MAP: ORGANIC CHEMISTRY (SMITH)

LibreTexts™

Map: Organic Chemistry (Smith)

The LibreTexts libraries are Powered by NICE CXOne and are supported by the Department of Education Open Textbook Pilot Project, the UC Davis Office of the Provost, the UC Davis Library, the California State University Affordable Learning Solutions Program, and Merlot. This material is based upon work supported by the National Science Foundation under Grant No. 1246120, 1525057, and 1413739.

Any opinions, findings, and conclusions or recommendations expressed in this material are those of the author(s) and do not necessarily reflect the views of the National Science Foundation nor the US Department of Education.

TABLE OF CONTENTS

5: Stereochemistry

6: Understanding Organic Reactions

7: Alkyl Halides and Nucleophilic Substitution

8: Alkyl Halides and Elimination Reactions

9: Alcohols, Ethers, and Epoxides

10: Alkenes

14: Conjugation, Resonance, and Dienes

15: Benzene and Aromatic Compounds

16: Electrophilic Aromatic Substitution

Licensing

*A detailed breakdown of this resource's licensing can be found in **Back Matter/Detailed Licensing**.*

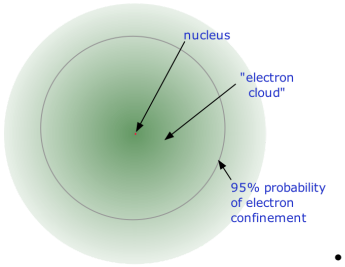
CHAPTER OVERVIEW

1: Structure and Bonding

1.1: The Periodic Table

The nuclear atom

The precise physical nature of atoms finally emerged from a series of elegant experiments carried out between 1895 and 1915. The most notable of these achievements was Ernest Rutherford's famous 1911 alpha-ray scattering experiment, which established that



- Almost all of the *mass* of an atom is contained within a tiny (and therefore extremely dense)*nucleus* which carries a positive electric charge whose value identifies each element and is known as the *atomic number* of the element.
- Almost all of the *volume* of an atom consists of empty space in which electrons, the fundamental carriers of negative electric charge, reside. The extremely small mass of the electron (1/1840 the mass of the hydrogen nucleus) causes it to behave as a quantum particle, which means that its location at any moment cannot be specified; the best we can do is describe its behavior in terms of the probability of its manifesting itself at any point in space. It is common (but somewhat misleading) to describe the volume of space in which the electrons of an atom have a significant probability of being found as the *electron cloud*. The latter has no definite outer boundary, so neither does the atom. The radius of an atom must be defined arbitrarily, such as the boundary in which the electron can be found with 95% probability. Atomic radii are typically 30-300 pm.

Protons and neutrons

The nucleus is itself composed of two kinds of particles. *Protons* are the carriers of positive electric charge in the nucleus; the proton charge is exactly the same as the electron charge, but of opposite sign. This means that in any [electrically neutral] atom, the number of protons in the nucleus (often referred to as the *nuclear charge*) is balanced by the same number of electrons outside the nucleus.

> *Because the electrons of an atom are in contact with the outside world, it is possible for one or more electrons to be lost, or some new ones to be added. The resulting electrically-charged atom is called an ion.*

The other nuclear particle is the *neutron*. As its name implies, this particle carries no electrical charge. Its mass is almost the same as that of the proton. Most nuclei contain roughly equal numbers of neutrons and protons, so we can say that these two particles together account for almost all the mass of the atom.

Atomic Number (Z)

What single parameter uniquely characterizes the atom of a given element? It is not the atom's relative mass, as we will see in the section on isotopes below. It is, rather, the number of protons in the nucleus, which we call the *atomic number* and denote by the symbol *Z*. Each proton carries an electric charge of +1, so the atomic number also specifies the electric charge of the nucleus. In the neutral atom, the *Z protons* within the nucleus are balanced by *Z electrons* outside it.

Atomic numbers were first worked out in 1913 by Henry Moseley, a young member of Rutherford's research group in Manchester.

Moseley searched for a measurable property of each element that increases linearly with atomic number. He found this in a class of X-rays emitted by an element when it is bombarded with electrons. The frequencies of these X-rays are unique to each element, and they increase uniformly in successive elements. Moseley found that the square roots of these frequencies give a straight line when plotted against Z; this enabled him to sort the elements in order of increasing atomic number.

You can think of the atomic number as a kind of serial number of an element, commencing at 1 for hydrogen and increasing by one for each successive element. The chemical name of the element and its symbol are uniquely tied to the atomic number; thus the symbol "Sr" stands for strontium, whose atoms all have $Z = 38$.

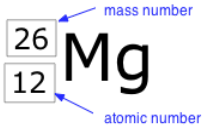
Mass number (A)

This is just the sum of the numbers of protons and neutrons in the nucleus. It is sometimes represented by the symbol *A*, so

in which *Z* is the atomic number and *N* is the *neutron number*.

Nuclides and their Symbols

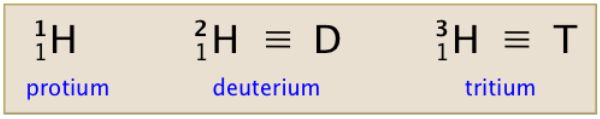
The term *nuclide* simply refers to any particular kind of nucleus. For example, a nucleus of atomic number 7 is a nuclide of nitrogen. Any nuclide is characterized by the pair of numbers (*Z* ,*A*). The element symbol depends on *Z* alone, so the symbol ^{26}Mg is used to specify the mass-26 nuclide of magnesium, whose name implies *Z*=12. A more explicit way of denoting a particular kind of nucleus is to add the atomic number as a subscript. Of course, this is somewhat redundant, since the symbol Mg **always** implies *Z*=12, but it is sometimes a convenience when discussing several nuclides.



Two nuclides having the **same** atomic number but different mass numbers are known as *isotopes*. Most elements occur in nature as mixtures of isotopes, but twenty-three of them (including beryllium and fluorine, shown in the table) are monoisotopic. For example, there are three *natural isotopes* of magnesium: ^{24}Mg (79% of all Mg atoms), ^{25}Mg (10%), and ^{26}Mg (11%); all three are present in all compounds of magnesium in about these same proportions.

	Z	mass numbers
H	1	1 2 3
He	2	3 4
Li	3	6 7
Be	4	9
B	5	10 11
C	6	12 13 14
N	7	14 15
O	8	16 17 18
F	9	19
Ne	10	20 21 22

Approximately 290 isotopes occur in nature. The two heavy isotopes of hydrogen are especially important— so much so that they have names and symbols of their own:



Deuterium accounts for only about 15 out of every one million atoms of hydrogen. Tritium, which is radioactive, is even less abundant. All the tritium on the earth is a by-product of the decay of other radioactive elements.

Atomic weights

Atoms are of course far too small to be weighed directly; weight measurements can only be made on the massive (but unknown) numbers of atoms that are observed in chemical reactions. The early combining-weight experiments of Dalton and others established that hydrogen is the lightest of the atoms, but the crude nature of the measurements and uncertainties about the formulas of many compounds made it difficult to develop a reliable scale of the relative weights of atoms. Even the most exacting

weight measurements we can make today are subject to experimental uncertainties that limit the precision to four significant figures at best.

The periodic table

The elements are arranged in a periodic table, which is probably the single most important learning aid in chemistry. It summarizes huge amounts of information about the elements in a way that facilitates the prediction of many of their properties and chemical reactions. The elements are arranged in seven horizontal rows, in order of increasing atomic number from left to right and top to bottom. The rows are called periods, and they are numbered from 1 to 7. The elements are stacked in such a way that elements with similar chemical properties form vertical columns, called groups, numbered from 1 to 18 (older periodic tables use a system based on roman numerals). Groups 1, 2, and 13–18 are the main group elements, listed as A in older tables. Groups 3–12 are in the middle of the periodic table and are the transition elements, listed as B in older tables. The two rows of 14 elements at the bottom of the periodic table are the lanthanides and the actinides, whose positions in the periodic table are indicated in group 3.

Atomic Orbitals

An orbital is the quantum mechanical refinement of Bohr's orbit. In contrast to his concept of a simple circular orbit with a fixed radius, orbitals are mathematically derived regions of space with different *probabilities* of having an electron.

One way of representing electron probability distributions was illustrated in Figure 6.5.2 for the 1*s* orbital of hydrogen. Because Ψ^2 gives the probability of finding an electron in a given volume of space (such as a cubic picometer), a plot of Ψ^2 versus distance from the nucleus (r) is a plot of the *probability density*. The 1*s* orbital is spherically symmetrical, so the probability of finding a 1*s* electron at any given point depends *only* on its distance from the nucleus. The probability density is greatest at $r = 0$ (at the nucleus) and decreases steadily with increasing distance. At very large values of r, the electron probability density is very small but *not* zero.

In contrast, we can calculate the *radial probability* (the probability of finding a 1*s* electron at a distance r from the nucleus) by adding together the probabilities of an electron being at all points on a series of x spherical shells of radius r_1, r_2, r_3,…, r_{x-1}, r_x. In effect, we are dividing the atom into very thin concentric shells, much like the layers of an onion (part (a) in Figure 6.6.1), and calculating the probability of finding an electron on each spherical shell. Recall that the electron probability density is greatest at $r = 0$ (part (b) in Figure 6.6.1), so the density of dots is greatest for the smallest spherical shells in part (a) in Figure 6.6.1. In contrast, the surface area of each spherical shell is equal to $4\pi r^2$, which increases very rapidly with increasing r (part (c) in Figure 6.6.1). Because the surface area of the spherical shells increases more rapidly with increasing r than the electron probability density decreases, the plot of radial probability has a maximum at a particular distance (part (d) in Figure 6.6.1). Most important, when r is very small, the surface area of a spherical shell is so small that the *total* probability of finding an electron close to the nucleus is very low; at the nucleus, the electron probability vanishes (part (d) in Figure 6.6.1).

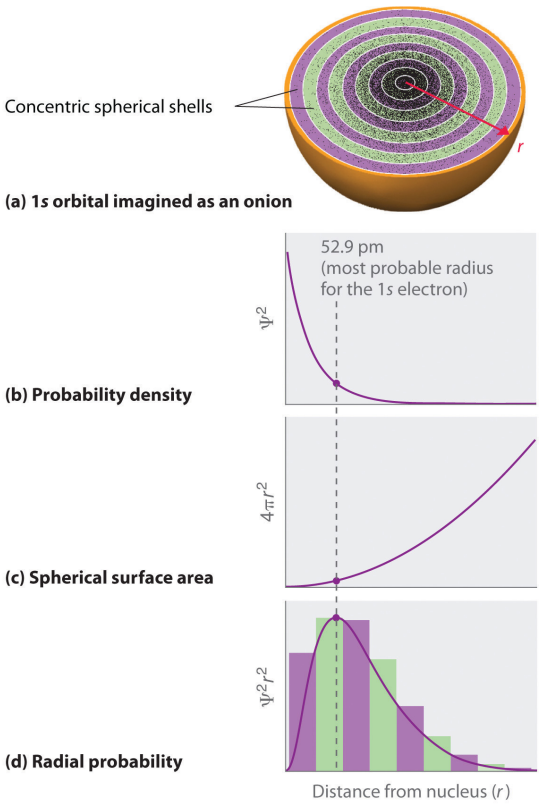


Figure 6.6.1 *Most Probable Radius for the Electron in the Ground State of the Hydrogen Atom. (a) Imagine dividing the atom's total volume into very thin concentric shells as shown in the onion drawing. (b) A plot of electron probability density Ψ^2 versus r shows that the electron probability density is greatest at r = 0 and falls off smoothly with increasing r. The density of the dots is therefore greatest in the innermost shells of the onion. (c) The surface area of each shell, given by $4\pi r^2$, increases rapidly with increasing r. (d) If we count the number of dots in each spherical shell, we obtain the total probability of finding the electron at a given value of r. Because the surface area of each shell increases more rapidly with increasing r than the electron probability density decreases, a plot of electron probability versus r (the radial probability) shows a peak. This peak corresponds to the most probable radius for the electron, 52.9 pm, which is exactly the radius predicted by Bohr's model of the hydrogen atom.*

For the hydrogen atom, the peak in the radial probability plot occurs at r = 0.529 Å (52.9 pm), which is exactly the radius calculated by Bohr for the n = 1 orbit. Thus the *most probable radius* obtained from quantum mechanics is identical to the radius calculated by classical mechanics. In Bohr's model, however, the electron was assumed to be at this distance 100% of the time, whereas in the Schrödinger model, it is at this distance only some of the time. The difference between the two models is attributable to the wavelike behavior of the electron and the Heisenberg uncertainty principle.

Figure 6.6.2 compares the electron probability densities for the hydrogen 1*s*, 2*s*, and 3*s* orbitals. Note that all three are spherically symmetrical. For the 2*s* and 3*s* orbitals, however (and for all other *s* orbitals as well), the electron probability density does not fall off smoothly with increasing *r*. Instead, a series of minima and maxima are observed in the radial probability plots (part (c) in Figure 6.6.2). The minima correspond to spherical nodes (regions of zero electron probability), which alternate with spherical regions of nonzero electron probability.

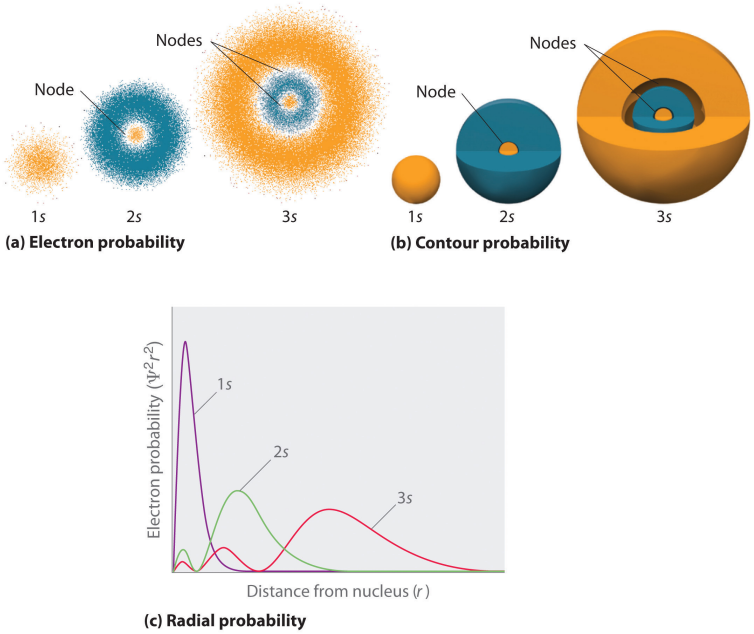


Figure 6.6.2: *Probability Densities for the 1s, 2s, and 3s Orbitals of the Hydrogen Atom. (a) The electron probability density in any plane that contains the nucleus is shown. Note the presence of circular regions, or nodes, where the probability density is zero. (b) Contour surfaces enclose 90% of the electron probability, which illustrates the different sizes of the 1s, 2s, and 3s orbitals. The cutaway drawings give partial views of the internal spherical nodes. The orange color corresponds to regions of space where the phase of the wave function is positive, and the blue color corresponds to regions of space where the phase of the wave function is negative. (c) In these plots of electron probability as a function of distance from the nucleus (r) in all directions (radial probability), the most probable radius increases as n increases, but the 2s and 3s orbitals have regions of significant electron probability at small values of r.*

s Orbitals

Three things happen to *s* orbitals as *n* increases (Figure 6.6.2):

1. They become larger, extending farther from the nucleus.
2. They contain more nodes. This is similar to a standing wave that has regions of significant amplitude separated by nodes, points with zero amplitude.
3. For a given atom, the *s* orbitals also become higher in energy as *n* increases because of their increased distance from the nucleus.

Orbitals are generally drawn as three-dimensional surfaces that enclose 90% of the electron density, as was shown for the hydrogen 1*s*, 2*s*, and 3*s* orbitals in part (b) in Figure 6.6.2. Although such drawings show the relative sizes of the orbitals, they do not normally show the spherical nodes in the 2*s* and 3*s* orbitals because the spherical nodes lie inside the 90% surface. Fortunately, the positions of the spherical nodes are not important for chemical bonding.

p Orbitals

Only *s* orbitals are spherically symmetrical. As the value of l increases, the number of orbitals in a given subshell increases, and the shapes of the orbitals become more complex. Because the 2*p* subshell has $l = 1$, with three values of m_l (−1, 0, and +1), there are three 2*p* orbitals.

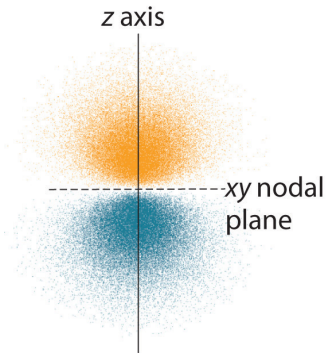


Figure 6.6.3: *Electron Probability Distribution for a Hydrogen 2p Orbital. The nodal plane of zero electron density separates the two lobes of the 2p orbital. As in Figure 6.6.2, the colors correspond to regions of space where the phase of the wave function is positive (orange) and negative (blue).*

The electron probability distribution for one of the hydrogen 2*p* orbitals is shown in Figure 6.6.3. Because this orbital has two lobes of electron density arranged along the *z* axis, with an electron density of zero in the *xy* plane (i.e., the *xy* plane is a nodal plane), it is a $2p_z$ orbital. As shown in Figure 6.6.4, the other two 2*p* orbitals have identical shapes, but they lie along the *x* axis ($2p_x$) and *y* axis ($2p_y$), respectively. Note that each *p* orbital has just one nodal plane. In each case, the phase of the wave function for each of the 2*p* orbitals is positive for the lobe that points along the positive axis and negative for the lobe that points along the negative axis. It is important to emphasize that these signs correspond to the *phase* of the wave that describes the electron motion, *not* to positive or negative charges.

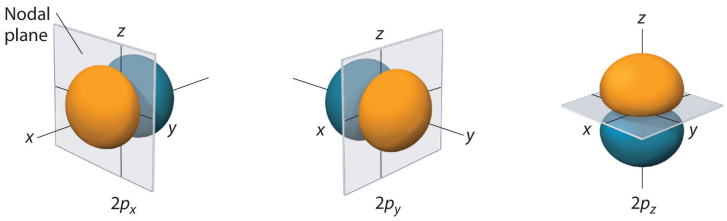


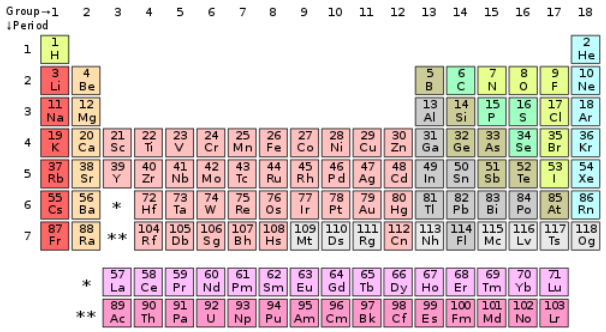
Figure 6.6.4 The Three Equivalent 2*p* Orbitals of the Hydrogen Atom

The surfaces shown enclose 90% of the total electron probability for the $2p_x$, $2p_y$, and $2p_z$ orbitals. Each orbital is oriented along the axis indicated by the subscript and a nodal plane that is perpendicular to that axis bisects each 2*p* orbital. The phase of the wave function is positive (orange) in the region of space where *x*, *y*, or *z* is positive and negative (blue) where *x*, *y*, or *z* is negative.

Just as with the *s* orbitals, the size and complexity of the *p* orbitals for any atom increase as the principal quantum number *n* increases. The shapes of the 90% probability surfaces of the 3*p*, 4*p*, and higher-energy *p* orbitals are, however, essentially the same as those shown in Figure 6.6.4.

The number of valence electrons

The number of valence electrons of an element can be determined by the periodic table group (vertical column) in which the element is categorized. With the exception of groups 3–12 (the transition metals), the units digit of the group number identifies how many valence electrons are associated with a neutral atom of an element listed under that particular column.



The periodic table of the chemical elements

Periodic table group	Valence electrons
Group 1 (I) (alkali metals)	1
Group 2 (II) (alkaline earth metals)	2
Groups 3-12 (transition metals)	2* (The 4s shell is complete and cannot hold any more electrons)
Group 13 (III) (boron group)	3
Group 14 (IV) (carbon group)	4
Group 15 (V) (pnictogens)	5
Group 16 (VI) (chalcogens)	6
Group 17 (VII) (halogens)	7
Group 18 (VIII or 0) (noble gases)	8**

** The general method for counting valence electrons is generally not useful for transition metals. Instead the modified d electron count method is used.*

*** Except for helium, which has only two valence electrons.*

Contributors

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

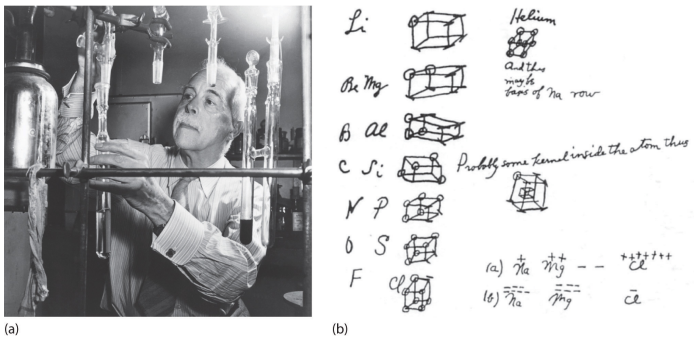
1.2: Bonding

Bonding Overview

Why are some substances chemically bonded molecules and others are an association of ions? The answer to this question depends upon the electronic structures of the atoms and nature of the chemical forces within the compounds. Although there are no sharply defined boundaries, chemical bonds are typically classified into three main types: ionic bonds, covalent bonds, and metallic bonds. In this chapter, each type of bond wil be discussed and the general properties found in typical substances in which the bond type occurs

1. Ionic bonds results from ***electrostatic forces that exist between ions of opposite charge***. These bonds typically involves a metal with a nonmetal
2. Covalent bonds ***result from the sharing of electrons between two atoms***. The bonds typically involves one nonmetallic element with another
3. Metallic bonds These bonds are found in solid metals (copper, iron, aluminum) with each metal bonded to several neighboring groups and bonding electrons free to move throughout the 3-dimensional structure.

Each bond classification is discussed in detail in subsequent sections of the chapter. Let's look at the preferred arrangements of electrons in atoms when they form chemical compounds.



(a) (b)

Figure 8.1.1 *G. N. Lewis and the Octet Rule. (a) Lewis is working in the laboratory. (b) In Lewis's original sketch for the octet rule, he initially placed the electrons at the corners of a cube rather than placing them as we do now.*

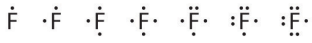
Lewis Symbols

At the beginning of the 20th century, the American chemist G. N. Lewis (1875–1946) devised a system of symbols—now called Lewis electron dot symbols, often shortened to *Lewis dot symbols*—that can be used for predicting the number of bonds formed by most elements in their compounds. Each Lewis dot symbol consists of the chemical symbol for an element surrounded by dots that represent its valence electrons.

Note
Lewis Dot symbols: • convenient representation of valence electrons • allows you to keep track of valence electrons during bond formation • consists of the chemical symbol for the element plus a dot for each valence electron

To write an element's Lewis dot symbol, we place dots representing its valence electrons, one at a time, around the element's chemical symbol. Up to four dots are placed above, below, to the left, and to the right of the symbol (in any order, as long as elements with four or fewer valence electrons have no more than one dot in each position). The next dots, for elements with more than four valence electrons, are again distributed one at a time, each paired with one of the first four. For example, the electron configuration for atomic sulfur is $[Ne]3s^2 3p^4$, thus there are ***six*** valence electrons. Its Lewis symbol would therefore be:

Fluorine, for example, with the electron configuration [He]$2s^2 2p^5$, has seven valence electrons, so its Lewis dot symbol is constructed as follows:



The number of dots in the Lewis dot symbol is the same as the number of valence electrons, which is the same as the last digit of the element's group number in the periodic table. Lewis dot symbols for the elements in period 2 are given in Figure 8.1.2.

Lewis used the unpaired dots to predict the number of bonds that an element will form in a compound. Consider the symbol for nitrogen in Figure 8.1.2. The Lewis dot symbol explains why nitrogen, with three unpaired valence electrons, tends to form compounds in which it shares the unpaired electrons to form three bonds. Boron, which also has three unpaired valence electrons in its Lewis dot symbol, also tends to form compounds with three bonds, whereas carbon, with four unpaired valence electrons in its Lewis dot symbol, tends to share all of its unpaired valence electrons by forming compounds in which it has four bonds.

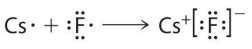
Element	Electron config.	Electron dot symbol
Li	[He]$2s^1$	
Be	[He]$2s^2$	
B	[He]$2s^2 2p^1$	
C	[He]$2s^2 2p^2$	
N	[He]$2s^2 2p^3$	
O	[He]$2s^2 2p^4$	
F	[He]$2s^2 2p^5$	
Ne	[He]$2s^2 2p^6$	

Figure 8.1.2: *Lewis Dot Symbols for the Elements in Period 2*

The Octet Rule

Lewis's major contribution to bonding theory was to recognize that atoms tend to lose, gain, or share electrons to reach a total of eight valence electrons, called an *octet*. This so-called octet rule explains the stoichiometry of most compounds in the *s* and *p* blocks of the periodic table. We now know from quantum mechanics that the number eight corresponds to one *ns* and three *np* valence orbitals, which together can accommodate a total of eight electrons. Remarkably, though, Lewis's insight was made nearly a decade before Rutherford proposed the nuclear model of the atom. An exception to the octet rule is helium, whose $1s^2$ electron configuration gives it a full $n = 1$ shell, and hydrogen, which tends to gain or share its one electron to achieve the electron configuration of helium.

Lewis dot symbols can also be used to represent the ions in ionic compounds. The reaction of cesium with fluorine, for example, to produce the ionic compound CsF can be written as follows:



No dots are shown on Cs^+ in the product because cesium has lost its single valence electron to fluorine. The transfer of this electron produces the Cs^+ ion, which has the valence electron configuration of Xe, and the F^- ion, which has a total of eight valence electrons (an octet) and the Ne electron configuration. This description is consistent with the statement that among the main group elements, ions in simple binary ionic compounds generally have the electron configurations of the nearest noble gas. The charge of each ion is written in the product, and the anion and its electrons are enclosed in brackets. This notation emphasizes that the ions are associated electrostatically; no electrons are shared between the two elements.

Note

Atoms often gain, lose, or share electrons to achieve the same number of electrons as the noble gas closest to them in the periodic table.

Ionic bonding

Ions are atoms or molecules which are electrically charged. **Cations** are positively charged and **anions** carry a negative charge. Ions form when atoms gain or lose electrons. Since electrons are negatively charged, an atom that loses one or more electrons will become positively charged; an atom that gains one or more electrons becomes negatively charged.

Ionic bonding is the attraction between positively- and negatively-charged **ions**. These oppositely charged ions attract each other to form ionic networks (or lattices). Electrostatics explains why this happens: opposite charges attract and like charges repel. When many ions attract each other, they form large, ordered, crystal lattices in which each ion is surrounded by ions of the opposite charge. Generally, when metals react with non-metals, electrons are transferred from the metals to the non-metals. The metals form positively-charged ions and the non-metals form negatively-charged ions.

Generating Ionic Bonds

Ionic bonds form when metals and non-metals chemically react. By definition, a metal is relatively stable if it loses electrons to form a complete valence shell and becomes positively charged. Likewise, a non-metal becomes stable by gaining electrons to complete its valence shell and become negatively charged. When metals and non-metals react, the metals lose electrons by transferring them to the non-metals, which gain them. Consequently, ions are formed, which instantly attract each other—ionic bonding.

Example 8.2.1a: Sodium Chloride

For example, in the reaction of Na (sodium) and Cl (chlorine), each Cl atom takes one electron from a Na atom. Therefore each Na becomes a Na^+ cation and each Cl atom becomes a Cl^- anion. Due to their opposite charges, they attract each other to form an ionic lattice. The formula (ratio of positive to negative ions) in the lattice is **NaCl**.

For full video of making NaCl from sodium metal and chlorine gase, see https://www.youtube.com/watch?v=WVonuBjCrNo. These ions are arranged in solid NaCl in a regular three-dimensional arrangement (or lattice):

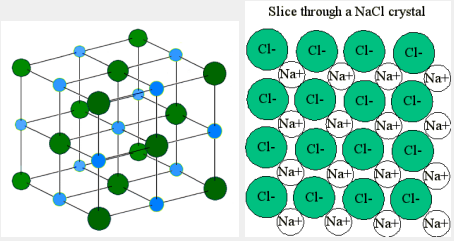
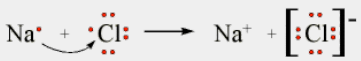


Figure: *NaCl lattice. (left) 3-D structure and (right) simple 2D slice through lattes. Images used with permission from Wikipedia and Mike Blaber.*

The chlorine has a high affinity for electrons, and the sodium has a low ionization potential. Thus the chlorine gains an electron from the sodium atom. This can be represented using ***electron-dot symbols*** (here we will consider one chlorine atom, rather than Cl_2):



The arrow indicates the transfer of the electron from sodium to chlorine to form the Na^+ metal ion and the Cl^- chloride ion. Each ion now has an **octet** of electrons in its valence shell:

- Na^+: $2s^2 2p^6$
- Cl^-: $3s^2 3p^6$

The importance of noble gas structures

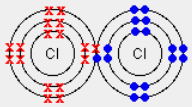
At a simple level a lot of importance is attached to the electronic structures of noble gases like neon or argon which have eight electrons in their outer energy levels (or two in the case of helium). These noble gas structures are thought of as being in some way a "desirable" thing for an atom to have.

You may well have been left with the strong impression that when other atoms react, they try to achieve noble gas structures. As well as achieving noble gas structures by transferring electrons from one atom to another as in ionic bonding, it is also possible for atoms to reach these stable structures by sharing electrons to give covalent bonds.

Some very simple covalent molecules

Chlorine

For example, two chlorine atoms could both achieve stable structures by sharing their single unpaired electron as in the diagram.

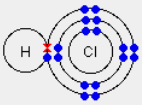


The fact that one chlorine has been drawn with electrons marked as crosses and the other as dots is simply to show where all the electrons come from. In reality there is no difference between them. The two chlorine atoms are said to be joined by a covalent bond. The reason that the two chlorine atoms stick together is that the shared pair of electrons is attracted to the nucleus of both chlorine atoms.

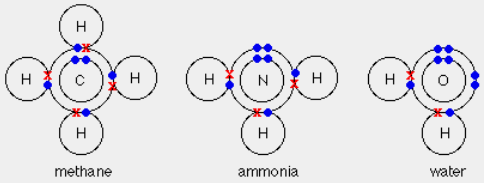
Hydrogen

Hydrogen atoms only need two electrons in their outer level to reach the noble gas structure of helium. Once again, the covalent bond holds the two atoms together because the pair of electrons is attracted to both nuclei.

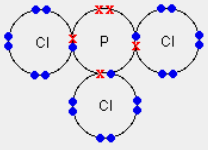
Hydrogen chloride



The hydrogen has a helium structure, and the chlorine an argon structure. Most of the simple molecules you draw do in fact have all their atoms with noble gas structures. For example:



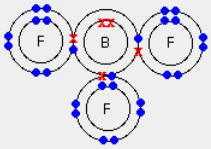
Even with a more complicated molecule like , there's no problem. In this case, only the outer electrons are shown for simplicity. Each atom in this structure has inner layers of electrons of 2, 8. Again, everything present has a noble gas structure.



Cases where the simple view throws up problems

Boron trifluoride, BF_3

A boron atom only has 3 electrons in its outer level, and there is no possibility of it reaching a noble gas structure by simple sharing of electrons. Is this a problem? No. The boron has formed the maximum number of bonds that it can in the circumstances, and this is a perfectly valid structure.

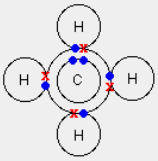


Energy is released whenever a covalent bond is formed. Because energy is being lost from the system, it becomes more stable after every covalent bond is made. It follows, therefore, that an atom will tend to make as many covalent bonds as possible. In the case of boron in BF_3, three bonds is the maximum possible because boron only has 3 electrons to share.
Note: You might perhaps wonder why boron doesn't form ionic bonds with fluorine instead. Boron doesn't form ions because the total energy needed to remove three electrons to form a B^{3+} ion is simply too great to be recoverable when attractions are set up between the boron and fluoride ions.

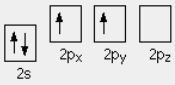
A more sophisticated view of covalent bonding

The bonding in methane, CH_4

What is wrong with the dots-and-crosses picture of bonding in methane?
We are starting with methane because it is the simplest case which illustrates the sort of processes involved. You will remember that the dots-and-crossed picture of methane looks like this.



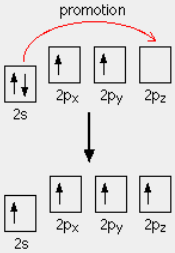
There is a serious mis-match between this structure and the modern electronic structure of carbon, $1s^2 2s^2 2p_x^1 2p_y^1$. The modern structure shows that there are only 2 unpaired electrons to share with hydrogens, instead of the 4 which the simple view requires.



You can see this more readily using the electrons-in-boxes notation. Only the 2-level electrons are shown. The $1s^2$ electrons are too deep inside the atom to be involved in bonding. The only electrons directly available for sharing are the 2p electrons. Why then isn't methane CH_2?

Promotion of an electron

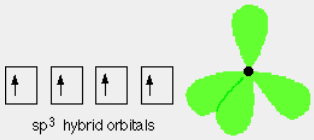
When bonds are formed, energy is released and the system becomes more stable. If carbon forms 4 bonds rather than 2, twice as much energy is released and so the resulting molecule becomes even more stable.
There is only a small energy gap between the 2s and 2p orbitals, and so it pays the carbon to provide a small amount of energy to promote an electron from the 2s to the empty 2p to give 4 unpaired electrons. The extra energy released when the bonds form more than compensates for the initial input.



The carbon atom is now said to be in an excited state. Now that we've got 4 unpaired electrons ready for bonding, another problem arises. In methane all the carbon-hydrogen bonds are identical, but our electrons are in two different kinds of orbitals. You aren't going to get four identical bonds unless you start from four identical orbitals.

Hybridization

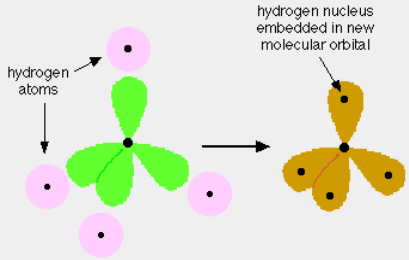
The electrons rearrange themselves again in a process called hybridization. This reorganizes the electrons into four identical hybrid orbitals called sp^3 hybrids (because they are made from one s orbital and three p orbitals). You should read "sp^3" as "s p three" - not as "s p cubed".



sp^3 hybrid orbitals look a bit like half a p orbital, and they arrange themselves in space so that they are as far apart as possible. You can picture the nucleus as being at the center of a tetrahedron (a triangularly based pyramid) with the orbitals pointing to the corners. For clarity, the nucleus is drawn far larger than it really is.

What happens when the bonds are formed?

Remember that hydrogen's electron is in a 1s orbital - a spherically symmetric region of space surrounding the nucleus where there is some fixed chance (say 95%) of finding the electron. When a covalent bond is formed, the atomic orbitals (the orbitals in the individual atoms) merge to produce a new molecular orbital which contains the electron pair which creates the bond.



Four molecular orbitals are formed, looking rather like the original sp^3 hybrids, but with a hydrogen nucleus embedded in each lobe. Each orbital holds the 2 electrons that we've previously drawn as a dot and a cross.
The principles involved - promotion of electrons if necessary, then hybridisation, followed by the formation of molecular orbitals - can be applied to any covalently-bound molecule.

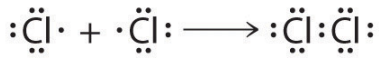
Contributors

- Mike Blaber (Florida State University)
- Jim Clark (Chemguide.co.uk)

1.3: Lewis Structures

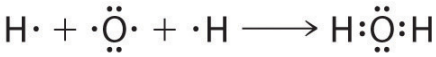
Using Lewis Dot Symbols to Describe Covalent Bonding

This sharing of electrons allowing atoms to "stick" together is the basis of covalent bonding. There is some intermediate distant, generally a bit longer than 0.1 nm, or if you prefer 100 pm, at which the attractive forces significantly outweigh the repulsive forces and a bond will be formed if both atoms can achieve a completen s2np6 configuration. It is this behavior that Lewis captured in his octet rule. The valence electron configurations of the constituent atoms of a covalent compound are important factors in determining its structure, stoichiometry, and properties. For example, chlorine, with seven valence electrons, is one electron short of an octet. If two chlorine atoms share their unpaired electrons by making a covalent bond and forming Cl2, they can each complete their valence shell:



Each chlorine atom now has an octet. The electron pair being shared by the atoms is called a bonding pair ; the other three pairs of electrons on each chlorine atom are called lone pairs. Lone pairs are not involved in covalent bonding. If both electrons in a covalent bond come from the same atom, the bond is called a coordinate covalent bond.

We can illustrate the formation of a water molecule from two hydrogen atoms and an oxygen atom using Lewis dot symbols:



The structure on the right is the Lewis electron structure, or Lewis structure, for H2O. With two bonding pairs and two lone pairs, the oxygen atom has now completed its octet. Moreover, by sharing a bonding pair with oxygen, each hydrogen atom now has a full valence shell of two electrons. Chemists usually indicate a bonding pair by a single line, as shown here for our two examples:

The following procedure can be used to construct Lewis electron structures for more complex molecules and ions:

1. Arrange the atoms to show specific connections. When there is a central atom, it is usually the least electronegative element in the compound. Chemists usually list this central atom first in the chemical formula (as in CCl4 and CO32−, which both have C as the central atom), which is another clue to the compound’s structure. Hydrogen and the halogens are almost always connected to only one other atom, so they are usually terminal rather than central.

Note the Pattern

The central atom is usually the least electronegative element in the molecule or ion; hydrogen and the halogens are usually terminal.

2. Determine the total number of valence electrons in the molecule or ion. Add together the valence electrons from each atom. (Recall from Chapter 2 that the number of valence electrons is indicated by the position of the element in the periodic table.) If the species is a polyatomic ion, remember to add or subtract the number of electrons necessary to give the total charge on the ion. For CO32−, for example, we add two electrons to the total because of the −2 charge.

3. Place a bonding pair of electrons between each pair of adjacent atoms to give a single bond. In H2O, for example, there is a bonding pair of electrons between oxygen and each hydrogen.

4. Beginning with the terminal atoms, add enough electrons to each atom to give each atom an octet (two for hydrogen). These electrons will usually be lone pairs.

5. If any electrons are left over, place them on the central atom. We explain in Section 4.6 that some atoms are able to accommodate more than eight electrons.

6. If the central atom has fewer electrons than an octet, use lone pairs from terminal atoms to form multiple (double or triple) bonds to the central atom to achieve an octet. This will not change the number of electrons on the terminal atoms.

Now let's apply this procedure to some particular compounds, beginning with one we have already discussed.

H_2O

1. Because H atoms are almost always terminal, the arrangement within the molecule must be HOH.

2. Each H atom (group 1) has 1 valence electron, and the O atom (group 16) has 6 valence electrons, for a total of 8 valence electrons.

3. Placing one bonding pair of electrons between the O atom and each H atom gives H:O:H, with 4 electrons left over.

4. Each H atom has a full valence shell of 2 electrons.

5. Adding the remaining 4 electrons to the oxygen (as two lone pairs) gives the following structure:

This is the Lewis structure we drew earlier. Because it gives oxygen an octet and each hydrogen two electrons, we do not need to use step 6.

OCl^-

1. With only two atoms in the molecule, there is no central atom.

2. Oxygen (group 16) has 6 valence electrons, and chlorine (group 17) has 7 valence electrons; we must add one more for the negative charge on the ion, giving a total of 14 valence electrons.

3. Placing a bonding pair of electrons between O and Cl gives O:Cl, with 12 electrons left over.

4. If we place six electrons (as three lone pairs) on each atom, we obtain the following structure:

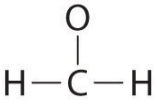
Each atom now has an octet of electrons, so steps 5 and 6 are not needed. The Lewis electron structure is drawn within brackets as is customary for an ion, with the overall charge indicated outside the brackets, and the bonding pair of electrons is indicated by a solid line. OCl^- is the hypochlorite ion, the active ingredient in chlorine laundry bleach and swimming pool disinfectant.

CH_2O

1. Because carbon is less electronegative than oxygen and hydrogen is normally terminal, C must be the central atom. One possible arrangement is as follows:

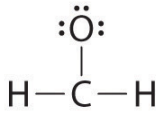
2. Each hydrogen atom (group 1) has one valence electron, carbon (group 14) has 4 valence electrons, and oxygen (group 16) has 6 valence electrons, for a total of [(2)(1) + 4 + 6] = 12 valence electrons.

3. Placing a bonding pair of electrons between each pair of bonded atoms gives the following:



Six electrons are used, and 6 are left over.

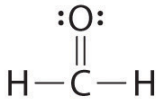
4. Adding all 6 remaining electrons to oxygen (as three lone pairs) gives the following:



Although oxygen now has an octet and each hydrogen has 2 electrons, carbon has only 6 electrons.

5. There are no electrons left to place on the central atom.

6. To give carbon an octet of electrons, we use one of the lone pairs of electrons on oxygen to form a carbon–oxygen double bond:



Both the oxygen and the carbon now have an octet of electrons, so this is an acceptable Lewis electron structure. The O has two bonding pairs and two lone pairs, and C has four bonding pairs. This is the structure of formaldehyde, which is used in embalming fluid.

An alternative structure can be drawn with one H bonded to O. Formal charges, discussed later in this section, suggest that such a structure is less stable than that shown previously.

Example

Write the Lewis electron structure for each species.

1. NCl_3
2. S_2^-
3. NOCl

Given: chemical species

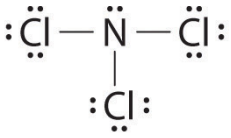
Asked for: Lewis electron structures

Strategy:

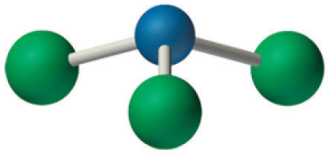
Use the six-step procedure to write the Lewis electron structure for each species.

Solution:

1. Nitrogen is less electronegative than chlorine, and halogen atoms are usually terminal, so nitrogen is the central atom. The nitrogen atom (group 15) has 5 valence electrons and each chlorine atom (group 17) has 7 valence electrons, for a total of 26 valence electrons. Using 2 electrons for each N–Cl bond and adding three lone pairs to each Cl account for (3 × 2) + (3 × 2 × 3) = 24 electrons. Rule 5 leads us to place the remaining 2 electrons on the central N:

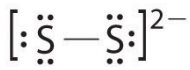


Nitrogen trichloride is an unstable oily liquid once used to bleach flour; this use is now prohibited in the United States.

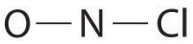


Nitrogen trichloride

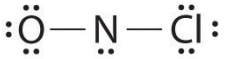
2. In a diatomic molecule or ion, we do not need to worry about a central atom. Each sulfur atom (group 16) contains 6 valence electrons, and we need to add 2 electrons for the −2 charge, giving a total of 14 valence electrons. Using 2 electrons for the S–S bond, we arrange the remaining 12 electrons as three lone pairs on each sulfur, giving each S atom an octet of electrons:



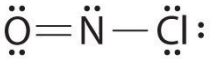
3. Because nitrogen is less electronegative than oxygen or chlorine, it is the central atom. The N atom (group 15) has 5 valence electrons, the O atom (group 16) has 6 valence electrons, and the Cl atom (group 17) has 7 valence electrons, giving a total of 18 valence electrons. Placing one bonding pair of electrons between each pair of bonded atoms uses 4 electrons and gives the following:



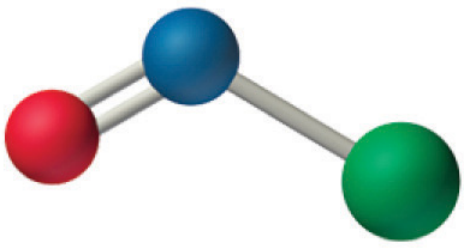
Adding three lone pairs each to oxygen and to chlorine uses 12 more electrons, leaving 2 electrons to place as a lone pair on nitrogen:



Because this Lewis structure has only 6 electrons around the central nitrogen, a lone pair of electrons on a terminal atom must be used to form a bonding pair. We could use a lone pair on either O or Cl. Because we have seen many structures in which O forms a double bond but none with a double bond to Cl, it is reasonable to select a lone pair from O to give the following:



All atoms now have octet configurations. This is the Lewis electron structure of nitrosyl chloride, a highly corrosive, reddish-orange gas.



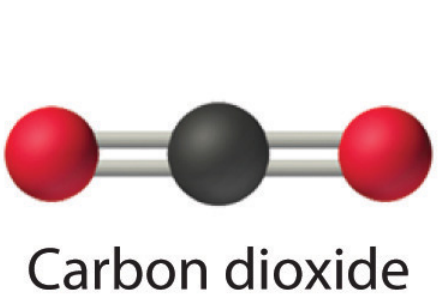
Nitrosyl chloride

Exercise

Write Lewis electron structures for CO_2 and SCl_2, a vile-smelling, unstable red liquid that is used in the manufacture of rubber.

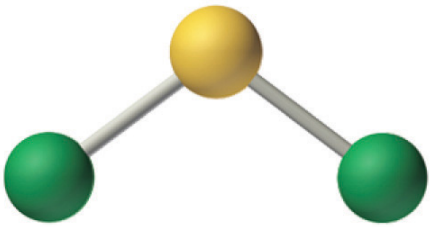
Answer:

1.



Carbon dioxide

2.



Sulfur dichloride

Formal Charges

It is sometimes possible to write more than one Lewis structure for a substance that does not violate the octet rule, as we saw for CH2O, but not every Lewis structure may be equally reasonable. In these situations, we can choose the most stable Lewis structure by considering the formal charge on the atoms, which is the difference between the number of valence electrons in the free atom and the number assigned to it in the Lewis electron structure. The formal charge is a way of computing the charge distribution within a Lewis structure; the sum of the formal charges on the atoms within a molecule or an ion must equal the overall charge on the molecule or ion. A formal charge does not represent a true charge on an atom in a covalent bond but is simply used to predict the most likely structure when a compound has more than one valid Lewis structure.

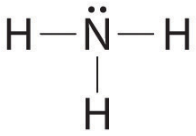
To calculate formal charges, we assign electrons in the molecule to individual atoms according to these rules:

- Nonbonding electrons are assigned to the atom on which they are located.
- Bonding electrons are divided equally between the bonded atoms.

For each atom, we then compute a formal charge:

$$\underset{}{\text{formal charge}} = \underset{(\text{free atom})}{\text{valence } e^-} - \underset{(\text{atom in Lewis structure})}{\left(\text{non-bonding } e^- + \frac{\text{bonding } e^-}{2}\right)} \qquad (5.3.1)$$

To illustrate this method, let's calculate the formal charge on the atoms in ammonia (NH3) whose Lewis electron structure is as follows:



Ammonia

A neutral nitrogen atom has five valence electrons (it is in group 15). From its Lewis electron structure, the nitrogen atom in ammonia has one lone pair and shares three bonding pairs with hydrogen atoms, so nitrogen itself is assigned a total of five

electrons [2 nonbonding e− + (6 bonding e−/2)]. Substituting into Equation 5.3.1, we obtain

$$formal\ charge\ (N) = 5\ valence\ e^- - \left(2\ non-bonding\ e^- + \frac{6\ bonding\ e^-}{2}\right) = 0 \qquad (4.4.2)$$

A neutral hydrogen atom has one valence electron. Each hydrogen atom in the molecule shares one pair of bonding electrons and is therefore assigned one electron [0 nonbonding e− + (2 bonding e−/2)]. Using Equation 4.4.1 to calculate the formal charge on hydrogen, we obtain

$$formal\ charge\ (H) = 1\ valence\ e^- - \left(0\ non-bonding\ e^- + \frac{2\ bonding\ e^-}{2}\right) = 0 \qquad (4.4.3)$$

The hydrogen atoms in ammonia have the same number of electrons as neutral hydrogen atoms, and so their formal charge is also zero. Adding together the formal charges should give us the overall charge on the molecule or ion. In this example, the nitrogen and each hydrogen has a formal charge of zero. When summed the overall charge is zero, which is consistent with the overall charge on the NH_3 molecule.

Typically, the structure with the most charges on the atoms closest to zero is the more stable Lewis structure. In cases where there are positive or negative formal charges on various atoms, stable structures generally have negative formal charges on the more electronegative atoms and positive formal charges on the less electronegative atoms. The next example further demonstrates how to calculate formal charges.

Example

Calculate the formal charges on each atom in the NH_4^+ ion.

Given: chemical species

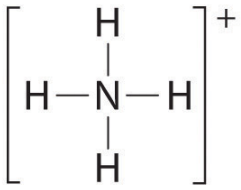
Asked for: formal charges

Strategy:

Identify the number of valence electrons in each atom in the NH_4^+ ion. Use the Lewis electron structure of NH_4^+ to identify the number of bonding and nonbonding electrons associated with each atom and then use Equation 4.4.1 to calculate the formal charge on each atom.

Solution:

The Lewis electron structure for the NH_4^+ion is as follows:



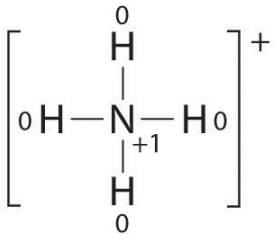
The nitrogen atom shares four bonding pairs of electrons, and a neutral nitrogen atom has five valence electrons. Using Equation 4.4.1, the formal charge on the nitrogen atom is therefore

formalcharge(N)=5−(0+82)=0

Each hydrogen atom in has one bonding pair. The formal charge on each hydrogen atom is therefore

formalcharge(H)=1−(0+22)=0

The formal charges on the atoms in the NH_4^+ ion are thus

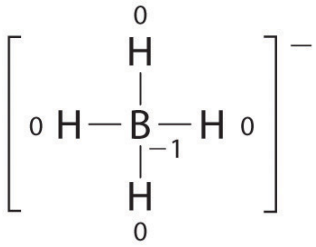


Adding together the formal charges on the atoms should give us the total charge on the molecule or ion. In this case, the sum of the formal charges is 0 + 1 + 0 + 0 + 0 = +1.

Exercise

Write the formal charges on all atoms in BH_4^-

Answer:



If an atom in a molecule or ion has the number of bonds that is typical for that atom (e.g., four bonds for carbon), its formal charge is zero.

Using Formal Charges to Distinguish between Lewis Structures

As an example of how formal charges can be used to determine the most stable Lewis structure for a substance, we can compare two possible structures for CO2. Both structures conform to the rules for Lewis electron structures.

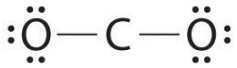
CO_2

1. C is less electronegative than O, so it is the central atom.

2. C has 4 valence electrons and each O has 6 valence electrons, for a total of 16 valence electrons.

3. Placing one electron pair between the C and each O gives O–C–O, with 12 electrons left over.

4. Dividing the remaining electrons between the O atoms gives three lone pairs on each atom:



This structure has an octet of electrons around each O atom but only 4 electrons around the C atom.

5. No electrons are left for the central atom.

6. To give the carbon atom an octet of electrons, we can convert two of the lone pairs on the oxygen atoms to bonding electron pairs. There are, however, two ways to do this. We can either take one electron pair from each oxygen to form a symmetrical structure or take both electron pairs from a single oxygen atom to give an asymmetrical structure:

Both Lewis electron structures give all three atoms an octet. How do we decide between these two possibilities? The formal charges for the two Lewis electron structures of CO2 are as follows:

Both Lewis structures have a net formal charge of zero, but the structure on the right has a +1 charge on the more electronegative atom (O). Thus the symmetrical Lewis structure on the left is predicted to be more stable, and it is, in fact, the structure observed experimentally. Remember, though, that formal charges do not represent the actual charges on atoms in a molecule or ion. They are used simply as a bookkeeping method for predicting the most stable Lewis structure for a compound.

Note the Pattern

The Lewis structure with the set of formal charges closest to zero is usually the most stable

Example

The thiocyanate ion (SCN^-), which is used in printing and as a corrosion inhibitor against acidic gases, has at least two possible Lewis electron structures. Draw two possible structures, assign formal charges on all atoms in both, and decide which is the preferred arrangement of electrons.

Given: chemical species

Asked for: Lewis electron structures, formal charges, and preferred arrangement

Strategy:

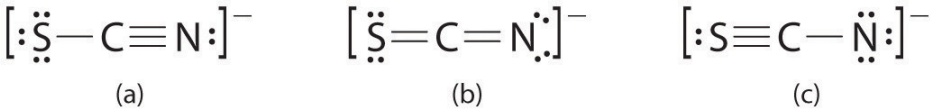
A Use the step-by-step procedure to write two plausible Lewis electron structures for SCN^-.

B Calculate the formal charge on each atom using Equation 4.4.1.

C Predict which structure is preferred based on the formal charge on each atom and its electronegativity relative to the other atoms present.

Solution:

A Possible Lewis structures for the SCN^- ion are as follows:



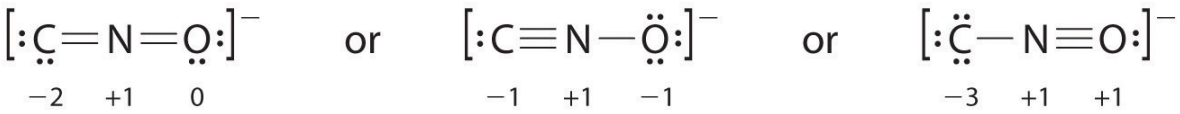
B We must calculate the formal charges on each atom to identify the more stable structure. If we begin with carbon, we notice that the carbon atom in each of these structures shares four bonding pairs, the number of bonds typical for carbon, so it has a formal charge of zero. Continuing with sulfur, we observe that in (a) the sulfur atom shares one bonding pair and has three lone pairs and has a total of six valence electrons. The formal charge on the sulfur atom is therefore $6−(6+22)=−1$.$5−(4+42)=−1$ In (c), nitrogen has a formal charge of −2.

C Which structure is preferred? Structure (b) is preferred because the negative charge is on the more electronegative atom (N), and it has lower formal charges on each atom as compared to structure (c): 0, −1 versus +1, −2.

Exercise

Salts containing the fulminate ion (CNO^-) are used in explosive detonators. Draw three Lewis electron structures for CNO^- and use formal charges to predict which is more stable. (Note: N is the central atom.)

Answer:



The second structure is predicted to be more stable.

Contributors

- Anonymous

1.4: Lewis Structures Continued

Three cases can be constructed that do not follow the octet rule, and as such, they are known as the exceptions to the octet rule. Following the Octet Rule for Lewis Dot Structures leads to the most accurate depictions of stable molecular and atomic structures and because of this we always want to use the octet rule when drawing Lewis Dot Structures. However, it is hard to imagine that one rule could be followed by all molecules. There is always an exception, and in this case, three exceptions. The octet rule is violated in these three scenarios:

1. When there are an odd number of valence electrons
2. When there are too few valence electrons
3. When there are too many valence electrons

Exception 1: Species with Odd Numbers of Electrons

The first exception to the Octet Rule is when there are an odd number of valence electrons. An example of this would be Nitrogen (II) Oxide (NO ,refer to figure one). Nitrogen has 5 valence electrons while Oxygen has 6. The total would be 11 valence electrons to be used. The Octet Rule for this molecule is fulfilled in the above example, however that is with 10 valence electrons. The last one does not know where to go. The lone electron is called an unpaired electron. But where should the unpaired electron go? The unpaired electron is usually placed in the Lewis Dot Structure so that each element in the structure will have the *lowest* formal charge possible. The formal charge is *the perceived charge on an individual atom in a molecule when atoms do not contribute equal numbers of electrons to the bonds they participate in*. The formula to find a formal charge is:

Formal Charge= [# of valence e^- the atom would have on its own] - [# of lone pair electrons on that atom]

- [# of bonds that atom participates in]

No formal charge at all is the most ideal situation. An example of a stable molecule with an odd number of valence electrons would be nitrogen monoxide. Nitrogen monoxide has 11 valence electrons. If you need more information about formal charges, see Lewis Structures. If we were to imagine nitrogen monoxide had ten valence electrons we would come up with the Lewis Structure (Figure 8.7.1):

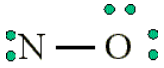


Figure 8.7.1. This is if Nitrogen monoxide has only *ten* valence electrons, which it does not.

Let's look at the formal charges of Figure 8.7.2 based on this Lewis structure. Nitrogen normally has five valence electrons. In Figure 8.7.1, it has two lone pair electrons and it participates in two bonds (a double bond) with oxygen. This results in nitrogen having a formal charge of +1. Oxygen normally has six valence electrons. In Figure 8.7.1, oxygen has four lone pair electrons and it participates in two bonds with nitrogen. Oxygen therefore has a formal charge of 0. The overall molecule here has a formal charge of +1 (+1 for nitrogen, 0 for oxygen. +1 + 0 = +1). However, if we add the eleventh electron to nitrogen (because we want the molecule to have the *lowest* total formal charge), it will bring both the nitrogen and the molecule's overall charges to zero, the most ideal formal charge situation. That is exactly what is done to get the correct Lewis structure for nitrogen monoxide (Figure 8.7.2):

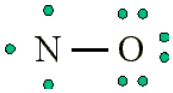


Figure 8.7.2. The proper Lewis structure for NO molecule

Free Radicals

There are actually very few stable molecules with odd numbers of electrons that exist, since that unpaired electron is willing to react with other unpaired electrons. Most odd electron species are highly reactive, which we call Free Radicals. Because of their instability, free radicals bond to atoms in which they can take an electron from in order to become stable, making them very chemically reactive. Radicals are found as both reactants and products, but generally react to form more stable molecules as soon as they can. In order to emphasize the existence of the unpaired electron, radicals are denoted with a dot in front of their chemical

symbol as with , the hydroxyl radical. An example of a radical you may by familiar with already is the gaseous chlorine atom, denoted . Interestingly, odd Number of Valence Electrons will result in the molecule being paramagnetic.

Exception 2: Incomplete Octets

The second exception to the Octet Rule is when there are too few valence electrons that results in an incomplete Octet. There are even more occasions where the octet rule does not give the most correct depiction of a molecule or ion. This is also the case with incomplete octets. Species with incomplete octets are pretty rare and generally are only found in some beryllium, aluminum, and boron compounds including the boron hydrides. Let's take a look at one such hydride, BH_3 (Borane).

If one was to make a Lewis structure for BH_3 following the basic strategies for drawing Lewis structures, one would probably come up with this structure (Figure 8.7.3):

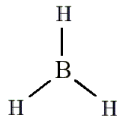


Figure 8.7.3

The problem with this structure is that boron has an incomplete octet; it only has six electrons around it. Hydrogen atoms can naturally only have only 2 electrons in their outermost shell (their version of an octet), and as such there are no spare electrons to form a double bond with boron. One might surmise that the failure of this structure to form complete octets must mean that this bond should be ionic instead of covalent. However, boron has an electronegativity that is very similar to hydrogen, meaning there is likely very little ionic character in the hydrogen to boron bonds, and as such this Lewis structure, though it does not fulfill the octet rule, is likely the best structure possible for depicting BH_3 with Lewis theory. One of the things that may account for BH_3's incomplete octet is that it is commonly a transitory species, formed temporarily in reactions that involve multiple steps.

Let's take a look at another incomplete octet situation dealing with boron, BF_3 (Boron trifluorine). Like with BH_3, the initial drawing of a Lewis structure of BF_3 will form a structure where boron has only six electrons around it (Figure 8.7.4).

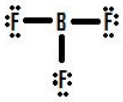


Figure 8.7.4

If you look Figure 8.7.4, you can see that the fluorine atoms possess extra lone pairs that they can use to make additional bonds with boron, and you might think that all you have to do is make one lone pair into a bond and the structure will be correct. If we add one double bond between boron and one of the fluorines we get the following Lewis Structure (Figure 8.7.5):

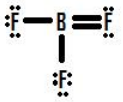


Figure 8.7.5

Each fluorine has eight electrons, and the boron atom has eight as well! Each atom has a perfect octet, right? Not so fast. We must examine the formal charges of this structure. The fluorine that shares a double bond with boron has six electrons around it (four from its two lone pairs of electrons and one each from its two bonds with boron). This is one less electron than the number of valence electrons it would have naturally (Group Seven elements have seven valence electrons), so it has a formal charge of +1. The two flourines that share single bonds with boron have seven electrons around them (six from their three lone pairs and one from their single bonds with boron). This is the same amount as the number of valence electrons they would have on their own, so they both have a formal charge of zero. Finally, boron has four electrons around it (one from each of its four bonds shared with fluorine). This is one more electron than the number of valence electrons that boron would have on its own, and as such boron has a formal charge of -1.

This structure is supported by the fact that the experimentally determined bond length of the boron to fluorine bonds in BF_3 is less than what would be typical for a single bond (see Bond Order and Lengths). However, this structure contradicts one of the major rules of formal charges: Negative formal charges are supposed to be found on the more electronegative atom(s) in a bond, but in the structure depicted in Figure 8.7.5, a *positive* formal charge is found on fluorine, which not only is the most electronegative element in the structure, but the most electronegative element in the entire periodic table ( ). Boron on the other hand, with the much lower electronegativity of 2.0, has the negative formal charge in this structure. This formal charge-electronegativity disagreement makes this double-bonded structure impossible.

However the large electronegativity difference here, as opposed to in BH_3, signifies significant polar bonds between boron and fluorine, which means there is a high ionic character to this molecule. This suggests the possibility of a semi-ionic structure such as seen in Figure 8.7.6:

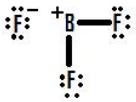


Figure 8.7.6

None of these three structures is the "correct" structure in this instance. The most "correct" structure is most likely a resonance of all three structures: the one with the incomplete octet (Figure 8.7.4), the one with the double bond (Figure 8.7.5), and the one with the ionic bond (Figure 8.7.6). The most contributing structure is probably the incomplete octet structure (due to Figure 8.7.5 being basically impossible and Figure 8.7.6 not matching up with the behavior and properties of BF_3). As you can see even when other possibilities exist, incomplete octets may best portray a molecular structure.

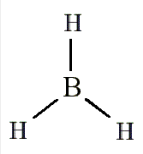
As a side note, it is important to note that BF_3 frequently bonds with a F^- ion in order to form BF_4^- rather than staying as BF_3. This structure completes boron's octet and it is more common in nature. This exemplifies the fact that incomplete octets are rare, and other configurations are typically more favorable, including bonding with additional ions as in the case of BF_3 .

Example 8.7.1:

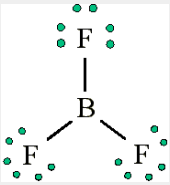
Draw the Lewis structure for boron trifluoride (BF_3).

SOLUTION

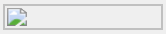
1. Add electrons (3*7) + 3 = **24**
2. Draw connectivities:



3. Add octets to outer atoms:

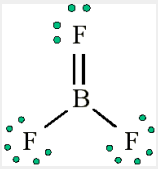


4. Add extra electrons (24-24=0) to central atom:



5. Does central electron have octet?

- NO. It has 6 electrons
- Add a multiple bond (double bond) to see if central atom can achieve an octet:

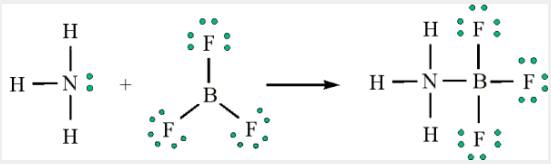


6. The central Boron now has an octet (there would be three resonance Lewis structures)

However...

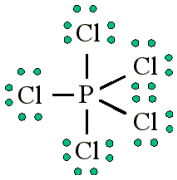
- In this structure with a double bond the fluorine atom is sharing extra electrons with the boron.
- The fluorine would have a '+' partial charge, and the boron a '-' partial charge, this is inconsistent with the electronegativities of fluorine and boron.
- Thus, ***the structure of BF_3, with single bonds, and 6 valence electrons around the central boron is the most likely structure***

BF_3 reacts strongly with compounds which have an unshared pair of electrons which can be used to form a bond with the boron:



Exception 3: Expanded Valence Shells

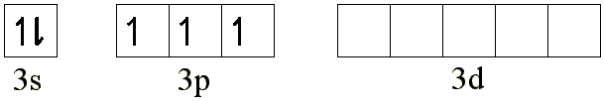
More common than incomplete octets are expanded octets where the central atom in a Lewis structure has more than eight electrons in its valence shell. In expanded octets, the central atom can have ten electrons, or even twelve. *Molecules with expanded octets involve highly electronegative terminal atoms, and a nonmetal central atom found in the third period or below*, which those terminal atoms bond to. For example, is a legitimate compound (whereas) is not:



Note

Expanded valence shells are observed **only** for elements in period 3 (i.e. n=3) and beyond

The 'octet' rule is based upon available n*s* and n*p* orbitals for valence electrons (2 electrons in the *s* orbitals, and 6 in the *p* orbitals). Beginning with the n=3 principle quantum number, the d orbitals become available (*l*=2). The orbital diagram for the valence shell of phosphorous is:



Hence, the third period elements occasionally exceed the octet rule by using their empty d orbitals to accommodate additional electrons. Size is also an important consideration:

- The larger the central atom, the larger the number of electrons which can surround it
- Expanded valence shells occur most often when the central atom is bonded to small electronegative atoms, such as F, Cl and O.

There is currently much scientific exploration and inquiry into the reason why expanded valence shells are found. The top area of interest is figuring out where the extra pair(s) of electrons are found. Many chemists think that there is not a very large energy difference between the 3p and 3d orbitals, and as such it is plausible for extra electrons to easily fill the 3d orbital when an expanded octet is more favorable than having a complete octet. This matter is still under hot debate, however and there is even debate as to what makes an expanded octet more favorable than a configuration that follows the octet rule.

One of the situations where expanded octet structures are treated as more favorable than Lewis structures that follow the octet rule is when the formal charges in the expanded octet structure are smaller than in a structure that adheres to the octet rule, or when there are less formal charges in the expanded octet than in the structure a structure that adheres to the octet rule.

Example 8.7.2: The ion

Such is the case for the sulfate ion, SO_4^{-2}. A strict adherence to the octet rule forms the following Lewis structure:

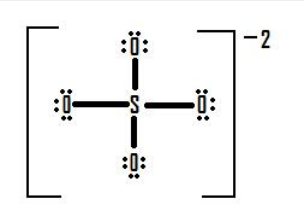


Figure 8.7.12

If we look at the formal charges on this molecule, we can see that all of the oxygen atoms have seven electrons around them (six from the three lone pairs and one from the bond with sulfur). This is one more electron than the number of valence electrons then they would have normally, and as such each of the oxygens in this structure has a formal charge of -1. Sulfur has four electrons around it in this structure (one from each of its four bonds) which is two electrons more than the number of valence electrons it would have normally, and as such it carries a formal charge of +2.

If instead we made a structure for the sulfate ion with an expanded octet, it would look like this:

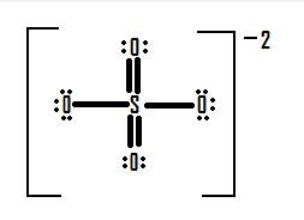


Figure 8.7.13

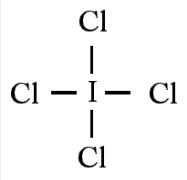
Looking at the formal charges for this structure, the sulfur ion has six electrons around it (one from each of its bonds). This is the same amount as the number of valence electrons it would have naturally. This leaves sulfur with a formal charge of zero. The two oxygens that have double bonds to sulfur have six electrons each around them (four from the two lone pairs and one each from the two bonds with sulfur). This is the same amount of electrons as the number of valence electrons that oxygen atoms have on their own, and as such both of these oxygen atoms have a formal charge of zero. The two oxygens with the single bonds to sulfur have seven electrons around them in this structure (six from the three lone pairs and one from the bond to sulfur). That is one electron more than the number of valence electrons that oxygen would have on its own, and as such those two oxygens carry a formal charge of -1. Remember that with formal charges, the goal is to keep the formal charges (or the difference between the formal charges of each atom) as small as possible. The number of and values of the formal charges on this structure (-1 and 0 (difference of 1) in Figure 8.7.12, as opposed to +2 and -1 (difference of 3) in Figure 8.7.12) is significantly lower than on the structure that follows the octet rule, and as such an expanded octet is plausible, and even preferred to a normal octet, in this case.

Example 8.7.3: The Ion

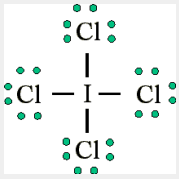
Draw the Lewis structure for ion.

SOLUTION

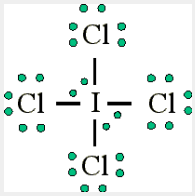
1. Count up the valence electrons: 7+(4*7)+1 = **36** electrons
2. Draw the connectivities:



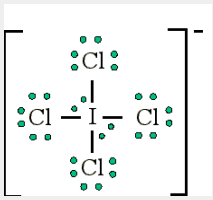
3. Add octet of electrons to outer atoms:



4. Add extra electrons (36-32=**4**) to central atom:



5. The ICl_4^- ion thus has 12 valence electrons around the central Iodine (in the 5*d* orbitals)



Expanded Lewis structures are also plausible depictions of molecules when experimentally determined bond lengths suggest partial double bond characters even when single bonds would already fully fill the octet of the central atom. Despite the cases for expanded octets, as mentioned for incomplete octets, it is important to keep in mind that, in general, the octet rule applies.

Contributors

- Mike Blaber (Florida State University)

1.5: Bond Length and Bond Strength

The Relationship between Bond Order and Bond Energy

The Relationship between Bond Order and Bond Energy

Table 8.6 Average Bond Energies (kJ/mol) for Commonly Encountered Bonds at 273 K

Single Bonds										Multiple Bonds	
H–H	432	C–C	346	N–N	≈167	O–O	≈142	F–F	155	C=C	602
H–C	411	C–Si	318	N–O	201	O–F	190	F–Cl	249	C≡C	835
H–Si	318	C–N	305	N–F	283	O–Cl	218	F–Br	249	C=N	615
H–N	386	C–O	358	N–Cl	313	O–Br	201	F–I	278	C≡N	887
H–P	≈322	C–S	272	N–Br	243	O–I	201	Cl–Cl	240	C=O	749
H–O	459	C–F	485	P–P	201	S–S	226	Cl–Br	216	C≡O	1072
H–S	363	C–Cl	327			S–F	284	Cl–I	208	N=N	418
H–F	565	C–Br	285			S–Cl	255	Br–Br	190	N≡N	942
H–Cl	428	C–I	213			S–Br	218	Br–I	175	N=O	607
H–Br	362	Si–Si	222					I–I	149	O=O	494
H–I	295	Si–O	452							S=O	532

Source: Data from J. E. Huheey, E. A. Keiter, and R. L. Keiter, *Inorganic Chemistry*, 4th ed. (1993).

1. Bonds between hydrogen and atoms in the same column of the periodic table decrease in strength as we go down the column. Thus an H–F bond is stronger than an H–I bond, H–C is stronger than H–Si, H–N is stronger than H–P, H–O is stronger than H–S, and so forth. The reason for this is that the region of space in which electrons are shared between two atoms becomes proportionally smaller as one of the atoms becomes larger (part (a) in Figure 8.11).
2. Bonds between like atoms usually become *weaker* as we go down a column (important exceptions are noted later). For example, the C–C single bond is stronger than the Si–Si single bond, which is stronger than the Ge–Ge bond, and so forth. As two bonded atoms become larger, the region between them occupied by bonding electrons becomes *proportionally* smaller, as illustrated in part (b) in Figure 8.11. Noteworthy exceptions are single bonds between the period 2 atoms of groups 15, 16, and 17 (i.e., N, O, F), which are unusually weak compared with single bonds between their larger congeners. It is likely that the N–N, O–O, and F–F single bonds are weaker than might be expected due to strong repulsive interactions between lone pairs of electrons on *adjacent* atoms. The trend in bond energies for the halogens is therefore

$$\text{Cl–Cl} > \text{Br–Br} > \text{F–F} > \text{I–I}$$

The Relationship between Bond Order and Bond Energy

Note
Bonds between hydrogen and atoms in a given column in the periodic table are weaker down the column; bonds between like atoms usually become weaker down a column.

The Relationship between Bond Order and Bond Energy

The Relationship between Bond Order and Bond Energy

The Relationship between Bond Order and Bond Energy

The Relationship between Bond Order and Bond Energy

Note
Bond strengths increase as bond order **increases**, while bond distances **decrease**.

Table: Average bond energies:

Bond	(kJ/mol)
C-F	485
C-Cl	328
C-Br	276
C-I	240
C-C	348
C-N	293
C-O	358
C-F	485
C-C	348
C=C	614
C≡C	839

Contributors

- Kim Song (UCD), Donald Le (UCD)

1.6: Electronegativity and Bond Polarity

Electronegativity

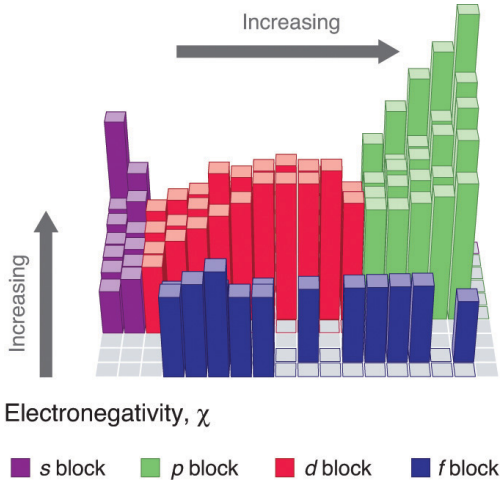
The elements with the highest ionization energies are generally those with the most negative electron affinities, which are located toward the upper right corner of the periodic table. Conversely, the elements with the lowest ionization energies are generally those with the least negative electron affinities and are located in the lower left corner of the periodic table.

Because the tendency of an element to gain or lose electrons is so important in determining its chemistry, various methods have been developed to quantitatively describe this tendency. The most important method uses a measurement called electronegativity (represented by the Greek letter *chi*, χ, pronounced "ky" as in "sky"), defined as the *relative* ability of an atom to attract electrons to itself *in a chemical compound*. Elements with high electronegativities tend to acquire electrons in chemical reactions and are found in the upper right corner of the periodic table. Elements with low electronegativities tend to lose electrons in chemical reactions and are found in the lower left corner of the periodic table.

Unlike ionization energy or electron affinity, the electronegativity of an atom is not a simple, fixed property that can be directly measured in a single experiment. In fact, an atom's electronegativity should depend to some extent on its chemical environment because the properties of an atom are influenced by its neighbors in a chemical compound. Nevertheless, when different methods for measuring the electronegativity of an atom are compared, they all tend to assign similar relative values to a given element. For example, all scales predict that fluorine has the highest electronegativity and cesium the lowest of the stable elements, which suggests that all the methods are measuring the same fundamental property.

Note

Electronegativity is defined as the ability of an atom in a particular molecule to attract electrons to itself. The **greater** the value, the **greater** the attractiveness for electrons.



Molecular Dipole Moments

You previously learned how to calculate the **dipole moments** of simple diatomic molecules. In more complex molecules with polar covalent bonds, the three-dimensional geometry and the compound's symmetry determine whether there is a net dipole moment. Mathematically, dipole moments are *vectors*; they possess both a *magnitude* and a *direction*. The dipole moment of a molecule is therefore the *vector sum* of the dipole moments of the individual bonds in the molecule. If the individual bond dipole moments cancel one another, there is no net dipole moment. Such is the case for CO_2, a linear molecule (part (a) in Figure 9.2.8). Each C–O bond in CO_2 is polar, yet experiments show that the CO_2 molecule has no dipole moment. Because the two C–O bond dipoles in CO_2 are equal in magnitude and oriented at 180° to each other, they cancel. As a result, the CO_2 molecule has no *net* dipole moment even though it has a substantial separation of charge. In contrast, the H_2O molecule is not linear (part (b) in Figure 9.2.8); it is bent in three-dimensional space, so the dipole moments do not cancel each other. Thus a molecule such as H_2O has a net dipole moment. We expect the concentration of negative charge to be on the oxygen, the more electronegative atom, and positive charge

on the two hydrogens. This charge polarization allows H_2O to hydrogen-bond to other polarized or charged species, including other water molecules.

Molecular Dipole Moments

Other examples of molecules with polar bonds are shown in Figure 9.2.9. In molecular geometries that are highly symmetrical (most notably tetrahedral and square planar, trigonal bipyramidal, and octahedral), individual bond dipole moments completely cancel, and there is no net dipole moment. Although a molecule like $CHCl_3$ is best described as tetrahedral, the atoms bonded to carbon are not identical. Consequently, the bond dipole moments cannot cancel one another, and the molecule has a dipole moment. Due to the arrangement of the bonds in molecules that have V-shaped, trigonal pyramidal, seesaw, T-shaped, and square pyramidal geometries, the bond dipole moments cannot cancel one another. Consequently, molecules with these geometries always have a nonzero dipole moment.

Molecular Dipole Moments

Note

Molecules with asymmetrical charge distributions have a net dipole moment.

Example

Which molecule(s) has a net dipole moment?

a. H_2S
b. NHF_2
c. BF_3

Given: three chemical compounds

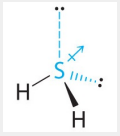
Asked for: net dipole moment

Strategy:

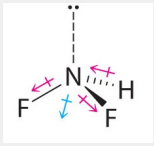
For each three-dimensional molecular geometry, predict whether the bond dipoles cancel. If they do not, then the molecule has a net dipole moment.

Solution:

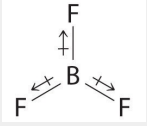
1. The total number of electrons around the central atom, S, is eight, which gives four electron pairs. Two of these electron pairs are bonding pairs and two are lone pairs, so the molecular geometry of H_2S is bent (Figure 9.2.6). The bond dipoles cannot cancel one another, so the molecule has a net dipole moment.



2. Difluoroamine has a trigonal pyramidal molecular geometry. Because there is one hydrogen and two fluorines, and because of the lone pair of electrons on nitrogen, the molecule is not symmetrical, and the bond dipoles of NHF_2 cannot cancel one another. This means that NHF_2 has a net dipole moment. We expect polarization from the two fluorine atoms, the most electronegative atoms in the periodic table, to have a greater affect on the net dipole moment than polarization from the lone pair of electrons on nitrogen.



3. The molecular geometry of BF_3 is trigonal planar. Because all the B–F bonds are equal and the molecule is highly symmetrical, the dipoles cancel one another in three-dimensional space. Thus BF_3 has a net dipole moment of zero:



Exercise

Which molecule(s) has a net dipole moment?

1. CH_3Cl
2. SO_3
3. XeO_3

Answer: CH_3Cl; XeO_3

Contributors

- *Mike Blaber* (*Florida State University*)

1.7: Polarity of Molecules

Dipole moments occur when there is a separation of charge. They can occur between two ions in an ionic bond or between atoms in a covalent bond; dipole moments arise from differences in electronegativity. The larger the difference in electronegativity, the larger the dipole moment. The distance between the charge separation is also a deciding factor into the size of the dipole moment. The dipole moment is a measure of the polarity of the molecule.

Introduction

When atoms in a molecule share electrons unequally, they create what is called a dipole moment. This occurs when one atom is more electronegative than another, resulting in that atom pulling more tightly on the shared pair of electrons, or when one atom has a lone pair of electrons and the difference of electronegativity vector points in the same way. One of the most common examples is the water molecule, made up of one oxygen atom and two hydrogen atoms. The differences in electronegativity and lone electrons give oxygen a partial negative charge and each hydrogen a partial positive charge.

Dipole Moment

When two electrical charges, of opposite sign and equal magnitude, are separated by a distance, a **dipole** is established. The size of a dipole is measured by its dipole moment ((\mu\)). Dipole moment is measured in debye units, which is equal to the distance between the charges multiplied by the charge (1 debye equals 3.34 x 10^{-30} coulomb-meters). The equation to figure out the dipole moment of a molecule is given below:

where

- is the dipole moment,
- is the magnitude of the charge, and
- is the distance between the charges.

The dipole moment acts in the direction of the vector quantity. An example of a polar molecule is . Because of the lone pair on oxygen, the structure of H_2O is bent, which means it is not symmetric. The vectors do not cancel each other out, making the molecule polar.

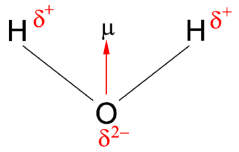


Figure 1: Dipole moment of water

The vector points from positive to negative, on both the molecular (net) dipole moment and the individual bond dipoles. The table above shows the electronegativity of some of the common elements. The larger the difference in electronegativity between the two atoms, the more electronegative that bond is. To be considered a polar bond, the difference in electronegativity must be large. The dipole moment points in the direction of the vector quantity of each of the bond electronegativities added together.

Example 1: Water

The water molecule picture from Figure 1 can be used to determine the direction and magnitude of the dipole moment. From the electronegativities of water and hydrogen, the difference is 1.2 for each of the hydrogen-oxygen bonds. Next, because the oxygen is the more electronegative atom, it exerts a greater pull on the shared electrons; it also has two lone pairs of electrons. From this, it can be concluded that the dipole moment points from between the two hydrogen atoms toward the oxygen atom. Using the equation above, the dipole moment is calculated to be 1.85 D by multiplying the distance between the oxygen and hydrogen atoms by the charge difference between them and then finding the components of each that point in the direction of the net dipole moment (remember the angle of the molecule is 104.5˚).
The bond moment of O-H bond =1.5 D, so the net dipole moment =2(1.5)×cos(104.5/2)=1.84 D.

Dipole Moments

It is relatively easy to measure dipole moments. Place substance between charged plates--polar molecules increase the charge stored on plates and the dipole moment can be obtained (has to do with capacitance). Polar molecules align themselves:

1. in an electric field
2. with respect to one another
3. with respect to ions

Nonpolar is not deflected; moderately polar acetone deflects slightly; highly polar water deflects strongly.

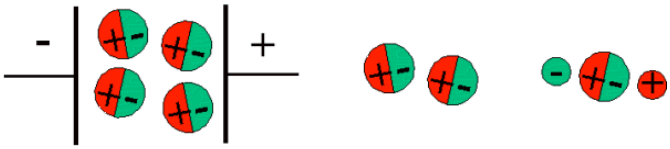


Figure 2: Polar molecules align themselves in an electric field (left), with respect to one another (middle), and with respect to ions (right)

When proton & electron close together, the dipole moment (degree of polarity) decreases. However, as proton & electron get farther apart, the dipole moment increases. In this case, the dipole moment calculated as:

The debye characterizes size of dipole moment. When a proton & electron 100 pm apart, the dipole moment is :

is a key reference value and represents a pure charge of +1 & -1 100 pm apart. If the charge separation were greater then the dipole moment increases (linearly):

- When proton & electron are separated by 120 pm,
- When proton & electron are separated by 150 pm,
- When proton & electron are separated by 200 pm,

Polarity and Structure of Molecules

The shape of a molecule and the polarity of its bonds determine the OVERALL POLARITY of that molecule. A molecule that contains polar bonds, might not have any overall polarity, depending upon its shape. The simple definition of whether a complex molecule is polar or not depends upon whether its overall centers of positive and negative charges overlap. If these centers lie at the same point in space, then the molecule has no overall polarity (and is non polar).

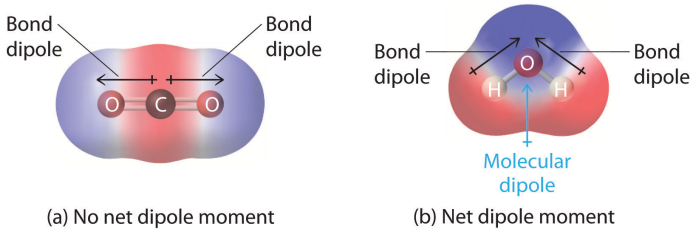


Figure 3: Charge distrubtions

If a molecule is completely symmetric, then the dipole moment vectors on each molecule will cancel each other out, making the molecule nonpolar. A molecule can only be polar if the structure of that molecule is not symmetric.

A good example of a nonpolar molecule that contains polar bonds is carbon dioxide. This is a linear molecule and the C=O bonds are, in fact, polar. The central carbon will have a net positive charge, and the two outer oxygens a net negative charge. However, since the molecule is linear, these two bond dipoles cancel each other out (i.e. vector addition of the dipoles equals zero). And the overall molecule has no dipole (.

Although a polar bond is a prerequisite for a molecule to have a dipole, not all molecules with polar bonds exhibit dipoles

Geometric Considerations

For molecules, where is the central atom and are all the same types of atoms, there are certain molecular geometries which are symmetric. Therefore, they will have no dipole even if the bonds are polar. These geometries include linear, trigonal planar, tetrahedral, octahedral and trigonal bipyramid.

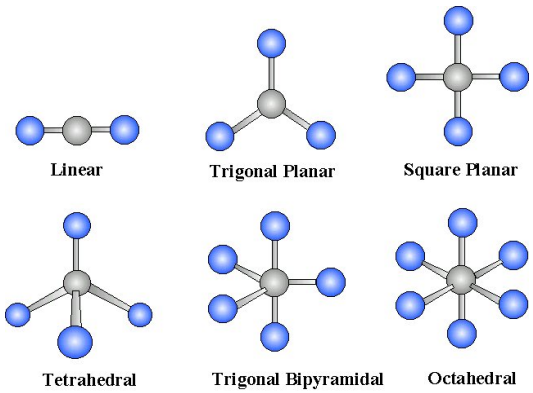
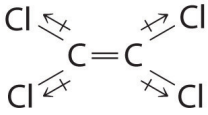


Figure 4: Molecular geometries with exact cancelation of polar bonding to generate a non-polar molecule ( )

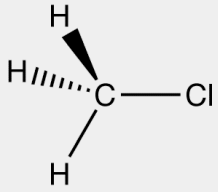
Example 2:

Although the C–Cl bonds are rather polar, the individual bond dipoles cancel one another in this symmetrical structure, and $Cl_2C{=}CCl_2$ does not have a net dipole moment.



Example 3:

C-Cl, the key polar bond, is 178 pm. Measurement reveals 1.87 D. From this data, % ionic character can be computed. If this bond were 100% ionic (based on proton & electron),



Example 4:

Since measurement 1.87 D,
% ionic = (1.7/8.54)x100 = 22%
u = 1.03 D (measured) H-Cl bond length 127 pm
If 100% ionic,

ionic = (1.03/6.09)x100 = 17%

Compound	Bond Length (Å)	Electronegativity Difference	Dipole Moment (D)
HF	0.92	1.9	1.82
HCl	1.27	0.9	1.08
HBr	1.41	0.7	0.82
HI	1.61	0.4	0.44

Although the bond length is ***increasing***, the dipole is ***decreasing*** as you move down the halogen group. The electronegativity decreases as we move down the group. Thus, the greater influence is the electronegativity of the two atoms (which influences the ***charge*** at the ends of the dipole).

Contributors

- *Mike Blaber (Florida State University)*

1.8: L-Dopa—A Representative Organic Molecule

An 3D image of L-Dopa can be found at ChemTube3D with many other molecules.

A discussion about the role L-Dopa plays in Parkinson's Disease and its discovery is covered in an article by Oleh Hornykiewicz in the Journal of Parkinson's Disease which can be read at PubMed

1.9: Resonance

Resonance Structures

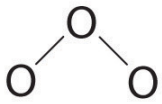
Sometimes, even when formal charges are considered, the bonding in some molecules or ions cannot be described by a single Lewis structure. Such is the case for ozone (O_3), an allotrope of oxygen with a V-shaped structure and an O–O–O angle of 117.5°.

O_3

1. We know that ozone has a V-shaped structure, so one O atom is central:

2. Each O atom has 6 valence electrons, for a total of 18 valence electrons.

3. Assigning one bonding pair of electrons to each oxygen–oxygen bond gives



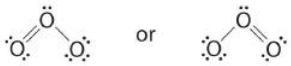
with 14 electrons left over.

4. If we place three lone pairs of electrons on each terminal oxygen, we obtain

and have 2 electrons left over.

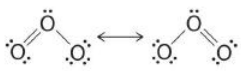
5. At this point, both terminal oxygen atoms have octets of electrons. We therefore place the last 2 electrons on the central atom:

6. The central oxygen has only 6 electrons. We must convert one lone pair on a terminal oxygen atom to a bonding pair of electrons —but which one? Depending on which one we choose, we obtain either

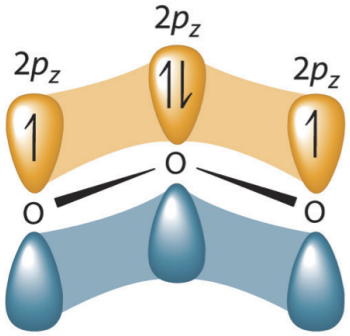


Which is correct? In fact, neither is correct. Both predict one O–O single bond and one O=O double bond. As you will learn in Section 4.8, if the bonds were of different types (one single and one double, for example), they would have different lengths. It turns out, however, that both O–O bond distances are identical, 127.2 pm, which is shorter than a typical O–O single bond (148 pm) and longer than the O=O double bond in O_2 (120.7 pm).

Equivalent Lewis dot structures, such as those of ozone, are called resonance structures . The position of the *atoms* is the same in the various resonance structures of a compound, but the position of the *electrons* is different. Double-headed arrows link the different resonance structures of a compound:



Before the development of quantum chemistry it was thought that the double-headed arrow indicates that the actual electronic structure is an *average* of those shown, or that the molecule oscillates between the two structures. Today we know that the electrons involved in the double bonds occupy an orbital that extends over all three oxygen molecules, combining *p* orbitals on all three.



Resonance Structures

We will discuss the formation of these molecular orbitals in the next chapter but it is important to understand that resonance structures are based on molecular orbitals not averages of different bonds between atoms. We describe the electrons in such molecular orbitals as being delocalized, that is they cannot be assigned to a bond between two atoms.

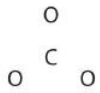
Note the Pattern

When it is possible to write more than one equivalent resonance structure for a molecule or ion, the actual structure involves a molecular orbital which is a linear combination of atomic orbitals from each of the atoms.

CO_3^{2-}

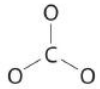
Like ozone, the electronic structure of the carbonate ion cannot be described by a single Lewis electron structure. Unlike O_3, though, the Lewis structures describing CO_3^{2-} has *three* equivalent representations.

1. Because carbon is the least electronegative element, we place it in the central position:

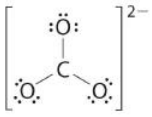


2. Carbon has 4 valence electrons, each oxygen has 6 valence electrons, and there are 2 more for the −2 charge. This gives 4 + (3 × 6) + 2 = 24 valence electrons.

3. Six electrons are used to form three bonding pairs between the oxygen atoms and the carbon:

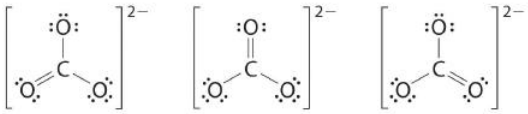


4. We divide the remaining 18 electrons equally among the three oxygen atoms by placing three lone pairs on each and indicating the −2 charge:

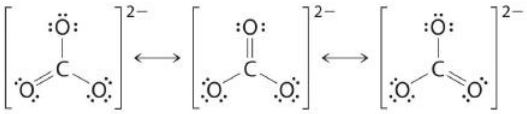


5. No electrons are left for the central atom.

6. At this point, the carbon atom has only 6 valence electrons, so we must take one lone pair from an oxygen and use it to form a carbon–oxygen double bond. In this case, however, there are *three* possible choices:



As with ozone, none of these structures describes the bonding exactly. Each predicts one carbon–oxygen double bond and two carbon–oxygen single bonds, but experimentally all C–O bond lengths are identical. We can write resonance structures (in this case, three of them) for the carbonate ion:



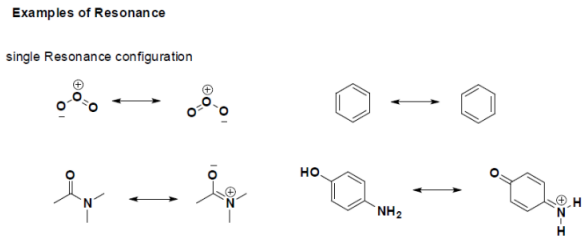
As the case for ozone, the actual structure involves the formation of a molecular orbital from p_z orbitals centered on each atom and sitting above and below the plane of the CO_3^{2-} ion.

CO_3^{2-}

Resonance structures are particularly common in oxoanions of the *p*-block elements, such as sulfate and phosphate, and in aromatic hydrocarbons, such as benzene and naphthalene.

Rules for estimating stability of resonance structures

1. The **greater the number of covalent bonds**, the greater the stability since more atoms will have complete octets
2. The structure with the **least number of formal charges** is more stable
3. The structure with the **least separation of formal charge** is more stable
4. A structure with a **negative charge on the more electronegative atom** will be more stable
5. **Positive charges on the least electronegative atom** (most electropositive) is more stable
6. **Resonance forms that are equivalent have no difference in stability and contribute equally.** (eg. benzene)



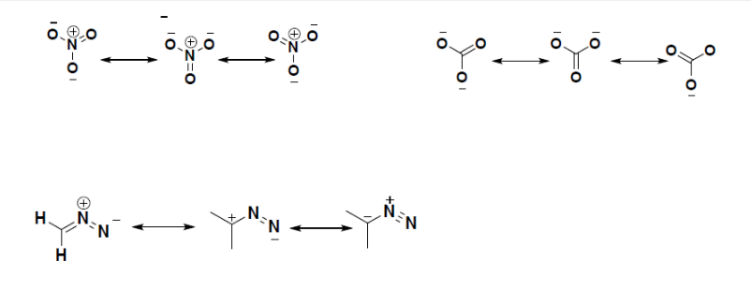
The above resonance structures show that the electrons are delocalized within the molecule and through this process the molecule gains extra stability. Ozone with both of its opposite charges creates a neutral molecule and through resonance it is a stable molecule. The extra electron that created the negative charge on either terminal oxygen can be delocalized by resonance through the terminal oxygens.

Benzene is an extremely stable molecule and it is accounted for its geometry and molecular orbital interaction, but most importantly it's due to its resonance structures. The delocalized electrons in the benzene ring make the molecule very stable and with its characteristics of a nucleophile, it will react with a strong electrophile only and after the first reactivity, the substituted benzene will depend on its resonance to direct the next position for the reaction to add a second substituent.

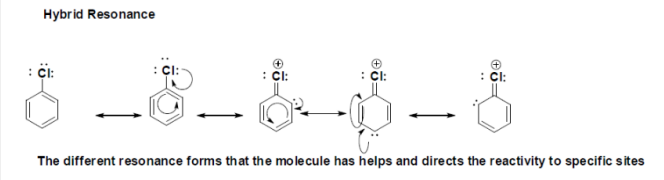
The next molecule, the Amide, is a very stable molecule that is present in most biological systems, mainly in proteins. By studies of NMR spectroscopy and X-Ray crystallography it is confirmed that the stability of the amide is due to resonance which through molecular orbital interaction creates almost a double bond between the Nitrogen and the carbon.

Example: Multiple Resonance of other Molecules

Molecules with more than one resonance form



Some structural resonance conformations are the major contributor or the dominant forms that the molecule exists. For example, if we look at the above rules for estimating the stability of a molecule, we see that for the third molecule the first and second forms are the major contributors for the overall stability of the molecule. The nitrogen is more electronegative than carbon so, it can handle the negative charge more than carbon. A carbon with a negative charge is the least favorable conformation for the molecule to exist, so the last resonance form contributes very little for the stability of the Ion.



The Hybrid Resonance forms show the different Lewis structures with the electron been delocalized. This is very important for the reactivity of chloro-benzene because in the presence of an electrophile it will react and the formation of another bond will be directed and determine by resonance. The long pair of electrons delocalized in the aromatic substituted ring is where it can potentially form a new bond with an electrophile, as it is shown there are three possible places that reactivity can take place, the first to react will take place at the *para* position with respect to the chloro substituent and then to either *ortho* position.

Contributors

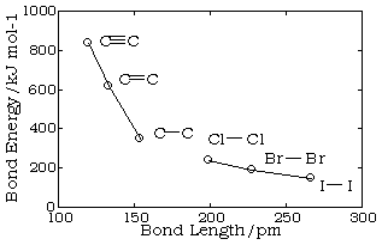
- Sharon Wei (UCD), Liza Chu (UCD)

1.10: Determining Molecular Shape

Bond lengths and angles

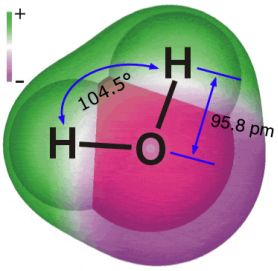
The length of a chemical bond the distance between the centers of the two bonded atoms (the *internuclear distance*.) Bond lengths have traditionally been expressed in Ångstrom units, but picometers are now preferred (1Å = 10^{-8} cm = 100 pm.) Bond lengths are typically in the range 1-2 Å or 100-200 pm. Even though the bond is vibrating, equilibrium bond lengths can be determined experimentally to within ±1 pm.

bond	Ave. Length	Ave. Energy/kJ mol^{-1}
H—H	74 pm	432
H—C	109 pm	415
H—N	101	390
H—O	96	460
H—Cl	127	428
H—Br	141	362
C—C	154	345
C=C	133	615
C≡C	120	835
N≡N	110	942
Cl—Cl	199	240
Br—Br	228	190
I—I	267	149



Bond lengths depend mainly on the sizes of the atoms, and secondarily on the bond strengths, the stronger bonds tending to be shorter. Bonds involving hydrogen can be quite short; The shortest bond of all, H–H, is only 74 pm. Multiply-bonded atoms are closer together than singly-bonded ones; this is a major criterion for experimentally determining the *multiplicity* of a bond. This trend is clearly evident in the above plot which depicts the sequence of carbon-carbon single, double, and triple bonds.

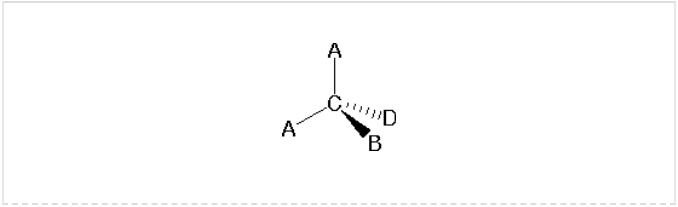
The most common method of measuring bond lengths in solids is by analysis of the diffraction or scattering of X-rays when they pass through the regularly-spaced atoms in the crystal. For gaseous molecules, neutron- or electron-diffraction can also be used.

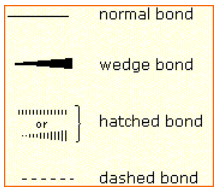


The complete structure of a molecule requires a specification of the coordinates of each of its atoms in three-dimensional space. This data can then be used by computer programs to construct *visualizations* of the molecule as discussed above. One such visualization of the water molecule, with bond distances and the HOH bond angle superimposed on a space-filling model, is shown here. (It is taken from an excellent reference source on water). The colors show the results of calculations that depict the way in which electron charge is distributed around the three nuclei.

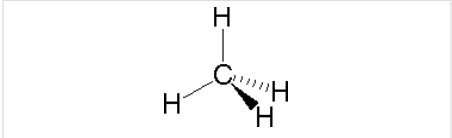
In most cases the focus of configuration is a carbon atom so the lines specifying bond directions will originate there. As defined in the diagram on the right, a simple straight line represents a bond lying approximately in the surface plane. The two bonds to substituents A in the structure on the left are of this kind. A wedge shaped bond is directed in front of this plane (thick end toward the viewer), as shown by the bond to substituent B; and a hatched bond is directed in back of the plane (away from the viewer), as shown by the bond to substituent D. Some texts and other sources may use a dashed bond in the same manner as we have defined the hatched bond, but this can be confusing because the dashed bond is often used to represent a partial bond (i.e. a covalent bond that is partially formed or partially broken).

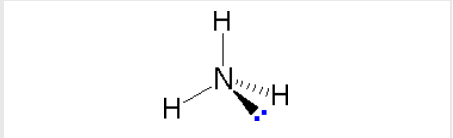
Molecular Shape

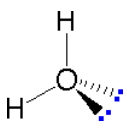




The following examples make use of this notation, and also illustrate the importance of including non-bonding valence shell electron pairs (colored blue) when viewing such configurations.

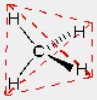
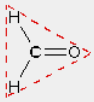






Methane	Ammonia	Water

Bonding configurations are readily predicted by valence-shell electron-pair repulsion theory, commonly referred to as **VSEPR** in most introductory chemistry texts. This simple model is based on the fact that electrons repel each other, and that it is reasonable to expect that the bonds and non-bonding valence electron pairs associated with a given atom will prefer to be as far apart as possible. The bonding configurations of carbon are easy to remember, since there are only three categories.

Configuration	Bonding Partners	Bond Angles	Example
Tetrahedral	4	109.5º	
Trigonal	3	120º	
Linear	2	180º	

In the three examples shown above, the central atom (carbon) does not have any non-bonding valence electrons; consequently the configuration may be estimated from the number of bonding partners alone. For molecules of water and ammonia, however, the non-bonding electrons must be included in the calculation. In each case there are four regions of electron density associated with the valence shell so that a tetrahedral bond angle is expected. The measured bond angles of these compounds (H_2O 104.5º & NH_3 107.3º) show that they are closer to being tetrahedral than trigonal or linear. Of course, it is the configuration of atoms (not electrons) that defines the the shape of a molecule, and in this sense ammonia is said to be pyramidal (not tetrahedral). The compound boron trifluoride, BF3, does not have non-bonding valence electrons and the configuration of its atoms is trigonal. Nice treatments of VSEPR theory have been provided by Oxford and Purdue. The best way to study the three-dimensional shapes of molecules is by using molecular models. Many kinds of model kits are available to students and professional chemists.

Two Electron Groups

Our first example is a molecule with two bonded atoms and no lone pairs of electrons, .

AX_2: BeH_2

1. The central atom, beryllium, contributes two valence electrons, and each hydrogen atom contributes one. The Lewis electron structure is

H:Be:H or H—Be—H

Lewis structure

2. There are two electron groups around the central atom. We see from Figure 9.2.2 that the arrangement that minimizes repulsions places the groups 180° apart.

3. Both groups around the central atom are bonding pairs (BP). Thus BeH_2 is designated as AX_2.

4. From Figure 9.2.3 we see that with two bonding pairs, the molecular geometry that minimizes repulsions in BeH_2 is *linear*.

AX_2: CO_2

1. The central atom, carbon, contributes four valence electrons, and each oxygen atom contributes six. The Lewis electron structure is

2. The carbon atom forms two double bonds. Each double bond is a group, so there are two electron groups around the central atom. Like BeH_2, the arrangement that minimizes repulsions places the groups 180° apart.

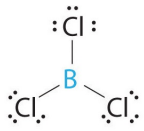
3. Once again, both groups around the central atom are bonding pairs (BP), so CO_2 is designated as AX_2.

4. VSEPR only recognizes groups around the *central* atom. Thus the lone pairs on the oxygen atoms do not influence the molecular geometry. With two bonding pairs on the central atom and no lone pairs, the molecular geometry of CO_2 is linear (Figure 9.2.3). The structure of CO_2 is shown in Figure 9.2.2.1.

Three Electron Groups

AX_3: BCl_3

1. The central atom, boron, contributes three valence electrons, and each chlorine atom contributes seven valence electrons. The Lewis electron structure is



Lewis structure

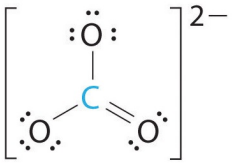
2. There are three electron groups around the central atom. To minimize repulsions, the groups are placed 120° apart (Figure 9.2.2).

3. All electron groups are bonding pairs (BP), so the structure is designated as AX_3.

4. From Figure 9.2.3 we see that with three bonding pairs around the central atom, the molecular geometry of BCl_3 is *trigonal planar*, as shown in Figure 9.2.2.1.

AX_3: CO_3^{2-}

1. The central atom, carbon, has four valence electrons, and each oxygen atom has six valence electrons. As you learned previously, the Lewis electron structure of one of three resonance forms is represented as

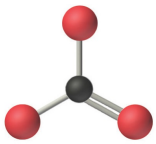


Lewis structure

2. The structure of CO_3^{2-} is a resonance hybrid. It has three identical bonds, each with a bond order of . We minimize repulsions by placing the three groups 120° apart (Figure 9.2.2).

3. All electron groups are bonding pairs (BP). With three bonding groups around the central atom, the structure is designated as AX_3.

4. We see from Figure 9.2.3 that the molecular geometry of CO_3^{2-} is trigonal planar.

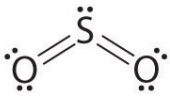


Molecular geometry
(trigonal planar)

In our next example we encounter the effects of lone pairs and multiple bonds on molecular geometry for the first time.

AX_2E: SO_2

1. The central atom, sulfur, has 6 valence electrons, as does each oxygen atom. With 18 valence electrons, the Lewis electron structure is shown below.



2. There are three electron groups around the central atom, two double bonds and one lone pair. We initially place the groups in a trigonal planar arrangement to minimize repulsions (Figure 9.2.2).

3. There are two bonding pairs and one lone pair, so the structure is designated as AX_2E. This designation has a total of three electron pairs, two X and one E. Because a lone pair is not shared by two nuclei, it occupies more space near the central atom than a bonding pair (Figure 9.2.4). Thus bonding pairs and lone pairs repel each other electrostatically in the order BP–BP < LP–BP < LP–LP. In SO_2, we have one BP–BP interaction and two LP–BP interactions.

4. The molecular geometry is described only by the positions of the nuclei, *not* by the positions of the lone pairs. Thus with two nuclei and one lone pair the shape is *bent*, or *V shaped*, which can be viewed as a trigonal planar arrangement with a missing vertex (Figures 9.2.2.1 and 9.2.3).

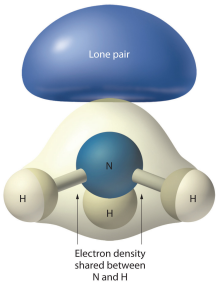
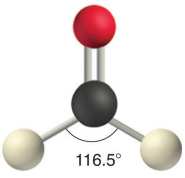


Figure 9.2.4: *The Difference in the Space Occupied by a Lone Pair of Electrons and by a Bonding Pair*

As with SO_2, this composite model of electron distribution and negative electrostatic potential in ammonia shows that a lone pair of electrons occupies a larger region of space around the nitrogen atom than does a bonding pair of electrons that is shared with a hydrogen atom.

Like lone pairs of electrons, multiple bonds occupy more space around the central atom than a single bond, which can cause other bond angles to be somewhat smaller than expected. This is because a multiple bond has a higher electron density than a single bond, so its electrons occupy more space than those of a single bond. For example, in a molecule such as CH_2O (AX_3), whose structure is shown below, the double bond repels the single bonds more strongly than the single bonds repel each other. This causes a deviation from ideal geometry (an H–C–H bond angle of 116.5° rather than 120°).

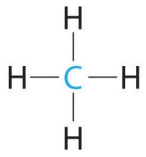


Four Electron Groups

One of the limitations of Lewis structures is that they depict molecules and ions in only two dimensions. With four electron groups, we must learn to show molecules and ions in three dimensions.

AX_4: CH_4

1. The central atom, carbon, contributes four valence electrons, and each hydrogen atom has one valence electron, so the full Lewis electron structure is

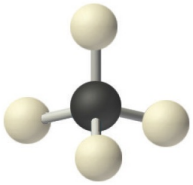


Lewis structure

2. There are four electron groups around the central atom. As shown in Figure 9.2.2, repulsions are minimized by placing the groups in the corners of a tetrahedron with bond angles of 109.5°.

3. All electron groups are bonding pairs, so the structure is designated as AX_4.

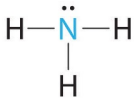
4. With four bonding pairs, the molecular geometry of methane is *tetrahedral* (Figure 9.2.3).



Molecular geometry
(tetrahedral)

AX_3E: NH_3

1. In ammonia, the central atom, nitrogen, has five valence electrons and each hydrogen donates one valence electron, producing the Lewis electron structure



Lewis structure

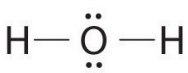
2. There are four electron groups around nitrogen, three bonding pairs and one lone pair. Repulsions are minimized by directing each hydrogen atom and the lone pair to the corners of a tetrahedron.

3. With three bonding pairs and one lone pair, the structure is designated as AX_3E. This designation has a total of four electron pairs, three X and one E. We expect the LP–BP interactions to cause the bonding pair angles to deviate significantly from the angles of a perfect tetrahedron.

4. There are three nuclei and one lone pair, so the molecular geometry is *trigonal pyramidal*. In essence, this is a tetrahedron with a vertex missing (Figure 9.2.3). However, the H–N–H bond angles are less than the ideal angle of 109.5° because of LP–BP repulsions (Figure 9.2.3 and Figure 9.2.4).

AX_2E_2: H_2O

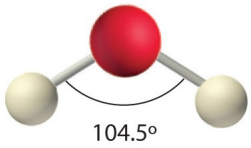
1. Oxygen has six valence electrons and each hydrogen has one valence electron, producing the Lewis electron structure



2. There are four groups around the central oxygen atom, two bonding pairs and two lone pairs. Repulsions are minimized by directing the bonding pairs and the lone pairs to the corners of a tetrahedron Figure 9.2.2.

3. With two bonding pairs and two lone pairs, the structure is designated as AX_2E_2 with a total of four electron pairs. Due to LP–LP, LP–BP, and BP–BP interactions, we expect a significant deviation from idealized tetrahedral angles.

4. With two hydrogen atoms and two lone pairs of electrons, the structure has significant lone pair interactions. There are two nuclei about the central atom, so the molecular shape is *bent*, or *V shaped*, with an H–O–H angle that is even less than the H–N–H angles in NH_3, as we would expect because of the presence of two lone pairs of electrons on the central atom rather than one.. This molecular shape is essentially a tetrahedron with two missing vertices.



Contributors

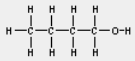
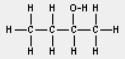
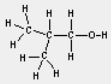
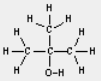
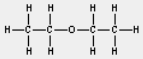
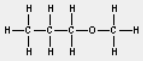
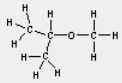
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

---

1.11: Drawing Organic Structures

It is necessary to draw structural formulas for organic compounds because in most cases a molecular formula does not uniquely represent a single compound. Different compounds having the same molecular formula are called **isomers**, and the prevalence of organic isomers reflects the extraordinary versatility of carbon in forming strong bonds to itself and to other elements. When the group of atoms that make up the molecules of different isomers are bonded together in fundamentally different ways, we refer to such compounds as **constitutional isomers**. There are seven constitutional isomers of $C_4H_{10}O$, and structural formulas for these are drawn in the following table. These formulas represent all known and possible $C_4H_{10}O$ compounds, and display a common structural feature. There are no double or triple bonds and no rings in any of these structures.

Structural Formulas for $C_4H_{10}O$ isomers

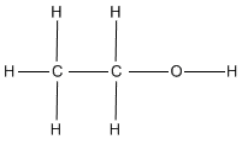
Kekulé Formula	Condensed Formula	Shorthand Formula
	$CH_3(CH_2)_3OH$	
	$C_2H_5CH(OH)CH_3$	
	$(CH_3)_2CHCH_2OH$	
	$(CH_3)_3COH$	
	$(C_2H_5)_2O$	
	$CH_3(CH_2)_2OCH_3$	
	$(CH_3)_2CHOCH_3$	

Simplification of structural formulas may be achieved without any loss of the information they convey. In **condensed structural formulas** the bonds to each carbon are omitted, but each distinct structural unit (group) is written with subscript numbers designating multiple substituents, including the hydrogens. **Shorthand (line) formulas** omit the symbols for carbon and hydrogen entirely. Each straight line segment represents a bond, the ends and intersections of the lines are carbon atoms, and the correct number of hydrogens is calculated from the tetravalency of carbon. Non-bonding valence shell electrons are omitted in these formulas.

Developing the ability to visualize a three-dimensional structure from two-dimensional formulas requires practice, and in most cases the aid of molecular models. As noted earlier, many kinds of model kits are available to students and professional chemists, and the beginning student is encouraged to obtain one.

Kekulé Formula

A structural formula displays the atoms of the molecule in the order they are bonded. It also depicts how the atoms are bonded to one another, for example single, double, and triple covalent bond. Covalent bonds are shown using lines. The number of dashes indicate whether the bond is a single, double, or triple covalent bond. Structural formulas are helpful because they explain the properties and structure of the compound which empirical and molecular formulas cannot always represent.

Ex. Kekulé Formula for Ethanol: 

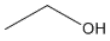
Condensed Formula

Condensed structural formulas show the order of atoms like a structural formula but are written in a single line to save space and make it more convenient and faster to write out. Condensed structural formulas are also helpful when showing that a group of atoms is connected to a single atom in a compound. When this happens, parenthesis are used around the group of atoms to show they are together.

Ex. Condensed Structural Formula for Ethanol: CH_3CH_2OH (Molecular Formula for Ethanol C_2H_6O).

Shorthand Formula

Because organic compounds can be complex at times, line-angle formulas are used to write carbon and hydrogen atoms more efficiently by replacing the letters with lines. A carbon atom is present wherever a line intersects another line. Hydrogen atoms are then assumed to complete each of carbon's four bonds. All other atoms that are connected to carbon atoms are written out. Line angle formulas help show structure and order of the atoms in a compound making the advantages and disadvantages similar to structural formulas.

Ex.Shorthand Formula for Ethanol: 

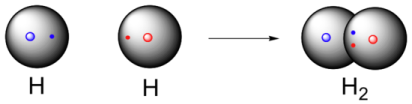
Contributors

- Jean Kim (UCD), Kristina Bonnett (UCD)

1.12: Hybridization

Formation of sigma bonds: the H_2 molecule

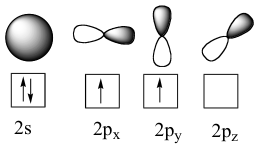
The simplest case to consider is the hydrogen molecule, H_2. When we say that the two electrons from each of the hydrogen atoms are shared to form a covalent bond between the two atoms, what we mean in valence bond theory terms is that the two spherical 1*s* orbitals overlap, allowing the two electrons to form a pair within the two overlapping orbitals.



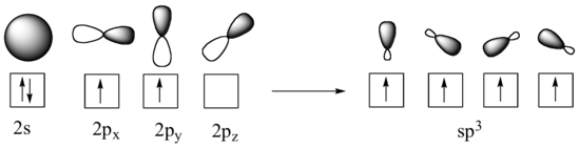
These two electrons are now attracted to the positive charge of *both* of the hydrogen nuclei, with the result that they serve as a sort of 'chemical glue' holding the two nuclei together.

Bonding in Methane

Now let's turn to methane, the simplest organic molecule. Recall the valence electron configuration of the central carbon:



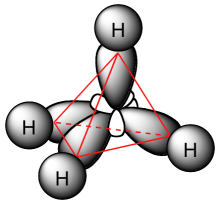
This picture, however, is problematic. How does the carbon form four bonds if it has only two half-filled *p* orbitals available for bonding? A hint comes from the experimental observation that the four C-H bonds in methane are arranged with tetrahedral geometry about the central carbon, and that each bond has the same length and strength. In order to explain this observation, valence bond theory relies on a concept called **orbital hybridization**. In this picture, the four valence orbitals of the carbon (one 2*s* and three 2*p* orbitals) combine mathematically (remember: orbitals are described by equations) to form four equivalent **hybrid orbitals**, which are named **sp^3 orbitals** because they are formed from mixing one s and three p orbitals. In the new electron configuration, each of the four valence electrons on the carbon occupies a single sp^3 orbital.



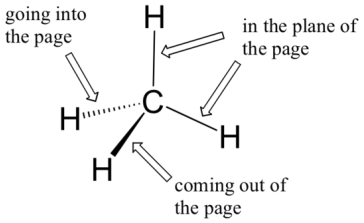
The sp^3 hybrid orbitals, like the *p* orbitals of which they are partially composed, are oblong in shape, and have two lobes of opposite sign. Unlike the *p* orbitals, however, the two lobes are of very different size. The larger lobes of the sp^3 hybrids are directed towards the four corners of a tetrahedron, meaning that the angle between any two orbitals is 109.5°.

This geometric arrangement makes perfect sense if you consider that it is precisely this angle that allows the four orbitals (and the electrons in them) to be as far apart from each other as possible.This is simply a restatement of the Valence Shell Electron Pair Repulsion (VSEPR) theory that you learned in General Chemistry: electron pairs (in orbitals) will arrange themselves in such a way as to remain as far apart as possible, due to negative-negative electrostatic repulsion.

Each C-H bond in methane, then, can be described as an overlap between a half-filled 1*s* orbital in a hydrogen atom and the larger lobe of one of the four half-filled sp^3 hybrid orbitals in the central carbon. The length of the carbon-hydrogen bonds in methane is 1.09 Å (1.09×10^{-10} m).



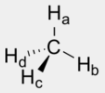
While previously we drew a Lewis structure of methane in two dimensions using lines to denote each covalent bond, we can now draw a more accurate structure in three dimensions, showing the tetrahedral bonding geometry. To do this on a two-dimensional page, though, we need to introduce a new drawing convention: the solid / dashed wedge system. In this convention, a solid wedge simply represents a bond that is meant to be pictured emerging from the plane of the page. A dashed wedge represents a bond that is meant to be pictured pointing into, or behind, the plane of the page. Normal lines imply bonds that lie in the plane of the page.

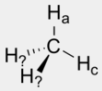


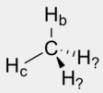
This system takes a little bit of getting used to, but with practice your eye will learn to immediately ‘see’ the third dimension being depicted.

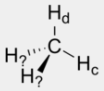
Example

Imagine that you could distinguish between the four hydrogens in a methane molecule, and labeled them H_a through H_d. In the images below, the *exact same* methane molecule is rotated and flipped in various positions. Draw the missing hydrogen atom labels. (It will be much easier to do this if you make a model.)



a) 

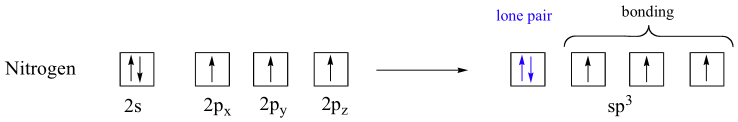
b) 

c) 

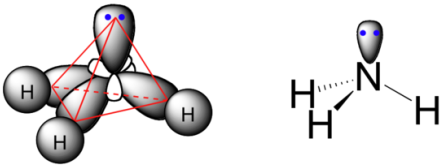
Example

Describe, with a picture and with words, the bonding in chloroform, $CHCl_3$.

Solutions

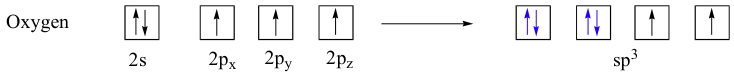


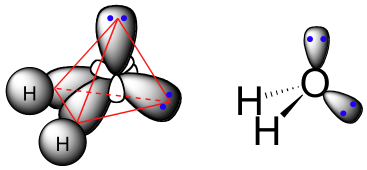
The bonding arrangement here is also tetrahedral: the three N-H bonds of ammonia can be pictured as forming the base of a trigonal pyramid, with the fourth orbital, containing the lone pair, forming the top of the pyramid.



Recall from your study of VSEPR theory in General Chemistry that the lone pair, with its slightly greater repulsive effect, 'pushes' the three N-H sbonds away from the top of the pyramid, meaning that the H-N-H bond angles are slightly less than tetrahedral, at 107.3˚ rather than 109.5˚.

VSEPR theory also predicts, accurately, that a water molecule is 'bent' at an angle of approximately 104.5˚. It would seem logical, then, to describe the bonding in water as occurring through the overlap of sp^3-hybrid orbitals on oxygen with 1sorbitals on the two hydrogen atoms. In this model, the two nonbonding lone pairs on oxygen would be located in sp^3 orbitals.





Some experimental evidence, however, suggests that the bonding orbitals on the oxygen are actually unhybridized 2*p* orbitals rather than sp^3 hybrids. Although this would seem to imply that the H-O-H bond angle should be 90˚ (remember that *p* orbitals are oriented perpendicular to one another), it appears that electrostatic repulsion has the effect of distorting this *p*-orbital angle to 104.5˚. Both the hybrid orbital and the nonhybrid orbital models present reasonable explanations for the observed bonding arrangement in water, so we will not concern ourselves any further with the distinction.

Example

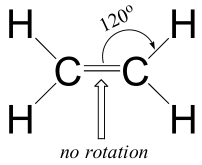
Draw, in the same style as the figures above, an orbital picture for the bonding in methylamine.

Solution

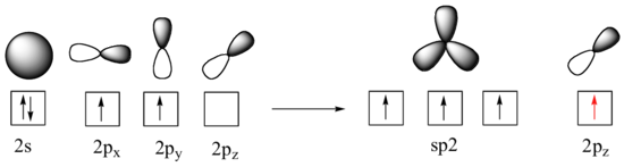
Formation of π bonds - sp^2 and sp hybridization

The valence bond theory, along with the hybrid orbital concept, does a very good job of describing double-bonded compounds such as ethene. Three experimentally observable characteristics of the ethene molecule need to be accounted for by a bonding model:

1. Ethene is a planar (flat) molecule.
2. Bond angles in ethene are approximately 120°, and the carbon-carbon bond length is 1.34 Å, significantly shorter than the 1.54 Å single carbon-carbon bond in ethane.
3. There is a significant barrier to rotation about the carbon-carbon double bond.

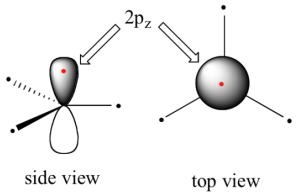


Clearly, these characteristics are not consistent with an sp^3 hybrid bonding picture for the two carbon atoms. Instead, the bonding in ethene is described by a model involving the participation of a different kind of hybrid orbital. Three atomic orbitals on each carbon – the 2*s*, $2p_x$ and $2p_y$ orbitals – combine to form three sp^2 hybrids, leaving the $2p_z$ orbital unhybridized.

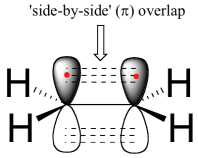


The three sp^2 hybrids are arranged with trigonal planar geometry, pointing to the three corners of an equilateral triangle, with angles of 120°between them. The unhybridized $2p_z$ orbital is *perpendicular* to this plane (in the next several figures, sp^2 orbitals

and the sigma bonds to which they contribute are represented by lines and wedges; only the $2p_z$ orbitals are shown in the 'space-filling' mode).

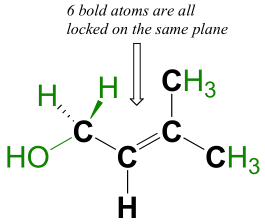


The carbon-carbon double bond in ethene consists of one sbond, formed by the overlap of two sp^2 orbitals, and a second bond, calleda **π (pi) bond**, which is formed by the *side-by-side* overlap of the two unhybridized $2p_z$ orbitals from each carbon.



spacefilling image of bonding in ethene

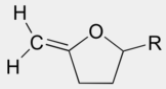
The pi bond does *not* have symmetrical symmetry. Because they are the result of side-by-side overlap (rather then end-to-end overlap like a sigma bond), *pi bonds are not free to rotate.* If rotation about this bond were to occur, it would involve disrupting the side-by-side overlap between the two $2p_z$ orbitals that make up the pi bond. The presence of the pi bond thus 'locks' the six atoms of ethene into the same plane. This argument extends to larger alkene groups: in each case, the six atoms of the group form a single plane.



Conversely, sbonds such as the carbon-carbon single bond in ethane (CH_3CH_3) exhibit free rotation, and can assume many different conformations, or shapes - this is one of the main subjects of Chapter 3.

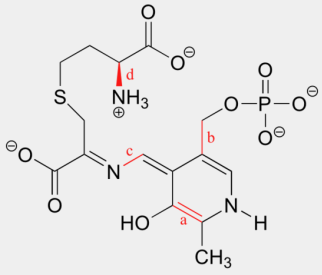
Example 1.20

Circle the six atoms in the molecule below that are 'locked' into the same plane.



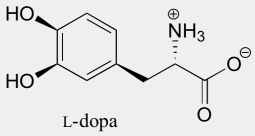
Example

What kinds of orbitals are overlapping in bonds a-d indicated below?



Example

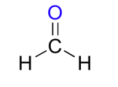
What is wrong with the way the following structure is drawn?



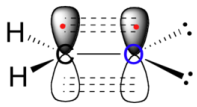
L-dopa

Solutions

A similar picture can be drawn for the bonding in carbonyl groups, such as formaldehyde. In this molecule, the carbon is sp^2-hybridized, and we will assume that the oxygen atom is also sp^2 hybridized. The carbon has three sigma bonds: two are formed by overlap between two of its sp^2 orbitals with the 1*s*orbital from each of the hydrogens, and the third sigma bond is formed by overlap between the remaining carbon sp^2 orbital and an sp^2 orbital on the oxygen. The two lone pairs on oxygen occupy its other two sp^2 orbitals.



formaldehyde



The pi bond is formed by side-by-side overlap of the unhybridized $2p_z$ orbitals on the carbon and the oxygen. Just like in alkenes, the $2p_z$ orbitals that form the pi bond are perpendicular to the plane formed by the sigma bonds.

Example

Describe and draw the bonding picture for the imine group shown below. Use the drawing of formaldehyde above as your guide.

Solution

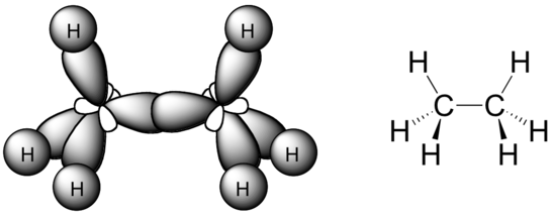
Contributors

- **Organic Chemistry With a Biological Emphasis** by Tim Soderberg (University of Minnesota, Morris)

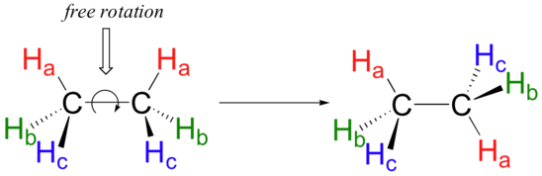
1.13: Ethane, Ethylene, and Acetylene

Bonding in Ethane

In the ethane molecule, the bonding picture according to valence orbital theory is very similar to that of methane. Both carbons are sp^3-hybridized, meaning that both have four bonds arranged with tetrahedral geometry. The carbon-carbon bond, with a bond length of 1.54 Å, is formed by overlap of one sp^3 orbital from each of the carbons, while the six carbon-hydrogen bonds are formed from overlaps between the remaining sp^3 orbitals on the two carbons and the 1*s* orbitals of hydrogen atoms. All of these are sigma bonds.



Because they are formed from the end-on-end overlap of two orbitals, *sigma bonds are free to rotate*. This means, in the case of ethane molecule, that the two methyl (CH_3) groups can be pictured as two wheels on a hub, each one able to rotate freely with respect to the other.



In chapter 3 we will learn more about the implications of rotational freedom in sigma bonds, when we discuss the 'conformation' of organic molecules.

The sp^3 bonding picture is also used to described the bonding in amines, including ammonia, the simplest amine. Just like the carbon atom in methane, the central nitrogen in ammonia is sp^3-hybridized. With nitrogen, however, there are five rather than four valence electrons to account for, meaning that three of the four hybrid orbitals are half-filled and available for bonding, while the fourth is fully occupied by a (non-bonding) pair of electrons.

C_2H_4, also known as ethylene or ethene, is a gaseous material created synthetically through steam cracking. In nature, it is released in trace amounts by plants to signal their fruits to ripen. Ethene consists of two sp^2-hybridized carbon atoms, which are sigma bonded to each other and to two hydrogen atoms each. The remaining unhybridized p orbitals on the carbon form a pi bond, which gives ethene its reactivity.

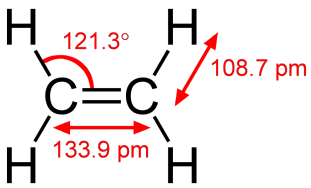
Bonding in Ethene

A key component of using Valence Bond Theory correctly is being able to use the Lewis dot diagram correctly. Ethene has a double bond between the carbons and single bonds between each hydrogen and carbon: each bond is represented by a pair of dots, which represent electrons. Each carbon requires a full octet and each hydrogen requires a pair of electrons. The correct Lewis structure for ethene is shown below:

For more information on how to use Lewis Dot Structures refer to http://chemwiki.ucdavis.edu/Wikitext...wis_Structures.

Valence Shell Electron Pair Repulsion (VSEPR) Theory is used to predict the bond angles and spatial positions of the carbon and hydrogen atoms of ethene and to determine the bond order of the carbon atoms (the number of bonds formed between them). Each carbon atom is of the general arrangement AX_3, where A is the central atom surrounded by three other atoms (denoted by X); compounds of this form adopt trigonal planar geometry, forming 120 degree bond angles. In order for the unhybridized p orbitals to

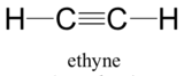
successfully overlap, the CH_2 must be coplanar: therefore, C_2H_4 is a planar molecule and each bond angle is about 120 degrees. The diagram below shows the bond lengths and hydrogen-carbon-carbon bond angles of ethene:



According to valence bond theory, two atoms form a covalent bond through the overlap of individual half-filled valence atomic orbitals, each containing one unpaired electron. In ethene, each hydrogen atom has one unpaired electron and each carbon is sp^2 hybridized with one electron each sp^2 orbital. The fourth electron is in the p orbital that will form the pi bond. The bond order for ethene is simply the number of bonds between each atom: the carbon-carbon bond has a bond order of two, and each carbon-hydrogen bond has a bond order of one. For more information see http://chemwiki.ucdavis.edu/Wikitexts/UCD_Chem_124A%3a_Kauzlarich/ChemWiki_Module_Topics/VSEPR

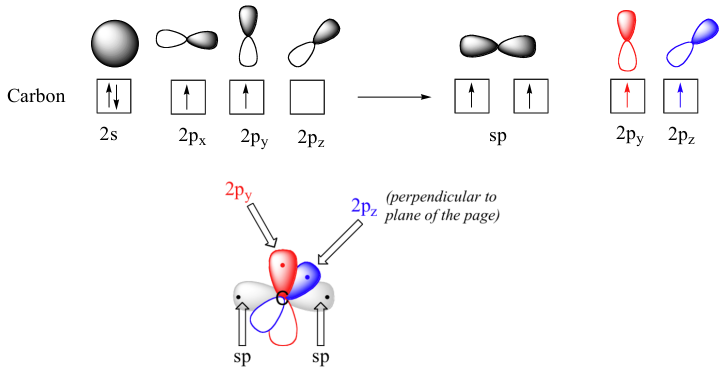
Bonding in acetylene

Finally, the hybrid orbital concept applies well to triple-bonded groups, such as alkynes and nitriles. Consider, for example, the structure of ethyne (common name acetylene), the simplest alkyne.

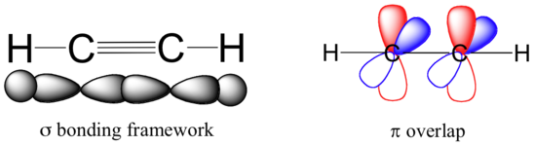


ethyne
(acetylene)

This molecule is linear: all four atoms lie in a straight line. The carbon-carbon triple bond is only 1.20Å long. In the hybrid orbital picture of acetylene, both carbons are **sp-hybridized**. In an sp-hybridized carbon, the 2*s* orbital combines with the $2p_x$ orbital to form two sp hybrid orbitals that are oriented at an angle of 180°with respect to each other (eg. along the x axis). The $2p_y$ and $2p_z$ orbitals remain unhybridized, and are oriented perpendicularly along the y and z axes, respectively.

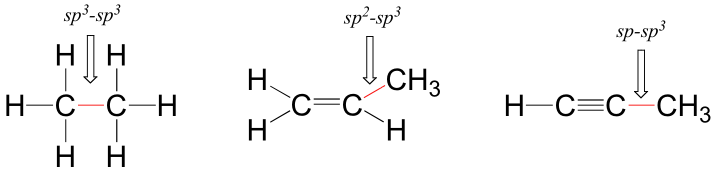


The C-C sigma bond, then, is formed by the overlap of one sp orbital from each of the carbons, while the two C-H sigma bonds are formed by the overlap of the second sp orbital on each carbon with a 1*s* orbital on a hydrogen. Each carbon atom still has two half-filled $2p_y$ and $2p_z$ orbitals, which are perpendicular both to each other and to the line formed by the sigma bonds. These two perpendicular pairs of *p* orbitals form two pi bonds between the carbons, resulting in a triple bond overall (one sigma bond plus two pi bonds).



σ bonding framework π overlap

The hybrid orbital concept nicely explains another experimental observation: single bonds adjacent to double and triple bonds are progressively shorter and stronger than ‘normal’ single bonds, such as the one in a simple alkane. The carbon-carbon bond in ethane (structure A below) results from the overlap of two sp^3 orbitals.



A B C

In alkene B, however, the carbon-carbon single bond is the result of overlap between an sp^2 orbital and an sp^3 orbital, while in alkyne C the carbon-carbon single bond is the result of overlap between an sp orbital and an sp^3 orbital. These are all single bonds, but the bond in molecule C is shorter and stronger than the one in B, which is in turn shorter and stronger than the one in A.

The explanation here is relatively straightforward. An sp orbital is composed of one *s* orbital and one *p* orbital, and thus it has 50% *s* character and 50% *p* character. sp^2 orbitals, by comparison, have 33% *s* character and 67% *p* character, while sp^3 orbitals have 25% *s* character and 75% *p* character. Because of their spherical shape, 2*s* orbitals are smaller, and hold electrons closer and 'tighter' to the nucleus, compared to 2*p* orbitals. Consequently, bonds involving sp + sp^3 overlap (as in alkyne C) are shorter and stronger than bonds involving sp^2 + sp^3 overlap (as in alkene B). Bonds involving sp^3-sp^3overlap (as in alkane A) are the longest and weakest of the group, because of the 75% '*p*' character of the hybrids.

Contributors

- **Organic Chemistry With a Biological Emphasis** by Tim Soderberg (University of Minnesota, Morris)

CHAPTER OVERVIEW

2: Acids and Bases

2.1: Brønsted–Lowry Acids and Bases

In 1923, chemists Johannes Brønsted and Martin Lowry independently developed definitions of acids and bases based on compounds abilities to either donate or accept protons (H^+ ions). Here, acids are defined as being able to donate protons in the form of hydrogen ions; whereas bases are defined as being able to accept protons. This took the Arrhenius definition one step further as water is no longer required to be present in the solution for acid and base reactions to occur.

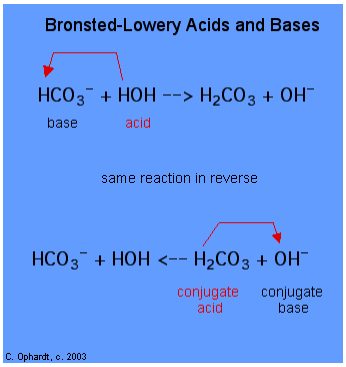
Brønsted-Lowery Definition

J.N. Brønsted and T.M. Lowry independently developed the theory of proton donors and proton acceptors in acid-base reactions, coincidentally in the same region and during the same year. The Arrhenius theory where acids and bases are defined by whether the molecule contains hydrogen and hydroxide ion is too limiting. The main effect of the Brønsted-Lowry definition is to identify the proton (H+) transfer occurring in the acid-base reaction. This is best illustrated in the following equation:

$$HA + Z \rightleftharpoons A^- + HZ^+ \tag{2.1.1}$$

Acid	Base	
Donates hydrogen ions	**Accepts hydrogen ions.**	
HCl^+	HOH →	$H_3O^+ + Cl^-$
HOH^+	NH_3→	$NH_4^+ + OH^-$

The determination of a substance as a Brønsted-Lowery acid or base can only be done by observing the reaction. In the case of the HOH it is a base in the first case and an acid in the second case.



To determine whether a substance is an acid or a base, count the hydrogens on each substance before and after the reaction. If the number of hydrogens has decreased that substance is the acid (donates hydrogen ions). If the number of hydrogens has increased that substance is the base (accepts hydrogen ions). These definitions are normally applied to the reactants on the left. If the reaction is viewed in reverse a new acid and base can be identified. The substances on the right side of the equation are called conjugate acid and conjugate base compared to those on the left. Also note that the original acid turns in the conjugate base after the reaction is over.

Acids are Proton Donors and Bases are Proton Acceptors

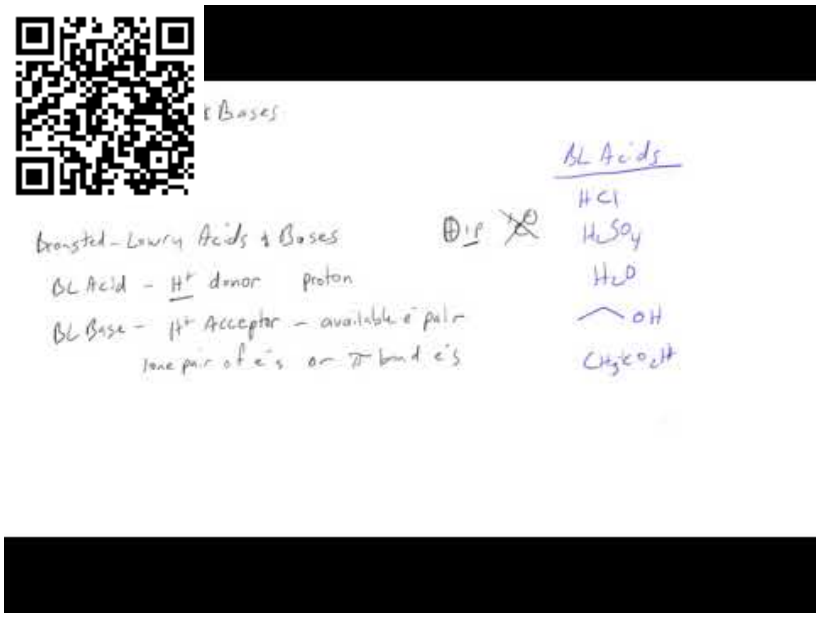
For a reaction to be in equilibrium a transfer of electrons needs to occur. The acid will give an electron away and the base will receive the electron. Acids and Bases that work together in this fashion are called a *conjugate pair* made up of *conjugate acids* and *conjugate bases*.

$$HA + Z \rightleftharpoons A^- + HZ^+ \tag{2.1.2}$$

A stands for an Acidic compound and Z stands for a Basic compound

- A Donates H to form HZ^+.
- Z Accepts H from A which forms HZ^+

- A^- becomes conjugate base of HA and in the reverse reaction it accepts a H from HZ to recreate HA in order to remain in equilibrium
- HZ^+ becomes a conjugate acid of Z and in the reverse reaction it donates a H to A^- recreating Z in order to remain in equilibrium



Questions

1. Why is HA an Acid?
2. Why is Z^- a Base?
3. How can A^- be a base when HA was and Acid?
4. How can HZ^+ be an acid when Z used to be a Base?

Now that we understand the concept, let's look at an an example with actual compounds!

$$HCl + H_2O \rightleftharpoons H_3O^+ + Cl^- \tag{2.1.3}$$

- HCL is the acid because it is donating a proton to H_2O
- H_2O is the base because H_2O is accepting a proton from HCL
- H_3O^+ is the conjugate acid because it is donating an acid to CL turn into it's conjugate acid H_2O
- Cl^- is the conjugate base because it accepts an H from H_3O to return to it's conjugate acid HCl

How can H_2O be a base? I thought it was neutral?

Answers

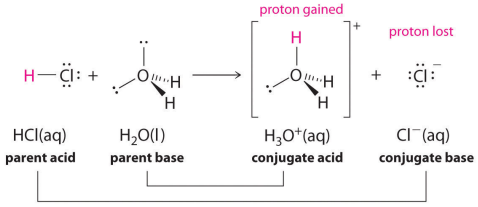
1. *It has a proton that can be transferred*
2. *It receives a proton from HA*
3. *A^- is a conjugate base because it is in need of a H in order to remain in equilibrium and return to HA*
4. *HZ^+ is a conjugate acid because it needs to donate or give away its proton in order to return to it's previous state of Z*
5. *In the* Brønsted-*Lowry Theory what makes a compound an element or a base is whether or not it donates or accepts protons. If the H_2O was in a different problem and was instead donating an H rather than accepting an H it would be an acid!*

Conjugate Acid–Base Pairs

In aqueous solutions, acids and bases can be defined in terms of the transfer of a proton from an acid to a base. Thus for every acidic species in an aqueous solution, there exists a species derived from the acid by the loss of a proton. These two species that differ by only a proton constitute a conjugate acid–base pair.

> *All acid–base reactions contain two conjugate acid–base pairs.*

For example, in the reaction of HCl with water, HCl, the parent acid, donates a proton to a water molecule, the parent base, thereby forming Cl^-. Thus HCl and Cl^- constitute a conjugate acid–base pair. By convention, we always write a conjugate acid–base pair as the acid followed by its conjugate base. In the reverse reaction, the Cl^- ion in solution acts as a base to accept a proton from H_2O and HCl. Thus H_3O^+ and H_2O constitute a second conjugate acid–base pair. In general, any acid–base reaction must contain two conjugate acid–base pairs, which in this case are HCl/Cl- and H_3O^+/H_2O.



Similarly, in the reaction of acetic acid with water, acetic acid donates a proton to water, which acts as the base. In the reverse reaction, H_3O^+ is the acid that donates a proton to the acetate ion, which acts as the base. Once again, we have two conjugate acid–base pairs: the parent acid and its conjugate base $(CH_3CO_2H/CH_3CO_2^-)$ and the parent base and its conjugate acid (H_3O^+/H_2O).

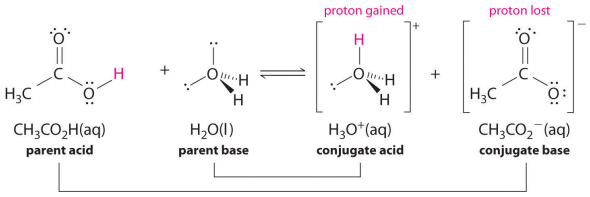


Figure 2.1.2

In the reaction of ammonia with water to give ammonium ions and hydroxide ions (Figure 16.3), ammonia acts as a base by accepting a proton from a water molecule, which in this case means that water is acting as an acid. In the reverse reaction, an ammonium ion acts as an acid by donating a proton to a hydroxide ion, and the hydroxide ion acts as a base. The conjugate acid–base pairs for this reaction are NH_4^+/NH_3 and H_2O/OH^-.

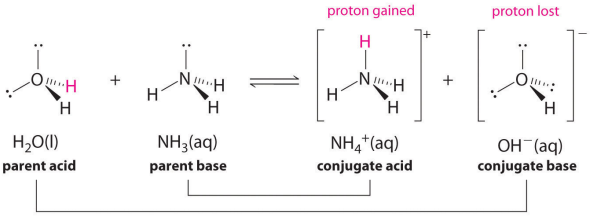


Figure 2.1.3: The Relative Strengths of Some Common Conjugate Acid–Base Pairs

Some common conjugate acid–base pairs are shown in Figure 2.1.4.

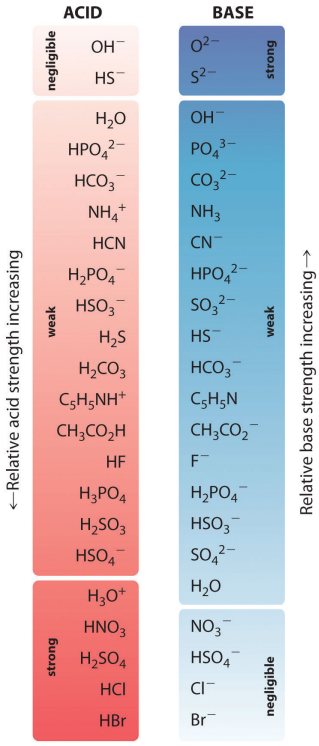


Figure 2.1.4: The strongest acids are at the bottom left, and the strongest bases are at the top right. The conjugate base of a strong acid is a very weak base, and, conversely, the conjugate acid of a strong base is a very weak acid.

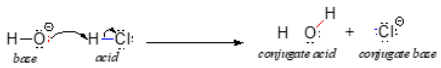
Contributors

- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Layne A. Morsch (University of Illinois Springfield)

2.2: Reactions of Brønsted–Lowry Acids and Bases

The Brønsted-Lowry definition of acidity

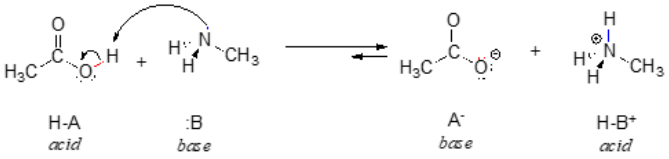
We'll begin our discussion of acid-base chemistry with a couple of essential definitions. The first of these definitions was proposed in 1923 by the Danish chemist Johannes Brønsted and the English chemist Thomas Lowry, and has come to be known as the Brønsted-Lowry definition of acids and bases. An acid, by the Brønsted-Lowry definition, is a species which is able to donate a proton (H^+), while a base is a proton acceptor. We have already discussed in the previous chapter one of the most familiar examples of a Brønsted-Lowry acid-base reaction, between hydrochloric acid and hydroxide ion:



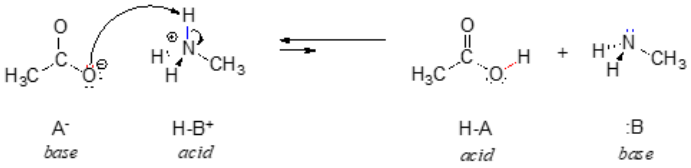
In this reaction, a proton is transferred from HCl (the acid, or proton *donor*) to hydroxide (the base, or proton *acceptor*). As we learned in the previous chapter, curved arrows depict the movement of electrons in this bond-breaking and bond-forming process.

After a Brønsted-Lowry acid donates a proton, what remains – in this case, a chloride ion – is called the **conjugate base**. Chloride is thus the conjugate base of hydrochloric acid. Conversely, when a Brønsted-Lowry base accepts a proton it is converted into its **conjugate acid** form: water is thus the conjugate acid of hydroxide.

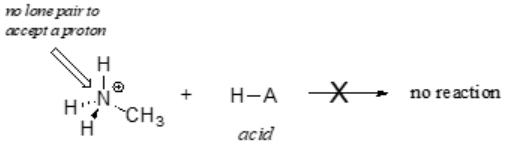
We can also talk about conjugate acid/base pairs: the two acid/base pairs involved in our first reaction are hydrochloric acid/chloride and hydroxide/water. In this next acid-base reaction, the two pairs involved are acetate/acetic acid and methyl ammonium/methylamine:



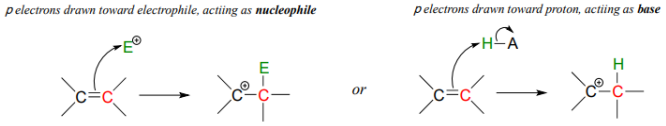
Throughout this text, we will often use the abbreviations HA and :B in order to refer in a general way to acidic and basic reactants:



In order to act as a proton acceptor, a base must have a reactive pair of electrons. In all of the examples we shall see in this chapter, this pair of electrons is a non-bonding lone pair, usually (but not always) on an oxygen, nitrogen, sulfur, or halogen atom. When acetate acts as a base in the reaction shown above, for example, one of its oxygen lone pairs is used to form a new bond to a proton. The same can be said for an amine acting as a base. Clearly, methyl ammonium ion cannot act as a base – it does not have a reactive pair of electrons with which to accept a new bond to a proton.



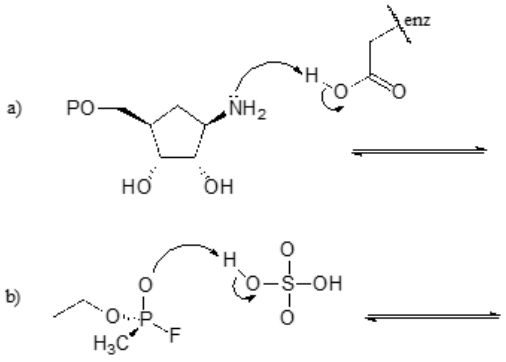
Later, in chapter 15, we will see several examples where the (relatively) reactive pair of electrons in a π bond act in a basic fashion.



In this chapter, we will concentrate on those bases with non-bonding (lone pair) electrons.

Example

Exercise 7.1: Draw structures for the missing conjugate acids or conjugate bases in the reactions below.



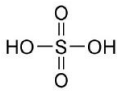
Solution

Contributors

- **Organic Chemistry With a Biological Emphasis** by Tim Soderberg (University of Minnesota, Morris)

2.3: Acid Strength and p K a pKa

You are no doubt aware that some acids are stronger than others. Sulfuric acid is strong enough to be used as a drain cleaner, as it will rapidly dissolve clogs of hair and other organic material.

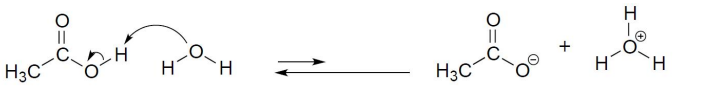


sulfuric acid

Not surprisingly, concentrated sulfuric acid will also cause painful burns if it touches your skin, and permanent damage if it gets in your eyes (there's a good reason for those safety goggles you wear in chemistry lab!). Acetic acid (vinegar), will also burn your skin and eyes, but is not nearly strong enough to make an effective drain cleaner. Water, which we know can act as a proton donor, is obviously not a very strong acid. Even hydroxide ion could *theoretically* act as an acid – it has, after all, a proton to donate – but this is not a reaction that we would normally consider to be relevant in anything but the most extreme conditions.

The relative acidity of different compounds or functional groups – in other words, their relative capacity to donate a proton to a common base under identical conditions – is quantified by a number called the **dissociation constant**, abbreviated $\mathbf{K_a}$. The common base chosen for comparison is water.

We will consider acetic acid as our first example. When a small amount of acetic acid is added to water, a proton-transfer event (acid-base reaction) occurs to some extent.



H-A acetic acid | :B water | A^- acetate ion | $H\text{-}B^+$ hydronium ion

Notice the phrase 'to some extent' – this reaction does *not* run to completion, with all of the acetic acid converted to acetate, its conjugate base. Rather, a *dynamic equilibrium* is reached, with proton transfer going in both directions (thus the two-way arrows) and finite concentrations of all four species in play. The nature of this equilibrium situation, as you recall from General Chemistry, is expressed by an equilibrium constant, K_{eq}. The equilibrium constant is actually a ratio of activities (represented by the symbol a), but activities are rarely used in courses other than analytical or physical chemistry. To simplify the discussion for general chemistry and organic chemistry courses, the activities of all of the solutes are replaced with molarities, and the activity of the solvent (usually water) is defined as having the value of 1.

In our example, we added a small amount of acetic acid to a large amount of water: water is the *solvent* for this reaction. Therefore, in the course of the reaction, the concentration of water changes very little, and the water can be treated as a pure solvent, which is always assigned an activity of 1. The acetic acid, acetate ion and hydronium ion are all *solutes*, and so their activities are approximated with molarities. The acid dissociation constant, or K_a, for acetic acid is therefore defined as:

$$K_{eq} = \frac{a_{CH_3COO^-} \cdot a_{H_3O^+}}{a_{CH_3COOH} \cdot a_{H_2O}} \approx \frac{[CH_3COO^-][H_3O^+]}{[CH_3COOH][1]} \tag{2.3.1}$$

Because dividing by 1 does not change the value of the constant, the "1" is usually not written, and K_a is written as:

$$K_{eq} = K_a = \frac{[CH_3COO^-][H_3O^+]}{[CH_3COOH]} = 1.75 \times 10^{-5} \tag{2.3.2}$$

In more general terms, the dissociation constant for a given acid is expressed as:

$$K_a = \frac{[A^-][H_3O^+]}{[HA]} \tag{2.3.3}$$

or

$$K_a = \frac{[A][H_3O^+]}{[HA^+]} \tag{2.3.4}$$

The first expression applies to a neutral acid such as like HCl or acetic acid, while the second applies to a cationic acid like ammonium (NH_4^+).

The value of $K_a = 1.75 \times 10^{-5}$ for acetic acid is very small - this means that very little dissociation actually takes place, and there is much more acetic acid in solution at equilibrium than there is acetate ion. Acetic acid is a relatively weak acid, at least when compared to sulfuric acid ($K_a = 10^9$) or hydrochloric acid ($K_a = 10^7$), both of which undergo essentially complete dissociation in water.

A number like 1.75×10^{-5} is not very easy either to say or to remember. Chemists have therefore come up with a more convenient term to express relative acidity: the **pK_a** value.

$$pK_a = -\log K_a$$

Doing the math, we find that the pK_a of acetic acid is 4.8. The use of pK_a values allows us to express the acidity of common compounds and functional groups on a numerical scale of about –10 (very strong acid) to 50 (not acidic at all). Table 7 at the end of the text lists exact or approximate pK_a values for different types of protons that you are likely to encounter in your study of organic and biological chemistry. Looking at Table 7, you see that the pK_a of carboxylic acids are in the 4-5 range, the pK_a of sulfuric acid is –10, and the pK_a of water is 14. Alkenes and alkanes, which are not acidic at all, have pK_a values above 30. *The lower the pK_a value, the stronger the acid.*

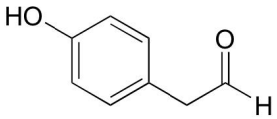
It is important to realize that pK_a is not at all the same thing as pH: the former is an inherent property of a compound or functional group, while the latter is the measure of the hydronium ion concentration in a particular aqueous solution:

$$pH = -\log [H_3O^+]$$

Any particular acid will always have the same pK_a (assuming that we are talking about an aqueous solution at room temperature) but different aqueous solutions of the acid could have different pH values, depending on how much acid is added to how much water.

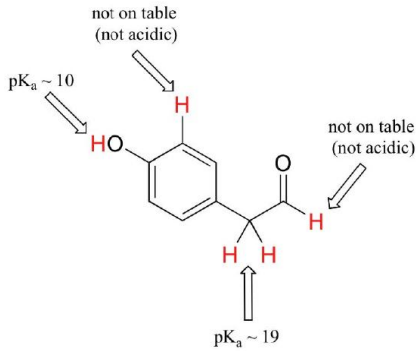
Our table of pK_a values will also allow us to compare the strengths of different bases by comparing the pK_avalues of their conjugate acids. The key idea to remember is this: *the stronger the conjugate acid, the weaker the conjugate base*. Sulfuric acid is the strongest acid on our list with a pK_a value of –10, so HSO_4^- is the weakest conjugate base. You can see that hydroxide ion is a stronger base than ammonia (NH_3), because ammonium (NH_4^+, $pK_a = 9.2$) is a stronger acid than water ($pK_a = 14.0$).

While Table 7 provides the pK_a values of only a limited number of compounds, it can be very useful as a starting point for estimating the acidity or basicity of just about any organic molecule. Here is where your familiarity with organic functional groups will come in very handy. What, for example, is the $pK_a$of cyclohexanol? It is not on the table, but as it is an alcohol it is probably somewhere near that of ethanol ($pK_a = 16$). Likewise, we can use Table 7 to predict that para-hydroxyphenyl acetaldehyde, an intermediate compound in the biosynthesis of morphine, has a pK_a in the neighborhood of 10, close to that of our reference compound, phenol.



p=hydroxyphenyl acetaldehyde

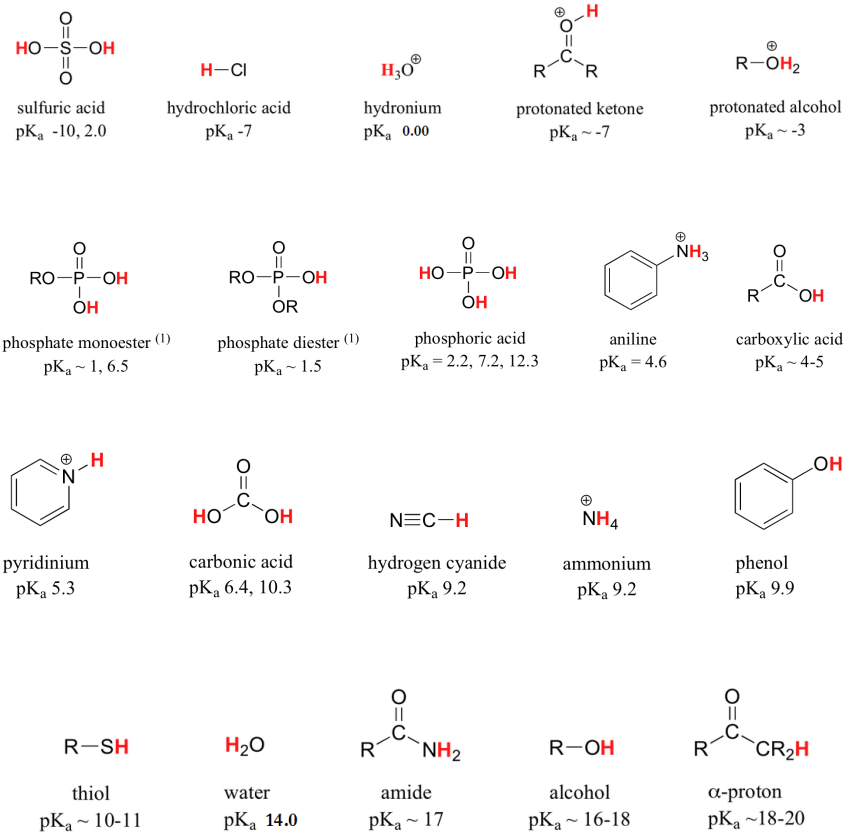
Notice in this example that we need to evaluate the potential acidity at *four* different locations on the molecule.

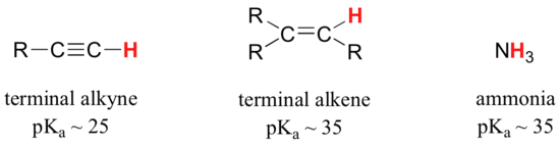


Aldehyde and aromatic protons are not at all acidic (pK_avalues are above 40 – not on our table). The two protons on the carbon next to the carbonyl are slightly acidic, with pK_a values around 19-20 according to the table. The most acidic proton is on the phenol group, so if the compound were to be subjected to a single molar equivalent of strong base, this is the proton that would be donated.

As you continue your study of organic chemistry, it will be a very good idea to commit to memory the approximate pK_a ranges of some important functional groups, including water, alcohols, phenols, ammonium, thiols, phosphates, carboxylic acids and carbons next to carbonyl groups (so-called a-carbons). These are the groups that you are most likely to see acting as acids or bases in biological organic reactions.

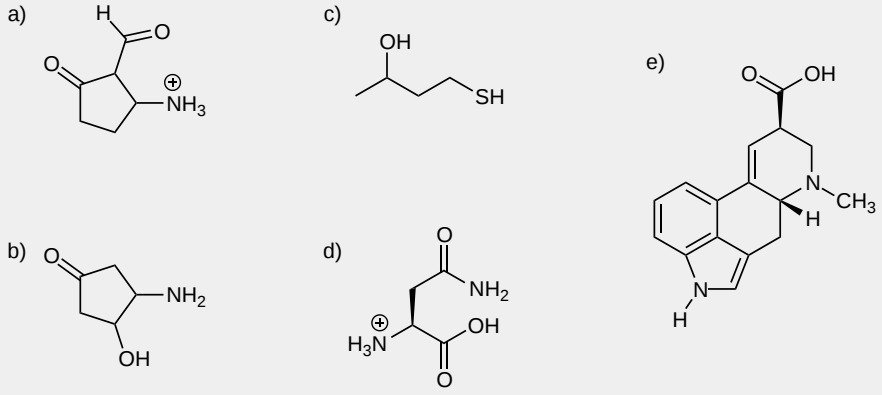
A word of caution: when using the pKa table, be absolutely sure that you are considering the correct conjugate acid/base pair. If you are asked to say something about the basicity of ammonia (NH_3) compared to that of ethoxide ion ($CH_3CH_2O^-$), for example, the relevant pK_a values to consider are 9.2 (the pK_a of ammonium ion) and 16 (the pK_a of ethanol). From these numbers, you know that ethoxide is the stronger base. Do not make the mistake of using the pK_a value of 38: this is the pK_a of ammonia *acting as an acid*, and tells you how basic the NH_2^- ion is (very basic!)





Example

Exercise 7.2: Using the pK_a table, estimate pK_a values for the most acidic group on the compounds below, and draw the structure of the conjugate base that results when this group donates a proton.



Solution

2.4: Predicting the Outcome of Acid–Base Reactions

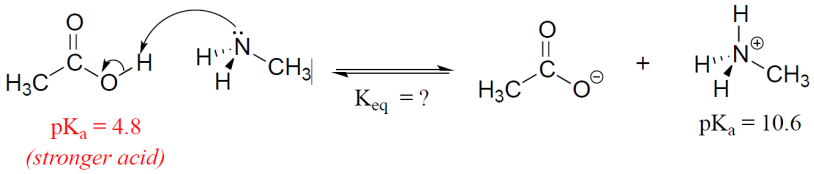
Using pK_a values to predict reaction equilibria

By definition, the pK_a value tells us the extent to which an acid will react with water as the base, but by extension, we can also calculate the equilibrium constant for a reaction between any acid-base pair. Mathematically, it can be shown that:

$$K_{eq} \text{ (for the acid base reaction in question)} = 10^{\Delta pKa}$$

where ΔpK_a = pK_a of product acid minus pK_a of reactant acid

Consider a reaction between methylamine and acetic acid:



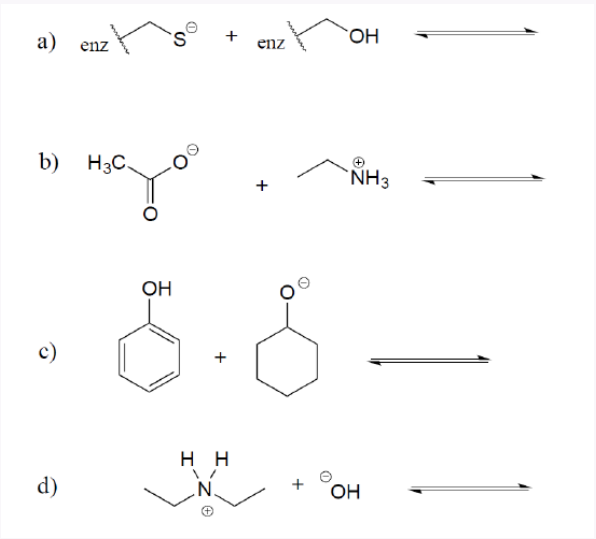
First, we need to identify the acid species on either side of the equation. On the left side, the acid is of course acetic acid, while on the right side the acid is methyl ammonium. The specific pK_a values for these acids are not on our very generalized pK_a table, but are given in the figure above. Without performing any calculations, you should be able to see that this equilibrium lies far to the right-hand side: acetic acid has a lower pK_a, is a stronger acid, and thus it wants to give up its proton more than methyl ammonium does. Doing the math, we see that

$$K_{eq} = 10^{\Delta pKa} = 10^{(10.6 - 4.8)} = 10^{5.8} = 6.3 \times 10^5$$

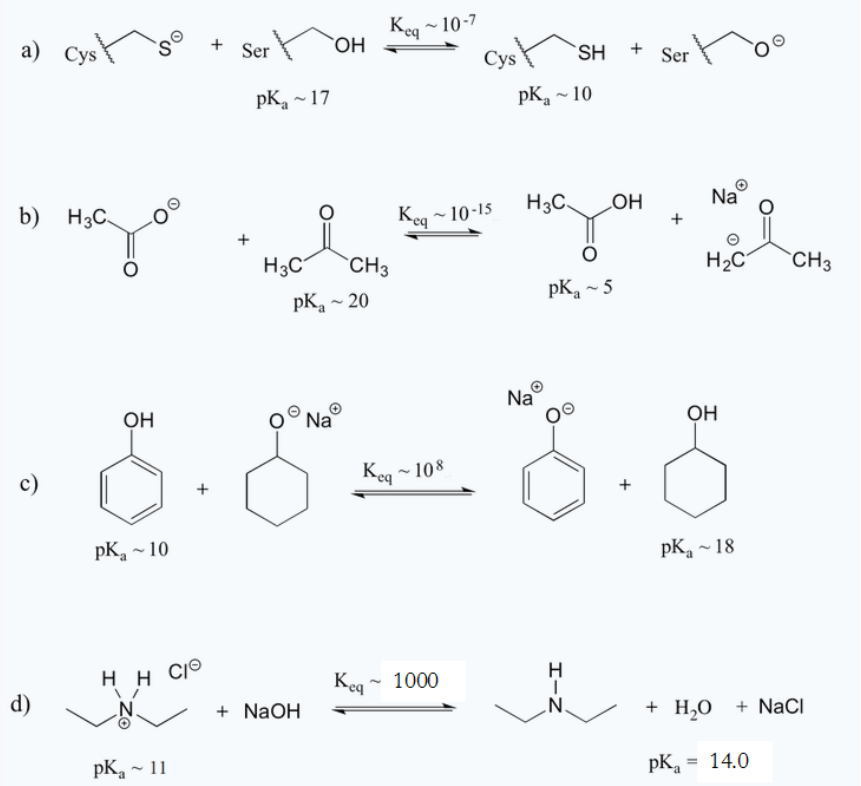
So K_{eq} is a very large number (much greater than 1) and the equilibrium lies far to the right-hand side of the equation, just as we had predicted. If you had just wanted to approximate an answer without bothering to look for a calculator, you could have noted that the difference in pK_a values is approximately 6, so the equilibrium constant should be somewhere in the order of 10^6, or one million. Using the pK_a table in this way, and making functional group-based pK_a approximations for molecules for which we don't have exact values, we can easily estimate the extent to which a given acid-base reaction will proceed.

Exercise 2.4.1

Show the products of the following acid-base reactions, and estimate the value of K_{eq}. Use the pKa table from Section 2.3 and/or from the Reference Tables.



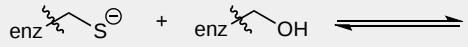
Answer

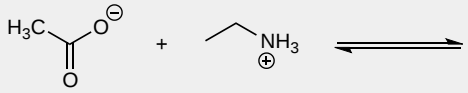


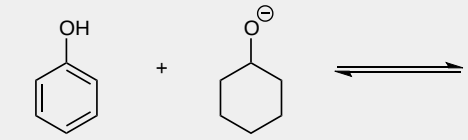
Add texts here. Do not delete this text first.

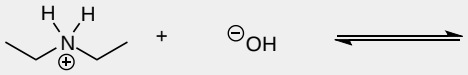
Example 7.3

Exercise 7.3 Show the products of the following acid-base reactions, and estimate the value of K_{eq}. Use the pKa table from Section 2.8 and/or from the Reference Tables.

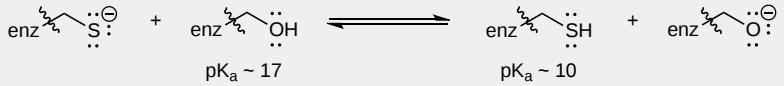
a) 

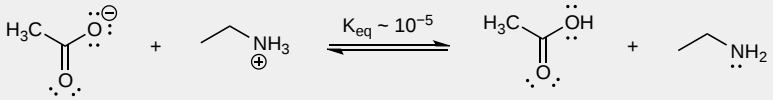
b) 

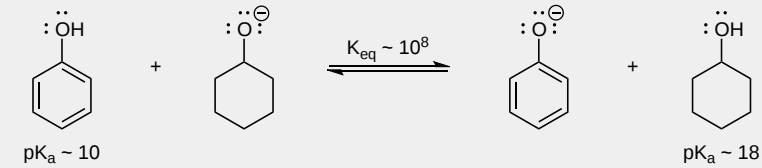
c) 

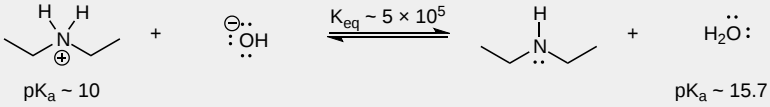
d) 

Solution

a) 

b) 

c) 

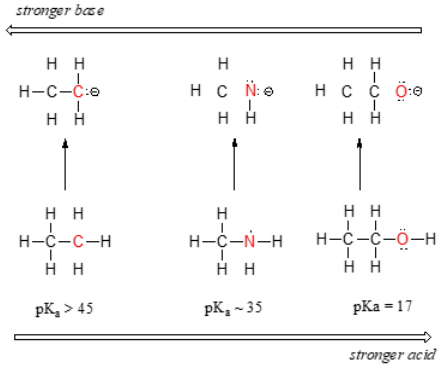
d) 

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

2.5: Factors That Determine Acid Strength

Periodic trends

First, we will focus on individual atoms, and think about trends associated with the position of an element on the periodic table. We'll use as our first models the simple organic compounds ethane, methylamine, and ethanol, but the concepts apply equally to more complex biomolecules, such as the side chains of alanine, lysine, and serine.



We can see a clear trend in acidity as we move from left to right along the second row of the periodic table from carbon to nitrogen to oxygen. The key to understanding this trend is to consider the hypothetical conjugate base in each case*: the more stable (weaker) the conjugate base, the stronger the acid*. Look at where the negative charge ends up in each conjugate base. In the ethyl anion, the negative charge is borne by carbon, while in the methylamine anion and ethoxide anion the charges are located on a nitrogen and an oxygen, respectively. Remember the periodic trend in electronegativity: it also increases as we move from left to right along a row, meaning that oxygen is the most electronegative of the three, and carbon the least. *The more electronegative an atom, the better it is able to bear a negative charge*. Thus, the ethoxide anion is the most stable (lowest energy, least basic) of the three conjugate bases, and the ethyl anion is the least stable (highest energy, most basic).

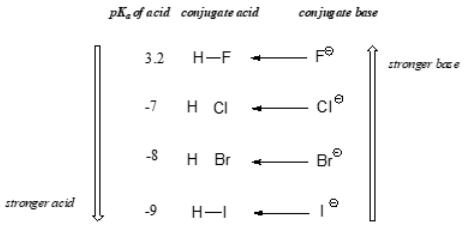
We can use the same set of ideas to explain the difference in basicity between water and ammonia.

$pK_a = -1.7 \quad H_3O^+ \rightleftharpoons H_2O + H^+$

$pK_a = 9.26 \quad NH_4^+ \rightleftharpoons NH_3 + H^+$

By looking at the pK_avalues for the appropriate conjugate acids, we know that ammonia is more basic than water. Oxygen, as the more electronegative element, holds more tightly to its lone pair than the nitrogen. The nitrogen lone pair, therefore, is more likely to break away and form a new bond to a proton - it is, in other words, more basic. Once again, a more reactive (stronger) conjugate base means a less reactive (weaker) conjugate acid.

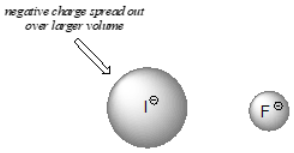
When moving vertically within a given column of the periodic table, we again observe a clear periodic trend in acidity. This is best illustrated with the halides: basicity, like electronegativity, increases as we move up the column.



Conversely, acidity in the haloacids increases as we move *down* the column.

In order to make sense of this trend, we will once again consider the stability of the conjugate bases. Because fluorine is the most electronegative halogen element, we might expect fluoride to also be the least basic halogen ion. But in fact, it is the *least* stable,

and the most basic! It turns out that when moving vertically in the periodic table, the *size* of the atom trumps its electronegativity with regard to basicity. The atomic radius of iodine is approximately twice that of fluorine, so in an iodine ion, the negative charge is spread out over a significantly larger volume:



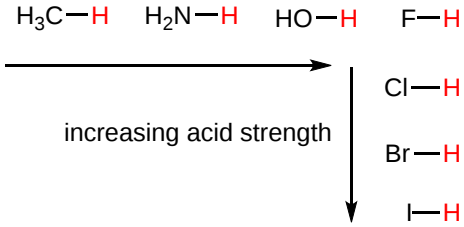
This illustrates a fundamental concept in organic chemistry that is important enough to put in red:

Electrostatic charges, whether positive or negative, are more stable when they are 'spread out' than when they are confined to one atom.

We will see this idea expressed again and again throughout our study of organic reactivity, in many different contexts. For now, the concept is applied only to the influence of atomic radius on anion stability. Because fluoride is the least stable (most basic) of the halide conjugate bases, HF is the least acidic of the haloacids, only slightly stronger than acetic acid. HI, with a pK_a of about -9, is one the strongest acids known.

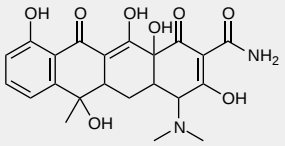
More importantly to the study of biological organic chemistry, this trend tells us that thiols are more acidic than alcohols. The pK_a of the thiol group on the cysteine side chain, for example, is approximately 8.3, while the pK_a for the hydroxyl on the serine side chain is on the order of 17.

To reiterate: acid strength increases as we move to the right along a row of the periodic table, and as we move down a column.



Example 7.6

Draw the structure of the conjugate base that would form if the compound below were to react with 1 molar equivalent of sodium hydroxide:

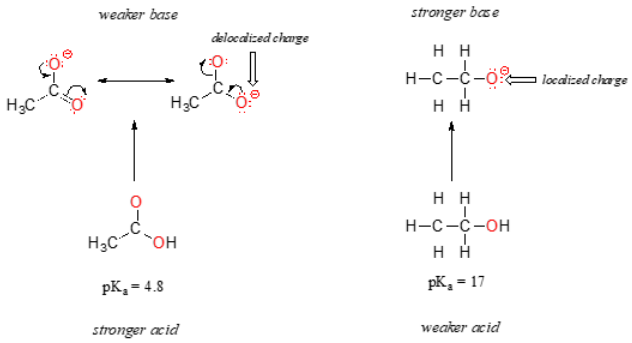


Solution

The Resonance Effect

In the previous section we focused our attention on periodic trends - the differences in acidity and basicity between groups where the exchangeable proton was bound to different elements. Now, it is time to think about how the structure of different organic groups contributes to their relative acidity or basicity, even when we are talking about the same element acting as the proton donor/acceptor. The first model pair we will consider is ethanol and acetic acid, but the conclusions we reach will be equally valid for all alcohol and carboxylic acid groups.

Despite the fact that they are both oxygen acids, the pK_a values of ethanol and acetic acid are very different. What makes a carboxylic acid so much more acidic than an alcohol? As before, we begin by considering the conjugate bases.

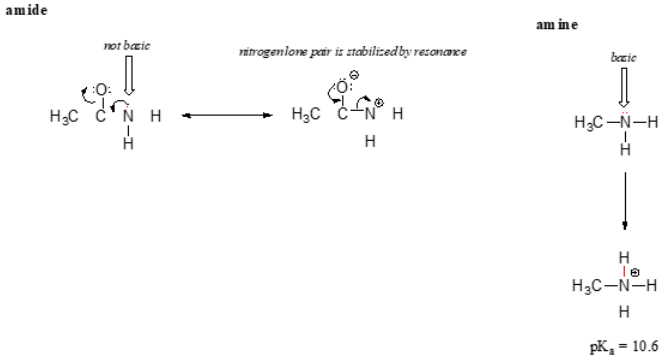


In both species, the negative charge on the conjugate base is held by an oxygen, so periodic trends cannot be invoked. For acetic acid, however, there is a key difference: a resonance contributor can be drawn in which the negative charge is localized on the second oxygen of the group. The two resonance forms for the conjugate base are equal in energy, according to our 'rules of resonance'. What this means, you may recall, is that the negative charge on the acetate ion is not located on one oxygen or the other: rather it is shared between the two. Chemists use the term 'delocalization of charge' to describe this situation. In the ethoxide ion, by contrast, the negative charge is 'locked' on the single oxygen – it has nowhere else to go.

Now is the time to think back to that statement from the previous section that was so important that it got printed in bold font in its own paragraph – in fact, it is so important that we'll just say it again: "Electrostatic charges, whether positive or negative, are more stable when they are 'spread out' than when they are confined to one atom." Now, we are seeing this concept in another context, where a charge is being 'spread out' (in other words, delocalized) *by resonance*, rather than simply by the size of the atom involved.

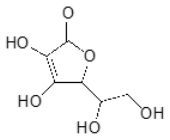
The delocalization of charge by resonance has a very powerful effect on the reactivity of organic molecules, enough to account for the difference of over 12 pK_a units between ethanol and acetic acid (and remember, pK_a is a log expression, so we are talking about a difference of over 10^{12} between the acidity constants for the two molecules). The acetate ion is that much more stable than the ethoxide ion, all due to the effects of resonance delocalization.

The resonance effect also nicely explains why a nitrogen atom is basic when it is in an amine, but *not* basic when it is part of an amide group. Recall that in an amide, there is significant double-bond character to the carbon-nitrogen bond, due to a second resonance contributor in which the nitrogen lone pair is part of a p bond.



While the electron lone pair of an amine nitrogen is 'stuck' in one place, the lone pair on an amide nitrogen is delocalized by resonance. Notice that in this case, we are extending our central statement to say that electron density – in the form of a lone pair – is stabilized by resonance delocalization, even though there is not a negative charge involved. Here's another way to think about it: the lone pair on an amide nitrogen is not available for bonding with a proton – these two electrons are too 'comfortable' being part of the delocalized pi-bonding system. The lone pair on an amine nitrogen, by contrast, is not part of a delocalized p system, and is very ready to form a bond with any acidic proton that might be nearby.

Often it requires some careful thought to predict the most acidic proton on a molecule. Ascorbic acid, also known as Vitamin C, has a pK_a of 4.1.

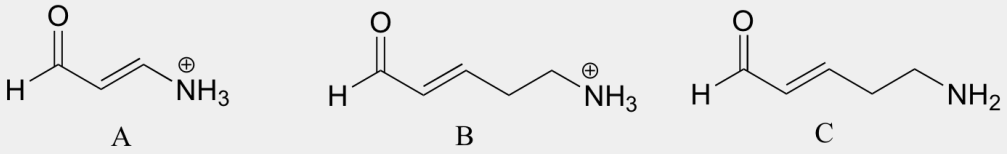


ascorbic acid
(Vitamin C)

There are four hydroxyl groups on this molecule – which one is the most acidic? If we consider all four possible conjugate bases, we find that there is only one for which we can delocalized the negative charge over *two* oxygen atoms.

Example 7.7

Rank the compounds below from most acidic to least acidic, and explain your reasoning.

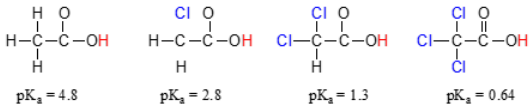


A B C

Solution

The inductive effect

Compare the pK_a values of acetic acid and its mono-, di-, and tri-chlorinated derivatives:



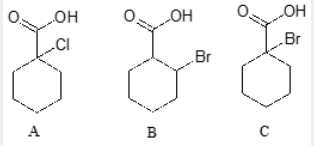
$pK_a = 4.8$ $pK_a = 2.8$ $pK_a = 1.3$ $pK_a = 0.64$

The presence of the chlorines clearly increases the acidity of the carboxylic acid group, but the argument here does not have to do with resonance delocalization, because no additional resonance contributors can be drawn for the chlorinated molecules. Rather, the explanation for this phenomenon involves something called the **inductive effect**. A chlorine atom is more electronegative than a hydrogen, and thus is able to 'induce', or 'pull' electron density towards itself, away from the carboxylate group. In effect, the chlorine atoms are helping to further spread out the electron density of the conjugate base, which as we know has a stabilizing effect. In this context, the chlorine substituent is called an **electron-withdrawing group**. Notice that the pK_a-lowering effect of each chlorine atom, while significant, is not as dramatic as the delocalizing resonance effect illustrated by the difference in pK_a values between an alcohol and a carboxylic acid. In general, *resonance effects are more powerful than inductive effects*.

The inductive electron-withdrawing effect of the chlorines takes place through covalent bonds, and its influence decreases markedly with distance – thus a chlorine two carbons away from a carboxylic acid group has a decreased effect compared to a chlorine just one carbon away.

Example

Rank the compounds below from most acidic to least acidic, and explain your reasoning.



A B C

Solution

- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- Layne A. Morsch (University of Illinois Springfield)

2.6: Common Acids and Bases

Acidity of Carboxylic Acids

The pK_a 's of some typical carboxylic acids are listed in the following table. When we compare these values with those of comparable alcohols, such as ethanol (pK_a = 16) and 2-methyl-2-propanol (pK_a = 19), it is clear that carboxylic acids are stronger acids by over ten powers of ten! Furthermore, electronegative substituents near the carboxyl group act to increase the acidity.

Compound	pK_a	Compound	pK_a
HCO_2H	3.75	$CH_3CH_2CH_2CO_2H$	4.82
CH_3CO_2H	4.74	$ClCH_2CH_2CH_2CO_2H$	4.53
FCH_2CO_2H	2.65	$CH_3CHClCH_2CO_2H$	4.05
$ClCH_2CO_2H$	2.85	$CH_3CH_2CHClCO_2H$	2.89
$BrCH_2CO_2H$	2.90	$C_6H_5CO_2H$	4.20
ICH_2CO_2H	3.10	$p\text{-}O_2NC_6H_4CO_2H$	3.45
Cl_3CCO_2H	0.77	$p\text{-}CH_3OC_6H_4CO_2H$	4.45

Contributors

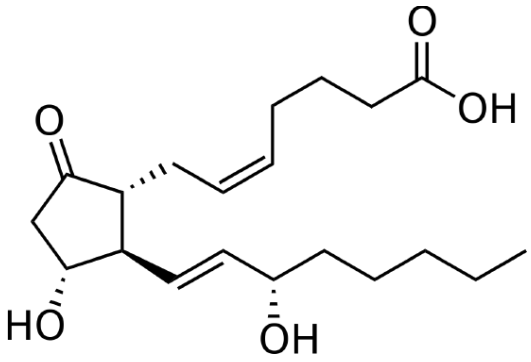
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

2.7: Aspirin

Prostaglandins were first discovered and isolated from human semen in the 1930s by Ulf von Euler of Sweden. Thinking they had come from the prostate gland, he named them prostaglandins. It has since been determined that they exist and are synthesized in virtually every cell of the body. Prostaglandins, are like hormones in that they act as chemical messengers, but do not move to other sites, but work right within the cells where they are synthesized.

Introduction

Prostaglandins are unsaturated carboxylic acids, consisting of of a 20 carbon skeleton that also contains a five member ring. They are biochemically synthesized from the fatty acid, arachidonic acid. See the graphic on the left. The unique shape of the arachidonic acid caused by a series of cis double bonds helps to put it into position to make the five member ring.



Structure of prostaglandin E2 (PGE_2)

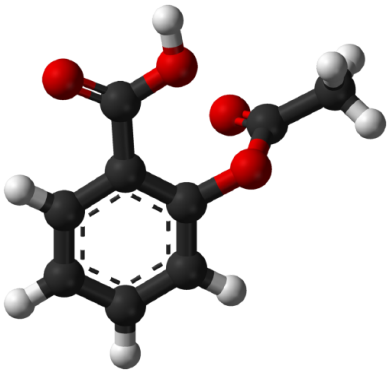
Prostaglandin Structure

Prostaglandins are unsaturated carboxylic acids, consisting of of a 20 carbon skeleton that also contains a five member ring and are based upon the fatty acid, arachidonic acid. There are a variety of structures one, two, or three double bonds. On the five member ring there may also be double bonds, a ketone, or alcohol groups. A typical structure is on the left graphic.

Functions of Prostaglandins

There are a variety of physiological effects including:

1. Activation of the inflammatory response, production of pain, and fever. When tissues are damaged, white blood cells flood to the site to try to minimize tissue destruction. Prostaglandins are produced as a result.
2. Blood clots form when a blood vessel is damaged. A type of prostaglandin called thromboxane stimulates constriction and clotting of platelets. Conversely, PGI2, is produced to have the opposite effect on the walls of blood vessels where clots should not be forming.
3. Certain prostaglandins are involved with the induction of labor and other reproductive processes. PGE2 causes uterine contractions and has been used to induce labor.
4. Prostaglandins are involved in several other organs such as the gastrointestinal tract (inhibit acid synthesis and increase secretion of protective mucus), increase blood flow in kidneys, and leukotriens promote constriction of bronchi associated with asthma.



Ball-and-stick model of the aspirin molecule, as found in the solid state. Single-crystal X-ray diffraction data from Kim, Y.; Machida, K.; Taga, T.; Osaki, K. (1985). "Structure Redetermination and Packing Analysis of Aspirin Crystal". Chem. Pharm. Bull. ***33*** *(7): 2641-2647. ISSN 1347-5223.*

Effects of Aspirin and other Pain Killers

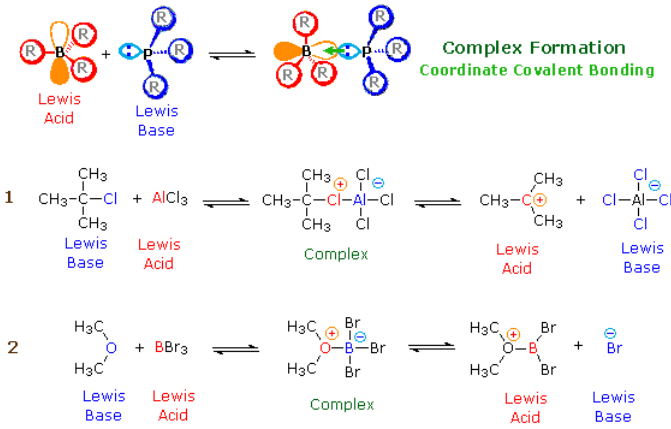
When you see that prostaglandins induce inflammation, pain, and fever, what comes to mind but aspirin. Aspirin blocks an enzyme called cyclooxygenase, COX-1 and COX-2, which is involved with the ring closure and addition of oxygen to arachidonic acid converting to prostaglandins. The acetyl group on aspirin is hydrolzed and then bonded to the alcohol group of serine as an ester. This has the effect of blocking the channel in the enzyme and arachidonic can not enter the active site of the enzyme. By inhibiting or blocking this enzyme, the synthesis of prostaglandins is blocked, which in turn relives some of the effects of pain and fever. Aspirin is also thought to inhibit the prostaglandin synthesis involved with unwanted blood clotting in coronary heart disease. At the same time an injury while taking aspirin may cause more extensive bleeding.

Contributors

Charles Ophardt (Professor Emeritus, Elmhurst College); Virtual Chembook

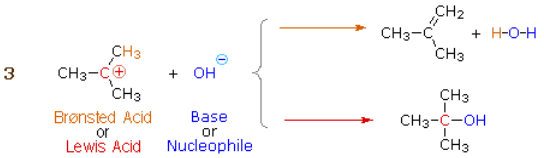
2.8: Lewis Acids and Bases

According to the Lewis theory, **an acid is an electron pair acceptor**, and **a base is an electron pair donor**. Lewis bases are also Brønsted bases; however, many Lewis acids, such as BF_3, $AlCl_3$ and Mg^{2+}, are not Brønsted acids. The product of a Lewis acid-base reaction, is a neutral, dipolar or charged complex, which may be a stable covalent molecule. As shown at the top of the following drawing, coordinate covalent bonding of a phosphorous Lewis base to a boron Lewis acid creates a complex in which the formal charge of boron is negative and that of phosphorous is positive. In this complex, boron acquires a neon valence shell configuration and phosphorous an argon configuration. If the substituents (R) on these atoms are not large, the complex will be favored at equilibrium. However, steric hindrance of bulky substituents may prohibit complex formation. The resulting mixture of non-bonded Lewis acid/base pairs has been termed "frustrated", and exhibits unusual chemical behavior.
Two examples of Lewis acid-base equilibria that play a role in chemical reactions are shown in equations 1 & 2 below.

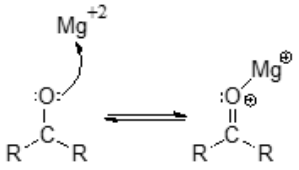


In the first example, an electron deficient aluminum atom bonds to a covalent chlorine atom by sharing one of its non-bonding valence electron pairs, and thus achieves an argon-like valence shell octet. Because this sharing is unilateral (chlorine contributes both electrons), both the aluminum and the chlorine have formal charges, as shown. If the carbon chlorine bond in this complex breaks with both the bonding electrons remaining with the more electronegative atom (chlorine), the carbon assumes a positive charge. We refer to such carbon species as **carbocations**. Carbocations are also Lewis acids, as the reverse reaction demonstrates.

Many carbocations (but not all) may also function as Brønsted acids. Equation 3 illustrates this dual behavior; the Lewis acidic site is colored red and three of the nine acidic hydrogen atoms are colored orange. In its Brønsted acid role the carbocation donates a proton to the base (hydroxide anion), and is converted to a stable neutral molecule having a carbon-carbon double bond.

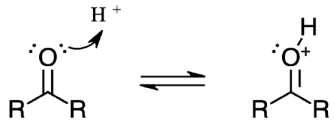


The interaction between a magnesium cation (Mg^{+2}) and a carbonyl oxygen is a common example of a Lewis acid-base reaction. The carbonyl oxygen (the Lewis base) donates a pair of electrons to the magnesium cation (the Lewis acid).



As we will see we begin the study of reactions involving carbonyl groups, this interaction has the very important effect of increasing the polarity of the carbon-oxygen double bond.

The Brønsted-Lowry equivalent of the reaction above is simply protonation of the carbonyl group. This, too, has the effect of increasing the polarity of the carbonyl double bond.



While it is important to be familiar with the Lewis definition, the focus throughout the remainder of this chapter will be on acid-base reactions of the Brønsted-Lowry type, where an actual proton transfer event takes place.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

CHAPTER OVERVIEW

3: Introduction to Organic Molecules and Functional Groups

Topic hierarchy

3.1: Functional Groups

Functional groups are atoms or small groups of atoms (two to four) that exhibit a characteristic reactivity when treated with certain reagents. A particular functional group will almost always display its characteristic chemical behavior when it is present in a compound. Because of their importance in understanding organic chemistry, functional groups have characteristic names that often carry over in the naming of individual compounds incorporating specific groups. In the following table the atoms of each functional group are colored red and the characteristic IUPAC nomenclature suffix that denotes some (but not all) functional groups is also colored.

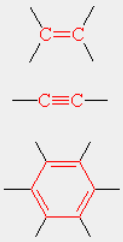
Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

3.2: An Overview of Functional Groups

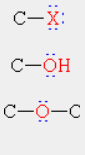
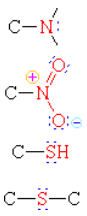
Functional groups

Functional Group Tables

Exclusively Carbon Functional Groups

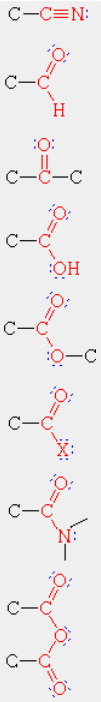
Group Formula	Class Name	Specific Example	IUPAC Name	Common Name
	Alkene	$H_2C{=}CH_2$	Ethene	Ethylene
	Alkyne	HC≡CH	Ethyne	Acetylene
	Arene	C_6H_6	Benzene	Benzene

Functional Groups with Single Bonds to Heteroatoms

Group Formula	Class Name	Specific Example	IUPAC Name	Common Name
	Halide	H_3C-I	Iodomethane	Methyl iodide
	Alcohol	CH_3CH_2OH	Ethanol	Ethyl alcohol
	Ether	$CH_3CH_2OCH_2CH_3$	Diethyl ether	Ether
	Amine	H_3C-NH_2	Aminomethane	Methylamine
	Nitro Compound	H_3C-NO_2	Nitromethane	
	Thiol	H_3C-SH	Methanethiol	Methyl mercaptan
	Sulfide	H_3C-S-CH_3	Dimethyl sulfid	

Functional Groups with Multiple Bonds to Heteroatoms

Group Formula	Class Name	Specific Example	IUPAC Name	Common Name
	Nitrile	H_3C-CN	Ethanenitrile	Acetonitrile
	Aldehyde	H_3CCHO	Ethanal	Acetaldehyde
	Ketone	H_3CCOCH_3	Propanone	Acetone

	Carboxylic Acid	H_3CCO_2H	Ethanoic Acid	Acetic acid
	Ester	$H_3CCO_2CH_2CH_3$	Ethyl ethanoate	Ethyl acetate
	Acid Halide	H_3CCOCl	Ethanoyl chloride	Acetyl chloride
	Amide	$H_3CCON(CH_3)_2$	N,N-Dimethylethanamide	N,N-Dimethylacetamide
	Acid Anhydride	$(H_3CCO)_2O$	Ethanoic anhydride	Acetic anhydride

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

3.3: Intermolecular Forces

Introduction

Introduction

> Note
>
> The properties of liquids are intermediate between those of gases and solids but are more similar to solids.

Introduction

Introduction

Introduction

Dipole–Dipole Interactions

Polar covalent bonds behave as if the bonded atoms have localized fractional charges that are equal but opposite (i.e., the two bonded atoms generate a *dipole*). If the structure of a molecule is such that the individual bond dipoles do not cancel one another, then the molecule has a net dipole moment. Molecules with net dipole moments tend to align themselves so that the positive end of one dipole is near the negative end of another and vice versa, as shown in part (a) in Figure 11.3. These arrangements are more stable than arrangements in which two positive or two negative ends are adjacent (part (c) in Figure 11.3). Hence dipole–dipole interactions, such as those in part (b) in Figure 11.3, are *attractive intermolecular interactions*, whereas those in part (d) in Figure 11.3 are *repulsive intermolecular interactions*. Because molecules in a liquid move freely and continuously, molecules always experience both attractive and repulsive dipole–dipole interactions simultaneously, as shown in Figure 11.4. On average, however, the attractive interactions dominate.

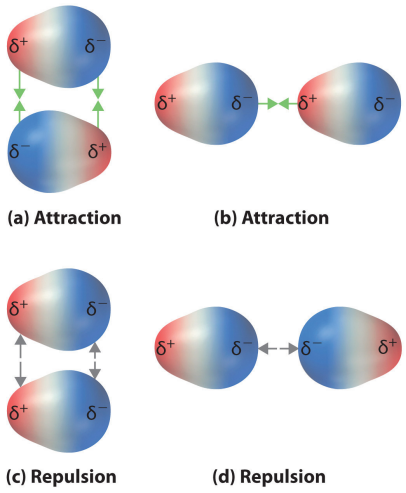


Figure 11.3 *Attractive and Repulsive Dipole–Dipole Interactions*

(a and b) Molecular orientations in which the positive end of one dipole (δ^+) is near the negative end of another (δ^-) (and vice versa) produce attractive interactions. (c and d) Molecular orientations that juxtapose the positive or negative ends of the dipoles on adjacent molecules produce repulsive interactions.

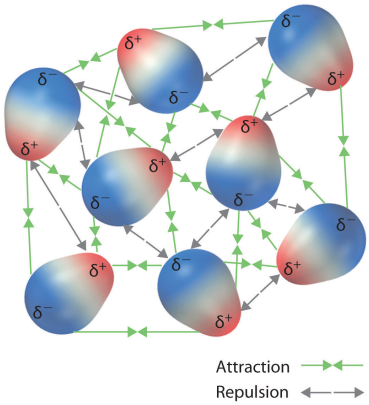


Figure 11.4 Both Attractive and Repulsive Dipole–Dipole Interactions Occur in a Liquid Sample with Many Molecules

Because each end of a dipole possesses only a fraction of the charge of an electron, dipole–dipole interactions are substantially weaker than the interactions between two ions, each of which has a charge of at least ±1, or between a dipole and an ion, in which one of the species has at least a full positive or negative charge. In addition, the attractive interaction between dipoles falls off much more rapidly with increasing distance than do the ion–ion interactions. Recall that the attractive energy between two ions is proportional to $1/r$, where r is the distance between the ions. Doubling the distance ($r \rightarrow 2r$) decreases the attractive energy by one-half. In contrast, the energy of the interaction of two dipoles is proportional to $1/r^6$, so doubling the distance between the dipoles decreases the strength of the interaction by 2^6, or 64-fold. Thus a substance such as HCl, which is partially held together by dipole–dipole interactions, is a gas at room temperature and 1 atm pressure, whereas NaCl, which is held together by interionic interactions, is a high-melting-point solid. Within a series of compounds of similar molar mass, the strength of the intermolecular interactions increases as the dipole moment of the molecules increases, as shown in Table 11.2. Using what we learned about predicting relative bond polarities from the electronegativities of the bonded atoms, we can make educated guesses about the relative boiling points of similar molecules.

Table 11.2 Relationships between the Dipole Moment and the Boiling Point for Organic Compounds of Similar Molar Mass

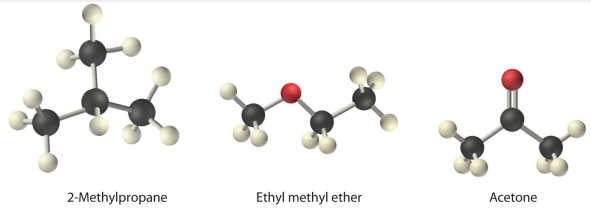
Compound	Molar Mass (g/mol)	Dipole Moment (D)	Boiling Point (K)
C_3H_6 (cyclopropane)	42	0	240
CH_3OCH_3 (dimethyl ether)	46	1.30	248
CH_3CN (acetonitrile)	41	3.9	355

Note

The attractive energy between two ions is proportional to $1/r$, whereas the attractive energy between two dipoles is proportional to $1/r^6$.

Example 1

Arrange ethyl methyl ether ($CH_3OCH_2CH_3$), 2-methylpropane [isobutane, $(CH_3)_2CHCH_3$], and acetone (CH_3COCH_3) in order of increasing boiling points. Their structures are as follows:



Given: compounds
Asked for: order of increasing boiling points
Strategy:
Compare the molar masses and the polarities of the compounds. Compounds with higher molar masses and that are polar will have the highest boiling points.
Solution:
The three compounds have essentially the same molar mass (58–60 g/mol), so we must look at differences in polarity to predict the strength of the intermolecular dipole–dipole interactions and thus the boiling points of the compounds. The first compound, 2-methylpropane, contains only C–H bonds, which are not very polar because C and H have similar electronegativities. It should therefore have a very small (but nonzero) dipole moment and a very low boiling point. Ethyl methyl ether has a structure similar to H_2O; it contains two polar C–O single bonds oriented at about a 109° angle to each other, in addition to relatively nonpolar C–H bonds. As a result, the C–O bond dipoles partially reinforce one another and generate a significant dipole moment that should give a moderately high boiling point. Acetone contains a polar C=O double bond oriented at about 120° to two methyl groups with nonpolar C–H bonds. The C–O bond dipole therefore corresponds to the molecular dipole, which should result in both a rather large dipole moment and a high boiling point. Thus we predict the following order of boiling points: 2-methylpropane < ethyl methyl ether < acetone. This result is in good agreement with the actual data: 2-methylpropane, boiling point = −11.7°C, and the dipole moment (μ) = 0.13 D; methyl ethyl ether, boiling point = 7.4°C and μ = 1.17 D; acetone, boiling point = 56.1°C and μ = 2.88 D.

Exercise 1

Arrange carbon tetrafluoride (CF_4), ethyl methyl sulfide ($CH_3SC_2H_5$), dimethyl sulfoxide [$(CH_3)_2S{=}O$], and 2-methylbutane [isopentane, $(CH_3)_2CHCH_2CH_3$] in order of decreasing boiling points.
Answer: dimethyl sulfoxide (boiling point = 189.9°C) > ethyl methyl sulfide (boiling point = 67°C) > 2-methylbutane (boiling point = 27.8°C) > carbon tetrafluoride (boiling point = −128°C)

London Dispersion Forces

Thus far we have considered only interactions between polar molecules, but other factors must be considered to explain why many nonpolar molecules, such as bromine, benzene, and hexane, are liquids at room temperature, and others, such as iodine and naphthalene, are solids. Even the noble gases can be liquefied or solidified at low temperatures, high pressures, or both (Table 11.3).

What kind of attractive forces can exist between nonpolar molecules or atoms? This question was answered by Fritz London (1900–1954), a German physicist who later worked in the United States. In 1930, London proposed that temporary fluctuations in the electron distributions within atoms and nonpolar molecules could result in the formation of short-lived instantaneous dipole moments, which produce attractive forces called London dispersion forces between otherwise nonpolar substances.

Table 11.3 Normal Melting and Boiling Points of Some Elements and Nonpolar Compounds

Substance	Molar Mass (g/mol)	Melting Point (°C)	Boiling Point (°C)
Ar	40	−189.4	−185.9
Xe	131	−111.8	−108.1
N_2	28	−210	−195.8
O_2	32	−218.8	−183.0

Substance	Molar Mass (g/mol)	Melting Point (°C)	Boiling Point (°C)
F_2	38	−219.7	−188.1
I_2	254	113.7	184.4
CH_4	16	−182.5	−161.5

Consider a pair of adjacent He atoms, for example. On average, the two electrons in each He atom are uniformly distributed around the nucleus. Because the electrons are in constant motion, however, their distribution in one atom is likely to be asymmetrical at any given instant, resulting in an instantaneous dipole moment. As shown in part (a) in Figure 11.5, the instantaneous dipole moment on one atom can interact with the electrons in an adjacent atom, pulling them toward the positive end of the instantaneous dipole or repelling them from the negative end. The net effect is that the first atom causes the temporary formation of a dipole, called an induced dipole, in the second. Interactions between these temporary dipoles cause atoms to be attracted to one another. These attractive interactions are weak and fall off rapidly with increasing distance. London was able to show with quantum mechanics that the attractive energy between molecules due to temporary dipole–induced dipole interactions falls off as $1/r^6$. Doubling the distance therefore decreases the attractive energy by 2^6, or 64-fold.

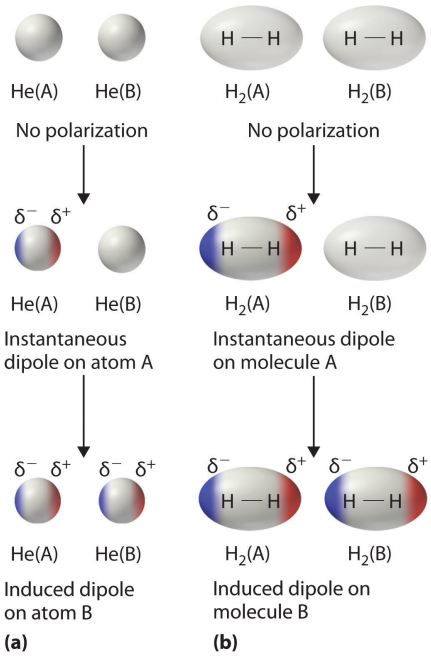


Figure 11.5 *Instantaneous Dipole Moments. The formation of an instantaneous dipole moment on one He atom (a) or an H_2 molecule (b) results in the formation of an induced dipole on an adjacent atom or molecule.*

Instantaneous dipole–induced dipole interactions between nonpolar molecules can produce intermolecular attractions just as they produce interatomic attractions in monatomic substances like Xe. This effect, illustrated for two H_2 molecules in part (b) in Figure 11.5, tends to become more pronounced as atomic and molecular masses increase (Table 11.3). For example, Xe boils at −108.1°C, whereas He boils at −269°C. The reason for this trend is that the strength of London dispersion forces is related to the ease with which the electron distribution in a given atom can be perturbed. In small atoms such as He, the two 1*s* electrons are held close to the nucleus in a very small volume, and electron–electron repulsions are strong enough to prevent significant asymmetry in their distribution. In larger atoms such as Xe, however, the outer electrons are much less strongly attracted to the nucleus because of filled intervening shells. As a result, it is relatively easy to temporarily deform the electron distribution to generate an instantaneous or induced dipole. The ease of deformation of the electron distribution in an atom or molecule is called its polarizability. Because the electron distribution is more easily perturbed in large, heavy species than in small, light species, we say that heavier substances tend to be much more *polarizable* than lighter ones.

Note
For similar substances, London dispersion forces get stronger with increasing molecular size.

The polarizability of a substance also determines how it interacts with ions and species that possess permanent dipoles. Thus London dispersion forces are responsible for the general trend toward higher boiling points with increased molecular mass and greater surface area in a homologous series of compounds, such as the alkanes (part (a) in Figure 11.6). The strengths of London dispersion forces also depend significantly on molecular shape because shape determines how much of one molecule can interact with its neighboring molecules at any given time. For example, part (b) in Figure 11.6 shows 2,2-dimethylpropane (neopentane) and *n*-pentane, both of which have the empirical formula C_5H_{12}. Neopentane is almost spherical, with a small surface area for intermolecular interactions, whereas *n*-pentane has an extended conformation that enables it to come into close contact with other *n*-pentane molecules. As a result, the boiling point of neopentane (9.5°C) is more than 25°C lower than the boiling point of *n*-pentane (36.1°C).

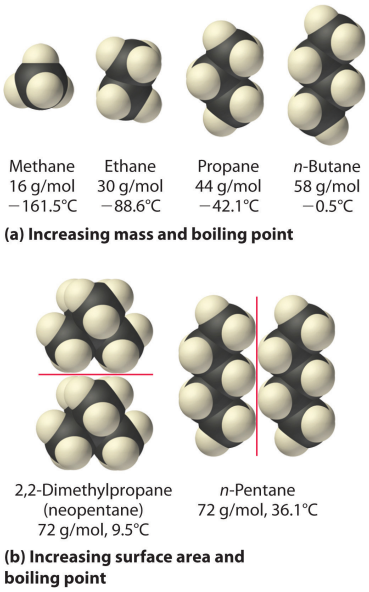


Figure 11.6 Mass and Surface Area Affect the Strength of London Dispersion Forces. (a) In this series of four simple alkanes, larger molecules have stronger London forces between them than smaller molecules and consequently higher boiling points. (b) Linear *n*-pentane molecules have a larger surface area and stronger intermolecular forces than spherical neopentane molecules. As a result, neopentane is a gas at room temperature, whereas *n*-pentane is a volatile liquid.

All molecules, whether polar or nonpolar, are attracted to one another by London dispersion forces in addition to any other attractive forces that may be present. In general, however, dipole–dipole interactions in small polar molecules are significantly stronger than London dispersion forces, so the former predominate.

Example 2

Arrange *n*-butane, propane, 2-methylpropane [isobutene, $(CH_3)_2CHCH_3$], and *n*-pentane in order of increasing boiling points.
Given: compounds
Asked for: order of increasing boiling points
Strategy:
Determine the intermolecular forces in the compounds and then arrange the compounds according to the strength of those forces. The substance with the weakest forces will have the lowest boiling point.
Solution:
The four compounds are alkanes and nonpolar, so London dispersion forces are the only important intermolecular forces. These forces are generally stronger with increasing molecular mass, so propane should have the lowest boiling point and *n*-pentane should have the highest, with the two butane isomers falling in between. Of the two butane isomers, 2-methylpropane is more compact, and *n*-butane has the more extended shape. Consequently, we expect intermolecular interactions for *n*-butane to be stronger due to its larger surface area, resulting in a higher boiling point. The overall order is thus as follows, with actual boiling points in parentheses: propane (−42.1°C) < 2-methylpropane (−11.7°C) < *n*-butane (−0.5°C) < *n*-pentane (36.1°C).

Exercise 2

Arrange GeH_4, $SiCl_4$, SiH_4, CH_4, and $GeCl_4$ in order of decreasing boiling points.
Answer: $GeCl_4$ (87°C) > $SiCl_4$ (57.6°C) > GeH_4 (−88.5°C) > SiH_4 (−111.8°C) > CH_4 (−161°C)

Hydrogen Bonds

Hydrogen Bonds

Hydrogen Bonds

Why do strong intermolecular forces produce such anomalously high boiling points and other unusual properties, such as high enthalpies of vaporization and high melting points? The answer lies in the highly polar nature of the bonds between hydrogen and very electronegative elements such as O, N, and F. The large difference in electronegativity results in a large partial positive charge on hydrogen and a correspondingly large partial negative charge on the O, N, or F atom. Consequently, H–O, H–N, and H–F bonds have very large bond dipoles that can interact strongly with one another. Because a hydrogen atom is so small, these dipoles can also approach one another more closely than most other dipoles. The combination of large bond dipoles and short dipole–dipole distances results in very strong dipole–dipole interactions called hydrogen bonds, as shown for ice in Figure 11.8. A hydrogen bond is usually indicated by a dotted line between the hydrogen atom attached to O, N, or F (the *hydrogen bond donor*) and the atom that has the lone pair of electrons (the *hydrogen bond acceptor*). Because each water molecule contains two hydrogen atoms and two lone pairs, a tetrahedral arrangement maximizes the number of hydrogen bonds that can be formed. In the structure of ice, each oxygen atom is surrounded by a distorted tetrahedron of hydrogen atoms that form bridges to the oxygen atoms of adjacent water molecules. The bridging hydrogen atoms are *not* equidistant from the two oxygen atoms they connect, however. Instead, each hydrogen atom is 101 pm from one oxygen and 174 pm from the other. In contrast, each oxygen atom is bonded to two H atoms at the shorter distance and two at the longer distance, corresponding to two O–H covalent bonds and two O···H hydrogen bonds from adjacent water molecules, respectively. The resulting open, cagelike structure of ice means that the solid is actually slightly less dense than the liquid, which explains why ice floats on water rather than sinks.

Hydrogen Bonds
Hydrogen Bonds

Hydrogen Bonds

Hydrogen Bonds

Hydrogen Bonds

Hydrogen Bonds

Exercise 4

Arrange 2,4-dimethylheptane, Ne, CS_2, Cl_2, and KBr in order of decreasing boiling points.
Answer: KBr (1435°C) > 2,4-dimethylheptane (132.9°C) > CS_2 (46.6°C) > Cl_2 (−34.6°C) > Ne (−246°C)

Summary

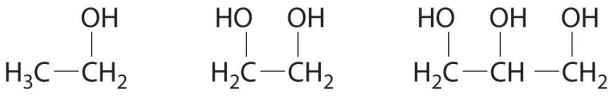
Molecules in liquids are held to other molecules by intermolecular interactions, which are weaker than the intramolecular interactions that hold the atoms together within molecules and polyatomic ions. Transitions between the solid and liquid or the liquid and gas phases are due to changes in intermolecular interactions but do not affect intramolecular interactions. The three major types of intermolecular interactions are dipole–dipole interactions, London dispersion forces (these two are often referred to collectively as **van der Waals forces**), and hydrogen bonds. **Dipole–dipole interactions** arise from the electrostatic interactions of the positive and negative ends of molecules with permanent dipole moments; their strength is proportional to the magnitude of the dipole moment and to $1/r^6$, where r is the distance between dipoles. **London dispersion forces** are due to the formation of **instantaneous dipole moments** in polar or nonpolar molecules as a result of short-lived fluctuations of electron charge distribution, which in turn cause the temporary formation of an **induced dipole** in adjacent molecules. Like dipole–dipole interactions, their energy falls off as $1/r^6$. Larger atoms tend to be more **polarizable** than smaller ones because their outer electrons are less tightly bound and are therefore more easily perturbed. **Hydrogen bonds** are especially strong dipole–dipole interactions between molecules that have hydrogen bonded to a highly electronegative atom, such as O, N, or F. The resulting partially positively charged H atom on one molecule (the *hydrogen bond donor*) can interact strongly with a lone pair of electrons of a partially negatively charged O, N, or F atom on adjacent molecules (the *hydrogen bond acceptor*). Because of strong

O · · · Hhydrogen bonding between water molecules, water has an unusually high boiling point, and ice has an open, cagelike structure that is less dense than liquid water.

Hydrogen Bonds

Conceptual Problems

1. What is the main difference between intramolecular interactions and intermolecular interactions? Which is typically stronger? How are changes of state affected by these different kinds of interactions?
2. Describe the three major kinds of intermolecular interactions discussed in this chapter and their major features. The hydrogen bond is actually an example of one of the other two types of interaction. Identify the kind of interaction that includes hydrogen bonds and explain why hydrogen bonds fall into this category.
3. Which are stronger—dipole–dipole interactions or London dispersion forces? Which are likely to be more important in a molecule with heavy atoms? Explain your answers.
4. Explain why hydrogen bonds are unusually strong compared to other dipole–dipole interactions. How does the strength of hydrogen bonds compare with the strength of covalent bonds?
5. Liquid water is essential for life as we know it, but based on its molecular mass, water should be a gas under standard conditions. Why is water a liquid rather than a gas under standard conditions?
6. Describe the effect of polarity, molecular mass, and hydrogen bonding on the melting point and boiling point of a substance.
7. Why are intermolecular interactions more important for liquids and solids than for gases? Under what conditions must these interactions be considered for gases?
8. Using acetic acid as an example, illustrate both attractive and repulsive intermolecular interactions. How does the boiling point of a substance depend on the magnitude of the repulsive intermolecular interactions?
9. In group 17, elemental fluorine and chlorine are gases, whereas bromine is a liquid and iodine is a solid. Why?
10. The boiling points of the anhydrous hydrogen halides are as follows: HF, 19°C; HCl, −85°C; HBr, −67°C; and HI, −34°C. Explain any trends in the data, as well as any deviations from that trend.
11. Identify the most important intermolecular interaction in each of the following.
    1. SO_2
    2. HF
    3. CO_2
    4. CCl_4
    5. CH_2Cl_2
12. Identify the most important intermolecular interaction in each of the following.
    1. LiF
    2. I_2
    3. ICl
    4. NH_3
    5. NH_2Cl
13. Would you expect London dispersion forces to be more important for Xe or Ne? Why? (The atomic radius of Ne is 38 pm, whereas that of Xe is 108 pm.)
14. Arrange Kr, Cl_2, H_2, N_2, Ne, and O_2 in order of increasing polarizability. Explain your reasoning.
15. Both water and methanol have anomalously high boiling points due to hydrogen bonding, but the boiling point of water is greater than that of methanol despite its lower molecular mass. Why? Draw the structures of these two compounds, including any lone pairs, and indicate potential hydrogen bonds.
16. The structures of ethanol, ethylene glycol, and glycerin are as follows:



Ethanol **Ethylene glycol** **Glycerin**

Arrange these compounds in order of increasing boiling point. Explain your rationale.

17. Do you expect the boiling point of H_2S to be higher or lower than that of H_2O? Justify your answer.
18. Ammonia (NH_3), methylamine (CH_3NH_2), and ethylamine ($CH_3CH_2NH_2$) are gases at room temperature, while propylamine ($CH_3CH_2CH_2NH_2$) is a liquid at room temperature. Explain these observations.
19. Why is it not advisable to freeze a sealed glass bottle that is completely filled with water? Use both macroscopic and microscopic models to explain your answer. Is a similar consideration required for a bottle containing pure ethanol? Why or why not?
20. Which compound in the following pairs will have the higher boiling point? Explain your reasoning.
    1. NH_3 or PH_3
    2. ethylene glycol ($HOCH_2CH_2OH$) or ethanol
    3. 2,2-dimethylpropanol [$CH_3C(CH_3)_2CH_2OH$] or *n*-butanol ($CH_3CH_2CH_2CH_2OH$)
21. Some recipes call for vigorous boiling, while others call for gentle simmering. What is the difference in the temperature of the cooking liquid between boiling and simmering? What is the difference in energy input?
22. Use the melting of a metal such as lead to explain the process of melting in terms of what is happening at the molecular level. As a piece of lead melts, the temperature of the metal remains constant, even though energy is being added continuously. Why?
23. How does the O–H distance in a hydrogen bond in liquid water compare with the O–H distance in the covalent O–H bond in the H_2O molecule? What effect does this have on the structure and density of ice?
24. 1. Explain why the hydrogen bonds in liquid HF are stronger than the corresponding intermolecular interactions in liquid HI.
    2. In which substance are the individual hydrogen bonds stronger: HF or H_2O? Explain your reasoning.
    3. For which substance will hydrogen bonding have the greater effect on the boiling point: HF or H_2O? Explain your reasoning.

Answers

1.
2.
3.
4.
5. Water is a liquid under standard conditions because of its unique ability to form four strong hydrogen bonds per molecule.
6.
7.
8.
9. As the atomic mass of the halogens increases, so does the number of electrons and the average distance of those electrons from the nucleus. Larger atoms with more electrons are more easily polarized than smaller atoms, and the increase in polarizability with atomic number increases the strength of London dispersion forces. These intermolecular interactions are strong enough to favor the condensed states for bromine and iodine under normal conditions of temperature and pressure.
10.
11. 1. The V-shaped SO_2 molecule has a large dipole moment due to the polar S=O bonds, so dipole–dipole interactions will be most important.
    2. The H–F bond is highly polar, and the fluorine atom has three lone pairs of electrons to act as hydrogen bond acceptors; hydrogen bonding will be most important.
    3. Although the C=O bonds are polar, this linear molecule has no net dipole moment; hence, London dispersion forces are most important.

4. This is a symmetrical molecule that has no net dipole moment, and the Cl atoms are relatively polarizable; thus, London dispersion forces will dominate.
5. This molecule has a small dipole moment, as well as polarizable Cl atoms. In such a case, dipole–dipole interactions and London dispersion forces are often comparable in magnitude.

12.
13.
14.

15. Water has two polar O–H bonds with H atoms that can act as hydrogen bond donors, plus two lone pairs of electrons that can act as hydrogen bond acceptors, giving a net of *four* hydrogen bonds per H_2O molecule. Although methanol also has two lone pairs of electrons on oxygen that can act as hydrogen bond acceptors, it only has one O–H bond with an H atom that can act as a hydrogen bond donor. Consequently, methanol can only form *two* hydrogen bonds per molecule on average, versus four for water. Hydrogen bonding therefore has a much greater effect on the boiling point of water.

16.
17.
18.
19.
20.

21. Vigorous boiling causes more water molecule to escape into the vapor phase, but does not affect the temperature of the liquid. Vigorous boiling requires a higher energy input than does gentle simmering.

Contributors

Anonymous

3.4: Physical Properties

The molecule is the smallest observable group of uniquely bonded atoms that represent the composition, configuration and characteristics of a pure compound. Our chief focus up to this point has been to discover and describe the ways in which atoms bond together to form molecules. Since all observable samples of compounds and mixtures contain a very large number of molecules (*ca.*!10^{20}), we must also concern ourselves with interactions between molecules, as well as with their individual structures. Indeed, many of the physical characteristics of compounds that are used to identify them (e.g. boiling points, melting points and solubilities) are due to intermolecular interactions.

All atoms and molecules have a weak attraction for one another, known as **van der Waals** attraction. This attractive force has its origin in the electrostatic attraction of the electrons of one molecule or atom for the nuclei of another. If there were no van der Waals forces, all matter would exist in a gaseous state, and life as we know it would not be possible. It should be noted that there are also smaller repulsive forces between molecules that increase rapidly at very small intermolecular distances.

Boiling & Melting Points

Boiling and Melting Points

For general purposes it is useful to consider temperature to be a measure of the kinetic energy of all the atoms and molecules in a given system. As temperature is increased, there is a corresponding increase in the vigor of translational and rotation motions of all molecules, as well as the vibrations of atoms and groups of atoms within molecules. Experience shows that many compounds exist normally as liquids and solids; and that even low-density gases, such as hydrogen and helium, can be liquified at sufficiently low temperature and high pressure. A clear conclusion to be drawn from this fact is that intermolecular attractive forces vary considerably, and that the boiling point of a compound is a measure of the strength of these forces. Thus, in order to break the intermolecular attractions that hold the molecules of a compound in the condensed liquid state, it is necessary to increase their kinetic energy by raising the sample temperature to the characteristic boiling point of the compound.

The following table illustrates some of the factors that influence the strength of intermolecular attractions. The formula of each entry is followed by its formula weight in parentheses and the boiling point in degrees Celsius. First there is molecular size. Large molecules have more electrons and nuclei that create van der Waals attractive forces, so their compounds usually have higher boiling points than similar compounds made up of smaller molecules. It is very important to apply this rule only to like compounds. The examples given in the first two rows are similar in that the molecules or atoms are spherical in shape and do not have permanent dipoles. Molecular shape is also important, as the second group of compounds illustrate. The upper row consists of roughly spherical molecules, whereas the isomers in the lower row have cylindrical or linear shaped molecules. The attractive forces between the latter group are generally greater. Finally, permanent molecular dipoles generated by polar covalent bonds result in even greater attractive forces between molecules, provided they have the mobility to line up in appropriate orientations. The last entries in the table compare non-polar hydrocarbons with equal-sized compounds having polar bonds to oxygen and nitrogen. Halogens also form polar bonds to carbon, but they also increase the molecular mass, making it difficult to distinguish among these factors.

Boiling Points (ºC) of Selected Elements and Compounds

Increasing Size				
Atomic	Ar (40) -186	Kr (83) -153	Xe (131) -109	
Molecular	CH_4 (16) -161	$(CH_3)_4C$ (72) 9.5	$(CH_3)_4Si$ (88) 27	CCl_4 (154) 77
Molecular Shape				
Spherical:	$(CH_3)_4C$ (72) 9.5	$(CH_3)_2CCl_2$ (113) 69	$(CH_3)_3CC(CH_3)_3$ (114) 106	
Linear:	$CH_3(CH_2)_3CH_3$ (72) 36	$Cl(CH_2)_3Cl$ (113) 121	$CH_3(CH_2)_6CH_3$ (114) 126	
Molecular Polarity				
Non-polar:	$H_2C=CH_2$ (28) -104	F_2 (38) -188	$CH_3C\equiv CCH_3$ (54) -32	CF_4 (88) -130
Polar:	$H_2C=O$ (30) -21	$CH_3CH=O$ (44) 20	$(CH_3)_3N$ (59) 3.5	$(CH_3)_2C=O$ (58) 56

	HC≡N (27) 26	$CH_3C{\equiv}N$ (41) 82	$(CH_2)_3O$ (58) 50	CH_3NO_2 (61) 101

The melting points of crystalline solids cannot be categorized in as simple a fashion as boiling points. The distance between molecules in a crystal lattice is small and regular, with intermolecular forces serving to constrain the motion of the molecules more severely than in the liquid state. Molecular size is important, but shape is also critical, since individual molecules need to fit together cooperatively for the attractive lattice forces to be large. Spherically shaped molecules generally have relatively high melting points, which in some cases approach the boiling point. This reflects the fact that spheres can pack together more closely than other shapes. This structure or shape sensitivity is one of the reasons that melting points are widely used to identify specific compounds. The data in the following table serves to illustrate these points.

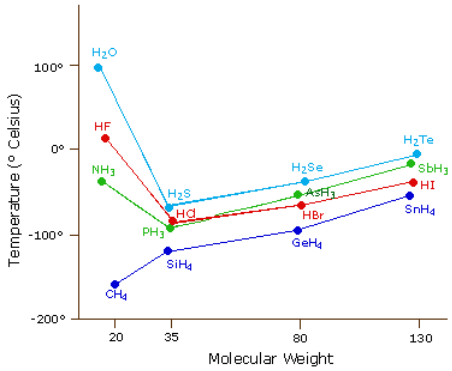
Compound	Formula	Boiling Point	Melting Point
pentane	$CH_3(CH_2)_3CH_3$	36ºC	–130ºC
hexane	$CH_3(CH_2)_4CH_3$	69ºC	–95ºC
heptane	$CH_3(CH_2)_5CH_3$	98ºC	–91ºC
octane	$CH_3(CH_2)_6CH_3$	126ºC	–57ºC
nonane	$CH_3(CH_2)_7CH_3$	151ºC	–54ºC
decane	$CH_3(CH_2)_8CH_3$	174ºC	–30ºC
tetramethylbutane	$(CH_3)_3C\text{-}C(CH_3)_3$	106ºC	+100ºC

Notice that the boiling points of the unbranched alkanes (pentane through decane) increase rather smoothly with molecular weight, but the melting points of the even-carbon chains increase more than those of the odd-carbon chains. Even-membered chains pack together in a uniform fashion more compactly than do odd-membered chains. The last compound, an isomer of octane, is nearly spherical and has an exceptionally high melting point (only 6º below the boiling point).

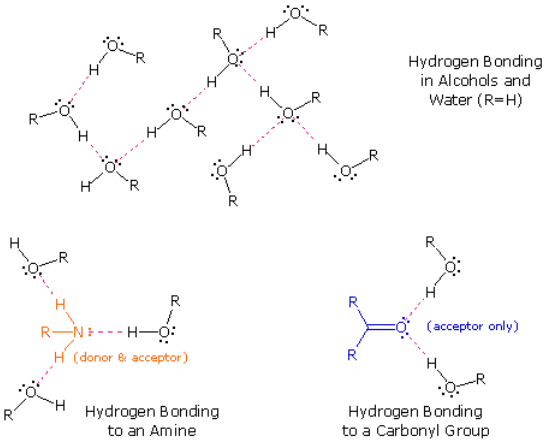
Hydrogen Bonding

Hydrogen Bonding

The most powerful intermolecular force influencing neutral (uncharged) molecules is the **hydrogen bond**. If we compare the boiling points of methane (CH_4) -161ºC, ammonia (NH_3) -33ºC, water (H_2O) 100ºC and hydrogen fluoride (HF) 19ºC, we see a greater variation for these similar sized molecules than expected from the data presented above for polar compounds. This is shown graphically in the following chart. Most of the simple hydrides of group IV, V, VI & VII elements display the expected rise in boiling point with molecular mass, but the hydrides of the most electronegative elements (nitrogen, oxygen and fluorine) have abnormally high boiling points for their mass.



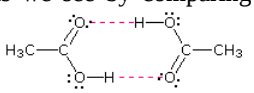
The exceptionally strong dipole-dipole attractions that cause this behavior are called the **hydrogen bond**. Hydrogen forms polar covalent bonds to more electronegative atoms such as oxygen, and because a hydrogen atom is quite small, the positive end of the bond dipole (the hydrogen) can approach neighboring nucleophilic or basic sites more closely than can other polar bonds. Coulombic forces are inversely proportional to the sixth power of the distance between dipoles, making these interactions relatively strong, although they are still weak (*ca.* 4 to 5 kcal per mole) compared with most covalent bonds. The unique properties of water are largely due to the strong hydrogen bonding that occurs between its molecules. In the following diagram the hydrogen bonds are depicted as magenta dashed lines.



The molecule providing a polar hydrogen for a hydrogen bond is called a **donor**. The molecule that provides the electron rich site to which the hydrogen is attracted is called an **acceptor**. Water and alcohols may serve as both donors and acceptors, whereas ethers, aldehydes, ketones and esters can function only as acceptors. Similarly, primary and secondary amines are both donors and acceptors, but tertiary amines function only as acceptors. Once you are able to recognize compounds that can exhibit intermolecular hydrogen bonding, the relatively high boiling points they exhibit become understandable. The data in the following table serve to illustrate this point.

Compound	Formula	Mol. Wt.	Boiling Point	Melting Point
dimethyl ether	CH_3OCH_3	46	–24ºC	–138ºC
ethanol	CH_3CH_2OH	46	78ºC	–130ºC
propanol	$CH_3(CH_2)_2OH$	60	98ºC	–127ºC
diethyl ether	$(CH_3CH_2)_2O$	74	34ºC	–116ºC
propyl amine	$CH_3(CH_2)_2NH_2$	59	48ºC	–83ºC
methylaminoethane	$CH_3CH_2NHCH_3$	59	37ºC	
trimethylamine	$(CH_3)_3N$	59	3ºC	–117ºC
ethylene glycol	$HOCH_2CH_2OH$	62	197ºC	–13ºC
acetic acid	CH_3CO_2H	60	118ºC	17ºC
ethylene diamine	$H_2NCH_2CH_2NH_2$	60	118ºC	8.5ºC

Alcohols boil considerably higher than comparably sized ethers (first two entries), and isomeric 1º, 2º & 3º-amines, respectively, show decreasing boiling points, with the two hydrogen bonding isomers being substantially higher boiling than the 3º-amine (entries 5 to 7). Also, O–H---O hydrogen bonds are clearly stronger than N–H---N hydrogen bonds, as we see by comparing propanol with the amines. As expected, the presence of two hydrogen bonding functions in a compound raises the boiling point even further. Acetic acid (the ninth entry) is an interesting case. A dimeric species, shown on the right, held together by two hydrogen bonds is a major component of the liquid state. If this



is an accurate representation of the composition of this compound then we would expect its boiling point to be equivalent to that of a $C_4H_8O_4$ compound (formula weight = 120). A suitable approximation of such a compound is found in tetramethoxymethane, $(CH_3O)_4C$, which is actually a bit larger (formula weight = 136) and has a boiling point of 114ºC. Thus, the dimeric hydrogen bonded structure appears to be a good representation of acetic acid in the condensed state.

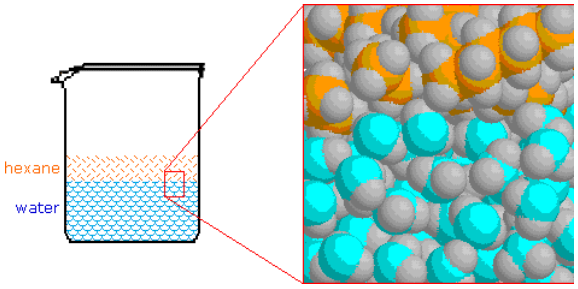
A related principle is worth noting at this point. Although the hydrogen bond is relatively weak (*ca.* 4 to 5 kcal per mole), when several such bonds exist the resulting structure can be quite robust. The hydrogen bonds between cellulose fibers confer great strength to wood and related materials.

Water Solubility

Solubility in Water

Water has been referred to as the "universal solvent", and its widespread distribution on this planet and essential role in life make it the benchmark for discussions of solubility. Water dissolves many ionic salts thanks to its high dielectric constant and ability to solvate ions. The former reduces the attraction between oppositely charged ions and the latter stabilizes the ions by binding to them and delocalizing charge density. Many organic compounds, especially alkanes and other hydrocarbons, are nearly insoluble in water. Organic compounds that are water soluble, such as most of those listed in the above table, generally have hydrogen bond acceptor and donor groups. The least soluble of the listed compounds is diethyl ether, which can serve only as a hydrogen bond acceptor and is 75% hydrocarbon in nature. Even so, diethyl ether is about two hundred times more soluble in water than is pentane.

The chief characteristic of water that influences these solubilities is the extensive hydrogen bonded association of its molecules with each other. This hydrogen bonded network is stabilized by the sum of all the hydrogen bond energies, and if nonpolar molecules such as hexane were inserted into the network they would destroy local structure without contributing any hydrogen bonds of their own. Of course, hexane molecules experience significant van der Waals attraction to neighboring molecules, but these attractive forces are much weaker than the hydrogen bond. Consequently, when hexane or other nonpolar compounds are mixed with water, the strong association forces of the water network exclude the nonpolar molecules, which must then exist in a separate phase. This is shown in the following illustration, and since hexane is less dense than water, the hexane phase floats on the water phase.



It is important to remember this tendency of water to exclude nonpolar molecules and groups, since it is a factor in the structure and behavior of many complex molecular systems. A common nomenclature used to describe molecules and regions within molecules is **hydrophilic** for polar, hydrogen bonding moieties and **hydrophobic** for nonpolar species.

Contributors

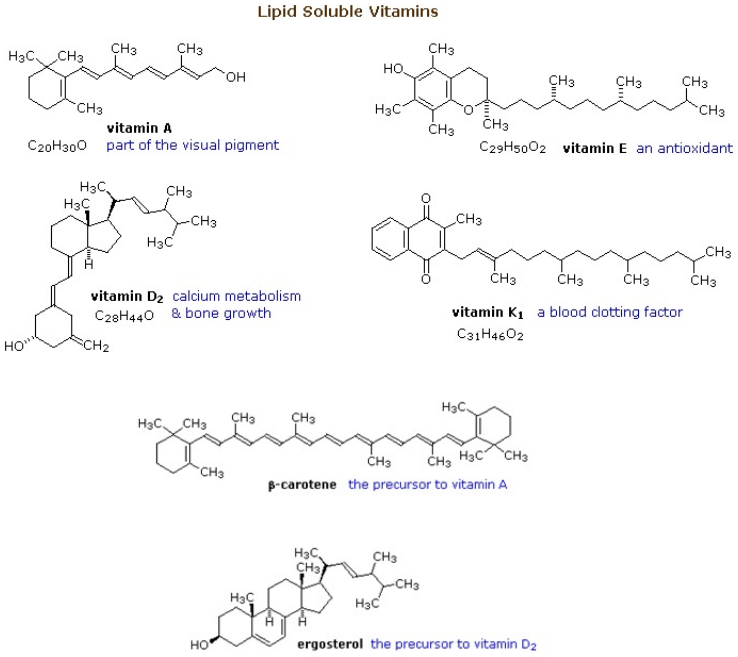
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

3.5: Application - Vitamins

The essential dietary substances called **vitamins** are commonly classified as "water soluble" or "fat soluble". Water soluble vitamins, such as vitamin C, are rapidly eliminated from the body and their dietary levels need to be relatively high. The recommended daily allotment (RDA) of vitamin C is 100 mg, and amounts as large as 2 to 3 g are taken by many people without adverse effects. The lipid soluble vitamins, shown in the diagram below, are not as easily eliminated and may accumulate to toxic levels if consumed in large quantity. The RDA for these vitamins are:

- Vitamin A 800 µg (upper limit ca. 3000 µg)
- Vitamin D 5 to 10 µg (upper limit ca. 2000 µg)
- Vitamin E 15 mg (upper limit ca. 1 g)
- Vitamin K 110 µg (upper limit not specified)

From this data it is clear that vitamins A and D, while essential to good health in proper amounts, can be very toxic. Vitamin D, for example, is used as a rat poison, and in equal weight is more than 100 times as poisonous as sodium cyanide.



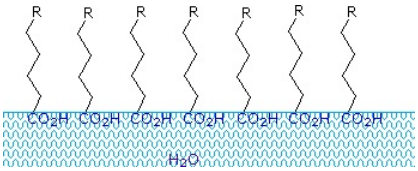
From the structures shown here, it should be clear that these compounds have more than a solubility connection with lipids. Vitamins A is a terpene, and vitamins E and K have long terpene chains attached to an aromatic moiety. The structure of vitamin D can be described as a steroid in which ring B is cut open and the remaining three rings remain unchanged. The precursors of vitamins A and D have been identified as the tetraterpene beta-carotene and the steroid ergosterol, respectively.

Contributors

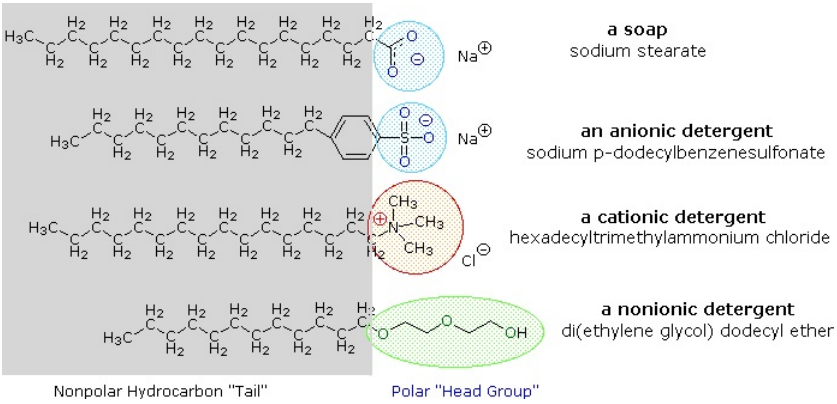
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

3.6: Application of Solubility- Soap

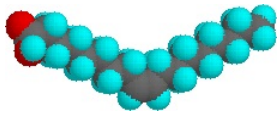
Carboxylic acids and salts having alkyl chains longer than eight carbons exhibit unusual behavior in water due to the presence of both hydrophilic (CO_2) and hydrophobic (alkyl) regions in the same molecule. Such molecules are termed **amphiphilic** (Gk. amphi = both) or **amphipathic**. Fatty acids made up of ten or more carbon atoms are nearly insoluble in water, and because of their lower density, float on the surface when mixed with water. Unlike paraffin or other alkanes, which tend to puddle on the waters surface, these fatty acids spread evenly over an extended water surface, eventually forming a monomolecular layer in which the polar carboxyl groups are hydrogen bonded at the water interface, and the hydrocarbon chains are aligned together away from the water. This behavior is illustrated in the diagram on the right. Substances that accumulate at water surfaces and change the surface properties are called **surfactants**.



Alkali metal salts of fatty acids are more soluble in water than the acids themselves, and the amphiphilic character of these substances also make them strong surfactants. The most common examples of such compounds are soaps and detergents, four of which are shown below. Note that each of these molecules has a nonpolar hydrocarbon chain, the "tail", and a polar (often ionic) "head group". The use of such compounds as cleaning agents is facilitated by their surfactant character, which lowers the surface tension of water, allowing it to penetrate and wet a variety of materials.



Very small amounts of these surfactants dissolve in water to give a random dispersion of solute molecules. However, when the concentration is increased an interesting change occurs. The surfactant molecules reversibly assemble into polymolecular aggregates called **micelles**. By gathering the hydrophobic chains together in the center of the micelle, disruption of the hydrogen bonded structure of liquid water is minimized, and the polar head groups extend into the surrounding water where they participate in hydrogen bonding. These micelles are often spherical in shape, but may also assume cylindrical and branched forms, as illustrated on the right. Here the polar head group is designated by a blue circle, and the nonpolar tail is a zig-zag black line.



The oldest amphiphilic cleaning agent known to humans is soap. Soap is manufactured by the base-catalyzed hydrolysis (saponification) of animal fat (see below). Before sodium hydroxide was commercially available, a boiling solution of potassium carbonate leached from wood ashes was used. Soft potassium soaps were then converted to the harder sodium soaps by washing with salt solution. The importance of soap to human civilization is documented by history, but some problems associated with its use have been recognized. One of these is caused by the weak acidity (pK_a ca. 4.9) of the fatty acids. Solutions of alkali metal soaps are slightly alkaline (pH 8 to 9) due to hydrolysis. If the pH of a soap solution is lowered by acidic contaminants, insoluble fatty acids precipitate and form a scum. A second problem is caused by the presence of calcium and magnesium salts in the water supply (hard water). These divalent cations cause aggregation of the micelles, which then deposit as a dirty scum.

These problems have been alleviated by the development of synthetic amphiphiles called detergents (or syndets). By using a much stronger acid for the polar head group, water solutions of the amphiphile are less sensitive to pH changes. Also the sulfonate functions used for virtually all anionic detergents confer greater solubility on micelles incorporating the alkaline earth cations found in hard water. Variations on the amphiphile theme have led to the development of other classes, such as the cationic and nonionic detergents shown above. Cationic detergents often exhibit germicidal properties, and their ability to change surface pH has made them useful as fabric softeners and hair conditioners. These versatile chemical "tools" have dramatically transformed the household and personal care cleaning product markets over the past fifty years.

Contributors

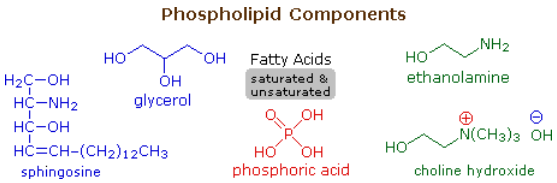
William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

3.7: Application- The Cell Membrane

Phospholipids

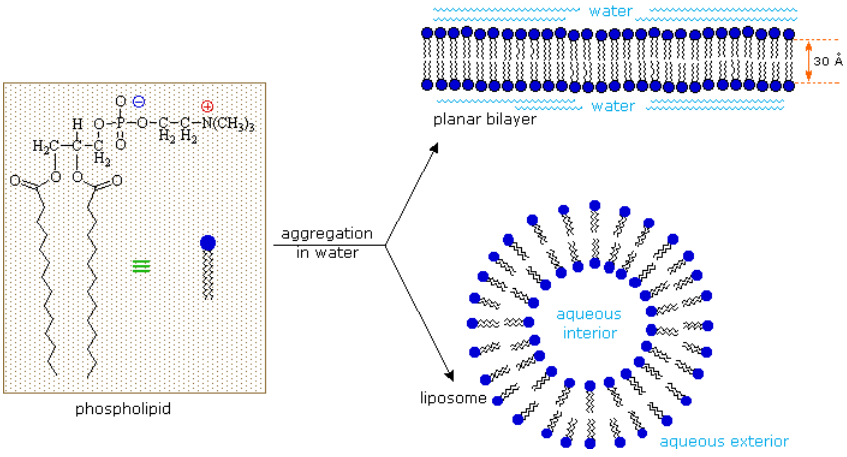
Phospholipids are the main constituents of cell membranes. They resemble the triglycerides in being ester or amide derivatives of glycerol or sphingosine with fatty acids and phosphoric acid. The phosphate moiety of the resulting phosphatidic acid is further esterified with ethanolamine, choline or serine in the phospholipid itself. The following diagram shows the structures of some of these components. Clicking on the diagram will change it to display structures for two representative phospholipids. Note that the fatty acid components (R & R') may be saturated or unsaturated.

To see a model of a phospholipid Click Here.

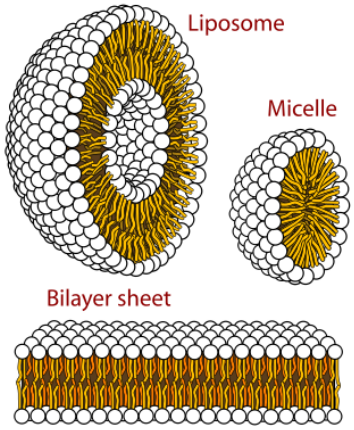


As ionic amphiphiles, phospholipids aggregate or self-assemble when mixed with water, but in a different manner than the soaps and detergents. Because of the two pendant alkyl chains present in phospholipids and the unusual mixed charges in their head groups, micelle formation is unfavorable relative to a bilayer structure. If a phospholipid is smeared over a small hole in a thin piece of plastic immersed in water, a stable planar bilayer of phospholipid molecules is created at the hole. As shown in the following diagram, the polar head groups on the faces of the bilayer contact water, and the hydrophobic alkyl chains form a nonpolar interior. The phospholipid molecules can move about in their half the bilayer, but there is a significant energy barrier preventing migration to the other side of the bilayer. **To see an enlarged segment of a phospholipid bilayer Click Here.**

This bilayer membrane structure is also found in aggregate structures called **liposomes**. Liposomes are microscopic vesicles consisting of an aqueous core enclosed in one or more phospholipid layers. They are formed when phospholipids are vigorously mixed with water. Unlike micelles, liposomes have both aqueous interiors and exteriors.



This bilayer membrane structure is also found in aggregate structures called **liposomes**. Liposomes are microscopic vesicles consisting of an aqueous core enclosed in one or more phospholipid layers. They are formed when phospholipids are vigorously mixed with water. Unlike micelles, liposomes have both aqueous interiors and exteriors.



A cell may be considered a very complex liposome. The bilayer membrane that separates the interior of a cell from the surrounding fluids is largely composed of phospholipids, but it incorporates many other components, such as cholesterol, that contribute to its structural integrity. Protein channels that permit the transport of various kinds of chemical species in and out of the cell are also important components of cell membranes.

The interior of a cell contains a variety of structures (organelles) that conduct chemical operations vital to the cells existence. Molecules bonded to the surfaces of cells serve to identify specific cells and facilitate interaction with external chemical entities. The sphingomyelins are also membrane lipids. They are the major component of the myelin sheath surrounding nerve fibers. Multiple Sclerosis is a devastating disease in which the myelin sheath is lost, causing eventual paralysis.

Ionophores

Because the health of cells depends on maintaining the proper levels of cations in intracellular fluids, any change that affects the normal flux of metal ions across cell membranes could well cause an organism to die. Molecules that facilitate the transport of metal ions across membranes are generally called **ionophores** (ion plus phore from the Greek phorein, meaning “to carry”). Many ionophores are potent antibiotics that can kill or inhibit the growth of bacteria. An example is valinomycin, a cyclic molecule with a central cavity lined with oxygen atoms (part (a) in Figure 21.14 "Valinomycin Is an Antibiotic That Functions Like an Ionophore") that is similar to the cavity of a crown ether (part (a) in Figure 13.7 "Crown Ethers and Cryptands"). Like a crown ether, valinomycin is highly selective: its affinity for K^+ is about 1000 times greater than that for Na^+. By increasing the flux of K^+ ions into cells, valinomycin disrupts the normal K^+ gradient across a cell membrane, thereby killing the cell (part (b) in Figure 21.14 "Valinomycin Is an Antibiotic That Functions Like an Ionophore").

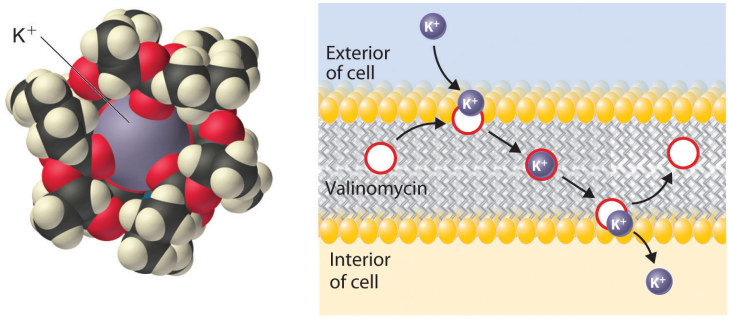


Figure 21.14 Valinomycin Is an Antibiotic That Functions Like an Ionophore

(a) This model of the structure of the K^+–valinomycin complex, determined by x-ray diffraction, shows how the valinomycin molecule wraps itself around the K^+ ion, shielding it from the environment, in a manner reminiscent of a crown ether complex. (For more information on the crown ethers, see Chapter 13 "Solutions", Section 13.2 "Solubility and Molecular Structure".) (b) Valinomycin kills bacteria by facilitating the transport of K^+ ions across the cell membrane, thereby disrupting the normal distribution of ions in the bacterium. At the surface of the membrane, valinomycin binds a K^+ ion. Because the hydrophobic exterior of the valinomycin molecule forms a “doughnut” that shields the positive charge of the metal ion, the K^+–valinomycin

complex is highly soluble in the nonpolar interior of the membrane. After the K^+–valinomycin complex diffuses across the membrane to the interior of the cell, the K^+ ion is released, and the valinomycin is free to diffuse back to the other side of the membrane to bind another K^+ ion. Valinomycin thereby destroys the normal K^+ gradient across the membrane, killing the cell.

Contributors

William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

3.8: Functional Groups and Reactivity

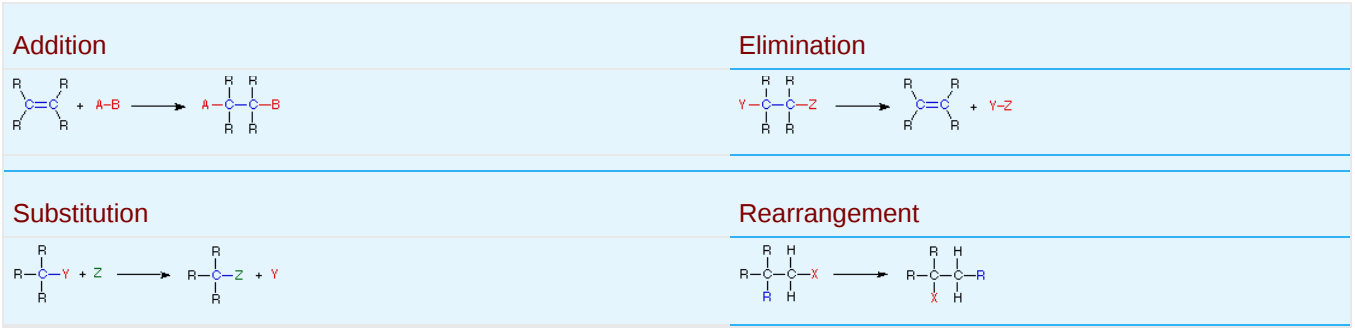
Organic chemistry encompasses a very large number of compounds (many millions), and our previous discussion and illustrations have focused on their structural characteristics. Now that we can recognize these actors (compounds), we turn to the roles they are inclined to play in the scientific drama staged by the multitude of chemical reactions that define organic chemistry.
We begin by defining some basic terms that will be used frequently as this subject is elaborated.

Chemical Reaction: A transformation resulting in a change of composition, constitution and/or configuration of a compound (referred to as the reactant or substrate).
Reactant or Substrate: The organic compound undergoing change in a chemical reaction. Other compounds may also be involved, and common reactive partners (reagents) may be identified. The reactant is often (but not always) the larger and more complex molecule in the reacting system. Most (or all) of the reactant molecule is normally incorporated as part of the product molecule.
Reagent: A common partner of the reactant in many chemical reactions. It may be organic or inorganic; small or large; gas, liquid or solid. The portion of a reagent that ends up being incorporated in the product may range from all to very little or none.
Product(s) The final form taken by the major reactant(s) of a reaction.
Reaction Conditions The environmental conditions, such as temperature, pressure, catalysts & solvent, under which a reaction progresses optimally. Catalysts are substances that accelerate the rate (velocity) of a chemical reaction without themselves being consumed or appearing as part of the reaction product. Catalysts do not change equilibria positions.

If you scan any organic textbook you will encounter what appears to be a very large, often intimidating, number of reactions. These are the "tools" of a chemist, and to use these tools effectively, we must organize them in a sensible manner and look for patterns of reactivity that permit us make plausible predictions. Most of these reactions occur at special sites of reactivity known as functional groups, and these constitute one organizational scheme that helps us catalog and remember reactions.

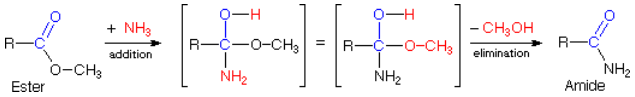
Ultimately, the best way to achieve proficiency in organic chemistry is to understand how reactions take place, and to recognize the various factors that influence their course.

First, we identify four broad classes of reactions based solely on the **structural change** occurring in the reactant molecules. This classification does not require knowledge or speculation concerning reaction paths or mechanisms. The four main reaction classes are **additions, eliminations, substitutions, and rearrangements.**

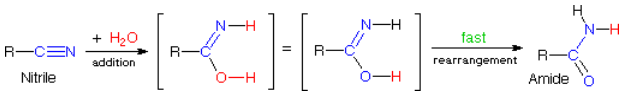


In an **addition** reaction the number of σ-bonds in the substrate molecule increases, usually at the expense of one or more π-bonds. The reverse is true of **elimination** reactions, *i.e.*the number of σ-bonds in the substrate decreases, and new π-bonds are often formed. **Substitution** reactions, as the name implies, are characterized by replacement of an atom or group (Y) by another atom or group (Z). Aside from these groups, the number of bonds does not change. A **rearrangement** reaction generates an isomer, and again the number of bonds normally does not change.

The examples illustrated above involve simple alkyl and alkene systems, but these reaction types are general for most functional groups, including those incorporating carbon-oxygen double bonds and carbon-nitrogen double and triple bonds. Some common reactions may actually be a combination of reaction types. The reaction of an ester with ammonia to give an amide, as shown below, appears to be a substitution reaction (Y = CH_3O & Z = NH_2); however, it is actually two reactions, an addition followed by an elimination.



The addition of water to a nitrile does not seem to fit any of the above reaction types, but it is simply a slow addition reaction followed by a rapid rearrangement, as shown in the following equation. Rapid rearrangements of this kind are called **tautomerizations**.



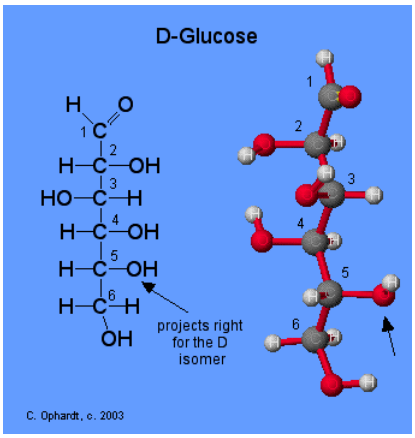
Contributors

William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

3.9: Biomolecules

Glucose

Glucose is initially synthesized by chlorophyll in plants using carbon dioxide from the air and sunlight as an energy source. Glucose is further converted to starch for storage.

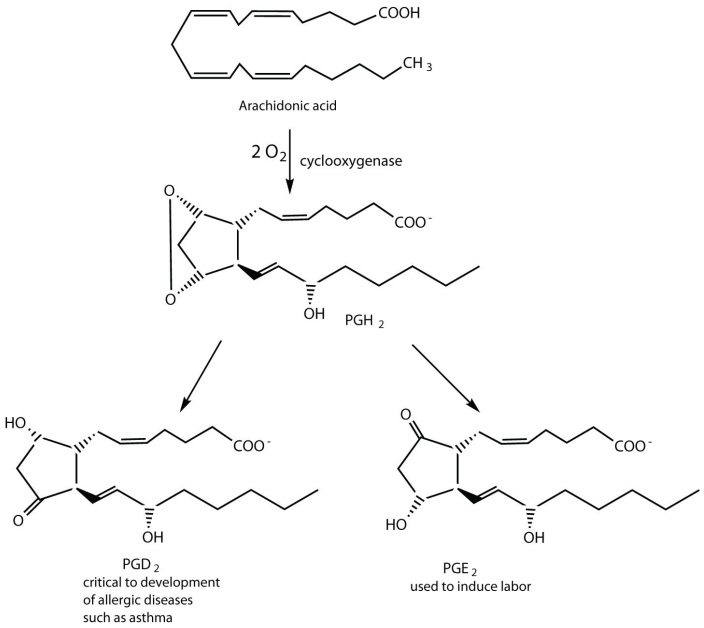


Prostaglandins

Prostaglandins are chemical messengers synthesized in the cells in which their physiological activity is expressed. They are unsaturated fatty acids containing 20 carbon atoms and are synthesized from arachidonic acid—a polyunsaturated fatty acid—when needed by a particular cell. They are called *prostaglandins* because they were originally isolated from semen found in the prostate gland. It is now known that they are synthesized in nearly all mammalian tissues and affect almost all organs in the body. The five major classes of prostaglandins are designated as PGA, PGB, PGE, PGF, and PGI. Subscripts are attached at the end of these abbreviations to denote the number of double bonds outside the five-carbon ring in a given prostaglandin.

The prostaglandins are among the most potent biological substances known. Slight structural differences give them highly distinct biological effects; however, all prostaglandins exhibit some ability to induce smooth muscle contraction, lower blood pressure, and contribute to the inflammatory response. Aspirin and other nonsteroidal anti-inflammatory agents, such as ibuprofen, obstruct the synthesis of prostaglandins by inhibiting cyclooxygenase, the enzyme needed for the initial step in the conversion of arachidonic acid to prostaglandins.

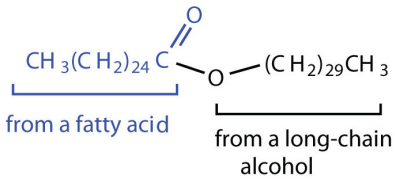
Their wide range of physiological activity has led to the synthesis of hundreds of prostaglandins and their analogs. Derivatives of PGE_2 are now used in the United States to induce labor. Other prostaglandins have been employed clinically to lower or increase blood pressure, inhibit stomach secretions, relieve nasal congestion, relieve asthma, and prevent the formation of blood clots, which are associated with heart attacks and strokes.



Waxes

Waxes

Waxes



Myricyl cerotate
(found in carnauba wax)

DNA

The secondary structure of DNA is actually very similar to the secondary structure of proteins. The protein single alpha helix structure held together by hydrogen bonds was discovered with the aid of X-ray diffraction studies. The X-ray diffraction patterns for DNA show somewhat similar patterns.

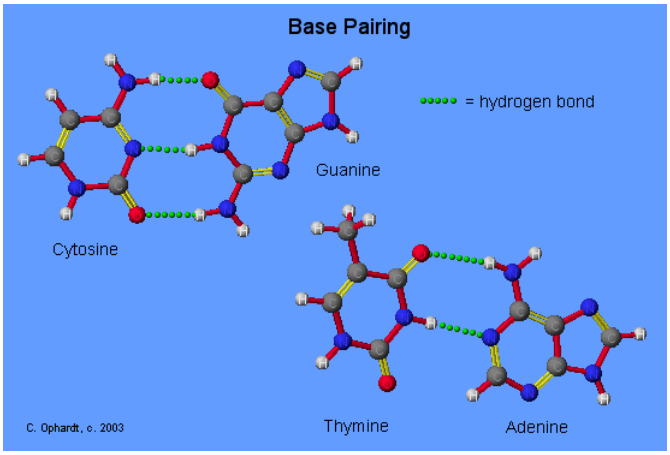
Introduction

In addition, chemical studies by E. Chargaff indicate several important clues about the structure of DNA. In the DNA of all organisms:

1. The concentration of adenine equals that of thymine.
2. The concentration of guanine equals that of cytosine.

Chargaff's findings clearly indicate that some type of heterocyclic amine base pairing exists in the DNA structure. X-ray diffraction data shows that a repeating helical pattern occurs every 34 Angstrom units with 10 subunits per turn. Each subunit occupies 3.4 Angstrom units which is the same amount of space occupied by a single nucleotide unit. Using Chargaff's information and the X-ray data in conjunction with building actual molecular models, Watson and Crick developed the double helix as a model for DNA.

The **double helix in DNA** consists of two right-handed polynucleotide chains that are coiled about the same axis. The heterocyclic amine bases project inward toward the center so that the base of one strand interacts or pairs with a base of the other strand. According to the chemical and X-ray data and model building exercises, only specific heterocyclic amine bases may be paired.

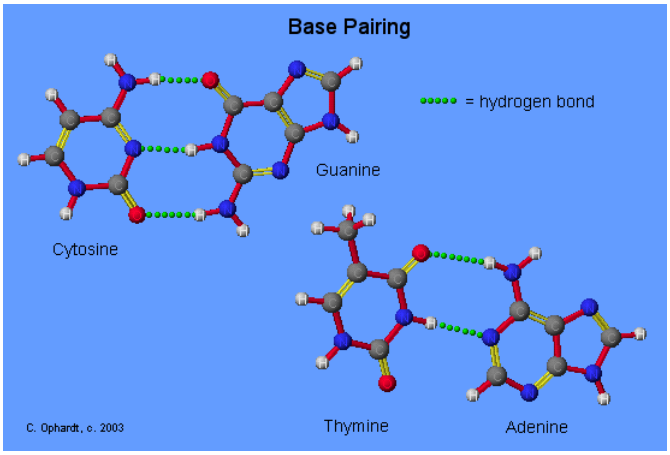


Base Pairing Principle

The Base Pairing Principle is that adenine pairs with thymine (A - T) and guanine pairs with cytosine (G - C)

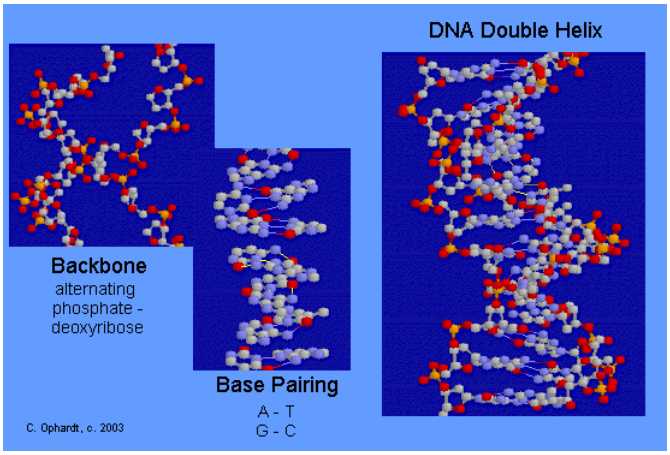
The base pairing is called complementary because there are specific geometry requirements in the formation of hydrogen bonds between the heterocylic amines. Heterocyclic amine base pairing is an application of the **hydrogen bonding principle**. In the structures for the complementary base pairs given in the graphic on the left, notice that the thymine - adenine pair interacts through two hydrogen bonds represented as (T=A) and that the cytosine-guanine pair interacts through three hydrogen bonds represented as (C≡G).

Although other base pairing-hydrogen bonding combinations may be possible, they are not utilized because the bond distances do not correspond to those given by the base pairs already cited. The diameter of the helix is 20 Angstroms.



DNA Double Helix

The double-stranded helical model for DNA is shown in the graphic on the left. The easiest way to visualize DNA is as an immensely long rope ladder, twisted into a cork-screw shape. The sides of the ladder are alternating sequences of deoxyribose and phosphate (backbone) while the rungs of the ladder (bases) are made in two parts with each part firmly attached to the side of the ladder. The parts in the rung are heterocyclic amines held in position by hydrogen bonding. Although most DNA exists as open ended double helices, some bacterial DNA has been found as a cyclic helix. Occasionally, DNA has also been found as a single strand.



Contributors

Charles Ophardt (Professor Emeritus, Elmhurst College); Virtual Chembook

CHAPTER OVERVIEW

4: Alkanes

Topic hierarchy

4.1: Alkanes—An Introduction

Alkanes are organic compounds that consist entirely of single-bonded carbon and hydrogen atoms and lack any other functional groups. Alkanes have the general formula C_nH_{2n+2} and can be subdivided into the following three groups: the **linear straight-chain alkanes**, **branched alkanes**, and **cycloalkanes**. Alkanes are also *saturated hydrocarbons*.

Cycloalkanes are cyclic hydrocarbons, meaning that the carbons of the molecule are arranged in the form of a ring. Cycloalkanes are also saturated, meaning that all of the carbons atoms that make up the ring are single bonded to other atoms (no double or triple bonds). There are also polycyclic alkanes, which are molecules that contain two or more cycloalkanes that are joined, forming multiple rings.

Molecular Formulas

Alkanes are the simplest family of hydrocarbons - compounds containing carbon and hydrogen only. Alkanes only contain carbon-hydrogen bonds and carbon-carbon single bonds. The first six alkanes are as follows:

methane	CH_4
ethane	C_2H_6
propane	C_3H_8
butane	C_4H_{10}
pentane	C_5H_{12}
hexane	C_6H_{14}

You can work out the formula of any of the alkanes using the general formula C_nH_{2n+2}

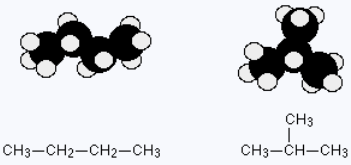
Isomerism

Isomers are molecules that have the same molecular formula, but have a different arrangement of the atoms in space. That excludes any different arrangements which are simply due to the molecule rotating as a whole, or rotating about particular bonds. For example, both of the following are the same molecule. They are not isomers. Both are butane.

All of the alkanes containing four or more carbon atoms show structural isomerism, meaning that there are two or more different structural formulae that you can draw for each molecular formula.

Example 1: Butane or MethylPropane

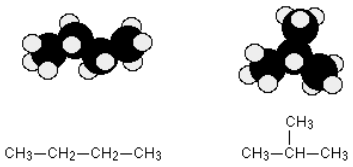
C_4H_{10} could be either of these two different molecules:



These are different molecules named butane (left) and 2-methylpropane (right).

There are also endless other possible ways that this molecule could twist itself. There is completely free rotation around all the carbon-carbon single bonds. If you had a model of a molecule in front of you, you would have to take it to pieces and rebuild it if you wanted to make an isomer of that molecule. If you can make an apparently different molecule just by rotating single bonds, it's not different - it's still the same molecule. In structural isomerism, the atoms are arranged in a completely different order. This is easier to see with specific examples. What follows looks at some of the ways that structural isomers can arise.

Constitutional isomers arise because of the possibility of branching in carbon chains. For example, there are two isomers of butane, C_4H_{10}. In one of them, the carbon atoms lie in a "straight chain" whereas in the other the chain is branched.

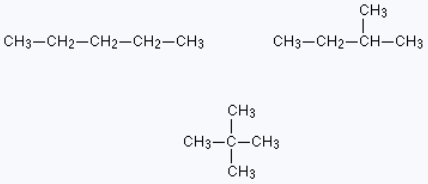


Be careful not to draw "false" isomers which are just twisted versions of the original molecule. For example, this structure is just the straight chain version of butane rotated about the central carbon-carbon bond.

You could easily see this with a model. This is the example we've already used at the top of this page.

Example 2: Constitutional Isomers in Pentane

Pentane, C_5H_{12}, has three chain isomers. If you think you can find any others, they are simply twisted versions of the ones below. If in doubt make some models.

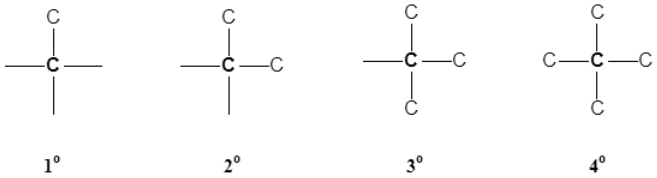


Examples of Simple Unbranched Alkanes

Name	Molecular Formula	Structural Formula	Isomers		Name	Molecular Formula	Structural Formula	Isomers
methane	CH_4	CH_4	1		hexane	C_6H_{14}	$CH_3(CH_2)_4CH_3$	5
ethane	C_2H_6	CH_3CH_3	1		heptane	C_7H_{16}	$CH_3(CH_2)_5CH_3$	9
propane	C_3H_8	$CH_3CH_2CH_3$	1		octane	C_8H_{18}	$CH_3(CH_2)_6CH_3$	18
butane	C_4H_{10}	$CH_3CH_2CH_2CH_3$	2		nonane	C_9H_{20}	$CH_3(CH_2)_7CH_3$	35
pentane	C_5H_{12}	$CH_3(CH_2)_3CH_3$	3		decane	$C_{10}H_{22}$	$CH_3(CH_2)_8CH_3$	75

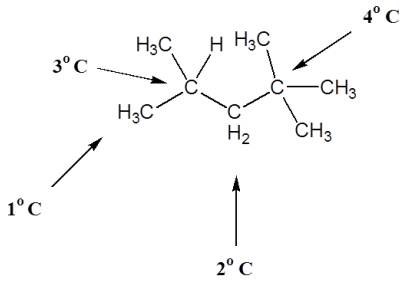
Classification of Carbon and Hydrogen Atoms

Carbons have a special terminology to describe how many other carbons they are attached to.

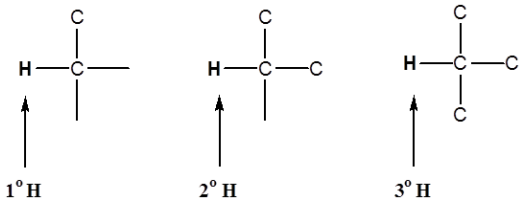


- Primary carbons (1°) attached to one other C atom
- Secondary carbons (2°) are attached to two other C's
- Tertiary carbons (3°) are attached to theree other C's
- Quaternary carbons (4°) are attached to four C's

For example, each of the three types of carbons are found in the 2,2 -dimethyl, 4-methylpentane molecule

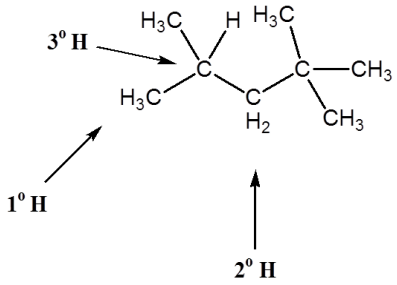


Hydrogen atoms are also classified in this manner. A hydrogen atom attached to a primary carbon atom is called a primary hydrogen; thus, isobutane, has nine primary hydrogens and one tertiary hydrogen.



- Primary hydrogens (1^o) are attached to carbons bonded to one other C atom
- Secondary hydrogens (2^o) are attached to carbons bonded to two other C's
- Tertiary hydrogens (3^o) are attached to carbons bonded to theree other C's

Each of the three types of carbons are found in the 2,2 -dimethyl, 4-methylpentane molecule



Contributors

Charles Ophardt (Professor Emeritus, Elmhurst College); Virtual Chembook

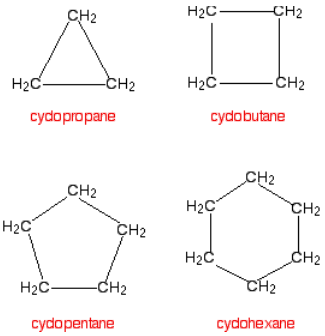
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)

4.2: Cycloalkanes

Cycloalkanes are cyclic hydrocarbons, meaning that the carbons of the molecule are arranged in the form of a ring. Cycloalkanes are also saturated, meaning that all of the carbons atoms that make up the ring are single bonded to other atoms (no double or triple bonds). There are also polycyclic alkanes, which are molecules that contain two or more cycloalkanes that are joined, forming multiple rings.

Introduction

Many organic compounds found in nature or created in a laboratory contain rings of carbon atoms with distinguishing chemical properties; these compounds are known as cycloalkanes. Cycloalkanes only contain carbon-hydrogen bonds and carbon-carbon single bonds, but in cycloalkanes, the carbon atoms are joined in a ring. The smallest cycloalkane is cyclopropane.



If you count the carbons and hydrogens, you will see that they no longer fit the general formula C_nH_{2n+2}. By joining the carbon atoms in a ring,two hydrogen atoms have been lost. The general formula for a cycloalkane is C_nH_{2n}. Cyclic compounds are not all flat molecules. All of the cycloalkanes, from cyclopentane upwards, exist as "puckered rings". Cyclohexane, for example, has a ring structure that looks like this:

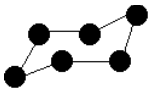
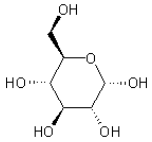
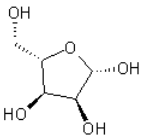
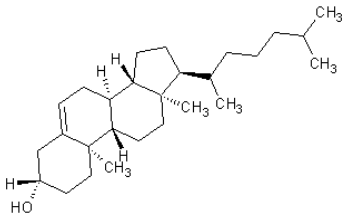


Figure 2: This is known as the "chair" form of cyclohexane from its shape, which vaguely resembles a chair. Note: The cyclohexane molecule is constantly changing, with the atom on the left, which is currently pointing down, flipping up, and the atom on the right flipping down. During this process, another (slightly less stable) form of cyclohexane is formed known as the "boat" form. In this arrangement, both of these atoms are either pointing up or down at the same time

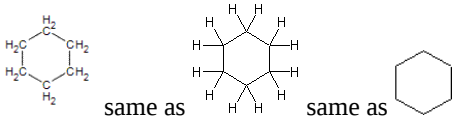
In addition to being saturated cyclic hydrocarbons, cycloalkanes may have multiple substituents or functional groups that further determine their unique chemical properties. The most common and useful cycloalkanes in organic chemistry are cyclopentane and cyclohexane, although other cycloalkanes varying in the number of carbons can be synthesized. Understanding cycloalkanes and their properties are crucial in that many of the biological processes that occur in most living things have cycloalkane-like structures.

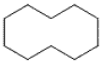
		
Glucose (6 carbon sugar)	Ribose (5 carbon sugar)	Cholesterol (polycyclic)

Although polycyclic compounds are important, they are highly complex and typically have common names accepted by IUPAC. However, the common names do not generally follow the basic IUPAC nomenclature rules. The general formula of the cycloalkanes is C_nH_{2n} where n is the number of carbons. The naming of cycloalkanes follows a simple set of rules that are built upon the same basic steps in naming alkanes. Cyclic hydrocarbons have the prefix "cyclo-".

Contents

For simplicity, cycloalkane molecules can be drawn in the form of skeletal structures in which each intersection between two lines is assumed to have a carbon atom with its corresponding number of hydrogens.



Cycloalkane	Molecular Formula	Basic Structure
Cyclopropane	C_3H_6	
Cyclobutane	C_4H_8	
Cyclopentane	C_5H_{10}	
Cyclohexane	C_6H_{12}	
Cycloheptane	C_7H_{14}	
Cyclooctane	C_8H_{16}	
Cyclononane	C_9H_{18}	
Cyclodecane	$C_{10}H_{20}$	

Contributors

- Jim Clark (Chemguide.co.uk)
- Pwint Zin

4.3: An Introduction to Nomenclature

The increasingly large number of organic compounds identified with each passing day, together with the fact that many of these compounds are isomers of other compounds, requires that a systematic nomenclature system be developed. Just as each distinct compound has a unique molecular structure which can be designated by a structural formula, each compound must be given a characteristic and unique name.

Introduction

As organic chemistry grew and developed, many compounds were given trivial names, which are now commonly used and recognized. Some examples are:

Name	Methane	Butane	Acetone	Toluene	Acetylene	Ethyl Alcohol
Formula	CH_4	C_4H_{10}	CH_3COCH_3	$CH_3C_6H_5$	C_2H_2	C_2H_5OH

Such **common names** often have their origin in the history of the science and the natural sources of specific compounds, but the relationship of these names to each other is arbitrary, and no rational or systematic principles underly their assignments.

The IUPAC Systematic Approach to Nomenclature

A rational nomenclature system should do at least two things. First, it should indicate how the carbon atoms of a given compound are bonded together in a characteristic lattice of chains and rings. Second, it should identify and locate any functional groups present in the compound. Since hydrogen is such a common component of organic compounds, its amount and locations can be assumed from the tetravalency of carbon, and need not be specified in most cases.

The IUPAC nomenclature system is a set of logical rules devised and used by organic chemists to circumvent problems caused by arbitrary nomenclature. Knowing these rules and given a structural formula, one should be able to write a unique name for every distinct compound. Likewise, given a IUPAC name, one should be able to write a structural formula. In general, an IUPAC name will have three essential features:

- A root or base indicating a major chain or ring of carbon atoms found in the molecular structure.
- A suffix or other element(s) designating functional groups that may be present in the compound.
- Names of substituent groups, other than hydrogen, that complete the molecular structure.

As an introduction to the IUPAC nomenclature system, we shall first consider compounds that have no specific functional groups. Such compounds are composed only of carbon and hydrogen atoms bonded together by sigma bonds (all carbons are sp^3 hybridized).

An excellent presentation of organic nomenclature is provided on a Nomenclature Page. created by Dave Woodcock. A full presentation of the IUPAC Rules is also available.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

4.4: Naming Alkanes

Alkanes

Hydrocarbons having no double or triple bond functional groups are classified as **alkanes** or **cycloalkanes**, depending on whether the carbon atoms of the molecule are arranged only in chains or also in rings. Although these hydrocarbons have no functional groups, they constitute the framework on which functional groups are located in other classes of compounds, and provide an ideal starting point for studying and naming organic compounds. The alkanes and cycloalkanes are also members of a larger class of compounds referred to as **aliphatic**. Simply put, aliphatic compounds are compounds that do not incorporate any aromatic rings in their molecular structure.

The following table lists the IUPAC names assigned to simple continuous-chain alkanes from C-1 to C-10. A common **"ane"** suffix identifies these compounds as alkanes. Longer chain alkanes are well known, and their names may be found in many reference and text books. The names **methane** through **decane** should be memorized, since they constitute the root of many IUPAC names. Fortunately, common numerical prefixes are used in naming chains of five or more carbon atoms.

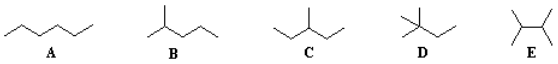
Table: Simple Unbranched Alkanes

Name	Molecular Formula	Structural Formula	Isomers	Name	Molecular Formula	Structural Formula	Isomers
meth**ane**	CH_4	CH_4	1	hex**ane**	C_6H_{14}	$CH_3(CH_2)_4CH_3$	5
eth**ane**	C_2H_6	CH_3CH_3	1	hept**ane**	C_7H_{16}	$CH_3(CH_2)_5CH_3$	9
prop**ane**	C_3H_8	$CH_3CH_2CH_3$	1	oct**ane**	C_8H_{18}	$CH_3(CH_2)_6CH_3$	18
but**ane**	C_4H_{10}	$CH_3CH_2CH_2CH_3$	2	non**ane**	C_9H_{20}	$CH_3(CH_2)_7CH_3$	35
pent**ane**	C_5H_{12}	$CH_3(CH_2)_3CH_3$	3	dec**ane**	$C_{10}H_{22}$	$CH_3(CH_2)_8CH_3$	75

Some important behavior trends and terminologies

1. The formulas and structures of these alkanes increase uniformly by a CH_2 increment.
2. A uniform variation of this kind in a series of compounds is called **homologous**.
3. These formulas all fit the $\mathbf{C_nH_{2n+2}}$ rule. This is also the highest possible H/C ratio for a stable hydrocarbon.
4. Since the H/C ratio in these compounds is at a maximum, we call them **saturated** (with hydrogen).

Beginning with butane (C_4H_{10}), and becoming more numerous with larger alkanes, we note the existence of alkane isomers. For example, there are five C_6H_{14} isomers, shown below as abbreviated line formulas (**A** through **E**):



Although these distinct compounds all have the same molecular formula, only one (**A**) can be called hexane. How then are we to name the others?

The **IUPAC** system requires first that we have names for simple unbranched chains, as noted above, and second that we have names for simple alkyl groups that may be attached to the chains. Examples of some common **alkyl groups** are given in the following table. Note that the "ane" suffix is replaced by "**yl**" in naming groups. The symbol **R** is used to designate a generic (unspecified) alkyl group.

Group	CH_3–	C_2H_5–	$CH_3CH_2CH_2$–	$(CH_3)_2CH$–	$CH_3CH_2CH_2CH_2$–	$(CH_3)_2CHCH_2$–	$CH_3CH_2CH(CH_3)$–	$(CH_3)_3C$–	R–
Name	Methyl	Ethyl	Propyl	Isopropyl	Butyl	Isobutyl	sec-Butyl	tert-Butyl	Alkyl

IUPAC Rules for Alkane Nomenclature

1. Find and name the longest continuous carbon chain.
2. Identify and name groups attached to this chain.
3. Number the chain consecutively, starting at the end nearest a substituent group.

4. Designate the location of each substituent group by an appropriate number and name.
5. Assemble the name, listing groups in alphabetical order.
The prefixes di, tri, tetra etc., used to designate several groups of the same kind, are not considered when alphabetizing.

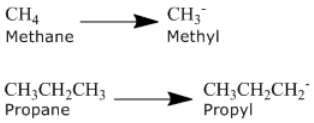
Halogen substituents are easily accommodated, using the names: fluoro (F-), chloro (Cl-), bromo (Br-) and iodo (I-).

Example 1: Halogen Substitution

For example, $(CH_3)_2CHCH_2CH_2Br$ would be named 1-bromo-3-methylbutane. If the halogen is bonded to a simple alkyl group an alternative "alkyl halide" name may be used. Thus, C_2H_5Cl may be named chloroethane (no locator number is needed for a two carbon chain) or ethyl chloride.
For the above isomers of hexane the IUPAC names are: **B** 2-methylpentane **C** 3-methylpentane **D** 2,2-dimethylbutane **E** 2,3-dimethylbutane

Alkyl Groups

Alkanes can be described by the general formula C_nH_{2n+2}. An alkyl group is formed by removing one hydrogen from the alkane chain and is described by the formula C_nH_{2n+1}. The removal of this hydrogen results in a stem change from **-ane** to **-yl**. Take a look at the following examples.



The same concept can be applied to any of the straight chain alkane names provided in the table above.

Name	Molecular Formula	Condensed Structural Formula
Methane	CH_4	CH_4
Ethane	C_2H_6	CH_3CH_3
Propane	C_3H_8	$CH_3CH_2CH_3$
Butane	C_4H_{10}	$CH_3(CH_2)_2CH_3$
Pentane	C_5H_{12}	$CH_3(CH_2)_3CH_3$
Hexane	C_6H_{14}	$CH_3(CH_2)_4CH_3$
Heptane	C_7H_{16}	$CH_3(CH_2)_5CH_3$
Octane	C_8H_{18}	$CH_3(CH_2)_6CH_3$
Nonane	C_9H_{20}	$CH_3(CH_2)_7CH_3$
Decane	$C_{10}H_{22}$	$CH_3(CH_2)_8CH_3$
Undecane	$C_{11}H_{24}$	$CH_3(CH_2)_9CH_3$
Dodecane	$C_{12}H_{26}$	$CH_3(CH_2)_{10}CH_3$
Tridecane	$C_{13}H_{28}$	$CH_3(CH_2)_{11}CH_3$
Tetradecane	$C_{14}H_{30}$	$CH_3(CH_2)_{12}CH_3$
Pentadecane	$C_{15}H_{32}$	$CH_3(CH_2)_{13}CH_3$
Hexadecane	$C_{16}H_{34}$	$CH_3(CH_2)_{14}CH_3$
Heptadecane	$C_{17}H_{36}$	$CH_3(CH_2)_{15}CH_3$
Octadecane	$C_{18}H_{38}$	$CH_3(CH_2)_{16}CH_3$

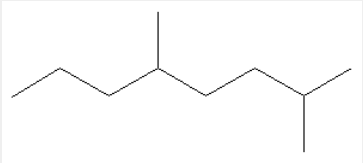
Nonadecane	$C_{19}H_{40}$	$CH_3(CH_2)_{17}CH_3$
Eicosane	$C_{20}H_{42}$	$CH_3(CH_2)_{18}CH_3$

Three Principles of Naming

1. Choose the longest, most substituted carbon chain containing a functional group.
2. A carbon bonded to a functional group must have the lowest possible carbon number. If there are no functional groups, then any substitute present must have the lowest possible number.
3. Take the alphabetical order into consideration; that is, after applying the first two rules given above, make sure that your substitutes and/or functional groups are written in alphabetical order.

Example 1

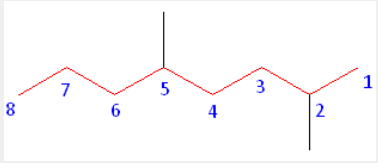
What is the name of the follow molecule?



SOLUTION

Rule #1: Choose the longest, most substituted carbon chain containing a functional group. This example does not contain any functional groups, so we only need to be concerned with choosing the longest, most substituted carbon chain. The longest carbon chain has been highlighted in red and consists of eight carbons.

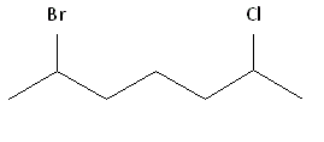
Rule #2: Carbons bonded to a functional group must have the lowest possible carbon number. If there are no functional groups, then any substitute present must have the lowest possible number. Because this example does not contain any functional groups, we only need to be concerned with the two substitutes present, that is, the two methyl groups. If we begin numbering the chain from the left, the methyls would be assigned the numbers 4 and 7, respectively. If we begin numbering the chain from the right, the methyls would be assigned the numbers 2 and 5. Therefore, to satisfy the second rule, numbering begins on the right side of the carbon chain as shown below. This gives the methyl groups the lowest possible numbering.



Rule 3: In this example, there is no need to utilize the third rule. Because the two substitutes are identical, neither takes alphabetical precedence with respect to numbering the carbons. This concept will become clearer in the following examples.

Example 2

What is the name of the follow molecule?

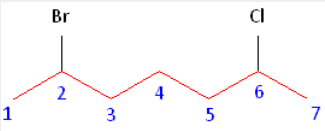


SOLUTION

Rule #1: Choose the longest, most substituted carbon chain containing a functional group. This example contains two functional groups, bromine and chlorine. The longest carbon chain has been highlighted in red and consists of seven carbons.

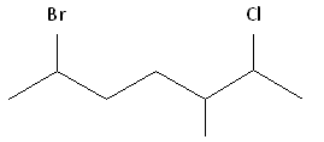
Rule #2: Carbons bonded to a functional group must have the lowest possible carbon number. If there are no functional groups, then any substitute present must have the lowest possible number. In this example, numbering the chain from the left or the right would satisfy this rule. If we number the chain from the left, bromine and chlorine would be assigned the second and sixth carbon positions, respectively. If we number the chain from the right, chlorine would be assigned the second position and bromine would be assigned the sixth position. In other words, whether we choose to number from the left or right, the functional groups occupy the second and sixth positions in the chain. To select the correct numbering scheme, we need to utilize the third rule.

Rule #3: After applying the first two rules, take the alphabetical order into consideration. Alphabetically, bromine comes before chlorine. Therefore, bromine is assigned the second carbon position, and chlorine is assigned the sixth carbon position.



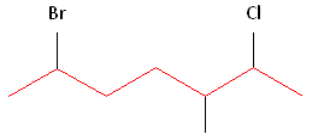
Example 3

What is the name of the follow molecule?

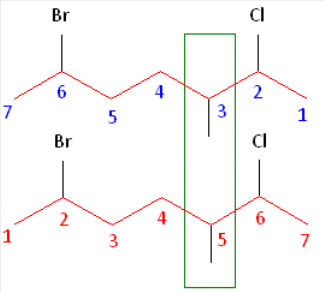


SOLUTION

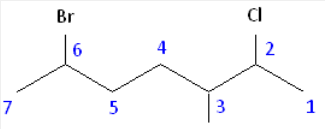
Rule #1: Choose the longest, most substituted carbon chain containing a functional group. This example contains two functional groups, bromine and chlorine, and one substitute, the methyl group. The longest carbon chain has been highlighted in red and consists of seven carbons.



Rule #2: Carbons bonded to a functional group must have the lowest possible carbon number. After taking functional groups into consideration, any substitutes present must have the lowest possible carbon number. This particular example illustrates the **point of difference principle**. If we number the chain from the left, bromine, the methyl group and chlorine would occupy the second, fifth and sixth positions, respectively. This concept is illustrated in the second drawing below. If we number the chain from the right, chlorine, the methyl group and bromine would occupy the second, third and sixth positions, respectively, which is illustrated in the first drawing below. The position of the methyl, therefore, becomes a **point of difference**. In the first drawing, the methyl occupies the third position. In the second drawing, the methyl occupies the fifth position. To satisfy the second rule, we want to choose the numbering scheme that provides the lowest possible numbering of this substitute. Therefore, the first of the two carbon chains shown below is correct.



Therefore, the first numbering scheme is the appropriate one to use.



Once you have determined the correct numbering of the carbons, it is often useful to make a list, including the functional groups, substitutes, and the name of the parent chain.

Rule #3: After applying the first two rules, take the alphabetical order into consideration. Alphabetically, bromine comes before chlorine. Therefore, bromine is assigned the second carbon position, and chlorine is assigned the sixth carbon position.

Parent chain: heptane 2-Chloro 3-Methyl 6-Bromo

Contributors

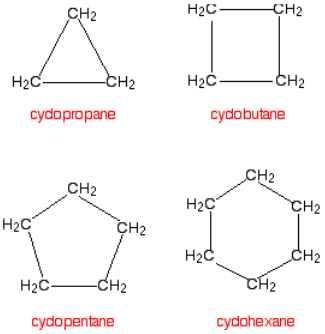
- Anonymous

4.5: Naming Cycloalkanes

Cycloalkanes are cyclic hydrocarbons, meaning that the carbons of the molecule are arranged in the form of a ring. Cycloalkanes are also saturated, meaning that all of the carbons atoms that make up the ring are single bonded to other atoms (no double or triple bonds). There are also polycyclic alkanes, which are molecules that contain two or more cycloalkanes that are joined, forming multiple rings.

Introduction

Many organic compounds found in nature or created in a laboratory contain rings of carbon atoms with distinguishing chemical properties; these compounds are known as cycloalkanes. Cycloalkanes only contain carbon-hydrogen bonds and carbon-carbon single bonds, but in cycloalkanes, the carbon atoms are joined in a ring. The smallest cycloalkane is cyclopropane.



If you count the carbons and hydrogens, you will see that they no longer fit the general formula C_nH_{2n+2}. By joining the carbon atoms in a ring,two hydrogen atoms have been lost. The general formula for a cycloalkane is C_nH_{2n}. Cyclic compounds are not all flat molecules. All of the cycloalkanes, from cyclopentane upwards, exist as "puckered rings". Cyclohexane, for example, has a ring structure that looks like this:

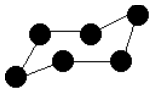
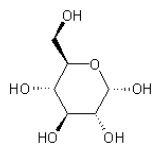
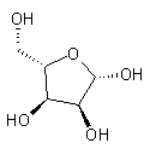
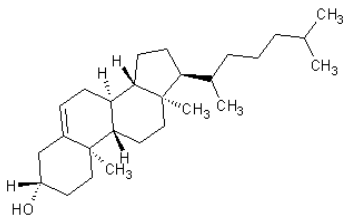


Figure 2: This is known as the "chair" form of cyclohexane from its shape, which vaguely resembles a chair. Note: The cyclohexane molecule is constantly changing, with the atom on the left, which is currently pointing down, flipping up, and the atom on the right flipping down. During this process, another (slightly less stable) form of cyclohexane is formed known as the "boat" form. In this arrangement, both of these atoms are either pointing up or down at the same time

In addition to being saturated cyclic hydrocarbons, cycloalkanes may have multiple substituents or functional groups that further determine their unique chemical properties. The most common and useful cycloalkanes in organic chemistry are cyclopentane and cyclohexane, although other cycloalkanes varying in the number of carbons can be synthesized. Understanding cycloalkanes and their properties are crucial in that many of the biological processes that occur in most living things have cycloalkane-like structures.

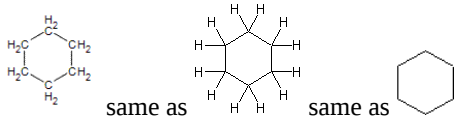
		
Glucose (6 carbon sugar)	Ribose (5 carbon sugar)	Cholesterol (polycyclic)

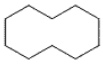
Although polycyclic compounds are important, they are highly complex and typically have common names accepted by IUPAC. However, the common names do not generally follow the basic IUPAC nomenclature rules. The general formula of the

cycloalkanes is C_nH_{2n} where n is the number of carbons. The naming of cycloalkanes follows a simple set of rules that are built upon the same basic steps in naming alkanes. Cyclic hydrocarbons have the prefix "cyclo-".

Contents

For simplicity, cycloalkane molecules can be drawn in the form of skeletal structures in which each intersection between two lines is assumed to have a carbon atom with its corresponding number of hydrogens.



Cycloalkane	Molecular Formula	Basic Structure
Cyclopropane	C_3H_6	
Cyclobutane	C_4H_8	
Cyclopentane	C_5H_{10}	
Cyclohexane	C_6H_{12}	
Cycloheptane	C_7H_{14}	
Cyclooctane	C_8H_{16}	
Cyclononane	C_9H_{18}	
Cyclodecane	$C_{10}H_{20}$	

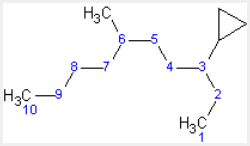
IUPAC Rules for Nomenclature

1. Determine the cycloalkane to use as the parent chain. The parent chain is the one with the highest number of carbon atoms. If there are two cycloalkanes, use the cycloalkane with the higher number of carbons as the parent chain.
2. If there is an alkyl straight chain that has a greater number of carbons than the cycloalkane, then the alkyl chain must be used as the primary parent chain. Cycloalkane acting as a substituent to an alkyl chain has an ending "-yl" and, therefore, must be named as a cycloalkyl.

Cycloalkane	Cycloalkyl
cyclopropane	cyclopropyl
cyclobutane	cyclobutyl
cyclopentane	cyclopentyl
cyclohexane	cyclohexyl
cycloheptane	cycloheptyl

cyclooctane	cyclooctyl
cyclononane	cyclononanyl
cyclodecane	cyclodecanyl

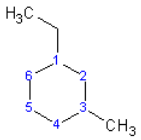
Example

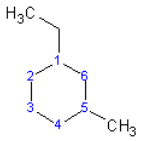


The longest straight chain contains 10 carbons, compared with cyclopropane, which only contains 3 carbons. Because cyclopropane is a substituent, it would be named a cyclopropyl-substituted alkane.

3) Determine any functional groups or other alkyl groups.

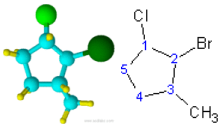
4) Number the carbons of the cycloalkane so that the carbons with functional groups or alkyl groups have the lowest possible number. A carbon with multiple substituents should have a lower number than a carbon with only one substituent or functional group. One way to make sure that the lowest number possible is assigned is to number the carbons so that when the numbers corresponding to the substituents are added, their sum is the lowest possible.



1-ethyl-3-methylcyclohexane (1+3=4) **NOT** 

1-ethyl-5-methylcyclohexane (1+5=6)

5) When naming the cycloalkane, the substituents and functional groups must be placed in alphabetical order.



(ex: 2-bromo-1-chloro-3-methylcyclopentane)

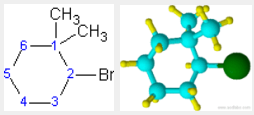
6) Indicate the carbon number with the functional group with the highest priority according to alphabetical order. A dash"-" must be placed between the numbers and the name of the substituent. After the carbon number and the dash, the name of the substituent can follow. When there is only one substituent on the parent chain, indicating the number of the carbon atoms with the substituent is not necessary.

(ex: 1-chlorocyclohexane or cholorocyclohexane is acceptable) 

7) If there is more than one of the same functional group on one carbon, write the number of the carbon two, three, or four times, depending on how many of the same functional group is present on that carbon. The numbers must be separated by commas, and the name of the functional group that follows must be separated by a dash. When there are two of the same functional group, the name must have the prefix "di". When there are three of the same functional group, the name must have the prefix "tri". When there are four of the same functional group, the name must have the prefix "tetra". However, these prefixes cannot be used when determining the alphabetical priorities.

There must always be commas between the numbers and the dashes that are between the numbers and the names.

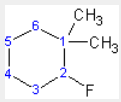
Example 2



(2-bromo-1,1-dimethylcyclohexane)

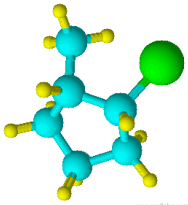
Notice that "f" of fluoro alphabetically precedes the "m" of methyl. Although "di" alphabetically precedes "f", it is not used in determining the alphabetical order.

Example 3



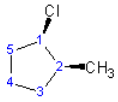
(2-fluoro-1,1,-dimethylcyclohexane **NOT** 1,1-dimethyl-2-fluorocyclohexane)

8) If the substituents of the cycloalkane are related by the cis or trans configuration, then indicate the configuration by placing "cis-" or "trans-" in front of the name of the structure.



Blue=Carbon Yellow=Hydrogen Green=Chlorine

Notice that chlorine and the methyl group are both pointed in the same direction on the axis of the molecule; therefore, they are cis.

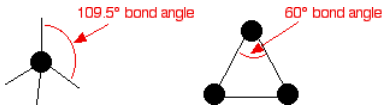


cis-1-chloro-2-methylcyclopentane

9) After all the functional groups and substituents have been mentioned with their corresponding numbers, the name of the cycloalkane can follow.

Reactivity

Cycloalkanes are very similar to the alkanes in reactivity, except for the very small ones, especially cyclopropane. Cyclopropane is significantly more reactive than what is expected because of the bond angles in the ring. Normally, when carbon forms four single bonds, the bond angles are approximately 109.5°. In cyclopropane, the bond angles are 60°.



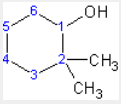
With the electron pairs this close together, there is a significant amount of repulsion between the bonding pairs joining the carbon atoms, making the bonds easier to break.

Alcohol Substituents on Cycloalkanes

Alcohol (-OH) substituents take the highest priority for carbon atom numbering in IUPAC nomenclature. The carbon atom with the alcohol substituent must be labeled as 1. Molecules containing an alcohol group have an ending "-ol", indicating the presence of an alcohol group. If there are two alcohol groups, the molecule will have a "di-" prefix before "-ol" (diol). If there are three alcohol groups, the molecule will have a "tri-" prefix before "-ol" (triol), etc.

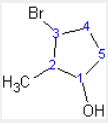
Example 4

The alcohol substituent is given the lowest number even though the two methyl groups are on the same carbon atom and labeling 1 on that carbon atom would give the lowest possible numbers. Numbering the location of the alcohol substituent is unnecessary because the ending "-ol" indicates the presence of one alcohol group on carbon atom number 1.



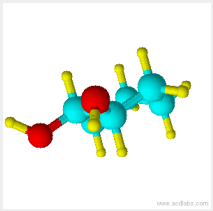
2,2-dimethylcyclohexanol **NOT** 1,1-dimethyl-cyclohexane-2-ol

Example 5

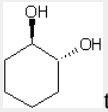


3-bromo-2-methylcyclopentanol **NOT** 1-bromo-2-methyl-cyclopentane-2-ol

Example 5



Blue=Carbon Yellow=Hydrogen Red=Oxygen



trans-cyclohexane-1,2-diol

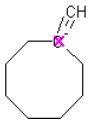
Other Substituents on Cycloalkanes

There are many other functional groups like alcohol, which are later covered in an organic chemistry course, and they determine the ending name of a molecule. The naming of these functional groups will be explained in depth later as their chemical properties are explained.

Name	Name ending
alkene	-ene
alkyne	-yne
alcohol	-ol
ether	-ether
nitrile	-nitrile
amine	-amine
aldehyde	-al
ketone	-one

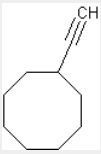
carboxylic acid	-oic acid
ester	-oate
amide	-amide

Although alkynes determine the name ending of a molecule, alkyne as a substituent on a cycloalkane is not possible because alkynes are planar and would require that the carbon that is part of the ring form 5 bonds, giving the carbon atom a negative charge.



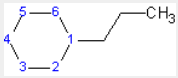
However, a cycloalkane with a triple bond-containing substituent is possible if the triple bond is not directly attached to the ring.

Example



ethynylcyclooctane

Example



1-propylcyclohexane

Summary

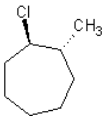
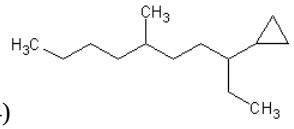
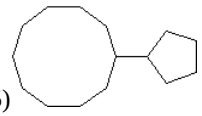
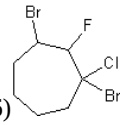
1. Determine the parent chain: the parent chain contains the most carbon atoms.
2. Number the substituents of the chain so that the sum of the numbers is the lowest possible.
3. Name the substituents and place them in alphabetical order.
4. If stereochemistry of the compound is shown, indicate the orientation as part of the nomenclature.
5. Cyclic hydrocarbons have the prefix "cyclo-" and have an "-alkane" ending unless there is an alcohol substituent present. When an alcohol substituent is present, the molecule has an "-ol" ending.

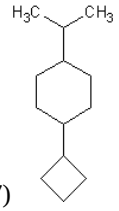
Glossary

- **alcohol**: An oxygen and hydrogenOH hydroxyl group that is bonded to a substituted alkyl group.
- **alkyl:** A structure that is formed when a hydrogen atom is removed from an alkane.
- **cyclic:** Chemical compounds arranged in the form of a ring or a closed chain form.
- **cycloalkanes:** Cyclic saturated hydrocarbons with a general formula of CnH(2n). Cycloalkanes are alkanes with carbon atoms attached in the form of a closed ring.
- **functional groups:** An atom or groups of atoms that substitute for a hydrogen atom in an organic compound, giving the compound unique chemical properties and determining its reactivity.
- **hydrocarbon:** A chemical compound containing only carbon and hydrogen atoms.
- **saturated**: All of the atoms that make up a compound are single bonded to the other atoms, with no double or triple bonds.
- **skeletal structure:** A simplified structure in which each intersection between two lines is assumed to have a carbon atom with its corresponding number of hydrogens.

Problems

Name the following structures. (Note: The structures are complex for practice purposes and may not be found in nature.)

1)  2)  3)  4)  5)  6) 

7) 

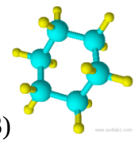
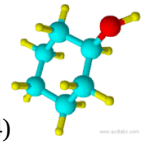
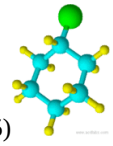
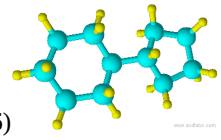
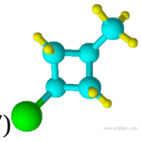
Draw the following structures.

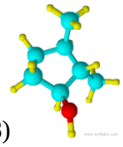
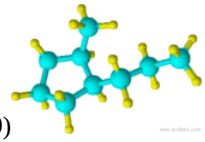
8) 1,1-dibromo-5-fluoro-3-butyl-7-methylcyclooctane 9) trans-1-bromo-2-chlorocyclopentane

10) 1,1-dibromo-2,3-dichloro-4-propylcyclobutane 11) 2-methyl-1-ethyl-1,3-dipropylcyclopentane 12) cycloheptane-1,3,5-triol

Name the following structures.

Blue=Carbon Yellow=Hydrogen Red=Oxygen Green=Chlorine

13)  14)  15)  16)  17) 

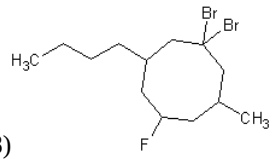
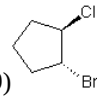
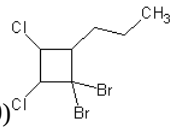
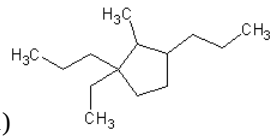
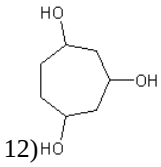
18)  19) 

Answers to Practice Problems

1) cyclodecane 2) chlorocyclopentane or 1-chlorocyclopentane 3) trans-1-chloro-2-methylcycloheptane

4) 3-cyclopropyl-6-methyldecane 5) cyclopentylcyclodecane or 1-cyclopentylcyclodecane 6) 1,3-dibromo-1-chloro-2-fluorocycloheptane

7) 1-cyclobutyl-4-isopropylcyclohexane

8)  9)  10)  11)  12) 

13) cyclohexane 14) cyclohexanol 15) chlorocyclohexane 16) cyclopentylcyclohexane 17) 1-chloro-3-methylcyclobutane

18) 2,3-dimethylcyclohexanol 19) cis-1-propyl-2-methylcyclopentane

Inside Links

- Nomenclature of Alcohols
- Nomenclature of Ethers
- Nomenclature of Esters
- Nomenclature of Alkenes
- Nomenclature of Ketones and Aldehydes
- Nomenclature of Alkynes

Outside links

- More Practice Problems on Nomenclature of Cycloalkanes
- Vollhardt, Schore. Organic Chemistry. 5th ed.
- Wikipedia: Cycloalkanes
- http://www.cem.msu.edu/~reusch/VirtualText/nomen1.htm
- http://www.chemguide.co.uk/organicprops/alkanes/background.html
- http://www.cem.msu.edu/~reusch/VirtualText/nomen1.htm
- http://science.csustan.edu/nhuy/chem...IVNamecyal.htm
- http://en.wikibooks.org/wiki/Organic...s/Cycloalkanes

References

1. ACD/ChemSketch Freeware, version 11.0, Advanced Chemistry Development, Inc., Toronto, ON, Canada, www.acdlabs.com, 2008.
2. Bruice, Paula Yurkanis. Oragnic Chemistry. 5th. CA. Prentice Hall, 2006.
3. Fryhle, C.B. and G. Solomons. Organic Chemistry. 9th ed. Danvers, MA: Wiley, 2008.
4. McMurry, John. Organic Chemistry. 7th ed. Belmont, California: Thomson Higher Education, 2008.
5. Sadava, Heller, Orians, Purves, Hillis. Life The Science of Biology. 8th ed. Sunderland, MA: W.H. Freeman, 2008.
6. Vollhardt, K. Peter C., and Neil E. Schore. Organic Chemistry. 5th ed. New York: W.H. Freeman, 2007.

Contributors

- Pwint Zin
- Jim Clark (ChemGuide)

4.6: Common Names

Using Common Names with Branched Alkanes

Certain branched alkanes have common names that are still widely used today. These common names make use of prefixes, such as ***iso***-, ***sec***-, ***tert***-, and ***neo***-. The prefix ***iso***-, which stands for isomer, is commonly given to 2-methyl alkanes. In other words, if there is methyl group located on the second carbon of a carbon chain, we can use the prefix ***iso***-. The prefix will be placed in front of the alkane name that indicates the *total* number of carbons. Examples:

- isopentane which is the same as 2-methylbutane
- isobutane which is the same as 2-methylpropane

To assign the prefixes ***sec***-, which stands for secondary, and ***tert***-, for tertiary, it is important that we first learn how to classify carbon molecules. If a carbon is attached to only one other carbon, it is called a **primary** carbon. If a carbon is attached to two other carbons, it is called a **seconday** carbon. A **tertiary** carbon is attached to three other carbons and last, a **quaternary** carbon is attached to four other carbons. Examples:

- 4-*sec*-butylheptane (30g)
- 4-*tert*-butyl-5-isopropylhexane (30d); if using this example, may want to move sec/tert after iso disc

The prefix ***neo***- refers to a substituent whose second-to-last carbon of the chain is trisubstituted (has three methyl groups attached to it). A neo-pentyl has five carbons total. Examples:

- neopentane
- neoheptane

4.7: Fossil Fuels

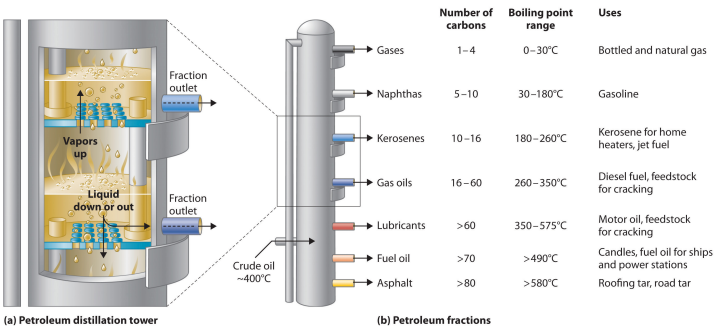
Petroleum

The petroleum that is pumped out of the ground at locations around the world is a complex mixture of several thousand organic compounds, including straight-chain alkanes, cycloalkanes, alkenes, and aromatic hydrocarbons with four to several hundred carbon atoms. The identities and relative abundances of the components vary depending on the source. So Texas crude oil is somewhat different from Saudi Arabian crude oil. In fact, the analysis of petroleum from different deposits can produce a "fingerprint" of each, which is useful in tracking down the sources of spilled crude oil. For example, Texas crude oil is "sweet," meaning that it contains a small amount of sulfur-containing molecules, whereas Saudi Arabian crude oil is "sour," meaning that it contains a relatively large amount of sulfur-containing molecules.

Gasoline

Petroleum is converted to useful products such as gasoline in three steps: distillation, cracking, and reforming. Recall from Chapter 1 "Introduction to Chemistry" that distillation separates compounds on the basis of their relative volatility, which is usually inversely proportional to their boiling points. Part (a) in Figure 2.23 "The Distillation of Petroleum" shows a cutaway drawing of a column used in the petroleum industry for separating the components of crude oil. The petroleum is heated to approximately 400°C (750°F), at which temperature it has become a mixture of liquid and vapor. This mixture, called the feedstock, is introduced into the refining tower. The most volatile components (those with the lowest boiling points) condense at the top of the column where it is cooler, while the less volatile components condense nearer the bottom. Some materials are so nonvolatile that they collect at the bottom without evaporating at all. Thus the composition of the liquid condensing at each level is different. These different fractions, each of which usually consists of a mixture of compounds with similar numbers of carbon atoms, are drawn off separately. Part (b) in Figure 2.23 "The Distillation of Petroleum" shows the typical fractions collected at refineries, the number of carbon atoms they contain, their boiling points, and their ultimate uses. These products range from gases used in natural and bottled gas to liquids used in fuels and lubricants to gummy solids used as tar on roads and roofs.

Figure 2.23 The Distillation of Petroleum



(a) This is a diagram of a distillation column used for separating petroleum fractions. (b) Petroleum fractions condense at different temperatures, depending on the number of carbon atoms in the molecules, and are drawn off from the column. The most volatile components (those with the lowest boiling points) condense at the top of the column, and the least volatile (those with the highest boiling points) condense at the bottom.

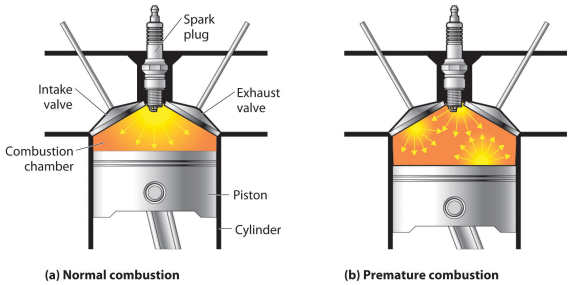
The economics of petroleum refining are complex. For example, the market demand for kerosene and lubricants is much lower than the demand for gasoline, yet all three fractions are obtained from the distillation column in comparable amounts. Furthermore, most gasolines and jet fuels are blends with very carefully controlled compositions that cannot vary as their original feedstocks did. To make petroleum refining more profitable, the less volatile, lower-value fractions must be converted to more volatile, higher-value mixtures that have carefully controlled formulas. The first process used to accomplish this transformation is cracking, in which the larger and heavier hydrocarbons in the kerosene and higher-boiling-point fractions are heated to temperatures as high as 900°C. High-temperature reactions cause the carbon–carbon bonds to break, which converts the compounds to lighter molecules similar to those in the gasoline fraction. Thus in cracking, a straight-chain alkane with a number of carbon atoms corresponding to the kerosene fraction is converted to a mixture of hydrocarbons with a number of carbon atoms corresponding to the lighter gasoline fraction. The second process used to increase the amount of valuable products is called reforming; it is the chemical conversion of straight-chain alkanes to either branched-chain alkanes or mixtures of aromatic hydrocarbons. Using metals such as platinum

brings about the necessary chemical reactions. The mixtures of products obtained from cracking and reforming are separated by fractional distillation.

Octane Ratings

The quality of a fuel is indicated by its octane rating, which is a measure of its ability to burn in a combustion engine without knocking or pinging. Knocking and pinging signal premature combustion (Figure 2.24 "The Burning of Gasoline in an Internal Combustion Engine"), which can be caused either by an engine malfunction or by a fuel that burns too fast. In either case, the gasoline-air mixture detonates at the wrong point in the engine cycle, which reduces the power output and can damage valves, pistons, bearings, and other engine components. The various gasoline formulations are designed to provide the mix of hydrocarbons least likely to cause knocking or pinging in a given type of engine performing at a particular level.

Figure 2.24 The Burning of Gasoline in an Internal Combustion Engine



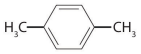
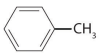
(a) Normally, fuel is ignited by the spark plug, and combustion spreads uniformly outward. (b) Gasoline with an octane rating that is too low for the engine can ignite prematurely, resulting in uneven burning that causes knocking and pinging.

The octane scale was established in 1927 using a standard test engine and two pure compounds: n-heptane and isooctane (2,2,4-trimethylpentane). n-Heptane, which causes a great deal of knocking on combustion, was assigned an octane rating of 0, whereas isooctane, a very smooth-burning fuel, was assigned an octane rating of 100. Chemists assign octane ratings to different blends of gasoline by burning a sample of each in a test engine and comparing the observed knocking with the amount of knocking caused by specific mixtures of n-heptane and isooctane. For example, the octane rating of a blend of 89% isooctane and 11% n-heptane is simply the average of the octane ratings of the components weighted by the relative amounts of each in the blend. Converting percentages to decimals, we obtain the octane rating of the mixture:

A gasoline that performs at the same level as a blend of 89% isooctane and 11% n-heptane is assigned an octane rating of 89; this represents an intermediate grade of gasoline. Regular gasoline typically has an octane rating of 87; premium has a rating of 93 or higher.

As shown in Figure 2.25 "The Octane Ratings of Some Hydrocarbons and Common Additives", many compounds that are now available have octane ratings greater than 100, which means they are better fuels than pure isooctane. In addition, antiknock agents, also called octane enhancers, have been developed. One of the most widely used for many years was tetraethyllead [$(C_2H_5)_4Pb$], which at approximately 3 g/gal gives a 10–15-point increase in octane rating. Since 1975, however, lead compounds have been phased out as gasoline additives because they are highly toxic. Other enhancers, such as methyl t-butyl ether (MTBE), have been developed to take their place. They combine a high octane rating with minimal corrosion to engine and fuel system parts. Unfortunately, when gasoline containing MTBE leaks from underground storage tanks, the result has been contamination of the groundwater in some locations, resulting in limitations or outright bans on the use of MTBE in certain areas. As a result, the use of alternative octane enhancers such as ethanol, which can be obtained from renewable resources such as corn, sugar cane, and, eventually, corn stalks and grasses, is increasing.

Figure 2.25 The Octane Ratings of Some Hydrocarbons and Common Additives

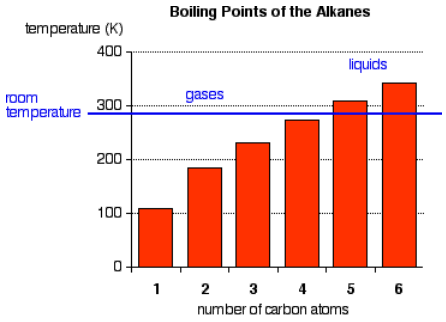
Name	Condensed Structural Formula	Octane Rating	Name	Condensed Structural Formula	Octane Rating
n-heptane	$CH_3CH_2CH_2CH_2CH_2CH_2CH_3$	0	*o*-xylene		107
n-hexane	$CH_3CH_2CH_2CH_2CH_2CH_3$	25	ethanol	CH_3CH_2OH	108
n-pentane	$CH_3CH_2CH_2CH_2CH_3$	62	*t*-butyl alcohol	$(CH_3)_3COH$	113
isooctane	$(CH_3)_3CCH_2CH(CH_3)_2$	100	*p*-xylene		116
benzene		106	methyl *t*-butyl ether	$H_3COC(CH_3)_3$	116
methanol	CH_3OH	107	toluene		118

4.8: Physical Properties of Alkanes

Alkanes are not very reactive and have little biological activity; all alkanes are colorless and odorless.

Boiling Points

The boiling points shown are for the "straight chain" isomers of which there is more than one. The first four alkanes are gases at room temperature, and solids do not begin to appear until about $C_{17}H_{36}$, but this is imprecise because different isomers typically have different melting and boiling points. By the time you get 17 carbons into an alkane, there are unbelievable numbers of isomers!



Cycloalkanes have boiling points that are approximately 20 K higher than the corresponding straight chain alkane.

There is not a significant electronegativity difference between carbon and hydrogen, thus, there is not any significant bond polarity. The molecules themselves also have very little polarity. A totally symmetrical molecule like methane is completely non-polar, meaning that the only attractions between one molecule and its neighbors will be Van der Waals dispersion forces. These forces will be very small for a molecule like methane but will increase as the molecules get bigger. Therefore, the boiling points of the alkanes increase with molecular size.

Where you have isomers, the more branched the chain, the lower the boiling point tends to be. Van der Waals dispersion forces are smaller for shorter molecules and only operate over very short distances between one molecule and its neighbors. It is more difficult for short, fat molecules (with lots of branching) to lie as close together as long, thin molecules.

Example

For example, the boiling points of the three isomers of C_5H_{12} are:

- pentane: 309.2 K
- 2-methylbutane: 301.0 K
- 2,2-dimethylpropane: 282.6 K

The slightly higher boiling points for the cycloalkanes are presumably because the molecules can get closer together because the ring structure makes them tidier and less "wriggly"!

Solubility

Alkanes (both alkanes and cycloalkanes) are virtually insoluble in water, but dissolve in organic solvents. However, liquid alkanes are good solvents for many other non-ionic organic compounds.

Solubility in Water

When a molecular substance dissolves in water, the following must occur:

- break the intermolecular forces within the substance. In the case of the alkanes, these are the Van der Waals dispersion forces.
- break the intermolecular forces in the water so that the substance can fit between the water molecules. In water, the primary intermolecular attractions are hydrogen bonds.

Breaking either of these attractions requires energy, although the amount of energy to break the Van der Waals dispersion forces in something like methane is relatively negligible; this is not true of the hydrogen bonds in water.

As something of a simplification, a substance will dissolve if there is enough energy released when new bonds are made between the substance and the water to compensate for what is used in breaking the original attractions. The only new attractions between the alkane and the water molecules are Van der Waals forces. These forces do not release a sufficient amount of energy to compensate for the energy required to break the hydrogen bonds in water. The alkane does not dissolve.

Note: This is a simplification because entropic effects are important when things dissolve.

Solubility in organic solvents

In most organic solvents, the primary forces of attraction between the solvent molecules are Van der Waals - either dispersion forces or dipole-dipole attractions. Therefore, when an alkane dissolves in an organic solvent, the Van der Waals forces are broken and are replaced by new Van der Waals forces. The two processes more or less cancel each other out energetically; thus, there is no barrier to solubility.

Contributors

Jim Clark (Chemguide.co.uk)

4.9: Conformations of Butane

Now let us consider butane, a slightly larger molecule. There are now three rotating carbon-carbon bonds to consider, but we will focus on the middle bond between C_2 and C_3. Below are two representations of butane in a conformation which puts the two CH_3 groups (C_1 and C_4) in the eclipsed position.

eclipsed (A)

This is the highest energy conformation for butane, due to what is called '**van der Waals repulsion**', or '**steric repulsion'**, between the two rather bulky methyl groups.

What is van der Waals repulsion? Didn't we just learn in Chapter 2 that the van der Waals force between two nonpolar groups is an *attractive* force? Consider this: you probably like to be near your friends, but no matter how close you are you probably don't want to share a one-room apartment with five of them. When the two methyl groups are brought too close together, the overall resulting noncovalent interaction is repulsive rather than attractive. The result is that their respective electron densities repel one another.

If we rotate the front, (blue) carbon by 60°clockwise, the butane molecule is now in a staggered conformation.

gauche

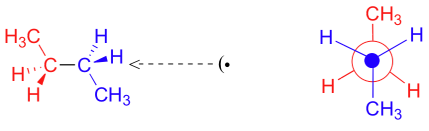
This is more specifically referred to as the '**gauche'** conformation of butane. Notice that although they are staggered, the two methyl groups are not as far apart as they could possibly be. There is still significant steric repulsion between the two bulky groups.

A further rotation of 60°gives us a second eclipsed conformation (B) in which both methyl groups are lined up with hydrogen atoms.

eclipsed (B)

Due to steric repulsion between methyl and hydrogen substituents, this eclipsed conformation B is higher in energy than the gauche conformation. However, because there is no methyl-to-methyl eclipsing, it is lower in energy than eclipsed conformation A.

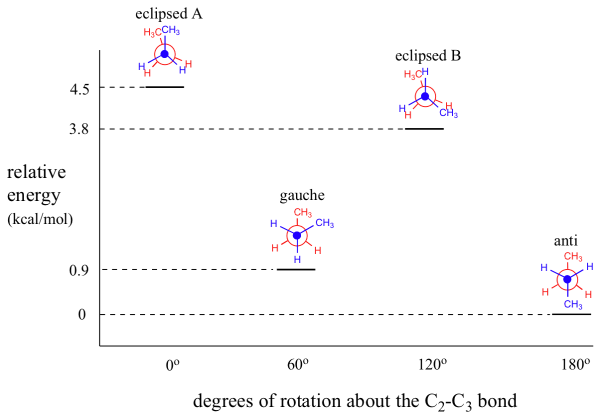
One more 60 rotation produces the 'anti' conformation, where the two methyl groups are positioned opposite each other and steric repulsion is minimized.



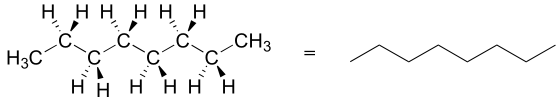
anti

This is the lowest energy conformation for butane.

The diagram below summarizes the relative energies for the various eclipsed, staggered, and gauche conformations.



At room temperature, butane is most likely to be in the lowest-energy anti conformation at any given moment in time, although the energy barrier between the anti and eclipsed conformations is not high enough to prevent constant rotation except at very low temperatures. For this reason (and also simply for ease of drawing), it is conventional to draw straight-chain alkanes in a zigzag form, which implies anti conformation at all carbon-carbon bonds.

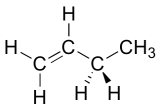


octane

Template:ExampleStart

Exercise 3.1: Draw Newman projections of the eclipsed and staggered conformations of propane.

Exercise 3.2: Draw a Newman projection, looking down the C_2-C_3 bond, of 1-butene in the conformation shown below.



Solutions
Template:ExampleEnd

The following diagram illustrates the change in potential energy that occurs with rotation about the C_2–C_3 bond.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

4.10: An Introduction to Cycloalkanes

Cycloalkanes have one or more rings of carbon atoms. The simplest examples of this class consist of a single, unsubstituted carbon ring, and these form a homologous series similar to the unbranched alkanes. The IUPAC names of the first five members of this series are given in the following table. The last (yellow shaded) column gives the general formula for a cycloalkane of any size. If a simple unbranched alkane is converted to a cycloalkane two hydrogen atoms, one from each end of the chain, must be lost. Hence the general formula for a cycloalkane composed of **n** carbons is $\mathbf{C_nH_{2n}}$. Although a cycloalkane has two fewer hydrogens than the equivalent alkane, each carbon is bonded to four other atoms so such compounds are still considered to be **saturated** with hydrogen.

Table 4.11.1: Examples of Simple Cycloalkanes

Name	Cyclopropane	Cyclobutane	Cyclopentane	Cyclohexane	Cycloheptane	Cycloalkane
Molecular Formula	C_3H_6	C_4H_8	C_5H_{10}	C_6H_{12}	C_7H_{14}	C_nH_{2n}
Structural Formula						$(CH_2)_n$
Line Formula						

The Baeyer Theory on the Strain in Cycloalkane Rings

Many of the properties of cyclopropane and its derivatives are similar to the properties of alkenes. In 1890, the famous German organic chemist, A. Baeyer, suggested that cyclopropane and cyclobutane derivatives are different from cyclopentane and cyclohexane, because their C—C—C angles cannot have the tetrahedral value of 109.5°. At the same time, Baeyer hypothesized that the difficulties encountered in synthesizing cycloalkane rings from C7 upward was the result of the angle strain that would be expected if the large rings were regular planar polygons (see Table 12-3). Baeyer also believed that cyclohexane had a planar structure like that shown in Figure 12-2, which would mean that the bond angles would have to deviate 10.5° from the tetrahedral value. However, in 1895, the then unknown chemist H. Sachse suggested that cyclohexane exists in the strain-free chair and boat forms discussed in Section 12-3. This suggestion was not accepted at the time because it led to the prediction of several possible isomers for compounds such as chlorocyclohexane (cf. Exercise 12-4). The idea that such isomers might act as a single substance, as the result of rapid equilibration, seemed like a needless complication, and it was not until 1918 that E. Mohr proposed a definitive way to distinguish between the Baeyer and Sachse cyclohexanes. As will be discussed in Section 12-9, the result, now known as the Sachse-Mohr theory, was complete confirmation of the idea of nonplanar large rings.

Table 12-3: Strain in Cycloalkane Rings and Heats of Combustion of Cycloalkanes

Compound		Angle Strain at each	Heat of Combustion (kcal/mol)	Heat of Combustion per (kcal/mol)	Total Strain (kcal/mol)
ethene	2	109.5	337.2	168.6	22.4
cyclopropane	3	49.5	499.9	166.6	27.7
cyclobutane	4	19.5	655.9	164.0	26.3
cyclopentane	5	1.5	793.4	158.7	6.5
cyclohexane	6	10.5	944.8	157.5	0.4
cycloheptane	7	19.1	1108.1	158.4	6.3

cyclooctane	8	25.5	1268.9	158.6	9.7
cyclononane	9	30.5	1429.5	158.8	12.9
cyclodecane	10	34.5	1586.1	158.6	12.1
cyclopentadecane	15	46.5	2362.5	157.5	1.5
open chain alkane				157.4	-

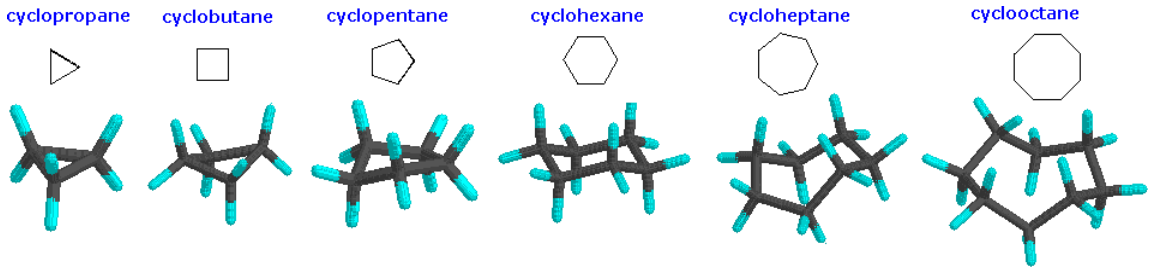
One of the most interesting developments in ‘the stereochemistry of organic compounds in recent years has been the demonstration that transcyclooctene (but not the cis isomer) can be resolved into stable chiral isomers (enantiomers, Section 5-IB). In general, a trans-cycloalkene would not be expected to be resolvable because of the possibility for formation of achiral conformations with a plane of symmetry. Any conformation with all of the carbons in a plane is such an achiral conformation (Figure 12-20a). However, when the chain connecting the ends of the double bond is short, as in trans-cyclooctene, steric hindrance and steric strain prevent easy.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

4.11: Cyclohexane

Although the customary line drawings of simple cycloalkanes are geometrical polygons, the actual shape of these compounds in most cases is very different.

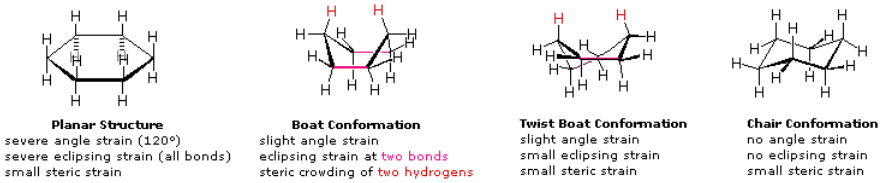


Cyclopropane is necessarily planar (flat), with the carbon atoms at the corners of an equilateral triangle. The 60º bond angles are much smaller than the optimum 109.5º angles of a normal tetrahedral carbon atom, and the resulting angle strain dramatically influences the chemical behavior of this cycloalkane. Cyclopropane also suffers substantial eclipsing strain, since all the carbon-carbon bonds are fully eclipsed. Cyclobutane reduces some bond-eclipsing strain by folding (the out-of-plane dihedral angle is about 25º), but the total eclipsing and angle strain remains high. Cyclopentane has very little angle strain (the angles of a pentagon are 108º), but its eclipsing strain would be large (about 10 kcal/mol) if it remained planar. Consequently, the five-membered ring adopts non-planar puckered conformations whenever possible.

Rings larger than cyclopentane would have angle strain if they were planar. However, this strain, together with the eclipsing strain inherent in a planar structure, can be relieved by puckering the ring. Cyclohexane is a good example of a carbocyclic system that virtually eliminates eclipsing and angle strain by adopting non-planar conformations. Cycloheptane and cyclooctane have greater strain than cyclohexane, in large part due to transannular crowding (steric hindrance by groups on opposite sides of the ring).

Conformations of Cyclohexane

A planar structure for cyclohexane is clearly improbable. The bond angles would necessarily be 120º, 10.5º larger than the ideal tetrahedral angle. Also, every carbon-carbon bond in such a structure would be eclipsed. The resulting angle and eclipsing strains would severely destabilize this structure. If two carbon atoms on opposite sides of the six-membered ring are lifted out of the plane of the ring, much of the angle strain can be eliminated.



Planar Structure
severe angle strain (120°)
severe eclipsing strain (all bonds)
small steric strain

Boat Conformation
slight angle strain
eclipsing strain at two bonds
steric crowding of two hydrogens

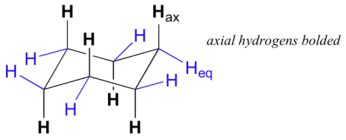
Twist Boat Conformation
slight angle strain
small eclipsing strain
small steric strain

Chair Conformation
no angle strain
no eclipsing strain
small steric strain

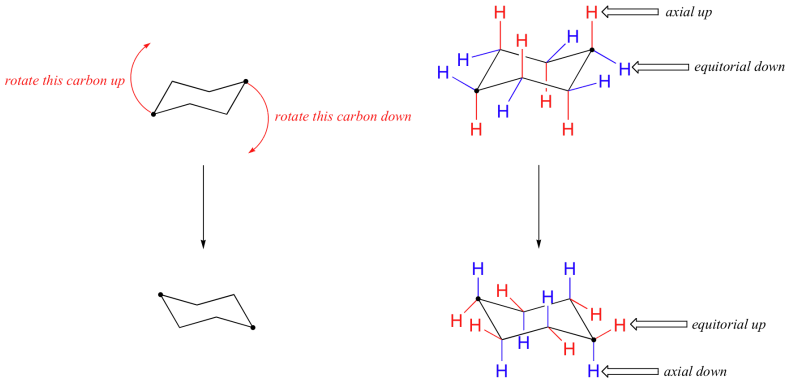
This boat structure still has two eclipsed bonds and severe steric crowding of two hydrogen atoms on the "bow" and "stern" of the boat. This steric crowding is often called steric hindrance. By twisting the boat conformation, the steric hindrance can be partially relieved, but the twist-boat conformer still retains some of the strains that characterize the boat conformer. Finally, by lifting one carbon above the ring plane and the other below the plane, a relatively strain-free 'chair' conformer is formed. This is the predominant structure adopted by molecules of cyclohexane.

Investigations concerning the conformations of cyclohexane were initiated by H. Sachse (1890) and E. Mohr (1918), but it was not until 1950 that a full treatment of the manifold consequences of interconverting chair conformers and the different orientations of pendent bonds was elucidated by D. H. R. Barton (Nobel Prize 1969 together with O. Hassel). The following discussion presents some of the essential features of this conformational analysis.

On careful examination of a chair conformation of cyclohexane, we find that the twelve hydrogens are not structurally equivalent. Six of them are located about the periphery of the carbon ring, and are termed equatorial. The other six are oriented above and below the approximate plane of the ring (three in each location), and are termed axial because they are aligned parallel to the symmetry axis of the ring.



In the figure above, the equatorial hydrogens are colored blue, and the axial hydrogens are in bold. Since there are two equivalent chair conformations of cyclohexane in rapid equilibrium, all twelve hydrogens have 50% equatorial and 50% axial character. The figure below illustrates how to convert a molecular model of cyclohexane between two different chair conformations - this is something that you should practice with models. Notice that a 'ring flip' causes equatorial hydrogens to become axial, and vice-versa.



How to draw stereo bonds ("up" and "down" bonds)

There are various ways to show these orientations. The solid (dark) "up wedge" I used is certainly common. Some people use an analogous "down wedge", which is light, to indicate a down bond; unfortunately, there is no agreement as to which way the wedge should point, and you are left relying on the lightness of the wedge to know it is "down". The "down bond" avoids this wedge ambiguity, and just uses some kind of light line. The down bond I used (e.g., in Figure 5B) is a dashed line; IUPAC encourages a series of parallel lines, something like A down bond of the type IUPAC prefers. It is a series of parallel lines.. What I did is a variation of what is recommended by IUPAC: http://www.chem.qmul.ac.uk/iupac/stereo/intro.html.

> *In **ISIS/Draw**, the "up wedge" and "down bond" that I used, along with other variations, are available from a tool button that may be labeled with any of them, depending on most recent use. It is located directly below the tool button for ordinary C-C bonds.*
>
> *In **Symyx Draw**, the "up wedge" and "down bond", along with other variations, are available from a tool button that may be labeled with any of them, depending on most recent use. It is located directly below the "Chain" tool button.*
>
> ***ChemSketch** provides up and down wedges, but not the simple up and down bonds discussed above. The wedges are available from the second toolbar across the top. For an expanded discussion of using these wedges, see the section of my ChemSketch Guide on Stereochemistry: Wedge bonds.*
>
> *As always, the information provided on these pages in intended to help you get started. Each program has more options for drawing bonds than discussed here. When you feel the need, look around!*

How to draw chairs

Most of the structures shown on this page were drawn with the free program **ISIS/Draw**. I have posted a guide to help you get started with ISIS/Draw. ISIS/Draw provides a simple cyclohexane (6-ring) hexagon template on the toolbar across the top. It provides templates for various 6-ring chair structures from the Templates menu; choose Rings. There are templates for simple

chairs, without substituents (e.g., Fig 1B), and for chairs showing all the substituents (e.g., Fig 2B). In either case, you can add, delete, or change things as you wish. Various kinds of stereo bonds (wedges and bars) are available by clicking the left-side tool button that is just below the regular C-C single bond button. It may have a wedge shown on it, but this will vary depending on how it has been used. To choose a type of stereo bond, click on the button and hold the mouse click; a new menu will appear to the right of the button.

The free drawing program **Symyx Draw**, the successor to ISIS/Draw, provides similar templates and tools. A basic chair structure is provided on the default template bar that is shown. More options are available by choosing the Rings template. See my page Symyx Draw for a general guide for getting started with this program.

The free drawing program **ChemSketch** provides similar templates and tools. To find the special templates for chairs, go to the **Templates** menu, choose **Template Window**, and then choose "Rings" from the drop-down menu near upper left. See my page ChemSketch for a general guide for getting started with this program.

If you want to draw chair structures by hand (and if you are going on in organic chemistry, you should)... Be careful. The precise zigs and zags, and the angles of substituents are all important. Your textbook may offer you some hints for how to draw chairs. A short item in the Journal of Chemical Education offers a nice trick, showing how the chair can be thought of as consisting of an M and a W. The article is V Dragojlovic, A method for drawing the cyclohexane ring and its substituents. J Chem Educ 78:923, 7/01. (I thank M Farooq Wahab, Chemistry, Univ Karachi, for suggesting that this article be noted here.)

Aside from drawing the basic chair, the key points in adding substituents are:

- Axial groups alternate up and down, and are shown "vertical".
- Equatorial groups are approximately horizontal, but actually somewhat distorted from that, so that the angle from the axial group is a bit more than a right angle -- reflecting the common 109 degree bond angle.
- As cautioned before, it is usually easier to draw and see what is happening at the four corners of the chair than at the two middle positions. Try to use the corners as much as possible.

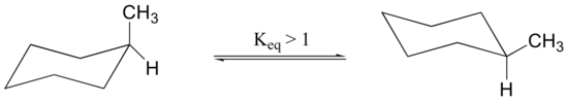
Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

---

4.12: Substituted Cycloalkanes

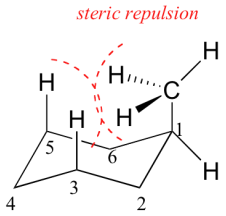
Because axial bonds are parallel to each other, substituents larger than hydrogen generally suffer greater steric crowding when they are oriented axial rather than equatorial. Consequently, ***substituted cyclohexanes will preferentially adopt conformations in which the larger substituents assume equatorial orientation***.



methyl group axial

methyl group equitorial (more stable)

When the methyl group in the structure above occupies an axial position it suffers steric crowding by the two axial hydrogens located on the same side of the ring.



The conformation in which the methyl group is equatorial is more stable, and thus the equilibrium lies in this direction.

The relative steric hindrance experienced by different substituent groups oriented in an axial versus equatorial location on cyclohexane may be determined by the conformational equilibrium of the compound. The corresponding equilibrium constant is related to the energy difference between the conformers, and collecting such data allows us to evaluate the relative tendency of substituents to exist in an equatorial or axial location.A table of these free energy values (sometimes referred to as A values) may be examined by clicking here.

Looking at the energy values in this table, it is clear that the apparent "size" of a substituent (in terms of its preference for equatorial over axial orientation) is influenced by its width and bond length to cyclohexane, as evidenced by the fact that an axial vinyl group is less hindered than ethyl, and iodine slightly less than chlorine.

We noted earlier that cycloalkanes having two or more substituents on different ring carbon atoms exist as a pair (sometimes more) of configurational stereoisomers. Now we must examine the way in which favorable ring conformations influence the properties of the configurational isomers. Remember, configurational stereoisomers are stable and do not easily interconvert, whereas, conformational isomers normally interconvert rapidly. In examining possible structures for substituted cyclohexanes, it is useful to follow two principles:

(i) Chair conformations are generally more stable than other possibilities.

(ii) Substituents on chair conformers prefer to occupy equatorial positions due to the increased steric hindrance of axial locations.

A Selection of AG° Values for the Change from Axial to Equatorial Orientation of Substituents for Monosubstituted Cyclohexanes

Substituent	$-\Delta G^o$ kcal/mol	Substituent	$-\Delta G^o$ kcal/mol
CH_3-	1.7	O_2N-	1.1
CH_2H_5-	1.8	$N\equiv C-$	0.2
$(CH_3)_2CH-$	2.2	CH_3O-	0.5
$(CH_3)_3C-$	≥ 5.0	HO_2C-	0.7
$F-$	0.3	$H_2C=CH-$	1.3
$Cl-$	0.5	C_6H_5-	3.0

Br^-	0.5		
I^-	0.5		

Chlorocyclohexane

This is an example of the next level of complexity, a mono-substituted cycloalkane. See Fig 3.

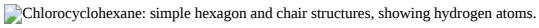


Figure 3

So what is new here? Not much, with the hexagon formula, Fig 3A. That type of formula shows the basic "connectivity" of the atoms -- who is connected to whom. This chemical has one Cl on the ring, and it does not matter where we show it. There is now only one H on that C, but since we are not showing H explicitly here, that is not an issue in drawing the structure. (It is an issue when you look at it and want to count H.)

With the chair formula (Fig 3B), which shows information not only about connectivity but also about conformation, there is important new information here. In a chair, there are two "types" of substituents: those pointing up or down, and called axial, and those pointing "outward", and called equatorial. I have shown the chlorine atom in an equatorial position. Why? Two reasons: it is what we would predict, and it is what is found. Why do we predict that the Cl is equatorial? Because it is bigger than H, and there is more room in the equatorial positions.

Helpful Hints...

If possible, examine a physical model of cyclohexane and chlorocyclohexane, so that you can see the axial and equatorial positions. Common ball and stick models are fine for this. It should be easy to see that the three axial H on one side can get very near each other.

If you do not have access to physical models, examining computer models can also be useful. See my RasMol page for a program and source of structures for this.

When putting substituents on chair structures, I encourage you to use the four corner positions of the chair as much as possible. It is easier to see the axial and equatorial relationship at the corners.

In Fig 3B I have shown the H atom that is on the same carbon as the Cl atom. This is perhaps not necessary, since the correct number of H atoms is understood, by counting bonds on C. But showing the H explicitly at key C atoms helps to make the structure clearer. This may be particularly important with hand-drawn structures. I often see structures where I am not sure whether a particular atom is shown axial or equatorial. But if both atoms at the position (the H as well as the Cl) are shown, then hopefully it becomes clearer which is which. I also encourage students who are not sure of their art work to annotate their drawing. Say what you mean. That allows me to distinguish whether you are unsure which direction things point or simply unsure how to draw them.)

> *Again, a reminder... For notes on how to draw chairs (by hand or using a drawing program), see the section E.2. Note: How to draw chairs.*

Dichlorocyclohexanes: an introduction

The next level of complexity is a di-substituted cycloalkane, "dichlorocyclohexane". The first question we must ask is which C the two chlorine substituents are on. For now, I want to discuss 1,3- dichlorocyclohexane. This introduces another issue: are the two Cl on the same side of the ring, or on opposite sides? We call these "cis" (same side) and "trans" (opposite sides). We focus on one of these, cis-1,3-dichlorocyclohexane. And for now, we will just look at hexagon structural formulas, leaving the question of conformation for later. Let's go through this one step at a time.

1,3-Dichlorocyclohexane

Our first attempt to draw 1,3-dichlorocyclohexane might look something like Fig 4.

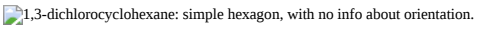


Figure 4

The structure in Fig 4 is indeed a dichlorocyclohexane. It is even a 1,3-dichlorocyclohexane. However, this structure provides no information about the orientation of the two Cl atoms relative to the plane of the ring. To show a specific isomer -- cis or trans -- we must somehow show how the two Cl atoms are oriented relative to the plane of the ring.

cis-1,3-Dichlorocyclohexane

Fig 5 shows two common ways to show how the substituents are oriented relative to the plane of the ring. The compound shown here is cis-1,3-dichlorocyclohexane.

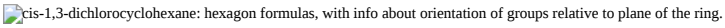


Figure 5

The basic idea in both of these is that we can imagine the ring to be planar, and then show the groups above or below the plane of the ring. How we show this is different in the two parts of Fig 5. In Fig 5A, we look at the ring "edge-on". The thick line for the bottom bond is intended to convey the edge-on view (or side view); this is sometimes omitted, especially with hand-drawn structures, but be careful then that the meaning is clear. Once we understand that we are now looking at the ring edge-on, it is clear that the two Cl atoms are both above the ring, hence cis. In Fig 5B, we view the ring "face-on" (or top view), and use special bond symbols -- "stereo bonds" -- to convey up and down: the heavy wedge -- an "up wedge" -- points upward, toward you, and the dashed bond -- a "down bond" -- points downward, away from you. Again, both Cl are "up", hence cis.

> *Notes...*
>
> *For some notes on how to draw the stereo bonds, see the section E.1. Note: How to draw stereo bonds ("up" and "down" bonds).*
>
> *In discussing Fig 5, I started by saying that we imagine the ring to be planar. Emphasize that cycloalkane rings are not really planar (except for cyclopropane rings). As so often,*

> *the structural formula represents the general layout of the atoms, but not the actual molecular geometry.*
>
> *Those with the Ouellette book can see examples of these two ways of showing up/down on p 81 (top) and p 80 (middle). Most organic chemistry books will show you this.*

The conformation of *cis*-1,3-dichlorocyclohexane

Fig 6, at the right, is one way to show this. Fig 6 shows features of the compound that we have already noted -- plus one more. Let's go through these features, emphasizing what is new.

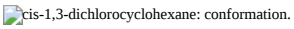


Figure 6

The structure shows *cis*-1,3-dichlorocyclohexane: a 6-ring; 2 Cl atoms, at positions 1 and 3; and cis, with both Cl on the same side of -- above -- the H that is on the same C.

> *I showed the 2 Cl atoms at corner positions, and I showed the H at the key positions explicitly. These points follow from some of the Helpful Hints discussed earlier. It is not required that you do these things, but they can make things easier for you -- and for anyone reading your structures.*

Now, what is new here? The conformation. We start with the notion that the conformation of cyclohexane derivatives is based on the "chair". At each position, one substituent is axial (loosely, perpendicular to the ring), and one is equatorial (loosely, in the plane of the ring). There is more room in the equatorial positions (not easily seen with these simple drawings, but ordinary ball and stick models do help with this point). Thus we try to put the larger substituents in the equatorial positions. In this case, we put the Cl equatorial and the H axial at each position 1 and position 3.

We are now done with this compound, cis-1,3-dichlorocyclohexane. However, we have missed one very important concern -- because it is not an issue in this case. So let's look at another compound.

cis-1,2-Dichlorocyclohexane

cis-1,2-Dichlorocyclohexane is like the previous compound, except that the two chloro groups are now at 1,2, rather than at 1,3.

Figure 7

Fig 7 shows a simple structural formula for 1,2-dichlorocyclohexane, without orientation. This is analogous to Fig 4 above for the 1,3 isomer.

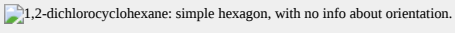


Figure 8

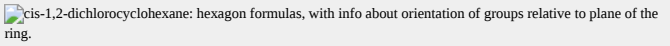


Fig 8 shows two ways to show the cis orientation in cis-1,2-dichlorocyclohexane. This Fig is analogous to Fig 5 above for the 1,3 isomer.

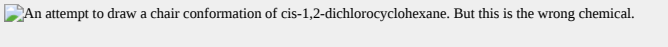
Figures 7 and 8 above introduce no new ideas or complications. These two figures should be straightforward.

So, what is the preferred conformation of cis-1,2-dichlorocyclohexane? This requires careful consideration; an important lesson from this exercise is to realize that we cannot propose a good conformation based simply on what we have learned so far.

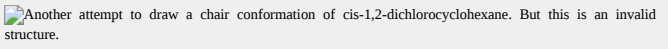
The two guidelines we have so far for conformation of 6-rings are:

- The carbon ring is in a chair.
- Larger substituents are in equatorial positions.

Let's explore the difficulty here by looking at some things people might naively draw.

Figure 9	Fig 9 shows an attempt to draw a chair conformation of cis-1,2-dichlorocyclohexane. It satisfies both of the guidelines listed above. But it is wrong.
 An attempt to draw a chair conformation of cis-1,2-dichlorocyclohexane. But this is the wrong chemical.	

Why is Fig 9 wrong? It is the wrong chemical. The structure shown in Fig 9 is trans, not cis. Look carefully at the 1 and 2 positions. At one of them, the H is above the Cl; at the other, the Cl is above the H. Trans. Wrong chemical. The structure shown in Fig 9 is not the requested chemical.

Figure 10	Fig 10 attempts to fix the problem with Fig 9. But it is also wrong.
 Another attempt to draw a chair conformation of cis-1,2-dichlorocyclohexane. But this is an invalid structure.	

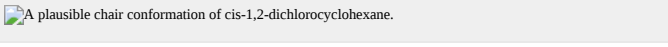
Why is Fig 10 wrong? After all, it seems to address the criteria presented. It contains both of the larger atoms (Cl) equatorial, and they are cis as desired. However, in Fig 10, the two axial groups on carbons # 1 and 2 (the two H that are shown) are both pointing up. This is impossible. In a valid chair, the axial groups alternate up/down as one goes around the ring; see Figure 2B, above. This follows from the tetrahedral bonding of C. *Adjacent axial groups*, as relevant here, *must point in opposite directions*; that condition is violated here. That is, Fig 10 is not a valid chair.

> *Those who find the above point new or surprising should check their textbook. If possible, look at models of cyclohexane and simple derivatives such as the one here. Figure 2B, above, is correct. In my experience, many students have not yet noticed this feature of chair conformations.*
>
> *If you think you have an alternative that is better (or even satisfactory), please show it to me. I suspect it will turn out to be equivalent to Fig 9 or Fig 10, above. But if you think it is good, let's discuss it.*

So now what? We have a contradiction. And that really is the most important point here. It is important to realize that we cannot draw a conformation for cis-1,2-dichlorocyclohexane which easily fits the criteria we have used so far: a chair, with large groups equatorial. So what do we do? Clearly, the conformation of this compound must, in some way, involve more issues than what we have considered so far.

Instructors and books will vary in how much further explanation they want to give on this matter. Therefore, how you proceed from here must take into account the preferences in your course. Here is one way to proceed.

One simple way to proceed is to re-examine the two criteria we have been using, and then state a generality about what to do in the event of a conflict. That generality is: use the chair, and then fit the groups as best you can. That is, try to put as many of the larger groups equatorial as you can, but realize that you may not get them all equatorial.

Figure 11	Fig 11 shows a plausible chair conformation of cis-1,2-dichlorocyclohexane.
 A plausible chair conformation of cis-1,2-dichlorocyclohexane.	

What have we accomplished here? First, this is the correct compound. Convince yourself that this really is cis-1,2-dichlorocyclohexane. In particular, it is cis because at each substituted position the Cl is "above" the H; that is, both Cl are on the

same side of the ring.

Second, this is a proper chair. Adjacent axial groups point in opposite directions. Only two of them are shown here: the axial Cl on the upper right C is "up", and the axial H on the lower right C is "down". Thus, these aspects satisfy the proper way to orient things, in general, on a cyclohexane chair.

How good a conformation is the one shown in Fig 11? Actually, it is quite good, in this case. The actual conformation has been measured, and it follows the basic ideas shown here.

Is this the end of the story? No, but it is about enough for now. The main purpose here was to show how one must carefully look at conformation, within the constraints of the specific isomer one is trying to draw. Some compounds cannot be easily drawn within the common "rules". cis-1,2-dichlorocyclohexane is one such example. In this case, we kept the basic chair conformation, but put one larger group in the less favored axial orientation. Measurements on many such chemicals have shown that the energetic penalty of moving a cyclohexane ring much away from the basic chair conformation is quite large -- certainly larger than the energetic penalty of putting one "somewhat large" group in an axial position. Of course, with larger groups or more groups, this might not hold.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- Robert Bruner (http://bbruner.org)

4.13: Oxidation of Alkanes

Oxidation and Reduction of Alkanes

You are undoubtedly already familiar with the general idea of oxidation and reduction: you learned in general chemistry that when a compound or atom is oxidized it loses electrons, and when it is reduced it gains electrons. You also know that oxidation and reduction reactions occur in pairs: if one species is oxidized, another must be reduced at the same time - thus the term 'redox reaction'.

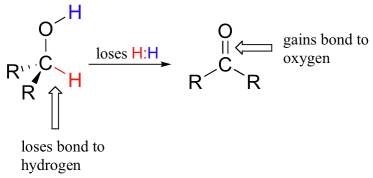
Most of the redox reactions you have seen previously in general chemistry probably involved the flow of electrons from one metal to another, such as the reaction between copper ion in solution and metallic zinc:

$$Cu^{+2}_{(aq)} + Zn_{(s)} \rightarrow Cu_{(s)} + Zn^{+2}_{(aq)}$$

In organic chemistry, redox reactions look a little different. Electrons in an organic redox reaction often are transferred in the form of a hydride ion - a proton and two electrons. Because they occur in conjunction with the transfer of a proton, these are commonly referred to as **hydrogenation** and **dehydrogenation** reactions: a hydride plus a proton adds up to a hydrogen (H_2) molecule. Be careful - do not confuse the terms hyd**rogen**ation and dehy**drogen**ation with hydration and dehydration - the latter refer to the gain and loss of a *water* molecule (and are *not* redox reactions), while the former refer to the gain and loss of a *hydrogen* molecule.

When a carbon atom in an organic compound loses a bond to hydrogen and gains a new bond to a heteroatom (or to another carbon), we say the compound has been dehydrogenated, or oxidized. A very common biochemical example is the oxidation of an alcohol to a ketone or aldehyde:

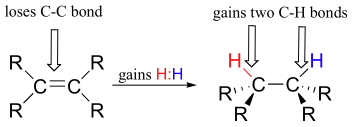
Dehydrogenation (oxidation) of an alcohol



When a carbon atom loses a bond to hydrogen and gains a bond to a heteroatom (or to another carbon atom), it is considered to be an oxidative process because hydrogen, of all the elements, is the least electronegative. Thus, in the process of dehydrogenation the carbon atom undergoes an overall loss of electron density - and loss of electrons is oxidation.

Conversely, when a carbon atom in an organic compound gains a bond to hydrogen and loses a bond to a heteroatom (or to another carbon atom), we say that the compound has been hydrogenated, or reduced. The hydrogenation of a ketone to an alcohol, for example, is overall the reverse of the alcohol dehydrogenation shown above. Illustrated below is another common possibility, the hydrogenation (reduction) of an alkene to an alkane.

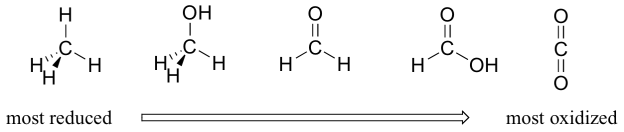
Hydrogenation (reduction) of an alkene



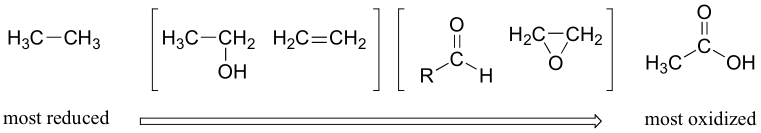
Hydrogenation results in *higher* electron density on a carbon atom(s), and thus we consider process to be one of reduction of the organic molecule.

Notice that neither hydrogenation nor dehydrogenation involves the gain or loss of an oxygen *atom*. Reactions which *do* involve gain or loss of one or more oxygen atoms are usually referred to as 'oxygenase' and 'reductase' reactions, and are the subject of section 16.10 and section 17.3.

For the most part, when talking about redox reactions in organic chemistry we are dealing with a small set of very recognizable functional group transformations. It is therefore very worthwhile to become familiar with the idea of 'oxidation states' as applied to organic functional groups. By comparing the relative number of bonds to hydrogen atoms, we can order the familiar functional groups according to oxidation state. We'll take a series of single carbon compounds as an example. Methane, with four carbon-hydrogen bonds, is highly reduced. Next in the series is methanol (one less carbon-hydrogen bond, one more carbon-oxygen bond), followed by formaldehyde, formate, and finally carbon dioxide at the highly oxidized end of the group.



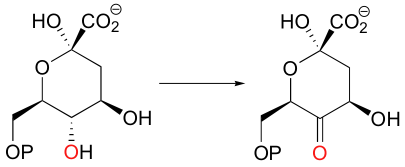
This pattern holds true for the relevant functional groups on organic molecules with two or more carbon atoms:



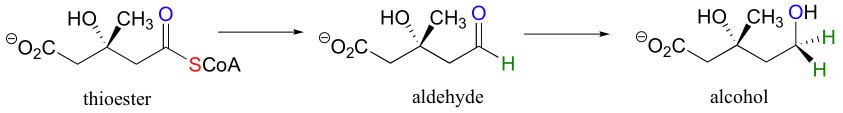
Alkanes are highly reduced, while alcohols - as well as alkenes, ethers, amines, sulfides, and phosphate esters - are one step up on the oxidation scale, followed by aldehydes/ketones/imines and epoxides, and finally by carboxylic acid derivatives (carbon dioxide, at the top of the oxidation list, is specific to the single carbon series).

Notice that in the series of two-carbon compounds above, ethanol and ethene are considered to be in the same oxidation state. You know already that alcohols and alkenes are interconverted by way of addition or elimination of water (section 14.1). When an alcohol is dehydrated to form an alkene, one of the two carbons loses a C-H bond and gains a C-C bond, and thus is oxidized. However, the other carbon loses a C-O bond and gains a C-C bond, and thus is considered to be reduced. Overall, therefore, there is no change to the oxidation state of the molecule.

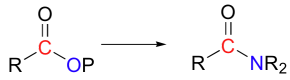
You should learn to recognize when a reaction involves a change in oxidation state in an organic reactant . Looking at the following transformation, for example, you should be able to quickly recognize that it is an oxidation: an alcohol functional group is converted to a ketone, which is one step up on the oxidation ladder.



Likewise, this next reaction involves the transformation of a carboxylic acid derivative (a thioester) first to an aldehyde, then to an alcohol: this is a *double* reduction, as the substrate loses two bonds to heteroatoms and gains two bonds to hydrogens.



An acyl transfer reaction (for example the conversion of an acyl phosphate to an amide) is *not* considered to be a redox reaction - the oxidation state of the organic molecule is does not change as substrate is converted to product, because a bond to one heteroatom (oxygen) has simply been traded for a bond to another heteroatom (nitrogen).



It is important to be able to recognize when an organic molecule is being oxidized or reduced, because this information tells you to look for the participation of a corresponding redox agent that is being reduced or oxidized- remember, oxidation and reduction always occur in tandem! We will soon learn in detail about the most important biochemical and laboratory redox agents.

Template:ExampleStart

Exercise 16.1: is an aldol condensation a redox reaction? Explain.

Exercise 16.2: Is the reaction catalyzed by squalene epoxidase a redox reaction? How about squalene cyclase? Explain.

Template:ExampleEnd

he combustion of carbon compounds, especially hydrocarbons, has been the most important source of heat energy for human civilizations throughout recorded history. The practical importance of this reaction cannot be denied, but the massive and uncontrolled chemical changes that take place in combustion make it difficult to deduce mechanistic paths. Using the combustion of propane as an example, we see from the following equation that every covalent bond in the reactants has been broken and an entirely new set of covalent bonds have formed in the products. No other common reaction involves such a profound and pervasive change, and the mechanism of combustion is so complex that chemists are just beginning to explore and understand some of its elementary features.

$$\mathrm{CH_3-CH_2-CH_3 + 5O_2 \rightarrow 3CO_2 + 4H_2O + heat} \tag{4.13.1}$$

Two points concerning this reaction are important:

1. Since all the covalent bonds in the reactant molecules are broken, the quantity of heat evolved in this reaction is related to the strength of these bonds (and, of course, the strength of the bonds formed in the products). Precise heats of combustion measurements can provide useful information about the structure of molecules.
2. The stoichiometry of the reactants is important. If insufficient oxygen is supplied some of the products will consist of the less oxidized carbon monoxide CO gas.

$$\mathrm{CH_3-CH_2-CH_3 + 4O_2 \rightarrow CO_2 + 2CO + 4H_2O + heat} \tag{4.13.2}$$

Heat of Combustion

From the previous discussion, we might expect isomers to have identical heats of combustion. However, a few simple measurements will disabuse this belief. Thus, the heat of combustion of pentane is –782 kcal/mole, but that of its 2,2-dimethylpropane (neopentane) isomer is –777 kcal/mole. Differences such as this reflect subtle structural variations, including the greater bond energy of 1º-C–H versus 2º-C–H bonds and steric crowding of neighboring groups. In small-ring cyclic compounds ring strain can be a major contributor to thermodynamic stability and chemical reactivity. The following table lists heat of combustion data for some simple cycloalkanes and compares these with the increase per CH_2 unit for long chain alkanes.

Cycloalkane $(CH_2)_n$	**CH_2 Units** n	**ΔH^{25°** kcal/mole	**ΔH^{25°** per CH_2 Unit	**Ring Strain** kcal/mole
Cyclopropane	n = 3	468.7	156.2	27.6
Cyclobutane	n = 4	614.3	153.6	26.4
Cyclopentane	n = 5	741.5	148.3	6.5
Cyclohexane	n = 6	882.1	147.0	0.0
Cycloheptane	n = 7	1035.4	147.9	6.3
Cyclooctane	n = 8	1186.0	148.2	9.6
Cyclononane	n = 9	1335.0	148.3	11.7
Cyclodecane	n = 10	1481	148.1	11.0
$CH_3(CH_2)_mCH_3$	m = large	—	147.0	0.0

The chief source of ring strain in smaller rings is angle strain and eclipsing strain. As noted elsewhere, cyclopropane and cyclobutane have large contributions of both strains, with angle strain being especially severe. Changes in chemical reactivity as a consequence of angle strain are dramatic in the case of cyclopropane, and are also evident for cyclobutane. Some examples are shown in the following diagram. The cyclopropane reactions are additions, many of which are initiated by electrophilic attack. The pyrolytic conversion of β-pinene to myrcene probably takes place by an initial rupture of the 1:6 bond, giving an allylic 3º-diradical, followed immediately by breaking of the 5:7 bond.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

4.14: Lipids—Part 1

Waxes

Waxes are esters of fatty acids with long chain monohydric alcohols (one hydroxyl group). Natural waxes are often mixtures of such esters, and may also contain hydrocarbons. The formulas for three well known waxes are given below, with the carboxylic acid moiety colored red and the alcohol colored blue.

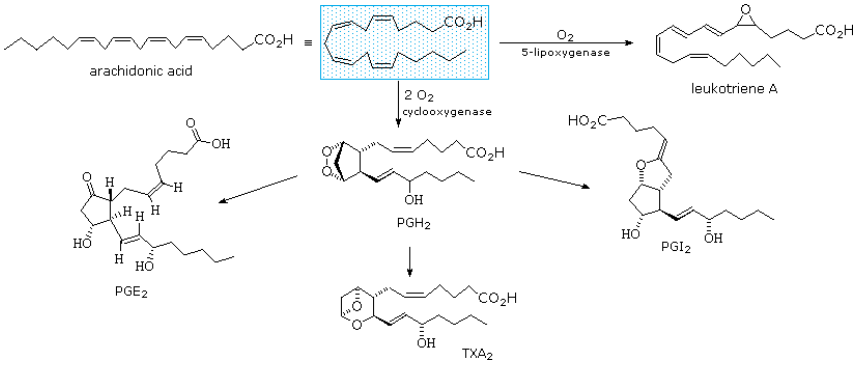
spermaceti		beeswax		carnuba wax
$CH_3(CH_2)_{14}CO_2$-$(CH_2)_{15}CH_3$		$CH_3(CH_2)_{24}CO_2$-$(CH_2)_{29}CH_3$		$CH_3(CH_2)_{30}CO_2$-$(CH_2)_{33}CH_3$

Waxes are widely distributed in nature. The leaves and fruits of many plants have waxy coatings, which may protect them from dehydration and small predators. The feathers of birds and the fur of some animals have similar coatings which serve as a water repellent. Carnuba wax is valued for its toughness and water resistance.

Prostaglandins Thromboxanes & Leukotrienes

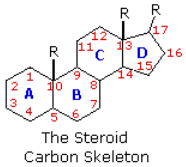
The members of this group of structurally related natural hormones have an extraordinary range of biological effects. They can lower gastric secretions, stimulate uterine contractions, lower blood pressure, influence blood clotting and induce asthma-like allergic responses. Because their genesis in body tissues is tied to the metabolism of the essential fatty acid arachadonic acid (5,8,11,14-eicosatetraenoic acid) they are classified as **eicosanoids**. Many properties of the common drug aspirin result from its effect on the cascade of reactions associated with these hormones.

The metabolic pathways by which arachidonic acid is converted to the various eicosanoids are complex and will not be discussed here. A rough outline of some of the transformations that take place is provided below. It is helpful to view arachadonic acid in the coiled conformation shown in the shaded box.



Leukotriene A is a precursor to other leukotriene derivatives by epoxide opening reactions. The prostaglandins are given systematic names that reflect their structure. The initially formed peroxide PGH_2 is a common intermediate to other prostaglandins, as well as thromboxanes such as TXA_2. **To see a model of prostaglandin PGE_2 Click Here**.

Steroids

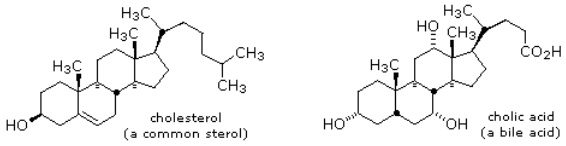


The Steroid Carbon Skeleton

The important class of lipids called **steroids** are actually metabolic derivatives of terpenes, but they are customarily treated as a separate group. Steroids may be recognized by their tetracyclic skeleton, consisting of three fused six-membered and one five-membered ring, as shown in the diagram to the right. The four rings are designated A, B, C & D as noted, and the peculiar numbering of the ring carbon atoms (shown in red) is the result of an earlier misassignment of the structure. The substituents designated by R are often alkyl groups, but may also have functionality. The R group at the A:B ring fusion is most commonly methyl or hydrogen, that at the C:D fusion is usually methyl. The substituent at C-17 varies considerably, and is usually larger than methyl if it is not a functional group. The most common locations of functional groups are C-3, C-4, C-7, C-11, C-12 & C-17. Ring A is sometimes aromatic. Since a number of tetracyclic triterpenes also have this tetracyclic structure, it cannot be considered a unique identifier.

Steroids are widely distributed in animals, where they are associated with a number of physiological processes. Examples of some important steroids are shown in the following diagram. Different kinds of steroids will be displayed by clicking the "Toggle Structures" button under the diagram. Norethindrone is a synthetic steroid, all the other examples occur naturally. A common strategy in pharmaceutical chemistry is to take a natural compound, having certain desired biological properties together with undesired side effects, and to modify its structure to enhance the desired characteristics and diminish the undesired. This is sometimes accomplished by trial and error.

The generic steroid structure drawn above has seven chiral stereocenters (carbons 5, 8, 9, 10, 13, 14 & 17), which means that it may have as many as 128 stereoisomers. With the exception of C-5, natural steroids generally have a single common configuration. This is shown in the last of the toggled displays, along with the preferred conformations of the rings.



Typical Animal Steroids

Toggle Structures

Chemical studies of the steroids were very important to our present understanding of the configurations and conformations of six-membered rings. Substituent groups at different sites on the tetracyclic skeleton will have axial or equatorial orientations that are fixed because of the rigid structure of the trans-fused rings. This fixed orientation influences chemical reactivity, largely due to the greater steric hindrance of axial groups versus their equatorial isomers. Thus an equatorial hydroxyl group is esterified more rapidly than its axial isomer.

To see a model of the steroid cholesterol Click Here

Contributors

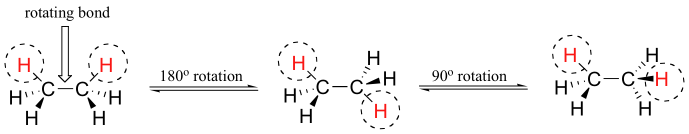
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

4.15: Conformations of Acyclic Alkanes—Ethane

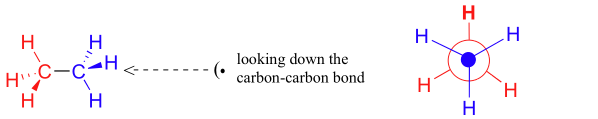
Conformational isomerism involves rotation about sigma bonds, and does not involve any differences in the connectivity or geometry of bonding. Two or more structures that are categorized as conformational isomers, or **conformers**, are really just two of the exact same molecule that differ only in terms of the angle about one or more sigma bonds.

Ethane Conformations

Although there are seven sigma bonds in the ethane molecule, rotation about the six carbon-hydrogen bonds does not result in any change in the shape of the molecule because the hydrogen atoms are essentially spherical. Rotation about the carbon-carbon bond, however, results in many different possible molecular conformations.



In order to better visualize these different conformations, it is convenient to use a drawing convention called the **Newman projection**. In a Newman projection, we look lengthwise down a specific bond of interest – in this case, the carbon-carbon bond in ethane. We depict the 'front' atom as a dot, and the 'back' atom as a larger circle.

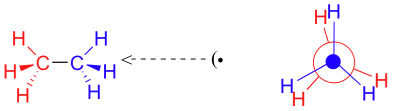


'staggered' conformation
(Newman projection)

The six carbon-hydrogen bonds are shown as solid lines protruding from the two carbons at 120°angles, which is what the actual tetrahedral geometry looks like when viewed from this perspective and flattened into two dimensions.

The lowest energy conformation of ethane, shown in the figure above, is called the 'staggered' conformation, in which all of the C-H bonds on the front carbon are positioned at dihedral angles of 60°relative to the C-H bonds on the back carbon. In this conformation, the distance between the bonds (and the electrons in them) is maximized.

If we now rotate the front CH_3 group 60°clockwise, the molecule is in the highest energy 'eclipsed' conformation, where the hydrogens on the front carbon are as close as possible to the hydrogens on the back carbon.



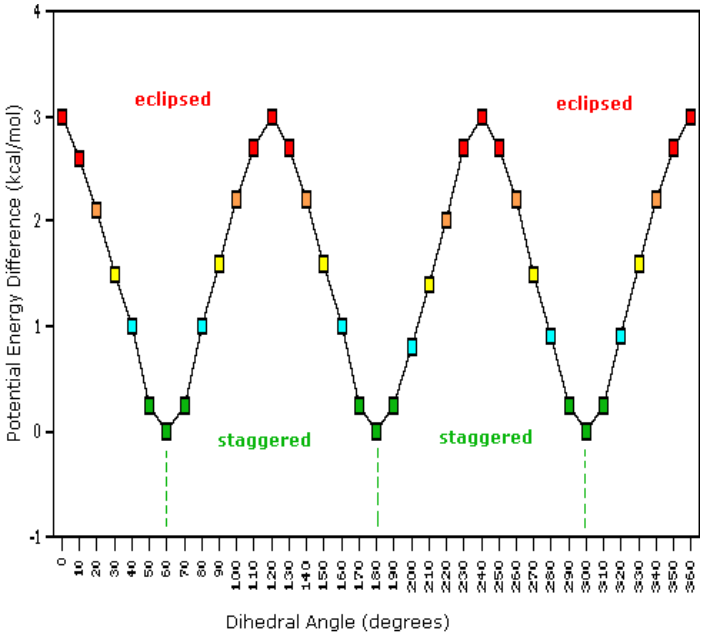
'eclipsed' conformation

This is the highest energy conformation because of unfavorable interactions between the electrons in the front and back C-H bonds. The energy of the eclipsed conformation is approximately 3 kcal/mol higher than that of the staggered conformation.

Another 60°rotation returns the molecule to a second eclipsed conformation. This process can be continued all around the 360°circle, with three possible eclipsed conformations and three staggered conformations, in addition to an infinite number of variations in between.

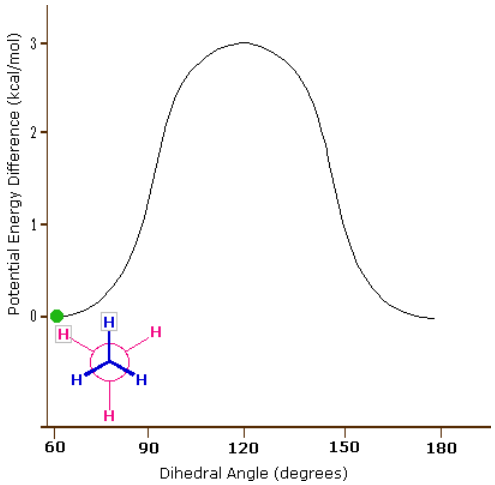
The carbon-carbon bond is not *completely* free to rotate – there is indeed a small, 3 kcal/mol barrier to rotation that must be overcome for the bond to rotate from one staggered conformation to another. This rotational barrier is not high enough to prevent constant rotation except at extremely cold temperatures. However, at any given moment the molecule is more likely to be in a staggered conformation - one of the rotational 'energy valleys' - than in any other state.

The potential energy associated with the various conformations of ethane varies with the dihedral angle of the bonds, as shown below.



Although the conformers of ethane are in rapid equilibrium with each other, the 3 kcal/mol energy difference leads to a substantial preponderance of staggered conformers (> 99.9%) at any given time.

The animation below illustrates the relationship between ethane's potential energy and its dihedral angle



Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

CHAPTER OVERVIEW

5: Stereochemistry

Topic hierarchy

5.1: Starch and Cellulose

The polysaccharides are the most abundant carbohydrates in nature and serve a variety of functions, such as energy storage or as components of plant cell walls. Polysaccharides are very large polymers composed of tens to thousands of monosaccharides joined together by glycosidic linkages. The three most abundant polysaccharides are starch, glycogen, and cellulose. These three are referred to as *homopolymers* because each yields only one type of monosaccharide (glucose) after complete hydrolysis. *Heteropolymers* may contain sugar acids, amino sugars, or noncarbohydrate substances in addition to monosaccharides. Heteropolymers are common in nature (gums, pectins, and other substances) but will not be discussed further in this textbook. The polysaccharides are nonreducing carbohydrates, are not sweet tasting, and do not undergo mutarotation.

Starch

Starch is the most important source of carbohydrates in the human diet and accounts for more than 50% of our carbohydrate intake. It occurs in plants in the form of granules, and these are particularly abundant in seeds (especially the cereal grains) and tubers, where they serve as a storage form of carbohydrates. The breakdown of starch to glucose nourishes the plant during periods of reduced photosynthetic activity. We often think of potatoes as a "starchy" food, yet other plants contain a much greater percentage of starch (potatoes 15%, wheat 55%, corn 65%, and rice 75%). Commercial starch is a white powder.

Starch is a mixture of two polymers: amylose and amylopectin. Natural starches consist of about 10%–30% amylase and 70%–90% amylopectin. Amylose is a linear polysaccharide composed entirely of D-glucose units joined by the α-1,4-glycosidic linkages we saw in maltose (part (a) of Figure 5.1.1). Experimental evidence indicates that amylose is not a straight chain of glucose units but instead is coiled like a spring, with six glucose monomers per turn (part (b) of Figure 5.1.1). When coiled in this fashion, amylose has just enough room in its core to accommodate an iodine molecule. The characteristic blue-violet color that appears when starch is treated with iodine is due to the formation of the amylose-iodine complex. This color test is sensitive enough to detect even minute amounts of starch in solution.

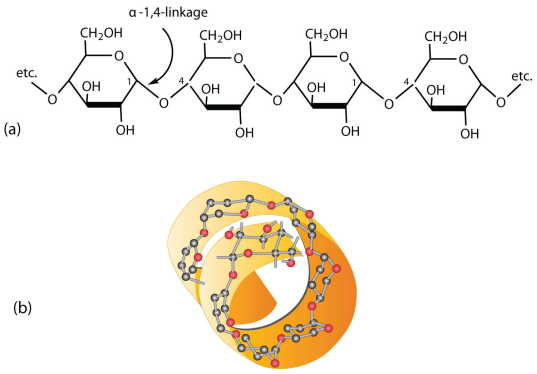


Figure 5.1.1: *Amylose. (a) Amylose is a linear chain of α-D-glucose units joined together by α-1,4-glycosidic bonds. (b) Because of hydrogen bonding, amylose acquires a spiral structure that contains six glucose units per turn.*

Amylopectin is a branched-chain polysaccharide composed of glucose units linked primarily by α-1,4-glycosidic bonds but with occasional α-1,6-glycosidic bonds, which are responsible for the branching. A molecule of amylopectin may contain many thousands of glucose units with branch points occurring about every 25–30 units (Figure 5.1.2). The helical structure of amylopectin is disrupted by the branching of the chain, so instead of the deep blue-violet color amylose gives with iodine, amylopectin produces a less intense reddish brown.

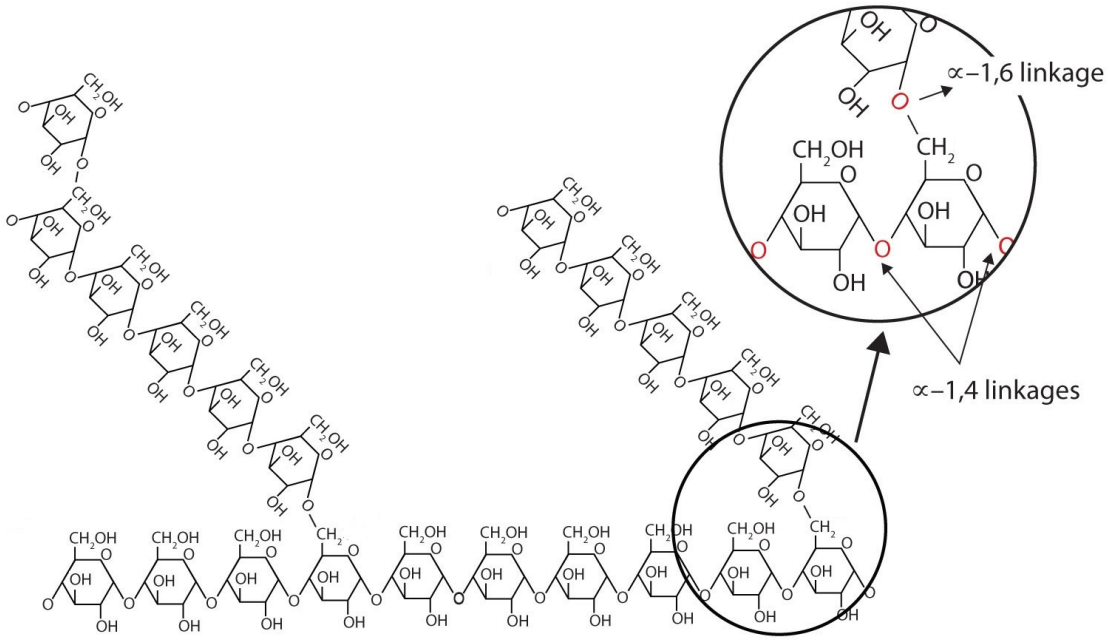


***Figure 5.1.2**: Representation of the Branching in Amylopectin and Glycogen. Both amylopectin and glycogen contain branch points that are linked through α-1,6-linkages. These branch points occur more often in glycogen.*

Dextrins are glucose polysaccharides of intermediate size. The shine and stiffness imparted to clothing by starch are due to the presence of dextrins formed when clothing is ironed. Because of their characteristic stickiness with wetting, dextrins are used as adhesives on stamps, envelopes, and labels; as binders to hold pills and tablets together; and as pastes. Dextrins are more easily digested than starch and are therefore used extensively in the commercial preparation of infant foods.

The complete hydrolysis of starch yields, in successive stages, glucose:

$$\text{starch} \rightarrow \text{dextrins} \rightarrow \text{maltose} \rightarrow \text{glucose}$$

In the human body, several enzymes known collectively as amylases degrade starch sequentially into usable glucose units.

Glycogen

Glycogen is the energy reserve carbohydrate of animals. Practically all mammalian cells contain some stored carbohydrates in the form of glycogen, but it is especially abundant in the liver (4%–8% by weight of tissue) and in skeletal muscle cells (0.5%–1.0%). Like starch in plants, glycogen is found as granules in liver and muscle cells. When fasting, animals draw on these glycogen reserves during the first day without food to obtain the glucose needed to maintain metabolic balance.

> **Note**
>
> About 70% of the total glycogen in the body is stored in muscle cells. Although the percentage of glycogen (by weight) is higher in the liver, the much greater mass of skeletal muscle stores a greater total amount of glycogen.

Glycogen is structurally quite similar to amylopectin, although glycogen is more highly branched (8–12 glucose units between branches) and the branches are shorter. When treated with iodine, glycogen gives a reddish brown color. Glycogen can be broken down into its D-glucose subunits by acid hydrolysis or by the same enzymes that catalyze the breakdown of starch. In animals, the enzyme phosphorylase catalyzes the breakdown of glycogen to phosphate esters of glucose.

Cellulose

Cellulose, a fibrous carbohydrate found in all plants, is the structural component of plant cell walls. Because the earth is covered with vegetation, cellulose is the most abundant of all carbohydrates, accounting for over 50% of all the carbon found in the vegetable kingdom. Cotton fibrils and filter paper are almost entirely cellulose (about 95%), wood is about 50% cellulose, and the dry weight of leaves is about 10%–20% cellulose. The largest use of cellulose is in the manufacture of paper and paper products.

Although the use of noncellulose synthetic fibers is increasing, rayon (made from cellulose) and cotton still account for over 70% of textile production.

Like amylose, cellulose is a linear polymer of glucose. It differs, however, in that the glucose units are joined by β-1,4-glycosidic linkages, producing a more extended structure than amylose (part (a) of Figure 5.1.3). This extreme linearity allows a great deal of hydrogen bonding between OH groups on adjacent chains, causing them to pack closely into fibers (part (b) of Figure 5.1.3). As a result, cellulose exhibits little interaction with water or any other solvent. Cotton and wood, for example, are completely insoluble in water and have considerable mechanical strength. Because cellulose does not have a helical structure, it does not bind to iodine to form a colored product.

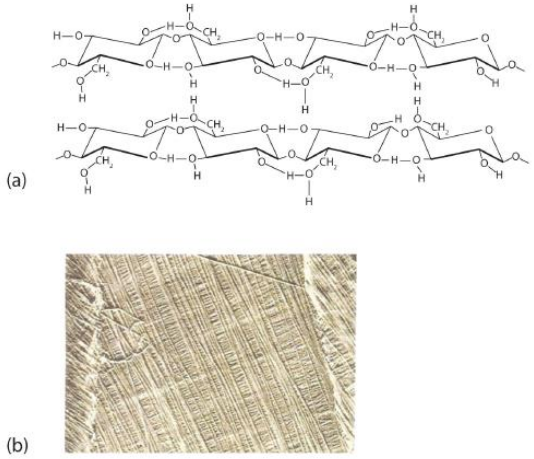


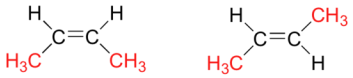
***Figure 5.1.3**: Cellulose. (a) There is extensive hydrogen bonding in the structure of cellulose. (b) In this electron micrograph of the cell wall of an alga, the wall consists of successive layers of cellulose fibers in parallel arrangement.*

Cellulose yields D-glucose after complete acid hydrolysis, yet humans are unable to metabolize cellulose as a source of glucose. Our digestive juices lack enzymes that can hydrolyze the β-glycosidic linkages found in cellulose, so although we can eat potatoes, we cannot eat grass. However, certain microorganisms can digest cellulose because they make the enzyme cellulase, which catalyzes the hydrolysis of cellulose. The presence of these microorganisms in the digestive tracts of herbivorous animals (such as cows, horses, and sheep) allows these animals to degrade the cellulose from plant material into glucose for energy. Termites also contain cellulase-secreting microorganisms and thus can subsist on a wood diet. This example once again demonstrates the extreme stereospecificity of biochemical processes.

5.2: The Two Major Classes of Isomers

Isomers are different compounds that have the same molecular formula. When the group of atoms that make up the molecules of different isomers are bonded together in fundamentally different ways, we refer to such compounds as constitutional isomers. For example, in the case of the C_4H_8hydrocarbons, most of the isomers are constitutional. Shorthand structures for four of these isomers are shown below with their IUPAC names.

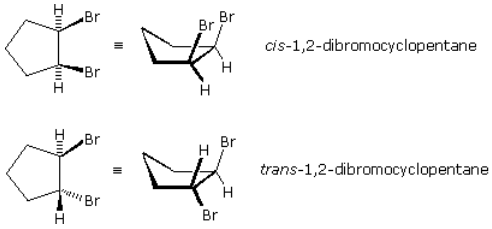
Note that the twelve atoms that make up these isomers are bonded in very different ways. As is true for all constitutional isomers, each different compound has a different IUPAC name. Furthermore, the molecular formula provides information about some of the structural features that must be present in the isomers. Since the formula C_4H_8 has two fewer hydrogens than the four-carbon alkane butane (C_4H_{10}), all the isomers having this composition must incorporate either a ring or a double bond. A fifth possible isomer of formula C_4H_8 is $CH_3CH{=}CHCH_3$. This would be named 2-butene according to the IUPAC rules; however, a close inspection of this molecule indicates it has two possible structures. These isomers may be isolated as distinct compounds, having characteristic and different properties. They are shown here with the designations *cis* and *trans*.



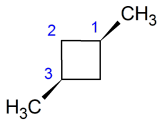
cis-2-butene *trans*-2-butene

The bonding patterns of the atoms in these two isomers are essentially equivalent, the only difference being the relative configuration of the two methyl groups and the two associated hydrogen atoms about the double bond. In the *cis* isomer the methyl groups are on the same side; whereas they are on opposite sides in the *trans* isomer. Isomers that differ only in the spatial orientation of their component atoms are called stereoisomers. Stereoisomers always require that an additional nomenclature prefix be added to the IUPAC name in order to indicate their spatial orientation.

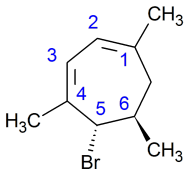
Stereoisomers are also observed in certain disubstituted (and higher substituted) cyclic compounds. Unlike the relatively flat molecules of alkenes, substituted cycloalkanes must be viewed as three-dimensional configurations in order to appreciate the spatial orientations of the substituents. By agreement, chemists use heavy, wedge-shaped bonds to indicate a substituent located above the average plane of the ring, and a hatched line for bonds to atoms or groups located below the ring. As in the case of the 2-butene stereoisomers, disubstituted cycloalkane stereoisomers may be designated by nomenclature prefixes such as *cis* and *trans*. The stereoisomeric 1,2-dibromocyclopentanes below are an example.



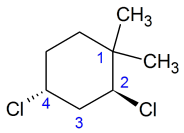
In general, if any two sp^3 carbons in a ring have two different substituent groups (not counting other ring atoms) stereoisomerism is possible. This is similar to the substitution pattern that gives rise to stereoisomers in alkenes; indeed, one might view a double bond as a two-membered ring. Four other examples of this kind of stereoisomerism in cyclic compounds are shown below.



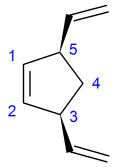
cis-1,3-dimethylcyclobutane



trans-5-bromo-1,4,6-trimethyl-1,3-cycloheptadiene

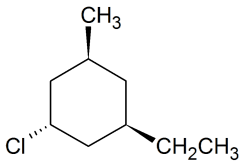


trans-2,4-dichloro-1,1-dimethylcyclohexane



cis-3,5-divinylcyclopentene

If more than two ring carbons have different substituents (not counting other ring atoms) the stereochemical notation distinguishing the various isomers becomes more complex. However, we can always state the relationship of any two substituents using cis or trans. For example, in the trisubstitutued cyclohexane below, we can say that the methyl group is *cis* to the ethyl group, and *trans* to the chlorine. We can also say that the ethyl group is *trans* to the chlorine. We cannot, however, designate the entire molecule as a *cis* or trans *isomer*.



Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

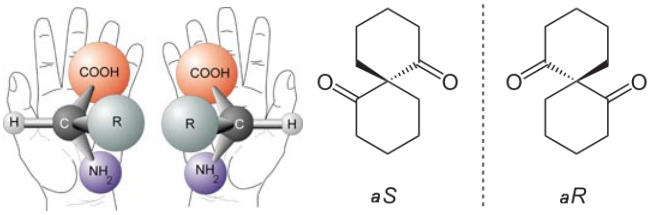
5.3: Looking Glass Chemistry—Chiral and Achiral Molecules

Stereoisomers are isomers that differ in spatial arrangement of atoms, rather than order of atomic connectivity. One of their most interesting type of isomer is the mirror-image stereoisomers, a non-superimposable set of two molecules that are mirror image of one another. The existance of these molecules are determined by concept known as **chirality**. The word "chiral" was derived from the Greek word for hand, because our hands display a good example of chirality since they are non-superimposable mirror images of each other.

Introduction

The opposite of chiral is **achiral**. Achiral objects are superimposable with their mirror images. For example, two pieces of paper are achiral. In contrast, chiral molecules, like our hands, are non superimposable mirror images of each other.

Try to line up your left hand perfectly with your right hand, so that the palms are both facing in the same directions. Spend about a minute doing this. Do you see that they cannot line up exactly? The same thing applies to some molecules



A Chiral molecule has a mirror image that cannot line up with it perfectly- the mirror images are non superimposable. The mirror images are called **enantiomers**.

But why are chiral molecules so interesting? A chiral molecule and its enantiomer have the same chemical and physical properties(boiling point, melting point,polarity, density etc...). It turns out that many of our biological molecules such as our DNA, amino acids and sugars, are chiral molecules.

It is pretty interesting that our hands seem to serve the same purpose but most people are only able to use one of their hands to write. Similarily this is true with chiral biological molecules and interactions. Just like your left hand will not fit properly in your right glove, one of the enantiomers of a molecule may not work the same way in your body.

This must mean that enantiomers have properties that make them unique to their mirror images. One of these properties is that they cannot have a **plane of symmetry** or an internal mirror plane. So, a chiral molecule cannot be divided in two mirror image halves. Another property of chiral molecules is optical activity.

Organic compounds, molecules created around a chain of carbon atom (more commonly known as carbon backbone), play an essential role in the chemistry of life. These molecules derive their importance from the energy they carry, mainly in a form of potential energy between atomic molecules. Since such potential force can be widely affected due to changes in atomic placement, it is important to understand the concept of an isomer, a molecule sharing same atomic make up as another but differing in structural arrangements. This article will be devoted to a specific isomers called stereoisomers and its property of chirality (Figure 1).

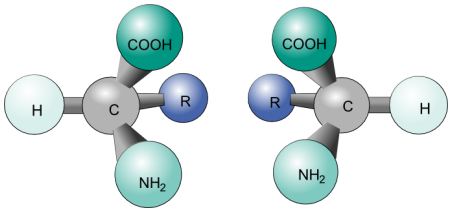


Figure 1. Two enantiomers of a tetrahedral complex.

The concepts of steroisomerism and chirality command great deal of importance in modern organic chemistry, as these ideas helps to understand the physical and theoretical reasons behind the formation and structures of numerous organic molecules, the main reason behind the energy embedded in these essential chemicals. In contrast to more well-known constitutional isomerism, which

develops isotopic compounds simply by different atomic connectivity, stereoisomerism generally maintains equal atomic connections and orders of building blocks as well as having same numbers of atoms and types of elements.

What, then, makes stereoisomers so unique? To answer this question, the learner must be able to think and imagine in not just two-dimensional images, but also three-dimensional space. This is due to the fact that stereoisomers are isomers because their atoms are different from others in terms of spatial arrangement.

Spatial Arrangement

First and foremost, one must understand the concept of spatial arrangement in order to understand stereoisomerism and chirality. Spatial arrangement of atoms concern how different atomic particles and molecules are situated about in the space around the organic compound, namely its carbon chain. In this sense, spatial arrangement of an organic molecule are different another if an atom is shifted in any three-dimensional direction by even one degree. This opens up a very broad possibility of different molecules, each with their unique placement of atoms in three-dimensional space .

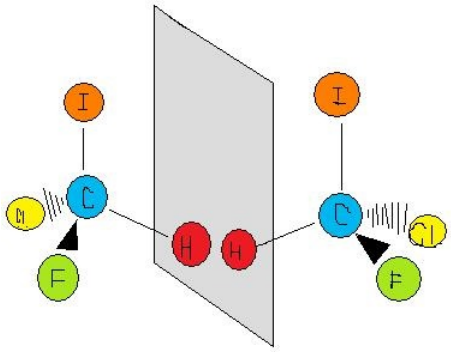
Stereoisomers

Stereoisomers are, as mentioned above, contain different types of isomers within itself, each with distinct characteristics that further separate each other as different chemical entities having different properties. Type called entaniomer are the previously-mentioned mirror-image stereoisomers, and will be explained in detail in this article. Another type, diastereomer, has different properties and will be introduced afterwards.

Enantiomers

This type of stereoisomer is the essential mirror-image, non-superimposable type of stereoisomer introduced in the beginning of the article. Figure 3 provides a perfect example; note that the gray plane in the middle demotes the mirror plane.

Figure 3.



Note that even if one were to flip over the left molecule over to the right, the atomic spatial arrangement will not be equal. This is equivalent to the left hand - right hand relationship, and is aptly referred to as 'handedness' in molecules. This can be somewhat counter-intuitive, so this article recommends the reader try the 'hand' example. Place both palm facing up, and hands next to each other. Now flip either side over to the other. One hand should be showing the back of the hand, while the other one is showing the palm. They are not same and non-superimposable.

This is where the concept of chirality comes in as one of the most essential and defining idea of stereoisomerism.

Chirality

Chirality essentially means 'mirror-image, non-superimposable molecules', and to say that a molecule is chiral is to say that its mirror image (it must have one) is not the same as it self. Whether a molecule is chiral or achiral depends upon a certain set of overlapping conditions. Figure 1 shows an example of two molecules, chiral and achiral, respectively. Notice the distinct characteristic of the achiral molecule: it possesses two atoms of same element. In theory and reality, if one were to create a plane that runs through the other two atoms, they will be able to create what is known as bisecting plane: The images on either side of the plan is the same as the other (Figure 4).

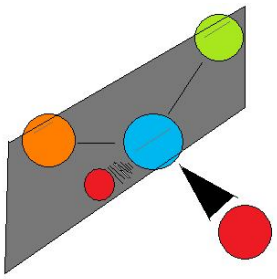


Figure 4.

In this case, the molecule is considered 'achiral'. In other words, to distinguish chiral molecule from an achiral molecule, one must search for the existence of the bisecting plane in a molecule. All chiral molecules are deprive of bisecting plane, whether simple or complex.

As a universal rule, no molecule with different surrounding atoms are achiral. Chirality is a simple but essential idea to support the concept of stereoisomerism, being used to explain one type of its kind. The chemical properties of the chiral molecule differs from its mirror image, and in this lies the significance of chilarity in relation to modern organic chemistry.

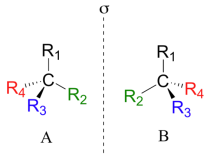
Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- Kristeen Pareja (UCD), Ifemayowa Aworanti (University Of Maryland Baltimore County)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

5.4: Stereogenic Centers

A consideration of the chirality of molecular configurations explains the curious stereoisomerism observed for lactic acid, carvone and a multitude of other organic compounds. Tetravalent carbons have a tetrahedral configuration. If all four substituent groups are the same, as in methane or tetrachloromethane, the configuration is that of a highly symmetric "regular tetrahedron". A regular tetrahedron several planes of symmetry and is achiral.

A carbon atom that is bonded to four different atoms or groups loses all symmetry, and is often referred to as an asymmetric carbon. The configuration of such a molecular unit is chiral, and the structure may exist in either a right-handed configuration or a left-handed configuration (one the mirror image of the other). This type of configurational stereoisomerism is termed enantiomorphism, and the non-identical, mirror-image pair of stereoisomers that result are called enantiomers. In the general figure below, A and B are nonsuperposable mirror images of one another, and thus are a pair of enantiomers.



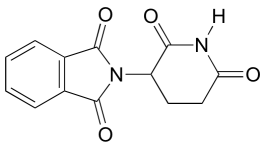
The structural formulas of lactic acid and carvone are drawn on the right with the asymmetric carbon colored red. Consequently, we find that these compounds exist as pairs of enantiomers. The presence of a single asymmetrically substituted carbon atom in a molecule is sufficient to render the whole configuration chiral, and modern terminology refers to such groupings as chiral centers. Most of the chiral centers we shall discuss are asymmetric carbon atoms, but it should be recognized that other tetrahedral or pyramidal atoms may become chiral centers if appropriately substituted. When more than one chiral center is present in a molecular structure, care must be taken to analyze their relationship before concluding that a specific molecular configuration is chiral or achiral. This aspect of stereoisomerism will be treated later.

A useful first step in examining structural formulas to determine whether stereoisomers may exist is to identify all stereogenic elements. A stereogenic element is a center, axis or plane that is a focus of stereoisomerism, such that an interchange of two groups attached to this feature leads to a stereoisomer. Stereogenic elements may be chiral or achiral. An asymmetric carbon is often a chiral stereogenic center, since interchanging any two substituent groups converts one enantiomer to the other. Alkenes having two different groups on each double bond carbon constitute an achiral stereogenic element, since interchanging substituents at one of the carbons changes the cis/trans configuration of the double bond.

Some of the structures in the figure above are chiral and some are achiral. First, try to identify all chiral stereogenic centers. Formulas having no chiral centers are necessarily achiral. Formulas having one chiral center are always chiral; and if two or more chiral centers are present in a given structure it is likely to be chiral, but in special cases, to be discussed later, may be achiral.

Structures F and G are achiral. The former has a plane of symmetry passing through the chlorine atom and bisecting the opposite carbon-carbon bond. The similar structure of compound E does not have such a symmetry plane, and the carbon bonded to the chlorine is a chiral center (the two ring segments connecting this carbon are not identical). Structure G is essentially flat. All the carbons except that of the methyl group are sp^2 hybridized, and therefore trigonal-planar in configuration. Compounds C, D & H have more than one chiral center, and are also chiral. Remember, all chiral structures may exist as a pair of enantiomers. Other configurational stereoisomers are possible if more than one stereogenic center is present in a structure.

In the 1960's, a drug called thalidomide was widely prescribed in the Western Europe to alleviate morning sickness in pregnant women.

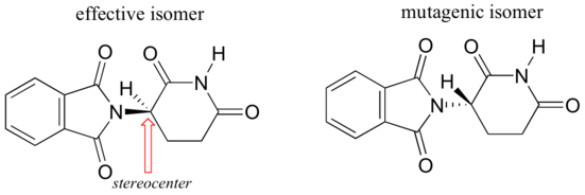


thalidomide

Thalidomide had previously been used in other countries as an antidepressant, and was believed to be safe and effective for both purposes. The drug was not approved for use in the U.S.A. It was not long, however, before doctors realized that something had

gone horribly wrong: many babies born to women who had taken thalidomide during pregnancy suffered from severe birth defects.

Researchers later realized the that problem lay in the fact that thalidomide was being provided as a mixture of two different isomeric forms.

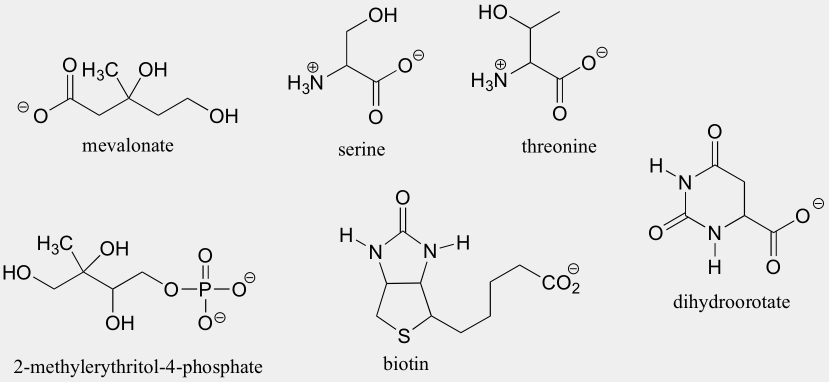


One of the isomers is an effective medication, the other caused the side effects. Both isomeric forms have the same molecular formula and the same atom-to-atom connectivity, so they are not constitutional isomers. Where they differ is in the arrangement in three-dimensional space about one tetrahedral, sp^3-hybridized carbon. These two forms of thalidomide are **stereoisomers**.

Note that the carbon in question has *four different substituents* (two of these just happen to be connected by a ring structure). Tetrahedral carbons with four different substituent groups are called **stereocenters**.

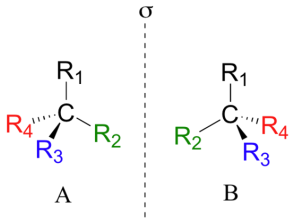
Example 1

Exercise 3.5: Locate all of the carbon stereocenters in the molecules below.

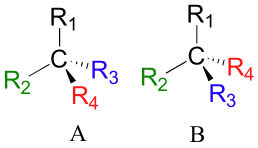


Solution

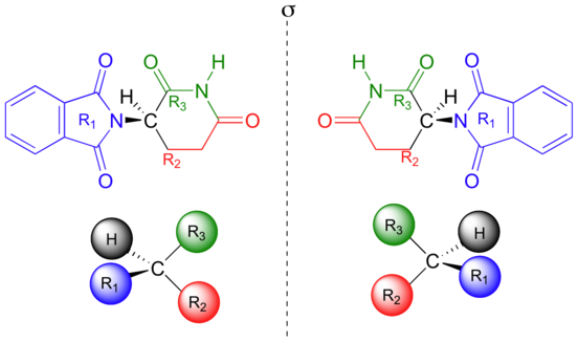
Looking at the structures of what we are referring to as the two isomers of thalidomide, you may not be entirely convinced that they are actually two different molecules. In order to convince ourselves that they are indeed different, let's create a generalized picture of a tetrahedral carbon stereocenter, with the four substituents designated R_1-R_4. The two stereoisomers of our simplified model look like this:



If you look carefully at the figure above, you will notice that molecule A and molecule B are mirror images of each other (the line labeled 's' represents a mirror plane). Furthermore, *they are not superimposable*: if we pick up molecule A, flip it around, and place it next to molecule B, we see that the two structures cannot be superimposed on each other. They are different molecules!



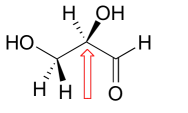
If you make models of the two stereoisomers of thalidomide and do the same thing, you will see that they too are mirror images, and cannot be superimposed (it well help to look at a color version of the figure below).



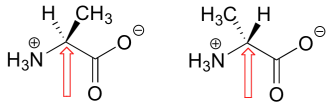
Thalidomide is a **chiral** molecule. Something is considered to be chiral if it cannot be superimposed on its own mirror image – in other words, if it is **asymmetric** (lacking in symmetry). The term 'chiral' is derived from the Greek word for 'handedness' – ie. right-handedness or left-handedness. Your hands are chiral: your right hand is a mirror image of your left hand, but if you place one hand on top of the other, both palms down, you see that they are not superimposable.

A pair of stereoisomers that are non-superimposable mirror images of one another are considered to have a specific type of stereoisomeric relationship – they are a pair of **enantiomers**. Thalidomide exists as a pair of enantiomers. On the macro level, your left and right hands are also a pair of enantiomers.

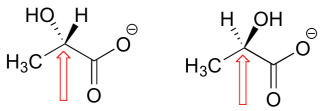
Here are some more examples of chiral molecules that exist as pairs of enantiomers. In each of these examples, there is a single stereocenter, indicated with an arrow. (Many molecules have more than one stereocenter, but we will get to that that a little later!)



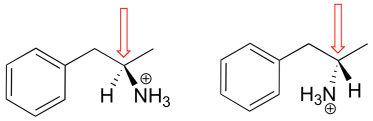
glyceraldehyde



alanine

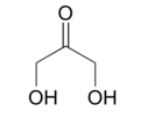


lactate

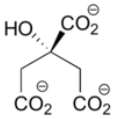


amphetamine

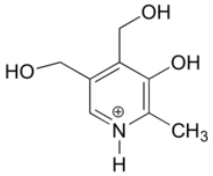
Here are some examples of molecules that are **achiral** (*not* chiral). Notice that none of these molecules has a stereocenter.



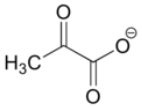
dihydroxyacetone



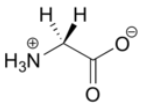
citrate



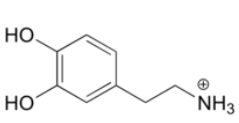
pyridoxine
(vitamin B_6)



pyruvate



glycine
(amino acid)



dopamine
(neurotransmitter)

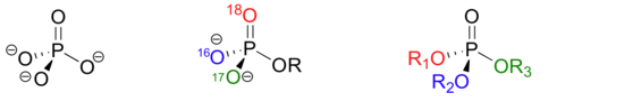
It is difficult to illustrate on the two dimensional page, but you will see if you build models of these achiral molecules that, in each case, there is at least one **plane of symmetry**, where one side of the plane is the mirror image of the other. Chirality is tied conceptually to the idea of asymmetry, and *any molecule that has a plane of symmetry cannot be chiral*. When looking for a plane

of symmetry, however, we must consider all possible conformations that a molecule could adopt. Even a very simple molecule like ethane, for example, is asymmetric in many of its countless potential conformations – but it has obvious symmetry in both the eclipsed and staggered conformations, and for this reason it is achiral.

Looking for planes of symmetry in a molecule is useful, but often difficult in practice. In most cases, the easiest way to decide whether a molecule is chiral or achiral is to look for one or more stereocenters - with a few rare exceptions (see section 3.7B), the general rule is that molecules with at least one stereocenter are chiral, and molecules with no stereocenters are achiral. Carbon stereocenters are also referred to quite frequently as **chiral carbons**.

When evaluating a molecule for chirality, it is important to recognize that the question of whether or not the dashed/solid wedge drawing convention is used is irrelevant. Chiral molecules are sometimes drawn without using wedges (although obviously this means that stereochemical information is being omitted). Conversely, wedges may be used on carbons that are not stereocenters – look, for example, at the drawings of glycine and citrate in the figure above. Just because you see dashed and solid wedges in a structure, do not automatically assume that you are looking at a stereocenter.

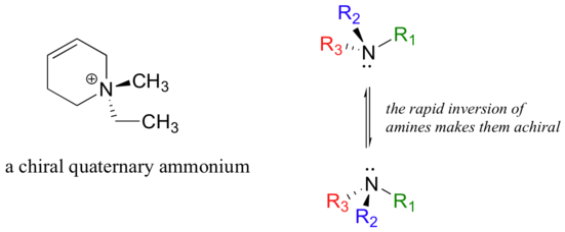
Other elements in addition to carbon can be stereocenters. The phosphorus center of phosphate ion and organic phosphate esters, for example, is tetrahedral, and thus is potentially a stereocenter.



phosphate (achiral) | labeled phosphate ester (chiral) | a chiral phosphate triester

We will see in chapter 10 how researchers, in order to investigate the stereochemistry of reactions at the phosphate center, incorporated sulfur and/or ^{17}O and ^{18}O isotopes of oxygen (the 'normal' isotope is ^{16}O) to create chiral phosphate groups. Phosphate triesters are chiral if the three substituent groups are different.

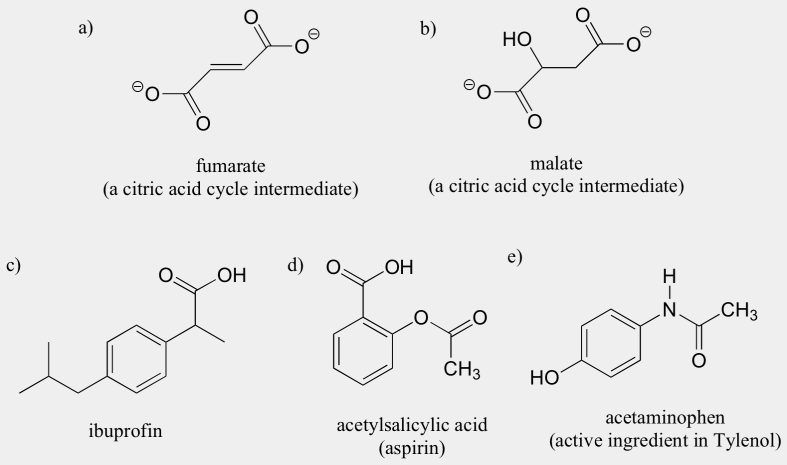
Asymmetric quaternary ammonium groups are also chiral. Amines, however, are not chiral, because they rapidly invert, or turn 'inside out', at room temperature.



a chiral quaternary ammonium

Example 2

Exercise 3.6: Label the molecules below as chiral or achiral, and locate all stereocenters.



a) fumarate (a citric acid cycle intermediate)

b) malate (a citric acid cycle intermediate)

c) ibuprofin

d) acetylsalicylic acid (aspirin)

e) acetaminophen (active ingredient in Tylenol)

Solution

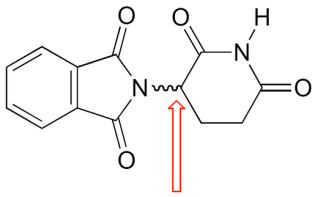
Internal Links

- Virtual Textbook of OChem

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

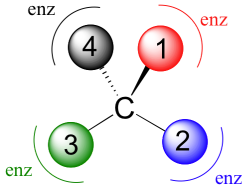
5.5: Stereogenic Centers in Cyclic Compounds

The thalidomide that was used in the 1960s to treat depression and morning sickness was sold as a 50:50 mixture of both the R and the S enantiomer – this is referred to as a **racemic mixture**. A 'squiggly' bond in a chemical structure indicates a racemic mixture - thus racemic (*R/S*) thalidomide would be drawn as:

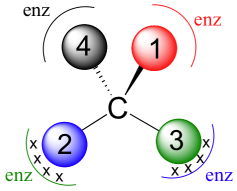


mixture of both R and S configurations at this stereocenter

The problem with racemic thalidomide, as we know, was that only the R enantiomer was an effective medicine, while the S enantiomer caused mutations in the developing fetus. How does such a seemingly trivial structural variation lead to such a dramatic (and in this case, tragic) difference in biological activity? Virtually all drugs work by interacting in some way with important proteins in our cells: they may bind to pain receptor proteins to block the transmission of pain signals, for instance, or clog up the active site of an enzyme that is involved in the synthesis of cholesterol. Proteins are chiral molecules, and are very sensitive to stereochemistry: just as a right-handed glove won't fit on your left hand, a protein that is able to bind tightly to (*R*)-thalidomide may not bind well at all to (*S*)-thalidomide (it will help to view a color version of the figure below).



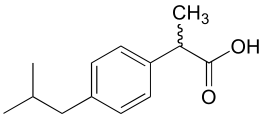
a protein that binds specifically to a chiral molecule . . .



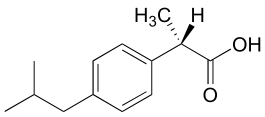
may not bind well at all to a different stereoisomer!

Instead, it seems that (*S*)-thalidomide interacts somehow with a protein involved in the development of a growing fetus, eventually causing the observed birth defects.

The over-the-counter painkiller ibuprofen is currently sold as a racemic mixture, but only the *S* enantiomer is effective.



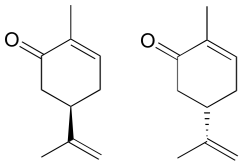
racemic ibuprofin



(S)-ibuprofin
(active enantiomer)

Fortunately, the *R* enantiomer does not produce any dangerous side effects, although its presence does seem to increase the amount of time that it takes for (*S*)-ibuprofen to take effect.

You can, with the assistance your instructor, directly experience the biological importance of stereoisomerism. Carvone is a chiral, plant-derived molecule that smells like spearmint in the *R* form and caraway (a spice) in the *S* form.



(R)-carvone (S)-carvone

The two enantiomers interact differently with smell receptor proteins in your nose, generating the transmission of different chemical signals to the olfactory center of your brain.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris) Template:HideTOC

5.6: Labeling Stereogenic Centers with R or S

To name the enantiomers of a compound unambiguously, their names must include the "handedness" of the molecule. The method for this is formally known as R/S nomenclature.

Introduction

The method of unambiguously assigning the handedness of molecules was originated by three chemists: R.S. Cahn, C. Ingold, and V. Prelog and, as such, is also often called the Cahn-Ingold-Prelog rules. In addition to the Cahn-Ingold system, there are two ways of experimentally determining the absolute configuration of an enantiomer:

1. X-ray diffraction analysis. Note that there is no correlation between the sign of rotation and the structure of a particular enantiomer.
2. Chemical correlation with a molecule whose structure has already been determined via X-ray diffraction.

However, for non-laboratory purposes, it is beneficial to focus on the R/S system. The sign of optical rotation, although different for the two enantiomers of a chiral molecule,at the same temperature, **cannot** be used to establish the absolute configuration of an enantiomer; this is because the sign of optical rotation for a particular enantiomer may change when the temperature changes.

Stereocenters are labeled R or S

The "right hand" and "left hand" nomenclature is used to name the enantiomers of a chiral compound. The stereocenters are labeled as R or S.

Consider the first picture: a curved arrow is drawn from the highest priority (*1*) substituent to the lowest priority *(4)* substituent. If the arrow points in a counterclockwise direction (**left** when leaving the 12 o' clock position), the configuration at stereocenter is considered ***S*** ("Sinister" → Latin= "left"). If, however, the arrow points clockwise,(**Right** when leaving the 12 o' clock position) then the stereocenter is labeled ***R*** ("Rectus" → Latin= "right").

The ***R*** *or* ***S*** is then added as a prefix, in parenthesis, to the name of the enantiomer of interest.

Example 1
(*R*)-2-Bromobutane (*S*)-2,3- Dihydroxypropanal

Sequence rules to assign priorities to substituents

Before applying the R and S nomenclature to a stereocenter, the substituents must be prioritized according to the following rules:

Rule 1

First, examine at the atoms directly attached to the stereocenter of the compound. A substituent with a higher atomic number takes precedence over a substituent with a lower atomic number. Hydrogen is the lowest possible priority substituent, because it has the lowest atomic number.

1. When dealing with isotopes, the atom with the higher atomic mass receives higher priority.
2. When visualizing the molecule, the lowest priority substituent should always point away from the viewer (a dashed line indicates this). To understand how this works or looks, imagine that a clock and a pole. Attach the pole to the back of the clock, so that when when looking at the face of the clock the pole points away from the viewer in the same way the lowest priority substituent should point away.
3. Then, draw an arrow from the highest priority atom to the 2nd highest priority atom to the 3rd highest priority atom. Because the 4th highest priority atom is placed in the back, the arrow should appear like it is going across the face of a clock. If it is

going clockwise, then it is an R-enantiomer; If it is going counterclockwise, it is an S-enantiomer.

When looking at a problem with wedges and dashes, if the lowest priority atom is not on the dashed line pointing away, the molecule must be rotated.
Remember that

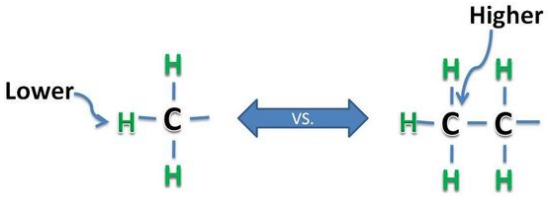
- Wedges indicate coming towards the viewer.
- Dashes indicate pointing away from the viewer.

Rule 2

If there are two substituents with equal rank, proceed along the two substituent chains until there is a point of difference. First, determine which of the chains has the first connection to an atom with the highest priority (the highest atomic number). That chain has the higher priority.

If the chains are similar, proceed down the chain, until a point of difference.

For example: an ethyl substituent takes priority over a methyl substituent. At the connectivity of the stereocenter, both have a carbon atom, which are equal in rank. Going down the chains, a methyl has only has hydrogen atoms attached to it, whereas the ethyl has another carbon atom. The carbon atom on the ethyl is the first point of difference and has a higher atomic number than hydrogen; therefore the ethyl takes priority over the methyl.



The "H-" (left) ranks lower than the "C-" (right) based on the first point of difference and their relative molecular weights

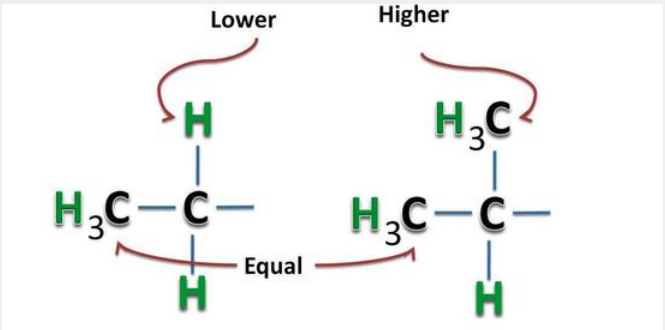
Rule 3

If a chain is connected to the same kind of atom twice or three times, check to see if the atom it is connected to has a greater atomic number than any of the atoms that the competing chain is connected to.

- If none of the atoms connected to the competing chain(s) at the same point has a greater atomic number: the chain bonded to the same atom multiple times has the greater priority
- If however, one of the atoms connected to the competing chain has a higher atomic number: that chain has the higher priority.

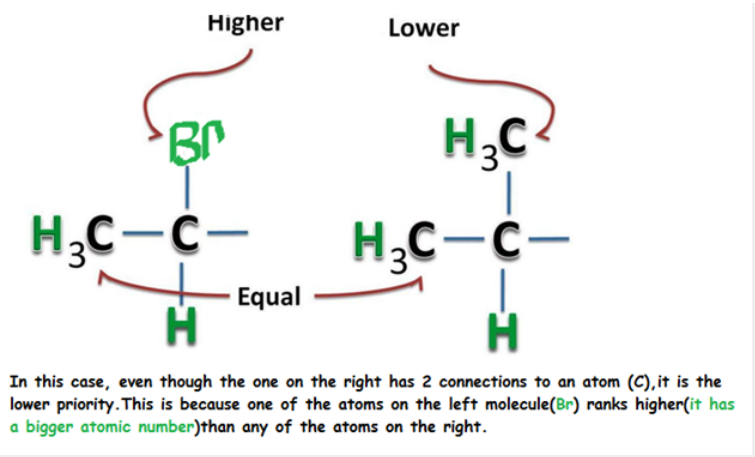
Example 2

A 1-methylethyl substituent takes precedence over an ethyl substituent. Connected to the first carbon atom, ethyl only has one other carbon, whereas the 1-methylethyl has two carbon atoms attached to the first; this is the first point of difference. Therefore, 1-methylethyl ranks higher in priority than ethyl, as shown below:



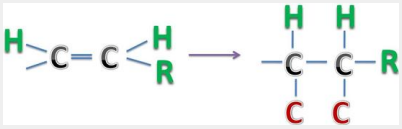
The "C-" (right) ranks higher than the "H-" (left) based on the first point of difference and their relative molecular weights.

However:



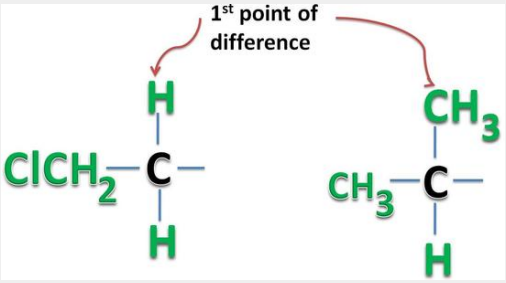
In this case, even though the one on the right has 2 connections to an atom (C), it is the lower priority. This is because one of the atoms on the left molecule(Br) ranks higher(it has a bigger atomic number)than any of the atoms on the right.

Remember that being double or triple bonded to an atom means that the atom is connected to the same atom twice. In such a case, follow the same method as above.

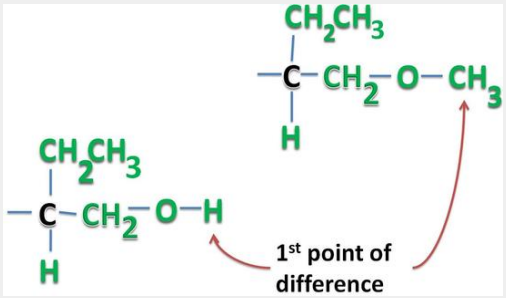


Caution!!

Keep in mind that priority is determined by the **first** point of difference along the two similar substituent chains. After the first point of difference, the rest of the chain is irrelevant.



When looking for the first point of difference on similar substituent chains, one may encounter branching. If there is branching, choose the branch that is higher in priority. If the two substituents have similar branches, rank the elements within the branches until a point of difference.



After all your substituents have been prioritized in the correct manner, you can now name/label the molecule **R** or **S.**

1. Put the lowest priority substituent in the back (dashed line).
2. Proceed from 1 to 2 to 3. (it is helpful to draw or imagine an arcing arrow that goes from 1--> 2-->3)
3. Determine if the direction from 1 to 2 to 3 clockwise or counterclockwise.

i) If it is **clockwise** it is **R.**
ii) if it is **counterclockwise** it is **S**.

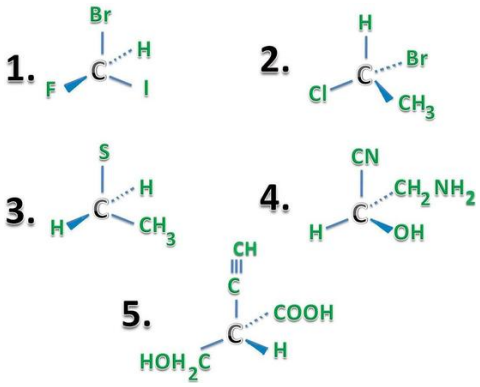
USE YOUR MODELING KIT: Models assist in visualizing the structure. When using a model, make sure the lowest priority is pointing away from you. Then determine the direction from the highest priority substituent to the lowest: clockwise (R) or counterclockwise (S).

IF YOU DO NOT HAVE A MODELING KIT: remember that the dashes mean the bond is going into the screen and the wedges means that bond is coming out of the screen. If the lowest priority bond is not pointing to the back, mentally rotate it so that it is. However, it is very useful when learning organic chemistry to use models.

If you have a modeling kit use it to help you solve the following practice problems.

Problems

Are the following R or S?



Solutions

1. **S:** I > Br > F > H. The lowest priority substituent, H, is already going towards the back. It turns left going from I to Br to F, so it's a S.
2. **R:** Br > Cl > CH_3 > H. You have to switch the H and Br in order to place the H, the lowest priority, in the back. Then, going from Br to Cl, CH_3 is turning to the right, giving you a R.
3. **Neither R or S**: This molecule is achiral. Only chiral molecules can be named R or S.
4. **R:** OH > CN > CH_2NH_2 > H. The H, the lowest priority, has to be switched to the back. Then, going from OH to CN to CH_2NH_2, you are turning right, giving you a R.
5. **(5) S:** $-COOH > -CH_2OH > C{\equiv}CH >$ H. Then, going from $-COOH$ to $-CH_2OH$ to $-C{\equiv}CH$ you are turning left, giving you a S configuration.

Outside links

- http://www.youtube.com/watch?v=EphUiPiQiCo
- http://en.wikipedia.org/wiki/Absolute_configuration

References

1. Schore and Vollhardt. *Organic Chemistry Structure and Function.* New York:W.H. Freeman and Company, 2007.
2. McMurry, John and Simanek, Eric. *Fundamentals of Organic Chemistry*. 6th Ed. Brooks Cole, 2006.

Contributors

- Ekta Patel (UCD), Ifemayowa Aworanti (University of Maryland Baltimore County)

5.7: Diastereomers

Diastereomers are stereoisomers that are not related as object and mirror image and are not enantiomers. Unlike enatiomers which **are mirror images** of each other and **non-sumperimposable**, diastereomers are **not mirror images** of each other and **non-superimposable**. Diastereomers can have different physical properties and reactivity. They have different melting points and boiling points and different densities. They have **two or more** stereocenters.

Introduction

It is easy to mistake between diasteromers and enantiomers. For example, we have four steroisomers of 3-bromo-2-butanol. The four possible combination are SS, RR, SR and RS (Figure 1). One of the molecule is the enantiomer of its mirror image molecule and diasteromer of each of the other two molecule (SS is enantiomer of RR and diasteromer of RS and SR). SS's mirror image is RR and they are not superimposable, so they are enantiomers. RS and SR are not mirror image of SS and are not superimposable to each other, so they are diasteromers.

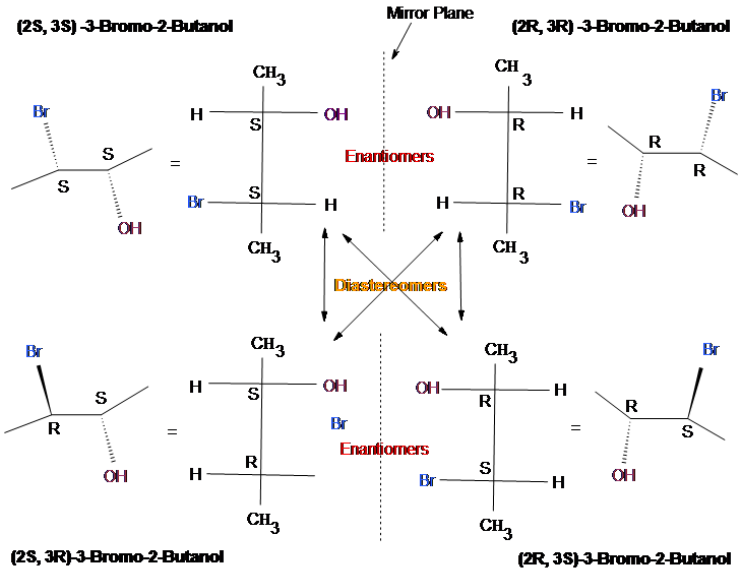


Figure 1

Diastereomers vs. Enantiomers

Tartaric acid, $C_4H_6O_6$, is an organic compound that can be found in grape, bananas, and in wine. The structures of tartaric acid itself is really interesting. Naturally, it is in the form of (R,R) stereocenters. Artificially, it can be in the meso form (R,S), which is achiral. R,R tartaric acid is enantiomer to is mirror image which is S,S tartaric acid and diasteromers to meso-tartaric acid (figure 2).

(R,R) and (S,S) tartaric acid have similar physical properties and reactivity. However, meso-tartaric acid have different physical properties and reactivity. For example, melting point of (R,R) & (S,S) tartaric is about 170 degree Celsius, and melting point of meso-tartaric acid is about 145 degree Celsius.

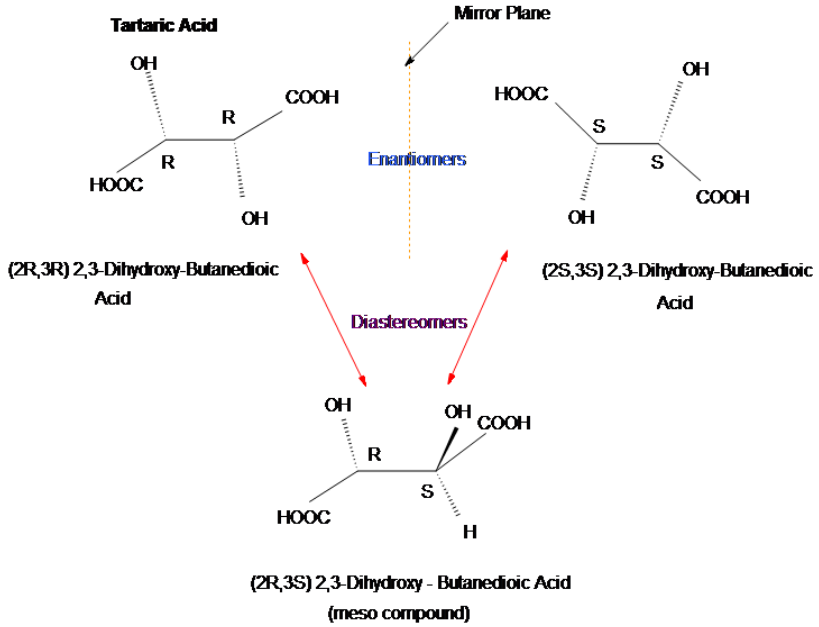
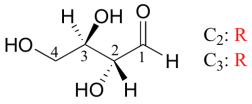


Figure 2

We turn our attention next to molecules which have more than one stereocenter. We will start with a common four-carbon sugar called D-erythrose.



D-erythrose

A note on sugar nomenclature: biochemists use a special system to refer to the stereochemistry of sugar molecules, employing names of historical origin in addition to the designators '*D*' and '*L*'. You will learn about this system if you take a biochemistry class. We will use the *D/L* designations here to refer to different sugars, but we won't worry about learning the system.

As you can see, *D*-erythrose is a chiral molecule: C_2 and C_3 are stereocenters, both of which have the *R* configuration. In addition, you should make a model to convince yourself that it is impossible to find a plane of symmetry through the molecule, regardless of the conformation. Does D-erythrose have an enantiomer? Of course it does – if it is a chiral molecule, it must. The enantiomer of erythrose is its mirror image, and is named L-erythrose (once again, you should use models to convince yourself that these mirror images of erythrose are not superimposable).

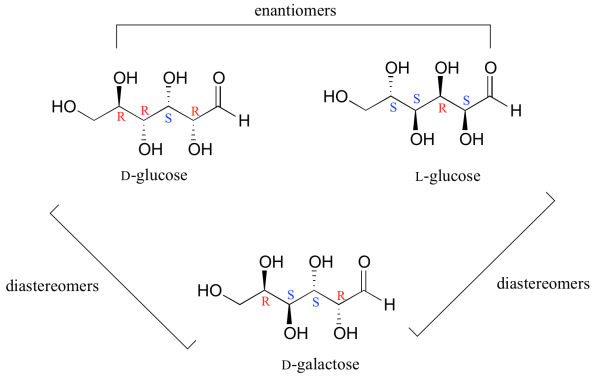
Notice that both chiral centers in L-erythrose both have the *S* configuration. *In a pair of enantiomers, **all** of the chiral centers are of the opposite configuration.*

What happens if we draw a stereoisomer of erythrose in which the configuration is *S* at C_2 and *R* at C_3? This stereoisomer, which is a sugar called D-threose, is *not* a mirror image of erythrose. D-threose is a **diastereomer** of both D-erythrose and L-erythrose.

The definition of diastereomers is simple: if two molecules are stereoisomers (same molecular formula, same connectivity, different arrangement of atoms in space) but are *not* enantiomers, then they are diastereomers by default. *In practical terms, this means that at least one - but not all - of the chiral centers are opposite in a pair of diastereomers.* By definition, two molecules that are diastereomers are *not* mirror images of each other.

L-threose, the enantiomer of D-threose, has the *R* configuration at C_2 and the *S* configuration at C_3. L-threose is a diastereomer of both erythrose enantiomers.

In general, a structure with *n* stereocenters will have 2^n different stereoisomers. (We are not considering, for the time being, the stereochemistry of double bonds – that will come later). For example, let's consider the glucose molecule in its open-chain form (recall that many sugar molecules can exist in either an open-chain or a cyclic form). There are two enantiomers of glucose, called D-glucose and L-glucose. The D-enantiomer is the common sugar that our bodies use for energy. It has $n = 4$ stereocenters, so therefore there are $2^n = 2^4 = 16$ possible stereoisomers (including D-glucose itself).

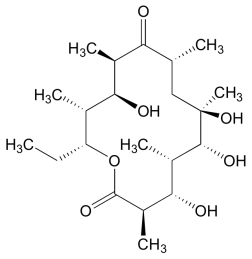


In L-glucose, all of the stereocenters are inverted relative to *D*-glucose. That leaves 14 diastereomers of D-glucose: these are molecules in which at least one, but not all, of the stereocenters are inverted relative to D-glucose. One of these 14 diastereomers, a sugar called *D*-galactose, is shown above: in D-galactose, one of four stereocenters is inverted relative to D-glucose. Diastereomers which differ in only one stereocenter (out of two or more) are called **epimers**. D-glucose and D-galactose can therefore be refered to as epimers as well as diastereomers.

Examples

Exercise 3.10: Draw the structure of L-galactose, the enantiomer of D-galactose.
Exercise 3.11: Draw the structure of two more diastereomers of D-glucose. One should be an epimer.
Solutions

Erythronolide B, a precursor to the 'macrocyclic' antibiotic erythromycin, has 10 stereocenters. It's enantiomer is that molecule in which all 10 stereocenters are inverted.



erythronolide B

In total, there are $2^{10} = 1024$ stereoisomers in the erythronolide B family: 1022 of these are diastereomers of the structure above, one is the enantiomer of the structure above, and the last ***is*** the structure above.

We know that enantiomers have identical physical properties and equal but opposite degrees of specific rotation. Diastereomers, in theory at least, have different physical properties – we stipulate 'in theory' because sometimes the physical properties of two or more diastereomers are so similar that it is very difficult to separate them. In addition, the specific rotations of diastereomers are unrelated – they could be the same sign or opposite signs, and similar in magnitude or very dissimilar.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

5.8: Meso Compounds

A meso compound is an achiral compound that has chiral centers. It is superimposed on its mirror image and is optically **inactive** although it contains two or more stereocenters.

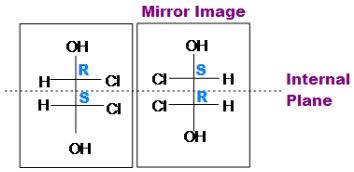
Introduction

In general, a meso compound should contain two or more identical substituted stereocenters. Also, it has an internal symmetry plane that divides the compound in half. These two halves reflect each other by the internal mirror. The stereochemistry of stereocenters should "cancel out". What it means here is that when we have an internal plane that splits the compound into two symmetrical sides, the stereochemistry of both left and right side should be opposite to each other, and therefore, result in **optically inactive**. Cyclic compounds may also be meso.

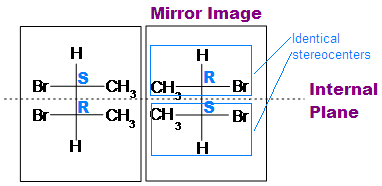
Identification

If A is a meso compound, it should have two or more stereocenters, an internal plane, and the stereochemistry should be R and S.

1. Look for an internal plane, or internal mirror, that lies in between the compound.
2. The stereochemistry (e.g. R or S) is very crucial in determining whether it is a meso compound or not. As mentioned above, a meso compound is optically inactive, so their stereochemistry should cancel out. For instance, R cancels S out in a meso compound with two stereocenters.

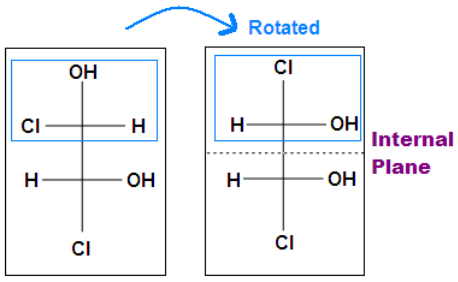


***trans*-1,2-dichloro-1,2-ethanediol**

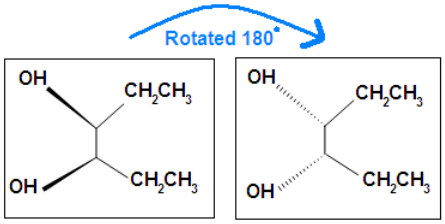


***(meso)*-2,3-dibromobutane**

Tips: An interesting thing about single bonds or sp^3-orbitals is that we can rotate the substituted groups that attached to a stereocenter around to recognize the internal plane. As the molecule is rotated, its stereochemistry does not change. For example:

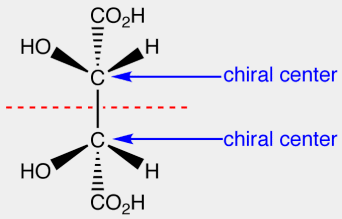


Another case is when we rotate the whole molecule by 180 degree. Both molecules below are still meso.



Remember the internal plane here is depicted on two dimensions. However, in reality, it is three dimensions, so be aware of it when we identify the internal mirror.

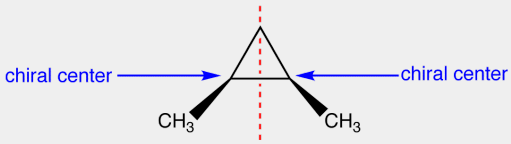
Example 1



1

1 has a plane of symmetry (the horizonatal plane going through the red broken line) and, therefore, is achiral; 1 has chiral centers. Thus, 1 is a meso compound.

Example 2

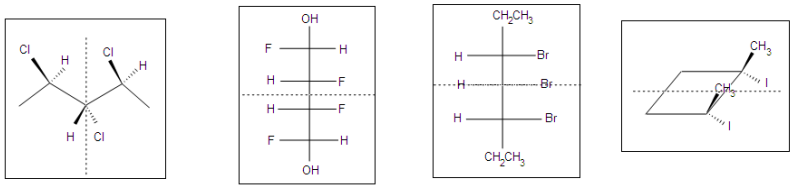


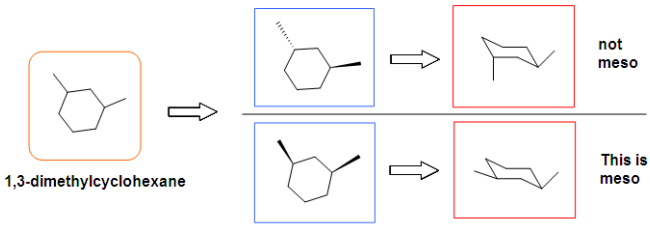
2

This molecules has a plane of symmetry (the vertical plane going through the red broken line perpendicular to the plane of the ring) and, therefore, is achiral, but has has two chiral centers. Thus, its is a meso compound.

Other Examples of meso compounds

Meso compounds can exist in many different forms such as pentane, butane, heptane, and even cyclobutane. They do not necessarily have to be two stereocenters, but can have more.



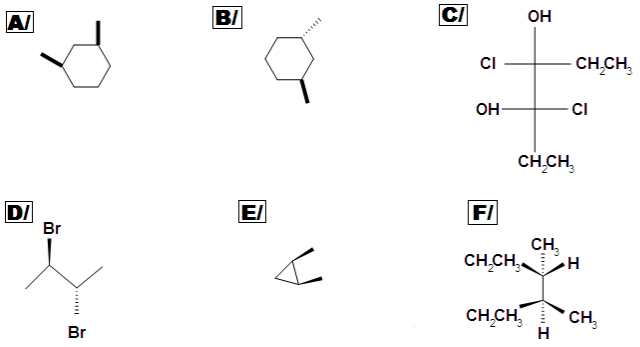


Optical Activity Analysis

When the optical activity of a meso compound is attempted to be determined with a polarimeter, the indicator will not show (+) or (-). It simply means there is no certain direction of rotation of the polarized light, neither levorotatory (-) and dexorotatory (+).

Problems

Beside meso, there are also other types of molecules: enantiomer, diastereomer, and identical. Determine if the following molecules are meso.



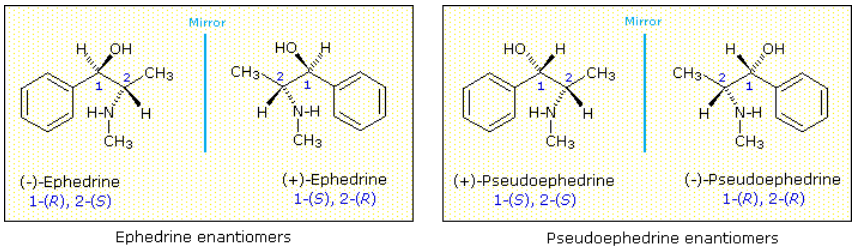
Answer key: A C, D, E are meso compounds.

Contributors

- Duy Dang
- Gamini Gunawardena from the OChemPal site (Utah Valley University)

5.9: R and S Assignments in Compounds with Two or More Stereogenic Centers

The Chinese shrub Ma Huang (Ephedra vulgaris) contains two physiologically active compounds ephedrine and pseudoephedrine. Both compounds are stereoisomers of 2-methylamino-1-phenyl-1-propanol, and both are optically active, one being levorotatory and the other dextrorotatory. Since the properties of these compounds (see below) are significantly different, they cannot be enantiomers. How, then, are we to classify these isomers and others like them?



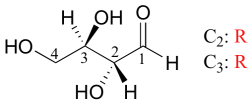
Stereoisomers of 2-methylamino-1-phenylpropanol

Ephedrine: m.p. 35 - 40 ° C, [α]D = –41°, moderate water solubility [this isomer may be referred to as (–)-ephedrine]

Pseudoephedrine: m.p. 119 ° C, [α]D = +52°, relatively insoluble in water [this isomer may be referred to as (+)-pseudoephedrine]

Since these two compounds are optically active, each must have an enantiomer. Although these missing stereoisomers were not present in the natural source, they have been prepared synthetically and have the expected identical physical properties and opposite-sign specific rotations with those listed above. The structural formula of 2-methylamino-1-phenylpropanol has two stereogenic carbons (#1 & #2). Each may assume an R or S configuration, so there are four stereoisomeric combinations possible. These are shown in the following illustration, together with the assignments that have been made on the basis of chemical interconversions

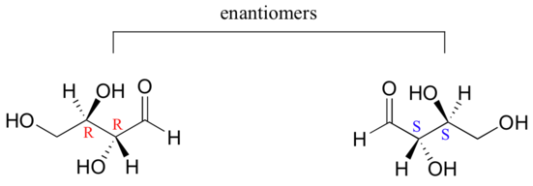
We turn our attention next to molecules which have more than one stereocenter. We will start with a common four-carbon sugar called D-erythrose.



D-erythrose

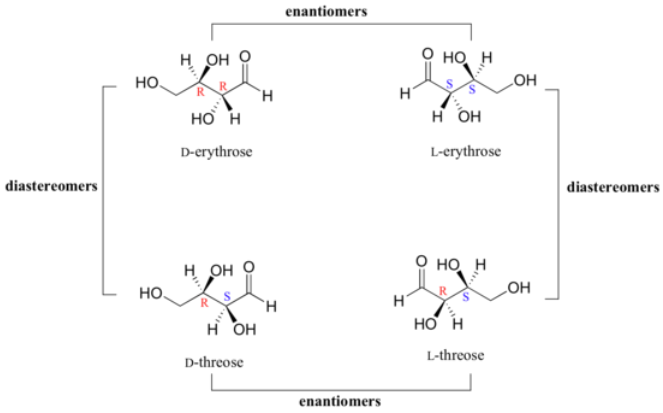
A note on sugar nomenclature: biochemists use a special system to refer to the stereochemistry of sugar molecules, employing names of historical origin in addition to the designators '*D*' and '*L*'. You will learn about this system if you take a biochemistry class. We will use the *D/L* designations here to refer to different sugars, but we won't worry about learning the system.

As you can see, *D*-erythrose is a chiral molecule: C_2 and C_3 are stereocenters, both of which have the *R* configuration. In addition, you should make a model to convince yourself that it is impossible to find a plane of symmetry through the molecule, regardless of the conformation. Does D-erythrose have an enantiomer? Of course it does – if it is a chiral molecule, it must. The enantiomer of erythrose is its mirror image, and is named L-erythrose (once again, you should use models to convince yourself that these mirror images of erythrose are not superimposable).



Notice that both chiral centers in L-erythrose both have the *S* configuration. *In a pair of enantiomers, **all** of the chiral centers are of the opposite configuration.*

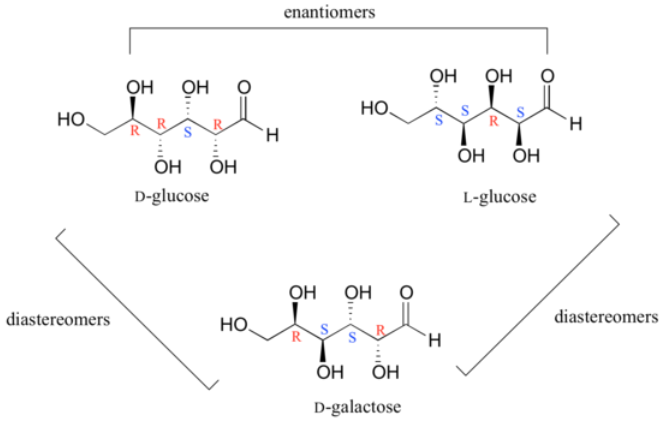
What happens if we draw a stereoisomer of erythrose in which the configuration is *S* at C_2 and *R* at C_3? This stereoisomer, which is a sugar called D-threose, is *not* a mirror image of erythrose. D-threose is a **diastereomer** of both D-erythrose and L-erythrose.



The definition of diastereomers is simple: if two molecules are stereoisomers (same molecular formula, same connectivity, different arrangement of atoms in space) but are *not* enantiomers, then they are diastereomers by default. *In practical terms, this means that at least one - but not all - of the chiral centers are opposite in a pair of diastereomers.* By definition, two molecules that are diastereomers are *not* mirror images of each other.

L-threose, the enantiomer of D-threose, has the *R* configuration at C_2 and the *S* configuration at C_3. L-threose is a diastereomer of both erythrose enantiomers.

In general, a structure with *n* stereocenters will have 2^n different stereoisomers. (We are not considering, for the time being, the stereochemistry of double bonds – that will come later). For example, let's consider the glucose molecule in its open-chain form (recall that many sugar molecules can exist in either an open-chain or a cyclic form). There are two enantiomers of glucose, called D-glucose and L-glucose. The D-enantiomer is the common sugar that our bodies use for energy. It has $n = 4$ stereocenters, so therefore there are $2^n = 2^4 = 16$ possible stereoisomers (including D-glucose itself).



In L-glucose, all of the stereocenters are inverted relative to *D*-glucose. That leaves 14 diastereomers of D-glucose: these are molecules in which at least one, but not all, of the stereocenters are inverted relative to D-glucose. One of these 14 diastereomers, a sugar called *D*-galactose, is shown above: in D-galactose, one of four stereocenters is inverted relative to D-glucose. Diastereomers which differ in only one stereocenter (out of two or more) are called **epimers**. D-glucose and D-galactose can therefore be refered to as epimers as well as diastereomers.

Examples

Exercise 3.10: Draw the structure of L-galactose, the enantiomer of D-galactose.
Exercise 3.11: Draw the structure of two more diastereomers of D-glucose. One should be an epimer.
Solutions

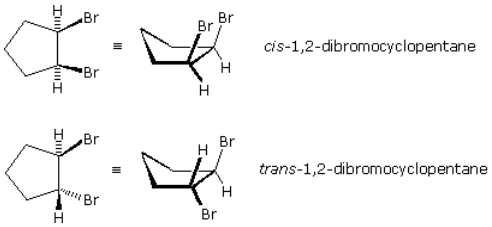
Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

---

5.10: Disubstituted Cycloalkanes

Configurational Stereoisomers of Cycloalkanes



Stereoisomers are also observed in certain disubstituted (and higher substituted) cyclic compounds. Unlike the relatively flat molecules of alkenes, substituted cycloalkanes must be viewed as three-dimensional configurations in order to appreciate the spatial orientations of the substituents. By agreement, chemists use heavy, **wedge-shaped** bonds to indicate a substituent located above the average plane of the ring (note that cycloalkanes larger than three carbons are not planar), and a **hatched line** for bonds to atoms or groups located below the ring. As in the case of the 2-butene stereoisomers, disubstituted cycloalkane stereoisomers may be designated by nomenclature prefixes such as *cis* and *trans*. The stereoisomeric 1,2-dibromocyclopentanes shown to the right are an example.

Many of the stereochemical concepts we have covered are illustrated nicely by looking at disubstituted cyclohexanes. We will now examine several dichlorocyclohexanes.

The 1,1-dichloro isomer has no centers of chirality. The 1,2- and 1,3-dichlorocyclohexanes each have two centers of chirality, bearing the same set of substituents. The cis & trans-1,4-dichlorocyclohexanes do not have any chiral centers, since the two ring groups on the substituted carbons are identical.

There are three configurational isomers of 1,2-dichlorocyclohexane and three configurational isomers of 1,3-dichlorocyclohexane. These are shown below:

1,2-substitution

1,3-substitution

All the 1,2-dichloro isomers are constitutional isomers of the 1,3-dichloro isomers. In each category (1,2- & 1,3-), the (R,R)-trans isomer and the (S,S)-trans isomer are enantiomers. The cis isomer is a diastereomer of the trans isomers.

Finally, all of these isomers may exist as a mixture of two (or more) conformational isomers.The chair conformer of the *cis* 1,2-dichloro isomer *appears* to be chiral. However, It exists as a 50:50 mixture of chair conformations, which interconvert so rapidly they cannot be resolved (ie. separated). In fact, a boat conformation can be constructued in which there exists a plane of symmetry, therefore the cis isomer is, over, achiral. Since the cis isomer has two centers of chirality (asymmetric carbons) but is achiral, it is a meso-compound. The corresponding trans isomers also exist as rapidly interconverting chiral conformations, but they are chiral. The diequatorial conformer predominates in each case, the (R,R) conformations being mirror images of the (S,S) conformations. All these conformations are diastereomeric with the cis conformations.

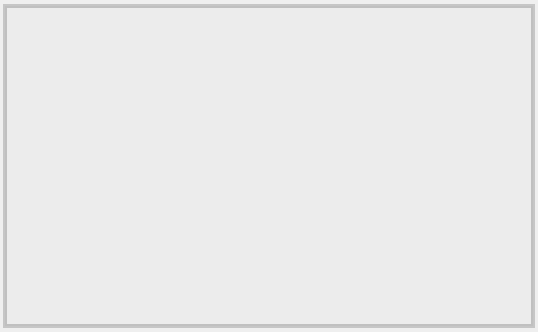
The diequatorial chair conformer of the *cis* 1,3-dichloro isomer is achiral. It is the major component of a fast equilibrium with the diaxial conformer, which is also achiral. This isomer is also a meso compound. The corresponding trans isomers also undergo a rapid conformational interconversion. For these isomers, however, this interconversion produces an identical conformer, so each enantiomer (R,R) and (S,S) has predominately a single chiral conformation. These enantiomeric conformations, both of which are chiral, are diastereomeric with the cis (meso) isomer.

Cyclic compounds can also be *meso*. One of many such examples is *cis*-1,2-dihydroxycyclohexane. Note, however, that if the hydroxyl groups are *trans* to each other, the molecule is chiral.

Fortunately for overworked organic chemistry students, the *meso* compound is a very special case, and it is difficult to find many naturally occurring examples. They do, however, seem to like showing up in organic chemistry exam questions.

Example

Exercise: Which of the molecules shown below are *meso*? Which are chiral? Which are achiral, but not *meso*?



Exercise: Draw the structure of another dimethylcyclopentane isomer that is *meso* (do not use structures from the previous problem).
Solutions

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- Robert Bruner (http://bbruner.org)

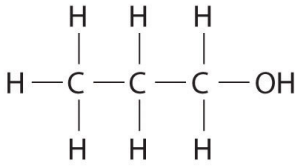
5.11: Isomers—A Summary

Conformational Isomers

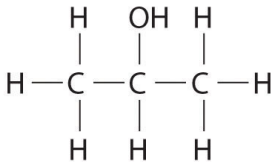
The C–C single bonds in ethane, propane, and other alkanes are formed by the overlap of an sp^3 hybrid orbital on one carbon atom with an sp^3 hybrid orbital on another carbon atom, forming a σ bond. Each sp^3 hybrid orbital is cylindrically symmetrical (all cross-sections are circles), resulting in a carbon–carbon single bond that is also cylindrically symmetrical about the C–C axis. Because rotation about the carbon–carbon single bond can occur without changing the overlap of the sp^3 hybrid orbitals, there is no significant electronic energy barrier to rotation. Consequently, many different arrangements of the atoms are possible, each corresponding to different degrees of rotation. Differences in three-dimensional structure resulting from rotation about a σ bond are called differences in conformation, and each different arrangement is called a conformational isomer (or conformer).

Structural Isomers

Unlike conformational isomers, which do not differ in connectivity, structural isomers differ in connectivity, as illustrated here for 1-propanol and 2-propanol. Although these two alcohols have the same molecular formula (C_3H_8O), the position of the –OH group differs, which leads to differences in their physical and chemical properties.

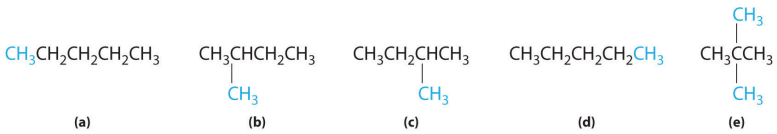


1-Propanol (*n*-propanol)



2-Propanol (isopropanol)

In the conversion of one structural isomer to another, at least one bond must be broken and reformed at a different position in the molecule. Consider, for example, the following five structures represented by the formula C_5H_{12}:



(a) **(b)** **(c)** **(d)** **(e)**

Of these structures, (a) and (d) represent the same compound, as do (b) and (c). No bonds have been broken and reformed; the molecules are simply rotated about a 180° vertical axis. Only three—n-pentane (a) and (d), 2-methylbutane (b) and (c), and 2,2-dimethylpropane (e)—are structural isomers. Because no bonds are broken in going from (a) to (d) or from (b) to (c), these alternative representations are not structural isomers. The three structural isomers—either (a) or (d), either (b) or (c), and (e)—have distinct physical and chemical properties.

Stereoisomers

Molecules with the same connectivity but different arrangements of the atoms in space are called stereoisomers. There are two types of stereoisomers: geometric and optical. Geometric isomers differ in the relative position(s) of substituents in a rigid molecule. Simple rotation about a C–C σ bond in an alkene, for example, cannot occur because of the presence of the π bond. The substituents are therefore rigidly locked into a particular spatial arrangement (part (a) in Figure 2.16. Thus a carbon–carbon multiple bond, or in some cases a ring, prevents one geometric isomer from being readily converted to the other. The members of

an isomeric pair are identified as either cis or trans, and interconversion between the two forms requires breaking and reforming one or more bonds. Because their structural difference causes them to have different physical and chemical properties, cis and trans isomers are actually two distinct chemical compounds.

> **Note**
>
> Stereoisomers have the same connectivity but different arrangements of atoms in space.

Optical isomers are molecules whose structures are mirror images but cannot be superimposed on one another in any orientation. Optical isomers have identical physical properties, although their chemical properties may differ in asymmetric environments. Molecules that are nonsuperimposable mirror images of each other are said to be chiral (pronounced “ky-ral,” from the Greek cheir, meaning “hand”). Examples of some familiar chiral objects are your hands, feet, and ears. As shown in part (a) in Figure 5.11.1., your left and right hands are nonsuperimposable mirror images. (Try putting your right shoe on your left foot—it just doesn’t work.) An achiral object is one that can be superimposed on its mirror image, as shown by the superimposed flasks in part (b) in Figure 5.11.1..

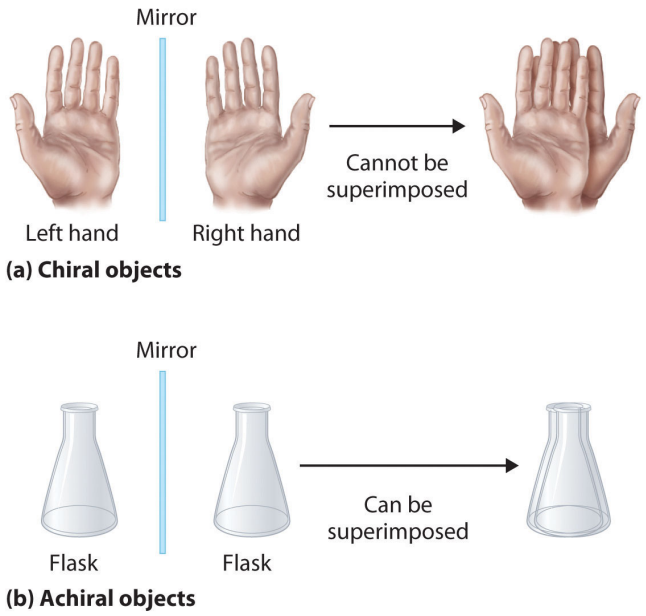


Figure 5.11.1*: Chiral and Achiral Objects. (a) Objects that are nonsuperimposable mirror images of each other are chiral, such as the left and the right hand. (b) The unmarked flask is achiral because it can be superimposed on its mirror image.*

Most chiral organic molecules have at least one carbon atom that is bonded to four different groups, as occurs in the bromochlorofluoromethane molecule shown in part (a) in Figure 5.11.2. This carbon, often designated by an asterisk in structural drawings, is called a chiral center or asymmetric carbon atom. If the bromine atom is replaced by another chlorine (part (b) in Figure 5.11.2), the molecule and its mirror image can now be superimposed by simple rotation. Thus the carbon is no longer a chiral center. Asymmetric carbon atoms are found in many naturally occurring molecules, such as lactic acid, which is present in milk and muscles, and nicotine, a component of tobacco. A molecule and its nonsuperimposable mirror image are called enantiomers (from the Greek enantiou, meaning “opposite”).

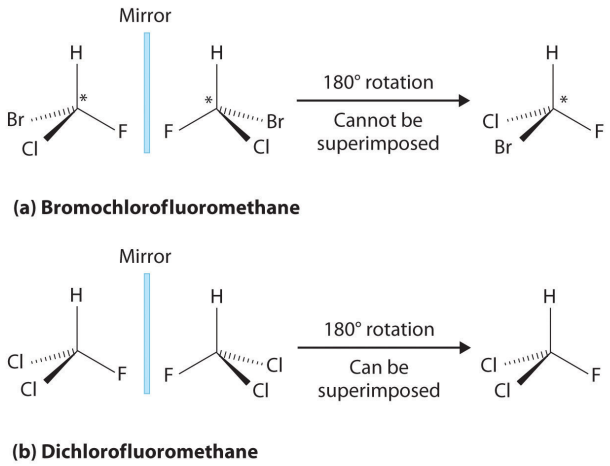


Figure 5.11.2: *Comparison of Chiral and Achiral Molecules. (a) Bromochlorofluoromethane is a chiral molecule whose stereocenter is designated with an asterisk. Rotation of its mirror image does not generate the original structure. To superimpose the mirror images, bonds must be broken and reformed. (b) In contrast, dichlorofluoromethane and its mirror image can be rotated so they are superimposable.*

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

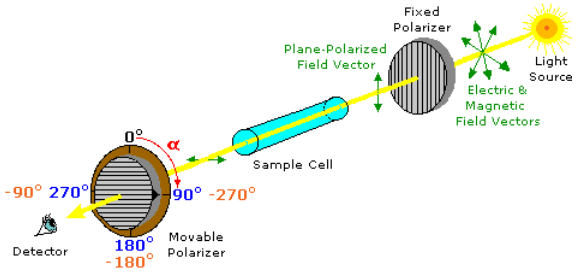
- Dan Chong

5.12: Physical Properties of Stereoisomers

Identifying and distinguishing enantiomers is inherently difficult, since their physical and chemical properties are largely identical. Fortunately, a nearly two hundred year old discovery by the French physicist Jean-Baptiste Biot has made this task much easier. This discovery disclosed that the right- and left-handed enantiomers of a chiral compound perturb plane-polarized light in opposite ways. This perturbation is unique to chiral molecules, and has been termed **optical activity**.

Polarimetry

Plane-polarized light is created by passing ordinary light through a polarizing device, which may be as simple as a lens taken from polarizing sun-glasses. Such devices transmit selectively only that component of a light beam having electrical and magnetic field vectors oscillating in a single plane. The plane of polarization can be determined by an instrument called a **polarimeter**, shown in the diagram below.



Monochromatic (single wavelength) light, is polarized by a fixed polarizer next to the light source. A sample cell holder is located in line with the light beam, followed by a movable polarizer (the analyzer) and an eyepiece through which the light intensity can be observed. In modern instruments an electronic light detector takes the place of the human eye. In the absence of a sample, the light intensity at the detector is at a maximum when the second (movable) polarizer is set parallel to the first polarizer (α = 0º). If the analyzer is turned 90º to the plane of initial polarization, all the light will be blocked from reaching the detector.

Chemists use polarimeters to investigate the influence of compounds (in the sample cell) on plane polarized light. Samples composed only of achiral molecules (e.g. water or hexane), have no effect on the polarized light beam. However, if a single enantiomer is examined (all sample molecules being right-handed, or all being left-handed), the plane of polarization is rotated in either a clockwise (positive) or counter-clockwise (negative) direction, and the analyzer must be turned an appropriate matching angle, **α**, if full light intensity is to reach the detector. In the above illustration, the sample has rotated the polarization plane clockwise by +90º, and the analyzer has been turned this amount to permit maximum light transmission.

The observed rotations (α) of enantiomers are opposite in direction. One enantiomer will rotate polarized light in a clockwise direction, termed **dextrorotatory** or (+), and its mirror-image partner in a counter-clockwise manner, termed **levorotatory** or (–). The prefixes dextro and levo come from the Latin *dexter*, meaning right, and *laevus*, for left, and are abbreviated *d* and *l* respectively. If equal quantities of each enantiomer are examined , using the same sample cell, then the magnitude of the rotations will be the same, with one being positive and the other negative. To be absolutely certain whether an observed rotation is positive or negative it is often necessary to make a second measurement using a different amount or concentration of the sample. In the above illustration, for example, α might be –90º or +270º rather than +90º. If the sample concentration is reduced by 10%, then the positive rotation would change to +81º (or +243º) while the negative rotation would change to –81º, and the correct α would be identified unambiguously.

Since it is not always possible to obtain or use samples of exactly the same size, the observed rotation is usually corrected to compensate for variations in sample quantity and cell length. Thus it is common practice to convert the observed rotation, α, to a **specific rotation, [α]**, by the following formula:

Specific Rotation =	$[\alpha]_D = \frac{\alpha}{l * c}$		where l = cell length in dm, c = concentration in g/ml
			D is the 589 nm light from a sodium lamp

Compounds that rotate the plane of polarized light are termed **optically active**. Each enantiomer of a stereoisomeric pair is optically active and has an equal but opposite-in-sign specific rotation. Specific rotations are useful in that they are experimentally determined constants that characterize and identify pure enantiomers. For example, the lactic acid and carvone enantiomers discussed earlier have the following specific rotations.

Carvone from caraway: $[\alpha]_D$ = +62.5º	this isomer may be referred to as (+)-carvone or *d*-carvone
Carvone from spearmint: $[\alpha]_D$ = –62.5º	this isomer may be referred to as (–)-carvone or *l*-carvone
Lactic acid from muscle tissue: $[\alpha]_D$ = +2.5º	this isomer may be referred to as (+)-lactic acid or *d*-lactic acid
Lactic acid from sour milk: $[\alpha]_D$ = –2.5º	this isomer may be referred to as (–)-lactic acid or *l*-lactic acid

A 50:50 mixture of enantiomers has no observable optical activity. Such mixtures are called **racemates** or racemic modifications, and are designated (±). When chiral compounds are created from achiral compounds, the products are racemic unless a single enantiomer of a chiral co-reactant or catalyst is involved in the reaction. The addition of HBr to either cis- or trans-2-butene is an example of racemic product formation (the chiral center is colored red in the following equation).

$CH_3CH{=}CHCH_3 + HBr$	⟶	(±) $CH_3CH_2CHBrCH_3$

Chiral organic compounds isolated from living organisms are usually optically active, indicating that one of the enantiomers predominates (often it is the only isomer present). This is a result of the action of chiral catalysts we call enzymes, and reflects the inherently chiral nature of life itself. Chiral synthetic compounds, on the other hand, are commonly racemates, unless they have been prepared from enantiomerically pure starting materials.

There are two ways in which the condition of a chiral substance may be changed:
1. A racemate may be separated into its component enantiomers. This process is called **resolution**.
2. A pure enantiomer may be transformed into its racemate. This process is called **racemization**.

Enantiomeric Excess

The "optical purity" is a comparison of the optical rotation of a pure sample of unknown stereochemistry versus the optical rotation of a sample of pure enantiomer. It is expressed as a percentage. If the sample only rotates plane-polarized light half as much as expected, the optical purity is 50%.

Because *R* and *S* enantiomers have equal but opposite optical activity, it naturally follows that a 50:50 racemic mixture of two enantiomers will have no observable optical activity. If we know the specific rotation for a chiral molecule, however, we can easily calculate the ratio of enantiomers present in a mixture of two enantiomers, based on its measured optical activity. When a mixture contains more of one enantiomer than the other, chemists often use the concept of **enantiomeric excess (ee)** to quantify the difference. Enantiomeric excess can be expressed as:

$$ee = \frac{(\%\text{ more abundant enantiomer} - 50) \times 100}{50}$$

For example, a mixture containing 60% *R* enantiomer (and 40% *S* enantiomer) has a 20% enantiomeric excess of R: ((60-50) x 100) / 50 = 20 %.

Expressed in terms of optical rotation (use absolute values):

$$ee = \frac{\text{specific rotation of mixture}}{\text{specific rotation of pure enantiomer}} \times 100$$

Example

The specific rotation of (*S*)-carvone is (+)61°, measured 'neat' (pure liquid sample, no solvent). The optical rotation of a neat sample of a mixture of *R* and *S* carvone is measured at (-)23°. Which enantiomer is in excess, and what is its ee? What are the percentages of (*R*)- and (*S*)-carvone in the sample?

Solution

Chiral molecules are often labeled according to the sign of their specific rotation, as in (*S*)-(+)-carvone and (*R*)-(-)-carvone, or (±)-carvone for the racemic mixture. However, there is no relationship whatsoever between a molecule's *R/S* designation and the sign of its specific rotation. Without performing a polarimetry experiment or looking in the literature, we would have no idea that (-)-carvone has the *R* configuration and (+)-carvone has the *S* configuration.

Separation of Chiral Compounds

As noted earlier, chiral compounds synthesized from achiral starting materials and reagents are generally racemic (i.e. a 50:50 mixture of enantiomers). Separation of racemates into their component enantiomers is a process called resolution. Since enantiomers have identical physical properties, such as solubility and melting point, resolution is extremely difficult. Diastereomers, on the other hand, have different physical properties, and this fact is used to achieve resolution of racemates. Reaction of a racemate with an enantiomerically pure chiral reagent gives a mixture of diastereomers, which can be separated. For example, if a racemic mixture of a chiral alcohol is reacted with a enantiomerically pure carboxylic acid, the result is a mixture of diastereomers: in this case, because the pure (R) entantiomer of the acid was used, the product is a mixture of (R-R) and (R-S) diastereomeric esters, which can, in theory, be separated by their different physical properties. Subsequent hydrolysis of each separated ester will yield the 'resolved' (enantiomerically pure) alcohols. The used in this technique are known as '

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

---

5.13: Chemical Properties of Enantiomers

Some Chiral Organic Molecules

There are a number of important biomolecules that could occur as enantiomers, including amino acids and sugars. In most cases, only one enantiomer occurs (although some fungi, for example, are able to produce mirror-image forms of these compounds). We will look later at some of these biomolecules, but first we will look at a compound that occurs naturally in both enantiomeric forms.

Carvone is a secondary metabolite. That means it is a naturally-occurring compound that is not directly connected to the very basic functions of a cell, such as self-replication or the production of energy. The role of secondary metabolites in nature is often difficult to determine. However, these compounds often play roles in self-defense, acting as deterrents against competitor species in a sort of small-scale chemical warfare scenario. They are also frequently used in communications; this role has been studied most extensively among insects, which use lots of compounds to send information to each other.

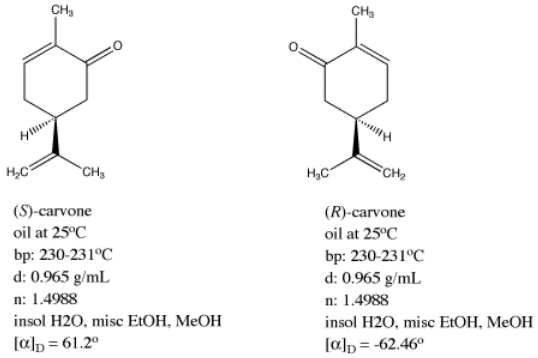


Figure SC5.1. The two naturally-occurring enantiomers of carvone.

Carvone is produced in two enantiomeric forms. One of these forms, called (-)-carvone, is found in mint leaves, and it is a principal contributor to the distinctive odor of mint. The other form, (+)-carvone, is found in caraway seeds. This form has a very different smell, and is typically used to flavour rye bread and other Eastern European foods.

Note that (+)-carvone is the same thing as (S)-carvone. The (+) designation is based on its positive optical rotation value, which is experimentally measured. The (S) designation is determined by the Cahn-Ingold-Prelog rules for designating stereochemistry, which deal with looking at the groups attached to a chiral center and assigning priority based on atomic number. However, carvone's chiral center actually has three carbons attached to it; they all have the same atomic number. We need a new rule to break the tie.

- If two substituent groups have the same atomic number, go one bond further to the next atom.
- If there is a difference among the second tier of atoms, stop.
- The group in which you have encountered a higher atomic number gets the highest priority.
- If there is not a clear difference, proceed one additional bond to the next set of atoms, and so on, until you find a difference.

In carvone, this decision tree works as follows:

- .The chiral center is connected to a H, a C, a C and a C.
- The H is lowest priority.
- One C eventually leads to a C=O. However, at the second bond from the chiral center, this C is connected to a C and two H's.
- A second C is also part of the six-membered ring, but the C=O is farther away in this direction. At the second bond from the chiral center, this C is connected to a C and two H's, just like the first one.
- The third C is part of a little three-carbon group attached to the six-membered ring. At the second bond from the chiral center, it is connected to only one H and has two bonds to another C (this is counted as two bonds to C and one to H).
- Those first two carbon groups are identical so far.

- However, the third group is different; it has an extra bond to C, whereas the others have an extra bond to H. C has a higher atomic number than H, so this group has higher priority.
- The second-highest priority is the branch that reaches the oxygen at the third bond from the chiral center.

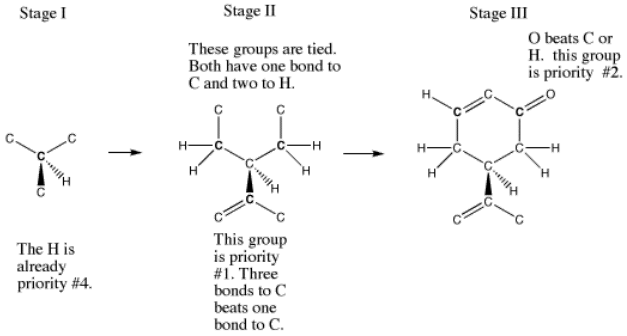


Figure SC5.2. Comparing atoms step-by-step to assign configuration.

How different, exactly, are these two compounds, (+)- and (-)-carvone? Are they completely different isomers, with different physical properties? In most ways, the answer is no. These two compounds have the same appearance (colourless oil), the same boiling point (230 ° C), the same refractive index (1.499) and specific gravity (0.965). However, they have optical rotations that are almost exactly opposite values.

- Two enantiomers have the same physical properties.
- Enantiomers have opposite optical rotations.

Clearly they have different biological properties; since they have slightly different odors, they must fit into slightly different nasal receptors, signaling to the brain whether the person next to you is chewing a stick of gum or a piece of rye bread. This different shape complimentarity is not surprising, just as it isn't surprising that a left hand only fits into a left handed baseball glove and not into a right handed one.

There are other reasons that we might concern ourselves with an understanding of enantiomers, apart from dietary and olfactory preferences. Perhaps the most dramatic example of the importance of enantiomers can be found in the case of thalidomide. Thalidomide was a drug commonly prescribed during the 1950's and 1960's in order to alleviate nausea and other symptoms of morning sickness. In fact, only one enantiomer of thalidomide had any therapeutic effect in this regard. The other enantiomer, apart from being therapeutically useless in this application, was subsequently found to be a teratogen, meaning it produces pronounced birth defects. This was obviously not a good thing to prescribe to pregnant women. Workers in the pharmaceutical industry are now much more aware of these kinds of consequences, although of course not all problems with drugs go undetected even through the extensive clinical trials required in the United States. Since the era of thalidomide, however, a tremendous amount of research in the field of synthetic organic chemistry has been devoted to methods of producing only one enantiomer of a useful compound and not the other. This effort probably represents the single biggest aim of synthetic organic chemistry through the last quarter century.

- Enantiomers may have very different biological properties.
- Obtaining enantiomerically pure compounds is very important in medicine and the pharmaceutical industry.

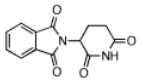


Figure SC5.3. Thalidomide.

Problem SC5.1.

1. Draw thalidomide and identify the chiral center with an asterisk.
2. Draw the two possible enantiomeric forms of thalidomide.

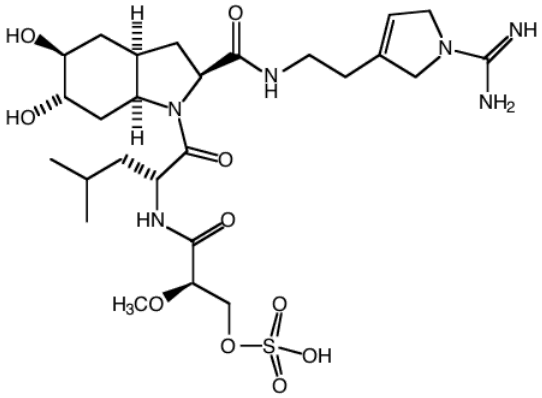
Problem SC5.2.

Draw the two enantiomeric forms of 2-butanol, $CH_3CH(OH)CH_2CH_3$. Label their configurations.

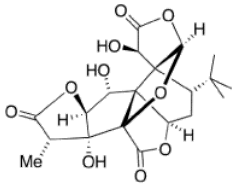
Problem SC5.3.

Sometimes, compounds have many chiral centers in them. For the following compounds, identify four chiral centers in each, mark them with asterisks, and identify each center as R or S configuration.

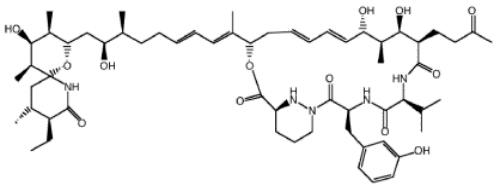
The following is the structure of dysinosin A, a potent thrombin inhibitor that consequently prevents blood clotting.



Ginkgolide B (below) is a secondary metabolite of the ginkgo tree, extracts of which are used in Chinese medicine.



Sanglifehrin A, shown below, is produced by a bacteria that may be found in the soil of coffee plantations in Malawi. It is also a promising candidate for the treatment of organ transplant patients owing to its potent immuno-suppressant activity.



Contributors

Chris P Schaller, Ph.D., (College of Saint Benedict / Saint John's University)

CHAPTER OVERVIEW

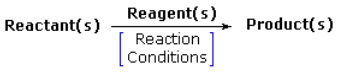
6: Understanding Organic Reactions

Topic hierarchy

6.1: Writing Equations for Organic Reactions

Organic chemistry encompasses a very large number of compounds (many millions), and our previous discussion and illustrations have focused on their structural characteristics. Now that we can recognize these actors (compounds), we turn to the roles they are inclined to play in the scientific drama staged by the multitude of chemical reactions that define organic chemistry.
We begin by defining some basic terms that will be used frequently as this subject is elaborated.

Chemical Reaction: A transformation resulting in a change of composition, constitution and/or configuration of a compound (referred to as the reactant or substrate).
Reactant or Substrate: The organic compound undergoing change in a chemical reaction. Other compounds may also be involved, and common reactive partners (reagents) may be identified. The reactant is often (but not always) the larger and more complex molecule in the reacting system. Most (or all) of the reactant molecule is normally incorporated as part of the product molecule.
Reagent: A common partner of the reactant in many chemical reactions. It may be organic or inorganic; small or large; gas, liquid or solid. The portion of a reagent that ends up being incorporated in the product may range from all to very little or none.
Product(s) The final form taken by the major reactant(s) of a reaction.
Reaction Conditions The environmental conditions, such as temperature, pressure, catalysts & solvent, under which a reaction progresses optimally. Catalysts are substances that accelerate the rate (velocity) of a chemical reaction without themselves being consumed or appearing as part of the reaction product. Catalysts do not change equilibria positions.

Chemical reactions are commonly written as equations:	

Contributors

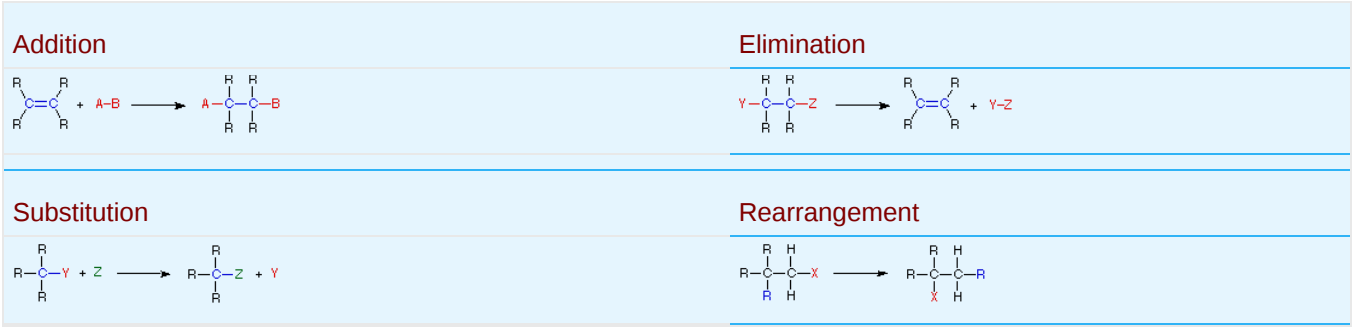
William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

6.2: Kinds of Organic Reactions

If you scan any organic textbook you will encounter what appears to be a very large, often intimidating, number of reactions. These are the "tools" of a chemist, and to use these tools effectively, we must organize them in a sensible manner and look for patterns of reactivity that permit us make plausible predictions. Most of these reactions occur at special sites of reactivity known as functional groups, and these constitute one organizational scheme that helps us catalog and remember reactions.

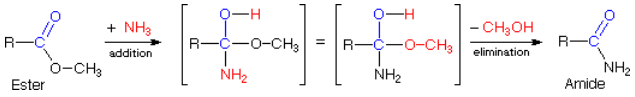
Ultimately, the best way to achieve proficiency in organic chemistry is to understand how reactions take place, and to recognize the various factors that influence their course.

First, we identify four broad classes of reactions based solely on the **structural change** occurring in the reactant molecules. This classification does not require knowledge or speculation concerning reaction paths or mechanisms. The four main reaction classes are **additions, eliminations, substitutions, and rearrangements.**

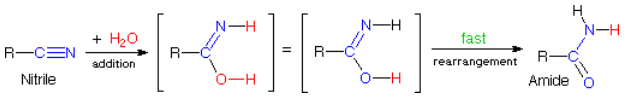


In an **addition** reaction the number of σ-bonds in the substrate molecule increases, usually at the expense of one or more π-bonds. The reverse is true of **elimination** reactions, *i.e.*the number of σ-bonds in the substrate decreases, and new π-bonds are often formed. **Substitution** reactions, as the name implies, are characterized by replacement of an atom or group (Y) by another atom or group (Z). Aside from these groups, the number of bonds does not change. A **rearrangement** reaction generates an isomer, and again the number of bonds normally does not change.

The examples illustrated above involve simple alkyl and alkene systems, but these reaction types are general for most functional groups, including those incorporating carbon-oxygen double bonds and carbon-nitrogen double and triple bonds. Some common reactions may actually be a combination of reaction types. The reaction of an ester with ammonia to give an amide, as shown below, appears to be a substitution reaction (Y = CH_3O & Z = NH_2); however, it is actually two reactions, an addition followed by an elimination.



The addition of water to a nitrile does not seem to fit any of the above reaction types, but it is simply a slow addition reaction followed by a rapid rearrangement, as shown in the following equation. Rapid rearrangements of this kind are called **tautomerizations**.



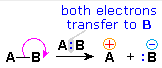
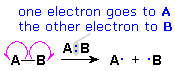
Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

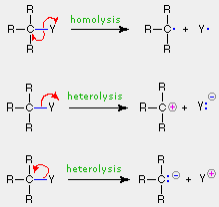
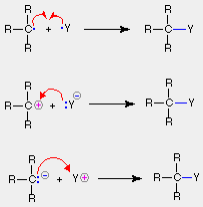
6.3: Bond Breaking and Bond Making

The Arrow Notation in Mechanisms

Since chemical reactions involve the breaking and making of bonds, a consideration of the movement of bonding (and non-bonding) valence shell electrons is essential to this understanding. It is now common practice to show the movement of electrons with curved arrows, and a sequence of equations depicting the consequences of such electron shifts is termed a **mechanism**. In general, two kinds of curved arrows are used in drawing mechanisms:

A full head on the arrow indicates the movement or shift of an electron pair:		
A partial head (fishhook) on the arrow indicates the shift of a single electron:		

The use of these symbols in bond-breaking and bond-making reactions is illustrated below. If a covalent single bond is broken so that one electron of the shared pair remains with each fragment, as in the first example, this bond-breaking is called **homolysis**. If the bond breaks with both electrons of the shared pair remaining with one fragment, as in the second and third examples, this is called **heterolysis**.

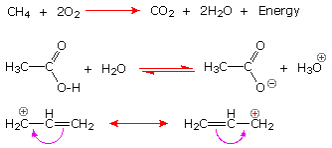
Bond-Breaking	**Bond-Making**
	

Other Arrow Symbols

Chemists also use arrow symbols for other purposes, and it is essential to use them correctly.

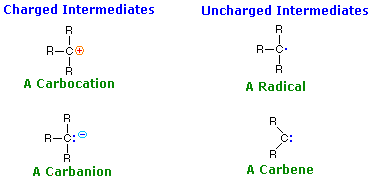
The Reaction Arrow	**The Equilibrium Arrow**	**The Resonance Arrow**
		

The following equations illustrate the proper use of these symbols:



Reactive Intermediates

The products of bond breaking, shown above, are not stable in the usual sense, and cannot be isolated for prolonged study. Such species are referred to as **reactive intermediates**, and are believed to be transient intermediates in many reactions. The general structures and names of four such intermediates are given below.



A pair of widely used terms, related to the Lewis acid-base notation, should also be introduced here.

> **Electrophile:** An electron deficient atom, ion or molecule that has an affinity for an electron pair, and will bond to a base or nucleophile.
> **Nucleophile:** An atom, ion or molecule that has an electron pair that may be donated in bonding to an electrophile (or Lewis acid).

Using these definitions, it is clear that carbocations (called carbonium ions in the older literature) are electrophiles and carbanions are nucleophiles. Carbenes have only a valence shell sextet of electrons and are therefore electron deficient. In this sense they are electrophiles, but the non-bonding electron pair also gives carbenes nucleophilic character. As a rule, the electrophilic character dominates carbene reactivity. Carbon radicals have only seven valence electrons,

and may be considered electron deficient; however, they do not in general bond to nucleophilic electron pairs, so their chemistry exhibits unique differences from that of conventional electrophiles. Radical intermediates are often called **free radicals**.

The importance of electrophile / nucleophile terminology comes from the fact that many organic reactions involve at some stage the bonding of a nucleophile to an electrophile, a process that generally leads to a stable intermediate or product. Reactions of this kind are sometimes called **ionic reactions**, since ionic reactants or products are often involved. Some common examples of ionic reactions and their mechanisms may be examined by Clicking Here

The shapes ideally assumed by these intermediates becomes important when considering the stereochemistry of reactions in which they play a role. A simple tetravalent compound like methane, CH_4, has a tetrahedral configuration. Carbocations have only three bonds to the charge bearing carbon, so it adopts a planar trigonal configuration. Carbanions are pyramidal in shape (tetrahedral if the electron pair is viewed as a substituent), but these species invert rapidly at room temperature, passing through a higher energy planar form in which the electron pair occupies a p-orbital. Radicals are intermediate in configuration, the energy difference between pyramidal and planar forms being very small. Since three points determine a plane, the shape of carbenes must be planar; however, the valence electron distribution varies.

Contributors

- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

6.4: Bond Dissociation Energy

The homolytic bond dissociation energy is the amount of energy needed to break apart one mole of covalently bonded gases into a pair of radicals. The SI units used to describe bond energy are kiloJoules per mole of bonds (kJ/Mol). It indicates how strongly the atoms are bonded to each other.

Introduction

Breaking a covalent bond between two partners, A-B, can occur either heterolytically, where the shared pair of electron goes with one partner or another

$$A-B \rightarrow A^{+} + B:^{-} \tag{6.4.1}$$

or

$$A-B \rightarrow A:^{-} + B^{+} \tag{6.4.2}$$

or homolytically, where one electron stays with each partner.

$$A-B \rightarrow A^{\bullet} + B^{\bullet} \tag{6.4.3}$$

The products of homolytic cleavage are radicals and the energy that is required to break the bond homolytically is called the Bond Dissociation Energy (BDE) and is a measure of the strength of the bond.

Calculation of the BDE

The BDE for a molecule A-B is calculated as the difference in the enthalpies of formation of the products and reactants for homolysis

$$BDE = \Delta_f H(A^{\bullet}) + \Delta_f H(B^{\bullet}) - \Delta_f H(A-B) \tag{6.4.4}$$

Officially, the IUPAC definition of bond dissociation energy refers to the energy change that occurs at 0 K, and the symbol is D_o. However, it is commonly referred to as BDE, the bond dissociation energy, and it is generally used, albeit imprecisely, interchangeably with the bond dissociation *enthalpy*, which generally refers to the enthalpy change at room temperature (298K). Although there are technically differences between BDEs at 0 K and 298 K, those difference are not large and generally do not affect interpretations of chemical processes.

Bond Breakage/Formation

Bond dissociation energy (or enthalpy) is a state function and consequently does not depend on the path by which it occurs. Therefore, the specific mechanism in how a bond breaks or is formed does not affect the BDE. Bond dissociation energies are useful in assessing the energetics of chemical processes. For chemical reactions, combining bond dissociation energies for bonds formed and bonds broken in a chemical reaction using Hess's Law can be used to estimate reaction enthalpies.

Example 6.4.1: Chlorination of Methane

Consider the chlorination of methane

$$CH_4 + Cl_2 \rightarrow CH_3Cl + HCl \tag{6.4.5}$$

the overall reaction thermochemistry can be calculated exactly by combining the BDEs for the bonds broken and bonds formed

$CH_4 \rightarrow CH_3^{\bullet} + H^{\bullet}$ BDE(CH_3-H)

$Cl_2 \rightarrow 2Cl^{\bullet}$ BDE(Cl_2)\]

$H^{\bullet} + Cl^{\bullet} \rightarrow HCl$ -BDE(HCl)

$CH_3^{\bullet} + Cl^{\bullet} \rightarrow CH_3Cl$ -BDE(CH_3-Cl)

$$CH_4 + Cl_2 \rightarrow CH_3Cl + HCl \tag{6.4.6}$$

$$\Delta H = BDE(R-H) + BDE(Cl_2) - BDE(HCl) - BDE(CH_3-Cl) \tag{6.4.7}$$

> Because reaction enthalpy is a state function, it does not matter what reactions are combined to make up the overall process using Hess's Law. However, BDEs are convenient to use because they are readily available.

Alternatively, BDEs can be used to assess individual steps of a mechanism. For example, an important step in free radical chlorination of alkanes is the abstraction of hydrogen from the alkane to form a free radical.

$$RH + Cl\bullet \rightarrow R\bullet + HCl$$

The energy change for this step is equal to the difference in the BDEs in RH and HCl

$$\Delta H = BDE(R-H) - BDE(HCl) \tag{6.4.8}$$

This relationship shows that the hydrogen abstraction step is more favorable when BDE(R-H) is smaller. The difference in energies accounts for the selectivity in the halogenation of hydrocarbons with different types of C-H bonds.

Representative C-H BDEs in Organic Molecules

R-H	D_o, kJ/mol	D_{298}, kJ/mol	**R-H**	D_o, kJ/mol	D_{298}, kJ/mol
CH_3-H	432.7±0.1	439.3±0.4	H_2C=CH-H	456.7±2.7	463.2±2.9
CH_3CH_2-H		423.0±1.7	C_6H_5-H	465.8±1.9	472.4±2.5
$(CH_3)_2$CH-H		412.5±1.7	HCCH	551.2±0.1	557.8±0.3
$(CH_3)_3$C-H		403.8±1.7			
			H_2C=CHCH_2-H		371.5±1.7
HC(O)-H		368.6±0.8	$C_6H_5CH_2$-H		375.3±2.5
CH_3C(O)-H		374.0±1.2			

Trends in C-H BDEs

It is important to remember that C-H BDEs refer to the energy it takes to break the bond, and is the difference in energy between the reactants and the products. Therefore, it is not appropriate to interpret BDEs solely in terms of the "stability of the radical products" as is often done.

Analysis of the BDEs shown in the table above shows that there are some systematic trends:

1. **BDEs vary with hybridization:** Bonds with sp^3 hybridized carbons are weakest and bonds with sp hybridized carbons are much stronger. The vinyl and phenyl C-H bonds are similar, reflecting their sp^2 hybridization. The correlation with hybridization can be viewed as a reflection of the C-H bond lengths. Longer bonds formed with sp^3 orbitals are consequently weaker. Shorter bonds formed with orbitals that have more s-character are similarly stronger.
2. **C-H BDEs vary with substitution:** Among sp^3 hybridized systems, methane has the strongest C-H bond. C-H bonds on primary carbons are stronger than those on secondary carbons, which are stronger than those on tertiary carbons.

Interpretation of C-H BDEs for sp^3 Hybridized Carbons

The interpretation of the BDEs in saturated molecules has been subject of recent controversy. As indicated above, the variation in BDEs with substitution has traditionally been interpreted as reflecting the stabilities of the alkyl radicals, with the assessment that more highly substituted radicals are more stable, as with carbocations. Although this is a popular explanation, it fails to account fo the fact the bonds to groups other than H do not show the same types of variation.

R	BDE(R-CH_3)	BDE(R-Cl)	BDE(R-Br)	BDE(R-OH)
CH_3-	377.0±0.4	350.2±0.4	301.7±1.3	385.3±0.4
CH_3CH_2-	372.4±1.7	354.8±2.1	302.9±2.5	393.3±1.7
$(CH_3)_2$CH-	370.7±1.7	356.5±2.1	309.2±2.9	399.6±1.7

R	BDE(R-CH_3)	BDE(R-Cl)	BDE(R-Br)	BDE(R-OH)
$(CH_3)_3C$-	366.1±1.7	355.2±2.9	303.8±2.5	400.8±1.7

Therefore, although C-CH_3 bonds get weaker with more substitution, the effect is not nearly as large as that observed with C-H bonds. The strengths of C-Cl and C-Br bonds are not affected by substitution, despite the fact that the same radicals are formed as when breaking C-H bonds, and the C-OH bonds in alcohols actually *increase* with more substitution.

Gronert has proposed that the variation in BDEs is alternately explained as resulting from destabilization of the reactants due to steric repulsion of the substituents, which is released in the nearly planar radicals.[1] Considering that BDEs reflect the relative energies of reactants and products, either explanation can account for the trend in BDEs.

Another factor that needs to be considered is the electronegativity. The Pauling definition of electronegativity says that the bond dissociation energy between unequal partners is going to be dependent on the difference in electrongativities, according to the expression

$$D_o(A-B) = \frac{D_o(A-A)+D_o(B-B)}{2} + (X_A - X_B)^2 \tag{6.4.9}$$

where X_A and X_B are the electronegativities and the bond energies are in eV. Therefore, the variation in BDEs can be interpreted as reflecting variation in the electronegativities of the different types of alkyl fragments.

There is likely some merit in all three interpretations. Since Gronert's original publication of his alternate explanation, there have been many desperate attempts to defend the radical stability explanation.

References

1. Gronert, S. *J. Org. Chem.* **2006**, *13*, 1209

Contributors

- Prof. Paul G. Wenthold (Purdue University)

6.5: Thermodynamics

Equilibrium Constant

For the hypothetical chemical reaction:

$$aA + bB \rightleftharpoons cC + dD \tag{6.5.1}$$

the equilibrium constant is defined as:

$$K_C = \frac{[C]^c[D]^d}{[A]^a[B]^b} \tag{6.5.2}$$

The notation [A] signifies the molar concentration of species A. An alternative expression for the equilibrium constant involves partial pressures:

$$K_P = \frac{P_C^c P_D^d}{P_A^a P_B^b} \tag{6.5.3}$$

Note that the expression for the equilibrium constant includes only solutes and gases; pure solids and liquids do not appear in the expression. For example, the equilibrium expression for the reaction

$$CaH_2(s) + 2H_2O(g) \rightleftharpoons Ca(OH)_2(s) + 2H_2(g) \tag{6.5.4}$$

is the following:

$$K_C = \frac{[H_2]^2}{[H_2O]^2} \tag{6.5.5}$$

Observe that the gas-phase species H_2O and H_2 appear in the expression but the solids CaH_2 and $Ca(OH)_2$ do not appear.

The equilibrium constant is most readily determined by allowing a reaction to reach equilibrium, measuring the concentrations of the various solution-phase or gas-phase reactants and products, and substituting these values into the Law of Mass Action.

Gibbs Energy

The interaction between enthalpy and entropy changes in chemical reactions is best observed by studying their influence on the equilibrium constants of reversible reactions. To this end a new thermodynamic function called **Free Energy** (or Gibbs Free Energy), symbol **ΔG**, is defined as shown in the first equation below. Two things should be apparent from this equation. First, in cases where the entropy change is small, ΔG ≅ ΔH. Second, the importance of ΔS in determining ΔG increases with increasing temperature.

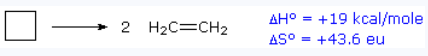
$$\Delta G^o = \Delta H^o - T\Delta S^o \tag{6.5.6}$$

where T is the absolute temperature measured in kelvin.

The free energy function provides improved insight into the thermodynamic driving forces that influence reactions. A negative ΔG° is characteristic of an **exergonic reaction**, one which is thermodynamically favorable and often spontaneous, as is the melting of ice at 1 °C. Likewise a positive ΔG° is characteristic of an **endergonic reaction**, one which requires an input of energy from the surroundings.

Example 6.5.1: Decomposition of Cyclobutane

For an example of the relationship of free energy to enthalpy consider the decomposition of cyclobutane to ethene, shown in the following equation. The standard state for all the compounds is gaseous.



This reaction is endothermic, but the increase in number of molecules from one (reactants) to two (products) results in a large positive ΔS°.

At 25 °C (298 °K), ΔG° = 19 kcal/mol – 298(43.6) cal/mole = 19 – 13 kcal/mole = +6 kcal/mole. Thus, the entropy change opposes the enthalpy change, but is not sufficient to change the sign of the resulting free energy change, which is endergonic.

Indeed, cyclobutane is perfectly stable when kept at room temperature.

Because the entropy contribution increases with temperature, this energetically unfavorable transformation can be made favorable by raising the temperature. At 200 ºC (473 ºK), ΔGº = 19 kcal/mol – 473(43.6) cal/mole = 19 – 20.6 kcal/mole = –1.6 kcal/mole. This is now an exergonic reaction, and the thermal cracking of cyclobutane to ethene is known to occur at higher temperatures.

$$\Delta G^{o} = -RT \ln K = -2.303 RT \log K \tag{6.5.1}$$

with

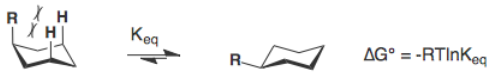
- R = 1.987 cal/ ºK mole
- T = temperature in ºK
- K = equilibrium constant

A second equation, shown above, is important because it demonstrates the fundamental relationship of ΔGº to the equilibrium constant, K. Because of the negative logarithmic relationship between these variables, a negative ΔGº generates a K>1, whereas a positive ΔGº generates a K<1. When ΔGº = 0, K = 1. Furthermore, small changes in ΔGº produce large changes in K. A change of 1.4 kcal/mole in ΔGº changes K by approximately a factor of 10. This interrelationship may be explored with the calculator on the right. Entering free energies outside the range -8 to 8 kcal/mole or equilibrium constants outside the range 10-6 to 900,000 will trigger an alert, indicating the large imbalance such numbers imply.

Substituted Cyclohexanes

A Values

Substituents on a cyclohexane prefer to be in the equatorial position. When a substituent is in the axial position, there are two gauche butane interactions more than when a substituent is in the equatorial position. We quantify the energy difference between the axial and equatorial conformations as the A-value, which is equivalent to the negative of the ΔG°, for the equilibrium shown below. Therefore the A-value, or -ΔG°, is the preference for the substituent to sit in the equatorial position.



Recall that the equilibrium constant is related to the change in Gibbs Energies for the reaction:

$$\Delta G^{o} = -RT \ln K_{eq} \tag{6.5.2}$$

The balance between reactants and products in a reaction will be determined by the free energy difference between the two sides of the reaction. The greater the free energy difference, the more the reaction will favor one side or the other (Table 6.5.1).

***Table 6.5.1**: Below is a table of A-values for some common substituents.*

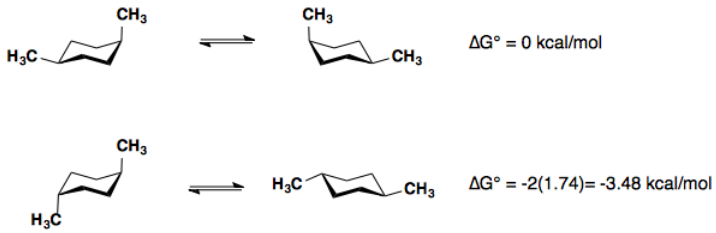
Substituent	ΔG° (kcal/mol)	A-value
-F	-0.28-0.24	0.24-0.28
-Cl	-0.53	0.53
-Br	-0.48	0.48
-I	-0.47	0.47
$-CH_3$ (-Me)	-1.8	1.8
$-CH_2CH_3$ (-Et)	-1.8	1.8
$-CH(CH_3)_2$ (-*i*-Pr)	-2.1	2.1
$-C(CH_3)_3$ (-*t*-Bu)	<-4.5	>4.5
$-CHCH_2$	-1.7	1.7

-CCH	-0.5	0.5
-CN	-0.25-0.15	0.15-0.25
$-C_6H_5$ (-Ph)	-2.9	2.9

Polysubstituted Cyclohexanes

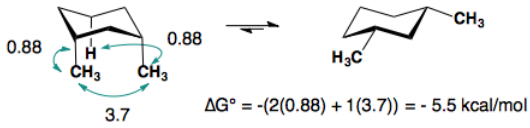
1,4-disubstitution

The A-values of the substituents are roughly additive in either the *cis*- or *trans*-diastereomers.



1,3-disubstitution

A-values are only additive in the *trans*-diastereomer:



When there are *cis*-substituents on the chair, there is a new interaction in the di-axial conformation:

In the above example, each methyl group has one 1,3-diaxial interaction with a hydrogen. The methyl groups also interact with each other. This new diaxial interaction is extremely unfavorable based on their steric interaction (see: double-gauche pentane conformation).

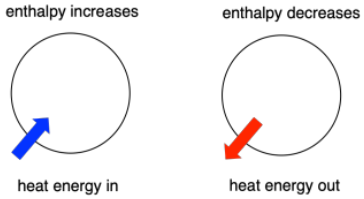
Contributors

- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Jim Clark (Chemguide.co.uk)

6.6: Enthalpy and Entropy

Enthalpy

Thermodynamics is the study of the relationship between heat (or energy) and work. Enthalpy is a central factor in thermodynamics. It is the heat content of a system. The heat that passes into or out of the system during a reaction is the enthalpy change. Whether the enthalpy of the system increases (i.e. when energy is added) or decreases (because energy is given off) is a crucial factor that determines whether a reaction can happen.



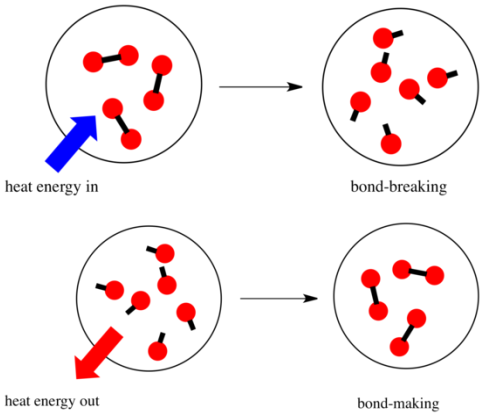
Sometimes, we call the energy of the molecules undergoing change the "internal enthalpy". Sometimes, we call it the "enthalpy of the system." These two phrases refer to the same thing. Similarly, the energy of the molecules that do not take part in the reaction is called the *"external enthalpy*" or the *"enthalpy of the surroundings"*.

Roughly speaking, the energy changes that we looked at in the introduction to thermodynamics were changes in enthalpy. We will see in the next section that there is another energetic factor, entropy, that we also need to consider in reactions. For now, we will just look at enthalpy.

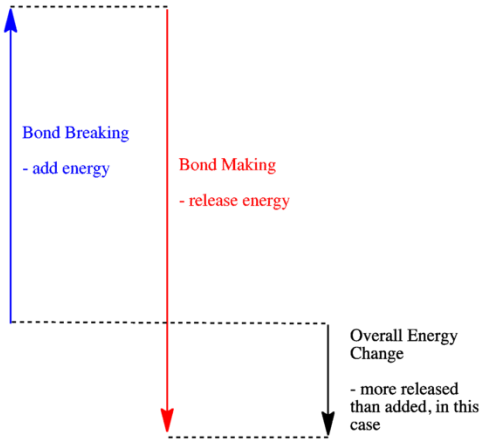
- Enthalpy is the heat content of a system.
- The enthalpy change of a reaction is roughly equivalent to the amount of energy lost or gained during the reaction.
- A reaction is favored if the enthalpy of the system decreases over the reaction.

That last statement is a lot like the description of energetics on the previous page. If a system undergoes a reaction and gives off energy, its own energy content decreases. It has less energy left over if it gave some away. Why does the energy of a set of molecules change when a reaction occurs? To answer that, we need to think about what happens in a chemical reaction.

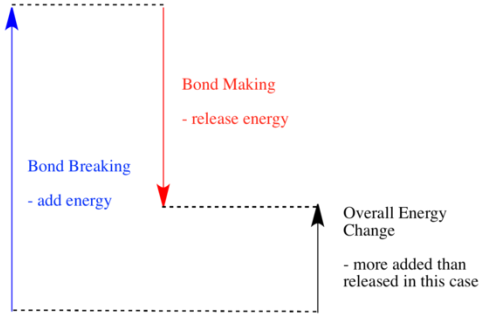
In a reaction, there is a change in chemical bonding. Some of the bonds in the reactants are broken, and new bonds are made to form the products. It costs energy to break bonds, but energy is released when new bonds are made.



Whether a reaction is able to go forward may depend on the balance between these bond-making and bond-breaking steps.



- A reaction is exothermic if more energy is released by formation of new bonds than is consumed by breaking old bonds.
- A reaction is exothermic if weaker bonds are traded for stronger ones.
- A reaction is endothermic if bond-breaking costs more energy than what is provided in bond-making.



Bond energies (the amount of energy that must be added in order to break a bond) are an important factor in determining whether a reaction will occur. Bond strengths are not always easy to predict, because the strength of a bond depends on a number of factors. However, lots of people have done lots of work measuring bond strengths, and they have collected the information in tables, so if you need to know how strong a bond is, you can just look up the information you need.

Bond	Bond Energy (kcal/mol)	Bond	Bond Energy (kcal/mol)
H-H	104	O-H	111
C-C	83	C-H	99
O=O	119	N-H	93
N=N	226	C=O	180

Example 6.6.1

Suppose you wanted to know whether the combustion of methane were an exothermic or endothermic reaction. I am going to guess that it's exothermic, because this reaction (and others like it) is used to provide heat for lots of homes by burning natural gas in furnaces.

Solution

The "combustion" of methane means that it is burned in air, so that it reacts with oxygen. The products of burning hydrocarbons are mostly carbon dioxide and water. The carbon atom in methane (CH_4) gets incorporated into a carbon dioxide molecule. The hydrogen atoms get incorporated into water molecules. There are four hydrogen atoms in methane, so that's enough to make two molecules of H_2O.

- Four C-H bonds must be broken in the combustion of methane.
- Four new O-H bonds are made when the hydrogens from methane are added into new water molecules.

- Two new C=O bonds are made when the carbon from methane is added into a CO_2 molecule.

The other piece of the puzzle is the oxygen source for the reaction. Oxygen is present in the atmosphere mostly as O_2. Because we need two oxygen atoms in the CO_2 molecule and two more oxygen atoms for the two water molecules, we need a total of four oxygen atoms for the reaction, which could be provided by two O_2 molecules.

- Two O=O bonds must be broken to provide the oxygen atoms for the products.

Altogether, that's four C-H and two O=O bonds broken, plus two C=O and four O-H bonds made. That's 4 x 99 kcal/mol for the C-H bonds and 2 x 119 kcal/mol for the O=O bonds, a total of 634 kJ/mol added. The reaction releases 2 x 180 kcal/mol for the C=O bonds and 4 x 111 kcla/mol for the OH bonds, totaling 804 kcal/mol. Overall, there is 170 kcal/mol more released than is consumed.

That means the reaction is exothermic, so it produces heat. It's probably a good way to heat your home.

Entropy

Observations of natural processes led a surprising number of chemists of the late 19th century (including Berthelot and Thomsen) to conclude that all spontaneous reactions must be exothermic since:

- **Objects roll downhill spontaneously** (i.e., energy is "lost" from the system)
- **Objects do not roll uphill spontaneously** (i.e., energy does not suddenly appear from nowhere)

If this were true all we would need to predict whether a reaction is spontaneous is the change of enthalpy. If ΔH were negative, the process should be able to occur by itself. If ΔH were positive, the reaction could not occur by itself.

Indeed, *almost* all exothermic reactions are spontaneous at standard thermodynamic conditions (1 atmosphere pressure) and 25^oC. However a number of common processes which are both endothermic and spontaneous are known. The most obvious are simple phase changes, like ice melting at room temperature. Also, many solids dissolve in water and simultaneously absorb heat.

So the energy is now dispersed among the molecules of liquid water which have access to all kinds of molecular motion states that were not available in the solid. At the same time, the ordered structure of the solid ice has given way to a much less organized flowing liquid.

But the actual change has occurred in the energy dispersal. This subtle property that matter possesses in terms of the way energy is dispersed in it is known as entropy. Entropy is sometimes erroneously referred to as "randomness" or even "disorder" but these descriptions do not fit the state of energy as well as they seem to describe some of the often obvious results.

> Just as reactions which form stronger bonds tend to occur spontaneously, energy is constantly being dispersed or "spread out" in any process which either happens on its own or which we make happen.

It is the **Second Law of Thermodynamics** which gives us the criterion we are seeking to decide whether a reaction will be spontaneous or not (well, almost...):

> In a spontaneous process the entropy of the universe increases.

The "universe" is a pretty big place. Recall the definitions we used when we introduced chemical thermodynamics. The system is that part of the universe on which we focus our attention--generally chemicals. The surroundings are everything else. Taken together they constitute the universe.

So the Second Law could be written this way for a spontaneous process:

$$\Delta S_{sys} + \Delta S_{surr} > 0 \tag{6.6.1}$$

Entropy trends and physical properties

(values in)

1. Entropy increases with mass

- $F_{2(g)}$ = 203 J/mol·K
- $Cl_{2(g)}$ = 224 J/mol·K
- $Br_{2\ (g)}$ = 245 J/mol·K
- $I_{2\ (g)}$ = 261 J/mol·K

2. Entropy increases with melting, vaporization or sublimation

- $I_{2(s)}$ = 117 J/mol·K vs. $I_{2(\ell)}$ = 261 J/mol·K and
- $H_2O_{(\ell)}$ = 70 J/mol·K vs. $H_2O_{(g)}$ = 189 J/mol·K

3. Entropy increases when solids or liquids dissolve in water

- CH3OH(ℓ) = 127 J/mol·K vs. $CH_3OH_{(aq)}$ = 132 J/mol·K and
- NaCl(s) = 72J/mol·K vs. Na+(aq) + Cl-(aq) = 115 J/mol·K

4. Entropy decreases when a gas is dissolved in water

- $HCl_{(g)}$ = 187 vs. $H^+_{(aq)}$ + $Cl^-_{(aq)}$ = 55

5. Entropy is lower in hard, brittle substances than in malleable solids like metals

- Diamond (C) = 2.4J/mol·K vs. Pb = 65 J/mol·K

6. Entropy increases with chemical complexity

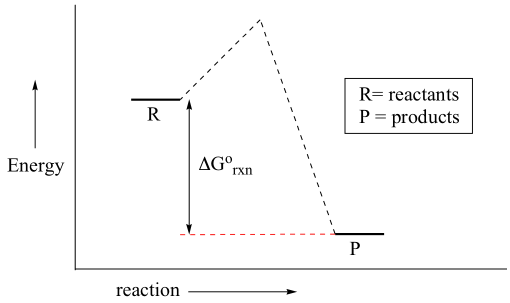
- $NaCl$ = 72 J/mol·K vs. $MgCl_2$ = 90 J/mol·K vs. $AlCl_3$ = 167 J/mol·K

Of course, the main issue here is how entropy *changes* during a process. This can be determined by calculation from standard entropy values (\(S^{\circ}\)) in the same way that enthalpy changes are calculated:

$$\sum S^o_{products} - \sum S^o_{reactants} = \Delta S^o_{rxn} \tag{6.6.2}$$

6.7: Energy Diagrams

You may recall from general chemistry that it is often convenient to describe chemical reactions with energy diagrams. In an energy diagram, the vertical axis represents the overall energy of the reactants, while the horizontal axis is the 'reaction coordinate', tracing from left to right the progress of the reaction from starting compounds to final products. The energy diagram for a typical one-step reaction might look like this:



Despite its apparent simplicity, this energy diagram conveys some very important ideas about the thermodynamics and kinetics of the reaction. Recall that when we talk about the **thermodynamics** of a reaction, we are concerned with the difference in energy between reactants and products, and whether a reaction is 'downhill' (exergonic, energy releasing) or 'uphill (endergonic, energy absorbing). When we talk about **kinetics**, on the other hand, we are concerned with the *rate* of the reaction, regardless of whether it is uphill or downhill thermodynamically.

First, let's review what this energy diagram tells us about the thermodynamics of the reaction illustrated by the energy diagram above. The energy level of the products is *lower* than that of the reactants. This tells us that the change in standard Gibbs Free Energy for the reaction (ΔG°_{rnx}) is negative. In other words, the reaction is exergonic, or 'downhill'. Recall that the ΔG°_{rnx} term encapsulates both ΔH°_{rnx}, the change in enthalpy (heat) and ΔS°_{rnx} , the change in entropy (disorder):

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \tag{6.7.1}$$

where T is the absolute temperature in Kelvin. For chemical processes where the entropy change is small (~0), the enthalpy change is essentially the same as the change in Gibbs Free Energy. Energy diagrams for these processes will often plot the enthalpy (H) instead of Free Energy for simplicity.

The standard Gibbs Free Energy change for a reaction can be related to the reaction's equilibrium constant (\(K_{eq}_) by a simple equation:

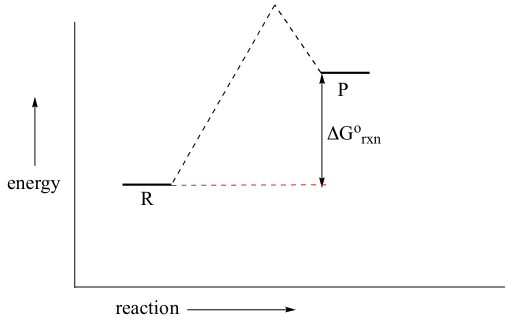
$$\Delta G^\circ = -RT \ln K_{eq} \tag{6.7.2}$$

where:

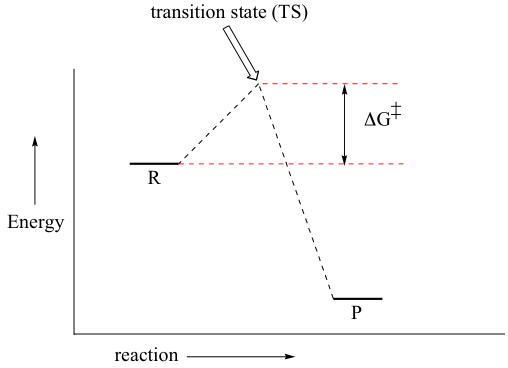
- K_{eq} = [product] / [reactant] at equilibrium
- R = 8.314 $J \times K^{-1} \times mol^{-1}$ *or* 1.987 $cal \times K^{-1} \times mol^{-1}$
- T = temperature in Kelvin (K)

If you do the math, you see that a negative value for ΔG°_{rnx} (an exergonic reaction) corresponds - as it should by intuition - to K_{eq} being greater than 1, an equilibrium constant which favors product formation.

In a hypothetical endergonic (energy-absorbing) reaction the products would have a higher energy than reactants and thus ΔG°_{rnx} would be positive and K_{eq} would be less than 1, favoring reactants.

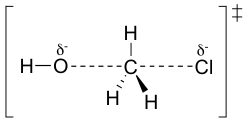


Now, let's move to kinetics. Look again at the energy diagram for exergonic reaction: although it is 'downhill' overall, it isn't a straight downhill run.



First, an 'energy barrier' must be overcome to get to the product side. The height of this energy barrier, you may recall, is called the '**activation energy'** ($\Delta G^{\ddagger}$). The activation energy is what determines the kinetics of a reaction: the higher the energy hill, the slower the reaction. At the very top of the energy barrier, the reaction is at its **transition state** (TS), which is the point at which the bonds are in the process of breaking and forming. The transition state is an '**activated complex'**: a transient and dynamic state that, unlike more stable species, does not have any definable lifetime. It may help to imagine a transition state as being analogous to the exact moment that a baseball is struck by a bat. Transition states are drawn with dotted lines representing bonds that are in the process of breaking or forming, and the drawing is often enclosed by brackets. Here is a picture of a likely transition state for a substitution reaction between hydroxide and chloromethane:

$$CH_3Cl + HO^- \rightarrow CH_3OH + Cl^- \tag{6.7.3}$$



This reaction involves a collision between *two* molecules: for this reason, we say that it has **second order kinetics**. The **rate expression** for this type of reaction is:

$$\text{rate} = k[\text{reactant 1}][\text{reactant 2}]$$

. . . which tells us that the rate of the reaction depends on the **rate constant** *k* as well as on the concentration of *both* reactants. The rate constant can be determined experimentally by measuring the rate of the reaction with different starting reactant concentrations. The rate constant depends on the activation energy, of course, but also on temperature: a higher temperature means a higher *k* and a faster reaction, all else being equal. This should make intuitive sense: when there is more heat energy in the system, more of the reactant molecules are able to get over the energy barrier.

Here is one more interesting and useful expression. Consider a simple reaction where the reactants are A and B, and the product is AB (this is referred to as a **condensation reaction**, because two molecules are coming together, or condensing). If we know the rate constant *k* for the forward reaction and the rate constant $k_{reverse}$ for the reverse reaction (where AB splits apart into A and B), we can simply take the quotient to find our equilibrium constant K_{eq}:

$$A + B \rightleftharpoons AB \qquad K_{eq} = \frac{[AB]}{[A]\,[B]} = \frac{k_{forward}}{k_{reverse}}$$

This too should make some intuitive sense; if the forward rate constant is higher than the reverse rate constant, equilibrium should lie towards products.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

Further Reading

MasterOrganicChemistry

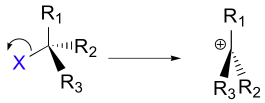
Equilibria

Websites

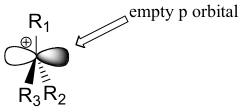
Reversible and irreversible reactions

6.8: Energy Diagram for a Two-Step Reaction Mechanism

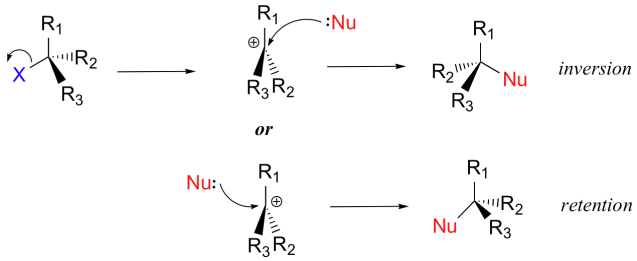
A second model for a nucleophilic substitution reaction is called the '**dissociative**', or '**S_N1**' mechanism: in this picture, the C-X bond breaks *first*, before the nucleophile approaches:



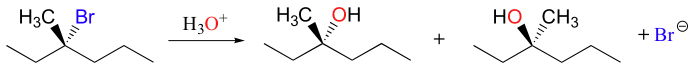
This results in the formation of a carbocation: because the central carbon has only three bonds, it bears a formal charge of +1. Recall that a carbocation should be pictured as sp^2 hybridized, with trigonal planar geometry. Perpendicular to the plane formed by the three sp^2 hybrid orbitals is an empty, unhybridized *p* orbital.



In the second step of this two-step reaction, the nucleophile attacks the empty, 'electron hungry' *p* orbital of the carbocation to form a new bond and return the carbon to tetrahedral geometry.

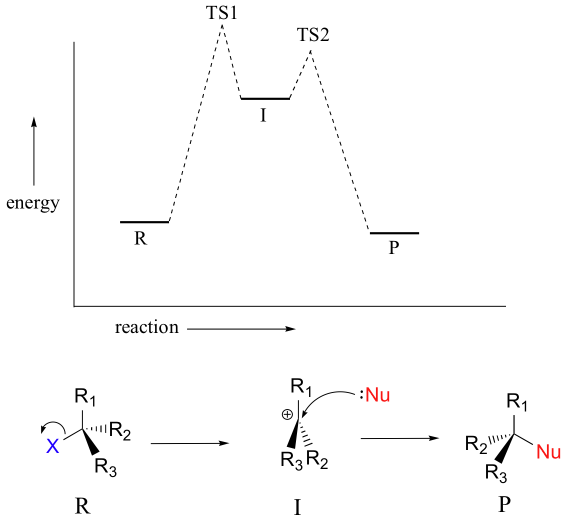


We saw that S_N2 reactions result specifically in inversion of stereochemistry at the electrophilic carbon center. What about the stereochemical outcome of S_N1 reactions? In the model S_N1 reaction shown above, the leaving group dissociates completely from the vicinity of the reaction before the nucleophile begins its attack. Because the leaving group is no longer in the picture, the nucleophile is free to attack from either side of the planar, sp^2-hybridized carbocation electrophile. This means that about half the time the product has the same stereochemical configuration as the starting material (retention of configuration), and about half the time the stereochemistry has been inverted. In other words, *racemization* has occurred at the carbon center. As an example, the tertiary alkyl bromide below would be expected to form a racemic mix of *R* and *S* alcohols after an S_N1 reaction with water as the incoming nucleophile.



Exercise
Draw the structure of the intermediate in the two-step nucleophilic substitution reaction above.

The S_N1 reaction we see an example of a reaction intermediate, a very important concept in the study of organic reaction mechanisms that was introduced earlier in the module on organic reactivity Recall that many important organic reactions do not occur in a single step; rather, they are the sum of two or more discreet bond-forming / bond-breaking steps, and involve transient intermediate species that go on to react very quickly. In the S_N1 reaction, the carbocation species is a reaction intermediate. A potential energy diagram for an S_N1 reaction shows that the carbocation intermediate can be visualized as a kind of valley in the path of the reaction, higher in energy than both the reactant and product but lower in energy than the two transition states.



Exercise

Draw structures representing TS1 and TS2 in the reaction above. Use the solid/dash wedge convention to show three dimensions.

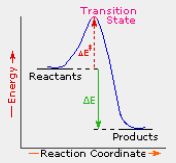
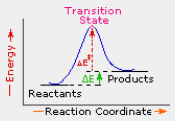
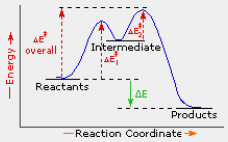
Recall that the first step of the reaction above, in which two charged species are formed from a neutral molecule, is much the slower of the two steps, and is therefore rate-determining. This is illustrated by the energy diagram, where the activation energy for the first step is higher than that for the second step. Also recall that an S_N1 reaction has *first order* kinetics, because the rate determining step involves one molecule splitting apart, not two molecules colliding

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

6.9: Kinetics

Activation Energy

Since exothermic reactions are energetically (thermodynamically) favored, a careless thinker might conclude that all such reactions will proceed spontaneously to their products. Were this true, no life would exist on Earth, because the numerous carbon compounds that are present in and essential to all living organisms would spontaneously combust in the presence of oxygen to give carbon dioxide-a more stable carbon compound. The combustion of methane (eq.1), for example, does not occur spontaneously, but requires an initiating energy in the form of a spark or flame. The flaw in this careless reasoning is that we have focused only on the initial (reactant) and final (product) states of reactions. To understand why some reactions occur readily (almost spontaneously), whereas other reactions are slow, even to the point of being unobservable, we need to consider the intermediate stages of reactions.

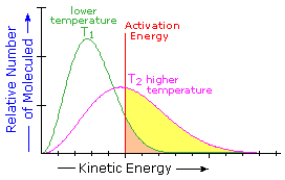
Exothermic Single Step Reaction	Endothermic Single Step Reaction	Exothermic Two Step Reaction
		

Every reaction in which bonds are broken will have a high energy **transition state** that must be reached before products can form. In order for the reactants to reach this transition state, energy must be supplied and reactant molecules must orient themselves in a suitable fashion. The energy needed to raise the reactants to the transition state energy level is called the **activation energy, $\Delta E^{\ddagger}$**. An example of a single-step exothermic reaction profile is shown on the left above, and a similar single-step profile for an endothermic reaction is in the center. The activation energy is drawn in red in each case, and the overall energy change (ΔE) is in green.

The profile becomes more complex when a multi-step reaction path is described. An example of a two-step reaction proceeding by way of a high energy intermediate is shown on the right above. Here there are two transition states, each with its own activation energy. The overall activation energy is the difference in energy between the reactant state and the highest energy transition state. We see now why the rate of a reaction may not correlate with its overall energy change. In the exothermic diagram on the left, a significant activation energy must be provided to initiate the reaction. Since the reaction is strongly exothermic, it will probably generate enough heat to keep going as long as reactants remain. The endothermic reaction in the center has a similar activation energy, but this will have to be supplied continuously for the reaction to proceed to completion.

What is the source of the activation energy that enables a chemical reaction to occur? Often it is heat, as noted above in reference to the flame or spark that initiates methane combustion. At room temperature, indeed at any temperature above absolute zero, the molecules of a compound have a total energy that is a combination of translational (kinetic) energy, internal vibrational and rotational energies, as well as electronic and nuclear energies. The temperature of a system is a measure of the average kinetic energy of all the atoms and molecules present in the system. As shown in the following diagram, the average kinetic energy increases and the distribution of energies broadens as the temperature is raised from T_1 to T_2. Portions of this thermal or kinetic energy provide the activation energy for many reactions, the concentration of suitably activated reactant molecules increasing with temperature, e.g. orange area for T_1 and yellow plus orange for T_2. (Note that the area under a curve or a part of a curve is proportional to the number of molecules represented.)

Distribution of Molecular Kinetic Energy
at Two Different Temperatures, T_1 & T_2



Reaction Rates and Kinetics

Chemical reactivity is the focus of chemistry, and the study of reaction rates provides essential information about this subject. Some reactions proceed so rapidly they seem to be instantaneous, whereas other reactions are so slow they are nearly unobservable. Most of the reactions described in this text take place in from 0.2 to 12 hours at 25 ºC. Temperature is important, since fast reactions may be slowed or stopped by cooling, and slow reactions are accelerated by heating. When a reaction occurs between two reactant species, it proceeds faster at higher concentrations of the reactants. These facts lead to the following general analysis of reaction rates.

Reaction Rate =	Number of Collisions between Reactant Molecules per Unit of Time	•	Fraction of Collisions with Sufficient Energy to pass the Transition State	•	an Orientational or Probability Factor

Since reacting molecules must collide to interact, and the necessary activation energy must come from the kinetic energy of the colliding molecules, the first two factors are obvious. The third (probability) factor incorporates the orientational requirements of the reaction. For example, the addition of bromine to a double bond at the end of a six-carbon chain (1-hexene) could only occur if the colliding molecules came together in a way that allowed the bromine molecule to interact with the pi-electrons of the double bond.

The collision frequency of reactant molecules will be proportional to their concentration in the reaction system. This aspect of a reaction rate may be incorporated in a **rate equation**, which may take several forms depending on the number of reactants. Three general examples are presented in the following table.

Reaction Type	Rate Equation	Reaction Order
A ———> B	Reaction Rate = k•[A]	First Order Reaction (no collision needed)
A + B ———> C + D	Reaction Rate = k•[A]*[B]	Second Order Reaction
A + A ———> D	Reaction Rate = k•$[A]^2$	Second Order Reaction

These rate equations take the form **Reaction Rate = k[X] ^{n}[Y] ^{m}**, where the proportionality constant **k** reflects the unique characteristics of a specific reaction, and is called **the rate constant**. The concentrations of reactants X and Y are [X] and [Y] respectively, and **n** & **m** are exponential numbers used to fit the rate equation to the experimental data. The sum n + m is termed the **kinetic order** of a reaction. The first example is a simple first order process. The next two examples are second order reactions, since n + m = 2. The kinetic order of a reaction is usually used to determine its molecularity.

In writing a rate equation we have disconnected the collision frequency term from the activation energy and probability factors defined above, which are necessarily incorporated in the rate constant k. This is demonstrated by the following equation.

$$\text{Rate Constant (k)} = A\, e^{-\Delta E^{\ddagger}/RT}$$

The complex parameter A incorporates the probability factor. Because of the exponential relationship of k and the activation energy small changes in $\Delta E^{\ddagger}$ will cause relatively large changes in reaction rate. An increase in temperature clearly acts to increase k, but of greater importance is the increase in average molecular kinetic energy such an increase produces. This was illustrated in a previous diagram, increase in temperature from T_1 to T_2 producing a larger proportion of reactant molecules having energies equal or greater than the activation energy (designated by the red line.

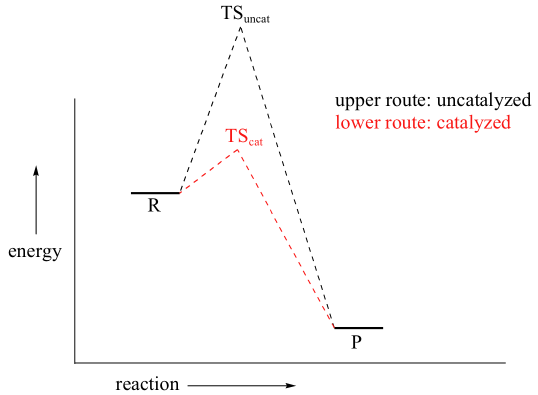
Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

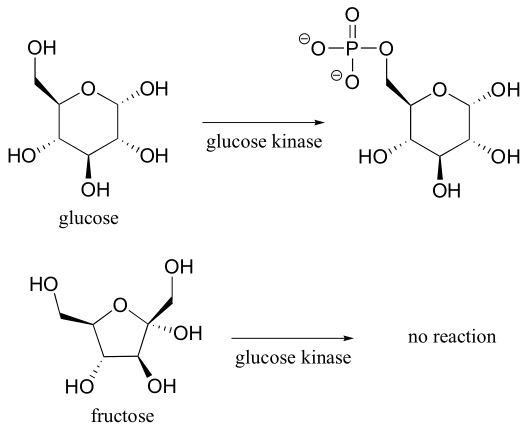
6.10: Catalysts

We come now to the subject of catalysis. Our hypothetical bowl of sugar (from section 6.2) is still stubbornly refusing to turn into carbon dioxide and water, even though by doing so it would reach a much more stable energy state. There are, in fact, two ways that we could speed up the process so as to avoid waiting several millennia for the reaction to reach completion. We could supply enough energy, in the form of heat from a flame, to push some of the sugar molecules over the high energy hill. Heat would be released from the resulting exothermic reaction, and this energy would push more molecules over their energy hills, and so on - the sugar would literally burn up.

A second way to make the reaction go faster is to employ a **catalyst**. You probably already know that a catalyst is an agent that causes a chemical reaction to go faster by lowering its activation energy.



How might you catalyze the conversion of sugar to carbon dioxide and water? It's not too hard – just eat the sugar, and let your digestive enzymes go to work catalyzing the many biochemical reactions involved in breaking it down. Enzymes are proteins, and are very effective catalysts. 'Very effective' in this context means very specific, and very fast. Most enzymes are very selective with respect to reactant molecules: they have evolved over millions of years to catalyze their specific reactions. An enzyme that attaches a phosphate group to glucose, for example, will not do anything at all to fructose (the details of these reactions are discussed in section 10.2B).



Glucose kinase is able to find and recognize glucose out of all of the other molecules floating around in the 'chemical soup' of a cell. A different enzyme, fructokinase, specifically catalyzes the phosphorylation of fructose.

We have already learned (section 3.9) that enzymes are very specific in terms of the stereochemistry of the reactions that they catalyze . Enzymes are also highly **regiospecific**, acting at only one specific part of a molecule. Notice that in the glucose kinase reaction above only one of the alcohol groups is phosphorylated.

Finally, enzymes are capable of truly amazing rate acceleration. Typical enzymes will speed up a reaction by anywhere from a million to a billion times, and the most efficient enzyme currently known to scientists is believed to accelerate its reaction by a factor of about 10^{17} (see *Chemical and Engineering News*, March 13, 2000, p. 42 for an interesting discussion about this enzyme, orotidine monophosphate decarboxylase).

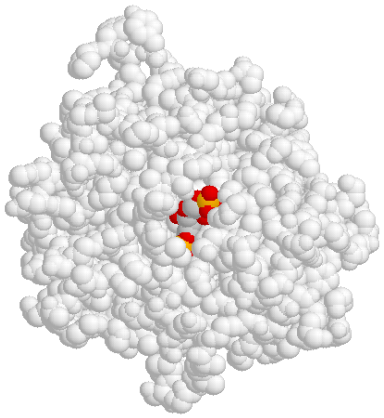
We will now begin an exploration of some of the basic ideas about how enzymes accomplish these amazing feats of catalysis, and these ideas will be revisited often throughout the rest of the text as we consider various examples of enzyme-catalyzed organic reactions. But in order to begin to understand how enzymes work, we will first need to learn (or review, as the case may be) a little bit about protein structure.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

6.11: Enzymes

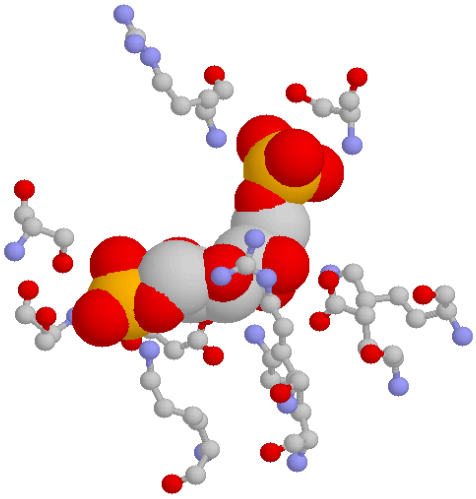
The active site

A critical element in the three-dimensional structure of any enzyme is the presence of an '**active site'**, which is a pocket, usually located in the interior of the protein, that serves as a docking point for the enzyme's **substrate**(s) ('substrate' is the term that biochemists use for a reactant molecule in an enzyme-catalyzed reaction). It is inside the active site pocket that enzymatic catalysis occurs. Shown below is an image of the glycolytic enzyme fructose-1,6-bisphosphate aldolase, with its substrate bound inside the active site pocket.

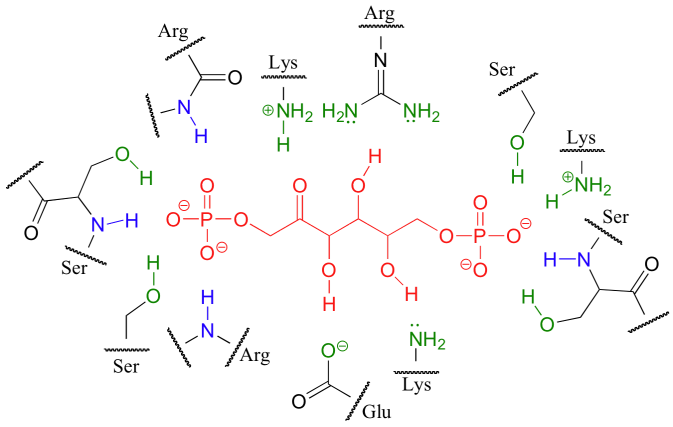


When the substrate binds to the active site, a large number of noncovalent interactions form with the amino acid residues that line the active site. The shape of the active site, and the enzyme-substrate interactions that form as a result of substrate binding, are *specific to the substrate-enzyme pair*: the active site has evolved to 'fit' one particular substrate and to catalyze one particular reaction. Other molecules do not fit in this active site nearly so well as fructose 1,6-bisphosphate.

Here are two close-up views of the same active site pocket, showing some of the specific hydrogen-bonding interactions between the substrate and active site amino acids. The first image below is a three-dimensional rendering directly from the crystal structure data. The substrate is shown in 'space-filling' style, while the active site amino acids are shown in the 'ball and stick' style. Hydrogens are not shown. The color scheme is grey for carbon, red for oxygen, blue for nitrogen, and orange for phosphorus.



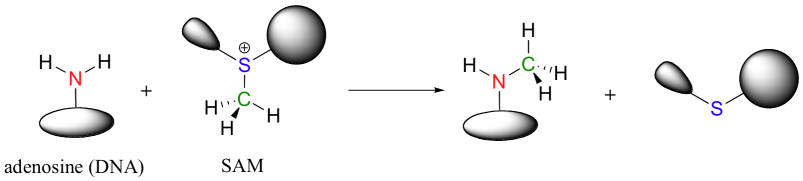
Below is a two-dimensional picture of the substrate (colored red) surrounded by hydrogen-bonding active site amino acids. Notice that both main chain and side chain groups contribute to hydrogen bonding: in this figure, main chain H-bonding groups are colored blue, and side chain H-bonding groups are colored green.



Looking at the last three images should give you some appreciation for the specific manner in which a substrate fits inside its active site.

Transition state stabilization

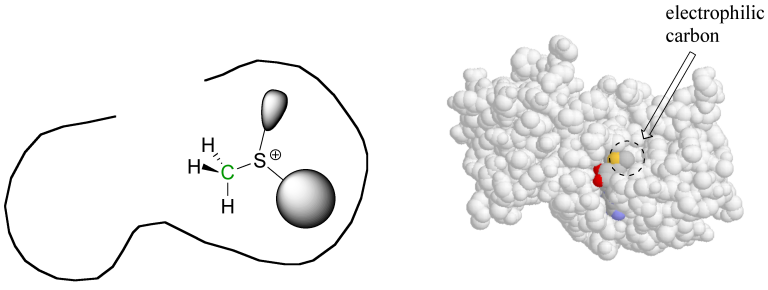
One of the most important ways that an enzyme catalyzes any given reaction is through entropy reduction: by bringing order to a disordered situation (remember that entropy is a component of Gibbs Free Energy, and thus a component of the activation energy). Let's turn again to our previous example (from section 6.1C) of a biochemical nucleophilic substitution reaction, the methylation of adenosine in DNA. The reaction is shown below with non-reactive sections of the molecules depicted by variously shaped 'bubbles' for the sake of simplicity.



adenosine (DNA) SAM

In order for this reaction to occur, the two substrates (reactants) must come into contact in precisely the right way. If they are both floating around free in solution, the likelihood of this occurring is very small – the entropy of the system is simply too high. In other words, this reaction takes place *very* slowly without the help of a catalyst.

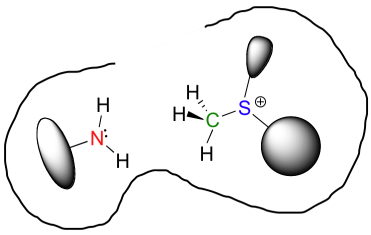
Here's where the enzyme's active site pocket comes into play. It is lined with various functional groups from the amino acid main and side chains, and has a very specific three-dimensional architecture that has evolved to bind to both of the substrates. If the SAM molecule, for example, diffuses into the active site, it can replace its (favorable) interactions with the surrounding water molecules with (even more favorable) new interactions with the functional groups lining the active site.



SAM bound in active site

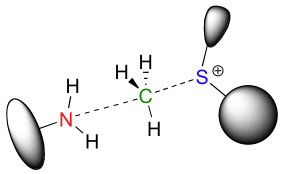
In a sense, SAM is moving from one solvent (water) to another 'solvent' (the active site), where many new energetically favorable interactions are possible. Remember: these new contacts between SAM and the active site groups are *highly specific* to SAM and SAM alone – no other molecule can 'fit' so well in this precise active site environment, and thus no other molecule will be likely to give up its contacts to water and bind to the active site.

The second substrate also has a specific spot reserved in the active site. (Because in this case the second substrate is a small segment of a long DNA molecule, the DNA-binding region of the active site is more of a 'groove' than a 'pocket').



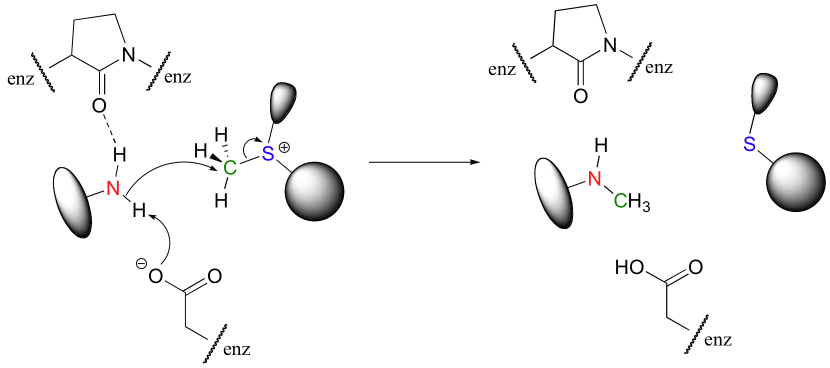
So now we have both substrates bound in the active site. But they are not just bound in any random orientation – they are specifically positioned relative to one another so that the nucleophilic nitrogen is held very close to the electrophilic carbon, with a free path of attack. What used to be a very disordered situation – two reactants diffusing freely in solution – is now a very highly ordered situation, with everything set up for the reaction to proceed. This is what is meant by entropy reduction: the entropic component of the energy barrier has been lowered.

Looking a bit deeper, though, it is not really the noncovalent interaction between enzyme and *substrate* that are responsible for catalysis. Remember: all catalysts, enzymes included, accelerate reactions by lowering the energy of the *transition state*. With this in mind, it should make sense that the primary job of an enzyme is to maximize favorable interactions with the transition state, *not* with the starting substrates. This does not imply that enzyme-substrate interactions are not strong, rather that enzyme-TS interactions are far *stronger*, often by several orders of magnitude. Think about it this way: if an enzyme were to bind to (and stabilize) its substrate(s) more tightly than it bound to (and stabilized) the transition state, it would actually *slow down* the reaction, because it would be *increasing* the energy difference between starting state and transition state. ***The enzyme has evolved to maximize favorable noncovalent interactions to the transition state***: in our example, this is the state in which the nucleophilic nitrogen is already beginning to attack the electrophilic carbon, and the carbon-sulfur bond has already begun to break.

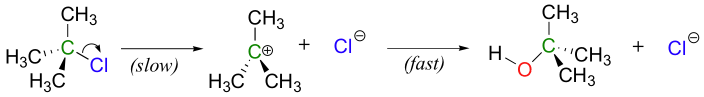


enzyme binds best to the transition state

In many enzymatic reactions, certain active site amino acid residues contribute to catalysis by *increasing the reactivity of the substrates*. Often, the catalytic role is that of acid and/or base. In our DNA methylation example, the nucleophilic nitrogen is deprotonated by a nearby aspartate side chain as it begins its nucleophilic attack on the methyl group of SAM. We will study nucleophilicity in greater detail in chapter 8, but it should make intuitive sense that deprotonating the amine increases the electron density of the nitrogen, making it *more nucleophilic*. Notice also in the figure below that the main chain carbonyl of an active site proline forms a hydrogen bond with the amine, which also has the effect of increasing the nitrogen's electron density and thus its nucleophilicity (*Nucleic Acids Res.* **2000**, *28*, 3950).

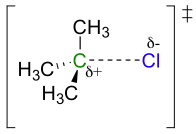


How does our picture of enzyme catalysis apply to multi-step reaction mechanisms? Although the two-step nucleophilic substitution reaction between *tert*-butyl chloride and hydroxide (section 6.1C) is not a biologically relevant process, let's pretend just for the sake of illustration that there is a hypothetical enzyme that catalyzes this reaction.



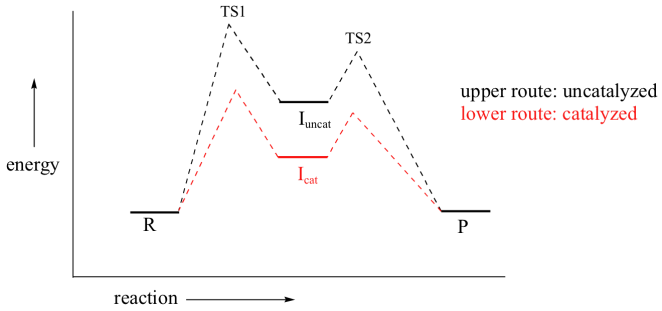
The same basic principles apply here: the enzyme binds best to the transition state. But therein lies the problem: there are two transition states! To which TS does the enzyme maximize its contacts?

Recall that the first step – the loss of the chloride leaving group to form the carbocation intermediate – is the slower, rate-limiting step. It is this step that our hypothetical enzyme needs to accelerate if it wants to accelerate the overall reaction, and it is thus the energy of TS1 that needs to be lowered.



enzyme maximizes interactions with TS1

By Hammond's postulate, we also know that the intermediate I is a close approximation of TS1. So the enzyme, by stabilizing the intermediate, will also stabilize TS1 (as well as TS2) and thereby accelerate the reaction.



If you read scientific papers about enzyme mechanisms, you will often see researchers discussing how an enzyme stabilizes a reaction intermediate. By virtue of Hammond's postulate, they are, at the same time, talking about how the enzyme lowers the energy of the transition state.

An additional note: although we have in this section been referring to SAM as a 'substrate' of the DNA methylation reaction, it is also often referred to as a **coenzyme**, or **cofactor**. These terms are used to describe small (relative to protein and DNA) biological organic molecules that bind specifically in the active site of an enzyme and help the enzyme to do its job. In the case of SAM, the job is methyl group donation. In addition to SAM, we will see many other examples of coenzymes in the coming chapters, a number of which - like ATP (adenosine triphosphate), coenzyme A, thiamine, and flavin - you have probably heard of before. The full structures of some common coenzymes are shown in table 6 in the tables section.

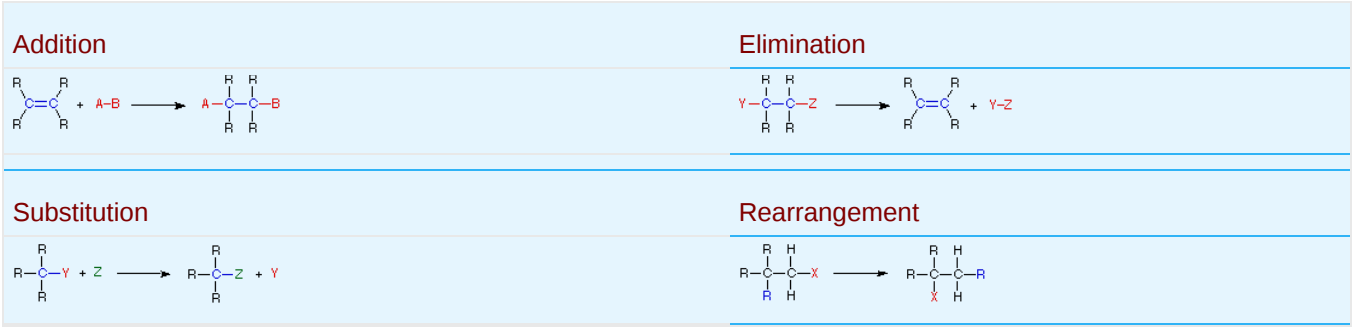
Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

6.12: Kinds of Organic Reactions

If you scan any organic textbook you will encounter what appears to be a very large, often intimidating, number of reactions. These are the "tools" of a chemist, and to use these tools effectively, we must organize them in a sensible manner and look for patterns of reactivity that permit us make plausible predictions. Most of these reactions occur at special sites of reactivity known as functional groups, and these constitute one organizational scheme that helps us catalog and remember reactions.

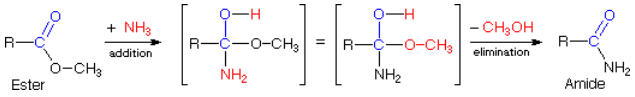
Ultimately, the best way to achieve proficiency in organic chemistry is to understand how reactions take place, and to recognize the various factors that influence their course.

First, we identify four broad classes of reactions based solely on the **structural change** occurring in the reactant molecules. This classification does not require knowledge or speculation concerning reaction paths or mechanisms. The four main reaction classes are **additions, eliminations, substitutions, and rearrangements.**

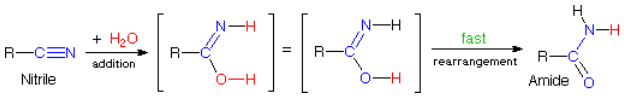


In an **addition** reaction the number of σ-bonds in the substrate molecule increases, usually at the expense of one or more π-bonds. The reverse is true of **elimination** reactions, *i.e.*the number of σ-bonds in the substrate decreases, and new π-bonds are often formed. **Substitution** reactions, as the name implies, are characterized by replacement of an atom or group (Y) by another atom or group (Z). Aside from these groups, the number of bonds does not change. A **rearrangement** reaction generates an isomer, and again the number of bonds normally does not change.

The examples illustrated above involve simple alkyl and alkene systems, but these reaction types are general for most functional groups, including those incorporating carbon-oxygen double bonds and carbon-nitrogen double and triple bonds. Some common reactions may actually be a combination of reaction types. The reaction of an ester with ammonia to give an amide, as shown below, appears to be a substitution reaction (Y = CH_3O & Z = NH_2); however, it is actually two reactions, an addition followed by an elimination.



The addition of water to a nitrile does not seem to fit any of the above reaction types, but it is simply a slow addition reaction followed by a rapid rearrangement, as shown in the following equation. Rapid rearrangements of this kind are called **tautomerizations**.



Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

6.13: Thermodynamics

Equilibrium Constant

For the hypothetical chemical reaction:

$$aA + bB \rightleftharpoons cC + dD \tag{6.5.1}$$

the equilibrium constant is defined as:

$$K_C = \frac{[C]^c[D]^d}{[A]^a[B]^b} \tag{6.5.2}$$

The notation [A] signifies the molar concentration of species A. An alternative expression for the equilibrium constant involves partial pressures:

$$K_P = \frac{P_C^c P_D^d}{P_A^a P_B^b} \tag{6.5.3}$$

Note that the expression for the equilibrium constant includes only solutes and gases; pure solids and liquids do not appear in the expression. For example, the equilibrium expression for the reaction

$$CaH_2(s) + 2H_2O(g) \rightleftharpoons Ca(OH)_2(s) + 2H_2(g) \tag{6.5.4}$$

is the following:

$$K_C = \frac{[H_2]^2}{[H_2O]^2} \tag{6.5.5}$$

Observe that the gas-phase species H_2O and H_2 appear in the expression but the solids CaH_2 and $Ca(OH)_2$ do not appear.

The equilibrium constant is most readily determined by allowing a reaction to reach equilibrium, measuring the concentrations of the various solution-phase or gas-phase reactants and products, and substituting these values into the Law of Mass Action.

Gibbs Energy

The interaction between enthalpy and entropy changes in chemical reactions is best observed by studying their influence on the equilibrium constants of reversible reactions. To this end a new thermodynamic function called **Free Energy** (or Gibbs Free Energy), symbol **ΔG**, is defined as shown in the first equation below. Two things should be apparent from this equation. First, in cases where the entropy change is small, ΔG ≅ ΔH. Second, the importance of ΔS in determining ΔG increases with increasing temperature.

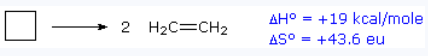
$$\Delta G^o = \Delta H^o - T\Delta S^o \tag{6.5.6}$$

where T is the absolute temperature measured in kelvin.

The free energy function provides improved insight into the thermodynamic driving forces that influence reactions. A negative ΔG° is characteristic of an **exergonic reaction**, one which is thermodynamically favorable and often spontaneous, as is the melting of ice at 1 °C. Likewise a positive ΔG° is characteristic of an **endergonic reaction**, one which requires an input of energy from the surroundings.

Example 6.5.1: Decomposition of Cyclobutane

For an example of the relationship of free energy to enthalpy consider the decomposition of cyclobutane to ethene, shown in the following equation. The standard state for all the compounds is gaseous.



This reaction is endothermic, but the increase in number of molecules from one (reactants) to two (products) results in a large positive ΔS°.

At 25 °C (298 °K), ΔG° = 19 kcal/mol – 298(43.6) cal/mole = 19 – 13 kcal/mole = +6 kcal/mole. Thus, the entropy change opposes the enthalpy change, but is not sufficient to change the sign of the resulting free energy change, which is endergonic.

Indeed, cyclobutane is perfectly stable when kept at room temperature.

Because the entropy contribution increases with temperature, this energetically unfavorable transformation can be made favorable by raising the temperature. At 200 ºC (473 ºK), ΔGº = 19 kcal/mol – 473(43.6) cal/mole = 19 – 20.6 kcal/mole = –1.6 kcal/mole. This is now an exergonic reaction, and the thermal cracking of cyclobutane to ethene is known to occur at higher temperatures.

$$\Delta G^{o} = -RT \ln K = -2.303 RT \log K \tag{6.13.1}$$

with

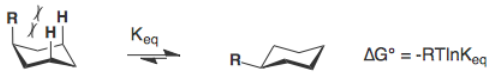
- R = 1.987 cal/ ºK mole
- T = temperature in ºK
- K = equilibrium constant

A second equation, shown above, is important because it demonstrates the fundamental relationship of ΔGº to the equilibrium constant, K. Because of the negative logarithmic relationship between these variables, a negative ΔGº generates a K>1, whereas a positive ΔGº generates a K<1. When ΔGº = 0, K = 1. Furthermore, small changes in ΔGº produce large changes in K. A change of 1.4 kcal/mole in ΔGº changes K by approximately a factor of 10. This interrelationship may be explored with the calculator on the right. Entering free energies outside the range -8 to 8 kcal/mole or equilibrium constants outside the range 10-6 to 900,000 will trigger an alert, indicating the large imbalance such numbers imply.

Substituted Cyclohexanes

A Values

Substituents on a cyclohexane prefer to be in the equatorial position. When a substituent is in the axial position, there are two gauche butane interactions more than when a substituent is in the equatorial position. We quantify the energy difference between the axial and equatorial conformations as the A-value, which is equivalent to the negative of the ΔG°, for the equilibrium shown below. Therefore the A-value, or -ΔG°, is the preference for the substituent to sit in the equatorial position.



Recall that the equilibrium constant is related to the change in Gibbs Energies for the reaction:

$$\Delta G^{o} = -RT \ln K_{eq} \tag{6.13.2}$$

The balance between reactants and products in a reaction will be determined by the free energy difference between the two sides of the reaction. The greater the free energy difference, the more the reaction will favor one side or the other (Table 6.5.1).

***Table 6.5.1**: Below is a table of A-values for some common substituents.*

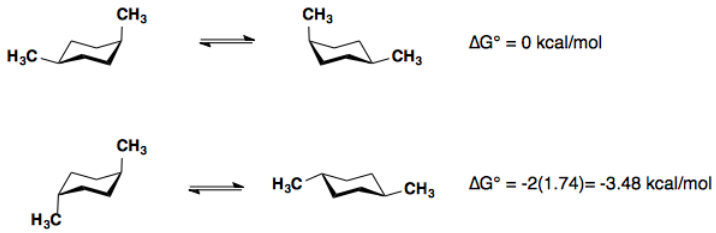
Substituent	ΔG° (kcal/mol)	A-value
-F	-0.28-0.24	0.24-0.28
-Cl	-0.53	0.53
-Br	-0.48	0.48
-I	-0.47	0.47
$-CH_3$ (-Me)	-1.8	1.8
$-CH_2CH_3$ (-Et)	-1.8	1.8
$-CH(CH_3)_2$ (-*i*-Pr)	-2.1	2.1
$-C(CH_3)_3$ (-*t*-Bu)	<-4.5	>4.5
$-CHCH_2$	-1.7	1.7

-CCH	-0.5	0.5
-CN	-0.25-0.15	0.15-0.25
$-C_6H_5$ (-Ph)	-2.9	2.9

Polysubstituted Cyclohexanes

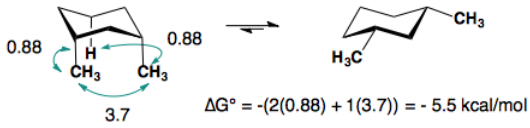
1,4-disubstitution

The A-values of the substituents are roughly additive in either the *cis*- or *trans*-diastereomers.



1,3-disubstitution

A-values are only additive in the *trans*-diastereomer:



When there are *cis*-substituents on the chair, there is a new interaction in the di-axial conformation:

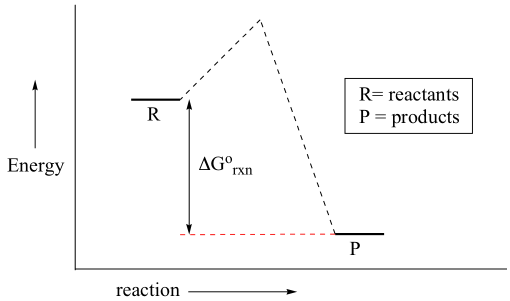
In the above example, each methyl group has one 1,3-diaxial interaction with a hydrogen. The methyl groups also interact with each other. This new diaxial interaction is extremely unfavorable based on their steric interaction (see: double-gauche pentane conformation).

Contributors

- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Jim Clark (Chemguide.co.uk)

6.14: Energy Diagrams

You may recall from general chemistry that it is often convenient to describe chemical reactions with energy diagrams. In an energy diagram, the vertical axis represents the overall energy of the reactants, while the horizontal axis is the 'reaction coordinate', tracing from left to right the progress of the reaction from starting compounds to final products. The energy diagram for a typical one-step reaction might look like this:



Despite its apparent simplicity, this energy diagram conveys some very important ideas about the thermodynamics and kinetics of the reaction. Recall that when we talk about the **thermodynamics** of a reaction, we are concerned with the difference in energy between reactants and products, and whether a reaction is 'downhill' (exergonic, energy releasing) or 'uphill (endergonic, energy absorbing). When we talk about **kinetics**, on the other hand, we are concerned with the *rate* of the reaction, regardless of whether it is uphill or downhill thermodynamically.

First, let's review what this energy diagram tells us about the thermodynamics of the reaction illustrated by the energy diagram above. The energy level of the products is *lower* than that of the reactants. This tells us that the change in standard Gibbs Free Energy for the reaction (ΔG°_{rnx}) is negative. In other words, the reaction is exergonic, or 'downhill'. Recall that the ΔG°_{rnx} term encapsulates both ΔH°_{rnx}, the change in enthalpy (heat) and ΔS°_{rnx} , the change in entropy (disorder):

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \tag{6.14.1}$$

where T is the absolute temperature in Kelvin. For chemical processes where the entropy change is small (~0), the enthalpy change is essentially the same as the change in Gibbs Free Energy. Energy diagrams for these processes will often plot the enthalpy (H) instead of Free Energy for simplicity.

The standard Gibbs Free Energy change for a reaction can be related to the reaction's equilibrium constant (\(K_{eq}_) by a simple equation:

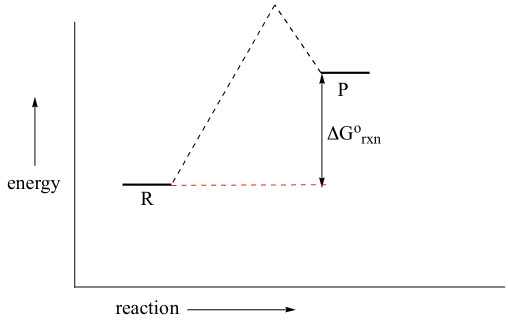
$$\Delta G^\circ = -RT \ln K_{eq} \tag{6.14.2}$$

where:

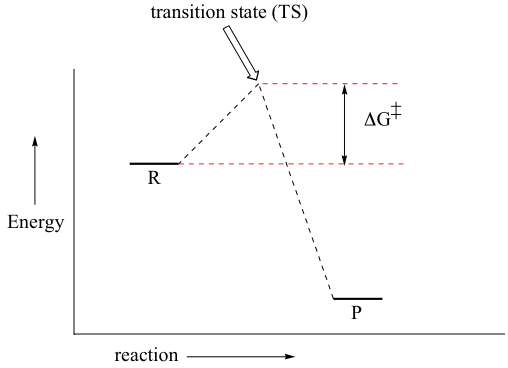
- K_{eq} = [product] / [reactant] at equilibrium
- R = 8.314 $J \times K^{-1} \times mol^{-1}$ *or* 1.987 $cal \times K^{-1} \times mol^{-1}$
- T = temperature in Kelvin (K)

If you do the math, you see that a negative value for ΔG°_{rnx} (an exergonic reaction) corresponds - as it should by intuition - to K_{eq} being greater than 1, an equilibrium constant which favors product formation.

In a hypothetical endergonic (energy-absorbing) reaction the products would have a higher energy than reactants and thus ΔG°_{rnx} would be positive and K_{eq} would be less than 1, favoring reactants.

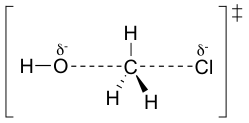


Now, let's move to kinetics. Look again at the energy diagram for exergonic reaction: although it is 'downhill' overall, it isn't a straight downhill run.



First, an 'energy barrier' must be overcome to get to the product side. The height of this energy barrier, you may recall, is called the '**activation energy'** ($\Delta G^{\ddagger}$). The activation energy is what determines the kinetics of a reaction: the higher the energy hill, the slower the reaction. At the very top of the energy barrier, the reaction is at its **transition state** (TS), which is the point at which the bonds are in the process of breaking and forming. The transition state is an '**activated complex'**: a transient and dynamic state that, unlike more stable species, does not have any definable lifetime. It may help to imagine a transition state as being analogous to the exact moment that a baseball is struck by a bat. Transition states are drawn with dotted lines representing bonds that are in the process of breaking or forming, and the drawing is often enclosed by brackets. Here is a picture of a likely transition state for a substitution reaction between hydroxide and chloromethane:

$$CH_3Cl + HO^- \rightarrow CH_3OH + Cl^- \tag{6.14.3}$$



This reaction involves a collision between *two* molecules: for this reason, we say that it has **second order kinetics**. The **rate expression** for this type of reaction is:

$$\text{rate} = k[\text{reactant 1}][\text{reactant 2}]$$

. . . which tells us that the rate of the reaction depends on the **rate constant** *k* as well as on the concentration of *both* reactants. The rate constant can be determined experimentally by measuring the rate of the reaction with different starting reactant concentrations. The rate constant depends on the activation energy, of course, but also on temperature: a higher temperature means a higher *k* and a faster reaction, all else being equal. This should make intuitive sense: when there is more heat energy in the system, more of the reactant molecules are able to get over the energy barrier.

Here is one more interesting and useful expression. Consider a simple reaction where the reactants are A and B, and the product is AB (this is referred to as a **condensation reaction**, because two molecules are coming together, or condensing). If we know the rate constant *k* for the forward reaction and the rate constant $k_{reverse}$ for the reverse reaction (where AB splits apart into A and B), we can simply take the quotient to find our equilibrium constant K_{eq}:

$$A + B \rightleftharpoons AB \qquad K_{eq} = \frac{[AB]}{[A]\,[B]} = \frac{k_{forward}}{k_{reverse}}$$

This too should make some intuitive sense; if the forward rate constant is higher than the reverse rate constant, equilibrium should lie towards products.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

Further Reading

MasterOrganicChemistry

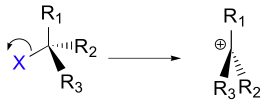
Equilibria

Websites

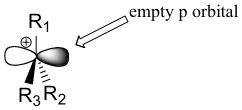
Reversible and irreversible reactions

6.15: Energy Diagram for a Two-Step Reaction Mechanism

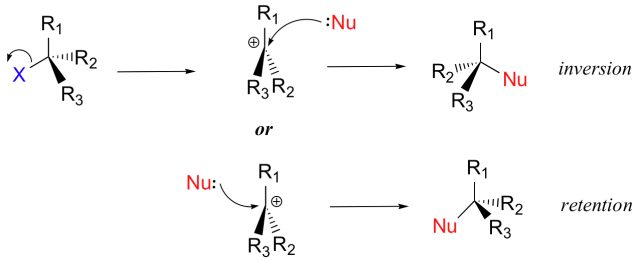
A second model for a nucleophilic substitution reaction is called the '**dissociative**', or '**S_N1**' mechanism: in this picture, the C-X bond breaks *first*, before the nucleophile approaches:



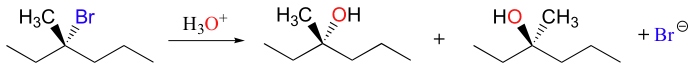
This results in the formation of a carbocation: because the central carbon has only three bonds, it bears a formal charge of +1. Recall that a carbocation should be pictured as sp^2 hybridized, with trigonal planar geometry. Perpendicular to the plane formed by the three sp^2 hybrid orbitals is an empty, unhybridized *p* orbital.



In the second step of this two-step reaction, the nucleophile attacks the empty, 'electron hungry' *p* orbital of the carbocation to form a new bond and return the carbon to tetrahedral geometry.

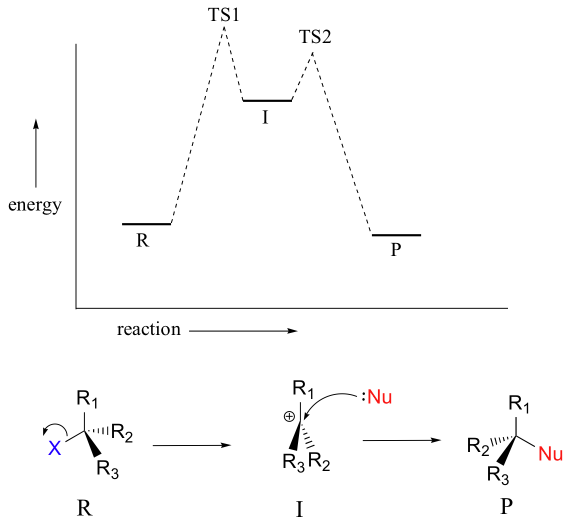


We saw that S_N2 reactions result specifically in inversion of stereochemistry at the electrophilic carbon center. What about the stereochemical outcome of S_N1 reactions? In the model S_N1 reaction shown above, the leaving group dissociates completely from the vicinity of the reaction before the nucleophile begins its attack. Because the leaving group is no longer in the picture, the nucleophile is free to attack from either side of the planar, sp^2-hybridized carbocation electrophile. This means that about half the time the product has the same stereochemical configuration as the starting material (retention of configuration), and about half the time the stereochemistry has been inverted. In other words, *racemization* has occurred at the carbon center. As an example, the tertiary alkyl bromide below would be expected to form a racemic mix of *R* and *S* alcohols after an S_N1 reaction with water as the incoming nucleophile.



Exercise
Draw the structure of the intermediate in the two-step nucleophilic substitution reaction above.

The S_N1 reaction we see an example of a reaction intermediate, a very important concept in the study of organic reaction mechanisms that was introduced earlier in the module on organic reactivity Recall that many important organic reactions do not occur in a single step; rather, they are the sum of two or more discreet bond-forming / bond-breaking steps, and involve transient intermediate species that go on to react very quickly. In the S_N1 reaction, the carbocation species is a reaction intermediate. A potential energy diagram for an S_N1 reaction shows that the carbocation intermediate can be visualized as a kind of valley in the path of the reaction, higher in energy than both the reactant and product but lower in energy than the two transition states.



Exercise

Draw structures representing TS1 and TS2 in the reaction above. Use the solid/dash wedge convention to show three dimensions.

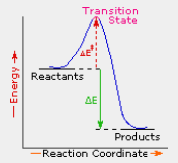
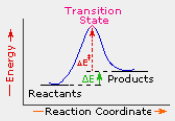
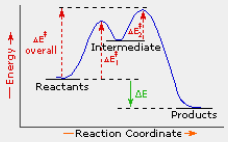
Recall that the first step of the reaction above, in which two charged species are formed from a neutral molecule, is much the slower of the two steps, and is therefore rate-determining. This is illustrated by the energy diagram, where the activation energy for the first step is higher than that for the second step. Also recall that an S_N1 reaction has *first order* kinetics, because the rate determining step involves one molecule splitting apart, not two molecules colliding

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

6.16: Kinetics

Activation Energy

Since exothermic reactions are energetically (thermodynamically) favored, a careless thinker might conclude that all such reactions will proceed spontaneously to their products. Were this true, no life would exist on Earth, because the numerous carbon compounds that are present in and essential to all living organisms would spontaneously combust in the presence of oxygen to give carbon dioxide-a more stable carbon compound. The combustion of methane (eq.1), for example, does not occur spontaneously, but requires an initiating energy in the form of a spark or flame. The flaw in this careless reasoning is that we have focused only on the initial (reactant) and final (product) states of reactions. To understand why some reactions occur readily (almost spontaneously), whereas other reactions are slow, even to the point of being unobservable, we need to consider the intermediate stages of reactions.

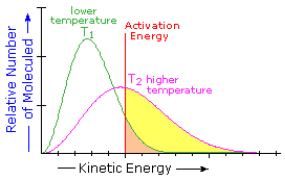
Exothermic Single Step Reaction	Endothermic Single Step Reaction	Exothermic Two Step Reaction
		

Every reaction in which bonds are broken will have a high energy **transition state** that must be reached before products can form. In order for the reactants to reach this transition state, energy must be supplied and reactant molecules must orient themselves in a suitable fashion. The energy needed to raise the reactants to the transition state energy level is called the **activation energy, $\Delta E^{\ddagger}$**. An example of a single-step exothermic reaction profile is shown on the left above, and a similar single-step profile for an endothermic reaction is in the center. The activation energy is drawn in red in each case, and the overall energy change (ΔE) is in green.

The profile becomes more complex when a multi-step reaction path is described. An example of a two-step reaction proceeding by way of a high energy intermediate is shown on the right above. Here there are two transition states, each with its own activation energy. The overall activation energy is the difference in energy between the reactant state and the highest energy transition state. We see now why the rate of a reaction may not correlate with its overall energy change. In the exothermic diagram on the left, a significant activation energy must be provided to initiate the reaction. Since the reaction is strongly exothermic, it will probably generate enough heat to keep going as long as reactants remain. The endothermic reaction in the center has a similar activation energy, but this will have to be supplied continuously for the reaction to proceed to completion.

What is the source of the activation energy that enables a chemical reaction to occur? Often it is heat, as noted above in reference to the flame or spark that initiates methane combustion. At room temperature, indeed at any temperature above absolute zero, the molecules of a compound have a total energy that is a combination of translational (kinetic) energy, internal vibrational and rotational energies, as well as electronic and nuclear energies. The temperature of a system is a measure of the average kinetic energy of all the atoms and molecules present in the system. As shown in the following diagram, the average kinetic energy increases and the distribution of energies broadens as the temperature is raised from T_1 to T_2. Portions of this thermal or kinetic energy provide the activation energy for many reactions, the concentration of suitably activated reactant molecules increasing with temperature, e.g. orange area for T_1 and yellow plus orange for T_2. (Note that the area under a curve or a part of a curve is proportional to the number of molecules represented.)

Distribution of Molecular Kinetic Energy
at Two Different Temperatures, T_1 & T_2



Reaction Rates and Kinetics

Chemical reactivity is the focus of chemistry, and the study of reaction rates provides essential information about this subject. Some reactions proceed so rapidly they seem to be instantaneous, whereas other reactions are so slow they are nearly unobservable. Most of the reactions described in this text take place in from 0.2 to 12 hours at 25 ºC. Temperature is important, since fast reactions may be slowed or stopped by cooling, and slow reactions are accelerated by heating. When a reaction occurs between two reactant species, it proceeds faster at higher concentrations of the reactants. These facts lead to the following general analysis of reaction rates.

Reaction Rate =	Number of Collisions between Reactant Molecules per Unit of Time	•	Fraction of Collisions with Sufficient Energy to pass the Transition State	•	an Orientational or Probability Factor

Since reacting molecules must collide to interact, and the necessary activation energy must come from the kinetic energy of the colliding molecules, the first two factors are obvious. The third (probability) factor incorporates the orientational requirements of the reaction. For example, the addition of bromine to a double bond at the end of a six-carbon chain (1-hexene) could only occur if the colliding molecules came together in a way that allowed the bromine molecule to interact with the pi-electrons of the double bond.

The collision frequency of reactant molecules will be proportional to their concentration in the reaction system. This aspect of a reaction rate may be incorporated in a **rate equation**, which may take several forms depending on the number of reactants. Three general examples are presented in the following table.

Reaction Type	Rate Equation	Reaction Order
A ———> B	Reaction Rate = k•[A]	First Order Reaction (no collision needed)
A + B ———> C + D	Reaction Rate = k•[A]*[B]	Second Order Reaction
A + A ———> D	Reaction Rate = k•$[A]^2$	Second Order Reaction

These rate equations take the form **Reaction Rate = k[X] ^{n}[Y] ^{m}**, where the proportionality constant **k** reflects the unique characteristics of a specific reaction, and is called **the rate constant**. The concentrations of reactants X and Y are [X] and [Y] respectively, and **n** & **m** are exponential numbers used to fit the rate equation to the experimental data. The sum n + m is termed the **kinetic order** of a reaction. The first example is a simple first order process. The next two examples are second order reactions, since n + m = 2. The kinetic order of a reaction is usually used to determine its molecularity.

In writing a rate equation we have disconnected the collision frequency term from the activation energy and probability factors defined above, which are necessarily incorporated in the rate constant k. This is demonstrated by the following equation.

$$\text{Rate Constant (k)} = A\, e^{-\Delta E^{\ddagger}/RT}$$

The complex parameter A incorporates the probability factor. Because of the exponential relationship of k and the activation energy small changes in $\Delta E^{\ddagger}$ will cause relatively large changes in reaction rate. An increase in temperature clearly acts to increase k, but of greater importance is the increase in average molecular kinetic energy such an increase produces. This was illustrated in a previous diagram, increase in temperature from T_1 to T_2 producing a larger proportion of reactant molecules having energies equal or greater than the activation energy (designated by the red line.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

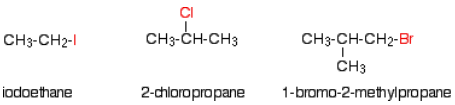
CHAPTER OVERVIEW

7: Alkyl Halides and Nucleophilic Substitution

Topic hierarchy

7.1: Introduction to Alkyl Halides

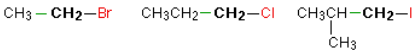
Alkyl halides are also known as haloalkanes. This page explains what they are and discusses their physical properties. alkyl halides are compounds in which one or more hydrogen atoms in an alkane have been replaced by halogen atoms (fluorine, chlorine, bromine or iodine). We will only look at compounds containing one halogen atom. For example:



alkyl halides fall into different classes depending on how the halogen atom is positioned on the chain of carbon atoms. There are some chemical differences between the various types.

Primary alkyl halides

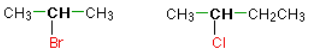
In a primary (1°) halogenoalkane, the carbon which carries the halogen atom is only attached to one other alkyl group.Some examples of primary alkyl halides include:



Notice that it doesn't matter how complicated the attached alkyl group is. In each case there is only one linkage to an alkyl group from the CH_2 group holding the halogen. There is an exception to this: CH_3Br and the other methyl halides are often counted as primary alkyl halides even though there are **no** alkyl groups attached to the carbon with the halogen on it.

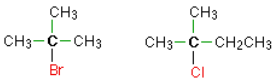
Secondary alkyl halides

In a secondary (2°) halogenoalkane, the carbon with the halogen attached is joined directly to two other alkyl groups, which may be the same or different. Examples:



Tertiary alkyl halides

In a tertiary (3°) halogenoalkane, the carbon atom holding the halogen is attached directly to three alkyl groups, which may be any combination of same or different. Examples:



Contributors

Jim Clark (Chemguide.co.uk)

7.2: Nomenclature

e Learning Objective is to name halogenated hydrocarbons given formulas and write formulas for these compounds given names.

Many organic compounds are closely related to the alkanes. As we noted in Section 12.7, alkanes react with halogens to produce halogenated hydrocarbons, the simplest of which have a single halogen atom substituted for a hydrogen atom of the alkane. Even more closely related are the cycloalkanes, compounds in which the carbon atoms are joined in a ring, or cyclic fashion.

The reactions of alkanes with halogens produce halogenated hydrocarbons, compounds in which one or more hydrogen atoms of a hydrocarbon have been replaced by halogen atoms:

CH_3CH_2Cl $CH_3CHBrCH_2Br$ CH_3CHICH_2Cl

The replacement of only one hydrogen atom gives an alkyl halide (or haloalkane). The *common names* of alkyl halides consist of two parts: the name of the alkyl group plus the stem of the name of the halogen, with the ending *-ide*. The IUPAC system uses the name of the parent alkane with a prefix indicating the halogen substituents, preceded by number indicating the substituent's location. The prefixes are *fluoro-*, *chloro-*, *bromo-*, and *iodo-*. Thus CH_3CH_2Cl has the common name ethyl chloride and the IUPAC name chloroethane. Alkyl halides with simple alkyl groups (one to four carbon atoms) are often called by common names. Those with a larger number of carbon atoms are usually given IUPAC names.

Example 3

Give the common and IUPAC names for each compound.

1. $CH_3CH_2CH_2Br$
2. $(CH_3)_2CHCl$

SOLUTION

1. The alkyl group ($CH_3CH_2CH_2$–) is a propyl group, and the halogen is bromine (Br). The common name is therefore propyl bromide. For the IUPAC name, the prefix for bromine (bromo) is combined with the name for a three-carbon chain (propane), preceded by a number identifying the carbon atom to which the Br atom is attached, so the IUPAC name is 1-bromopropane.
2. The alkyl group [$(CH_3)_2CH$–] has three carbon atoms, with a chlorine (Cl) atom attached to the middle carbon atom. The alkyl group is therefore isopropyl, and the common name of the compound is isopropyl chloride. For the IUPAC name, the Cl atom (prefix *chloro-*) attached to the middle (second) carbon atom of a propane chain results in 2-chloropropane.

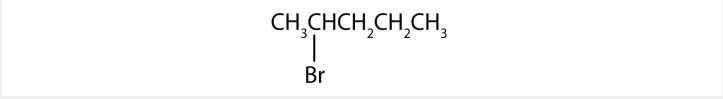
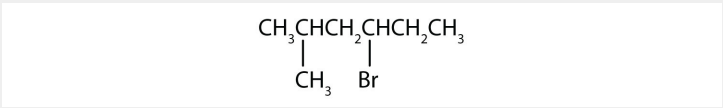
Skill-Building Exercise

Give common and IUPAC names for each compound.

1. CH_3CH_2I
2. $CH_3CH_2CH_2CH_2F$

Example 4

Give the IUPAC name for each compound.

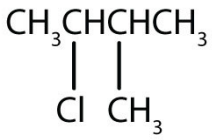
1. 
2. 

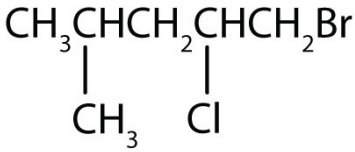
SOLUTION

1. The parent alkane has five carbon atoms in the longest continuous chain; it is pentane. A bromo (Br) group is attached to the second carbon atom of the chain. The IUPAC name is 2-bromopentane.
2. The parent alkane is hexane. Methyl (CH_3) and bromo (Br) groups are attached to the second and fourth carbon atoms, respectively. Listing the substituents in alphabetical order gives the name 4-bromo-2-methylhexane.

Skill-Building Exercise

Give the IUPAC name for each compound.

1. 

2. 

A wide variety of interesting and often useful compounds have one or more halogen atoms per molecule. For example, methane (CH_4) can react with chlorine (Cl_2), replacing one, two, three, or all four hydrogen atoms with Cl atoms. Several halogenated products derived from methane and ethane (CH_3CH_3) are listed in Table 12.6 "Some Halogenated Hydrocarbons", along with some of their uses.

Table 12.6 Some Halogenated Hydrocarbons

Formula	Common Name	IUPAC Name	Some Important Uses
Derived from CH_4			
CH_3Cl	methyl chloride	chloromethane	refrigerant; the manufacture of silicones, methyl cellulose, and synthetic rubber
CH_2Cl_2	methylene chloride	dichloromethane	laboratory and industrial solvent
$CHCl_3$	chloroform	trichloromethane	industrial solvent
CCl_4	carbon tetrachloride	tetrachloromethane	dry-cleaning solvent and fire extinguishers (but no longer recommended for use)
$CBrF_3$	halon-1301	bromotrifluoromethane	fire extinguisher systems
CCl_3F	chlorofluorocarbon-11 (CFC-11)	trichlorofluoromethane	foaming plastics
CCl_2F_2	chlorofluorocarbon-12 (CFC-12)	dichlorodifluoromethane	refrigerant
Derived from CH_3CH_3			
CH_3CH_2Cl	ethyl chloride	chloroethane	local anesthetic
$ClCH_2CH_2Cl$	ethylene dichloride	1,2-dichloroethane	solvent for rubber
CCl_3CH_3	methylchloroform	1,1,1-trichloroethane	solvent for cleaning computer chips and molds for shaping plastic

Contributors

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

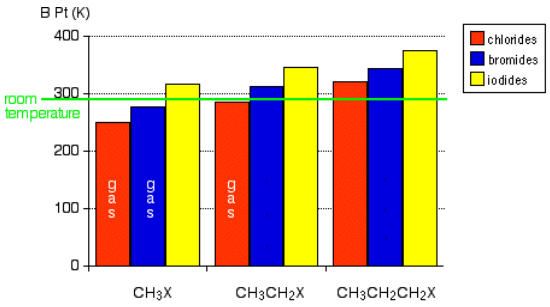
- Jim Clark (Chemguide.co.uk)

7.3: Physical Properties

Physical properties of alkyl halides

Boiling Points

The chart shows the boiling points of some simple alkyl halides.



Notice that three of these have boiling points below room temperature (taken as being about 20°C). These will be gases at room temperature. All the others you are likely to come across are liquids. Remember:

- the only methyl halide which is a liquid is iodomethane;
- chloroethane is a gas.

The patterns in boiling point reflect the patterns in intermolecular attractions.

van der Waals dispersion forces

These attractions get stronger as the molecules get longer and have more electrons. That increases the sizes of the temporary dipoles that are set up. This is why the boiling points increase as the number of carbon atoms in the chains increases. Look at the chart for a particular type of halide (a chloride, for example). Dispersion forces get stronger as you go from 1 to 2 to 3 carbons in the chain. It takes more energy to overcome them, and so the boiling points rise.

The increase in boiling point as you go from a chloride to a bromide to an iodide (for a given number of carbon atoms) is also because of the increase in number of electrons leading to larger dispersion forces. There are lots more electrons in, for example, iodomethane than there are in chloromethane - count them!

van der Waals dipole-dipole attractions

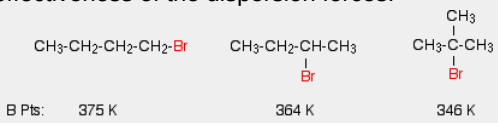
The carbon-halogen bonds (apart from the carbon-iodine bond) are polar, because the electron pair is pulled closer to the halogen atom than the carbon. This is because (apart from iodine) the halogens are more electronegative than carbon. The electronegativity values are:

C	2.5		F	4.0
			Cl	3.0
			Br	2.8
			I	2.5

This means that in addition to the dispersion forces there will be forces due to the attractions between the permanent dipoles (except in the iodide case). The size of those dipole-dipole attractions will fall as the bonds get less polar (as you go from chloride to bromide to iodide, for example). Nevertheless, the boiling points rise! This shows that the effect of the permanent dipole-dipole attractions is much less important than that of the temporary dipoles which cause the dispersion forces. The large increase in number of electrons by the time you get to the iodide completely outweighs the loss of any permanent dipoles in the molecules.

Example 1: Boiling Points of Some Isomers

The examples show that the boiling points fall as the isomers go from a primary to a secondary to a tertiary halogenoalkane. This is a simple result of the fall in the effectiveness of the dispersion forces.



The temporary dipoles are greatest for the longest molecule. The attractions are also stronger if the molecules can lie closely together. The tertiary halogenoalkane is very short and fat, and won't have much close contact with its neighbours.

Solubility

Solubility in water

The alkyl halides are at best only slightly soluble in water. For a halogenoalkane to dissolve in water you have to break attractions between the halogenoalkane molecules (van der Waals dispersion and dipole-dipole interactions) and break the hydrogen bonds between water molecules. Both of these cost energy.

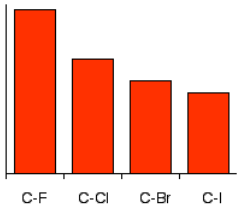
Energy is released when new attractions are set up between the halogenoalkane and the water molecules. These will only be dispersion forces and dipole-dipole interactions. These aren't as strong as the original hydrogen bonds in the water, and so not as much energy is released as was used to separate the water molecules. The energetics of the change are sufficiently "unprofitable" that very little dissolves.

Solubility in organic solvents

alkyl halides tend to dissolve in organic solvents because the new intermolecular attractions have much the same strength as the ones being broken in the separate halogenoalkane and solvent.

Chemical Reactivity

The pattern in strengths of the four carbon-halogen bonds are:



Notice that bond strength falls as you go from C-F to C-I, and notice how much stronger the carbon-fluorine bond is than the rest. To react with the alkyl halides, the carbon-halogen bond has got to be broken. Because that gets easier as you go from fluoride to chloride to bromide to iodide, the compounds get more reactive in that order. Iodoalkanes are the most reactive and fluoroalkanes are the least. In fact, fluoroalkanes are so unreactive that we shall pretty well ignore them completely from now on in this section!

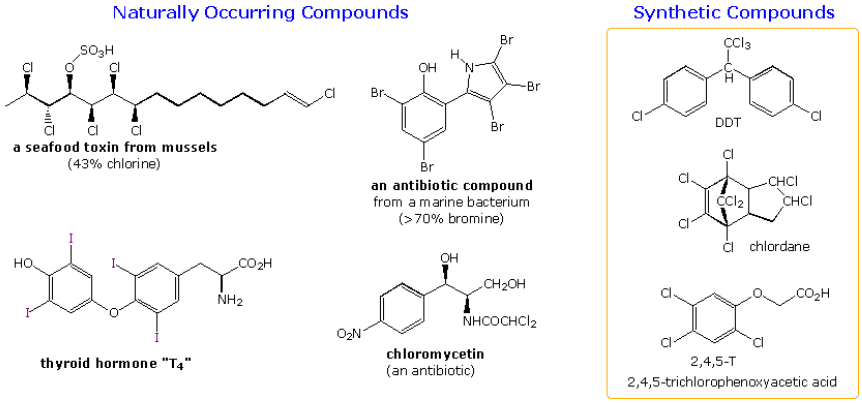
Contributors

- Jim Clark (Chemguide.co.uk)

7.4: Interesting Alkyl Halides

Halogen containing organic compounds are relatively rare in terrestrial plants and animals. The thyroid hormones T_3 and T_4 are exceptions; as is fluoroacetate, the toxic agent in the South African shrub *Dichapetalum cymosum*, known as "gifblaar". However, the halogen rich environment of the ocean has produced many interesting natural products incorporating large amounts of halogen. Some examples are shown below.

The ocean is the largest known source for atmospheric methyl bromide and methyl iodide. Furthermore, the ocean is also estimated to supply 10-20% of atmospheric methyl chloride, with other significant contributions coming from biomass burning, salt marshes and wood-rotting fungi. Many subsequent chemical and biological processes produce poly-halogenated methanes.



Synthetic organic halogen compounds are readily available by direct halogenation of hydrocarbons and by addition reactions to alkenes and alkynes. Many of these have proven useful as intermediates in traditional synthetic processes. Some halogen compounds, shown in the box. have been used as pesticides, but their persistence in the environment, once applied, has led to restrictions, including banning, of their use in developed countries. Because DDT is a cheap and effective mosquito control agent, underdeveloped countries in Africa and Latin America have experienced a dramatic increase in malaria deaths following its removal, and arguments are made for returning it to limited use. 2,4,5-T and 2,4-D are common herbicides that are sold by most garden stores. Other organic halogen compounds that have been implicated in environmental damage include the polychloro- and polybromo-biphenyls (PCBs and PBBs), used as heat transfer fluids and fire retardants; and freons (e.g. CCl_2F_2 and other chlorofluorocarbons) used as refrigeration gases and fire extinguishing agents.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

7.5: The Polar Carbon–Halogen Bond

Halogens and the Character of the Carbon-Halogen Bond

With respect to electronegativity, halogens are more electronegative than carbons. This results in a carbon-halogen bond that is polarized. As shown in the image below, carbon atom has a partial positive charge, while the halogen has a partial negative charge.

The Polar C-X Bond

The following image shows the relationship between the halogens and electronegativity. Notice, as we move up the periodic table from iodine to fluorine, electronegativity increases.

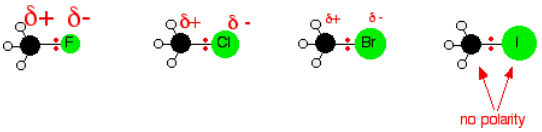
Electronegativity	I	<	Br	<	Cl	<	F

The following image shows the relationships between bond length, bond strength, and molecular size. As we progress down the periodic table from fluorine to iodine, molecular size increases. As a result, we also see an increase in bond length. Conversely, as molecular size increases and we get longer bonds, the strength of those bonds decreases.

Bond length	C-F	<	C-Cl	<	C-Br	<	C-I
Bond strength	C-I	<	C-Br	<	C-Cl	<	C-F
Molecular size	F	<	Cl	<	Br	<	I

The influence of bond polarity

Of the four halogens, fluorine is the most electronegative and iodine the least. That means that the electron pair in the carbon-fluorine bond will be dragged most towards the halogen end. Looking at the methyl halides as simple examples:



The electronegativities of carbon and iodine are equal and so there will be no separation of charge on the bond.

One of the important set of reactions of alkyl halides involves replacing the halogen by something else - substitution reactions. These reactions involve either:

- the carbon-halogen bond breaking to give positive and negative ions. The ion with the positively charged carbon atom then reacts with something either fully or slightly negatively charged.
- something either fully or negatively charged attracted to the slightly positive carbon atom and pushing off the halogen atom.

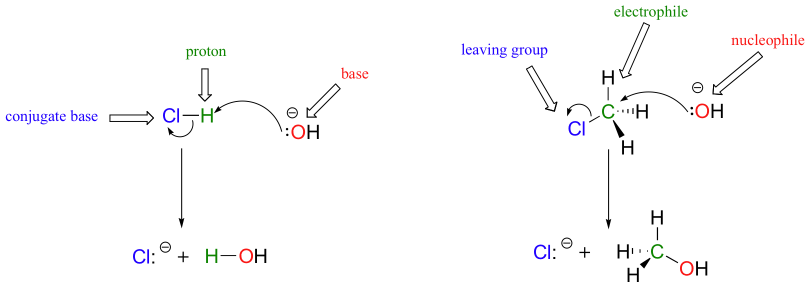
You might have thought that either of these would be more effective in the case of the carbon-fluorine bond with the quite large amounts of positive and negative charge already present. But that's not so - quite the opposite is true! The thing that governs the reactivity is the strength of the bonds which have to be broken. If is difficult to break a carbon-fluorine bond, but easy to break a carbon-iodine one.

Contributors

- Rachael Curtis (UC Davis)
- Jim Clark (Chemguide.co.uk)

7.6: General Features of Nucleophilic Substitution

In many ways, the proton transfer process in a Brønsted-Lowry acid-base reaction can be thought of as simply a special kind of nucleophilic substitution reaction, one in which the electrophile is a hydrogen rather than a carbon.



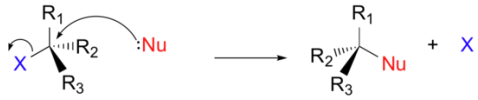
acid-base reaction **nucleophilic substitution**

In both reaction types, we are looking at very similar players: an electron-rich species (the nucleophile/base) attacks an electron-poor species (the electrophile/proton), driving off the leaving group/conjugate base.

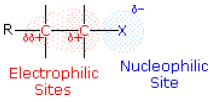
In the next few sections, we are going to be discussing some general aspects of nucleophilic substitution reactions, and in doing so it will simplify things greatly if we can use some abbreviations and generalizations before we dive into real examples.

Instead of showing a specific nucleophile like hydroxide, we will simply refer to the nucleophilic reactant as 'Nu'. In a similar fashion, we will call the leaving group 'X'. We will see as we study actual reactions that leaving groups are sometimes negatively charged, sometimes neutral, and sometimes positively charged. We will also see some examples of nucleophiles that are negatively charged and some that are neutral. Therefore, in this general picture we will not include a charge designation on the 'X' or 'Nu' species. In the same way, we will see later that nucleophiles and leaving groups are sometimes protonated and sometimes not, so for now, for the sake of simplicity, we will not include protons on 'Nu' or 'X'. We will generalize the three other groups bonded on the electrophilic central carbon as R_1, R_2, and R_3: these symbols could represent hydrogens as well as alkyl groups. Finally, in order to keep figures from becoming too crowded, we will use in most cases the line structure convention in which the central, electrophilic carbon is not drawn out as a 'C'.

Here, then, is the generalized picture of a concerted (single-step) nucleophilic substitution reaction:

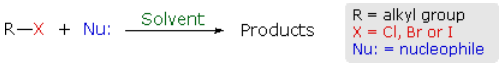


The functional group of alkyl halides is a carbon-halogen bond, the common halogens being fluorine, chlorine, bromine and iodine. With the exception of iodine, these halogens have electronegativities significantly greater than carbon. Consequently, this functional group is polarized so that the carbon is electrophilic and the halogen is nucleophilic, as shown in the drawing on the right. Two characteristics other than electronegativity also have an important influence on the chemical behavior of these compounds. The first of these is covalent bond strength. The strongest of the carbon-halogen covalent bonds is that to fluorine. Remarkably, this is the strongest common single bond to carbon, being roughly 30 kcal/mole stronger than a carbon-carbon bond and about 15 kcal/mole stronger than a carbon-hydrogen bond. Because of this, **alkyl fluorides and fluorocarbons in general are chemically and thermodynamically quite stable**, and do not share any of the reactivity patterns shown by the other alkyl halides. The carbon-chlorine covalent bond is slightly weaker than a carbon-carbon bond, and the bonds to the other halogens are weaker still, the bond to iodine being about 33% weaker. The second factor to be considered is the relative stability of the corresponding halide anions, which is likely the form in which these electronegative atoms will be replaced. This stability may be estimated from the relative acidities of the H-X acids, assuming that the strongest acid releases the most stable conjugate base (halide anion). With the exception of HF (pK_a = 3.2), all the hydrohalic acids are very strong, small differences being in the direction HCl < HBr < HI.



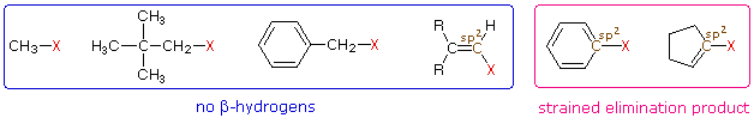
In order to understand why some combinations of alkyl halides and nucleophiles give a substitution reaction, whereas other combinations give elimination, and still others give no observable reaction, we must investigate systematically the way in which

changes in reaction variables perturb the course of the reaction. The following general equation summarizes the factors that will be important in such an investigation.



One conclusion, relating the structure of the R-group to possible products, should be immediately obvious. **If R- has no beta-hydrogens an elimination reaction is not possible**, unless a structural rearrangement occurs first. The first four halides shown on the left below do not give elimination reactions on treatment with base, because they have no β-hydrogens. The two halides on the right do not normally undergo such reactions because the potential elimination products have highly strained double or triple bonds.

It is also worth noting that sp^2 hybridized C–X compounds, such as the three on the right, do not normally undergo nucleophilic substitution reactions, unless other functional groups perturb the double bond(s).



Using the general reaction shown above as our reference, we can identify the following variables and observables.

Variables	**R** change α-carbon from 1º to 2º to 3º if the α-carbon is a chiral center, set as (*R*) or (*S*) **X** change from Cl to Br to I (F is relatively unreactive) **Nu:** change from anion to neutral; change basicity; change polarizability **Solvent** polar vs. non-polar; protic vs. non-protic
Observables	**Products** substitution, elimination, no reaction. **Stereospecificity** if the α-carbon is a chiral center what happens to its configuration? **Reaction Rate** measure as a function of reactant concentration.

When several reaction variables may be changed, it is important to isolate the effects of each during the course of study. In other words: **only one variable should be changed at a time**, the others being held as constant as possible. For example, we can examine the effect of changing the halogen substituent from Cl to Br to I, using ethyl as a common R–group, cyanide anion as a common nucleophile, and ethanol as a common solvent. We would find a common substitution product, C_2H_5–CN, in all cases, but the speed or rate of the reaction would increase in the order: Cl < Br < I. This reactivity order reflects both the strength of the C–X bond, and the stability of $X^{(-)}$ as a leaving group, and leads to the general conclusion that alkyl iodides are the most reactive members of this functional class.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

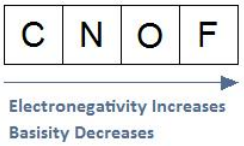
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

7.7: The Leaving Group

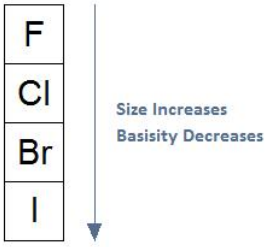
Our general discussion of nucleophilic substitution reactions, we have until now been designating the leaving group simply as “X". As you may imagine, however, the nature of the leaving group is an important consideration: if the C-X bond does not break, the new bond between the nucleophile and electrophilic carbon cannot form, regardless of whether the substitution is S_N1 or S_N2. In this module, we are focusing on substitution reactions in which the leaving group is a halogen ion, although many reactions are known, both in the laboratory and in biochemical processes, in which the leaving group is something other than a halogen.

In order to understand the nature of the leaving group, it is important to first discuss factors that help determine whether a species will be a strong base or weak base. If you remember from general chemistry, a Lewis base is defined as a species that donates a pair of electrons to form a covalent bond. The factors that will determine whether a species wants to share its electrons or not include electronegativity, size, and resonance.

As Electronegativity Increases, Basicity Decreases: In general, if we move from the left of the periodic table to the right of the periodic table as shown in the diagram below, electronegativity increases. As electronegativity increases, basicity will decrease, meaning a species will be less likely to act as base; that is, the species will be less likely to share its electrons.



As Size Increases, Basicity Decreases: In general, if we move from the top of the periodic table to the bottom of the periodic table as shown in the diagram below, the size of an atom will increase. As size increases, basicity will decrease, meaning a species will be less likely to act as a base; that is, the species will be less likely to share its electrons.

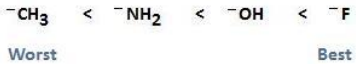


Resonance Decreases Basicity: The third factor to consider in determining whether or not a species will be a strong or weak base is resonance. As you may remember from general chemistry, the formation of a resonance stabilized structure results in a species that is less willing to share its electrons. Since strong bases, by definition, want to share their electrons, resonance stabilized structures are weak bases.Edit section

Now that we understand how electronegativity, size, and resonance affect basicity, we can combine these concepts with the fact that weak bases make the best leaving groups. Think about why this might be true. In order for a leaving group to leave, it must be able to accept electrons. A strong bases wants to donate electrons; therefore, the leaving group must be a weak base. We will now revisit electronegativity, size, and resonance, moving our focus to the leaving group, as well providing actual examples.

> **Note**
>
> As the Electronegativity of the group *Increases*, The propensity of the Leaving Group to Leave *Increases*

As mentioned previously, if we move from left to right on the periodic table, electronegativity increases. With an increase in electronegativity, basisity decreases, and the ability of the leaving group to leave increases. This is because an increase in electronegativity results in a species that wants to hold onto its electrons rather than donate them. The following diagram illustrates this concept, showing $^-CH_3$ to be the worst leaving group and F^- to be the best leaving group. This particular example should only be used to facilitate your understanding of this concept. In real reaction mechanisms, these groups are not good leaving groups at all. For example, fluoride is such a poor leaving group that S_N2 reactions of fluoroalkanes are rarely observed.

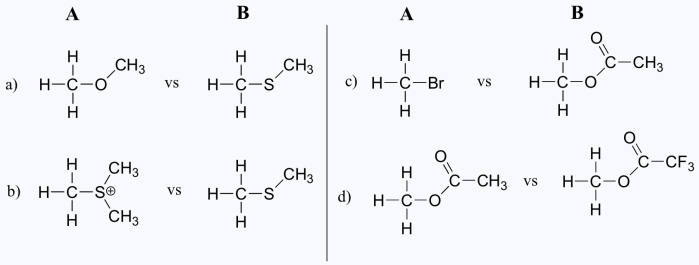


As Size Increases, The Ability of the Leaving Group to Leave Increases: Here we revisit the effect size has on basicity. If we move down the periodic table, size increases. With an increase in size, basicity decreases, and the ability of the leaving group to leave increases. The relationship among the following halogens, unlike the previous example, is true to what we will see in upcoming reaction mechanisms.

F	<	Cl	<	Br	<	I
Worst		Fair		Good		Excellent

Example 7.7.1

In each pair (A and B) below, which electrophile would be expected to react more rapidly in an S_N2 reaction with the thiol group of cysteine as the common nucleophile?



Solution (8.13)

Contributor

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

7.8: The Nucleophile

What is a nucleophile?

Nucleophilic functional groups are those which have electron-rich atoms able to donate a pair of electrons to form a new covalent bond. In both laboratory and biological organic chemistry, the most relevant nucleophilic atoms are oxygen, nitrogen, and sulfur, and the most common nucleophilic functional groups are water, alcohols, phenols, amines, thiols, and occasionally carboxylates. More specifically in laboratory reactions, halide and azide (N_3^-) anions are commonly seen acting as nucleophiles.

Of course, carbons can also be nucleophiles - otherwise how could new carbon-carbon bonds be formed in the synthesis of large organic molecules like DNA or fatty acids? Enolate ions (section 7.5) are the most common carbon nucleophiles in biochemical reactions, while the cyanide ion (CN^-) is just one example of a carbon nucleophile commonly used in the laboratory. Reactions with carbon nucleophiles will be dealt with in chapters 13 and 14, however - in this chapter and the next, we will concentrate on non-carbon nucleophiles.

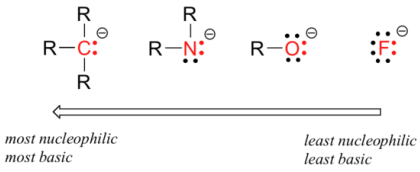
When thinking about nucleophiles, the first thing to recognize is that, for the most part, the same quality of 'electron-richness' that makes a something nucleophilic also makes it basic: *nucleophiles can be bases, and bases can be nucleophiles*. It should not be surprising, then, that most of the trends in basicity that we have already discussed also apply to nucleophilicity.

Protonation states and nucleophilicity

The protonation state of a nucleophilic atom has a very large effect on its nucleophilicity. This is an idea that makes intuitive sense: a hydroxide ion is much more nucleophilic (and basic) than a water molecule, because the negatively charged oxygen on the hydroxide ion carries greater electron density than the oxygen atom of a neutral water molecule. In practical terms, this means that a hydroxide nucleophile will react in an S_N2 reaction with methyl bromide much faster (about 10,000 times faster) than a water nucleophile.

Periodic trends and solvent effects in nucleophilicity

There are predictable periodic trends in nucleophilicity. Moving horizontally across the second row of the table, the trend in nucleophilicity parallels the trend in basicity:

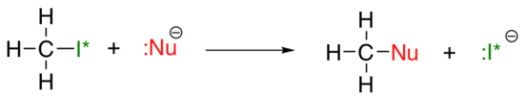


The reasoning behind the horizontal nucleophilicity trend is the same as the reasoning behind the basicity trend: more electronegative elements hold their electrons more tightly, and are less able to donate them to form a new bond.

This horizontal trends also tells us that amines are more nucleophilic than alcohols, although both groups commonly act as nucleophiles in both laboratory and biochemical reactions.

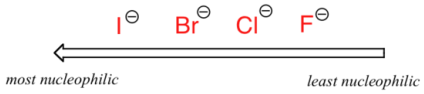
Recall that the basicity of atoms decreases as we move vertically down a column on the periodic table: thiolate ions are less basic than alkoxide ions, for example, and bromide ion is less basic than chloride ion, which in turn is less basic than fluoride ion. Recall also that this trend can be explained by considering the increasing size of the 'electron cloud' around the larger ions: the electron density inherent in the negative charge is spread around a larger area, which tends to increase stability (and thus reduce basicity).

The vertical periodic trend for nucleophilicity is somewhat more complicated that that for basicity: depending on the solvent that the reaction is taking place in, the nucleophilicity trend can go in either direction. Let's take the simple example of the SN2 reaction below:



. . .where Nu^- is one of the halide ions: fluoride, chloride, bromide, or iodide, and the leaving group I* is a radioactive isotope of iodine (which allows us to distinguish the leaving group from the nucleophile in that case where both are iodide). If this reaction is

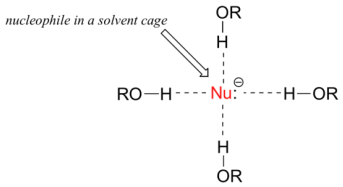
occurring in a **protic solvent** (that is, a solvent that has a hydrogen bonded to an oxygen or nitrogen - water, methanol and ethanol are the most important examples), then the reaction will go fastest when iodide is the nucleophile, and slowest when fluoride is the nucleophile, reflecting the relative strength of the nucleophile.



Relative nucleophilicity in a protic solvent

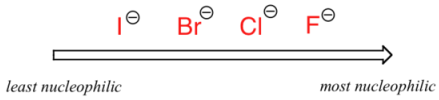
This of course, is opposite that of the vertical periodic trend for basicity, where iodide is the *least* basic. What is going on here? Shouldn't the stronger base, with its more reactive unbonded valence electrons, also be the stronger nucleophile?

As mentioned above, it all has to do with the solvent. Remember, we are talking now about the reaction running in a *protic* solvent like ethanol. Protic solvent molecules form very strong ion-dipole interactions with the negatively-charged nucleophile, essentially creating a 'solvent cage' around the nucleophile:



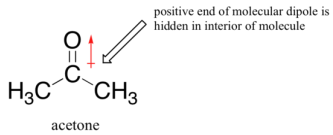
In order for the nucleophile to attack the electrophile, it must break free, at least in part, from its solvent cage. The lone pair electrons on the larger, less basic iodide ion interact less tightly with the protons on the protic solvent molecules - thus the iodide nucleophile is better able to break free from its solvent cage compared the smaller, more basic fluoride ion, whose lone pair electrons are bound more tightly to the protons of the cage.

The picture changes if we switch to a **polar aprotic solvent**, such as acetone, in which there is a molecular dipole but *no hydrogens bound to oxygen or nitrogen*. Now, fluoride is the best nucleophile, and iodide the weakest.



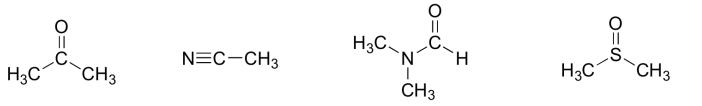
Relative nucleophilicity in a polar aprotic solvent

The reason for the reversal is that, with an aprotic solvent, the ion-dipole interactions between solvent and nucleophile are much weaker: the positive end of the solvent's dipole is hidden in the interior of the molecule, and thus it is shielded from the negative charge of the nucleophile.



A weaker solvent-nucleophile interaction means a weaker solvent cage for the nucleophile to break through, so the solvent effect is much less important, and the more basic fluoride ion is also the better nucleophile.

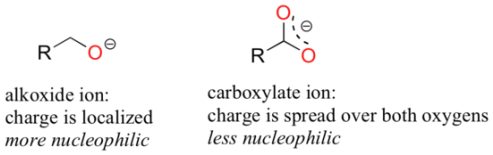
Why not use a completely nonpolar solvent, such as hexane, for this reaction, so that the solvent cage is eliminated completely? The answer to this is simple - the nucleophile needs to be in solution in order to react at an appreciable rate with the electrophile, and a solvent such as hexane will not solvate an a charged (or highly polar) nucleophile at all. That is why chemists use polar aprotic solvents for nucleophilic substitution reactions in the laboratory: they are polar enough to solvate the nucleophile, but not so polar as to lock it away in an impenetrable solvent cage. In addition to acetone, three other commonly used polar aprotic solvents are acetonitrile, dimethylformamide (DMF), and dimethyl sulfoxide (DMSO).



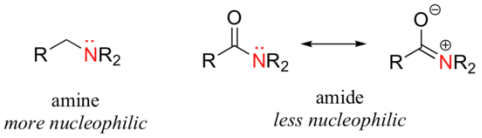
In biological chemistry, where the solvent is protic (water), the most important implication of the periodic trends in nucleophilicity is that thiols are more powerful nucleophiles than alcohols. The thiol group in a cysteine amino acid, for example, is a powerful nucleophile and often acts as a nucleophile in enzymatic reactions, and of course negatively-charged thiolates (RS^-) are even more nucleophilic. This is not to say that the hydroxyl groups on serine, threonine, and tyrosine do not also act as nucleophiles - they do.

Resonance effects on nucleophilicity

Resonance effects also come into play when comparing the inherent nucleophilicity of different molecules. The reasoning involved is the same as that which we used to understand resonance effects on basicity. If the electron lone pair on a heteroatom is delocalized by resonance, it is inherently less reactive - meaning less nucleophilic, and also less basic. An alkoxide ion, for example, is more nucleophilic and more basic than a carboxylate group, even though in both cases the nucleophilic atom is a negatively charged oxygen. In the alkoxide, the negative charge is localized on a single oxygen, while in the carboxylate the charge is delocalized over two oxygen atoms by resonance.

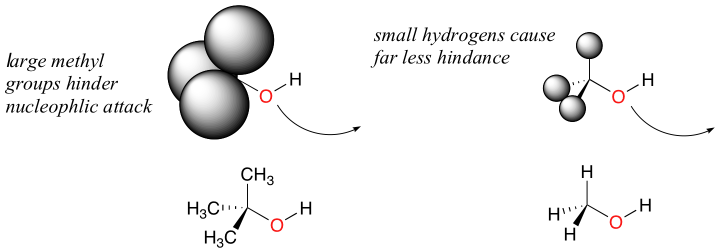


The nitrogen atom on an amide is less nucleophilic than the nitrogen of an amine, due to the resonance stabilization of the nitrogen lone pair provided by the amide carbonyl group.



Steric effects on nucleophilicity

Steric hindrance is an important consideration when evaluating nucleophility. For example, *tert*-butanol is less potent as a nucleophile than methanol. This is because the comparatively bulky methyl groups on the tertiary alcohol effectively block the route of attack by the nucleophilic oxygen, slowing the reaction down considerably (imagine trying to walk through a narrow doorway while carrying three large suitcases!).



It is not surprising that it is more common to observe serines acting as nucleophiles in enzymatic reactions compared to threonines - the former is a primary alcohol, while the latter is a secondary alcohol.

Example 7.8.1

Which is the better nucleophile - a cysteine side chain or a methionine side chain? Explain.

Example 7.8.2

In each of the following pairs of molecules/ions, which is the better nucleophile in a reaction with CH_3Br in acetone solvent? Explain your choice.

a. phenolate ion (deprotonated phenol) or benzoate ion (deprotonated benzoic acid)
b. water and hydronium ion
c. trimethylamine and triethylamine
d. chloride anion and iodide anion
e. CH_3NH^- and CH_3CH_2NH

Contributors

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

7.9: Possible Mechanisms for Nucleophilic Substitution

7.10: Two Mechanisms for Nucleophilic Substitution

The S_N2 Mechanism

As described in the previous section, a majority of the reactions thus far described appear to proceed by a common single-step mechanism. This mechanism is referred to as the **S_N2** mechanism, where **S** stands for **S**ubstitution, **N** stands for **N**ucleophilic and **2** stands for **bi**molecular. Other features of the S_N2 mechanism are inversion at the alpha-carbon, increased reactivity with increasing nucleophilicity of the nucleophilic reagent and steric hindrance to rear-side bonding, especially in tertiary and neopentyl halides. Although reaction **3** exhibits second order kinetics, it is an elimination reaction and must therefore proceed by a very different mechanism, which will be described later.

The S_N1 Mechanism

Reaction **7**, shown at the end of the previous section, is clearly different from the other cases we have examined. It not only shows first order kinetics, but the chiral 3º-alkyl bromide reactant undergoes substitution by the modest nucleophile water with extensive racemization. In all of these features this reaction fails to meet the characteristics of the S_N2 mechanism. A similar example is found in the hydrolysis of tert-butyl chloride, shown below. Note that the initial substitution product in this reaction is actually a hydronium ion, which rapidly transfers a proton to the chloride anion. This second acid-base proton transfer is often omitted in writing the overall equation, as in the case of reaction **7** above.

$$(CH_3)_3C\text{-}Cl + H_2O \longrightarrow (CH_3)_3C\text{-}OH_2^{(+)} + Cl^{(-)} \longrightarrow (CH_3)_3C\text{-}OH + HCl$$

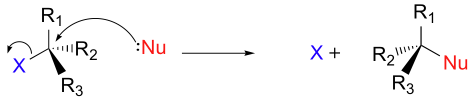
Contributors

- Jim Clark (Chemguide.co.uk)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

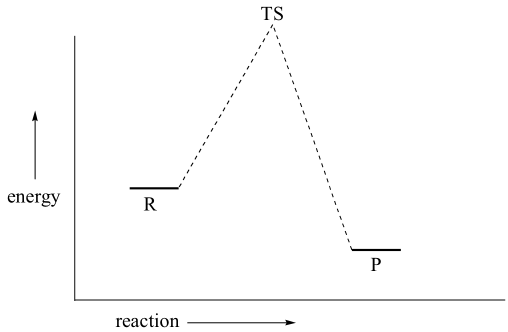
7.11: The S N 2 SN2 Mechanism

The S_N2 mechanism

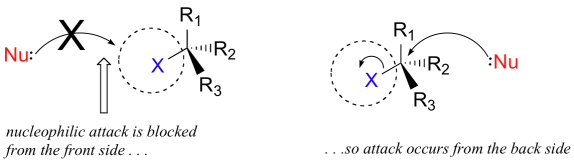
There are two mechanistic models for how an alkyl halide can undergo nucleophilic substitution. In the first picture, the reaction takes place in a single step, and bond-forming and bond-breaking occur simultaneously. (In all figures in this section, 'X' indicates a halogen substituent).



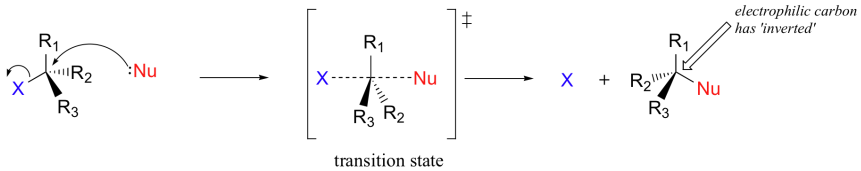
This is called an '**S_N2**' mechanism. In the term S_N2, S stands for 'substitution', the subscript N stands for 'nucleophilic', and the number 2 refers to the fact that this is a **bimolecular reaction**: the overall rate depends on a step in which two separate molecules (the nucleophile and the electrophile) collide. A potential energy diagram for this reaction shows the transition state (TS) as the highest point on the pathway from reactants to products.



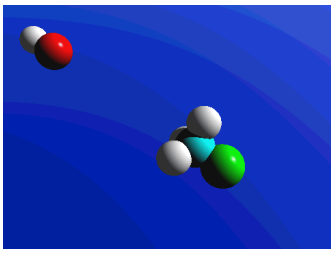
If you look carefully at the progress of the S_N2 reaction, you will realize something very important about the outcome. The nucleophile, being an electron-rich species, must attack the electrophilic carbon from the *back side* relative to the location of the leaving group. Approach from the front side simply doesn't work: the leaving group - which is also an electron-rich group - blocks the way.



The result of this backside attack is that the stereochemical configuration at the central carbon *inverts* as the reaction proceeds. In a sense, the molecule is turned inside out. At the transition state, the electrophilic carbon and the three 'R' substituents all lie on the same plane.

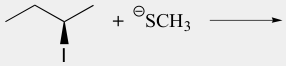


What this means is that S_N2 reactions whether enzyme catalyzed or not, are inherently stereoselective: when the substitution takes place at a stereocenter, we can confidently predict the stereochemical configuration of the product. Below is an animation illustrating the principles we have just learned, showing the S_N2 reaction between hydroxide ion and methyl iodide. Notice how backside attack by the hydroxide nucleophile results in inversion at the tetrahedral carbon electrophile.



Exercise

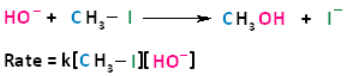
Predict the structure of the product in this S_N2 reaction. Be sure to specify stereochemistry.



We will be contrasting about two types of nucleophilic substitution reactions. One type is referred to as **unimolecular nucleophilic substitution (S_N1)**, whereby the rate determining step is unimolecular and **bimolecular nucleophilic substitution (S_N2)**, whereby the rate determining step is bimolecular. We will begin our discussion with S_N2 reactions, and discuss S_N1 reactions elsewhere.

Biomolecular Nucleophilic Substitution Reactions and Kinetics

In the term S_N2, the S stands for substitution, the N stands for nucleophilic, and the number two stands for bimolecular, meaning there are two molecules involved in the rate determining step. The rate of bimolecular nucleophilic substitution reactions depends on the concentration of both the haloalkane and the nucleophile. To understand how the rate depends on the concentrations of both the haloalkane and the nucleophile, let us look at the following example. The hydroxide ion is the nucleophile and methyl iodide is the haloalkane.



$$\text{Rate} = k[CH_3{-}I][HO^-]$$

If we were to double the concentration of either the haloalkane or the nucleophile, we can see that the rate of the reaction would proceed twice as fast as the initial rate.

$$\text{Rate}_1 = k[CH_3{-}I][HO^-]$$
$$\text{Rate}_2 = 2k[CH_3{-}I][HO^-]$$
$$\text{Rate}_2 = 2\,\text{Rate}_1$$

If we were to double the concentration of both the haloalkane and the nucleophile, we can see that the rate of the reaction would proceed four times as fast as the initial rate.

$$\text{Rate}_1 = k[CH_3{-}I][HO^-]$$
$$\text{Rate}_2 = 4k[CH_3{-}I][HO^-]$$
$$\text{Rate}_2 = 4\,\text{Rate}_1$$

The bimolecular nucleophilic substitution reaction follows second-order kinetics; that is, the rate of the reaction depends on the concentration of two first-order reactants. In the case of bimolecular nucleophilic substitution, these two reactants are the haloalkane and the nucleophile. For further clarification on reaction kinetics, the following links may facilitate your understanding of rate laws, rate constants, and second-order kinetics:

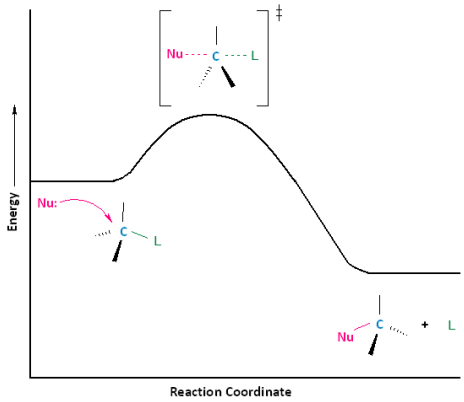
- Definition of a Reaction Rate
- Rate Laws and Rate Constants
- The Determination of the Rate Law
- Second-Order Reactions

Bimolecular Nucleophilic Substitution Reactions Are Concerted

Bimolecular nucleophilic substitution (SN_2) reactions are **concerted**, meaning they are a **one step process**. This means that the process whereby the nucleophile attacks and the leaving group leaves is simultaneous. Hence, the bond-making between the

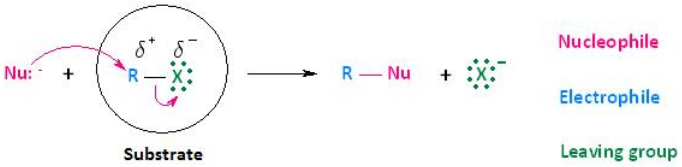
nucleophile and the electrophilic carbon occurs at the same time as the bond-breaking between the electophilic carbon and the halogen.

The potential energy diagram for an SN_2 reaction is shown below. Upon nucleophilic attack, a single transition state is formed. A transition state, unlike a reaction intermediate, is a very short-lived species that cannot be isolated or directly observed. Again, this is a single-step, concerted process with the occurrence of a single transition state.

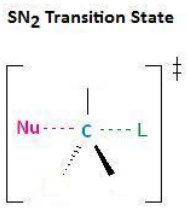


Sterrically Hindered Substrates Will Reduce the S_N2 Reaction Rate

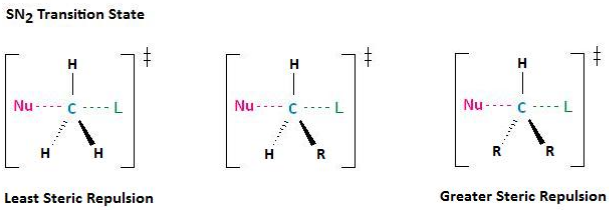
Now that we have discussed the effects that the leaving group, nucleophile, and solvent have on biomolecular nucleophilic substitution (S_N2) reactions, it's time to turn our attention to how the substrate affects the reaction. Although the substrate, in the case of nucleophilic substitution of haloalkanes, is considered to be the entire molecule circled below, we will be paying particular attention to the alkyl portion of the substrate. In other words, we are most interested in the electrophilic center that bears the leaving group.



In the section Kinetics of Nucleophilic Substitution Reactions, we learned that the SN_2 transition state is very crowded. Recall that there are a total of five groups around the electrophilic center, the nucleophile, the leaving group, and three substituents.

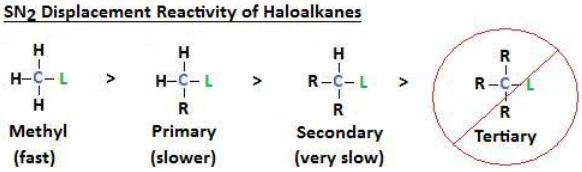


If each of the three substituents in this transition state were small hydrogen atoms, as illustrated in the first example below, there would be little steric repulsion between the incoming nucleophile and the electrophilic center, thereby increasing the ease at which the nucleophilic substitution reaction can occur. Remember, for the SN_2 reaction to occur, the nucleophile must be able to attack the electrophilic center, resulting in the expulsion of the leaving group. If one of the hydrogens, however, were replaced with an R group, such as a methyl or ethyl group, there would be an increase in steric repulsion with the incoming nucleophile. If two of the hydrogens were replaced by R groups, there would be an even greater increase in steric repulsion with the incoming nucleophile.



How does steric hindrance affect the rate at which an SN_2 reaction will occur? As each hydrogen is replaced by an R group, the rate of reaction is significantly diminished. This is because the addition of one or two R groups shields the backside of the electrophilic carbon, impeding nucleophilic attack.

The diagram below illustrates this concept, showing that electrophilic carbons attached to three hydrogen atoms results in faster nucleophilic substitution reactions, in comparison to primary and secondary haloalkanes, which result in nucleophilic substitution reactions that occur at slower or much slower rates, respectively. Notice that a tertiary haloalkane, that which has three R groups attached, does not undergo nucleophilic substitution reactions at all. The addition of a third R group to this molecule creates a carbon that is entirely blocked.



Substitutes on Neighboring Carbons Slow Nucleophilic Substitution Reactions

Previously we learned that adding R groups to the electrophilic carbon results in nucleophilic substitution reactions that occur at a slower rate. What if R groups are added to neighboring carbons? It turns out that the addition of substitutes on neighboring carbons will slow nucleophilic substitution reactions as well.

In the example below, 2-methyl-1-bromopropane differs from 1-bromopropane in that it has a methyl group attached to the carbon that neighbors the electrophilic carbon. The addition of this methyl group results in a significant decrease in the rate of a nucleophilic substitution reaction.

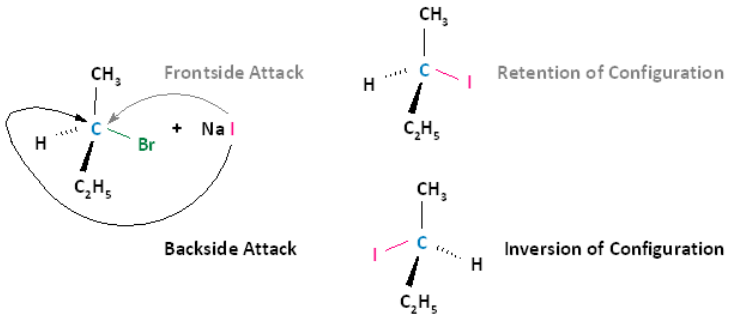
If R groups were added to carbons farther away from the electrophilic carbon, we would still see a decrease in the reaction rate. However, branching at carbons farther away from the electrophilic carbon would have a much smaller effect.

Frontside vs. Backside Attacks

A biomolecular nucleophilic substitution (S_N2) reaction is a type of nucleophilic substitution whereby a lone pair of electrons on a nucleophile attacks an electron deficient electrophilic center and bonds to it, resulting in the expulsion of a leaving group. It is possible for the nucleophile to attack the electrophilic center in two ways.

- **Frontside Attack:** In a frontside attack, the nucleophile attacks the electrophilic center on the same side as the leaving group. When a frontside attack occurs, the stereochemistry of the product remains the same; that is, we have retention of configuration.
- **Backside Attack:** In a backside attack, the nucleophile attacks the electrophilic center on the side that is opposite to the leaving group. When a backside attack occurs, the stereochemistry of the product does not stay the same. There is inversion of configuration.

The following diagram illustrates these two types of nucleophilic attacks, where the frontside attack results in retention of configuration; that is, the product has the same configuration as the substrate. The backside attack results in inversion of configuration, where the product's configuration is opposite that of the substrate.

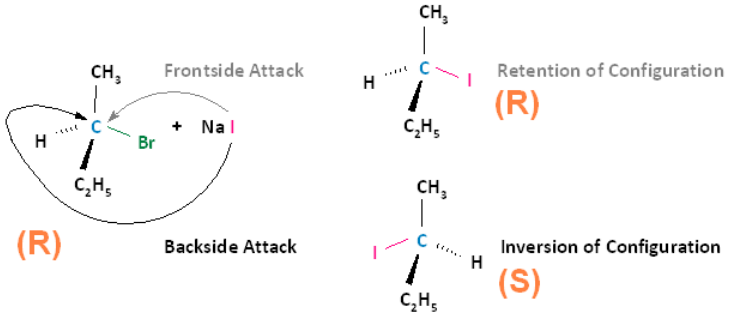


Experimental Observation: All S_N2 Reactions Proceed With Nucleophilic Backside Attacks

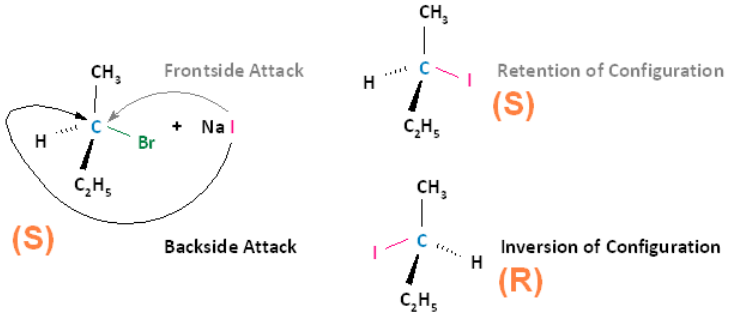
Experimental observation shows that all S_N2 reactions proceed with inversion of configuration; that is, the nucleophile will always attack from the backside in all S_N2 reactions. To think about why this might be true, remember that the nucleophile has a lone pair of electrons to be shared with the electrophilic center, and the leaving group is going to take a lone pair of electrons with it upon leaving. Because like charges repel each other, the nucleophile will always proceed by a backside displacement mechanism.

S_N2 Reactions Are Stereospecific

The S_N2 reaction is stereospecific. A stereospecific reaction is one in which different stereoisomers react to give different stereoisomers of the product. For example, if the substrate is an R enantiomer, a frontside nucleophilic attack results in retention of configuration, and the formation of the R enantiomer. A backside nucleophilic attack results in inversion of configuration, and the formation of the S enantiomer.



Conversely, if the substrate is an S enantiomer, a frontside nucleophilic attack results in retention of configuration, and the formation of the S enantiomer. A backside nucleophilic attack results in inversion of configuration, and the formation of the R enantiomer.



In conclusion, S_N2 reactions that begin with the R enantiomer as the substrate will form the S enantiomer as the product. Those that begin with the S enantiomer as the substrate will form the R enantiomer as the product. This concept also applies to substrates that are *cis* and substrates that are *trans*. If the *cis* configuration is the substrate, the resulting product will be *trans*. Conversely, if the *trans* configuration is the substrate, the resulting product will be *cis*.

Contributors

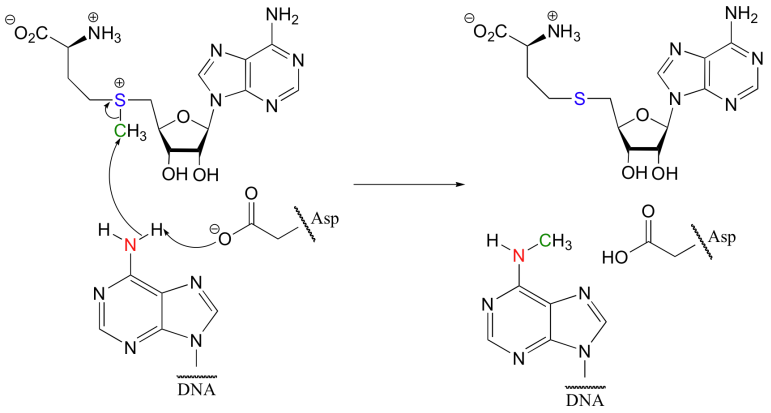
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Jim Clark (Chemguide.co.uk)

John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

7.12: Application- Useful \(S_{N}2\) Reactions

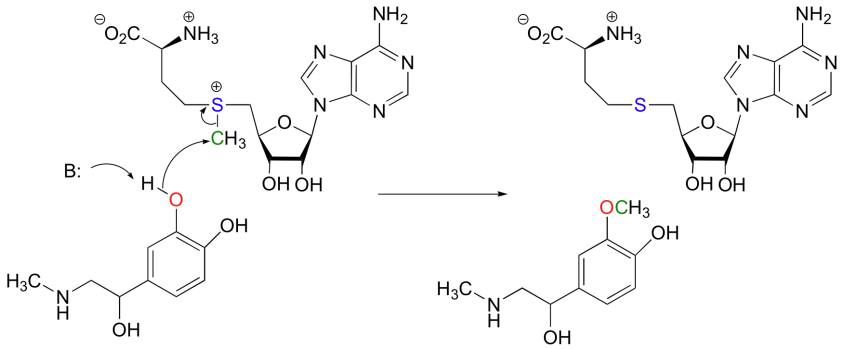
SAM methyltransferases

Some of the most important examples of S_N2 reactions in biochemistry are those catalyzed by S-adenosyl methionine (SAM) – dependent methyltransferase enzymes. We have already seen, in chapter 6 and again in chapter 8, how a methyl group is transferred in an S_N2 reaction from SAM to the amine group on the nucleotide base adenosine:



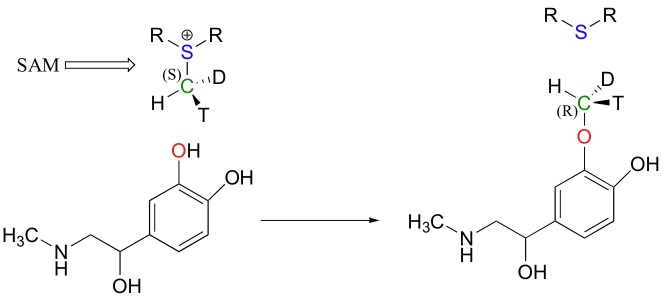
(*Nucleic Acids Res*. **2000**, *28*, 3950).

Another SAM-dependent methylation reaction is catalyzed by an enzyme called catechol-O-methyltransferase. The substrate here is epinephrine, also known as adrenaline.



Notice that in this example, the attacking nucleophile is an alcohol rather than an amine (that's why the enzyme is called an O-methyltransferase). In both cases, though, a basic amino acid side chain is positioned in the active site in just the right place to deprotonate the nucleophilic group as it attacks, increasing its nucleophilicity. The electrophile in both reactions is a methyl carbon, so there is little steric hindrance to slow down the nucleophilic attack. The methyl carbon is electrophilic because it is bonded to a positively-charged sulfur, which is a powerful electron withdrawing group. The positive charge on the sulfur also makes it an excellent leaving group, as the resulting product will be a neutral and very stable sulfide. All in all, in both reactions we have a reasonably good nucleophile, an electron-poor, unhindered electrophile, and an excellent leaving group.

Because the electrophilic carbon in these reactions is a methyl carbon, a stepwise S_N1-like mechanism is extremely unlikely: a methyl carbocation is very high in energy and thus is not a reasonable intermediate to propose. We can confidently predict that this reaction is S_N2. Does this S_N2 reaction occur, as expected, with inversion of stereochemistry? Of course, the electrophilic methyl carbon in these reactions is achiral, so inversion is not apparent. To demonstrate inversion, the following experiment has been carried out with catechol-O-methyltransferase:



Here, the methyl group of SAM was made to be chiral by incorporating hydrogen isotopes tritium (^{3}H, T) and deuterium (^{2}H, D). The researchers determined that the reaction occurred with inversion of configuration, as expected for an S_N2 displacement (*J. Biol. Chem.* **1980,** *255*, 9124).

Example

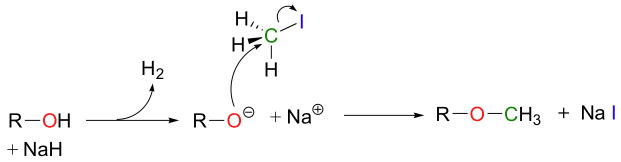
Exercise 9.1: SAM is formed by a nucleophilic substitution reaction between methionine and adenosine triphosphate (ATP). Propose a mechanism for this reaction.

Solution

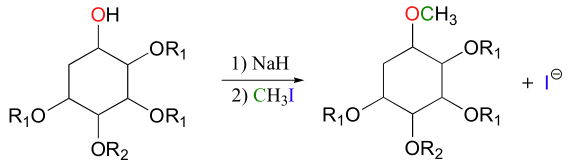
EOF expected: /content/body/div[3]/span, line 1, column 20
(click for details)

9.1B: Synthetic parallel – the Williamson ether synthesis

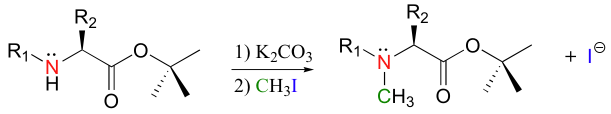
Synthetic organic chemists often use reactions in the laboratory that are conceptually very similar to the SAM-dependent methylation reactions described above. In what is referred to as "O-methylation", an alcohol is first deprotonated by a strong base, typically sodium hydride (this is essentially an irreversible deprotonation, as the hydrogen gas produced can easily be removed from the reaction vessel).



The alkoxide ion, a powerful nucleophile, is then allowed to attack the electrophilic carbon in iodomethane, displacing iodide in an S_N2 reaction. Recall (section 7.3A) that iodide ion is the least basic - and thus the best leaving group - among the halogens commonly used in the synthetic lab. CH_3I is one of the most commonly used lab reagents for methyl transfer reactions, and is the lab equivalent of SAM. In the synthesis of a modified analog of the signaling molecule *myo*-inisitol triphosphate, an alcohol group was methylated using sodium hydride and iodomethane (*Carbohydrate Research* **2004,** *339*, 51):



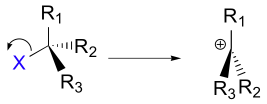
Methylation of amines (N-methylation) by iodomethane is also possible. A recent study concerning the optimization of peptide synthesis methods involved the following reaction (*J. Org. Chem.* **2000** *65*, 2309):



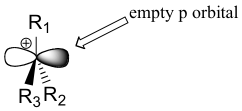
7.13: The S N 1 SN1 Mechanism

The S_N1 mechanism

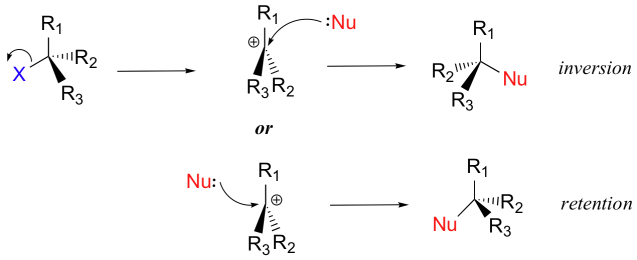
A second model for a nucleophilic substitution reaction is called the '**dissociative**', or '**S_N1**' mechanism: in this picture, the C-X bond breaks *first*, before the nucleophile approaches:



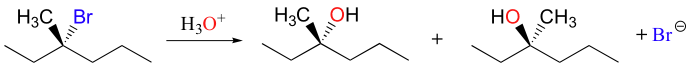
This results in the formation of a carbocation: because the central carbon has only three bonds, it bears a formal charge of +1. Recall that a carbocation should be pictured as sp^2 hybridized, with trigonal planar geometry. Perpendicular to the plane formed by the three sp^2 hybrid orbitals is an empty, unhybridized *p* orbital.



In the second step of this two-step reaction, the nucleophile attacks the empty, 'electron hungry' *p* orbital of the carbocation to form a new bond and return the carbon to tetrahedral geometry.

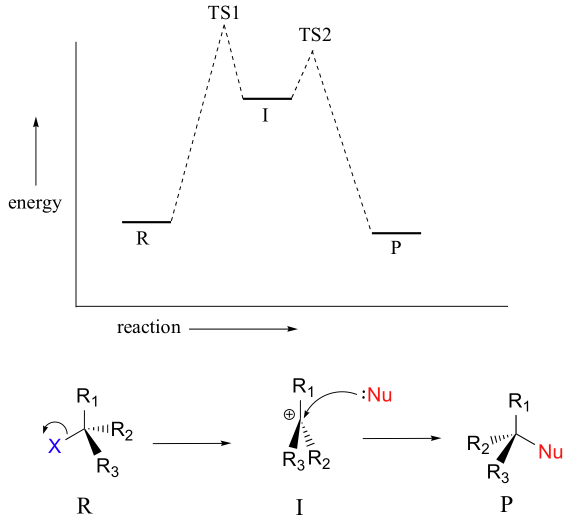


We saw that S_N2 reactions result specifically in inversion of stereochemistry at the electrophilic carbon center. What about the stereochemical outcome of S_N1 reactions? In the model S_N1 reaction shown above, the leaving group dissociates completely from the vicinity of the reaction before the nucleophile begins its attack. Because the leaving group is no longer in the picture, the nucleophile is free to attack from either side of the planar, sp^2-hybridized carbocation electrophile. This means that about half the time the product has the same stereochemical configuration as the starting material (retention of configuration), and about half the time the stereochemistry has been inverted. In other words, *racemization* has occurred at the carbon center. As an example, the tertiary alkyl bromide below would be expected to form a racemic mix of *R* and *S* alcohols after an S_N1 reaction with water as the incoming nucleophile.



Exercise
Draw the structure of the intermediate in the two-step nucleophilic substitution reaction above.

The S_N1 reaction we see an example of a reaction intermediate, a very important concept in the study of organic reaction mechanisms that was introduced earlier in the module on organic reactivity Recall that many important organic reactions do not occur in a single step; rather, they are the sum of two or more discreet bond-forming / bond-breaking steps, and involve transient intermediate species that go on to react very quickly. In the S_N1 reaction, the carbocation species is a reaction intermediate. A potential energy diagram for an S_N1 reaction shows that the carbocation intermediate can be visualized as a kind of valley in the path of the reaction, higher in energy than both the reactant and product but lower in energy than the two transition states.



Exercise

Draw structures representing TS1 and TS2 in the reaction above. Use the solid/dash wedge convention to show three dimensions.

Recall that the first step of the reaction above, in which two charged species are formed from a neutral molecule, is much the slower of the two steps, and is therefore rate-determining. This is illustrated by the energy diagram, where the activation energy for the first step is higher than that for the second step. Also recall that an S_N1 reaction has *first order* kinetics, because the rate determining step involves one molecule splitting apart, not two molecules colliding.

Exercise

Consider two nucleophilic substitutions that occur uncatalyzed in solution. Assume that reaction A is S_N2, and reaction B is S_N1. Predict, in each case, what would happen to the rate of the reaction if the concentration of the nucleophile were doubled, while all other conditions remained constant.

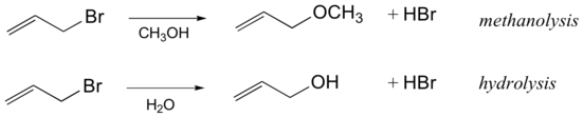
A: $CH_3I + CH_3S^{\ominus} \xrightarrow{S_N2}$

B: $(CH_3)_3CBr + CH_3SH \xrightarrow{S_N1}$

Influence of the solvent in an SN1 reaction

Since the hydrogen atom in a polar protic solvent is highly positively charged, it can interact with the anionic nucleophile which would negatively affect an SN2, but it does not affect an SN1 reaction because the nucleophile is not a part of the rate-determining step. Polar protic solvents actually speed up the rate of the unimolecular substitution reaction because the large dipole moment of the solvent helps to stabilize the transition state. The highly positive and highly negative parts interact with the substrate to lower the energy of the transition state. Since the carbocation is unstable, anything that can stabilize this even a little will speed up the reaction.

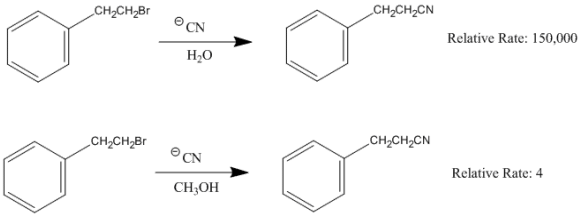
Sometimes in an SN1 reaction the solvent acts as the nucleophile. This is called a solvolysis reaction.The S_N1 reaction of allyl bromide in methanol is an example of what we would call **methanolysis**, while if water is the solvent the reaction would be called **hydrolysis**:



The polarity and the ability of the solvent to stabilize the intermediate carbocation is very important as shown by the relative rate data for the solvolysis (see table below). The dielectric constant of a solvent roughly provides a measure of the solvent's polarity. A dielectric constant below 15 is usually considered non-polar. Basically, the dielectric constant can be thought of as the solvent's ability to reduce the internal charge of the solvent. So for our purposes, the higher the dielectric constant the more polar the substance and in the case of S_N1 reactions, the faster the rate.

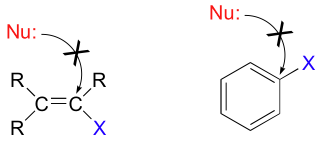
Solvent	Dielectric Constant	Relative Rate
• CH_3CO_2H • CH_3OH • H_2O	• 6 • 33 • 78	• 1 • 4 • 150,000

Below is the same reaction conducted in two different solvents and the relative rate that corresponds with it.



Exercise
Draw a complete curved-arrow mechanism for the methanolysis reaction of allyl bromide shown above.

One more important point must be made before continuing: nucleophilic substitutions as a rule occur at sp^3-hybridized carbons, and *not* where the leaving group is attached to an sp^2-hybridized carbon::



Bonds on sp^2-hybridized carbons are inherently shorter and stronger than bonds on sp^3-hybridized carbons, meaning that it is harder to break the C-X bond in these substrates. S_N2 reactions of this type are unlikely also because the (hypothetical) electrophilic carbon is protected from nucleophilic attack by electron density in the p bond. S_N1 reactions are highly unlikely, because the resulting carbocation intermediate, which would be sp-hybridized, would be very unstable (we'll discuss the relative stability of carbocation intermediates in a later section of this module).

Before we look at some real-life nucleophilic substitution reactions in the next chapter, we will spend some time in the remainder of this module focusing more closely on the three principal partners in the nucleophilic substitution reaction: the nucleophile, the electrophile, and the leaving group.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

7.14: Carbocation Stability

Stability of carbocation intermediates

We know that the rate-limiting step of an S_N1 reaction is the first step - formation of the this carbocation intermediate. The rate of this step – and therefore, the rate of the overall substitution reaction – depends on the activation energy for the process in which the bond between the carbon and the leaving group breaks and a carbocation forms. According to Hammond's postulate (section 6.2B), the more stable the carbocation intermediate is, the faster this first bond-breaking step will occur. In other words, the likelihood of a nucleophilic substitution reaction proceeding by a dissociative (S_N1) mechanism depends to a large degree on the stability of the carbocation intermediate that forms.

The critical question now becomes, *what stabilizes a carbocation?*

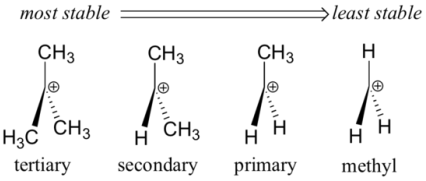
So if it takes an electron *withdrawing* group to stabilize a negative charge, what will stabilize a positive charge? An electron *donating* group!

Electron Donating Group: stabilizes a carbocation

Electron Withdrawing Group: *de*stabilizes a carbocation

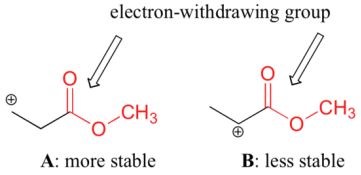
A positively charged species such as a carbocation is very electron-poor, and thus anything which donates electron density to the center of electron poverty will help to stabilize it. Conversely, a carbocation will be *destabilized* by an electron withdrawing group.

Alkyl groups – methyl, ethyl, and the like – are weak electron donating groups, and thus stabilize nearby carbocations. What this means is that, in general, *more substituted carbocations are more stable*: a tert-butyl carbocation, for example, is more stable than an isopropyl carbocation. Primary carbocations are highly unstable and not often observed as reaction intermediates; methyl carbocations are even less stable.



Alkyl groups are electron donating and carbocation-stabilizing because the electrons around the neighboring carbons are drawn towards the nearby positive charge, thus slightly reducing the electron poverty of the positively-charged carbon.

It is not accurate to say, however, that carbocations with higher substitution are *always* more stable than those with less substitution. Just as electron-donating groups can stabilize a carbocation, electron-withdrawing groups act to destabilize carbocations. Carbonyl groups are electron-withdrawing by inductive effects, due to the polarity of the C=O double bond. It is possible to demonstrate in the laboratory (see section 16.1D) that carbocation A below is more stable than carbocation B, even though A is a primary carbocation and B is secondary.

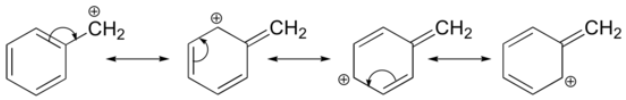


A: more stable **B**: less stable

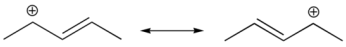
The difference in stability can be explained by considering the electron-withdrawing inductive effect of the ester carbonyl. Recall that inductive effects - whether electron-withdrawing or donating - are relayed through covalent bonds and that the strength of the effect decreases rapidly as the number of intermediary bonds increases. In other words, the effect decreases with distance. In species B the positive charge is closer to the carbonyl group, thus the destabilizing electron-withdrawing effect is stronger than it is in species A.

In the next chapter we will see how the carbocation-destabilizing effect of electron-withdrawing fluorine substituents can be used in experiments designed to address the question of whether a biochemical nucleophilic substitution reaction is S_N1 or S_N2.

Stabilization of a carbocation can also occur through resonance effects, and as we have already discussed in the acid-base chapter, resonance effects as a rule are more powerful than inductive effects. Consider the simple case of a **benzylic** carbocation:

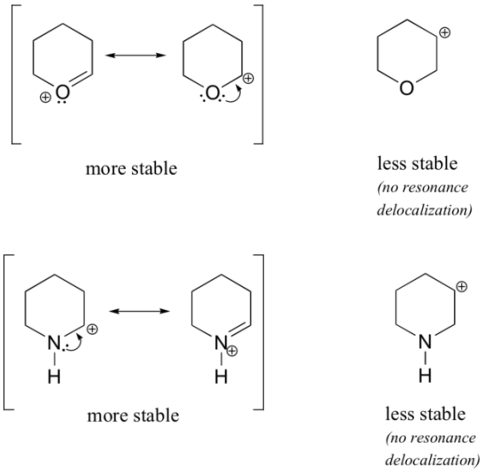


This carbocation is comparatively stable. In this case, electron donation is a resonance effect. Three additional resonance structures can be drawn for this carbocation in which the positive charge is located on one of three aromatic carbons. The positive charge is not isolated on the benzylic carbon, rather it is delocalized around the aromatic structure: this delocalization of charge results in significant stabilization. As a result, benzylic and **allylic** carbocations (where the positively charged carbon is conjugated to one or more non-aromatic double bonds) are significantly more stable than even tertiary alkyl carbocations.



an allylic carbocation

Because heteroatoms such as oxygen and nitrogen are more electronegative than carbon, you might expect that they would by definition be electron withdrawing groups that destabilize carbocations. In fact, the opposite is often true: if the oxygen or nitrogen atom is in the correct position, the overall effect is carbocation stabilization. This is due to the fact that although these heteroatoms are electron *withdrawing* groups by induction, they are electron *donating* groups by resonance, and it is this resonance effect which is more powerful. (We previously encountered this same idea when considering the relative acidity and basicity of phenols and aromatic amines in section 7.4). Consider the two pairs of carbocation species below:



more stable

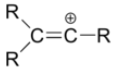
less stable
(no resonance delocalization)

more stable

less stable
(no resonance delocalization)

In the more stable carbocations, the heteroatom acts as an electron donating group by resonance: in effect, the lone pair on the heteroatom is available to delocalize the positive charge. In the less stable carbocations the positively-charged carbon is more than one bond away from the heteroatom, and thus no resonance effects are possible. In fact, in these carbocation species the heteroatoms actually *destabilize* the positive charge, because they are electron withdrawing by induction.

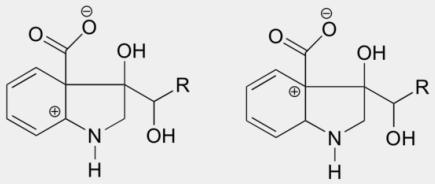
Finally, **vinylic** carbocations, in which the positive charge resides on a double-bonded carbon, are very unstable and thus unlikely to form as intermediates in any reaction.



a vinylic carbocation
(very unstable)

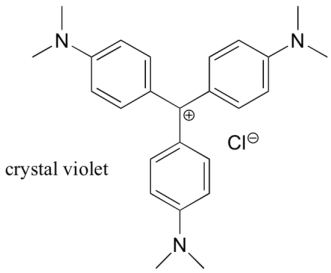
Example 8.10

Exercise 8.10: In which of the structures below is the carbocation expected to be more stable? Explain.



Solution

For the most part, carbocations are very high-energy, transient intermediate species in organic reactions. However, there are some unusual examples of very stable carbocations that take the form of organic salts. Crystal violet is the common name for the chloride salt of the carbocation whose structure is shown below. Notice the structural possibilities for extensive resonance delocalization of the positive charge, and the presence of three electron-donating amine groups.



Example 8.11

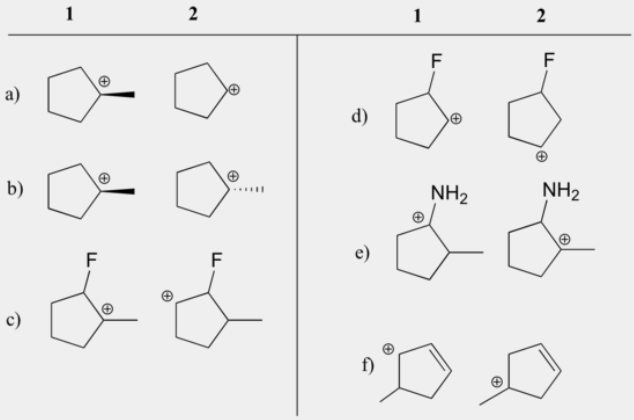
Draw a resonance structure of the crystal violet cation in which the positive charge is delocalized to one of the nitrogen atoms.

Solution

When considering the possibility that a nucleophilic substitution reaction proceeds *via* an S_N1 pathway, it is critical to evaluate the stability of the hypothetical carbocation intermediate. If this intermediate is not sufficiently stable, an S_N1 mechanism must be considered unlikely, and the reaction probably proceeds by an S_N2 mechanism. In the next chapter we will see several examples of biologically important S_N1 reactions in which the positively charged intermediate is stabilized by inductive and resonance effects inherent in its own molecular structure.

Example 8.12

State which carbocation in each pair below is more stable, or if they are expected to be approximately equal. Explain your reasoning.

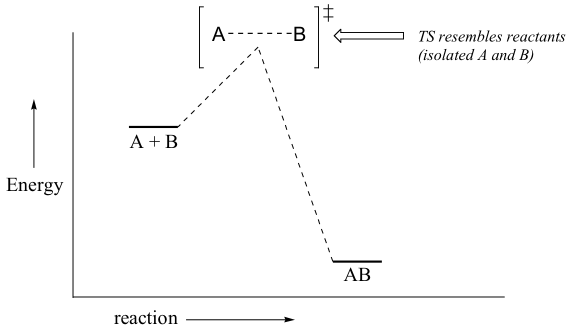


Solution

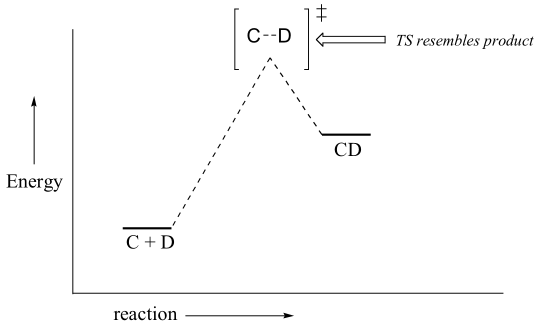
Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

7.15: The Hammond Postulate

Now, back to transition states. Chemists are often very interested in trying to learn about what the transition state for a given reaction looks like, but addressing this question requires an indirect approach because the transition state itself cannot be observed. In order to gain some insight into what a particular transition state looks like, chemists often invoke the **Hammond postulate**, which states that *a transition state resembles the structure of the nearest stable species*. For an exergonic reaction, therefore, the transition state resembles the reactants more than it does the products.



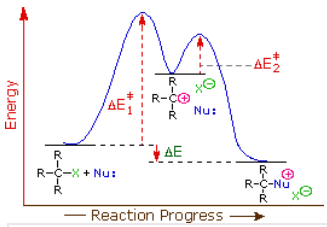
If we consider a hypothetical exergonic reaction between compounds A and B to form AB, the distance between A and B would be relatively large at the transition state, resembling the starting state where A and B are two isolated species. In the hypothetical endergonic reaction between C and D to form CD, however, the bond formation process would be much further along at the TS point, resembling the product.



The Hammond Postulate is a very simplistic idea, which relies on an assumption that potential energy surfaces are parabolic. Although such an assumption is not rigorously true, it is fairly reliable and allows chemists to make energetic arguments about transition states by employing arguments about the stability of a related species. Since the formation of a reactive intermediate is very reliably **endergonic**, arguments about the stability of reactive intermediates can serve as proxy arguments about transition state stability.

The Hammond Postulate and the S_N1 Reaction

the Hammond postulate suggests that the activation energy of the rate-determining first step will be inversely proportional to the stability of the carbocation intermediate. The stability of carbocations was discussed earlier, and a qualitative relationship is given below:



Carbocation Stability	$CH_3^{(+)}$	<	$CH_3CH_2^{(+)}$	<	$(CH_3)_2CH^{(+)}$	≈	$CH_2{=}CH{-}CH_2^{(+)}$	<	$C_6H_5CH_2^{(+)}$	≈	$(CH_3)_3C^{(+)}$

Consequently, we expect that 3º-alkyl halides will be more reactive than their 2º and 1º-counterparts in reactions that follow an S_N1 mechanism. This is opposite to the reactivity order observed for the S_N2 mechanism. Allylic and benzylic halides are exceptionally reactive by either mechanism.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

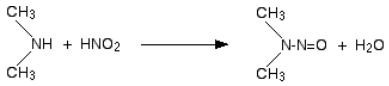
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

---

7.16: Application- S N 1 SN1 Reactions, Nitrosamines, and Cancer

Secondary amines and nitrous acid

This time there isn't any gas produced. Instead, you get a yellow oil called a nitrosamine. These compounds are powerful carcinogens - avoid them! For example:



Contributors

Jim Clark (Chemguide.co.uk)

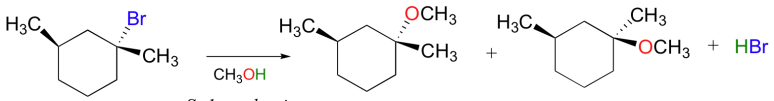
7.17: When Is the Mechanism S N 1 SN1 or S N 2 SN2 ?

Predicting S_N1 vs. S_N2 mechanisms; competition between nucleophilic substitution and elimination reactions

When considering whether a nucleophilic substitution is likely to occur via an S_N1 or S_N2 mechanism, we really need to consider three factors:

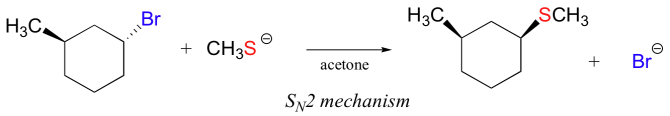
1. **The electrophile:** when the leaving group is attached to a methyl group or a primary carbon, an S_N2 mechanism is favored (here the electrophile is unhindered by surrounded groups, and any carbocation intermediate would be high-energy and thus unlikely). When the leaving group is attached to a tertiary, allylic, or benzylic carbon, a carbocation intermediate will be relatively stable and thus an S_N1 mechanism is favored.
2. **The nucleophile**: powerful nucleophiles, especially those with negative charges, favor the S_N2 mechanism. Weaker nucleophiles such as water or alcohols favor the S_N1 mechanism.
3. **The solvent**: Polar aprotic solvents favor the S_N2 mechanism by enhancing the reactivity of the nucleophile. Polar protic solvents favor the S_N1 mechanism by stabilizing the carbocation intermediate. S_N1 reactions are frequently solvolysis reactions.

For example, the reaction below has a tertiary alkyl bromide as the electrophile, a weak nucleophile, and a polar protic solvent (we'll assume that methanol is the solvent). Thus we'd confidently predict an S_N1 reaction mechanism. Because substitution occurs at a chiral carbon, we can also predict that the reaction will proceed with racemization.



S_N1 mechanism

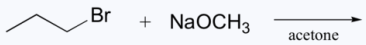
In the reaction below, on the other hand, the electrophile is a secondary alkyl bromide – with these, both S_N1 and S_N2 mechanisms are possible, depending on the nucleophile and the solvent. In this example, the nucleophile (a thiolate anion) is strong, and a polar protic solvent is used – so the S_N2 mechanism is heavily favored. The reaction is expected to proceed with inversion of configuration.

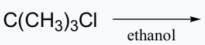


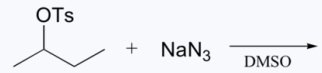
S_N2 mechanism

Example 7.17.1

Determine whether each substitution reaction shown below is likely to proceed by an S_N1 or S_N2 mechanism.

a) 

b) 

c) 

Solution

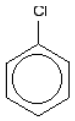
Contributors

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

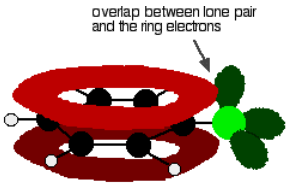
7.18: Vinyl Halides and Aryl Halides

Nucleophilic substitution in the aryl halides

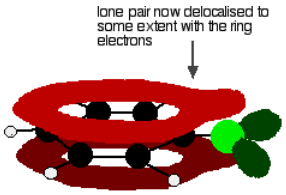
We'll look in some detail at the structure of chlorobenzene. Bromobenzene and iodobenzene are just the same. The simplest way to draw the structure of chlorobenzene is:



To understand chlorobenzene properly, you need to dig a bit deeper than this. There is an interaction between the delocalised electrons in the benzene ring and one of the lone pairs on the chlorine atom. This overlaps with the delocalised ring electron system . . .



to giving a structure rather like this:



This delocalisation is by no means complete, but it does have a significant effect on the properties of both the carbon-chlorine bond and the polarity of the molecule. The delocalisation introduces some extra bonding between the carbon and the chlorine, making the bond stronger. This has a major effect on the reactions of compounds like chlorobenzene.

There is also some movement of electrons away from the chlorine towards the ring. Chlorine is quite electronegative and usually draws electrons in the carbon-chlorine bond towards itself. In this case, this is offset to some extent by the movement of electrons back towards the ring in the delocalisation. The molecule is less polar than you would otherwise have expected.

Simple aryl halides like chlorobenzene are very resistant to nucleophilic substitution. It is possible to replace the chlorine by -OH, but only under very severe industrial conditions - for example at 200°C and 200 atmospheres. In the lab, these reactions do not happen. There are two reasons for this - depending on which of the above mechanisms you are talking about.

1. **The extra strength of the carbon-halogen bond in aryl halides**: The carbon-chlorine bond in chlorobenzene is stronger than you might expect. There is an interaction between one of the lone pairs on the chlorine atom and the delocalized ring electrons, and this strengthens the bond. Both of the mechanisms above involve breaking the carbon-halogen bond at some stage. The more difficult it is to break, the slower the reaction will be.
2. **Repulsion by the ring electrons:** This will only apply if the hydroxide ion attacked the chlorobenzene by a mechanism like the first one described above. In that mechanism, the hydroxide ion attacks the slightly positive carbon that the halogen atom is attached to.If the halogen atom is attached to a benzene ring, the incoming hydroxide ion is going to be faced with the delocalized ring electrons above and below that carbon atom. The negative hydroxide ion will simply be repelled. That particular mechanism is simply a non-starter!

Contributors

Jim Clark (Chemguide.co.uk)

7.19: Organic Synthesis

Wöhler synthesis of Urea in 1828 heralded the birth of modern chemistry. The Art of synthesis is as old as Organic chemistry itself. Natural product chemistry is firmly rooted in the science of degrading a molecule to known smaller molecules using known chemical reactions and conforming the assigned structure by chemical synthesis from small, well known molecules using well established synthetic chemistry techniques. Once this art of synthesizing a molecule was mastered, chemists attempted to modify bioactive molecules in an attempt to develop new drugs and also to unravel the mystery of biomolecular interactions. Until the middle of the 20th Century, organic chemists approached the task of synthesis of molecules as independent tailor made projects, guided mainly by chemical intuition and a sound knowledge of chemical reactions. During this period, a strong foundation was laid for the development of mechanistic principles of organic reactions, new reactions and reagents. More than a century of such intensive studies on the chemistry of carbohydrates, alkaloids, terpenes and steroids laid the foundation for the development of logical approaches for the synthesis of molecules.

The job of a synthetic chemist is akin to that of an architect (or civil engineer). While the architect could actually see the building he is constructing, a molecular architect called Chemist is handicapped by the fact that the molecule he is synthesizing is too small to be seen even through the most powerful microscope developed to date. With such a limitation, how does he ‘see’ the developing structure? For this purpose, a chemist makes use of spectroscopic tools. How does he cut, tailor and glue the components on a molecule that he cannot see? For this purpose chemists have developed molecular level tools called Reagents and Reactions. How does he clean the debris and produce pure molecules? This feat is achieved by crystallization, distillation and extensive use of Chromatography techniques. A mastery over several such techniques enables the molecular architect (popularly known as organic chemist) to achieve the challenging task of synthesizing the mirade molecular structures encountered in Natural Products Chemistry, Drug Chemistry and modern Molecular Materials. In this task, he is further guided by several ‘thumb rules’ that chemists have evolved over the past two centuries. The discussions on the topics **Name Reactions, Reagents** for synthesis, **Spectroscopy** and **Chromatography** are beyond the scope of this write-up. Let us begin with a brief look at some of the important ***‘Rules’*** *in organic chemistry that guide us in planning organic synthesis.* We would then discuss Protection and Deprotection of some important functional groups. We could then move on to the Logic of planning Organic Synthesis.

Contributors

- Prof. R Balaji Rao (Department of Chemistry, Banaras Hindu University, Varanasi) as part of Information and Communication Technology

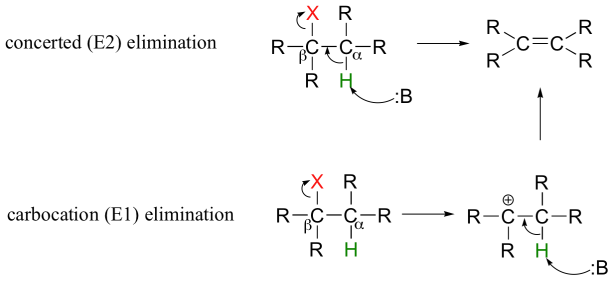
CHAPTER OVERVIEW

8: Alkyl Halides and Elimination Reactions

Topic hierarchy

8.1: General Features of Elimination

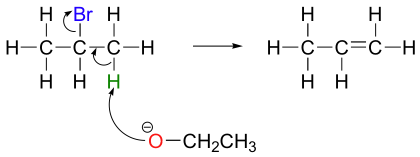
So far in this chapter, we have seen several examples of carbanion-intermediate (E1cb) beta-elimination reactions, in which the first step was proton abstraction at a carbon positioned ato an electron-withdrawing carbonyl or imine. Elimination reactions are also possible at positions that are isolated from carbonyls or any other electron-withdrawing groups. This type of elimination can be described by two model mechanisms: it can occur in a single concerted step (proton abstraction at C_α occurring at the same time as $C\beta$-X bond cleavage), or in two steps ($C\beta$-X bond cleavage occurring first to form a carbocation intermediate, which is then 'quenched' by proton abstraction at the alpha-carbon).



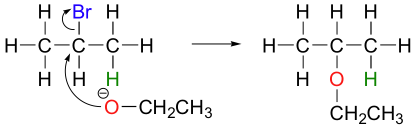
These mechanisms, termed E2 and E1, respectively, are important in laboratory organic chemistry, but are less common in biological chemistry. As explained below, which mechanism actually occurs in a laboratory reaction will depend on the identity of the R groups (ie., whether the alkyl halide is primary, secondary, tertiary, etc.) as well as on the characteristics of the base.

E1 and E2 reactions in the laboratory

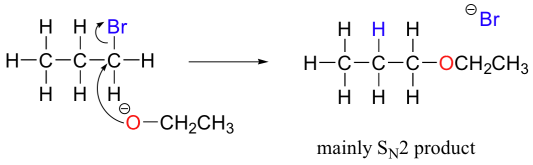
E2 elimination reactions in the laboratory are carried out with relatively strong bases, such as alkoxides (deprotonated alcohols). 2-bromopropane will react with ethoxide, for example, to give propene.



Propene is not the only product of this reaction, however - the ethoxide will also to some extent act as a nucleophile in an S_N2 reaction.

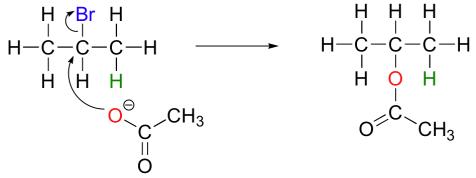


Chemists carrying out nonenzymatic nucleophilic substitution or elimination reactions always have to be aware of the competition between the two mechanisms, because bases can also be nucleophiles, and vice-versa. However, a chemist can tip the scales in one direction or another by carefully choosing reagents. Primary carbon electrophiles like 1-bromopropane, for example, are much more likely to undergo substitution (by the S_N2 mechanism) than elimination (by the E2 mechanism) – this is because the electrophilic carbon is unhindered and a good target for a nucleophile.

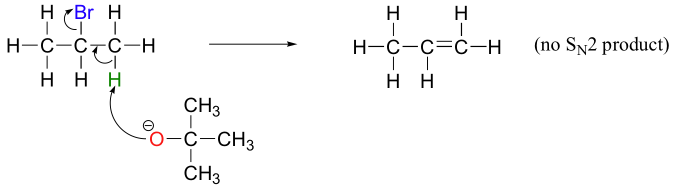


S_N1 and E1 mechanisms are unlikely with such compounds because of the relative instability of primary carbocations.

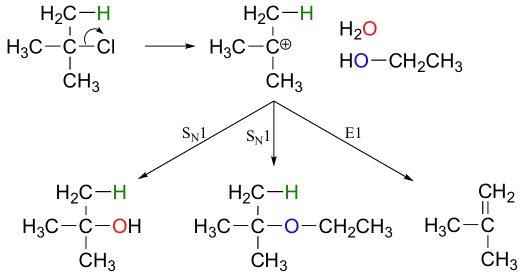
The nature of the electron-rich species is also critical. Acetate, for example, is a weak base but a reasonably good nucleophile, and will react with 2-bromopropane mainly as a nucleophile.



In order to direct the reaction towards elimination, a strong *hindered* base such as tert-butoxide can be used. The bulkiness of tert-butoxide makes it difficult for the oxygen to reach the carbon (in other words, to act as a nucleophile). It is more likely to pluck off a proton, which is much more accessible than the electrophilic carbon).



E1 reactions occur by the same kinds of carbocation-favoring conditions that have already been described for S_N1 reactions (section 9.4): a secondary or tertiary substrate, a protic solvent, and a relatively weak base/nucleophile. In fact, E1 and S_N1 reactions generally occur simultaneously, giving a mixture of substitution and elimination products after formation of a common carbocation intermediate. When tert-butyl chloride is stirred in a mixture of ethanol and water, for example, a mixture of S_N1 products (tert-butyl alcohol and tert-butyl ethyl ether) and E1 product (2-methylpropene) results.

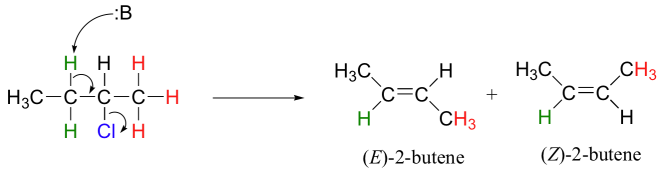


Template:ExampleStart

Exercise 14.4: A straightforward functional group conversion that is often carried out in the undergraduate organic lab is the phosphoric acid-catalyzed dehydration of cyclohexanol to form cyclohexene. No solvent is necessary in this reaction - pure liquid cyclohexanol is simply stirred together with a few drops of concentrated phosphoric acid. In order to drive the equilibrium of this reversible reaction towards the desired product, cyclohexene is distilled out of the reaction mixture as it forms (the boiling point of cyclohexene is 83 ^oC, significantly lower than that of anything else in the reaction solution). Any cyclohexyl phosphate that might form from the competing S_N1 reaction remains in the flask, and is eventually converted to cyclohexene over time. Draw a mechanism for the cyclohexene synthesis reaction described above. Also, draw a mechanism showing how the undesired cyclohexyl phosphate could form.

Template:ExampleEnd

Next, let's put aside the issue of competition between nucleophilic substitution and elimination, and focus on the regioselectivity of elimination reactions. In many cases an elimination reaction can result in more than one constitutional isomer or stereoisomer. The elimination products of 2-chloropentane provide a good example:

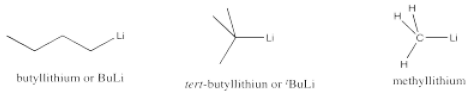


This reaction is both regiospecific and stereospecific. In general**,** *more substituted alkenes are more stable*, and as a result, the product mixture will contain less 1-butene than 2-butene (this is the regiochemical aspect of the outcome, and is often referred to as **Zaitsev's rule**). In addition, we already know that *trans* (*E*) alkenes are generally more stable than *cis* (*Z*) alkenes (section 3.7C), so we can predict that more of the *E* product will form compared to the *Z* product.

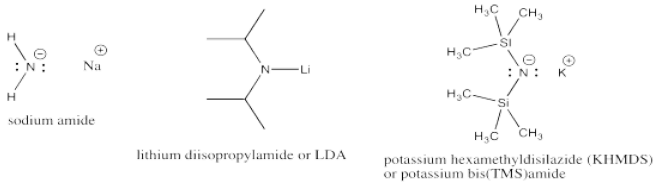
Why might a reaction undergo elimination rather than substitution? The most important reason concerns the nature of the nucleophile. The more basic the nucleophile, the more likely it will induce elimination.

- Basic nucleophiles lead to elimination.

Very strong bases include carbon and nitrogen anions and semi-anions. Examples include butyllithium and sodium amide. Very strong bases are highly likely to engage in elimination, rather than substitution.



Strong bases include non-stabilized oxygen anions. Examples include sodium hydroxide as well as alkoxides such as potassium tert-butoxide or sodium ethoxide. Strong bases favour elimination, too. Nevertheless, they can sometimes undergo either elimination or substitution, depending on other factors (see below).



Weak bases include cyanide, stabilized oxygen anions such as carboxylates and aryloxides, fluoride ion and neutral amines. Weak bases are much more likely to undergo substitution than elimination.

Very weak bases include heavy halides such as chloride, bromide or iodide, as well as phosphorus and sulfur nucleophiles. Very weak bases undergo elimination only rarely.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- Prof. Steven Farmer (Sonoma State University)

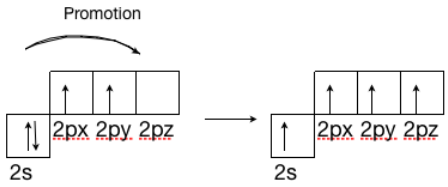
8.2: Alkenes—The Products of Elimination Reactions

Ethene is the formal IUPAC name for $H_2C{=}CH_2$, but it also goes by a common name: Ethylene. The name Ethylene is used because it is like an ethyl group (CH_2CH_3) but there is a double bond between the two carbon atoms in it. Ethene has the formula C_2H_4 and is the simplest alkene because it has the fewest carbons (two) necessary for a carbon-carbon double bond.

Introduction

Bonding in carbon is covalent, containing either sigma or π bonds. Carbon can make single, double, or triple bonds. The number of bonds it makes determines the structure. With four single bonds, carbon has a tetrahedral structure, while with one double bond it's structure is trigonal planar, and with a triple bond it has a linear structure.

A solitary carbon atom has four electrons, two in the 2s orbital, and one in each of the $2p_x$ and $2p_y$ orbitals, leaving the $2p_z$ orbital empty. A single carbon atom can make up to four bonds, but by looking at its electron configuration this would not be possible because there are only two electrons available to bond with. The other two are in a lone pair state, making them much less reactive to another electron that is by itself. Well it is, in order to make the four bonds, the carbon atom promotes one of the 2s electrons into the empty $2p_z$ orbital, leaving the carbon with four unpaired electrons allowing it to now form four bonds. The electron is not promoted spontaneously. It becomes promoted when a photon of light with the correct wavelength hits the carbon atom. When this photon hits the carbon atom it gives the atom enough energy to promote one of the lone pair electrons to the $2p_z$ orbital.



Sigma and Pi Bonds

All the bonds in Ethene are covalent, meaning that they are all formed by two adjacent atoms sharing their valence electrons. As opposed to ionic bonds which hold atoms together through the attraction of two ions of opposite charges.

Sigma bonds are created when there is overlap of similar orbitals, orbitals that are aligned along the inter-nuclear axis. Common sigma bonds are $s+s$, p_z+p_z and $s+p_z$, z is the axis of the bond on the xyz-plane of the atom.

π bonds are created when there is adequate overlap of similar, adjacent p orbitals, such as p_x+p_x and p_y+p_y. Each p orbital has two lobes, one usually indicated by a + and the other indicated by a - (sometimes one may be shaded while the other is not). This + and - (shaded, not shaded) are only meant to indicate the opposite phase ϕ the wave functions, they **do not** indicate any type of electrical charge. For a π bond to form both lobes of the p orbital must overlap, + with + and - with -. When a + lobe overlaps with a - lobe this creates an anti-bonding orbital interaction which is much higher in energy, and therefore not a desirable interaction.

Usually there can be no π bonds between two atoms without having at least one sigma bond present first. But there are special cases such as dicarbon (C_2) where the central bond is a π bond not a sigma bond, but in cases like these the two atoms want to have as much orbital overlap as possible so the bond lengths between the atoms are smaller than what is normally expected.

The π bond in ethene is weak compared to the sigma bond between the two carbons. This weakness makes the π bond and the overall molecule a site of comparatively high chemical reactivity to an array of different substances. This is due to the high electron density in the π bond, and because it is a weak bond with high electron density the π bond will easily break in order to form two separate sigma bonds. Sites such as these are referred to as functional groups or functionalities. These groups have characteristic properties and they control the reactivity of the molecule as a whole. How these functional groups and other reactants form various products are an important concept in organic chemistry.

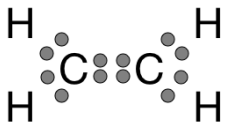
Orbital Bonding in Ethene

Ethene is made up of four $1s^1$ Hydrogen atoms and two $2s^2$ $2p_x{}^1$ $2p_y{}^2$ carbon atoms. These carbon atoms already have four electrons, but they each want to get four more so that they have a full eight in the valence shell. Having eight valence electrons around carbon gives the atom itself the same electron configuration as neon, a noble gas. Carbon wants to have the same

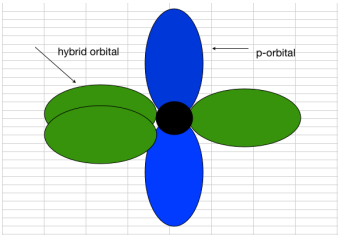
configuration as Neon because when it has eight valence electrons carbon is at its most stable, lowest energy state, it has all of the electrons that it wants, so it is no longer reactive.

Structure of Ethene

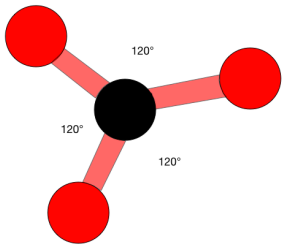
Ethene is not a very complicated molecule. It contains two carbon atoms that are double bonded to each other, with each of these atoms also bonded to two Hydrogen atoms.



This forms a total of three bonds to each carbon atom, giving them an sp^2 hybridization. Since the carbon atom is forming three sigma bonds instead of the four that it can, it only needs to hybridize three of its outer orbitals, instead of four. It does this by using the $2s$ electron and two of the $2p$ electrons, leaving the other unchanged. This new orbital is called an sp^2 hybrid because that's exactly what it is, it is made from one s orbital and two p orbitals.



When atoms are an sp^2 hybrid they have a trigonal planar structure. These structures are very similar to a 'peace' sign, there is a central atom with three atoms around it, all on one plane. Trigonal planar molecules have an ideal bond angle of 120° on each side.



The H-C-H bond angle is 117°, which is very close to the ideal 120° of a carbon with sp^2 hybridization. The other two angles (H-C=C) are both 121.5°.

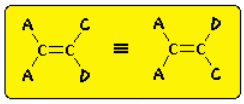
Rigidity in Ethene

There is rigidity in the Ethene molecule due to the double-bonded carbons. In Ethane there are two carbons that share a single bond, this allows the two Methyl groups to rotate with respect to each other. These different conformations result in higher and lower energy forms of Ethane. In Ethene there is no free rotation about the carbon-carbon sigma bond. There is no rotation because there is also a π bond along with the sigma bond between the two carbons. A π bond is only formed when there is adequate overlap between both top and bottom p-orbitals. In order for there to be free rotation the p-orbitals would have to go through a phase where they are 90° from each other, which would break the π bond because there would be no overlap. Since the π bond is essential to the structure of Ethene it must not break, so there can be not free rotation about the carbon-carbon sigma bond.

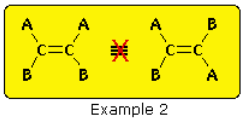
Configurational Stereoisomers of Alkenes

The carbon-carbon double bond is formed between two sp^2 hybridized carbons, and consists of two occupied molecular orbitals, a sigma orbital and a pi orbital. Rotation of the end groups of a double bond relative to each other destroys the p-orbital overlap that creates the pi orbital or bond. Because the pi bond has a bond energy of roughly 60 kcal/mole, this resistance to rotation stabilizes the planar configuration of this functional group. As a result, certain disubstituted alkenes may exist as a pair of configurational stereoisomers, often designated cis and trans. **The essential requirement for this stereoisomerism is that each carbon of the**

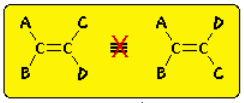
double bond must have two different substituent groups (one may be hydrogen). This is illustrated by the following general formulas. In the first example, the left-hand double bond carbon has two identical substituents (**A**) so stereoisomerism about the double bond is not possible (reversing substituents on the right-hand carbon gives the same configuration). In the next two examples, each double bond carbon atom has two different substituent groups and stereoisomerism exists, regardless of whether the two substituents on one carbon are the same as those on the other.



Example 1

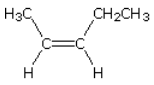


Example 2

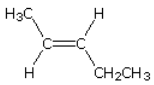


Example 3

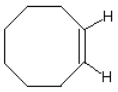
Some examples of this configurational stereoisomerism (sometimes called geometric isomerism) are shown below. Note that cycloalkenes smaller than eight carbons cannot exist in a stable trans configuration due to ring strain. A similar restriction holds against cycloalkynes smaller than ten carbons. Since alkynes are linear, there is no stereoisomerism associated with the carbon-carbon triple bond.



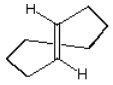
cis-2-pentene



trans-2-pentene



cis-cyclooctene

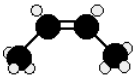


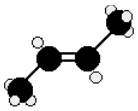
trans-cyclooctene

Geometric (cis-trans) isomerism

The carbon-carbon double bond doesn't allow any rotation about it. That means that it is possible to have the CH_3 groups on either end of the molecule locked either on one side of the molecule or opposite each other.

These are called cis-but-2-ene (where the groups are on the same side) or trans-but-2-ene (where they are on opposite sides).

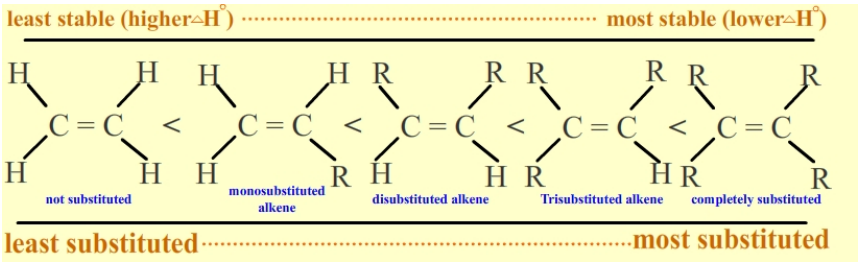

cis-but-2-ene


trans-but-2-ene

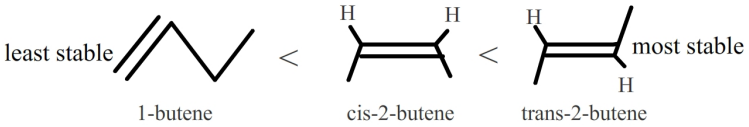
Cis-but-2-ene is also known as (Z)-but-2-ene; trans-but-2-ene is also known as (E)-but-2-ene. For an explanation of the two ways of naming these two compounds, follow the link in the box below.

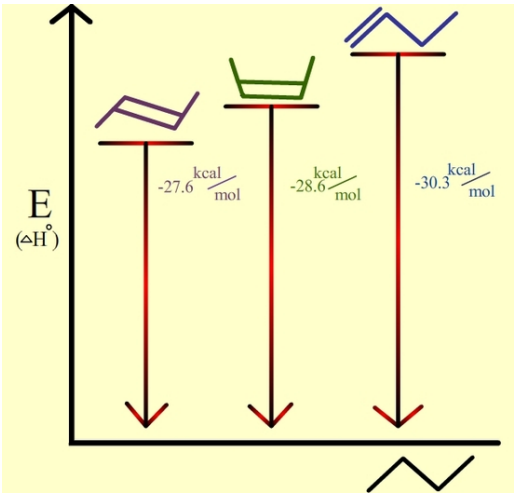
Stability of Alkenes

The stability of alkene can be determined by measuring the amount of energy associated with the hydrogenation of the molecule. Since the double bond is breaking in this reaction, the energy released in hydrogenation is proportional to the energy in the double bond of the molecule. This is a useful tool because heats of hydrogenation can be measured very accurately. The ?H° is usually around -30 kcal/mol for alkenes. Stability is simply a measure of energy. Lower energy molecules are more stable than higher energy molecules. More substituted alkenes are more stable than less substituted ones due to hyperconjugation. They have a lower heat of hydrogenation. The following illustrates stability of alkenes with various substituents:



In disubstituted alkenes, trans isomers are more stable than cis isomers due to steric hindrance. Also, internal alkenes are more stable than terminal ones. See the following isomers of butene:





Trans-2-butene is the most stable because it has the lowest heat of hydrogenation.

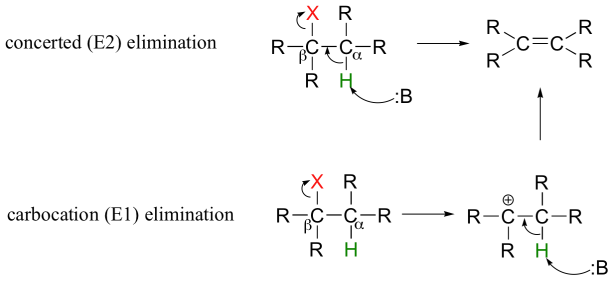
Note: In cycloalkenes smaller than cyclooctene, the cis isomers are more stable than the trans as a result of ring strain.

Contributors

- Anna Manis (2009)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

8.3: The Mechanisms of Elimination

So far in this chapter, we have seen several examples of carbanion-intermediate (E1cb) beta-elimination reactions, in which the first step was proton abstraction at a carbon positioned ato an electron-withdrawing carbonyl or imine. Elimination reactions are also possible at positions that are isolated from carbonyls or any other electron-withdrawing groups. This type of elimination can be described by two model mechanisms: it can occur in a single concerted step (proton abstraction at C_α occurring at the same time as $C\beta$-X bond cleavage), or in two steps ($C\beta$-X bond cleavage occurring first to form a carbocation intermediate, which is then 'quenched' by proton abstraction at the alpha-carbon).



These mechanisms, termed E2 and E1, respectively, are important in laboratory organic chemistry, but are less common in biological chemistry. As explained below, which mechanism actually occurs in a laboratory reaction will depend on the identity of the R groups (ie., whether the alkyl halide is primary, secondary, tertiary, etc.) as well as on the characteristics of the base.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

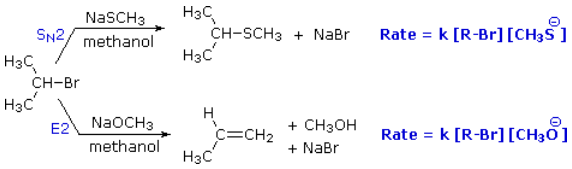
8.4: The E 2 E2 Mechanism

E2, bimolecular elimination, was proposed in the 1920s by British chemist Christopher Kelk Ingold. Unlike E1 reactions, E2 reactions remove two subsituents with the addition of a strong base, resulting in an alkene.

Introduction

E2 reactions are typically seen with secondary and tertiary alkyl halides, but a hindered base is necessary with a primary halide. The mechanism by which it occurs is a single step **concerted** reaction with one transition state. The rate at which this mechanism occurs is second order kinetics, and depends on both the base and alkyl halide. A good leaving group is required because it is involved in the rate determining step. The leaving groups must be coplanar in order to form a pi bond; carbons go from sp^3 to sp^2 hybridization states.

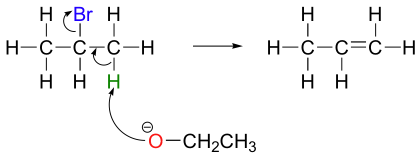
To get a clearer picture of the interplay of these factors involved in a a reaction between a nucleophile/base and an alkyl halide, consider the reaction of a 2º-alkyl halide, isopropyl bromide, with two different nucleophiles. In one pathway, a methanethiolate nucleophile substitutes for bromine in an S_N2 reaction. In the other (bottom) pathway, methoxide ion acts as a base (rather than as a nucleophile) in an elimination reaction. As we will soon see, the mechanism of this reaction is single-step, and is referred to as the E2 mechanism.



General Reaction

Below is a mechanistic diagram of an elimination reaction by the E2 pathway:

.

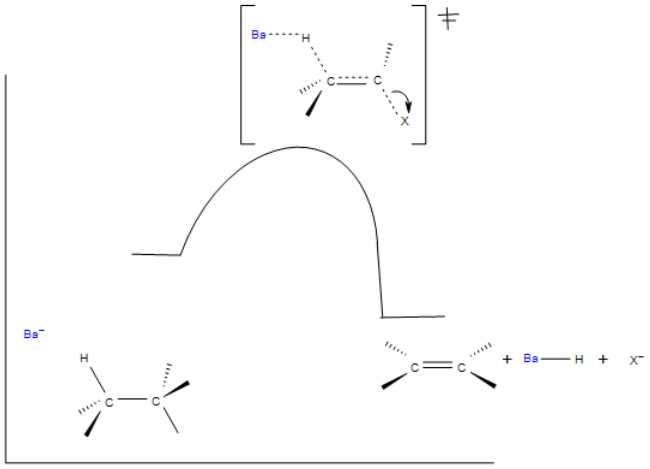


In this reaction Ba represents the base and Br representents a leaving group, typically a halogen. There is one transition state that shows the concerted reaction for the base attracting the hydrogen and the halogen taking the electrons from the bond. The product be both eclipse and staggered depending on the transition states. Eclipsed products have a synperiplanar transition states, while staggered products have antiperiplanar transition states. Staggered conformation is usually the major product because of its lower energy confirmation.

An E2 reaction has certain requirements to proceed:

- A strong base is necessary especially necessary for primary alkyl halides. Secondary and tertirary primary halides will procede with E2 in the precesence of a base (OH-, RO-, R_2N-)
- Both leaving groups should be on the same plane, this allows the double bond to form in the reaction. In the reaction above you can see both leaving groups are in the plane of the carbons.
- Follows Zaitsev's rule, the most substituted alkene is usually the major product.
- Hoffman Rule, if a strically hindered base will result in the least substituted product.

E2 Reaction Coordinate



The Leaving Group Effect in E2 Reactions

As Size Increases, The Ability of the Leaving Group to Leave Increases: Here we revisit the effect size has on basicity. If we move down the periodic table, size increases. With an increase in size, basicity decreases, and the ability of the leaving group to leave increases. The relationship among the following halogens, unlike the previous example, is true to what we will see in upcoming reaction mechanisms.

F	<	Cl	<	Br	<	I
Worst		Fair		Good		Excellent

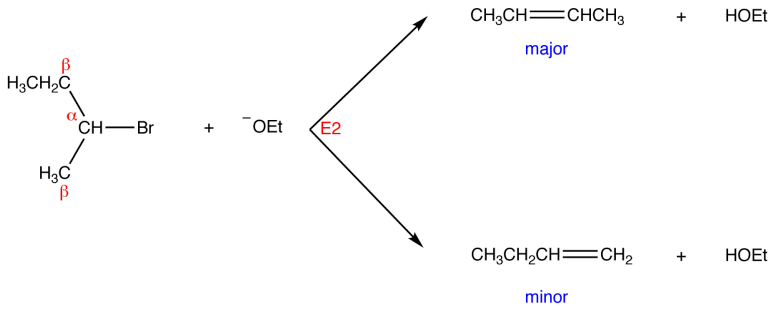
Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

8.5: The Zaitsev Rule

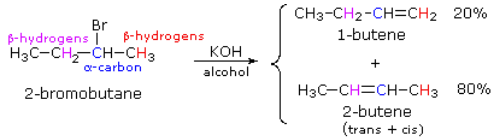
Zaitsev's Rule can be used to predict the regiochemistry of elimination reactions.

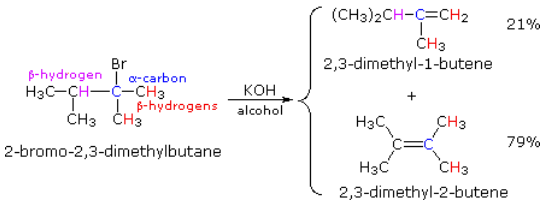
Introduction

Zaitsev's or Saytzev's (anglicized spelling) rule is an empirical rule used to predict regioselectivity of 1,2-elimination reactions occurring via the E1 or E2 mechanisms. It states that in a regioselective E1 or E2 reaction the major product is the more stable alkene, (i.e., the alkene with the more highly substituted double bond). For example:



If two or more structurally distinct groups of beta-hydrogens are present in a given reactant, then several constitutionally isomeric alkenes may be formed by an E2 elimination. This situation is illustrated by the 2-bromobutane and 2-bromo-2,3-dimethylbutane elimination examples given below.





By using the strongly basic hydroxide nucleophile, we direct these reactions toward elimination. In both cases there are two different sets of beta-hydrogens available to the elimination reaction (these are colored red and magenta and the alpha carbon is blue). If the rate of each possible elimination was the same, we might expect the amounts of the isomeric elimination products to reflect the number of hydrogens that could participate in that reaction. For example, since there are three 1°-hydrogens (red) and two 2°-hydrogens (magenta) on beta-carbons in 2-bromobutane, statistics would suggest a 3:2 ratio of 1-butene and 2-butene in the products. This is not observed, and the latter predominates by 4:1. This departure from statistical expectation is even more pronounced in the second example, where there are six 1°-beta-hydrogens compared with one 3°-hydrogen. These results point to a strong regioselectivity favoring the more highly substituted product double bond, an empirical statement generally called the **Zaitsev Rule**.

Contributors

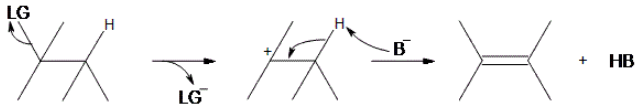
- Gamini Gunawardena from the OChemPal site (Utah Valley University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

8.6: The E 1 E1 Mechanism

Unimolecular Elimination (E1) is a reaction in which the removal of an HX substituent results in the formation of a double bond. It is similar to a unimolecular nucleophilic substitution reaction (S_N1) in various ways. One being the formation of a carbocation intermediate. Also, the only rate determining (slow) step is the dissociation of the leaving group to form a carbocation, hence the name unimolecular. Thus, since these two reactions behave similarly, they compete against each other. Many times, both these reactions will occur simultaneously to form different products from a single reaction. However, one can be favored over another through thermodynamic control. Although Elimination entails two types of reactions, E1 and E2, we will focus mainly on E1 reactions with some reference to E2.

General Reaction

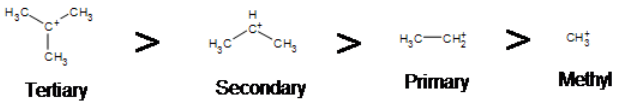
An E1 reaction involves the deprotonation of a hydrogen nearby (usually one carbon away, or the beta position) the carbocation resulting in the formation of an alkene product. In order to accomplish this, a Lewis base is required. For a simplified model, we'll take B to be a Lewis base, and LG to be a halogen leaving group.



As can be seen above, the preliminary step is the leaving group (LG) leaving on its own. Because it takes the electrons in the bond along with it, the carbon that was attached to it loses its electron, making it a carbocation. Once it becomes a carbocation, a Lewis Base (B^-) deprotonates the intermediate carbocation at the beta position, which then donates its electrons to the neighboring C-C bond, forming a double bond. Unlike E2 reactions, which require the proton to be *anti* to the leaving group, E1 reactions only require a neighboring hydrogen. This is due to the fact that the leaving group has already left the molecule. The final product is an alkene along with the HB byproduct.

Reactivity

Due to the fact that E1 reactions create a carbocation intermediate, rules present in S_N1 reactions still apply.

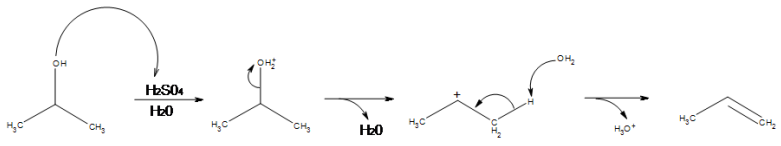


As expected, tertiary carbocations are favored over secondary, primary and methyl's. This is due to the phenomena of hyperconjugation, which essentially allows a nearby C-C or C-H bond to interact with the p orbital of the carbon to bring the electrons down to a lower energy state. Thus, this has a stabilizing effect on the molecule as a whole. In general, primary and methyl carbocations do not proceed through the E1 pathway for this reason, unless there is a means of carbocation rearrangement to move the positive charge to a nearby carbon. Secondary and Tertiary carbons form more stable carbocations, thus this formation occurs quite rapidly.

Secondary carbocations can be subject to the E2 reaction pathway, but this generally occurs in the presence of a good / strong base. Adding a weak base to the reaction disfavors E2, essentially pushing towards the E1 pathway. In many instances, solvolysis occurs rather than using a base to deprotonate. This means heat is added to the solution, and the solvent itself deprotonates a hydrogen. The medium can effect the pathway of the reaction as well. Polar protic solvents may be used to hinder nucleophiles, thus disfavoring E2 / S_n2 from occurring.

Acid catalyzed dehydration of secondary / tertiary alcohols

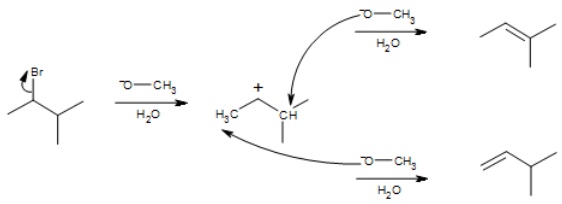
We'll take a look at a mechanism involving solvolysis during an E1 reaction of Propanol in Sulfuric Acid.



- Step 1: The OH group on the pentanol is hydrated by H_2SO_4. This allows the OH to become an H_2O, which is a better leaving group.
- Step 2: Once the OH has been hydrated, the H_2O molecule leaves, taking its electrons with it. This creates a carbocation intermediate on the attached carbon.
- Step 3: Another H_2O molecule comes in to deprotonate the beta carbon, which then donates its electrons to the neighboring C-C bond. The carbons are rehybridized from sp^3 to sp^2, and thus a pi bond is formed between them.

Mechanism for Alkyl Halides

This mechanism is a common application of E1 reactions in the synthesis of an alkene.



Once again, we see the basic 2 steps of the E1 mechanism.

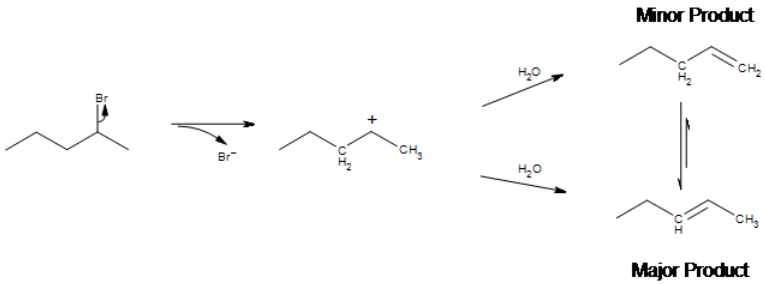
1. The leaving group leaves along with its electrons to form a carbocation intermediate.
2. A base deprotonates a beta carbon to form a pi bond.

In this case we see a mixture of products rather than one discrete one. This is the case because the carbocation has two nearby carbons that are capable of being deprotonated, but that only one forms a major product (more stable).

How are Regiochemistry & Stereochemistry involved?

In terms of regiochemistry, Zaitsev's rule states that although more than one product can be formed during alkene synthesis, the more substituted alkene is the major product. This infers that the hydrogen on the most substituted carbon is the most probable to be deprotonated, thus allowing for the most substituted alkene to be formed.

Unlike E2 reactions, E1 is not stereospecific. Thus, a hydrogen is not required to be anti-periplanar to the leaving group.



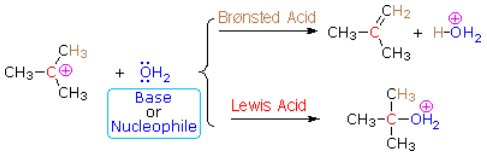
In this mechanism, we can see two possible pathways for the reaction. One in which the methyl on the right is deprotonated, and another in which the CH_2 on the left is deprotonated. Either one leads to a plausible resultant product, however, only one forms a major product. As stated by **Zaitsev's rule**, deprotonation of the most substituted carbon results in the most substituted alkene. This then becomes the most stable product due to hyperconjugation, and is also more common than the minor product.

Contributors

- Satish Balasubramanian

8.7: S N 1 SN1 and E 1 E1 Reactions

The E1 mechanism is nearly identical to the S_N1 mechanism, differing only in the course of reaction taken by the carbocation intermediate. As shown by the following equations, a carbocation bearing beta-hydrogens may function either as a Lewis acid (electrophile), as it does in the S_N1 reaction, or a Brønsted acid, as in the E1 reaction.



Thus, hydrolysis of tert-butyl chloride in a mixed solvent of water and acetonitrile gives a mixture of 2-methyl-2-propanol (60%) and 2-methylpropene (40%) at a rate independent of the water concentration. The alcohol is the product of an S_N1 reaction and the alkene is the product of the E1 reaction. The characteristics of these two reaction mechanisms are similar, as expected. They both show first order kinetics; neither is much influenced by a change in the nucleophile/base; and both are relatively non-stereospecific.

$(CH_3)_3C–Cl + H_2O \longrightarrow [\ (CH_3)_3C(+)\ ] + Cl^{(-)} + H_2O \longrightarrow (CH_3)_3C–OH + (CH_3)_2C{=}CH_2 + HCl + H_2O$

To summarize, when carbocation intermediates are formed one can expect them to react further by one or more of the following modes:

1. The cation may bond to a nucleophile to give a substitution product.
2. The cation may transfer a beta-proton to a base, giving an alkene product.
3. The cation may rearrange to a more stable carbocation, and then react by mode #1 or #2.

Since the S_N1 and E1 reactions proceed via the same carbocation intermediate, the product ratios are difficult to control and both substitution and elimination usually take place.

Having discussed the many factors that influence nucleophilic substitution and elimination reactions of alkyl halides, we must now consider the practical problem of predicting the most likely outcome when a given alkyl halide is reacted with a given nucleophile. As we noted earlier, several variables must be considered, **the most important being the structure of the alkyl group and the nature of the nucleophilic reactant**. The nature of the halogen substituent on the alkyl halide is usually not very significant if it is Cl, Br or I. In cases where both S_N2 and E2 reactions compete, chlorides generally give more elimination than do iodides, since the greater electronegativity of chlorine increases the acidity of beta-hydrogens. Indeed, although alkyl fluorides are relatively unreactive, when reactions with basic nucleophiles are forced, elimination occurs (note the high electronegativity of fluorine).

Contributors

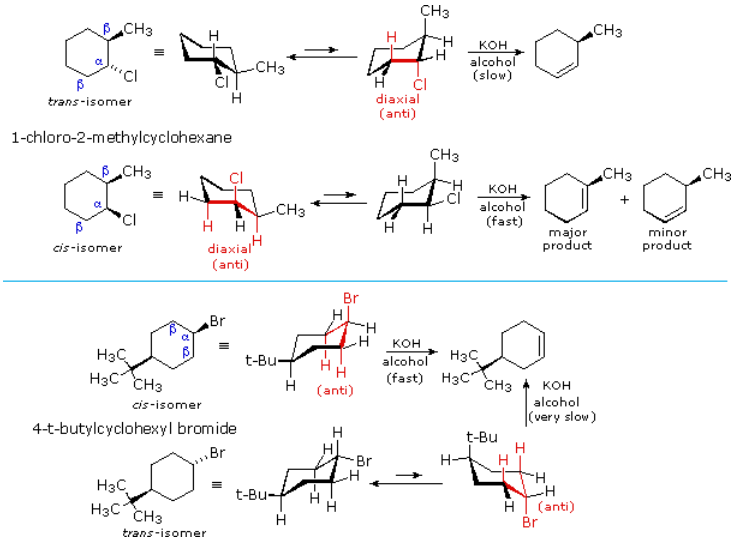
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

8.8: Stereochemistry of the \(E_2\) Reaction

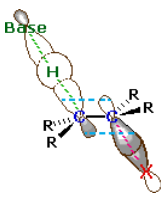
Stereochemistry of the E_2 Reaction

E2 elimination reactions of certain isomeric cycloalkyl halides show unusual rates and regioselectivity that are not explained by the principles thus far discussed. For example, trans-2-methyl-1-chlorocyclohexane reacts with alcoholic KOH at a much slower rate than does its cis-isomer. Furthermore, the product from elimination of the trans-isomer is 3-methylcyclohexene (not predicted by the Zaitsev rule), whereas the cis-isomer gives the predicted 1-methylcyclohexene as the chief product. These differences are described by the first two equations in the following diagram.

Unlike open chain structures, cyclic compounds generally restrict the spatial orientation of ring substituents to relatively few arrangements. Consequently, reactions conducted on such substrates often provide us with information about the preferred orientation of reactant species in the transition state. Stereoisomers are particularly suitable in this respect, so the results shown here contain important information about the E2 transition state.



The most sensible interpretation of the elimination reactions of 2- and 4-substituted halocyclohexanes is that this reaction prefers an **anti orientation** of the halogen and the beta-hydrogen which is attacked by the base. These anti orientations are colored in red in the above equations. The compounds used here all have six-membered rings, so the anti orientation of groups requires that they assume a diaxial conformation. The observed differences in rate are the result of a steric preference for equatorial orientation of large substituents, which reduces the effective concentration of conformers having an axial halogen. In the case of the 1-bromo-4-tert-butylcyclohexane isomers, the tert-butyl group is so large that it will always assume an equatorial orientation, leaving the bromine to be axial in the cis-isomer and equatorial in the trans. Because of symmetry, the two axial beta-hydrogens in the cis-isomer react equally with base, resulting in rapid elimination to the same alkene (actually a racemic mixture). This reflects the fixed anti orientation of these hydrogens to the chlorine atom. To assume a conformation having an axial bromine the trans-isomer must tolerate serious crowding distortions. Such conformers are therefore present in extremely low concentration, and the rate of elimination is very slow. Indeed, substitution by hydroxide anion predominates.



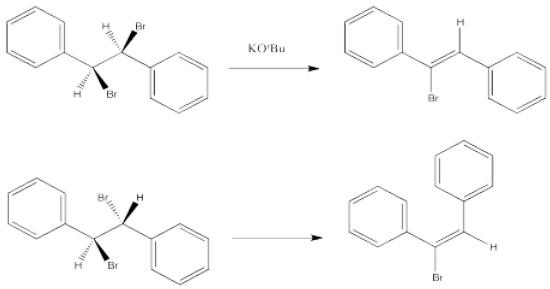
A similar analysis of the 1-chloro-2-methylcyclohexane isomers explains both the rate and regioselectivity differences. Both the chlorine and methyl groups may assume an equatorial orientation in a chair conformation of the trans-isomer, as shown in the top equation. The axial chlorine needed for the E2 elimination is present only in the less stable alternative chair conformer, but this structure has only one axial beta-hydrogen (colored red), and the resulting elimination gives 3-methylcyclohexene. In the cis-isomer the smaller chlorine atom assumes an axial position in the more stable chair conformation, and here there are two axial beta hydrogens. The more stable 1-methylcyclohexene is therefore the predominant product, and the overall rate of elimination is relatively fast.

An orbital drawing of the anti-transition state is shown on the right. Note that the base attacks the alkyl halide from the side opposite the halogen, just as in the S_N2 mechanism. In this drawing the α and β carbon atoms are undergoing a rehybridization from sp^3 to sp^2 and the developing π-bond is drawn as dashed light blue lines. The symbol **R** represents an alkyl group or hydrogen. Since both the base and the alkyl halide are present in this transition state, the reaction is bimolecular and should exhibit

second order kinetics. We should note in passing that a syn-transition state would also provide good orbital overlap for elimination, and in some cases where an anti-orientation is prohibited by structural constraints *syn*-elimination has been observed.

Instead, in an E_2 reaction, stereochemistry of the double bond -- that is, whether the *E* or *Z* isomer results -- is dictated by the stereochemistry of the starting material, if it is diastereomeric. In other words, if the carbon with the hydrogen and the carbon with the halogen are both chiral, then one diastereomer will lead to one product, and the other diastereomer will lead to the other product.

The following reactions of potassium ethoxide with dibromostilbene (1,2-dibromo-1,2-diphenylethane) both occurred via an E_2 mechanism. Two different diastereomers were used. Two different stereoisomers (*E* vs. *Z*) resulted.



Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)

8.9: When is the Mechanism E 1 E1 or E 2 E2

8.10: E 2 E2 Reactions and Alkyne Synthesis

Alkynes can be a useful functional group to synthesize due to some of their antibacterial, antiparasitic, and antifungal properties. One simple method for alkyne synthesis is by double elimination from a dihaloalkane.

Introduction

One case in which elimination can occur is when a haloalkane is put in contact with a nucleophile. The table below is used to determine which situations will result in elimination and the formation of a π bond.

Elimination: Haloalkane-Nucleophile Reaction

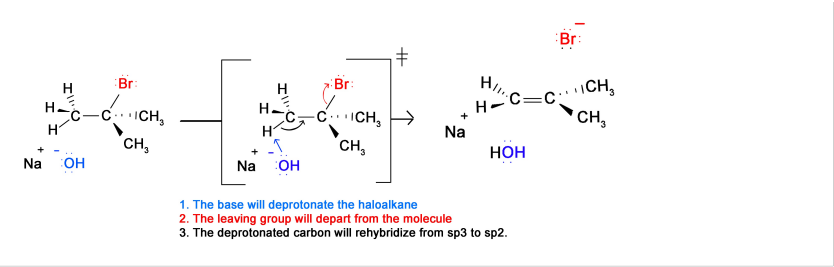
Type of Haloalkane	Weak Base, Poor Nucleophile	Weak Base, Good Nucleophile	Strong, Unhindered Base	Strong, Hindered Base
Primary				
Unhindered				E2
Branched			E2	E2
Secondary	E1		E2	E2
Tertiary	E1	E1	E2	E2

* Empty Box means no elimination or Pi bond forms

To synthesize alkynes from dihaloalkanes we use dehydrohalogenation. The majority of these reactions take place using alkoxide bases (other strong bases can also be used) with high temperatures. This combination results in the majority of the product being from the E2 mechanism.

E2 Mechanism

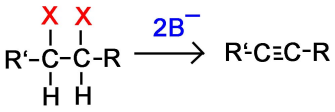
Recall that the E2 mechanism is a concerted reaction (occurs in 1 step). However, in this 1 step there are 3 different changes in the molecule. This is the reaction between 2-Bromo-2-methylpropane and Sodium Hyrdoxide.



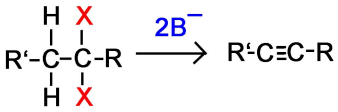
This is a brief review of the E2 reaction. For further information on why the reaction proceeds as it does visit the E2 reaction page. Now, if we apply this concept using 2 halides on vicinal or geminal carbons, the E2 reaction will take place twice resulting in the formation of 2 Pi bonds and thus an Alkyne.

Dihaloalkane Elimination

This is a general picture of the reaction taking place without any of the mechanisms shown.

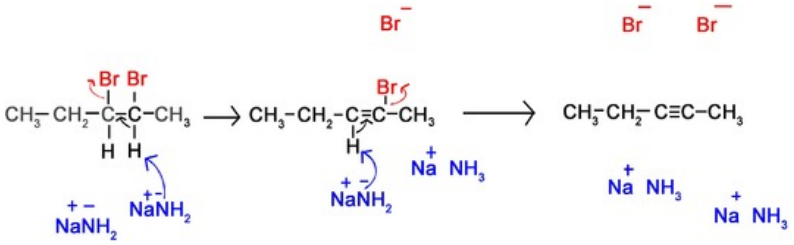


or



* With a terminal haloalkane the equation above is modified in that 3 equivalents of base will be used instead of 2.

Lets look at the mechanism of a reaction between 2,3-Dibromopentane with sodium amide in liquid ammonia.

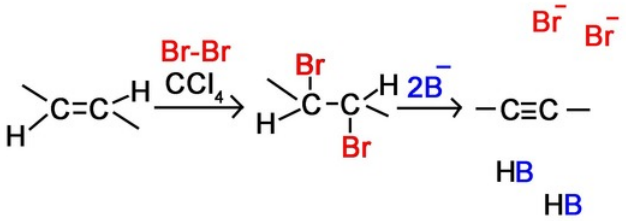


- Liquid ammonia is not part of the reaction, but is used as a solvent
- Notice the intermediate of the alkyne synthesis. It is stereospecifically in its anti form. Because the second proton and halogen are pulled off the molecule this is unimportant to the synthesis of alkynes. For more information on this see the page on preparation of alkenes from haloalkanes.

Preparation of Alkynes from Alkenes

Lastly, we will briefly look at how to prepare alkynes from alkenes. This is a simple process using first halogenation of the alkene bond to form the dihaloalkane, and next, using the double elimination process to protonate the alkane and from the 2 Pi bonds.

This first process is gone over in much greater detail in the page on halogenation of an alkene. In general, chlorine or bromine is used with an inert halogenated solvent like chloromethane to create a vicinal dihalide from an alkene. The vicinal dihalide formed is the reactant needed to produce the alkyene using double elimination, as covered previously on this page.

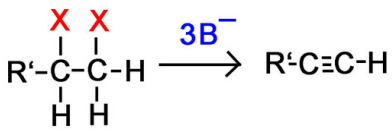


In The Lab

Due to the strong base and high temperatures needed for this reaction to take place, the triple bond may change positions. An example of this is when reactants that should form a terminal alkyne, form a 2-Alkyne instead. The use of $NaNH_2$ in liquid NH_3 is used in order to prevent this from happening due to its lower reacting temperature. Even so, most chemists will prefer to use nucleophilic substitution instead of elimination when trying to form a terminal alkyne.

Questions

Question 1: Why would we need 3 bases for every terminal dihaloalkane instead of 2 in order to form an alkyne?

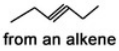


Question 2: What are the major products of the following reactions:

a.) 1,2-Dibromopentane with sodium amide in liquid ammonia

b.) 1-Pentene first with Br_2 and chloromethane, followed by sodium ethoxide (Na^+ $^-O\text{-}CH_2CH_3$)

Question 3: What would be good starting molecules for the synthesis of the following molecules:

a.) 
from an alkene

b.) 
from a dihaloalkane

Question 4: Use a 6 carbon diene to synthesize a 6 carbon molecule with 2 terminal alkynes.

Answers

Answer 1: Remember that hydrogen atoms on terminal alkynes make the alkyne acidic. One of the base molecules will pull off the terminal hydrogen instead of one of the halides like we want.

Answer 2:

a.) 1-Pentyne

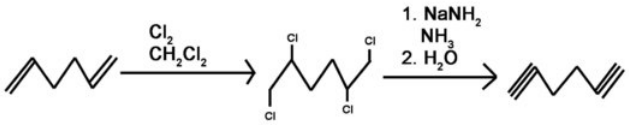
b.) 1-Pentyne

Answer 3:

a.) 

b.) 

Answer 4: Bromine or chlorine can be used with different inert solvents for the halogenation. This can be done using many different bases. Liquid ammonia is used as a solvent and needs to be followed by an aqueous work-up.



8.11: When Is the Reaction S N 1 SN1 , S N 2 SN2 , E 1 E1 , or E 2 E2 ?

Having discussed the many factors that influence nucleophilic substitution and elimination reactions of alkyl halides, we must now consider the practical problem of predicting the most likely outcome when a given alkyl halide is reacted with a given nucleophile. As we noted earlier, several variables must be considered, **the most important being the structure of the alkyl group and the nature of the nucleophilic reactant**.In general, in order for an SN1 or E1 reaction to occur, the relevant carbocation intermediate must be relatively stable. Strong nucleophile favor substitution, and strong bases, especially strong hindered bases (such as tert-butoxide) favor elimination.

The nature of the halogen substituent on the alkyl halide is usually not very significant if it is Cl, Br or I. In cases where both S_N2 and E2 reactions compete, chlorides generally give more elimination than do iodides, since the greater electronegativity of chlorine increases the acidity of beta-hydrogens. Indeed, although alkyl fluorides are relatively unreactive, when reactions with basic nucleophiles are forced, elimination occurs (note the high electronegativity of fluorine).

The following table summarizes the expected outcome of alkyl halide reactions with nucleophiles. It is assumed that the alkyl halides have one or more beta-hydrogens, making elimination possible; and that low dielectric solvents (e.g. acetone, ethanol, tetrahydrofuran & ethyl acetate) are used. When a high dielectric solvent would significantly influence the reaction this is noted in red. **Note that halogens bonded to sp^2 or sp hybridized carbon atoms do not normally undergo substitution or elimination reactions with nucleophilic reagents**.

Nucleophile Alkyl Group	**Anionic Nucleophiles** (Weak Bases: I^-, Br^-, SCN^-, N_3^-, $CH_3CO_2^-$, RS^-, CN^- etc.) pK_a's from -9 to 10 (left to right)	**Anionic Nucleophiles** (Strong Bases: HO^-, RO^-) pK_a's > 15	**Neutral Nucleophiles** (H_2O, ROH, RSH, R_3N) pK_a's ranging from -2 to 11
Primary RCH_2–	Rapid S_N2 substitution. The rate may be reduced by substitution of β-carbons, as in the case of neopentyl.	Rapid S_N2 substitution. E2 elimination may also occur. *e.g.* $ClCH_2CH_2Cl + KOH \longrightarrow CH_2{=}CHCl$	S_N2 substitution. (N ≈ S >>O)
Secondary R_2CH–	S_N2 substitution and / or E2 elimination (depending on the basicity of the nucleophile). Bases weaker than acetate (pK_a = 4.8) give less elimination. The rate of substitution may be reduced by branching at the β-carbons, and this will increase elimination.	E2 elimination will dominate.	S_N2 substitution. (N ≈ S >>O) In high dielectric ionizing solvents, such as water, dimethyl sulfoxide & acetonitrile, S_N1 and E1 products may be formed slowly.
Tertiary R_3C–	E2 elimination will dominate with most nucleophiles (even if they are weak bases). No S_N2 substitution due to steric hindrance. In high dielectric ionizing solvents, such as water, dimethyl sulfoxide & acetonitrile, S_N1 and E1 products may be expected.	E2 elimination will dominate. No S_N2 substitution will occur. In high dielectric ionizing solvents S_N1 and E1 products may be formed.	E2 elimination with nitrogen nucleophiles (they are bases). No S_N2 substitution. In high dielectric ionizing solvents S_N1 and E1 products may be formed.

Allyl $H_2C{=}CHCH_2{-}$	Rapid S_N2 substitution for 1º and 2º-halides. For 3º-halides a very slow S_N2 substitution or, if the nucleophile is moderately basic, E2 elimination. In high dielectric ionizing solvents, such as water, dimethyl sulfoxide & acetonitrile, S_N1 and E1 products may be observed.	Rapid S_N2 substitution for 1º halides. E2 elimination will compete with substitution in 2º-halides, and dominate in the case of 3º-halides. In high dielectric ionizing solvents S_N1 and E1 products may be formed.	Nitrogen and sulfur nucleophiles will give S_N2 substitution in the case of 1º and 2º-halides. 3º-halides will probably give E2 elimination with nitrogen nucleophiles (they are bases). In high dielectric ionizing solvents S_N1 and E1 products may be formed. Water hydrolysis will be favorable for 2º & 3º-halides.
Benzyl $C_6H_5CH_2{-}$	Rapid S_N2 substitution for 1º and 2º-halides. For 3º-halides a very slow S_N2 substitution or, if the nucleophile is moderately basic, E2 elimination. In high dielectric ionizing solvents, such as water, dimethyl sulfoxide & acetonitrile, S_N1 and E1 products may be observed.	Rapid S_N2 substitution for 1º halides (note there are no β hydrogens). E2 elimination will compete with substitution in 2º-halides, and dominate in the case of 3º-halides. In high dielectric ionizing solvents S_N1 and E1 products may be formed.	Nitrogen and sulfur nucleophiles will give S_N2 substitution in the case of 1º and 2º-halides. 3º-halides will probably give E2 elimination with nitrogen nucleophiles (they are bases). In high dielectric ionizing solvents S_N1 and E1 products may be formed. Water hydrolysis will be favorable for 2º & 3º-halides.

Contributors

William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

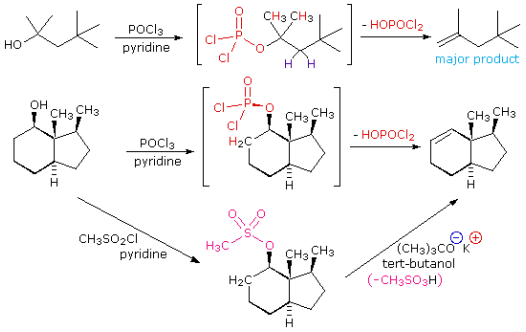
CHAPTER OVERVIEW

9: Alcohols, Ethers, and Epoxides

Topic hierarchy

9.1: Dehydration Using POC l 3 POCl3 and Pyridine

The E2 elimination of 3º-alcohols under relatively non-acidic conditions may be accomplished by treatment with phosphorous oxychloride ($POCl_3$) in pyridine. This procedure is also effective with hindered 2º-alcohols, but for unhindered and 1º-alcohols an S_N2 chloride ion substitution of the chlorophosphate intermediate competes with elimination. Examples of these and related reactions are given in the following figure. The first equation shows the dehydration of a 3º-alcohol. The predominance of the non-Zaitsev product (less substituted double bond) is presumed due to steric hindrance of the methylene group hydrogen atoms, which interferes with the approach of base at that site. The second example shows two elimination procedures applied to the same 2º-alcohol. The first uses the single step $POCl_3$ method, which works well in this case because S_N2 substitution is retarded by steric hindrance. The second method is another example in which an intermediate sulfonate ester confers halogen-like reactivity on an alcohol. In every case the anionic leaving group is the conjugate base of a strong acid.



Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

9.2: Conversion of Alcohols to Alkyl Halides with HX

When alcohols react with a hydrogen halide, a substitution takes place producing an alkyl halide and water:


Figure

Scope of Reaction

- The order of reactivity of alcohols is 3° > 2° > 1° methyl.
- The order of reactivity of the hydrogen halides is HI > HBr > HCl (HF is generally unreactive).

The reaction is acid catalyzed. Alcohols react with the strongly acidic hydrogen halides HCl, HBr, and HI, but they do not react with nonacidic NaCl, NaBr, or NaI. Primary and secondary alcohols can be converted to alkyl chlorides and bromides by allowing them to react with a mixture of a sodium halide and sulfuric acid:


Figure

Mechanisms of the Reactions of Alcohols with HX

Secondary, tertiary, allylic, and benzylic alcohols appear to react by a mechanism that involves the formation of a carbocation, in an S_N1 reaction with the protonated alcohol acting as the substrate.

The S_N1 mechanism is illustrated by the reaction tert-butyl alcohol and aqueous hydrochloric acid (H_3O^+, Cl^-). The first two steps in this S_n1 substitution mechanism are protonation of the alcohol to form an oxonium ion. Although the oxonium ion is formed by protonation of the alcohol, it can also be viewed as a Lewis acid-base complex between the cation (R^+) and H_2O. Protonation of the alcohol converts a poor leaving group (OH-) to a good leaving group (\)H_2O_), which makes the dissociation step of the S_N1 mechanism more favorable.


Figure

In step 3, the carbocation reacts with a nucleophile (a halide ion) to complete the substitution.


Figure

When we convert an alcohol to an alkyl halide, we carry out the reaction in the presence of acid and in the presence of halide ions, and not at elevated temperature. Halide ions are good nucleophiles (they are much stronger nucleophiles than water), and since halide ions are present in high concentration, most of the carbocations react with an electron pair of a halide ion to form a more stable species, the alkyl halide product. The overall result is an S_n1 reaction.

Primary Alcohols

Not all acid-catalyzed conversions of alcohols to alkyl halides proceed through the formation of carbocations. Primary alcohols and methanol react to form alkyl halides under acidic conditions by an S_N2 mechanism.

In these reactions the function of the acid is to produce a *protonated alcohol*. The halide ion then displaces a molecule of water (a good leaving group) from carbon; this produces an alkyl halide:


Figure

Again, acid is required. Although halide ions (particularly iodide and bromide ions) are strong nucleophiles, they are not strong enough to carry out substitution reactions with alcohols themselves. Direct displacement of the hydroxyl group does not occur because the leaving group would have to be a strongly basic hydroxide ion:

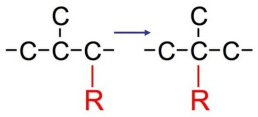

Figure

We can see now why the reactions of alcohols with hydrogen halides are acid-promoted.

Carbocation rearrangements are extremely common in organic chemistry reactions are are defined as the movement of a carbocation from an unstable state to a more stable state through the use of various structural reorganizational "shifts" within the molecule. Once the carbocation has shifted over to a different carbon, we can say that there is a structural isomer of the initial molecule. However, this phenomenon is not as simple as it sounds.

Carbocation Rearrangement in the SN1 Reaction

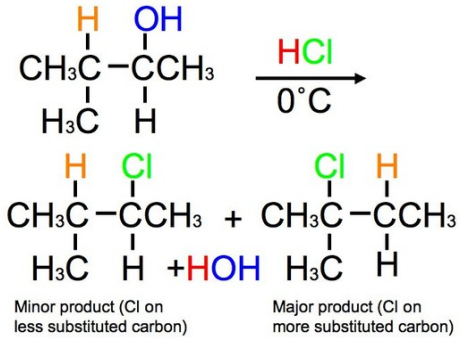
Whenever alcohols are subject to transformation into various carbocations, the carbocations are subject to a phenomenon known as carbocation rearrangement. A carbocation, in brief, holds the positive charge in the molecule that is attached to three other groups and bears a sextet rather than an octet. However, we do see carbocation rearrangements in reactions that do not contain alcohol as well. Those, on the other hand, require more difficult explanations than the two listed below. There are two types of rearrangements: hydride shift and alkyl shift. These rearrangements usualy occur in many types of carbocations. Once rearranged, the molecules can also undergo further unimolecular substitution (S_N1) or unimolecular elimination (E1). Though, most of the time we see either a simple or complex mixture of products. We can expect two products before undergoing carbocation rearrangement, but once undergoing this phenomenon, we see the major product.



Hydride Shift

Whenever a nucleophile attacks some molecules, we typically see *two* products. However, in most cases, we normally see both a major product and a minor product. The major product is typically the rearranged product that is *more substituted* (aka more stable). The minor product, in contract, is typically the normal product that is *less substituted* (aka less stable).

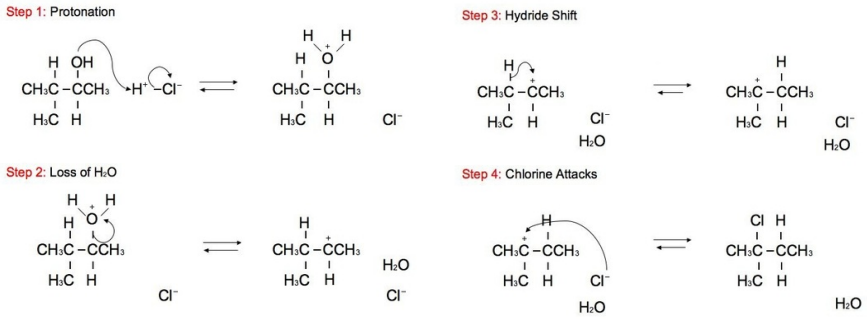
The reaction: We see that the formed carbocations can undergo rearrangements called **hydride shift**. This means that the two electron hydrogen from the unimolecular substitution moves over to the *neighboring* carbon. We see the phenomenon of hydride shift typically with the reaction of an alcohol and hydrogen halides, which include HBr, HCl, and HI. HF is typically not used because of its instability and its fast reactivity rate. Below is an example of a reaction between an alcohol and hydrogen chloride:



GREEN (Cl) = nucleophile **BLUE (OH)** = leaving group **ORANGE (H)** = hydride shift proton **RED(H)** = remaining proton

The alcohol portion (-OH) has been substituted with the nucleophilic Cl atom. However, it is not a direct substitution of the OH atom as seen in S_N2 reactions. In this S_N1 reaction, we see that the leaving group, -OH, forms a carbocation on Carbon #3 after receiving a proton from the nucleophile to produce an alkyloxonium ion. Before the Cl atom attacks, the hydrogen atom attached to the Carbon atom directly adjacent to the original Carbon (preferably the more stable Carbon), Carbon #2, can undergo hydride shift. The hydrogen and the carbocation formally switch positions. The Cl atom can now attack the carbocation, in which it forms the more stable structure because of hyperconjugation. The carbocation, in this case, is most stable because it attaches to the tertiary carbon (being attached to 3 different carbons). However, we can still see small amounts of the minor, unstable product. The

mechanism for hydride shift occurs in *multiple steps* that includes various intermediates and transition states. Below is the mechanism for the given reaction above:



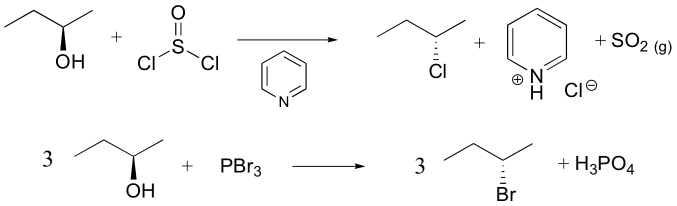
Contributors

- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Jim Clark (Chemguide.co.uk)

9.3: Conversion of Alcohols to Alkyl Halides with SOC l 2 SOCl2 and PB r 3 PBr3

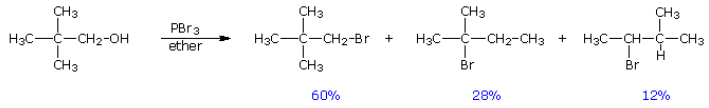
The most common methods for converting 1º- and 2º-alcohols to the corresponding chloro and bromo alkanes (*i.e.* replacement of the hydroxyl group) are treatments with thionyl chloride and phosphorus tribromide, respectively. These reagents are generally preferred over the use of concentrated HX due to the harsh acidity of these hydrohalic acids and the carbocation rearrangements associated with their use.

Synthetic organic chemists, when they want to convert an alcohol into a better leaving group, have several methods to choose from. One common strategy is to convert the alcohol into an alkyl chloride or bromide, using thionyl chloride or phosphorus tribromide:

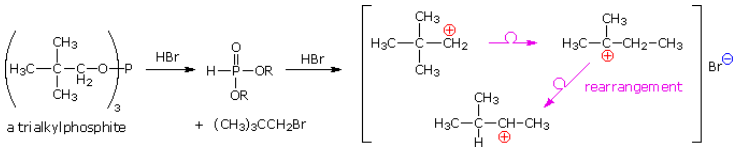


Drawbacks to using PBr_3 and $SOCl_2$

Despite their general usefulness, phosphorous tribromide and thionyl chloride have shortcomings. Hindered 1º- and 2º-alcohols react sluggishly with the former, and may form rearrangement products, as noted in the following equation.



Below, an abbreviated mechanism for the reaction is displayed. The initially formed trialkylphosphite ester may be isolated if the HBr byproduct is scavenged by base. In the presence of HBr a series of acid-base and S_N2 reactions take place, along with the transient formation of carbocation intermediates. Rearrangement (pink arrows) of the carbocations leads to isomeric products.



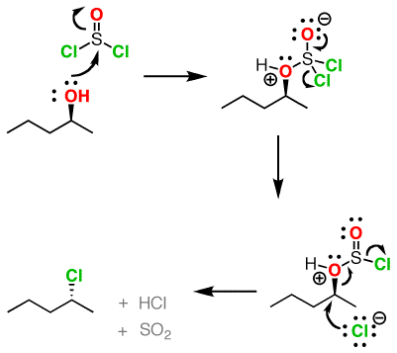
Reaction of thionyl chloride with chiral 2º-alcohols has been observed to proceed with either inversion or retention. In the presence of a base such as pyridine, the intermediate chlorosulfite ester reacts to form an "pyridinium" salt, which undergoes a relatively clean S_N2 reaction to the inverted chloride. In ether and similar solvents the chlorosulfite reacts with retention of configuration, presumably by way of a tight or intimate ion pair. This is classified as an $\mathbf{S_Ni}$ reaction (nucleophilic substitution internal). The carbocation partner in the ion pair may also rearrange. These reactions are illustrated by the following equations. An alternative explanation for the retention of configuration, involving an initial solvent molecule displacement of the chlorosulfite group (as SO_2 and chloride anion), followed by chloride ion displacement of the solvent moiety, has been suggested. In this case, two inversions lead to retention.

Example 1: Conversion of Alcohols to Alkyl Chlorides

There's one important thing to note here: see the stereochemistry? It's been inverted.*(white lie alert – see below) That's an important difference between $SOCl_2$ and TsCl, which leaves the stereochemistry alone. We'll get to the root cause of that in a moment, but in the meantime, can you think of a mechanism which results in inversion of configuration at carbon?

Formation of Alkyl Chlorides

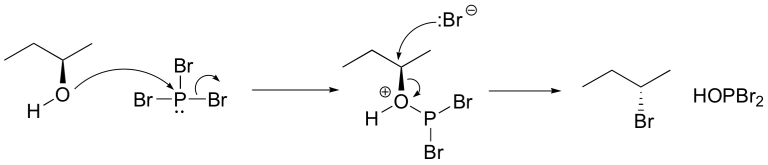
Since the reaction proceeds through a backside attack (S_N2), there is inversion of configuration at the carbon



The mechanism for formation of acid chlorides from carboxylic acids is similar. The conversion of caboxylic acids to acid chlorides is similar, but proceeds through a [1,2]-addition of chloride ion to the carbonyl carbon followed by [1,2]-elimination to give the acid chloride, SO_2 and HCl

Formation of Alkyl Bromides

The PBr_3 reaction is thought to involve two successive S_N2-like steps:



Notice that these reactions result in inversion of stereochemistry in the resulting alkyl halide.

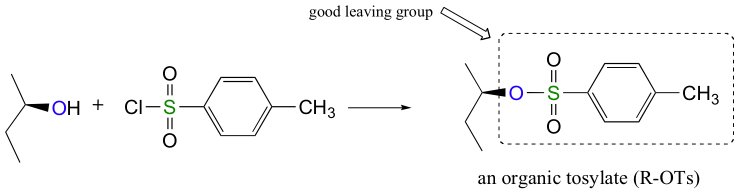
Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

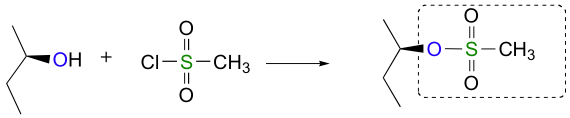
---

9.4: Tosylate—Another Good Leaving Group

Alternatively, we can transform an alcohol group into sulfonic ester using *para*-toluene sulfonyl chloride (Ts-Cl) or methanesulfonyl chloride (Ms-Cl), creating what is termed an organic **tosylate** or **mesylate:**



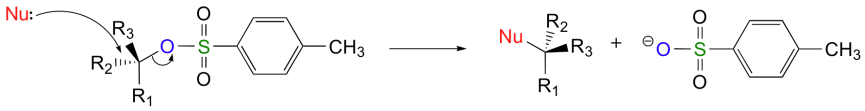
an organic tosylate (R-OTs)



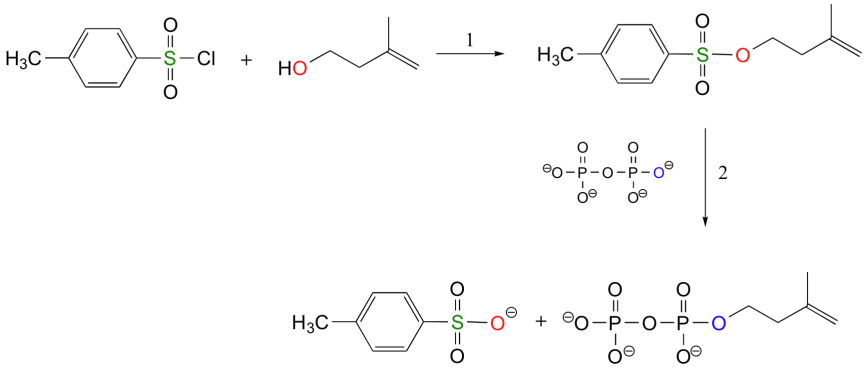
an organic mesylate (R-OMs)

Again, you'll have a chance to work a mechanism for tosylate and mesylate formation in the chapter 12 problems. Notice, though, that unlike the halogenation reactions above, conversion of an alcohol to a tosylate or mesylate proceeds with retention of configuration at the electrophilic carbon.

Chlorides, bromides, and tosylate / mesylate groups are excellent leaving groups in nucleophilic substitution reactions, due to resonance delocalization of the developing negative charge on the leaving oxygen.

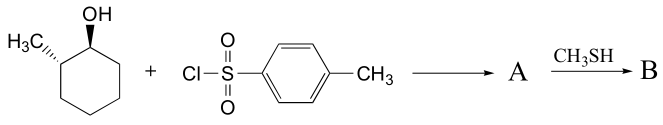


The laboratory synthesis of isopentenyl diphosphate - the 'building block' molecule used by nature for the construction of isoprenoid molecules such as cholesterol and b-carotene - was accomplished by first converting the alcohol into an organic tosylate (step 1), then displacing the tosylate group with an inorganic pyrophosphate nucleophile (step 2) (*J. Org. Chem* **1986**, *51*, 4768).



Example	

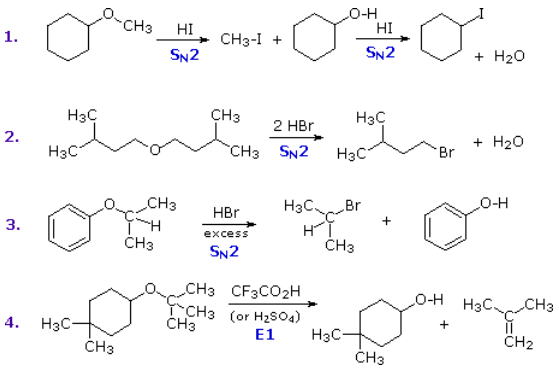
Exercise 8.14: Predict the structures of A and B in the following reaction:



Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

9.5: Reaction of Ethers with Strong Acid

The most common reaction of ethers is cleavage of the C–O bond by strong acids. This may occur by S_N1 or E1 mechanisms for 3º-alkyl groups or by an S_N2 mechanism for 1º-alkyl groups. Some examples are shown in the following diagram. The conjugate acid of the ether is an intermediate in all these reactions, just as conjugate acids were intermediates in certain alcohol reactions.



The first two reactions proceed by a sequence of S_N2 steps in which the iodide or bromide anion displaces an alcohol in the first step, and then converts the conjugate acid of that alcohol to an alkyl halide in the second. Since S_N2 reactions are favored at least hindered sites, the methyl group in example #1 is cleaved first. The 2º-alkyl group in example #3 is probably cleaved by an S_N2 mechanism, but the S_N1 alternative cannot be ruled out. The phenol formed in this reaction does not react further, since S_N2, S_N1 and E1 reactions do not take place on aromatic rings. The last example shows the cleavage of a 3º-alkyl group by a strong acid. Acids having poorly nucleophilic conjugate bases are often chosen for this purpose so that E1 products are favored. The reaction shown here (#4) is the reverse of the tert-butyl ether preparation described earlier.

Contributors

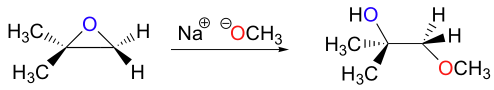
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

9.6: Reactions of Epoxides

Epoxide ring-opening reactions - S_N1 vs. S_N2, regioselectivity, and stereoselectivity

The nonenzymatic ring-opening reactions of epoxides provide a nice overview of many of the concepts we have seen already in this chapter. Ring-opening reactions can proceed by either S_N2 or S_N1 mechanisms, depending on the nature of the epoxide and on the reaction conditions. If the epoxide is asymmetric, the structure of the product will vary according to which mechanism dominates. When an asymmetric epoxide undergoes solvolysis in basic methanol, ring-opening occurs by an S_N2 mechanism, and the *less* substituted carbon is the site of nucleophilic attack, leading to what we will refer to as product B:

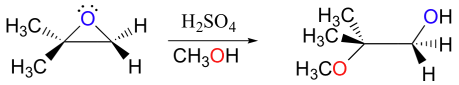
basic ring-opening:



product **B**

Conversely, when solvolysis occurs in acidic methanol, the reaction occurs by a mechanism with substantial S_N1 character, and the *more* substituted carbon is the site of attack. As a result, product A predominates.

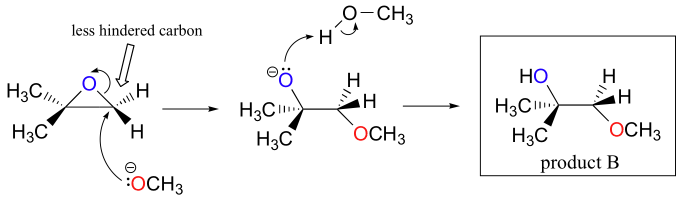
acidic ring-opening:



product **A**

These are both good examples of **regioselective reactions**. In a regioselective reaction, two (or more) different constitutional isomers are possible as products, but one is formed preferentially (or sometimes exclusively).

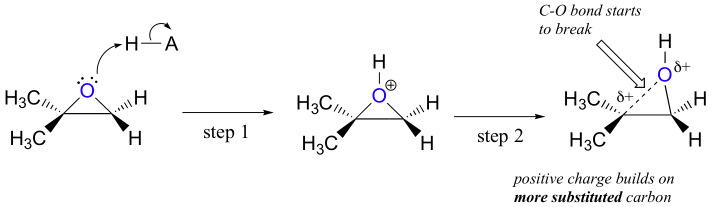
Let us examine the basic, S_N2 case first. The leaving group is an alkoxide anion, because there is no acid available to protonate the oxygen prior to ring opening. An alkoxide is a poor leaving group, and thus the ring is unlikely to open without a 'push' from the nucleophile.



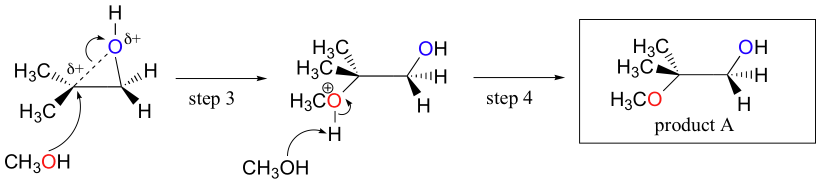
The nucleophile itself is potent: a deprotonated, negatively charged methoxide ion. When a nucleophilic substitution reaction involves a poor leaving group and a powerful nucleophile, it is very likely to proceed by an S_N2 mechanism.

What about the electrophile? There are two electrophilic carbons in the epoxide, but the best target for the nucleophile in an S_N2 reaction is the carbon that is *least hindered*. This accounts for the observed regiochemical outcome. Like in other S_N2 reactions, nucleophilic attack takes place from the backside, resulting in inversion at the electrophilic carbon.

Probably the best way to depict the acid-catalyzed epoxide ring-opening reaction is as a hybrid, or cross, between an S_N2 and S_N1 mechanism. First, the oxygen is protonated, creating a good leaving group (step 1 below) . Then the carbon-oxygen bond begins to break (step 2) and positive charge begins to build up on the more substituted carbon (recall the discussion from section 8.4B about carbocation stability).



Unlike in an S_N1 reaction, the nucleophile attacks the electrophilic carbon (step 3) before a complete carbocation intermediate has a chance to form.



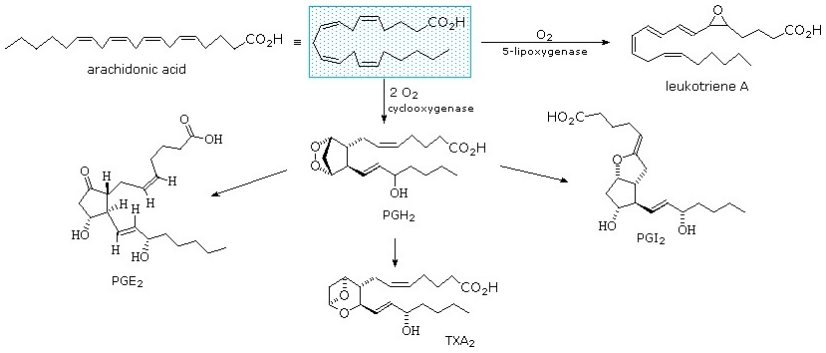
Attack takes place preferentially from the backside (like in an S_N2 reaction) because the carbon-oxygen bond is still to some degree in place, and the oxygen blocks attack from the front side. Notice, however, how the regiochemical outcome is different from the base-catalyzed reaction: in the acid-catalyzed process, the nucleophile attacks the more substituted carbon because it is this carbon that holds a greater degree of positive charge.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

9.7: Application- Epoxides, Leukotrienes, and Asthma

The members of this group of structurally related natural hormones have an extraordinary range of biological effects. They can lower gastric secretions, stimulate uterine contractions, lower blood pressure, influence blood clotting and induce asthma-like allergic responses. Because their genesis in body tissues is tied to the metabolism of the essential fatty acid arachadonic acid (5,8,11,14-eicosatetraenoic acid) they are classified as eicosanoids. Many properties of the common drug aspirin result from its effect on the cascade of reactions associated with these hormones.

The metabolic pathways by which arachidonic acid is converted to the various eicosanoids are complex and will not be discussed here. A rough outline of some of the transformations that take place is provided below. It is helpful to view arachadonic acid in the coiled conformation shown in the shaded box.



Leukotriene A is a precursor to other leukotriene derivatives by epoxide opening reactions. The prostaglandins are given systematic names that reflect their structure. The initially formed peroxide PGH_2 is a common intermediate to other prostaglandins, as well as thromboxanes such as TXA_2.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

9.8: Application- Benzo[a]pyrene, Epoxides, and Cancer

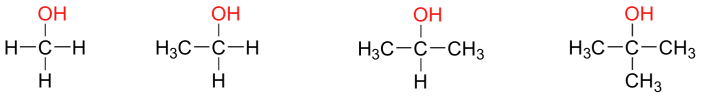
To Your Health: Polycyclic Aromatic Hydrocarbons and Cancer

The intense heating required for distilling coal tar results in the formation of PAHs. For many years, it has been known that workers in coal-tar refineries are susceptible to a type of skin cancer known as tar cancer. Investigations have shown that a number of PAHs are carcinogens. One of the most active carcinogenic compounds, benzopyrene, occurs in coal tar and has also been isolated from cigarette smoke, automobile exhaust gases, and charcoal-broiled steaks. It is estimated that more than 1,000 t of benzopyrene are emitted into the air over the United States each year. Only a few milligrams of benzopyrene per kilogram of body weight are required to induce cancer in experimental animals.

9.9: Introduction

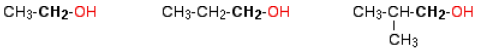
Alcohols

We have already seen the simplest possible example of an **alcohol** functional group in methanol. In the alcohol functional group, a carbon is single-bonded to an OH group (this OH group, by itself, is referred to as a **hydroxyl**). If the central carbon in an alcohol is bonded to only one other carbon, we call the group a primary alcohol. In secondary alcohols and tertiary alcohols, the central carbon is bonded to two and three carbons, respectively. Methanol, of course, is in class by itself in this respect.



Primary alcohols

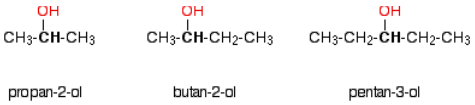
In a primary (1°) alcohol, the carbon atom that carries the -OH group is only attached to one alkyl group. Some examples of primary alcohols are shown below:



Notice that the complexity of the attached alkyl group is irrelevant. In each case there is only one linkage to an alkyl group from the CH_2 group holding the -OH group. There is an exception to this. Methanol, CH_3OH, is counted as a primary alcohol even though there are no alkyl groups attached to the the -OH carbon atom.

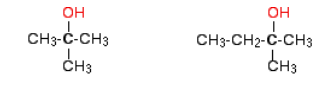
Secondary alcohols

In a secondary (2°) alcohol, the carbon atom with the -OH group attached is joined directly to two alkyl groups, which may be the same or different. Examples include the following:



Tertiary alcohols

In a tertiary (3°) alcohol, the carbon atom holding the -OH group is attached directly to three alkyl groups, which may be any combination of the same or different groups. Examples of tertiary alcohols are given below:



Ethers

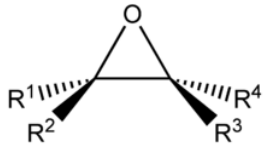
Ethers

Ethers

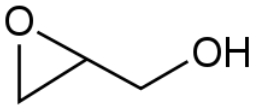
Ethers

Epoxides

An **epoxide** is a cyclic ether with three ring atoms. These rings approximately define an equilateral triangle, which makes it highly strained. The strained ring makes epoxides more reactive than other ethers. Simple epoxides are named from the parent compound ethylene oxide or oxirane, such as in *chloromethyloxirane*. As a functional group, epoxides feature the *epoxy* prefix, such as in the compound *1,2-epoxycycloheptane*, which can also be called *cycloheptene epoxide*, or simply *cycloheptene oxide*.



A generic epoxide.



The chemical structure of the epoxide glycidol, a common chemical intermediate

A polymer formed by reacting epoxide units is called a *polyepoxide* or an *epoxy*. Epoxy resins are used as adhesives and structural materials. Polymerization of an epoxide gives a polyether, for example ethylene oxide polymerizes to give polyethylene glycol, also known as polyethylene oxide.

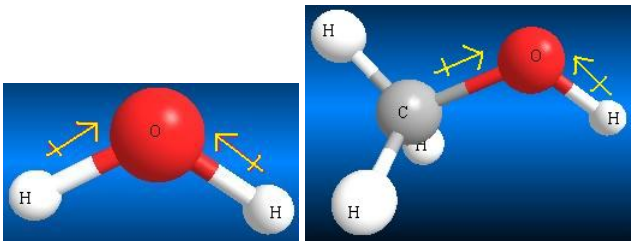
Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- Jim Clark (Chemguide.co.uk)

9.10: Structure and Bonding

Structure of Alcohols

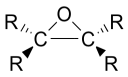
The structure of an alcohol resembles that of water. With both alcohol and water, the bond angles reflect the effect of electron repulsion and increasing steric bulk of the substituents on the central oxygen atom. The electronegativity of oxygen contributes to the unsymmetrical distribution of charge, creating a partial positive charge on hydrogen and a partial negative charge on oxygen. This uneven distribution of electron density in the O-H bond creates a dipole. In addition, because of the high electronegativity of oxygen relative to that of carbon, the O-H bond is shorter (1.41 Å for C-O vs. 1.51 Å for C-C) and stronger ($\Delta H^o_{O\text{-}H}$ = 104 kcal mol^{-1} for C-O vs. $\Delta H^o_{C\text{-}H}$ = 98 kcal mol^{-1} for C-C).



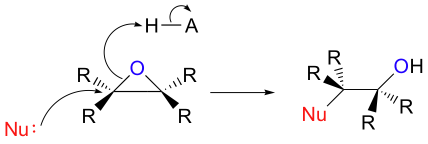
Water Methanol

Structure of Epoxides

Structure of Epoxides



The carbons in an epoxide group are very reactive electrophiles, due in large part to the fact that substantial ring strain is relieved when the ring opens upon nucleophilic attack.



Structure of Ethers

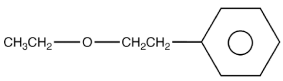
Ethers are a class of organic compounds that contain an oxygen between two alkyl groups. They have the formula R-O-R', with R's being the alkyl groups. these compounds are used in dye, perfumes, oils, waxes and industrial use. Ethers are named as alkoxyalkanes.

An aliphatic ether is an ether in the molecule of which there are no aryl groups on the ether group.

eg:

An ether molecule may contain aryl groups, nevertheless, be an aliphatic ether.

eg:



Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- Jaspreet Dheri
- Gamini Gunawardena from the OChemPal site (Utah Valley University)

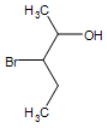
9.11: Nomenclature

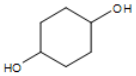
Naming Alcohols

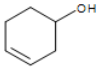
1. Find the longest chain containing the hydroxy group (OH). If there is a chain with more carbons than the one containing the OH group it will be named as a subsitutent.
2. Place the OH on the lowest possible number for the chain. With the exception of carbonyl groups such as ketones and aldehydes, the alcohol or hydroxy groups have first priority for naming.
3. When naming a cyclic structure, the -OH is assumed to be on the first carbon unless the carbonyl group is present, in which case the later will get priority at the first carbon.
4. When multiple -OH groups are on the cyclic structure, number the carbons on which the -OH groups reside.
5. Remove the final **e** from the parent alkane chain and add **-ol**. When multiple alcohols are present use **di, tri,** et.c before the **ol,** after the parent name. ex. 2,3-hexan**diol.** If a carbonyl group is present, the -OH group is named with the prefix "hydroxy," with the carbonyl group attached to the parent chain name so that it ends with **-al** or **-one.**

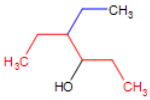
Ethan**e**: CH_3CH_3 ----->Ethan**ol**:  (the alcohol found in beer, wine and other consumed sprits)

Secondary alcohol:  2-propanol

Other functional groups on an alcohol:  3-bromo-2-pentanol

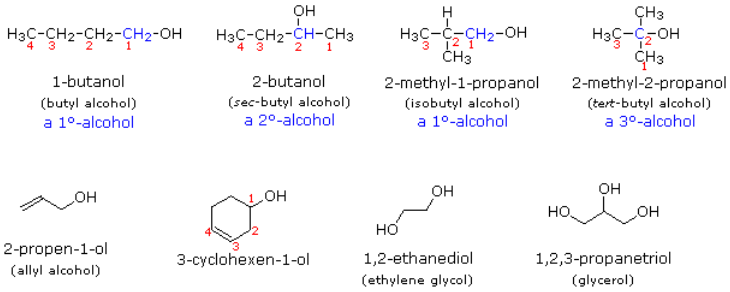
Cyclic alcohol (two -OH groups):  cyclohexan-1,4-diol

Other functional group on the cyclic structure:  3-hex**ene**ol (the alkene is in **bold** and indicated by numbering the carbon closest to the alcohol)

A complex alcohol:  4-ethyl-3hexanol (the parent chain is in red and the substituent is in blue)

In the IUPAC system of nomenclature, functional groups are normally designated in one of two ways. The presence of the function may be indicated by a characteristic suffix and a location number. This is common for the carbon-carbon double and triple bonds which have the respective suffixes **-ene** and **-yne**. Halogens, on the other hand, do not have a suffix and are named as substituents, for example: $(CH_3)_2C{=}CHCHClCH_3$ is 4-chloro-2-methyl-2-pentene.

Alcohols are usually named by the first procedure and are designated by an **-ol** suffix, as in ethanol, CH_3CH_2OH (note that a locator number is unnecessary on a two-carbon chain). On longer chains the location of the hydroxyl group determines chain numbering. For example: $(CH_3)_2C{=}CHCH(OH)CH_3$ is 4-methyl-3-penten-2-ol. Other examples of IUPAC nomenclature are shown below, together with the common names often used for some of the simpler compounds. For the mono-functional alcohols, this common system consists of naming the **alkyl group** followed by the word **alcohol**. Alcohols may also be classified as primary, **1º**, secondary, **2º**, and tertiary, **3º**, in the same manner as alkyl halides. This terminology refers to alkyl substitution of the carbon atom bearing the hydroxyl group (colored blue in the illustration).



Many functional groups have a characteristic suffix designator, and only one such suffix (other than "-ene" and "-yne") may be used in a name. When the hydroxyl functional group is present together with a function of higher nomenclature priority, it must be cited and located by the prefix **hydroxy** and an appropriate number. For example, lactic acid has the IUPAC name 2-hydroxypropanoic acid.

Naming Ethers

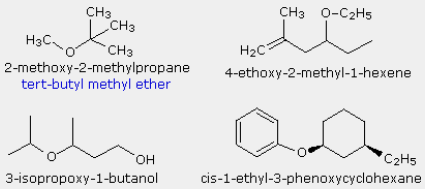
Ethers are compounds having two alkyl or aryl groups bonded to an oxygen atom, as in the formula R^1–O–R^2. The ether functional group does not have a characteristic IUPAC nomenclature suffix, so it is necessary to designate it as a substituent. To do so the common alkoxy substituents are given names derived from their alkyl component (below):

Alkyl Group	Name		Alkoxy Group	Name
CH_3–	Methyl		CH_3O–	Methoxy
CH_3CH_2–	Ethyl		CH_3CH_2O–	Ethoxy
$(CH_3)_2CH$–	Isopropyl		$(CH_3)_2CHO$–	Isopropoxy
$(CH_3)_3C$–	tert-Butyl		$(CH_3)_3CO$–	tert-Butoxy
C_6H_5–	Phenyl		C_6H_5O–	Phenoxy

The smaller, shorter alkyl group becomes the alkoxy substituent. The larger, longer alkyl group side becomes the alkane base name. Each alkyl group on each side of the oxygen is numbered separately. The numbering priority is given to the carbon closest to the oxgen. The alkoxy side (shorter side) has an "-oxy" ending with its corresponding alkyl group. For example, $CH_3CH_2CH_2CH_2CH_2$-O-$CH_2CH_2CH_3$ is 1-propoxypentane. If there is cis or trans stereochemistry, the same rule still applies.

Example

Examples are: $CH_3CH_2OCH_2CH_3$, diethyl ether (sometimes referred to as ether), and $CH_3OCH_2CH_2OCH_3$, ethylene glycol dimethyl ether (glyme).



Common names

Simple ethers are given common names in which the alkyl groups bonded to the oxygen are named in alphabetical order followed by the word "ether". The top left example shows the common name in blue under the IUPAC name. Many simple ethers are symmetrical, in that the two alkyl substituents are the same. These are named as "dialkyl ethers".

Heterocycles

In cyclic ethers (heterocycles), one or more carbons are replaced with oxygen. Often, it's called heteroatoms, when carbon is replaced by an oxygen or any atom other than carbon or hydrogen. In this case, the stem is called the oxacycloalkane, where the prefix "oxa-" is an indicator of the replacement of the carbon by an oxygen in the ring. These compounds are numbered starting at the oxygen and continues around the ring. For example,

1,4-dioxacyclohexane

1-oxacyclopentane

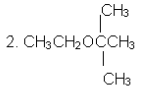
If a substituent is an alcohol, the alcohol has higher priority. However, if a substituent is a halide, ether has higher priority. If there is both an alcohol group and a halide, alcohol has higher priority. The numbering begins with the end that is closest to the higher priority substituent. There are ethers that are contain multiple ether groups that are called cyclic polyethers or crown ethers. These are also named using the IUPAC system.

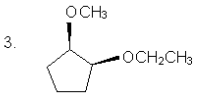
hyl sulphide. Sulphides are chemically more reactive than ethers, reflecting the greater nucleophilicity of sulfur relative to oxygen.

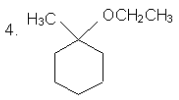
Problems

Name the following ethers:

1. $CH_3CH_2OCH_2CH_3$



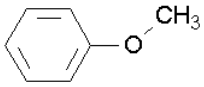




(Answers to problems above: 1. diethyl ether; 2. 2-ethoxy-2-methyl-1-propane; 3. cis-1-ethoxy-2-methoxycyclopentane; 4. 1-ethoxy-1-methylcyclohexane; 5. oxacyclopropane; 6. 2,2-Dimethyloxacyclopropane)

Common names of some ethers

anisole (try naming anisole by the other two conventions. J)



oxirane

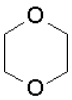
1,2-epoxyethane, ethylene oxide, dimethylene oxide, oxacyclopropane,

furan (this compound is aromatic)

tetrahydrofuran

oxacyclopentane, 1,4-epoxybutane, tetramethylene oxide,

dioxane



1,4-dioxacyclohexane

Contributors

- Abhiram Kondajji (UCD)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

9.12: Physical Properties

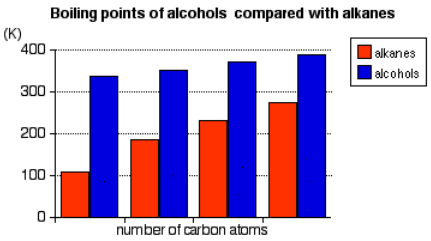
Physical properties of alcohols

Boiling Points

The chart below shows the boiling points of the following simple primary alcohols with up to 4 carbon atoms:

CH_3OH	CH_3CH_2OH	$CH_3CH_2CH_2OH$	$CH_3CH_2CH_2CH_2OH$
methanol	ethanol	propan-1-ol	butan-1-ol

These boiling points are compared with those of the equivalent alkanes (methane to butane) with the same number of carbon atoms.



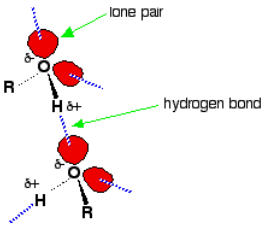
Notice that:

- The boiling point of an alcohol is always significantly higher than that of the analogous alkane.
- The boiling points of the alcohols increase as the number of carbon atoms increases.

The patterns in boiling point reflect the patterns in intermolecular attractions.

Hydrogen bonding

Hydrogen bonding occurs between molecules in which a hydrogen atom is attached to a strongly electronegative element: fluorine, oxygen or nitrogen. In the case of alcohols, hydrogen bonds occur between the partially-positive hydrogen atoms and lone pairs on oxygen atoms of other molecules.



The hydrogen atoms are slightly positive because the bonding electrons are pulled toward the very electronegative oxygen atoms. In alkanes, the only intermolecular forces are van der Waals dispersion forces. Hydrogen bonds are much stronger than these, and therefore it takes more energy to separate alcohol molecules than it does to separate alkane molecules. This the main reason for higher boiling points in alcohols.

The effect of van der Waals forces

- **Boiling points of the alcohols**: Hydrogen bonding is not the only intermolecular force alcohols experience. There are also van der Waals dispersion forces and dipole-dipole interactions. The hydrogen bonding and dipole-dipole interactions are much the same for all alcohols, but dispersion forces increase as the alcohols get bigger. These attractions get stronger as the molecules get longer and have more electrons. This increases the sizes of the temporary dipoles formed. This is why the boiling points increase as the number of carbon atoms in the chains increases. It takes more energy to overcome the dispersion forces, and thus the boiling points rise.
- **Comparison between alkanes and alcohols**: Even without any hydrogen bonding or dipole-dipole interactions, the boiling point of the alcohol would be higher than the corresponding alkane with the same number of carbon atoms.

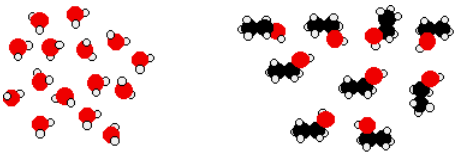
Compare ethane and ethanol:

Ethanol is a longer molecule, and the oxygen atom brings with it an extra 8 electrons. Both of these increase the size of the van der Waals dispersion forces, and subsequently the boiling point. A more accurate measurement of the effect of the hydrogen bonding on boiling point would be a comparison of ethanol with propane rather than ethane. The lengths of the two molecules are more similar, and the number of electrons is exactly the same.

Solubility of alcohols in water

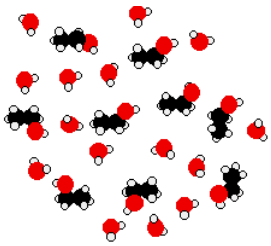
Small alcohols are completely soluble in water; mixing the two in any proportion generates a single solution. However, solubility decreases as the length of the hydrocarbon chain in the alcohol increases. At four carbon atoms and beyond, the decrease in solubility is noticeable; a two-layered substance may appear in a test tube when the two are mixed.

Consider ethanol as a typical small alcohol. In both pure water and pure ethanol the main intermolecular attractions are hydrogen bonds.



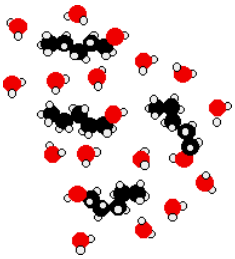
Both of these are held together mainly by hydrogen bonding.

In order to mix the two, the hydrogen bonds between water molecules and the hydrogen bonds between ethanol molecules must be broken. Energy is required for both of these processes. However, when the molecules are mixed, new hydrogen bonds are formed between water molecules and ethanol molecules.



New hydrogen bonds are set up between ethanol and water molecules.

The energy released when these new hydrogen bonds form approximately compensates for the energy needed to break the original interactions. In addition, there is an increase in the disorder of the system, an increase in entropy. This is another factor in deciding whether chemical processes occur. Consider a hypothetical situation involving 5-carbon alcohol molecules.



The hydrocarbon chains are forced between water molecules, breaking hydrogen bonds between those water molecules. The -OH ends of the alcohol molecules can form new hydrogen bonds with water molecules, but the hydrocarbon "tail" does not form hydrogen bonds. This means that many of the original hydrogen bonds being broken are never replaced by new ones.

In place of those original hydrogen bonds are merely van der Waals dispersion forces between the water and the hydrocarbon "tails." These attractions are much weaker, and unable to furnish enough energy to compensate for the broken hydrogen bonds. Even allowing for the increase in disorder, the process becomes less feasible. As the length of the alcohol increases, this situation becomes more pronounced, and thus the solubility decreases.

Comparisons of Alcohols and Ethers

Comparisons of Alcohols and Ethers

Table 14.4 Comparison of Boiling Points of Alkanes, Alcohols, and Ethers

Condensed Structural Formula	Name	Molar Mass	Boiling Point (°C)	Intermolecular Hydrogen Bonding in Pure Liquid?
$CH_3CH_2CH_3$	propane	44	–42	no
CH_3OCH_3	dimethyl ether	46	–25	no
CH_3CH_2OH	ethyl alcohol	46	78	yes
$CH_3CH_2CH_2CH_2CH_3$	pentane	72	36	no
$CH_3CH_2OCH_2CH_3$	diethyl ether	74	35	no
$CH_3CH_2CH_2CH_2OH$	butyl alcohol	74	117	yes

Comparisons of Alcohols and Ethers

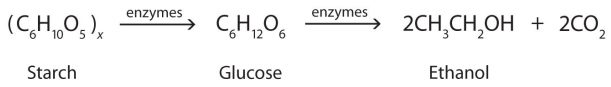
Contributors

- Jim Clark (Chemguide.co.uk)

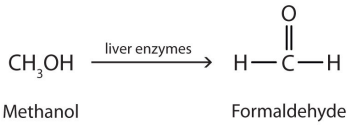
9.13: Interesting Alcohols, Ethers, and Epoxides

Alcohols Produced by Fermentation

In addition to its preparation from ethylene, ethanol is made by the fermentation of sugars or starch from various sources (potatoes, corn, wheat, rice, etc.). Fermentation is catalyzed by enzymes found in yeast and proceeds by an elaborate multistep mechanism. We can represent the overall process as follows:



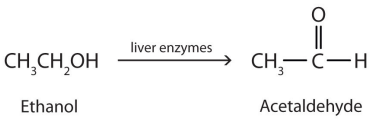
Methanol is quite poisonous to humans. Ingestion of as little as 15 mL of methanol can cause blindness, and 30 mL (1 oz) can cause death. However, the usual fatal dose is 100 to 150 mL. The main reason for methanol's toxicity is that we have liver enzymes that catalyze its oxidation to formaldehyde, the simplest member of the aldehyde family:



Formaldehyde reacts rapidly with the components of cells, coagulating proteins in much the same way that cooking coagulates an egg. This property of formaldehyde accounts for much of the toxicity of methanol.

> **Note**
>
> Organic and biochemical equations are frequently written showing only the organic reactants and products. In this way, we focus attention on the organic starting material and product, rather than on balancing complicated equations.

Alcohols Produced by Fermentation



Alcohols Produced by Fermentation

Alcohols Produced by Fermentation

Ethylene Glycol

Polyhydric alcohols in which the hydroxyl groups are situated on different carbons are relatively stable, and, as we might expect for substances with multiple polar groups, they have high boiling points and considerable water solubility, but low solubility in nonpolar solvents:

1,2-Diols are prepared from alkenes by oxidation with reagents such as osmium tetroxide, potassium permanganate, or hydrogen peroxide. However, ethylene glycol is made on a commercial scale from oxacyclopropane, which in turn is made by air oxidation of ethene at high temperatures over a silver oxide catalyst.

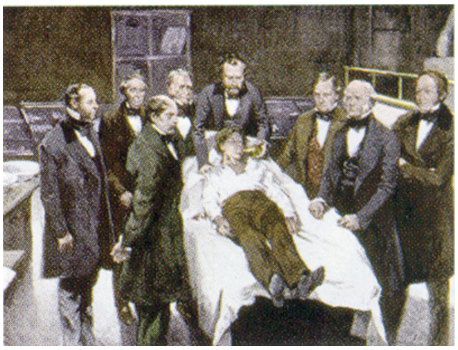
Ethylene glycol has important commercial uses. It is an excellent permanent antifreeze for automotive cooling systems because it is miscible with water in all proportions and a 50% solution freezes at —34° (—29°F). It also is used as a solvent and as an intermediate in the production of polymers (polyesters) and other products.

Ethylene oxide

The most important and simplest epoxide is ethylene oxide which is prepared on an industrial scale by catalytic oxidation of ethylene by air.

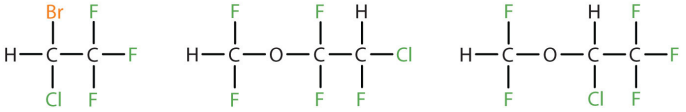
Ethers as General Anesthetics

A *general anesthetic* acts on the brain to produce unconsciousness and a general insensitivity to feeling or pain. Diethyl ether ($CH_3CH_2OCH_2CH_3$) was the first general anesthetic to be used.



William Morton, a Boston dentist, introduced diethyl ether into surgical practice in 1846. This painting shows an operation in Boston in 1846 in which diethyl ether was used as an anesthetic. Inhalation of ether vapor produces unconsciousness by depressing the activity of the central nervous system. Source: Painting of William Morton by Ernest Board, from http://commons.wikimedia.org/wiki/Fi...Ether_1846.jpg.

Diethyl ether is relatively safe because there is a fairly wide gap between the dose that produces an effective level of anesthesia and the lethal dose. However, because it is highly flammable and has the added disadvantage of causing nausea, it has been replaced by newer inhalant anesthetics, including the fluorine-containing compounds halothane, enflurane, and isoflurane. Unfortunately, the safety of these compounds for operating room personnel has been questioned. For example, female operating room workers exposed to halothane suffer a higher rate of miscarriages than women in the general population.



These three modern, inhalant, halogen-containing, anesthetic compounds are less flammable than diethyl ether.

Crown Ethers

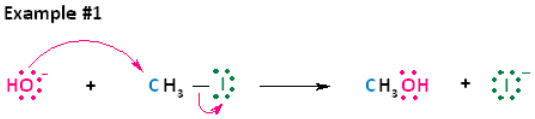
Ethers as General Anesthetics

Ethers as General Anesthetics
Ethers as General Anesthetics

9.14: Preparation of Alcohols, Ethers, and Epoxides

Alcohols are prepared by S_N2 reaction

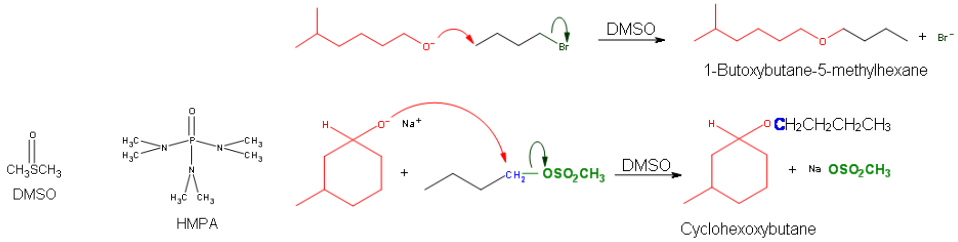
Alkyl halides can be converted to alcohols by using S_N2 reactions with OH^- as a nucleophile. Substrates that undergo substitution by SN1 reaction can be converted to alcohols using water as the nucleophile (and it can even be the solvent). Recall that S_N1 reactions are promoted in polar, protic solvents.



Ethers are prepared by S_N2 reaction

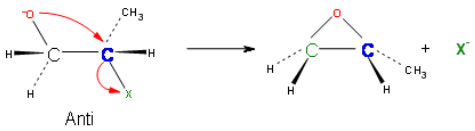
Williamson Ether Reactions involve an alkoxide that reacts with a primary haloalkane or a sulfonate ester. Alkoxides consist of the conjugate base of an alcohol and are comprised of an R group bonded to an oxygen atom. They are written as $RO^–$, where R is the organic substituent.

Ethers can be synthesized in standard S_N2 conditions by coupling an alkoxide with a haloalkane/sulfonate ester. The alcohol that supplies the electron rich alkoxide can be used as the solvent, as well as dimethyl sulfoxide (DMSO) or hexamethylphosphoric triamide (HMPA).



Epoxides are prepared by an SN2

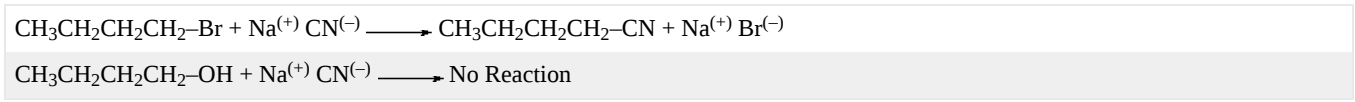
S_n2 reactions are characterized by the *inversion* of stereochemistry at the site of the leaving group. Williamson Ether synthesis is not an exception to this rule and the reaction is set in motion by the backside attack of the nucleophile. This requires that the nucleophile and the electrophile are in anti-configuration.



9.15: General Features—Reactions of Alcohols, Ethers, and Epoxides

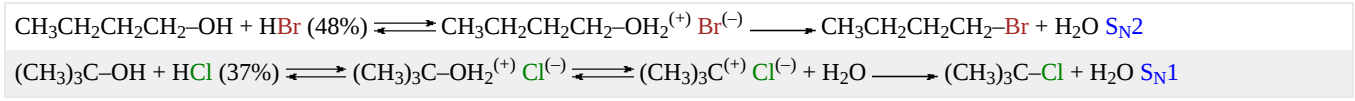
Alcohols as a leaving group

Despite this promising background evidence, alcohols do not undergo the same S_N2 reactions commonly observed with alkyl halides. For example, the rapid S_N2 reaction of 1-bromobutane with sodium cyanide, shown below, has no parallel when 1-butanol is treated with sodium cyanide. In fact, ethyl alcohol is often used as a solvent for alkyl halide substitution reactions such as this.

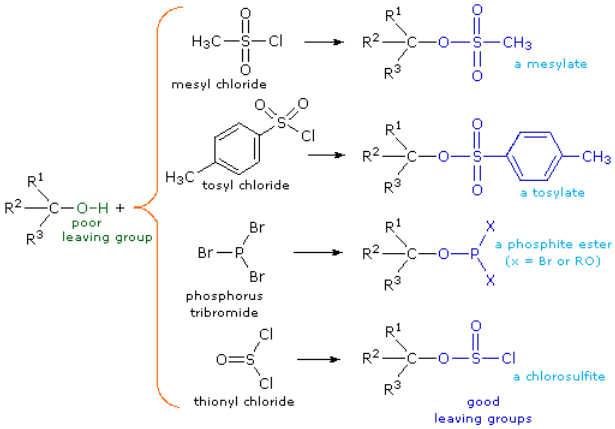


The key factor here is the stability of the leaving anion (bromide vs. hydroxide). HBr is a much stronger acid than water (by more than 18 orders of magnitude), and this difference is reflected in reactions that generate their respective conjugate bases. The weaker base, bromide, is more stable, and its release in a substitution or elimination reaction is much more favorable than that of hydroxide ion, a stronger and less stable base.

A clear step toward improving the reactivity of alcohols in S_N2 reactions would be to modify the –OH functional group in a way that improves its stability as a leaving anion. One such modification is to conduct the substitution reaction in strong acid, converting –OH to $–OH_2^{(+)}$. Because the hydronium ion ($H_3O^{(+)}$) is a much stronger acid than water, its conjugate base (H_2O) is a better leaving group than hydroxide ion. The only problem with this strategy is that many nucleophiles, including cyanide, are deactivated by protonation in strong acid, effectively removing the nucleophilic co-reactant needed for the substitution. The strong acids HCl, HBr and HI are not subject to this difficulty because their conjugate bases are good nucleophiles and are even weaker bases than alcohols. The following equations illustrate some substitution reactions of alcohols that may be effected by these acids. As with alkyl halides, the nucleophilic substitution of 1º-alcohols proceeds by an S_N2 mechanism, whereas 3º-alcohols react by an S_N1 mechanism. Reactions of 2º-alcohols may occur by both mechanisms and often produce some rearranged products. The numbers in parentheses next to the mineral acid formulas represent the weight percentage of a concentrated aqueous solution, the form in which these acids are normally used.

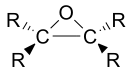


Although these reactions are sometimes referred to as "acid-catalyzed," this is not strictly correct. In the overall transformation a strong HX acid is converted to water, a very weak acid, so at least a stoichiometric quantity of HX is required for a complete conversion of alcohol to alkyl halide. The necessity of using equivalent quantities of very strong acids in this reaction limits its usefulness to simple alcohols of the type shown above. Alcohols with acid sensitive groups do not, of course, tolerate such treatment. Nevertheless, the idea of modifying the -OH functional group to improve its stability as a leaving anion can be pursued in other directions. The following diagram shows some modifications that have proven effective. In each case the hydroxyl group is converted to an ester of a strong acid. The first two examples show the sulfonate esters described earlier. The third and fourth examples show the formation of a phosphite ester (X represents remaining bromines or additional alcohol substituents) and a chlorosulfite ester respectively. All of these leaving groups (colored blue) have conjugate acids that are much stronger than water (by 13 to 16 powers of ten) so the leaving anion is correspondingly more stable than hydroxide ion. The mesylate and tosylate compounds are particularly useful in that they may be used in substitution reactions with a wide variety of nucleophiles. The intermediates produced in reactions of alcohols with phosphorus tribromide and thionyl chloride (last two examples) are seldom isolated, and these reactions continue on to alkyl bromide and chloride products.

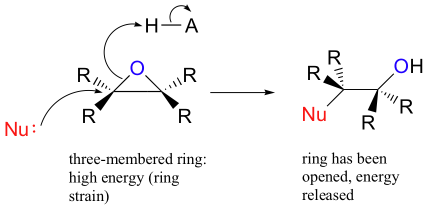


Epoxides as a "Leaving Group"

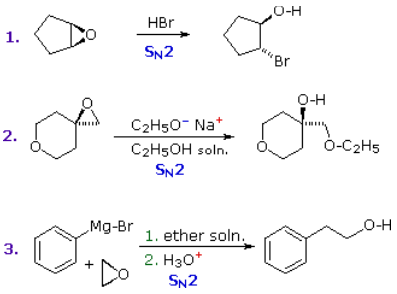
Epoxides (oxiranes) are three-membered cyclic ethers that are easily prepared from alkenes by reaction with peracids. Because of the large angle strain in this small ring, epoxides undergo acid and base-catalyzed C–O bond cleavage more easily than do larger ring ethers. Among the following examples, the first is unexceptional except for the fact that it occurs under milder conditions and more rapidly than other ether cleavages. The second and third examples clearly show the exceptional reactivity of epoxides, since unstrained ethers present in the same reactant or as solvent do not react. The aqueous acid used to work up the third reaction, following the Grignard reagent cleavage of the ethylene oxide, simply neutralizes the magnesium salt of the alcohol product.



The carbons in an epoxide group are very reactive electrophiles, due in large part to the fact that substantial ring strain is relieved when the ring opens upon nucleophilic attack.



Examples



Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

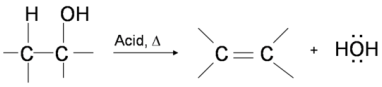
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

9.16: Dehydration of Alcohols to Alkenes

One way to synthesize alkenes is by dehydration of alcohols, a process in which alcohols undergo E1 or E2 mechanisms to lose water and form a double bond.

Introduction

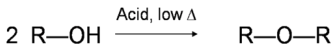
The dehydration reaction of alcohols to generate alkene proceeds by heating the alcohols in the presence of a strong acid, such as sulfuric or phosphoric acid, at high temperatures.



The required range of reaction temperature decreases with increasing substitution of the hydroxy-containing carbon:

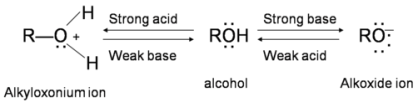
- 1° alcohols: 170° - 180°C
- 2° alcohols: 100°– 140 °C
- 3° alcohols: 25°– 80°C

If the reaction is not sufficiently heated, the alcohols do not dehydrate to form alkenes, but react with one another to form ethers (e.g., the Williamson Ether Synthesis).



Alcohol as a Base

Alcohols are amphoteric; they can act both as acid or base. The lone pair of electrons on oxygen atom makes the –OH group weakly basic. Oxygen can donate two electrons to an electron-deficient proton. Thus, in the presence of a strong acid, R—OH acts as a base and protonates into the very acidic alkyloxonium ion $^{+}OH_2$ (The pKa value of a tertiary protonated alcohol can go as low as -3.8). This basic characteristic of alcohol is essential for its dehydration reaction with an acid to form alkenes.



Mechanism for the Dehydration of Alcohol into Alkene

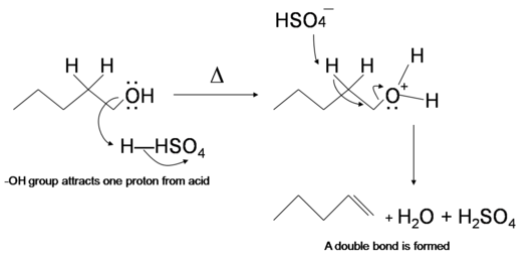
Different types of alcohols may dehydrate through a slightly different mechanism pathway. However, the general idea behind each dehydration reaction is that the –OH group in the alcohol donates two electrons to H^+ from the acid reagent, forming an alkyloxonium ion. This ion acts as a very good leaving group which leaves to form a carbocation. The deprotonated acid (the nucleophile) then attacks the hydrogen adjacent to the carbocation and form a double bond.

Primary alcohols undergo bimolecular elimination (E2 mechanism) while secondary and tertiary alcohols undergo unimolecular elimination (E1 mechanism). The relative reactivity of alcohols in dehydration reaction is ranked as the following

Methanol < primary < secondary < tertiary

Primary alcohol dehydrates through the E2 mechanism

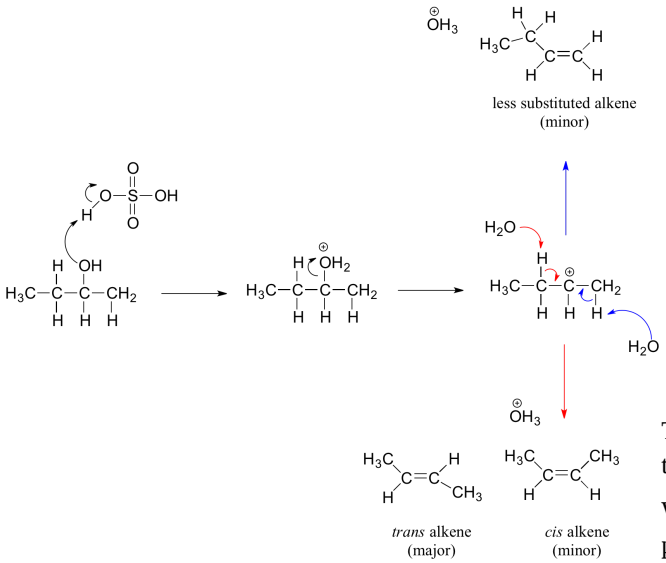
Oxygen donates two electrons to a proton from sulfuric acid H_2SO_4, forming an alkyloxonium ion. Then the nucleophile HSO_4^- back-side attacks one adjacent hydrogen and the alkyloxonium ion leaves in a concerted process, making a double bond.



Secondary and tertiary alcohols dehydrate through the E1 mechanism

Similarly to the reaction above, secondary and tertiary –OH protonate to form alkyloxonium ions. However, in this case the ion leaves first and forms a carbocation as the reaction intermediate. The water molecule (which is a stronger base than the HSO_4^- ion) then abstracts a proton from an adjacent carbon, forming a double bond. Notice in the mechanism below that the aleke formed depends on which proton is abstracted: the red arrows show formation of the more substituted 2-butene, while the blue arrows show formation of the less substituted 1-butene. Recall the general rule that more substituted alkenes are more stable than less substituted alkenes, and *trans* alkenes are more stable than *cis* alkenes. Thereore, the *trans* diastereomer of the 2-butene product is most abundant.

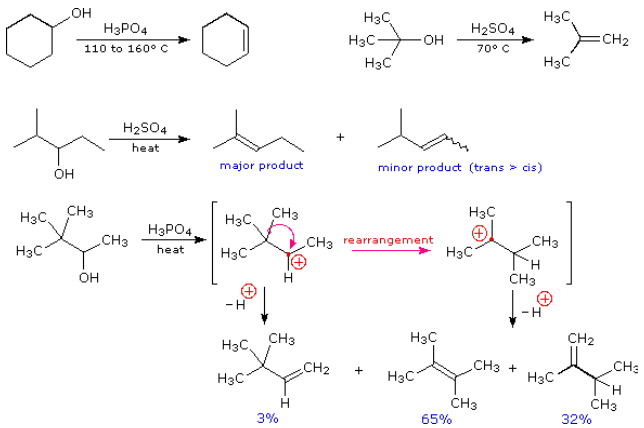
Dehydration reaction of secondary alcohol



The dehydration mechanism for a tertiary alcohol is analogous to that shown above for a secondary alcohol.

When more than one alkene product are possible, the favored product is usually the thermodynamically most stable alkene. More-substituted alkenes are favored over less-substituted ones; and trans-substituted alkenes are preferred compared to cis-substituted ones.

1. Since the C=C bond is not free to rotate, cis-substituted alkenes are less stable than trans-subsituted alkenes because of steric hindrance (spatial interfererence) between two bulky substituents on the same side of the double bond (as seen in the cis product in the above figure). Trans-substituted alkenes reduce this effect of spatial interference by separating the two bulky substituents on each side of the double bond (for further explanation on the rigidity of C=C bond, see Structure and Bonding in Ethene- The pi Bond).
2. Heats of hydrogenation of differently-substituted alkene isomers are lowest for more-substituted alkenes, suggesting that they are more stable than less-substituted alkenes and thus are the major products in an elimination reaction. This is partly because in more --substituted alkenes, the p orbitals of the pi bond are stabilized by neighboring alkyl substituents, a phenomenon similar to hyperconjugation (see also Catalytic Hydrogenation of Alkenes: Relative Stabilities of Double Bond).
3.



Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

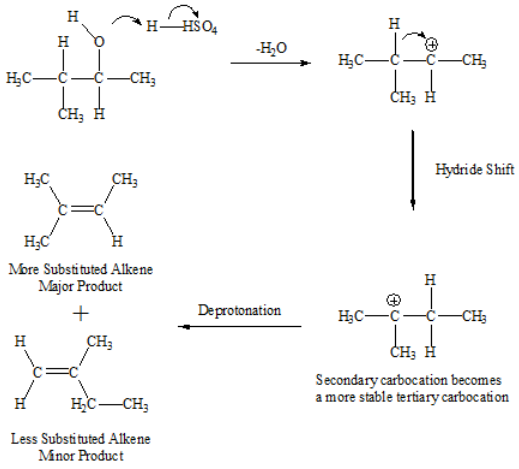
- Thuy Hoang
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)

9.17: Carbocation Rearrangements

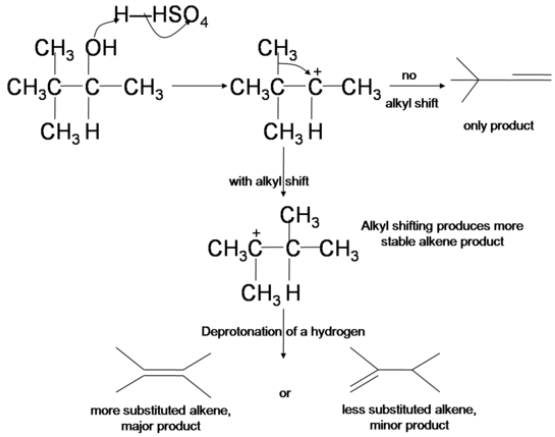
Hydride and Alkyl Shifts

Since the dehydration reaction of alcohol has a carbocation intermediate, hydride or alkyl shifts can occur which relocates the carbocation to a more stable position. The dehydrated products therefore are a mixture of alkenes, with and without carbocation rearrangement. Tertiary cation is more stable than secondary cation, which in turn is more stable than primary cation due to a phenomenon known as hyperconjugation, where the interaction between the filled orbitals of neighboring carbons and the singly occupied p orbital in the carbocation stabilizes the positive charge in carbocation.

- In hydride shifts, a secondary or tertiary hydrogen from a carbon next to the original carbocation takes both of its electrons to the cation site, swapping place with the carbocation and renders it a more stable secondary or tertiary cation.



Similarly, when there is no hydride available for hydride shifting, an alkyl group can take its bonding electrons and swap place with an adjacent cation, a process known as alkyl shift.



Consider the major product of the addition of HCl to 3,3-dimethyl-1-butene:

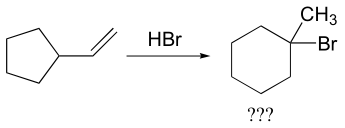
This may not be the result that you would have predicted, based on what we have learned so far about electrophilic additions! Most likely, you would at first predict that the sole product of the reaction would be the first one shown above, 3-chloro-2,2-

dimethylbutane. Why does the second product (2-chloro-2,3-dimethylbutane) form also?

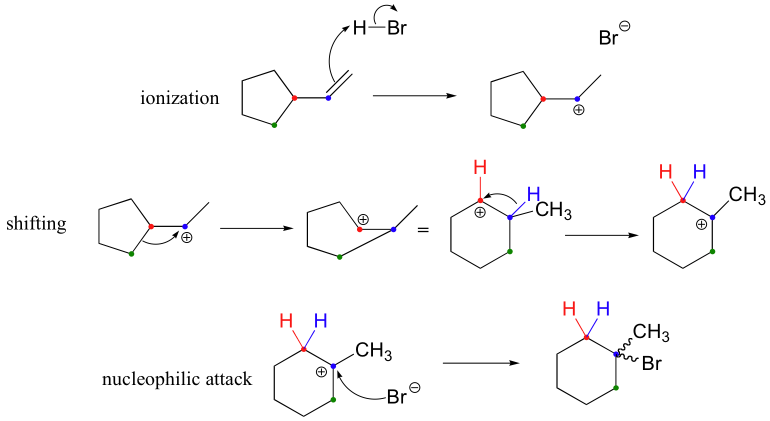
The answer lies in the observation that formation of carbocations is sometimes accompanied by a structural rearrangement. Such rearrangements take place by a shift of a neighboring alkyl group or hydrogen, and are favored *when the rearranged carbocation is more stable than the initial carbocation.* As you can see in the mechanism below, this holds true in the case of the 3,3-dimethyl-1-butene addition, and explains why the 2-chloro product is actaully the *major* product: more of it forms than the minor 3-chloro product.

Protonation of the alkene leads to a secondary carbocation, but a methyl shift to a lower-energy tertiary carbocation occurs faster than nucleophilic attack by chlorine, so that when chlorine does attack it does so at carbon #3, rather than carbon #2.

In most examples of carbocation rearrangements that you are likely to encounter, the shifting species is a hydride or methyl group. However, pretty much any alkyl group is capable of shifting. Sometimes, the entire side of a ring will shift over in a ring-expanding rearrangement. Consider the following electrophilic addition of HBr to an alkene: right off the bat, it is very hard to see what is going on here.



Taking into account the possibility of rearrangement, however, we can see how the observed product forms.



The first 1,2-alkyl shift is driven by the expansion of a five-membered ring to a six-membered ring, which has slightly less ring strain. A hydride shift then converts a secondary carbocation to a tertiary carbocation, which is the electrophile ultimately attacked by the bromide nucleophile.

Another factor that may induce rearrangement of carbocation intermediates is strain. The addition of HCl to α-pinene, the major hydrocarbon component of turpentine, gives the rearranged product, bornyl chloride, in high yield. This rearrangement converts a 3º-carbocation to a 2º-carbocation, a transformation that is normally unfavorable. However, the rearrangement also expands a strained four-membered ring to a much less-strained five-membered ring, and this relief of strain provides a driving force for the rearrangement.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- Thuy Hoang
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)

CHAPTER OVERVIEW

10: Alkenes

10.1: Introduction

This is an introductory page about alkenes such as ethene, propene and the rest. It deals with their formulae and isomerism, their physical properties, and an introduction to their chemical reactivity.

What are alkenes?

Alkenes are a family of hydrocarbons (compounds containing carbon and hydrogen only) containing a carbon-carbon double bond. The first two are:

ethene	C_2H_4
propene	C_3H_6

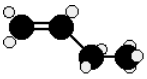
You can work out the formula of any of them using: C_nH_{2n} The table is limited to the first two, because after that there are isomers which affect the names.

Isomerism in the alkenes

Structural isomerism

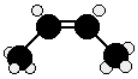
All the alkenes with 4 or more carbon atoms in them show structural isomerism. This means that there are two or more different structural formulae that you can draw for each molecular formula.

For example, with C_4H_8, it isn't too difficult to come up with these three structural isomers:



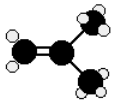
$CH_2=CH-CH_2-CH_3$

but-1-ene



$CH_3-CH=CH-CH_3$

but-2-ene



$CH_2=C(CH_3)_2$

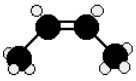
2-methylpropene

There is, however, another isomer. But-2-ene also exhibits geometric isomerism.

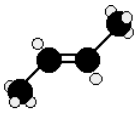
Geometric (cis-trans) isomerism

The carbon-carbon double bond doesn't allow any rotation about it. That means that it is possible to have the CH_3 groups on either end of the molecule locked either on one side of the molecule or opposite each other.

These are called cis-but-2-ene (where the groups are on the same side) or trans-but-2-ene (where they are on opposite sides).



cis-but-2-ene



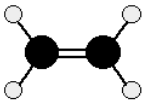
trans-but-2-ene

Cis-but-2-ene is also known as (Z)-but-2-ene; trans-but-2-ene is also known as (E)-but-2-ene. For an explanation of the two ways of naming these two compounds, follow the link in the box below..

Chemical Reactivity

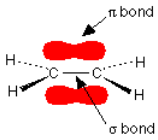
Bonding in the alkenes

We just need to look at ethene, because what is true of C=C in ethene will be equally true of C=C in more complicated alkenes. Ethene is often modeled like this:



The double bond between the carbon atoms is, of course, two pairs of shared electrons. What the diagram doesn't show is that the two pairs aren't the same as each other.

One of the pairs of electrons is held on the line between the two carbon nuclei as you would expect, but the other is held in a molecular orbital above and below the plane of the molecule. A molecular orbital is a region of space within the molecule where there is a high probability of finding a particular pair of electrons.



In this diagram, the line between the two carbon atoms represents a normal bond - the pair of shared electrons lies in a molecular orbital on the line between the two nuclei where you would expect them to be. This sort of bond is called a sigma bond.

The other pair of electrons is found somewhere in the shaded part above and below the plane of the molecule. This bond is called a pi bond. The electrons in the pi bond are free to move around anywhere in this shaded region and can move freely from one half to the other.

The pi electrons are not as fully under the control of the carbon nuclei as the electrons in the sigma bond and, because they lie exposed above and below the rest of the molecule, they are relatively open to attack by other things.

Contributors

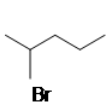
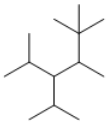
Jim Clark (Chemguide.co.uk)

10.2: Calculating Degrees of Unsaturation

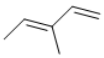
There are many ways one can go about determining the structure of an unknown organic molecule. Although, nuclear magnetic resonance (NMR) and infrared radiation (IR) are the primary ways of determining molecular structures, calculating the degrees of unsaturation is useful information since knowing the degrees of unsaturation make it easier for one to figure out the molecular structure; it helps one double-check the number of π bonds and/or cyclic rings.

Saturated vs. Unsaturated Molecules

In the lab, saturation may be thought of as the point when a solution cannot dissolve anymore of a substance added to it. In terms of degrees of unsaturation, a molecule only containing single bonds with no rings is considered saturated.

$CH_3CH_2CH_3$			1-methyoxypentane

Unlike saturated molecules, unsaturated molecules contain double bond(s), triple bond(s) and/or ring(s).

$CH_3CH{=}CHCH_3$				3-chloro-5-octyne

Calculating Degrees of Unsaturation (DoU)

Degree of Unsaturation (DoU) is also known as **Double Bond Equivalent**. If the molecular formula is given, plug in the numbers into this formula:

$$DoU = \frac{2C + 2 + N - X - H}{2} \tag{10.2.1}$$

- C is the number of carbons
- N is the number of nitrogens
- X is the number of halogens (F, Cl, Br, I)
- H is the number of hydrogens

As stated before, a saturated molecule contains only single bonds and no rings. Another way of interpreting this is that a saturated molecule has the maximum number of hydrogen atoms possible to be an acyclic alkane. Thus, the number of hydrogens can be represented by 2C+2, which is the general molecular representation of an alkane. As an example, for the molecular formula C_3H_4 the number of actual hydrogens needed for the compound to be saturated is 8 *[2C+2=(2x3)+2=8]*. The compound needs 4 more hydrogens in order to be fully saturated *(expected number of hydrogens-observed number of hydrogens=8-4=4)*. Degrees of unsaturation is equal to 2, or half the number of hydrogens the molecule needs to be classified as saturated. Hence, the DoB formula divides by 2. The formula subtracts the number of X's because a halogen (X) replaces a hydrogen in a compound. For instance, in chloroethane, C_2H_5Cl, there is one less hydrogen compared to ethane, C_2H_6.

For a compound to be saturated, there is one more hydrogen in a molecule when nitrogen is present. Therefore, we add the number of nitrogens (N). This can be seen with C_3H_9N compared to C_3H_8. Oxygen and sulfur are not included in the formula because saturation is unaffected by these elements. As seen in alcohols, the same number of hydrogens in ethanol, C_2H_5OH, matches the number of hydrogens in ethane, C_2H_6.

The following chart illustrates the possible combinations of the number of double bond(s), triple bond(s), and/or ring(s) for a given degree of unsaturation. Each row corresponds to a different combination.

- One degree of unsaturation is equivalent to 1 ring or 1 double bond (1 π bond).
- Two degrees of unsaturation is equivalent to 2 double bonds, 1 ring and 1 double bond, 2 rings, or 1 triple bond (2 π bonds).

DoU	Possible combinations of rings/ bonds		
	# of rings	# of double bonds	# of triple bonds
1	1	0	0
	0	1	0
2	2	0	0
	0	2	0
	0	0	1
	1	1	0
3	3	0	0
	2	1	0
	1	2	0
	0	1	1
	0	3	0
	1	0	1

Remember, the degrees of unsaturation only gives the sum of double bonds, triple bonds and/or rings. For instance, a degree of unsaturation of 3 can contain 3 rings, 2 rings+1 double bond, 1 ring+2 double bonds, 1 ring+1 triple bond, 1 double bond+1 triple bond, *or* 3 double bonds.

Example: Benzene

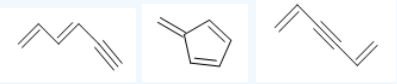
What is the Degree of Unsaturation for Benzene?

Solution

The molecular formula for benzene is C_6H_6. Thus,

DoU= 4, where C=6, N=0,X=0, and H=6. 1 DoB can equal 1 ring or 1 double bond. This corresponds to benzene containing 1 ring and 3 double bonds.

However, when given the molecular formula C_6H_6, benzene is only one of many possible structures (isomers). The following structures all have DoB of 4 and have the same molecular formula as benzene.

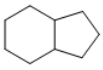
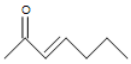
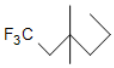


References

1. Vollhardt, K. P.C. & Shore, N. (2007). *Organic Chemistry* (5thEd.). New York: W. H. Freeman. (473-474)
2. Shore, N. (2007). *Study Guide and Solutions Manual for Organic Chemistry* (5th Ed.). New York: W.H. Freeman. (201)

Problems

1. Are the following molecules saturated or unsaturated:

1.  (b.)  (c.)  (d.) $C_{10}H_6N_4$

2. Using the molecules from 1., give the degrees of unsaturation for each.
3. Calculate the degrees of unsaturation for the following molecular formulas:
    1. (a.) C_9H_{20} (b.) C_7H_8 (c.) C_5H_7Cl (d.) $C_9H_9NO_4$
4. Using the molecular formulas from 3, are the molecules unsaturated or saturated.
5. Using the molecular formulas from 3, if the molecules are unsaturated, how many rings/double bonds/triple bonds are predicted?

Answers

1.

(a.) **unsaturated** (E*ven though rings only contain single bonds, rings are considered unsaturated.)*

(b.) **unsaturated**

(c.) **saturated**

(d.) **unsaturated**

2. *If the molecular structure is given, the easiest way to solve is to count the number of double bonds, triple bonds and/or rings. However, you can also determine the molecular formula and solve for the degrees of unsaturation by using the formula.*

(a.) **2**

(b.) **2** *(one double bond and the double bond from the carbonyl)*

(c.) **0**

(d.) **10**

3. *Use the formula to solve*

(a.) **0**

(b.) **4**

(c.) **2**

(d.) **6**

4.

(a.) **saturated**

(b.) **unsaturated**

(c.) **unsaturated**

(d.) **unsaturated**

5.

(a.) **0** (Remember-a saturated molecule only contains single bonds)

(b.) *The molecule can contain any of these combinations* **(i) 4 double bonds (ii) 4 rings (iii) 2 double bonds+2 rings (iv) 1 double bond+3 rings (v) 3 double bonds+1 ring (vi) 1 triple bond+2 rings (vii) 2 triple bonds (viii) 1 triple bond+1 double bond+1 ring (ix) 1 triple bond+2 double bonds**

(c.) **(i) 1 triple bond (ii) 1 ring+1 double bond (iii) 2 rings (iv) 2 double bonds**

(d.) **(i) 3 triple bonds (ii) 2 triple bonds+2 double bonds (iii) 2 triple bonds+1 double bond+1 ring (iv)...** *(As you can see, the degrees of unsaturation only gives the sum of double bonds, triple bonds and/or ring. Thus, the formula may give numerous possible structures for a given molecular formula.)*

Contributors

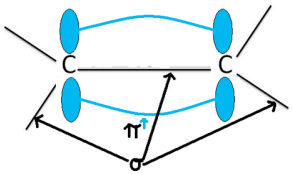
- Kim Quach (UCD)

10.3: Nomenclature

Alkenes contain carbon-carbon double bonds and are unsaturated hydrocarbons with the molecular formula is C_nH_{2n}. This is also the same molecular formula as cycloalkanes. Alkenes are named by dropping the -ane ending of the parent and adding -ene.

Introduction

The parent structure is the longest chain containing both carbon atoms of the double bond. The two carbon atoms of a double bond and the four atoms attached to them lie in a plane, with bond angles of approximately 120° A double bond consists of one sigma bond formed by overlap of sp^2 hybrid orbitals and one pi bond formed by overlap of parallel 2 p orbitals



The Basic Rules

For straight chain alkenes, it is the same basic rules as nomenclature of alkanes except change the suffix to "-ene."

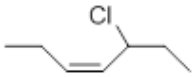
i. Find the Longest Carbon Chain that Contains the Carbon Carbon double bond. If you have two ties for longest Carbon chain, and both chains contain a Carbon Carbon double bond, then identify the most substituted chain.

ii. Give the lowest possible number to the Carbon Carbon double bond.

1. Do not need to number cycloalkenes because it is understood that the double bond is in the one position.
2. Alkenes that have the same molecular formula but the location of the doble bonds are different means they are constitutional isomers.
3. Functional Groups with higher priority:

iii. Add substituents and their position to the alkene as prefixes. Of course remember to give the lowest numbers possible. And remember to name them in alphabetical order when writting them.

iv. Next is identifying stereoisomers. when there are only two non hydrogen attachments to the alkene then use cis and trans to name the molecule.



In this diagram this is a cis conformation. It has both the substituents going upward. This molecule would be called (cis) 5-chloro-3-heptene.)

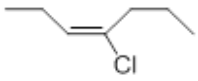
Trans would look like this

v. On the other hand if there are 3 or 4 non-hydrogen different atoms attached to the alkene then use the E, Z system.

E (entgegen) means the higher priority groups are opposite one another relative to the double bond.

Z (zusammen) means the higher priority groups are on the same side relative to the double bond.

(You could think of Z as Zame Zide to help memorize it.)



In this example it is E-4-chloro-3-heptene. It is E because the Chlorine and the CH_2CH_3 are the two higher priorities and they are on opposite sides.

vi. A hydroxyl group gets precedence over th double bond. Therefore alkenes containing alchol groups are called alkenols. And the prefix becomes --enol. And this means that now the alcohol gets lowest priority over the alkene.

vii. Lastly remember that alkene substituents are called alkenyl. Suffix --enyl.

Here is a chart containing the systemic name for the first twenty straight chain alkenes.

Name	Molecular formula
Ethene	C_2H_4
Propene	C_3H_6
Butene	C_4H_8
Pentene	C_5H_{10}
Hexene	C_6H_{12}
Heptene	C_7H_{14}
Octene	C_8H_{16}
Nonene	C_9H_{18}
Decene	$C_{10}H_{20}$
Undecene	$C_{11}H_{22}$
Dodecene	$C_{12}H_{24}$
Tridecene	$C_{13}H_{26}$
Tetradecene	$C_{14}H_{28}$
Pentadecene	$C_{15}H_{30}$
Hexadecene	$C_{16}H_{32}$
Heptadecene	$C_{17}H_{34}$
Octadecene	$C_{18}H_{36}$
Nonadecene	$C_{19}H_{38}$
Eicosene	$C_{20}H_{40}$

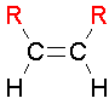
Did you notice how there is no methene? Because it is impossible for a Carbon to have a double bond with nothing.

Geometric Isomers

Double bonds can exist as geometric isomers and these isomers are designated by using either the cis / trans designation or the modern E / Z designation.

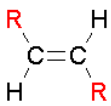
cis Isomers

.The two largest groups are on the same side of the double bond.



trans Isomers

...The two largest groups are on opposite sides of the double bond.



E/Z nomenclature

E = entgegan ("trans") Z = zusamen ("cis")

Priority of groups is based on the atomic mass of attached atoms (not the size of the group). An atom attached by a multiple bond is counted once for each bond.

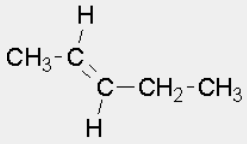
fluorine atom > isopropyl group > n-hexyl group

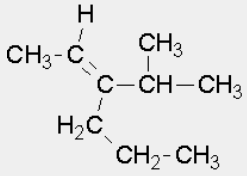
deuterium atom > hydrogen atom

$$-CH_2-CH=CH_2 > -CH_2CH_2CH_3$$

Example 1

Try to name the following compounds using both conventions...

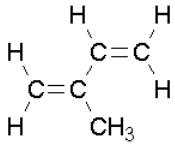




Common names

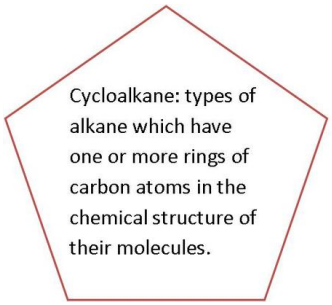
Remove the -ane suffix and add -ylene. There are a couple of unique ones like ethenyl's common name is vinyl and 2-propenyl's common name is allyl. That you should know are...

- vinyl substituent $H_2C=CH-$
- allyl substituent $H_2C=CH-CH_2-$
- allene molecule $H_2C=C=CH_2$
- isoprene



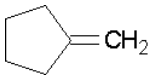
Endocyclic Alkenes

Endocyclic double bonds have both carbons in the ring and exocyclic double bonds have only one carbon as part of the ring.

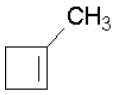


Cyclopentene is an example of an endocyclic double bond.

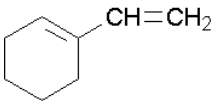
Methylenecylopentane is an example of an exocyclic double bond.



Name the following compounds...

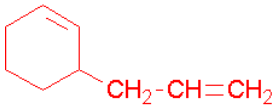


1-methylcyclobutene. The methyl group places the double bond. It is correct to also name this compound as 1-methylcyclobut-1-ene.

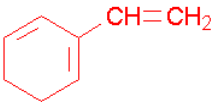


1-ethenylcyclohexene, the methyl group places the double bond. It is correct to also name this compound as 1-ethenylcyclohex-1-ene. A common name would be 1-vinylcyclohexene.

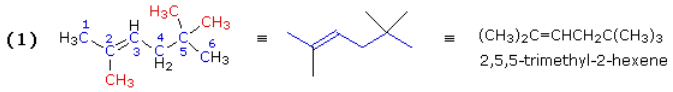
Try to draw structures for the following compounds...



- 2-vinyl-1,3-cyclohexadiene

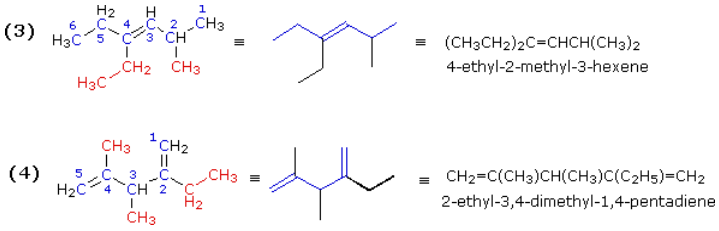


Examples



Both these compounds have double bonds, making them alkenes. In example (1) the longest chain consists of six carbons, so the root name of this compound will be hexene. Three methyl substituents (colored red) are present. Numbering the six-carbon chain begins at the end nearest the double bond (the left end), so the methyl groups are located on carbons 2 & 5. The IUPAC name is therefore: 2,5,5-trimethyl-2-hexene.

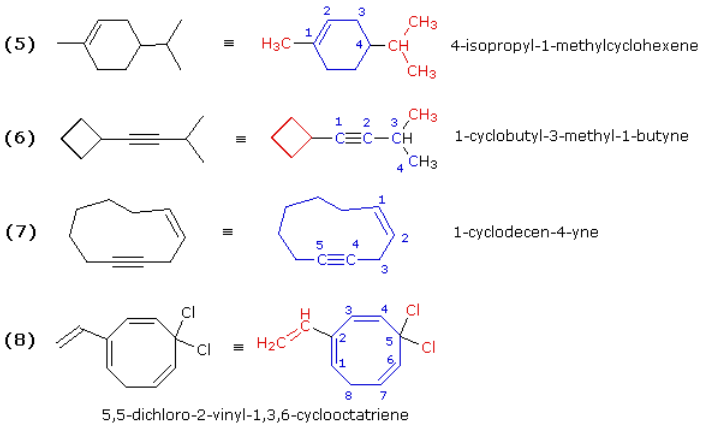
In example (2) the longest chain incorporating both carbon atoms of the double bond has a length of five. There is a seven-carbon chain, but it contains only one of the double bond carbon atoms. Consequently, the root name of this compound will be pentene. There is a propyl substituent on the inside double bond carbon atom (#2), so the IUPAC name is: 2-propyl-1-pentene.



The double bond in example (3) is located in the center of a six-carbon chain. The double bond would therefore have a locator number of 3 regardless of the end chosen to begin numbering. The right hand end is selected because it gives the lowest first-

substituent number (2 for the methyl as compared with 3 for the ethyl if numbering were started from the left). The IUPAC name is assigned as shown.

Example (4) is a diene (two double bonds). Both double bonds must be contained in the longest chain, which is therefore five- rather than six-carbons in length. The second and fourth carbons of this 1,4-pentadiene are both substituted, so the numbering begins at the end nearest the alphabetically first-cited substituent (the ethyl group).



These examples include rings of carbon atoms as well as some carbon-carbon triple bonds. Example (6) is best named as an alkyne bearing a cyclobutyl substituent. Example (7) is simply a ten-membered ring containing both a double and a triple bond. The double bond is cited first in the IUPAC name, so numbering begins with those two carbons in the direction that gives the triple bond carbons the lowest locator numbers. Because of the linear geometry of a triple bond, a-ten membered ring is the smallest ring in which this functional group is easily accommodated. Example (8) is a cyclooctatriene (three double bonds in an eight-membered ring). The numbering must begin with one of the end carbons of the conjugated diene moiety (adjacent double bonds), because in this way the double bond carbon atoms are assigned the smallest possible locator numbers (1, 2, 3, 4, 6 & 7). Of the two ways in which this can be done, we choose the one that gives the vinyl substituent the lower number.

Outside links

- http://www.vanderbilt.edu/AnS/Chemis...0a/alkenes.pdf

References

1. Vollhardt, Peter, and Neil E. Schore. Organic Chemistry: Structure and Function. 5th Edition. New York: W. H. Freeman & Company, 2007.

Problems

Try to name the following compounds...

1-pentene or pent-1-ene

2-ethyl-1-hexene or 2-ethylhex-1-ene

Try to draw structures for the following compounds...

- 2-pentene

$$CH_3–CH=CH–CH_2–CH_3$$

- 3-heptene

$$CH_3–CH_2–CH=CH–CH_2–CH_2–CH_3$$

b. Give the double bond the lowest possible numbers regardless of substituent placement.

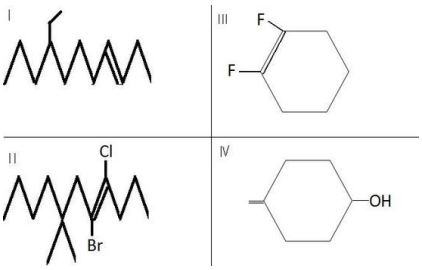
• Try to name the following compound...

J

• Try to draw a structure for the following compound...

4-methyl-2-pentene J

Name the following structures:



v. Draw (Z)-5-Chloro-3-ethly-4-hexen-2-ol.

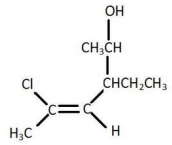
Answers

I. trans-8-ethyl-3-undecene

II. E-5-bromo-4-chloro-7,7-dimethyl-4-undecene

III. Z-1,2-difluoro-cyclohexene

IV. 4-ethenylcyclohexanol.



V.

Contributors

- S. Devarajan (UCD)

Richard Banks (Boise State University)

10.4: Physical Properties

Physical state

Ethene, Propene, and Butene exists as colorless gases. Members of the 5 or more carbons such as Pentene, Hexene, and Heptene are liquid, and members of the 15 carbons or more are solids.

Density

Alkenes are lighter than water, therefore, are insoluble in water. Alkenes are only soluble in nonpolar solvent.

Solubility

Alkenes are virtually insoluble in water, but dissolve in organic solvents. The reasons for this are exactly the same as for the alkanes.

Boiling Points

The boiling point of each alkene is very similar to that of the alkane with the same number of carbon atoms. Ethene, propene and the various butenes are gases at room temperature. All the rest that you are likely to come across are liquids.

Boiling points of alkenes depends on more molecular mass (chain length). The more intermolecular mass is added, the higher the boiling point. Intermolecular forces of alkenes gets stronger with increase in the size of the molecules.

Compound	Boiling points (oC)
Ethene	-104
Propene	-47
Trans-2-Butene	0.9
Cis-2-butene	3.7
Trans 1,2-dichlorobutene	155
Cis 1,2-dichlorobutene	152
1-Pentene	30
Trans-2-Pentene	36
Cis-2-Pentene	37
1-Heptene	115
3-Octene	122
3-Nonene	147
5-Decene	170

In each case, the alkene has a boiling point which is a small number of degrees lower than the corresponding alkane. The only attractions involved are Van der Waals dispersion forces, and these depend on the shape of the molecule and the number of electrons it contains. Each alkene has 2 fewer electrons than the alkane with the same number of carbons.

Melting Points

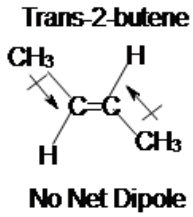
Melting points of alkenes depends on the packaging of the molecules. Alkenes have similar melting points to that of alkanes, however, in cis isomers molecules are package in a U-bending shape, therefore, will display a lower melting points to that of the trans isomers.

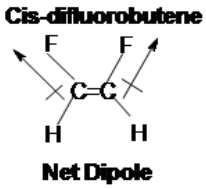
Compound	Melting Points (0C)

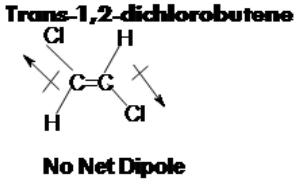
Ethene	-169
Propene	-185
Butene	-138
1-Pentene	-165
Trans-2-Pentene	-135
Cis-2-Pentene	-180
1-Heptene	-119
3-Octene	-101.9
3-Nonene	-81.4
5-Decene	-66.3

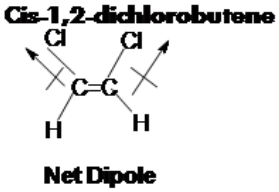
Polarity

Chemical structure and fuctional groups can affect the polarity of alkenes compounds. The sp^2 carbon is much more electron-withdrawing than the sp3 hybridize orbitals, therefore, creates a weak dipole along the substituent weak alkenly carbon bond. The two individual dipoles together form a net molecular dipole. In trans-subsituted alkenes, the dipole cancel each other out. In cis-subsituted alkenes there is a net dipole, therefore contributing to higher boiling in cis-isomers than trans-isomers.









Contributors

- Trung Nguyen
- Jim Clark (Chemguide.co.uk)

10.5: Interesting Alkenes

Ethene

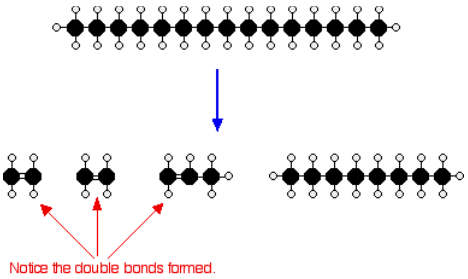
Cracking is the name given to breaking up large hydrocarbon molecules into smaller and more useful bits. This is achieved by using high pressures and temperatures without a catalyst, or lower temperatures and pressures in the presence of a catalyst. The source of the large hydrocarbon molecules is often the naphtha fraction or the gas oil fraction from the fractional distillation of crude oil (petroleum). These fractions are obtained from the distillation process as liquids, but are re-vaporized before cracking.

There is not any single unique reaction happening in the cracker. The hydrocarbon molecules are broken up in a fairly random way to produce mixtures of smaller hydrocarbons, some of which have carbon-carbon double bonds. One possible reaction involving the hydrocarbon $C_{15}H_{32}$ might be:

$$C_{15}H_{32} \longrightarrow 2C_2H_4 + C_3H_6 + C_8H_{18}$$

ethene propene octane

Or, showing more clearly what happens to the various atoms and bonds:

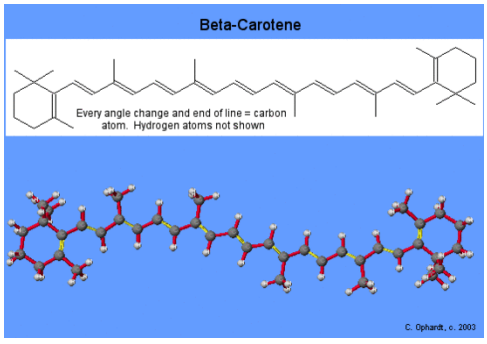


This is only one way in which this particular molecule might break up. The ethene and propene are important materials for making plastics or producing other organic chemicals. You will remember that during the polymeriation of ethene, thousands of ethene molecules join together to make poly(ethene) - commonly called polythene. The reaction is done at high pressures in the presence of a trace of oxygen as an initiator.

$$n CH_2{=}CH_2 \longrightarrow [\text{-}CH_2\text{-}CH_2\text{-}]_n$$

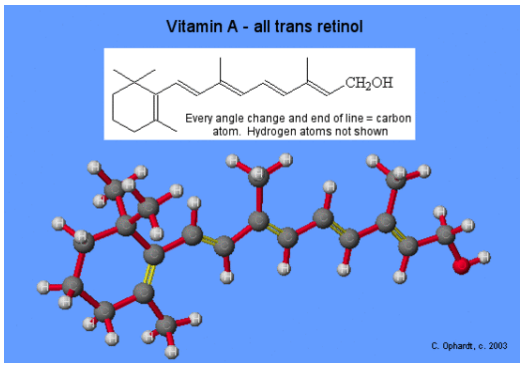
Beta-Carotene

The long chain of alternating double bonds (conjugated) is responsible for the orange color of beta-carotene. The conjugated chain in carotenoids means that they absorb in the visible region - green/blue part of the spectrum. So β-carotene appears orange, because the red/yellow colors are reflected back to us.



Vitamin A

Vitamin A has several functions in the body. The most well known is its role in vision - hence carrots "make you able to see in the dark". The retinol is oxidized to its aldehyde, retinal, which complexes with a molecule in the eye called opsin. When a photon of light hits the complex, the retinal changes from the 11-cis form to the all-trans form, initiating a chain of events which results in the transmission of an impulse up the optic nerve. A more detailed explanation is in Photochemical Events.



Other roles of vitamin A are much less well understood. It is known to be involved in the synthesis of certain glycoproteins, and that deficiency leads to abnormal bone development, disorders of the reproductive system, xerophthalmia (a drying condition of the cornea of the eye) and ultimately death.

Vitamin A is required for healthy skin and mucus membranes, and for night vision. Its absence from diet leads to a loss in weight and failure of growth in young animals, to the eye diseases; xerophthalmia, and night blindness, and to a general susceptibility to infections. It is thought to help prevent the development of cancer. Good sources of carotene, such as green vegetables are good potential sources of vitamin A. Vitamin A is also synthetically manufactured by extraction from fish-liver oil and by synthesis from beta-ionone.

Contributors

- Jim Clark (Chemguide.co.uk)
- Charles Ophardt, Professor Emeritus, Elmhurst College; Virtual Chembook

10.6: Lipids—Part 2

Fatty acids are merely carboxylic acids with long hydrocarbon chains. The hydrocarbon chain length may vary from 10-30 carbons (most usual is 12-18). The non-polar hydrocarbon alkane chain is an important counter balance to the polar acid functional group. In acids with only a few carbons, the acid functional group dominates and gives the whole molecule a polar character. However, in fatty acids, the non-polar hydrocarbon chain gives the molecule a non-polar character.

Introduction

The most common fatty acids are listed. Note that there are two groups of fatty acids--saturated and unsaturated. Recall that the term **unsaturated** refers to the presence of one or more double bonds between carbons as in alkenes. A **saturated fatty acid** has all bonding positions between carbons occupied by hydrogens.

The melting points for the saturated fatty acids follow the **boiling point principle** observed previously. Melting point principle: **as the molecular weight increases, the melting point increases.** This observed in the series lauric (C12), palmitic (C16), stearic (C18). Room temperature is 25°C, Lauric acid which melts at 44° is still a solid, while arachidonic acid has long since melted at -50°, so it is a liquid at room temperature.

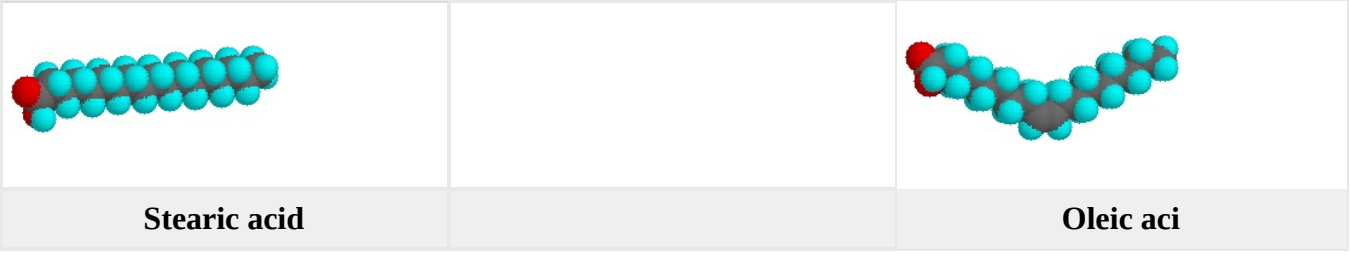
Table 1: Common Fatty Acids

Saturated Fatty Acids		
Formula	**Common Name**	**Melting Point**
$CH_3(CH_2)_{10}CO_2H$	lauric acid	45 °C
$CH_3(CH_2)_{12}CO_2H$	myristic acid	55 °C
$CH_3(CH_2)_{14}CO_2H$	palmitic acid	63 °C
$CH_3(CH_2)_{16}CO_2H$	stearic acid	69 °C
$CH_3(CH_2)_{18}CO_2H$	arachidic acid	76 °C

Unsaturated Fatty Acids		
Formula	**Common Name**	**Melting Point**
$CH_3(CH_2)_5CH=CH(CH_2)_7CO_2H$	palmitoleic acid	0 °C
$CH_3(CH_2)_7CH=CH(CH_2)_7CO_2H$	oleic acid	13 °C
$CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7CO_2H$	linoleic acid	-5 °C
$CH_3CH_2CH=CHCH_2CH=CHCH_2CH=CH(CH_2)_7CO_2H$	linolenic acid	-11 °C
$CH_3(CH_2)_4(CH=CHCH_2)_4(CH_2)_2CO_2H$	arachidonic acid	-49 °C

Melting Points of Saturated vs. Unsaturated Fatty Acids

Note that as a group, the **unsaturated fatty acids have lower melting points than the saturated fatty acids**. The reason for this phenomenon can be found by a careful consideration of molecular geometries. The tetrahedral bond angles on carbon results in a molecular geometry for saturated fatty acids that is relatively linear although with zigzags.



Stearic acid **Oleic aci**

This molecular structure allows many fatty acid molecules to be rather closely "stacked" together. As a result, close intermolecular interactions result in relatively high melting points.

On the other hand, the introduction of one or more double bonds in the hydrocarbon chain in unsaturated fatty acids results in one or more "bends" in the molecule. The geometry of the double bond is almost always a cis configuration in natural fatty acids. and these molecules do not "stack" very well. The intermolecular interactions are much weaker than saturated molecules. As a result, the melting points are much lower for unsaturated fatty acids.

Percent Fatty Acid Present in Triglycerides					
Fat or Oil	Saturated		Unsaturated		
	Palmitic	Stearic	Oleic	Linoleic	Other
Animal Origin					
Butter	29	9	27	4	31
Lard	30	18	41	6	5
Beef	32	25	38	3	2
Vegatable Origin					
Corn oil	10	4	34	48	4
Soybean	7	3	25	56	9
Peanut	7	5	60	21	7
Olive	6	4	83	7	-

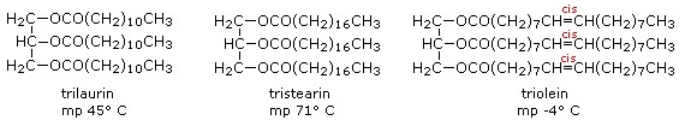
Saturated vs. Unsaturated Fatty Acids in Fats and Oils

The triesters of fatty acids with glycerol (1,2,3-trihydroxypropane) compose the class of lipids known as fats and oils. These **triglycerides** (or triacylglycerols) are found in both plants and animals, and compose one of the major food groups of our diet. Triglycerides that are solid or semisolid at room temperature are classified as fats, and occur predominantly in animals. Those triglycerides that are liquid are called oils and originate chiefly in plants, although triglycerides from fish are also largely oils. Some examples of the composition of triglycerides from various sources are given in the following table.

	Saturated Acids (%)					Unsaturated Acids (%)		
Source	**C_{10} & less**	**C_{12} lauric**	**C_{14} myristic**	**C_{16} palmitic**	**C_{18} stearic**	**C_{18} oleic**	**C_{18} linoleic**	**C_{18} unsaturated**
Animal Fats								
butter	15	2	11	30	9	27	4	1
lard	-	-	1	27	15	48	6	2
human fat	-	1	3	25	8	46	10	3
herring oil	-	-	7	12	1	2	20	52
Plant Oils								
coconut	-	50	18	8	2	6	1	-
corn	-	-	1	10	3	50	34	-
olive	-	-	-	7	2	85	5	-
palm	-	-	2	41	5	43	7	-
peanut	-	-	-	8	3	56	26	7

safflower	-	-	-	3	3	19	76	-

As might be expected from the properties of the fatty acids, fats have a predominance of saturated fatty acids, and oils are composed largely of unsaturated acids. Thus, the melting points of triglycerides reflect their composition, as shown by the following examples. Natural mixed triglycerides have somewhat lower melting points, the melting point of lard being near 30 ° C, whereas olive oil melts near -6 ° C. Since fats are valued over oils by some Northern European and North American populations, vegetable oils are extensively converted to solid triglycerides (e.g. Crisco) by partial hydrogenation of their unsaturated components. Some of the remaining double bonds are isomerized (to trans) in this operation. These saturated and trans-fatty acid glycerides in the diet have been linked to long-term health issues such as atherosclerosis.



Triglycerides having three identical acyl chains, such as tristearin and triolein (above), are called "simple", while those composed of different acyl chains are called "mixed". If the acyl chains at the end hydroxyl groups (1 & 3) of glycerol are different, the center carbon becomes a chiral center and enantiomeric configurations must be recognized.

The hydrogenation of vegetable oils to produce semisolid products has had unintended consequences. Although the hydrogenation imparts desirable features such as spreadability, texture, "mouth feel," and increased shelf life to naturally liquid vegetable oils, it introduces some serious health problems. These occur when the cis-double bonds in the fatty acid chains are not completely saturated in the hydrogenation process. The catalysts used to effect the addition of hydrogen isomerize the remaining double bonds to their trans configuration. These unnatural trans-fats appear to to be associated with increased heart disease, cancer, diabetes and obesity, as well as immune response and reproductive problems.

Contributors

- Charles Ophardt, Professor Emeritus, Elmhurst College; Virtual Chembook
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

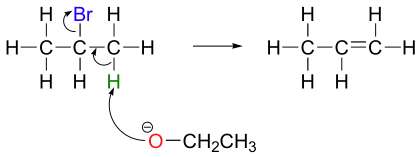
10.7: Preparation of Alkenes

E2 Reaction

E2 reactions are typically seen with secondary and tertiary alkyl halides, but a hindered base is necessary with a primary halide. The mechanism by which it occurs is a single step **concerted** reaction with one transition state. The rate at which this mechanism occurs is second order kinetics, and depends on both the base and alkyl halide. A good leaving group is required because it is involved in the rate determining step. The leaving groups must be coplanar in order to form a pi bond; carbons go from sp^3 to sp^2 hybridization states.

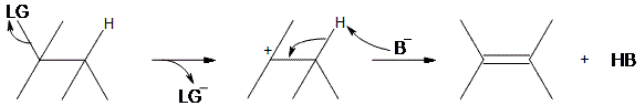
To get a clearer picture of the interplay of these factors involved in a a reaction between a nucleophile/base and an alkyl halide, consider the reaction of a 2º-alkyl halide, isopropyl bromide, with two different nucleophiles. In one pathway, a methanethiolate nucleophile substitutes for bromine in an S_N2 reaction. In the other (bottom) pathway, methoxide ion acts as a base (rather than as a nucleophile) in an elimination reaction. As we will soon see, the mechanism of this reaction is single-step, and is referred to as the E2 mechanism.

.



E1 Reaction

An E1 reaction involves the deprotonation of a hydrogen nearby (usually one carbon away, or the beta position) the carbocation resulting in the formation of an alkene product. In order to accomplish this, a Lewis base is required. For a simplified model, we'll take B to be a Lewis base, and LG to be a halogen leaving group.

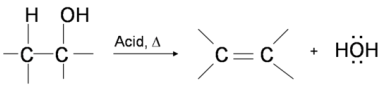


As can be seen above, the preliminary step is the leaving group (LG) leaving on its own. Because it takes the electrons in the bond along with it, the carbon that was attached to it loses its electron, making it a carbocation. Once it becomes a carbocation, a Lewis Base ( ) deprotonates the intermediate carbocation at the beta position, which then donates its electrons to the neighboring C-C bond, forming a double bond. Unlike E2 reactions, which require the proton to be *anti* to the leaving group, E1 reactions only require a neighboring hydrogen. This is due to the fact that the leaving group has already left the molecule. The final product is an alkene along with the HB byproduct.

Dehydration

One way to synthesize alkenes is by dehydration of alcohols, a process in which alcohols undergo E1 or E2 mechanisms to lose water and form a double bond.

The dehydration reaction of alcohols to generate alkene proceeds by heating the alcohols in the presence of a strong acid, such as sulfuric or phosphoric acid, at high temperatures.



Primary alcohol dehydrates through the E2 mechanism

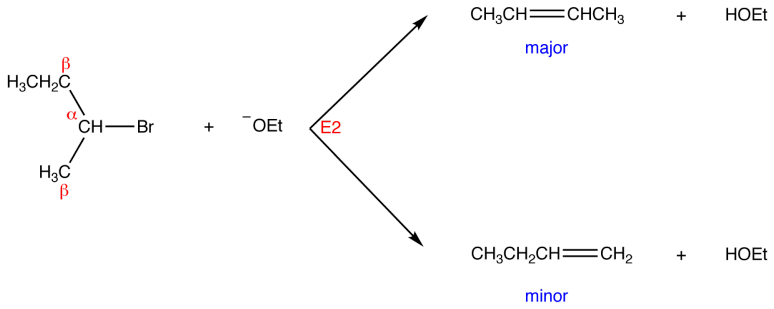
Oxygen donates two electrons to a proton from sulfuric acid H_2SO_4, forming an alkyloxonium ion. Then the nucleophile HSO_4^- back-side attacks one adjacent hydrogen and the alkyloxonium ion leaves in a concerted process, making a double bond.

Secondary and tertiary alcohols dehydrate through the E1 mechanism

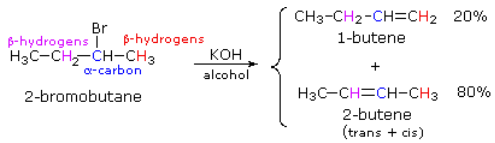
Similarly to the reaction above, secondary and tertiary –OH protonate to form alkyloxonium ions. However, in this case the ion leaves first and forms a carbocation as the reaction intermediate. The water molecule (which is a stronger base than the HSO_4^- ion) then abstracts a proton from an adjacent carbon, forming a double bond. Notice in the mechanism below that the aleke formed depends on which proton is abstracted: the red arrows show formation of the more substituted 2-butene, while the blue arrows show formation of the less substituted 1-butene. Recall the general rule that more substituted alkenes are more stable than less substituted alkenes, and *trans* alkenes are more stable than *cis* alkenes. Thereore, the *trans* diastereomer of the 2-butene product is most abundant.

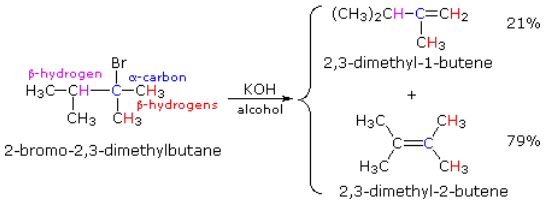
Zaitsev's Rule

Zaitsev's or Saytzev's (anglicized spelling) rule is an empirical rule used to predict regioselectivity of 1,2-elimination reactions occurring via the E1 or E2 mechanisms. It states that in a regioselective E1 or E2 reaction the major product is the more stable alkene, (i.e., the alkene with the more highly substituted double bond). For example:



If two or more structurally distinct groups of beta-hydrogens are present in a given reactant, then several constitutionally isomeric alkenes may be formed by an E2 elimination. This situation is illustrated by the 2-bromobutane and 2-bromo-2,3-dimethylbutane elimination examples given below.





Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

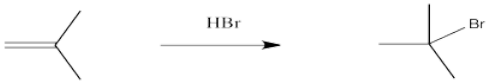
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Gamini Gunawardena from the OChemPal site (Utah Valley University)

10.8: Introduction to Addition Reactions

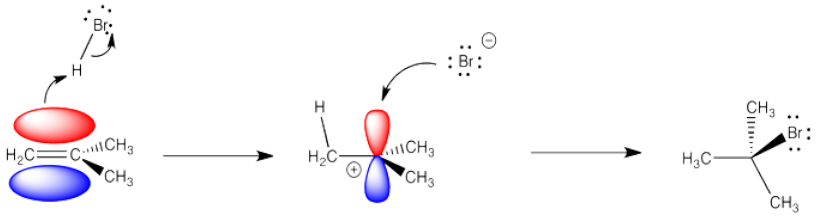
Alkenes are found throughout nature. They form the basis of many natural products, such as terpenes, which play a variety of roles in the lives of plants and insects. The C=C bonds of alkenes are very different from the C=O bonds that are also common in nature. The C=C bonds of alkenes are electron-rich and nucleophilic, in contrast to the electron-poor C=O bonds of carbohydrates, fatty acids and proteins. That difference plays a role in how terpenes form in nature.

Alkenes, or olefins, are also a major product of the petroleum industry. Reactions of alkenes form the basis for a significant porion of our manufacturing economy. Commonly used plastics such as polyethylene, polypropylene and polystyrene are all formed through the reactions of alkenes. These materials continue to find use in our society because of their valuable properties, such as high strength, flexibility and low weight.

Alkenes undergo addition reactions like carbonyls do. Often, they add a proton to one end of the double bond and another group to the other end. These reactions happen in slightly different ways, however.



Alkenes are reactive because they have a high-lying pair of π-bonding electrons. These electrons are loosely held, being high in energy compared to σ-bonds. The fact that they are not located between the carbon nuclei, but are found above and below the plane of the double bond, also makes these electrons more accessible.



Alkenes can donate their electrons to strong electrophiles other than protons, too. Sometimes their reactivity pattern is a little different than the simple addition across the double bond, but that straightforward pattern is what we will focus on in this chapter.

10.9: Hydrohalogenation—Electrophilic Addition of HX

his page looks at the reaction of the carbon-carbon double bond in alkenes such as ethene with hydrogen halides such as hydrogen chloride and hydrogen bromide.

Symmetrical alkenes (like ethene or but-2-ene) are dealt with first. These are alkenes where identical groups are attached to each end of the carbon-carbon double bond.

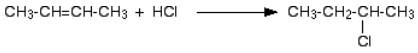
Addition to symmetrical alkenes

What happens?

All alkenes undergo addition reactions with the hydrogen halides. A hydrogen atom joins to one of the carbon atoms originally in the double bond, and a halogen atom to the other.

For example, with ethene and hydrogen chloride, you get chloroethane:

With but-2-ene you get 2-chlorobutane:



What happens if you add the hydrogen to the carbon atom at the right-hand end of the double bond, and the chlorine to the left-hand end? You would still have the same product.

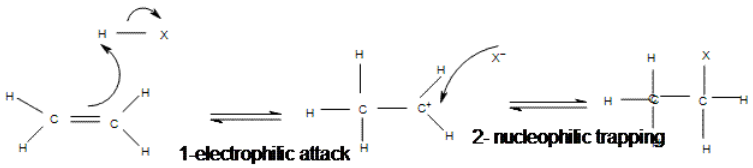
The chlorine would be on a carbon atom next to the end of the chain - you would simply have drawn the molecule flipped over in space.

That would be different of the alkene was unsymmetrical - that's why we have to look at them separately.

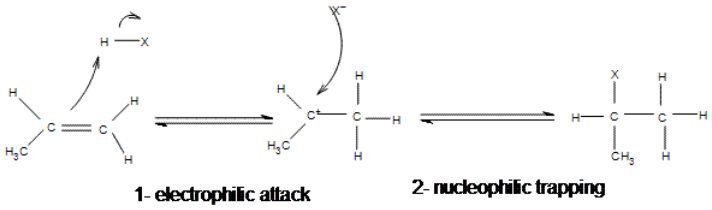
Mechanism

The addition of hydrogen halides is one of the easiest electrophilic addition reactions because it uses the simplest electrophile: the proton. Hydrogen halides provide both a electrophile (proton) and a nucleophile (halide). First, the electrophile will attack the double bond and take up a set of electrons, attaching it to the molecule (1). This is basically the reverse of the last step in the E1 reaction (deprotonation step). The resulting molecule will have a single carbon- carbon bond with a positive charge on one of them (carbocation). The next step is when the nucleophile (halide) bonds to the carbocation, producing a new molecule with both the original hydrogen and halide attached to the organic reactant (2). The second step will only occur if a good nucleophile is used.

Mechanism of Electrophilic Addition of Hydrogen Halide to Ethene



Mechanism of Electrophilic Addition of Hydrogen Halide to Propene



All of the halides (HBr, HCl, HI, HF) can participate in this reaction and add on in the same manner. Although different halides do have different rates of reaction, due to the H-X bond getting weaker as X gets larger (poor overlap of orbitals)s.

Reaction rates

Variation of rates when you change the halogen

Reaction rates increase in the order HF - HCl - HBr - HI. Hydrogen fluoride reacts much more slowly than the other three, and is normally ignored in talking about these reactions.

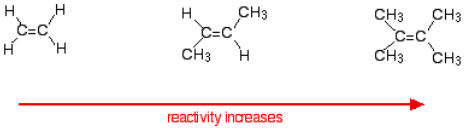
When the hydrogen halides react with alkenes, the hydrogen-halogen bond has to be broken. The bond strength falls as you go from HF to HI, and the hydrogen-fluorine bond is particularly strong. Because it is difficult to break the bond between the hydrogen and the fluorine, the addition of HF is bound to be slow.

Variation of rates when you change the alkene

This applies to unsymmetrical alkenes as well as to symmetrical ones. For simplicity the examples given below are all symmetrical ones- but they don't have to be.

Reaction rates increase as the alkene gets more complicated - in the sense of the number of alkyl groups (such as methyl groups) attached to the carbon atoms at either end of the double bond.

For example:



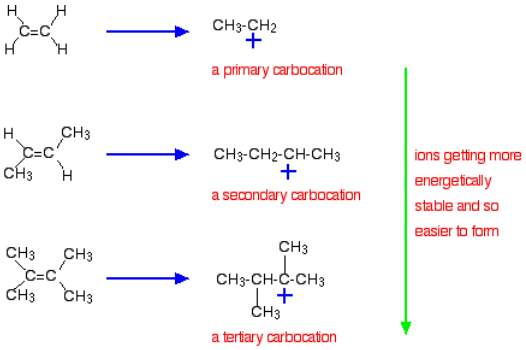
There are two ways of looking at the reasons for this - both of which need you to know about the mechanism for the reactions.

Alkenes react because the electrons in the pi bond attract things with any degree of positive charge. Anything which increases the electron density around the double bond will help this.

Alkyl groups have a tendency to "push" electrons away from themselves towards the double bond. The more alkyl groups you have, the more negative the area around the double bonds becomes.

The more negatively charged that region becomes, the more it will attract molecules like hydrogen chloride.

The more important reason, though, lies in the stability of the intermediate ion formed during the reaction. The three examples given above produce these carbocations (carbonium ions) at the half-way stage of the reaction:



The stability of the intermediate ions governs the activation energy for the reaction. As you go towards the more complicated alkenes, the activation energy for the reaction falls. That means that the reactions become faster.

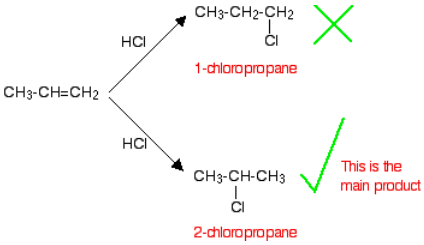
Addition to unsymmetrical alkenes

What happens?

In terms of reaction conditions and the factors affecting the rates of the reaction, there is no difference whatsoever between these alkenes and the symmetrical ones described above. The problem comes with the orientation of the addition - in other words, which way around the hydrogen and the halogen add across the double bond.

Orientation of addition

If HCl adds to an unsymmetrical alkene like propene, there are two possible ways it could add. However, in practice, there is only one major product.



This is in line with Markovnikov's Rule which says:

> When a compound HX is added to an unsymmetrical alkene, the hydrogen becomes attached to the carbon with the most hydrogens attached to it already.

In this case, the hydrogen becomes attached to the CH_2 group, because the CH_2 group has more hydrogens than the CH group.

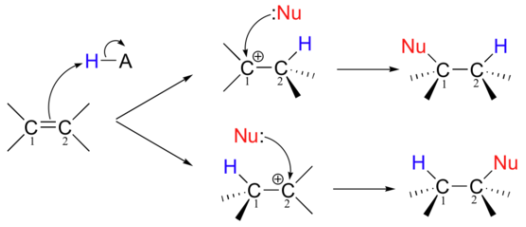
Notice that only the hydrogens directly attached to the carbon atoms at either end of the double bond count. The ones in the CH_3 group are totally irrelevant.

Contributors

- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Jim Clark (Chemguide.co.uk)

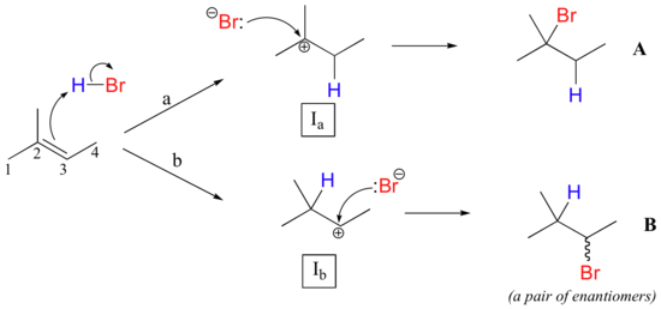
10.10: Markovnikov's Rule

very important regarding electrophilic addition reactions is that if the starting alkene is asymmetrical, there are two possible courses that could be followed, depending on which of the two alkene carbons forms the new sigma bond in the first step.

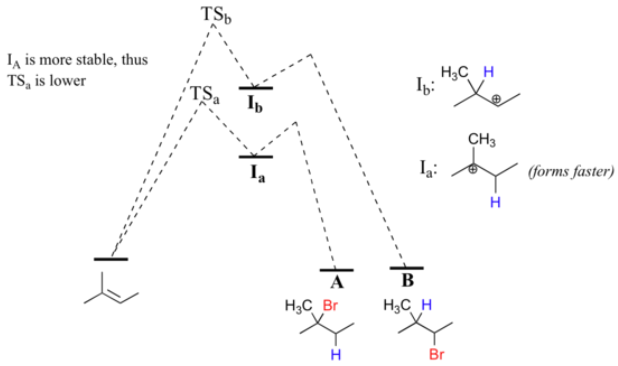


Of course, the two reaction courses involve two different carbocation intermediates, which may have different energy levels. Two different products are possible, and in general *the product which predominates will be the one that is derived from the lower-energy carbocation intermediate*.

This important regiochemical principle is nicely illustrated by a simple electrophilic addition that is commonly carried out in the organic laboratory: the conversion of an alkene to an alkyl bromide by electrophilic addition of HBr to the double bond. Let's look at a hypothetical addition of HBr to 2-methyl-2-butene, pictured below. Two different regiochemical outcomes are possible:

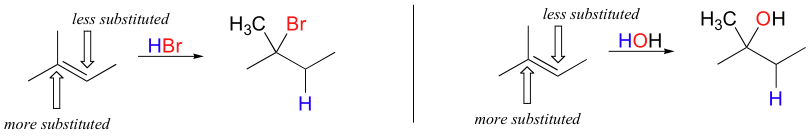


The initial protonation step could follow two different pathways, resulting in two different carbocation intermediates: pathway '**a**' gives a tertiary carbocation intermediate (I_a), while pathway '**b**' gives a secondary carbocation intermediate (I_b) We know already that the tertiary carbocation is more stable (in other words, lower in energy). According to the Hammond postulate, this implies that the activation energy for pathway **a** is lower than in pathway **b**, meaning in turn that I_a forms *faster*.



Because the protonation step is the rate determining step for the reaction, the tertiary alkyl bromide A will form much faster than the secondary alkyl halide B, and thus A will be the predominant product observed in this reaction. This is a good example of a non-enzymatic organic reaction that is highly regiospecific.

In the example above, the difference in carbocation stability can be accounted for by the electron-donating effects of the extra methyl group on one side of the double bond. It is generally observed that, in electrophilic addition of acids (including water) to asymmetrical alkenes, the *more substituted* carbon is the one that ends up bonded to the heteroatom of the acid, while the less substituted carbon is protonated.

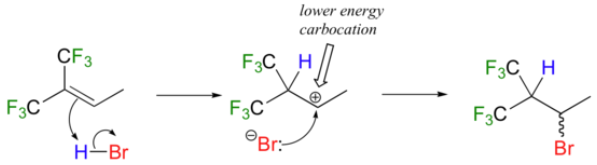


This rule of thumb is known as **Markovnikov's rule**, after the Russian chemist Vladimir Markovnikov who proposed it in 1869.

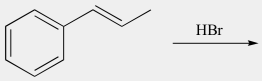
While it is useful in many cases, Markovikov's rule does not apply to all possible electrophilic additions. It is more accurate to use the more general principle that has already been stated above:

When an asymmetrical alkene undergoes electrophilic addition, the product that predominates is the one that results from the more stable of the two possible carbocation intermediates.

How is this different from Markovnikov's original rule? Consider the following hypothetical reaction, which is similar to the HBr addition shown above except that the six methyl hydrogens on the left side of the double bond have been replaced by highly electron-withdrawing fluorines.



Now when HBr is added, it is the *less* substituted carbocation that forms faster in the rate-determining protonation step, because in this intermediate the carbon bearing the positive charge is located further away from the electron-withdrawing, *cation-destabilizing* fluorines. As a result, the predominant product is the secondary rather than the tertiary bromoalkane. This would be referred to as an 'anti-Markovnikov' addition product, because it 'breaks' Markovnikov's rule.

Example
Predict the product of the following reaction: 

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

10.11: Stereochemistry of Electrophilic Addition of HX

As illustrated in the drawing below, the pi-bond fixes the carbon-carbon double bond in a planar configuration, and does not permit free rotation about the double bond itself. We see then that addition reactions to this function might occur in three different ways, depending on the relative orientation of the atoms or groups that add to the carbons of the double bond: (i) they may bond from the same side, (ii) they may bond from opposite sides, or (iii) they may bond randomly from both sides. The first two possibilities are examples of stereoselectivity, the first being termed **syn-addition**, and the second **anti-addition**. Since initial electrophilic attack on the double bond may occur equally well from either side, it is in the second step (or stage) of the reaction (bonding of the nucleophile) that stereoselectivity may be imposed.

If the two-step mechanism described above is correct, and if the carbocation intermediate is sufficiently long-lived to freely-rotate about the sigma-bond component of the original double bond, we would expect to find random or non-stereoselective addition in the products. On the other hand, if the intermediate is short-lived and factors such as steric hindrance or neighboring group interactions favor one side in the second step, then stereoselectivity in product formation is likely. The following table summarizes the results obtained from many studies, the formula HX refers to all the strong Brønsted acids. The interesting differences in stereoselectivity noted here provide further insight into the mechanisms of these addition reactions.

Reagent	H–X	X_2	HO–X	RS–Cl	$Hg(OAc)_2$	BH_3
Stereoselectivity	mixed	anti	anti	anti	anti	syn

Contributors

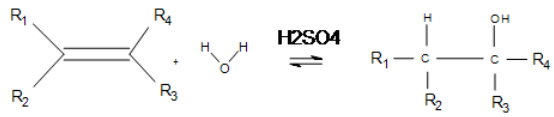
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

10.12: Hydration—Electrophilic Addition of Water

Electrophilic hydration is the act of adding electrophilic hydrogen from a non-nucleophilic strong acid (a reusable catalyst, examples of which include sulfuric and phosphoric acid) and applying appropriate temperatures to break the alkene's double bond. After a carbocation is formed, water bonds with the carbocation to form a 1º, 2º, or 3º alcohol on the alkane.

What Is Electrophilic Hydration?

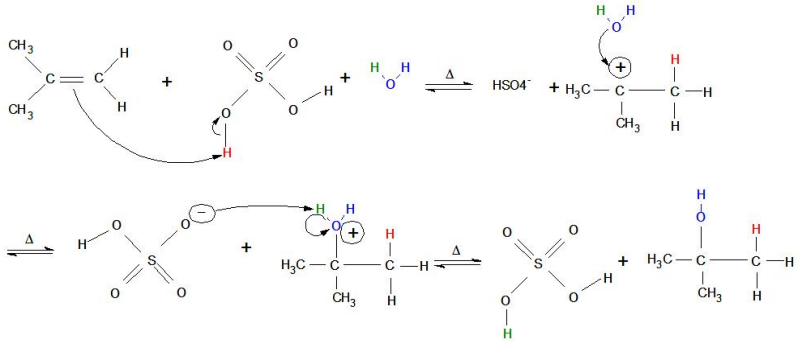
Electrophilic hydration is the reverse dehydration of alcohols and has practical application in making alcohols for fuels and reagents for other reactions. The basic reaction under certain temperatures (given below) is the following:



The phrase "electrophilic" literally means "electron loving" (whereas "nucleophilic" means "nucleus loving"). Electrophilic hydrogen is essentially a proton: a hydrogen atom stripped of its electrons. Electrophilic hydrogen is commonly used to help break double bonds or restore catalysts (see S_N2 for more details).

How Does Electrophilic Hydration Work?

Mechanism for 3º Alcohol (1º and 2º mechanisms are similar):



Temperatures for Types of Alcohol Synthesis

Heat is used to catalyze electrophilic hydration; because the reaction is in equilibrium with the dehydration of an alcohol, which requires higher temperatures to form an alkene, lower temperatures are required to form an alcohol. *The exact temperatures used are highly variable and depend on the product being formed.*

- Primary Alcohol: Less than 170ºC
- Secondary Alcohol: Less than 100ºC
- Tertiary Alcohol: Less than 25ºC

But...Why Does Electrophilic Hydration Work?

- An alkene placed in an aqueous non-nucleophilic strong acid immediately "reaches out" with its double bond and attacks one of the acid's hydrogen atoms (meanwhile, the bond between oxygen and hydrogen performs heterolytic cleavage toward the oxygen—in other words, both electrons from the oxygen/hydrogen single bond move onto the oxygen atom).
- A carbocation is formed on the original alkene (now alkane) in the more-substituted position, where the oxygen end of water attacks with its 4 non-bonded valence electrons (oxygen has 6 total valence electrons because it is found in Group 6 on the periodic table and the second row down: two electrons in a 2s-orbital and four in 2p-orbitals. Oxygen donates one valence electron to each bond it forms, leaving four 4 non-bonded valence electrons).
- After the blue oxygen atom forms its third bond with the more-substituted carbon, it develops a positive charge (3 bonds and 2 valence electrons give the blue oxygen atom a formal charge of +1).

- The bond between the green hydrogen and the blue oxygen undergoes heterolytic cleavage, and both the electrons from the bond move onto the blue oxygen. The now negatively-charged strong acid picks up the green electrophilic hydrogen.
- Now that the reaction is complete, the non-nucleophilic strong acid is regenerated as a catalyst and an alcohol forms on the most substituted carbon of the current alkane. At lower temperatures, more alcohol product can be formed.

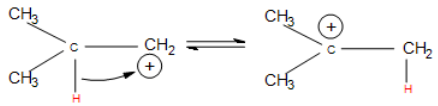
What is Regiochemistry and How Does It Apply?

Regiochemistry deals with where the substituent bonds on the product. **Zaitsev**'s and **Markovnikov**'s rules address regiochemistry, but Zaitsev's rule applies when synthesizing an alkene while Markovnikov's rule describes where the substituent bonds onto the product. In the case of electrophilic hydration, Markovnikov's rule is the only rule that *directly* applies. See the following for an in-depth explanation of regiochemistry Markovnikov explanation: Radical Additions--Anti-Markovnikov Product Formation

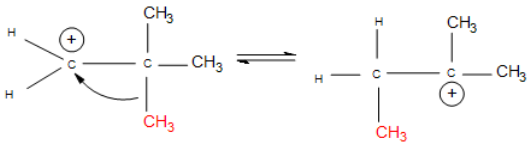
In the mechanism for a 3º alcohol shown above, the red H is added to the least-substituted carbon connected to the nucleophilic double bonds (it has less carbons attached to it). This means that the carbocation forms on the 3º carbon, causing it to be highly stabilized by *hyperconjugation*—electrons in nearby sigma (single) bonds help fill the empty p-orbital of the carbocation, which lessens the positive charge. More substitution on a carbon means more sigma bonds are available to "help out" (by using overlap) with the positive charge, which creates greater *carbocation stability*. In other words, **carbocations form on the most substituted carbon** connected to the double bond. Carbocations are also stabilized by resonance, but resonance is not a large factor in this case because any carbon-carbon double bonds are used to initiate the reaction, and other double bonded molecules can cause a completely different reaction.

If the carbocation does originally form on the less substituted part of the alkene, carbocation rearrangements occur to form more substituted products:

- **Hydride shifts:** a hydrogen atom bonded to a carbon atom next to the carbocation leaves that carbon to bond with the carbocation (after the hydrogen has taken both electrons from the single bond, it is known as a hydride). This changes the once neighboring carbon to a carbocation, and the former carbocation becomes a neighboring carbon atom.



- **Alkyl shifts:** if no hydrogen atoms are available for a hydride shift, an entire methyl group performs the same shift.

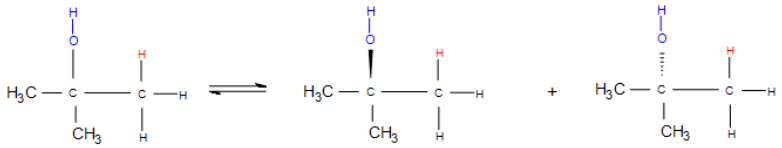


The nucleophile attacks the positive charge formed on the most substituted carbon connected to the double bond, because the nucleophile is seeking that positive charge. In the mechanism for a 3º alcohol shown above, water is the nucleophile. When the green H is removed from the water molecule, the alcohol attached to the most substituted carbon. Hence, **electrophilic hydration follows Markovnikov's rule.**

What is Stereochemistry and How Does It Apply?

Stereochemistry deals with how the substituent bonds on the product directionally. Dashes and wedges denote stereochemistry by showing whether the molecule or atom is going into or out of the plane of the board. Whenever the bond is a simple single straight line, the molecule that is bonded is equally likely to be found going into the plane of the board as it is out of the plane of the board. This indicates that **the product is a racemic mixture**.

Electrophilic hydration adopts a stereochemistry wherein the substituent is equally likely to bond pointing into the plane of the board as it is pointing out of the plane of the board. The 3º alcohol product could look like either of the following products:



Note: Whenever a straight line is used along with dashes and wedges on the same molecule, it could be denoting that the straight line bond is in the same plane as the board. Practice with a molecular model kit and attempting the practice problems at the end can help eliminate any ambiguity.

Is this a Reversible Synthesis?

Electrophilic hydration is reversible because an alkene in water is in equilibrium with the alcohol product. To sway the equilibrium one way or another, the temperature or the concentration of the non-nucleophilic strong acid can be changed. For example:

- Less sulfuric or phosphoric acid and an excess of water help synthesize more alcohol product.
- Lower temperatures help synthesize more alcohol product.

Is There a Better Way to Add Water to Synthesize an Alcohol From an Alkene?

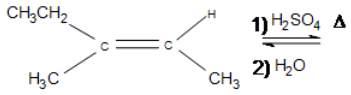
A more efficient pathway does exist: see Oxymercuration - Demercuration: A Special Electrophilic Addition. Oxymercuration does not allow for rearrangements, but it does require the use of mercury, which is highly toxic. Detractions for using electrophilic hydration to make alcohols include:

- Allowing for carbocation rearrangements
- Poor yields due to the reactants and products being in equilibrium
- Allowing for product mixtures (such as an (R)-enantiomer and an (S)-enantiomer)
- Using sulfuric or phosphoric acid

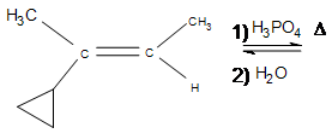
Problems

Predict the product of each reaction.

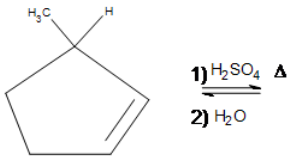
1)



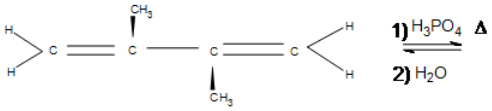
2) How does the cyclopropane group affect the reaction?



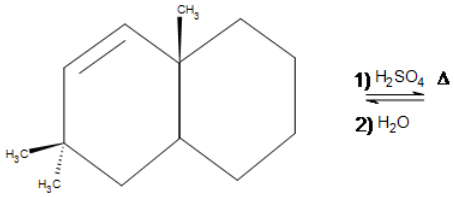
3) (Hint: What is different about this problem?)



4) (Hint: Consider stereochemistry.)

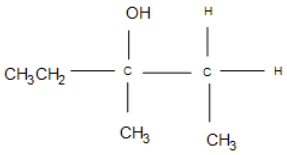


5) Indicate any shifts as well as the major product:

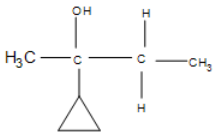


Answers to Practice Problems

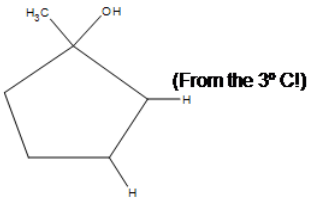
1) This is a basic electrophilic hydration.



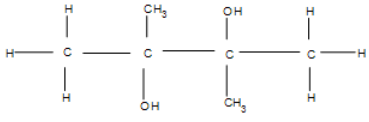
2) The answer is additional side products, but **the major product formed is still the same** (the product shown). Depending on the temperatures used, the cyclopropane may open up into a straight chain, which makes it unlikely that the major product will form (after the reaction, it is unlikely that the 3º carbon will remain as such).



3) A hydride shift actually occurs from the top of the 1-methylcyclopentane to where the carbocation had formed.

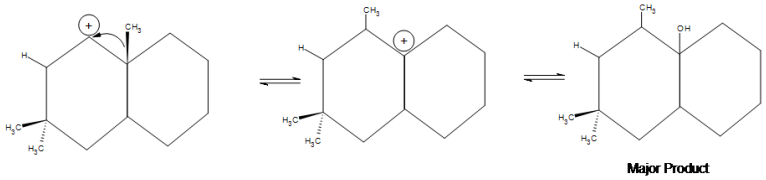


4) **This reaction will have poor yields due to a very unstable intermediate**. For a brief moment, carbocations can form on the two center carbons, which are more stable than the outer two carbons. The carbocations have an sp^2 hybridization, and when the water is added on, the carbons change their hybridization to sp^3. This makes the methyl and alcohol groups equally likely to be found going into or out of the plane of the paper- the product is racemic.



5) In the first picture shown below, an alkyl shift occurs but a hydride shift (which occurs faster) is possible. Why doesn't a hydride shift occur? The answer is because **the alkyl shift leads to a more stable product**. There is a noticeable amount of side product

that forms where the two methyl groups are, but the major product shown below is still the most significant due to the hyperconjugation that occurs by being in between the two cyclohexanes.



References

1. Vollhardt and Schore. Organic Chemistry, Structure and Function- Fifth Edition. New York: W. H. Freeman and Company, 2007.
2. Krow, Grant. "Sulfuric Acid." Encyclopedia of Reagents for Organic Synthesis. Philadelphia, Pennsylvania: John Wiley & Sons, 2001.

Outside Links

- http://en.wikipedia.org/wiki/Electrophile
- http://www.youtube.com/watch?v=Z7xskJnGDEM
- For more on Hyperconjugation: http://en.wikipedia.org/wiki/Hyperconjugation
- For more on Markovnikov's Rule: http://en.wikipedia.org/wiki/Markovnikov_rule
- For more on Zaitsev's Rule: http://en.wikipedia.org/wiki/Zaitsev%27s_rule

Contributors

- Lance Peery (UCD)

10.13: Halogenation—Addition of Halogen

Halogens can act as electrophiles to attack a double bond in alkene. Double bond represents a region of electron density and therefore functions as a nucleophile. How is it possible for a halogen to obtain positive charge to be an electrophile?

Introduction

As halogen molecule, for example Br_2, approaches a double bond of the alkene, electrons in the double bond repel electrons in bromine molecule causing polarization of the halogen bond. This creates a dipolar moment in the halogen molecule bond. Heterolytic bond cleavage occurs and one of the halogens obtains positive charge and reacts as an electrophile. The reaction of the addition is not regioselective but stereoselective.Stereochemistry of this addition can be explained by the mechanism of the reaction.In the first step electrophilic halogen with a positive charge approaches the double carbon bond and 2 p orbitals of the halogen, bond with two carbon atoms and create a cyclic ion with a halogen as the intermediate step. In the second step, halogen with the negative charge attacks any of the two carbons in the cyclic ion from the back side of the cycle as in the S_N2 reaction. Therefore stereochemistry of the product is **vicinial dihalides through anti** addition.

$$R_2C{=}CR_2 + X_2 \rightarrow R_2CX{-}CR_2X \tag{10.13.1}$$

Halogens that are commonly used in this type of the reaction are: Br and Cl. In thermodynamical terms I is too slow for this reaction because of the size of its atom, and F is too vigorous and explosive.

Solvents that are used for this type of electrophilic halogenation are inert (e.g., CCl_4) can be used in this reaction.

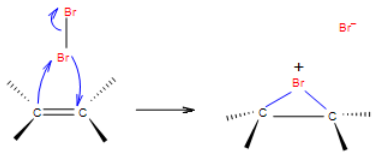
Because halogen with negative charge can attack any carbon from the opposite side of the cycle it creates a mixture of steric products.Optically inactive starting material produce optically inactive achiral products (meso) or a racemic mixture.

Electrophilic addition mechanism consists of two steps.

Before constructing the mechanism let us summarize conditions for this reaction. We will use Br_2 in our example for halogenation of ethylene.

Nucleophile	Double bond in alkene
Electrophile	Br_2, Cl_2
Regiochemistry	not relevant
Stereochemistry	**ANTI**

Step 1: In the first step of the addition the Br-Br bond polarizes, heterolytic cleavage occurs and Br with the positive charge forms a intermediate cycle with the double bond.



Step 2: In the second step, bromide anion attacks any carbon of the bridged bromonium ion from the back side of the cycle. Cycle opens up and two halogens are in the position **anti**.

Summary

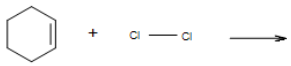
Hallogens can act as electrophiles due to polarizability of their covalent bond.Addition of halogens is stereospecific and produces vicinial dihalides with anti addition.Cis starting material will give mixture of enantiomers and trans produces a meso compound.

References

1. Vollhard,K.Peter C., and Neil E.Schore.Organic Chemistry:Structure and Function.New Yourk: W.H.Freeman and Company 2007
2. Chemestry-A Europian Journal 9 (2003) :1036-1044

Problems

1.What is the mechanism of adding Cl_2 to the cyclohexene?

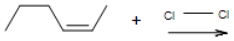


2.A reaction of Br_2 molecule in an inert solvent with alkene follows?

a) syn addition

b) anti addition

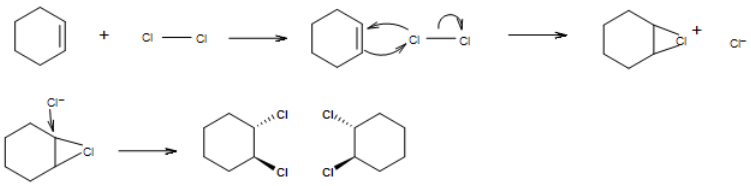
c) Morkovnikov rule

3) 

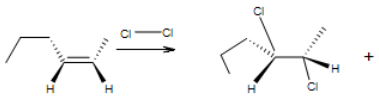
4) 

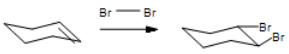
Key:

1.



2. b

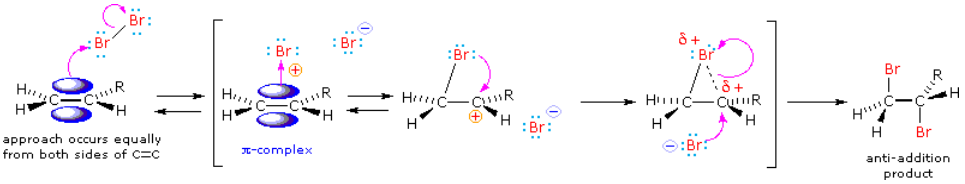
3.  enantiomer

4. 

10.14: Stereochemistry of Halogenation

The halogens chlorine and bromine add rapidly to a wide variety of alkenes without inducing the kinds of structural rearrangements (carbocation shifts) noted for strong acids - this is because a discreet carbocation intermediate does not form in these reactions. The stereoselectivity of halogen additions is strongly anti, as shown in many of the following examples.

We can account both for the high stereoselectivity and the lack of rearrangement in these reactions by proposing a stabilizing interaction between the developing carbocation center and the electron rich halogen atom on the adjacent carbon. This interaction delocalizes the positive charge on the intermediate and blocks halide ion attack from the *syn*-location.



The stabilization provided by the halogen-carbocation bonding makes rearrangement unlikely, and in a few cases three-membered cyclic halonium cations have been isolated and identified as true intermediates. A resonance description of such a bromonium ion intermediate is shown below. The positive charge is delocalized over all the atoms of the ring, but should be concentrated at the more substituted carbon (where positive charge is more stable), and this is the site to which the nucleophile will bond.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

10.15: Halohydrin Formation

The proton is not the only electrophilic species that initiates addition reactions to the double bond of alkenes. Lewis acids like the halogens, boron hydrides and certain transition metal ions are able to bond to the alkene pi-electrons, and the resulting complexes rearrange or are attacked by nucleophiles to give addition products.The electrophilic character of the halogens is well known. Chlorine (Cl_2) and bromine(Br_2) react selectively with the double bond of alkenes, and these reactions are what we will focus on. Fluorine adds uncontrollably with alkenes,and the addition of iodine is unfavorable, so these are not useful preparative methods.

The addition of chlorine and bromine to alkenes, as shown below, proceeds by an initial electrophilic attack on the pi-electrons of the double bond. Dihalo-compounds in which the halogens are bound to adjacent carbons are called vicinal, from the Latin *vicinalis*, meaning neighboring.

$$R_2C{=}CR_2 + X_2 \longrightarrow R_2CX\text{-}CR_2X$$

Other halogen-containing reagents which add to double bonds include hypohalous acids, HOX, and sulfenyl chlorides, RSCl. These reagents are unsymmetrical, so their addition to unsymmetrical double bonds may in principle take place in two ways. In practice, these addition reactions are regioselective, with one of the two possible constitutionally isomeric products being favored. The electrophilic moiety in both of these reagents is the halogen.

$$(CH_3)_2C{=}CH_2 + HOBr \longrightarrow (CH_3)_2COH\text{-}CH_2Br$$

$$(CH_3)_2C{=}CH_2 + C_6H_5SCl \longrightarrow (CH_3)_2CCl\text{-}CH_2SC_6H_5$$

The regioselectivity of the above reactions may be explained by the same mechanism we used to rationalize the Markovnikov rule. Thus, bonding of an electrophilic species to the double bond of an alkene should result in preferential formation of the more stable (more highly substituted) carbocation, and this intermediate should then combine rapidly with a nucleophilic species to produce the addition product.

To apply this mechanism we need to determine the electrophilic moiety in each of the reagents. By using electronegativity differences we can dissect common addition reagents into electrophilic and nucleophilic moieties, a**s shown on the right**. In the case of hypochlorous and hypobromous acids (HOX), these weak Brønsted acids (pKa's ca. 8) do not react as proton donors; and since oxygen is more electronegative than chlorine or bromine, the electrophile will be a halide cation. The nucleophilic species that bonds to the intermediate carbocation is then hydroxide ion, or more likely water (the usual solvent for these reagents), and the products are called halohydrins. Sulfenyl chlorides add in the opposite manner because the electrophile is a sulfur cation, RS(+), whereas the nucleophilic moiety is chloride anion (chlorine is more electronegative than sulfur).

Below are some examples illustrating the addition of various electrophilic halogen reagents to alkene groups. Notice the specific regiochemistry of the products, as explained above.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

10.16: Hydroboration–Oxidation

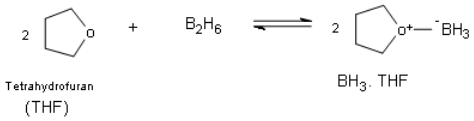
Hydroboration-Oxidation is a two step pathway used to produce alcohols. The reaction proceeds in an Anti-Markovnikov manner, where the hydrogen (from BH_3 or BHR_2) attaches to the more substituted carbon and the boron attaches to the least substituted carbon in the alkene bouble bond. Furthermore, the borane acts as a lewis acid by accepting two electrons in its empty p orbital from an alkene that is electron rich. This process allows boron to have an electron octet. A very interesting characteristic of this process is that it does not require any activation by a catalyst. The Hydroboration mechanism has the elements of both hydrogenation and electrophilic addition and it is a stereospecific (***syn addition),*** meaning that the hydroboration takes place on the same face of the double bond, this leads ***cis*** stereochemistry.

Introduction

Hydroboration-oxidation of alkenes has been a very valuable laboratory method for the stereoselectivity and regioselectivity of alkenes. An Additional feature of this reaction is that it occurs without rearrangement.

The Borane Complex

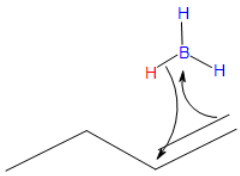
First off it is very imporatnt to understand little bit about the structure and the properties of the borane molecule. Borane exists naturally as a very toxic gas and it exists as dimer of the general formula B_2H_6 (diborane). Additionally, the dimer B_2H_6ignites spontaneously in air. Borane is commercially available in ether and tetrahydrofuran (THF), in these solutions the borane can exist as a lewis acid-base complex, which allows boron to have an electron octet.



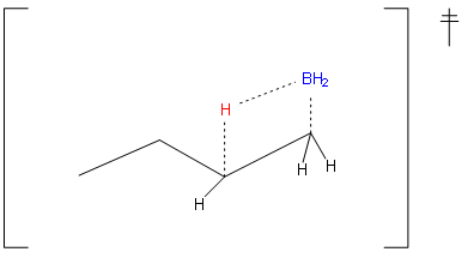
The Mechanism

Step #1

- Part #1: Hydroboration of the alkene. In this first step the addittion of the borane to the alkene is initiated and prceeds as a concerted reaction because bond breaking and bond formation occurs at the same time. This part consists of the vacant 2p orbital of the boron electrophile pairing with the electron pair of the ? bondof the nucleophile.

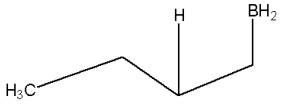


Transition state



*** Note that a carbocation is not formed. Therefore, no rearrangement takes place.**

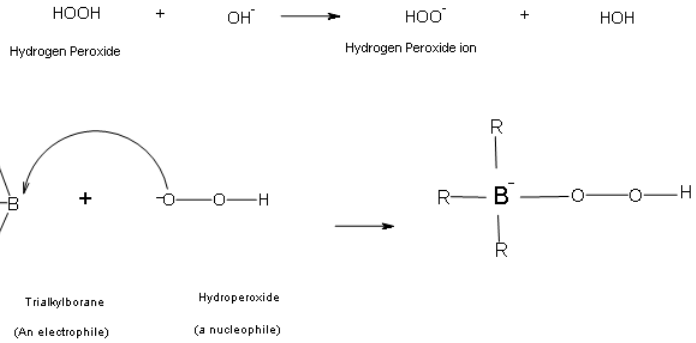
- Part #2: The Anti Markovnikov addition of Boron. The boron adds to the less substituted carbon of the alkene, which then places the hydrogen on the more substituted carbon. Both, the boron and the hydrogen add simultaneously on the same face of the double bond (syn addition).



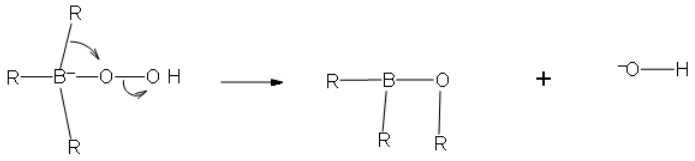
Oxidation of the Trialkylborane by Hydrogen Peroxide

Step #2

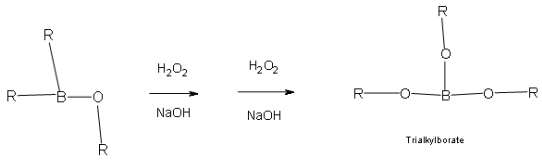
- Part #1: the first part of this mechanism deals with the donation of a pair of electrons from the hydrogen peroxide ion. the hydrogen peroxide is the nucleophile in this reaction because it is the electron donor to the newly formed trialkylborane that resulted from hydroboration.



- Part 2: In this second part of the mechanism, a rearrangement of an R group with its pair of bonding electrons to an adjacent oxygen results in the removal of a hydroxide ion.



Two more of these reactions with hydroperoxide will occur in order give a trialkylborate



- Part 3: This is the final part of the Oxidation process. In this part the trialkylborate reacts with aqueous NaOH to give the alcohol and sodium borate.

If you need additional visuals to aid you in understanding the mechanism, click on the outside links provided here that will take you to other pages and media that are very helpful as well.

Stereochemistry of hydroboration

The hydroboration reaction is among the few simple addition reactions that proceed cleanly in a *syn* fashion. As noted above, this is a single-step reaction. Since the bonding of the double bond carbons to boron and hydrogen is concerted, it follows that the geometry of this addition must be syn. Furthermore, rearrangements are unlikely inasmuch as a discrete carbocation intermediate is never formed. These features are illustrated for the hydroboration of α-pinene.

Since the hydroboration procedure is most commonly used to hydrate alkenes in an anti-Markovnikov fashion, we also need to know the stereoselectivity of the second oxidation reaction, which substitutes a hydroxyl group for the boron atom. Independent study has shown this reaction takes place with retention of configuration so the overall addition of water is also syn.

The hydroboration of α-pinene also provides a nice example of steric hindrance control in a chemical reaction. In the less complex alkenes used in earlier examples the plane of the double bond was often a plane of symmetry, and addition reagents could approach with equal ease from either side. In this case, one of the methyl groups bonded to C-6 (colored blue in the equation) covers one face of the double bond, blocking any approach from that side. All reagents that add to this double bond must therefore approach from the side opposite this methyl.

Outside links

- http://en.wikipedia.org/wiki/Hydroboration-oxidation
- http://bcs.whfreeman.com/vollhardtsc...2/12010-03.htm
- http://www.chemhelper.com/hydroboration.html
- http://www.cartage.org.lb/en/themes/...roboration.htm
- http://www.organic-chemistry.org/nam...oboration.shtm

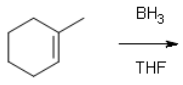
References

1. Vollhardt, Peter, and Neil Shore. Organic Chemistry: Structure and Function. 5th. New York: W.H. Freeman and Company, 2007.
2. Foote, S. Christopher, and William H. Brown. Organic Chemistry. 5th. Belmont, CA: Brooks/Cole Cengage Learning, 2005.
3. Bruice, Paula Yurkanis. Oragnic Chemistry. 5th. CA. Prentice Hall, 2006.
4. Bergbreiter E. David , and David P. Rainville. Stereochemistry of hydroboration-oxidation of terminal alkenes. *J. Org. Chem.*, 1976, 41 (18), pp 3031–3033
5. Ilich, Predrag-Peter; Rickertsen, Lucas S., and Becker Erienne. Polar Addition to C=C Group: Why Is Anti-Markovnikov Hydroboration-Oxidation of Alkenes Not "Anti-"? Journal of Chemical Education., 2006, v83, n11, pg 1681-1685

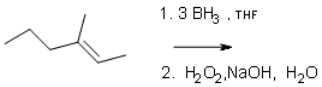
Problems

What are the products of these following reactions?

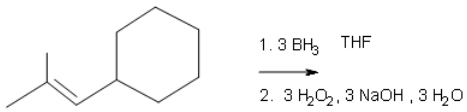
#1.



#2.

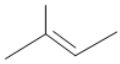


#3.



Draw the structural formulas for the alcohols that result from hydroboration-oxidation of the alkenes shown.

#4.

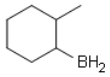


#5. (E)-3-methyl-2-pentene

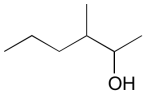
If you need clarification or a reminder on the nomenclature of alkenes refer to the link below on naming the alkenes.

Answers

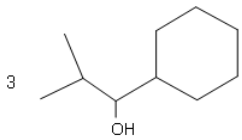
#1.



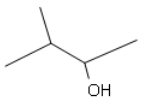
#2.



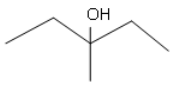
#3.



#4.



#5.



Contributors

- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Jim Clark (Chemguide.co.uk)

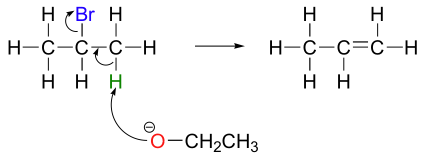
10.17: Keeping Track of Reactions

E2 Reaction

E2 reactions are typically seen with secondary and tertiary alkyl halides, but a hindered base is necessary with a primary halide. The mechanism by which it occurs is a single step **concerted** reaction with one transition state. The rate at which this mechanism occurs is second order kinetics, and depends on both the base and alkyl halide. A good leaving group is required because it is involved in the rate determining step. The leaving groups must be coplanar in order to form a pi bond; carbons go from sp^3 to sp^2 hybridization states.

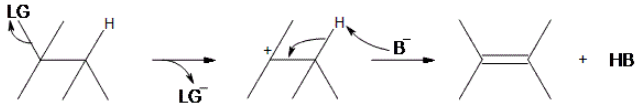
To get a clearer picture of the interplay of these factors involved in a a reaction between a nucleophile/base and an alkyl halide, consider the reaction of a 2º-alkyl halide, isopropyl bromide, with two different nucleophiles. In one pathway, a methanethiolate nucleophile substitutes for bromine in an S_N2 reaction. In the other (bottom) pathway, methoxide ion acts as a base (rather than as a nucleophile) in an elimination reaction. As we will soon see, the mechanism of this reaction is single-step, and is referred to as the E2 mechanism.

.



E1 Reaction

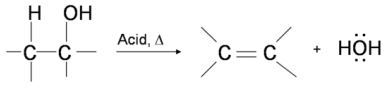
An E1 reaction involves the deprotonation of a hydrogen nearby (usually one carbon away, or the beta position) the carbocation resulting in the formation of an alkene product. In order to accomplish this, a Lewis base is required. For a simplified model, we'll take B to be a Lewis base, and LG to be a halogen leaving group.



As can be seen above, the preliminary step is the leaving group (LG) leaving on its own. Because it takes the electrons in the bond along with it, the carbon that was attached to it loses its electron, making it a carbocation. Once it becomes a carbocation, a Lewis Base ( ) deprotonates the intermediate carbocation at the beta position, which then donates its electrons to the neighboring C-C bond, forming a double bond. Unlike E2 reactions, which require the proton to be *anti* to the leaving group, E1 reactions only require a neighboring hydrogen. This is due to the fact that the leaving group has already left the molecule. The final product is an alkene along with the HB byproduct.

Dehydration

One way to synthesize alkenes is by dehydration of alcohols, a process in which alcohols undergo E1 or E2 mechanisms to lose water and form a double bond. The dehydration reaction of alcohols to generate alkene proceeds by heating the alcohols in the presence of a strong acid, such as sulfuric or phosphoric acid, at high temperatures.



Primary alcohol dehydrates through the E2 mechanism

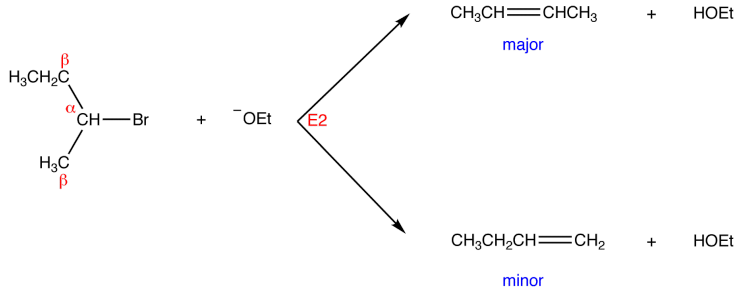
Oxygen donates two electrons to a proton from sulfuric acid H_2SO_4, forming an alkyloxonium ion. Then the nucleophile HSO_4^- back-side attacks one adjacent hydrogen and the alkyloxonium ion leaves in a concerted process, making a double bond.

Secondary and tertiary alcohols dehydrate through the E1 mechanism

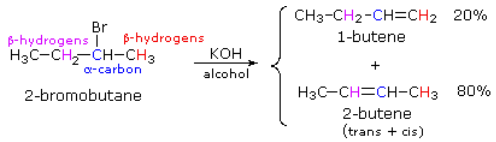
Similarly to the reaction above, secondary and tertiary –OH protonate to form alkyloxonium ions. However, in this case the ion leaves first and forms a carbocation as the reaction intermediate. The water molecule (which is a stronger base than the HSO_4^- ion) then abstracts a proton from an adjacent carbon, forming a double bond. Notice in the mechanism below that the aleke formed depends on which proton is abstracted: the red arrows show formation of the more substituted 2-butene, while the blue arrows show formation of the less substituted 1-butene. Recall the general rule that more substituted alkenes are more stable than less substituted alkenes, and *trans* alkenes are more stable than *cis* alkenes. Thereore, the *trans* diastereomer of the 2-butene product is most abundant.

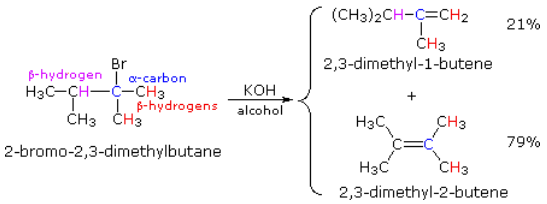
Zaitsev's Rule

Zaitsev's or Saytzev's (anglicized spelling) rule is an empirical rule used to predict regioselectivity of 1,2-elimination reactions occurring via the E1 or E2 mechanisms. It states that in a regioselective E1 or E2 reaction the major product is the more stable alkene, (i.e., the alkene with the more highly substituted double bond). For example:



If two or more structurally distinct groups of beta-hydrogens are present in a given reactant, then several constitutionally isomeric alkenes may be formed by an E2 elimination. This situation is illustrated by the 2-bromobutane and 2-bromo-2,3-dimethylbutane elimination examples given below.





Contributors

- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Gamini Gunawardena from the OChemPal site (Utah Valley University)

10.18: Alkenes in Organic Synthesis

Disconnection of bonds

Having chosen the TARGET molecule for synthesis, the next exercise is to draw out synthetic plans that would summarize all reasonable routes for its synthesis. During the past few decades, chemists have been working on a process called RETROSYNTHESIS. Retrosynthesis could be described as a logical Disconnection at strategic bonds in such a way that the process would progressively lead to easily available starting material(s) through several synthetic plans. Each plan thus evolved, describes a 'ROUTE' based on a retrosynthesis. Each disconnection leads to a simplified structure. The logic of such disconnections forms the basis for the retroanalysis of a given target molecule. Natural products have provided chemists with a large variety of structures, having complex functionalities and stereochemistry. This area has provided several challenging targets for development of these concepts. The underlining principle in devising logical approaches for synthetic routes is very much akin to the following simple problem. Let us have a look of the following big block, which is made by assembling several small blocks **(Fig 1.4.2.1)**. You could easily see that the large block could be broken down in different ways and then reassembled to give the same original block.

Fig 1.4.2.1

Now let us try and extend the same approach for the synthesis of a simple molecule. Let us look into three possible 'disconnections' for a cyclohexane ring as shown in **Fig 1.4.2.2**.

Fig 1.4.2.2

In the above analysis we have attempted to develop three ways of disconnecting the six membered ring. Have we thus created three pathways for the synthesis of cyclohexane ring? Do such disconnections make chemical sense? The background of an organic chemist should enable him to read the process as a chemical reaction in the reverse (or 'retro-') direction. The dots in the above structures could represent a carbonium ion, a carbanion, a free radical or a more complex reaction (such as a pericyclic reaction or a rearrangement). Applying such chemical thinking could open up several plausible reactions. Let us look into path b, which resulted from cleavage of one sigma bond. An anionic cyclisation route alone exposes several candidates as suitable intermediates for the formation of this linkage. The above analysis describes only three paths out of the large number of alternate cleavage routes that are available. An extended analysis shown below indicates more such possibilities **(Fig 1.4.2.3)**. Each such intermediate could be subjected to further disconnection process and the process continued until we reach a reasonably small, easily available starting materials. Thus, a complete 'SYNTHETIC TREE' could be constructed that would summarize all possible routes for the given target molecule.

Fig 1.4.2.3

1.4.3 Efficiency of a route

A route is said to be efficient when the ‘overall yield’ of the total process is the best amongst all routes investigated. This would depend not only on the number of steps involved in the synthesis, but also on the type of strategy followed. The strategy could involve a ‘linear syntheses’ involving only consequential steps or a ‘convergent syntheses’ involving fewer consequential steps. **Fig 1.4.3.1** shown below depicts a few patterns that could be recognized in such synthetic trees. When each disconnection process leads to only one feasible intermediate and the process proceeds in this fashion

Fig 1.4.3.1

all the way to one set of starting materials (SM), the process is called a Linear Synthesis. On the other hand, when an intermediate could be disconnected in two or more ways leading to different intermediates, branching occurs in the plan. The processes could be continued all the way to SMs. In such routes different branches of the synthetic pathways converge towards an intermediate. Such schemes are called Convergent Syntheses.

The flow charts shown below **(Fig 1.4.3.2)** depicts a hypothetical 5-step synthesis by the above two strategies. Assuming a very good yield (90%) at each step (this is rarely seen in real projects), a linier synthesis gives 59% overall yield, whereas a convergent synthesis gives 73% overall yield for the same number of steps..

Fig 1.4.3.2

1.4.4 Problem of substituents and stereoisomers

The situation becomes more complex when you consider the possibility of unwanted isomers generated at different steps of the synthesis. The overall yield drops down considerably for the synthesis of the right isomer. Reactions that yield single isomers (Diastereospecific reactions) in good yields are therefore preferred. Some reactions like the Diels Alder Reaction generate several stereopoints (points at which stereoisomers are generated) simultaneously in one step in a highly predictable manner. Such reactions are highly valued in planning synthetic strategies because several desirable structural features are introduced in one step. Where one pure enantiomer is the target, the situation is again complex. A pure compound in the final step could still have 50% unwanted enantiomer, thus leading to a drastic drop in the efficiency of the route. In such cases, it is desirable to separate the optical isomers as early

in the route as possible, along the synthetic route. This is the main merit of the Chiron Approach, in which the right starting material is chosen from an easily available, cheap 'chiral pool'. We would discuss this aspect after we have understood the logic of planning syntheses. Given these parameters, you could now decide on the most efficient route for any given target.

Molecules of interest are often more complex than the plain cyclohexane ring discussed above. They may have substituents and functional groups at specified points and even specific stereochemical points. Construction of a synthetic tree should ideally accommodate all these parameters to give efficient routes. Let us look into a slightly more complex example shown in **Fig 1.4.4.1** . The ketone **1.4.4.1A** is required as an intermediate in a synthesis. Unlike the plain cyclohexane discussed above, the substitution pattern and the keto- group in this molecule impose some restrictions on disconnection processes.

Fig 1.4.4.1

Cleavage a: This route implies attack of an anion of methylisopropylketone on a bromo-component. *Cleavage b:* This route implies simple regiospecific methylation of a larger ketone that bears all remaining structural elements. *Cleavage c:* This route implies three different possibilities. Route C-1 envisages an acylonium unit, which could come from an acid halide or an ester. Route C-2 implies an umpolung reaction at the acyl unit. Route C-3 suggests an oxidation of a secondary alcohol, which could be obtained through a Grignard-type reaction. *Cleavage d:* This implies a Micheal addition.

Each of these routes could be further developed backwards to complete the synthetic tree. These are just a few plausible routes to illustrate an important point that the details on the structure would restrict the possible cleavages to some strategic points. Notable contributions towards planning organic syntheses came from E.J. Corey's school. These developments have been compiles by Corey in a book by the title LOgIC OF CHEMICAL SYNTHESIS. These and several related presentations on this topic should be taken as guidelines. They are devised after analyzing most of the known approaches published in the literature and identifying a pattern in the logic. They need not restrict the scope for new possibilities. Some of the important strategies are outlined below.

1.4.5 Preliminary scan

When a synthetic chemist looks at the given Target, he should first ponder on some preliminary steps to simplify the problem on hand. Is the molecule polymeric? See whether the whole molecule could be split into monomeric units, which could be coupled by a known reaction. This is easily seen in the case of peptides, nucleotides and organic polymers. This could also be true to other natural products. In molecules like C-Toxiferin 1 **(1.4.5.1A) (Fig 1.4.5.1)**, the point of dimerisation is obvious. In several other cases, a deeper insight is required to identify the monomeric units, as is the case with Usnic acid **(1.4.5.1B)**. In the case of the macrolide antibiotic Nonactin **(1.4.5.1C)**, this strategy reduces the possibilities to the synthesis of a monomeric unit **(1.4.5.1D)**. The overall structure has S4 symmetry and is achiral even though assembled from chiral precursors. Both (+)-nonactic acid and (−)-nonactic acid **(1.4.5.1D)** are needed to construct the macrocycle and they are joined head-to-tail in an alternating (+)-(−)-(+)-(−) pattern. (see J. Am. Chem. Soc., 131, 17155 (2009) and references cited therein).

Fig 1.4.5.1

Is a part of the structure already solved? Critical study of the literature may often reveal that the same molecule or a closely related one has been solved. R.B. Woodward synthesized **(1.4.5.2C)** as a key intermediate in an elegant synthesis of Reserpine **(1.4.5.2A)**. The same intermediate compound **(1.4.5.2C)** became the key starting compound for Velluz et.al., in the synthesis of Deserpidine **(1.4.5.2B) (Fig 1.4.5.2)**.

Fig 1.4.5.2

Such strategies reduce the time taken for the synthesis of new drug candidates. These strategies are often used in natural product chemistry and drug chemistry. Once the preliminary scan is complete, the target molecule could be disconnected at Strategic Bonds.

1.4.6 Strategic Bonds, Retrons and Transforms

STRATEGIC BONDS are the bonds that are cleaved to arrive at suitable Starting Materials (SM) or SYNTHONS. For the purpose of bond disconnection, Corey has suggested that the structure could be classified according to the sub-structures generated by known chemical reactions. He called the sub-structures RETRONS and the chemical transformations that generate these Retrons were called TRANSFORMS. A short list of Transforms and Retrons are given below (TABLE 1.4.6.1). Note that when Transforms generate Retrons, the product may have new STEREOPOINTS (stereochemical details) generated that may need critical appraisal.

Fig 1.4.6.1

The structure of the target could be such that the Retron and the corresponding Transforms could be easily visualized and directly applied. In some cases, the Transforms or the Retrons may not be obvious. In several syntheses, transformations do not simplify the molecule, but they facilitate the process of synthesis. For example, a keto- group could be generated through modification of a -CH-NO_2 unit through a Nef reaction. This generates a new set of Retron / transforms pair. A few such transforms are listed below, along with the nomenclature suggested by Corey **(Fig 1.4.6.2)**.

Fig 1.4.6.2

A Rearrangement Reaction could be a powerful method for generating suitable new sub-structures. In the following example, a suitable Pinacol Retron, needed for the rearrangement is obtained through an acyloin transform **(Fig 1.4.6.3)**. Such rearrangement Retrons are often not obvious to inexperienced eyes.

Fig 1.4.6.3

Some transforms may be necessary to protect (acetals for ketones), modify (reduction of a ketone to alcohol to avoid an Aldol condensation during a Claisen condensation) or transpose a structural element such as a stereopoint (e.g. S_N2 inversion, epimerization etc.,) or shifting a functional group. Such transforms do not simplify the given structural unit. At times, activation at specific points on the structure may be introduced to bring about a C-C bond formation and later the extra group may be removed. For example, consider the following retrosynthesis in which an extra ester group has been introduced to facilitate a Dieckmann Retron. In complex targets, combinations of such strategies could prove to be a very productive strategy in planning retrosynthesis. Witness the chemical modification strategy shown below for an efficient stereospecific synthesis of a trisubstituted olefin **(Fig 1.4.6.4)**

Fig 1.4.6.4

Fig 1.4.6.4 Examples for FGA / FGR strategies for complex targets

Amongst the molecular architectures, the bridged-rings pose a complex challenge in Structure-Based disconnection procedures. Corey has suggested guidelines for efficient disconnections of strategic bonds.

A bond cleavage for retrosynthesis should lead to simplified structures, preferably bearing five- or six-membered rings. The medium and large rings are difficult to synthesize stereospecifically. Amongst the common rings, a six-membered ring is easily approached and manipulated to large and small rings. Simultaneous cleavage of two bonds, suggesting cycloaddition – retrons are often more efficient. Some cleavages of strategic bonds are shown in **Fig 1.4.6.5**, suggesting good and poor cleavage strategies based on this approach. However, these guidelines are not restrictive.

Fig 1.4.6.5

Fig 1.4.6.5: Some cleavages at strategic bonds on bridged-ring systems.

Identifying Retron – Transform sets in a given target molecule is therefore a critical component in retrosynthesis. Such an approach could often generate several synthetic routes. The merit of this approach is that starting materials do not prejudice this logic. Retrosyntheses thus developed could throws open several routes that need further critical scrutiny on the basis of known facts.

Identification of Retrons / Transforms sets provided the prerequisite for computer assisted programs designed for generating retrosynthetic routes. A list of Retrons and the corresponding transforms were interlinked and the data was stored in the computer. All known reactions were thus analyzed for their Retron / Transform characteristics and documented. The appropriate literature citations were also documented and linked. Based on these inputs, computer programs were designed to generate retrosynthetic routes for any given structure. Several such programs are now available in the market to help chemists generate synthetic strategies. Given any structure, these programs generate several routes. Once the scientist identifies the specific routes of interest for further analysis, the program generates detailed synthetic steps, reagents required and the appropriate citations. In spite of such powerful artificial intelligence, the intelligence and intuitive genius of a chemist is still capable of generating a new strategy, not yet programmed. Again, human intelligence is still a critical input for the analysis the routes generated using a computer. Based on the experience of the chemists' team, their projected aim of the project and facilities available, the routes are further screened.

Contributors

- Prof. R Balaji Rao (Department of Chemistry, Banaras Hindu University, Varanasi) as part of Information and Communication Technology

CHAPTER OVERVIEW

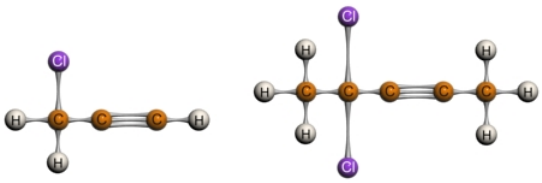
11: Alkynes

Topic hierarchy

11.1: Introduction

The simplest alkyne—a hydrocarbon with carbon-to-carbon triple bond—has the molecular formula C_2H_2 and is known by its common name—acetylene. Its structure is H–C≡C–H.

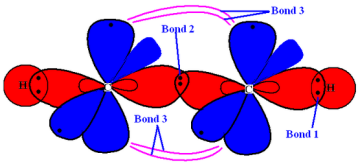
Terminal Alkyne: Internal Alkyne:

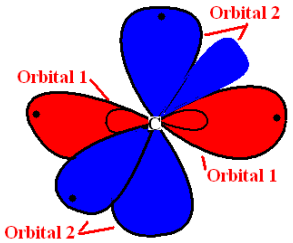


3-chloro-1-propyne 4,4-dichloro-2-pentyne

Bonding and Hybridization

Bond	Name	Location	Overlap
Bond 1	s (? bond) bond	Formed between 2 sp orbitals of carbon and hydrogen atoms	End-on overlap
Bond 2	S (? bond) bond	Formed between the 2 sp orbital of 2 unsaturated Carbon atoms.	End-on overlap
Bond 3	p-bonds (? bonds)	Formed between the 2 p-orbitals among the carbon atoms	Side-on overlap





Orbital	Name	Location
Orbital 1	sp hybrid orbitals	Formed in the linear structure model of carbon atom
Orbital 2	p-orbitals	Formed on each carbon

Contributors

- Jim Clark (Chemguide.co.uk)

11.2: Nomenclature

Alkynes are organic molecules made of the functional group carbon-carbon triple bonds and are written in the empirical formula of C_nH_{2n-2}. They are unsaturated hydrocarbons. Like alkenes have the suffix –ene, alkynes use the ending –yne; this suffix is used when there is only one alkyne in the molecule.

Introduction

HC ≡ CH

Here are the molecular formulas and names of the first ten carbon straight chain alkynes.

Name	Molecular Formula
Ethyne	C_2H_2
Propyne	C_3H_4
1-Butyne	C_4H_6
1-Pentyne	C_5H_8
1-Hexyne	C_6H_{10}
1-Heptyne	C_7H_{12}
1-Octyne	C_8H_{14}
1-Nonyne	C_9H_{16}
1-Decyne	$C_{10}H_{18}$

The more commonly used name for ethyne is acetylene, which used industrially.

Naming Alkynes

Like previously mentioned, the IUPAC rules are used for the naming of alkynes.

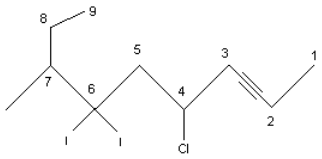
Rule 1

Find the longest carbon chain that includes both carbons of the triple bond.

Rule 2

Number the longest chain starting at the end closest to the triple bond. A 1-alkyne is referred to as a terminal alkyne and alkynes at any other position are called internal alkynes.

For example:

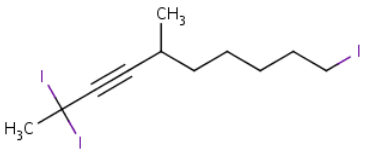


4-chloro-6-diiodo-7-methyl-2-nonyne

Rule 3

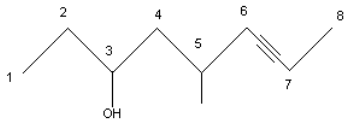
After numbering the longest chain with the lowest number assigned to the alkyne, label each of the substituents at its corresponding carbon. While writing out the name of the molecule, arrange the substituents in alphabetical order. If there are more than one of the same substituent use the prefixes di, tri, and tetra for two, three, and four substituents respectively. These prefixes are not taken into account in the alphabetical order.

For example:



1-triiodo-4-dimethyl-2-nonyne

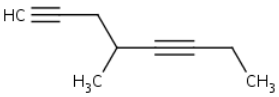
If there is an alcohol present in the molecule, number the longest chain starting at the end closest to it, and follow the same rules. However, the suffix would be –ynol, because the alcohol group takes priority over the triple bond.



5- methyl-7-octyn-3-ol

When there are two triple bonds in the molecule, find the longest carbon chain including both the triple bonds. Number the longest chain starting at the end closest to the triple bond that appears first. The suffix that would be used to name this molecule would be –diyne.

For example:

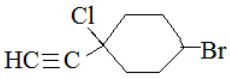


4-methyl-1,5-octadiyne

Rule 4

Substituents containing a triple bond are called alkynyl.

For example:



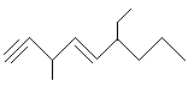
1-chloro-1-ethynyl-4-bromocyclohexane

Here is a table with a few of the alkynyl substituents:

Name	Molecule
Ethynyl	-C?CH
2- Propynyl	-CH_2C?CH
2-Butynyl	-CH_3C?CH_2CH_3

Rule 5

A molecule that contains both double and triple bonds is called an alkenyne. The chain can be numbered starting with the end closest to the functional group that appears first. For example:



6-ethyl-3-methyl-1,4-nonenyne

Outside links

- http://en.wikipedia.org/wiki/Alkyne
- http://www.cem.msu.edu/~reusch/VirtualText/nomen1.htm

Reference

1. Vollhardt, Peter, and Neil E. Schore. Organic Chemistry: Structure and Function. 5th Edition. New York: W. H. Freeman & Company, 2007.

Problems

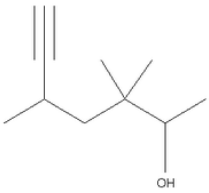
Name or draw out the following molecules:

1. 4,4-dimethyl-2-pentyne

2. 4-Penten-1-yne

3. 1-ethyl-3-dimethylnonyne

4.



Contributors

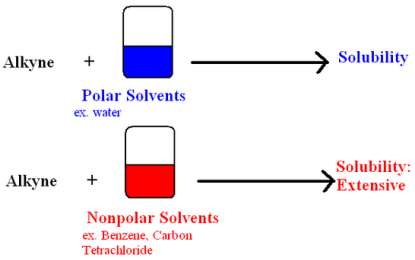
- A. Sheth and S. Sujit (UCD)

11.3: Physical Properties

The characteristic of the triple bond helps to explain the properties and bonding in the alkynes.

Importance of Triple Bonds

Hybridization due to triple bonds allows the uniqueness of alkyne structure. This triple bond contributes to the nonpolar bonding strength, linear, and the acidity of alkynes. Physical Properties include nonpolar due to slight solubility in polar solvents and insoluble in water. This solubility in water and polar solvents is a characteristic feature to alkenes as well. Alkynes dissolve in organic solvents.

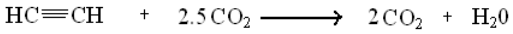


Boiling Points

Compared to alkanes and alkenes, alkynes have a slightly higher boiling point. Ethane has a boiling point of -88.6 ?C, while Ethene is -103.7 ?C and Ethyne has a higher boiling point of -84.0 ?C.

Alkynes are High In Energy

Alkynes are involved in a high release of energy because of repulsion of electrons. The content of energy involved in the alkyne molecule contributes to this high amount of energy. The pi-bonds however, do not encompass a great amount of energy even though the concentration is small within the molecule. The combustion of Ethyne is a major contributor from CO_2, water, and the ethyne molecule



??H = -311 kcal/mol

To help understand the relative stabilities of alkyne isomers, heats of hydrogenation must be used. Hydrogenation of the least energy, results in the release of the internal alkyne. With the result of the production of butane, the stability of internal versus terminal alkynes has significant relative stability due to hyperconjugation.

Outside links

- http://www.ucc.ie/academic/chem/dolc...t/alkynes.html
- http://www.cliffsnotes.com/WileyCDA/...eId-22631.html

References

1. Bloch, D.R. Organic chemistry demystified, New York : McGraw-Hill, 2006.
2. Vollhardt. Schore, Organic Chemistry Structure and Function Fifth Edition, New York: W.H. Freeman and Company, 2007.

Problems

1. What is the carbon-carbon, carbon-hydrogen bond length for alkyne? Is it shorter or longer than alkane and alkene?
2. Which is the most acidic and most stable, alkane, alkene, or alkyne? And depends on what?
3. How many pi bonds and sigma bonds are involved in the structure of ethyne?
4. Why is the carbon-hydrogen bond so short?
5. What is the alkyne triple bond characterizes by? How is this contribute to the weakness of the pi bonds?
6. How is heat of hydrogenation effects the stability of the alkyne?

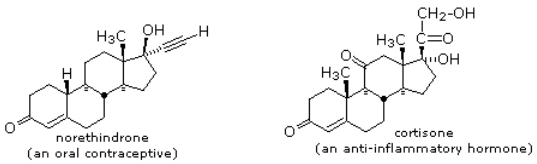
Contributors

- Bao Kha Nguyen, Garrett M. Chin

11.4: Interesting Alkynes

The important class of lipids called **steroids** are actually metabolic derivatives of terpenes, but they are customarily treated as a separate group. Steroids may be recognized by their tetracyclic skeleton, consisting of three fused six-membered and one five-membered ring.

Steroids are widely distributed in animals, where they are associated with a number of physiological processes. Examples of some important steroids are shown in the following diagram. Norethindrone is a synthetic steroid, all the other examples occur naturally. A common strategy in pharmaceutical chemistry is to take a natural compound, having certain desired biological properties together with undesired side effects, and to modify its structure to enhance the desired characteristics and diminish the undesired. This is sometimes accomplished by trial and error.



Medicinally Useful Steroids

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

11.5: Preparation of Alkynes

lkynes can be a useful functional group to synthesize due to some of their antibacterial, antiparasitic, and antifungal properties. One simple method for alkyne synthesis is by double elimination from a dihaloalkane.

Introduction

One case in which elimination can occur is when a haloalkane is put in contact with a nucleophile. The table below is used to determine which situations will result in elimination and the formation of a π bond.

Elimination: Haloalkane-Nucleophile Reaction

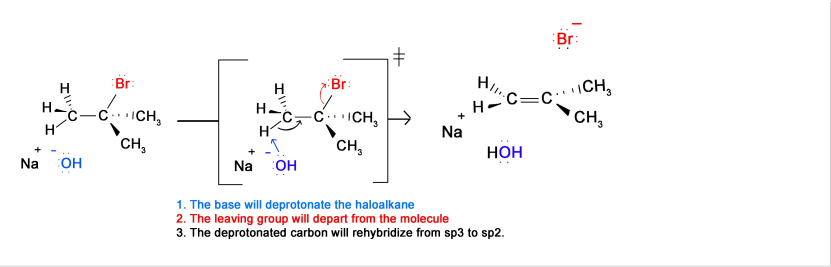
Type of Haloalkane	Weak Base, Poor Nucleophile	Weak Base, Good Nucleophile	Strong, Unhindered Base	Strong, Hindered Base
Primary				
Unhindered				E2
Branched			E2	E2
Secondary	E1		E2	E2
Tertiary	E1	E1	E2	E2

* Empty Box means no elimination or Pi bond forms

To synthesize alkynes from dihaloalkanes we use dehydrohalogenation. The majority of these reactions take place using alkoxide bases (other strong bases can also be used) with high temperatures. This combination results in the majority of the product being from the E2 mechanism.

E2 Mechanism

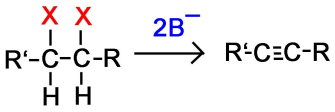
Recall that the E2 mechanism is a concerted reaction (occurs in 1 step). However, in this 1 step there are 3 different changes in the molecule. This is the reaction between 2-Bromo-2-methylpropane and Sodium Hyrdoxide.



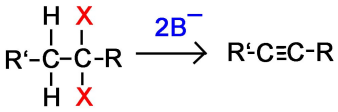
This is a brief review of the E2 reaction. For further information on why the reaction proceeds as it does visit the E2 reaction page. Now, if we apply this concept using 2 halides on vicinal or geminal carbons, the E2 reaction will take place twice resulting in the formation of 2 Pi bonds and thus an Alkyne.

Dihaloalkane Elimination

This is a general picture of the reaction taking place without any of the mechanisms shown.

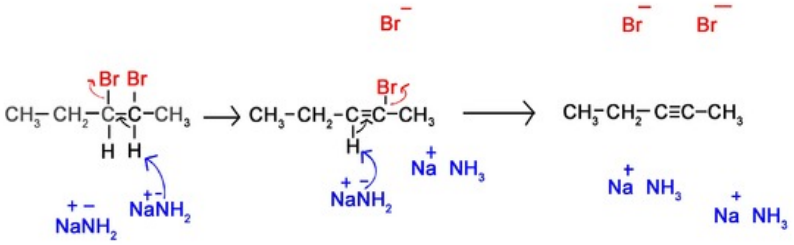


or



* With a terminal haloalkane the equation above is modified in that 3 equivalents of base will be used instead of 2.

Lets look at the mechanism of a reaction between 2,3-Dibromopentane with sodium amide in liquid ammonia.

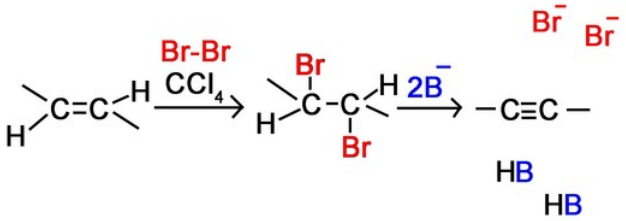


- Liquid ammonia is not part of the reaction, but is used as a solvent
- Notice the intermediate of the alkyne synthesis. It is stereospecifically in its anti form. Because the second proton and halogen are pulled off the molecule this is unimportant to the synthesis of alkynes. For more information on this see the page on preparation of alkenes from haloalkanes.

Preparation of Alkynes from Alkenes

Lastly, we will briefly look at how to prepare alkynes from alkenes. This is a simple process using first halogenation of the alkene bond to form the dihaloalkane, and next, using the double elimination process to protonate the alkane and from the 2 Pi bonds.

This first process is gone over in much greater detail in the page on halogenation of an alkene. In general, chlorine or bromine is used with an inert halogenated solvent like chloromethane to create a vicinal dihalide from an alkene. The vicinal dihalide formed is the reactant needed to produce the alkyene using double elimination, as covered previously on this page.

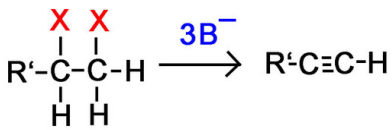


In The Lab

Due to the strong base and high temperatures needed for this reaction to take place, the triple bond may change positions. An example of this is when reactants that should form a terminal alkyne, form a 2-Alkyne instead. The use of $NaNH_2$ in liquid NH_3 is used in order to prevent this from happening due to its lower reacting temperature. Even so, most chemists will prefer to use nucleophilic substitution instead of elimination when trying to form a terminal alkyne.

Questions

Question 1: Why would we need 3 bases for every terminal dihaloalkane instead of 2 in order to form an alkyne?

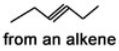


Question 2: What are the major products of the following reactions:

a.) 1,2-Dibromopentane with sodium amide in liquid ammonia

b.) 1-Pentene first with Br_2 and chloromethane, followed by sodium ethoxide (Na^+ ^-O-CH_2CH_3)

Question 3: What would be good starting molecules for the synthesis of the following molecules:

a.) 
from an alkene

b.) 
from a dihaloalkane

Question 4: Use a 6 carbon diene to synthesize a 6 carbon molecule with 2 terminal alkynes.

Answers

Answer 1: Remember that hydrogen atoms on terminal alkynes make the alkyne acidic. One of the base molecules will pull off the terminal hydrogen instead of one of the halides like we want.

Answer 2:

a.) 1-Pentyne

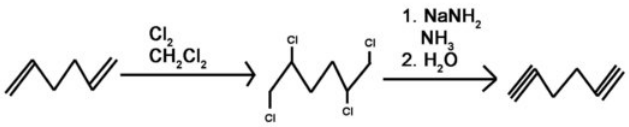
b.) 1-Pentyne

Answer 3:

a.) 

b.) 

Answer 4: Bromine or chlorine can be used with different inert solvents for the halogenation. This can be done using many different bases. Liquid ammonia is used as a solvent and needs to be followed by an aqueous work-up.



Outside links

- http://en.wikipedia.org/wiki/Alkyne

References

1. Vollhardt, Peter, and Neil Shore. Organic Chemistry: Structure and Function. 5th. New York: W.H. Freeman and Company, 2007.
2. Daley, Richard, and Sally Daley. "13.8 Elimination of Organohalogens." Organic Chemistry. Daley. 5 July 2005. 21 Feb. 2009. <http://www.ochem4free.info/node/143>.

11.6: Introduction to Alkyne Reactions

Alkanes are undoubtedly the weakest Brønsted acids commonly encountered in organic chemistry. It is difficult to measure such weak acids, but estimates put the pK_a of ethane at about 48. Hybridizing the carbon so as to increase the s-character of the C-H increases the acidity, with the greatest change occurring for the sp-C-H groups found in terminal alkynes. Thus, the pK_a of ethene is estimated at 44, and the pK_a of ethyne (acetylene) is found to be 25, making it 10^{23} times stronger an acid than ethane. This increase in acidity permits the isolation of insoluble silver and copper salts of such compounds.

$$RC{\equiv}C\text{-}H + Ag(NH_3)_2^{(+)} \text{ (in } NH_4OH) \rightarrow RC{\equiv}C\text{-}Ag \text{ (insoluble)} + NH_3 + NH_4^{(+)}$$

Despite the dramatic increase in acidity of terminal alkynes relative to other hydrocarbons, they are still very weak acids, especially when compared with water, which is roughly a billion times more acidic. If we wish to prepare nucleophilic salts of terminal alkynes for use in synthesis, it will therefore be necessary to use a much stronger base than hydroxide (or ethoxide) anion. Such a base is sodium amide ($NaNH_2$), discussed above, and its reactions with terminal alkynes may be conducted in liquid ammonia or ether as solvents. The products of this acid-base reaction are ammonia and a sodium acetylide salt. Because the acetylide anion is a powerful nucleophile it may displace halide ions from 1º-alkyl halides to give a more highly substituted alkyne as a product (S_N2 reaction). This synthesis application is described in the following equations. The first two equations show how acetylene can be converted to propyne; the last two equations present a synthesis of 2-pentyne from propyne.

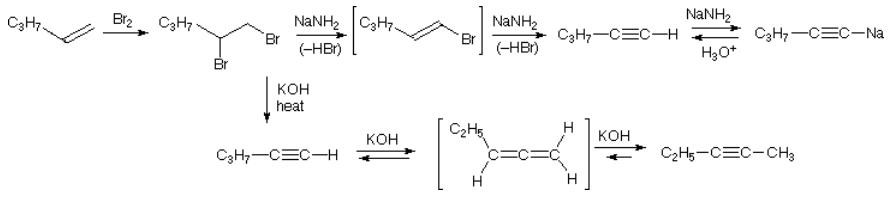
$H\text{-}C{\equiv}C\text{-}H + NaNH_2$ (in ammonia or ether) $\rightarrow H\text{-}C{\equiv}C\text{-}Na$ (sodium acetylide) $+ NH_3$
$H\text{-}C{\equiv}C\text{-}Na + CH_3\text{-}I \rightarrow H\text{-}C{\equiv}C\text{-}CH_3 + NaI$
$CH_3\text{-}C{\equiv}C\text{-}H + NaNH_2$ (in ammonia or ether) $\rightarrow CH_3\text{-}C{\equiv}C\text{-}Na$ (sodium propynylide) $+ NH_3$
$CH_3\text{-}C{\equiv}C\text{-}Na + C_2H_5\text{-}Br \rightarrow CH_3\text{-}C{\equiv}C\text{-}C_2H_5 + NaBr$

Because $RC{\equiv}C{:}^{(-)}\ Na^{(+)}$ is a very strong base (roughly a billion times stronger than NaOH), its use as a nucleophile in S_N2 reactions is limited to 1º-alkyl halides; 2º and 3º-alkyl halides undergo elimination by an E2 mechanism.

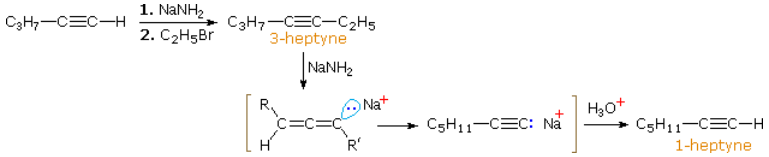
The enhanced acidity of terminal alkynes relative to alkanes also leads to metal exchange reactions when these compounds are treated with organolithium or Grignard reagents. This exchange, shown below in equation 1, can be interpreted as an acid-base reaction which, as expected, proceeds in the direction of the weaker acid and the weaker base. This factor clearly limits the usefulness of Grignard or lithium reagents when a terminal triple bond is present, as in equation 2.

1) $RC{\equiv}C\text{-}H + C_2H_5MgBr$ (in ether) $\rightarrow RC{\equiv}C\text{-}MgBr + C_2H_6$
2) $HC{\equiv}C\text{-}CH_2CH_2Br + Mg$ (in ether) $\rightarrow$ [$HC{\equiv}C\text{-}CH_2CH_2MgBr$] $\rightarrow BrMgC{\equiv}C\text{-}CH_2CH_2H$

The acidity of terminal alkynes also plays a role in product determination when vicinal (or geminal) dihalides undergo base induced bis-elimination reactions. The following example illustrates eliminations of this kind starting from 1,2-dibromopentane, prepared from 1-pentene by addition of bromine. The initial elimination presumably forms 1-bromo-1-pentene, since base attack at the more acidic and less hindered 1 º-carbon should be favored. The second elimination then produces 1-pentyne. If the very strong base sodium amide is used, the terminal alkyne is trapped as its sodium salt, from which it may be released by mild acid treatment. However, if the weaker base KOH is used for the elimination, the terminal alkyne salt is not formed, or is formed reversibly, and the initially generated 1-pentyne rearranges to the more stable 2-pentyne via an allene intermediate.



In the case of non-terminal alkynes, sodium and potassium amide, and related strong bases from 1 º-amines, are able to abstract protons from carbon atoms adjacent to the triple bond. The resulting allenic carbanions undergo rapid proton transfer equilibria, leading to the relatively stable terminal alkyne conjugate base. This isomerization may be used to prepare longer chain 1-alkynes, as shown in the following conversion of 3-heptyne to 1-heptyne. The R and R' substituents on the allenic intermediate range from propyl to hydrogen, as the proton transfers proceed.



Conjugate base anions of terminal alkynes (acetylide anions) are nucleophiles, and can do both nucleophilic substitution and nucleophilic addition reactions.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

11.7: Addition of Hydrogen Halides

Reaction 1: Addition of Hydrogen Halide to an Alkyne

Summary: Reactivity order of hydrogen halides: HI > HB r> HCl > HF.

Follows Markovnikov's rule:

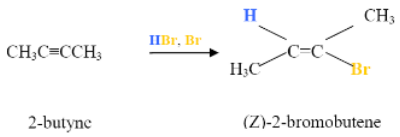
- Hydrogen adds to the carbon with the greatest number of hydrogens, the halogen adds to the carbon with fewest hydrogens.
- Protination occurs on the more stable carbocation. With the addition of HX, haloalkenes form.
- With the addition of excess HX, you get *anti* addition forming a geminal dihaloalkane.

Addition of a HX to an Internal Alkyne

As described in Figure 1, the π electrons will attack the hydrogen of the HBr and because this is a symmetric molecule it does not matter which carbon it adds to, but in an asymmetric molecule the hydrogen will covalently bond to the carbon with the most hydrogens. Once the hydrogen is covalently bonded to one of the carbons, you will get a carbocation intermediate (not shown, but will look the same as depicted in Figure 1) on the other carbon. Again, this is a symmetric molecule and if it were asymmetric, which carbon would have the positive charge?

The final step is the addition of the Bromine, which is a good nucleophile because it has electrons to donate or share. Bromine, therefore attacks the carbocation intermediate placing it on the highly substituted carbon. As a result, you get 2-bromobutene from your 2-butyne reactant, as shown below.

Figure 2



2-butyne (Z)-2-bromobutene

Now, what if you have excess HBr?

Addition due to excess HX present ? yields a geminal dihaloalkane

Figure 3

(Z)-2-bromobutene 2,2-Dibromobutane

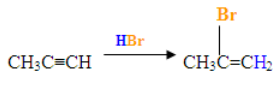
Here, the electrophilic addition proceeds with the same steps used to achieve the product in Addition of a HX to an Internal Alkyne. The π electrons attacked the hydrogen, adding it to the carbon on the left (shown in blue). Why was hydrogen added to the carbon on left and the one on the right bonded to the Bromine?

Now, you will have your carbocation intermediate, which is followed by the attack of the Bromine to the carbon on the right resulting in a haloalkane product.

Addition of HX to Terminal Alkyne

- Here is an addition of HBr to an asymmetric molecule.
- First, try to make sense of how the reactant went to product and then take a look at the mechanism.

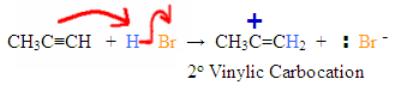
Figure 4



Propyne 2-Bromopropene

Mechanism:

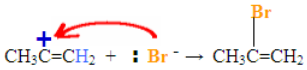
1)



2° Vinylic Carbocation

The π electrons are attacking the hydrogen, depicted by the electron pushing arrows and the Bromine gains a negative charge. The carbocation intermediate forms a positive charge on the left carbon after the hydrogen was added to the carbon with the most hydrogen substituents.

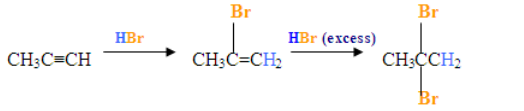
2)



The Bromine, which has a negative charge, attacks the positively charged carbocation forming the final product with the nucleophile on the more substituted carbon.

Addition due to excess HBr present

Figure 5

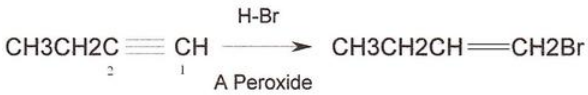


Propyne 2-Bromopropene 2,2-Dibromopropane

Most Hydrogen halide reactions with alkynes occur in a Markovnikov-manner in which the halide attaches to the most substituted carbon since it is the most positively polarized. A more substituted carbon has more bonds attached to 1) carbons or 2) electron-donating groups such as Fluorine and other halides. However, there are two specific reactions among alkynes where anti-Markovnikov reactions take place: the radical addition of HBr and Hydroboration Oxidation reactions. For alkynes, an anti-Markovnikov addition takes place on a terminal alkyne, an alkyne on the end of a chain.

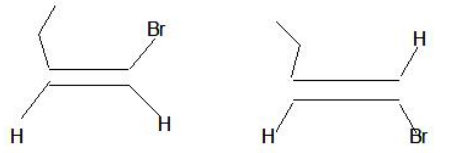
HBr Addition With Radical Yields 1-bromoalkene

The Br of the Hydrogen Bromide (H-Br) attaches to the less substituted 1-carbon of the terminal alkyne shown below in an anti-Markovnikov manner while the Hydrogen proton attaches to the second carbon. As mentioned above, the first carbon is the less substituted carbon since it has fewer bonds attached to carbons and other substituents. The H-Br reagent must also be reacted with heat or some other radicial initiator such as a peroxide in order for this reaction to proceed in this manner. This presence of the radical or heat leads to the anti-Markovnikov addition since it produces the most stable reaction. For more on Anti-Markovnikov additions:Radical Additions--Anti-Markovnikov Product Formation



The product of a terminal alkyne that is reacted with a peroxide (or light) and H-Br is a 1-bromoalkene.

Regioselectivity: The Bromine can attach in a ***syn*** or ***anti*** manner which means the resulting alkene can be both ***cis*** and ***trans***. ***Syn*** addition is when both Hydrogens attach to the same face or side of the double bond (i.e. ***cis***) while the ***anti*** addition is when they attach on opposite sides of the bond (***trans***).



Cis-1-bromo-1-butene *Trans*-1-bromo-1-butene

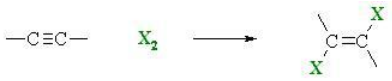
Contributors

- Prof. Hilton Weiss (Bard College)
- Aleksandra Milman
- Ali Alvandi

11.8: Addition of Halogen

Reaction: Halogenation of Alkynes

Summary:

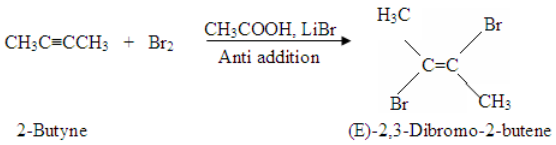


- Stereoslectivity: anti addition
- Reaction proceeds via cyclic halonium ion

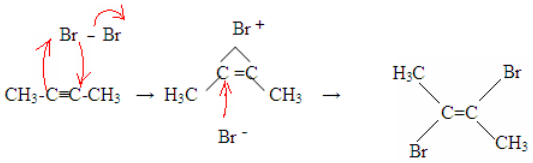
Addition of Br_2

- The addition of Br_2 to an alkyne is analogous to adding Br_2 to an alkene.
- Once Br_2 approaches the nucleophilic alkyne, it becomes polarized.
- The π electrons, from the triple bond, can now attack the polarized bromine forming a C-Br bond and displacing the bromine ion.
- Now, you will get an intermediate electrophilic carbocation, which will immediately react with the bromine ion giving you the dibromo product.

Figure 6



Mechanism:



First, you see the polarized Br_2 being attacked by the π electrons. Once you form the C-Br bond, the other bromine is released as a bromine ion. The intermediate here is a bromonium ion, which is electrophilic and reacts with the bromine ion giving you the dibromo product.

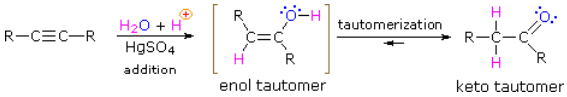
Contributors

- Prof. Hilton Weiss (Bard College)
- Aleksandra Milman

11.9: Addition of Water

Reaction: Hydration of Alkynes

As with alkenes,hydration (addition of water) to alkynes requires a strong acid, usually sulfuric acid, and is facilitated by mercuric sulfate. However, unlike the additions to double bonds which give alcohol products, addition of water to alkynes gives ketone products (except for acetylene which yields acetaldehyde). The explanation for this deviation lies in **enol-keto tautomerization**, illustrated by the following equation. The initial product from the addition of water to an alkyne is an enol (a compound having a hydroxyl substituent attached to a double-bond), and this immediately rearranges to the more stable keto tautomer.

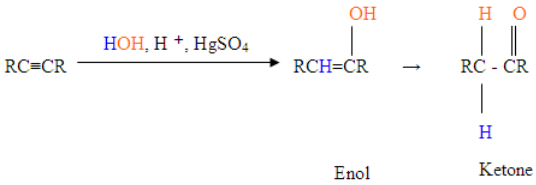


Tautomers are defined as rapidly interconverted constitutional isomers, usually distinguished by a different bonding location for a labile hydrogen atom (colored red here) and a differently located double bond. The equilibrium between tautomers is not only rapid under normal conditions, but it often strongly favors one of the isomers (acetone, for example, is 99.999% keto tautomer). Even in such one-sided equilibria, evidence for the presence of the minor tautomer comes from the chemical behavior of the compound. Tautomeric equilibria are catalyzed by traces of acids or bases that are generally present in most chemical samples. The three examples shown below illustrate these reactions for different substitutions of the triple-bond. The tautomerization step is indicated by a red arrow. For terminal alkynes the addition of water follows the Markovnikov rule, as in the second example below, and the final product ia a methyl ketone (except for acetylene, shown in the first example). For internal alkynes (the triple-bond is within a longer chain) the addition of water is not regioselective. If the triple-bond is not symmetrically located (i.e. if R & R' in the third equation are not the same) two isomeric ketones will be formed.

$HC{\equiv}CH + H_2O + HgSO_4$ & H_2SO_4 ———> [$H_2C{=}CHOH$] ———> $H_3C\text{-}CH{=}O$
$RC{\equiv}CH + H_2O + HgSO_4$ & H_2SO_4 ———> [$RC(OH){=}CH_2$] ———> $RC(=O)CH_3$
$RC{\equiv}CR' + H_2O + HgSO_4$ & H_2SO_4 ———> [$RHC{=}C(OH)R' + RC(OH){=}CHR'$] ———> $RCH_2\text{-}C(=O)R' + RC(=O)\text{-}CH_2R'$

With the addition of water, alkynes can be hydrated to form enols that spontaneously tautomerize to ketones. Reaction is catalyzed by mercury ions. Follows Markovnikov's Rule: Terminal alkynes give methyl ketones

Figure 7

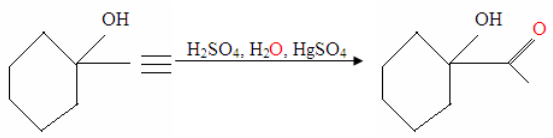


- The first step is an acid/base reaction where the electrons of the triple bond acts as a Lewis base and attacks the proton therefore protinating the carbon with the most hydrogen substituents.
- The second step is the attack of the nucleophilic water molecule on the electrophilic carbocation, which creates an oxonium ion.
- Next you deprotonate by a base, generating an alcohol called an enol, which then tautomerizes into a ketone.
- Tautomerism is a simultaneous proton and double bond shift, which goes from the enol form to the keto isomer form as shown above in Figure 7.

Now let's look at some Hydration Reactions.

Hydration of Terminal Alkyne produces methyl ketones

Figure 8

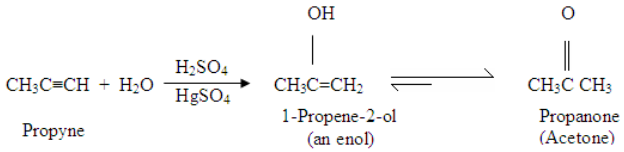


91%

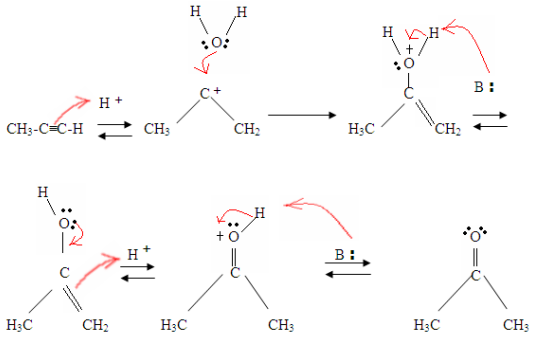
Just as described in Figure 7 the electrons will attack a proton, forming a carbocation, which then gets attacked by the nucleophilic water molecules. After deprotination, we generate an enol, which then tautomerizes into the ketone form shown.

Hydration of Alkyne

Figure 9



Mechanism:



As you can see here, the electrons of the triple bond are attacking the proton, which forms a covalent bond on the carbon with the most hydrogen substituents. Once the hydrogen is bound you have a carbocation, which gets attacked by the water molecule. Now you have a positive charge on the oxygen which results in a base coming in and deprotinating the molecule. Once deprotinated, you have an enol, which then gets tautomerized.

Tautomerism is shown here when the proton gets attacked by the double bond electrons forming a covalent bond between the carbon and the hydrogen on the less substituted carbon. Electrons from the Oxygen end up moving to the carbon, forming a double bond with carbon and giving itself a positive charge, which then gets attacked by the base. The base deprotinates the Oxygen resulting in the more stable final product at equilibrium, which is a ketone.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Hilton Weiss (Bard College)
- Aleksandra Milman

11.10: Hydroboration–Oxidation

Hydroboration Reactions

Diborane reacts readily with alkynes, but the formation of substituted alkene products leaves open the possibility of a second addition reaction. A clever technique for avoiding this event takes advantage of the fact that alkynes do not generally suffer from steric hindrance near the triple-bond (the configuration of this functional group is linear). Consequently, large or bulky electrophilic reagents add easily to the triple-bond, but the resulting alkene is necessarily more crowded or sterically hindered and resists further additions. The bulky hydroboration reagent needed for this strategy is prepared by reaction of diborane with 2-methyl-2-butene, a highly branched alkene. Because of the alkyl branching, only two alkenes add to a BH_3 moiety (steric hindrance again), leaving one B-H covalent bond available for reaction with an alkyne, as shown below. The resulting dialkyl borane is called disiamylborane, a contraction of di-secondary-isoamylborane (amyl is an old name for pentyl).

$$2\ (CH_3)_2C{=}CHCH_3 + BH_3 \text{ in ether} \longrightarrow [\ (CH_3)_2CH\text{-}CH(CH_3)\ ]_2B\text{-}H$$ *disiamylborane*

An important application of disiamylborane is its addition reaction to terminal alkynes. As with alkenes, the B-H reagent group adds in an apparently anti-Markovnikov manner, due to the fact that the boron is the electrophile, not the hydrogen. Further addition to the resulting boron-substituted alkene does not occur, and the usual oxidative removal of boron by alkaline hydrogen peroxide gives an enol which rapidly rearranges to the aldehyde tautomer. Thus, by the proper choice of reagents, terminal alkynes may be converted either to methyl ketones (mercuric ion catalyzed hydration) or aldehydes (hydroboration followed by oxidation).

$$RC{\equiv}CH + (C_5H_{11})_2B\text{-}H \longrightarrow [\ RCH{=}CH\text{-}B(C_5H_{11})_2\ ] + H_2O_2\ \&\ NaOH \longrightarrow [\ RCH{=}CH\text{-}OH\ ] \longrightarrow RCH_2\text{-}CH{=}O$$

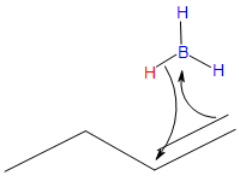
Hydroboration of internal alkynes is not a particularly useful procedure because a mixture of products will often be obtained, unless the triple-bond is symmetrically substituted. Mercuric ion catalyzed hydration gives similar results.

Hydroboration-Oxidation is a two step pathway used to produce alcohols. The reaction proceeds in an Anti-Markovnikov manner, where the hydrogen (from BH_3 or BHR_2) attaches to the more substituted carbon and the boron attaches to the least substituted carbon in the alkene bouble bond. Furthermore, the borane acts as a lewis acid by accepting two electrons in its empty p orbital from an alkene that is electron rich. This process allows boron to have an electron octet. A very interesting characteristic of this process is that it does not require any activation by a catalyst. The Hydroboration mechanism has the elements of both hydrogenation and electrophilic addition and it is a stereospecific (***syn addition),*** meaning that the hydroboration takes place on the same face of the double bond, this leads ***cis*** stereochemistry.

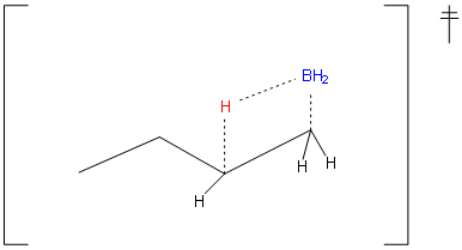
The Mechanism

Step #1

- Part #1: Hydroboration of the alkene. In this first step the addittion of the borane to the alkene is initiated and prceeds as a concerted reaction because bond breaking and bond formation occurs at the same time. This part consists of the vacant 2p orbital of the boron electrophile pairing with the electron pair of the ? bondof the nucleophile.

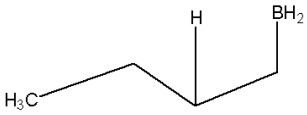


Transition state



*** Note that a carbocation is not formed. Therefore, no rearrangement takes place.**

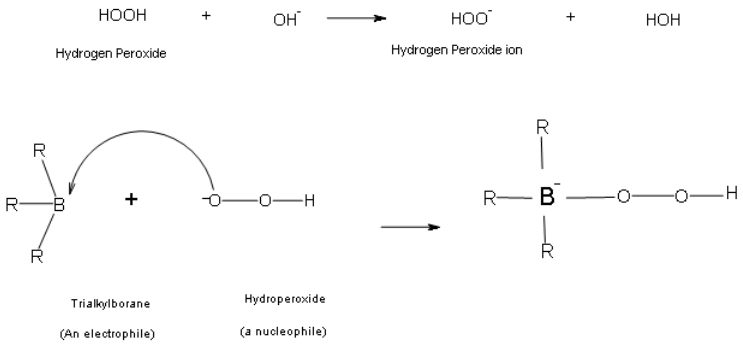
- Part #2: The Anti Markovnikov addition of Boron. The boron adds to the less substituted carbon of the alkene, which then places the hydrogen on the more substituted carbon. Both, the boron and the hydrogen add simultaneously on the same face of the double bond (syn addition).



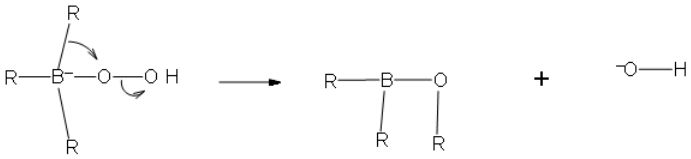
Oxidation of the Trialkylborane by Hydrogen Peroxide

Step #2

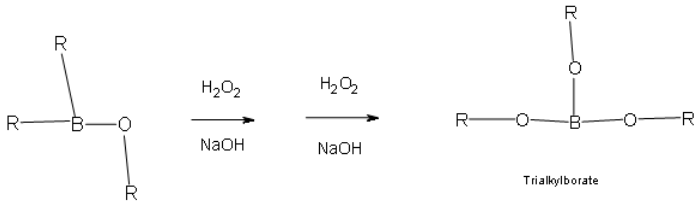
- Part #1: the first part of this mechanism deals with the donation of a pair of electrons from the hydrogen peroxide ion. the hydrogen peroxide is the nucleophile in this reaction because it is the electron donor to the newly formed trialkylborane that resulted from hydroboration.



- Part 2: In this second part of the mechanism, a rearrangement of an R group with its pair of bonding electrons to an adjacent oxygen results in the removal of a hydroxide ion.



Two more of these reactions with hydroperoxide will occur in order give a trialkylborate

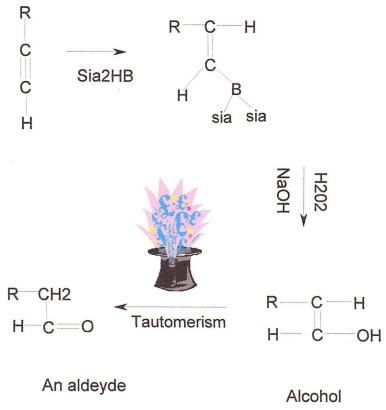


- Part 3: This is the final part of the Oxidation process. In this part the trialkylborate reacts with aqueous NaOH to give the alcohol and sodium borate.

If you need additional visuals to aid you in understanding the mechanism, click on the outside links provided here that will take you to other pages and media that are very helpful as well.

Stereospecific Hydroboration Oxidation of Alkynes

Step 1: Hydroboration of terminal alkynes reacts in an anti-Markovnikov fashion in which the Boron attacks the less substituted carbon which is the least hindered. It is a stereospecific reaction where ***syn*** addition is observed as the hydroboration occurs on the same side of the alkyne and results in ***cis*** stereochemistry. However, a bulky borane reagent needs to be used to stop at the alkenyl-borane stage. Otherwise, a second hydroboration will occur. In this example, diisoamyl borane or $HBsia_2$, a fairly large and sterically-hindered borane reagent, is used. Both of the alkyne's pi bonds will undergo hydroboration if BH_3 (borane) is used by itself.



Step 2: Oxidation is the next step that occurs. The resulting alkylborane is oxidized to a vinyl alcohol due to the reaction with a hydroxide in a basic solution such as aqueous sodium hydroxide. A vinyl alcohol is an alcohol that has both an alkene and an -OH group. After the vinyl alcohol is formed, tautomerization takes place. Tautomerism is the interconversion of isomeric compounds due to the migration of a proton. The alcohol, which in this case is a terminal enol, **spontaneously and rapidly rearranges** due to tautomerism to become an aldehyde since the aldehyde form is much more stable than the enol.

For additional information on hydroboration oxidation: Hydroboration Oxidation

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Gilbert Torres (UCD)
- Ali Alvandi

11.11: Reaction of Acetylide Anions

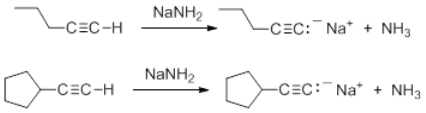
Acidity of Terminal Alkynes: Formation of Acetylide Anions

Terminal alkynes are much more acidic than most other hydrocarbons. Removal of the proton leads to the formation of an acetylide anion, $RC{\equiv}C{:}^-$. The origin of the enhanced acidity can be attributed to the stability of the acetylide anion, which has the unpaired electrons in an sp hybridized orbital. The stability results from occupying an orbital with a high degree of s-orbital character.

There is a strong correlation between s-character in the orbital containing the non-bonding electrons in the anion and the acidity of hydrocarbons. The enhanced acidity with greater s-character occurs despite the fact that the homolytic C-H BDE is larger.

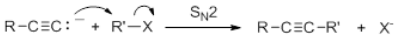
Compound	Conjugate Base	Hybridization	"s Character"	pKa	C-H BDE (kJ/mol)
CH_3CH_3	$CH_3CH_2^-$	sp^3	25%	50	410
CH_2CH_2	CH_2CH^-	sp^2	33%	44	473
HCCH	HCC^-	sp	50%	25	523

Consequently, acetylide anions can be readily formed by deprotonation using a sufficiently strong base. Amide anion (NH_2^-), in the form of $NaNH_2$ is commonly used for the formation of acetylide anions.

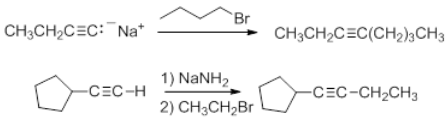


Nucleophilic Substitution Reactions of Acetylides

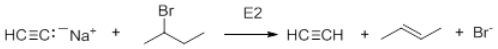
Acetylide anions are strong bases and strong nucleophiles. Therefore, they are able to displace halides and other leaving groups in substitution reactions. The product is a substituted alkyne.



Because the ion is a very strong base, the substitution reaction is most efficient with methyl or primary halides without substitution near the reaction center,

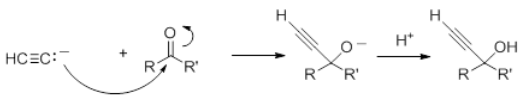


Secondary, tertiary or even bulky primary substrates will give elimination by the E2 mechanism.



Nucleophilic Addition of Acetylides to Carbonyls

Acetylide anions will add to aldehydes and ketones to form alkoxides, which, upon protonation, give propargyl alcohols.



With aldehydes and non-symmetric ketones, in the absence of chiral catalyst, the product will be a racemic mixture of the two enantiomers.

Problems

1. The pK_a of ammonia is 35. Estimate the equilibrium constant for the deprotonation of pent-1-yne by amide, as shown above.

Answers

1. Assuming the pK_a of pent-1-yne is about 25, then the difference in pK_as is 10. Since pentyne is more acidic, the formation of the acetylide will be favored at equilibrium, so the equilibrium constant for the reaction is about 10^{10}

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Paul G. Wenthold (Purdue University)

11.12: Synthesis

'There could be ART in Organic Synthesis' declared the inimitable monarch of organic synthesis, Professor R.B. Woodward. His school unveiled several elegant approaches covering a variety of complex structures and broke new grounds to define the art of organic synthesis. 'If organic synthesis is a branch of science, what is the LOGIC of organic synthesis?' marveled several others. The development of the concept of logical approaches towards synthesis has been evolving over the past several decades. A few stalwarts focused their attention on this theme and attempted to evolve a pattern to define this logic. There is no doubt that all of us who dabble with synthesis contribute our small bit in the magnificent direction. A few names stand out in our minds for their outstanding contributions. Notable contributions came from the schools of J.A. Marshal, E.J. Wenkert, G. Stock, S Hanessian, E.E. van Tamalen, S. Masamune, R.B. Woodward, E.J. Corey and several others. More focused on this theme were the contributions from the school of E.J. Corey.

The period 1960 – 1990 witnessed the evolution of this thought and the concept bloomed into a full-fledged topic that now merits a separate space in college curriculum. Earlier developments focused on the idea of *ANTITHETIC APPROACHES* and perfected the art of DISCONNECTION via RETROSYNTHESIS. This led to logical approaches for the construction of *SYNTHETIC TREES* that summarized various possible approaches for the proposed Target structure. All disconnections may not lead to good routes for synthesis. Once the synthetic tree was constructed, the individual branches were analyzed critically. The reactions involved were looked into, to study their feasibility in the laboratory, their mechanistic pathways were analyzed to understand the conformational and stereochemical implications on the outcome of each step involved and the time / cost factors of the proposed routes were also estimated. The possible areas of pitfall were identified and the literature was critically scanned to make sure that the steps contemplated were already known or feasible on the basis of known chemistry. In some cases, model compounds were first constructed to study the feasibility of the particular reaction, before embarking on the synthesis of the complex molecular architecture. Thus a long process of logical planning is now put in place before the start of the actual synthetic project. In spite of all these careful and lengthy preparations, an experienced chemist is still weary of the Damocles Sword of synthesis viz., the likely failure of a critical step in the proposed route(s), resulting in total failure of the entire project. All achievements are 10% inspiration and 90% perspiration. For these brave molecular engineers, sometimes also called chemists, these long-drawn programs and possible perils of failures are still worth, for the perspiration is enough reward.

A sound knowledge of mechanistic organic chemistry, detailed information on the art and science of functional group transformations, bond formation and cleavage reactions, mastery over separation and purification techniques and a sound knowledge of spectroscopic analysis are all essential basics for the synthesis of molecules. A synthetic chemist should also be aware of developments in synthetic strategies generated over the years for different groups of compounds, which include Rules and guidelines governing synthesis. Since organic chemistry has a strong impact on the development of other sister disciplines like pharmacy, biochemistry and material science, an ability to understand one or more of these areas and interact with them using their terminologies is also an added virtue for a synthetic chemist. With achievements from synthesis of strained molecules (once considered difficult (if not impossible) to synthesize, to the synthesis of complex, highly functionalized and unstable molecules, an organic chemist could now confidently say that he could synthesize any molecule that is theoretically feasible. This is the current status of the power of organic synthesis. Based on the task assigned to the chemist, he would select a Target molecule for investigation and devise suitable routes for synthesis.

Disconnection of bonds

Having chosen the TARGET molecule for synthesis, the next exercise is to draw out synthetic plans that would summarize all reasonable routes for its synthesis. During the past few decades, chemists have been working on a process called RETROSYNTHESIS. Retrosynthesis could be described as a logical Disconnection at strategic bonds in such a way that the process would progressively lead to easily available starting material(s) through several synthetic plans. Each plan thus evolved, describes a 'ROUTE' based on a retrosynthesis. Each disconnection leads to a simplified structure. The logic of such disconnections forms the basis for the retroanalysis of a given target molecule. Natural products have provided chemists with a large variety of structures, having complex functionalities and stereochemistry. This area has provided several challenging targets for development of these concepts. The underlining principle in devising logical approaches for synthetic routes is very much akin to the following simple problem. Let us have a look of the following big block, which is made by assembling several small blocks **(Fig 1.4.2.1)**. You could easily see that the large block could be broken down in different ways and then reassembled to give the same original block.

Fig 1.4.2.1

Now let us try and extend the same approach for the synthesis of a simple molecule. Let us look into three possible 'disconnections' for a cyclohexane ring as shown in **Fig 1.4.2.2**.

Fig 1.4.2.2

In the above analysis we have attempted to develop three ways of disconnecting the six membered ring. Have we thus created three pathways for the synthesis of cyclohexane ring? Do such disconnections make chemical sense? The background of an organic chemist should enable him to read the process as a chemical reaction in the reverse (or 'retro-') direction. The dots in the above structures could represent a carbonium ion, a carbanion, a free radical or a more complex reaction (such as a pericyclic reaction or a rearrangement). Applying such chemical thinking could open up several plausible reactions. Let us look into path b, which resulted from cleavage of one sigma bond. An anionic cyclisation route alone exposes several candidates as suitable intermediates for the formation of this linkage. The above analysis describes only three paths out of the large number of alternate cleavage routes that are available. An extended analysis shown below indicates more such possibilities **(Fig 1.4.2.3)**. Each such intermediate could be subjected to further disconnection process and the process continued until we reach a reasonably small, easily available starting materials. Thus, a complete 'SYNTHETIC TREE' could be constructed that would summarize all possible routes for the given target molecule.

Fig 1.4.2.3

Efficiency of a route

A route is said to be efficient when the 'overall yield' of the total process is the best amongst all routes investigated. This would depend not only on the number of steps involved in the synthesis, but also on the type of strategy followed. The strategy could involve a 'linear syntheses' involving only consequential steps or a 'convergent syntheses' involving fewer consequential steps. **Fig 1.4.3.1** shown below depicts a few patterns that could be recognized in such synthetic trees. When each disconnection process leads to only one feasible intermediate and the process proceeds in this fashion

Fig 1.4.3.1

all the way to one set of starting materials (SM), the process is called a Linear Synthesis. On the other hand, when an intermediate could be disconnected in two or more ways leading to different intermediates, branching occurs in the plan. The processes could be continued all the way to SMs. In such routes different branches of the synthetic pathways converge towards

an intermediate. Such schemes are called Convergent Syntheses.

The flow charts shown below **(Fig 1.4.3.2)** depicts a hypothetical 5-step synthesis by the above two strategies. Assuming a very good yield (90%) at each step (this is rarely seen in real projects), a linier synthesis gives 59% overall yield, whereas a convergent synthesis gives 73% overall yield for the same number of steps..

Contributors

- Prof. R Balaji Rao (Department of Chemistry, Banaras Hindu University, Varanasi) as part of Information and Communication Technology

CHAPTER OVERVIEW

12: Oxidation and Reduction

Topic hierarchy

12.1: Introduction

Solutions to exercises

You are undoubtedly already familiar with the general idea of oxidation and reduction: you learned in general chemistry that when a compound or atom is oxidized it loses electrons, and when it is reduced it gains electrons. You also know that oxidation and reduction reactions occur in pairs: if one species is oxidized, another must be reduced at the same time - thus the term 'redox reaction'.

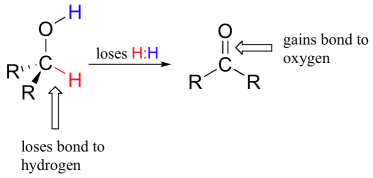
Most of the redox reactions you have seen previously in general chemistry probably involved the flow of electrons from one metal to another, such as the reaction between copper ion in solution and metallic zinc:

$$Cu^{+2}_{(aq)} + Zn_{(s)} \rightarrow Cu_{(s)} + Zn^{+2}_{(aq)}$$

In organic chemistry, redox reactions look a little different. Electrons in an organic redox reaction often are transferred in the form of a hydride ion - a proton and two electrons. Because they occur in conjunction with the transfer of a proton, these are commonly referred to as **hydrogenation** and **dehydrogenation** reactions: a hydride plus a proton adds up to a hydrogen (H_2) molecule. Be careful - do not confuse the terms hyd**rogen**ation and dehy**drogen**ation with hydration and dehydration - the latter refer to the gain and loss of a *water* molecule (and are *not* redox reactions), while the former refer to the gain and loss of a *hydrogen* molecule.

When a carbon atom in an organic compound loses a bond to hydrogen and gains a new bond to a heteroatom (or to another carbon), we say the compound has been dehydrogenated, or oxidized. A very common biochemical example is the oxidation of an alcohol to a ketone or aldehyde:

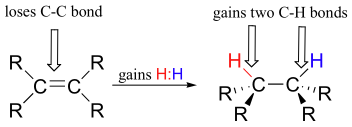
Dehydrogenation (oxidation) of an alcohol



When a carbon atom loses a bond to hydrogen and gains a bond to a heteroatom (or to another carbon atom), it is considered to be an oxidative process because hydrogen, of all the elements, is the least electronegative. Thus, in the process of dehydrogenation the carbon atom undergoes an overall loss of electron density - and loss of electrons is oxidation.

Conversely, when a carbon atom in an organic compound gains a bond to hydrogen and loses a bond to a heteroatom (or to another carbon atom), we say that the compound has been hydrogenated, or reduced. The hydrogenation of a ketone to an alcohol, for example, is overall the reverse of the alcohol dehydrogenation shown above. Illustrated below is another common possibility, the hydrogenation (reduction) of an alkene to an alkane.

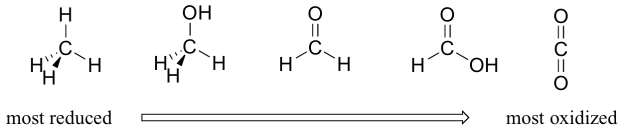
Hydrogenation (reduction) of an alkene



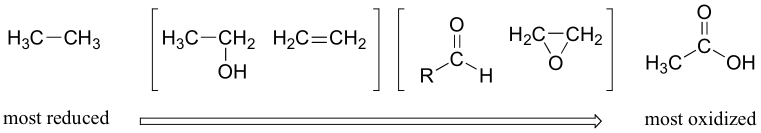
Hydrogenation results in *higher* electron density on a carbon atom(s), and thus we consider process to be one of reduction of the organic molecule.

Notice that neither hydrogenation nor dehydrogenation involves the gain or loss of an oxygen *atom*. Reactions which *do* involve gain or loss of one or more oxygen atoms are usually referred to as 'oxygenase' and 'reductase' reactions, and are the subject of section 16.10 and section 17.3.

For the most part, when talking about redox reactions in organic chemistry we are dealing with a small set of very recognizable functional group transformations. It is therefore very worthwhile to become familiar with the idea of 'oxidation states' as applied to organic functional groups. By comparing the relative number of bonds to hydrogen atoms, we can order the familiar functional groups according to oxidation state. We'll take a series of single carbon compounds as an example. Methane, with four carbon-hydrogen bonds, is highly reduced. Next in the series is methanol (one less carbon-hydrogen bond, one more carbon-oxygen bond), followed by formaldehyde, formate, and finally carbon dioxide at the highly oxidized end of the group.



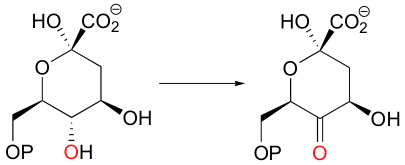
This pattern holds true for the relevant functional groups on organic molecules with two or more carbon atoms:



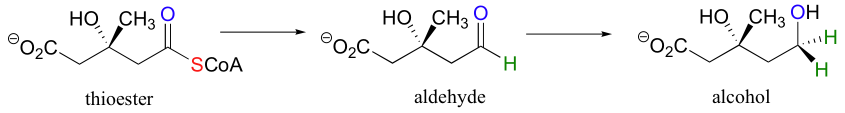
Alkanes are highly reduced, while alcohols - as well as alkenes, ethers, amines, sulfides, and phosphate esters - are one step up on the oxidation scale, followed by aldehydes/ketones/imines and epoxides, and finally by carboxylic acid derivatives (carbon dioxide, at the top of the oxidation list, is specific to the single carbon series).

Notice that in the series of two-carbon compounds above, ethanol and ethene are considered to be in the same oxidation state. You know already that alcohols and alkenes are interconverted by way of addition or elimination of water (section 14.1). When an alcohol is dehydrated to form an alkene, one of the two carbons loses a C-H bond and gains a C-C bond, and thus is oxidized. However, the other carbon loses a C-O bond and gains a C-C bond, and thus is considered to be reduced. Overall, therefore, there is no change to the oxidation state of the molecule.

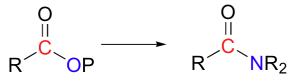
You should learn to recognize when a reaction involves a change in oxidation state in an organic reactant . Looking at the following transformation, for example, you should be able to quickly recognize that it is an oxidation: an alcohol functional group is converted to a ketone, which is one step up on the oxidation ladder.



Likewise, this next reaction involves the transformation of a carboxylic acid derivative (a thioester) first to an aldehyde, then to an alcohol: this is a *double* reduction, as the substrate loses two bonds to heteroatoms and gains two bonds to hydrogens.



An acyl transfer reaction (for example the conversion of an acyl phosphate to an amide) is *not* considered to be a redox reaction - the oxidation state of the organic molecule is does not change as substrate is converted to product, because a bond to one heteroatom (oxygen) has simply been traded for a bond to another heteroatom (nitrogen).



carbon is in same oxidation state - not a redox reaction

It is important to be able to recognize when an organic molecule is being oxidized or reduced, because this information tells you to look for the participation of a corresponding redox agent that is being reduced or oxidized- remember, oxidation and reduction always occur in tandem! We will soon learn in detail about the most important biochemical and laboratory redox agents.

Template:ExampleStart

Exercise 16.1: is an aldol condensation a redox reaction? Explain.

Exercise 16.2: Is the reaction catalyzed by squalene epoxidase a redox reaction? How about squalene cyclase? Explain.

Template:ExampleEnd

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

12.2: Reducing Agents

Liquid Ammonia Solutions

A remarkable feature of the alkali metals is their ability to dissolve reversibly in liquid ammonia. Just as in their reactions with water, reacting alkali metals with liquid ammonia eventually produces hydrogen gas and the metal salt of the conjugate base of the solvent—in this case, the amide ion (NH_2^-) rather than hydroxide:

$$M(s) + NH_3(l) \rightarrow \tfrac{1}{2}H_2(g) + M^+(am) + NH_2^-(am) \tag{12.2.1}$$

where the (am) designation refers to an ammonia solution, analogous to (aq) used to indicate aqueous solutions. Without a catalyst, the reaction in Equation 12.2.1 tends to be rather slow. In many cases, the alkali metal amide salt (MNH_2) is not very soluble in liquid ammonia and precipitates, but when dissolved, very concentrated solutions of the alkali metal are produced. One mole of Cs metal, for example, will dissolve in as little as 53 mL (40 g) of liquid ammonia. The pure metal is easily recovered when the ammonia evaporates.

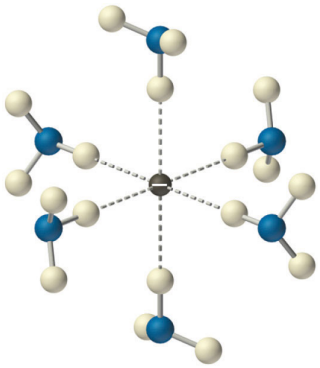


Figure 12.2.1: Solvated electrons. The presence of solvated electrons (e^-, NH_3) in solutions of alkali metals in liquid ammonia is indicated by the intense color of the solution and its electrical conductivity. (CC BY-SA-NC 3.0; anonymous)

Solutions of alkali metals in liquid ammonia are intensely colored and good conductors of electricity due to the presence of solvated electrons (e^-, NH_3), which are not attached to single atoms. A solvated electron is loosely associated with a cavity in the ammonia solvent that is stabilized by hydrogen bonds. Alkali metal–liquid ammonia solutions of about 3 M or less are deep blue (Figure 12.2.2) and conduct electricity about 10 times better than an aqueous $NaCl$ solution because of the high mobility of the solvated electrons. As the concentration of the metal increases above 3 M, the color changes to metallic bronze or gold, and the conductivity increases to a value comparable with that of the pure liquid metals.

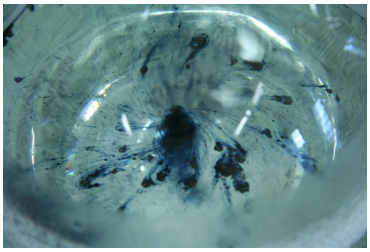
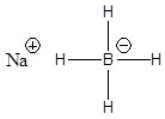
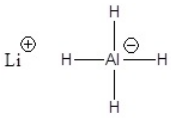


Figure 12.2.2: Alkali Metal–Liquid Ammonia Solutions. Most metals are insoluble in virtually all solvents, but the alkali metals (and the heavier alkaline earth metals) dissolve readily in liquid ammonia to form solvated metal cations and solvated electrons, which give the solution a deep blue color. Image copyrighted by the Klein research group (Christian Joest, 2013).

The most common sources of the hydride nucleophile are lithium aluminum hydride ($LiAlH_4$) and sodium borohydride ($NaBH_4$). Note! The hydride anion is not present during this reaction; rather, these reagents serve as a source of hydride due to the presence of a polar metal-hydrogen bond. Because aluminum is less electronegative than boron, the Al-H bond in $LiAlH_4$ is more polar, thereby, making $LiAlH_4$ a stronger reducing agent.



Sodium Borohydride



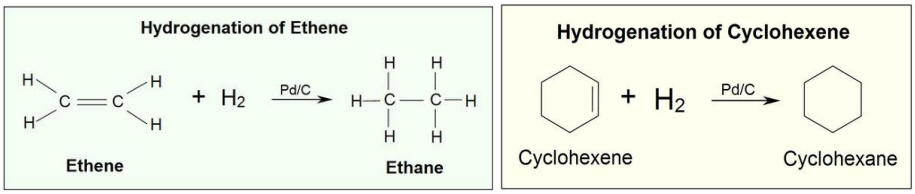
Lithium Aluminum Hydride

Hydride Nucleophile

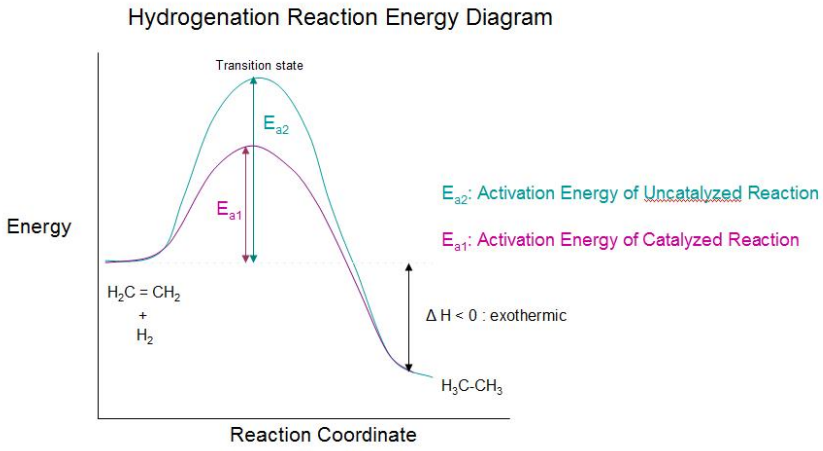
12.3: Reduction of Alkenes

Addition of hydrogen to a carbon-carbon double bond is called hydrogenation. The overall effect of such an addition is the reductive removal of the double bond functional group. Regioselectivity is not an issue, since the same group (a hydrogen atom) is bonded to each of the double bond carbons. The simplest source of two hydrogen atoms is molecular hydrogen (H_2), but mixing alkenes with hydrogen does not result in any discernible reaction. Although the overall hydrogenation reaction is exothermic, a high activation energy prevents it from taking place under normal conditions. This restriction may be circumvented by the use of a catalyst, as shown in the following diagram.

An example of an alkene addition reaction is a process called hydrogenation.In a hydrogenation reaction, two hydrogen atoms are added across the double bond of an alkene, resulting in a saturated alkane. Hydrogenation of a double bond is a thermodynamically favorable reaction because it forms a more stable (lower energy) product. In other words, the energy of the product is lower than the energy of the reactant; thus it is exothermic (heat is released). The heat released is called the heat of hydrogenation, which is an indicator of a molecule's stability.



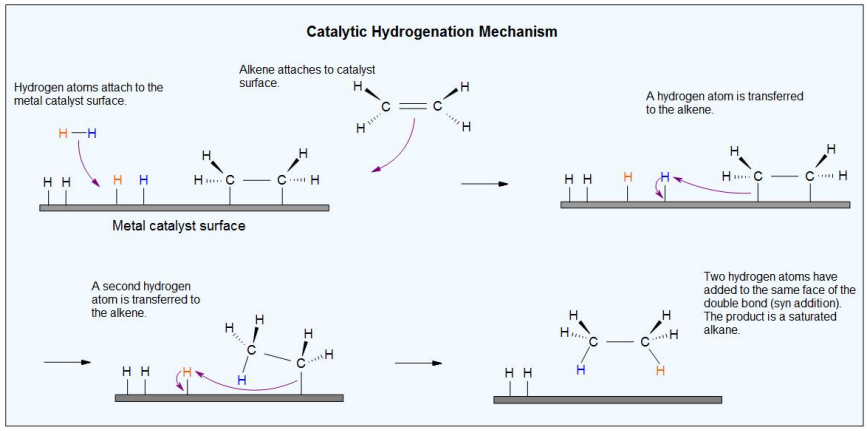
Catalysts are substances that changes the rate (velocity) of a chemical reaction without being consumed or appearing as part of the product. Catalysts act by lowering the activation energy of reactions, but they do not change the relative potential energy of the reactants and products. Finely divided metals, such as platinum, palladium and nickel, are among the most widely used hydrogenation catalysts. Catalytic hydrogenation takes place in at least two stages, as depicted in the diagram. First, the alkene must be adsorbed on the surface of the catalyst along with some of the hydrogen. Next, two hydrogens shift from the metal surface to the carbons of the double bond, and the resulting saturated hydrocarbon, which is more weakly adsorbed, leaves the catalyst surface. The exact nature and timing of the last events is not well understood.



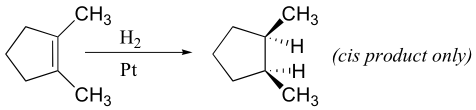
A catalyst lowers the activation energy needed for the reacting molecules to reach the transition state. The addition of a catalyst enables the hydrogenation reaction to occur, that otherwise, would not.

As shown in the energy diagram, the hydrogenation of alkenes is exothermic, and heat is released corresponding to the ΔE (colored green) in the diagram. This heat of reaction can be used to evaluate the thermodynamic stability of alkenes having different numbers of alkyl substituents on the double bond. For example, the following table lists the heats of hydrogenation for three C_5H_{10} alkenes which give the same alkane product (2-methylbutane). Since a large heat of reaction indicates a high energy reactant, these heats are inversely proportional to the stabilities of the alkene isomers. To a rough approximation, we see that each alkyl substituent on a double bond stabilizes this functional group by a bit more than 1 kcal/mole.

Alkene Isomer	$(CH_3)_2CHCH=CH_2$ 3-methyl-1-butene	$CH_2=C(CH_3)CH_2CH_3$ 2-methyl-1-butene	$(CH_3)_2C=CHCH_3$ 2-methyl-2-butene
Heat of Reaction (ΔH^o)	–30.3 kcal/mole	–28.5 kcal/mole	–26.9 kcal/mole



From the mechanism shown here we would expect the addition of hydrogen to occur with syn-stereoselectivity. This is often true, but the hydrogenation catalysts may also cause isomerization of the double bond prior to hydrogen addition, in which case stereoselectivity may be uncertain.



(cis product only)

Contributors

- Prof. Steven Farmer (Sonoma State University)
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Jim Clark (Chemguide.co.uk)

12.4: Application- Hydrogenation of Oils

Introduction

In the late 1970's the lipid hypothesis came in to existences. The lipid hypothesis states that eating saturated fats leads to elevated LDL(Low Density Lipoprotein) which is perceived to be bad cholesterol. This will result in coronary heart disease which is hardening and narrowing of arteries resulting in heart attack. Fats were eventually classified in to 2 categories, "healthy fats" and "unhealthy fats". Unhealthy fats where perceived to be saturated fats, healthy fats where perceived to be unsaturated fats.

A meta-analysis of 72 studies with over 103,052 people have found no validity in the lipid hypothesis. The conclusion of the Meta-Analysis was,"In contrast to current recommendations, this systematic review found no evidence that saturated fat increases the risk of coronary disease, or that polyunsaturated fats have a cardio protective effect."[1]

Dietary fats play a critical role in human health. They help keep cells healthy, help with brain development, help with the use of fat soluble vitamins, and they help cushion organs protecting them against blunt trauma. Fats come in multiple forms, Saturated, Unsaturated and trans fats just to name a few.

Hydrogenation Reaction

Unsaturated fatty acids may be converted to saturated fatty acids by the relatively simple hydrogenation reaction. Recall that the addition of hydrogen to an alkene (unsaturated) results in an alkane (saturated). A simple hydrogenation reaction is:

$$H_2C{=}CH_2 + H_2 \rightarrow CH_3CH_3$$

alkene plus hydrogen yields an alkane

Saturated Fats

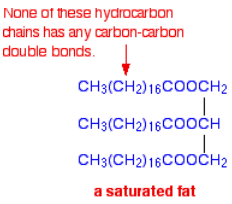
Saturated fats are solid at room temperature due to their molecular shape. The term saturated is in reference to an Sp3 carbon chain that has its remaining Sp3 orbitals bonded with hydrogen atoms. Thus the term "saturated". It's "saturated" with hydrogen.

Saturated fats have a chain like structure which allows them to stack very well forming a solid at room temperature. Unsaturated fats are not linear due to double bonded carbons which results in a different molecular shape because the Sp2 carbons are trigonal planar, not tetrahedral(Sp3 carbons) as the carbons are in saturated fats. This change in structure will cause the fat molecules to not stack very well resulting in fats that are liquid at room temperature. Butter is mostly saturated fat, that's why it's solid at room temperature. Olive Oil is liquid at room temperature, thus it's an unsaturated fat. An unsaturated fat can be made in to a saturated fat by a Hydrogenation process.

These are similar molecules, differing in their melting points. If the compound is a solid at room temperature, you usually call it a fat. If it is a liquid, it is often described as an oil.

Their melting points are largely determined by the presence of carbon-carbon double bonds in the molecule. The higher the number of carbon-carbon double bonds, the lower the melting point.

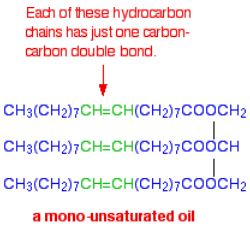
If there aren't any carbon-carbon double bonds, the substance is said to be saturated. A typical saturated fat might have the structure:



Molecules of this sort are usually solid at room temperature.

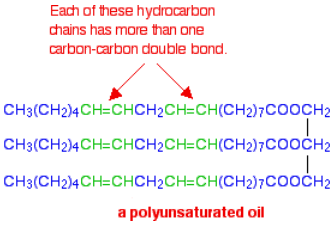
If there is only one carbon-carbon double bond in each of the hydrocarbon chains, it is called a mono-unsaturated fat (or mono-unsaturated oil, because it is likely to be a liquid at room temperature.)

A typical mono-unsaturated oil might be:



If there are two or more carbon-carbon double bonds in each chain, then it is said to be polyunsaturated.

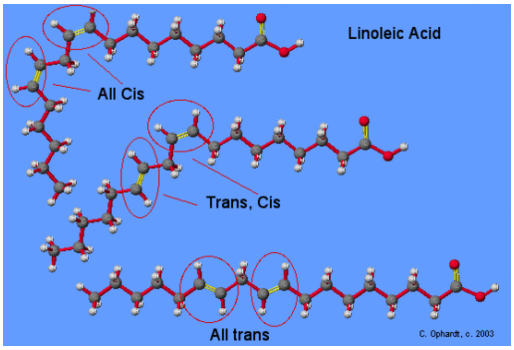
For example:



For simplicity, in all these diagrams, all three hydrocarbon chains in each molecule are the same. That doesn't have to be the case - you can have a mixture of types of chain in the same molecule.

Trans Fat

A major health concern during the hydrogenation process is the production of trans fats. Trans fats are the result of a side reaction with the catalyst of the hydrogenation process. This is the result of an unsaturated fat which is normally found as a cis isomer converts to a trans isomer of the unsaturated fat. Isomers are molecules that have the same molecular formula but are bonded together differently. Focusing on the Sp2 double bonded carbons, a cis isomer has the hydrogens on the same side. Due to the added energy from the hydrogenation process, the activation energy is reached to convert the cis isomers of the unsaturated fat to a trans isomer of the unsaturated fat. The effect is putting one of the hydrogens on the opposite side of one of the carbons. This results in a trans configuration of the double bonded carbons. The human body doesn't recognized trans fats.



Although the trans fatty acids are chemically "monounsaturated" or "polyunsaturated" they are considered so different from the cis monounsaturated or polyunsaturated fatty acids that they can not be legally designated as unsaturated for purposes of labeling. Most of the trans fatty acids (although chemically still unsaturated) produced by the partial hydrogenation process are now classified in the same category as saturated fats.

The major negative is that trans fat tends to raise "bad" LDL- cholesterol and lower "good" HDL-cholesterol, although not as much as saturated fat. Trans fat are found in margarine, baked goods such as doughnuts and Danish pastry, deep-fried foods like fried chicken and French-fried potatoes, snack chips, imitation cheese, and confectionery fats.

Margarine manufacture

Some margarine is made by hydrogenating carbon-carbon double bonds in animal or vegetable fats and oils. You can recognise the presence of this in foods because the ingredients list will include words showing that it contains "hydrogenated vegetable oils" or "hydrogenated fats".

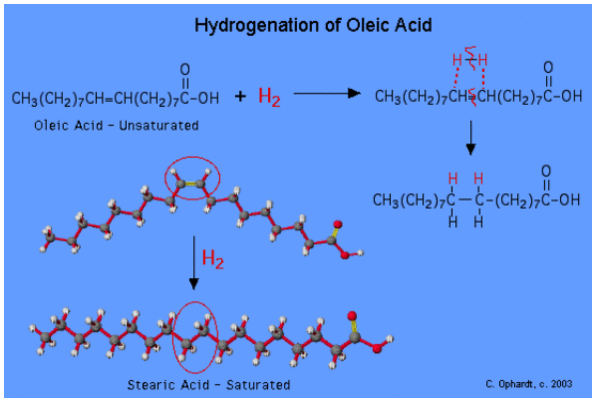
The impression is sometimes given that all margarine is made by hydrogenation - that's simply not true.

Vegetable oils often contain high proportions of polyunsaturated and mono-unsaturated fats (oils), and as a result are liquids at room temperature. That makes them messy to spread on your bread or toast, and inconvenient for some baking purposes.

You can "harden" (raise the melting point of) the oil by hydrogenating it in the presence of a nickel catalyst. Conditions (like the precise temperature, or the length of time the hydrogen is passed through the oil) are carefully controlled so that some, but not necessarily all, of the carbon-carbon double bonds are hydrogenated.

This produces a "partially hydrogenated oil" or "partially hydrogenated fat".

You need to hydrogenate enough of the bonds to give the final texture you want. However, there are possible health benefits in eating mono-unsaturated or polyunsaturated fats or oils rather than saturated ones - so you wouldn't want to remove all the carbon-carbon double bonds.



The downside of hydrogenation as a means of hardening fats and oils

There are some probable health risks from eating hydrogenated fats or oils. Consumers are becoming more aware of this, and manufacturers are increasingly finding alternative ways of converting oils into spreadable solids.

One of the problems arises from the hydrogenation process.

The double bonds in unsaturated fats and oils tend to have the groups around them arranged in the "cis" form.

The relatively high temperatures used in the hydrogenation process tend to flip some of the carbon-carbon double bonds into the "trans" form. If these particular bonds aren't hydrogenated during the process, they will still be present in the final margarine in molecules of trans fats.

The consumption of trans fats has been shown to increase cholesterol levels (particularly of the more harmful LDL form) - leading to an increased risk of heart disease.

Any process which tends to increase the amount of trans fat in the diet is best avoided. Read food labels, and avoid any food which contains (or is cooked in) hydrogenated oil or hydrogenated fat.

Problems

1. After the hydrogenation of an unsaturated fatty acid, would it exist at room temperature as a liquid or solid?

   Answer

2. Write the hydrogenation reaction for linoleic acid to hydrogenate all of the double bonds. What is the new name for this fatty acid? Hint: count carbons.

   Answer

3. Compare a "hard" type margarine vs. a "soft" margarine. Which has the most double bonds?

   Answer

4. Which is the most saturated?

   Answer

References

1. http://www.ncbi.nlm.nih.gov/pubmedhe...link-unproven/

2.

Contributors

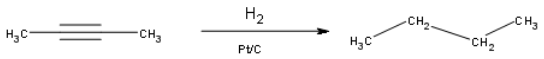
- Charles Ophardt, Professor Emeritus, Elmhurst College; Virtual Chembook
- Antonio Rodriguez
- Jim Clark (Chemguide.co.uk)

12.5: Reduction of Alkynes

Reactions between alkynes and catalysts are a common source of alkene formation. Because alkynes differ from alkenes on account of their two procurable π bonds, alkynes are more susceptible to additions. Aside from turning them into alkenes, these catalysts affect the arrangement of substituents on the newly formed alkene molecule. Depending on which catalyst is used, the catalysts cause anti- or syn-addition of hydrogens. Alkynes can readily undergo additions because of their availability of two π bonds.

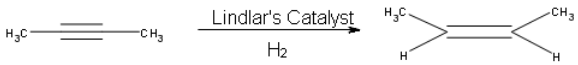
Hydrogenation of an Alkyne

Alkynes can be fully hydrogenated into alkanes with the help of a platinum catalyst. However, the use of two other catalysts can be used to hydrogenate alkynes to alkanes. These catalysts are: Palladium dispersed on carbon (Pd/C) and finely dispersed nickel (Raney-Ni).

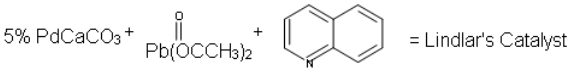


Hydrogenation of an Alkyne to a Cis-Alkene

Because hydrogenation is an interruptible process involving a series of steps, hydrogenation can be stopped, using modified catalysts (e.g., Lindlar's Catalyst) at the transitional alkene stage. Lindar's catalyst has three components: Palladium-Calcium Carbonate, lead acetate and quinoline. The quinoline serves to prevent complete hydrogenation of the alkyne to an alkane. Lindlar's Catalyst transforms an alkyne to a cis-alkene.

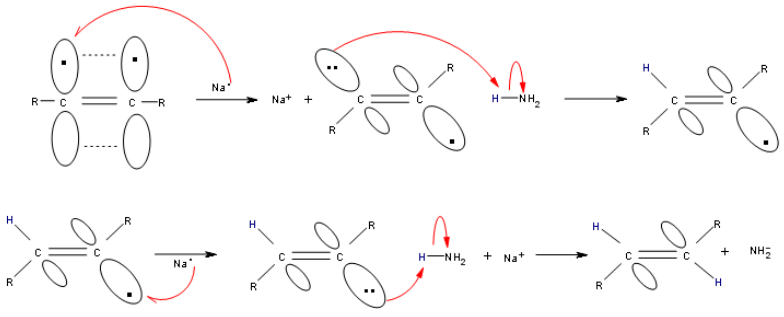


Lindlar's Catalyst:



Hydrogenation of an Alkyne to a Trans-Alkene

Alkynes can be reduced to trans-alkenes with the use of sodium dissolved in an ammonia solvent. An Na radical donates an electron to one of the P bonds in a carbon-carbon triple bond. This forms an anion, which can be protonated by a hydrogen in an ammonia solvent. This prompts another Na radical to donate an electron to the second P orbital. Soon after this anion is also protonated by a hydrogen from the ammonia solvent, resulting in a trans-alkene.

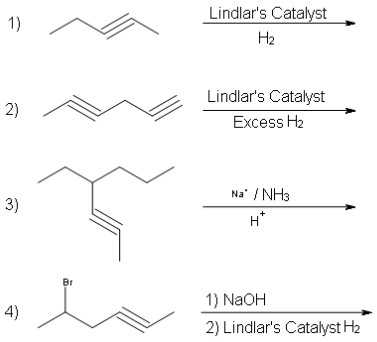


References

- Ternay, Andrew L. Contemporary Organic Chemistry. 2nd ed. Saunders, 1979
- Vollhardt, K. Peter C., and Neil E. Schore. Organic Chemistry: Structure and Function. New York: W.H. Freeman and Company, 2007.

- Williams, Jonathon M.J. Preparation of Alkenes: A Practical Approach. Illustrated ed. Oxford UP, 1996.

Problems



5) What is the role of quinoline in hydrogenation of an alkyn

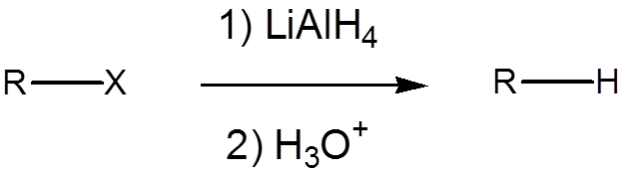
Contributors

- Ravjot Takhar (UCD)

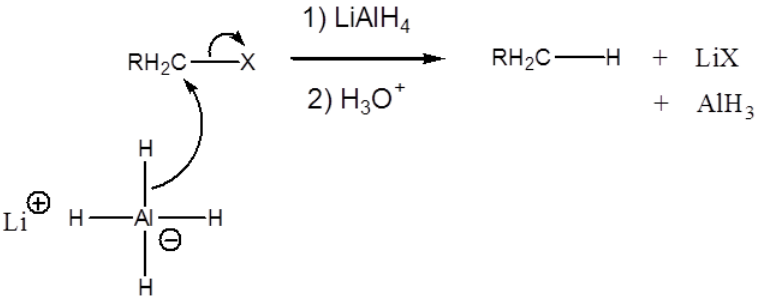
12.6: The Reduction of Polar C–X σ Bonds

Reduction of Halides

Alkyl halides can be reduced to alkanes through reaction with hydrife reagents, most commonly $LiAlH_4$

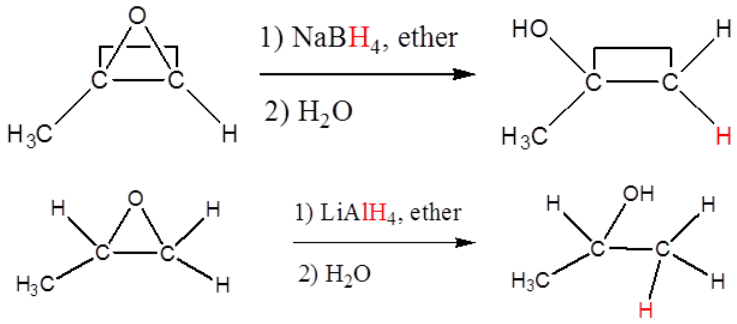


Mechanism



Hydride addition to epoxides

The hydride attacks the less substituted side of the epoxide. The H and OH are anti to each other.



Contributors

- Prof. Steven Farmer (Sonoma State University)

12.7: Oxidizing Agents

The laboratory oxidation of an alcohol to form an aldehyde or ketone is mechanistically different from the biochemical oxidations with $NAD(P)^+$ that we saw earlier in this chapter. The general picture of laboratory oxidations is illustrated below. Essentially what happens is that the hydroxide hydrogen of the alcohol is replaced by a leaving group (X in the figure below).

Then, a base can abstract the proton bound to the alcohol carbon, which results in elimination of the X leaving group and formation of a new carbon-oxygen double bond. As you can see by looking closely at this general mechanism, *tertiary alcohols cannot be oxidized in this way* – there is no hydrogen to abstract in the final step!

A common method for oxidizing secondary alcohols to ketones uses **chromic acid** (**H_2CrO_4**) as the oxidizing agent. Chromic acid, also known as **Jones reagent**, is prepared by adding chromium trioxide (CrO_3) to aqueous sulfuric acid.

A mechanism for the chromic acid oxidation of a ketone is shown below.

Note that the chromium reagent has lost two bonds to oxygen in this reaction, and thus has been reduced (it *must* have been reduced - it is the oxidizing agent!).

Ketones are not oxidized by chromic acid, so the reaction stops at the ketone stage. In contrast, primary alcohols are oxidized by chromic acid first to aldehydes, then straight on to carboxylic acids.

It is actually the hydride form of the aldehyde that is oxidized (recall from section 11.3 that aldehydes in aqueous solution exist in rapid equilibrium with their hydrate forms).

One of the hydroxyl groups of the hydrate attacks chromic acid, and the reaction proceeds essentially as shown for the oxidation of a secondary alcohol.

Under some conditions, chromic acid will even oxidize a carbon in the benzylic position to a carboxylic acid (notice that a carbon-carbon bond is broken in this transformation).

A number of other common oxidizing agents are discussed below.

The **pyridinium chlorochromate (PCC)** and **Swern oxidation** reactions are useful for oxidizing primary alcohols to aldehydes. Further oxidation of the aldehyde to the carboxylic acid stage does not occur with these reagents, because the reactions are carried out in anhydrous (water-free) organic solvents such as dichloromethane, and therefore the hydrate form of the aldehyde is not able to form.

The Swern oxidation uses dimethylsulfoxide and oxalyl chloride, followed by addition of a base such as triethylamine. The actual oxidizing species in this reaction is the dimethylchlorosulfonium ion, which forms from dimethylsulfoxide and oxalyl chloride.

You will be asked to propose a mechanism for these reactions in the end of chapter problems.

Pyridinium chlorochromate is generated by combining chromium trioxide, hydrochloric acid, and pyridine.

The PCC and Swern oxidation conditions can both also be used to oxidize secondary alcohols to ketones.

Silver ion, Ag(I), is often used to oxidize aldehydes to carboxylic acid. Two common reaction conditions are:

The set of reagents in the latter reaction conditions are commonly known as '**Tollens' reagent**'.

Alkenes are oxidized to *cis*-1,2-diols by **osmium tetroxide (OsO_4)**. The stereospecificity is due to the formation of a cyclic osmate ester intermediate. Osmium tetroxide is used in catalytic amounts, and is regenerated by N-methylmorpholine-N-oxide.

cis-1,2-diol compounds can be oxidized to dialdehydes (or diketones, depending on the substitution of the starting diol) using **periodic acid**:

Alkenes can also be oxidized by treatment with ozone, O_3. In **ozonolysis**, the carbon-carbon double bond is cleaved, and the alkene carbons are converted to aldehydes:

Dimethyl sulfide or zinc is added in the work-up stage of the reaction in order to reduce hydrogen peroxide, which is formed in the reaction, to water.

Alternatively, hydrogen peroxide and aqueous base can be added in the workup to obtain carboxylic acids:

Potassium permanganate ($KMnO_4$) is another very powerful oxidizing agent that will oxidize primary alcohols and aldehydes to carboxylic acids. KMnO4 is also useful for oxidative cleavage of alkenes to ketones and carboxylic acids:

Finally, alkenes can be oxidized to epoxides using a '**peroxyacid**' such as *m*-chloroperoxybenzoic acid. Notice the presence of a third oxygen in the peroxyacid functional group.

The mechanism is similar to that of the biological epoxidation catalyzed by squalene epoxidase (section 16.10A), with the π electrons in the alkene double bond attacking the 'outer' oxygen of the peroxyacid and cleaving the reactive O-O peroxide bond.

Uncatalyzed epoxidation of an asymmetric alkene generally results in two diastereomeric epoxide products, with the epoxide adding either from above or below the plane of the alkene.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

12.8: Epoxidation

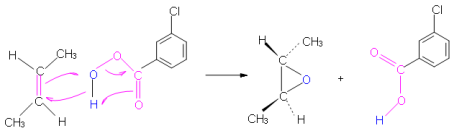
Oxacyclopropane rings, also called epoxide rings, are useful reagents that may be opened by further reaction to form anti vicinal diols. One way to synthesize oxacyclopropane rings is through the reaction of an alkene with peroxycarboxylic acid.

Oxacyclopropane Synthesis by Peroxycarboxylic Acid

Oxacyclopropane synthesis by peroxycarboxylic acid requires an alkene and a peroxycarboxylic acid as well as an appropriate solvent. The peroxycarboxylic acid has the unique property of having an electropositive oxygen atom on the COOH group. The reaction is initiated by the electrophilic oxygen atom reacting with the nucleophilic carbon-carbon double bond. The mechanism involves a concerted reaction with a four-part, circular transition state. The result is that the originally electropositive oxygen atom ends up in the oxacyclopropane ring and the COOH group becomes COH.

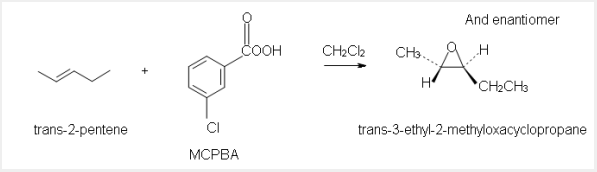
Mechanism

Peroxycarboxylic acids are generally unstable. An exception is meta-chloroperoxybenzoic acid, shown in the mechanism above. Often abbreviated MCPBA, it is a stable crystalline solid. Consequently, MCPBA is popular for laboratory use. However, MCPBA can be explosive under some conditions.



Peroxycarboxylic acids are sometimes replaced in industrial applications by monoperphthalic acid, or the monoperoxyphthalate ion bound to magnesium, which gives magnesium monoperoxyphthalate (MMPP). In either case, a nonaqueous solvent such as chloroform, ether, acetone, or dioxane is used. This is because in an aqueous medium with any acid or base catalyst present, the epoxide ring is hydrolyzed to form a vicinal diol, a molecule with two OH groups on neighboring carbons. (For more explanation of how this reaction leads to vicinal diols, see below.) However, in a nonaqueous solvent, the hydrolysis is prevented and the epoxide ring can be isolated as the product. Reaction yields from this reaction are usually about 75%. The reaction rate is affected by the nature of the alkene, with more nucleophilic double bonds resulting in faster reactions.

Example



Since the transfer of oxygen is to the same side of the double bond, the resulting oxacyclopropane ring will have the same stereochemistry as the starting alkene. A good way to think of this is that the alkene is rotated so that some constituents are coming forward and some are behind. Then, the oxygen is inserted on top. (See the product of the above reaction.) One way the epoxide ring can be opened is by an acid catalyzed oxidation-hydrolysis. Oxidation-hydrolysis gives a vicinal diol, a molecule with OH groups on neighboring carbons. For this reaction, the dihydroxylation is *anti* since, due to steric hindrance, the ring is attacked from the side opposite the existing oxygen atom. Thus, if the starting alkene is trans, the resulting vicinal diol will have one S and one R stereocenter. But, if the starting alkene is cis, the resulting vicinal diol will have a racemic mixture of S, S and R, R enantiomers.

The Synthesis of Disparlure using epoxidation

The gypsy moth (Porthytria dispar) is a serious pest of the forests. In 1976 B.A. Bierl et.al., (Science, 170,88 (1970)) isolated the sex pheromone from extracts of 78,000 tips of the last two abdominal segments of female moths. The structure was assigned as **1.5.1.** Later, the precursor molecule – the cis-olefin was also

Fig 1.5.1

isolates from the same source. A laboratory bioassay from synthetic materials showed that just 2 pg of 1.5.1 was enough to elicit bioactivity. Since the availability of the molecule from natural sources was very minute even for structure elucidation problems and study its anticipated role as pest control molecule, there was intense interest in an efficient synthesis of this molecule. Some disconnections for this simple molecule are depicted in **Fig 1.5.2.**

Fig 1.5.2

Epoxides could be made from corresponding olefins. In this case, the olefin should be Z-olefin. When synthesis of such olefins are not stereospecific, direct epoxidation using peroxides would yield a mixture of α- and β-epoxide from both isomeric olefins. To avoid such mixtures at the last stage, one should introduce selectivity at an early stage of the synthesis.

The first attempt was directed towards synthesis of the appropriate olefin and epoxidation (B.A. Bierl et.al., (Science, 170, 88 (1970)). The stereoselectivity was unsatisfactory (Fig 1.5.3). This necessitated extensive purification.

References

1. Royals, E. 1954. Advanced Organic Chemistry. New York: Prentice Hall. 948 p.
2. Streitwieser, A. and C. Heathcock. 1981. Introduction to Organic Chemistry. 2nd ed. New York: Macmillan Publishing Co. 1258 p.
3. Vollhardt, K. and N. Schore. 2007. Organic Chemistry: Structure and Function. 5th ed. New York: W.H. Freeman and Company. 1254 p.
4. Wheland, G. 1949. Advanced Organic Chemistry. 3rd ed. New York: John Wiley & Sons. 871 p.

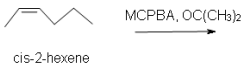
Outside Links

- http://en.wikipedia.org/wiki/Peroxycarboxylic_acid
- http://en.wikipedia.org/wiki/Epoxide

Problems

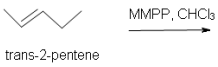
1. Predict the product of the reaction of cis-2-hexene with MCPBA (meta-chloroperoxybenzoic acid)

a) in acetone solvent.

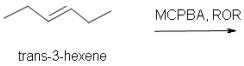


b) in an aqueous medium with acid or base catalyst present.

2. Predict the product of the reaction of trans-2-pentene with magnesium monoperoxyphthalate (MMPP) in a chloroform solvent.



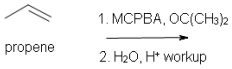
3. Predict the product of the reaction of trans-3-hexene with MCPBA in ether solvent.



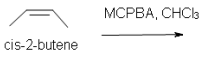
4. Predict the reaction of propene with MCPBA.

a) in acetone solvent

b) after aqueous work-up.

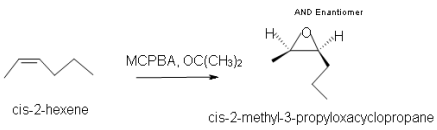


5. Predict the reaction of cis-2-butene in chloroform solvent.

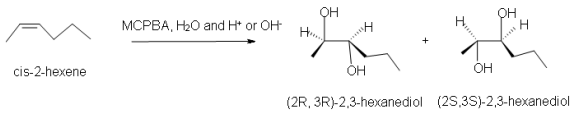


Answers

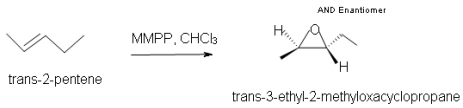
1. a) Cis-2-methyl-3-propyloxacyclopropane



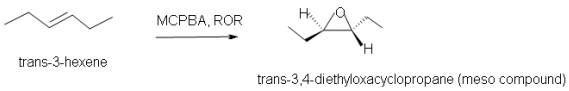
b) Racemic (2R,3R)-2,3-hexanediol and (2S,3S)-2,3-hexanediol



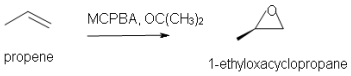
2. Trans-3-ethyl-2-methyloxacyclopropane.



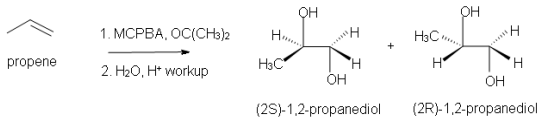
3. Trans-3,4-diethyloxacyclopropane.



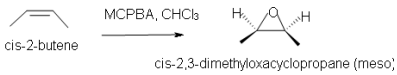
4. a) 1-ethyl-oxacyclopropane



b) Racemic (2S)-1,2-propandiol and (2R)-1,2-propanediol



5. Cis-2,3-dimethyloxacyclopropane



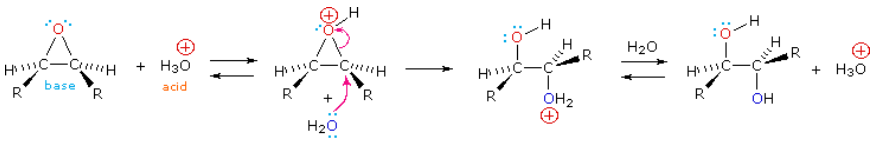
Contributors

- Kristen Perano

12.9: Dihydroxylation

Anti Dihydroxylation

Epoxides may be cleaved by aqueous acid to give glycols that are often diastereomeric with those prepared by the syn-hydroxylation reaction described above. Proton transfer from the acid catalyst generates the conjugate acid of the epoxide, which is attacked by nucleophiles such as water in the same way that the cyclic bromonium ion described above undergoes reaction. The result is **anti-hydroxylation** of the double bond, in contrast to the syn-stereoselectivity of the earlier method. In the following equation this procedure is illustrated for a cis-disubstituted epoxide, which, of course, could be prepared from the corresponding cis-alkene. This hydration of an epoxide does not change the oxidation state of any atoms or groups.

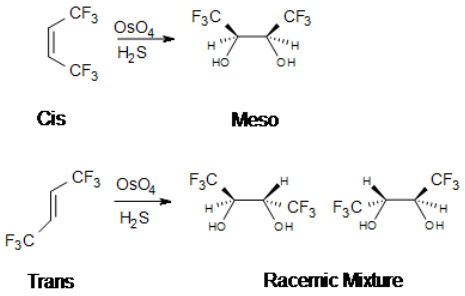


Syn Dihydroxylation

Osmium tetroxide oxidizes alkenes to give glycols through syn addition. A glycol, also known as a vicinal diol, is a compound with two -OH groups on adjacent carbons.

Introduction

The reaction with OsO_4 is a concerted process that has a cyclic intermediate and no rearrangements. Vicinal syn dihydroxylation complements the epoxide-hydrolysis sequence which constitutes an *anti* dihydroxylation of an alkene. When an alkene reacts with osmium tetroxide, stereocenters can form in the glycol product. Cis alkenes give meso products and trans alkenes give racemic mixtures.



OsO_4 is formed slowly when osmium powder reacts with gasoues O_2 at ambient temperature. Reaction of bulk solid requires heating to 400 °C:

$$Os_{(s)} + 2O_{2\ (g)} \rightarrow OS_4 \tag{12.9.1}$$

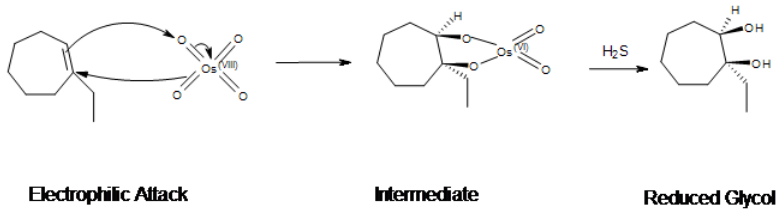
Since Osmium tetroxide is expensive and highly toxic, the reaction with alkenes has been modified. Catalytic amounts of OsO_4 and stoichiometric amounts of an oxidizing agent such as hydrogen peroxide are now used to eliminate some hazards. Also, an older reagent that was used instead of OsO_4 was potassium permanganate, $KMnO_4$. Although syn diols will result from the reaction of $KMnO_4$ and an alkene, potassium permanganate is less useful since it gives poor yields of the product because of *overoxidation*.

Mechanism

- Electrophilic attack on the alkene
  - Pi bond of the alkene acts as the nucleophile and reacts with osmium (VIII) tetroxide (OsO_4)
  - 2 electrons from the double bond flows toward the osmium metal

- In the process, 3 electron pairs move simultaneously
  - Cyclic ester with Os (VI) is produced
- Reduction
  - H_2S reduces the cyclic ester
    - $NaHSO_4$ with H_2O may be used
  - Forms the syn-1,2-diol (glycol)

Example: Dihydroxylation of 1-ethyl-1-cycloheptene



Hydroxylation of alkenes

Dihydroxylated products (glycols) are obtained by reaction with aqueous potassium permanganate (pH > 8) or osmium tetroxide in pyridine solution. Both reactions appear to proceed by the same mechanism (shown below); the metallocyclic intermediate may be isolated in the osmium reaction. In basic solution the purple permanganate anion is reduced to the green manganate ion, providing a nice color test for the double bond functional group. From the mechanism shown here we would expect syn-stereoselectivity in the bonding to oxygen, and regioselectivity is not an issue.

When viewed in context with the previously discussed addition reactions, the hydroxylation reaction might seem implausible. Permanganate and osmium tetroxide have similar configurations, in which the metal atom occupies the center of a tetrahedral grouping of negatively charged oxygen atoms. How, then, would such a species interact with the nucleophilic pi-electrons of a double bond? A possible explanation is that an empty d-orbital of the electrophilic metal atom extends well beyond the surrounding oxygen atoms and initiates electron transfer from the double bond to the metal, in much the same fashion noted above for platinum. Back-bonding of the nucleophilic oxygens to the antibonding π*-orbital completes this interaction. The result is formation of a metallocyclic intermediate, as shown above.

Chemical Highlight

Antitumor drugs have been formed by using dihydroxylation. This method has been applied to the enantioselective synthesis of ovalicin, which is a class of fungal-derived products called antiangiogenesis agents. These antitumor products can cut off the blood supply to solid tumors. A derivative of ovalicin, TNP-470, is chemically stable, nontoxic, and noninflammatory. TNP-470 has been used in research to determine its effectiveness in treating cancer of the breast, brain, cervix, liver, and prostate.

Outside links

- http://en.wikipedia.org/wiki/Osmium_tetroxide
- http://www.chm.bris.ac.uk/motm/oso4/oso4v.htm
- http://www.organic-chemistry.org/che...tetroxide.shtm

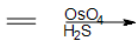
References

1. Dehestani, Ahmad et al. (2005). Ligand-assisted reduction of osmium tetroxide with molecular hydrogen via a [3+2] mechanism. *Journal of the American Chemical Society, 2005, 127 (10)*, 3423-3432.
2. Sorrell, Thomas, N. Organic Chemistry. New York: University Science Books, 2006.
3. Vollhardt, Peter, and Neil E. Schore. Organic Chemistry: Structure and Function. 5th Edition. New York: W. H. Freeman & Company, 2007.

Problems

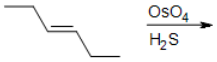
Questions:

1. Give the major product.

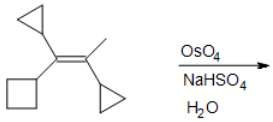


2. What is the product in the dihydroxylation of (Z)-3-hexene?

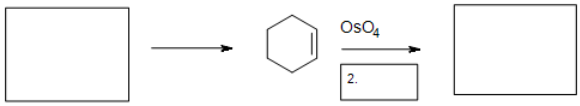
3. What is the product in the dihydroxylation of (E)-3-hexene?



4. Draw the intermediate of this reaction.

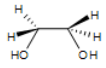


5. Fill in the missing reactants, reagents, and product.

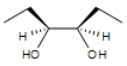


Solutions

1. A syn-1,2-ethanediol is formed. There is no stereocenter in this particular reaction. The OH groups are on the same side.

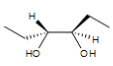


2. Meso-3,4-hexanediol is formed. There are 2 stereocenters in this reaction.

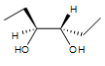


(3S, 4R)

3. A racemic mixture of 3,4-hexanediol is formed. There are 2 stereocenters in both products.

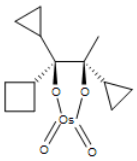


(3R, 4R)

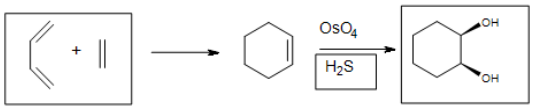


(3S, 4S)

4. A cyclic osmic ester is formed.



5. The Diels-Alder cycloaddition reaction is needed in the first box to form the cyclohexene. The second box needs a reagent to reduce the intermediate cyclic ester (not shown). The third box has the product: 1,2-cyclohexanediol.

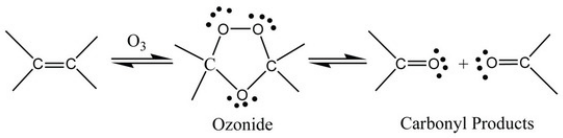


Contributors

- Shivam Nand
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

12.10: Oxidative Cleavage of Alkenes

Ozonolysis is a method of oxidatively cleaving alkenes or alkynes using ozone (O_3), a reactive allotrope of oxygen. The process allows for carbon-carbon double or triple bonds to be replaced by double bonds with oxygen. This reaction is often used to identify the structure of unknown alkenes. by breaking them down into smaller, more easily identifiable pieces. Ozonolysis also occurs naturally and would break down repeated units used in rubber and other polymers. On an industrial scale, azelaic acid and pelargonic acids are produced from ozonolysis.

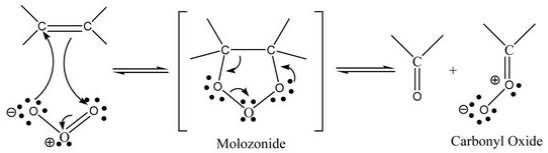


Introduction

The gaseous ozone is first passed through the desired alkene solution in either methanol or dichloromethane. The first intermediate product is an ozonide molecule which is then further reduced to carbonyl products. This results in the breaking of the Carbon-Carbon double bond and is replaced by a Carbon-Oxygen double bond instead.

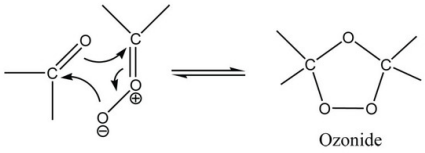
Reaction Mechanism

Step 1:



The first step in the mechanism of ozonolysis is the initial electrophilic addition of ozone to the Carbon-Carbon double bond, which then form the molozonide intermediate. Due to the unstable molozonide molecule, it continues further with the reaction and breaks apart to form a carbonyl and a carbonyl oxide molecule.

Step 2:

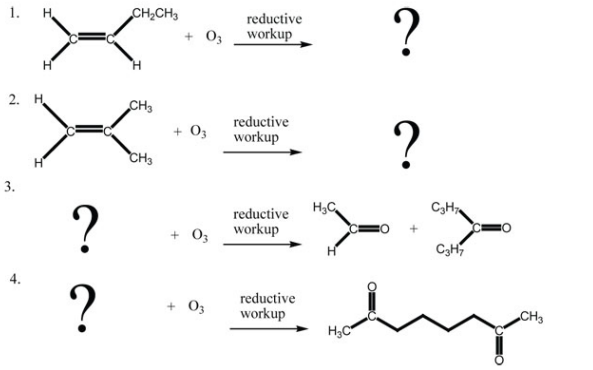


The carbonyl and the carbonyl oxide rearranges itself and reforms to create the stable ozonide intermediate. A reductive workup could then be performed to convert convert the ozonide molecule into the desired carbonyl products.

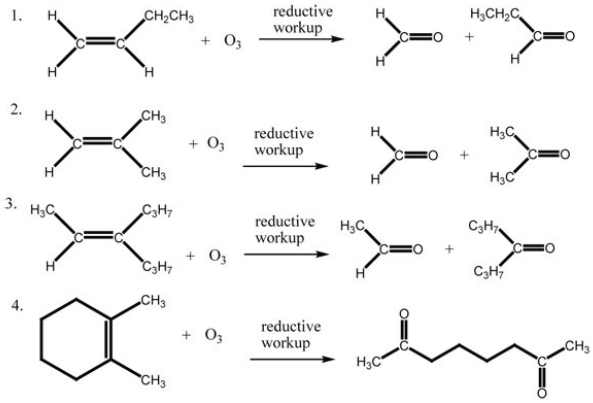
References

1. Vollhardt, K., Schore, N. Organic Chemistry: Structure and Function. 5th ed. New York, NY: W. H. Freeman and Company, 2007.
2. Shore, N. Study Guide and Solutions Manual for Organic Chemistry. 5th ed. New York, NY: W.H. Freeman and Company, 2007.

Problems

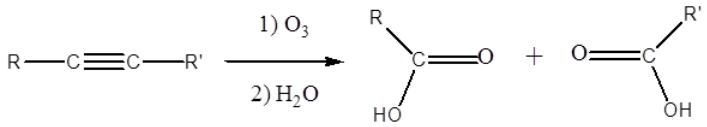


Answers

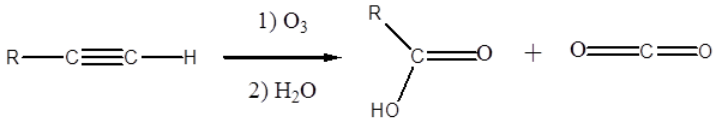


12.11: Oxidative Cleavage of Alkynes

Alkynes can also undergo oxidative cleavage. Internal alkynes form carboxylic acids **(RCOOH)** and terminal alkynes form carboxylic acids and **CO_2**.

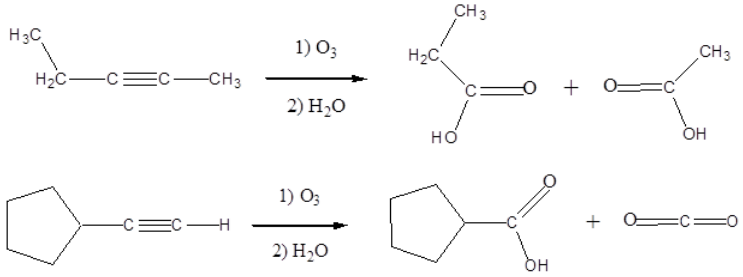


Internal Alkyne — Carboxylic Acids



Terminal Alkyne

Examples



Contributors

- Prof. Steven Farmer (Sonoma State University)

12.12: Oxidation of Alcohols

This page looks at the oxidation of alcohols using acidified sodium or potassium dichromate(VI) solution. This reaction is used to make aldehydes, ketones and carboxylic acids, and as a way of distinguishing between primary, secondary and tertiary alcohols.

Oxidizing the different types of alcohols

The oxidizing agent used in these reactions is normally a solution of sodium or potassium dichromate(VI) acidified with dilute sulfuric acid. If oxidation occurs, the orange solution containing the dichromate(VI) ions is reduced to a green solution containing chromium(III) ions. The electron-half-equation for this reaction is

$$Cr_2O_7^{2-} + 14H^+ + 6e^- \rightarrow 2Cr^{3+} + 7H_2O \tag{12.12.1}$$

Oxidizing agents

$K_2C_r2O_7$ potassium dichromate

CrO3 Chromium Trioxide

Both of these are used along with

H_2SO_4, H_2O

1^o alcohol → Carboxylic acid

2^o alcohol → Ketone

3^o alcohol → No reaction

Primary alcohols

Primary alcohols can be oxidized to either aldehydes or carboxylic acids depending on the reaction conditions. In the case of the formation of carboxylic acids, the alcohol is first oxidized to an aldehyde which is then oxidized further to the acid.

Full oxidation to carboxylic acids

You need to use an excess of the oxidizing agent and make sure that the aldehyde formed as the half-way product stays in the mixture. The alcohol is heated under reflux with an excess of the oxidizing agent. When the reaction is complete, the carboxylic acid is distilled off. The full equation for the oxidation of ethanol to ethanoic acid is:

$$3CH_3CH_2OH + 2Cr_2O_7^{2-} + 16H+ \rightarrow 3CH_3COOH + 4Cr^{3+} + 11H_2O \tag{12.12.2}$$

The more usual simplified version looks like this:

$$CH_3CH_2OH + 2[O] \rightarrow CH_3COOH + H_2O \tag{12.12.3}$$

Alternatively, you could write separate equations for the two stages of the reaction - the formation of ethanal and then its subsequent oxidation.

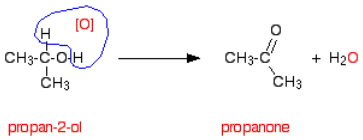
$$CH_3CH_2OH + [O] \rightarrow CH_3CHO + H_2O \tag{12.12.4}$$

$$CH_3CHO + [O] \rightarrow CH_3COOH \tag{12.12.5}$$

This is what is happening in the second stage:

Secondary alcohols

Secondary alcohols are oxidized to ketones - and that's it. For example, if you heat the secondary alcohol propan-2-ol with sodium or potassium dichromate(VI) solution acidified with dilute sulfuric acid, you get propanone formed. Playing around with the reaction conditions makes no difference whatsoever to the product. Using the simple version of the equation and showing the relationship between the structures:

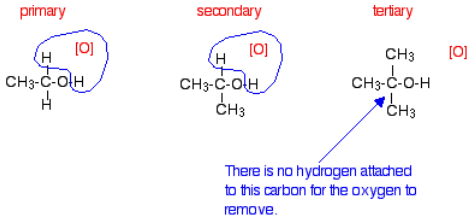


If you look back at the second stage of the primary alcohol reaction, you will see that an oxygen "slotted in" between the carbon and the hydrogen in the aldehyde group to produce the carboxylic acid. In this case, there is no such hydrogen - and the reaction has nowhere further to go.

Tertiary alcohols

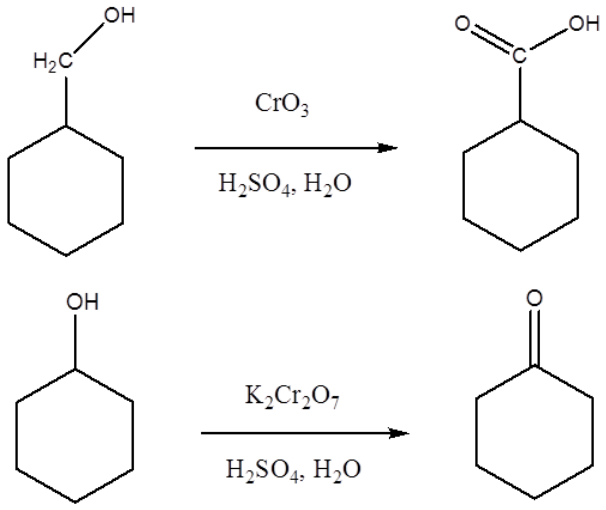
Tertiary alcohols are not oxidized by acidified sodium or potassium dichromate(VI) solution - there is no reaction whatsoever. If you look at what is happening with primary and secondary alcohols, you will see that the oxidizing agent is removing the hydrogen from the -OH group, and a hydrogen from the carbon atom attached to the -OH. Tertiary alcohols don't have a hydrogen atom attached to that carbon.

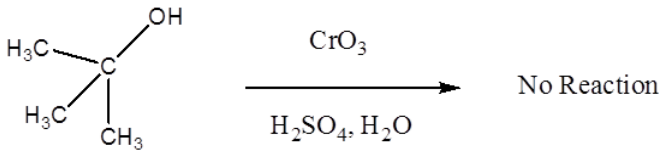
You need to be able to remove those two particular hydrogen atoms in order to set up the carbon-oxygen double bond.



Mechanism

Examples



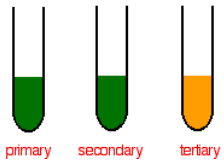


Using these reactions as a test for the different types of alcohol

First you have to be sure that you have actually got an alcohol by testing for the -OH group. You would need to show that it was a neutral liquid, free of water and that it reacted with solid phosphorus(V) chloride to produce a burst of acidic steamy hydrogen chloride fumes. You would then add a few drops of the alcohol to a test tube containing potassium dichromate(VI) solution acidified with dilute sulfuric acid. The tube would be warmed in a hot water bath.

Picking out the tertiary alcohol

In the case of a primary or secondary alcohol, the orange solution turns green. With a tertiary alcohol there is no color change. After heating:

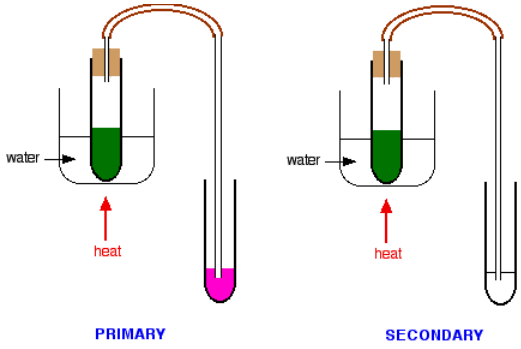


Distinguishing between the primary and secondary alcohols

You need to produce enough of the aldehyde (from oxidation of a primary alcohol) or ketone (from a secondary alcohol) to be able to test them. There are various things which aldehydes do which ketones don't. These include the reactions with Tollens' reagent, Fehling's solution and Benedict's solution, and are covered on a separate page.

These tests can be a bit of a bother to carry out and the results are not always as clear-cut as the books say. A much simpler but fairly reliable test is to use *Schiff's reagent*. Schiff's reagent is a fuchsin dye decolorized by passing sulfur dioxide through it. In the presence of even small amounts of an aldehyde, it turns bright magenta.

It must, however, be used absolutely cold, because ketones react with it very slowly to give the same color. If you heat it, obviously the change is faster - and potentially confusing. While you are warming the reaction mixture in the hot water bath, you can pass any vapours produced through some Schiff's reagent.



- If the Schiff's reagent quickly becomes magenta, then you are producing an aldehyde from a primary alcohol.
- If there is no color change in the Schiff's reagent, or only a trace of pink color within a minute or so, then you are not producing an aldehyde, and so haven't got a primary alcohol.

Because of the color change to the acidified potassium dichromate(VI) solution, you must therefore have a secondary alcohol. You should check the result as soon as the potassium dichromate(VI) solution turns green - if you leave it too long, the Schiff's reagent might start to change color in the secondary alcohol case as well.

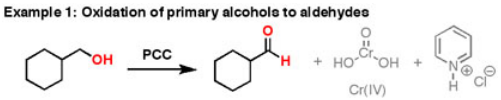
Formation of Aldehydes using PCC

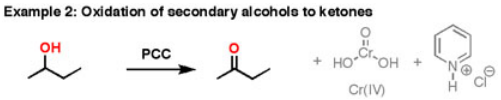
Pyridinium chlorochromate (PCC) is a milder version of chromic acid.

PCC (Pyridinium Chlorochromate)

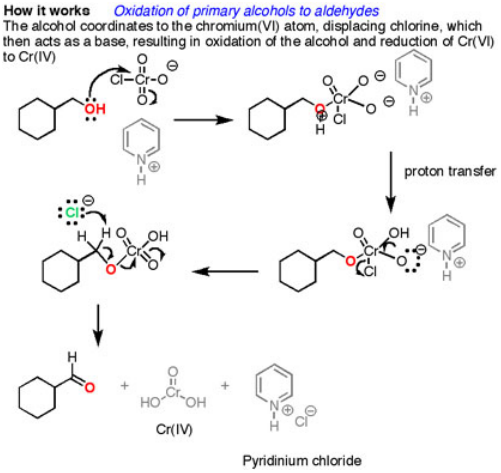
PCC oxidizes alcohols one rung up the oxidation ladder, from primary alcohols to aldehydes and from secondary alcohols to ketones. Unlike chromic acid, PCC will not oxidize aldehydes to carboxylic acids. Similar to or the same as: CrO_3 and pyridine (the Collins reagent) will also oxidize primary alcohols to aldehydes. Here are two examples of PCC in action.

- If you add one equivalent of PCC to either of these alcohols, you obtain the oxidized version. The byproducts (featured in grey) are Cr(IV) as well as pyridinium hydrochloride.
- One has to be careful with the amount of water present in the reaction. If water were present, it can ad to the aldehyde to make the hydrate, which could be further oxidized by a second equivalent of PCC were it present. This is not a concern with ketones, since there is no H directly bonded to C.





How does it work? Oxidation reactions of this sort are actually a kind of elimination reaction. We're going from a carbon-oxygen single bond to a carbon-oxygen double bond. The elimination reaction can occur because we're putting a good leaving group on the oxygen, namely the chromium, which will be displaced when the neighboring C-H bond is broken with a base.



The first step is attack of oxygen on the chromium to form the Cr-O bond. Secondly, a proton on the (now positive) OH is transferred to one of the oxygens of the chromium, possibly through the intermediacy of the pyridinium salt. A chloride ion is then displaced, in a reaction reminiscent of a 1,2 elimination reaction, to form what is known as a chromate ester.

The C-O double bond is formed when a base removes the proton on the carbon adjacent to the oxygen. [aside: I've drawn the base as Cl(-) although there are certainly other species which could also act as bases here (such as an alcohol). It is also possible for pyridine to be used as the base here, although only very low concentrations of the deprotonated form will be present under these

acidic conditions.] The electrons from the C-H bond move to form the C-O bond, and in the process break the O-Cr bond, and Cr(VI) becomes Cr(IV) in the process (drawn here as O=Cr(OH)2).

Real life notes: If you end up using PCC in the lab, don't forget to add molecular sieves or Celite or some other solid to the bottom of the flask, because otherwise you get a nasty brown tar that is a real major pain to clean up. The toxicity and mess associated with chromium has spurred the development of other alternatives like TPAP, IBX, DMP, and a host of other neat reagents you generally don't learn about until grad school.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- Prof. Steven Farmer (Sonoma State University)

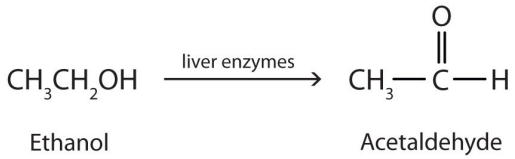
James Ashenhurst (MasterOrganicChemistry.com)

- Jim Clark (Chemguide.co.uk)

12.13: Green Chemistry

12.14: Application- The Oxidation of Ethanol

Ethanol is oxidized in the liver to acetaldehyde:



The acetaldehyde is in turn oxidized to acetic acid ($HC_2H_3O_2$), a normal constituent of cells, which is then oxidized to carbon dioxide and water. Even so, ethanol is potentially toxic to humans. The rapid ingestion of 1 pt (about 500 mL) of pure ethanol would kill most people, and acute ethanol poisoning kills several hundred people each year—often those engaged in some sort of drinking contest. Ethanol freely crosses into the brain, where it depresses the respiratory control center, resulting in failure of the respiratory muscles in the lungs and hence suffocation. Ethanol is believed to act on nerve cell membranes, causing a diminution in speech, thought, cognition, and judgment.

Rubbing alcohol is usually a 70% aqueous solution of isopropyl alcohol. It has a high vapor pressure, and its rapid evaporation from the skin produces a cooling effect. It is toxic when ingested but, compared to methanol, is less readily absorbed through the skin.

12.15: Sharpless Epoxidation

Epoxides are very useful intermediates in organic synthesis. Because most naturally occurring molecules (including those with medicinal properties) are chiral, control of stereochemistry is one of the most important challenges facing a synthetic chemist attempting to synthesize a naturally occurring molecule in the laboratory. In what was arguably one of the most important discoveries in synthetic organic chemistry in recent decades, Barry Sharpless of Stanford University reported in 1980 that he and his colleagues had developed a method to stereoselectively epoxidize asymmetric alkenes which contained an alcohol in the allylic position. The '**Sharpless asymmetric oxidation**' is achieved with the use of a chiral catalyst composed of (+) or (-) diethyltartrate and an organotitanium compound (*J. Am. Chem. Soc*. **1980**, *102*, 5974). Depending on which stereoisomer of diethyltartrate is used, the peroxyacid oxygen tends to add to either the top or bottom plane of the alkene.

This technique allows for the specific introduction of two new stereocenters at an alkene position, which as you can imagine makes it an extremely useful synthetic tool.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

CHAPTER OVERVIEW

13: Radical Reactions

Topic hierarchy

13.1: Introduction

In chemistry, a **radical** (more precisely, a **free radical**) is an atom, molecule, or ion that has unpaired valence electrons or an open electron shell, and therefore may be seen as having one or more "dangling" covalent bonds.

With some exceptions, these "dangling" bonds make free radicals highly chemically reactive towards other substances, or even towards themselves: their molecules will often spontaneously dimerize or polymerize if they come in contact with each other. Most radicals are reasonably stable only at very low concentrations in inert media or in a vacuum.

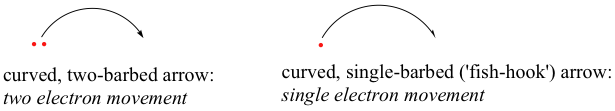
Free radicals may be created in a number of ways, including synthesis with very dilute or rarefied reagents, reactions at very low temperatures, or breakup of larger molecules. The latter can be affected by any process that puts enough energy into the parent molecule, such as ionizing radiation, heat, electrical discharges, electrolysis, and chemical reactions. Indeed, radicals are intermediate stages in many chemical reactions.

History

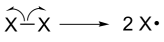
The first organic free radical identified was triphenylmethyl radical. This species was discovered by Moses Gomberg in 1900 at the University of Michigan USA. Historically, the term *radical* in radical theory was also used for bound parts of the molecule, especially when they remain unchanged in reactions. These are now called functional groups. For example, methyl alcohol was described as consisting of a methyl "radical" and a hydroxyl "radical". Neither are radicals in the modern chemical sense, as they are permanently bound to each other, and have no unpaired, reactive electrons; however, they can be observed as radicals in mass spectrometry when broken apart by irradiation with energetic electrons.

Depiction in chemical reactions

In this chapter, we will learn about some reactions in which the key steps involve the movement of *single* electrons. You may recall from way back in section 6.1A that single electron movement is depicted by a single-barbed'**fish-hook**' arrow (as opposed to the familiar double-barbed arrows that we have been using throughout the book to show two-electron movement).

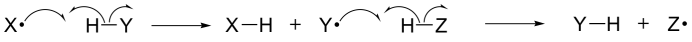


Single-electron mechanisms involve the formation and subsequent reaction of free radical species, highly unstable intermediates that contain an unpaired electron. We will learn in this chapter how free radicals are often formed from **homolytic cleavage**, an event where the two electrons in a breaking covalent bond move in opposite directions.



(In contrast, essentially all of the reactions we have studied up to now involve bond-breaking events in which both electrons move in the same direction: this is called **heterolytic cleavage**).

We will also learn that many single-electron mechanisms take the form of a radical chain reaction, in which one radical causes the formation of a second radical, which in turn causes the formation of a third radical, and so on.

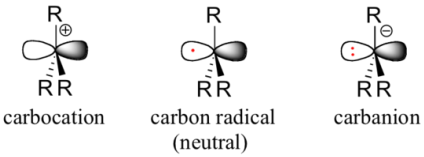


The high reactivity of free radical species and their ability to initiate chain reactions is often beneficial - we will learn in this chapter about radical polymerization reactions that form useful materials such as plexiglass and polyproylene fabric. We will also learn about radical reactions that are harmful, such as the degradation of atmospheric ozone by freon, and the oxidative damage done to lipids and DNA in our bodies by free radicals species. Finally, we will see how some enzymes use bound metals to catalyze high e

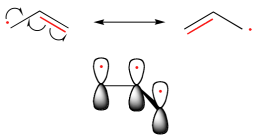
The geometry and relative stability of carbon radicals

As organic chemists, we are particularly interested in radical intermediates in which the unpaired electron resides on a carbon atom. Experimental evidence indicates that the three bonds in a carbon radical have trigonal planar geometry, and therefore the carbon is considered to be sp^2-hybridized with the unpaired electron occupying the perpendicular, unhybridized $2p_z$orbital. Contrast this

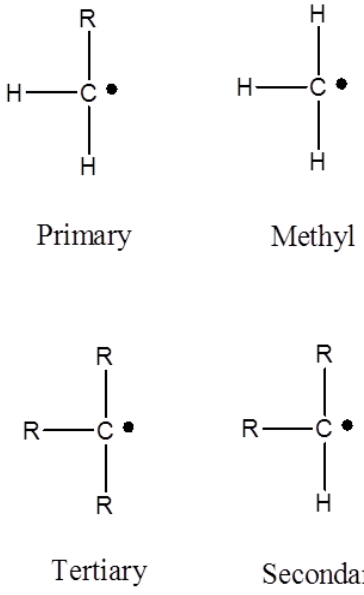
picture with carbocation and carbanion intermediates, which are both also trigonal planar but whose $2p_z$ orbitals contain zero or two electrons, respectively.



The trend in the stability of carbon radicals parallels that of carbocations (section 8.4B): tertiary radicals, for example, are more stable than secondary radicals, followed by primary and methyl radicals. This should make intuitive sense, because radicals, like carbocations, can be considered to be electron deficient, and thus are stabilized by the electron-donating effects of nearby alkyl groups. Benzylic and allylic radicals are more stable than alkyl radicals due to resonance effects - an unpaired electron can be delocalized over a system of conjugated pi bonds. An allylic radical, for example, can be pictured as a system of three parallel $2p_z$ orbitals sharing three electrons.

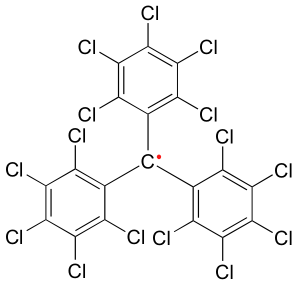


Trends in radical stability



Allyic & Benzlic > 3^o > 2^o > 1^o > Methyl

Template:ExampleStart
Exercise 17.1: Draw the structure of a benzylic radical compound, and then draw a resonance form showing how the radical is stabilized.
Template:ExampleEnd
With enough resonance stabilization, radicals can be made that are quite unreactive. One example of an inert organic radical structure is shown below.



In this molecule, the already extensive resonance stabilization is further enhanced by the ability of the chlorine atoms to shield the radical center from external reagents. The radical is, in some sense, inside a protective 'cage'.

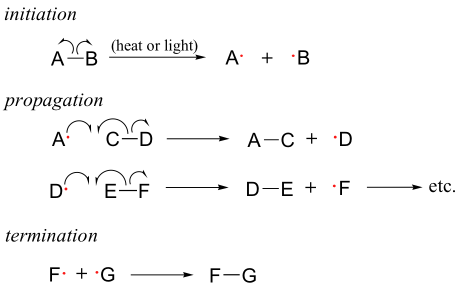
Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- Prof. Steven Farmer (Sonoma State University)

13.2: General Features of Radical Reactions

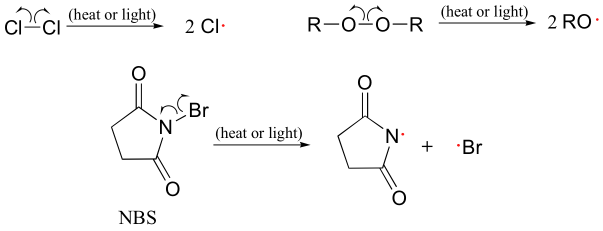
The three phases of radical chain reactions

Because of their high reactivity, free radicals have the potential to be both extremely powerful chemical tools and extremely harmful contaminants. Much of the power of free radical species stems from the natural tendency of radical processes to occur in a chain reaction fashion. **Radical chain reactions** have three distinct phases: initiation, propagation, and termination.

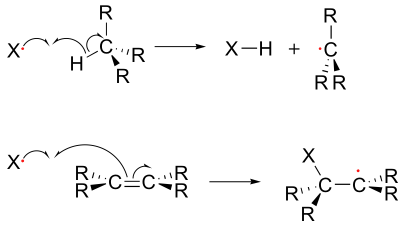


The **initiation phase** describes the step that initially creates a radical species. In most cases, this is a homolytic cleavage event, and takes place very rarely due to the high energy barriers involved. Often the influence of heat, UV radiation, or a metal-containing catalyst is necessary to overcome the energy barrier.

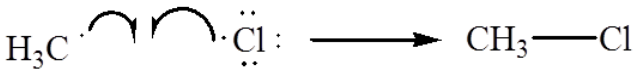
Molecular chlorine and bromine will both undergo homolytic cleavage to form radicals when subjected to heat or light. Other functional groups which also tend to form radicals when exposed to heat or light are chlorofluorocarbons, peroxides, and the halogenated amide N-bromosuccinimide (NBS).



The **propagation phase** describes the 'chain' part of chain reactions. Once a reactive free radical is generated, it can react with stable molecules to form new free radicals. These new free radicals go on to generate yet more free radicals, and so on. Propagation steps often involve hydrogen abstraction or addition of the radical to double bonds.



Chain termination occurs when two free radical species react with each other to form a stable, non-radical adduct. Although this is a very thermodynamically downhill event, it is also very rare due to the low concentration of radical species and the small likelihood of two radicals colliding with one another. In other words, the Gibbs free energy barrier is very high for this reaction, mostly due to entropic rather than enthalpic considerations. The active sites of enzymes, of course, can evolve to overcome this entropic barrier by positioning two radical intermediates adjacent to one another.



Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- Prof. Steven Farmer (Sonoma State University)

13.3: Halogenation of Alkanes

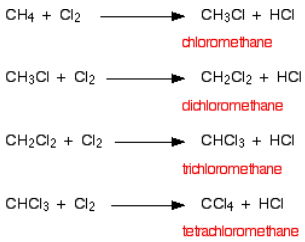
Methane and chlorine

If a mixture of methane and chlorine is exposed to a flame, it explodes - producing carbon and hydrogen chloride. This is not a very useful reaction! The reaction we are going to explore is a more gentle one between methane and chlorine in the presence of ultraviolet light - typically sunlight. This is a good example of a photochemical reaction - a reaction brought about by light.

$$CH_4 + Cl_2 + \text{energy} \rightarrow CH_3Cl + HC$$

The organic product is chloromethane. One of the hydrogen atoms in the methane has been replaced by a chlorine atom, so this is a substitution reaction. However, the reaction doesn't stop there, and all the hydrogens in the methane can in turn be replaced by chlorine atoms. Multiple substitution is dealt with on a separate page, and you will find a link to that at the bottom of this page.

Substitution reactions happen in which hydrogen atoms in the methane are replaced one at a time by chlorine atoms. You end up with a mixture of chloromethane, dichloromethane, trichloromethane and tetrachloromethane.



The original mixture of a colorless and a green gas would produce steamy fumes of hydrogen chloride and a mist of organic liquids. All of the organic products are liquid at room temperature with the exception of the chloromethane which is a gas.

If you were using bromine, you could either mix methane with bromine vapor, or bubble the methane through liquid bromine - in either case, exposed to UV light. The original mixture of gases would, of course, be red-brown rather than green.

You wouldn't choose to use these reactions as a means of preparing these organic compounds in the lab because the mixture of products would be too tedious to separate. The mechanisms for the reactions are explained on separate pages.

Contributors

Jim Clark (Chemguide.co.uk)

13.4: The Mechanism of Halogenation

lkanes (the most basic of all organic compounds) undergo very few reactions. One of these reactions is halogenation, or the substitution of a single hydrogen on the alkane for a single halogen to form a haloalkane. This reaction is very important in organic chemistry because it opens a gateway to further chemical reactions.

Introduction

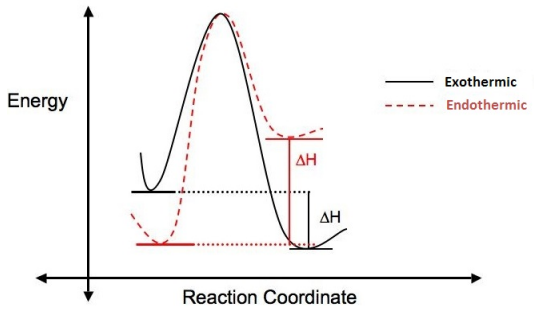
While the reactions possible with alkanes are few, there are many reactions that involve haloalkanes. In order to better understand the mechanism (a detailed look at the step by step process through which a reaction occurs), we will closely examine the chlorination of methane. When methane (CH_4) and chlorine (Cl_2) are mixed together in the absence of light at room temperature nothing happens. However, if the conditions are changed, so that either the reaction is taking place at high temperatures (denoted by Δ) or there is ultra violet irradiation, a product is formed, chloromethane (CH_3Cl).

Energetics

Why does this reaction occur? Is the reaction favorable? A way to answer these questions is to look at the change in enthalpy (ΔH) that occurs when the reaction takes place.

$$\Delta H = (\text{Energy put into reaction}) - (\text{Energy given off from reaction})$$

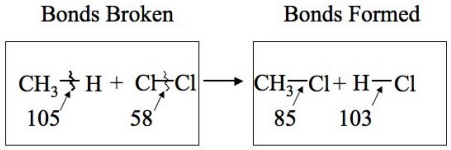
If more energy is put into a reaction than is given off, the ΔH is positive, the reaction is endothermic and not energetically favorable. If more energy is given off in the reaction than was put in, the ΔH is negative, the reaction is said to be exothermic and is considered favorable. The figure below illustrates the difference between endothermic and exothermic reactions.



ΔH can also be calculated using bond dissociation energies (ΔH°):

$$\Delta H = \sum \Delta H^\circ \text{ of bonds broken} - \sum \Delta H^\circ \text{ of bonds formed} \tag{13.4.1}$$

Let's look at our specific example of the chlorination of methane to determine if it is endothermic or exothermic:



Change in enthalpy = (105 + 58) - (85 + 103)
= -25kcal/mol

Since, the ΔH for the chlorination of methane is negative, the reaction is exothermic. Energetically this reaction is favorable. In order to better understand this reaction we need to look at the mechanism (a detailed step by step look at the reaction showing how it occurs) by which the reaction occurs.

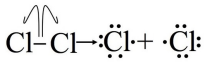
Radical Chain Mechanism

The reaction proceeds through the radical chain mechanism. The radical chain mechanism is characterized by three steps: **initiation**, **propagation** and **termination**. Initiation requires an input of energy but after that the reaction is self-sustaining. The

first propagation step uses up one of the products from initiation, and the second propagation step makes another one, thus the cycle can continue until indefinitely.

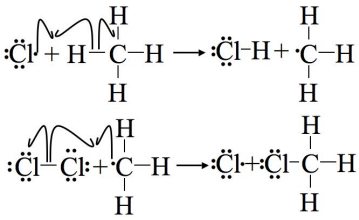
Step 1: Initiation

Initiation breaks the bond between the chlorine molecule (Cl_2). For this step to occur energy must be put in, this step is not energetically favorable. After this step, the reaction can occur continuously (as long as reactants provide) without input of more energy. It is important to note that this part of the mechanism cannot occur without some external energy input, through light or heat.

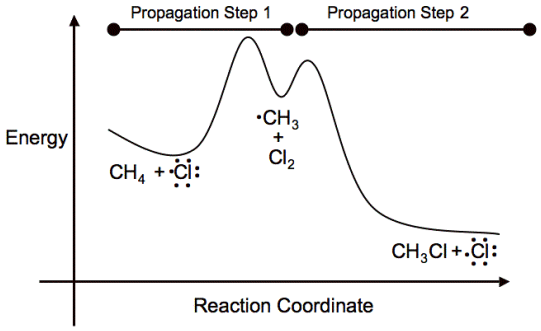


Step 2: Propagation

The next two steps in the mechanism are called propagation steps. In the first propagation step, a chlorine radical combines with a hydrogen on the methane. This gives hydrochloric acid (HCl, the inorganic product of this reaction) and the methyl radical. In the second propagation step more of the chlorine starting material (Cl_2) is used, one of the chlorine atoms becomes a radical and the other combines with the methyl radical.

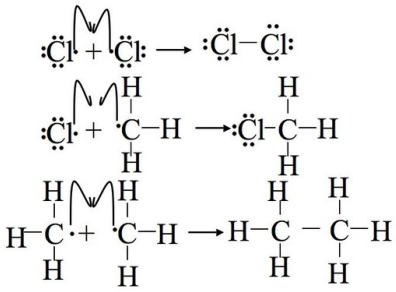


The first propagation step is endothermic, meaning it takes in heat (requires 2 kcal/mol) and is not energetically favorable. In contrast the second propagation step is exothermic, releasing 27 kcal/mol. Since the second propagation step is so exothermic, it occurs very quickly. The second propagation step uses up a product from the first propagation step (the methyl radical) and following Le Chatelier's principle, when the product of the first step is removed the equilibrium is shifted towards it's products. This principle is what governs the unfavorable first propagation step's occurance.



Step 3: Termination

In the termination steps, all the remaining radicals combine (in all possible manners) to form more product (CH_3Cl), more reactant (Cl_2) and even combinations of the two methyl radicals to form a side product of ethane (CH_3CH_3).



Problems with the Chlorination of Methane

The chlorination of methane does not necessarily stop after one chlorination. It may actually be very hard to get a monosubstituted chloromethane. Instead di-, tri- and even tetra-chloromethanes are formed. One way to avoid this problem is to use a much higher concentration of methane in comparison to chloride. This reduces the chance of a chlorine radical running into a chloromethane and starting the mechanism over again to form a dichloromethane. Through this method of controlling product ratios one is able to have a relative amount of control over the product.

References

1. Matyjaszewski, Krzysztof, Wojciech Jakubowski, Ke Min, Wei Tang, Jinyu Huang, Wade A. Braunecker, and Nicolay V. Tsarevsky. "Diminishing Catalyst Concentration in Atom Transfer Radical Polymerization with Reducing Agents." Proceedings of the National Academy of Sciences of the United States of America 103 (2006): 15309-5314.
2. Morgan, G. T. "A State Experiment in Chemical Research." Science 72 (1930): 379-90.
3. Phillips, Francis C. "# Researches upon the Chemical Properties of Gases." Researches upon the Chemical Properties of Gases 17 (1893): 149-236.

Outside Links

- Video of Mechanism: http://www.jbpub.com/organic-online/...s/chlormet.htm
- Wikipedia of Radical Chain Mechanism: http://en.wikipedia.org/wiki/Free_ra...l_halogenation
- Wikipedia of Le Chatelier's Principle: http://en.wikipedia.org/wiki/Le_Chat...#Concentration

Problems

Answers to these questions are in an attached slide

1. Write out the complete mechanism for the chlorination of methane.
2. Explain, in your own words, how the first propagation step can occur without input of energy if it is energetically unfavorable.
3. Compounds other than chlorine and methane go through halogenation with the radical chain mechanism. Write out a generalized equation for the halogenation of RH with X_2including all the different steps of the mechanism.
4. Which step of the radical chain mechanism requires outside energy? What can be used as this energy?
5. Having learned how to calculate the change in enthalpy for the chlorination of methane apply your knowledge and using the table provided below calculate the change in enthalpy for the bromination of ethane.

Compound	Bond Dissociation Energy (kcal/mol)
CH_3CH_2-H	101
CH_3CH_2-Br	70
H-Br	87
Br_2	46

Contributors

- Kristen Kelley and Britt Farquharson

13.5: Chlorination of Other Alkanes

When alkanes larger than ethane are halogenated, isomeric products are formed. Thus chlorination of propane gives both 1-chloropropane and 2-chloropropane as mono-chlorinated products. Four constitutionally isomeric dichlorinated products are possible, and **five constitutional isomers** exist for the trichlorinated propanes. Can you write structural formulas for the four dichlorinated isomers?

$$CH_3CH_2CH_3 + 2Cl_2 \rightarrow \text{Four } C_3H_6Cl_2 \text{ isomers} + 2HCl \tag{13.5.1}$$

The halogenation of propane discloses an interesting feature of these reactions. **All the hydrogens in a complex alkane do not exhibit equal reactivity**. For example, propane has eight hydrogens, six of them being structurally equivalent **primary**, and the other two being **secondary**. If all these hydrogen atoms were equally reactive, halogenation should give a 3:1 ratio of 1-halopropane to 2-halopropane mono-halogenated products, reflecting the primary/secondary numbers. This is not what we observe. Light-induced gas phase chlorination at 25 ºC gives 45% 1-chloropropane and 55% 2-chloropropane.

CH_3-CH_2-CH_3 + Cl_2 → 45% CH_3-CH_2-CH_2Cl + 55% CH_3-$CHCl$-CH_3

The results of bromination (light-induced at 25 ºC) are even more suprising, with 2-bromopropane accounting for 97% of the mono-bromo product.

CH_3-CH_2-CH_3 + Br_2 → 3% CH_3-CH_2-CH_2Br + 97% CH_3-$CHBr$-CH_3

These results suggest strongly that 2º-hydrogens are inherently more reactive than 1º-hydrogens, by a factor of about 3:1. Further experiments showed that 3º-hydrogens are even more reactive toward halogen atoms. Thus, light-induced chlorination of 2-methylpropane gave predominantly (65%) 2-chloro-2-methylpropane, the substitution product of the sole 3º-hydrogen, despite the presence of nine 1º-hydrogens in the molecule.

$(CH_3)_3CH$ + Cl_2 → 65% $(CH_3)_3CCl$ + 35% $(CH_3)_2CHCH_2Cl$

If you are uncertain about the terms primary (1º), secondary (2º) & tertiary (3º) Click Here.

It should be clear from a review of the two steps that make up the free radical chain reaction for halogenation that the first step (hydrogen abstraction) is the **product determining step**. Once a carbon radical is formed, subsequent bonding to a halogen atom (in the second step) can only occur at the radical site. Consequently, an understanding of the preference for substitution at 2º and 3º-carbon atoms must come from an analysis of this first step.

First Step: R_3CH + $X\cdot$ → $R_3C\cdot$ + H-X

Second Step: $R_3C\cdot$ + X_2 → R_3CX + $X\cdot$

Since the H-X product is common to all possible reactions, differences in reactivity can only be attributed to differences in C-H bond dissociation energies. In our previous discussion of bond energy we assumed average values for all bonds of a given kind, but now we see that this is not strictly true. In the case of carbon-hydrogen bonds, there are significant differences, and the specific dissociation energies (energy required to break a bond homolytically) for various kinds of C-H bonds have been measured. These values are given in the following table.

R (in R–H)	methyl	ethyl	i-propyl	t-butyl	phenyl	benzyl	allyl	vinyl
Bond Dissociation Energy (kcal/mole)	103	98	95	93	110	85	88	112

The difference in C-H bond dissociation energy reported for primary (1º), secondary (2º) and tertiary (3º) sites agrees with the halogenation observations reported above, in that we would expect weaker bonds to be broken more easily than are strong bonds. By this reasoning we would expect benzylic and allylic sites to be exceptionally reactive in free radical halogenation, as experiments have shown. The methyl group of toluene, $C_6H_5CH_3$, is readily chlorinated or brominated in the presence of free radical initiators (usually peroxides), and ethylbenzene is similarly chlorinated at the benzylic location exclusively. The hydrogens bonded to the aromatic ring (referred to as phenyl hydrogens above) have relatively high bond dissociation energies and are not substituted.

$C_6H_5CH_2CH_3$ + Cl_2 → $C_6H_5CHClCH_3$ + HCl

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

13.6: Chlorination versus Bromination

A Free Radical Substitution Reaction

This page gives you the facts and a simple, uncluttered mechanism for the free radical substitution reaction between methane and bromine. This reaction between methane and bromine happens in the presence of ultraviolet light - typically sunlight. This is a good example of a photochemical reaction - a reaction brought about by light.

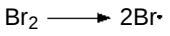
$$CH_4 + Br_2 \rightarrow CH_3Br + HBr \tag{13.6.1}$$

The organic product is bromomethane. One of the hydrogen atoms in the methane has been replaced by a bromine atom, so this is a substitution reaction. However, the reaction doesn't stop there, and all the hydrogens in the methane can in turn be replaced by bromine atoms.

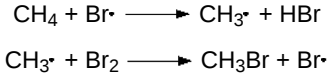
The mechanism

The mechanism involves a chain reaction. During a chain reaction, for every reactive species you start off with, a new one is generated at the end - and this keeps the process going.The over-all process is known as free radical substitution, or as a free radical chain reaction.

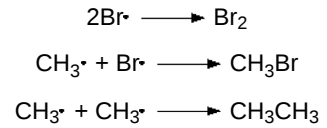
- **Chain initiation:** The chain is initiated (started) by UV light breaking a bromine molecule into free radicals.



- **Chain propagation reactions:** These are the reactions which keep the chain going.



- **Chain termination reactions:** These are reactions which remove free radicals from the system without replacing them by new ones.



Selectivity

When alkanes larger than ethane are halogenated, isomeric products are formed. Thus chlorination of propane gives both 1-chloropropane and 2-chloropropane as mono-chlorinated products. Four constitutionally isomeric dichlorinated products are possible, and **five constitutional isomers** exist for the trichlorinated propanes. Can you write structural formulas for the four dichlorinated isomers?

$$CH_3CH_2CH_3 + 2Cl_2 \rightarrow \text{Four } C_3H_6Cl_2 \text{ isomers} + 2HCl \tag{13.6.2}$$

The halogenation of propane discloses an interesting feature of these reactions. **All the hydrogens in a complex alkane do not exhibit equal reactivity**. For example, propane has eight hydrogens, six of them being structurally equivalent **primary**, and the other two being **secondary**. If all these hydrogen atoms were equally reactive, halogenation should give a 3:1 ratio of 1-halopropane to 2-halopropane mono-halogenated products, reflecting the primary/secondary numbers. This is not what we observe. Light-induced gas phase chlorination at 25 ºC gives 45% 1-chloropropane and 55% 2-chloropropane.

CH_3-CH_2-CH_3 + Cl_2 → 45% CH_3-CH_2-CH_2Cl + 55% CH_3-$CHCl$-CH_3

The results of bromination (light-induced at 25 ºC) are even more suprising, with 2-bromopropane accounting for 97% of the mono-bromo product.

CH_3-CH_2-CH_3 + Br_2 → 3% CH_3-CH_2-CH_2Br + 97% CH_3-$CHBr$-CH_3

These results suggest strongly that 2º-hydrogens are inherently more reactive than 1º-hydrogens, by a factor of about 3:1. Further experiments showed that 3º-hydrogens are even more reactive toward halogen atoms. Thus, light-induced chlorination of 2-

methylpropane gave predominantly (65%) 2-chloro-2-methylpropane, the substitution product of the sole 3º-hydrogen, despite the presence of nine 1º-hydrogens in the molecule.

$(CH_3)_3CH + Cl_2 \rightarrow 65\% (CH_3)_3CCl + 35\% (CH_3)_2CHCH_2Cl$

Contributors

Jim Clark (Chemguide.co.uk)

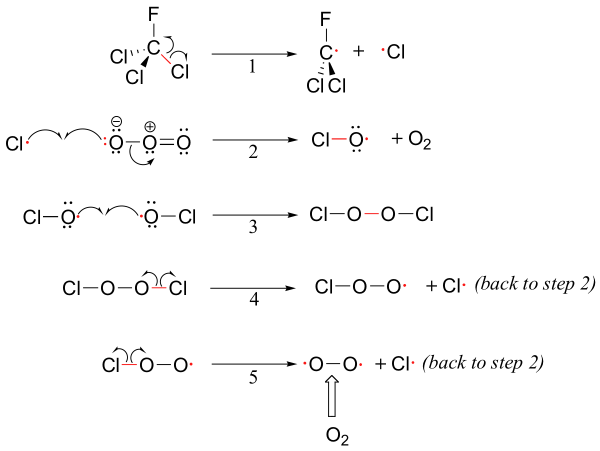
13.7: Halogenation as a Tool in Organic Synthesis

13.8: The Stereochemistry of Halogenation Reactions

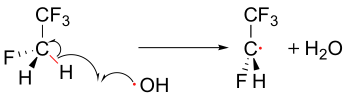
13.9: Application- The Ozone Layer and CFCs

The high reactivity of free radicals and the multiplicative nature of radical chain reactions can be useful in the synthesis of materials such as polyethylene plastic - but these same factors can also result in dangerous consequences. You are probably aware of the danger posed to the earth's protective stratospheric ozone layer by the use of chlorofluorocarbons (CFCs) as refrigerants and propellants in aerosol spray cans. Freon-11, or $CFCl_3$, is a typical CFC that was widely used until fairly recently. It can take months or years for a CFC molecule to drift up into the stratosphere from the surface of the earth, and of course the concentration of CFCs at this altitude is very low. Ozone, on the other hand, is continually being formed in the stratosphere. Why all the concern, then, about destruction of the ozone layer - how could such a small amount of CFCs possibly do significant damage? The problem lies in the fact that the process by which ozone is destroyed is a chain reaction, so that a single CFC molecule can initiate the destruction of many ozone molecules before a chain termination event occurs.

Although there are several different processes by which the ozone destruction process might occur, the most important is believed to be the chain reaction shown below.



To address the problem of ozone destruction, scientists are developing new organohalogen refrigerant compounds that are less stable than the older CFCs like Freon-11, in the hope that the new compounds will break down in the lower atmosphere before they reach an altitude where they can harm the ozone layer. Most of the new compounds contain carbon-hydrogen bonds, which are subject to homolytic cleavage initiated by hydroxide radicals present in the lower atmosphere.

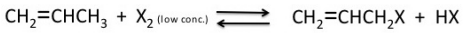


This degradation occurs *before* the refrigerant molecules have a chance to drift up to the stratosphere where the ozone plays its important protective role. The degradation products are quite unstable and quickly degrade further, by a variety of mechanisms, into relatively harmless by-products. The hydroxide radical is sometimes referred to as an atmospheric 'detergent' due to its ability to degrade refrigerants and other volatile organic pollutants which have escaped into the atmosphere.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

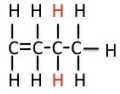
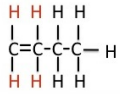
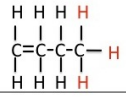
13.10: Radical Halogenation at an Allylic Carbon

When halogens are in the presence of unsaturated molecules such as alkenes, the expected reaction is addition to the double bond carbons resulting in a vicinal dihalide (halogens on adjacent carbons). However, when the halogen concentration is low enough, alkenes containing allylic hydrogens undergo substitution at the allylic position rather than addition at the double bond. The product is an allylic halide (halogen on carbon next to double bond carbons), which is acquired through a radical chain mechanism.



Why Substitution of Allylic Hydrogens?

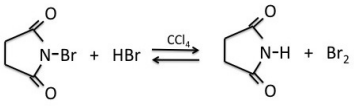
As the table below shows, the dissociation energy for the allylic C-H bond is lower than the dissociation energies for the C-H bonds at the vinylic and alkylic positions. This is because the radical formed when the allylic hydrogen is removed is resonance-stabilized. Hence, given that the halogen concentration is low, substitution at the allylic position is favored over competing reactions. However, when the halogen concentration is high, addition at the double bond is favored because a polar reaction outcompetes the radical chain reaction.

Type of Hydrogen	Dissociation Energy (DH^o)
allylic 	88 kcal/mol
vinylic 	106 kcal/mol
alkylic 	98 kcal/mol

Radical Allylic Bromination (Wohl-Ziegler Reaction)

Preparation of Bromine (low concentration)

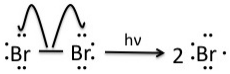
NBS (N-bromosuccinimide) is the most commonly used reagent to produce low concentrations of bromine. When suspended in tetrachloride (CCl_4), NBS reacts with trace amounts of HBr to produce a low enough concentration of bromine to facilitate the allylic bromination reaction.



Allylic Bromination Mechanism

Step 1: Initiation

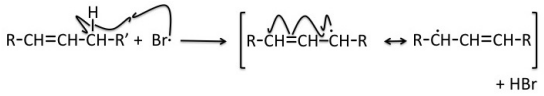
Once the pre-initiation step involving NBS produces small quantities of Br_2, the bromine molecules are homolytically cleaved by light to produce bromine radicals.



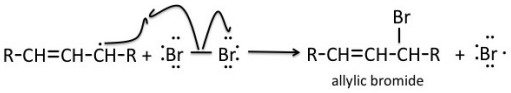
Step 2: Propagation

One bromine radical produced by homolytic cleavage in the initiation step removes an allylic hydrogen of the alkene molecule. A radical intermediate is generated, which is stabilized by resonance. The stability provided by delocalization of the radical in the

alkene intermediate is the reason that substitution at the allylic position is favored over competing reactions such as addition at the double bond.

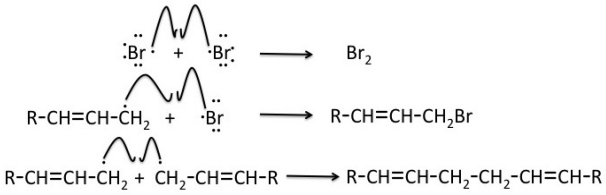


The intermediate radical then reacts with a Br_2 molecule to generate the allylic bromide product and regenerate the bromine radical, which continues the radical chain mechanism. If the alkene reactant is asymmetric, two distinct product isomers are formed.



Step 3: Termination

The radical chain mechanism of allylic bromination can be terminated by any of the possible steps shown below.



Radical Allylic Chlorination

Like bromination, chlorination at the allylic position of an alkene is achieved when low concentrations of Cl_2 are present. The reaction is run at high temperatures to achieve the desired results.

Industrial Uses

Allylic chlorination has important practical applications in industry. Since chlorine is inexpensive, allylic chlorinations of alkenes have been used in the industrial production of valuable products. For example, 3-chloropropene, which is necessary for the synthesis of products such as epoxy resin, is acquired through radical allylic chlorination (shown below).

Problems (Answers are attached as a file)

1. Cyclooctene undergoes radical allylic bromination. Write out the complete mechanism including reactants, intermediates and products.
2. Predict the two products of the allylic chlorination reaction of 1-heptene.
3. What conditions are required for allylic halogenation to occur? Why does this reaction outcompete other possible reactions such as addition when these conditions are met?
4. Predict the product of the allylic bromination reaction of 2-benzylheptane. (Hint: How are benzylic hydrogens similar to allylic hydrogens?)
5. The reactant 5-isopropyl-1-hexene generates the products 3-bromo-5-isopropyl-1-hexene and 1-bromo-5-isopropyl-2-hexene. What reagents were used in this reaction?

References

1. Djerassi, Carl. "Brominations with N-Bromosuccinimide and Related Compounds - The Wohl-Ziegler Reaction." Chemical Reviews 43 (1948):271-314.
2. Easton, Christopher J., Alison J. Edwards, Stephen B. McNabb, Martin C. Merrett, Jenny L. O'Connell, Gregory W. Simpson, Jamie S. Simpson, and Anthony C. Willis. "Allylic halogenation of unsaturated amino acids." Organic and Biomolecular Chemistry (2003). RSC Publishing. 9 June 2003. Royal Society of Chemistry. 25 Feb. 2009.
3. Kent, Doug. Allylic Bromination. Chem 118B Workshop. Learning Skills Center. 3 Feb. 2009.
4. Li, Chao-Jun, and Tak-Hang Chan. Comprehensive Organic Reactions in Aqueous Media. New York: Wiley-Interscience, 2007.

5. Vollhardt, Peter C., and Neil E. Schore. Organic Chemistry: Structure and Function. 5th ed. New York: W.H. Freeman and Company, 2007.

Outside Links

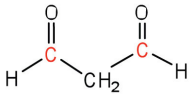
- http://en.wikipedia.org/wiki/N-Bromo...de#Preparation
- http://en.wikipedia.org/wiki/Wohl-Ziegler_reaction
- http://www.mhhe.com/physsci/chemistr...10allylic.html

13.11: Application- Oxidation of Unsaturated Lipids

Fats and oils that are in contact with moist air at room temperature eventually undergo oxidation and hydrolysis reactions that cause them to turn rancid, acquiring a characteristic disagreeable odor. One cause of the odor is the release of volatile fatty acids by hydrolysis of the ester bonds. Butter, for example, releases foul-smelling butyric, caprylic, and capric acids. Microorganisms present in the air furnish lipases that catalyze this process. Hydrolytic rancidity can easily be prevented by covering the fat or oil and keeping it in a refrigerator.

Another cause of volatile, odorous compounds is the oxidation of the unsaturated fatty acid components, particularly the readily oxidized structural unit

in polyunsaturated fatty acids, such as linoleic and linolenic acids. One particularly offensive product, formed by the oxidative cleavage of both double bonds in this unit, is a compound called *malonaldehyde*.



Malonaldehyde

Rancidity is a major concern of the food industry, which is why food chemists are always seeking new and better antioxidants, substances added in very small amounts (0.001%–0.01%) to prevent oxidation and thus suppress rancidity. Antioxidants are compounds whose affinity for oxygen is greater than that of the lipids in the food; thus they function by preferentially depleting the supply of oxygen absorbed into the product. Because vitamin E has antioxidant properties, it helps reduce damage to lipids in the body, particularly to unsaturated fatty acids found in cell membrane lipids.

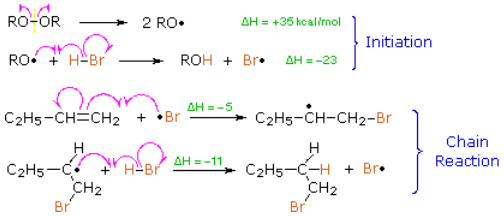
Contributors

- Anonymous

13.12: Application- Antioxidants

13.13: Radical Addition Reactions to Double Bonds

Protons and other electrophiles are not the only reactive species that initiate addition reactions to carbon-carbon double bonds. Curiously, this first became evident as a result of conflicting reports concerning the regioselectivity of HBr additions. As noted earlier, the acid-induced addition of HBr to 1-butene gave predominantly 2-bromobutane, the Markovnikov Rule product. However, in some early experiments in which peroxide contaminated reactants were used, 1-bromobutane was the chief product. Further study showed that an alternative radical chain-reaction, initiated by peroxides, was responsible for the anti-Markovnikov product. This is shown by the following equations.



The weak O–O bond of a peroxide initiator is broken homolytically by thermal or hight energy. The resulting alkoxy radical then abstracts a hydrogen atom from HBr in a strongly exothermic reaction. Once a bromine atom is formed it adds to the π-bond of the alkene in the first step of a chain reaction. This addition is regioselective, giving the more stable carbon radical as an intermediate. The second step is carbon radical abstraction of another hydrogen from HBr, generating the anti-Markovnikov alkyl bromide and a new bromine atom. Each of the steps in this chain reaction is exothermic, so once started the process continues until radicals are lost to termination events.

This free radical chain addition competes very favorably with the slower ionic addition of HBr described earlier, especially in non-polar solvents. It is important to note, however, that HBr is unique in this respect. The radical addition process is unfavorable for HCl and HI because one of the chain steps becomes endothermic (the second for HCl & the first for HI).

Other radical addition reactions to alkenes have been observed, one example being the peroxide induced addition of carbon tetrachloride shown in the following equation

$$RCH{=}CH_2 + CCl_4 \text{ (peroxide initiator)} \longrightarrow RCHClCH_2CCl_3$$

The best known and most important use of free radical addition to alkenes is probably polymerization. Since the addition of carbon radicals to double bonds is energetically favorable, concentrated solutions of alkenes are prone to radical-initiated polymerization, as illustrated for propene by the following equation. The blue colored R-group represents an initiating radical species or a growing polymer chain; the propene monomers are colored maroon. The addition always occurs so that the more stable radical intermediate is formed.

$$R\dot{C}H_2(CH_3)CH + CH_3CH{=}CH_2 \longrightarrow RCH_2(CH_3)CH\text{-}CH_2(CH_3)\dot{C}H + CH_3CH{=}CH_2 \longrightarrow RCH_2(CH_3)CHCH_2(CH_3)CH\text{-}CH_2(CH_3)\dot{C}H \longrightarrow \textbf{etc.}$$

Anti-Markovnikov rule describes the regiochemistry where the substituent is bonded to a less substituted carbon, rather than the more substitued carbon. This process is quite unusual, as carboncations which are commonly formed during alkene, or alkyne reactions tend to favor the more substitued carbon. This is because substituted carbocation allow more hyperconjugation and indution to happen, making the carbocation more stable.

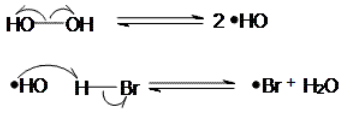
Introduction

This process was first explained by Morris Selig Karasch in his paper: 'The Addition of Hydrogen Bromide to Allyl Bromide' in 1933.[1] Examples of Anti-Markovnikov includes Hydroboration-Oxidation and Radical Addition of HBr. A free radical is any chemical substance with unpaired electron. The more substituents the carbon is connected to, the more substituted is that carbon. For example: Tertiary carbon (most substituted), Secondary carbon (medium substituted), primary carbon (least substituted)

Anti-Markovnikov Radical Addition of Haloalkane can ONLY happen to HBr and there MUST be presence of Hydrogen Peroxide (H_2O_2). Hydrogen Peroxide is essential for this process, as it is the chemical which starts off the chain reaction in the initiation step. **HI and HCl cannot** be used in radical reactions, because in their radical reaction one of the radical reaction steps: Initiation is

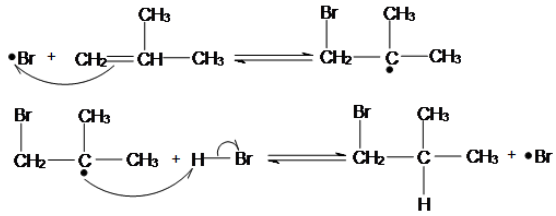
Endothermic, as recalled from Chem 118A, this means the reaction is unfavorable. To demonstrate the anti-Markovnikov regiochemistry, I will use 2-Methylprop-1-ene as an example below:

Initiation Steps



Hydrogen Peroxide is an unstable molecule, if we heat it, or shine it with sunlight, two free radicals of OH will be formed. These OH radicals will go on and attack HBr, which will take the Hydrogen and create a Bromine radical. Hydrogen radical do not form as they tend to be extremely unstable with only one electron, thus bromine radical which is more stable will be readily formed.

Propagation Steps



The Bromine Radical will go on and attack the LESS SUBSTITUTED carbon of the alkene. This is because after the bromine radical attacked the alkene a carbon radical will be formed. A carbon radical is more stable when it is at a more substituted carbon due to induction and hyperconjugation. Thus, the radical will be formed at the more substituted carbon, while the bromine is bonded to the less substituted carbon. After a carbon radical is formed, it will go on and attack the hydrogen of a HBr, which a bromine radical will be formed again.

Termination Steps

There are also Termination Steps, but we do not concern about the termination steps as they are just the radicals combining to create waste products. For example two bromine radical combined to give bromine. This radical addition of bromine to alkene by radical addition reaction will go on until all the alkene turns into bromoalkane, and this process will take some time to finish.

References

1. K. Peter C. Vollhardt, Neil E. Schore; Organic Chemistry: Structure and Function Fifth Edition; W. H. Freeman and Campany, 2007
2. Micheal Vokin; Nuffield Advance Chemistry Student's Book Forth Edition; Person Education Limited, 2004

Outside Links

1. http://en.wikipedia.org/wiki/Morris_S._Kharasch

Problems

Please give the product(s) of the reactions below:

1. CH_3-C(CH_3)=CH-CH_3 + HBr + H_2O_2 ==> ?
2. CH_3-C(CH_3)=CH-CH_3 + HI + H_2O_2 ==> ?
3. CH_3-C(CH_3)=CH-CH_3 + HCl + H_2O_2 ==> ?
4. CH_3-CH=CH-CH_3 + HBr + H_2O_2 ==> ?
5. CH_3-C(CH_3)=CH-CH_3 + HBr ==> ?

Answers

1. CH_3-CH(CH_3)-CHBr-CH_3 (Anti-Markovnikov)
2. CH_3-C(CH_3)I-CH_2-CH_3 (Markovnikov)
3. CH_3-C(CH_3)Cl-CH_2-CH_3 (Markovnikov)
4. CH_3-CHBr-CH-CH_3 or CH_3-CH-CHBr-CH_3 (Both molecules are the same)
5. CH_3-C(CH_3)Br-CH_2-CH_3 (Markovnikov)

References

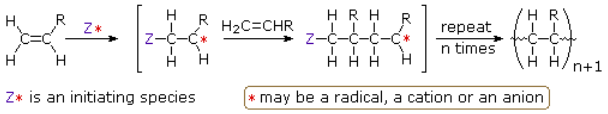
1. http://uncyclopedia.wikia.com/wiki/Organic_chemistry
2. http://uncyclopedia.wikia.com/wiki/Chemistry

Contributors

- Kelvin Kan (UCD)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

13.14: Polymers and Polymerization

All the monomers from which addition polymers are made are alkenes or functionally substituted alkenes. The most common and thermodynamically favored chemical transformations of alkenes are addition reactions. Many of these addition reactions are known to proceed in a stepwise fashion by way of reactive intermediates, and this is the mechanism followed by most polymerizations. A general diagram illustrating this assembly of linear macromolecules, which supports the name chain growth polymers, is presented here. Since a pi-bond in the monomer is converted to a sigma-bond in the polymer, the polymerization reaction is usually exothermic by 8 to 20 kcal/mol. Indeed, cases of explosively uncontrolled polymerizations have been reported.

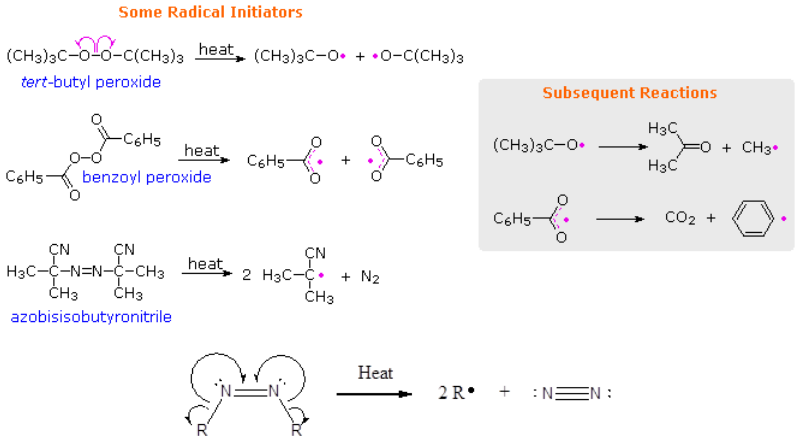


It is useful to distinguish four polymerization procedures fitting this general description.

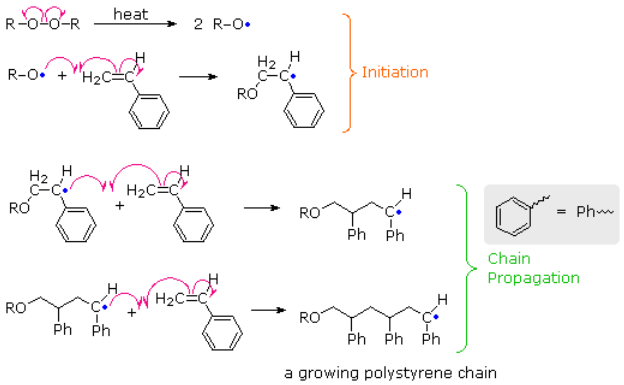
• Radical Polymerization The initiator is a radical, and the propagating site of reactivity (*) is a carbon radical.
• Cationic Polymerization The initiator is an acid, and the propagating site of reactivity (*) is a carbocation.
• Anionic Polymerization The initiator is a nucleophile, and the propagating site of reactivity (*) is a carbanion.
• Coordination Catalytic Polymerization The initiator is a transition metal complex, and the propagating site of reactivity (*) is a terminal catalytic complex.

Radical Chain-Growth Polymerization

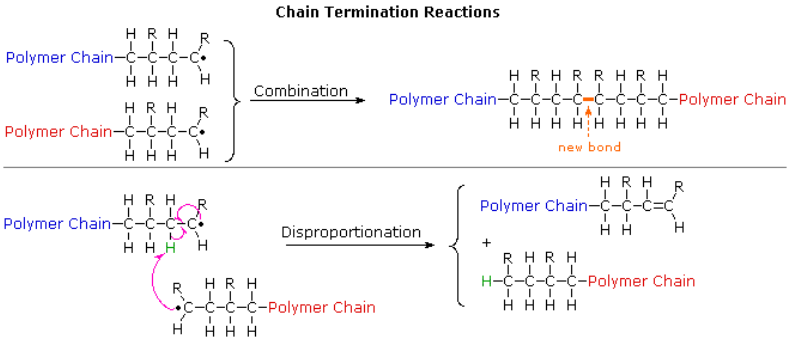
Virtually all of the monomers described above are subject to radical polymerization. Since this can be initiated by traces of oxygen or other minor impurities, pure samples of these compounds are often "stabilized" by small amounts of radical inhibitors to avoid unwanted reaction. When radical polymerization is desired, it must be started by using a radical initiator, such as a peroxide or certain azo compounds. The formulas of some common initiators, and equations showing the formation of radical species from these initiators are presented below.



By using small amounts of initiators, a wide variety of monomers can be polymerized. One example of this radical polymerization is the conversion of styrene to polystyrene, shown in the following diagram. The first two equations illustrate the initiation process, and the last two equations are examples of chain propagation. Each monomer unit adds to the growing chain in a manner that generates the most stable radical. Since carbon radicals are stabilized by substituents of many kinds, the preference for head-to-tail regioselectivity in most addition polymerizations is understandable. Because radicals are tolerant of many functional groups and solvents (including water), radical polymerizations are widely used in the chemical industry.

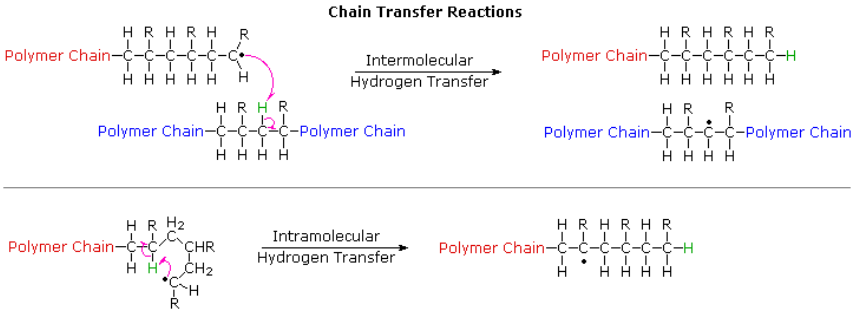


In principle, once started a radical polymerization might be expected to continue unchecked, producing a few extremely long chain polymers. In practice, larger numbers of moderately sized chains are formed, indicating that chain-terminating reactions must be taking place. The most common termination processes are Radical Combination and Disproportionation. These reactions are illustrated by the following equations. The growing polymer chains are colored blue and red, and the hydrogen atom transferred in disproportionation is colored green. Note that in both types of termination two reactive radical sites are removed by simultaneous conversion to stable product(s). Since the concentration of radical species in a polymerization reaction is small relative to other reactants (e.g. monomers, solvents and terminated chains), the rate at which these radical-radical termination reactions occurs is very small, and most growing chains achieve moderate length before termination.



The relative importance of these terminations varies with the nature of the monomer undergoing polymerization. For acrylonitrile and styrene combination is the major process. However, methyl methacrylate and vinyl acetate are terminated chiefly by disproportionation.

Another reaction that diverts radical chain-growth polymerizations from producing linear macromolecules is called chain transfer. As the name implies, this reaction moves a carbon radical from one location to another by an intermolecular or intramolecular hydrogen atom transfer (colored green). These possibilities are demonstrated by the following equations



Chain transfer reactions are especially prevalent in the high pressure radical polymerization of ethylene, which is the method used to make LDPE (low density polyethylene). The 1º-radical at the end of a growing chain is converted to a more stable 2º-radical by hydrogen atom transfer. Further polymerization at the new radical site generates a side chain radical, and this may in turn lead to creation of other side chains by chain transfer reactions. As a result, the morphology of LDPE is an amorphous network of highly branched macromolecules.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

CHAPTER OVERVIEW

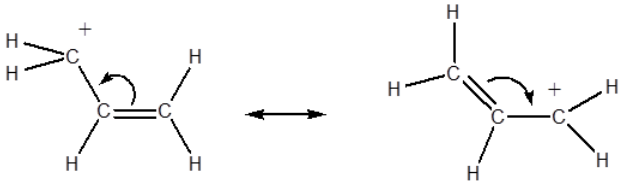
14: Conjugation, Resonance, and Dienes

14.1: Conjugation

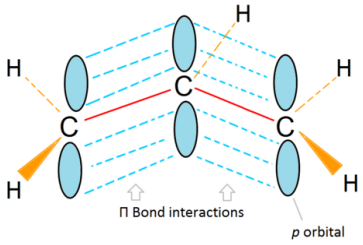
Allylic Carbocation

Conjugation occurs when p orbital on three or more adjacent atoms can overlap Conjugation tends to stabilize molecules

Allylic carbocations are a common conjugated system.



The positive charge of a carbocation is contained in a P orbital of a sp^2 hybridized carbon. This allows for overlap with double bonds. The positive charge is more stable because it is spread over 2 carbons.



Molecular Orbitals of an Allylic Carbocation

The stability of the carbocation of propene is due to a conjugated π electron system. A "double bond" doesn't really exist. Instead, it is a group of 3 adjacent, overlapping, non-hybridized *p* orbitals we call a **conjugated π electron system**. You can clearly see the interactions between all three of the *p* orbitals from the three carbons resulting in a really stable cation. It all comes down to where the location of the electron-deficient carbon is.

Molecular orbital descriptions can explain allylic stability in yet another way using 2-propenyl. Fig.6

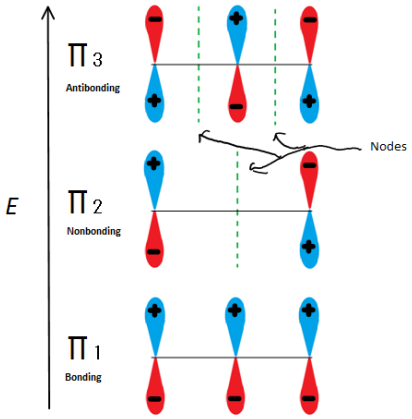


Fig.6 Shows the 3 possible Molecular orbitals of 2-propenyl

If we just take the π molecular orbital and not any of the s, we get three of them. π_1 is bonding with no nodes, π_2 is nonbonding (In other words, the same energy as a regular *p*-orbital) with a node, and π_3 is antibonding with 2 nodes (none of the orbitals are interacting). The first two electrons will go into the π_1 molecular orbital, regardless of whether it is a cation, radical, or anion. If it

is a radical or anion, the next electron goes into the π_2 molecular orbital. The last anion electron goes into the nonbonding orbital also. So no matter what kind of carbon center exists, no electron will ever go into the antibonding orbital.

The Bonding orbitals are the lowest energy orbitals and are favorable, which is why they are filled first. Even though the nonbonding orbitals can be filled, the overall energy of the system is still lower and more stable due to the filled bonding molecular orbitals.

This figure also shows that π_2 is the only molecular orbital where the electrion differs, and it is also where a single node passes through the middle. Because of this, the charges of the molecule are mainly on the two terminal carbons and not the middle carbon.

This molecular orbital description can also illustrate the stability of allylic carbon centers in figure 7.

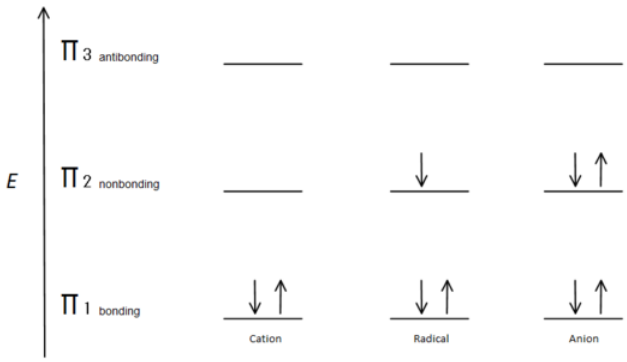
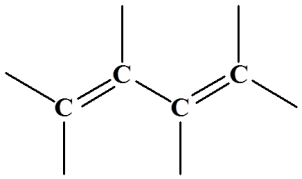


Fig.7 diagram showing how the electrons fill based on the Aufbau principle.

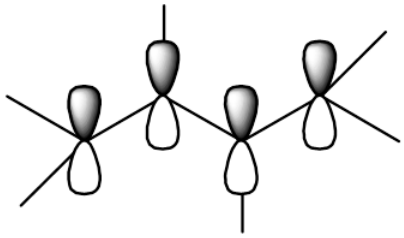
The π bonding orbital is lower in energy than the nonbonding *p* orbital. Since every carbon center shown has two electrons in the lower energy, bonding π orbitals, the energy of each system is lowered overall (and thus more stable), regardless of cation, radical, or anion.

1,3-Dienes

Conjugated double bonds are separated by a single bond. 1,3-dienes are an excellent example of a conjugated system. Each carbon in 1,3 dienes are sp^2 hybridized and therefore have one *p* orbital. The four *p* orbitals in 1,3-butadiene overlap to form a conjugated system.

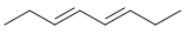


1,3-Diene



Conjugated vs. Nonconjugated Dienes

Conjugated dienes are two double bonds separated by a single bond



3,5-octadiene

Nonconjugated (Isolated) Dienes are two double bonds are separated by more than one single bond.

2,5-heptadiene

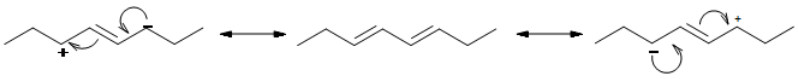
When using electrostatic potential maps, it is observed that the pi electron density overlap is closer together and delocalized in conjugated dienes, while in non conjugated dienes the pi electron density is located differently across the molecule. Since having more electron density delocalized makes the molecule more stable conjugated dienes are more stable than non conjugated

For example in 1,3-butadiene the carbons with the single bond are sp2 hybridized unlike in nonconjugated dienes where the carbons with single bonds are sp3 hybridized. This difference in hybridization shows that the conjugated dienes have more 's' character and draw in more of the pi electrons, thus making the single bond stronger and shorter than an ordinary alkane C-C bond (1.54Å).

Stability of Conjugated Dienes

Conjugated dienes are more stable than non conjugated dienes (both isolated and cumulated) due to factors such as delocalization of charge through resonance and hybridization energy. This can also explain why allylic radicals are much more stable than secondary or even tertiary carbocations. This is all due to the positioning of the pi orbitals and ability for overlap to occur to strengthen the single bond between the two double bonds.

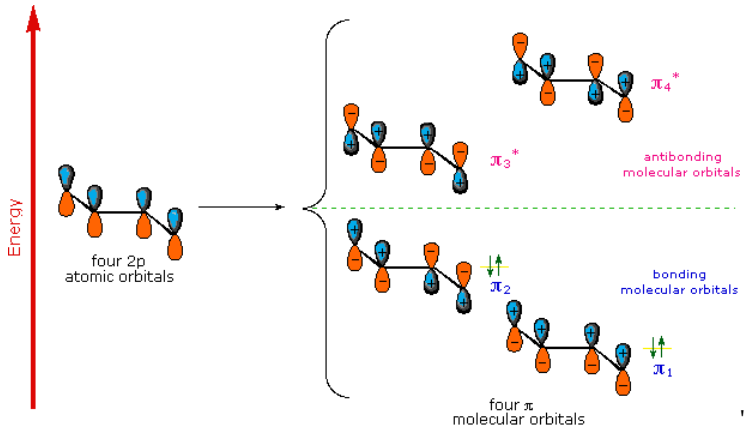
The resonance structure shown below gives a good understanding of how the charge is delocalized across the four carbons in this conjugated diene. This delocalization of charges stablizes the conjugated diene:



Along with resonance, hybridization energy effect the stability of the compound. For example in 1,3-butadiene the carbons with the single bond are sp2 hybridized unlike in nonconjugated dienes where the carbons with single bonds are sp3 hybridized. This difference in hybridization shows that the conjugated dienes have more 's' character and draw in more of the pi electrons, thus making the single bond stronger and shorter than an ordinary alkane C-C bond (1.54Å).

Molecular Orbitals of 1,3 Dienes

A molecular orbital model for 1,3-butadiene is shown below. Note that the lobes of the four p-orbital components in each pi-orbital are colored differently and carry a plus or minus sign. This distinction refers to different phases, defined by the mathematical wave equations for such orbitals. Regions in which adjacent orbital lobes undergo a phase change are called **nodes**. Orbital electron density is zero in such regions. Thus a single p-orbital has a node at the nucleus, and all the pi-orbitals shown here have a nodal plane that is defined by the atoms of the diene. This is the only nodal surface in the lowest energy pi-orbital, π_1. Higher energy pi-orbitals have an increasing number of nodes.

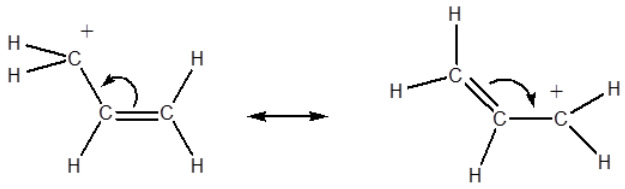


Contributors

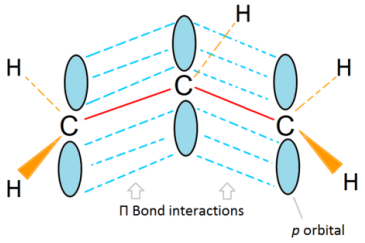
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)
- Jim Clark (Chemguide.co.uk)
- Jeffrey Hu

14.2: Resonance and Allylic Carbocations

Conjugation occurs when p orbital on three or more adjacent atoms can overlap Conjugation tends to stabilize molecules. Allylic carbocations are a common conjugated system.

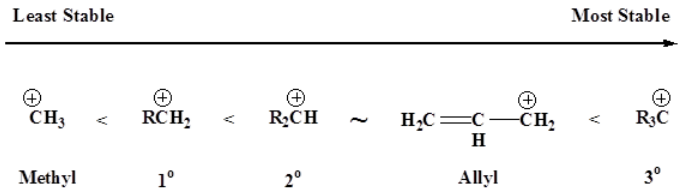


The positive charge of a carbocation is contained in a P orbital of a sp^2 hybrizied carbon. This allows for overlap with double bonds. The positive charge is more stable because it is spread over 2 carbons.



The true structure of the conjugated allyl carbocation is a hybrid of of the two resonance structure so the positive charge is delocalized over the two terminal carbons. This delocalization stablizes the allyl carbocation making it more stable than a normal primary carbocation.

Relative Stabilities of Carbocations



Contributors

- Prof. Steven Farmer (Sonoma State University)
- Jim Clark (Chemguide.co.uk)
- Jeffrey Hu

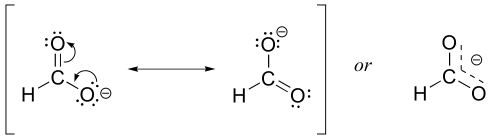
14.3: Common Examples of Resonance

1) Three atoms in a A=B-C where C is and atom with a *p* orbital.

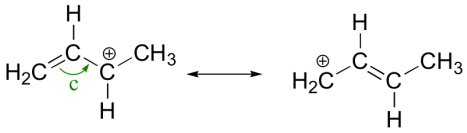
There are two major resonance possible. The two structure differ in the lcoation of the double bond. The anion, cation, or radical is stabilized by declocaliztion.

Examples

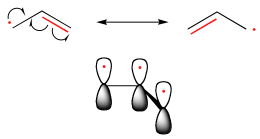
Carboxylate Anion



Allylic carbocation

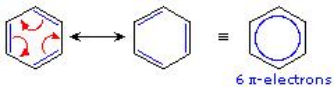


Allyic radical

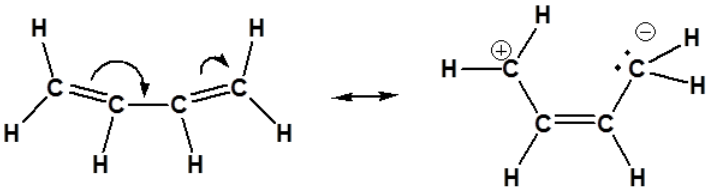


2) Conjugated double bonds

The benzene ring has two resonance structures which can be drawn by moving elections in a cyclic manner.

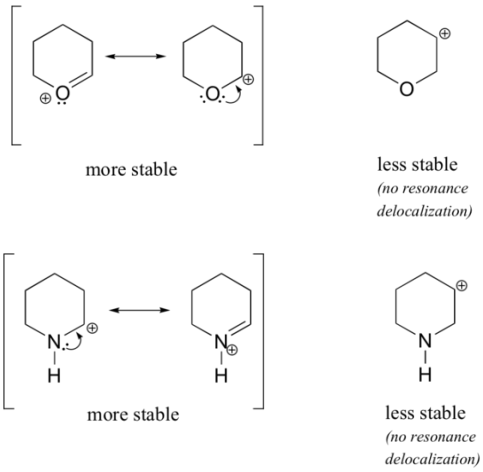


Conjugated double bonds contain multiple resonance structures.



3) Cations adjacent of an atom with lone pair electons.

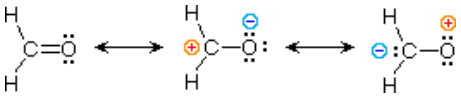
Because heteroatoms such as oxygen and nitrogen are more electronegative than carbon, you might expect that they would by definition be electron withdrawing groups that destabilize carbocations. In fact, the opposite is often true: if the oxygen or nitrogen atom is in the correct position, the overall effect is carbocation stabilization. This is due to the fact that although these heteroatoms are electron *withdrawing* groups by induction, they are electron *donating* groups by resonance, and it is this resonance effect which is more powerful. (We previously encountered this same idea when considering the relative acidity and basicity of phenols and aromatic amines in section 7.4). Consider the two pairs of carbocation species below:



In the more stable carbocations, the heteroatom acts as an electron donating group by resonance: in effect, the lone pair on the heteroatom is available to delocalize the positive charge. In the less stable carbocations the positively-charged carbon is more than one bond away from the heteroatom, and thus no resonance effects are possible. In fact, in these carbocation species the heteroatoms actually *destabilize* the positive charge, because they are electron withdrawing by induction

4) Double bonds with one atom more electronegative that the other

Multiple resonance structures are possible which causes a charge separation in the molecule.



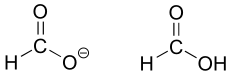
Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)
- Jim Clark (Chemguide.co.uk)

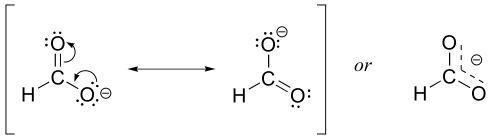
14.4: The Resonance Hybrid

Resonance contributors for the carboxylate group

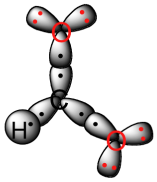
The convention of drawing two or more resonance contributors to approximate a single structure may seem a bit clumsy to you at this point, but as you gain experience you will see that the practice is actually very useful when discussing the manner in which many functional groups react. Let's next consider the carboxylate ion (the conjugate base of a carboxylic acid). As our example, we will use formate, the simplest possible carboxylate-containing molecule. The conjugate acid of formate is formic acid, which causes the painful sting you felt if you have ever been bitten by an ant.



Usually, you will see carboxylate groups drawn with one carbon-oxygen double bond and one carbon-oxygen single bond, with a negative formal charge located on the single-bonded oxygen. In actuality, however, the two carbon-oxygen bonds are the same length, and although there is indeed an overall negative formal charge on the group, it is shared equally between the two oxygens. Therefore, the carboxylate can be more accurately depicted by a *pair* of resonance contributors. Alternatively, a single structure can be used, with a dashed line depicting the resonance-delocalized π bond and the negative charge located in between the two oxygens.

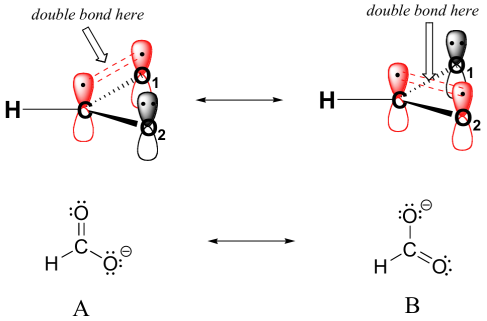


Let's see if we can correlate these drawing conventions to a valence bond theory picture of the bonding in a carboxylate group. We know that the carbon must be sp^2-hybridized, (the bond angles are close to 120˚, and the molecule is planar), and we will treat both oxygens as being sp^2-hybridized as well. Both carbon-oxygen sbonds, then, are formed from the overlap of carbon sp^2 orbitals and oxygen sp^2 orbitals.



the σ-bonding framework of formate

In addition, the carbon and both oxygens each have an unhybridized $2p_z$ orbital situated perpendicular to the plane of the sigma bonds. These three $2p_z$ orbitals are parallel to each other, and can overlap in a side-by-side fashion to form a delocalized pi bond.

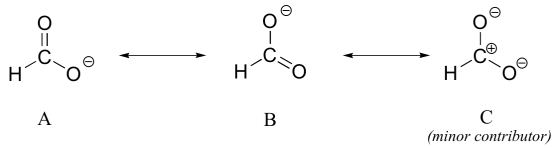


Resonance contributor A shows oxygen #1 sharing a pair of electrons with carbon in a pi bond, and oxygen #2 holding a lone pair of electrons in its $2p_z$ orbital. Resonance contributor B, on the other hand, shows oxygen #2 participating in the pi bond with carbon, and oxygen #1 holding a lone pair in its $2p_z$ orbital. Overall, the situation is one of *three parallel, overlapping $2p_z$ orbitals*

sharing four delocalized pi electrons. Because there is one more electron than there are $2p_z$ orbitals, the system has an overall charge of –1. This is the kind of 3D picture that resonance contributors are used to approximate, and once you get some practice you should be able to quickly visualize overlapping $2p_z$ orbitals and delocalized pi electrons whenever you see resonance structures being used. In this text, carboxylate groups will usually be drawn showing only one resonance contributor for the sake of simplicity, but you should always keep in mind that the two C-O bonds are equal, and that the negative charge is delocalized to both oxygens.

Major vs minor resonance contributors

Different resonance contributors do not always make the same contribution to the overall structure of the hybrid. If one resonance structure is more stable (lower in energy) than another, then the first will come closer to depicting the 'real' (hybrid) structure than the second. In the case of carboxylates, contributors A and B are equivalent to each other in terms of their relative stability and therefore their relative contribution to the hybrid structure. However, there is a third resonance contributor 'C' that we have not considered yet, in which the carbon bears a positive formal charge and both oxygens are single-bonded and bear negative charges.



Structure C is relatively less stable, and therefore makes a less important contribution to the overall structure of the hybrid relative to A and B.

How do we know that structure C is the less stable, and thus the 'minor' contributor? There are four basic rules which you need to learn in order to evaluate the relative stability of different resonance contributors. We will number them 5-8 so that they may be added to in the 'rules for resonance' list from section 2.2C.

> 5) The carbon in contributor C does not have an octet – in general, resonance contributors in which a carbon does not fulfill the octet rule are relatively less important.
>
> 6) In structure C, a separation of charge has been introduced that is not present in A or B. In general, resonance contributors in which there is a greater separation of charge are relatively less important.
>
> 7) In structure C, there are no double bonds. In general, a resonance structure with a lower number of multiple bonds is relatively less important.

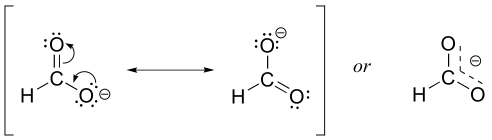
There is one more important rule that does not apply to this particular example, but we will list it here in the interest of completeness (we will soon see an actual example).

> 8) The resonance contributor in which a negative formal charge is located on a more electronegative atom (such as oxygen or nitrogen) is more stable than one in which the negative charge is located on a less electronegative atom (such as carbon).

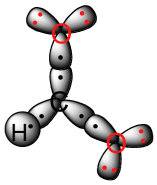
When discussing other examples of resonance contributors, we will often see cases where one form is less stable – but these minor resonance contributors can still be very relevant in explaining properties of structure or reactivity, and should not be disregarded.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

14.5: Electron Delocalization, Hybridization, and Geometry

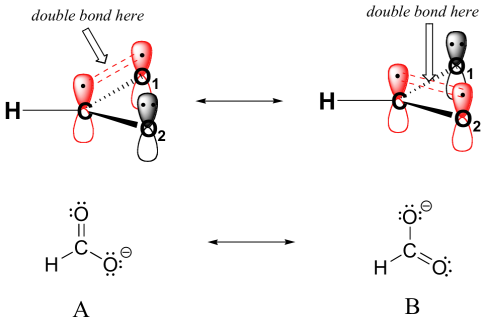


Let's see if we can correlate these drawing conventions to a valence bond theory picture of the bonding in a carboxylate group. We know that the carbon must be sp^2-hybridized, (the bond angles are close to 120˚, and the molecule is planar), and we will treat both oxygens as being sp^2-hybridized as well. Both carbon-oxygen sbonds, then, are formed from the overlap of carbon sp^2 orbitals and oxygen sp^2 orbitals.



the σ-bonding framework of formate

In addition, the carbon and both oxygens each have an unhybridized $2p_z$ orbital situated perpendicular to the plane of the sigma bonds. These three $2p_z$ orbitals are parallel to each other, and can overlap in a side-by-side fashion to form a delocalized pi bond.



Resonance contributor A shows oxygen #1 sharing a pair of electrons with carbon in a pi bond, and oxygen #2 holding a lone pair of electrons in its $2p_z$ orbital. Resonance contributor B, on the other hand, shows oxygen #2 participating in the pi bond with carbon, and oxygen #1 holding a lone pair in its $2p_z$ orbital. Overall, the situation is one of *three parallel, overlapping $2p_z$ orbitals sharing four delocalized pi electrons*. Because there is one more electron than there are $2p_z$ orbitals, the system has an overall charge of –1. This is the kind of 3D picture that resonance contributors are used to approximate, and once you get some practice you should be able to quickly visualize overlapping $2p_z$ orbitals and delocalized pi electrons whenever you see resonance structures being used. In this text, carboxylate groups will usually be drawn showing only one resonance contributor for the sake of simplicity, but you should always keep in mind that the two C-O bonds are equal, and that the negative charge is delocalized to both oxygens.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

14.6: Conjugated Dienes

When considering compounds having two or more double bonds in a molecule, it is useful to identify three distinct ways in which these functions may be oriented with respect to each other. First, the double bonds may be separated by one or more sp3-hybridized carbon atoms, as in 1,5-hexadiene. In this circumstance each double bond behaves independently of the other, and we refer to them as isolated. A second relationship has the double bonds connected to each other by a single bond, as in 1,3-hexadiene, and we refer to this arrangement as conjugated. Finally, two double bonds might share a carbon atom, as in 1,2-hexadiene. The central carbon atom in such a system is sp-hybridized, and we call such double bonds cumulated.

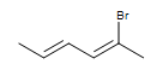
Dienes can adopt two possible conformations through rotation about the single bond joining the two double bonds: the *s-cis* and the *s-trans* conformations.

The energy barrier to isomerization is normally low, and the *s-trans* conformer is often more stable than the s-cis conformer.

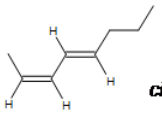
Naming Dienes

First identify the longest chain containing both carbons with double bonds in the compound. Then give the lowest possible number for the location of the carbons with double bonds and any other functional groups present (remember when naming alkenes that some groups take priority such as alcohols). Do not forget stereochemistry or any other orientation of the double bond such as (E/Z,cis or trans).

Examples:

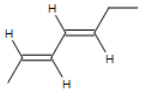


2-Bromo-2,4-hexadiene



cis-2-*trans*-4-octadiene

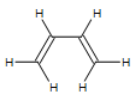
1,3-cyclopentadiene



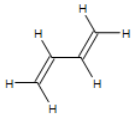
trans-2,4-heptadiene

Different conformations of Conjugated Dienes

There are two different conformations of conjugated dienes which are s-*cis* and s-*trans* conformations. s-*cis* is when the double bonds are cis in reference to the single bond and s-*trans* is when the two double bonds are trans in reference to the single bond. The cis conformation is less stable due to the steric interation of hydrogens on carbon. One important use of the cis conformation of a conjugated diene is that it is used diels-alder cycloaddition reactions. Even though the trans conformation is more stable the cis conformation is used because of the molecule's ability to interconvert and rotate about the single bond.



s-*cis*



s-*trans*

Contributors

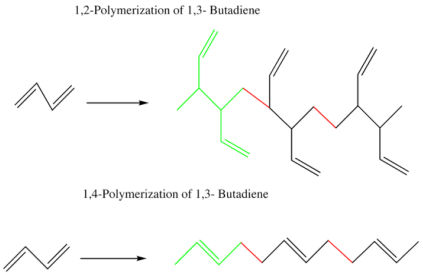
- Shravan Rao
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

14.7: Interesting Dienes and Polyenes

Conjugated dienes (alkenes with two double bonds and a single bond in between) can be polymerized to form important compounds like rubber. This takes place, in different forms, both in nature and in the laboratory. Interactions between double bonds on multiple chains leads to cross-linkage which creates elasticity within the compound.

Polymerization of 1,3-Butadiene

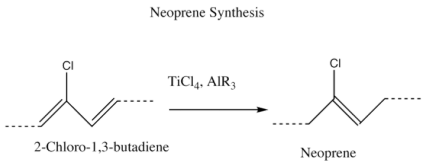
For rubber compounds to be synthesized, 1,3-butadiene must be polymerized. Below is a simple illustration of how this compound is formed into a chain. The 1,4 polymerization is much more useful to polymerization reactions.



Above, the green structures represent the base units of the polymers that are synthesized and the red represents the bonds between these units which form these polymers. Whether the 1,3 product or the 1,4 product is formed depends on whether the reaction is thermally or kinetically controlled.

Synthetic Rubber

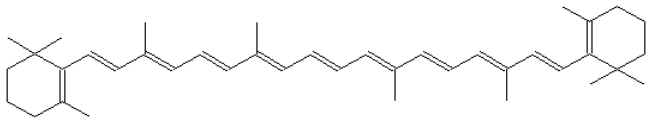
The most important synthetic rubber is Neoprene which is produced by the polymerization of 2-chloro-1,3-butadiene.



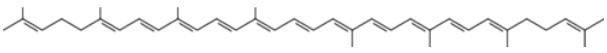
In this illustration, the dashed lines represent repetition of the same base units, so both the products and reactants are polymers. The reaction proceeds with a mechanism similar to the Friedel-Crafts mechanism. Cross-linkage between the chlorine atom of one chain and the double bond of another contributes to the overall elasticity of neoprene. This cross-linkage occurs as the chains lie next to each other at random angles, and the attractions between double bonds prevent them from sliding back and forth.

Colored molecules

The counjugated double bonds in beta-carotene produce the orange color in carrots. The conjugated double bons in lycopene produce the red color in tomatoes.



ß carotene



lycopene

Outside links

- "Dienes," http://en.wikipedia.org/wiki/Diene
- "Rubber," http://en.wikipedia.org/wiki/Rubber

- "Neoprene," http://en.wikipedia.org/wiki/Neoprene

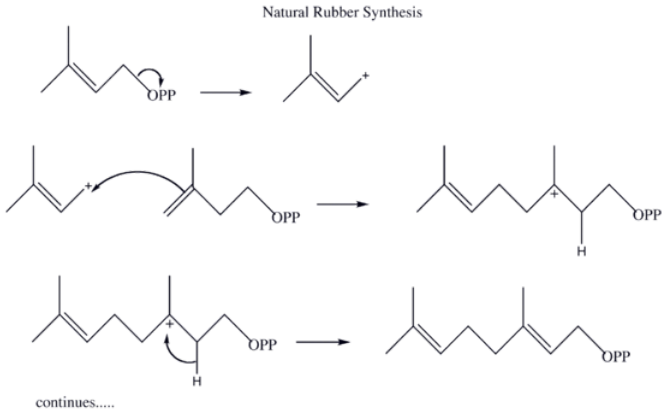
References

1. Vollhardt, Peter, and Neil E. Schore. Organic Chemistry: Structure and Function. New York: W. H. Freeman & Company, 2007.
2. Buehr, Walter. Rubber: Natural and Synthetic. Morrow, 1964.

Problem

Draw out the mechanism for the natural synthesis of rubber from 3-methyl-3-butenyl pyrophosphate and 2-methyl-1,3-butadiene. Show the movement of electrons with arrows.

Answer



14.8: The Carbon–Carbon σ Bond Length in 1,3-Butadiene

The conjugated diene has 2 double bonds with one single C-C bond between them. This structure offers stability because the two pi bonds can transfer electrons through the two carbons that are sp^2 hybridized with a single bond which results in electron delocalization. Extended P orbital sharing makes this diene more stable than the isolated dienes. The more stable molecule also has lower energy and a shorter bond length.

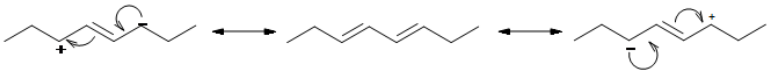
Contributors

- Natasha Singh

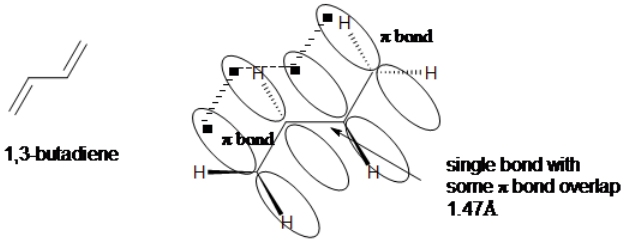
14.9: Stability of Conjugated Dienes

Conjugated dienes are more stable than non conjugated dienes (both isolated and cumulated) due to factors such as delocalization of charge through resonance and hybridization energy. This can also explain why allylic radicals are much more stable than secondary or even tertiary carbocations. This is all due to the positioning of the pi orbitals and ability for overlap to occur to strengthen the single bond between the two double bonds.

The resonance structure shown below gives a good understanding of how the charge is delocalized across the four carbons in this conjugated diene. This delocalization of charges stablizes the conjugated diene:

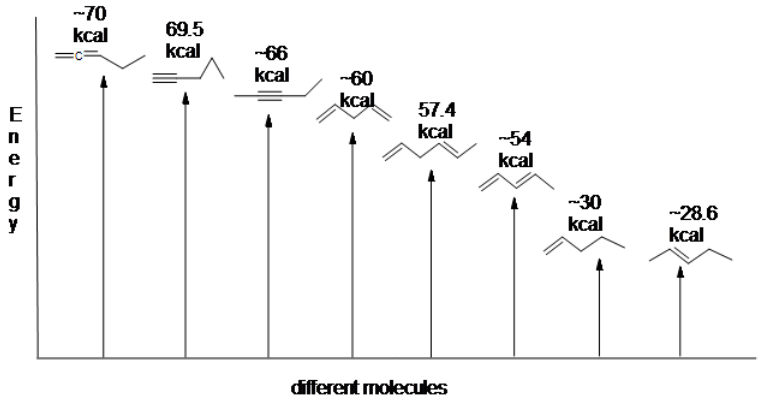


Along with resonance, hybridization energy effect the stability of the compound. For example in 1,3-butadiene the carbons with the single bond are sp2 hybridized unlike in nonconjugated dienes where the carbons with single bonds are sp3 hybridized. This difference in hybridization shows that the conjugated dienes have more 's' character and draw in more of the pi electrons, thus making the single bond stronger and shorter than an ordinary alkane C-C bond (1.54Å).



Another useful resource to consider are the heats of hydrogenation of different arrangements of double bonds. Since the higher the heat of hydrogenation the less stable the compound, it is shown below that conjugated dienes (~54 kcal) have a lower heat of hydrogenation than their isolated (~60 kcal) and cumulated diene (~70 kcal) counterparts.

Here is an energy diagram comparing different types of bonds with their heats of hydrogenation to show relative stability of each molecule:



The stabilization of dienes by conjugation is less dramatic than the aromatic stabilization of benzene. Nevertheless, similar resonance and molecular orbital descriptions of conjugation may be written.

Contributors

- Shravan Rao

14.10: Electrophilic Addition- 1,2- Versus 1,4-Addition

Addition reactions of isolated dienes proceed more or less as expected from the behavior of simple alkenes. Thus, if one molar equivalent of 1,5-hexadiene is treated with one equivalent of bromine a mixture of 5,6-dibromo-1-hexene, 1,2,5,6-tetrabromohexane and unreacted diene is obtained, with the dibromo compound being the major product (about 50%)

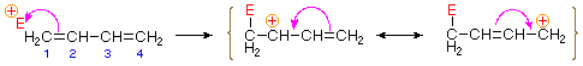
fig

Similar reactions of conjugated dienes, on the other hand, often give unexpected products. The addition of bromine to 1,3-butadiene is an example. As shown below, a roughly 50:50 mixture of 3,4-dibromo-1-butene (the expected product) and 1,4-dibromo-2-butene (chiefly the E-isomer) is obtained. The latter compound is remarkable in that the remaining double bond is found in a location where there was no double bond in the reactant. This interesting relocation requires an explanation.

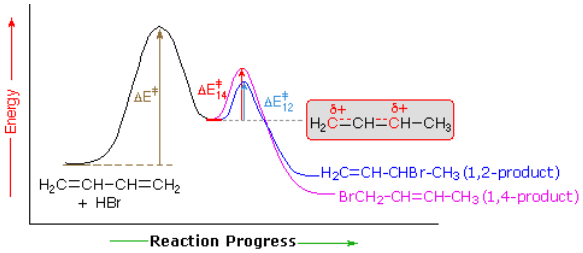
CH_2=CH-CH=CH_2 + Br_2 ⟶	$BrCH_2CHBr$-CH=CH_2 +	$BrCH_2CH$=$CHCH_2Br$
	3,4-dibromo-1-butene	1,4-dibromo-2-butene

The expected addition product from reactions of this kind is the result of **1,2-addition**, i.e. bonding to the adjacent carbons of a double bond. The unexpected product comes from **1,4-addition**, i.e. bonding at the terminal carbon atoms of a conjugated diene with a shift of the remaining double bond to the 2,3-location. (These numbers refer to the four carbons of the conjugated diene and are not IUPAC nomenclature numbers.) Product compositions are often temperature dependent: at 40 oC, 85% of the product mixture in the addition reaction above is the 1,4 product, whereas at 0 oC, only about 30% is the 1,4 product.

Bonding of an electrophilic atom or group to one of the end carbon atoms of a conjugated diene (carbon #1 in the figure below) generates an allyl cation intermediate. Such cations are stabilized by charge delocalization, and it is this delocalization that accounts for the 1,4-addition product produced in such addition reactions. As shown in the diagram, the positive charge is distributed over carbons #2 and #4 so it is at these sites that the nucleophilic component bonds. Note that resonance stabilization of the allyl cation is greater than comparable stabilization of 1,3-butadiene, because charge is delocalized in the former, but created and separated in the latter.



An explanation for the temperature influence is shown in the following energy diagram for the addition of HBr to 1,3-butadiene. The initial step in which a proton bonds to carbon #1 is the **rate determining step**, as indicated by the large activation energy (light gray arrow). The second faster step is the **product determining step**, and there are two reaction paths (colored blue for 1,2-addition and magenta for 1,4-addition). The 1,2-addition has a smaller activation energy than 1,4-addition - it occurs faster than 1,4 addition, because the bromide nucleophile is closer to carbon #2 then to carbon #4. However, the 1,4-product is more stable than the 1,2-product. At low temperatures, the products are formed irreversibly and reflect the relative rates of the two competing reactions. This is termed **kinetic control**. At higher temperatures, equilibrium is established between the products, and the **thermodynamically favored** 1,4-product dominates.



When a conjugated diene is attacked by an electrophile, the resulting products are a mixture of 1,2 and 1,4 isomers. Kinetics and Thermodynamics control a reaction when there are two products under different reaction conditions. The Kinetic product (Product A) will be formed fast, and the Thermodynamic product (Product B) will be formed more slowly. Usually the first product formed is the more stable favored product, but in this case, the slower product formed is the more stable product; Product B.

Introduction

Like nonconjugated dienes, conjugated dienes are subject to attack by electrophiles. In fact, conjugated electrophiles experience relatively greater kinetic reactivity when reacted with electrophiles than nonconjugated dienes do. Upon electrophilic addition, the conjugated diene forms a mixture of two products—the kinetic product and the thermodynamic product—whose ratio is determined by the conditions of reaction. A reaction yielding more thermodynamic product is under thermodynamic control, and likewise, a reaction that yields more kinetic product is under kinetic control.

Basic Reaction

Detailed Mechanism

Conclusion

The reactivity of conjugated dienes (hydrocarbons that contain two double bonds) varies depending on the location of double bonds and temperature of the reaction.These reactions can produce both thermodynamic and kinetic products. Isolated double bonds provide dienes with less stability thermodynamically than conjugated dienes. However, they are more reactive kinetically in the presence of electrophiles and other reagents. This is a result of Markovnikov addition to one of the double bonds. A carbocation is formed after a double bond is opened. This carbocation has two resonance structures and addition can occur at either of the positive carbons.

Practice Problems

1. Write out the products of 1,2 addition and 1,4- addition of a) HBr and Br. b) DBr to 1,3-cyclo-hexadiene. What is unusual about the products of 1,2- and 1,4- addition of HX to unsubstituted cyclic 1,3-dienes?
2. Is the 1,2-addition product formed more rapidly at higher temperatures, even though it is the 1,4-addition product that predominates under these conditions?
3. Why is the 1,4-addition product the thermodynamically more stable product?
4. Out of the following radical cations which one is not a reasonable resonance structure?

5. Addition of 1 equivalent of Bromine to 2,4-hexadiene at 0 degrees C gives 4,5-dibromo-2-hexene plus an isomer. Which of the following is that isomer:

a. 5,5-dibromo-2-hexene
b. 2,5-dibromo-3-hexene
c. 2,2-dibromo-3-hexene

d. 2,3-dibromo-4-hexene

6. Which of the following will be the kinetically favored product from the depicted reaction?

7. Addition of HBr to 2,3-dimethyl-1,3-cyclohexadiene may occur in the absence or presence of peroxides. In each case two isomeric $C_8H_{13}Br$ products are obtained. Which of the following is a common product from both reactions?

8. and 9.

8. The kinetically controlled product in the above reaction is:

a. 3-Chloro-1-Butene
b. 1-Chloro-2-Butene

9. For the reaction in question 8, which one is the result of 1,4-addition?

a. 3-Chloro-1-Butene
b. 1-Chloro-2-Butene

Answers to Problems

1. A) Same product for both modes of addition.

B) Both cis and trans isomers will form.

Addition of the HX to unsubstituted cycloalka-1,3-dienes in either 1,2- or 1,4- manner gives the same product becasuse of symmetry.

2. Yes. the Kinetic Product will still form faster but in this case there will be enough energy to form the thermodynamic product because the thermodynamic product is still more stable.

3. The 1,4- product is more thermodynamically stable because there are two alkyl groups on each side of the double bond. This form offers stability to the overall structure.

4. All of these isomers are viable.

5. D

6. C

7. D

8. A

9. B

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Jim Clark (Chemguide.co.uk)
- Natasha Singh

14.11: Kinetic Versus Thermodynamic Products

Kinetic and Thermodynamic Products

Kinetic products form the fastest. They usually occur at or below 0°C. This is also known as the 1,2-adduct because the substituents are added to the first and second carbons. Kinetic products contain a terminal double bond and the reaction is irreversible. Thermodynamic products form at higher temperatures, generally greater than 40 °C. These are known are the 1,4-adducts because they add to the first and fourth carbons. Thermodynamic products contain an internal double bond and the reaction is reversible. Also, when reactions are carried out, thermodynamic products are more stable than kinetic products because they are more substituted.

Figure 1: Conditions at 0 °C:

Final Products:

- 1,2 Addition (Kinetic controlled product)
- 1,4 Addition (Thermodynamic controlled product)

The reason for the two products is the difference in their activation energies. The reaction will go through to completion on the easiest path and in this case that is the Kinetic path. This path has a much lower Activation Energy which means that less is required to have the product formed. This product- Product A, is not the most stable form however. Over time, the amount of Product B- the more stable one, will increase and the Product A will decrease.

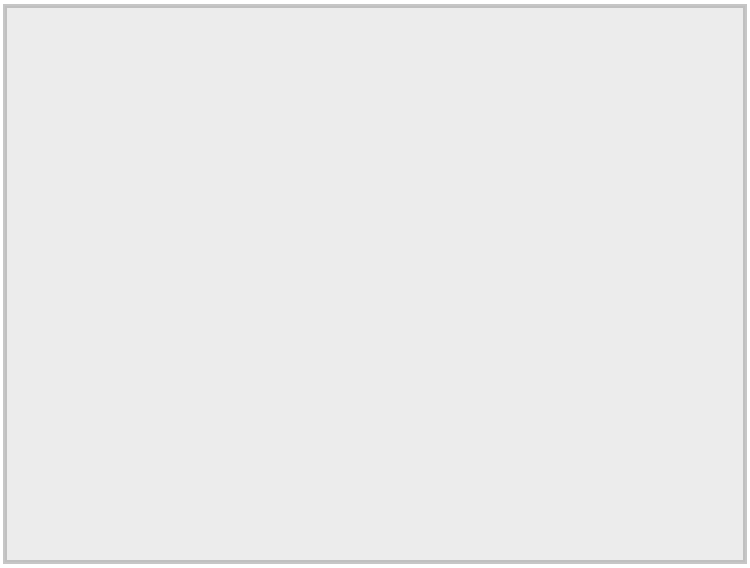


Figure 2: Potential Energy profiles

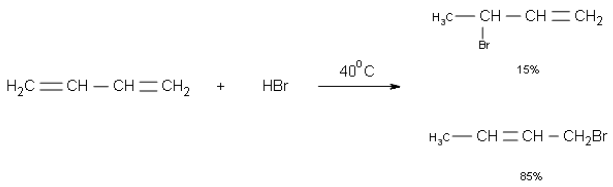
Understanding the Reaction Coordinate Diagram

1. **Major product at low temperatures- 1, 2 Bromobutene:** The main product at low temperatures is Kinetically controlled. This means that there is not enough energy to overcome the Activation Energy of the Thermodynamic product even though it is the more stable product.
2. **98% product:** At a low temperature the amount of energy in the reaction is not enough to get a large amount of the product over into the Thermodynamic Isomer. One of the two factors that influences the outcome of the reaction is the rate of product formation which is the Kinetic control. The Proximity Effect makes it so that the when the H is taken from the Br by the double bond, the Br is left close to the C2 and, in order to take away the positive charge, the C2 bonds with it quickly forming 1,2-Bromobutene.
3. **2% product:**The Thermodynamic Isomer is not favored at low temperatures because the Rate of Reaction is based on the Activation Energy. The Activation Energy of the Thermodynamic Isomer is higher than the Kinetic and therefore will happen a lot slower.
4. **The Intermediate is low in energy due to charge delocalization:** The charge is delocalized across the three Carbons so the positive charge is not only on one Carbon. The Br will attack at the 2 and 4 positions.
5. **Kinetic Higher Energy product:** The product formed Kinetically is less stable than the Thermodynamic product. The double bond in the Kinetic Product is only connected to one single bond which means that it has left of an Allylic effect on the overall structure.
6. **Thermodynamic Lower Energy Product:** The Thermodynamic product has two Alkyl groups bonded to the double bond. This has a stabilizing effect on the molecule.
7. **Major Product at high temperatures- 1,4 bromobutene:** This is the Thermodynamic Product that does not occur rapidly due to the Resonance Structure required to form the final product. If the reaction is left to go through equilibrium this product will predominate. It is not based on the physical conditions of the reaction and that is why it is the Thermodynamic product.

Table 1: Conjugated Dienese: Kinetics vs. Thermodynamic Conditions

Kinetic and Thermodynamic Product Ratios

To ensure the greatest possible yield of thermodynamic products, the reaction should be carried out at a temperature of 40°C or greater. This is known as thermodynamic control. At higher temperatures and longer reaction times, thermodynamic products are favored. On the contrary, at lower temperatures, one would tend to see a greater yield of kinetic products. These products are generally formed at or around 0°C. Carrying out reactions around these temperatures is known as kinetic control and kinetic products form before thermodynamic products.



Since the thermodynamic product contains an internal double bond, it is more stable than the kinetic product, and this is due to **hyperconjugation** with neighboring atoms. Additionally, a higher activation energy results in the thermodynamic product forming slower than the kinetic product. Therefore, a thermodynamically controlled reaction gives a more stable product and kinetically controlled reaction gives a less stable product.

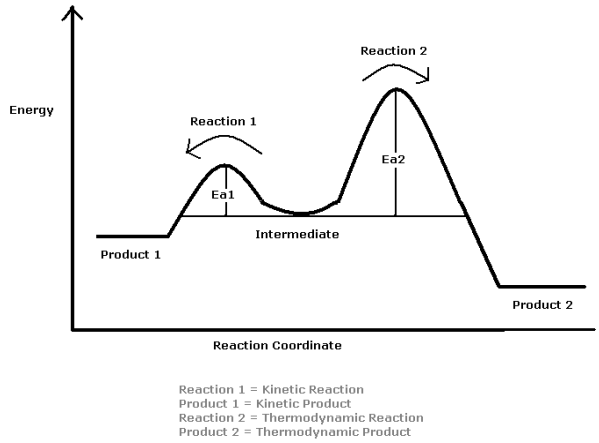


Figure: The various temperature conditions that may instigate a change or speed up the reaction

The conjugated diene has 2 double bonds with one single C-C bond between them. This structure offers stability because the two pi bonds can transfer electrons through the two carbons that are sp^2 hybridized with a single bond which results in electron delocalization. Extended P orbital sharing makes this diene more stable than the isolated dienes. The more stable molecule also has lower energy and a shorter bond length.

Figure 4:

The p electrons reach out to the electrophile and form a bond that in turn forms a Carbocation. The Markovnikov Addition states that the most stable carbocation is most likely to be formed with the charge going on the more substituted carbon. The difference

between a conjugated diene and an alkene is that there is still a double bond left after the reaction has completed.

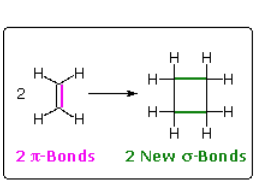
- The Kinetic product is formed more quickly because it has a more stable carbocation to begin with. Due to resonance forms, the most stable isomer is the one with the double bond in the center of the molecule. As the reaction completes under normal conditions, the more likely product is the one formed with the most stable carbocation.
- The Kinetic isomer product. While the carbocation is more stable, the final product is not. The double bond ends up on a primary carbon. It would have more stabilizing effect if it were in the middle which is why it tries to get there.

Contributors

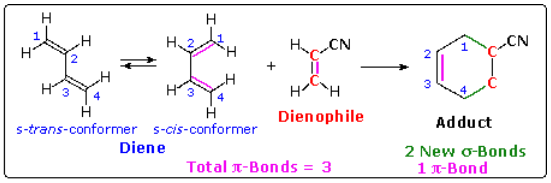
- Natasha Singh

14.12: The Diels–Alder Reaction

The unique character of conjugated dienes manifests itself dramatically in the **Diels-Alder Cycloaddition Reaction**. A cycloaddition reaction is the concerted bonding together of two independent pi-electron systems to form a new ring of atoms. When this occurs, two pi-bonds are converted to two sigma-bonds, the simplest example being the hypothetical combination of two ethene molecules to give cyclobutane. This does not occur under normal conditions, but the cycloaddition of 1,3-butadiene to cyanoethene (acrylonitrile) does, and this is an example of the Diels-Alder reaction. The following diagram illustrates two cycloadditions, and introduces several terms that are useful in discussing reactions of this kind.



A [2+2] Cycloaddition



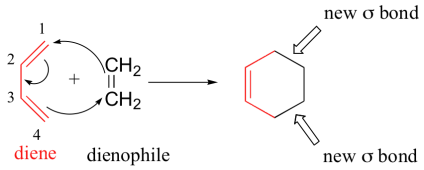
A [4+2] Cycloaddition

In the hypothetical ethylene dimerization on the left, each reactant molecule has a pi-bond (colored orange) occupied by two electrons. The cycloaddition converts these pi-bonds into new sigma-bonds (colored green), and this transformation is then designated a [2+2] cycloaddition, to enumerate the reactant pi-electrons that change their bonding location.
The Diels-Alder reaction is an important and widely used method for making six-membered rings, as shown on the right. The reactants used in such reactions are a conjugated diene, simply referred to as the **diene**, and a double or triple bond coreactant called the **dienophile**, because it combines with (has an affinity for) the diene. The Diels-Alder cycloaddition is classified as a [4+2] process because the diene has four pi-electrons that shift position in the reaction and the dienophile has two.

The Diels-Alder reaction is a single step process, so the diene component must adopt an s-cisconformation in order for the end carbon atoms (#1 & #4) to bond simultaneously to the dienophile. For many acyclic dienes the s-trans conformer is more stable than the s-cis conformer (due to steric crowding of the end groups), but the two are generally in rapid equilibrium, permitting the use of all but the most hindered dienes as reactants in Diels-Alder reactions. In its usual form, the diene component is electron rich, and the best dienophiles are electron poor due to electron withdrawing substituents such as CN, C=O & NO_2. The initial bonding interaction reflects this electron imbalance, with the two new sigma-bonds being formed simultaneously, but not necessarily at equal rates.

Mechanism

We end this chapter with a discussion of a type of reaction that is different from anything we have seen before. In the Diels-Alder cycloaddition reaction, a conjugated diene reacts with an alkene to form a ring structure.



In a Diels-Alder reaction, the alkene reacting partner is referred to as the **dienophile**. Essentially, this process involves overlap of the 2p orbitals on carbons 1 and 4 of the diene with 2p orbitals on the two sp^2-hybridized carbons of the dienophile. Both of these new overlaps end up forming new sigma bonds, and a new pi bond is formed between carbon 2 and 3 of the diene.

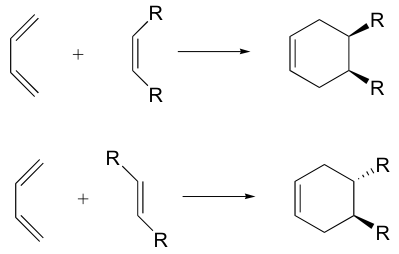
One of the most important things to understand about this process is that it is *concerted* – all of the electron rearrangement takes place at once, with no carbocation intermediates.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

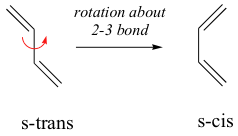
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

14.13: Specific Rules Governing the Diels–Alder Reaction

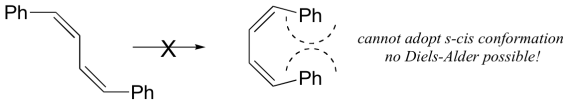
The Diels-Alder reaction is enormously useful for synthetic organic chemists, not only because ring-forming reactions are useful in general but also because in many cases two new stereocenters are formed, and the reaction is inherently stereospecific. A *cis* dienophile will generate a ring with *cis* substitution, while a *trans* dienophile will generate a ring with *trans* substitution:



In order for a Diels-Alder reaction to occur, the diene molecule must adopt what is called the **s-cis conformation**:

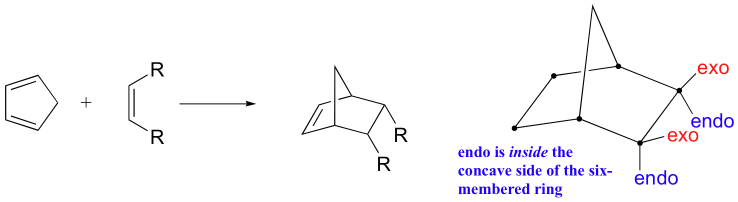


The s-cis conformation is higher in energy than the s-trans conformation, due to steric hindrance. For some dienes, extreme steric hindrance causes the s-cis conformation to be highly strained, and for this reason such dienes do not readily undergo Diels-Alder reactions.



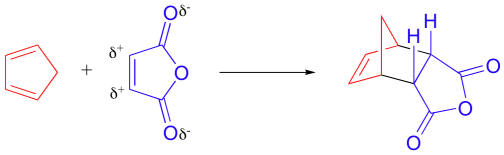
Cyclic dienes, on the other hand, are 'locked' in the s-cis conformation, and are especially reactive. The result of a Diels-Alder reaction involving a cyclic diene is a **bicyclic** structure:

Here, we see another element of stereopecificity: Diels-Alder reactions with cyclic dienes favor the formation of bicyclic structures in which substituents are in the **endo position**.



The endo position on a bicyclic structure refers to the position that is *inside* the concave shape of the larger (six-membered) ring. As you might predict, the **exo position** refers to the *outside* position.

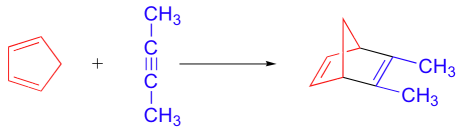
The rate at which a Diels-Alder reaction takes place depends on electronic as well as steric factors. A particularly rapid Diels-Alder reaction takes place between cyclopentadiene and maleic anhydride.



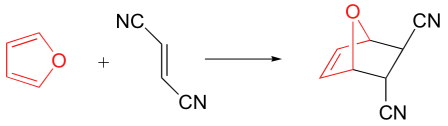
We already know that cyclopentadiene is a good diene because of its inherent s-cis conformation. Maleic anhydride is also a very good dienophile, because the electron-withdrawing effect of the carbonyl groups causes the two alkene carbons to be electron-poor, and thus a good target for attack by the pi electrons in the diene.

In general, Diels-Alder reactions proceed fastest with electron-donating groups on the diene (eg. alkyl groups) and electron-withdrawing groups on the dienophile.

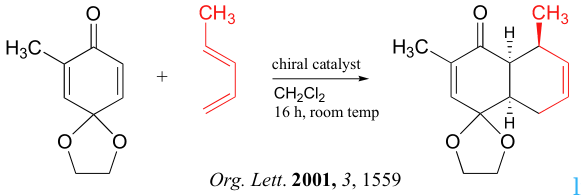
Alkynes can also serve as dienophiles in Diels-Alder reactions:



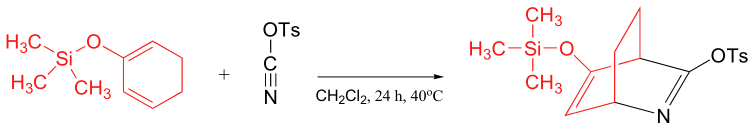
Below are just three examples of Diels-Alder reactions that have been reported in recent years:



J. Med. Chem. **2008,** *51*, 424 link

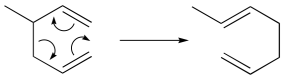


Org. Lett. **2001,** *3*, 1559 link



J. Org. Chem. **2003,** *68,* 8256 link

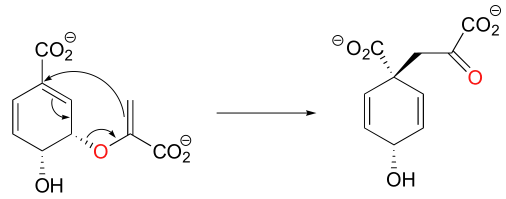
The Diels-Alder reaction is just one example of a **pericyclic** reaction: this is a general term that refers to concerted rearrangements that proceed though cyclic transition states. Two well-studied intramolecular pericyclic reactions are known as the Cope rearrangement . . .



. . .and the Claisen rearrangement (when an oxygen is involved):

Notice that the both of these reactions require compounds in which two double bonds are separated by three single bonds.

Pericyclic reactions are rare in biological chemistry, but here is one example: the Claisen rearrangement catalyzed by chorismate mutase in the aromatic amino acid biosynthetic pathway.

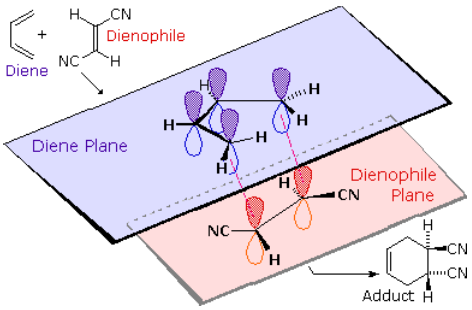


chorismate prephenate

The study of pericyclic reactions is an area of physical organic chemistry that blossomed in the mid-1960s, due mainly to the work of R.B. Woodward, Roald Hoffman, and Kenichi Fukui. The **Woodward-Hoffman rules** for pericyclic reactions (and a simplified version introduced by Fukui) use molecular orbital theory to explain why some pericyclic processes take place and others do not. A full discussion is beyond the scope of this text, but if you go on to study organic chemistry at the advanced undergraduate or graduate level you are sure to be introduced to this fascinating area of inquiry.

Stereochemistry of the Diels-Alder reaction

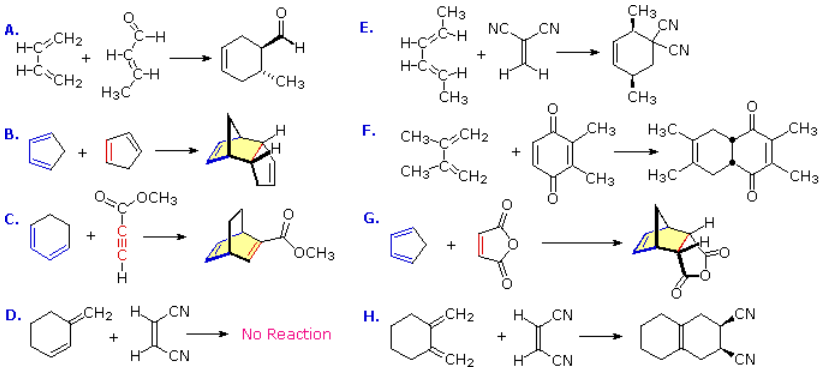
We noted earlier that addition reactions of alkenes often exhibited stereoselectivity, in that the reagent elements in some cases added syn and in other cases anti to the the plane of the double bond. Both reactants in the Diels-Alder reaction may demonstrate stereoisomerism, and when they do it is found that the relative configurations of the reactants are preserved in the product (the adduct). The following drawing illustrates this fact for the reaction of 1,3-butadiene with (E)-dicyanoethene. The trans relationship of the cyano groups in the dienophile is preserved in the six-membered ring of the adduct. Likewise, if the terminal carbons of the diene bear substituents, their relative configuration will be retained in the adduct. Using the earlier terminology, we could say that bonding to both the diene and the dienophile is syn. An alternative description, however, refers to the planar nature of both reactants and terms the bonding in each case to be **suprafacial** (i.e. to or from the same face of each plane). This stereospecificity also confirms the synchronous nature of the 1,4-bonding that takes place.



The essential characteristics of the Diels-Alder cycloaddition reaction may be summarized as follows:

(i) The reaction always creates a new six-membered ring. When intramolecular, another ring may also be formed.
(ii) The diene component must be able to assume a s-cis conformation.
(iii) Electron withdrawing groups on the dienophile facilitate reaction.
(iv) Electron donating groups on the diene facilitate reaction.
(v) Steric hindrance at the bonding sites may inhibit or prevent reaction.
(vi) The reaction is stereospecific with respect to substituent configuration in both the dienophile and the diene.

These features are illustrated by the following eight examples, one of which does not give a Diels-Alder cycloaddition.



There is no reaction in example **D** because this diene cannot adopt an s-cis orientation. In examples **B, C, F, G & H** at least one of the reactants is cyclic so that the product has more than one ring, but the newly formed ring is always six-membered. In example **B** the the same cyclic compound acts as both the diene colored blue) and the dienophile (colored red). The adduct has three rings, two of which are the five-membered rings present in the reactant, and the third is the new six-membered ring (shaded light yellow). Example **C** has an alkyne as a dienophile (colored red), so the adduct retains a double bond at that location. This double bond could still serve as a dienophile, but in the present case the diene is sufficiently hindered to retard a second cycloaddition. The quinone dienophile in reaction **F** has two dienophilic double bonds. However, the double bond with two methyl substituents is less reactive than the unsubstituted dienophile due in part to the electron donating properties of the methyl groups and in part to steric hindrance. The stereospecificity of the Diels-Alder reaction is demonstrated by examples **A, E & H**. In **A & H** the stereogenic centers lie on the dienophile, whereas in **E** these centers are on the diene. In all cases the configuration of the reactant is preserved in the adduct.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

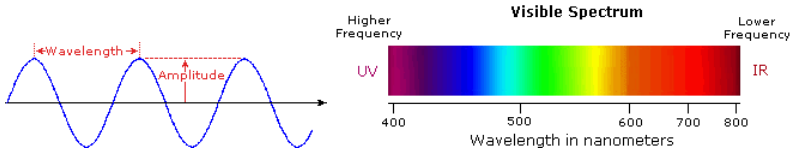
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

---

14.14: Other Facts About the Diels–Alder Reaction

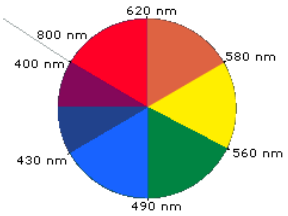
14.15: Conjugated Dienes and Ultraviolet Light

Electromagnetic radiation such as visible light is commonly treated as a wave phenomenon, characterized by a wavelength or frequency. **Wavelength** is defined on the left below, as the distance between adjacent peaks (or troughs), and may be designated in meters, centimeters or nanometers (10^{-9} meters). **Frequency** is the number of wave cycles that travel past a fixed point per unit of time, and is usually given in cycles per second, or hertz (Hz). Visible wavelengths cover a range from approximately 400 to 800 nm. The longest visible wavelength is red and the shortest is violet. Other common colors of the spectrum, in order of decreasing wavelength, may be remembered by the mnemonic: **ROY G BIV**. The wavelengths of what we perceive as particular colors in the visible portion of the spectrum are displayed and listed below. In horizontal diagrams, such as the one on the bottom left, wavelength will increase on moving from left to right.



- **Violet:** 400 - 420 nm
- **Indigo:** 420 - 440 nm
- **Blue:** 440 - 490 nm
- **Green:** 490 - 570 nm
- **Yellow:** 570 - 585 nm
- **Orange:** 585 - 620 nm
- **Red:** 620 - 780 nm

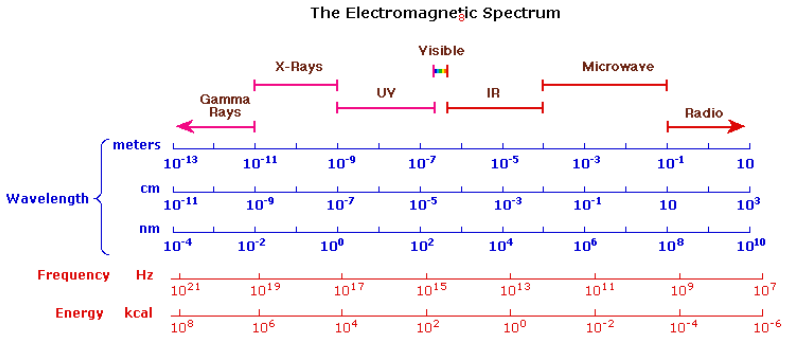
When white light passes through or is reflected by a colored substance, a characteristic portion of the mixed wavelengths is absorbed. The remaining light will then assume the complementary color to the wavelength(s) absorbed. This relationship is demonstrated by the color wheel shown below. Here, complementary colors are diametrically opposite each other. Thus, absorption of 420-430 nm light renders a substance yellow, and absorption of 500-520 nm light makes it red. Green is unique in that it can be created by absoption close to 400 nm as well as absorption near 800 nm.



Early humans valued colored pigments, and used them for decorative purposes. Many of these were inorganic minerals, but several important organic dyes were also known. These included the crimson pigment, kermesic acid, the blue dye, indigo, and the yellow saffron pigment, crocetin. A rare dibromo-indigo derivative, punicin, was used to color the robes of the royal and wealthy. The deep orange hydrocarbon carotene is widely distributed in plants, but is not sufficiently stable to be used as permanent pigment, other than for food coloring. A common feature of all these colored compounds, displayed below, is a system of **extensively conjugated π-electrons**.

The Electromagnetic Spectrum

The visible spectrum constitutes but a small part of the total radiation spectrum. Most of the radiation that surrounds us cannot be seen, but can be detected by dedicated sensing instruments. This **electromagnetic spectrum** ranges from very short wavelengths (including gamma and x-rays) to very long wavelengths (including microwaves and broadcast radio waves). The following chart displays many of the important regions of this spectrum, and demonstrates the inverse relationship between wavelength and frequency (shown in the top equation below the chart).



The energy associated with a given segment of the spectrum is proportional to its frequency. The bottom equation describes this relationship, which provides the energy carried by a photon of a given wavelength of radiation.

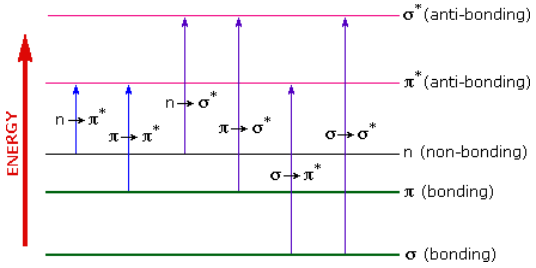
$\upsilon = c/\lambda$ υ=frequency, λ=wavelength, c=velocity of light ($c = 3 \cdot 10^{10}$ cm/sec)
$\Delta E = h\upsilon$ E=energy, υ=frequency, h=Planck's constant ($h = 6.6 \cdot 10^{-27}$ erg sec)

To obtain specific frequency, wavelength and energy values use this calculator.

UV-Visible Absorption Spectra

To understand why some compounds are colored and others are not, and to determine the relationship of conjugation to color, we must make accurate measurements of light absorption at different wavelengths in and near the visible part of the spectrum. Commercial optical spectrometers enable such experiments to be conducted with ease, and usually survey both the near ultraviolet and visible portions of the spectrum. For a description of a UV-Visible spectrometer Click Here.

The visible region of the spectrum comprises photon energies of 36 to 72 kcal/mole, and the near ultraviolet region, out to 200 nm, extends this energy range to 143 kcal/mole. Ultraviolet radiation having wavelengths less than 200 nm is difficult to handle, and is seldom used as a routine tool for structural analysis.



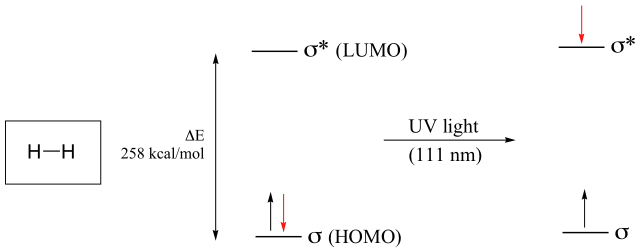
The energies noted above are sufficient to promote or excite a molecular electron to a higher energy orbital. Consequently, absorption spectroscopy carried out in this region is sometimes called "electronic spectroscopy". A diagram showing the various kinds of electronic excitation that may occur in organic molecules is shown on the left. Of the six transitions outlined, only the two lowest energy ones (left-most, colored blue) are achieved by the energies available in the 200 to 800 nm spectrum. As a rule, energetically favored electron promotion will be from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO), and the resulting species is called an **excited state**. For a review of molecular orbitals click here.

When sample molecules are exposed to light having an energy that matches a possible electronic transition within the molecule, some of the light energy will be absorbed as the electron is promoted to a higher energy orbital. An optical spectrometer records the wavelengths at which absorption occurs, together with the degree of absorption at each wavelength. The resulting spectrum is presented as a graph of absorbance (A) versus wavelength, as in the isoprene spectrum shown below. Since isoprene is colorless, it does not absorb in the visible part of the spectrum and this region is not displayed on the graph. **Absorbance** usually ranges from 0 (no absorption) to 2 (99% absorption), and is precisely defined in context with spectrometer operation.

Electronic transitions

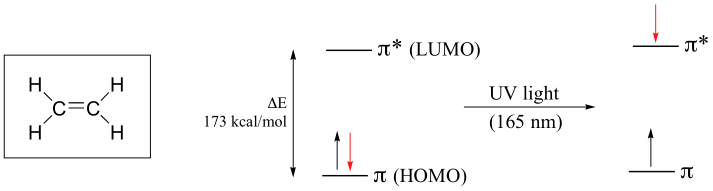
Let's take as our first example the simple case of molecular hydrogen, H_2. As you may recall from section 2.1A, the molecular orbital picture for the hydrogen molecule consists of one bonding σ MO, and a higher energy antibonding σ* MO. When the

molecule is in the ground state, both electrons are paired in the lower-energy bonding orbital – this is the Highest Occupied Molecular Orbital (HOMO). The antibonding σ* orbital, in turn, is the Lowest Unoccupied Molecular Orbital (LUMO).



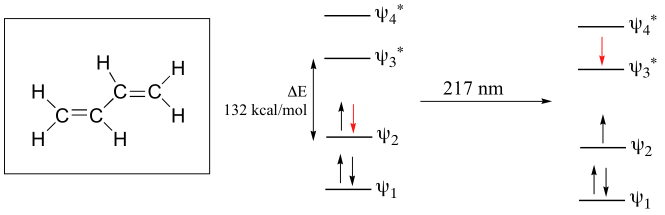
If the molecule is exposed to light of a wavelength with energy equal to **ΔE**, the HOMO-LUMO energy gap, this wavelength will be absorbed and the energy used to bump one of the electrons from the HOMO to the LUMO – in other words, from the σ to the σ* orbital. This is referred to as a **σ - σ* transition**. **ΔE** for this electronic transition is 258 kcal/mol, corresponding to light with a wavelength of 111 nm.

When a double-bonded molecule such as ethene (common name ethylene) absorbs light, it undergoes a **π - π* transition.** Because π- π* energy gaps are narrower than σ - σ* gaps, ethene absorbs light at 165 nm - a longer wavelength than molecular hydrogen.



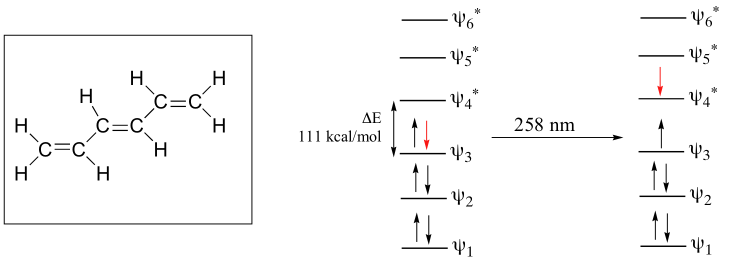
The electronic transitions of both molecular hydrogen and ethene are too energetic to be accurately recorded by standard UV spectrophotometers, which generally have a range of 220 – 700 nm. Where UV-vis spectroscopy becomes useful to most organic and biological chemists is in the study of molecules with conjugated pi systems. In these groups, the energy gap for π -π* transitions is smaller than for isolated double bonds, and thus the wavelength absorbed is longer. Molecules or parts of molecules that absorb light strongly in the UV-vis region are called **chromophores**.

Let's revisit the MO picture for 1,3-butadiene, the simplest conjugated system (see section 2.1B). Recall that we can draw a diagram showing the four pi MO's that result from combining the four $2p_z$ atomic orbitals. The lower two orbitals are bonding, while the upper two are antibonding.

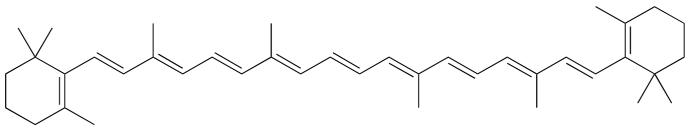


Comparing this MO picture to that of ethene, our isolated pi-bond example, we see that the HOMO-LUMO energy gap is indeed smaller for the conjugated system. 1,3-butadiene absorbs UV light with a wavelength of 217 nm.

As conjugated pi systems become larger, the energy gap for a π - π* transition becomes increasingly narrow, and the wavelength of light absorbed correspondingly becomes longer. The absorbance due to the π - π* transition in 1,3,5-hexatriene, for example, occurs at 258 nm, corresponding to a **ΔE** of 111 kcal/mol.

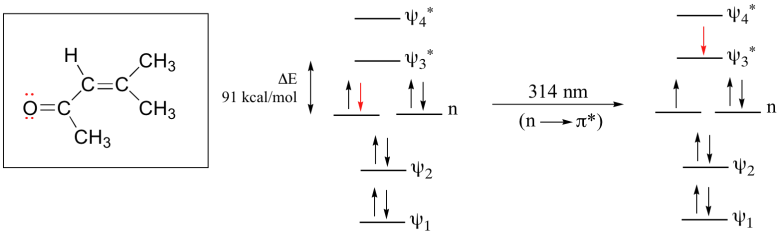


In molecules with extended pi systems, the HOMO-LUMO energy gap becomes so small that absorption occurs in the visible rather then the UV region of the electromagnetic spectrum. Beta-carotene, with its system of 11 conjugated double bonds, absorbs light with wavelengths in the blue region of the visible spectrum while allowing other visible wavelengths – mainly those in the red-yellow region - to be transmitted. This is why carrots are orange.



β-carotene

The conjugated pi system in 4-methyl-3-penten-2-one gives rise to a strong UV absorbance at 236 nm due to a π - π* transition. However, this molecule also absorbs at 314 nm. This second absorbance is due to the transition of a non-bonding (lone pair) electron on the oxygen up to a π* antibonding MO:

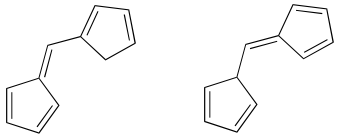


This is referred to as an **n - π* transition**. The nonbonding (n) MO's are higher in energy than the highest bonding p orbitals, so the energy gap for an n - π* transition is smaller that that of a π - π* transition – and thus the n - π* peak is at a longer wavelength. In general, n - π* transitions are weaker (less light absorbed) than those due to π - π* transitions.

Template:ExampleStart

Exercise 4.3: How large is the π - π* transition in 4-methyl-3-penten-2-one?

Exercise 4.4: Which of the following molecules would you expect absorb at a longer wavelength in the UV region of the electromagnetic spectrum? Explain your answer.



A B

Solution

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

Template:ExampleEnd

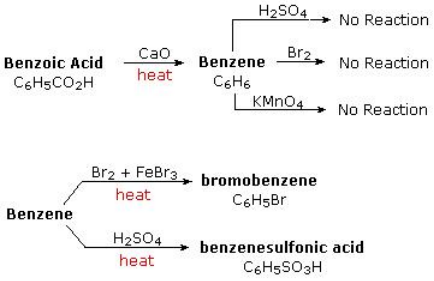
CHAPTER OVERVIEW

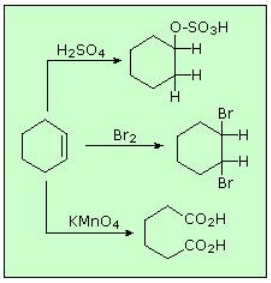
15: Benzene and Aromatic Compounds

Topic hierarchy

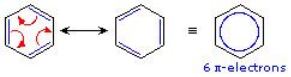
15.1: Background

Because of the low hydrogen to carbon ratio in aromatic compounds (note that the H:C ratio in an alkane is >2), chemists expected their structural formulas would contain a large number of double or triple bonds. Since double bonds are easily cleaved by oxidative reagents such as potassium permanganate or ozone, and rapidly add bromine and chlorine, these reactions were applied to these aromatic compounds. Surprisingly, products that appeared to retain many of the double bonds were obtained, and these compounds exhibited a high degree of chemical stability compared with known alkenes and cycloalkenes (aliphatic compounds). On treatment with hot permanganate solution, cinnamaldehyde gave a stable, crystalline $C_7H_6O_2$ compound, now called benzoic acid. The H:C ratio in benzoic acid is <1, again suggesting the presence of several double bonds. Benzoic acid was eventually converted to the stable hydrocarbon benzene, C_6H_6, which also proved unreactive to common double bond transformations, as shown below. For comparison, reactions of cyclohexene, a typical alkene, with these reagents are also shown (green box). As experimental evidence for a wide assortment of compounds was acquired, those incorporating this exceptionally stable six-carbon core came to be called "aromatic".



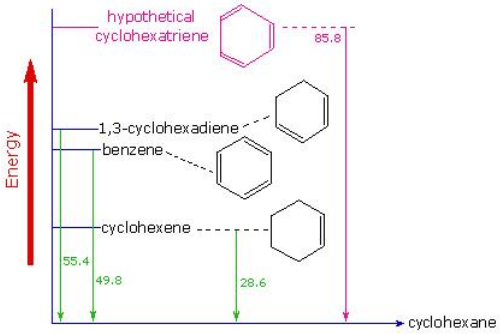


If benzene is forced to react by increasing the temperature and/or by addition of a catalyst, It undergoes **substitution reactions** rather than the addition reactions that are typical of alkenes. This further confirms the previous indication that the six-carbon benzene core is unusually stable to chemical modification. The conceptual contradiction presented by a high degree of unsaturation (low H:C ratio) and high chemical stability for benzene and related compounds remained an unsolved puzzle for many years. Eventually, the presently accepted structure of a regular-hexagonal, planar ring of carbons was adopted, and the exceptional thermodynamic and chemical stability of this system was attributed to resonance stabilization of a conjugated cyclic triene.

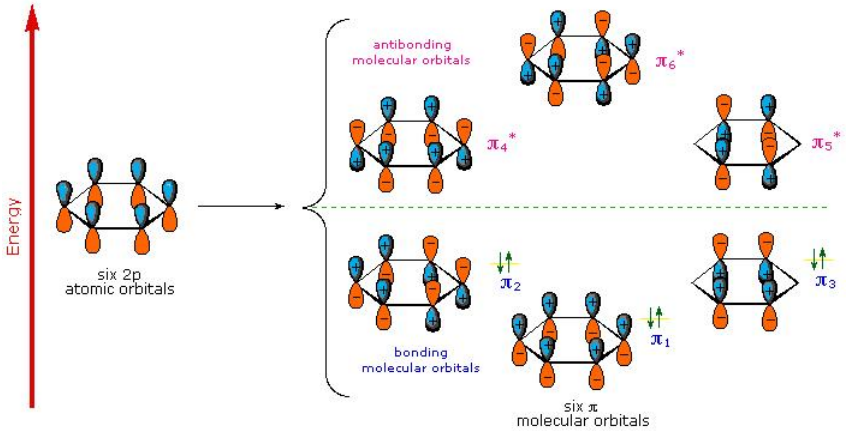
Benzene:	

Here, two structurally and energetically equivalent electronic structures for a stable compound are written, but no single structure provides an accurate or even an adequate representation of the true molecule. The six-membered ring in benzene is a perfect hexagon (all carbon-carbon bonds have an identical length of 1.40 Å). The cyclohexatriene contributors would be expected to show alternating bond lengths, the double bonds being shorter (1.34 Å) than the single bonds (1.54 Å). An alternative representation for benzene (circle within a hexagon) emphasizes the pi-electron delocalization in this molecule, and has the advantage of being a single diagram. In cases such as these, the electron delocalization described by resonance enhances the stability of the molecules, and compounds composed of such molecules often show exceptional stability and related properties.

Evidence for the enhanced thermodynamic stability of benzene was obtained from measurements of the heat released when double bonds in a six-carbon ring are hydrogenated (hydrogen is added catalytically) to give cyclohexane as a common product. In the following diagram cyclohexane represents a low-energy reference point. Addition of hydrogen to cyclohexene produces cyclohexane and releases heat amounting to 28.6 kcal per mole. If we take this value to represent the energy cost of introducing one double bond into a six-carbon ring, we would expect a cyclohexadiene to release 57.2 kcal per mole on complete hydrogenation, and 1,3,5-cyclohexatriene to release 85.8 kcal per mole. These **heats of hydrogenation** would reflect the relative thermodynamic stability of the compounds. In practice, 1,3-cyclohexadiene is slightly more stable than expected, by about 2 kcal, presumably due to conjugation of the double bonds. **Benzene, however, is an extraordinary 36 kcal/mole more stable than expected**. This sort of stability enhancement is now accepted as a characteristic of all aromatic compounds.



A molecular orbital description of benzene provides a more satisfying and more general treatment of "aromaticity". We know that benzene has a planar hexagonal structure in which all the carbon atoms are sp^2 hybridized, and all the carbon-carbon bonds are equal in length. As shown below, the remaining cyclic array of six p-orbitals (one on each carbon) overlap to generate six molecular orbitals, three bonding and three antibonding. The plus and minus signs shown in the diagram do not represent electrostatic charge, but refer to phase signs in the equations that describe these orbitals (in the diagram the phases are also color coded). When the phases correspond, the orbitals overlap to generate a common region of like phase, with those orbitals having the greatest overlap (e.g. π_1) being lowest in energy. The remaining carbon valence electrons then occupy these molecular orbitals in pairs, resulting in a fully occupied (6 electrons) set of bonding molecular orbitals. It is this completely filled set of bonding orbitals, or **closed shell**, that gives the benzene ring its thermodynamic and chemical stability, just as a filled valence shell octet confers stability on the inert gases.



The Molecular Orbitals of Benzene

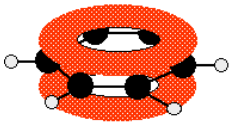
Contributors

William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

15.2: The Structure of Benzene

Among the many distinctive features of benzene, its aromaticity is the major contributor to why it is so unreactive. This section will try to clarify the theory of aromaticity and why aromaticity gives unique qualities that make these conjugated alkenes inert to compounds such as Br_2 and even hydrochloric acid. It will also go into detail about the unusually large resonance energy due to the six conjugated carbons of benzene.

The delocalization of the p-orbital carbons on the sp^2 hybridized carbons is what gives the aromatic qualities of benzene.

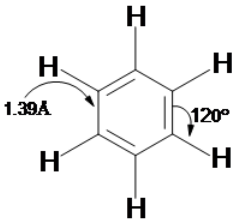


This diagram shows one of the molecular orbitals containing two of the delocalized electrons, which may be found anywhere within the two "doughnuts". The other molecular orbitals are almost never drawn.

- Benzene, C_6H_6, is a planar molecule containing a ring of six carbon atoms, each with a hydrogen atom attached.

  The six carbon atoms form a perfectly regular hexagon. All of the carbon-carbon bonds have exactly the same lengths - somewhere between single and double bonds.
- There are delocalized electrons above and below the plane of the ring.
- The presence of the delocalized electrons makes benzene particularly stable.
- Benzene resists addition reactions because those reactions would involve breaking the delocalization and losing that stability.
- Benzene is represented by this symbol, where the circle represents the delocalized electrons, and each corner of the hexagon has a carbon atom with a hydrogen attached.

Basic Structure of Benzene



Because of the aromaticity of benzene, the resulting molecule is planar in shape with each C-C bond being 1.39 Å in length and each bond angle being 120°. You might ask yourselves how it's possible to have all of the bonds to be the same length if the ring is conjugated with both single (1.47 Å) and double (1.34 Å), but it is important to note that there are no distinct single or double bonds within the benzene. Rather, the delocalization of the ring makes each count as one and a half bonds between the carbons which makes sense because experimentally we find that the actual bond length is somewhere in between a single and double bond. Finally, there are a total of six p-orbital electrons that form the stabilizing electron clouds above and below the aromatic ring.

Contributors

Jim Clark (Chemguide.co.uk)

15.3: Nomenclature of Benzene Derivatives

Unlike aliphatic organics, nomenclature of benzene-derived compounds can be confusing because a single aromatic compound can have multiple possible names (such as common and systematic names) be associated with its structure. In these sections, we will analyze some of the ways these compounds can be named.

Simple Benzene Naming

Some common substituents, like NO_2, Br, and Cl, can be named this way when it is attached to a phenyl group. Long chain carbons attached can also be named this way. The general format for this kind of naming is:

(positions of substituents (if >1)- + # (di, tri, ...) + substituent)$_n$ + benzene.

For example, chlorine (Cl) attached to a phenyl group would be named **chlorobenzene (chloro + benzene)**. Since there is only one substituent on the benzene ring, we do not have to indicate its position on the benzene ring (as it can freely rotate around and you would end up getting the same compound.)

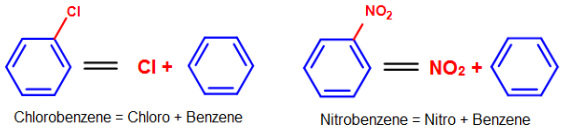


Figure 8. Example of simple benzene naming with chlorine and NO_2 as substituents.

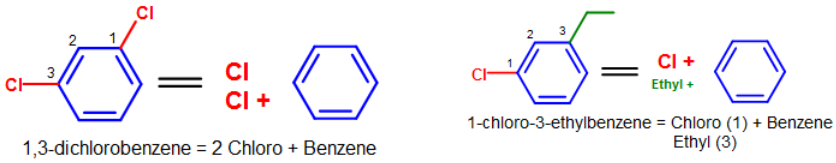


Figure 9. More complicated simple benzene naming examples - Note that standard nomenclature priority rules are applied here, causing the numbering of carbons to switch. See Nomenclature of Organic Compounds for a review on naming and priority rules.

Ortho-, Meta-, Para- (OMP) Nomenclature for Disubstituted Benzenes

Instead of using numbers to indicate substituents on a benzene ring, ***ortho- (o-), meta- (m-), or para (p-)*** can be used in place of positional markers when there are **two** substituents on the benzene ring (disubstituted benzenes). They are defined as the following:

- ***ortho- (o-):*** 1,2- (next to each other in a benzene ring)
- ***meta- (m):*** 1,3- (separated by one carbon in a benzene ring)
- ***para- (p):*** 1,4- (across from each other in a benzene ring)

Using the same example above in figure 9a (1,3-dichlorobenzene), we can use the ortho-, meta-, para- nomenclature to transform the chemical name into m-dichlorobenzene, as shown in the figure below.

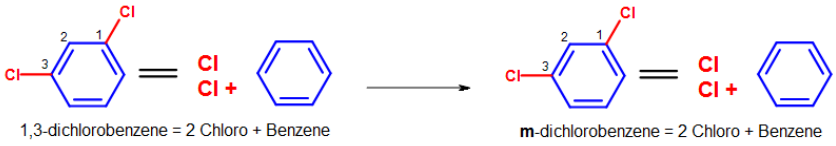


Figure 10. Transformation of 1,3-dichlorobenzene into m-dichlorobenzene.

Here are some other examples of ortho-, meta-, para- nomenclature used in context:

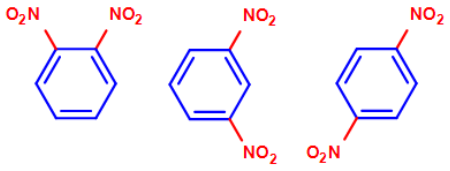


Figure 11. Example of o-, m-, p- nomenclature.
Listed in order:
1) o-dinitrobenzene
2) m-dinitrobenzene
3) p-dinitrobenzene

However, the substituents used in ortho-, meta-, para- nomenclature do not have to be the same. For example, we can use chlorine and a nitro group as substituents in the benzene ring.

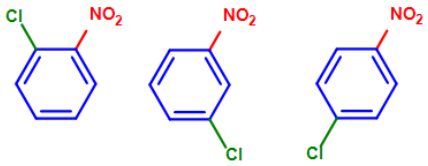
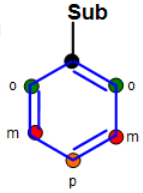


Figure 12. Example of o-, m-, p- nomenclature.
Listed in order:
1) o-nitrochlorobenzene
2) m-nitrochlorobenzene
3) p-nitrochlorobenzene
Note that the two substituents do not have to be the same.

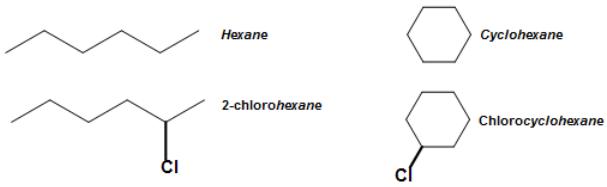
In conclusion, these can be pieced together into a summary diagram, as shown below:

Figure 13. A benzene ring with a primary substituent and the possible locations for the secondary substituent.
As shown:
1,2- (green) = ortho, o-
1,3- (red) = meta, m-
1,4- (orange) = para, p-
For clarity, the benzene ring has been rotated 30° relatively to the other benzenes in this article.



Base Name Nomenclature

In addition to simple benzene naming and OMP nomenclature, benzene derived compounds are also sometimes used as **bases**. The concept of a base is similar to the nomenclature of aliphatic and cyclic compounds, where the parent for the organic compound is used as a base (a name for its chemical name. For example, the following compounds have the base names ***hexane*** and ***cyclohexane***, respectively. See Nomenclature of Organic Compounds for a review on naming organic compounds.



Benzene, similar to these compounds shown above, also has base names from its derived compounds. **Phenol (C_6H_5OH)**, as introduced previously in this article, for example, serves as a base when other substituents are attached to it. This is best illustrated in the diagram below.

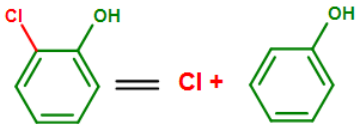


Figure 14. An example showing phenol as a base in its chemical name. Note how benzene no longer serves as a base when an OH group is added to the benzene ring.

Alternatively, we can use the numbering system to indicate this compound. When the numbering system is used, the carbon where the substituent is attached on the base will be given the first priority and named as carbon #1 (C_1). The normal priority rules then apply in the nomenclature process (give the rest of the substituents the lowest numbering as you could).

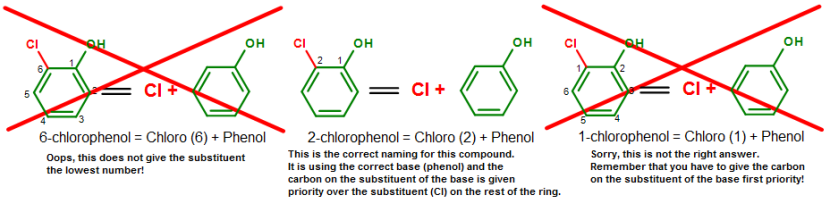


Figure 15. The naming process for 2-chlorophenol (o-chlorophenol). Note that 2-chlorophenol = o-chlorophenol.

Below is a list of commonly seen benzene-derived compounds. Some of these mono-substituted compounds (labeled in red and green), such as phenol or toluene, can be used in place of benzene for the chemical's base name.

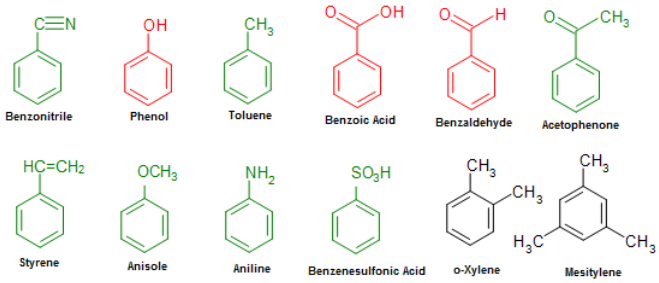


Figure 16. Common benzene derived compounds with various substituents.

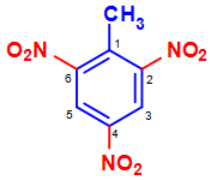


Figure 17. 2,4,6-Trinitrotoluene, or **TNT**, a common explosive used for both industrial and military purposes, is consisted of a **toluene** base (labeled in blue), along with three **nitro** groups attached as substituents (labeled in red).
The explosive is characteristic for its resistance to external shock and friction, making it useful in many applications where other highly sensitive explosives would simultaneously detonate.

Common vs. Systematic (IUPAC) Nomenclature

According to the indexing preferences of the *Chemical Abstracts*, **phenol, benzaldehyde, and benzoic acid (labeled in red in Figure 16)** are some of the common names that are retained in the IUPAC (systematic) nomenclature. Other names such as toluene, styrene, naphthalene, or phenanthrene can also be seen in the IUPAC system in the same way. While the use of other common names are usually acceptable in IUPAC, their use are discouraged in the nomenclature of compounds.

Nomenclature for compounds which has such discouraged names will be named by the simple benzene naming system. An example of this would include **toluene derivatives like TNT.** (Note that toluene by itself is retained by the IUPAC nomenclature, but its derivatives, which contains additional substituents on the benzene ring, might be excluded from the convention). For this reason, the **common chemical name** 2,4,6-trinitrotoluene, or TNT, as shown in figure 17, would not be advisable under the IUPAC (**systematic**) nomenclature.

To correctly name TNT under the IUPAC system, the simple benzene naming system should be used:

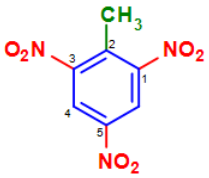


Figure 18. TNT, as named under the IUPAC nomenclature. Note that since the IUPAC nomenclature does not recognize toluene as the primary base of this compound, substituent priorities are reverted to normal defaults.
As a result, TNT in IUPAC is named (systematic name):
2-methyl-1,3,5-trinitrobenzene

Figure 18. Systematic (IUPAC) name of 2,4,6-trinitrotoluene (common name), or TNT.
Note that the methyl group is individually named due to the exclusion of toluene from the IUPAC nomenclature.

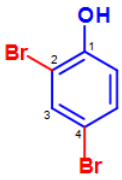


Figure 19. 2,4-dibromophenol, as shown in this diagram, is valid in both the common nomenclature as well as the IUPAC nomenclature. As mentioned previously, **phenol, benzoic acid, and benzaldehyde** substituents are allowed to be used in the IUPAC naming conventions and the base naming priority rules are applied in the nomenclature process.

Figure 19. The common name 2,4-dibromophenol, is shared by the IUPAC systematic nomenclature. Only substituents **phenol, benzoic acid, and benzaldehyde** share this commonality.

Since the IUPAC nomenclature primarily rely on the simple benzene naming system for the nomenclature of different benzene derived compounds, the OMP (ortho-, meta-, para-) system is not accepted in the IUPAC nomenclature. For this reason, the OMP system will yield common names that can be converted to systematic names by using the same method as above. For example, o-Xylene from the OMP system can be named 1,2-dimethylbenzene by using simple benzene naming (IUPAC standard).

The Phenyl and Benzyl Groups

The Phenyl Group

As mentioned previously, the phenyl group (Ph-R, C_6H_5-R) can be formed by removing a hydrogen from benzene and attaching a substituent to where the hydrogen was removed. To this phenomenon, we can name compounds formed this way by applying this rule: **(phenyl + substituent)**. For example, a chlorine attached in this manner would be named **phenyl chloride**, and a bromine attached in this manner would be named **phenyl bromide**. (See below diagram)

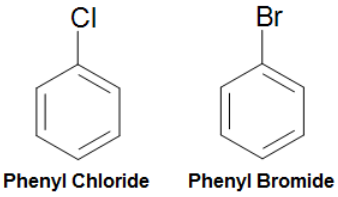


Figure 20. Naming of Phenyl Chloride and Phenyl Bromide

While compounds like these are usually named by simple benzene type naming (chlorobenzene and bromobenzene), the phenyl group naming is usually applied to benzene rings where a substituent with six or more carbons is attached, such as in the diagram below.

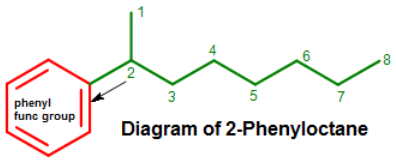


Figure 21. Diagram of 2-phenyloctane.

Although the diagram above might be a little daunting to understand at first, it is not as difficult as it seems after careful analysis of the structure is made. By looking for the longest chain in the compound, it should be clear that the longest chain is eight (8) carbons long (octane, as shown in green) and that a benzene ring is attached to the second position of this longest chain (labeled in red). As this rule suggests that the benzene ring will act as a function group (a substituent) whenever a substituent of more than six (6) carbons is attached to it, the name "benzene" is changed to **phenyl** and is used the same way as any other substituents, such as **methyl, ethyl, or bromo.** Putting it all together, the name can be derived as: **2-phenyloctane** (phenyl is attached at the second position of the longest carbon chain, octane).

The Benzyl Group

The benzyl group (abbv. Bn), similar to the phenyl group, is formed by manipulating the benzene ring. In the case of the benzyl group, it is formed by taking the phenyl group and adding a CH_2 group to where the hydrogen was removed. Its molecular fragment can be written as $C_6H_5CH_2$-R, $PhCH_2$-R, or Bn-R. Nomenclature of benzyl group based compounds are very similar to the phenyl group compounds. For example, a chlorine attached to a benzyl group would simply be called benzyl chloride, whereas an OH group attached to a benzyl group would simply be called benzyl alcohol.

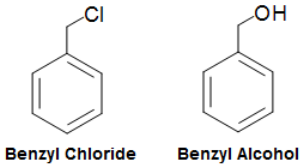


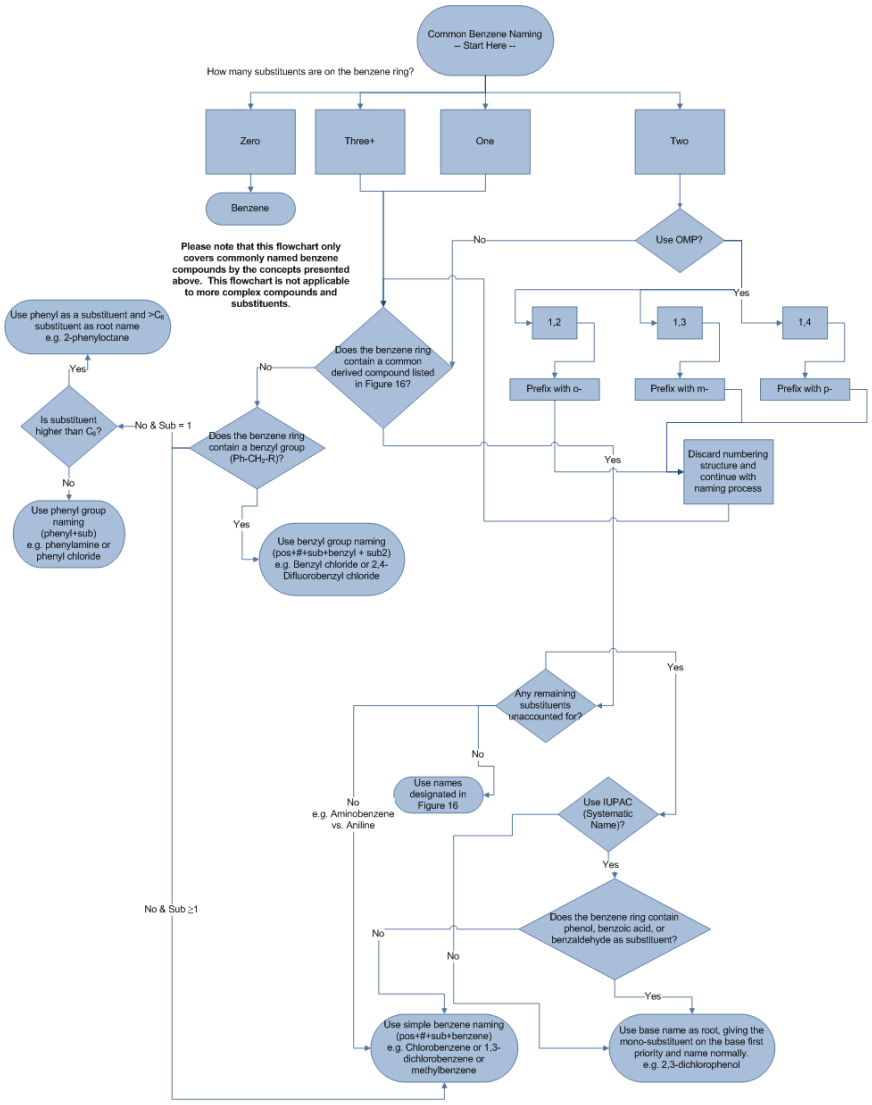
Figure 22. Benzyl Group Nomenclature

Additionally, other substituents can attach on the benzene ring in the presence of the benzyl group. An example of this can be seen in the figure below:

Figure 23. Nomenclature of 2,4-difluorobenzyl chloride. Similar to the base name nomenclatures system, the carbon in which th base substitutent is attached on the benzene ring is given the first priority and the rest of the substituents are given the lowest number order possible.

Similar to the base name nomenclature system, the carbon in which the base substituent is attached on the benzene ring is given the first priority and the rest of the substituents are given the lowest number order possible. Under this consideration, the above compound can be named: **2,4-difluorobenzyl chloride.**

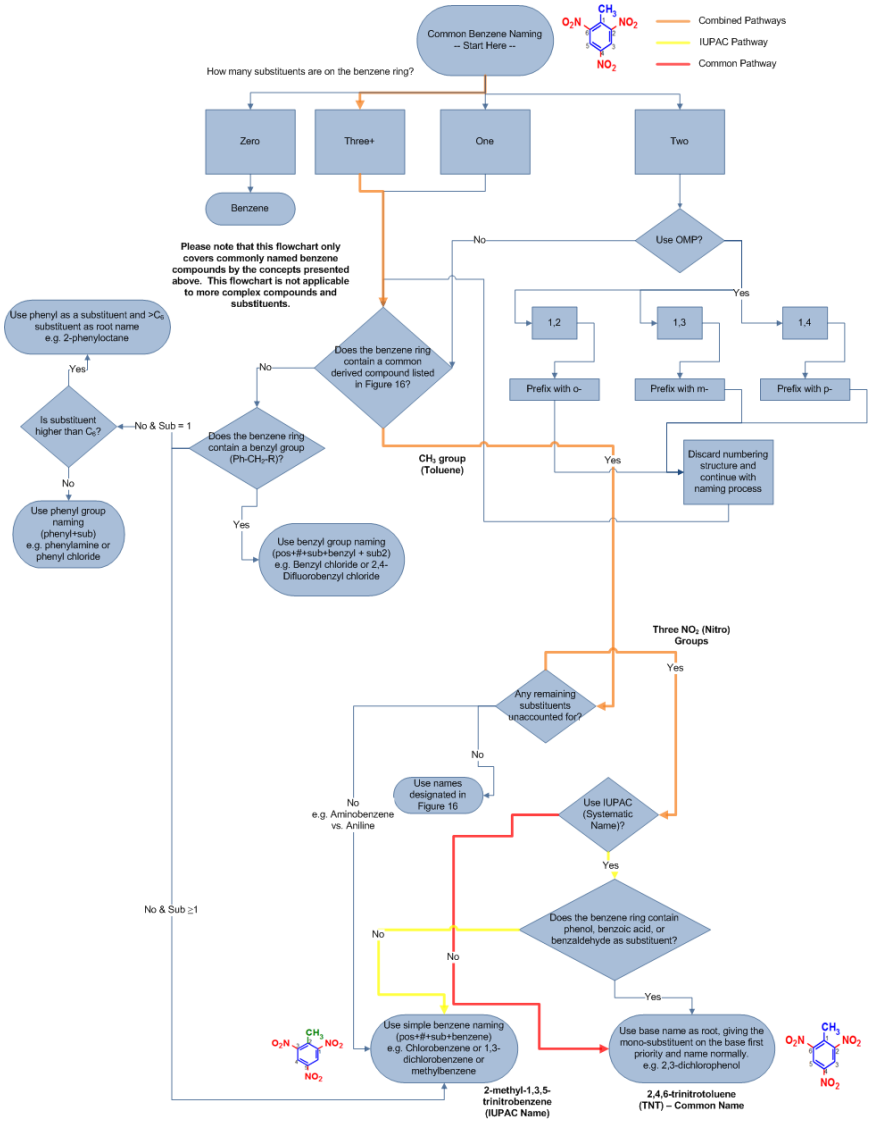
Commonly Named Benzene Compounds Nomenclature Summary Flowchart



Summary Flowchart (Figure 24). Summary of nomenclature rules used in commonly benzene derived compounds. As benzene derived compounds can be extremely complex, only compounds covered in this article and other commonly named compounds can be named using this flowchart.

Determination of Common and Systematic Names using Flowchart

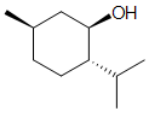
To demonstrate how this flowchart can be used to name TNT in its common and systematic (IUPAC) name, a replica of the flowchart with the appropriate flow paths are shown below:



References

1. Nicolaou, K. C., & Montagnon, T. (2008). *Molecules That Changed the World.* KGaA, Weinheim: Wiley-VCH. p. 54
2. Pitman, V. (2004). *Aromatherapy.* Great Britain, UK: Nelson Thornes. p.135-136
3. Burton, G. (2000). *Chemical Ideas.* Bicester, Oxon: Heinemann. p.290-292
4. Vollhardt, K. P.C. & Shore, N. (2007). *Organic Chemistry* (5th Ed.). New York: W. H. Freeman. p. 667-669
5. Schnaubelt, K. (1999). *Medical Aromatherapy.* Berkeley, CA: Frog Books. p. 211-213
6. Patrick, G. L. (2004). *Organic Chemistry.* New York, NY: Taylor & Francis. p. 135-136
7. Talbott, S. M. (2002). *A Guide to Understanding Dietary Supplements.* Binghamton, NY: Haworth Press. p. 616-619
8. Lifton, R. J. (2000). *The Nazi doctors.* New York, NY: Basic Books. p. 255-261
9. Myers, R. L., & Myers, R. L. (2007). *The 100 most important chemical compounds.* Westport, CT: Greenwood Publishing Group. p. 281-282

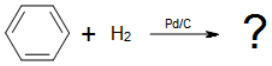
Practice Problems



Q1) (True/False) The compound above contains a benzene ring and thus is aromatic.

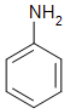
Q2) Benzene unusual stability is caused by how many conjugated pi bonds in its cyclic ring? ____

Q3) Menthol, a topical analgesic used in many ointments for the relief of pain, releases a peppermint aroma upon exposure to the air. Based on this conclusion, can you imply that a benzene ring is present in its chemical structure? Why or why not?

Q4) 

Q5) At normal conditions, benzene has ___ resonance structures.

Q6) Which of the following name(s) is/are correct for the following compound?

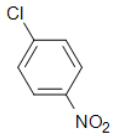


a) nitrohydride benzene
b) phenylamine
c) phenylamide
d) aniline
e) nitrogenhydrogen benzene
f) All of the above is correct

Q7) Convert 1,4-dimethylbenzene into its common name.

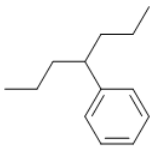
Q8) TNT's common name is: _____

Q9) Name the following compound using OMP nomenclature:

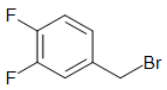


Q10) Draw the structure of 2,4-dinitrotoluene.

Q11) Name the following compound:



Q12) Which of the following is the correct name for the following compound?



a) 3,4-difluorobenzyl bromide
b) 1,2-difluorobenzyl bromide
c) 4,5-difluorobenzyl bromide
d) 1,2-difluoroethyl bromide
e) 5,6-difluoroethyl bromide
f) 4,5-difluoroethyl bromide

Q13) (True/False) Benzyl chloride can be abbreviated Bz-Cl.

Q14) Benzoic Acid has what R group attached to its phenyl functional group?

Q15) (True/False) A single aromatic compound can have multiple names indicating its structure.

Q16) List the corresponding positions for the OMP system (o-, m-, p-).

Q17) A scientist has conducted an experiment on an unknown compound. He was able to determine that the unknown compound contains a cyclic ring in its structure as well as an alcohol (-OH) group attached to the ring. What is the unknown compound?
a) Cyclohexanol
b) Cyclicheptanol
c) Phenol
d) Methanol
e) Bleach
f) Cannot determine from the above information

Q18) Which of the following statements is **false** for the compound, phenol?
a) Phenol is a benzene derived compound.
b) Phenol can be made by attaching an -OH group to a phenyl group.
c) Phenol is highly toxic to the body even in small doses.
d) Phenol can be used as a catalyst in the hydrogenation of benzene into cyclohexane.
e) Phenol is used as an antiseptic in minute doses.
f) Phenol is amongst one of the three common names retained in the IUPAC nomenclature.

Answer Key to Practice Questions

Q1) False, this compound does not contain a benzene ring in its structure.

Q2) 3

Q3) No, a substance that is fragrant does not imply a benzene ring is in its structure. See camphor example (figure 1)

Q4) No reaction, benzene requires a special catalyst to be hydrogenated due to its unusual stability given by its three conjugated pi bonds.

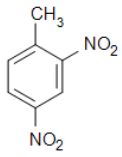
Q5) 2

Q6) b, d

Q7) p-Xylene

Q8) 2,4,6-trinitrotoluene

Q9) p-chloronitrobenzene

Q10) 

Q11) 4-phenylheptane

Q12) a

Q13) False, the correct abbreviation for the benzyl group is Bn, not Bz. The correct abbreviation for Benzyl chloride is Bn-Cl.

Q14) COOH

Q15) True. TNT, for example, has the common name 2,4,6-trinitrotoluene and its systematic name is 2-methyl-1,3,5-trinitrobenzene.

Q16) Ortho - 1,2 ; Meta - 1,3 ; Para - 1,4

Q17) The correct answer is f). We cannot determine what structure this is since the question does not tell us what kind of cyclic ring the -OH group is attached on. Just as cyclohexane can be cyclic, benzene and cycloheptane can also be cyclic.

Q18) d

Contributors

- David Lam

15.4: Spectroscopic Properties

The chemical shifts of aromatic protons

Some protons resonate much further downfield than can be accounted for simply by the deshielding effect of nearby electronegative atoms. Vinylic protons (those directly bonded to an alkene carbon) and aromatic (benzylic) protons are dramatic examples.

We'll consider the aromatic proton first. Recall that in benzene and many other aromatic structures, a sextet of pelectrons is delocalized around the ring. When the molecule is exposed to B_0, these pelectrons begin to circulate in a **ring current**, generating their own induced magnetic field that opposes B_0. In this case, however, the induced field of the pelectrons does not shield the benzylic protons from B_0 as you might expect– rather, it causes the protons to experience a *stronger* magnetic field in the direction of B_0 – in other words, it *adds* to B_0 rather than subtracting from it.

To understand how this happens, we need to understand the concept of **diamagnetic anisotropy** (anisotropy means `non-uniformity`). So far, we have been picturing magnetic fields as being oriented in a uniform direction. This is only true over a small area. If we step back and take a wider view, however, we see that the lines of force in a magnetic field are actually anisotropic. They start in the 'north' direction, then loop around like a snake biting its own tail.

If we are at point A in the figure above, we feel a magnetic field pointing in a northerly direction. If we are at point B, however, we feel a field pointing to the south.

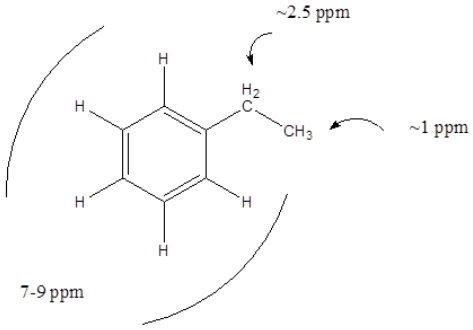
In the induced field generated by the aromatic ring current, the benzylic protons are at the equivalent of ‘point B’ – this means that the induced current in this region of space is oriented in the *same* direction as B_0.

In total, the benzylic protons are subjected to three magnetic fields: the applied field (B_0) and the induced field from the pelectrons pointing in one direction, and the induced field of the non-aromatic electrons pointing in the opposite (shielding) direction. The end

result is that benzylic protons, due to the anisotropy of the induced field generated by the ring current, appear to be highly deshielded. Their chemical shift is far downfield, in the 6.5-8 ppm region.

Characteristic NMR Absorption of Benzene Derivatives

Hydrogens directly attached to an arene ring show up about 7-9 PPM in the NMR. **This is called the aromatic region.** Hydrogen environments directly bonded to an arene ring show up about 2.5 PPM.



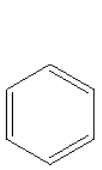
Charateristic IR Absorption of Benzene Derivatives

Arenes produce an characteristic C=C absorption about 1680-1600 1/cm

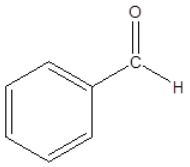
Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- Prof. Steven Farmer (Sonoma State University)

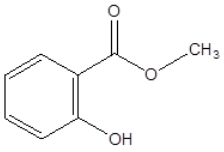
15.5: Interesting Aromatic Compounds



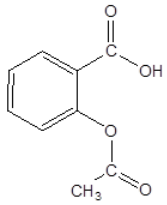
Benzene
a Carcinogen



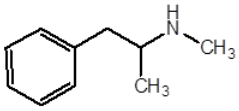
Benzaldehyde
The smell and taste of almonds.



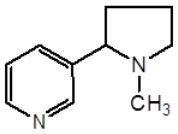
Methyl salicylate
(Oil of wintergreen)



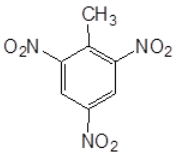
Asprin
A Pain killer



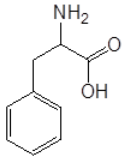
Methamphetamine
A stimulant



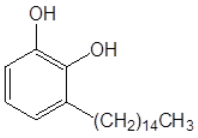
Nicotine
A poison



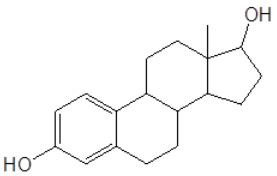
1,3,5-Trinitrotoluene (TNT)
An Explosive



Phenylalanine
An amino acid



An Urushiol
One of the allergic components found in Poison Oak



Estradiol
A Female Hormone

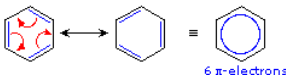
Contributors

- Prof. Steven Farmer (Sonoma State University)

15.6: Benzene's Unusual Stability

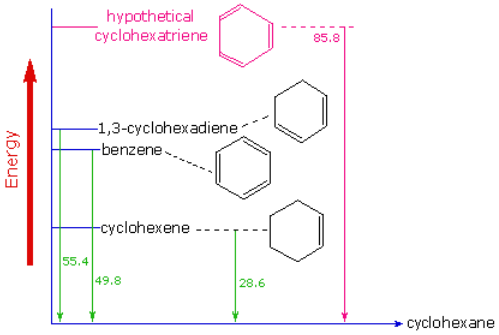
If benzene is forced to react by increasing the temperature and/or by addition of a catalyst, It undergoes **substitution reactions** rather than the addition reactions that are typical of alkenes. This further confirms the previous indication that the six-carbon benzene core is unusually stable to chemical modification. The conceptual contradiction presented by a high degree of unsaturation (low H:C ratio) and high chemical stability for benzene and related compounds remained an unsolved puzzle for many years. Eventually, the presently accepted structure of a regular-hexagonal, planar ring of carbons was adopted, and the exceptional thermodynamic and chemical stability of this system was attributed to resonance stabilization of a conjugated cyclic triene.

Benzene:



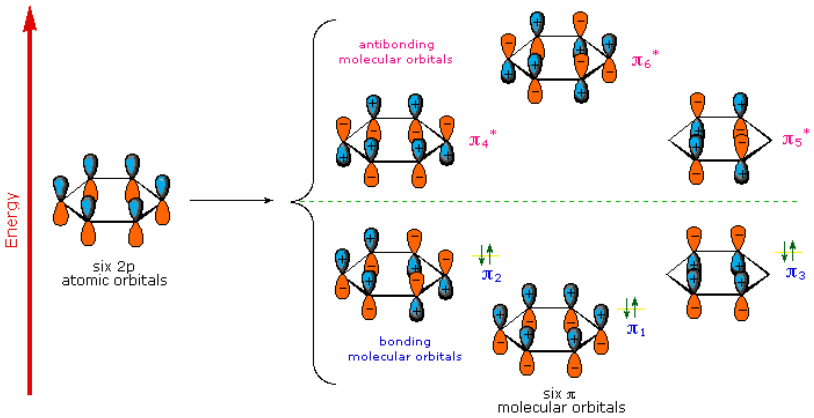
Here, two structurally and energetically equivalent electronic structures for a stable compound are written, but no single structure provides an accurate or even an adequate representation of the true molecule. The six-membered ring in benzene is a perfect hexagon (all carbon-carbon bonds have an identical length of 1.40 Å). The cyclohexatriene contributors would be expected to show alternating bond lengths, the double bonds being shorter (1.34 Å) than the single bonds (1.54 Å). An alternative representation for benzene (circle within a hexagon) emphasizes the pi-electron delocalization in this molecule, and has the advantage of being a single diagram. In cases such as these, the electron delocalization described by resonance enhances the stability of the molecules, and compounds composed of such molecules often show exceptional stability and related properties.

Evidence for the enhanced thermodynamic stability of benzene was obtained from measurements of the heat released when double bonds in a six-carbon ring are hydrogenated (hydrogen is added catalytically) to give cyclohexane as a common product. In the following diagram cyclohexane represents a low-energy reference point. Addition of hydrogen to cyclohexene produces cyclohexane and releases heat amounting to 28.6 kcal per mole. If we take this value to represent the energy cost of introducing one double bond into a six-carbon ring, we would expect a cyclohexadiene to release 57.2 kcal per mole on complete hydrogenation, and 1,3,5-cyclohexatriene to release 85.8 kcal per mole. These **heats of hydrogenation** would reflect the relative thermodynamic stability of the compounds. In practice, 1,3-cyclohexadiene is slightly more stable than expected, by about 2 kcal, presumably due to conjugation of the double bonds. **Benzene, however, is an extraordinary 36 kcal/mole more stable than expected**. This sort of stability enhancement is now accepted as a characteristic of all aromatic compounds.



A molecular orbital description of benzene provides a more satisfying and more general treatment of "aromaticity". We know that benzene has a planar hexagonal structure in which all the carbon atoms are sp^2 hybridized, and all the carbon-carbon bonds are equal in length. As shown below, the remaining cyclic array of six p-orbitals (one on each carbon) overlap to generate six molecular orbitals, three bonding and three antibonding. The plus and minus signs shown in the diagram do not represent electrostatic charge, but refer to phase signs in the equations that describe these orbitals (in the diagram the phases are also color coded). When the phases correspond, the orbitals overlap to generate a common region of like phase, with those orbitals having the greatest overlap (e.g. π_1) being lowest in energy. The remaining carbon valence electrons then occupy these molecular orbitals in pairs, resulting in a fully occupied (6 electrons) set of bonding molecular orbitals. It is this completely filled set of bonding orbitals, or **closed shell**, that gives the benzene ring its thermodynamic and chemical stability, just as a filled valence shell octet confers stability on the inert gases.

The Molecular Orbitals of Benzene



Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

15.7: The Criteria for Aromaticity - Hückel's Rule

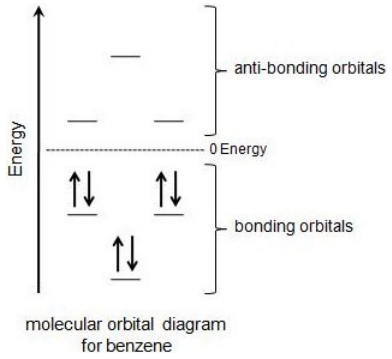
In 1931, German chemist and physicist Erich Hückel proposed a theory to help determine if a planar ring molecule would have aromatic properties. His rule states that if a cyclic, planar molecule has 4n+2 π electrons, it is considered aromatic. This rule would come to be known as Hückel's Rule.

Four Criteria for Aromaticity

When deciding if a compound is aromatic, go through the following checklist. If the compound does not meet all the following criteria, it is likely not aromatic.

1. The molecule is cyclic (a ring of atoms)
2. The molecule is planar (all atoms in the molecule lie in the same plane)
3. The molecule is fully conjugated (p orbitals at every atom in the ring)
4. The molecule has $4n+2\ \pi$ electrons ($n = 0$ or any positive integer)

According to Hückel's Molecular Orbital Theory, a compound is particularly stable if all of its bonding molecular orbitals are filled with paired electrons. This is true of aromatic compounds, meaning they are quite stable. With aromatic compounds, 2 electrons fill the lowest energy molecular orbital, and 4 electrons fill each subsequent energy level (the number of subsequent energy levels is denoted by *n*), leaving all bonding orbitals filled and no anti-bonding orbitals occupied. This gives a total of 4n+2 π electrons. You can see how this works with the molecular orbital diagram for the aromatic compound, benzene, below. Benzene has 6 π electrons. Its first 2 π electrons fill the lowest energy orbital, and it has 4 π electrons remaining. These 4 fill in the orbitals of the succeeding energy level. Notice how all of its bonding orbitals are filled, but none of the anti-bonding orbitals have any electrons.



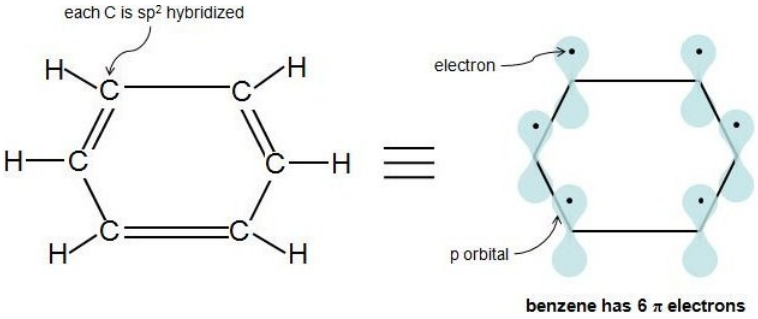
molecular orbital diagram for benzene

To apply the 4n+2 rule, first count the number of π electrons in the molecule. Then, set this number equal to 4n+2 and solve for n. If is 0 or any positive integer (1, 2, 3,...), the rule has been met. For example, benzene has six π electrons:

$$4n+2 = 6$$
$$4n = 4$$
$$n = 1$$

For benzene, we find that $n = 1$, which is a positive integer, so the rule is met.

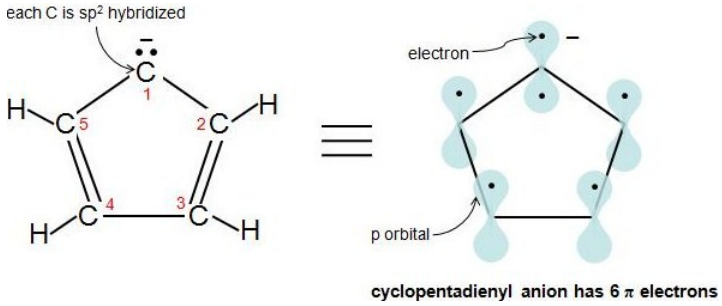
Perhaps the toughest part of Hückel's Rule is figuring out which electrons in the compound are actually π electrons. Once this is figured out, the rule is quite straightforward. π electrons lie in p orbitals. Sp^2 hybridized atoms have 1 p orbital each. So if every molecule in the cyclic compound is sp^2 hybridized, this means the molecule is fully conjugated (has 1 p orbital at each atom), and the electrons in these p orbitals are the π electrons. A simple way to know if an atom is sp^2 hybridized is to see if it has 3 attached atoms and no lone pairs of electrons. This video provides a very nice tutorial on how to determine an atom's hybridization. In a cyclic hydrocarbon compound with alternating single and double bonds, each carbon is attached to 1 hydrogen and 2 other carbons. Therefore, each carbon is sp^2 hybridized and has a p orbital. Let's look at our previous example, benzene:



Each double bond (π bond) always contributes 2 π electrons. Benzene has 3 double bonds, so it has 6 π electrons.

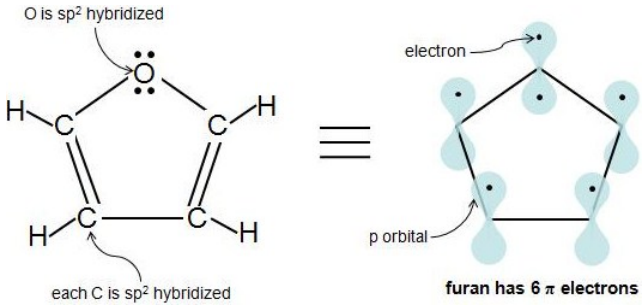
Aromatic Ions

Hückel's Rule also applies to ions. As long as a compound has 4n+2 π electrons, it does not matter if the molecule is neutral or has a charge. For example, cyclopentadienyl anion is an aromatic ion. How do we know that it is fully conjugated? That is, how do we know that each atom in this molecule has 1 p orbital? Let's look at the following figure. Carbons 2-5 are sp^2 hybridized because they have 3 attached atoms and have no lone electron pairs. What about carbon 1? Another simple rule to determine if an atom is sp^2 hybridized is if an atom has 1 or more lone pairs and is attached to an sp^2 hybridized atom, then that atom is sp^2 hybridized also. This video explains the rule very clearly. Therefore, carbon 1 has a p orbital. Cyclopentadienyl anion has 6 π electrons and fulfills the 4n+2 rule.



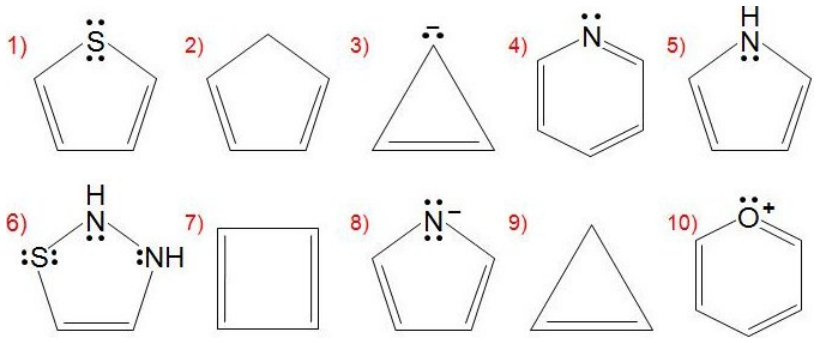
Heterocyclic Aromatic Compounds

So far, you have encountered many carbon homocyclic rings, but compounds with elements other than carbon in the ring can also be aromatic, as long as they fulfill the criteria for aromaticity. These molecules are called heterocyclic compounds because they contain 1 or more different atoms other than carbon in the ring. A common example is furan, which contains an oxygen atom. We know that all carbons in furan are sp^2 hybridized. But is the oxygen atom sp^2 hybridized? The oxygen has at least 1 lone electron pair and is attached to an sp^2 hybridized atom, so it is sp^2 hybridized as well. Notice how oxygen has 2 lone pairs of electrons. How many of those electrons are π electrons? An sp^2 hybridized atom only has 1 p orbital, which can only hold 2 electrons, so we know that 1 electron pair is in the p orbital, while the other pair is in an sp^2 orbital. So, only 1 of oxygen's 2 lone electron pairs are π electrons. Furan has 6 π electrons and fulfills the 4n+2 rule.



Problems

Using the criteria for aromaticity, determine if the following molecules are aromatic:



Answers

1. Aromatic - only 1 of S's lone pairs counts as π electrons, so there are 6 π electrons, n=1
2. Not aromatic - not fully conjugated, top C is sp^3 hybridized
3. Not aromatic - top C is sp^2 hybridized, but there are 4 π electrons, n=1/2
4. Aromatic - N is using its 1 p orbital for the electrons in the double bond, so its lone pair of electrons are not π electrons, there are 6 π electrons, n=1
5. Aromatic - there are 6 π electrons, n=1
6. Not aromatic - all atoms are sp^2 hybridized, but only 1 of S's lone pairs counts as π electrons, so there 8 π electrons, n=1.5
7. Not aromatic - there are 4 π electrons, n=1/2
8. Aromatic - only 1 of N's lone pairs counts as π electrons, so there are 6 π electrons, n=1
9. Not aromatic - not fully conjugated, top C is sp^3 hybridized
10. Aromatic - O is using its 1 p orbital for the elections in the double bond, so its lone pair of electrons are not π electrons, there are 6 π electrons, n=1

References

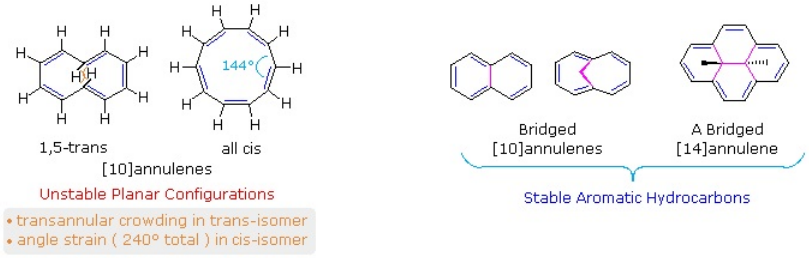
1. Vollhardt, Peter, and Neil E. Schore. Organic Chemistry: Structure and Function. 5th ed. New York: W. H. Freeman & Company, 2007.
2. Berson, Jerome. Chemical Creativity: Ideas from the Work of Woodward, Hückel, Meerwein, and Others. New York: Wiley-VCH, 1999.
3. Badger, G.M. Aromatic Character and Aromaticity. London, England: Cambridge University Press, 1969.
4. Lewis, David and David Peters. Facts and Theories of Aromaticity. London, England: Macmillan Press, 1975.

Contributors

- Ramie Hosein

15.8: Examples of Aromatic Compounds

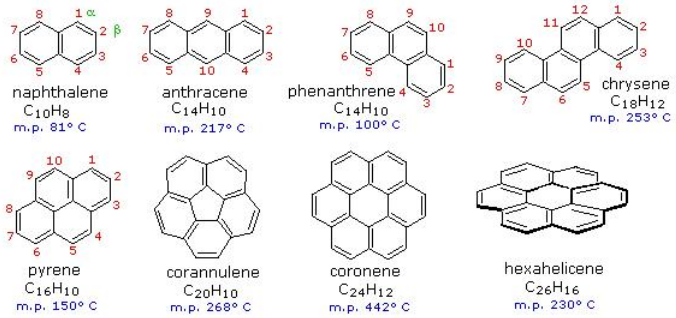
Aromatic Compound with a single ring



Aromatic Compounds with more than one ring

Benzene rings may be joined together (fused) to give larger polycyclic aromatic compounds. A few examples are drawn below, together with the approved numbering scheme for substituted derivatives. The peripheral carbon atoms (numbered in all but the last three examples) are all bonded to hydrogen atoms. Unlike benzene, all the C-C bond lengths in these fused ring aromatics are not the same, and there is some localization of the pi-electrons.

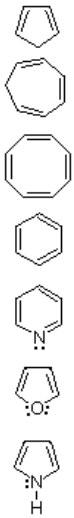
The six benzene rings in coronene are fused in a planar ring; whereas the six rings in hexahelicene are not joined in a larger ring, but assume a helical turn, due to the crowding together of the terminal ring atoms. This helical configuration renders the hexahelicene molecule chiral, and it has been resolved into stable enantiomers.



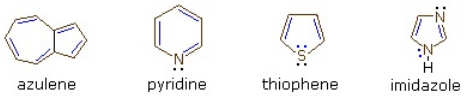
Aromatic Heterocycles

Many unsaturated cyclic compounds have exceptional properties that we now consider characteristic of "aromatic" systems. The following cases are illustrative:

Compound	Structural Formula	Reaction with Br_2	Thermodynamic Stabilization
1,3-Cyclopentadiene		Addition (0 ºC)	Slight
1,3,5-Cycloheptatriene		Addition (0 ºC)	Slight
1,3,5,7-Cyclooctatetraene		Addition (0 ºC)	Slight
Benzene		Substitution	Large
Pyridine		Substitution	Large

Furan		Substitution (0 ºC)	Moderate
Pyrrole		Substitution	Moderate

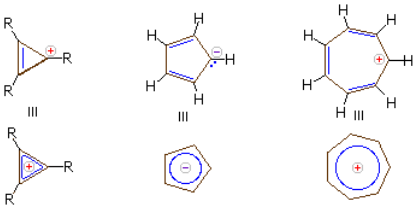
Benzene is the archetypical aromatic compound. It is planar, bond angles=120º, all carbon atoms in the ring are sp^2 hybridized, and the pi-orbitals are occupied by 6 electrons. The aromatic heterocycle pyridine is similar to benzene, and is often used as a weak base for scavenging protons. Furan and pyrrole have heterocyclic five-membered rings, in which the heteroatom has at least one pair of non-bonding valence shell electrons. By hybridizing this heteroatom to a sp2 state, a p-orbital occupied by a pair of electrons and oriented parallel to the carbon p-orbitals is created. The resulting planar ring meets the first requirement for aromaticity, and the π-system is occupied by 6 electrons, 4 from the two double bonds and 2 from the heteroatom, thus satisfying the Hückel Rule.



Four illustrative examples of aromatic compounds are shown above. The sp2 hybridized ring atoms are connected by brown bonds, the π-electron pairs and bonds that constitute the aromatic ring are colored blue. Electron pairs that are not part of the aromatic π-electron system are black. The first example is azulene, a blue-colored 10 π-electron aromatic hydrocarbon isomeric with naphthalene. The second and third compounds are heterocycles having aromatic properties. Pyridine has a benzene-like six-membered ring incorporating one nitrogen atom. The non-bonding electron pair on the nitrogen is not part of the aromatic π-electron sextet, and may bond to a proton or other electrophile without disrupting the aromatic system. In the case of thiophene, a sulfur analog of furan, one of the sulfur electron pairs (colored blue) participates in the aromatic ring π-electron conjugation. The last compound is imidazole, a heterocycle having two nitrogen atoms. Note that only one of the nitrogen non-bonding electron pairs is used for the aromatic π-electron sextet. The other electron pair (colored black) behaves similarly to the electron pair in pyridine.

Charged Aromatic Compounds

Carbanions and carbocations may also show aromatic stabilization. Some examples are:



The three-membered ring cation has 2 π-electrons and is surprisingly stable, considering its ring strain. Cyclopentadiene is as acidic as ethanol, reflecting the stability of its 6 π-electron conjugate base. Salts of cycloheptatrienyl cation (tropylium ion) are stable in water solution, again reflecting the stability of this 6 π-electron cation.

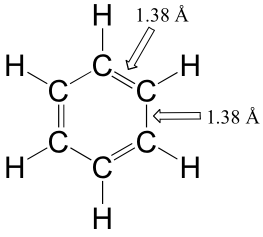
Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

15.9: What Is the Basis of Hückel's Rule?

Aromaticity

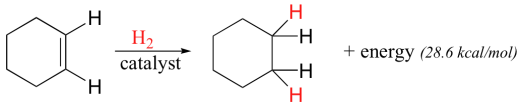
Molecular orbital theory is especially helpful in explaining the unique properties of a class of compounds called aromatics. Benzene, a common organic solvent, is the simplest example of an aromatic compound.



benzene

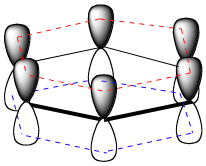
Although it is most often drawn with three double bonds and three single bonds, it is known that all of the carbon-carbon bonds in benzene are exactly the same length - 1.38 Å. This is shorter than a typical carbon-carbon single bond (about 1.54 Å), and slightly longer than a typical carbon-carbon double bond (about 1.34 Å).

In addition, the π bonds in benzene are significantly less reactive than isolated or conjugated π bonds in most alkenes. To illustrate this unique stability, we will make use of the idea of 'heat of hydrogenation'. The carbon-carbon double bond in an alkene can be converted to a single bond through a process called 'catalytic hydrogenation' –essentially adding a molecule of H_2 to the double bond.



We will learn more about how this process occurs, both in the laboratory and in living cells, later in the text (section 16.5). For now, what is important to understand is that the hydrogenation process is *exothermic*: the alkane is lower in energy than the alkene, so hydrogenating the double bond results in the release of energy in the form of heat. Converting one mole of cyclohexene to cyclohexane, for example, releases 28.6 kilocalories. If the benzene molecule is considered to be a six-membered ring with three isolated double bonds, the heat of hydrogenation should theoretically be three times this value, or 85.8 kcal/mol. The actual heat of hydrogenation of benzene, however, is only 49.8 kcal/mol, or 36 kcal/mol less than what we would expect if using the isolated double bond model. Something about the structure of benzene makes these π bonds especially stable. This 'something' has a name: it is called 'aromaticity'.

What exactly is this 'aromatic' property that makes the pbonds in benzene so much less reactive than those in alkenes? In a large part, the answer to this question lies in the fact that benzene is a *cyclic* molecule in which all of the ring atoms are sp^2-hybridized. This allows the π electrons to be delocalized in molecular orbitals that extend all the way around the ring, above and below the plane of the ring. For this to happen, of course, the ring must be planar – otherwise the $2p_z$ orbitals couldn't overlap properly. Benzene is indeed known to be a flat molecule.

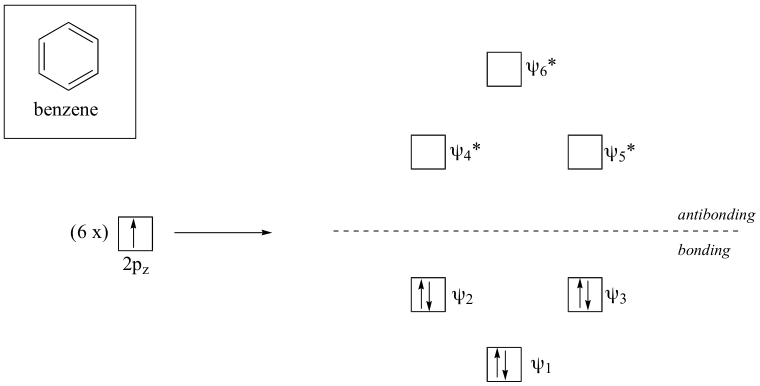


π electrons delocalized around the ring, above and below the plane

Do all cyclic molecules with alternating single and double bonds have this same aromatic stability? Quite simply, the answer is 'no'. The eight-membered cyclooctatetraene ring shown below is *not* flat, and its π bonds are much more reactive than those of benzene.

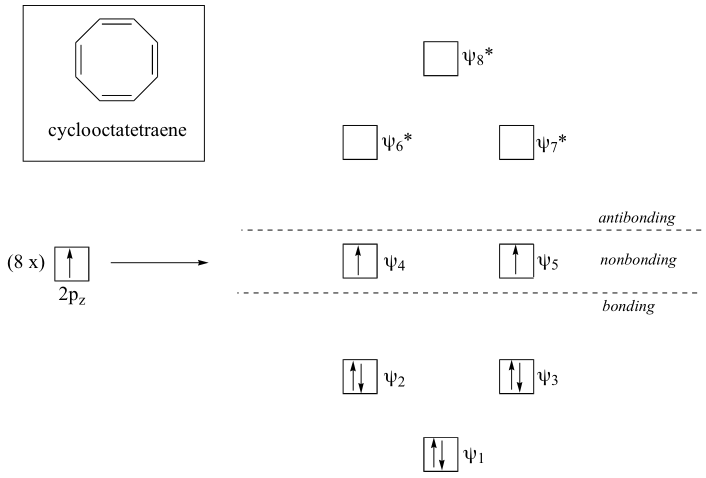
cyclooctatetraene

Clearly it takes something more to be aromatic, and this can best be explained with molecular orbital theory. Let's look at an energy diagram for the molecular orbitals containing the π electrons in benzene.



Quantum mechanical calculations conclude that the six molecular orbitals in benzene, formed from six atomic $2p_z$ orbitals, occupy four separate energy levels. Ψ_1 and Ψ_6* have unique energy levels, while the Ψ_2- Ψ_3 and Ψ_4*-Ψ_5* pairs are **degenerate** (more than one orbital at the same energy level). When we use the *aufbau* principle to fill up these orbitals with the six π electrons in benzene, we see that the bonding orbitals are completely filled, and the antibonding orbitals are empty. This gives us a good clue to the source of the special stability of benzene: a full set of bonding MO's is similar in many ways to the 'full shell' of electrons possessed by the very stable noble gases like helium, neon, and argon.

Now, let's do the same thing for cyclooctatetraene, which we have already learned is not aromatic.



The result of molecular orbital calculations tells us that the lowest and highest energy MOs (Ψ_1 and Ψ_8*) have unique energy levels, while the other six come in degenerate pairs. Notice that $\psi_4$and $\psi_5$are at the same energy level as the isolated $2p_z$ atomic orbitals: these are therefore neither bonding nor antibonding, rather they are referred to as **nonbonding MOs**. Filling up the MOs with the eight π electrons in the molecule, we find that the last two electrons are unpaired and fall into the two degenerate nonbonding orbitals. Because we don't have a perfect filled shell of bonding MOs, our molecule is not aromatic. As a consequence, each of the double bonds in cyclooctatetraene acts more like an *isolated* double bond.

Here, then, are the conditions that must be satisfied for a molecule to be considered aromatic:

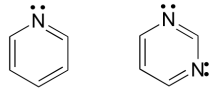
1. It must have a cyclic structure.
2. The ring must be planar.
3. Each atom in the ring must be sp^2-hybridized, so that π electrons can be delocalized around the ring.

4. The number of π electrons in the ring must be such that, in the ground state of the molecule, all bonding MOs are completely filled, and all nonbonding and antibonding MOs are completely empty.

It turns out that, in order to satisfy condition #4, the ring must contain a specific number of π electrons. The set of possible numbers is quite easy to remember - the rule is simply $4n+2$, where n is any positive integer (this is known as the **Hückel rule**, named after Erich Hückel, a German scientist who studied aromatic compounds in the 1930's). Thus, if $n = 0$, the first Hückel number is (4 x 0) + 2, or 2. If $n = 1$, the Hückel number is (4 x 1) + 2, or 6 (the Hückel number for benzene). The series continues with 10, 14, 18, 22, and so on. Cyclooctatetraene has eight π electrons, which is *not* a Hückel number. Because 6 is such a common Hückel number, chemists often use the term **'aromatic sextet'**.

Benzene is best visualized as a planar ring made up of carbon-carbon sbonds, with two 'donut-like' rings of fully delocalized π electron density above and below the plane of the ring (the fact that there is a ring of π electron density on *both* sides of the molecule stems from the fact that the overlapping *p* orbitals have two lobes, and the electron density is located in both). This general picture is valid not just for benzene but for all other aromatic structures as well.

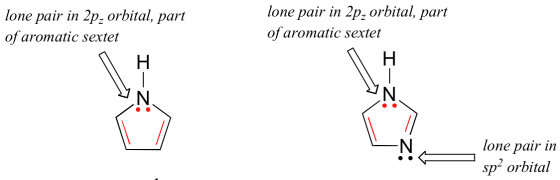
Let's look at some different aromatic compounds other than benzene. Pyridine and pyrimidine both fulfill all of the criteria for aromaticity.



pyridine pyrimidine

In both of these molecules, the nitrogen atoms are sp^2 hybridized, with the lone pair occupying an sp^2 orbital and therefore not counted among the aromatic sextet. The Hückel number for both pyridine and pyrimidine is six.

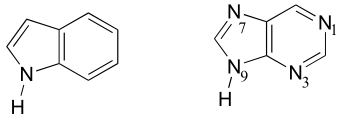
Rings do not necessarily need to be 6-membered in order to have six π electrons. Pyrrole and imidizole, for example, are both aromatic 5-membered rings with six π electrons.



pyrrole imidazole

The nitrogen atoms in both of these molecules are sp^2-hybridized (as they must be for the rings to be aromatic). In pyrrole, the lone pair can be thought of as occupying a $2p_z$ orbital, and thus both of these electrons contribute to the aromatic π system. In imidazole, one lone pair occupies a $2p_z$ orbital and is part of the aromatic sextet, while the second occupies one of the sp^2 orbitals and is not part of the sextet.

Molecules with more then one ring can also fulfill the Hückel criteria, and often have many of the same properties as monocyclic aromatic compounds, including a planar structure. Indole (a functional group in the amino acid tryptophan) and purine (a functional group in guanine and adenine DNA/RNA bases) both have a total of ten π electrons delocalized around two rings.

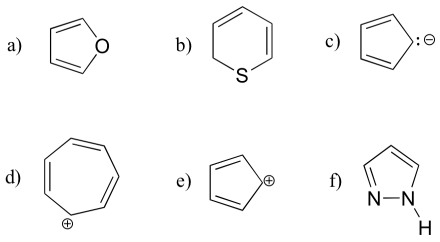


indole purine

The nitrogen in indole and the N_9 nitrogen in purine both contribute a pair of electrons to the π system. The N_1, N_3, and N_7 nitrogens of purine, in contrast, hold their lone pair in sp^2 orbitals, outside of the aromatic system.

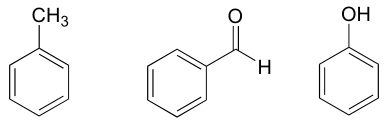
Example	

Exercise 2.2: Are the following molecules likely to be aromatic? Explain, using Huckel's criteria. and orbital drawings. Hint: Ions can also be aromatic!



Solution

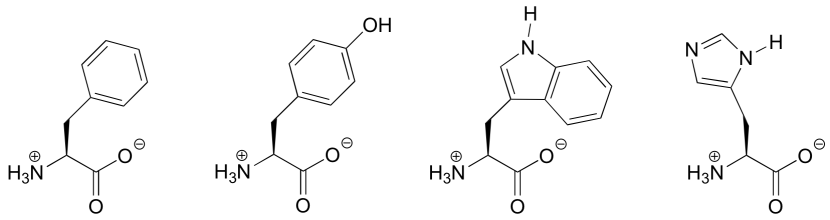
Up to now we have been talking about molecules in which the entire structure makes up an aromatic system. However, in organic chemistry we will more often encounter examples of molecules which have both aromatic *and* nonaromatic parts. Toluene, a common organic solvent (which is much safer to use than benzene) is simply a benzene ring with a methyl substituent. Benzyaldehyde is benzene with an aldehyde substituent, and phenol is benzene with a hydroxyl substituent.



toluene benzaldehyde phenol

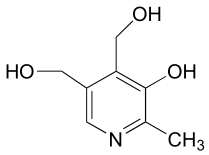
In these 'substituted benzene' compounds, the entire molecule is not aromatic, just the benzene ring part.

When a benzene ring is part of a larger molecule, it is called a 'phenyl' group. The amino acid phenylalanine, for example, contains a phenyl group. The amino acids tyrosine, tryptophan, and histidine contain phenol, indole, and imidazole groups, respectively.



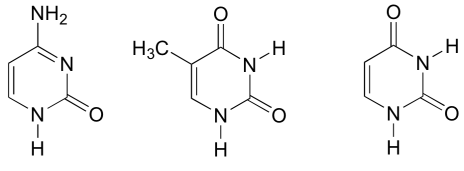
phenylalanine tyrosine tryptophan histidine

Pyridoxine, commonly known as vitamin B_6, is a substituted pyridine.

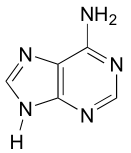


pyridoxine
(vitamin B_6)

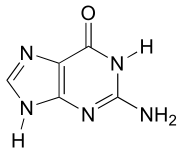
The DNA and RNA bases are based on pyrimidine (cytosine, thymine, and uracil) and purine (adenine and guanine).



cytosine thymine uracil



adenine



guanine

The flat, aromatic structure of these bases plays a critical role in the overall structure and function of DNA and RNA.

Contributors

- **Organic Chemistry With a Biological Emphasis** by Tim Soderberg (University of Minnesota, Morris)

15.10: The Inscribed Polygon Method for Predicting Aromaticity

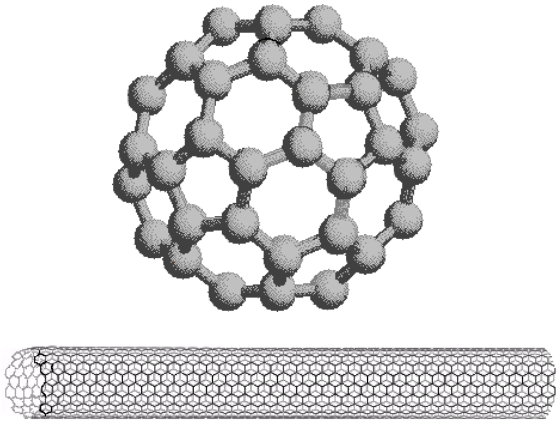
15.11: Buckminsterfullerene—Is It Aromatic?

If we extend the structure of corannulene by adding similar cycles of five benzene rings, the curvature of the resulting molecule should increase, and eventually close into a sphere of carbon atoms. The archetypical compound of this kind (C_{60}) has been named **buckminsterfullerene** because of its resemblance to the geodesic structures created by Buckminster Fuller. It is a member of a family of similar carbon structures that are called **fullerenes**. These materials represent a third class of carbon allotropes. Alternating views of the C_{60} fullerene structure are shown on the right, together with a soccer ball-like representation of the 12 five and 20 six-membered rings composing its surface. Precise measurement by Atomic Force Microscopy (AFM) has shown that the C-C bond lengths of the six-membered rings are not all equal, and depend on whether the ring is fused to a five or six-membered beighbor. By clicking on this graphic, a model of C_{60} will be displayed.

Although C_{60} is composed of fused benzene rings its chemical reactivity resembles that of the cycloalkenes more than benzene. Indeed, exposure to light and oxygen slowly degrade fullerenes to cage opened products. Most of the reactions thus far reported for C_{60} involve addition to, rather than substitution of, the core structure. These reactions include hydrogenation, bromination and hydroxylation. Strain introduced by the curvature of the surface may be responsible for the enhanced reactivity of C_{60}.

. Larger fullerenes, such as C_{70}, C_{76}, C_{82} & C_{84}have ellipsoidal or distorted spherical structures, and fullerene-like assemblies up to C_{240} have been detected. A fascinating aspect of these structures is that the space within the carbon cage may hold atoms, ions or small molecules. Such species are called **endohedral fullerenes**. The cavity of C_{60} is relatively small, but encapsulated helium, lithium and atomic nitrogen compounds have been observed. Larger fullerenes are found to encapsulate lanthanide metal atoms.

Interest in the fullerenes has led to the discovery of a related group of carbon structures referred to as nanotubes. As shown in the following illustration, nanotubes may be viewed as rolled up segments of graphite. The chief structural components are six-membered rings, but changes in tube diameter, branching into side tubes and the capping of tube ends is accomplished by fusion with five and seven-membered rings. Many interesting applications of these unusual structures have been proposed.



CHAPTER OVERVIEW

16: Electrophilic Aromatic Substitution

Topic hierarchy

16.1: Limitations on Electrophilic Substitution Reactions with Substituted Benzenes

Over reaction of Aniline and Phenol

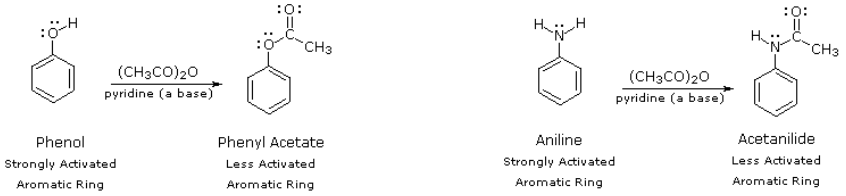
The strongest activating and ortho/para-directing substituents are the amino (-NH_2) and hydroxyl (-OH) groups. Direct nitration of phenol (hydroxybenzene) by dilute nitric acid gives modest yields of nitrated phenols and considerable oxidative decomposition to tarry materials; aniline (aminobenzene) is largely destroyed. Bromination of both phenol and aniline is difficult to control, with di- and tri-bromo products forming readily. Because of their high nucleophilic reactivity, aniline and phenol undergo substitution reactions with iodine, a halogen that is normally unreactive with benzene derivatives. The mixed halogen iodine chloride (ICl) provides a more electrophilic iodine moiety, and is effective in iodinating aromatic rings having less powerful activating substituents.

$C_6H_5–NH_2 + I_2 + NaHCO_3$		⟶	p-I–C_6H_4–NH_2 + NaI + CO_2 + H_2O

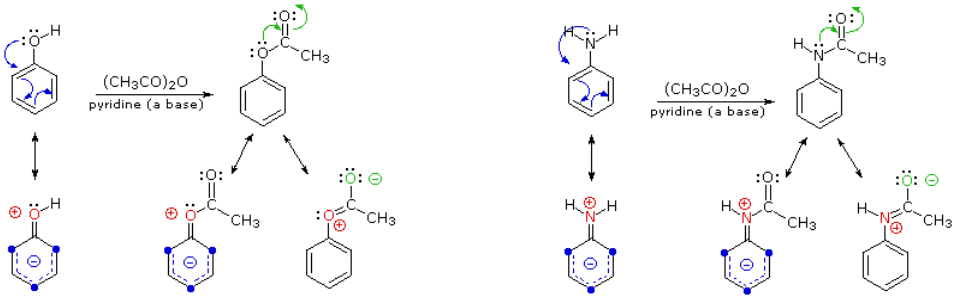
By acetylating the heteroatom substituent on phenol and aniline, its activating influence can be substantially attenuated. For example, acetylation of aniline gives acetanilide (first step in the following equation), which undergoes nitration at low temperature, yielding the para-nitro product in high yield. The modifying acetyl group can then be removed by acid-catalyzed hydrolysis (last step), to yield para-nitroaniline. Although the activating influence of the amino group has been reduced by this procedure, the acetyl derivative remains an ortho/para-directing and activating substituent.

$C_6H_5–NH_2 + (CH_3CO)_2O$	pyridine (a base)	$C_6H_5–NHCOCH_3$	HNO_3 , 5 ºC ⟶	p-$O_2N–C_6H_4–NHCOCH_3$	$H_3O^{(+)}$ & heat	p-$O_2N–C_6H_4–NH$

The following diagram illustrates how the acetyl group acts to attenuate the overall electron donating character of oxygen and nitrogen. The non-bonding valence electron pairs that are responsible for the high reactivity of these compounds (blue arrows) are diverted to the adjacent carbonyl group (green arrows). However, the overall influence of the modified substituent is still activating



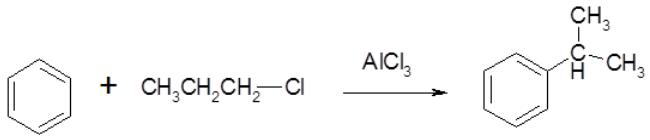
and ortho/para-directing.



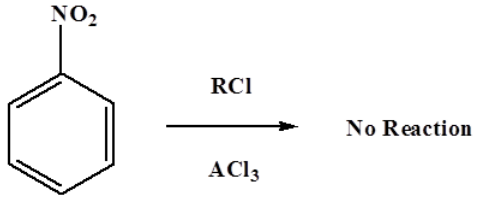
Some limitations of Friedel-Crafts Alkylation

There are possibilities of carbocation rearrangements when you are trying to add a carbon chain greater than two carbons. The rearrangements occur due to hydride shifts and methyl shifts. For example, the product of a Friedel-Crafts Alkylation will show an

iso rearrangement when adding a three carbon chain as a substituent. One way to resolve these problems is through Friedel-Crafts Acylation.



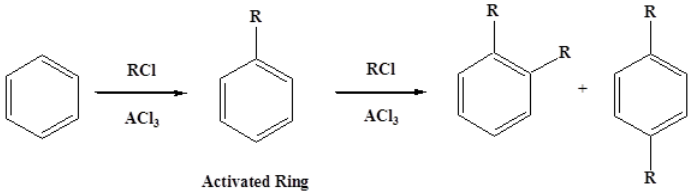
Also, the reaction will only work if the ring you are adding a substituent to is not deactivated. Friedel-Crafts fails when used with compounds such as nitrobenzene and other strong deactivating systems.



Friedel-Crafts reactions cannot be preformed then the aromatic ring contains a NH_2, NHR, or NR_2 substituent. The lone pair electrons on the amines react with the Lewis acid $AlCl_3$. This places a positive charge next to the benzene ring, which is so strongly activating that the Friedel-Crafts reaction cannot occur.

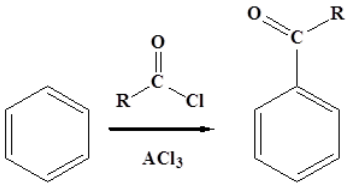
The positive charge strongly deactivates the benzene ring

Lastly, Friedel-Crafts alkylation can undergo polyalkylation. The reaction adds an electron donating alkyl group, which activates the benzene ring to further alkylation.



Activated Ring

This problem does not occure during Friedel-Crafts Acylation because an acyl group is deactivating. The prevents further actylations.



Dectivated Ring

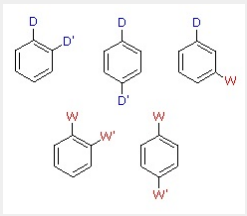
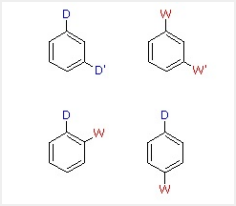
Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)

16.2: Disubstituted Benzenes

Orientational Interaction of Substituents

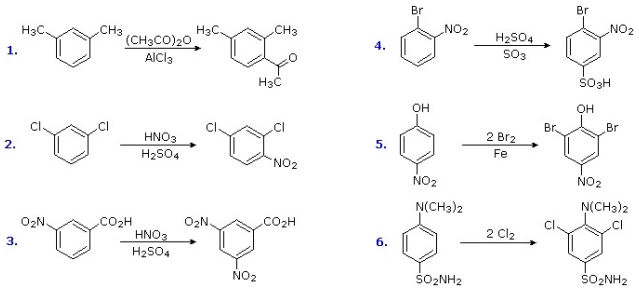
When a benzene ring has two substituent groups, each exerts an influence on subsequent substitution reactions. The activation or deactivation of the ring can be predicted more or less by the sum of the individual effects of these substituents. The site at which a new substituent is introduced depends on the orientation of the existing groups and their individual directing effects. We can identify two general behavior categories, as shown in the following table. Thus, the groups may be oriented in such a manner that their directing influences act in concert, reinforcing the outcome; or are opposed (antagonistic) to each other. Note that the orientations in each category change depending on whether the groups have similar or opposite individual directing effects.

Antagonistic or Non-Cooperative	**Reinforcing or Cooperative**
	

D = Electron Donating Group (ortho/para-directing)
W = Electron Withdrawing Group (meta-directing)

Reinforcing or Cooperative Substitutions

The products from substitution reactions of compounds having a reinforcing orientation of substituents are easier to predict than those having antagonistic substituents. For example, the six equations shown below are all examples of reinforcing or cooperative directing effects operating in the expected manner. Symmetry, as in the first two cases, makes it easy to predict the site at which substitution is likely to occur. Note that if two different sites are favored, substitution will usually occur at the one that is least hindered by ortho groups.

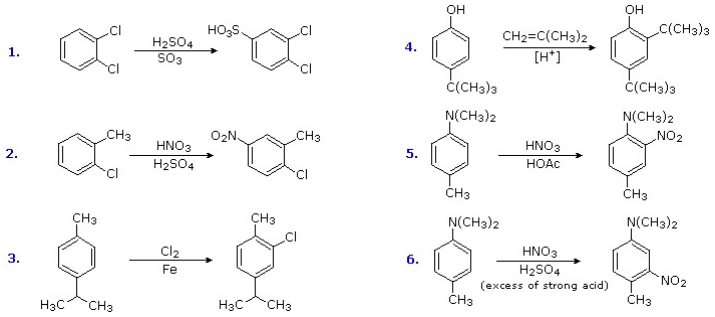


The first three examples have two similar directing groups in a meta-relationship to each other. In examples 4 through 6, oppositely directing groups have an ortho or para-relationship. The major products of electrophilic substitution, as shown, are the sum of the individual group effects. The strongly activating hydroxyl (–OH) and amino ($–NH_2$) substituents favor dihalogenation in examples 5 and six.

Antagonistic or Non-Cooperative Substitutions

Substitution reactions of compounds having an antagonistic orientation of substituents require a more careful analysis. If the substituents are identical, as in example 1 below, the symmetry of the molecule will again simplify the decision. When one substituent has a pair of non-bonding electrons available for adjacent charge stabilization, it will normally exert the product

determining influence, examples 2, 4 & 5, even though it may be overall deactivating (case 2). Case 3 reflects a combination of steric hindrance and the superior innate stabilizing ability of methyl groups relative to other alkyl substituents. Example 6 is interesting in that it demonstrates the conversion of an activating ortho/para-directing group into a deactivating meta-directing "onium" cation [–$NH(CH_3)_2^{(+)}$] in a strong acid environment.



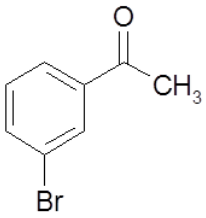
Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

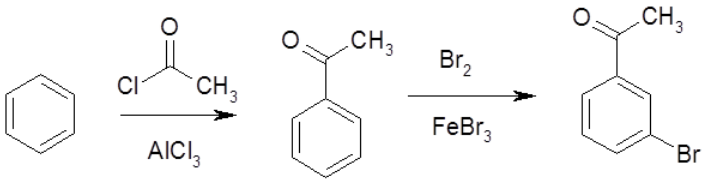
16.3: Synthesis of Benzene Derivatives

When we synthesize benzene derivatives with two or more substituents the effect of directing groups must be taken into account. Often the order of reactions can change the products produced.

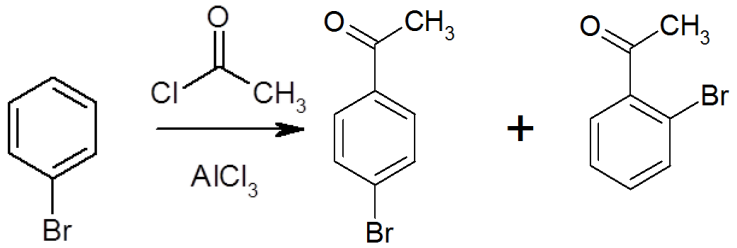
From benzene synthesize:



Two reactions an acylation and a bromination. In this case the two substituents are meta to each other. This means that the effects of a meta directing groups must be utilized. Of the two reactions the acylation puts a meta director on the benzene ring. The means the acylation need to come first.



If the reaction is reversed an ortho/para directing bromine is added first. The end products are different.

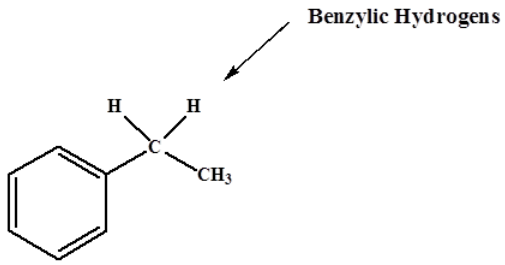


Contributors

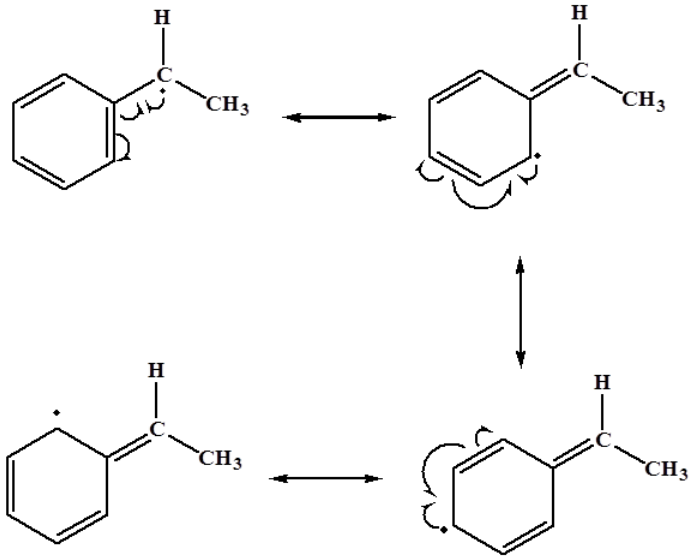
- Prof. Steven Farmer (Sonoma State University)

16.4: Halogenation of Alkyl Benzenes

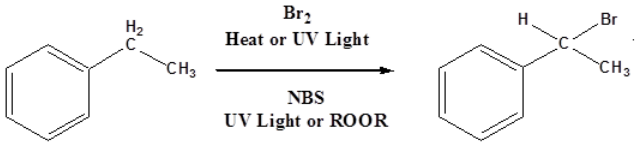
The benzylic C-H bonds weaker than most sp^3 hybridized C-H. This is because the radical formed from homolysis is resonance stabilized.



Resonance stabilization of the benzylic radical

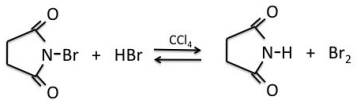


Because of the weak C-H bonds, benzylic hydrogens can form benzylic halides under radical conditions.



NBS as a Bromine Source

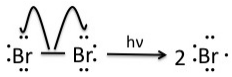
NBS (N-bromosuccinimide) is the most commonly used reagent to produce low concentrations of bromine. When suspended in tetrachloride (CCl_4), NBS reacts with trace amounts of HBr to produce a low enough concentration of bromine to facilitate the allylic bromination reaction.



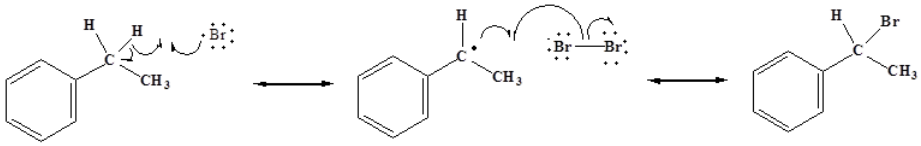
Allylic Bromination Mechanism

Step 1: Initiation

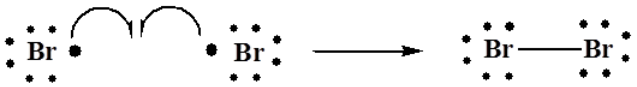
Once the pre-initiation step involving NBS produces small quantities of Br_2, the bromine molecules are homolytically cleaved by light to produce bromine radicals.



Step 2 and 3: Propagation



Step 4: Termination



Contributors

- Prof. Steven Farmer (Sonoma State University)

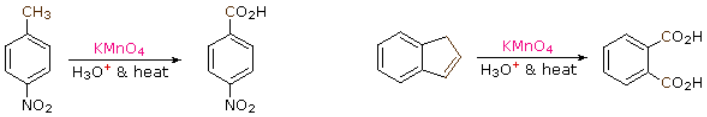
16.5: Oxidation and Reduction of Substituted Benzenes

Oxidation of Alkyl Side-Chains

The benzylic hydrogens of alkyl substituents on a benzene ring are activated toward free radical attack, as noted earlier. Furthermore, , and E1 reactions ofbenzylic halides, show enhanced reactivity, due to the adjacent aromatic ring. The possibility that these observations reflect a general benzylic activation is supported by the susceptibility of alkyl side-chains to oxidative degradation, as shown in the following examples (the oxidized side chain is colored). Such oxidations are normally effected by hot acidic pemanganate solutions, but for large scale industrial operations catalyzed air-oxidations are preferred. Interestingly, if the benzylic position is completely substituted this oxidative degradation does not occur (second equation, the substituted benzylic carbon is colored blue).

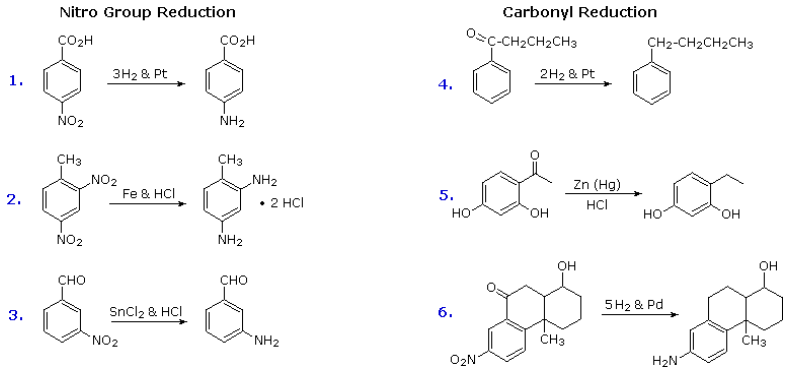
$C_6H_5–CH_2CH_2CH_2CH_3 + KMnO_4 + H_3O^{(+)}$ & heat	$C_6H_5–CO_2H + CO_2$
p-$(CH_3)_3C–C_6H_4–CH_3 + KMnO_4 + H_3O^{(+)}$ & heat	p-$(CH_3)_3C–C_6H_4–CO_2H$

These equations are not balanced. The permanganate oxidant is reduced, usually to Mn(IV) or Mn(II). Two other examples of this reaction are given below, and illustrate its usefulness in preparing substituted benzoic acids.



Reduction of Nitro Groups and Aryl Ketones

Electrophilic nitration and Friedel-Crafts acylation reactions introduce deactivating, meta-directing substituents on an aromatic ring. The attached atoms are in a high oxidation state, and their reduction converts these electron withdrawing functions into electron donating amino and alkyl groups. Reduction is easily achieved either by catalytic hydrogenation (H2 + catalyst), or with reducing metals in acid. Examples of these reductions are shown here, equation 6 demonstrating the simultaneous reduction of both functions. Note that the butylbenzene product in equation 4 cannot be generated by direct Friedel-Crafts alkylation due to carbocation rearrangement. The zinc used in ketone reductions, such as 5, is usually activated by alloying with mercury (a process known as amalgamation).



Several alternative methods for reducing nitro groups to amines are known. These include zinc or tin in dilute mineral acid, and sodium sulfide in ammonium hydroxide solution. The procedures described above are sufficient for most cases.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

16.6: Multistep Synthesis

From benzene make *m*-bromoaniline:

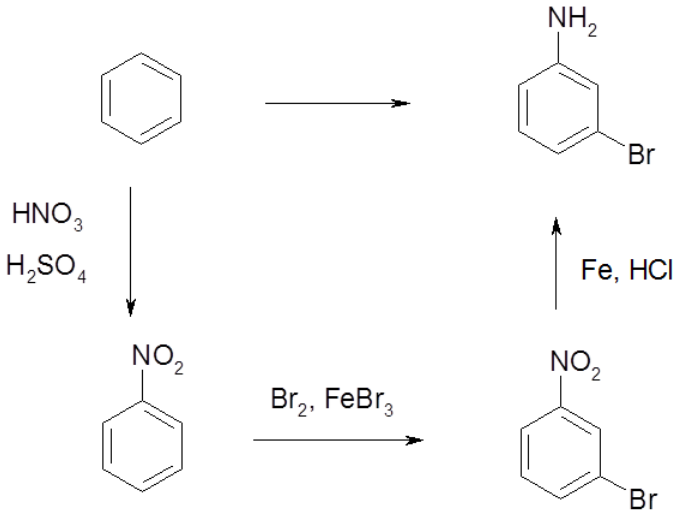
In this reaction three reactions are required.

1) A nitration

2) A conversion from the nitro group to an amine

3) A bromination

Because the end product is meta a meta directing group must be utilized. Of the nitro, bromine, and amine group, only the nitro group is meta direction. This means that the first step need to be the nitration and not the bromination. Also, the conversion of the nitro group to an amine must occur last because the amine group is ortho/para direction.



From benzene make *p*-nitropropylbenzene

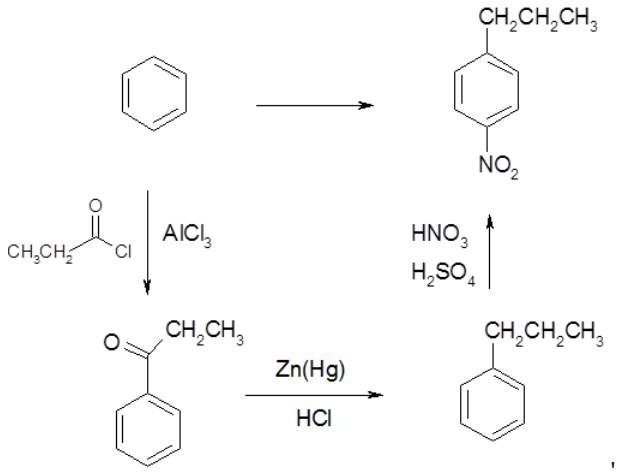
In this reaction three reactions are required.

1) A Friedel Crafts acylation

2) A conversion from the acyl group to an alkane

3) A nitration

Because the propyl group has more than two carbons, it must be added in two steps. A Friedel Crafts acylation followed by a Clemmensen Reduction. Remeber that Friedel Crafts reactions are hindered if the benzene ring is strongly deactivated. This means that the acyl group must go on first. Because the end product is para a para directing group must be utilized. Of the nitro, acyl, and alkane group, only the alkane group is meta direction. This means that the acyl group must be converted to an alkane prior to the nitration step.



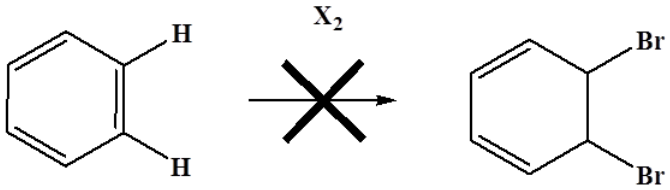
Contributors

- Prof. Steven Farmer (Sonoma State University)

16.7: Electrophilic Aromatic Substitution

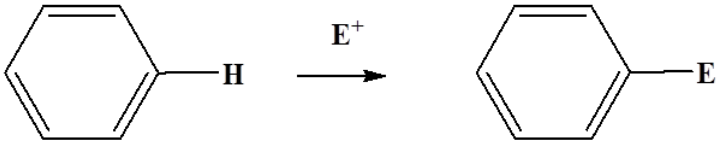
Bensene contains six pi electrons which are delocalized in six p orbitals above and below the plane of the benzene ring.

The six pi electrons obey Huckel's rule so benzene is especially stable. This means that the aromatic ring want to be retained during reactions. Because of this benzene does not undergo addition like other unsaturated hydrocarbons.



Non-Aromatic

Benzene can undergo electrophilic aromatic substitution because aromaticity is maintained.



Product is Aromatic

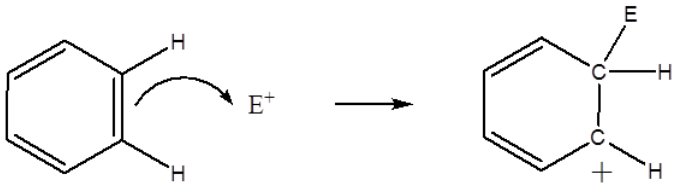
Contributors

- Prof. Steven Farmer (Sonoma State University)

16.8: The General Mechanism

The General Mechanism

Step 1 (Slow)



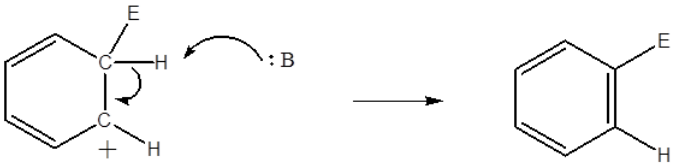
Arenium Ion

The e- in the pi bond attacks the electrophile

One carbon gets a positive charge the other forms a C-E bond

This forms the arenium ion.
The arenium ion is conjugated but not aromatic.

Step 2 (Fast)

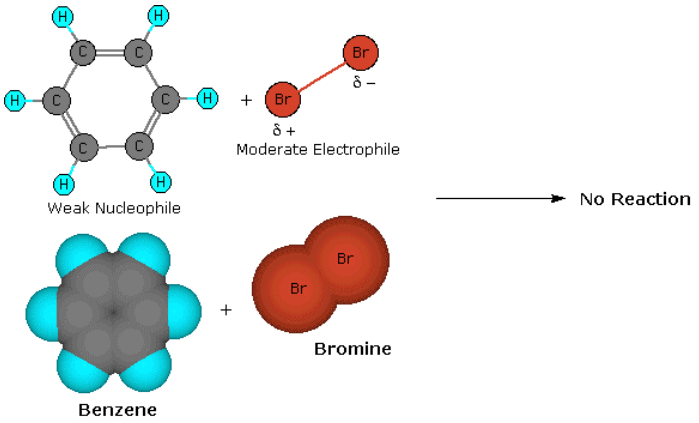


The LPE on a base attacks the hydrogen.

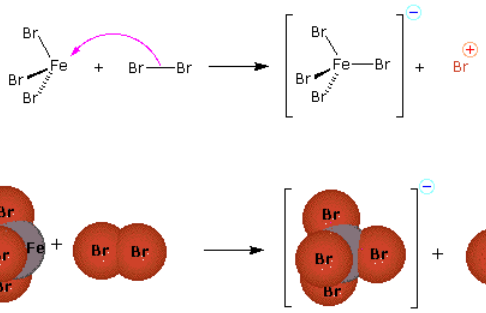
This causes the e- in the C-H bond to form a C-C double bond and aromaticity is reformed

A Detailed discussion of the Mechanism for Electrophilic Substitution Reactions of Benzene

A two-step mechanism has been proposed for these electrophilic substitution reactions. In the first, slow or rate-determining, step the electrophile forms a sigma-bond to the benzene ring, generating a positively charged **benzenonium intermediate**. In the second, fast step, a proton is removed from this intermediate, yielding a substituted benzene ring. The following four-part illustration shows this mechanism for the bromination reaction. Also, an animated diagram may be viewed.

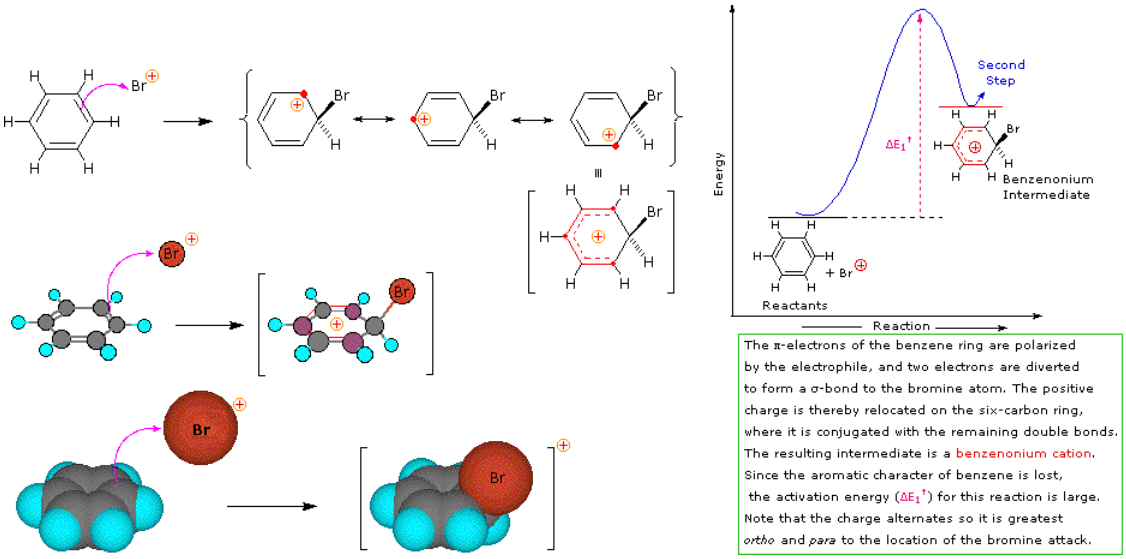


The bromine molecule is polarized so that one end is electrophilic and the other nucleophilic. Although the electrophilic end reacts easily with simple alkenes and dienes, it fails to react with the more stable and weaker nucleophilic π-electron system of benzene.

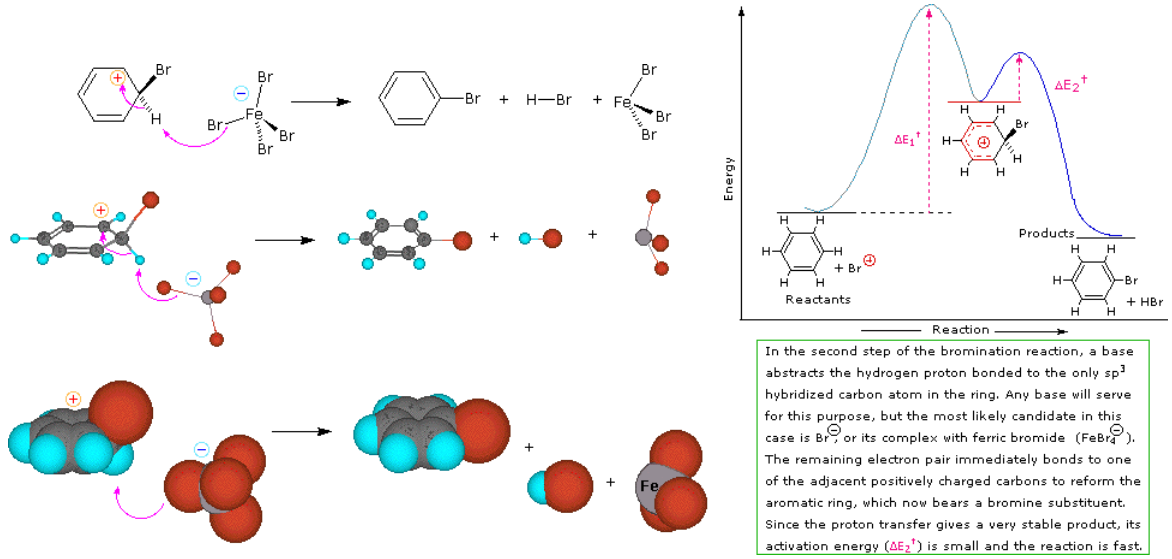


Ferric bromide and other Lewis acids enhance the electrophilic strength of bromine by forming a complex anion, in this case $FeBr_4^{\ominus}$. At the same time, this complexation creates the strongly electrophilic bromine cation, which reacts with nucleophiles.

Preliminary step: Formation of the strongly electrophilic bromine cation



Step 1: The electrophile forms a sigma-bond to the benzene ring, generating a positively charged benzenonium intermediate



Step 2: A proton is removed from this intermediate, yielding a substituted benzene ring

This mechanism for electrophilic aromatic substitution should be considered in context with other mechanisms involving carbocation intermediates. These include S_N1 and E1 reactions of alkyl halides, and Brønsted acid addition reactions of alkenes.

To summarize, when carbocation intermediates are formed one can expect them to react further by one or more of the following modes:

1. The cation may bond to a nucleophile to give a substitution or addition product.
2. The cation may transfer a proton to a base, giving a double bond product.
3. The cation may rearrange to a more stable carbocation, and then react by mode #1 or #2.

S_N1 and E1 reactions are respective examples of the first two modes of reaction. The second step of alkene addition reactions proceeds by the first mode, and any of these three reactions may exhibit molecular rearrangement if an initial unstable carbocation is formed. The carbocation intermediate in electrophilic aromatic substitution (the benzenonium ion) is stabilized by charge delocalization (resonance) so it is not subject to rearrangement. In principle it could react by either mode 1 or 2, but the energetic advantage of reforming an aromatic ring leads to exclusive reaction by mode 2 (*ie.* proton loss).

Other Examples of Electophilic Aromatic Substitution

Many other substitution reactions of benzene have been observed, the five most useful are listed below (chlorination and bromination are the most common halogenation reactions). Since the reagents and conditions employed in these reactions are electrophilic, these reactions are commonly referred to as **Electrophilic Aromatic Substitution**. The catalysts and co-reagents serve to generate the strong electrophilic species needed to effect the initial step of the substitution. The specific electrophile believed to function in each type of reaction is listed in the right hand column.

Reaction Type	Typical Equation				Electrophile $E^{(+)}$
Halogenation:	C_6H_6	+ Cl_2 & heat $FeCl_3$ catalyst	———>	C_6H_5Cl + HCl Chlorobenzene	$Cl^{(+)}$ or $Br^{(+)}$
Nitration:	C_6H_6	+ HNO_3 & heat H_2SO_4 catalyst	———>	$C_6H_5NO_2$ + H_2O Nitrobenzene	$NO_2^{(+)}$
Sulfonation:	C_6H_6	+ H_2SO_4 + SO_3 & heat	———>	$C_6H_5SO_3H$ + H_2O Benzenesulfonic acid	$SO_3H^{(+)}$
Alkylation: Friedel-Crafts	C_6H_6	+ R-Cl & heat $AlCl_3$ catalyst	———>	C_6H_5-R + HCl An Arene	$R^{(+)}$

Acylation: Friedel-Crafts	C_6H_6	+ RCOCl & heat $AlCl_3$ catalyst	———>	C_6H_5COR + HCl An Aryl Ketone	$RCO^{(+)}$

Contributors

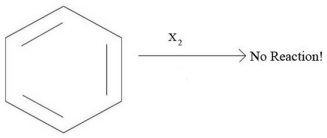
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

16.9: Halogenation

Halogenation is an example of electrophillic aromatic substitution. In electrophilic aromatic substitutions, a benzene is attacked by an electrophile which results in substition of hydrogens. However, halogens are not electrophillic enough to break the aromaticity of benzenes, which require a catalyst to activate.

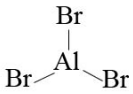
Activation of Halogen

(where X= Br or Cl, we will discuss further in detail later why other members of the halogen family Flourine and Iodine are not used in halogenation of benzenes)

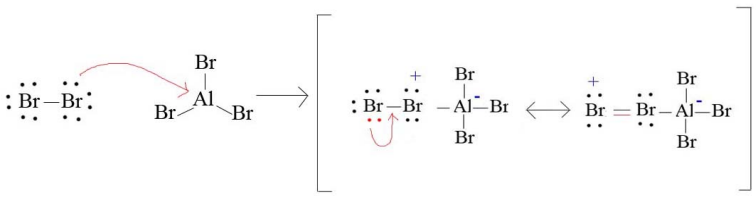


Hence, Halogen needs the help and aid of Lewis Acidic Catalysts to activate it to become a very strong electrophile. Examples of these activated halogens are Ferric Hallides (FeX_3) Aluminum Halides (AlX_3) where X= Br or Cl. In the following examples, the halogen we will look at is Bromine.

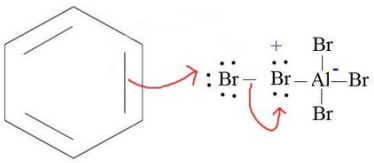
In the example of bromine, in order to make bromine electrophillic enough to react with benzene, we use the aid of an aluminum halide such as aluminum bromide.

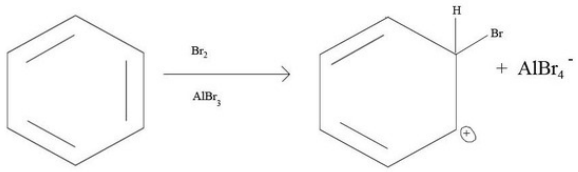


With aluminum bromide as a Lewis acid, we can mix Br_2 with $AlBr_3$ to give us Br^+. The presence of Br^+ is a much better electrophile than Br_2 alone. Bromination is acheived with the help of $AlBr_3$ (Lewis acid catalysts) as it polarizes the Br-Br bond. The polarization causes polarization causes the bromine atoms within the Br-Br bond to become more electrophillic. The presence of Br^+ compared to Br_2 alone is a much better electrophille that can then react with benzene.

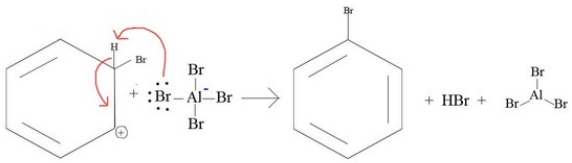


As the bromine has now become more electrophillic after activation of a catalyst, an electrophillic attack by the benzene occurs at the terminal bromine of Br-Br-$AlBr_3$. This allows the other bromine atom to leave with the $AlBr_3$ as a good leaving group, $AlBr_4$-.





After the electrophilic attack of bromide to the benzene, the hydrogen on the same carbon as bromine substitutes the carbocation in which resulted from the attack. Hence it being an electrophilic aromatic SUBSTITUTION. Since the by-product aluminum tetrabromide is a strong nucleophile, it pulls of a proton from the Hydrogen on the same carbon as bromine.



In the end, $AlBr_3$was not consumed by the reaction and is regenerated. It serves as our catalyst in the halogenation of benzenes.

Dissociation Energies of Halogens and its Effect on Halogenation of Benzenes

The electrophillic bromination of benzenes is an exothermic reaction. Considering the exothermic rates of aromatic halogenation decreasing down the periodic table in the Halogen family, Flourination is the most exothermic and Iodination would be the least. Being so exothermic, a reaction of flourine with benzene is explosive! For iodine, electrophillic iodination is generally endothermic, hence a reaction is often not possible. Similar to bromide, chlorination would require the aid of an activating presence such as Alumnium Chloride or Ferric Chloride. The mechanism of this reaction is the same as with Bromination of benzene.

Outside links

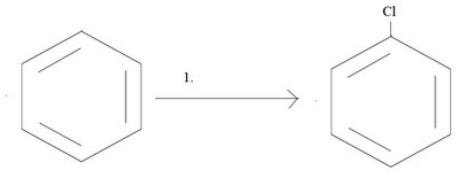
- http://www.chemguide.co.uk/mechanism...ogenation.html
- http://en.wikipedia.org/wiki/Electro...c_halogenation

References

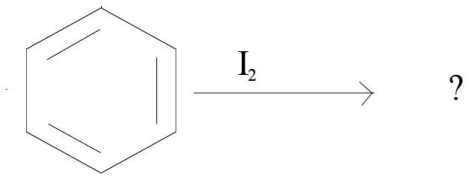
1. Vollhardt, Peter, and Neil Shore. Organic Chemistry: Structure and Function. 5th Edition. New York: W.H. Freeman and Company, 2007.

Problems

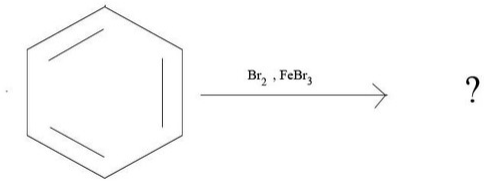
1. What reagents would you need to get the given product?



2. What product would result from the given reagents?



3. What is the major product given the reagents below?



4. Draw the formatin of Cl^+ from $AlCl_3$ and Cl_2

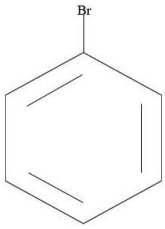
5. Draw the mechanism of the reaction between Cl^+ and a benzene.

Solutions

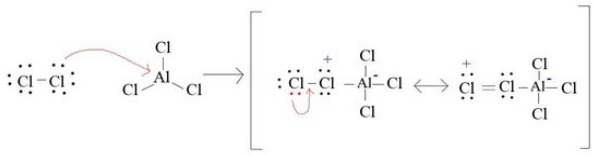
1. Cl_2 and AlCl3 or Cl_2 and $FeCl_3$

2. No Reaction

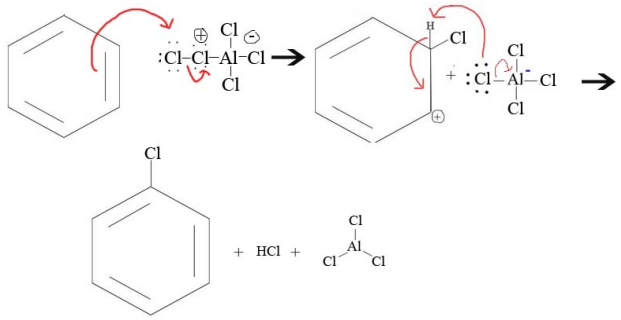
3.



4.



5.



Contributors

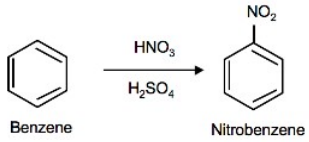
- Catherine Nguyen

16.10: Nitration and Sulfonation

Nitration and sulfonation of benzene are two examples of electrophilic aromatic substitution. The nitronium ion (NO_2^+) and sulfur trioxide (SO_3) are the electrophiles and individually react with benzene to give nitrobenzene and benzenesulfonic acid respectively.

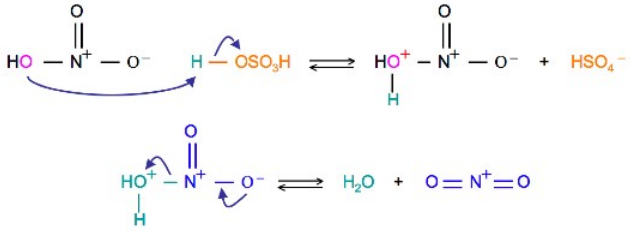
Nitration of Benzene

The source of the nitronium ion is through the protonation of nitric acid by sulfuric acid, which causes the loss of a water molecule and formation of a nitronium ion.



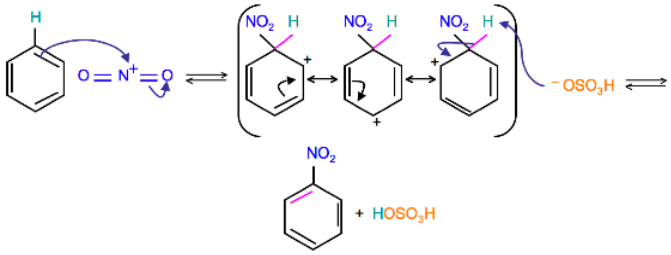
Sulfuric Acid Activation of Nitric Acid

The first step in the nitration of benzene is to activate $HNO_3$with sulfuric acid to produce a stronger electrophile, the nitronium ion.



Because the nitronium ion is a good electrophile, it is attacked by benzene to produce Nitrobenzene.

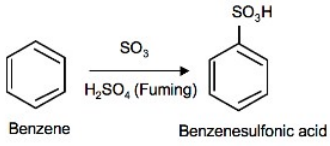
Mechanism



(Resonance forms of the intermediate can be seen in the generalized electrophilic aromatic substitution)

Sulfonation of Benzene

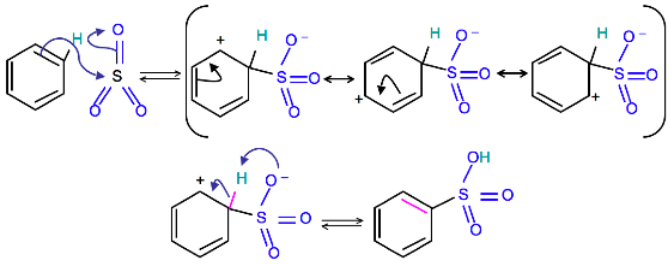
Sulfonation is a reversible reaction that produces benzenesulfonic acid by adding sulfur trioxide and fuming sulfuric acid. The reaction is reversed by adding hot aqueous acid to benzenesulfonic acid to produce benzene.



Mechanism

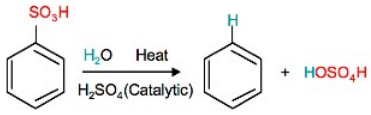
To produce benzenesulfonic acid from benzene, fuming sulfuric acid and sulfur trioxide are added. Fuming sulfuric acid, also refered to as *oleum*, is a concentrated solution of dissolved sulfur trioxide in sulfuric acid. The sulfur in sulfur trioxide is

electrophilic because the oxygens pull electrons away from it because oxygen is very electronegative. The benzene attacks the sulfur (and subsequent proton transfers occur) to produce benzenesulfonic acid.



Reverse Sulfonation

Sulfonation of benzene is a reversible reaction. Sulfur trioxide readily reacts with water to produce sulfuric acid and heat. Therefore, by adding heat to benzenesulfonic acid in diluted aqueous sulfuric acid the reaction is reversed.



Further Applications of Nitration and Sulfonation

Nitration is used to add nitrogen to a benzene ring, which can be used further in substitution reactions. The nitro group acts as a ring deactivator. Having nitrogen present in a ring is very useful because it can be used as a directing group as well as a masked amino group. The products of aromatic nitrations are very important intermediates in industrial chemistry.

Because sulfonation is a reversible reaction, it can also be used in further substitution reactions in the form of a directing blocking group because it can be easily removed. The sulfonic group blocks the carbon from being attacked by other substituents and after the reaction is completed it can be removed by reverse sulfonation. Benzenesulfonic acids are also used in the synthesis of detergents, dyes, and sulfa drugs. Bezenesulfonyl Chloride is a precursor to sulfonamides, which are used in chemotherapy.

Outside Links

Aromatic Sulfonation

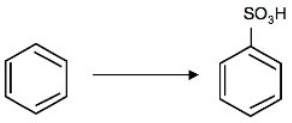
- Wikipedia: http://en.wikipedia.org/wiki/Aromatic_sulfonation
- Video: http://www.youtube.com/watch?v=s1qJ1...eature=related
- Interactive 3D Reaction: http://www.chemtube3d.com/Electrophi...20benzene.html

Aromatic Nitration

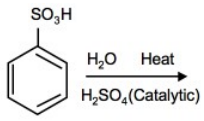
- Wikipedia: http://en.wikipedia.org/wiki/Nitration
- Video: http://www.youtube.com/watch?v=i7ucl...eature=related
- Interactive 3D Reaction: http://www.chemtube3d.com/Electrophi...20benzene.html

Problems

1. What is/are the required reagent(s)for the following reaction:



2. What is the product of the following reaction:



3. Why is it important that the nitration of benzene by nitric acid occurs in sulfuric acid?

4. Write a detailed mechanism for the sulfonation of benzene, including all resonance forms.

5. Draw an energy diagram for the nitration of benzene. Draw the intermediates, starting materials, and products. Label the transition states. (For questions 1 and 2 see Electrophilic Aromatic Substitution for hints)

For other problems involving Electrophilic Aromatic Substitution and similar reactions see:

- Electrophilic Aromatic Substitution
- Activating and Deactivating Benzene Rings
- Electrophilic Attack on Disubstituted Benzenes

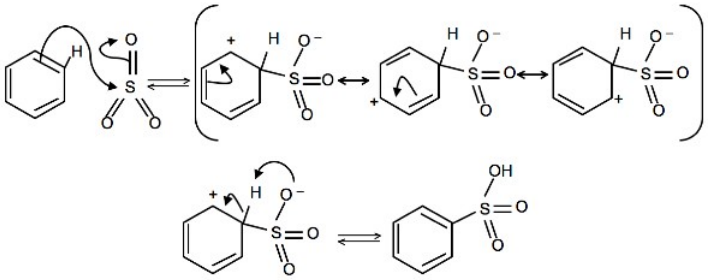
Solutions

1. SO_3 and H_2SO_4 (fuming)

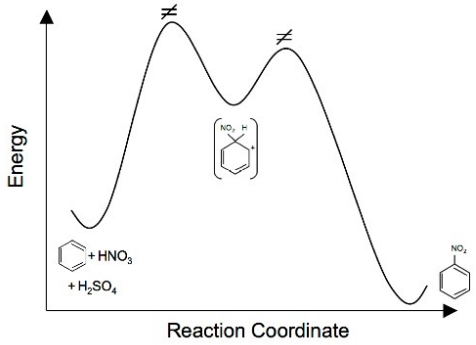
2.

3. Sulfuric acid is needed in order for a good electrophile to form. Sulfuric acid protonates nitric acid to form the nitronium ion (water molecule is lost). The nitronium ion is a very good electrophile and is open to attack by benzene. Without sulfuric acid the reaction would not occur.

4.



5.



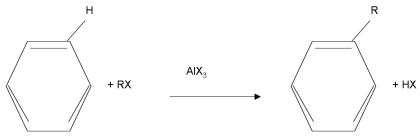
References

1. Laali, Kenneth K., and Volkar J. Gettwert. “Electrophilic Nitration of Aromatics in Ionic Liquid Solvents.” The Journal of Organic Chemistry 66 (Dec. 2000): 35-40. American Chemical Society.
2. Malhotra, Ripudaman, Subhash C. Narang, and George A. Olah. Nitration: Methods and Mechanisms. New York: VCH Publishers, Inc., 1989.
3. Sauls, Thomas W., Walter H. Rueggeberg, and Samuel L. Norwood. “On the Mechanism of Sulfonation of the Aromatic Nucleus and Sulfone Formation.” The Journal of Organic Chemistry 66 (1955): 455-465. American Chemical Society.
4. Vollhardt, Peter. Organic Chemistry : Structure and Function. 5th ed. Boston: W. H. Freeman & Company, 2007.

16.11: Friedel–Crafts Alkylation and Friedel–Crafts Acylation

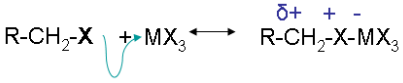
Friedel-Crafts Alkylation

Friedel-Crafts Alkylation was first discovered by French scientist Charles Friedel and his partner, American scientist James Crafts, in 1877. This reaction allowed for the formation of alkyl benzenes from alkyl halides, but was plagued with unwanted supplemental activity that reduced its efficiency.



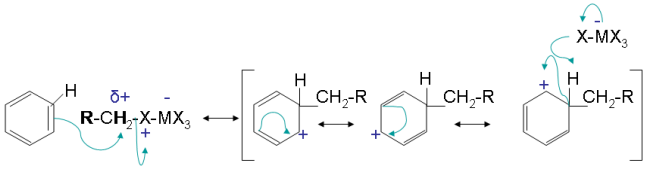
The mechanism takes place as follows:

Step one:



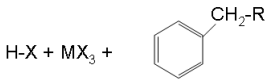
The first step creates a cabocation that acts as the electrophile in the reaction. This step activates the haloalkane. Secondary and teriary halides only form the free cabocation in the step.

Step two



The second step has an electrophilic attack on the benzene that results in multiple resonance forms. The halogen reactions with the intermediate and picks up the hydrogen to eliminate the positive charge.

Finish



The final step shown above is the results of the end of step and shows the final products.

The reactivity of haloalkanes increases as you move up the periodic table and increase polarity. This means that an RF haloalkane is most reactive followed by RCl then RBr and finally RI. This means that the Lewis acids used as catalysts in Friedel-Crafts Alkylation reactions tend have similar halogen combinations such as BF_3, $SbCl_5$, $AlCl_3$, $SbCl_5$, and $AlBr_3$, all of which are commonly used in these reactions.

Some limitations of Friedel-Crafts Alkylation

There are possibilities of carbocation rearrangements when you are trying to add a carbon chain greater than two carbons. The rearrangements occur due to hydride shifts and methyl shifts. For example, the product of a Friedel-Crafts Alkylation will show an iso rearrangement when adding a three carbon chain as a substituent. Also, the reaction will only work if the ring you are adding a substituent to is not deactivated. For a look at substituents that activating or deactivating Benzene Rings.

The three key limitations of Friedel-Crafts alkylation are:

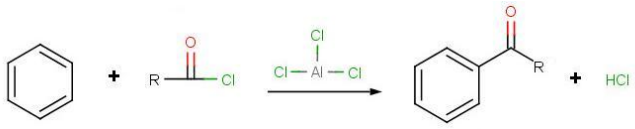
1. Carbocation Rearrangement - Only certain alkylbenzenes can be made due to the tendency of cations to rearrange.

2. **Compound Limitations** - Friedel-Crafts fails when used with compounds such as nitrobenzene and other strong deactivating systems.
3. **Polyalkylation** - Products of Friedel-Crafts are even more reactive than starting material. Alkyl groups produced in Friedel-Crafts Alkylation are electron-donating substituents meaning that the products are more susceptible to electrophilic attack than what we began with. For synthetic purposes, this is a big dissapointment.

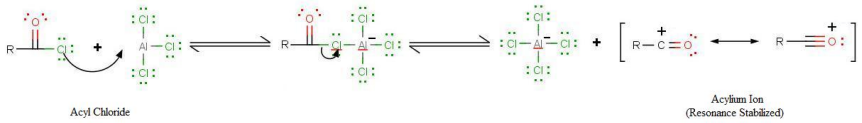
To remedy these limitations, a new and improved reaction was devised: The Friedel-Crafts Acylation. (also known as Friedel-Crafts Alkanoylation).

Friedel-Crafts Acylation

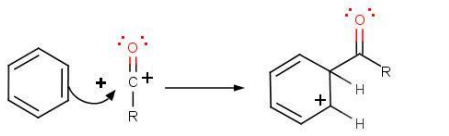
The goal of the reaction is the following:



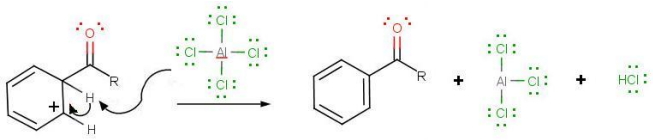
The very first step involves the formation of the acylium ion which will later react with benzene:



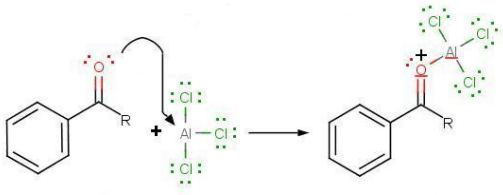
The second step involves the attack of the acylium ion on benzene as a new electrophile to form one complex:



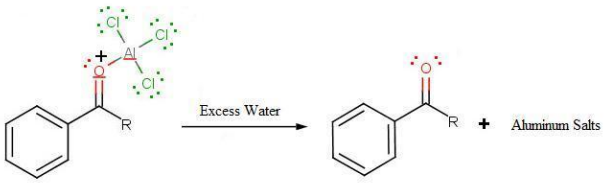
The third step involves the departure of the proton in order for aromaticity to return to benzene:



During the third step, $AlCl_4$ returns to remove a proton from the benzene ring, which enables the ring to return to aromaticity. In doing so, the original $AlCl_3$ is regenerated for use again, along with HCl. Most importantly, we have the first part of the final product of the reaction, which is a ketone. Thie first part of the product is the complex with aluminum chloride as shown:



The final step involves the addition of water to liberate the final product as the acylbenzene:

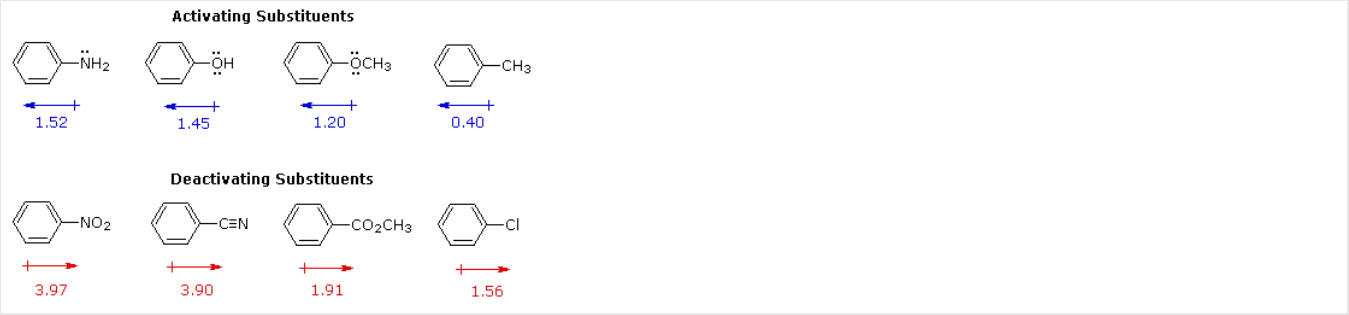


Because the acylium ion (as was shown in step one) is stabilized by resonance, no rearrangement occurs (Limitation 1). Also, because of of the deactivation of the product, it is no longer susceptible to electrophilic attack and hence, is no longer susceptible to electrophilic attack and hence, no longer goes into further reactions (Limitation 3). However, as not all is perfect, Limitation 2 still prevails where Friedel-Crafts Acylation fails with strong deactivating rings.

16.12: Substituted Benzenes

When substituted benzene compounds undergo electrophilic substitution reactions of the kind discussed above, **two related features must be considered:**

I. The first is the relative reactivity of the compound compared with benzene itself. Experiments have shown that substituents on a benzene ring can influence reactivity in a profound manner. For example, a hydroxy or methoxy substituent increases the rate of electrophilic substitution about ten thousand fold, as illustrated by the case of anisole in the virtual demonstration (above). In contrast, a nitro substituent decreases the ring's reactivity by roughly a million. This **activation** or **deactivation** of the benzene ring toward electrophilic substitution may be correlated with the electron donating or electron withdrawing influence of the substituents, as measured by molecular dipole moments. In the following diagram we see that electron donating substituents (blue dipoles) activate the benzene ring toward electrophilic attack, and electron withdrawing substituents (red dipoles) deactivate the ring (make it less reactive to electrophilic attack).

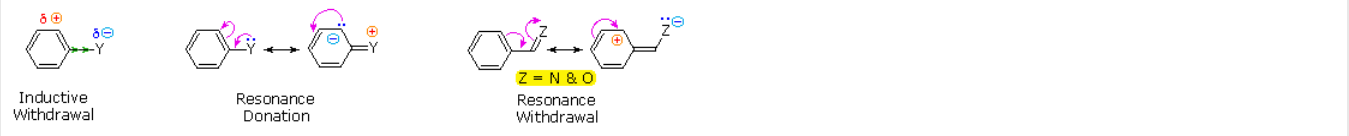


The influence a substituent exerts on the reactivity of a benzene ring may be explained by the interaction of two effects:

The first is the **inductive effect** of the substituent. Most elements other than metals and carbon have a significantly greater electronegativity than hydrogen. Consequently, substituents in which nitrogen, oxygen and halogen atoms form sigma-bonds to the aromatic ring exert an inductive electron withdrawal, which deactivates the ring (left-hand diagram below).

The second effect is the result of **conjugation** of a substituent function with the aromatic ring. This conjugative interaction facilitates electron pair donation or withdrawal, to or from the benzene ring, in a manner different from the inductive shift. If the atom bonded to the ring has one or more non-bonding valence shell electron pairs, as do nitrogen, oxygen and the halogens, electrons may flow into the aromatic ring by p-π conjugation (resonance), as in the middle diagram. Finally, polar double and triple bonds conjugated with the benzene ring may withdraw electrons, as in the right-hand diagram. Note that in the resonance examples all the contributors are not shown. In both cases the charge distribution in the benzene ring is greatest at sites ortho and para to the substituent.

In the case of the nitrogen and oxygen activating groups displayed in the top row of the previous diagram, electron donation by resonance dominates the inductive effect and these compounds show exceptional reactivity in electrophilic substitution reactions. Although halogen atoms have non-bonding valence electron pairs that participate in p-π conjugation, their strong inductive effect predominates, and compounds such as chlorobenzene are less reactive than benzene. The three examples on the left of the bottom row (in the same diagram) are examples of electron withdrawal by conjugation to polar double or triple bonds, and in these cases the inductive effect further enhances the deactivation of the benzene ring. Alkyl substituents such as methyl increase the nucleophilicity of aromatic rings in the same fashion as they act on double bonds.

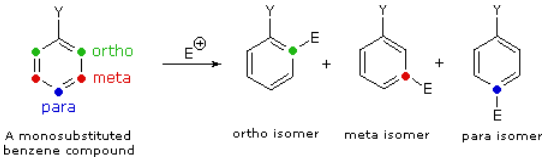


Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

16.13: Electrophilic Aromatic Substitution of Substituted Benzenes

II. The second factor that becomes important in reactions of substituted benzenes concerns the site at which electrophilic substitution occurs. Since a mono-substituted benzene ring has two equivalent ortho-sites, two equivalent meta-sites and a unique para-site, three possible constitutional isomers may be formed in such a substitution. If reaction occurs equally well at all available sites, the expected statistical mixture of isomeric products would be 40% ortho, 40% meta and 20% para. Again we find that the nature of the substituent influences this product ratio in a dramatic fashion. Bromination of methoxybenzene (anisole) is very fast and gives mainly the para-bromo isomer, accompanied by 10% of the ortho-isomer and only a trace of the meta-isomer. Bromination of nitrobenzene requires strong heating and produces the meta-bromo isomer as the chief product.



Some additional examples of product isomer distribution in other electrophilic substitutions are given in the table below. It is important to note here that the reaction conditions for these substitution reactions are not the same, and must be adjusted to fit the reactivity of the reactant C_6H_5-Y. The high reactivity of anisole, for example, requires that the first two reactions be conducted under very mild conditions (low temperature and little or no catalyst). The nitrobenzene reactant in the third example is very unreactive, so rather harsh reaction conditions must be used to accomplish that reaction.

Y in C_6H_5–Y	Reaction	% Ortho-Product	% Meta-Product	% Para-Product
–O–CH_3	Nitration	30–40	0–2	60–70
–O–CH_3	F-C Acylation	5–10	0–5	90–95
–NO_2	Nitration	5–8	90–95	0–5
–CH_3	Nitration	55–65	1–5	35–45
–CH_3	Sulfonation	30–35	5–10	60–65
–CH_3	F-C Acylation	10–15	2–8	85–90
–Br	Nitration	35–45	0–4	55–65
–Br	Chlorination	40–45	5–10	50–60

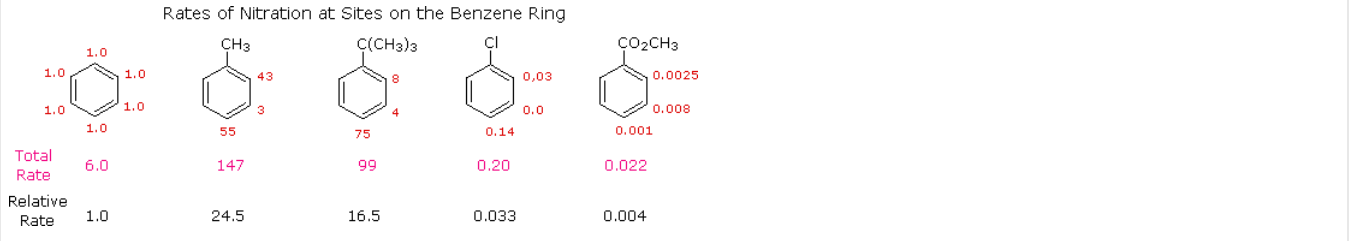
These observations, and many others like them, have led chemists to formulate an empirical classification of the various substituent groups commonly encountered in aromatic substitution reactions. Thus, substituents that activate the benzene ring toward electrophilic attack generally direct substitution to the ortho and para locations. With some exceptions, such as the halogens, deactivating substituents direct substitution to the meta location. The following table summarizes this classification.

Orientation and Reactivity Effects of Ring Substituents

Activating Substituents ortho & para-Orientation			Deactivating Substituents meta-Orientation			Deactivating Substituents ortho & para-Orientation	
–$O^{(-)}$	–NH_2		–NO_2	–CO_2H			–F
–OH	–NR_2		–$NR_3^{(+)}$	–CO_2R			–Cl
–OR	–$NHCOCH_3$		–$PR_3^{(+)}$	–$CONH_2$			–Br
–OC_6H_5	–R		–$SR_2^{(+)}$	–CHO			–I
–$OCOCH_3$	–C_6H_5		–SO_3H	–COR			–CH_2Cl
			–SO_2R	–CN			–$CH{=}CHNO_2$

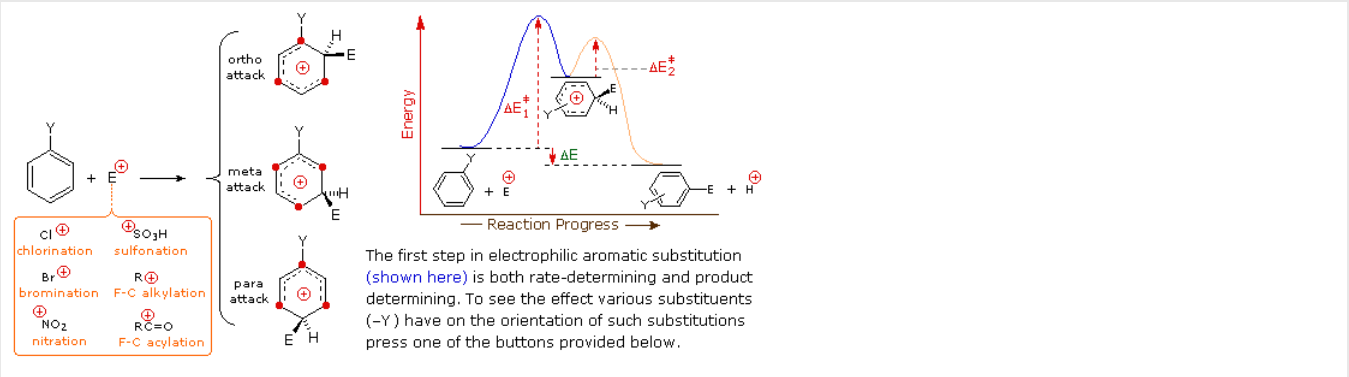
The information summarized in the above table is very useful for rationalizing and predicting the course of aromatic substitution reactions, but in practice most chemists find it desirable to understand the underlying physical principles that contribute to this empirical classification. We have already analyzed the activating or deactivating properties of substituents in terms of inductive and resonance effects, and these same factors may be used to rationalize their influence on substitution orientation.

The first thing to recognize is that the proportions of ortho, meta and para substitution in a given case reflect the relative rates of substitution at each of these sites. If we use the nitration of benzene as a reference, we can assign the rate of reaction at one of the carbons to be 1.0. Since there are six equivalent carbons in benzene, the total rate would be 6.0. If we examine the nitration of toluene, tert-butylbenzene, chlorobenzene and ethyl benzoate in the same manner, we can assign relative rates to the ortho, meta and para sites in each of these compounds. These relative rates are shown (colored red) in the following illustration, and the total rate given below each structure reflects the 2 to 1 ratio of ortho and meta sites to the para position. The overall relative rates of reaction, referenced to benzene as 1.0, are calculated by dividing by six. Clearly, the alkyl substituents activate the benzene ring in the nitration reaction, and the chlorine and ester substituents deactivate the ring.



From rate data of this kind, it is a simple matter to calculate the proportions of the three substitution isomers. Toluene gives 58.5% ortho-nitrotoluene, 37% para-nitrotoluene and only 4.5% of the meta isomer. The increased bulk of the tert-butyl group hinders attack at the ortho-sites, the overall product mixture being 16% ortho, 8% meta and 75% para-nitro product. Although chlorobenzene is much less reactive than benzene, the rate of ortho and para-substitution greatly exceeds that of meta-substitution, giving a product mixture of 30% ortho and 70% para-nitrochlorobenzene. Finally, the benzoic ester gave predominantly the meta-nitro product (73%) accompanied by the ortho (22%) and para (5%) isomers, as shown by the relative rates. Equivalent rate and product studies for other substitution reactions lead to similar conclusions. For example, electrophilic chlorination of toluene occurs hundreds of times faster than chlorination of benzene, but the relative rates are such that the products are 60% ortho-chlorotoluene, 39% para and 1% meta-isomers, a ratio similar to that observed for nitration.

The manner in which specific substituents influence the orientation of electrophilic substitution of a benzene ring is shown in the following interactive diagram. As noted on the opening illustration, the product-determining step in the substitution mechanism is the first step, which is also the slow or rate determining step. It is not surprising, therefore, that there is a rough correlation between the rate-enhancing effect of a substituent and its site directing influence. The exact influence of a given substituent is best seen by looking at its interactions with the delocalized positive charge on the benzenonium intermediates generated by bonding to the electrophile at each of the three substitution sites. This can be done for seven representative substituents by using the selection buttons underneath the diagram.



In the case of alkyl substituents, charge stabilization is greatest when the alkyl group is bonded to one of the positively charged carbons of the benzenonium intermediate. This happens only for ortho and para electrophilic attack, so such substituents favor formation of those products. Interestingly, primary alkyl substituents, especially methyl, provide greater stabilization of an adjacent

charge than do more substituted groups (note the greater reactivity of toluene compared with tert-butylbenzene).

Nitro (NO_2), sulfonic acid (SO_3H) and carbonyl (C=O) substituents have a full or partial positive charge on the atom bonded to the aromatic ring. Structures in which like-charges are close to each other are destabilized by charge repulsion, so these substituents inhibit ortho and para substitution more than meta substitution. Consequently, meta-products predominate when electrophilic substitution is forced to occur.

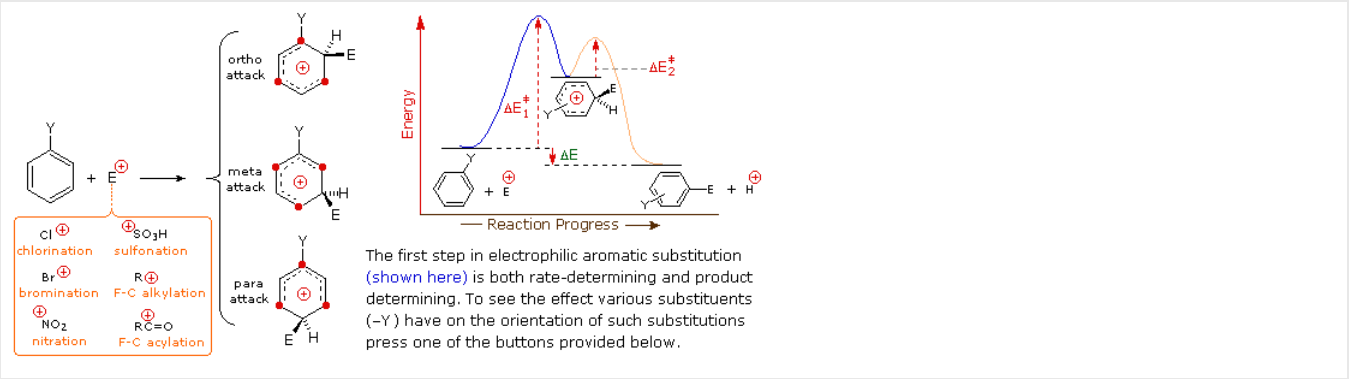
Halogen (X), OR and NR_2 substituents all exert a destabilizing inductive effect on an adjacent positive charge, due to the high electronegativity of the substituent atoms. By itself, this would favor meta-substitution; however, these substituent atoms all have non-bonding valence electron pairs which serve to stabilize an adjacent positive charge by pi-bonding, with resulting delocalization of charge. Consequently, all these substituents direct substitution to ortho and para sites. The balance between inductive electron withdrawal and p-π conjugation is such that the nitrogen and oxygen substituents have an overall stabilizing influence on the benzenonium intermediate and increase the rate of substitution markedly; whereas halogen substituents have an overall destabilizing influence.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

16.14: Why Substituents Activate or Deactivate a Benzene Ring

The manner in which specific substituents influence the orientation of electrophilic substitution of a benzene ring is shown in the following interactive diagram. As noted on the opening illustration, the product-determining step in the substitution mechanism is the first step, which is also the slow or rate determining step. It is not surprising, therefore, that there is a rough correlation between the rate-enhancing effect of a substituent and its site directing influence. The exact influence of a given substituent is best seen by looking at its interactions with the delocalized positive charge on the benzenonium intermediates generated by bonding to the electrophile at each of the three substitution sites. This can be done for seven representative substituents by using the selection buttons underneath the diagram.



In the case of alkyl substituents, charge stabilization is greatest when the alkyl group is bonded to one of the positively charged carbons of the benzenonium intermediate. This happens only for ortho and para electrophilic attack, so such substituents favor formation of those products. Interestingly, primary alkyl substituents, especially methyl, provide greater stabilization of an adjacent charge than do more substituted groups (note the greater reactivity of toluene compared with tert-butylbenzene).

Nitro (NO_2), sulfonic acid (SO_3H) and carbonyl (C=O) substituents have a full or partial positive charge on the atom bonded to the aromatic ring. Structures in which like-charges are close to each other are destabilized by charge repulsion, so these substituents inhibit ortho and para substitution more than meta substitution. Consequently, meta-products predominate when electrophilic substitution is forced to occur.

Halogen (X), OR and NR_2 substituents all exert a destabilizing inductive effect on an adjacent positive charge, due to the high electronegativity of the substituent atoms. By itself, this would favor meta-substitution; however, these substituent atoms all have non-bonding valence electron pairs which serve to stabilize an adjacent positive charge by pi-bonding, with resulting delocalization of charge. Consequently, all these substituents direct substitution to ortho and para sites. The balance between inductive electron withdrawal and p-π conjugation is such that the nitrogen and oxygen substituents have an overall stabilizing influence on the benzenonium intermediate and increase the rate of substitution markedly; whereas halogen substituents have an overall destabilizing influence.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

16.15: Orientation Effects in Substituted Benzenes

Substituted rings are divided into two groups based on the type of the substituent that the ring carries:

- **Activated rings**: the substituents on the ring are groups that donate electrons.
- **Deactivated rings**: the substituents on the ring are groups that withdraw electrons.

Introduction

Examples of activating groups in the relative order from the most activating group to the least activating:

$$-NH_2, -NR_2 > -OH, -OR > -NHCOR > -CH_3 \text{ and other alkyl groups}$$

with R as alkyl groups (C_nH_{2n+1})

Examples of deactivating groups in the relative order from the most deactivating to the least deactivating:

$$-NO_2, -CF_3 > -COR, -CN, -CO_2R, -SO_3H > \text{Halogens}$$

with R as alkyl groups (C_nH_{2n+1})

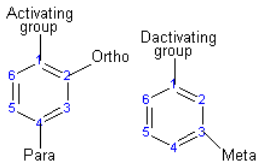
The order of reactivity among Halogens from the more reactive (least deactivating substituent) to the least reactive (most deactivating substituent) halogen is:

$$F > Cl > Br > I$$

The order of reactivity of the benzene rings toward the electrophilic substitution when it is substituted with a halogen groups, follows the order of electronegativity. The ring that is substituted with the most electronegative halogen is the most reactive ring (less deactivating substituent) and the ring that is substituted with the least electronegatvie halogen is the least reactive ring (more deactivating substituent), when we compare rings with halogen substituents. Also the size of the halogen effects the reactivity of the benzene ring that the halogen is attached to. As the size of the halogen increase, the reactivity of the ring decreases.

The direction of the reaction

The activating group directs the reaction to the ortho or para position, which means the electrophile substitute the hydrogen that is on carbon 2 or carbon 4. The deactivating group directs the reaction to the meta position, which means the electrophile substitute the hydrogen that is on carbon 3 with the exception of the halogens that is a deactivating group but directs the ortho or para substitution.

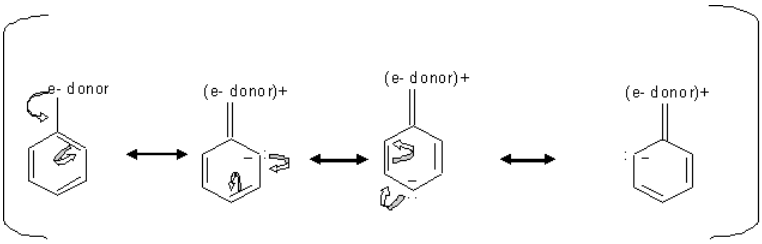


Substituents determine the reaction direction by resonance or inductive effect

Resonance effect is the conjugation between the ring and the substituent, which means the delocalizing of the π electrons between the ring and the substituent. Inductive effect is the withdraw of the sigma (the single bond) electrons away from the ring toward the substituent, due to the higher electronegativity of the substituent compared to the carbon of the ring.

Activating groups (ortho or para directors)

When the substituents like -OH have an unshared pair of electrons, the resonance effect is stronger than the inductive effect which make these substituents stronger activators, since this resonance effect direct the electron toward the ring. In cases where the subtituents is esters or amides, they are less activating because they form resonance structure that pull the electron density away from the ring.

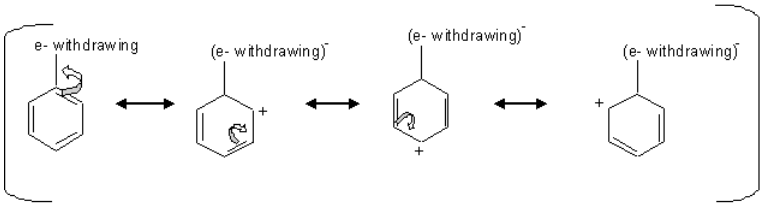


By looking at the mechanism above, we can see how groups donating electron direct the ortho, para electrophilic substition. Since the electrons locatinn transfer between the ortho and para carbons, then the electrophile prefer attacking the carbon that has the free electron.

Inductive effect of alkyl groups activates the direction of the ortho or para substitution, which is when s electrons gets pushed toward the ring.

Deactivating group (meta directors)

The deactivating groups deactivate the ring by the inductive effect in the presence of an electronegative atom that withdraws the electrons away from the ring.



we can see from the mechanism above that when there is an electron withdraw from the ring, that leaves the carbons at the ortho, para positions with a positive charge which is unfavorable for the electrophile, so the electrophile attacks the carbon at the meta positions.

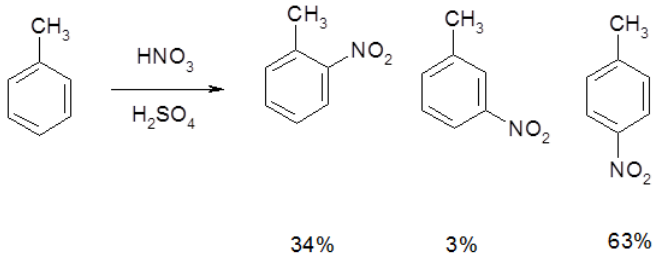
Halogens are an exception of the deactivating group that directs the ortho or para substitution. The halogens deactivate the ring by inductive effect not by the resonance even though they have an unpaired pair of electrons. The unpaired pair of electrons gets donated to the ring, but the inductive effect pulls away the s electrons from the ring by the electronegativity of the halogens.

Substituents determine the reactivity of rings

The reaction of a substituted ring with an activating group is faster than benzene. On the other hand, a substituted ring with a deactivated group is slower than benzene.

Activating groups speed up the reaction because of the resonance effect. The presence of the unpaired electrons that can be donated to the ring, stabilize the carbocation in the transition state. Thus; stabilizing the intermediate step, speeds up the reaction; and this is due to the decrease of the activating energy. On the other hand, the deactivating groups, withdraw the electrons away from the carbocation formed in the intermediate step, thus; the activation energy is increased which slows down the reaction.

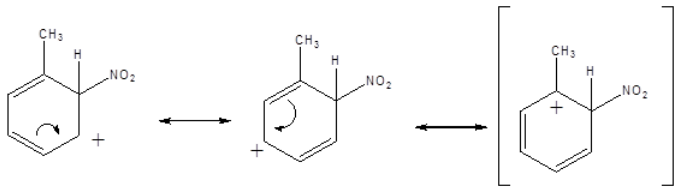
The CH_3Group is and ortho, para Director



Alkyl groups are Inductive activators

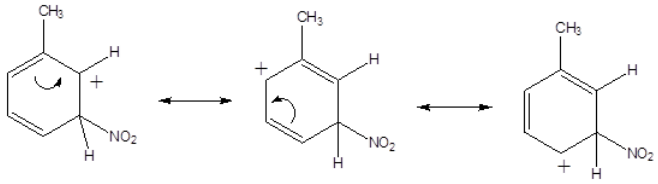
With o/p attack the form a tertiary arenium carbocation which speeds up the reaction

Ortho Attack

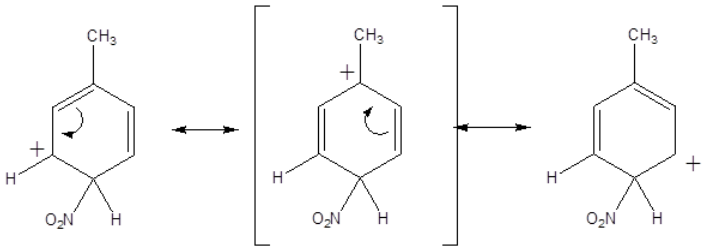


Tertiary Carbocation

Meta Attack

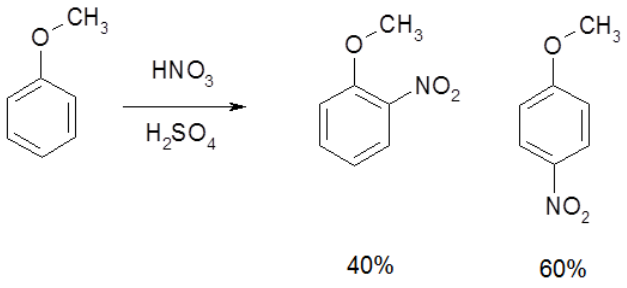


Para Attack



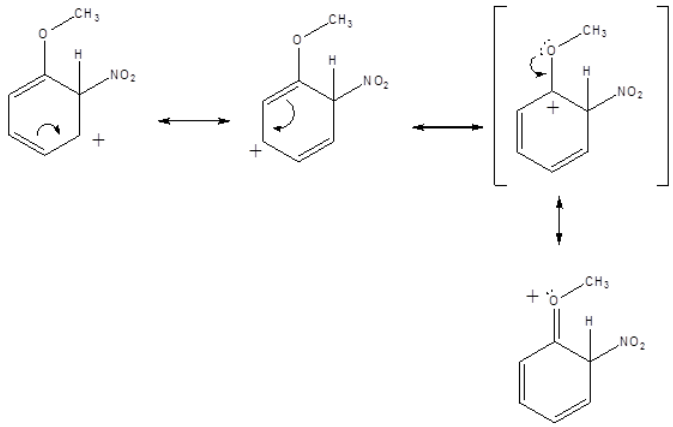
Tertiary Carbocation

The O-CH_3 Group is an ortho, para Director

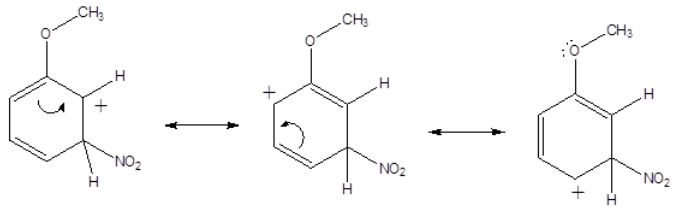


Ortho and Para producst produces a resonance structure which stabilizes the arenium ion. This causes the ortho and para products for form faster than meta. Generally, the para product is preferred because of steric effects.

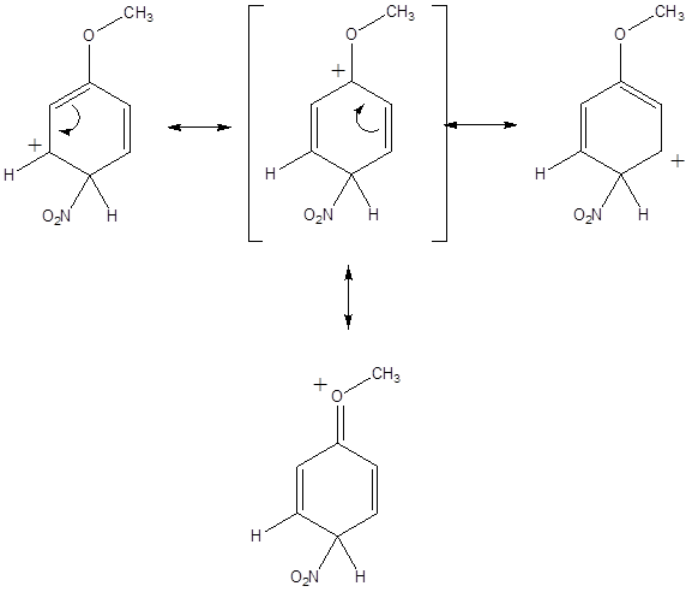
Ortho Attack



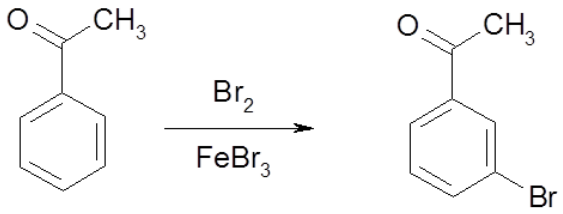
Meta Attack



Para Attack



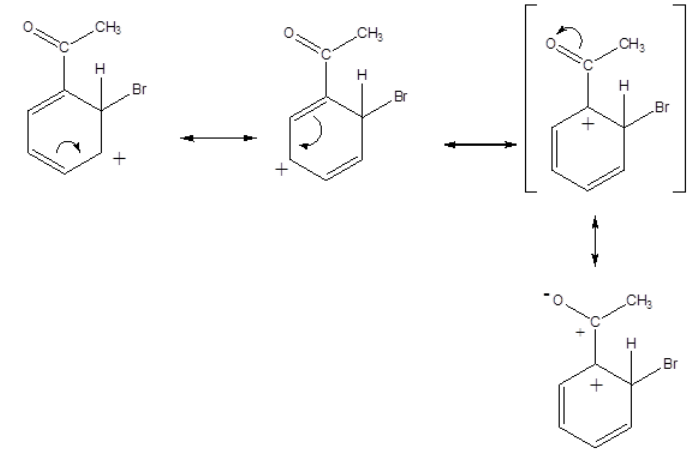
Acyl groups are meta Directors



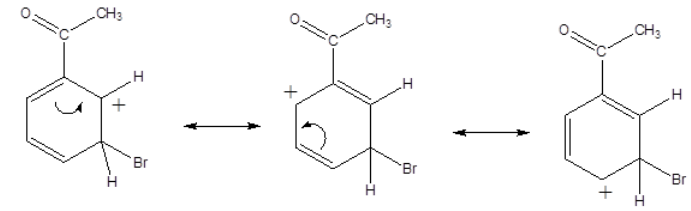
72%

Acyl groups are resonance deactivators. Ortho and para attack produces a resonance structure which places the arenium cation next to and additional cation. This destabilizes the arenium cation and slows down ortho and para reaction. By default the meta product forms faster because it lacks this destablizing resonance structure.

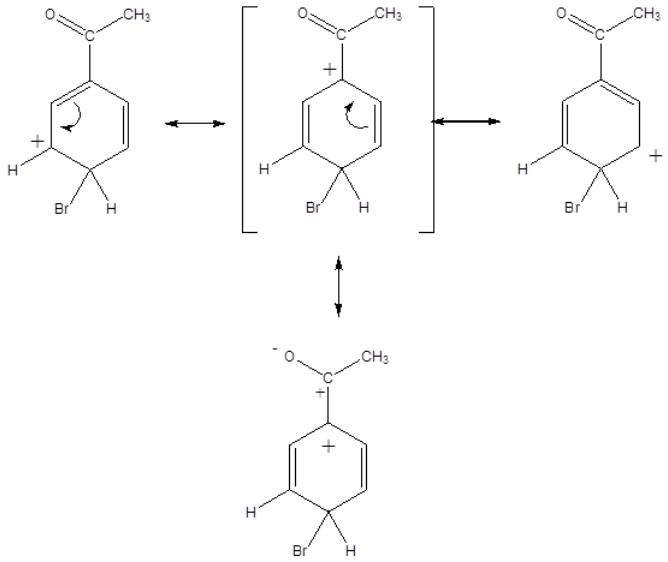
Ortho Attack



Meta Attack



Para Attack



References

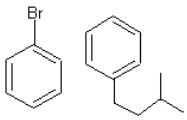
1. Schore, N.E. and P.C. Vollhardt. 2007. *Organic Chemistry, structure and function*, 5th ed. New York,NY: W.H. Freeman and Company.
2. Fryhle, C.B. and G. Solomons. 2008. *Organic Chemistry*, 9th ed.Danvers,MA: Wiley.

Outside Links

- http://en.wikipedia.org/wiki/Activating_group
- http://en.wikipedia.org/wiki/Deactivating_group
- http://www.columbia.edu/itc/chemistry/c3045/client_edit/ppt/PDF/12_12_14.pdf

Problems

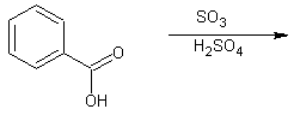
1. Predict the direction of the electrophile substition on these rings:



2. Which nitration product is going to form faster?

    nitration of aniline or nitration of nitrobenzene?

3. Predict the product of the following two sulfonation reactions:

A. 

4. Classify these two groups as activating or deactivating groups:

    A. alcohol

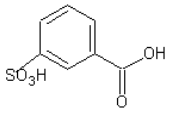
    B. ester

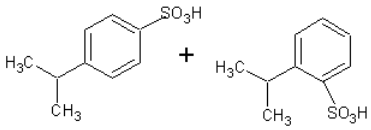
5. By which effect does trichloride effect a monosubstituted ring?

Answers

1. The first substitution is going to be ortho and/or para substitution since we have a halogen subtituent. The second substition is going to be ortho and/or para substitution also since we have an alkyl substituent.

2. The nitration of aniline is going to be faster than the nitration of nitrobenzene, since the aniline is a ring with NH_2 substituent and nitrobenzene is a ring with NO_2 substiuent. As described above $NH_2$is an activating group which speeds up the reaction and NO_2 is deactivating group that slows down the reaction.

3. A. the product is 

B. the product is 

4. A. alcohol is an activating group.

B. ester is a deactivating group.

5. Trichloride deactivate a monosubstitued ring by inductive effect.

Contributors

- Lana Alawwad (UCD)
- Prof. Steven Farmer (Sonoma State University)

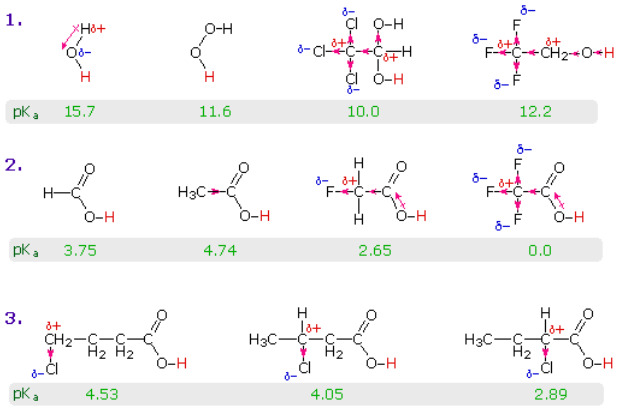
CHAPTER OVERVIEW

17: Carboxylic Acids and the Acidity of the O–H Bond

Topic hierarchy

17.1: Inductive Effects in Aliphatic Carboxylic Acids

The resonance effect described here is undoubtedly the major contributor to the exceptional acidity of carboxylic acids. However, inductive effects also play a role. For example, alcohols have pK_a's of 16 or greater but their acidity is increased by electron withdrawing substituents on the alkyl group. The following diagram illustrates this factor for several simple inorganic and organic compounds (row #1), and shows how inductive electron withdrawal may also increase the acidity of carboxylic acids (rows #2 & 3). The acidic hydrogen is colored red in all examples.



Water is less acidic than hydrogen peroxide because hydrogen is less electronegative than oxygen, and the covalent bond joining these atoms is polarized in the manner shown. Alcohols are slightly less acidic than water, due to the poor electronegativity of carbon, but chloral hydrate, $Cl_3CCH(OH)_2$, and 2,2,2,-trifluoroethanol are significantly more acidic than water, due to inductive electron withdrawal by the electronegative halogens (and the second oxygen in chloral hydrate). In the case of carboxylic acids, if the electrophilic character of the carbonyl carbon is decreased the acidity of the carboxylic acid will also decrease. Similarly, an increase in its electrophilicity will increase the acidity of the acid. Acetic acid is ten times weaker an acid than formic acid (first two entries in the second row), confirming the electron donating character of an alkyl group relative to hydrogen, as noted earlier in a discussion of carbocation stability. Electronegative substituents increase acidity by inductive electron withdrawal. As expected, the higher the electronegativity of the substituent the greater the increase in acidity (F > Cl > Br > I), and the closer the substituent is to the carboxyl group the greater is its effect (isomers in the 3rd row). Substituents also influence the acidity of benzoic acid derivatives, but resonance effects compete with inductive effects. The methoxy group is electron donating and the nitro group is electron withdrawing (last three entries in the table of pK_a values).

For additional information about substituent effects on the acidity of carboxylic acids Click Here

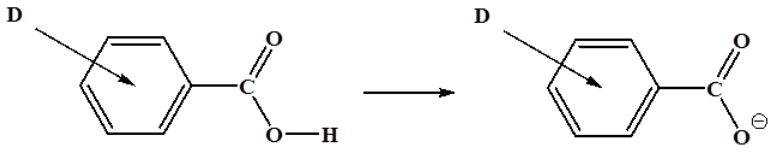
Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

17.2: Substituted Benzoic Acids

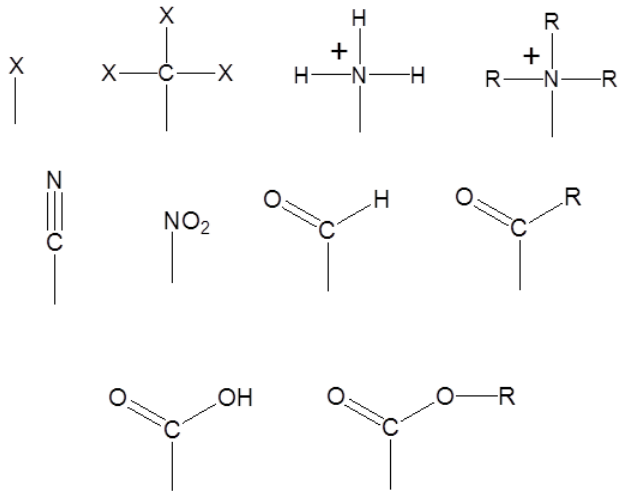
Electron-withdrawing groups

The conjugate base of benzoic acid is destabilized by electron-donating groups. This makes the acid less acidic



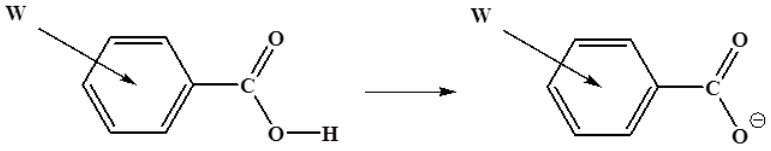
D is Electron-Donating Group **The carboxylate anion is destabilized**

Electron-withdrawing groups deactivate the benzene ring to electrophilic attack and make benzoic acids more acidic.



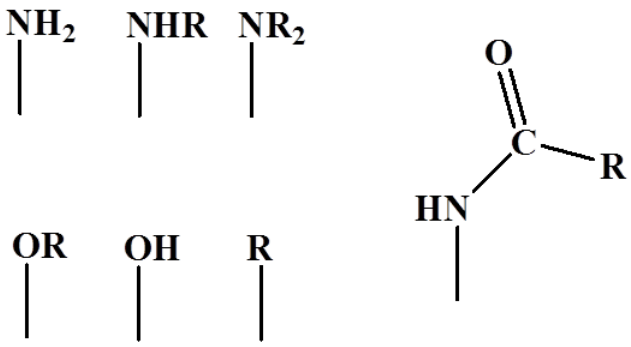
Electron-donating groups

The conjugate base of benzoic acid is stabilized by electron-withdrawing groups. This makes the acid more acidic



W is an Electron-Withdrawing Group **The carboxylate anion is destabilized**

Electron-withdrawing groups activate the benzene ring to electrophilic attack and make benzoic acids less acidic.



Contributors

- Prof. Steven Farmer (Sonoma State University)

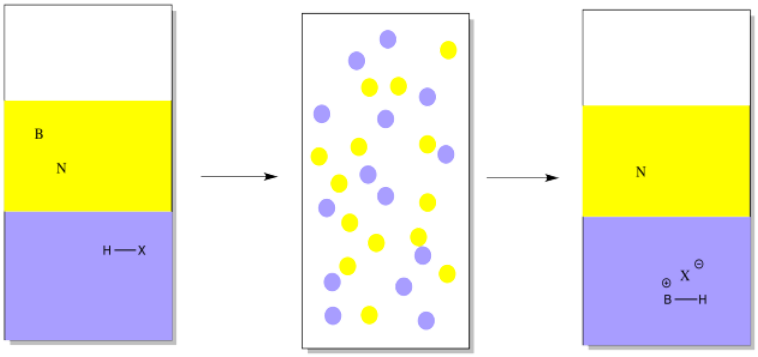
17.3: Extraction

An acid-base extraction is a type of liquid-liquid extraction. It typically involves different solubility levels in water and an organic solvent. The organic solvent may be any carbon-based liqiuid that does not dissolve very well in water; common ones are ether, ethyl acetate, or dichloromethane.

Acid-base extraction is typically used to separate organic compounds from each other based on their acid-base properties. The method rests on the assumption that most organic compounds are more soluble in organic solvents than they are in water. However, if the organic compound is rendered ionic, it becomes more soluble in water than in the organic solvent. These compounds can easily be made into ions either by adding a proton (an H^+ ion), making the compound into a positive ion, or by removing a proton, making the compound into a negative ion.

Suppose you have a mixture of two compounds. There is a neutral one which doesn't react with any acids or bases. There is also a basic one, which reacts with acids by picking up a proton. In this case, a proton might be added via reaction with a strong mineral acid (represented by HX in the drawing). Suppose an aqueous solution of mineral acid, such as HCl, were shaken vigorously with an ethereal solution of an organic base and an organic neutral. The proton would be transferred to a basic compound, but not to a neutral one. The basic compound would become ionic, and more water-soluble.

Note that in the drawing, the ether is represented in yellow, whereas the water is shown in blue. The water is on the bottom in this case because water has a higher density than ether, so it will sink to the bottom (along with anything dissolved in it). Some organic solvents do have a higher density than water, so the aqueous solution would float to the top in those case.



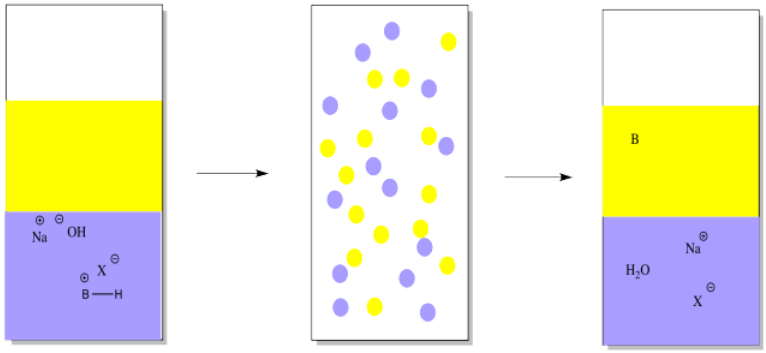
As a result, the ethereal solution would contain only the neutral compound, not the basic one. The neutral compound could be isolated simply by evaporating the ether.

However, as a practical matter, the ether would have to be dried first. What's the difference between evaporating and drying? Have you ever been to the beach or taken a shower? Drying refers to the removal of water. This step is necessary because ether tends to dissolve a lot of water in it. Once the ether has been evaporated, there would be some neutral compound, but it would be mixed with water.

Water removal is most easily done by adding a drying agent, such as magnesium sulfate or sodium sulfate. The water sticks to these solids, which are then filtered off.

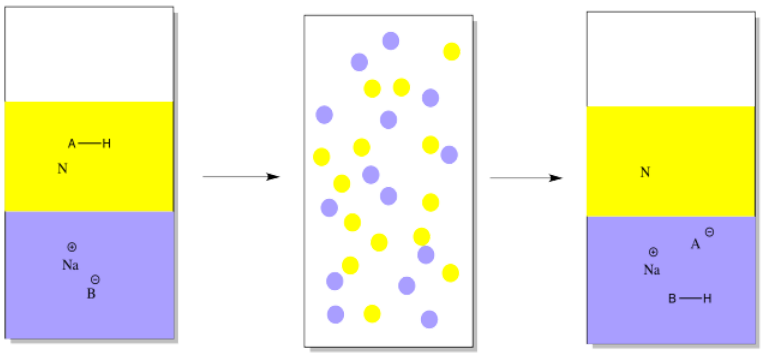
Now the neutral compound is alone in the ether. Evaporation of the ether gives the pure, neutral compound.

However, the basic compound is stuck in the water, and it isn't the same compound anymore. It's an ion, now. If we want the original compound in a pure form, we need to take that proton away. That can be done by adding a mineral base, such as sodium hydroxide.



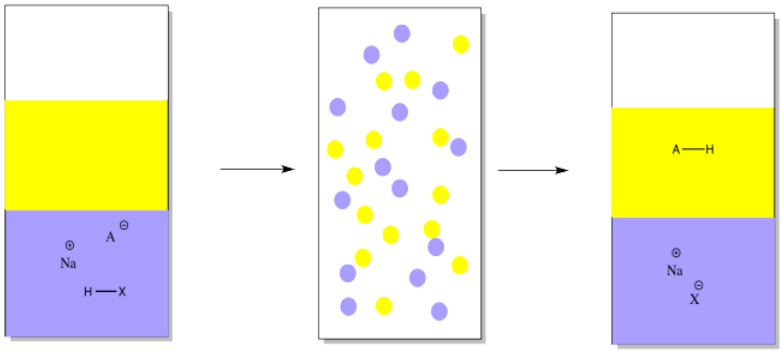
The mineral base will remove the proton, leaving the original organic compound. The organic compound is uncharged and not as soluble in water anymore. It will go back into the ether layer.

Conversely, we might have a mixture of an acidic organic compound and a neutral compound to start out with. In that case, we would add a mineral base in the first place, to take a proton away from the acidic compound. The mineral base might be something like sodium hydroxide or sodium bicarbonate. In the drawing, it is just represented as Na^+ B^-.



The acidic compound becomes ionic and water-soluble when it loses a proton. That leaves the neutral compound alone.

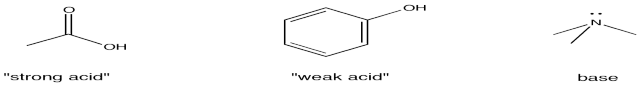
To get that acidic compound back, we would add a mineral acid such as hydrochloric acid in order to restore the missing proton.



Just as in the other case, the ether layer containing a pure compound could be separated, dried and evaporated in order to provide the pure compound.

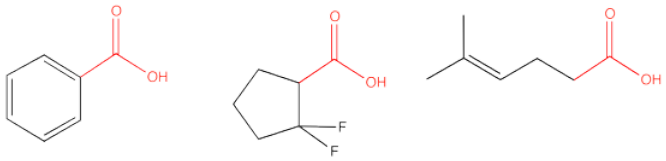
Acidity

But how do we know whether something is an organic acid or a base? Common structural features of organic acids and bases are displayed below.

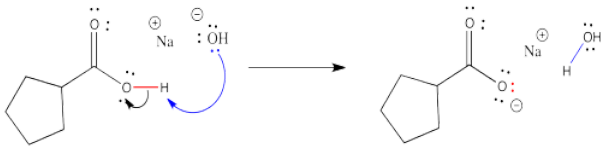


Note that the terms, "strong acid" and "weak acid", are relative with organic compounds. Sometimes, the term, "strong acid", designates a compound that completely ionizes in solution, so that it automatically gives up a H^+ ion and forms an ionic compound. Hydrochloric acid, HCl, in water is a good example. That isn't true here; none of these acids ionize very easily on their own, and they appear in solution just as they do above, with just a small minority of molecules forming H^+ and an anion. In this case, the term just compares one group of acidic compounds (called carboxylic acids) to another group of acidic compounds (called phenols). Carboxylic acids are more likely to give up protons than are phenols, so carboxylic acids are referred to in this context as "strong" and phenols as "weak".

The carboxylic acid group contains a C=O (a carbonyl) with an additional OH group attached to the carbon. Examples are shown below.

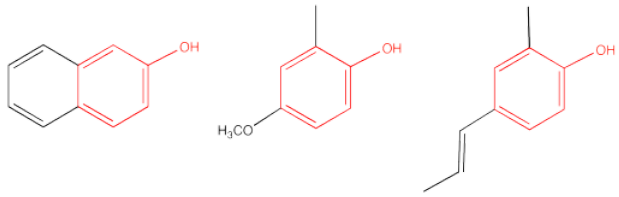


When carboxylic acids are treated with mineral bases such as sodium hydroxide, the carboxylic OH group gives up a proton to the hydroxide, forming a water molecule. The electrons in the O-H bond stay behind, putting a negative charge on the resulting carboxylate anion. The salt that forms is much more water soluble.

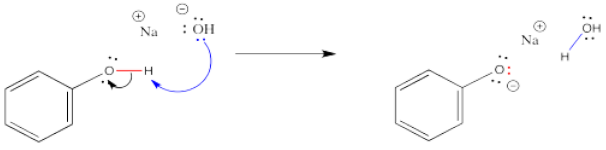


This reaction is completely reversible. A mineral acid, such as HCl, could provide protons to the carboxylate anion. The carboxylate ion would use a pair of electrons to bind to a proton, and the compound would become a neutral (as in uncharged) carboxylic acid again.

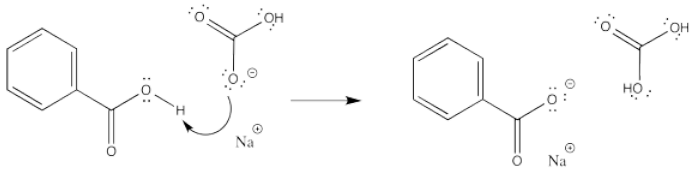
Phenols also contain an OH group, but instead of being attached to a C=O group, the OH is attached to a benzene (a six-carbon ring with three double bonds). Examples are shown below.



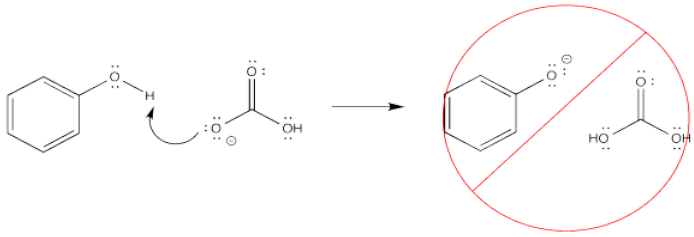
Phenols react with bases in the same way as do carboxylic acids, just not so as easily.



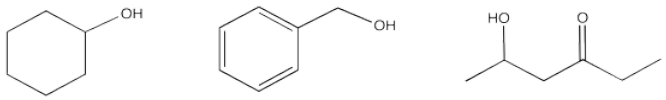
Because phenols do not react as easily as carboxylic acids, there are situations in which a carboxylic acid would react with a base but a phenol would not. For example, carboxylic acids react even with weak bases such as sodium bicarbonate (baking soda).



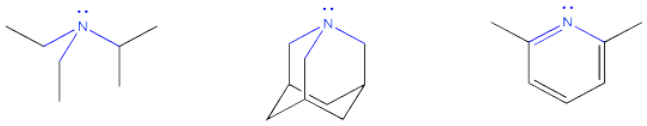
Phenols, on the other hand, do no such thing.



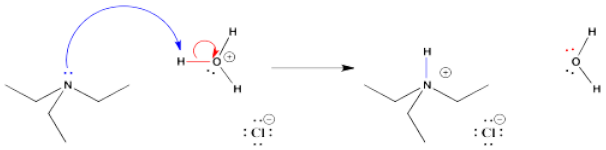
If the OH is attached to a carbon in an organic compound, but it is not attached to either a C=O or a benzene ring, it is not acidic enough to be removed to an appreciable extent. That is true even if there is a carbonyl or a benzene somewhere else in the molecule. As a result, acid-base extraction is not possible in these cases.



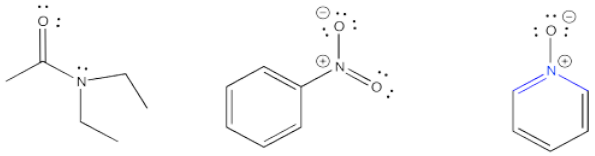
Organic bases are compounds that contain nitrogen atoms. In order to be basic, the nitrogen atom must have a lone pair. The lone pair is needed in order to make a bond with the proton.



Once the lone pair has donated to the proton to form a bond with it, the nitrogen compound becomes positively charged. It then becomes more water-soluble.



If the nitrogen does not have a lone pair, it is unable to bond to a proton. However, some compounds that do have a lone pair on the nitrogen still can't donate their lone pair to make a bond to the hydrogen. Most often that's because of a very electronegative oxygen atom nearby. The attraction of the oxygen for the lone pair makes the lone pair less able to donate to another atom. There can also be other reasons, especially involving electron delocalization or aromaticity that makes the lone pair unavailable for bonding.

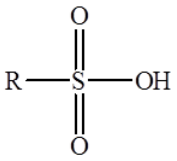


Contributors

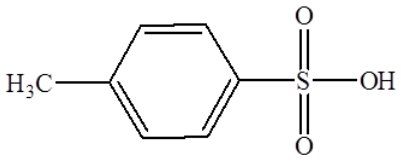
Chris P Schaller, Ph.D., (College of Saint Benedict / Saint John's University)

17.4: Sulfonic Acids

Sulfonic acids are similar to carboxylic acids and have the general structure of RSO_3H. Sulfonic acids are very strong acids (pKa ~ -7). The most common sulfonic acid is p-toluenesulfonic acid.

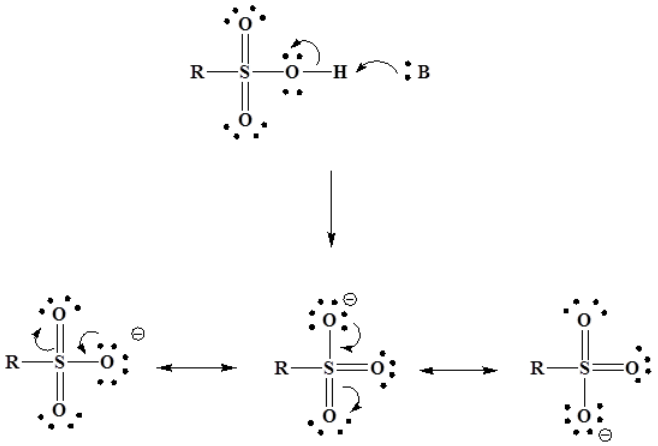


General Structure of Sulfonic Acids



p-Toluenesulfonic acid (TsOH)

The conjugate bases of sulfonic acids are called sulfonate anions and are resonance stabilized. Consequently, sulfonate anions make good leaving groups.



The sulfonate anion has three major resonance structures.

Contributors

- Prof. Steven Farmer (Sonoma State University)

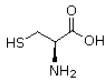
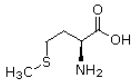
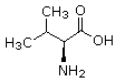
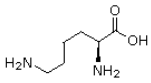
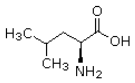
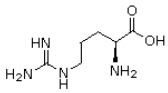
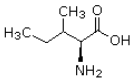
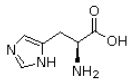
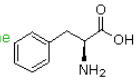
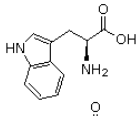
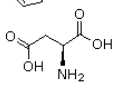
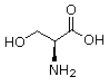
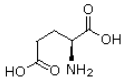
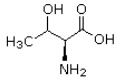
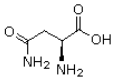
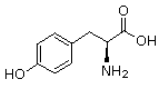
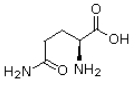
17.5: Amino Acids

Common amino acids

There are 20 common amino acids. They are composed of C, H, O, N and S atoms. They are structurally and chemically different, and also differ in size and volume. Some are branched structures, some are linear, some have ring structures. One of the 20 common amino acids is actually an imino acid. A typical grouping of their chemical nature is as follows:

- Nonpolar (hydrocarbons and one sulfur-containing amino acid). Dispersion forces and hydrophobic effects predominate in their interactions. They cannot H-bond with water and these side chains have a characteristic hydrophobic effect in water.
- Polar uncharged. Contain functional groups that can H-bond with water and other amino acids. Include C, H, O, N and S atoms.
- Acidic. Contain a carboxylic acid functional group with a negative charge at neutral pH. Can H-bond with water, can form ionic interactions, and can also serve as nucleophiles or participate in acid-base chemistry.
- Basic. Nitrogen containing bases (e.g. guanidino, imidazole or amino groups) with a net positive charge at neutral pH. Can serve as proton donors in chemical reactions, and form ionic interactions.

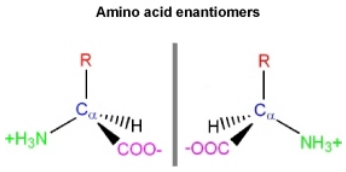
The amino acids have a name, as well as a three letter or single letter mnemonic code:

Name	Formula	Abbreviations		Name	Formula	Abbreviations	
Glycine		Gly	G	Cysteine		Cys	C
Alanine		Ala	A	Methionine		Met	M
Valine		Val	V	Lysine		Lys	K
Leucine		Leu	L	Arginine		Arg	R
Isoleucine		Ile	I	Histidine		His	H
Phenylalanine		Phe	F	Tryptophan		Trp	W
Proline		Pro	P	Aspartic Acid		Asp	D
Serine		Ser	S	Glutamic Acid		Glu	E
Threonine		Thr	T	Asparagine		Asn	N
Tyrosine		Tyr	Y	Glutamine		Gln	Q

Strereochemistry in amino acids

With the exception of glycine, all the 19 other common amino acids have a uniquely different functional group on the central tetrahedral alpha carbon (i.e. Ca)

- The C a is termed "chiral" to indicate there are four different constituents and that the Ca is asymmetric
- Since the C a is asymmetric there exists two possible, non-superimposable, mirror images of the amino acids:

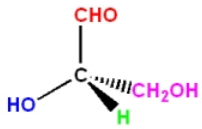


- How are these two uniquely different structures distinguished?

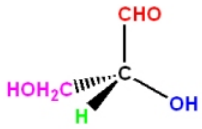
The D, L system

Glyceraldehyde contains a chiral carbon, and therefore, there are two enantiomers of this molecule.

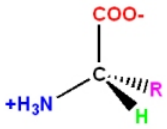
- One is labeled the "L" form, and the other the "D" form
- This is the frame of reference used to describe amino acid enantiomers as being either the "L" or "D" form



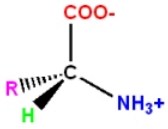
L-Glyceraldehyde



D-Glyceraldehyde



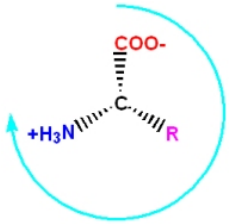
L-Amino acid



D-Amino acid

Even though the two enantiomers would seem to be essentially equivalent to each other, all common amino acids are found in the "L" enantiomer in living systems

- When looking down the H-C
- a bond towards the Ca there is a mnemonic to identify the L-enantiomer of amino acids (note: in this view the three functional groups are pointing away from you, and not towards you; the H atom is omitted for clarity - but it would be in front of the C)



- Starting with the carbonyl functional group, and going clockwise around the C
- a of the L-enantiomer, the three functional groups spell out the word CORN.
- If you follow the above instructions, it will spell out CONR (a silly, meaningless word) for the D-enantiomer

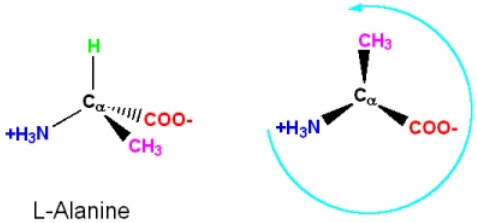
The R,S system of naming chiral centers

- A relative ranking of the "priority" of various functional groups is given as:

SH > OH > NH2 > COOH > CHO > CH2OH > CH3 > H

- A chiral center has four different functional groups. Identify the functional group with the lowest priority
- View the chiral center down the bond from the chiral center to the lowest priority atom
- don't confuse this with the CORN mnemonic method of identifying the L-amino acid chirality by viewing from the H to the Ca)
- Assign priorities to the three other functional groups connected to the chiral center, using the above ranking

- If the priorities of these other groups goes in a clockwise rotation, the chirality is "R". If the priorities of these other groups goes counterclockwise, the chirality is "S". (Note that this assignment has nothing to do with optical activity, and is not using L-glyceraldehyde as a reference molecule)



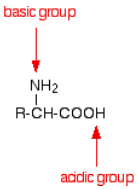
Spectroscopic properties of amino acids

This refers to the ability of amino acids to absorb or emit electromagnetic energy at different wavelengths (i.e. energies)

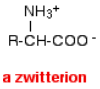
- No amino acids absorb light in the visible spectrum (i.e. they are "colorless").
- If proteins have color (e.g. hemoglobin is red) it is because they contain a bound, non-protein atom, ion or molecule; iron in this case)
- All amino acids absorb in the infrared region (longer wavelengths, weaker energy than visible light)
- Some amino acids absorb in the ultraviolet spectrum (shorter wavelengths, higher energy than visible light)
  - Absorption occurs as electrons rise to higher energy states
  - Electrons in aromatic ring structures absorb in the u.v. spectrum. Such structures comprise the side chains of
  - tryptophan, tyrosine and phenylalanine.

Amino acids as zwitterions

An amino acid has both a basic amine group and an acidic carboxylic acid group.



There is an internal transfer of a hydrogen ion from the -COOH group to the $-NH_2$ group to leave an ion with both a negative charge and a positive charge. This is called a zwitterion.

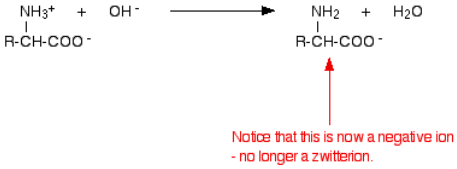


a zwitterion

This is the form that amino acids exist in even in the solid state. If you dissolve the amino acid in water, a simple solution also contains this ion. A zwitterion is a compound with no overall electrical charge, but which contains separate parts which are positively and negatively charged.

Adding an alkali to an amino acid solution

If you increase the pH of a solution of an amino acid by adding hydroxide ions, the hydrogen ion is removed from the $-NH_3^+$ group.

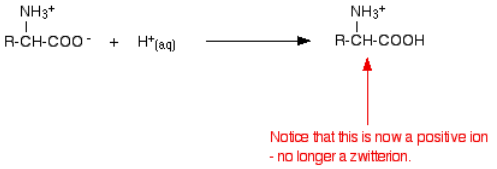


You could show that the amino acid now existed as a negative ion using electrophoresis. In its simplest form, electrophoresis can just consist of a piece of moistened filter paper on a microscope slide with a crocodile clip at each end attached to a battery. A drop of amino acid solution is placed in the center of the paper.

Although the amino acid solution is colourless, its position after a time can be found by spraying it with a solution of ninhydrin. If the paper is allowed to dry and then heated gently, the amino acid shows up as a coloured spot. The amino acid would be found to travel towards the anode (the positive electrode).

Adding an acid to an amino acid solution

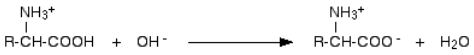
If you decrease the pH by adding an acid to a solution of an amino acid, the $-COO^-$ part of the zwitterion picks up a hydrogen ion.



This time, during electrophoresis, the amino acid would move towards the cathode (the negative electrode).

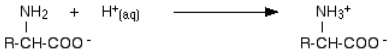
Shifting the pH from one extreme to the other

Suppose you start with the ion we've just produced under acidic conditions and slowly add alkali to it. That ion contains two acidic hydrogens - the one in the -COOH group and the one in the $-NH_3^+$ group. The more acidic of these is the one in the -COOH group, and so that is removed first - and you get back to the zwitterion.

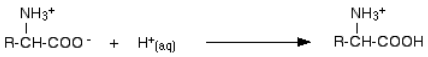


So when you have added just the right amount of alkali, the amino acid no longer has a net positive or negative charge. That means that it wouldn't move towards either the cathode or anode during electrophoresis. The pH at which this lack of movement during electrophoresis happens is known as the isoelectric point of the amino acid. This pH varies from amino acid to amino acid. If you go on adding hydroxide ions, you will get the reaction we've already seen, in which a hydrogen ion is removed from the $-NH_3^+$ group.

You can, of course, reverse the whole process by adding an acid to the ion we've just finished up with. That ion contains two basic groups - the $-NH_2$ group and the $-COO^-$ group. The $-NH_2$ group is the stronger base, and so picks up hydrogen ions first. That leads you back to the zwitterion again.



. . . and, of course, you can keep going by then adding a hydrogen ion to the $-COO^-$ group.



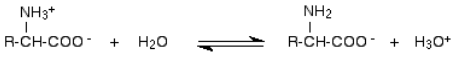
The Isoelectric Point

As defined above, the isoelectric point, **pI**, is the pH of an aqueous solution of an amino acid (or peptide) at which the molecules on average have no net charge. In other words, the positively charged groups are exactly balanced by the negatively charged groups. For simple amino acids such as alanine, the pI is an average of the pK_a's of the carboxyl (2.34) and ammonium (9.69) groups. Thus, the pI for alanine is calculated to be: (2.34 + 9.69)/2 = 6.02, the experimentally determined value. If additional acidic or basic groups are present as side-chain functions, the pI is the average of the pK_a's of the two most similar acids. To assist in determining similarity we define two classes of acids. The first consists of acids that are neutral in their protonated form (e.g. CO_2H & SH). The second includes acids that are positively charged in their protonated state (e.g. $-NH_3^+$). In the case of aspartic acid, the similar acids are the alpha-carboxyl function (pK_a = 2.1) and the side-chain carboxyl function (pK_a = 3.9), so pI = (2.1 +

3.9)/2 = 3.0. For arginine, the similar acids are the guanidinium species on the side-chain (pK_a = 12.5) and the alpha-ammonium function (pK_a = 9.0), so the calculated pI = (12.5 + 9.0)/2 = 10.75.

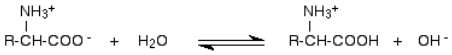
Why isn't the isoelectric point of an amino acid at pH 7?

When an amino acid dissolves in water, the situation is a little bit more complicated than we tend to pretend at this level. The zwitterion interacts with water molecules - acting as both an acid and a base. As an acid:



The $-NH_3^+$ group is a weak acid and donates a hydrogen ion to a water molecule. Because it is only a weak acid, the position of equilibrium will lie to the left.

As a base:



The $-COO^-$ group is a weak base and takes a hydrogen ion from a water molecule. Again, the equilibrium lies to the left.

When you dissolve an amino acid in water, both of these reactions are happening. However, the positions of the two equilibria aren't identical - they vary depending on the influence of the "R" group. In practice, for the simple amino acids we have been talking about, the position of the first equilibrium lies a bit further to the right than the second one. That means that there will be rather more of the negative ion from the amino acid in the solution than the positive one.

In those circumstances, if you carried out electrophoresis on the unmodified solution, there would be a slight drift of amino acid towards the positive electrode (the anode). To stop that, you need to cut down the amount of the negative ion so that the concentrations of the two ions are identical. You can do that by adding a very small amount of acid to the solution, moving the position of the first equilibrium further to the left. Typically, the pH has to be lowered to about 6 to achieve this. For glycine, for example, the isoelectric point is pH 6.07; for alanine, 6.11; and for serine, 5.68.

Contributors

- Jim Clark (Chemguide.co.uk)

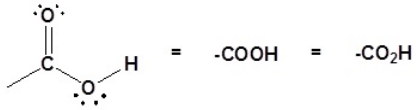
Charles Ophardt (Professor Emeritus, Elmhurst College); Virtual Chembook

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

17.6: Structure and Bonding

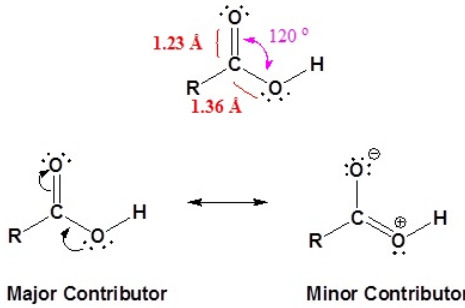
Structure of the carboxyl acid group

Carboxylic acids are organic compounds which incorporate a carboxyl functional group, CO_2H. The name carboxyl comes from the fact that a carbonyl and a hydroxyl group are attached to the same carbon.



Carboxyl Group

The carbon and oxygen in the carbonyl are both sp2 hybridized which give a carbonyl group a basic trigonal shape. The hydroxyl oxygen is also sp2 hybridized which allows one of its lone pair electrons to conjugate with the pi system of the carbonyl group. This make the carboxyl group planar an can represented with the following resonance structure.



Major Contributor Minor Contributor

Carboxylic acids are named such because they can donate a hydrogen to produce a carboxylate ion. The factors which affect the acidity of carboxylic acids will be discussed later.

Carboxylic acid Carboxylate ion

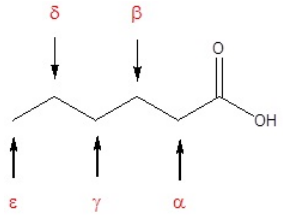
Contributors

- Prof. Steven Farmer (Sonoma State University)

17.7: Nomenclature

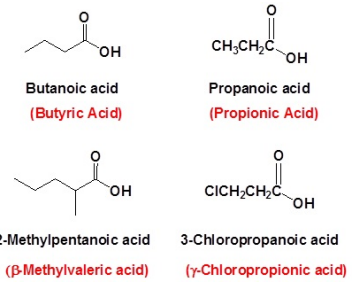
The IUPAC system of nomenclature assigns a characteristic suffix to these classes. The **–e** ending is removed from the name of the parent chain and is replaced **-anoic acid**. Since a carboxylic acid group must always lie at the end of a carbon chain, it is always is given the #1 location position in numbering and it is not necessary to include it in the name.

Many carboxylic acids are called by the common names. These names were chosen by chemists to usually describe a source of where the compound is found. In common names of aldehydes, carbon atoms near the carboxyl group are often designated by Greek letters. The atom adjacent to the carbonyl function is alpha, the next removed is beta and so on.



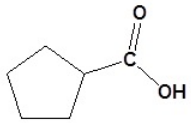
Formula	Common Name	Source	IUPAC Name	Melting Point	Boiling Point
HCO_2H	formic acid	ants (L. formica)	methanoic acid	8.4 ºC	101 ºC
CH_3CO_2H	acetic acid	vinegar (L. acetum)	ethanoic acid	16.6 ºC	118 ºC
$CH_3CH_2CO_2H$	propionic acid	milk (Gk. protus prion)	propanoic acid	-20.8 ºC	141 ºC
$CH_3(CH_2)_2CO_2H$	butyric acid	butter (L. butyrum)	butanoic acid	-5.5 ºC	164 ºC
$CH_3(CH_2)_3CO_2H$	valeric acid	valerian root	pentanoic acid	-34.5 ºC	186 ºC
$CH_3(CH_2)_4CO_2H$	caproic acid	goats (L. caper)	hexanoic acid	-4.0 ºC	205 ºC
$CH_3(CH_2)_5CO_2H$	enanthic acid	vines (Gk. oenanthe)	heptanoic acid	-7.5 ºC	223 ºC
$CH_3(CH_2)_6CO_2H$	caprylic acid	goats (L. caper)	octanoic acid	16.3 ºC	239 ºC
$CH_3(CH_2)_7CO_2H$	pelargonic acid	pelargonium (an herb)	nonanoic acid	12.0 ºC	253 ºC
$CH_3(CH_2)_8CO_2H$	capric acid	goats (L. caper)	decanoic acid	31.0 ºC	219 ºC

Example (Common Names Are in Red)

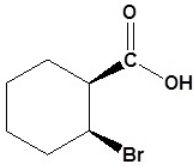


Naming carboxyl groups added to a ring

When a carboxyl group is added to a ring the suffix **-carboxylic acid** is added to the name of the cyclic compound. The ring carbon attached to the carboxyl group is given the #1 location number.



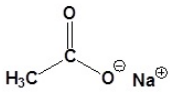
Cyclopentanecarboxylic acid



Cis-2-Bromocyclohexanecarboylic acid

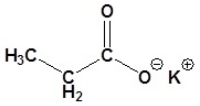
Naming carboxylates

Salts of carboxylic acids are named by writing the name of the cation followed by the name of the acid with the **–ic acid** ending replaced by an **–ate** ending. This is true for both the IUPAC and Common nomenclature systems.



Sodium ethanoate

(Sodium Acetate)

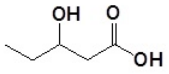


Potassium Propanoate

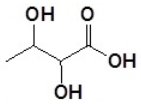
(Potassium propionate)

Naming carboxylic acids which contain other functional groups

Carboxylic acids are given the highest nomenclature priority by the IUPAC system. This means that the carboxyl group is given the lowest possible location number and the appropriate nomenclature suffix is included. In the case of molecules containing carboxylic acid and alcohol functional groups the OH is named as a hydroxyl substituent. However, the **l** in hydroxyl is generally removed.

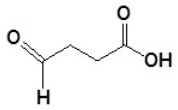


3-Hydroxypentanoic acid

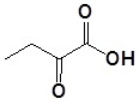


2,3-Dihydroxybutanoic acid

In the case of molecules containing a carboxylic acid and aldehydes and/or ketones functional groups the carbonyl is named as a "Oxo" substituent.

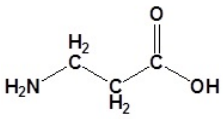


4-Oxobutanoic acid

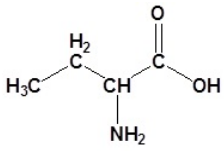


2-Oxobutanoic acid

In the case of molecules containing a carboxylic acid an amine functional group the amine is named as an "amino" substituent.



3-Aminopropanoic acid

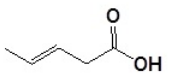


2-Aminobutanoic acid

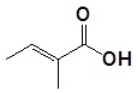
When carboxylic acids are included with an alkene the following order is followed:

(Location number of the alkene)-(Prefix name for the longest carbon chain minus the -ane ending)-(an –enoic acid ending to indicate the presence of an alkene and carboxylic acid)

Remember that the carboxylic acid has priority so it should get the lowest possible location number. Also, remember that cis/tran or E/Z nomenclature for the alkene needs to be included if necessary.



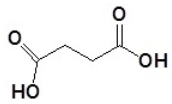
Trans-3-pentenoic acid



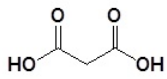
(E)-2-Methyl-2-butenoic acid

Naming dicarboxylic acids

For dicarboxylic acids the location numbers for both carboxyl groups are omitted because both functional groups are expected to occupy the ends of the parent chain. The ending **–dioic acid** is added to the end of the parent chain.



Butanedioic acid



Propanedioic acid

Contributors

- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

17.8: Physical Properties

Physical Properties of Some Carboxylic Acids

Formula	Common Name	Source	IUPAC Name	Melting Point	Boiling Point
HCO_2H	formic acid	ants (L. formica)	methanoic acid	8.4 ºC	101 ºC
CH_3CO_2H	acetic acid	vinegar (L. acetum)	ethanoic acid	16.6 ºC	118 ºC
$CH_3CH_2CO_2H$	propionic acid	milk (Gk. protus prion)	propanoic acid	-20.8 ºC	141 ºC
$CH_3(CH_2)_2CO_2H$	butyric acid	butter (L. butyrum)	butanoic acid	-5.5 ºC	164 ºC
$CH_3(CH_2)_3CO_2H$	valeric acid	valerian root	pentanoic acid	-34.5 ºC	186 ºC
$CH_3(CH_2)_4CO_2H$	caproic acid	goats (L. caper)	hexanoic acid	-4.0 ºC	205 ºC
$CH_3(CH_2)_5CO_2H$	enanthic acid	vines (Gk. oenanthe)	heptanoic acid	-7.5 ºC	223 ºC
$CH_3(CH_2)_6CO_2H$	caprylic acid	goats (L. caper)	octanoic acid	16.3 ºC	239 ºC
$CH_3(CH_2)_7CO_2H$	pelargonic acid	pelargonium (an herb)	nonanoic acid	12.0 ºC	253 ºC
$CH_3(CH_2)_8CO_2H$	capric acid	goats (L. caper)	decanoic acid	31.0 ºC	219 ºC

Saturated			Unsaturated		
Formula	Common Name	Melting Point	Formula	Common Name	Melting Point
$CH_3(CH_2)_{10}CO_2H$	lauric acid	45 ºC	$CH_3(CH_2)_5CH{=}CH(CH_2)_7CO_2H$	palmitoleic acid	0 ºC
$CH_3(CH_2)_{12}CO_2H$	myristic acid	55 ºC	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$	oleic acid	13 ºC
$CH_3(CH_2)_{14}CO_2H$	palmitic acid	63 ºC	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$	linoleic acid	-5 ºC
$CH_3(CH_2)_{16}CO_2H$	stearic acid	69 ºC	$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$	linolenic acid	-11 ºC
$CH_3(CH_2)_{18}CO_2H$	arachidic acid	76 ºC	$CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2CO_2H$	arachidonic acid	-49 ºC

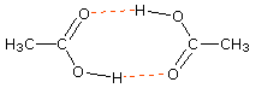
The table at the beginning of this page gave the melting and boiling points for a homologous group of carboxylic acids having from one to ten carbon atoms. The boiling points increased with size in a regular manner, but the melting points did not. Unbranched acids made up of an even number of carbon atoms have melting points higher than the odd numbered homologs having one more or one less carbon. This reflects differences in intermolecular attractive forces in the crystalline state. In the table of fatty acids we see that the presence of a cis-double bond significantly lowers the melting point of a compound. Thus, palmitoleic acid melts over 60º lower than palmitic acid, and similar decreases occur for the C_{18} and C_{20} compounds. Again, changes in crystal packing and intermolecular forces are responsible.

The factors that influence the relative boiling points and water solubilities of various types of compounds were discussed earlier. In general, dipolar attractive forces between molecules act to increase the boiling point of a given compound, with hydrogen bonds being an extreme example. Hydrogen bonding is also a major factor in the water solubility of covalent compounds To refresh your understanding of these principles Click Here. The following table lists a few examples of these properties for some similar sized polar compounds (the non-polar hydrocarbon hexane is provided for comparison).

Physical Properties of Some Organic Compounds

Formula	IUPAC Name	Molecular Weight	Boiling Point	Water Solubility
$CH_3(CH_2)_2CO_2H$	butanoic acid	88	164 ºC	very soluble
$CH_3(CH_2)_4OH$	1-pentanol	88	138 ºC	slightly soluble
$CH_3(CH_2)_3CHO$	pentanal	86	103 ºC	slightly soluble
$CH_3CO_2C_2H_5$	ethyl ethanoate	88	77 ºC	moderately soluble
$CH_3CH_2CO_2CH_3$	methyl propanoate	88	80 ºC	slightly soluble
$CH_3(CH_2)_2CONH_2$	butanamide	87	216 ºC	soluble
$CH_3CON(CH_3)_2$	N,N-dimethylethanamide	87	165 ºC	very soluble
$CH_3(CH_2)_4NH_2$	1-aminobutane	87	103 ºC	very soluble
$CH_3(CH_2)_3CN$	pentanenitrile	83	140 ºC	slightly soluble
$CH_3(CH_2)_4CH_3$	hexane	86	69 ºC	insoluble

The first five entries all have oxygen functional groups, and the relatively high boiling points of the first two is clearly due to hydrogen bonding. Carboxylic acids have exceptionally high boiling points, due in large part to dimeric associations involving two hydrogen bonds. A structural formula for the dimer of acetic acid is shown here. When the mouse pointer passes over the drawing, an electron cloud diagram will appear. The high boiling points of the amides and nitriles are due in large part to strong dipole attractions, supplemented in some cases by hydrogen bonding.



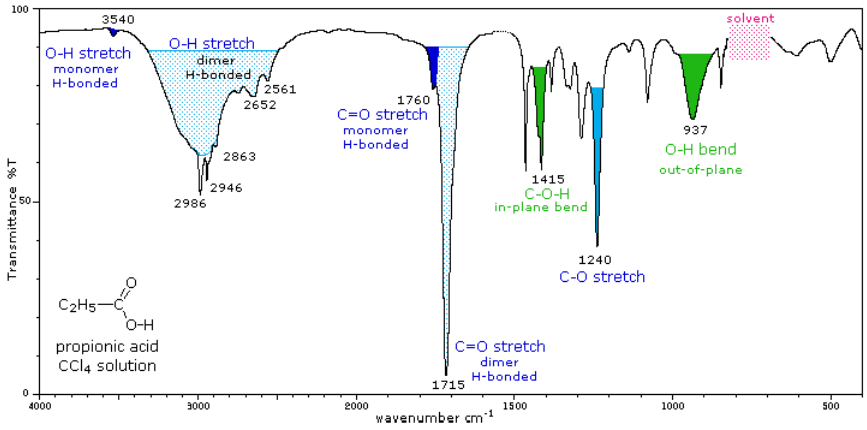
Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

17.9: Spectroscopic Properties

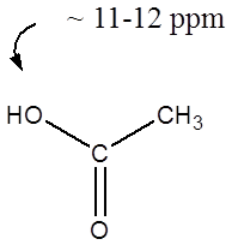
IR

The carboxyl group is associated with two characteristic infrared stretching absorptions which change markedly with hydrogen bonding. The spectrum of a CCl_4 solution of propionic acid (propanoic acid), shown below, is illustrative. Carboxylic acids exist predominantly as hydrogen bonded dimers in condensed phases. The O-H stretching absorption for such dimers is very strong and broad, extending from 2500 to 3300 cm^{-1}. This absorption overlaps the sharper C-H stretching peaks, which may be seen extending beyond the O-H envelope at 2990, 2950 and 2870 cm^{-1}. The smaller peaks protruding near 2655 and 2560 are characteristic of the dimer. In ether solvents a sharper hydrogen bonded monomer absorption near 3500 cm^{-1} is observed, due to competition of the ether oxygen as a hydrogen bond acceptor. The carbonyl stretching frequency of the dimer is found near 1710 cm^{-1}, but is increased by 25 cm^{-1} or more in the monomeric state. Other characteristic stretching and bending absorptions are marked in the spectrum.

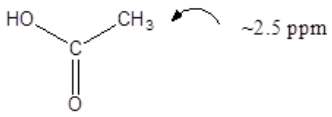


NMR

The combination of anisotropy and electronegativity causes the O-H hydrogen in a carboxylic acid to be very deshielded.



Hydrogen environments adjacent to a carboxylic acid are shifted to the region of 2.5-3.0 ppm.Deshielding occurs due to the fact that the sp^2 hybridized carbon the the carboxylic acid is more electronegative than a sp^3 hybridized carbon.



Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)

17.10: Interesting Carboxylic Acids

Carboxylic acids are widespread in nature, often combined with other functional groups. Simple alkyl carboxylic acids, composed of four to ten carbon atoms, are liquids or low melting solids having very unpleasant odors. The **fatty acids** are important components of the biomolecules known as **lipids**, especially fats and oils. As shown in the following table, these long-chain carboxylic acids are usually referred to by their common names, which in most cases reflect their sources. A mnemonic phrase for the C_{10} to C_{20} natural fatty acids capric, lauric, myristic, palmitic, stearic and arachidic is: "**C**urly, **L**arry & **M**oe **P**erform **S**illy **A**ntics" (note that the names of the three stooges are in alphabetical order).

Interestingly, the molecules of most natural fatty acids have an even number of carbon atoms. Analogous compounds composed of odd numbers of carbon atoms are perfectly stable and have been made synthetically. Since nature makes these long-chain acids by linking together acetate units, it is not surprising that the carbon atoms composing the natural products are multiples of two. The double bonds in the unsaturated compounds listed on the right are all cis (or Z).

FATTY ACIDS

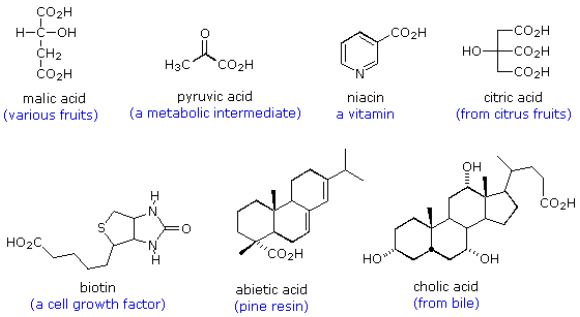
Saturated

Formula	Common Name	Melting Point
$CH_3(CH_2)_{10}CO_2H$	lauric acid	45 ºC
$CH_3(CH_2)_{12}CO_2H$	myristic acid	55 ºC
$CH_3(CH_2)_{14}CO_2H$	palmitic acid	63 ºC
$CH_3(CH_2)_{16}CO_2H$	stearic acid	69 ºC
$CH_3(CH_2)_{18}CO_2H$	arachidic acid	76 ºC

Unsaturated

Formula	Common Name	Melting Point
$CH_3(CH_2)_5CH=CH(CH_2)_7CO_2H$	palmitoleic acid	0 ºC
$CH_3(CH_2)_7CH=CH(CH_2)_7CO_2H$	oleic acid	13 ºC
$CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7CO_2H$	linoleic acid	-5 ºC
$CH_3CH_2CH=CHCH_2CH=CHCH_2CH=CH(CH_2)_7CO_2H$	linolenic acid	-11 ºC
$CH_3(CH_2)_4(CH=CHCH_2)_4(CH_2)_2CO_2H$	arachidonic acid	-49 ºC

The following formulas are examples of other naturally occurring carboxylic acids. The molecular structures range from simple to complex, often incorporate a variety of other functional groups, and many are chiral.



Contributors

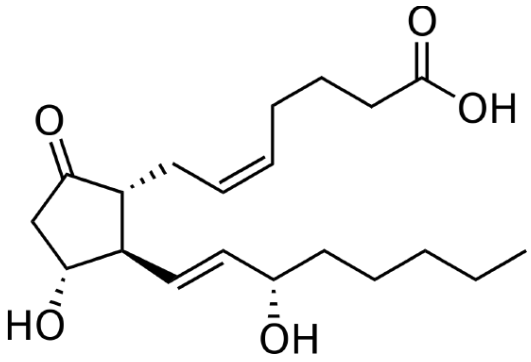
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

17.11: Aspirin, Arachidonic Acid, and Prostaglandins

Prostaglandins were first discovered and isolated from human semen in the 1930s by Ulf von Euler of Sweden. Thinking they had come from the prostate gland, he named them prostaglandins. It has since been determined that they exist and are synthesized in virtually every cell of the body. Prostaglandins, are like hormones in that they act as chemical messengers, but do not move to other sites, but work right within the cells where they are synthesized.

Introduction

Prostaglandins are unsaturated carboxylic acids, consisting of of a 20 carbon skeleton that also contains a five member ring. They are biochemically synthesized from the fatty acid, arachidonic acid. See the graphic on the left. The unique shape of the arachidonic acid caused by a series of cis double bonds helps to put it into position to make the five member ring.



Structure of prostaglandin E2 (PGE_2)

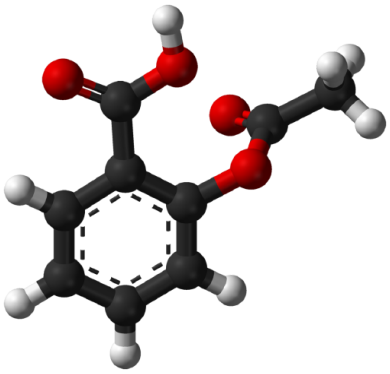
Prostaglandin Structure

Prostaglandins are unsaturated carboxylic acids, consisting of of a 20 carbon skeleton that also contains a five member ring and are based upon the fatty acid, arachidonic acid. There are a variety of structures one, two, or three double bonds. On the five member ring there may also be double bonds, a ketone, or alcohol groups. A typical structure is on the left graphic.

Functions of Prostaglandins

There are a variety of physiological effects including:

1. Activation of the inflammatory response, production of pain, and fever. When tissues are damaged, white blood cells flood to the site to try to minimize tissue destruction. Prostaglandins are produced as a result.
2. Blood clots form when a blood vessel is damaged. A type of prostaglandin called thromboxane stimulates constriction and clotting of platelets. Conversely, PGI2, is produced to have the opposite effect on the walls of blood vessels where clots should not be forming.
3. Certain prostaglandins are involved with the induction of labor and other reproductive processes. PGE2 causes uterine contractions and has been used to induce labor.
4. Prostaglandins are involved in several other organs such as the gastrointestinal tract (inhibit acid synthesis and increase secretion of protective mucus), increase blood flow in kidneys, and leukotriens promote constriction of bronchi associated with asthma.



Ball-and-stick model of the aspirin molecule, as found in the solid state. Single-crystal X-ray diffraction data from Kim, Y.; Machida, K.; Taga, T.; Osaki, K. (1985). "Structure Redetermination and Packing Analysis of Aspirin Crystal". Chem. Pharm. Bull. ***33*** *(7): 2641-2647. ISSN 1347-5223.*

Effects of Aspirin and other Pain Killers

When you see that prostaglandins induce inflammation, pain, and fever, what comes to mind but aspirin. Aspirin blocks an enzyme called cyclooxygenase, COX-1 and COX-2, which is involved with the ring closure and addition of oxygen to arachidonic acid converting to prostaglandins. The acetyl group on aspirin is hydrolzed and then bonded to the alcohol group of serine as an ester. This has the effect of blocking the channel in the enzyme and arachidonic can not enter the active site of the enzyme. By inhibiting or blocking this enzyme, the synthesis of prostaglandins is blocked, which in turn relives some of the effects of pain and fever. Aspirin is also thought to inhibit the prostaglandin synthesis involved with unwanted blood clotting in coronary heart disease. At the same time an injury while taking aspirin may cause more extensive bleeding.

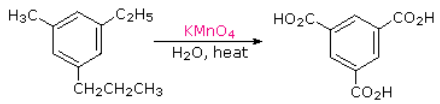
Contributors

Charles Ophardt (Professor Emeritus, Elmhurst College); Virtual Chembook

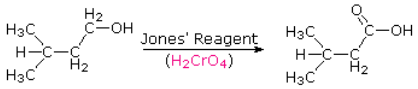
17.12: Preparation of Carboxylic Acids

The carbon atom of a carboxyl group has a high oxidation state. It is not surprising, therefore, that many of the chemical reactions used for their preparation are oxidations. Such reactions have been discussed in previous sections of this text, and the following diagram summarizes most of these. To review the previous discussion of any of these reaction classes simply click on the number (**1** to **4**) or descriptive heading for the group.

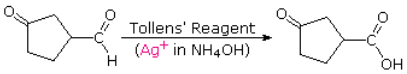
1. Oxidation of Arene Side-Chains



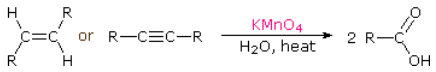
2. Oxidation of 1°-Alcohols



3. Oxidation of Aldehydes

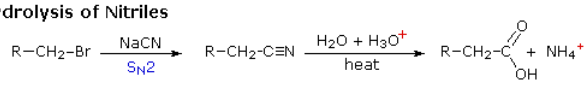


4. Oxidative Cleavage of Alkenes and Alkynes

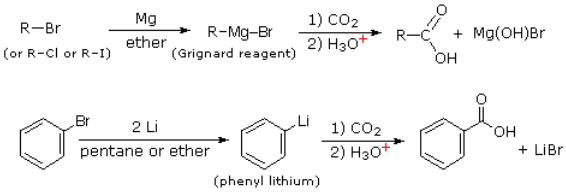


Two other useful procedures for preparing carboxylic acids involve hydrolysis of nitriles and carboxylation of organometallic intermediates. As shown in the following diagram, both methods begin with an organic halogen compound and the carboxyl group eventually replaces the halogen. Both methods require two steps, but are complementary in that the nitrile intermediate in the first procedure is generated by a S_N2 reaction, in which cyanide anion is a nucleophilic precursor of the carboxyl group. The hydrolysis may be either acid or base-catalyzed, but the latter give a carboxylate salt as the initial product.
In the second procedure the electrophilic halide is first transformed into a strongly nucleophilic metal derivative, and this adds to carbon dioxide (an electrophile). The initial product is a salt of the carboxylic acid, which must then be released by treatment with strong aqueous acid.

Hydrolysis of Nitriles



Carboxylation of Organometallic Reagents



An existing carboxylic acid may be elongated by one methylene group, using a homologation procedure called the **Arndt-Eistert reaction**. To learn about this useful method Click Here.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

17.13: Reactions of Carboxylic Acids—General Features

Salt Formation

Because of their enhanced acidity, carboxylic acids react with bases to form ionic salts, as shown in the following equations. In the case of alkali metal hydroxides and simple amines (or ammonia) the resulting salts have pronounced ionic character and are usually soluble in water. Heavy metals such as silver, mercury and lead form salts having more covalent character (3rd example), and the water solubility is reduced, especially for acids composed of four or more carbon atoms.

RCO_2H	+	$NaHCO_3$	⟶	$RCO_2^{(-)}\ Na^{(+)} + CO_2 + H_2O$
RCO_2H	+	$(CH_3)_3N$:	⟶	$RCO_2^{(-)}\ (CH_3)_3NH^{(+)}$
RCO_2H	+	AgOH	⟶	$RCO_2^{\delta(-)}\ Ag^{\delta(+)} + H_2O$

Carboxylic acids and salts having alkyl chains longer than six carbons exhibit unusual behavior in water due to the presence of both hydrophilic (CO_2) and hydrophobic (alkyl) regions in the same molecule. Such molecules are termed **amphiphilic** (Gk. amphi = both) or **amphipathic**. Depending on the nature of the hydrophilic portion these compounds may form monolayers on the water surface or sphere-like clusters, called micelles, in solution.

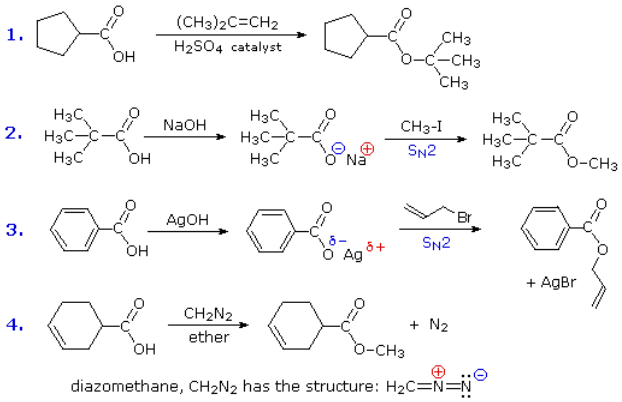
Substitution of the Hydroxyl Hydrogen

This reaction class could be termed **electrophilic substitution at oxygen**, and is defined as follows (E is an electrophile). Some examples of this substitution are provided in equations (1) through (4).

$RCO_2–H + E^{(+)}$	⟶	$RCO_2–E + H^{(+)}$

If E is a strong electrophile, as in the first equation, it will attack the nucleophilic oxygen of the carboxylic acid directly, giving a positively charged intermediate which then loses a proton. If E is a weak electrophile, such as an alkyl halide, it is necessary to convert the carboxylic acid to the more nucleophilic carboxylate anion to facilitate the substitution. This is the procedure used in reactions 2 and 3. Equation 4 illustrates the use of the reagent diazomethane (CH_2N_2) for the preparation of methyl esters. This toxic and explosive gas is always used as an ether solution (bright yellow in color). The reaction is easily followed by the evolution of nitrogen gas and the disappearance of the reagent's color. This reaction is believed to proceed by the rapid bonding of a strong electrophile to a carboxylate anion.

The nature of S_N2 reactions, as in equations 2 & 3, has been described elsewhere. The mechanisms of reactions 1 & 4 will be displayed by clicking the "Toggle Mechanism" button below the diagram.



Mechanism Toggle | Other Examples

Alkynes may also serve as electrophiles in substitution reactions of this kind, as illustrated by the synthesis of vinyl acetate from acetylene. Intramolecular carboxyl group additions to alkenes generate cyclic esters known as **lactones**. Five-membered (gamma) and six-membered (delta) lactones are most commonly formed. Electrophilic species such as acids or halogens are necessary

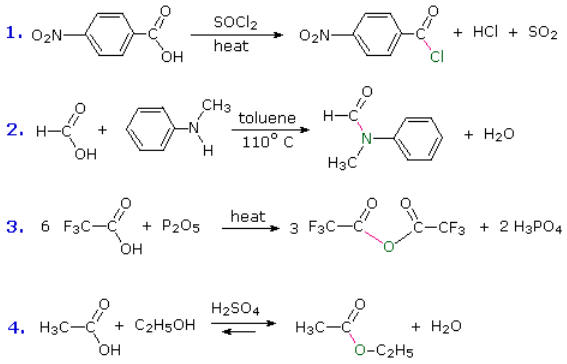
initiators of lactonizations. Even the weak electrophile iodine initiates iodolactonization of γ,δ- and δ,ε-unsaturated acids. Examples of these reactions will be displayed by clicking the "Other Examples" button.

Substitution of the Hydroxyl Group

Reactions in which the hydroxyl group of a carboxylic acid is replaced by another nucleophilic group are important for preparing functional derivatives of carboxylic acids. The alcohols provide a useful reference chemistry against which this class of transformations may be evaluated. In general, the hydroxyl group proved to be a poor leaving group, and virtually all alcohol reactions in which it was lost involved a prior conversion of –OH to a better leaving group. This has proven to be true for the carboxylic acids as well.

Four examples of these hydroxyl substitution reactions are presented by the following equations. In each example, the new bond to the carbonyl group is colored magenta and the nucleophilic atom that has replaced the hydroxyl oxygen is colored green. The hydroxyl moiety is often lost as water, but in reaction #1 the hydrogen is lost as HCl and the oxygen as SO_2. This reaction parallels a similar transformation of alcohols to alkyl chlorides, although its mechanism is different. Other reagents that produce a similar conversion to acyl halides are PCl_5 and $SOBr_2$.

The amide and anhydride formations shown in equations #2 & 3 require strong heating, and milder procedures that accomplish these transformations will be described in the next chapter.



Esterification Mechanism

Reaction #4 is called **esterification**, since it is commonly used to convert carboxylic acids to their ester derivatives. Esters may be prepared in many different ways; indeed, equations #1 and #4 in the previous diagram illustrate the formation of tert-butyl and methyl esters respectively. The acid-catalyzed formation of ethyl acetate from acetic acid and ethanol shown here is reversible, with an equilibrium constant near 2. The reaction can be forced to completion by removing the water as it is formed. This type of esterification is often referred to as **Fischer esterification**. As expected, the reverse reaction, **acid-catalyzed ester hydrolysis**, can be carried out by adding excess water.

A thoughtful examination of this reaction (#4) leads one to question why it is classified as a hydroxyl substitution rather than a hydrogen substitution. The following equations, in which the hydroxyl oxygen atom of the carboxylic acid is colored red and that of the alcohol is colored blue, illustrate this distinction (note that the starting compounds are in the center).

H_2O + CH_3CO-OCH_2CH_3	H-substitution ←	CH_3CO-OH + CH_3CH_2-OH	HO-substitution →	CH_3CO-OCH_2CH_3 + H_2O

In order to classify this reaction correctly and establish a plausible mechanism, the oxygen atom of the alcohol was isotopically labeled as ^{18}O (colored blue in our equation). Since this oxygen is found in the ester product and not the water, the hydroxyl group of the acid must have been replaced in the substitution. A mechanism for this general esterification reaction will be displayed on clicking the "Esterification Mechanism" button; also, once the mechanism diagram is displayed, a reaction coordinate for it can be seen by clicking the head of the green "energy diagram" arrow. Addition-elimination mechanisms of this kind proceed by way of tetrahedral intermediates (such as A and B in the mechanism diagram) and are common in acyl substitution reactions. Acid catalysis is necessary to increase the electrophilic character of the carboxyl carbon atom, so it will bond more rapidly to the

nucleophilic oxygen of the alcohol. Base catalysis is not useful because base converts the acid to its carboxylate anion conjugate base, a species in which the electrophilic character of the carbon is reduced.

Since a tetrahedral intermediate occupies more space than a planar carbonyl group, we would expect the rate of this reaction to be retarded when bulky reactants are used. To test this prediction the esterification of acetic acid was compared with that of 2,2-dimethylpropanoic acid, $(CH_3)_3CO_2H$. Here the relatively small methyl group of acetic acid is replaced by a larger tert-butyl group, and the bulkier acid reacted fifty times slower than acetic acid. Increasing the bulk of the alcohol reactant results in a similar rate reduction.

Contributors

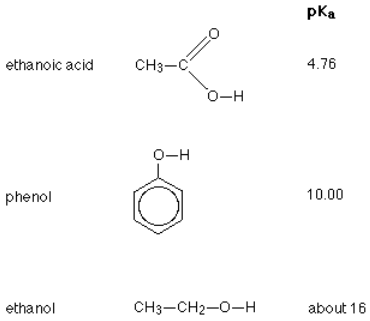
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

17.14: Carboxylic Acids—Strong Organic Brønsted–Lowry Acids

Comparing the strengths of weak acids

The strengths of weak acids are measured on the pK_a scale. The smaller the number on this scale, the stronger the acid is.

Three of the compounds we shall be looking at, together with their pK_a values are:



Remember - the smaller the number the stronger the acid. Comparing the other two to ethanoic acid, you will see that phenol is very much weaker with a pK_a of 10.00, and ethanol is so weak with a pK_a of about 16 that it hardly counts as acidic at all!

Acidity of Carboxylic Acids

The pK_a 's of some typical carboxylic acids are listed in the following table. When we compare these values with those of comparable alcohols, such as ethanol (pK_a = 16) and 2-methyl-2-propanol (pK_a = 19), it is clear that carboxylic acids are stronger acids by over ten powers of ten! Furthermore, electronegative substituents near the carboxyl group act to increase the acidity.

Compound	pK_a	Compound	pK_a
HCO_2H	3.75	$CH_3CH_2CH_2CO_2H$	4.82
CH_3CO_2H	4.74	$ClCH_2CH_2CH_2CO_2H$	4.53
FCH_2CO_2H	2.65	$CH_3CHClCH_2CO_2H$	4.05
$ClCH_2CO_2H$	2.85	$CH_3CH_2CHClCO_2H$	2.89
$BrCH_2CO_2H$	2.90	$C_6H_5CO_2H$	4.20
ICH_2CO_2H	3.10	$p\text{-}O_2NC_6H_4CO_2H$	3.45
Cl_3CCO_2H	0.77	$p\text{-}CH_3OC_6H_4CO_2H$	4.45

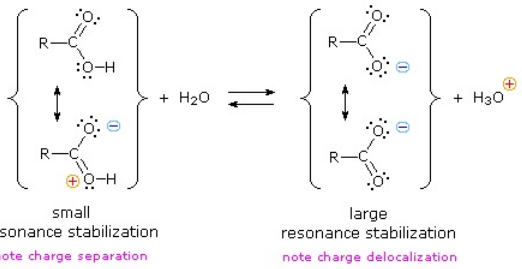
Why should the presence of a carbonyl group adjacent to a hydroxyl group have such a profound effect on the acidity of the hydroxyl proton? To answer this question we must return to the nature of acid-base equilibria and the definition of pK_a , illustrated by the general equations given below. These relationships were described in an previous section of this text.

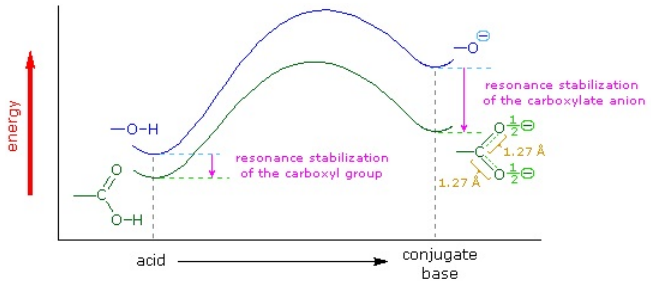
$$H\text{–}A + H_2O \rightleftharpoons H_3O^{\oplus} + A:^{\ominus} \qquad K_{eq} = \frac{[H_3O^{\oplus}]\,[A:^{\ominus}]}{[HA]\,[H_2O]}$$

$$K_a = \frac{[H_3O^{\oplus}]\,[A:^{\ominus}]}{[HA]} \qquad pK_a = -\log K_a = \log\left(\frac{1}{K_a}\right)$$

We know that an equilibrium favors the thermodynamically more stable side, and that the magnitude of the equilibrium constant reflects the energy difference between the components of each side. In an acid base equilibrium the equilibrium always favors the weaker acid and base (these are the more stable components). Water is the standard base used for pK_a measurements; consequently, anything that stabilizes the conjugate base ($A:^{(-)}$) of an acid will necessarily make that acid (H–A) stronger and shift the equilibrium to the right. Both the carboxyl group and the carboxylate anion are stabilized by resonance, but the stabilization of the anion is much greater than that of the neutral function, as shown in the following diagram. In the carboxylate anion the two

contributing structures have equal weight in the hybrid, and the C–O bonds are of equal length (between a double and a single bond). This stabilization leads to a markedly increased acidity, as illustrated by the energy diagram displayed by clicking the "Toggle Display" button.





mpounds like alcohols and phenol which contain an -OH group attached to a hydrocarbon are very weak acids. Alcohols are so weakly acidic that, for normal lab purposes, their acidity can be virtually ignored. However, phenol is sufficiently acidic for it to have recognizably acidic properties - even if it is still a very weak acid. A hydrogen ion can break away from the -OH group and transfer to a base.

The pKa of ethanol is about 17, while the pKa of acetic acid is about 5: this is a 10^{12}-fold difference in the two acidity constants. In both compounds, the acidic proton is bonded to an oxygen atom. How can they be so different in terms of acidity?

We begin by considering the conjugate bases.

In both species, the negative charge on the conjugate base is held by an oxygen, so periodic trends cannot be invoked. For acetic acid, however, there is a key difference: a resonance contributor can be drawn in which the negative charge is localized on the second oxygen of the group. The two resonance forms for the conjugate base are equal in energy. What this means is that the negative charge on the acetate ion is not located on one oxygen or the other: rather it is shared between the two. Chemists use the term ‘delocalization of charge’ to describe this situation. In the ethoxide ion, by contrast, the negative charge is ‘locked’ on the single oxygen – it has nowhere else to go.

Recall the findamental idea that electrostatic charges, whether positive or negative, are more stable when they are ‘spread out’ than when they are confined to one atom. Here, a charge is being ‘spread out’ (in other words, delocalized) *by resonance*, rather than simply by the size of the atom involved.

The delocalization of charge by resonance has a very powerful effect on the reactivity of organic molecules, enough to account for the difference of over 12 pK_a units between ethanol and acetic acid. The acetate ion is that much more stable than the ethoxide ion, all due to the effects of resonance delocalization.

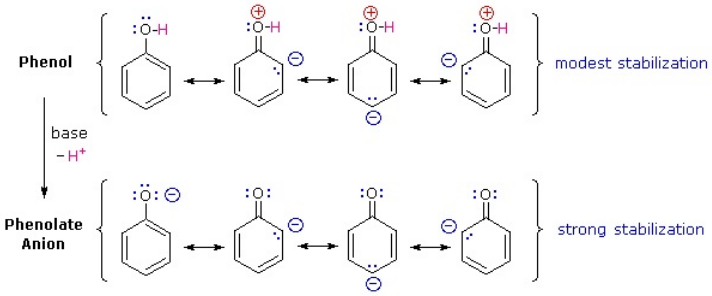
The resonance effect also explains why a nitrogen atom is much more basic when it is in an amine, but *not* significantly basic when it is part of an amide group. Recall that in an amide, there is significant double-bond character to the carbon-nitrogen bond, due to a second resonance contributor in which the nitrogen lone pair is part of a p bond.

While the electron lone pair of an amine nitrogen is ‘stuck’ in one place, the lone pair on an amide nitrogen is delocalized by resonance. Notice that in this case, we are extending our central statement to say that electron density – in the form of a lone pair – is stabilized by resonance delocalization, even though there is not a negative charge involved. Here’s another way to think about it: the lone pair on an amide nitrogen is not available for bonding with a proton – these two electrons are too ‘comfortable’ being part of the delocalized pi-bonding system. The lone pair on an amine nitrogen, by contrast, is not part of a delocalized pi system, and is very ready to form a bond with any acidic proton that might be nearby.

Why is phenol acidic?

Compounds like alcohols and phenol which contain an -OH group attached to a hydrocarbon are very weak acids. Alcohols are so weakly acidic that, for normal lab purposes, their acidity can be virtually ignored. However, phenol is sufficiently acidic for it to have recognizably acidic properties - even if it is still a very weak acid. A hydrogen ion can break away from the -OH group and transfer to a base. For example, in solution in water:

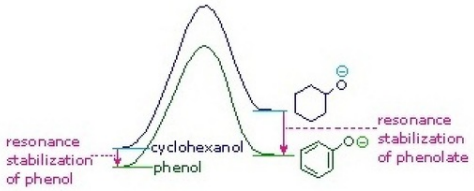
Phenol is a very weak acid and the position of equilibrium lies well to the left. Phenol can lose a hydrogen ion because the phenoxide ion formed is stabilised to some extent. The negative charge on the oxygen atom is delocalised around the ring. The more stable the ion is, the more likely it is to form. One of the lone pairs on the oxygen atom overlaps with the delocalised electrons on the benzene ring.



This overlap leads to a delocalization which extends from the ring out over the oxygen atom. As a result, the negative charge is no longer entirely localized on the oxygen, but is spread out around the whole ion.

Spreading the charge around makes the ion more stable than it would be if all the charge remained on the oxygen. However, oxygen is the most electronegative element in the ion and the delocalized electrons will be drawn towards it. That means that there will still be a lot of charge around the oxygen which will tend to attract the hydrogen ion back again. That is why phenol is only a very weak acid.

Why is phenol a much stronger acid than cyclohexanol? To answer this question we must evaluate the manner in which an oxygen substituent interacts with the benzene ring. As noted in our earlier treatment of electrophilic aromatic substitution reactions, an oxygen substituent enhances the reactivity of the ring and favors electrophile attack at ortho and para sites. It was proposed that resonance delocalization of an oxygen non-bonded electron pair into the pi-electron system of the aromatic ring was responsible for this substituent effect. A similar set of resonance structures for the phenolate anion conjugate base appears below the phenol structures.



The resonance stabilization in these two cases is very different. An important principle of resonance is that charge separation diminishes the importance of canonical contributors to the resonance hybrid and reduces the overall stabilization. The contributing structures to the phenol hybrid all suffer charge separation, resulting in very modest stabilization of this compound. On the other hand, the phenolate anion is already charged, and the canonical contributors act to disperse the charge, resulting in a substantial stabilization of this species. The conjugate bases of simple alcohols are not stabilized by charge delocalization, so the acidity of these compounds is similar to that of water. An energy diagram showing the effect of resonance on cyclohexanol and phenol acidities is shown on the right. Since the resonance stabilization of the phenolate conjugate base is much greater than the stabilization of phenol itself, the acidity of phenol relative to cyclohexanol is increased. Supporting evidence that the phenolate negative charge is delocalized on the ortho and para carbons of the benzene ring comes from the influence of electron-withdrawing substituents at those sites.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Jim Clark (Chemguide.co.uk)

CHAPTER OVERVIEW

18: Introduction to Carbonyl Chemistry; Organometallic Reagents; Oxidation and Reduction

Topic hierarchy

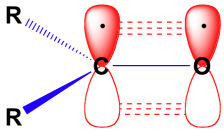
18.1: Introduction

A carbonyl group is a chemically organic functional group composed of a carbon atom double-bonded to an oxygen atom --> [**C=O**] The simplest carbonyl groups are aldehydes and ketones usually attached to another carbon compound. These structures can be found in many aromatic compounds contributing to smell and taste.

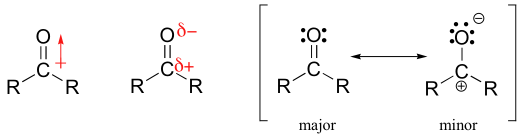
The Carbonyl Group

C=O is prone to additions and nucleophillic attack because or carbon's positive charge and oxygen's negative charge. The resonance of the carbon partial positive charge allows the negative charge on the nucleophile to attack the Carbonyl group and become a part of the structure and a positive charge (usually a proton hydrogen) attacks the oxygen. Just a reminder, the nucleophile is a good acid therefore "likes protons" so it will attack the side with a positive charge.

Before we consider in detail the reactivity of aldehydes and ketones, we need to look back and remind ourselves of what the bonding picture looks like in a carbonyl. Carbonyl carbons are sp^2 hybridized, with the three sp^2 orbitals forming soverlaps with orbitals on the oxygen and on the two carbon or hydrogen atoms. These three bonds adopt trigonal planar geometry. The remaining unhybridized 2p orbital on the central carbonyl carbon is perpendicular to this plane, and forms a ‘side-by-side’ pbond with a 2p orbital on the oxygen.

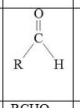
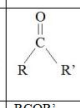
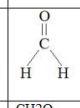
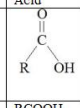
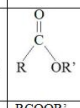
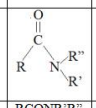
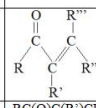
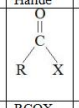
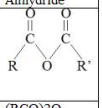


The carbon-oxygen double bond is polar: oxygen is more electronegative than carbon, so electron density is higher on the oxygen side of the bond and lower on the carbon side. Recall that bond polarity can be depicted with a dipole arrow, or by showing the oxygen as holding a partial negative charge and the carbonyl carbon a partial positive charge.



A third way to illustrate the carbon-oxygen dipole is to consider the two main resonance contributors of a carbonyl group: the major form, which is what you typically see drawn in Lewis structures, and a minor but very important contributor in which both electrons in the pbond are localized on the oxygen, giving it a full negative charge. The latter depiction shows the carbon with an empty 2p orbital and a full positive charge.

Some Carbonyl Compounds

Compound	Aldehyde	Ketone	Formaldehyde	Carboxylic Acid	Ester	Amide	Enone	Acyl Halide	Acid Anhydride
Structure									
General Formula	RCHO	RCOR’	CH2O	RCOOH	RCOOR’	RCONR’R”	RC(O)C(R’)CR”R”’	RCOX	(RCO)2O

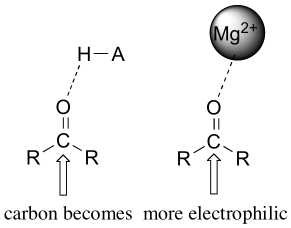
Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- Prof. Steven Farmer (Sonoma State University)

18.2: General Reactions of Carbonyl Compounds

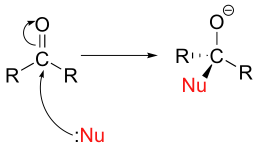
Nucleophilic Addition to Aldehydes and Ketones

The result of carbonyl bond polarization, however it is depicted, is straightforward to predict. The carbon, because it is electron-poor, is an electrophile: it is a great target for attack by an electron-rich nucleophilic group. Because the oxygen end of the carbonyl double bond bears a partial negative charge, anything that can help to stabilize this charge by accepting some of the electron density will increase the bond's polarity and make the carbon more electrophilic. Very often a general acid group serves this purpose, donating a proton to the carbonyl oxygen.

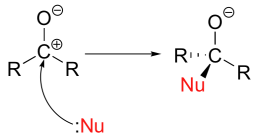


The same effect can also be achieved if a Lewis acid, such as a magnesium ion, is located near the carbonyl oxygen.

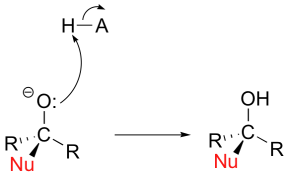
Unlike the situation in a nucleophilic substitution reaction, when a nucleophile attacks an aldehyde or ketone carbon there is no leaving group – the incoming nucleophile simply 'pushes' the electrons in the pi bond up to the oxygen.



Alternatively, if you start with the minor resonance contributor, you can picture this as an attack by a nucleophile on a carbocation.



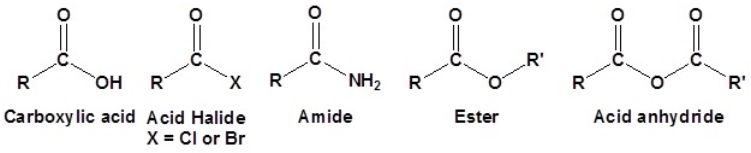
After the carbonyl is attacked by the nucleophile, the negatively charged oxygen has the capacity to act as a nucleophile. However, most commonly the oxygen acts instead as a base, abstracting a proton from a nearby acid group in the solvent or enzyme active site.



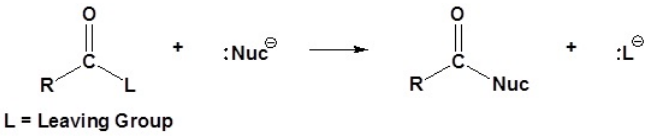
This very common type of reaction is called a **nucleophilic addition**. In many biologically relevant examples of nucleophilic addition to carbonyls, the nucleophile is an alcohol oxygen or an amine nitrogen, or occasionally a thiol sulfur. In one very important reaction type known as an aldol reaction (which we will learn about in section 13.3) the nucleophile attacking the carbonyl is a resonance-stabilized carbanion. In this chapter, we will concentrate on reactions where the nucleophile is an oxygen or nitrogen.

Nucleophilic Substitution of RCOZ (Z = Leaving Group)

Carbonyl compounds with leaving groups have reactions similar to aldehydes and ketones. The main difference is the presence of an electronegative substituent that can act as a leaving group during a nucleophile substitution reaction. Although there are many types of carboxylic acid derivatives known, this article focuses on four: acid halides, acid anhydrides, esters, and amides.

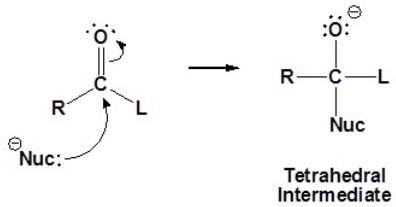


General reaction

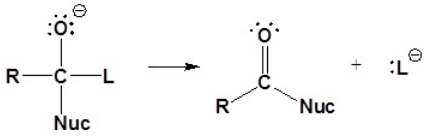


General mechanism

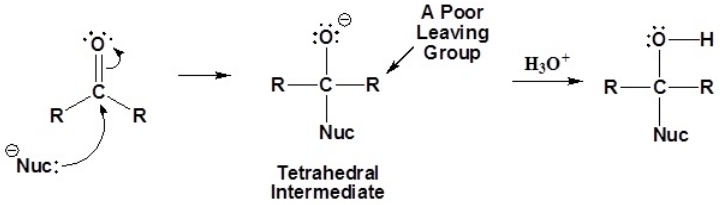
1) Nucleophilic attack on the carbonyl



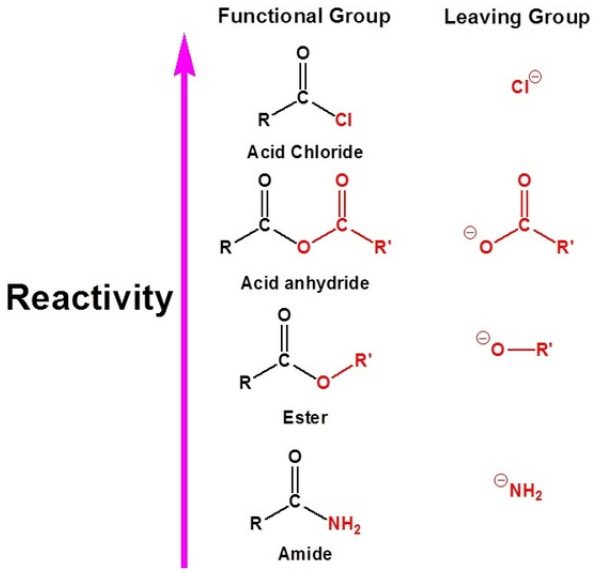
2) Leaving group is removed



Although aldehydes and ketones also contain carbonyls, their chemistry is distinctly different because they do not contain suitable leaving groups. Once a tetrahedral intermediate is formed, aldehydes and ketones cannot reform their carbonyls. Because of this, aldehydes and ketones typically undergo nucleophilic additions and not substitutions.



The relative reactivity of carboxylic acid derivatives toward nucleophile substitutions is related to the electronegative leaving group's ability to activate the carbonyl. The more electronegative leaving groups withdraw electron density from the carbonyl, thereby increasing its electrophilicity.



Contributors

- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Prof. Steven Farmer (Sonoma State University)

18.3: A Preview of Oxidation and Reduction

Solutions to exercises

You are undoubtedly already familiar with the general idea of oxidation and reduction: you learned in general chemistry that when a compound or atom is oxidized it loses electrons, and when it is reduced it gains electrons. You also know that oxidation and reduction reactions occur in pairs: if one species is oxidized, another must be reduced at the same time - thus the term 'redox reaction'.

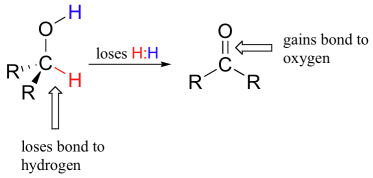
Most of the redox reactions you have seen previously in general chemistry probably involved the flow of electrons from one metal to another, such as the reaction between copper ion in solution and metallic zinc:

$$Cu^{+2}_{(aq)} + Zn_{(s)} \rightarrow Cu_{(s)} + Zn^{+2}_{(aq)}$$

In organic chemistry, redox reactions look a little different. Electrons in an organic redox reaction often are transferred in the form of a hydride ion - a proton and two electrons. Because they occur in conjunction with the transfer of a proton, these are commonly referred to as **hydrogenation** and **dehydrogenation** reactions: a hydride plus a proton adds up to a hydrogen (H_2) molecule. Be careful - do not confuse the terms hyd**rogen**ation and dehy**drogen**ation with hydration and dehydration - the latter refer to the gain and loss of a *water* molecule (and are *not* redox reactions), while the former refer to the gain and loss of a *hydrogen* molecule.

When a carbon atom in an organic compound loses a bond to hydrogen and gains a new bond to a heteroatom (or to another carbon), we say the compound has been dehydrogenated, or oxidized. A very common biochemical example is the oxidation of an alcohol to a ketone or aldehyde:

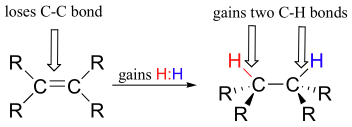
Dehydrogenation (oxidation) of an alcohol



When a carbon atom loses a bond to hydrogen and gains a bond to a heteroatom (or to another carbon atom), it is considered to be an oxidative process because hydrogen, of all the elements, is the least electronegative. Thus, in the process of dehydrogenation the carbon atom undergoes an overall loss of electron density - and loss of electrons is oxidation.

Conversely, when a carbon atom in an organic compound gains a bond to hydrogen and loses a bond to a heteroatom (or to another carbon atom), we say that the compound has been hydrogenated, or reduced. The hydrogenation of a ketone to an alcohol, for example, is overall the reverse of the alcohol dehydrogenation shown above. Illustrated below is another common possibility, the hydrogenation (reduction) of an alkene to an alkane.

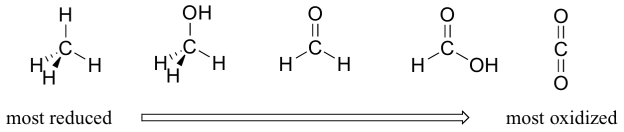
Hydrogenation (reduction) of an alkene



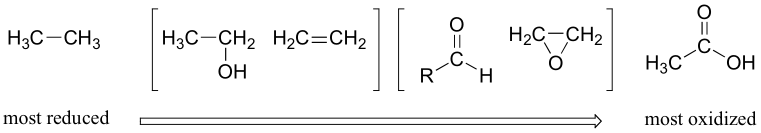
Hydrogenation results in *higher* electron density on a carbon atom(s), and thus we consider process to be one of reduction of the organic molecule.

Notice that neither hydrogenation nor dehydrogenation involves the gain or loss of an oxygen *atom*. Reactions which *do* involve gain or loss of one or more oxygen atoms are usually referred to as 'oxygenase' and 'reductase' reactions, and are the subject of section 16.10 and section 17.3.

For the most part, when talking about redox reactions in organic chemistry we are dealing with a small set of very recognizable functional group transformations. It is therefore very worthwhile to become familiar with the idea of 'oxidation states' as applied to organic functional groups. By comparing the relative number of bonds to hydrogen atoms, we can order the familiar functional groups according to oxidation state. We'll take a series of single carbon compounds as an example. Methane, with four carbon-hydrogen bonds, is highly reduced. Next in the series is methanol (one less carbon-hydrogen bond, one more carbon-oxygen bond), followed by formaldehyde, formate, and finally carbon dioxide at the highly oxidized end of the group.



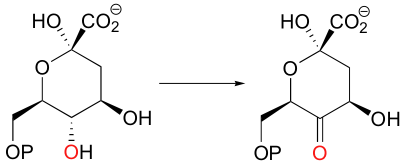
This pattern holds true for the relevant functional groups on organic molecules with two or more carbon atoms:



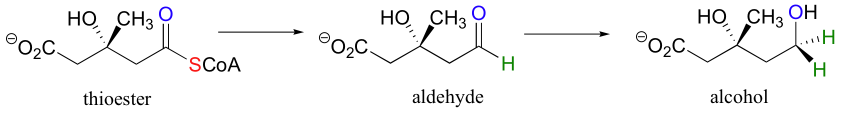
Alkanes are highly reduced, while alcohols - as well as alkenes, ethers, amines, sulfides, and phosphate esters - are one step up on the oxidation scale, followed by aldehydes/ketones/imines and epoxides, and finally by carboxylic acid derivatives (carbon dioxide, at the top of the oxidation list, is specific to the single carbon series).

Notice that in the series of two-carbon compounds above, ethanol and ethene are considered to be in the same oxidation state. You know already that alcohols and alkenes are interconverted by way of addition or elimination of water (section 14.1). When an alcohol is dehydrated to form an alkene, one of the two carbons loses a C-H bond and gains a C-C bond, and thus is oxidized. However, the other carbon loses a C-O bond and gains a C-C bond, and thus is considered to be reduced. Overall, therefore, there is no change to the oxidation state of the molecule.

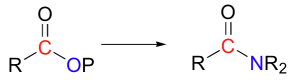
You should learn to recognize when a reaction involves a change in oxidation state in an organic reactant . Looking at the following transformation, for example, you should be able to quickly recognize that it is an oxidation: an alcohol functional group is converted to a ketone, which is one step up on the oxidation ladder.



Likewise, this next reaction involves the transformation of a carboxylic acid derivative (a thioester) first to an aldehyde, then to an alcohol: this is a *double* reduction, as the substrate loses two bonds to heteroatoms and gains two bonds to hydrogens.



An acyl transfer reaction (for example the conversion of an acyl phosphate to an amide) is *not* considered to be a redox reaction - the oxidation state of the organic molecule is does not change as substrate is converted to product, because a bond to one heteroatom (oxygen) has simply been traded for a bond to another heteroatom (nitrogen).



carbon is in same oxidation state - not a redox reaction

It is important to be able to recognize when an organic molecule is being oxidized or reduced, because this information tells you to look for the participation of a corresponding redox agent that is being reduced or oxidized- remember, oxidation and reduction always occur in tandem! We will soon learn in detail about the most important biochemical and laboratory redox agents.

{template.ExampleStart()}}

Exercise 16.1: is an aldol condensation a redox reaction? Explain.

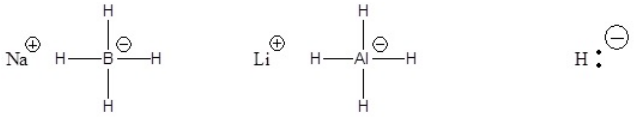
Exercise 16.2: Is the reaction catalyzed by squalene epoxidase a redox reaction? How about squalene cyclase? Explain.

Template:ExampleEnd

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

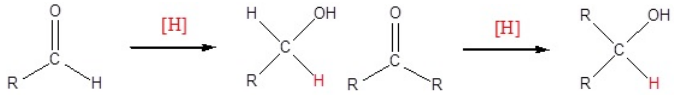
18.4: Reduction of Aldehydes and Ketones

he most common sources of the hydride Nucleophile are lithium aluminum hydride ($LiAlH_4$) and sodium borohydride ($NaBH_4$). Note! The hydride anion is not present during this reaction; rather, these reagents serve as a source of hydride due to the presence of a polar metal-hydrogen bond. Because aluminum is less electronegative than boron, the Al-H bond in $LiAlH_4$ is more polar, thereby, making $LiAlH_4$ a stronger reducing agent.



Sodium Borohydride **Lithium Aluminum Hydride** **Hydride Nucleophile**

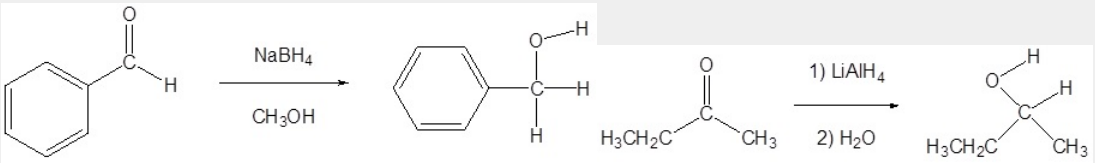
Addition of a hydride anion ($H:^-$) to an aldehyde or ketone gives an alkoxide anion, which on protonation yields the corresponding alcohol. Aldehydes produce 1°-alcohols and ketones produce 2°-alcohols.



Aldehyde **1° Alcohol** **Ketone** **2° Alcohol**

In metal hydrides reductions the resulting alkoxide salts are insoluble and need to be hydrolyzed (with care) before the alcohol product can be isolated. In the sodium borohydride reduction the methanol solvent system achieves this hydrolysis automatically. In the lithium aluminum hydride reduction water is usually added in a second step. The lithium, sodium, boron and aluminum end up as soluble inorganic salts at the end of either reaction. Note! $LiAlH_4$ and $NaBH_4$ are both capable of reducing aldehydes and ketones to the corresponding alcohol.

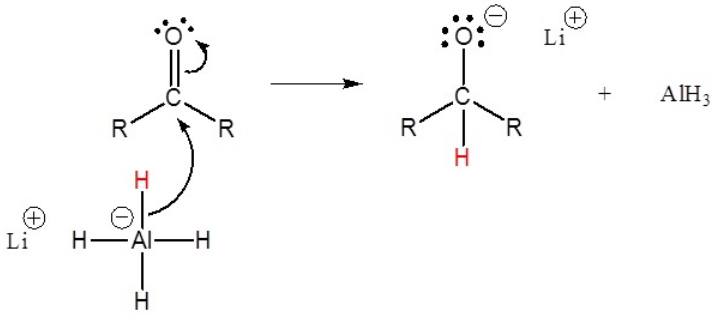
Example 1



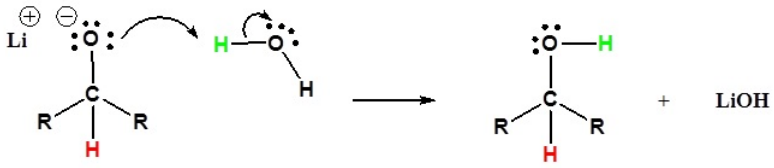
Mechanism

This mechanism is for a $LiAlH_4$ reduction. The mechanism for a $NaBH_4$ reduction is the same except methanol is the proton source used in the second step.

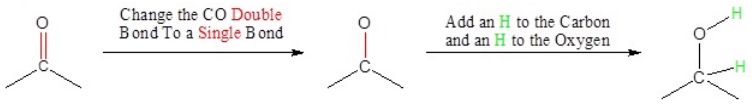
1) Nucleopilic attack by the hydride anion



2) The alkoxide is protonated



Going from Reactants to Products Simplified



Properties of Hydride Sources

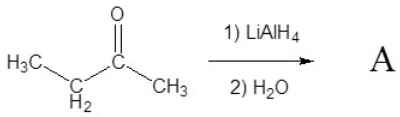
Two practical sources of hydride-like reactivity are the complex metal hydrides lithium aluminum hydride ($LiAlH_4$) and sodium borohydride ($NaBH_4$). These are both white (or near white) solids, which are prepared from lithium or sodium hydrides by reaction with aluminum or boron halides and esters. Lithium aluminum hydride is by far the most reactive of the two compounds, reacting violently with water, alcohols and other acidic groups with the evolution of hydrogen gas. The following table summarizes some important characteristics of these useful reagents.

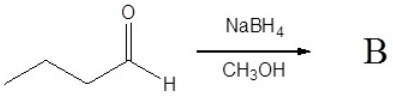
It would be great to convert this table to text.

Reagent	Preferred Solvents	Functions Reduced	Reaction Work-up
Sodium Borohydride $NaBH_4$	ethanol; aqueous ethanol 15% NaOH; diglyme avoid strong acids	aldehydes to 1°-alcohols ketones to 2°-alcohols inert to most other functions	**1)** simple neutralization **2)** extraction of product
Lithium Aluminum Hydride $LiAlH_4$	ether; THF avoid alcohols and amines avoid halogenated compounds avoid strong acids	aldehydes to 1°-alcohols ketones to 2°-alcohols carboxylic acids to 1°-alcohols esters to alcohols epoxides to alcohols nitriles & amides to amines halides & tosylates to alkanes most functions react	**1)** careful addition of water **2)** remove aluminum salts **3)** extraction of product

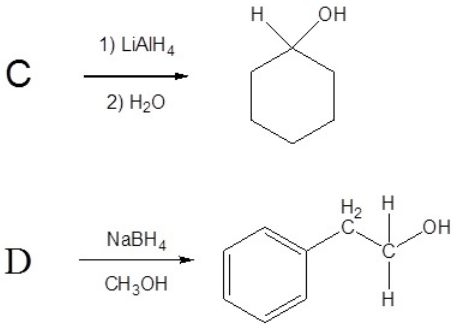
Problems

1) Please draw the products of the following reactions:

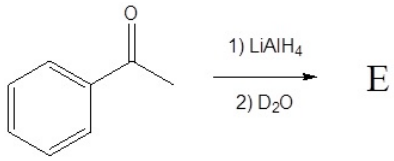




2) Please draw the structure of the molecule which must be reacted to produce the product.

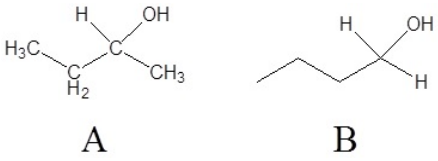


3) Deuterium oxide (D_2O) is a form of water where the hydrogens have been replaced by deuteriums. For the following $LiAlH_4$ reduction the water typically used has been replaced by deuterium oxide. Please draw the product of the reaction and place the deuterium in the proper location. Hint! Look at the mechanism of the reaction.

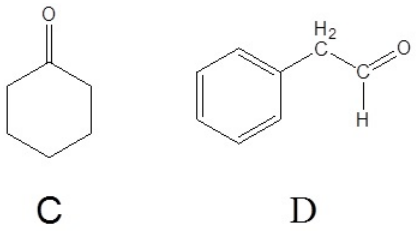


Answers

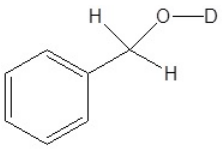
1)



2)



3)

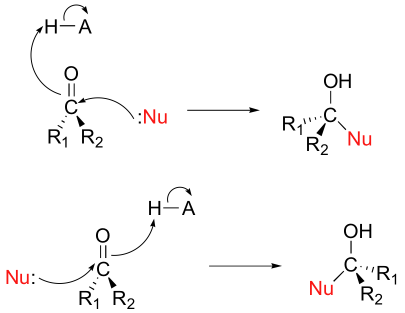


Contributors

- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

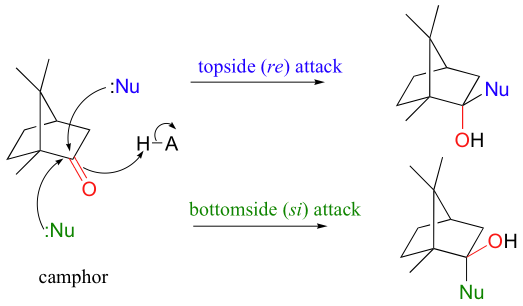
18.5: The Stereochemistry of Carbonyl Reduction

Notice that in the course of the nucleophilic addition pictured above, the hybridization of the carbonyl carbon changes from sp^2 to sp^3, meaning that the bond geometry changes from trigonal planar to tetrahedral. It is also important to note that if the starting carbonyl is asymmetric (in other words, if the two R groups are not equivalent), then a new stereocenter has been created. The configuration of the new stereocenter depends upon which side of the carbonyl plane the nucleophile attacks from.



If the reaction is catalyzed by an enzyme, the stereochemistry of addition is tightly controlled, and leads to one specific stereoisomer - this is because the nucleophilic and electrophilic substrates are bound in a specific positions within the active site, so that attack must occur specifically from one side. If, however, the reaction occurs uncatalyzed in solution, then either side of the carbonyl is equally likely to be attacked, and the result will be a 50:50 racemic mixture.

This is the rule for most nonenzymatic reactions, but as with most rules, there are exceptions. If, for example, the geometry of the carbonyl-containing molecule is constrained in such a way that approach by the nucleophile is less hindered from one side, a 50:50 racemic mixture will not necessarily result. Consider camphor, the distinctive-smelling compound found in many cosmetics and skin creams.



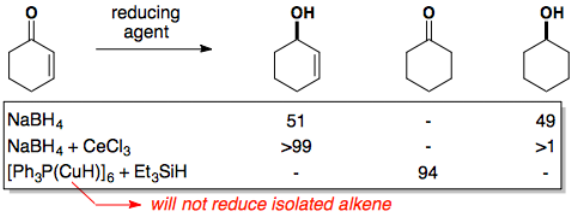
Upon inspection it is clear that topside attack and bottom side attack by a nucleophile are nonequivalent in terms of steric hindrance. A relatively simple experiment shows that, when the incoming nucleophile is a hydride ion from the common synthetic reducing agent sodium borohydride (a reaction type we will study in a later chapter), the product of bottom side attack predominates by a ratio of about 6 to 1 (see section 16.4D for more details on this experiment). We can infer from this result that approach from the bottom (*si*) face of the carbonyl in camphor is less hindered.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

18.6: Enantioselective Carbonyl Reductions

Chemoselective Reductions

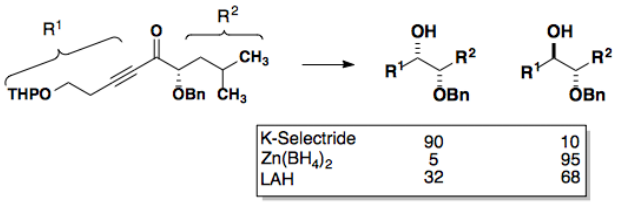
Enones present unique challenges as reducing agents can also attack the alkene giving a mixture of products. Methods to selectively reduce the ketone (Luche Reduction) and the alkene (Stryker Reduction) have been developed.



Diastereoselective Reductions

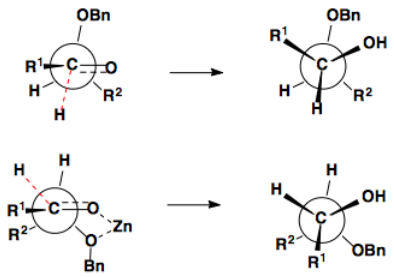
Acyclic Compounds

Reductions of aldehydes and ketones follow the same selectivity models as the addition of unstabilized carbon nucleophiles to these functional groups. Non-chelating reducing agents ($NaBH_4$, $LiAH_4$, etc.) show Felkin-Anh selectivity while reducing agents which can chelate ($Zn(BH_4)_2$) show Cram Chelate selectivity.



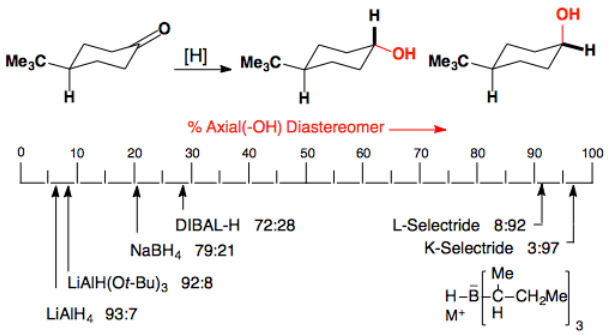
Tetrahedron Lett., **1985**, *26*,5139-5142.

As seen in the example above, lithium will sometimes chelate.

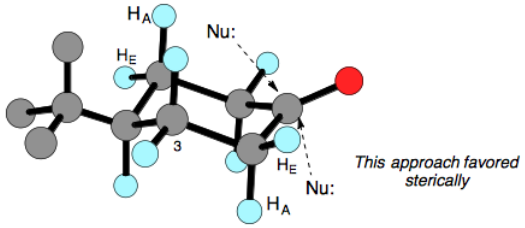


Cyclohexanones

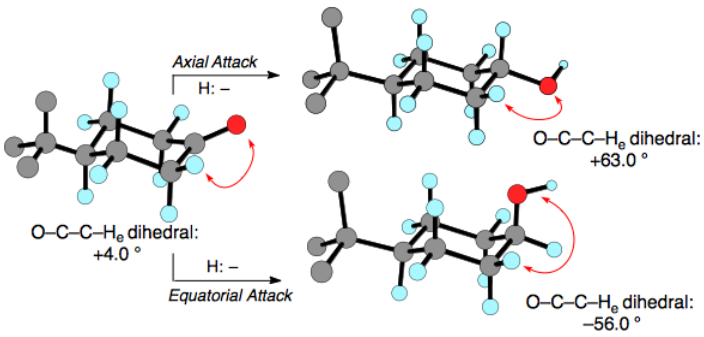
Hydrides can approach cyclohexanones from the axial or equatorial face of the ketone.



It has been obvserved that increasingly bulky hydride reagents prefer to attack from the equatorial face of the carbonyl. This is rationalized by the increased steric demand of a nucleophile approaching from the axial face of the carbonyl as it encounters the axial substituents (H in this case) at the 3 and 5 positions.

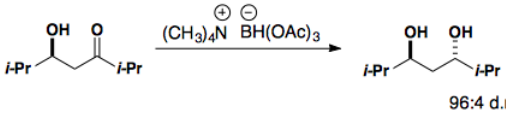


This argument would thus seem to always argue for attack from the equatorial face, but we must also take into consideration any developing torsional strain through the transition state. Attack from the axial face avoids developing eclipsing interactions between the C–O bond and the C–H_E bonds at the 2 and 6 positions. Attack from the equatorial face forces the C–O bond to travel past the C–H_E bonds to sit in the chair conformation. We can see this below as the dihedral angle in the starting cyclhexanone starts as a positive number and ends up as a negative number which shows that the C–O bond must have gone through an eclipsing conformation to reach its final position. Axial attack does not cause a change in sign of the dihedral angle, thus avoiding any eclipsing interactions in the transition state.

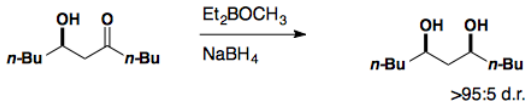


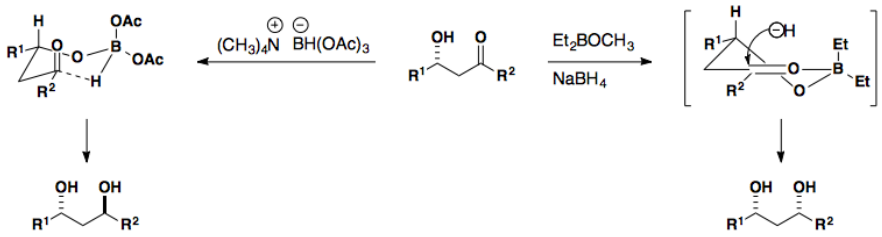
We can thus predict that small hydride reagents, such as $LiAlH_4$, will prefer to attack from the axial face as the torsional strain in the transition state is the dominant interaction while large hydride reagents, such as H–BR_4, will attack from the equatorial face as the steric interactions from the reagent's approach are now the dominant interaction.

Substrate Directed Reductions



J. Am. Chem. Soc., **1988**, *110*, 3560-3578.

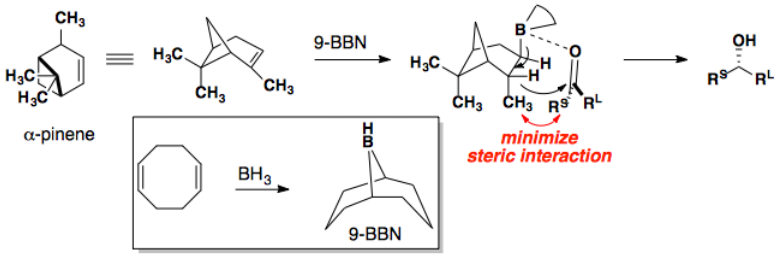


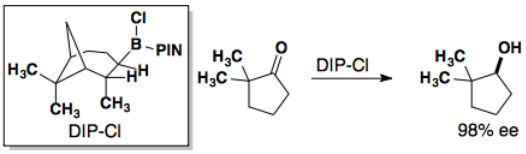


Tetrahedron Lett., **1987**, *28*, 155-158.

Enantioselective Reductions

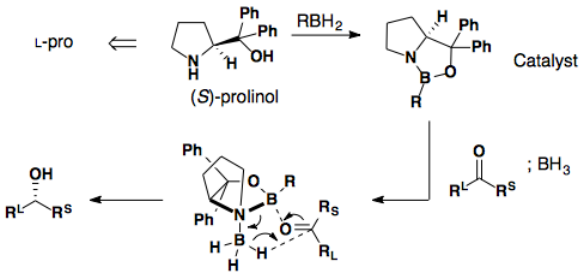
Chiral Boronates



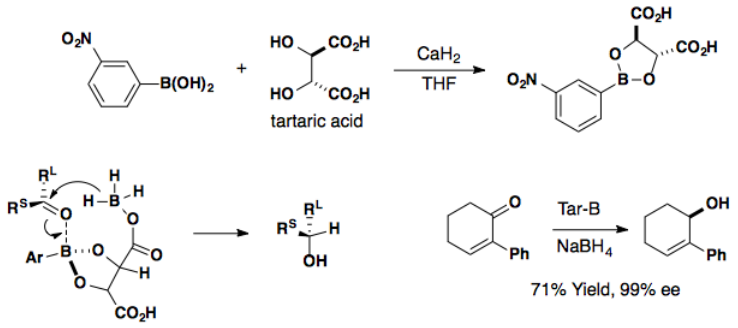


If the selectivity from these reactions is the opposite of your desired product, you can use a Mitsunobu Reaction to invert the stereocenter.

Corey-Bakshi-Shibata (CBS) Reductions

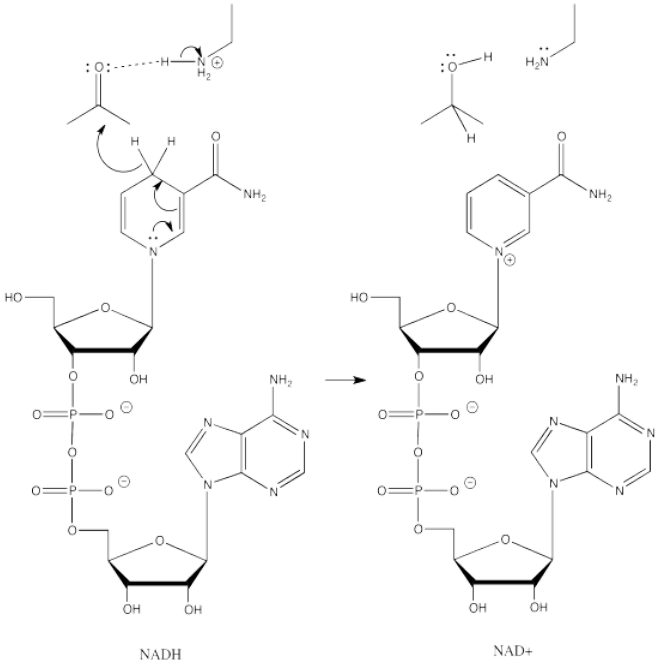


Tar-B



Biological Reduction

Addition to a carbonyl by a semi-anionic hydride, such as $NaBH_4$, results in conversion of the carbonyl compound to an alcohol. The hydride from the BH_4^- anion acts as a nucleophile, adding H^- to the carbonyl carbon. A proton source can then protonate the oxygen of the resulting alkoxide ion, forming an alcohol.



Formally, that process is referred to as a reduction. Reduction generally means a reaction in which electrons are added to a compound; the compound that gains electrons is said to be reduced. Because hydride can be thought of as a proton plus two electrons, we can think of conversion of a ketone or an aldehyde to an alcohol as a two-electron reduction. An aldehyde plus two electrons and two protons becomes an alcohol.

Aldehydes, ketones and alcohols are very common features in biological molecules. Converting between these compounds is a frequent event in many biological pathways. However, semi-anionic compounds like sodium borohydride don't exist in the cell. Instead, a number of biological hydride donors play a similar role.

NADH is a common biological reducing agent. NADH is an acronym for nicotinamide adenine dinucleotide hydride. Insetad of an anionic donor that provides a hydride to a carbonyl, NADH is actually a neutral donor. It supplies a hydride to the carbonyl under very specific circumstances. In doing so, it forms a cation, NAD^+.

Contributors

- Stephen Laws
- Michael Di Maso (UC Davis)

- Jared Shaw (UC Davis)

18.7: Reduction of Carboxylic Acids and Their Derivatives

Since relatively few methods exist for the reduction of carboxylic acid derivatives to aldehydes, it would be useful to modify the reactivity and solubility of LAH to permit partial reductions of this kind to be achieved. The most fruitful approach to this end has been to attach alkoxy or alkyl groups on the aluminum. This not only modifies the reactivity of the reagent as a hydride donor, but also increases its solubility in nonpolar solvents. Two such reagents will be mentioned here; the reactive hydride atom is colored blue.

Lithium tri-tert-butoxyaluminohydride (LtBAH), $LiAl[OC(CH_3)_3]_3\mathbf{H}$: Soluble in THF, diglyme & ether.

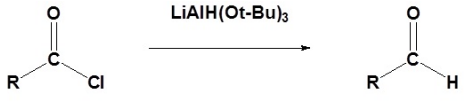
Diisobutylaluminum hydride (DIBAH), $[(CH_3)_2CHCH_2]_2Al\mathbf{H}$: Soluble in toluene, THF & ether.

Each of these reagents carries one equivalent of hydride. The first (LtBAH) is a complex metal hydride, but the second is simply an alkyl derivative of aluminum hydride. In practice, both reagents are used in equimolar amounts, and usually at temperatures well below 0 ºC. The following examples illustrate how aldehydes may be prepared from carboxylic acid derivatives by careful application of these reagents. A temperature of -78 ºC is easily maintained by using dry-ice as a coolant.

Reduction of Acid Chlorides and Esters

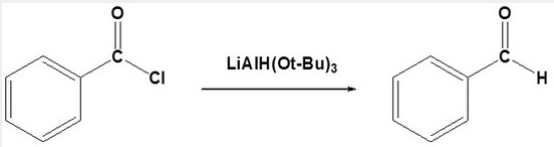
Acid chlorides can be converted to aldehydes using lithium tri-tert-butoxyaluminum hydride ($LiAlH(Ot\text{-}Bu)_3$). The hydride source ($LiAlH(Ot\text{-}Bu)_3$) is a weaker reducing agent than lithium aluminum hydride. Because acid chlorides are highly activated they still react with the hydride source; however, the formed aldehyde will react slowly, which allows for its isolation.

General Reaction:



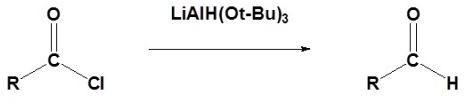
Acid Chloride Aldehyde

Example 1



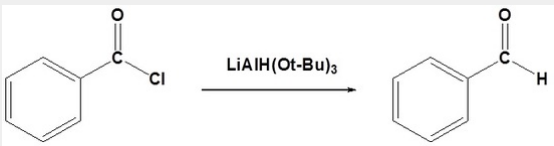
Acid chlorides can be converted to aldehydes using lithium tri-tert-butoxyaluminum hydride ($LiAlH(Ot\text{-}Bu)_3$). The hydride source ($LiAlH(Ot\text{-}Bu)_3$) is a weaker reducing agent than lithium aluminum hydride. Because acid chlorides are highly activated they still react with the hydride source; however, the formed aldehyde will react slowly, which allows for its isolation.

General Reaction:

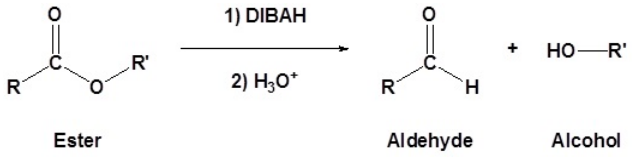


Acid Chloride Aldehyde

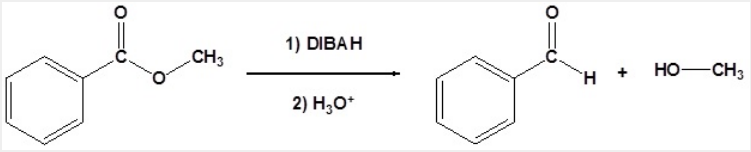
Example 1



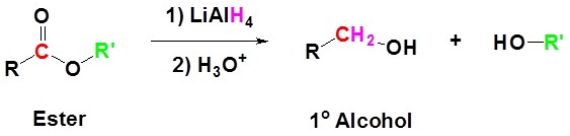
Esters can be converted to aldehydes using diisobutylaluminum hydride (DIBAH). The reaction is usually carried out at -78 ^{o}C to prevent reaction with the aldehyde product.



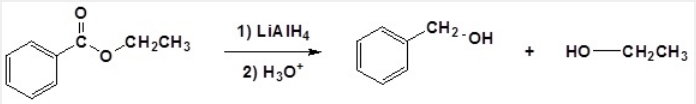
Example 1:



Esters can be converted to 1^{o} alcohols using $LiAlH_4$, while sodium borohydride ($NaBH_4$) is not a strong enough reducing agent to perform this reaction.

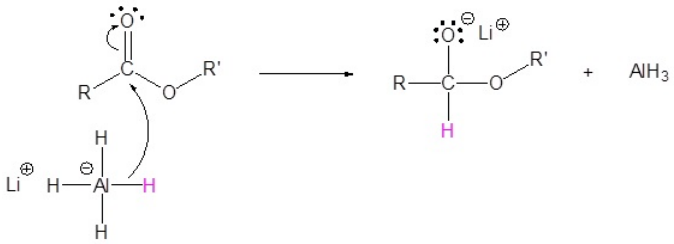


Example 1:

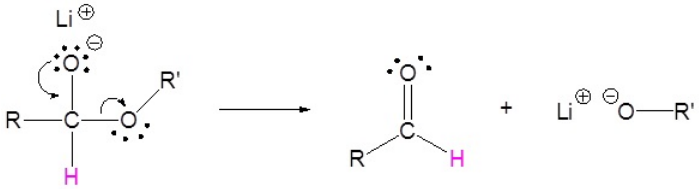


Mechanism

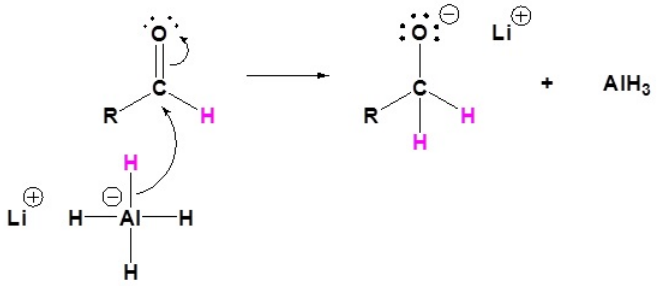
1) Nucleophilic attack by the hydride



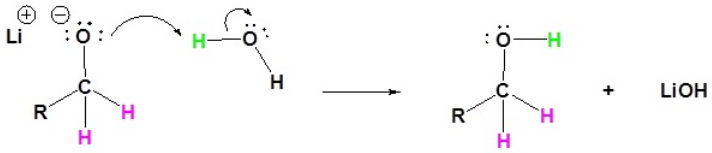
2) Leaving group removal



3) Nucleopilic attack by the hydride anion

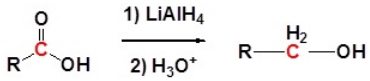


4) The alkoxide is protonated

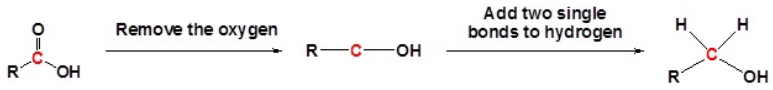


Reduction of Carboxylic Acids and Amides

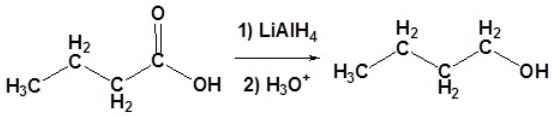
Carboxylic acids can be converted to 1^o alcohols using Lithium aluminum hydride ($LiAlH_4$). Note that $NaBH_4$ is not strong enough to convert carboxylic acids or esters to alcohols. An aldehyde is produced as an intermediate during this reaction, but it cannot be isolated because it is more reactive than the original carboxylic acid.



Going from reactant to products simplified

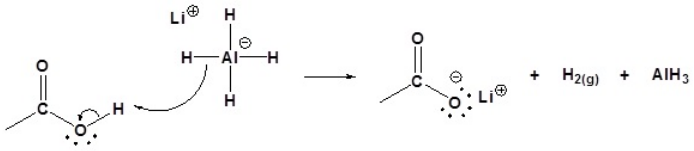


Example

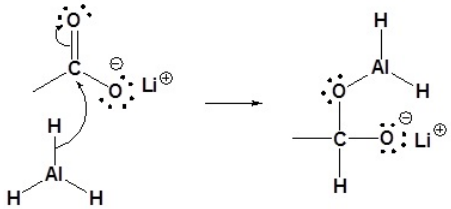


Possible Mechanism

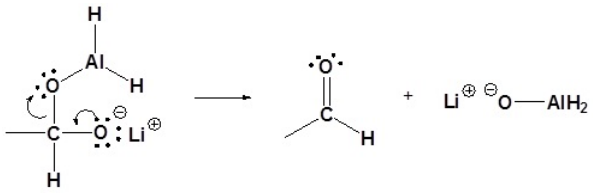
1) Deprotonation



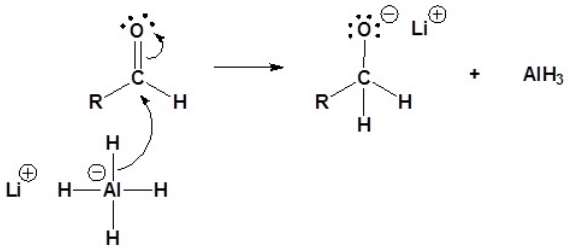
2) Nucleopilic attack by the hydride anion



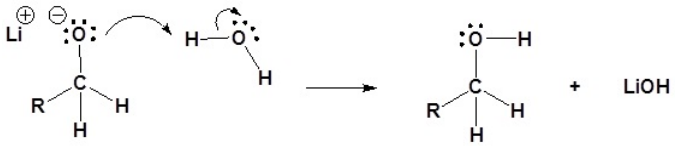
3) Leaving group removal



4) Nucleopilic attack by the hydride anion

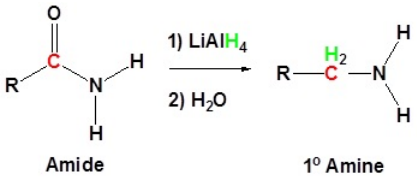


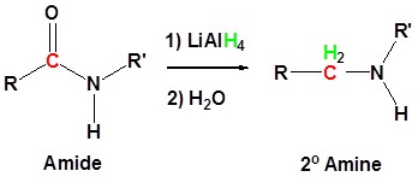
5) The alkoxide is protonated

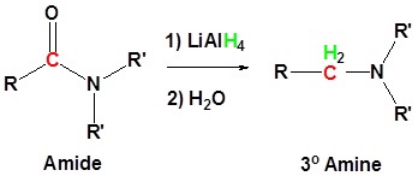


Amides can be converted to 1°, 2° or 3° amines using $LiAlH_4$.

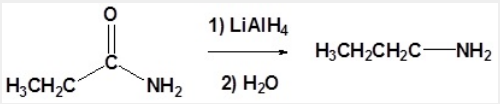
General Reaction



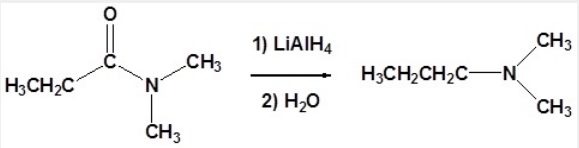




Example 1: Amide Reductions

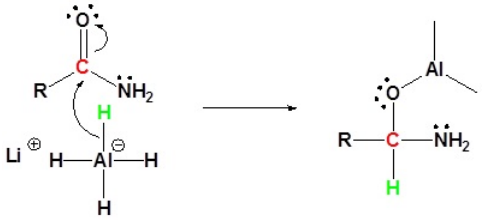


Alkyl groups attached to the nitrogen do not affect the reaction.

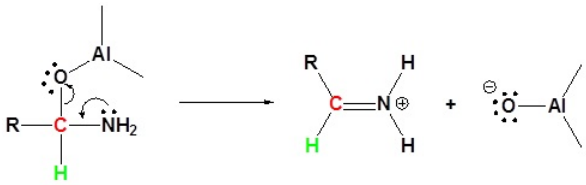


Mechanism

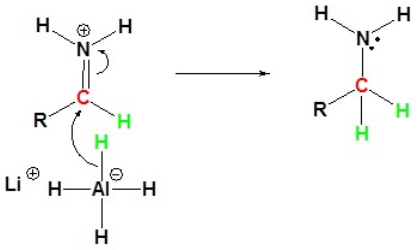
1) Nucleophilic attach by the hydride



2) Leaving group removal



3) Nucleophilic attach by the hydride



Contributors

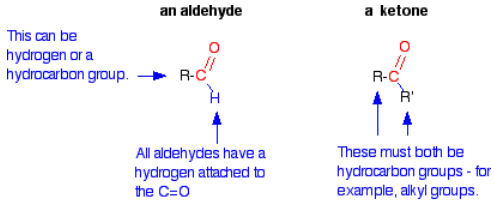
- Prof. Steven Farmer (Sonoma State University)

18.8: Oxidation of Aldehydes

This page looks at ways of distinguishing between aldehydes and ketones using oxidizing agents such as acidified potassium dichromate(VI) solution, Tollens' reagent, Fehling's solution and Benedict's solution.

Why do aldehydes and ketones behave differently?

You will remember that the difference between an aldehyde and a ketone is the presence of a hydrogen atom attached to the carbon-oxygen double bond in the aldehyde. Ketones don't have that hydrogen.

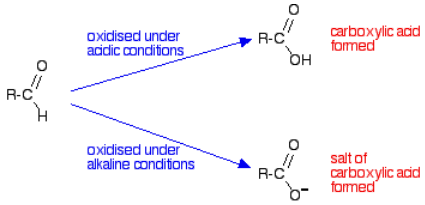


The presence of that hydrogen atom makes aldehydes very easy to oxidize. Or, put another way, they are strong reducing agents. However, because ketones do not have that particular hydrogen atom, they are resistant to oxidation, and only very strong oxidizing agents like potassium manganate(VII) solution (potassium permanganate solution) oxidize ketones. However, they do it in a destructive way, breaking carbon-carbon bonds.

Provided you avoid using these powerful oxidizing agents, you can easily tell the difference between an aldehyde and a ketone. Aldehydes are easily oxidized by all sorts of different oxidizing agents and ketones are not.

What is formed when aldehydes are oxidized?

It depends on whether the reaction is done under acidic or alkaline conditions. Under acidic conditions, the aldehyde is oxidized to a carboxylic acid. Under alkaline conditions, this couldn't form because it would react with the alkali. A salt is formed instead.



Building equations for the oxidation reactions

If you need to work out the equations for these reactions, the only reliable way of building them is to use electron-half-equations. The half-equation for the oxidation of the aldehyde obviously varies depending on whether you are doing the reaction under acidic or alkaline conditions.

Under acidic conditions it is:

$$RCHO + H_2O \rightarrow RCOOH + 2H^+ + 2e^- \tag{18.8.1}$$

. . . and under alkaline conditions:

$$RCHO + 3OH^- \rightarrow RCOO^- + 2H_2O + 2e^- \tag{18.8.2}$$

These half-equations are then combined with the half-equations from whatever oxidizing agent you are using. Examples are given in detail below.

Specific examples

In each of the following examples, we are assuming that you know that you have either an aldehyde or a ketone. There are lots of other things which could also give positive results. Assuming that you know it has to be one or the other, in each case, a ketone does nothing. Only an aldehyde gives a positive result.

Using acidified potassium dichromate(VI) solution

A small amount of potassium dichromate(VI) solution is acidified with dilute sulphuric acid and a few drops of the aldehyde or ketone are added. If nothing happens in the cold, the mixture is warmed gently for a couple of minutes - for example, in a beaker of hot water.

ketone	No change in the orange solution.
aldehyde	Orange solution turns green.

The orange dichromate(VI) ions have been reduced to green chromium(III) ions by the aldehyde. In turn the aldehyde is oxidized to the corresponding carboxylic acid. The electron-half-equation for the reduction of dichromate(VI) ions is:

$$Cr_2O_7^{2-} + 14H^+ + 6e^- \rightarrow 2Cr^{3+} + 7H_2O \tag{18.8.3}$$

Combining that with the half-equation for the oxidation of an aldehyde under acidic conditions:

$$RCHO + H_2O \rightarrow RCOOH + 2H^+ + 2e^- \tag{18.8.4}$$

. . . gives the overall equation:

$$2RCHO + Cr_2O_7^{2-} + 8H^+ \rightarrow 3RCOOH + 2Cr^{3+} + 4H_2O \tag{18.8.5}$$

Using Tollens' reagent (the silver mirror test)

Tollens' reagent contains the diamminesilver(I) ion, $[Ag(NH_3)_2]^+$. This is made from silver(I) nitrate solution. You add a drop of sodium hydroxide solution to give a precipitate of silver(I) oxide, and then add just enough dilute ammonia solution to redissolve the precipitate. To carry out the test, you add a few drops of the aldehyde or ketone to the freshly prepared reagent, and warm gently in a hot water bath for a few minutes.

ketone	No change in the colourless solution.
aldehyde	The colourless solution produces a grey precipitate of silver, or a silver mirror on the test tube.

Aldehydes reduce the diamminesilver(I) ion to metallic silver. Because the solution is alkaline, the aldehyde itself is oxidized to a salt of the corresponding carboxylic acid. The electron-half-equation for the reduction of of the diamminesilver(I) ions to silver is:

$$Ag(NH_3)_2^+ + e^- \rightarrow Ag + 2NH_3 \tag{18.8.6}$$

Combining that with the half-equation for the oxidation of an aldehyde under alkaline conditions:

$$RCHO + 3OH^- \rightarrow RCOO^- + 2H_2O + 2e^- \tag{18.8.7}$$

gives the overall equation:

$$2Ag(NH_3)_2^+ + RCHO + 3OH^- \rightarrow 2Ag + RCOO^- + 4H_2O + 2H_2O \tag{18.8.8}$$

Using Fehling's solution or Benedict's solution

Fehling's solution and Benedict's solution are variants of essentially the same thing. Both contain complexed copper(II) ions in an alkaline solution.

- Fehling's solution contains copper(II) ions complexed with tartrate ions in sodium hydroxide solution. Complexing the copper(II) ions with tartrate ions prevents precipitation of copper(II) hydroxide.
- Benedict's solution contains copper(II) ions complexed with citrate ions in sodium carbonate solution. Again, complexing the copper(II) ions prevents the formation of a precipitate - this time of copper(II) carbonate.

Both solutions are used in the same way. A few drops of the aldehyde or ketone are added to the reagent, and the mixture is warmed gently in a hot water bath for a few minutes.

ketone	No change in the blue solution.

aldehyde	The blue solution produces a dark red precipitate of copper(I) oxide.

Aldehydes reduce the complexed copper(II) ion to copper(I) oxide. Because the solution is alkaline, the aldehyde itself is oxidized to a salt of the corresponding carboxylic acid. The equations for these reactions are always simplified to avoid having to write in the formulae for the tartrate or citrate ions in the copper complexes. The electron-half-equations for both Fehling's solution and Benedict's solution can be written as:

$$2Cu^{2+}_{complexed} + 2OH^- + 2e^- \rightarrow Cu_2O + H_2O \tag{18.8.9}$$

Combining that with the half-equation for the oxidation of an aldehyde under alkaline conditions:

$$RCHO + 3OH^- \rightarrow RCOO^- + 2H_2O + 2e^- \tag{18.8.10}$$

to give the overall equation:

$$RCHO + 2Cu^{2+}_{complexed} + 5OH^- \rightarrow RCOO^- + Cu_2O + 3H_2O \tag{18.8.11}$$

Contributors

Jim Clark (Chemguide.co.uk)

18.9: Organometallic Reagents

The alkali metals (Li, Na, K etc.) and the alkaline earth metals (Mg and Ca, together with Zn) are good reducing agents, the former being stronger than the latter. These same metals reduce the carbon-halogen bonds of alkyl halides. The halogen is converted to a halide anion, and the carbon bonds to the metal which has characteristics similar to a carbanion (R:-).

Formation of Organometallic Reagents

Many organometallic reagents are commercially available, however, it is often necessary to make then. The following equations illustrate these reactions for the commonly used metals lithium and magnesium (R may be hydrogen or alkyl groups in any combination).

- **An Alkyl Lithium Reagent**

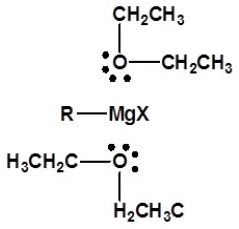
$$\mathrm{R_3C{-}X + 2\,Li \rightarrow R_3C{-}Li + LiX} \tag{18.9.1}$$

- **A Grignard Regent**

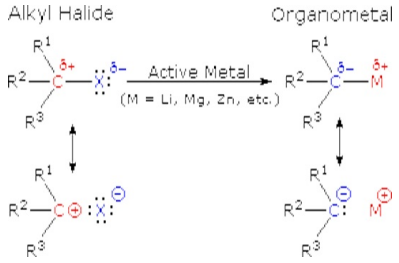
$$\mathrm{R_3C{-}X + Mg \rightarrow R_3C{-}MgX} \tag{18.9.2}$$

Halide reactivity in these reactions increases in the order: Cl < Br < I and Fluorides are usually not used. The alkyl magnesium halides described in the second reaction are called Grignard Reagents after the French chemist, Victor Grignard, who discovered them and received the Nobel prize in 1912 for this work. The other metals mentioned above react in a similar manner, but Grignard and Alky Lithium Reagents most widely used. Although the formulas drawn here for the alkyl lithium and Grignard reagents reflect the stoichiometry of the reactions and are widely used in the chemical literature, they do not accurately depict the structural nature of these remarkable substances. Mixtures of polymeric and other associated and complexed species are in equilibrium under the conditions normally used for their preparation.

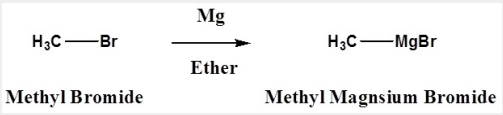
A suitable solvent must be used. For alkyl lithium formation pentane or hexane are usually used. Diethyl ether can also be used but the subsequent alkyl lithium reagent must be used immediately after preparation due to an interaction with the solvent. Ethyl ether or THF are essential for Grignard reagent formation. Lone pair electrons from two ether molecules form a complex with the magnesium in the Grignard reagent (As pictured below). This complex helps stabilize the organometallic and increases its ability to react.

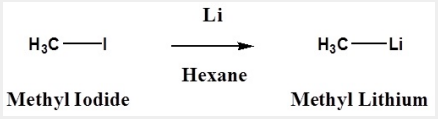


These reactions are obviously substitution reactions, but they cannot be classified as nucleophilic substitutions, as were the earlier reactions of alkyl halides. Because the functional carbon atom has been reduced, the polarity of the resulting functional group is inverted (an originally electrophilic carbon becomes nucleophilic). This change, shown below, makes alkyl lithium and Grignard reagents excellent nucleophiles and useful reactants in synthesis.

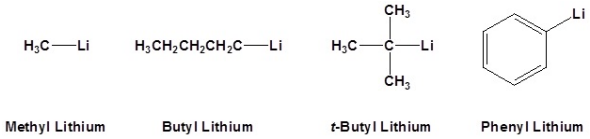


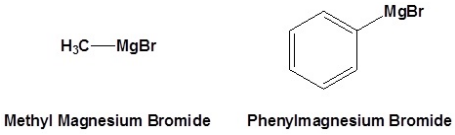
Examples





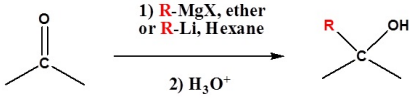
Common Organometallic Reagents





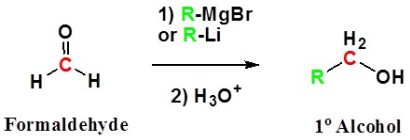
Reaction of Organometallic Reagents with Various Carbonyls

Because organometallic reagents react as their corresponding carbanion, they are excellent nucleophiles. The basic reaction involves the nucleophilic attack of the carbanionic carbon in the organometallic reagent with the electrophilic carbon in the carbonyl to form alcohols.

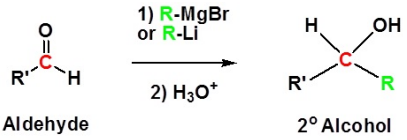


Both Grignard and Organolithium Reagents will perform these reactions

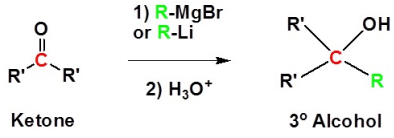
Addition to formaldehyde gives 1o alcohols



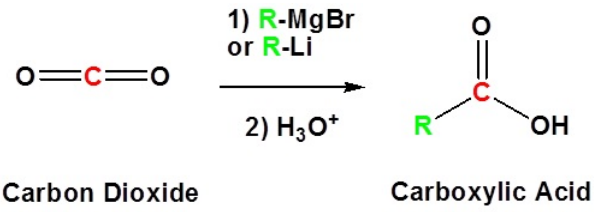
Addition to aldehydes gives 2^{o} alcohols



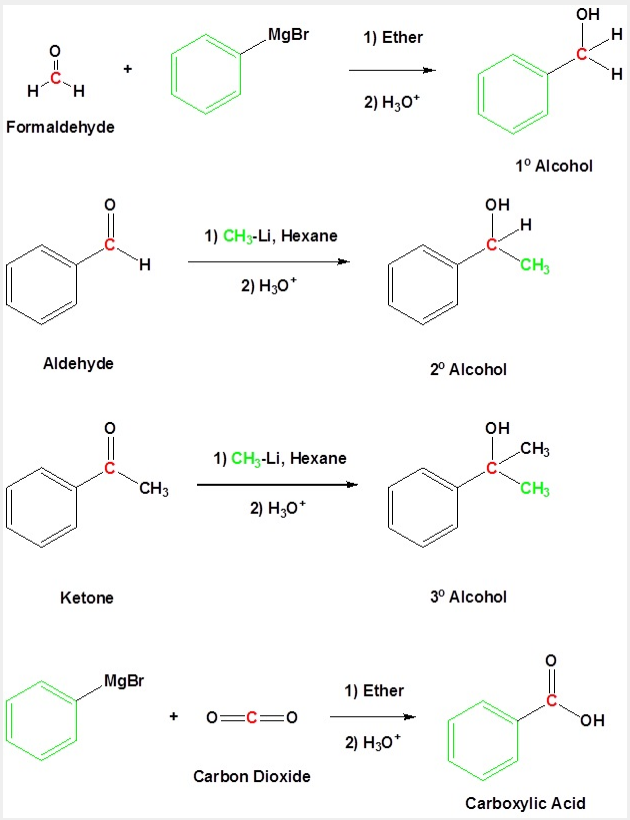
Addition to ketones gives 3o alcohols



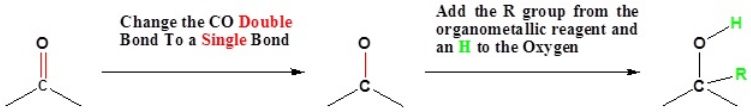
Addition to carbon dioxide (CO_2) forms a carboxylic acid



Examples



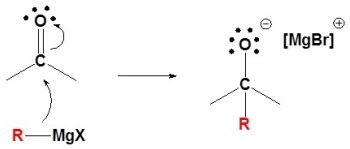
Going from Reactants to Products Simplified



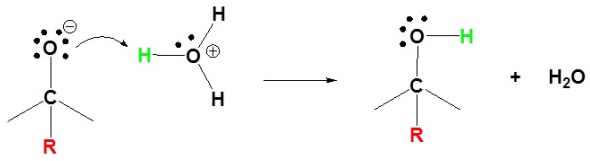
Mechanism for the Addition to Carbonyls

The mechanism for a Grignard agent is shown. The mechanism for an organometallic reagent is the same.

1) Nucleophilic attack



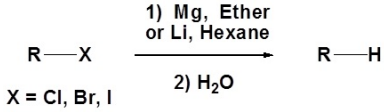
2) Protonation



Organometallic Reagents as Bases

These reagents are very strong bases (pKa's of saturated hydrocarbons range from 42 to 50). Although not usually done with Grignard reagents, organolithium reagents can be used as strong bases. Both Grignard reagents and organolithium reagents react with water to form the corresponding hydrocarbon. This is why so much care is needed to insure dry glassware and solvents when working with organometallic reagents.

In fact, the reactivity of Grignard reagents and organolithium reagents can be exploited to create a new method for the conversion of halogens to the corresponding hydrocarbon (illustrated below). The halogen is converted to an organometallic reagent and then subsequently reacted with water to from an alkane.



Conjugate base anions of terminal alkynes (acetylide anions) are nucleophiles, and can do both nucleophilic substitution and nucleophilic addition reactions.

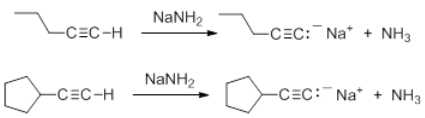
Formation of Acetylide Anions

Terminal alkynes are much more acidic than most other hydrocarbons. Removal of the proton leads to the formation of an acetylide anion, $RC{\equiv}C:^-$. The origin of the enhanced acidity can be attributed to the stability of the acetylide anion, which has the unpaired electrons in an sp hybridized orbital. The stability results from occupying an orbital with a high degree of s-orbital character.

There is a strong correlation between s-character in the orbital containing the non-bonding electrons in the anion and the acidity of hydrocarbons. The enhanced acidity with greater s-character occurs despite the fact that the homolytic C-H BDE is larger.

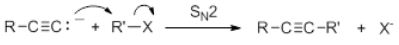
Compound	Conjugate Base	Hybridization	"s Character"	pKa	C-H BDE (kJ/mol)
CH_3CH_3	$CH_3CH_2^-$	sp^3	25%	50	410
CH_2CH_2	CH_2CH^-	sp^2	33%	44	473
HCCH	HCC^-	sp	50%	25	523

Consequently, acetylide anions can be readily formed by deprotonation using a sufficiently strong base. Amide anion (NH_2^-), in the form of $NaNH_2$ is commonly used for the formation of acetylide anions.

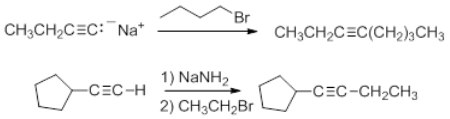


Nucleophilic Substitution Reactions of Acetylides

Acetylide anions are strong bases and strong nucleophiles. Therefore, they are able to displace halides and other leaving groups in substitution reactions. The product is a substituted alkyne.



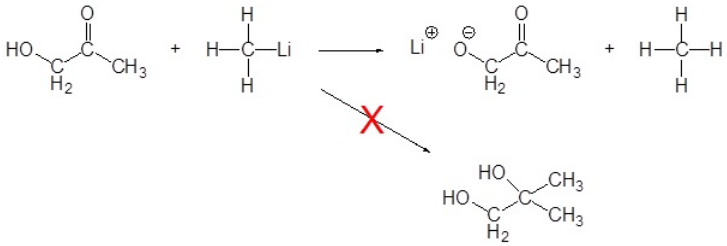
Because the ion is a very strong base, the substitution reaction is most efficient with methyl or primary halides without substitution near the reaction center,



Secondary, tertiary or even bulky primary substrates will give elimination by the E2 mechanism.

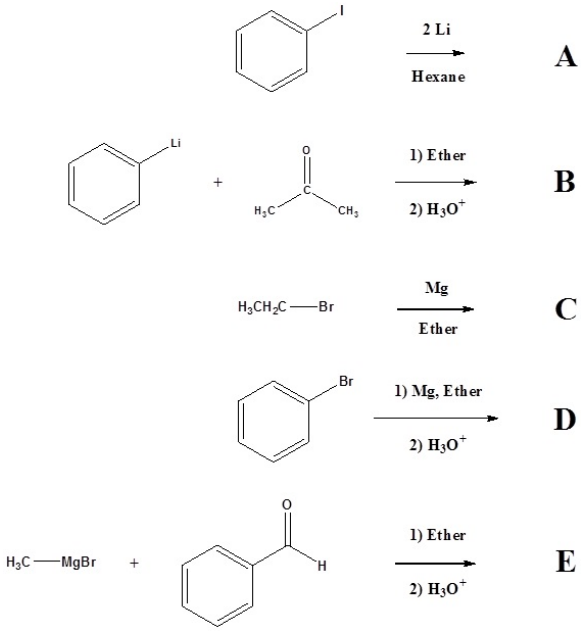
Limitation of Organometallic Reagents

As discussed above, Grignard and organolithium reagents are powerful bases. Because of this they cannot be used as nucleophiles on compounds which contain acidic hydrogens. If they are used they will act as a base and deprotonate the acidic hydrogen rather than act as a nucleophile and attack the carbonyl. A partial list of functional groups which cannot be used are: alcohols, amides, 1o amines, 2o amines, carboxylic acids, and terminal alkynes.

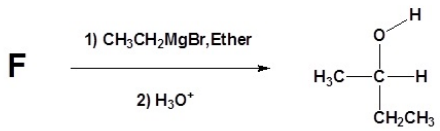


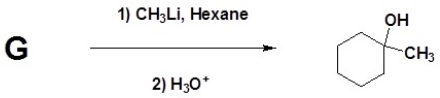
Problems

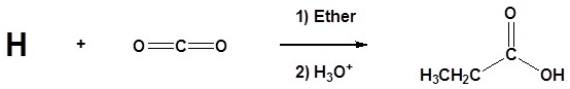
1) Please write the product of the following reactions.

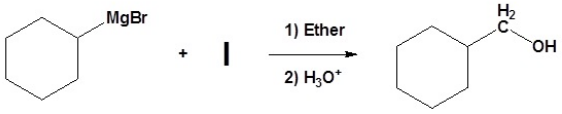


2) Please indicate the starting material required to produce the product.

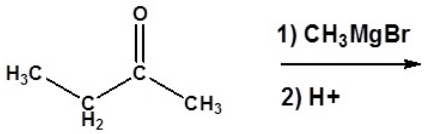




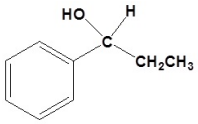




3) Please give a detailed mechanism and the final product of this reaction

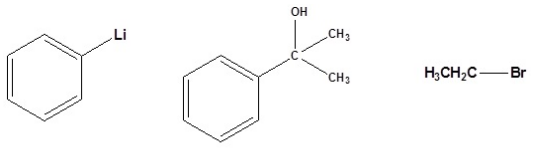


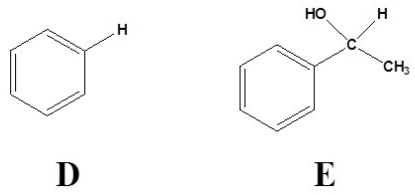
4) Please show two sets of reactants which could be used to synthesize the following molecule using a Grignard reaction.



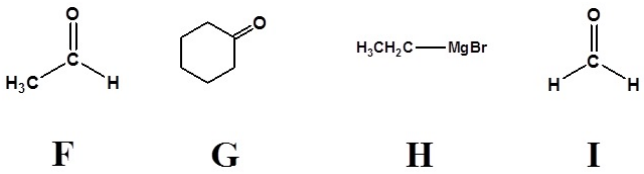
Answers

1)



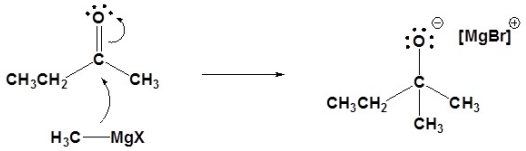


2)

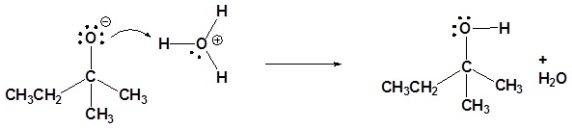


3)

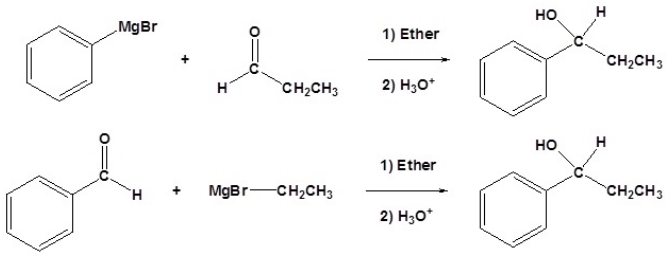
Nucleophilic attack



Protonation



4)

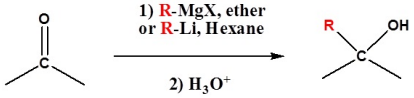


Contributors

- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

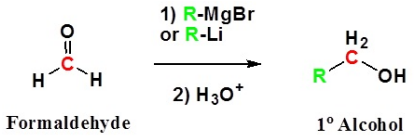
18.10: Reaction of Organometallic Reagents with Aldehydes and Ketones

Because organometallic reagents react as their corresponding carbanion, they are excellent nucleophiles. The basic reaction involves the nucleophilic attack of the carbanionic carbon in the organometallic reagent with the electrophilic carbon in the carbonyl to form alcohols.

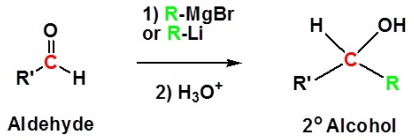


Both Grignard and Organolithium Reagents will perform these reactions

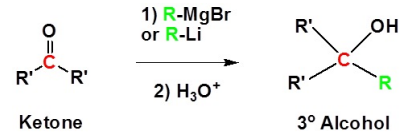
Addition to formaldehyde gives 1o alcohols



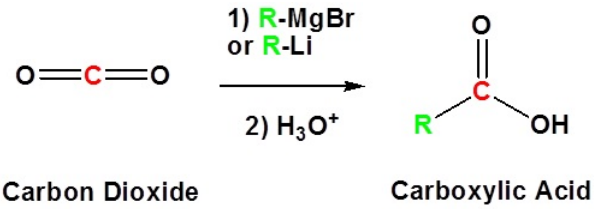
Addition to aldehydes gives 2° alcohols



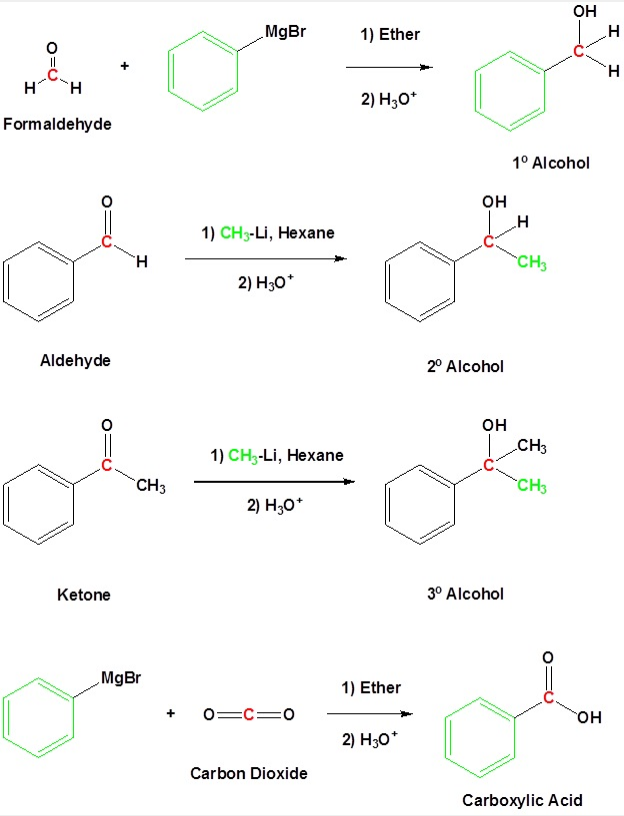
Addition to ketones gives 3o alcohols



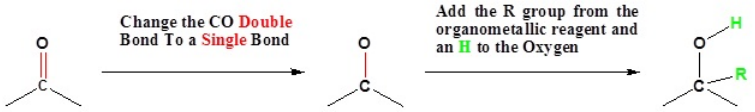
Addition to carbon dioxide (CO_2) forms a carboxylic acid



Examples



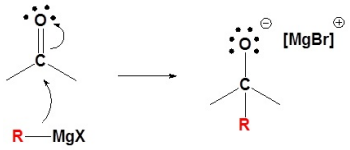
Going from Reactants to Products Simplified



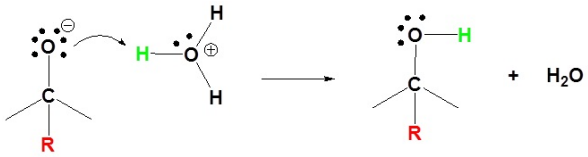
Mechanism for the Addition to Carbonyls

The mechanism for a Grignard agent is shown. The mechanism for an organometallic reagent is the same.

1) Nucleophilic attack

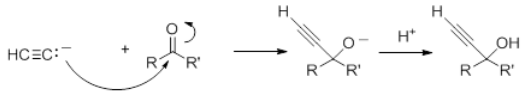


2) Protonation



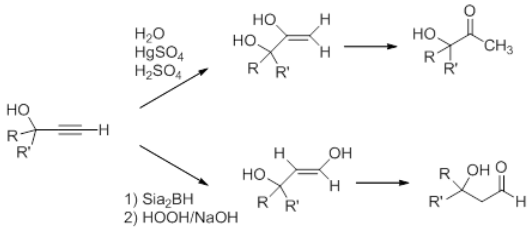
Nucleophilic Addition of Acetylides to Carbonyls

Acetylide anions will add to aldehydes and ketones to form alkoxides, which, upon protonation, give propargyl alcohols.



With aldehydes and non-symmetric ketones, in the absence of chiral catalyst, the product will be a racemic mixture of the two enantiomers.

The triple bond in the propargyl alcohol can be modified by using the reactivity of the alkyne. For example, Markovnikov and anti-Markovnikov hydration of the triple bond leads to formation of the hydroxy-substituted ketone and aldehyde, respectively, after enol-keto tautomerization.



Contributors

- Prof. Steven Farmer (Sonoma State University)
- Prof. Paul G. Wenthold (Purdue University)

18.11: Retrosynthetic Analysis of Grignard Products

Disconnection of bonds

Having chosen the TARGET molecule for synthesis, the next exercise is to draw out synthetic plans that would summarize all reasonable routes for its synthesis. During the past few decades, chemists have been working on a process called RETROSYNTHESIS. Retrosynthesis could be described as a logical Disconnection at strategic bonds in such a way that the process would progressively lead to easily available starting material(s) through several synthetic plans. Each plan thus evolved, describes a 'ROUTE' based on a retrosynthesis. Each disconnection leads to a simplified structure. The logic of such disconnections forms the basis for the retroanalysis of a given target molecule. Natural products have provided chemists with a large variety of structures, having complex functionalities and stereochemistry. This area has provided several challenging targets for development of these concepts. The underlining principle in devising logical approaches for synthetic routes is very much akin to the following simple problem. Let us have a look of the following big block, which is made by assembling several small blocks **(Fig 1.4.2.1)**. You could easily see that the large block could be broken down in different ways and then reassembled to give the same original block.

Fig 1.4.2.1

Now let us try and extend the same approach for the synthesis of a simple molecule. Let us look into three possible 'disconnections' for a cyclohexane ring as shown in **Fig 1.4.2.2**.

Fig 1.4.2.2

In the above analysis we have attempted to develop three ways of disconnecting the six membered ring. Have we thus created three pathways for the synthesis of cyclohexane ring? Do such disconnections make chemical sense? The background of an organic chemist should enable him to read the process as a chemical reaction in the reverse (or 'retro-') direction. The dots in the above structures could represent a carbonium ion, a carbanion, a free radical or a more complex reaction (such as a pericyclic reaction or a rearrangement). Applying such chemical thinking could open up several plausible reactions. Let us look into path b, which resulted from cleavage of one sigma bond. An anionic cyclisation route alone exposes several candidates as suitable intermediates for the formation of this linkage. The above analysis describes only three paths out of the large number of alternate cleavage routes that are available. An extended analysis shown below indicates more such possibilities **(Fig 1.4.2.3)**. Each such intermediate could be subjected to further disconnection process and the process continued until we reach a reasonably small, easily available starting materials. Thus, a complete 'SYNTHETIC TREE' could be constructed that would summarize all possible routes for the given target molecule.

Fig 1.4.2.3

1.4.3 Efficiency of a route

A route is said to be efficient when the ‘overall yield’ of the total process is the best amongst all routes investigated. This would depend not only on the number of steps involved in the synthesis, but also on the type of strategy followed. The strategy could involve a ‘linear syntheses’ involving only consequential steps or a ‘convergent syntheses’ involving fewer consequential steps. **Fig 1.4.3.1** shown below depicts a few patterns that could be recognized in such synthetic trees. When each disconnection process leads to only one feasible intermediate and the process proceeds in this fashion

Fig 1.4.3.1

all the way to one set of starting materials (SM), the process is called a Linear Synthesis. On the other hand, when an intermediate could be disconnected in two or more ways leading to different intermediates, branching occurs in the plan. The processes could be continued all the way to SMs. In such routes different branches of the synthetic pathways converge towards an intermediate. Such schemes are called Convergent Syntheses.

The flow charts shown below **(Fig 1.4.3.2)** depicts a hypothetical 5-step synthesis by the above two strategies. Assuming a very good yield (90%) at each step (this is rarely seen in real projects), a linier synthesis gives 59% overall yield, whereas a convergent synthesis gives 73% overall yield for the same number of steps..

Fig 1.4.3.2

1.4.4 Problem of substituents and stereoisomers

The situation becomes more complex when you consider the possibility of unwanted isomers generated at different steps of the synthesis. The overall yield drops down considerably for the synthesis of the right isomer. Reactions that yield single isomers (Diastereospecific reactions) in good yields are therefore preferred. Some reactions like the Diels Alder Reaction generate several stereopoints (points at which stereoisomers are generated) simultaneously in one step in a highly predictable manner. Such reactions are highly valued in planning synthetic strategies because several desirable structural features are introduced in one step. Where one pure enantiomer is the target, the situation is again complex. A pure compound in the final step could still have 50% unwanted enantiomer, thus leading to a drastic drop in the efficiency of the route. In such cases, it is desirable to separate the optical isomers as early

in the route as possible, along the synthetic route. This is the main merit of the Chiron Approach, in which the right starting material is chosen from an easily available, cheap 'chiral pool'. We would discuss this aspect after we have understood the logic of planning syntheses. Given these parameters, you could now decide on the most efficient route for any given target.

Molecules of interest are often more complex than the plain cyclohexane ring discussed above. They may have substituents and functional groups at specified points and even specific stereochemical points. Construction of a synthetic tree should ideally accommodate all these parameters to give efficient routes. Let us look into a slightly more complex example shown in **Fig 1.4.4.1** . The ketone **1.4.4.1A** is required as an intermediate in a synthesis. Unlike the plain cyclohexane discussed above, the substitution pattern and the keto- group in this molecule impose some restrictions on disconnection processes.

Fig 1.4.4.1

Cleavage a: This route implies attack of an anion of methylisopropylketone on a bromo-component. *Cleavage b:* This route implies simple regiospecific methylation of a larger ketone that bears all remaining structural elements. *Cleavage c:* This route implies three different possibilities. Route C-1 envisages an acylonium unit, which could come from an acid halide or an ester. Route C-2 implies an umpolung reaction at the acyl unit. Route C-3 suggests an oxidation of a secondary alcohol, which could be obtained through a Grignard-type reaction. *Cleavage d:* This implies a Micheal addition.

Each of these routes could be further developed backwards to complete the synthetic tree. These are just a few plausible routes to illustrate an important point that the details on the structure would restrict the possible cleavages to some strategic points. Notable contributions towards planning organic syntheses came from E.J. Corey's school. These developments have been compiles by Corey in a book by the title LOgIC OF CHEMICAL SYNTHESIS. These and several related presentations on this topic should be taken as guidelines. They are devised after analyzing most of the known approaches published in the literature and identifying a pattern in the logic. They need not restrict the scope for new possibilities. Some of the important strategies are outlined below.

1.4.5 Preliminary scan

When a synthetic chemist looks at the given Target, he should first ponder on some preliminary steps to simplify the problem on hand. Is the molecule polymeric? See whether the whole molecule could be split into monomeric units, which could be coupled by a known reaction. This is easily seen in the case of peptides, nucleotides and organic polymers. This could also be true to other natural products. In molecules like C-Toxiferin 1 **(1.4.5.1A) (Fig 1.4.5.1)**, the point of dimerisation is obvious. In several other cases, a deeper insight is required to identify the monomeric units, as is the case with Usnic acid **(1.4.5.1B)**. In the case of the macrolide antibiotic Nonactin **(1.4.5.1C)**, this strategy reduces the possibilities to the synthesis of a monomeric unit **(1.4.5.1D)**. The overall structure has S4 symmetry and is achiral even though assembled from chiral precursors. Both (+)-nonactic acid and (−)-nonactic acid **(1.4.5.1D)** are needed to construct the macrocycle and they are joined head-to-tail in an alternating (+)-(−)-(+)-(−) pattern. (see J. Am. Chem. Soc., 131, 17155 (2009) and references cited therein).

Fig 1.4.5.1

Is a part of the structure already solved? Critical study of the literature may often reveal that the same molecule or a closely related one has been solved. R.B. Woodward synthesized **(1.4.5.2C)** as a key intermediate in an elegant synthesis of Reserpine **(1.4.5.2A)**. The same intermediate compound **(1.4.5.2C)** became the key starting compound for Velluz et.al., in the synthesis of Deserpidine **(1.4.5.2B) (Fig 1.4.5.2)**.

Fig 1.4.5.2

Such strategies reduce the time taken for the synthesis of new drug candidates. These strategies are often used in natural product chemistry and drug chemistry. Once the preliminary scan is complete, the target molecule could be disconnected at Strategic Bonds.

1.4.6 Strategic Bonds, Retrons and Transforms

STRATEGIC BONDS are the bonds that are cleaved to arrive at suitable Starting Materials (SM) or SYNTHONS. For the purpose of bond disconnection, Corey has suggested that the structure could be classified according to the sub-structures generated by known chemical reactions. He called the sub-structures RETRONS and the chemical transformations that generate these Retrons were called TRANSFORMS. A short list of Transforms and Retrons are given below (TABLE 1.4.6.1). Note that when Transforms generate Retrons, the product may have new STEREOPOINTS (stereochemical details) generated that may need critical appraisal.

Fig 1.4.6.1

The structure of the target could be such that the Retron and the corresponding Transforms could be easily visualized and directly applied. In some cases, the Transforms or the Retrons may not be obvious. In several syntheses, transformations do not simplify the molecule, but they facilitate the process of synthesis. For example, a keto- group could be generated through modification of a -CH-NO_2 unit through a Nef reaction. This generates a new set of Retron / transforms pair. A few such transforms are listed below, along with the nomenclature suggested by Corey **(Fig 1.4.6.2)**.

Fig 1.4.6.2

A Rearrangement Reaction could be a powerful method for generating suitable new sub-structures. In the following example, a suitable Pinacol Retron, needed for the rearrangement is obtained through an acyloin transform **(Fig 1.4.6.3)**. Such rearrangement Retrons are often not obvious to inexperienced eyes.

Fig 1.4.6.3

Some transforms may be necessary to protect (acetals for ketones), modify (reduction of a ketone to alcohol to avoid an Aldol condensation during a Claisen condensation) or transpose a structural element such as a stereopoint (e.g. S_N2 inversion, epimerization etc.,) or shifting a functional group. Such transforms do not simplify the given structural unit. At times, activation at specific points on the structure may be introduced to bring about a C-C bond formation and later the extra group may be removed. For example, consider the following retrosynthesis in which an extra ester group has been introduced to facilitate a Dieckmann Retron. In complex targets, combinations of such strategies could prove to be a very productive strategy in planning retrosynthesis. Witness the chemical modification strategy shown below for an efficient stereospecific synthesis of a trisubstituted olefin **(Fig 1.4.6.4)**

Fig 1.4.6.4

Fig 1.4.6.4 Examples for FGA / FGR strategies for complex targets

Amongst the molecular architectures, the bridged-rings pose a complex challenge in Structure-Based disconnection procedures. Corey has suggested guidelines for efficient disconnections of strategic bonds.

A bond cleavage for retrosynthesis should lead to simplified structures, preferably bearing five- or six-membered rings. The medium and large rings are difficult to synthesize stereospecifically. Amongst the common rings, a six-membered ring is easily approached and manipulated to large and small rings. Simultaneous cleavage of two bonds, suggesting cycloaddition – retrons are often more efficient. Some cleavages of strategic bonds are shown in **Fig 1.4.6.5**, suggesting good and poor cleavage strategies based on this approach. However, these guidelines are not restrictive.

Fig 1.4.6.5

Fig 1.4.6.5: Some cleavages at strategic bonds on bridged-ring systems.

Identifying Retron – Transform sets in a given target molecule is therefore a critical component in retrosynthesis. Such an approach could often generate several synthetic routes. The merit of this approach is that starting materials do not prejudice this logic. Retrosyntheses thus developed could throws open several routes that need further critical scrutiny on the basis of known facts.

Identification of Retrons / Transforms sets provided the prerequisite for computer assisted programs designed for generating retrosynthetic routes. A list of Retrons and the corresponding transforms were interlinked and the data was stored in the computer. All known reactions were thus analyzed for their Retron / Transform characteristics and documented. The appropriate literature citations were also documented and linked. Based on these inputs, computer programs were designed to generate retrosynthetic routes for any given structure. Several such programs are now available in the market to help chemists generate synthetic strategies. Given any structure, these programs generate several routes. Once the scientist identifies the specific routes of interest for further analysis, the program generates detailed synthetic steps, reagents required and the appropriate citations. In spite of such powerful artificial intelligence, the intelligence and intuitive genius of a chemist is still capable of generating a new strategy, not yet programmed. Again, human intelligence is still a critical input for the analysis the routes generated using a computer. Based on the experience of the chemists' team, their projected aim of the project and facilities available, the routes are further screened.

Contributors

- Prof. R Balaji Rao (Department of Chemistry, Banaras Hindu University, Varanasi) as part of Information and Communication Technology

18.12: Protecting Groups

Compound **1.4.1.4A** illustrates several important points in Protection / Deprotection protocol. Both the functional groups could react with a Grignard Reagent. Carboxylic acid group would first react with one mole of the Grignard Reagent to give a carboxylate anion salt. This anion does not react any further with the reagent. When two moles of Grignard Reagent are added to the reaction mixture, the second mole attacks the ketone to give a tertiary alcohol. On aqueous work-up, the acid group is regenerated. Thus, the first mole of the reagent provides a selective transient protection for the –COOH group. Once the acid group is esterified, such selectivity towards this reagent is lost. The reagent attacks at both sites. If reaction is desired only at the ester site, the keto- group should be selectively protected as an acetal. In the next step, the grignard reaction is carried out. Now the reagent has only one group available for reaction. On treatment with acid, the ketal protection in the intermediate compound is also hydrolyzed to regenerated the keto- group.

Fig 1.4.1.4

Protection of Aldehydes and Ketones

Since alcohols, aldehydes and ketones are the most frequently manipulated functional groups in organic synthesis, a great deal of work has appeared in their protection / deprotection strategies. In this discussion let us focus on the classes of protecting groups rather than an exhaustive treatment of all the protections.

Acetals

There are two general methods for the introduction of this protection. Transketalation is the method of choice when acetals (ketals) with methanol are desired. Acetone is the by-product, which has to be removed to shift the equilibrium to the right hand side. This is achieved by refluxing with a large excess of the acetonide reagent. Acetone formed is constantly distilled. In the case of cyclic diols, the water formed is continuously removed using a Dean-Stork condenser **(Fig 1.4.1.6)**.

Fig 1.4.1.6

The rate of formation of ketals from ketones and 1,2-ethanediol (ethylene glycol), 1,3-propanediol and 2,2-dimethyl-1,3-propanediol are different. So is the deketalation reaction. This has enabled chemists to selectively work at one center. The following examples from steroid chemistry illustrate these points **(Fig 1.4.1.7)**.

Fig 1.4.1.7

The demand for **Green Chemistry processes** has prompted search for new green procedures. Some examples from recent literature are given here **(Fig 1.4.1.8)**.

Fig 1.4.1.8

Thioketals

Compared with their oxygen analogues, thioketals markedly differ in their chemistry. The formation as well as deprotection is promoted by suitable Lewis acids. The thioacetals are markedly stable under deketalation conditions, thus paving way for selective operations at two different centers. When conjugated ketones are involved, the ketal formation (as well as deprotection) proceeds with double bond migration. On the other hand, thioketals are formed and deketalated without double bond migration **(Fig 1.4.1.9)**.

Fig 1.4.1.9

Silyl Ethers (R – OSiR_3)

The oxygen – silicon sigma bond is stable to lithium and Grignard reagents, nucleophiles and hydride reagents but very unstable to water and mild aqueous acid and base conditions. A silyl ether of secondary alcohol is less reactive than that of a primary alcohol. The O – trimethylsilyl (O – SiMe3) was first protection of this class. **(Fig 1.4.1.24)**.

Fig 1.4.1.24

Replacement of methyl group with other alkyl and aryl groups gives a large variety of silyl ether with varying degrees of stability towards hydrolysis **(Fig 1.4.1.25)**.

Fig 1.4.1.25

The following examples illustrate the selectivity in formation and hydrolysis of this group **(Fig 1.4.1.26)**.

Fig 1.4.1.26

Contributors

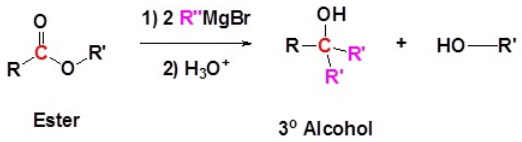
- Prof. R Balaji Rao (Department of Chemistry, Banaras Hindu University, Varanasi) as part of Information and Communication Technology

18.13: Reaction of Organometallic Reagents with Carboxylic Acid Derivatives

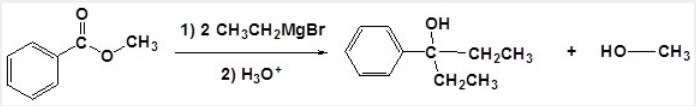
Addition of Grignard reagents convert esters to 3^{o} alcohols.

In effect the Grignard reagent adds twice.

General Reaction

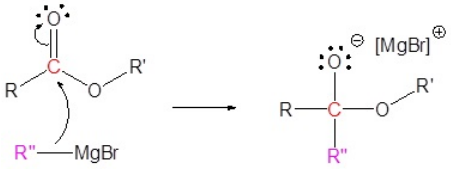


Example 1:

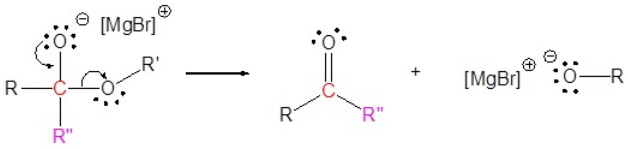


Mechanism

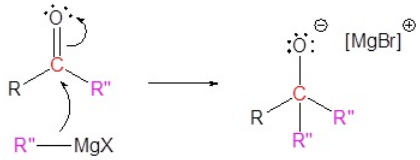
1) Nucleophilic attack



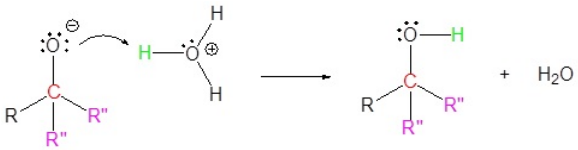
2) Leaving group removal



3) Nucleophilic attack

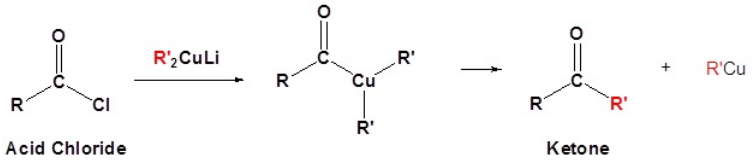


4) Protonation

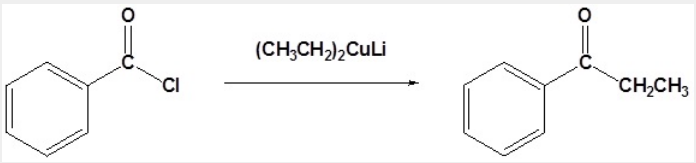


Organocuprate reagents convert acid chlorides to ketones

General Reaction



Example 1:



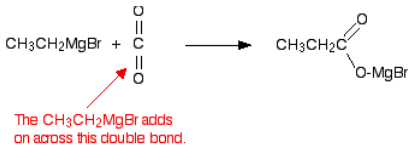
Contributors

- Prof. Steven Farmer (Sonoma State University)

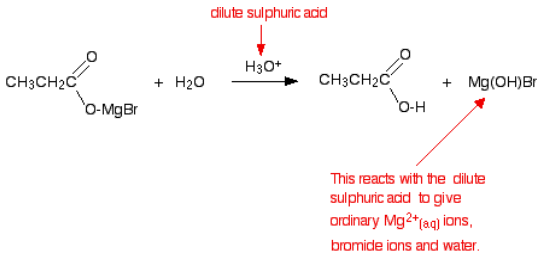
18.14: Reaction of Organometallic Reagents with Other Compounds

Organometallic reagents and carbon dioxide

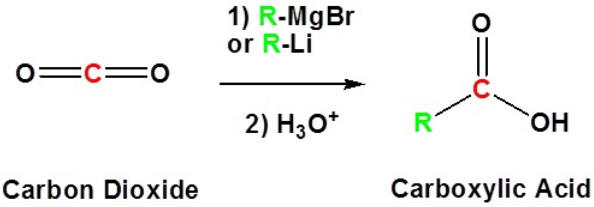
Grignard reagents react with carbon dioxide in two stages. In the first, you get an addition of the Grignard reagent to the carbon dioxide. Dry carbon dioxide is bubbled through a solution of the Grignard reagent in ethoxyethane, made as described above. For example:



The product is then hydrolyzed (reacted with water) in the presence of a dilute acid. Typically, you would add dilute sulphuric acid or dilute hydrochloric acid to the solution formed by the reaction with the CO_2. A carboxylic acid is produced with one more carbon than the original Grignard reagent. The usually quoted equation is (without the red bits):



Almost all sources quote the formation of a basic halide such as Mg(OH)Br as the other product of the reaction. That's actually misleading because these compounds react with dilute acids. What you end up with would be a mixture of ordinary hydrated magnesium ions, halide ions and sulfate or chloride ions - depending on which dilute acid you added.



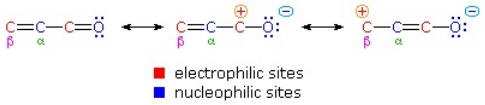
Contributors

- Jim Clark (Chemguide.co.uk)
- Prof. Steven Farmer (Sonoma State University)

18.15: α,β-Unsaturated Carbonyl Compounds

Introduction

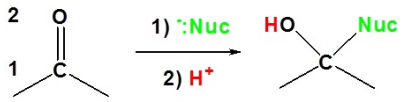
One of the largest and most diverse classes of reactions is composed of nucleophilic additions to a carbonyl group. Conjugation of a double bond to a carbonyl group transmits the electrophilic character of the carbonyl carbon to the beta-carbon of the double bond. These conjugated carbonyl are called enones or α, β unsaturated carbonyls. A resonance description of this transmission is shown below.



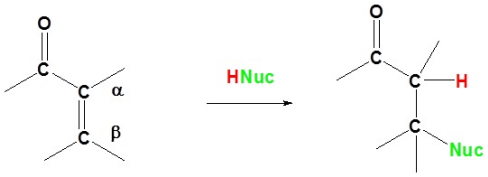
From this formula it should be clear that nucleophiles may attack either at the carbonyl carbon, as for any aldehyde, ketone or carboxylic acid derivative, or at the beta-carbon. These two modes of reaction are referred to as 1,2-addition and 1,4-addition respectively. A 1,4-addition is also called a conjugate addition.

Basic reaction of 1,2 addition

Here the nucleophile adds to the carbon which is in the one position. The hydrogen adds to the oxygen which is in the two position.



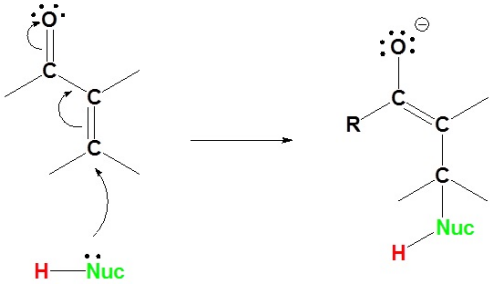
Basic reaction of 1,4 addition



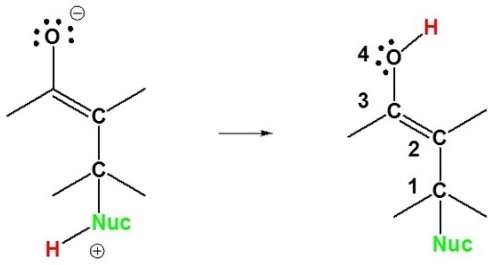
In 1,4 addition the Nucleophile is added to the carbon β to the carbonyl while the hydrogen is added to the carbon α to the carbonyl.

Mechanism for 1,4 addition

1) Nucleophilic attack on the carbon β to the carbonyl

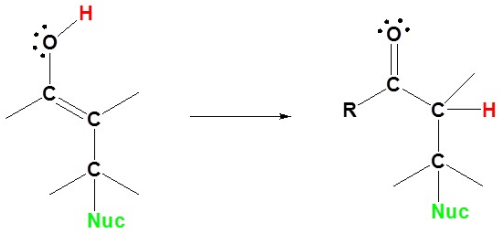


2) Proton Transfer

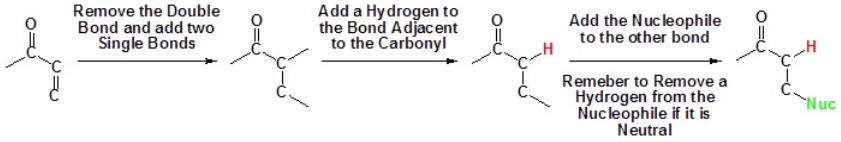


Here we can see why this addition is called 1,4. The nucleophile bonds to the carbon in the one position and the hydrogen adds to the oxygen in the four position.

3) Tautomerization



Going from reactant to products simplified



1,2 Vs. 1,4 addition

Whether 1,2 or 1,4-addition occurs depends on multiple variables but mostly it is determined by the nature of the nucleophile. During the addition of a nucleophile there is a competition between 1,2 and 1,4 addition products. If the nucleophile is a strong base, such as Grignard reagents, both the 1,2 and 1,4 reactions are irreversible and therefor are under kinetic control. Since 1,2-additions to the carbonyl group are fast, we would expect to find a predominance of 1,2-products from these reactions.

If the nucleophile is a weak base, such as alcohols or amines, then the 1,2 addition is usually reversible. This means the competition between 1,2 and 1,4 addition is under thermodynamic control. In this case 1,4-addition dominates because the stable carbonyl group is retained.

Gilman Reagents

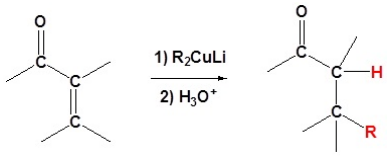
Another important reaction exhibited by organometallic reagents is metal exchange. Organolithium reagents react with cuprous iodide to give a lithium dimethylcopper reagent, which is referred to as a Gilman reagent. Gilman reagents are a source of carbanion like nucleophiles similar to Grignard and Organo lithium reagents. However, the reactivity of organocuprate reagents is slightly different and this difference will be exploited in different situations. In the case of α, β unsaturated carbonyls organocuprate reagents allow for an 1,4 addition of an alkyl group. As we will see later Grignard and Organolithium reagents add alkyl groups 1,2 to α, β unsaturated carbonyls

Organocuprate reagents are made from the reaction of organolithium reagents and CuI

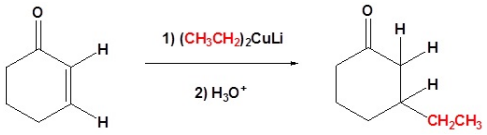
$$2\ RLi + CuI \longrightarrow R_2CuLi + LiI$$

This acts as a source of R:$^-$

$$2\ CH_3LI + CuI \longrightarrow (CH_3)_2CuLI + LiI$$

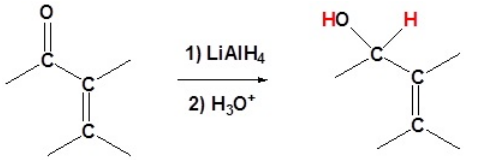


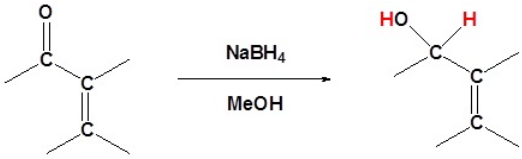
Example



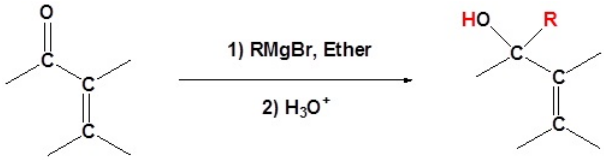
Nucleophiles which add 1,2 to α, β unsaturated carbonyls

Metal Hydrides

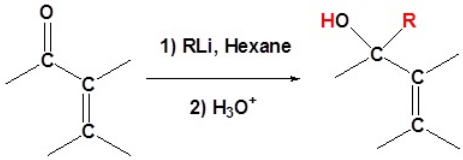




Grignard Reagents



Organolithium Reagents



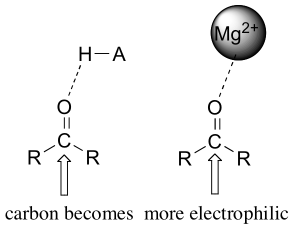
Contributors

- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

18.16: Summary—The Reactions of Organometallic Reagents

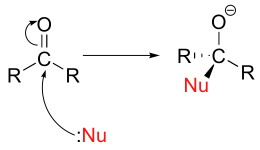
Nucleophilic Addition to Aldehydes and Ketones

The result of carbonyl bond polarization, however it is depicted, is straightforward to predict. The carbon, because it is electron-poor, is an electrophile: it is a great target for attack by an electron-rich nucleophilic group. Because the oxygen end of the carbonyl double bond bears a partial negative charge, anything that can help to stabilize this charge by accepting some of the electron density will increase the bond's polarity and make the carbon more electrophilic. Very often a general acid group serves this purpose, donating a proton to the carbonyl oxygen.

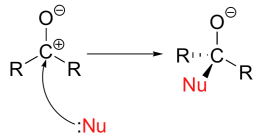


The same effect can also be achieved if a Lewis acid, such as a magnesium ion, is located near the carbonyl oxygen.

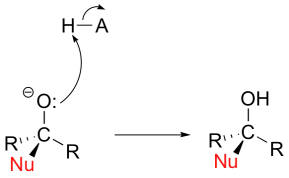
Unlike the situation in a nucleophilic substitution reaction, when a nucleophile attacks an aldehyde or ketone carbon there is no leaving group – the incoming nucleophile simply 'pushes' the electrons in the pi bond up to the oxygen.



Alternatively, if you start with the minor resonance contributor, you can picture this as an attack by a nucleophile on a carbocation.



After the carbonyl is attacked by the nucleophile, the negatively charged oxygen has the capacity to act as a nucleophile. However, most commonly the oxygen acts instead as a base, abstracting a proton from a nearby acid group in the solvent or enzyme active site.

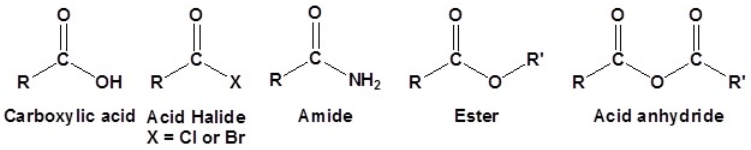


This very common type of reaction is called a **nucleophilic addition**. In many biologically relevant examples of nucleophilic addition to carbonyls, the nucleophile is an alcohol oxygen or an amine nitrogen, or occasionally a thiol sulfur. In one very important reaction type known as an aldol reaction (which we will learn about in section 13.3) the nucleophile attacking the carbonyl is a resonance-stabilized carbanion. In this chapter, we will concentrate on reactions where the nucleophile is an oxygen or nitrogen.

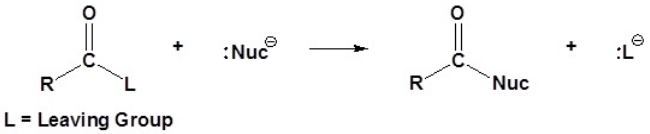
1. Nucleophilic Addition to Aldehydes and Ketones
2. Nucleophilic Substitution of RCOZ (Z = Leaving Group)
3. General reaction

Nucleophilic Substitution of RCOZ (Z = Leaving Group)

Carbonyl compounds with leaving groups have reactions similar to aldehydes and ketones. The main difference is the presence of an electronegative substituent that can act as a leaving group during a nucleophile substitution reaction. Although there are many types of carboxylic acid derivatives known, this article focuses on four: acid halides, acid anhydrides, esters, and amides.



General reaction



Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- Prof. Steven Farmer (Sonoma State University)

18.17: Synthesis

Disconnection of bonds

Having chosen the TARGET molecule for synthesis, the next exercise is to draw out synthetic plans that would summarize all reasonable routes for its synthesis. During the past few decades, chemists have been working on a process called RETROSYNTHESIS. Retrosynthesis could be described as a logical Disconnection at strategic bonds in such a way that the process would progressively lead to easily available starting material(s) through several synthetic plans. Each plan thus evolved, describes a 'ROUTE' based on a retrosynthesis. Each disconnection leads to a simplified structure. The logic of such disconnections forms the basis for the retroanalysis of a given target molecule. Natural products have provided chemists with a large variety of structures, having complex functionalities and stereochemistry. This area has provided several challenging targets for development of these concepts. The underlining principle in devising logical approaches for synthetic routes is very much akin to the following simple problem. Let us have a look of the following big block, which is made by assembling several small blocks **(Fig 1.4.2.1)**. You could easily see that the large block could be broken down in different ways and then reassembled to give the same original block.

Fig 1.4.2.1

Now let us try and extend the same approach for the synthesis of a simple molecule. Let us look into three possible 'disconnections' for a cyclohexane ring as shown in **Fig 1.4.2.2**.

Fig 1.4.2.2

In the above analysis we have attempted to develop three ways of disconnecting the six membered ring. Have we thus created three pathways for the synthesis of cyclohexane ring? Do such disconnections make chemical sense? The background of an organic chemist should enable him to read the process as a chemical reaction in the reverse (or 'retro-') direction. The dots in the above structures could represent a carbonium ion, a carbanion, a free radical or a more complex reaction (such as a pericyclic reaction or a rearrangement). Applying such chemical thinking could open up several plausible reactions. Let us look into path b, which resulted from cleavage of one sigma bond. An anionic cyclisation route alone exposes several candidates as suitable intermediates for the formation of this linkage. The above analysis describes only three paths out of the large number of alternate cleavage routes that are available. An extended analysis shown below indicates more such possibilities **(Fig 1.4.2.3)**. Each such intermediate could be subjected to further disconnection process and the process continued until we reach a reasonably small, easily available starting materials. Thus, a complete 'SYNTHETIC TREE' could be constructed that would summarize all possible routes for the given target molecule.

Fig 1.4.2.3

1.4.3 Efficiency of a route

A route is said to be efficient when the ‘overall yield’ of the total process is the best amongst all routes investigated. This would depend not only on the number of steps involved in the synthesis, but also on the type of strategy followed. The strategy could involve a ‘linear syntheses’ involving only consequential steps or a ‘convergent syntheses’ involving fewer consequential steps. **Fig 1.4.3.1** shown below depicts a few patterns that could be recognized in such synthetic trees. When each disconnection process leads to only one feasible intermediate and the process proceeds in this fashion

Fig 1.4.3.1

all the way to one set of starting materials (SM), the process is called a Linear Synthesis. On the other hand, when an intermediate could be disconnected in two or more ways leading to different intermediates, branching occurs in the plan. The processes could be continued all the way to SMs. In such routes different branches of the synthetic pathways converge towards an intermediate. Such schemes are called Convergent Syntheses.

The flow charts shown below **(Fig 1.4.3.2)** depicts a hypothetical 5-step synthesis by the above two strategies. Assuming a very good yield (90%) at each step (this is rarely seen in real projects), a linier synthesis gives 59% overall yield, whereas a convergent synthesis gives 73% overall yield for the same number of steps..

Fig 1.4.3.2

1.4.4 Problem of substituents and stereoisomers

The situation becomes more complex when you consider the possibility of unwanted isomers generated at different steps of the synthesis. The overall yield drops down considerably for the synthesis of the right isomer. Reactions that yield single isomers (Diastereospecific reactions) in good yields are therefore preferred. Some reactions like the Diels Alder Reaction generate several stereopoints (points at which stereoisomers are generated) simultaneously in one step in a highly predictable manner. Such reactions are highly valued in planning synthetic strategies because several desirable structural features are introduced in one step. Where one pure enantiomer is the target, the situation is again complex. A pure compound in the final step could still have 50% unwanted enantiomer, thus leading to a drastic drop in the efficiency of the route. In such cases, it is desirable to separate the optical isomers as early

in the route as possible, along the synthetic route. This is the main merit of the Chiron Approach, in which the right starting material is chosen from an easily available, cheap 'chiral pool'. We would discuss this aspect after we have understood the logic of planning syntheses. Given these parameters, you could now decide on the most efficient route for any given target.

Molecules of interest are often more complex than the plain cyclohexane ring discussed above. They may have substituents and functional groups at specified points and even specific stereochemical points. Construction of a synthetic tree should ideally accommodate all these parameters to give efficient routes. Let us look into a slightly more complex example shown in **Fig 1.4.4.1** . The ketone **1.4.4.1A** is required as an intermediate in a synthesis. Unlike the plain cyclohexane discussed above, the substitution pattern and the keto- group in this molecule impose some restrictions on disconnection processes.

Fig 1.4.4.1

Cleavage a: This route implies attack of an anion of methylisopropylketone on a bromo-component. *Cleavage b:* This route implies simple regiospecific methylation of a larger ketone that bears all remaining structural elements. *Cleavage c:* This route implies three different possibilities. Route C-1 envisages an acylonium unit, which could come from an acid halide or an ester. Route C-2 implies an umpolung reaction at the acyl unit. Route C-3 suggests an oxidation of a secondary alcohol, which could be obtained through a Grignard-type reaction. *Cleavage d:* This implies a Micheal addition.

Each of these routes could be further developed backwards to complete the synthetic tree. These are just a few plausible routes to illustrate an important point that the details on the structure would restrict the possible cleavages to some strategic points. Notable contributions towards planning organic syntheses came from E.J. Corey's school. These developments have been compiles by Corey in a book by the title LOgIC OF CHEMICAL SYNTHESIS. These and several related presentations on this topic should be taken as guidelines. They are devised after analyzing most of the known approaches published in the literature and identifying a pattern in the logic. They need not restrict the scope for new possibilities. Some of the important strategies are outlined below.

Contributors

- Prof. R Balaji Rao (Department of Chemistry, Banaras Hindu University, Varanasi) as part of Information and Communication Technology

CHAPTER OVERVIEW

19: Aldehydes and Ketones—Nucleophilic Addition

Topic hierarchy

19.1: The Wittig Reaction

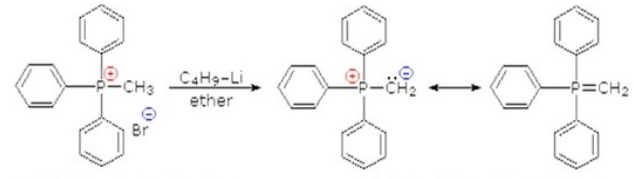
Organophosphorus ylides react with aldehydes or ketones to give substituted alkenes in a transformation called the Wittig reaction. This reaction is named for George Wittig who was awarded the Nobel prize for this work in 1979. A principal advantage of alkene synthesis by the Wittig reaction is that the location of the double bond is absolutely fixed, in contrast to the mixtures often produced by alcohol dehydration.

Preparation of Phosphorus Ylides

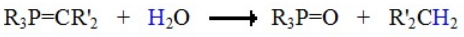
It has been noted that dipolar phosphorus compounds are stabilized by p-d bonding. This bonding stabilization extends to carbanions adjacent to phosphonium centers, and the zwitterionic conjugate bases derived from such cations are known as ylides. An **ylide** is defined as a compound with opposite charges on adjacent atoms both of which have complete octets. For the Wittig reaction discussed below an organophosphorus ylide, also called Wittig reagents, will be used. The ability of phosphorus to hold more than eight valence electrons allows for a resonance structure to be drawn forming a double bonded structure.

An Ylide

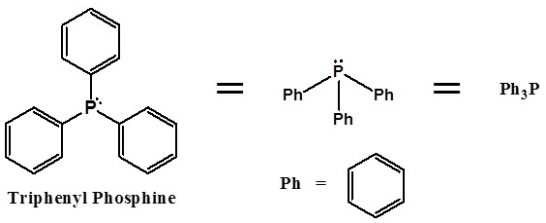
The stabilization of the carbanion provided by the phosphorus causes an increase in acidity (pKa ~35). Very strong bases, such as butyl lithium, are required for complete formation of ylides.



The ylides shown here are all strong bases. Like other strongly basic organic reagents, they are protonated by water and alcohols, and are sensitive to oxygen. Water decomposes phosphorous ylides to hydrocarbons and phosphine oxides, as shown.

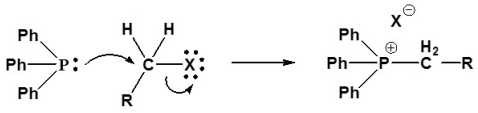


Although many ylides are commercially available it is often necessary to create them synthetically. Ylides can be synthesized from an alkyl halide and a trialkyl phosphine. Typically triphenyl phosphine is used to synthesize ylides. Because a S_N2 reaction is used in the ylide synthesis methyl and primary halides perform the best. Secondary halides can also be used but the yields are generally lower. This should be considered when planning out a synthesis which involves a synthesized Wittig reagent.

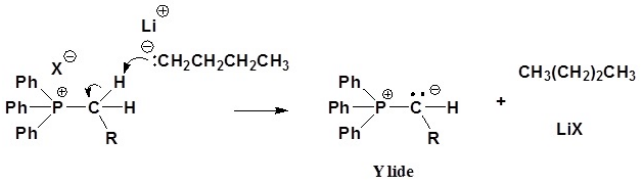


Mechanism of ylide formation

1) S_N2 reaction

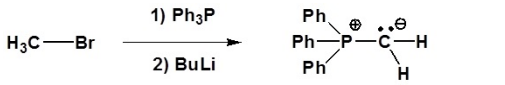


2) Deprotonation



Ylide

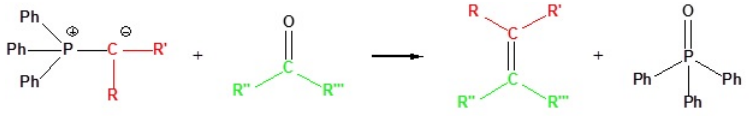
Examples of ylide formation



Methyltriphenylphosphonium bromide

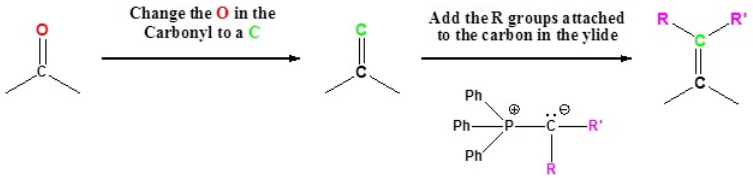
The Wittig Reaction

The most important use of ylides in synthesis comes from their reactions with aldehydes and ketones, which are initiated in every case by a covalent bonding of the nucleophilic alpha-carbon to the electrophilic carbonyl carbon. Ylides react to give substituted alkenes in a transformation called the Wittig reaction. This reaction is named for George Wittig who was awarded the Nobel prize for this work in 1979. A principal advantage of alkene synthesis by the Wittig reaction is that the location of the double bond is absolutely fixed, in contrast to the mixtures often produced by alcohol dehydration.

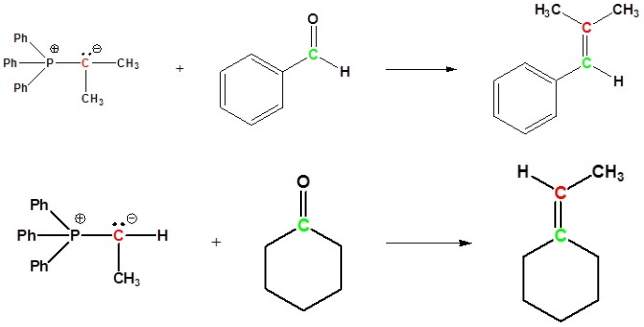


Ylide | Aldehyde or Ketone | Alkene | Triphenyl-phosphine oxide

Going from reactants to products simplified



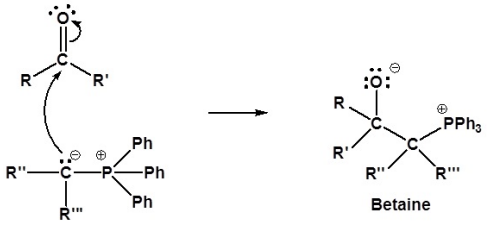
Examples of the Wittig reaction



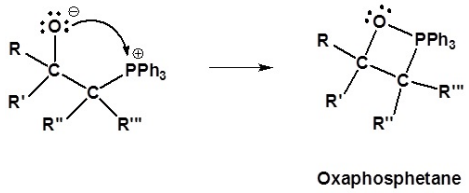
Mechanism of the Wittig reaction

Following the initial carbon-carbon bond formation, two intermediates have been identified for the Wittig reaction, a dipolar charge-separated species called a betaine and a four-membered heterocyclic structure referred to as an oxaphosphatane. Cleavage of the oxaphosphatane to alkene and phosphine oxide products is exothermic and irreversible.

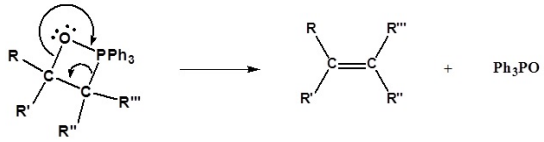
1) Nucleophillic attack on the carbonyl



2) Formation of a 4 membered ring

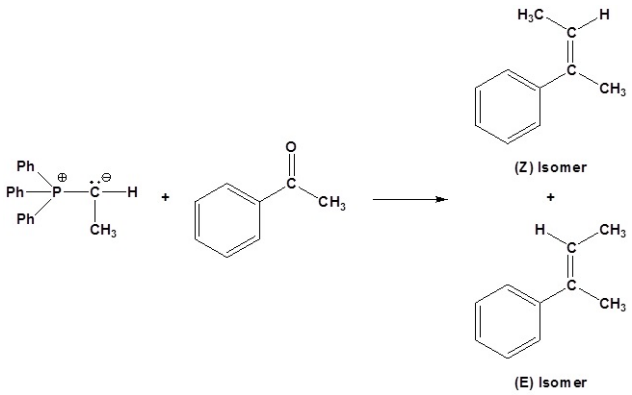


3) Formation of the alkene



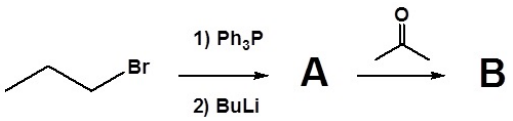
Limitation of the Wittig reaction

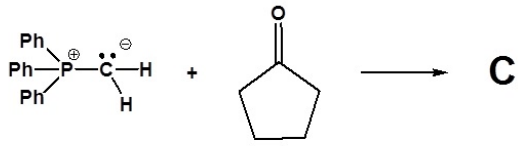
If possible both E and Z isomer of the double bond will be formed. This should be considered when planning a synthesis involving a Wittig Reaction.

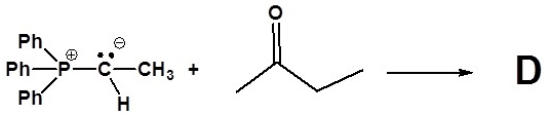


Problems

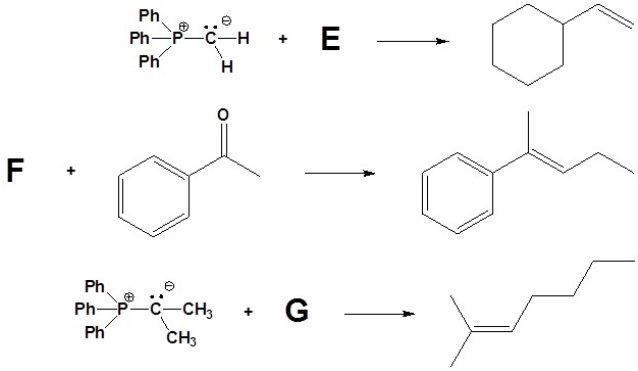
1) Please write the product of the following reactions.







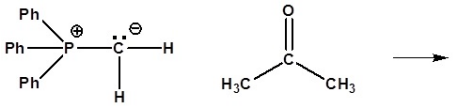
2) Please indicate the starting material required to produce the product.



3) Please draw the structure of the oxaphosphetane which is made during the mechanism of the reaction given that produces product **C**.

4) Please draw the structure of the betaine which is made during the mechanism of the reaction given that produces product **D**.

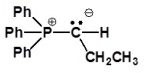
5) Please give a detailed mechanism and the final product of this reaction

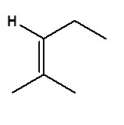


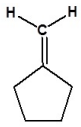
6) It has been shown that reacting and epoxide with triphenylphosphine forms an alkene. Please propose a mechanism for this reaction. Review the section on epoxide reactions if you need help.

Answers

1)



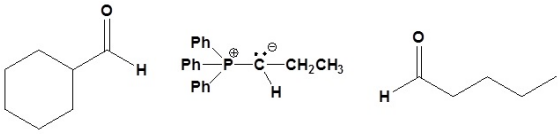




A **B** **C**

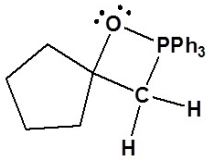
D

2)

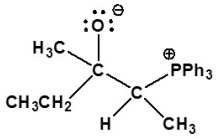


E **F** **G**

3)

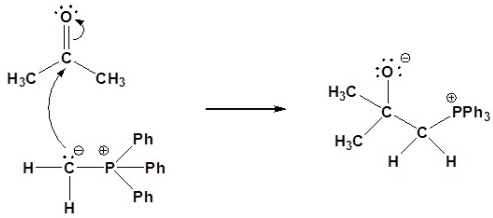


4)

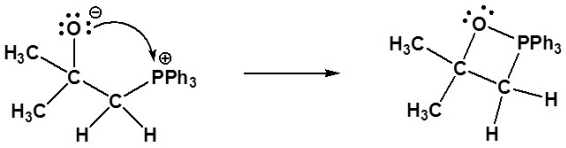


5)

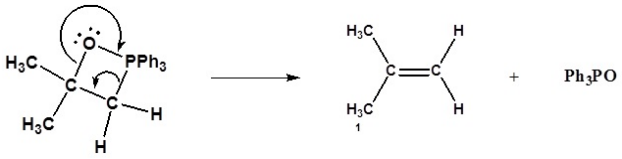
Nucleophillic attack on the carbonyl



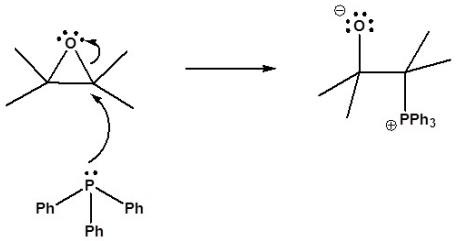
Formation of a 4 membered ring



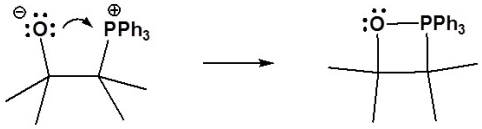
Formation of the alkene



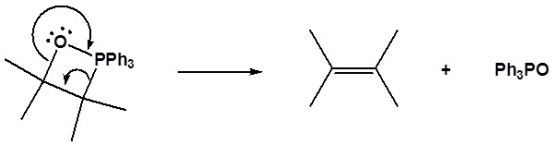
6) Nucleophillic attack on the epoxide



Formation of a 4 membered ring



Formation of the alkene

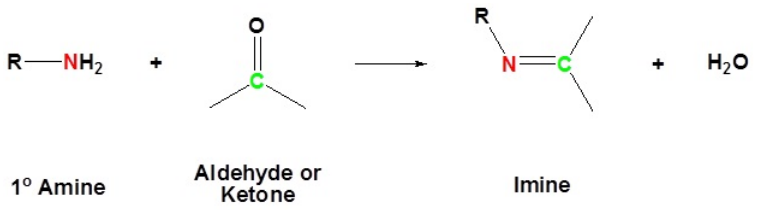


Contributors

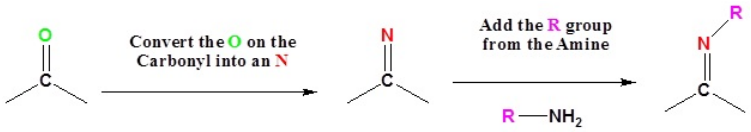
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

19.2: Addition of 1° Amines

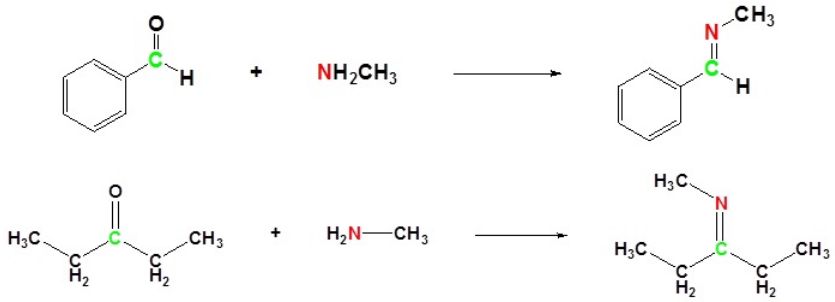
The reaction of aldehydes and ketones with ammonia or 1°-amines forms imine derivatives, also known as Schiff bases (compounds having a C=N function). Water is eliminated in the reaction, which is acid-catalyzed and reversible in the same sense as acetal formation. The pH for reactions which form imine compounds must be carefully controlled. The rate at which these imine compounds are formed is generally greatest near a pH of 5, and drops at higher and lower pH's. At high pH there will not be enough acid to protonate the OH in the intermediate to allow for removal as H_2O. At low pH most of the amine reactant will be tied up as its ammonium conjugate acid and will become non-nucleophilic.



Converting reactants to products simply

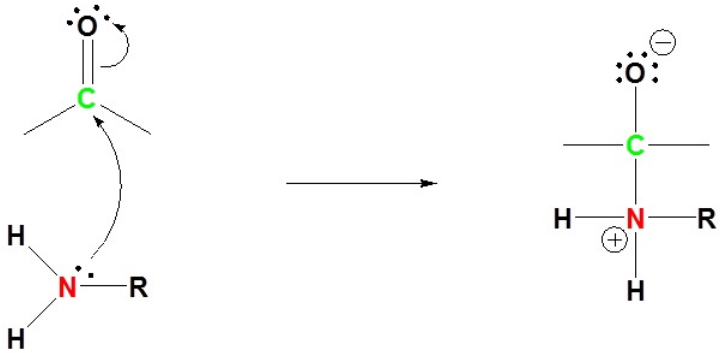


Examples of imine forming reactions

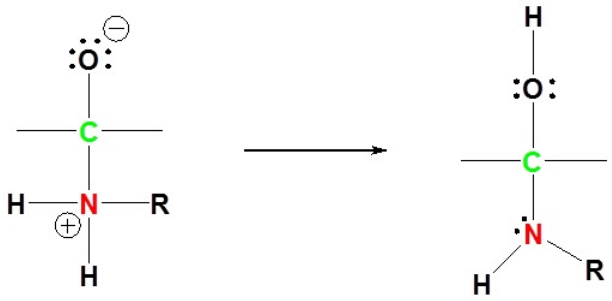


Mechanism of imine formation

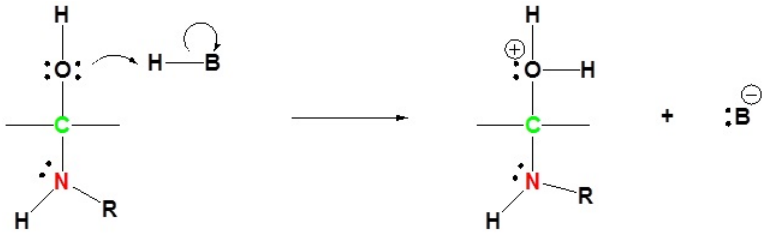
1) Nucleophilic attack



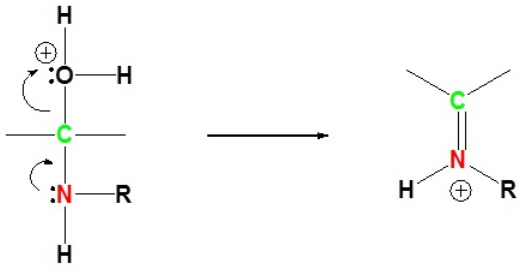
2) Proton transfer



3) Protonation of OH



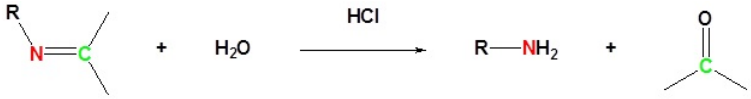
4) Removal of water



5) Deprotonation

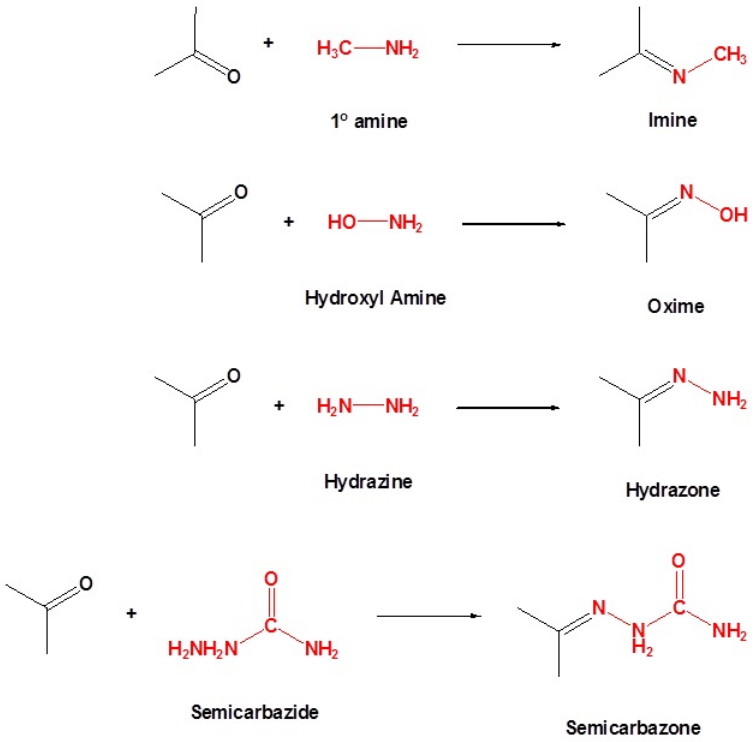
Reversibility of imine forming reactions

Imines can be hydrolyzed back to the corresponding primary amine under acidic conditons.



Reactions involving other reagents of the type Y-NH_2

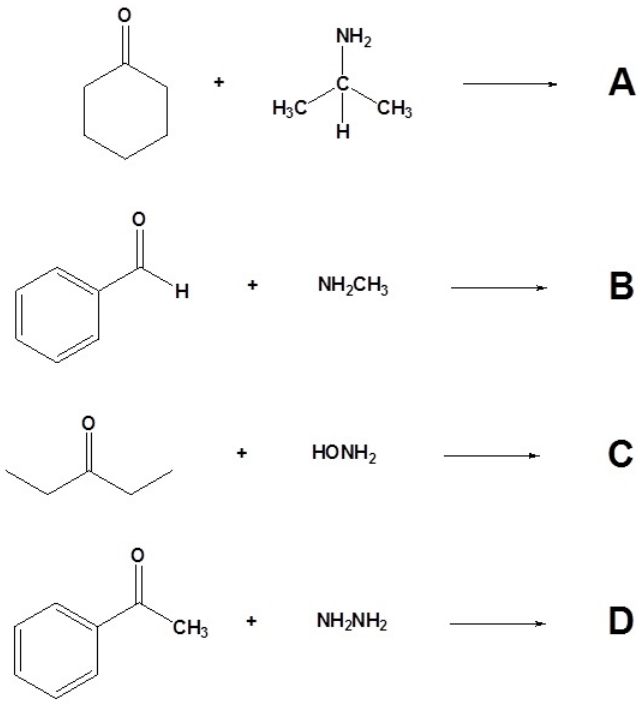
Imines are sometimes difficult to isolate and purify due to their sensitivity to hydrolysis. Consequently, other reagents of the type Y–NH_2 have been studied, and found to give stable products (R_2C=N–Y) useful in characterizing the aldehydes and ketones from which they are prepared. Some of these reagents are listed in the following table, together with the structures and names of their carbonyl reaction products. Hydrazones are used as part of the Wolff-Kishner reduction and will be discussed in more detail in another module.



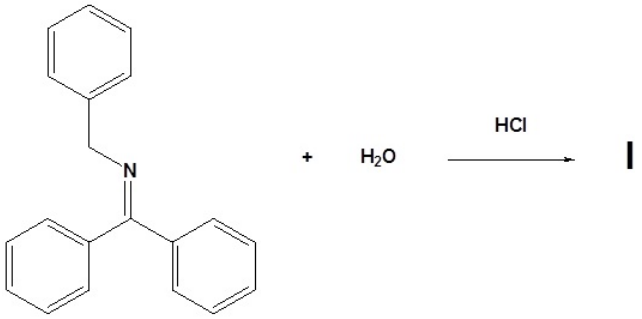
With the exception of unsubstituted hydrazones, these derivatives are easily prepared and are often crystalline solids - even when the parent aldehyde or ketone is a liquid. Since melting points can be determined more quickly and precisely than boiling points, derivatives such as these are useful for comparison and identification of carbonyl compounds. It should be noted that although semicarbazide has two amino groups ($-NH_2$) only one of them is a reactive amine. The other is amide-like and is deactivated by the adjacent carbonyl group.

Problems

1)Please draw the products of the following reactions.



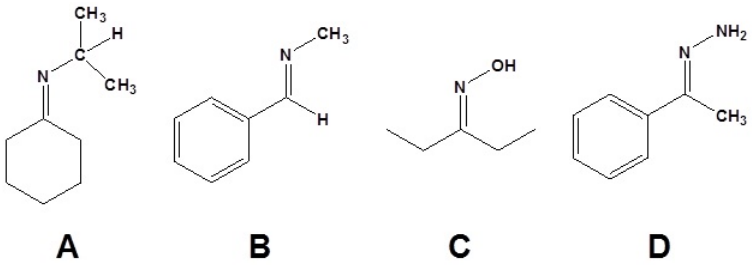
2) Please draw the structure of the reactant needed to produce the indicated product.



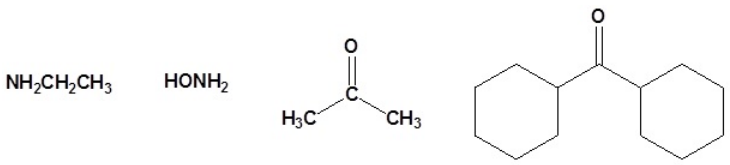
3) Please draw the products of the following reactions.

Answers

1)



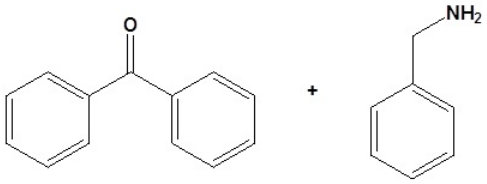
2)



E F G H

3)

I



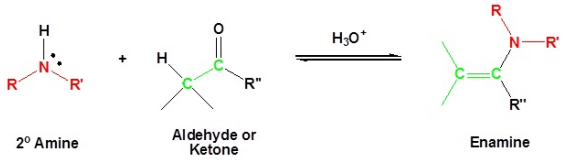
Contributors

- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

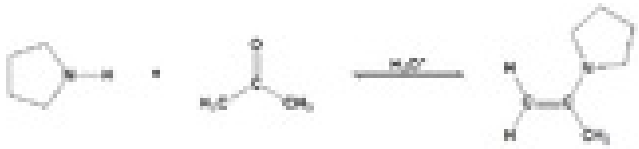
19.3: Addition of 2° Amines

Introduction

Most aldehydes and ketones react with 2º-amines to give products known as **enamines**. It should be noted that, like acetal formation, these are acid-catalyzed reversible reactions in which water is lost. Consequently, enamines are easily converted back to their carbonyl precursors by acid-catalyzed hydrolysis.

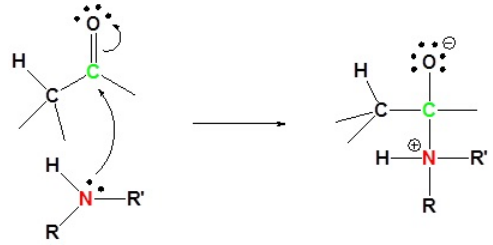


Example	

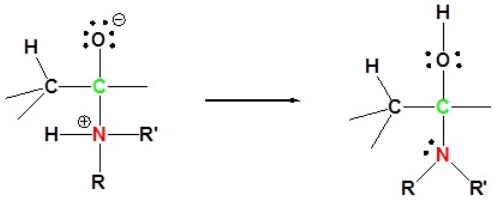


Mechanism

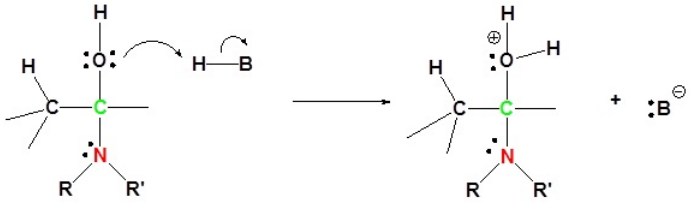
1) Nuleophilic attack



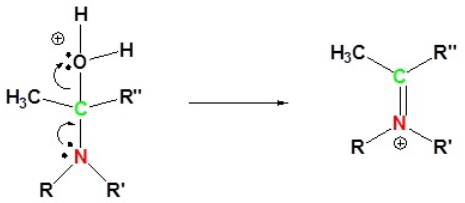
2) Proton transfer



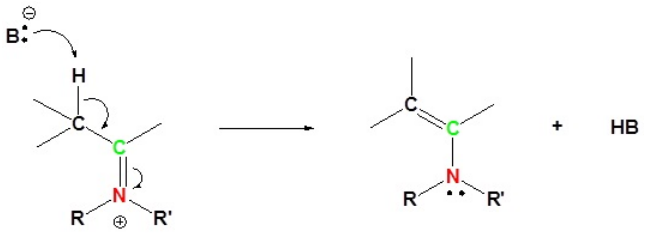
3) Protonation of OH



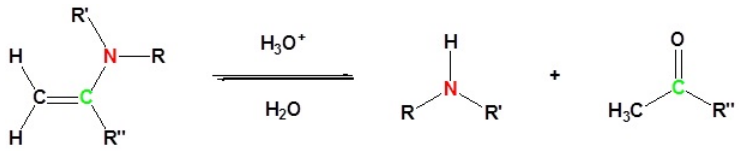
4) Removal of water



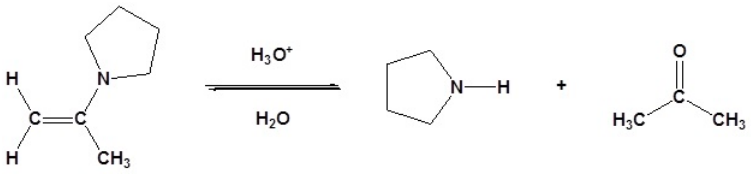
5) Deprotonation



Reversibility of Enamines

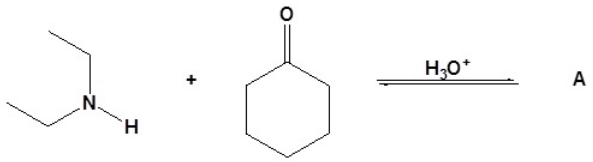


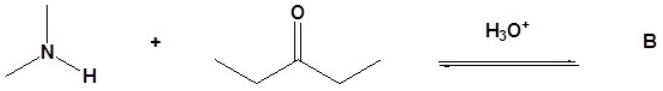
Example	



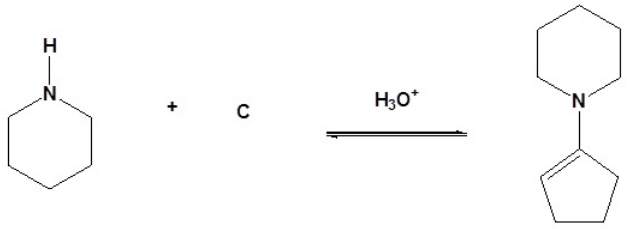
Problems

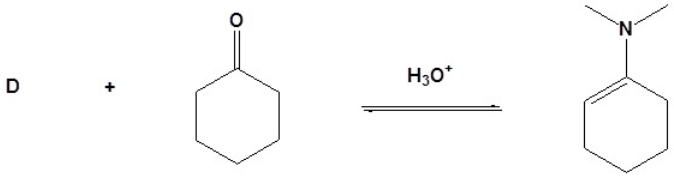
1) Please draw the products for the following reactions.





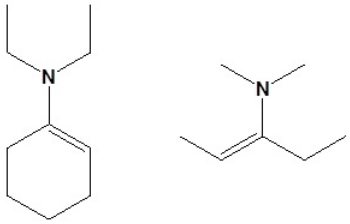
2) Please give the structure of the reactant needed to product the following product





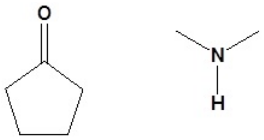
Answers

1)



A B

2)



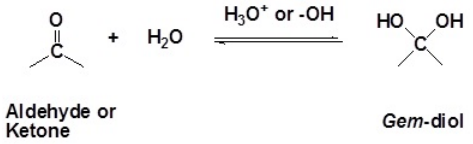
C D

Contributors

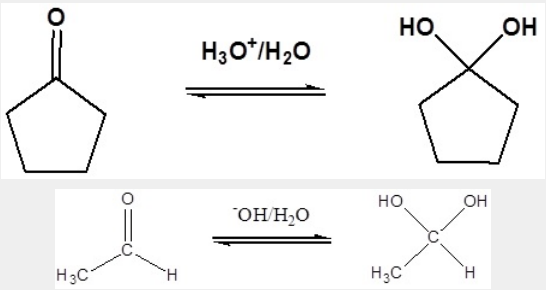
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

19.4: Addition of H 2 O H2O —Hydration

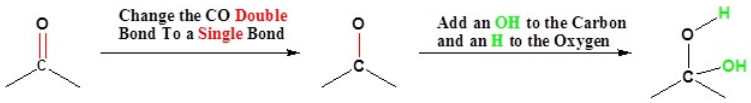
It has been demonstrated that water, in the presence of an acid or a base, adds rapidly to the carbonyl function of aldehydes and ketones establishing a reversible equilibrium with a **hydrate** (geminal-diol or *gem*-diol). The word germinal or gem comes from the Latin word for twin, *geminus*.



Example 1

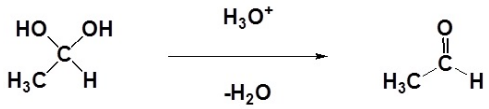


Going from Reactants to Products Simplified



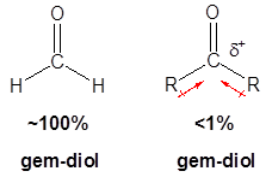
Reversibility of the Reaction

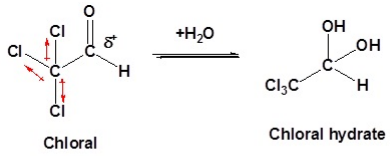
Isolation of *gem*-diols is difficult because the reaction is reversibly. Removal of the water during a reaction can cause the conversion of a gem-diol back to the corresponding carbonyl.

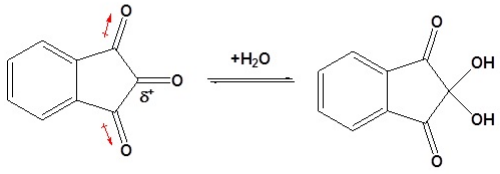


Factors Affecting the *Gem*-diol Equilibrium

In most cases the resulting *gem*-diol is unstable relative to the reactants and cannot be isolated. Exceptions to this rule exist, one being formaldehyde where the weaker pi-component of the carbonyl double bond, relative to other aldehydes or ketones, and the small size of the hydrogen substituents favor addition. Thus, a solution of formaldehyde in water (formalin) is almost exclusively the hydrate, or polymers of the hydrate. The addition of electron donating alkyl groups stabilized the partial positive charge on the carbonyl carbon and decreases the amount of *gem*-diol product at equilibrium. Because of this ketones tend to form less than 1% of the hydrate at equilibrium. Likewise, the addition of strong electron-withdrawing groups destabilizes the carbonyl and tends to form stable *gem*-diols. Two examples of this are chloral, and 1,2,3-indantrione. It should be noted that chloral hydrate is a sedative and has been added to alcoholic beverages to make a “Knock-out” drink also called a Mickey Finn. Also, ninhydrin is commonly used by forensic investigators to resolve finger prints.





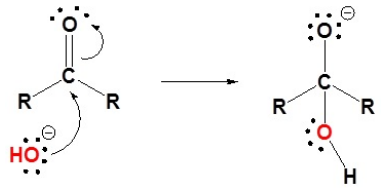


Mechanism of *Gem*-diol Formation

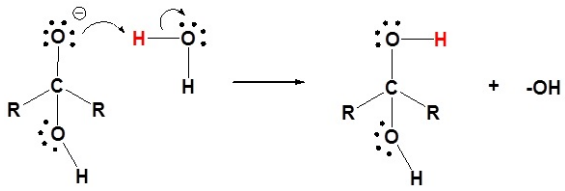
The mechanism is catalyzed by the addition of an acid or base. Note! This may speed up the reaction but is has not effect on the equilibriums discussed above. Basic conditions speed up the reaction because hydroxide is a better nucleophilic than water. Acidic conditions speed up the reaction because the protonated carbonyl is more electrophilic.

Basic conditions

1) Nucleophilic attack by hydroxide

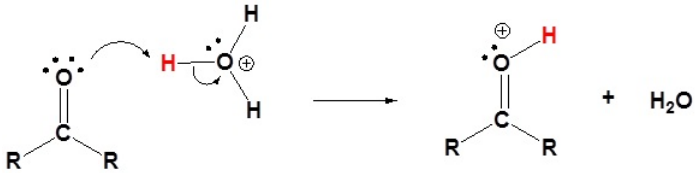


2) Protonation of the alkoxide

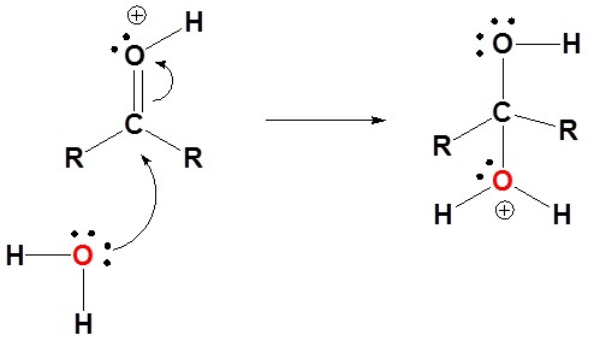


Acidic conditions

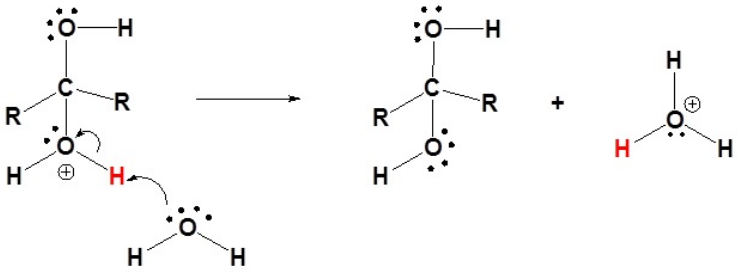
1) Protonation of the carbonyl



2) Nucleophilic attack by water

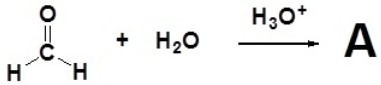


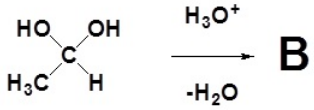
3) Deprotonation

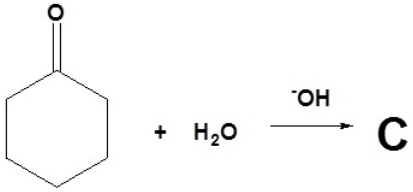


Problems

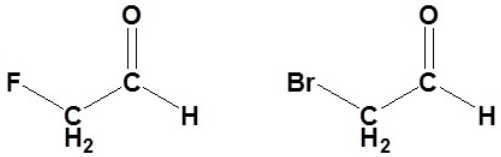
1) Draw the expected products of the following reactions.



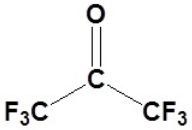




2) Of the following pairs of molecules which would you expect to form a larger percentage of *gem*-diol at equilibrium? Please explain your answer.

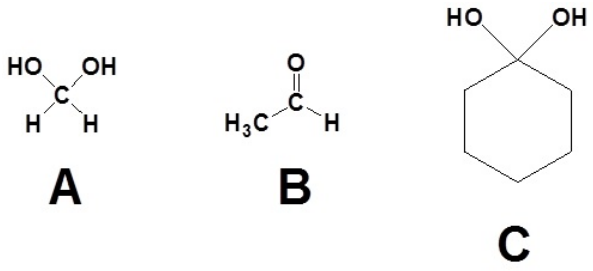


3) Would you expect the following molecule to form appreciable amount of *gem*-diol in water? Please explain your answer.



Answers

1)



2) The compound on the left would. Fluorine is more electronegative than bromine and would remove more electron density from the carbonyl carbon. This would destabilize the carbonyl allowing for more *gem*-diol to form.

3) Although ketones tend to not form *gem*-diols this compound exists almost entirely in the *gem*-diol form when placed in water. Ketones tend to not form *gem*-diols because of the stabilizing effect of the electron donating alkyl group. However, in this case the electron donating effects of alkyl group is dominated by the presence of six highly electronegative fluorines.

Contributors

- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

19.5: Addition of Alcohols—Acetal Formation

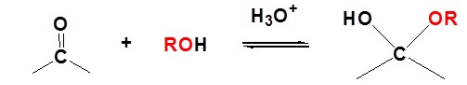
In this organic chemistry topic, we shall see how alcohols (R-OH) add to carbonyl groups. Carbonyl groups are characterized by a carbon-oxygen double bond. The two main functional groups that consist of this carbon-oxygen double bond are Aldehydes and Ketones.

Introduction

It has been demonstrated that water adds rapidly to the carbonyl function of aldehydes and ketones to form geminal-diol. In a similar reaction alcohols add reversibly to aldehydes and ketones to form hemiacetals (h*emi*, Greek, half). This reaction can continue by adding another alcohol to form an acetal. Hemiacetals and acetals are important functional groups because they appear in sugars.

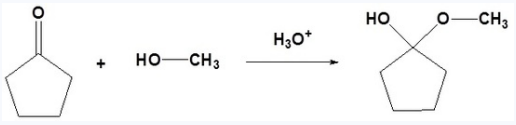
To achieve effective hemiacetal or acetal formation, two additional features must be implemented. First, an acid catalyst must be used because alcohol is a weak nucleophile; and second, the water produced with the acetal must be removed from the reaction by a process such as a molecular sieves or a **Dean-Stark trap**. The latter is important, since acetal formation is reversible. Indeed, once pure hemiacetal or acetals are obtained they may be hydrolyzed back to their starting components by treatment with aqueous acid and an excess of water.

Formation of Hemiacetals

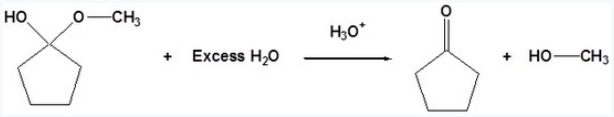


Aldehyde or Ketone **Hemi-Acetal**

Example 1: Formation of Hemiacetals

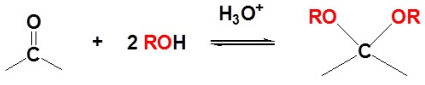


Example 2: Hemiacetal Reversibility



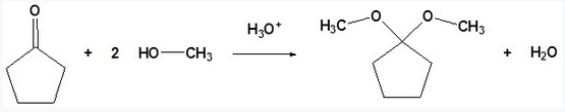
Formation of Acetals

Acetals are geminal-diether derivatives of aldehydes or ketones, formed by reaction with two equivalents (or an excess amount) of an alcohol and elimination of water. Ketone derivatives of this kind were once called ketals, but modern usage has dropped that term. It is important to note that a hemiacetal is formed as an intermediate during the formation of an acetal.

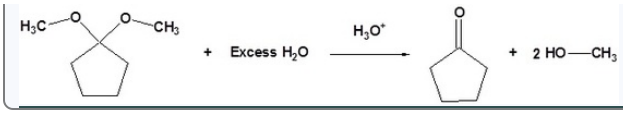


Aldehyde or Ketone **Acetal**

Example 3: Formation of Acetals



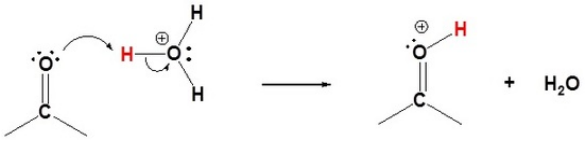
Example 4: Acetal Reversibility



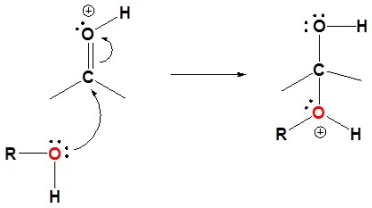
Mechanism for Hemiacetal and Acetal Formation

The mechanism shown here applies to both acetal and hemiacetal formation

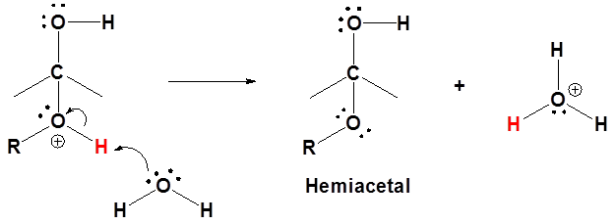
1) Protonation of the carbonyl



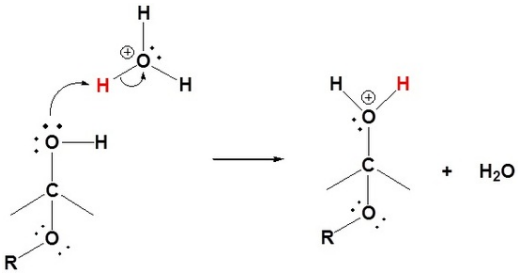
2) Nucleophilic attack by the alcohol



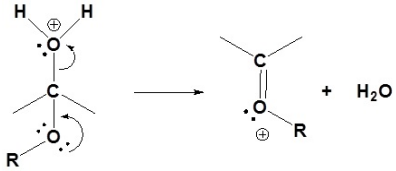
3) Deprotonation to form a hemiacetal



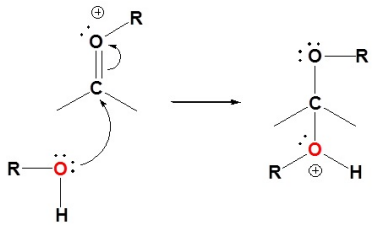
4) Protonation of the alcohol



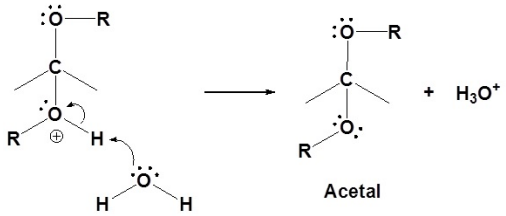
5) Removal of water



6) Nucleophilic attack by the alcohol



7) Deprotonation by water



Contributors

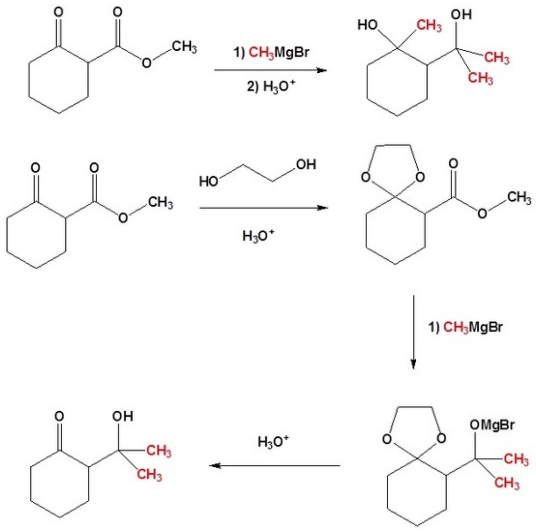
- Prof. Steven Farmer (Sonoma State University)

19.6: Acetals as Protecting Groups

Acetals as Protecting Groups

The importance of acetals as carbonyl derivatives lies chiefly in their stability and lack of reactivity in neutral to strongly basic environments. As long as they are not treated by acids, especially aqueous acid, acetals exhibit all the lack of reactivity associated with ethers in general. Among the most useful and characteristic reactions of aldehydes and ketones is their reactivity toward strongly nucleophilic (and basic) metallo-hydride, alkyl and aryl reagents. If the carbonyl functional group is converted to an acetal these powerful reagents have no effect; thus, acetals are excellent protective groups, when these irreversible addition reactions must be prevented.

In the following example we would like a Grignard reagent to react with the ester and not the ketone. This cannot be done without a protecting group because Grignard reagents react with esters and ketones.



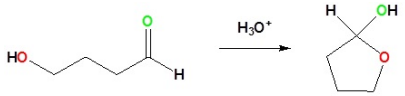
Contributors

- Prof. Steven Farmer (Sonoma State University)

19.7: Cyclic Hemiacetals

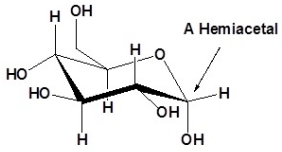
Formation of Cyclic Hemiacetal and Acetals

Molecules which have an alcohol and a carbonyl can undergo an intramolecular reaction to form a cyclic hemiacetal.



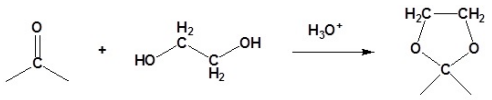
Cyclic Hemiacetal

Intramolecular Hemiacetal formation is common in sugar chemistry. For example, the common sugar glucose exists in the cylcic manner more than 99% of the time in a mixture of aqueous solution.



D-Glucose

Carbonyls reacting with diol produce a cyclic acetal. A common diol used to form cyclic acetals is ethylene glycol.



Ethylene Glycol

Cyclic Acetal

Contributors

- Prof. Steven Farmer (Sonoma State University)

19.8: An Introduction to Carbohydrates

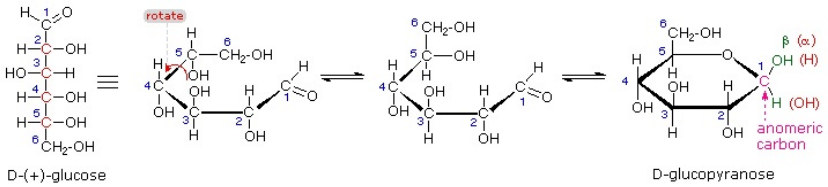
Carbohydrates are the most abundant class of organic compounds found in living organisms. They originate as products of photosynthesis, an endothermic reductive condensation of carbon dioxide requiring light energy and the pigment chlorophyll.

$$nCO_2 + nH_2O + \text{Energy} \rightarrow C_nH_{2n}O_n + nO_2 \tag{19.8.1}$$

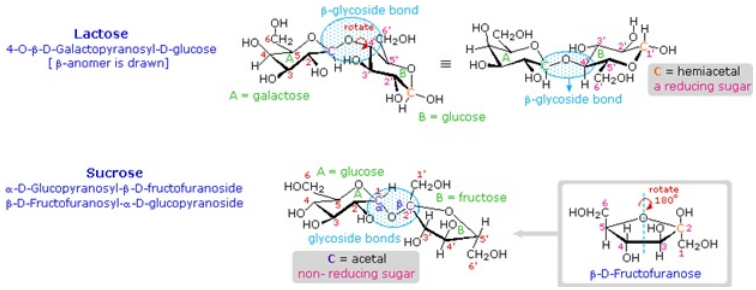
As noted here, the formulas of many carbohydrates can be written as carbon hydrates, $C_n(H_2O)_n$, hence their name. The carbohydrates are a major source of metabolic energy, both for plants and for animals that depend on plants for food. Aside from the sugars and starches that meet this vital nutritional role, carbohydrates also serve as a structural material (cellulose), a component of the energy transport compound ATP/ADP, recognition sites on cell surfaces, and one of three essential components of DNA and RNA.

The most useful carbohydrate classification scheme divides the carbohydrates into groups according to the number of individual simple sugar units. **Monosaccharides** contain a single unit; **disaccharides** contain two sugar units; and **polysaccharides** contain many sugar units as in polymers - most contain glucose as the monosaccharide unit.

Some sugars can undergo a intermolecular cyclization to form a hemi-acetal. The hemiacetal carbon atom (C-1) becomes a new stereogenic center, commonly referred to as the anomeric carbon, and the α and β-isomers are called anomers.



Disaccharides made up of other sugars are known, but glucose is often one of the components. Two important examples of such mixed disaccharides are displayed above. Lactose, also known as milk sugar, is a galactose-glucose compound joined as a beta-glycoside. It is a reducing sugar because of the hemiacetal function remaining in the glucose moiety. Many adults, particularly those from regions where milk is not a dietary staple, have a metabolic intolerance for lactose. Infants have a digestive enzyme which cleaves the beta-glycoside bond in lactose, but production of this enzyme stops with weaning. Sucrose, or cane sugar, is our most commonly used sweetening agent. It is a non-reducing disaccharide composed of glucose and fructose joined at the anomeric carbon of each by glycoside bonds (one alpha and one beta). In the formula shown here the fructose ring has been rotated 180º from its conventional perspective.



Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

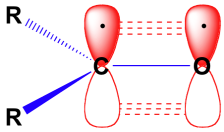
19.9: Introduction

A carbonyl group is a chemically organic functional group composed of a carbon atom double-bonded to an oxygen atom --> [**C=O**] The simplest carbonyl groups are aldehydes and ketones usually attached to another carbon compound. These structures can be found in many aromatic compounds contributing to smell and taste.

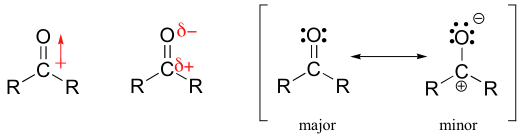
The Carbonyl Group

C=O is prone to additions and nucleophillic attack because or carbon's positive charge and oxygen's negative charge. The resonance of the carbon partial positive charge allows the negative charge on the nucleophile to attack the Carbonyl group and become a part of the structure and a positive charge (usually a proton hydrogen) attacks the oxygen. Just a reminder, the nucleophile is a good acid therefore "likes protons" so it will attack the side with a positive charge.

Before we consider in detail the reactivity of aldehydes and ketones, we need to look back and remind ourselves of what the bonding picture looks like in a carbonyl. Carbonyl carbons are sp^2 hybridized, with the three sp^2 orbitals forming soverlaps with orbitals on the oxygen and on the two carbon or hydrogen atoms. These three bonds adopt trigonal planar geometry. The remaining unhybridized 2p orbital on the central carbonyl carbon is perpendicular to this plane, and forms a ‘side-by-side’ pbond with a 2p orbital on the oxygen.



The carbon-oxygen double bond is polar: oxygen is more electronegative than carbon, so electron density is higher on the oxygen side of the bond and lower on the carbon side. Recall that bond polarity can be depicted with a dipole arrow, or by showing the oxygen as holding a partial negative charge and the carbonyl carbon a partial positive charge.



A third way to illustrate the carbon-oxygen dipole is to consider the two main resonance contributors of a carbonyl group: the major form, which is what you typically see drawn in Lewis structures, and a minor but very important contributor in which both electrons in the pbond are localized on the oxygen, giving it a full negative charge. The latter depiction shows the carbon with an empty 2p orbital and a full positive charge.

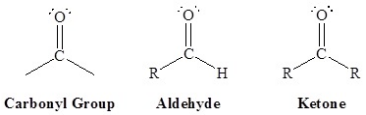
Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

19.10: Nomenclature

he most potent and varied odors are aldehydes. Ketones are widely used as industrial solvents. Aldehydes and ketones contain the carbonyl group. Aldehydes are considered the most important functional group. They are often called the formyl or methanoyl group. Aldehydes derive their name from the *dehyd*ration of *al*cohols. Aldehydes contain the carbonyl group bonded to at least one hydrogen atom. Ketones contain the carbonyl group bonded to two carbon atoms.

Introduction

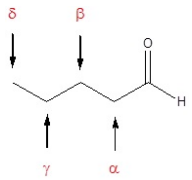
Aldehydes and ketones are organic compounds which incorporate a **carbonyl functional group**, C=O. The carbon atom of this group has two remaining bonds that may be occupied by hydrogen, alkyl or aryl substituents. If at least one of these substituents is hydrogen, the compound is an **aldehyde**. If neither is hydrogen, the compound is a **ketone**.



Naming Aldehydes

The IUPAC system of nomenclature assigns a characteristic suffix ***-al*** to aldehydes. For example, $H_2C=O$ is methan**al**, more commonly called formaldehyde. Since an aldehyde carbonyl group must always lie at the end of a carbon chain, it is always is given the #1 location position in numbering and it is not necessary to include it in the name. There are several simple carbonyl containing compounds which have common names which are retained by IUPAC.

Also, there is a common method for naming aldehydes and ketones. For aldehydes common parent chain names, similar to those used for carboxylic acids, are used and the suffix ***–aldehyde*** is added to the end. In common names of aldehydes, carbon atoms near the carbonyl group are often designated by Greek letters. The atom adjacent to the carbonyl function is alpha, the next removed is beta and so on.



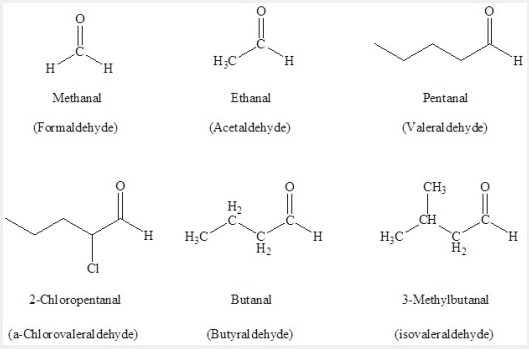
If the aldehyde moiety  (-CHO) is attached to a ring the suffix ***–carbaldehyde*** is added to the name of the ring. The carbon attached to this moiety will get the #1 location number in naming the ring.

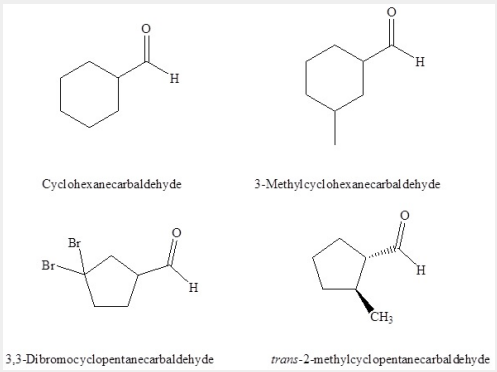
Summary of Aldehyde Nomenclature rules

1. Aldehydes take their name from their parent alkane chains. The ***-e*** is removed from the end and is replaced with ***-al***.
2. The aldehyde funtional group is given the #1 numbering location and this number is not included in the name.
3. For the common name of aldehydes start with the common parent chain name and add the suffix ***-aldehyde***. Substituent positions are shown with Greek letters.
4. When the -CHO functional group is attached to a ring the suffix ***-carbaldehyde*** is added, and the carbon attached to that group is C1.

Example 1

The IUPAC system names are given on top while the common name is given on the bottom in parentheses.





Naming Ketones

The IUPAC system of nomenclature assigns a characteristic suffix of **-one** to ketones. A ketone carbonyl function may be located anywhere within a chain or ring, and its position is usually given by a location number. Chain numbering normally starts from the end nearest the carbonyl group. Very simple ketones, such as propanone and phenylethanone do not require a locator number, since there is only one possible site for a ketone carbonyl function

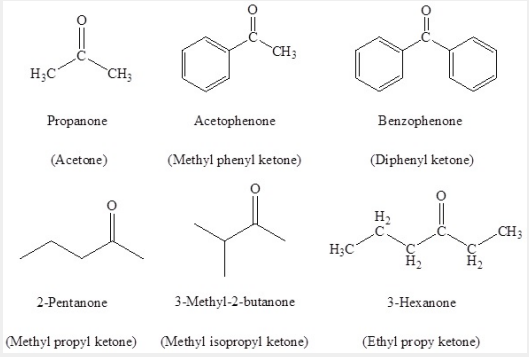
The common names for ketones are formed by naming both alkyl groups attached to the carbonyl then adding the suffix **-ketone**. The attached alkyl groups are arranged in the name alphabetically.

Summary of Ketone Nomenclature rules

1. Ketones take their name from their parent alkane chains. The ending ***-e*** is removed and replaced with ***-one***.
2. The common name for ketones are simply the **substituent groups listed alphabetically + *ketone*.**
3. Some common ketones are known by their generic names. Such as the fact that *propanone* is commonly referred to as *acetone*.

Example 2

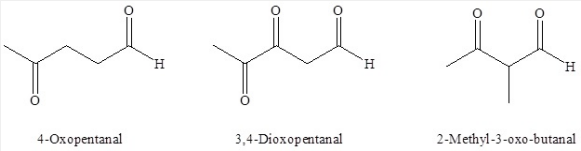
The IUPAC system names are given on top while the common name is given on the bottom in parentheses.



Naming Aldehydes and Ketones in the Same Molecule

As with many molecules with two or more functional groups, one is given priority while the other is named as a substituent. Because aldehydes have a higher priority than ketones, molecules which contain both functional groups are named as aldehydes and the ketone is named as an **"oxo"** substituent. It is not necessary to give the aldehyde functional group a location number, however, it is usually necessary to give a location number to the ketone.

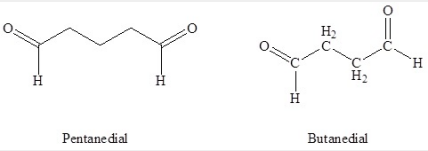
Example 3



Naming Dialdehydes and Diketones

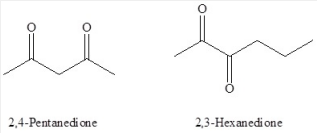
For dialdehydes the location numbers for both carbonyls are omitted because the aldehyde functional groups are expected to occupy the ends of the parent chain. The ending **–dial** is added to the end of the parent chain name.

Example 4



For diketones both carbonyls require a location number. The ending **-dione** or **-dial** is added to the end of the parent chain.

Example 5

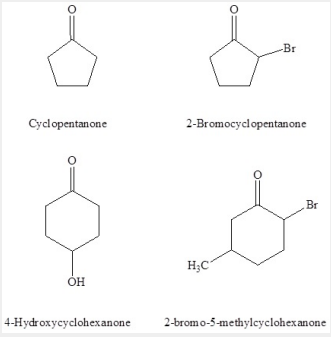


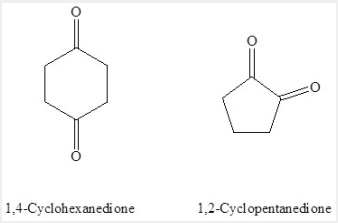
Naming Cyclic Ketones and Diketones

In cyclic ketones the carbonyl group is assigned location position #1, and this number is not included in the name, unless more than one carbonyl group is present. The rest of the ring is numbered to give substituents the lowest possible location numbers. Remember the prefix **cyclo** is included before the parent chain name to indicate that it is in a ring. As with other ketones the **–e** ending is replaced with the **–one** to indicate the presence of a ketone.

With cycloalkanes which contain two ketones both carbonyls need to be given a location numbers. Also, an **–e** is not removed from the end but the suffix **–dione** is added.

Example 6

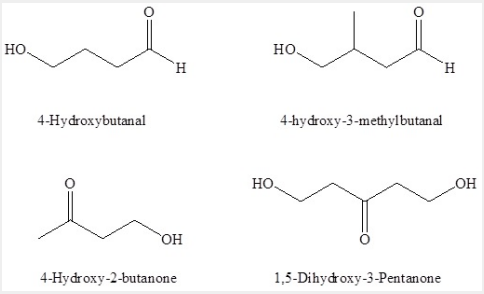




Naming Carbonyls and Hydroxyls in the Same Molecule

When and aldehyde or ketone is present in a molecule which also contains an alcohol functional group the carbonyl is given nomenclature priority by the IUPAC system. This means that the carbonyl is given the lowest possible location number and the appropriate nomenclature suffix is included. In the case of alcohols the **OH** is named as a **hydroxyl** substituent. However, the **l** in hydroxyl is generally removed.

Example 7



Naming Carbonyls and Alkenes in the Same Molecule

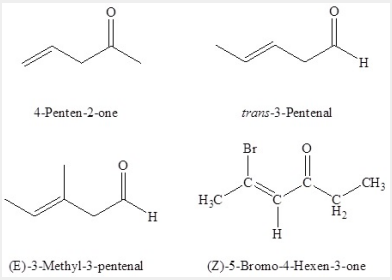
When and aldehyde or ketone is present in a molecule which also contains analkene functional group the carbonyl is given nomenclature priority by the IUPAC system. This means that the carbonyl is given the lowest possible location number and the appropriate nomenclature suffix is included.

When carbonyls are included with an alkene the following order is followed:

(Location number of the alkene)-(Prefix name for the longest carbon chain minus the **-ane** ending)-(an **-en** ending to indicate the presence of an alkene)-(the location number of the carbonyl if a ketone is present)-(either an **–one** or and **-anal** ending).

Remember that the carbonyl has priority so it should get the lowest possible location number. Also, remember that cis/tran or E/Z nomenclature for the alkene needs to be included if necessary.

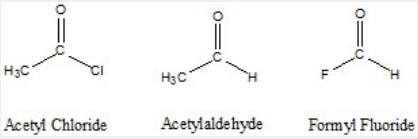
Example 8



Aldehydes and Ketones as Fragments

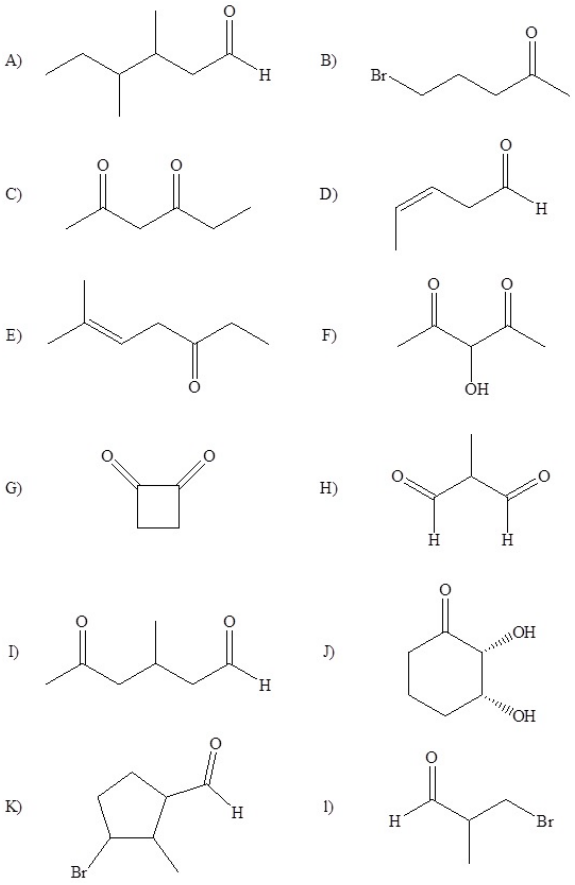
- *Alkanoyl* is the common name of the fragment, though the older naming, *acyl*, is still widely used.
- *Formyl* is the common name of the fragment.
- *Acety* is the common name of the CH_3-C=O- fragment.

Example 9



Additional Examples of Carbonyl Nomenclature

1) Please give the IUPAC name for each compound:



Answers for Question 1

A. 3,4-Dimethylhexanal
B. 5-Bromo-2-pentanone
C. 2,4-Hexanedione
D. cis-3-Penenal
E. 6-methyl-5-Hepten-3-one
F. 3-hydroxy-2,4-Pentanedione
G. 1,2-Cyclobutanedione
H. 2-methyl-Propanedial
I. 3-methyl-5-oxo-Hexanal
J. cis-2,3-dihydroxycyclohexanone
K. 2-methylcyclopentanecarboaldehyde
L. 3-bromo-2-methylpropanal

2) Please give the structure corresponding to each name:

A) Butanal

B) 2-Hydroxycyclopentanone

C) 2,3-Pentanedione

D) 1,3-Cyclohexanedione

E) 3,4-Dihydoxy-2-butanone

F) (E) 3-methyl-2-Hepten-4-one

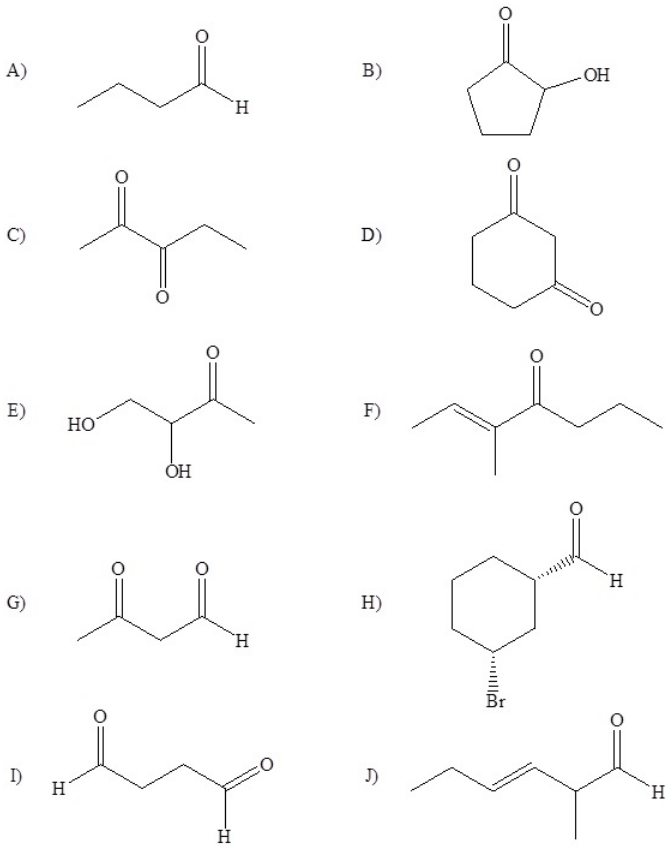
G) 3-Oxobutanal

H) *cis*-3-Bromocyclohexanecarboaldehyde

I) Butanedial

J) *trans*-2-methyl-3-Hexenal

Answers to question 2:



References

1. Vollhardt, K. Peter C., and Neil E. Schore. Organic Chemistry. 5th ed. New York: W.H. Freeman, 2007.
2. Zumdahl, Steven S., and Susan A. Zumdahl. Chemistry. 6th ed. Boston: Houghton Mifflin College Division, 2002.

Contributors

- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

19.11: Physical Properties

Introduction

A comparison of the properties and reactivity of aldehydes and ketones with those of the alkenes is warranted, since both have a double bond functional group. Because of the greater electronegativity of oxygen, the carbonyl group is polar, and aldehydes and ketones have larger molecular dipole moments (D) than do alkenes. The resonance structures in Figure 1 illustrate this polarity, and the relative dipole moments of formaldehyde, other aldehydes and ketones confirm the stabilizing influence that alkyl substituents have on carbocations (the larger the dipole moment the greater the polar character of the carbonyl group). We expect, therefore, that aldehydes and ketones will have higher boiling points than similar sized alkenes. Furthermore, the presence of oxygen with its non-bonding electron pairs makes aldehydes and ketones hydrogen-bond acceptors, and should increase their water solubility relative to hydrocarbons. Specific examples of these relationships are provided in the following table.

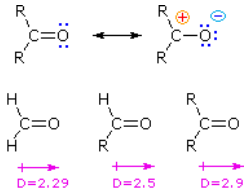


Figure 1: Resonance structures

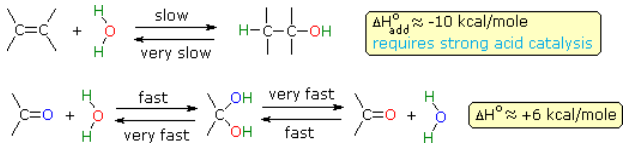
Compound	Mol. Wt.	Boiling Point	Water Solubility
$(CH_3)_2C=CH_2$	56	-7.0 ºC	0.04 g/100
$(CH_3)_2C=O$	58	56.5 ºC	infinite
$CH_3CH_2CH_2CH=CH_2$	70	30.0 ºC	0.03 g/100
$CH_3CH_2CH_2CH=O$	72	76.0 ºC	7 g/100
	96	103.0 ºC	insoluble
	98	155.6 ºC	5 g/100

The polarity of the carbonyl group also has a profound effect on its chemical reactivity, compared with the non-polar double bonds of alkenes. Thus, reversible addition of water to the carbonyl function is fast, whereas water addition to alkenes is immeasurably slow in the absence of a strong acid catalyst. Curiously, relative bond energies influence the thermodynamics of such addition reactions in the opposite sense.

The C=C of alkenes has an average bond energy of 146 kcal/mole. Since a C–C σ-bond has a bond energy of 83 kcal/mole, the π-bond energy may be estimated at 63 kcal/mole (i.e. less than the energy of the sigma bond). The C=O bond energy of a carbonyl group, on the other hand, varies with its location, as follows:

$H_2C=O$	**170 kcal/mole**
RCH=O	**175 kcal/mole**
$R_2C=O$	**180 kcal/mole**

The C–O σ-bond is found to have an average bond energy of 86 kcal/mole. Consequently, with the exception of formaldehyde, the carbonyl function of aldehydes and ketones has a π-bond energy greater than that of the sigma-bond, in contrast to the pi-sigma relationship in C=C. This suggests that addition reactions to carbonyl groups should be thermodynamically disfavored, as is the case for the addition of water. All of this is summarized in the following diagram (ΔH^o values are for the addition reaction).



Although the addition of water to an alkene is exothermic and gives a stable product (an alcohol), the uncatalyzed reaction is extremely slow due to a high activation energy. The reverse reaction (dehydration of an alcohol) is even slower, and because of the kinetic barrier, both reactions are practical only in the presence of a strong acid.

In contrast, both the endothermic addition of water to a carbonyl function, and the exothermic elimination of water from the resulting geminal-diol are fast. The inherent polarity of the carbonyl group, together with its increased basicity (compared with alkenes), lowers the transition state energy for both reactions, with a resulting increase in rate. Acids and bases catalyze both the addition and elimination of water. Proof that rapid and reversible addition of water to carbonyl compounds occurs is provided by experiments using isotopically labeled water. If a carbonyl reactant composed of ^{16}O (colored blue above) is treated with water incorporating the ^{18}O isotope (colored red above), a rapid exchange of the oxygen isotope occurs. This can only be explained by the addition-elimination mechanism shown here.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

19.12: Spectroscopic Properties

IR Spectra

The carbonyl stretching vibration band C=O of saturated aliphatic ketones appears:

- C=O stretch - aliphatic ketones 1715 cm^{-1}

- ?, ?-unsaturated ketones 1685-1666 cm^{-1}

Figure 8. shows the spectrum of 2-butanone. This is a saturated ketone, and the C=O band appears at 1715.

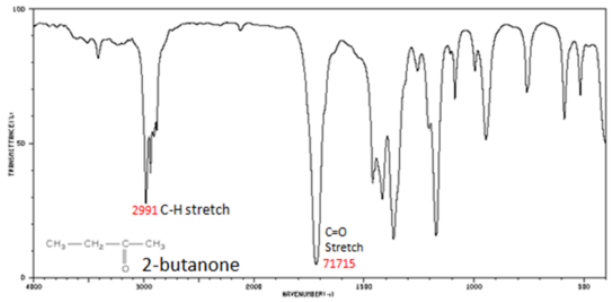


Figure 8. Infrared Spectrum of 2-Butanone

If a compound is suspected to be an aldehyde, a peak always appears around 2720 cm^{-1} which often appears as a shoulder-type peak just to the right of the alkyl C–H stretches.

- H–C=O stretch 2830-2695 cm^{-1}
- C=O stretch:
  - aliphatic aldehydes 1740-1720 cm^{-1}
  - alpha, beta-unsaturated aldehydes 1710-1685 cm^{-1}

Figure 9. shows the spectrum of butyraldehyde.

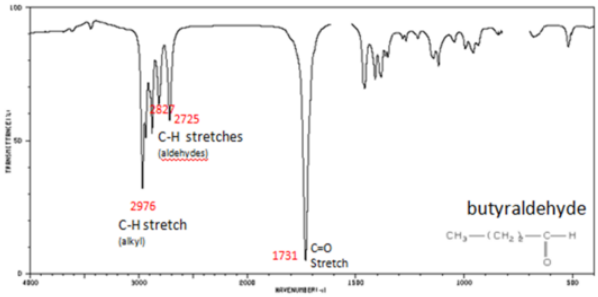
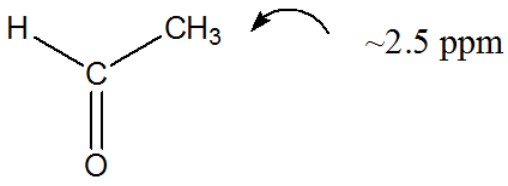


Figure 9. Infrared Spectrum of Butyraldehyde

NMR Spectra

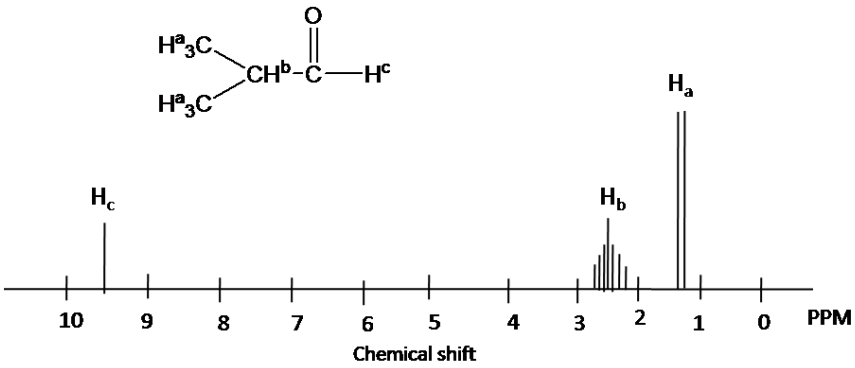
Hydrogens attached to carbon adjacent to the sp^2 hybridized carbon in aldehydes and ketones usually show up 2.0-2.5 ppm.



.

Aldehyde hydrogens are highly deshielded and appear far downfield as 9-10 ppm.

Example



Chemical shift of each protons is predicted by ^{1}H chemical shift ranges (H_a): chemical shift of methyl groups (1.1 ppm). (H_b) The chemical shift of the -CH- group move downfield due to effect an adjacent aldehyde group: (2.4 ppm). The chemical shift of aldehyde hydrogen is highly deshielded (9.6 ppm).

4) Splitting pattern is determined by (N+1) rule: Ha is split into two peaks by H_b(#of proton=1). H_b has the septet pattern by H_a (#of proton=6). H_c has one peak.(Note that H_c has doublet pattern by H_b due to vicinal proton-proton coupling.)

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)

19.13: Interesting Aldehydes and Ketones

Aldehydes and ketones are widespread in nature and are often combined with other functional groups. Examples of naturally occurring molecules which contain a aldehyde or ketone functional group are shown in the following two figures. The compounds in the figure 1 are found chiefly in plants or microorganisms and those in the figure 2 have animal origins. Many of these molecular structures are chiral.

When chiral compounds are found in nature they are usually enantiomerically pure, although different sources may yield different enantiomers. For example, carvone is found as its levorotatory (R)-enantiomer in spearmint oil, whereas, caraway seeds contain the dextrorotatory (S)-enantiomer. In this case the change of the stereochemistry causes a drastic change in the perceived scent. Aldehydes and ketones are known for their sweet and sometimes pungent odors. The odor from vanilla extract comes from the molecule vanillin. Likewise, benzaldehyde provides a strong scent of almonds and is this author's favorite chemical smell. Because of their pleasant fragrances aldehyde and ketone containing molecules are often found in perfumes. However, not all of the fragrances are pleasing. In particular, 2-Heptanone provides part of the sharp scent from blue cheese and (R)-Muscone is part of the musky smell from the Himalayan musk deer. Lastly, ketones show up in many important hormones such as progesterone (a female sex hormone) and testosterone (a male sex hormone). Notice how subtle differences in structure can cause drastic changes in biological activity. The ketone functionality also shows up in the anti-inflammatory steroid, Cortisone.

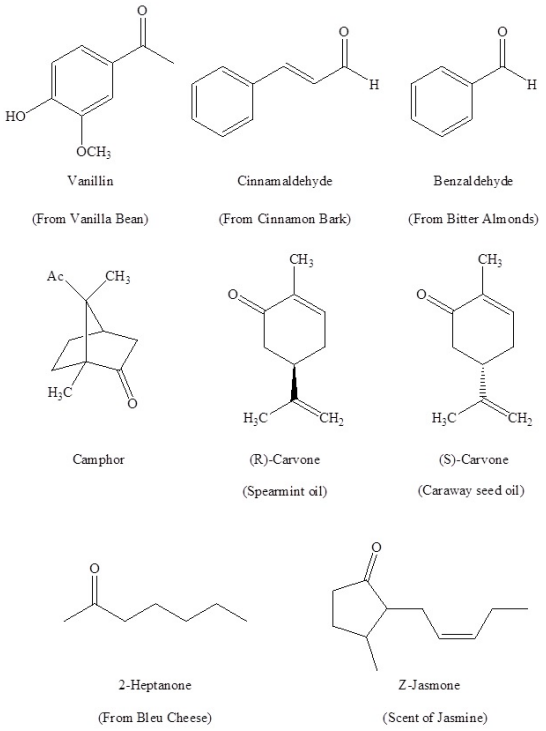


Figure 1. Aldehyde and ketone containing molecules isolated from plant sources.

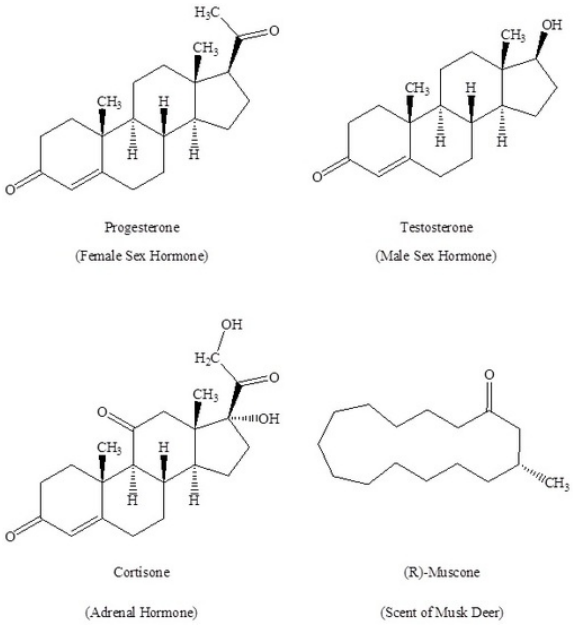


Figure 2. Aldehyde and ketone containing molecules isolated from animal sources.

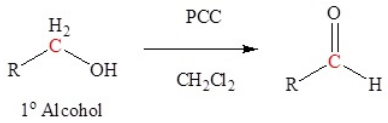
Contributors

- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

19.14: Preparation of Aldehydes and Ketones

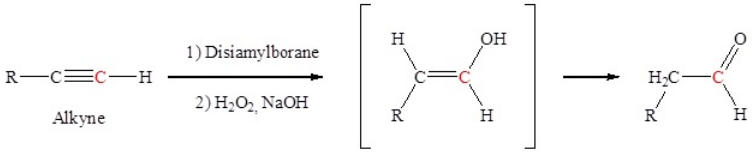
Aldehydes and ketones can be prepared using a wide variety of reactions. Although these reactions are discussed in greater detail in other sections, they are listed here as a summary and to help with planning multistep synthetic pathways. Please use the appropriate links to see more details about the reactions.

Oxidation of 1^o alcohols with PCC to form aldehydes

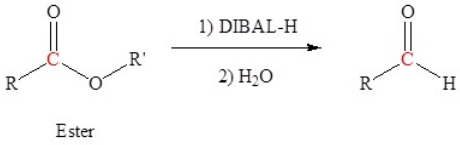


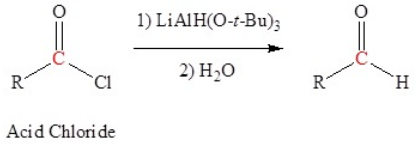
Hydration of an alkyne to form aldehydes

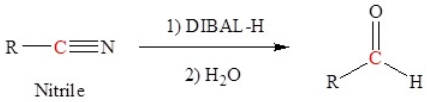
Anti-Markovnikov addition of a hydroxyl group to an alkyne forms an aldehyde. The addition of a hydroxyl group to an alkyne causes tautomerization which subsequently forms a carbonyl.



Reduction of an ester, acid chloride or nitrile to form aldehydes

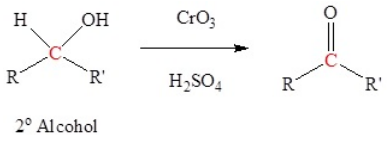






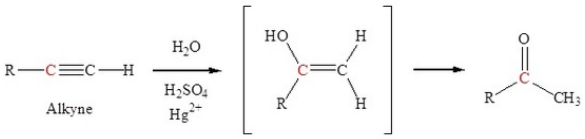
Oxidation of 2^o alcohols to form ketones

Typically uses Jones reagent (CrO_3 in H_2SO_4) but many other reagents can be used

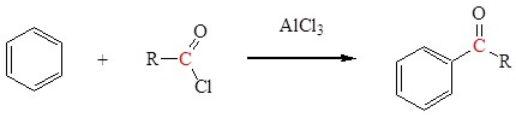


Hydration of an alkyne to form ketones

The addition of a hydroxyl group to an alkyne causes tautomerization which subsequently forms a carbonyl. Markovnikov addition of a hydroxyl group to an alkyne forms a ketone.

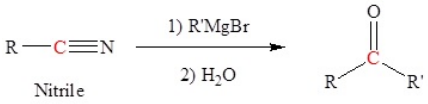


Friedel-Crafts acylation to form a ketone

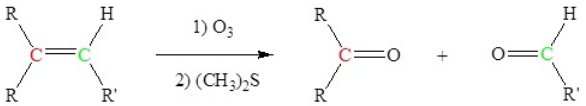


Acid Chloride

Reaction of Grignard reagents with nitriles to form ketones



Alkenes can be cleaved using ozone (O_3) to form aldehydes and/or ketones



Alkene

This is an example of a Ozonolysis reaction.

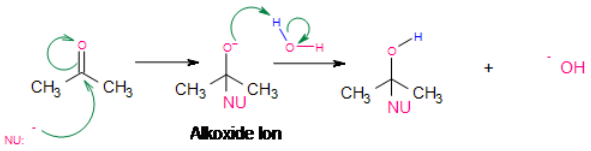
Contributors

- Prof. Steven Farmer (Sonoma State University)

19.15: Reactions of Aldehydes and Ketones—General Considerations

Reaction at the Carbonyl Carbon

Under neutral or basic conditions, nucleophilic attack of the electrophilic carbon takes place. As the nucleophile approaches the electrophilic carbon, two valence electrons from the nucleophile form a covalent bond to the carbon. As this occurs, the electron pair from the pie bond transfers completely over to the oxygen which produces the intermediate alkoxide ion. This alkoxide ion, with a negative charge on oxygen is susceptible to protonation from a protic solvent like water or alcohol, giving the final addition reaction.

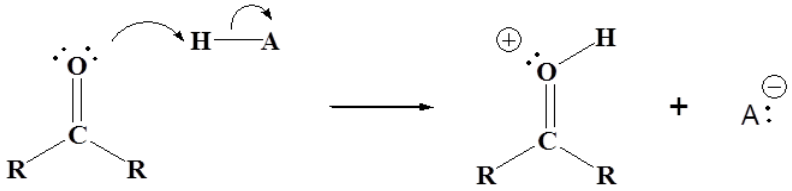


Electrophilic Addition-Protonation

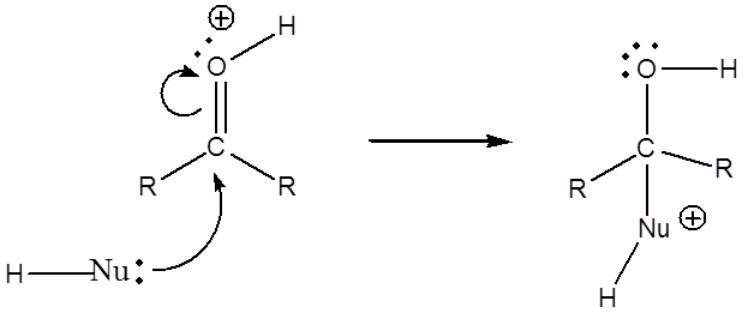
Under acidic conditions, electrophilic attack of the carbonyl oxygen takes place. Initially, protonation of the carbonyl group at the oxygen takes place because of excess H+ all around. Once protonation has occurred, nucleophilic attack by the nucleophile finishes the addition reaction. It should be noted that electrophilic attack is extremely unlikely, however, a few carbonyl groups do become protonated initially to initiate addition through electrophilic attack. This type of reaction works best when the reagent being used is a very mildly basic nucleophile.

Mechanism

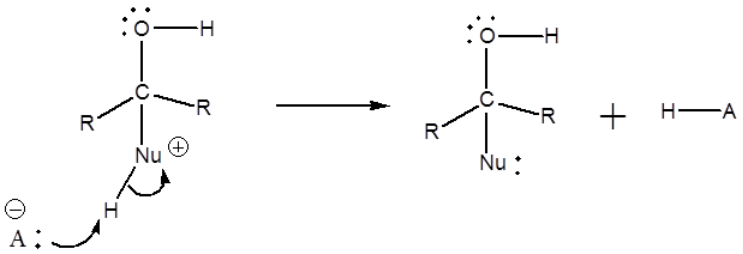
1) Protonation of the carbonyl



2) Nuc addition



3) Deprotonation

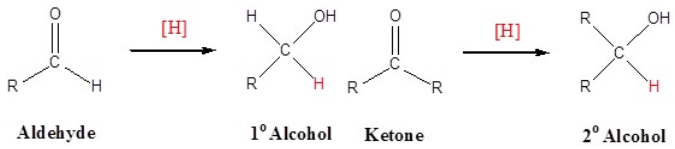


Contributors

- Prof. Steven Farmer (Sonoma State University)

19.16: Nucleophilic Addition of H– and R——A Review

Addition of a hydride anion ($H:^-$) to an aldehyde or ketone gives an alkoxide anion, which on protonation yields the corresponding alcohol. Aldehydes produce 1º-alcohols and ketones produce 2º-alcohols.

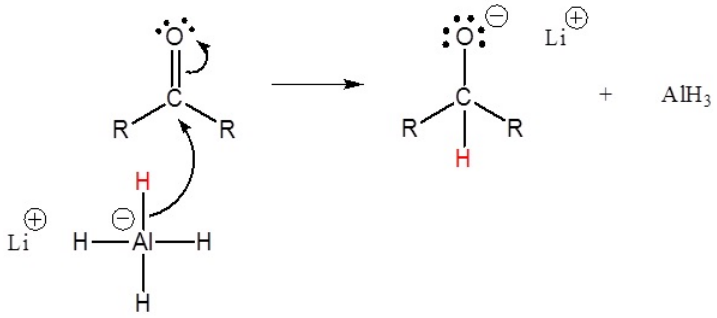


In metal hydrides reductions the resulting alkoxide salts are insoluble and need to be hydrolyzed (with care) before the alcohol product can be isolated. In the sodium borohydride reduction the methanol solvent system achieves this hydrolysis automatically. In the lithium aluminum hydride reduction water is usually added in a second step. The lithium, sodium, boron and aluminum end up as soluble inorganic salts at the end of either reaction. Note! $LiAlH_4$ and $NaBH_4$ are both capable of reducing aldehydes and ketones to the corresponding alcohol.

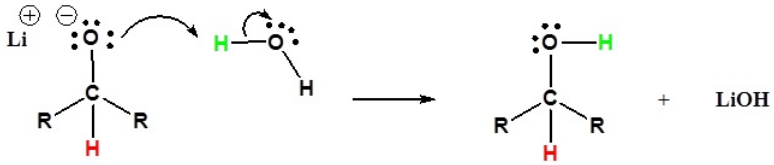
Mechanism

This mechanism is for a $LiAlH_4$ reduction. The mechanism for a $NaBH_4$ reduction is the same except methanol is the proton source used in the second step.

1) Nucleopilic attack by the hydride anion

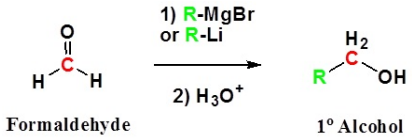


2) The alkoxide is protonated

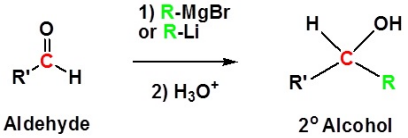


Addition of a organometallic reagent to an aldehyde or ketone gives an alkoxide anion, which on protonation yields the corresponding alcohol. Aldehydes produce 2º-alcohols and ketones produce 3º-alcohols.

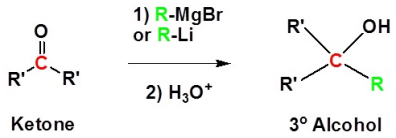
Addition to formaldehyde gives 1o alcohols



Addition to aldehydes gives 2º alcohols

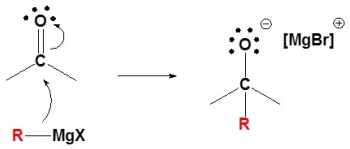


Addition to ketones gives 3^{o} alcohols

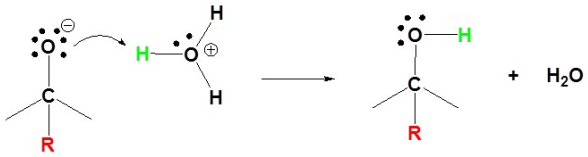


Mechanism

1) Nucleophilic attack



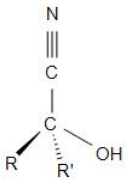
2) Protonation



Contributors

- Prof. Steven Farmer (Sonoma State University)

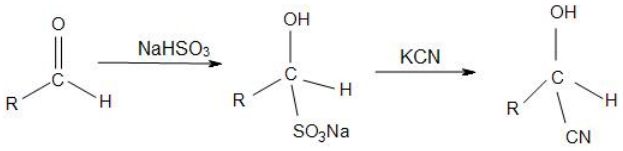
19.17: Nucleophilic Addition of –CN



Cyanohydrins have the structural formula of $R_2C(OH)CN$. The "R" on the formula represents an alkyl, aryl, or hydrogen. In order to form a cyanohydrin, a hydrogen cyanide adds reversibly to the carbonyl group of an organic compound thus forming a hydroxyalkanenitrile adducts (commonly known and called as cyanohydrins).

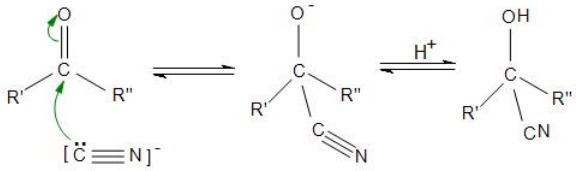
Introduction

Cyanohydrin reactions occurs when an aldehyde or ketone gets treated by a cyanide anion (such as HCN) or a nitrile forming a cyanohydrin product. This special reaction is a nucleophilic addition, where the nucleophilic CN^- attacks the electrophilic carbonyl carbon on the ketone, following a protonation by HCN, thereby the cyanide anion being regenerated. This reaction is also reversible.



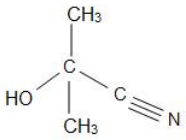
Cyanohydrins are also intermediates for the Strecker amino acid synthesis. The preparation of displacements of sulfite by cyanide salts are also followed under cyanohydrins.

Mechanism of Cyanohydrin Formation

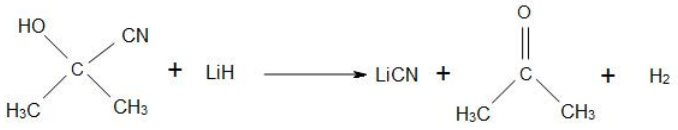


Acid-catalysed hydrolysis of silylated cyanohydrins has recently been shown to give cyanohydrins instead of ketones; thus an efficient synthesis of cyanohydrins has been found which works with even highly hindered ketones.

Acetone Cyanohydrins

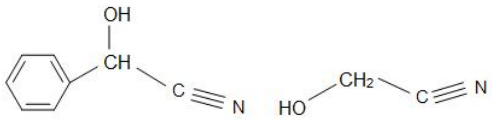


Acetone cyanohydrins (ACH) have the structural formula of $(CH_3)_2C(OH)CN$. It is an organic compound serves in the production of methyl methacrylate (also known as acrylic). It is classified as an extremely hazardous substance, since it rapidly decomposes when it's in contact with water. In ACH, sulfuric acid is treated to give the sulfate ester of the methacrylamid. Preparations of other cyanohydrins are also used from ACH: for HACN to Michael acceptors and for the formylation of arenas. The treatment with lithium hydride affords anhydrous lithium cyanide.



Other Cyanohydrins

Other cyanohydrins, excluding acetone cyanohydrins, are: mandelonitrile and glycolonitrile.



Mandelonitrile have a structural formula of $C_6H_5CH(OH)CN$ and occur in pits of some fruits. Glycolonitrile is an organic compound with the structural formula of $HOCH_2CN$, which is the simplest cyanohydrin that is derived by formaldehydes.

Contributors

- Kathy Wong (UCD)

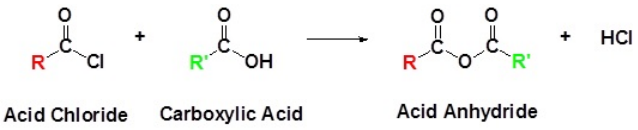
CHAPTER OVERVIEW

20: Carboxylic Acids and Their Derivatives— Nucleophilic Acyl Substitution

Topic hierarchy

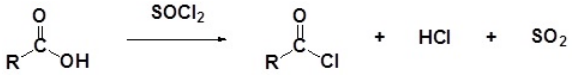
20.1: Reactions of Carboxylic Acids

Acid Chlorides react with carboxylic acids to form anhydrides

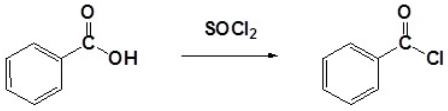


Carboxylic acids react with Thionyl Chloride ($SOCl_2$) to form acid chlorides.

During the reaction the hydroxyl group of the carboxylic acid is converted to a chlorosulfite intermediate making it a better leaving group. The chloride anion produced during the reaction acts a nucleophile.

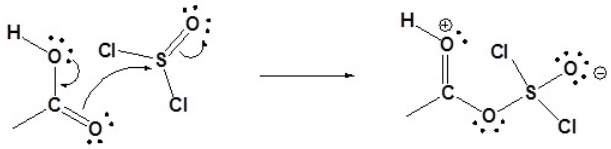


Example

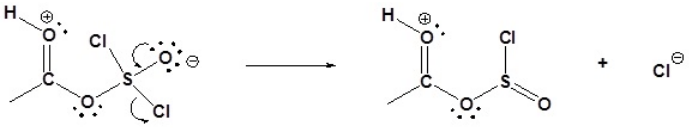


Mechanism

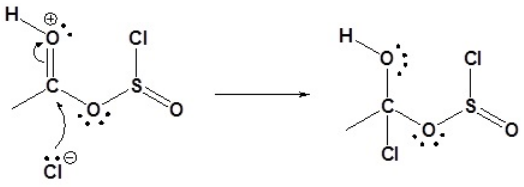
1) Nucleophilic attack on Thionyl Chloride



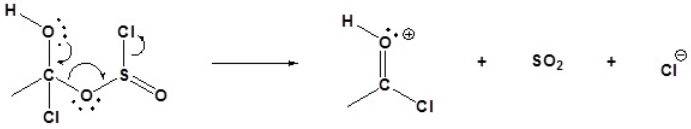
2) Removal of Cl leaving group



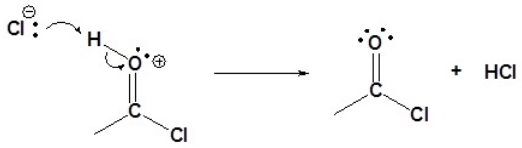
3) Nucleophilic attack on the carbonyl



4) Leaving group removal



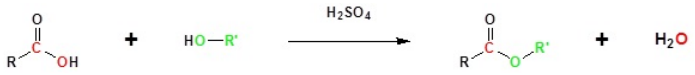
5) Deprotonation



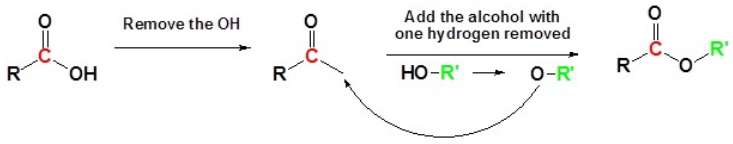
Carboxylic acids can react with alcohols to form esters in a process called Fischer esterification.

Usually the alcohol is used as the reaction solvent. An acid catalyst is required.

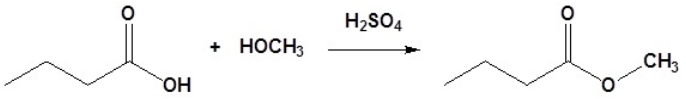
Basic Reaction



Going from reactants to products simplified

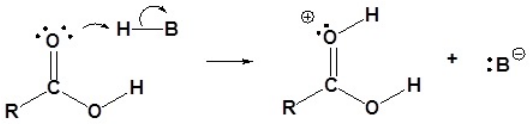


Example

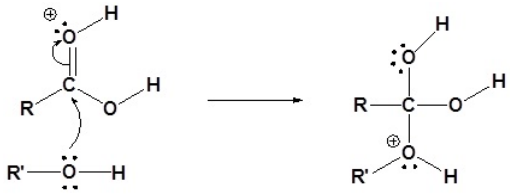


Mechanism

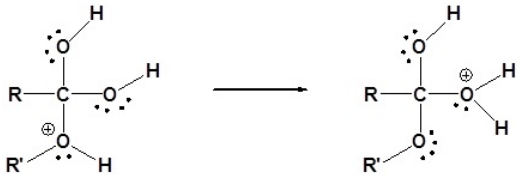
1) Protonation of the carbonyl by the acid. The carbonyl is now activated toward nucleophilic attack.



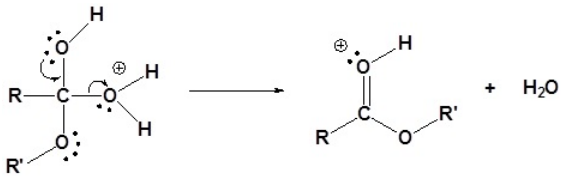
2) Nucleophilic attack on the carbonyl



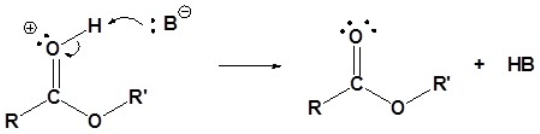
3) Proton transfer



4) Water leaves



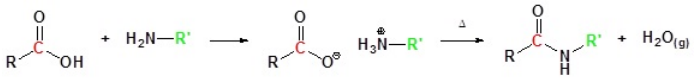
5) Deprotonation



Conversion of Carboxylic Acids to Amides

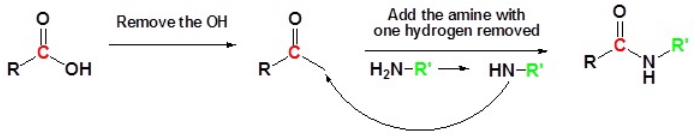
The direct reaction of a carboxylic acid with an amine would be expected to be difficult because the basic amine would deprotonate the carboxylic acid to form a highly unreactive carboxylate. However when the ammonium carboxylate salt is heated to a temperature above 100 ^{o}C water is driven off and an amide is formed.

General Reaction



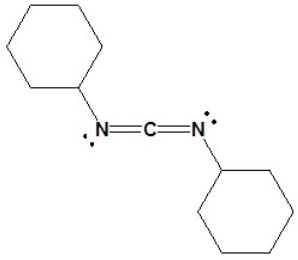
Ammonium Carboxylate Salt

Going from reactants to products simply



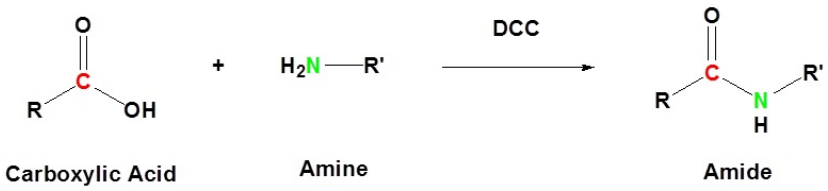
Conversion of Carboxylic acids to amide using DCC as an activating agent

The direct conversion of a carboxylic acid to an amide is difficult because amines are basic and tend to convert carboxylic acids to their highly unreactive carboxylates. In this reaction the carboxylic acid adds to the DCC molecule to form a good leaving group which can then be displaced by an amine during nucleophilic substitution. DCC induced coupling to form an amide linkage is an important reaction in the synthesis of peptides.

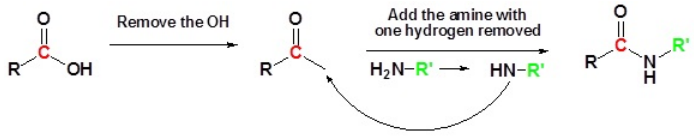


Dicyclohexylcarbodiimide (DCC)

Basic reaction

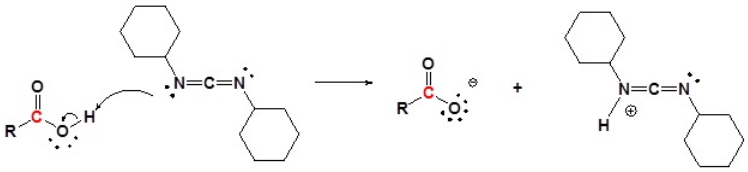


Going from reactants to products simplified

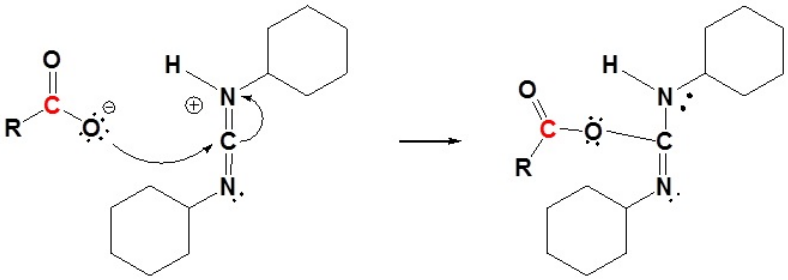


Mechanism

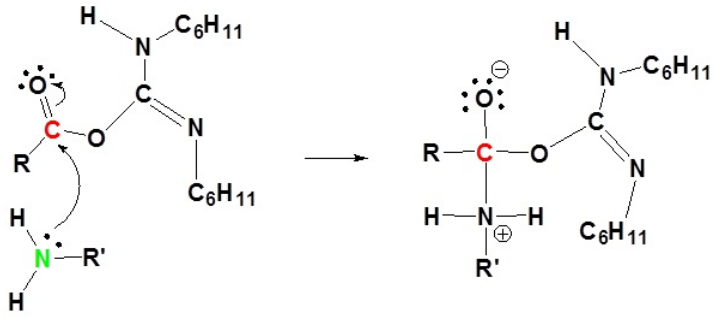
1) Deprotonation



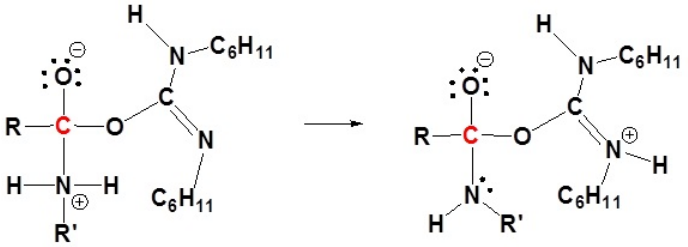
2) Nucleophilic attack by the carboxylate



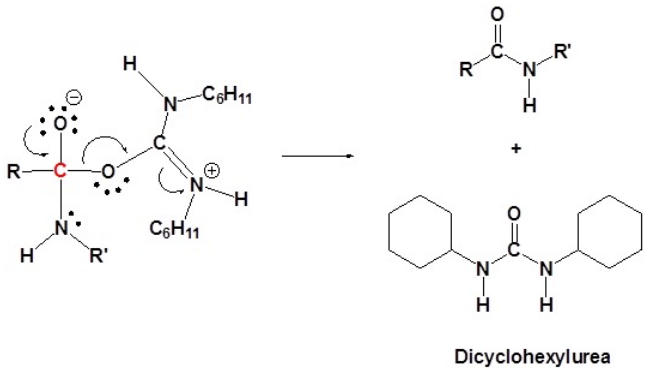
3) Nucleophilic attack by the amine



4) Proton transfer



5) Leaving group removal



Dicyclohexylurea

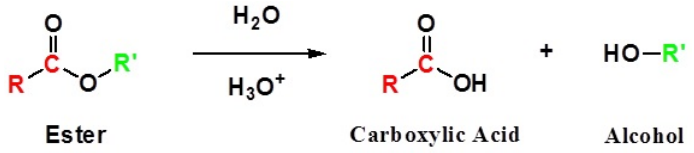
Contributors

- Prof. Steven Farmer (Sonoma State University)

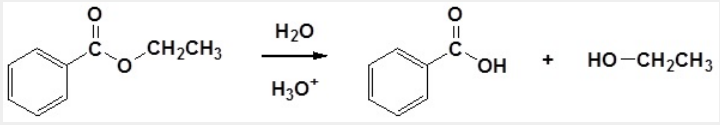
20.2: Reactions of Esters

Esters can be cleaved back into a carboxylic acid and an alcohol by reaction with water and a catalytic amount of acid.

General Reaction

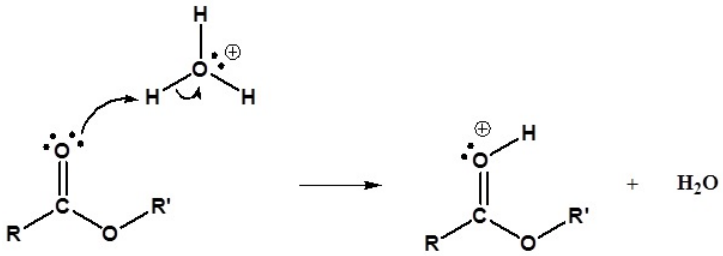


Example 1:

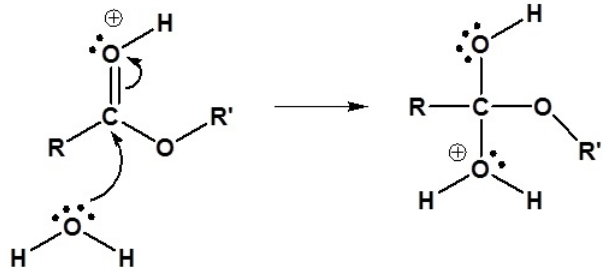


Mechanism

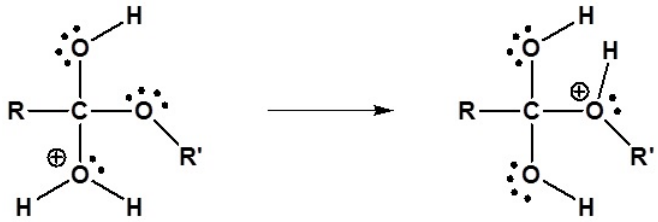
1) Protonation of the Carbonyl



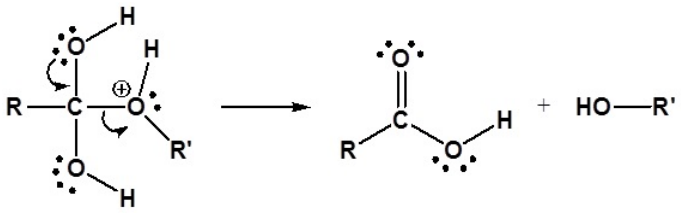
2) Nucleophilic attack by water



3) Proton transfer



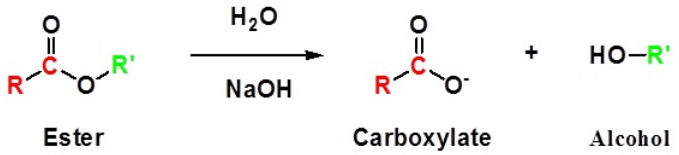
4) Leaving group removal



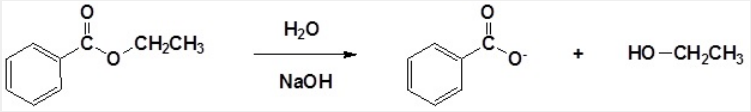
Esters can be cleaved back into a carboxylic acid and an alcohol by reaction with water and a base

The reaction is called a saponification from the Latin *sapo* which means soap. The name comes from the fact that soap used to me made by the ester hydrolysis of fats. Due to the basic conditions a carboxylate ion is made rather than a carboxylic acid.

General reaction

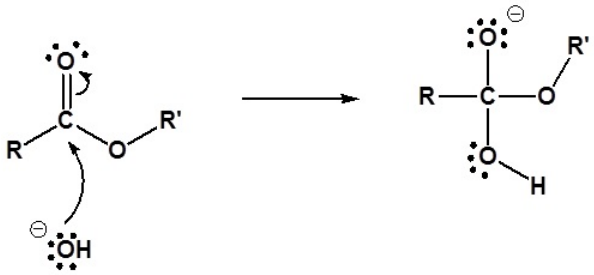


Example 1:

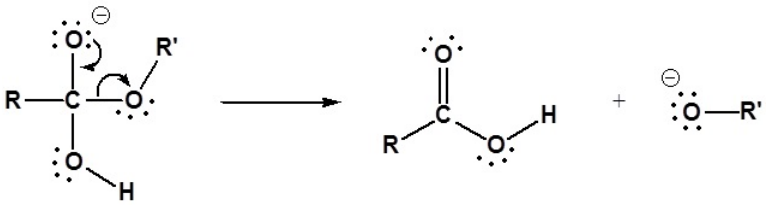


Mechanism

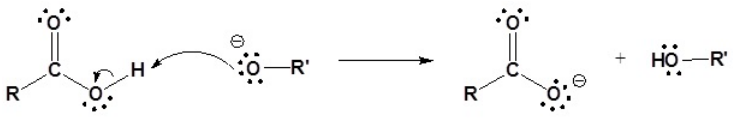
1) Nucleophilic attack by hydroxide



2) Leaving group removal



3) Deprotonation



Contributors

- Prof. Steven Farmer (Sonoma State University)

20.3: Application- Lipid Hydrolysis

Soap is a mixture of sodium salts of various naturally occurring fatty acids. Air bubbles added to a molten soap will decrease the density of the soap and thus it will float on water. If the fatty acid salt has potassium rather than sodium, a softer lather is the result. Soap is produced by a saponification or basic hydrolysis reaction of a fat or oil. Currently, sodium carbonate or sodium hydroxide is used to neutralize the fatty acid and convert it to the salt.

Introduction

General overall hydrolysis reaction:

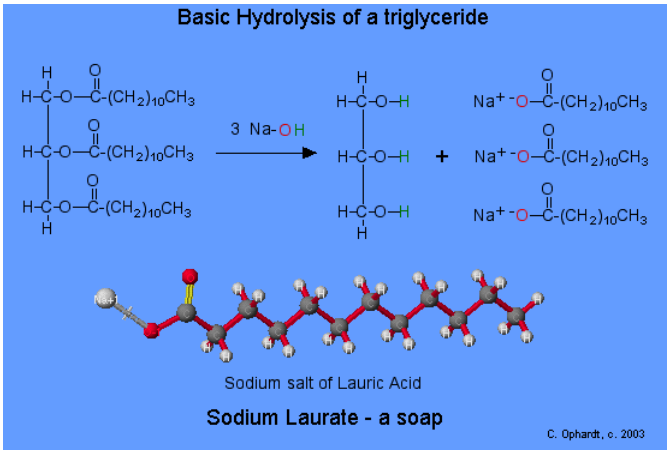
fat + NaOH → glycerol + sodium salt of fatty acid

Although the reaction is shown as a one step reaction, it is in fact two steps. The net effect as that the ester bonds are broken. The glycerol turns back into an alcohol (addition of the green H's). The fatty acid portion is turned into a salt because of the presence of a basic solution of the NaOH. In the carboxyl group, one oxygen (red) now has a negative charge that attracts the positive sodium ion.

Types of Soap

The type of fatty acid and length of the carbon chain determines the unique properties of various soaps. Tallow or animal fats give primarily sodium stearate (18 carbons) a very hard, insoluble soap. Fatty acids with longer chains are even more insoluble. As a matter of fact, zinc stearate is used in talcum powders because it is water repellent.

Coconut oil is a source of lauric acid (12 carbons) which can be made into sodium laurate. This soap is very soluble and will lather easily even in sea water. Fatty acids with only 10 or fewer carbons are not used in soaps because they irritate the skin and have objectionable odors.



Contributors

Charles Ophardt (Professor Emeritus, Elmhurst College); Virtual Chembook

20.4: Reactions of Amides

This page describes the hydrolysis of amides under both acidic and alkaline conditions. It also describes the use of alkaline hydrolysis in testing for amides.

What is hydrolysis?

Technically, hydrolysis is a reaction with water. That is exactly what happens when amides are hydrolyzed in the presence of dilute acids such as dilute hydrochloric acid. The acid acts as a catalyst for the reaction between the amide and water. The alkaline hydrolysis of amides actually involves reaction with hydroxide ions, but the result is similar enough that it is still classed as hydrolysis.

Hydrolysis under acidic conditions

Taking ethanamide as a typical amide. If ethanamide is heated with a dilute acid (such as dilute hydrochloric acid), ethanoic acid is formed together with ammonium ions. So, if you were using hydrochloric acid, the final solution would contain ammonium chloride and ethanoic acid.

$$CH_3CONH_2 + H_2O + HCl\ rightarrow CH_3COOH + NH_4^+Cl^- \tag{20.4.1}$$

Hydrolysis under alkaline conditions

Also, if ethanamide is heated with sodium hydroxide solution, ammonia gas is given off and you are left with a solution containing sodium ethanoate.

$$CH_3CONH_2 + NaOH\ rightarrow CH_3COONa + NH_3 \tag{20.4.2}$$

Using alkaline hydrolysis to test for an amide

If you add sodium hydroxide solution to an unknown organic compound, and it gives off ammonia on heating (but not immediately in the cold), then it is an amide. You can recognize the ammonia by smell and because it turns red litmus paper blue.

The possible confusion using this test is with ammonium salts. Ammonium salts also produce ammonia with sodium hydroxide solution, but in this case there is always enough ammonia produced in the cold for the smell to be immediately obvious.

Contributors

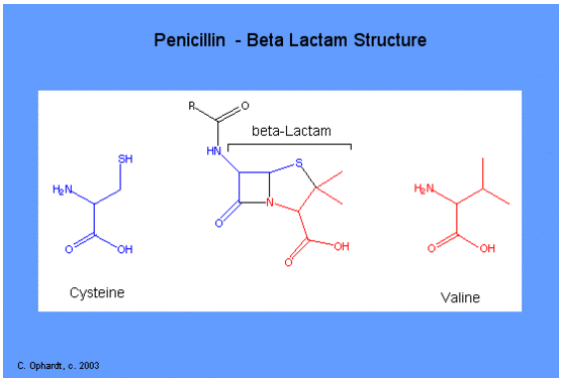
Jim Clark (Chemguide.co.uk)

20.5: Application- The Mechanism of Action of β-Lactam Antibiotics

Antibiotics are specific chemical substances derived from or produced by living organisms that are capable of inhibiting the life processes of other organisms. The first antibiotics were isolated from microorganisms but some are now obtained from higher plants and animals. Over 3,000 antibiotics have been identified but only a few dozen are used in medicine. Antibiotics are the most widely prescribed class of drugs comprising 12% of the prescriptions in the United States. The penicillins were the first antibiotics discovered as natural products from the mold Penicillium.

Introduction

In 1928, Sir Alexander Fleming, professor of bacteriology at St. Mary's Hospital in London, was culturing Staphylococcus aureus. He noticed zones of inhibition where mold spores were growing. He named the mold Penicillium rubrum. It was determined that a secretion of the mold was effective against Gram-positive bacteria.



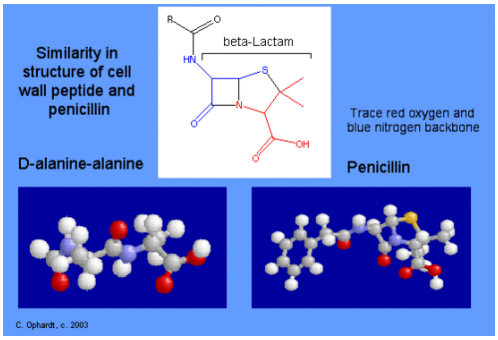
Penicillins as well as cephalosporins are called beta-lactam antibiotics and are characterized by three fundamental structural requirements: the fused beta-lactam structure (shown in the blue and red rings, a free carboxyl acid group (shown in red bottom right), and one or more substituted amino acid side chains (shown in black). The lactam structure can also be viewed as the covalent bonding of pieces of two amino acids - cysteine (blue) and valine (red).

Penicillin-G where R = an ethyl pheny group, is the most potent of all penicillin derivatives. It has several shortcomings and is effective only against gram-positive bacteria. It may be broken down in the stomach by gastric acids and is poorly and irregularly absorbed into the blood stream. In addition many disease producing staphylococci are able to produce an enzyme capable of inactivating penicillin-G. Various semisynthetic derivatives have been produced which overcome these shortcomings.

Powerful electron-attracting groups attached to the amino acid side chain such as in phenethicillin prevent acid attack. A bulky group attached to the amino acid side chain provides steric hindrance which interferes with the enzyme attachment which would deactivate the pencillins i.e. methicillin. Refer to Table 2 for the structures. Finally if the polar character is increased as in ampicillin or carbenicillin, there is a greater activity against Gram-negative bacteria.

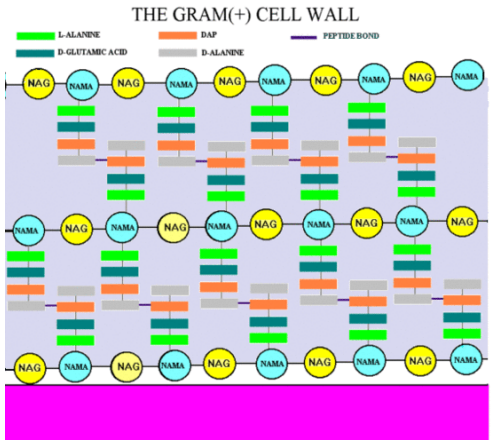
Penicillin Mode of Action

All penicillin derivatives produce their bacteriocidal effects by inhibition of bacterial cell wall synthesis. Specifically, the cross linking of peptides on the mucosaccharide chains is prevented. If cell walls are improperly made cell walls allow water to flow into the cell causing it to burst. Resemblances between a segment of penicillin structure and the backbone of a peptide chain have been used to explain the mechanism of action of beta-lactam antibiotics. The structures of a beta-lactam antibiotic and a peptide are shown on the left for comparison. Follow the trace of the red oxygens and blue nitrogen atoms.



Gram-positive bacteria possess a thick cell wall composed of a cellulose-like structural sugar polymer covalently bound to short peptide units in layers.The polysaccharide portion of the peptidoglycan structure is made of repeating units of N-acetylglucosamine linked b-1,4 to N-acetylmuramic acid (NAG-NAM). The peptide varies, but begins with L-Ala and ends with D-Ala. In the middle is a dibasic amino acid, diaminopimelate (DAP). DAP (orange) provides a linkage to the D-Ala (gray) residue on an adjacent peptide.

The bacterial cell wall synthesis is completed when a cross link between two peptide chains attached to polysaccharide backbones is formed. The cross linking is catalyzed by the enzyme transpeptidase. First the terminal alanine from each peptide is hydrolyzed and secondly one alanine is joined to lysine through an amide bond.



Penicillin binds at the active site of the transpeptidase enzyme that cross-links the peptidoglycan strands. It does this by mimicking the D-alanyl-D-alanine residues that would normally bind to this site. Penicillin irreversibly inhibits the enzyme transpeptidase by reacting with a serine residue in the transpeptidase. This reaction is irreversible and so the growth of the bacterial cell wall is inhibited. Since mammal cells do not have the same type of cell walls, penicillin specifically inhibits only bacterial cell wall synthesis.

Bacterial Resistance

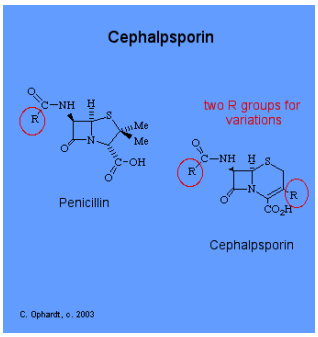
As early as the 1940s, bacteria began to combat the effectiveness of penicillin. Penicillinases (or beta-lactamases) are enzymes produced by structurally susceptable bacteria which renders penicillin useless by hydrolysing the peptide bond in the beta-lactam ring of the nucleus. Penicillinase is a response of bacterial adaptation to its adverse environment, namely the presence of a substance which inhibits its growth. Many other antibiotics are also rendered ineffective because of this same type of resistance.

Severe Allergic Shock

It is estimated that between 300-500 people die each year from penicillin-induced anaphylaxis, a severe allergic shock reaction to penicillin. In afflicted individuals, the beta-lactam ring binds to serum proteins, initiating an IgE-mediated inflammatory response. Penicillin and ala-ala peptide - Chime in new window

Cephalosporins

Cephalosporins are the second major group of beta-lactam antibiotics. They differ from penicillins by having the beta-lactam ring as a 6 member ring. The other difference, which is more significant from a medicinal chemistry stand point, is the existence of a functional group (R) at position 3 of the fused ring system. This now allows for molecular variations to effect changes in properties by diversifying the groups at position 3.



The first member of the newer series of beta-lactams was isolated in 1956 from extracts of Cephalosporium acremonium, a sewer fungus. Like penicillin, cephalosporins are valuable because of their low toxicity and their broad spectrum of action against various diseases. In this way, cephalosporin is very similar to penicillin. Cephalosporins are one of the most widely used antibiotics, and economically speaking, has about 29% of the antibiotic market. The cephalosporins are possibly the single most important group of antibiotics today and are equal in importance to penicillin.

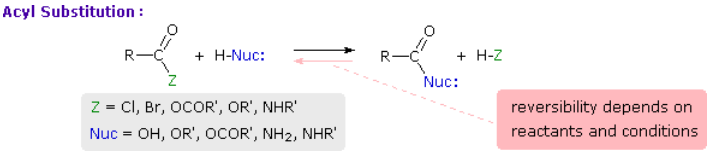
The structure and mode of action of the cephalosporins are similar to that of penicillin. They affect bacterial growth by inhibiting cell wall synthesis, in Gram-positive and negative bacteria. Some brand names include: cefachlor, cefadroxil, cefoxitin, ceftriaxone. Cephalexin - Chime in new window

Contributors

Charles Ophardt (Professor Emeritus, Elmhurst College); Virtual Chembook

20.6: Summary of Nucleophilic Acyl Substitution Reactions

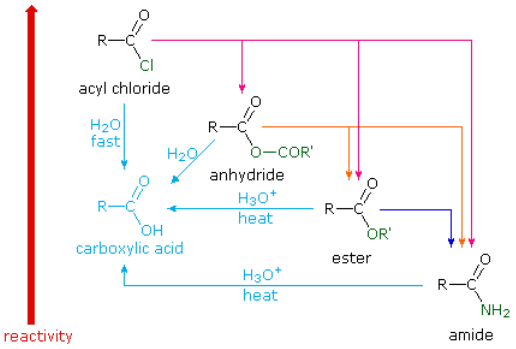
This is probably the single most important reaction of carboxylic acid derivatives. The overall transformation is defined by the following equation, and may be classified either as **nucleophilic substitution at an acyl group** or as **acylation of a nucleophile**. For certain nucleophilic reagents the reaction may assume other names as well. If Nuc-H is water the reaction is often called **hydrolysis**, if Nuc–H is an alcohol the reaction is called **alcoholysis**, and for ammonia and amines it is called **aminolysis**.



Different carboxylic acid derivatives have very different reactivities, acyl chlorides and bromides being the most reactive and amides the least reactive, as noted in the following qualitatively ordered list. The change in reactivity is dramatic. In homogeneous solvent systems, reaction of acyl chlorides with water occurs rapidly, and does not require heating or catalysts. Amides, on the other hand, react with water only in the presence of strong acid or base catalysts and external heating.

Reactivity: acyl halides > anhydrides >> esters ≈ acids >> amides

Because of these differences, the conversion of one type of acid derivative into another is generally restricted to those outlined in the following diagram. Methods for converting carboxylic acids into these derivatives were shown in a previous section, but the amide and anhydride preparations were not general and required strong heating. A better and more general anhydride synthesis can be achieved from acyl chlorides, and amides are easily made from any of the more reactive derivatives. Specific examples of these conversions will be displayed by clicking on the product formula. The carboxylic acids themselves are not an essential part of this diagram, although all the derivatives shown can be hydrolyzed to the carboxylic acid state (light blue formulas and reaction arrows). Base catalyzed hydrolysis produces carboxylate salts.



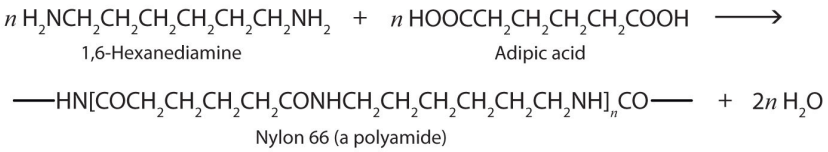
Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

20.7: Natural and Synthetic Fibers

Polyamides

Polyamides

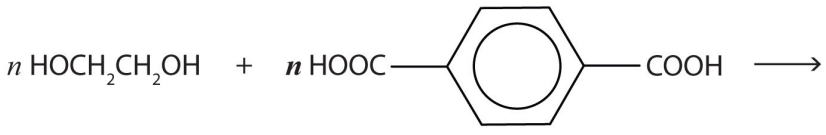


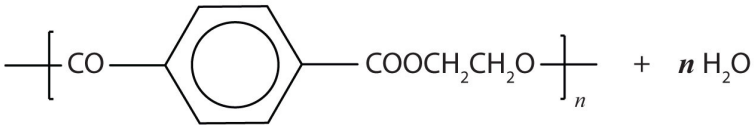
Some polyamides are known as *nylons*. Nylons are among the most widely used synthetic fibers—for example, they are used in ropes, sails, carpets, clothing, tires, brushes, and parachutes. They also can be molded into blocks for use in electrical equipment, gears, bearings, and valves.

Polyesters

A commercially important esterification reaction is condensation polymerization, in which a reaction occurs between a dicarboxylic acid and a dihydric alcohol (diol), with the elimination of water. Such a reaction yields an ester that contains a free (unreacted) carboxyl group at one end and a free alcohol group at the other end. Further condensation reactions then occur, producing polyester polymers.

The most important polyester, polyethylene terephthalate (PET), is made from terephthalic acid and ethylene glycol monomers:





Polyethylene terephthalate

Polyester molecules make excellent fibers and are used in many fabrics. A knitted polyester tube, which is biologically inert, can be used in surgery to repair or replace diseased sections of blood vessels. PET is used to make bottles for soda pop and other beverages. It is also formed into films called Mylar. When magnetically coated, Mylar tape is used in audio- and videocassettes. Synthetic arteries can be made from PET, polytetrafluoroethylene, and other polymers.

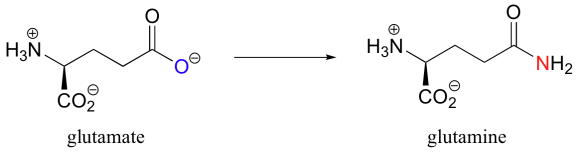
Contributors

John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

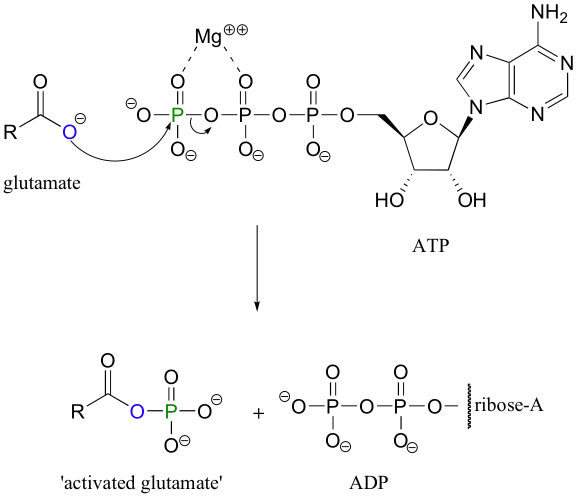
20.8: Biological Acylation Reactions

Glutamine synthetase

You have already learned that the carboxylate functional group is a very unreactive substrate for an enzyme-catalyzed acyl substitution reactions. How, then, does a living system accomplish an 'uphill' reaction such as the one shown below, where glutamate (a carboxylate) is converted to glutamine (an amide)?

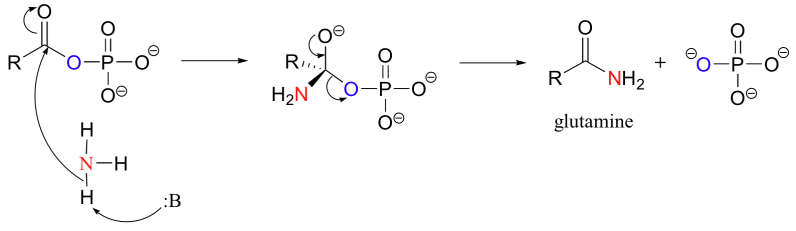


It turns out that this conversion is not carried out directly. Rather, the first conversion is from a carboxylate (the *least* reactive acyl transfer substrate) to an acyl phosphate (the *most* reactive acyl transfer substrate). This transformation requires a reaction that we are familiar with from chapter 10: phosphorylation of a carboxylate oxygen with ATP as the phosphate donor.

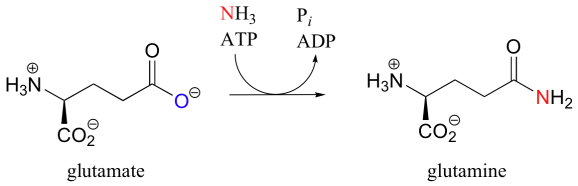


Note that this is just one of the many ways that ATP is used as a energy storage unit: in order to make a high energy acyl phosphate molecule from a low energy carboxylate, the cell must 'spend' the energy of one ATP molecule.

The acyl phosphate version of glutamate is now ready to be converted directly to an amide (glutamine) *via* a nucleophilic acyl substitution reaction, as an ammonia molecule attacks the carbonyl and the phosphate is expelled.

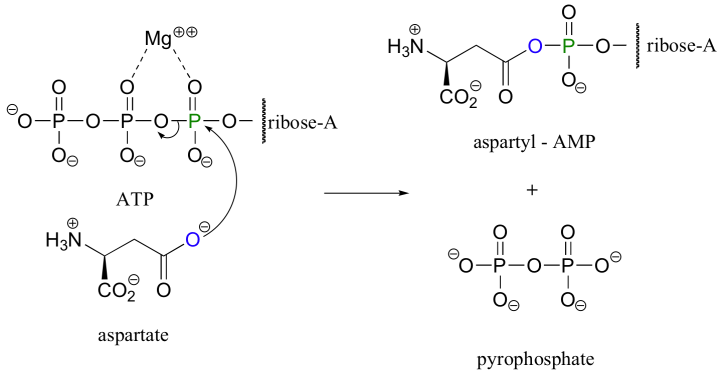


Overall, this reaction can be written as:



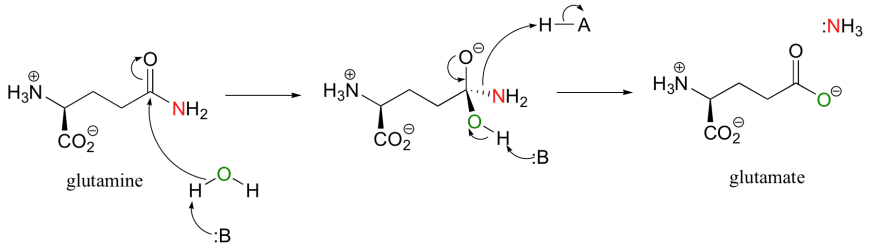
Asparagine synthetase

Another common form of activated carboxylate group is an acyl adenosine phosphate. Consider another amino acid reaction, the conversion of aspartate to asparagine. In the first step, the carboxylate group of aspartate must be activated:

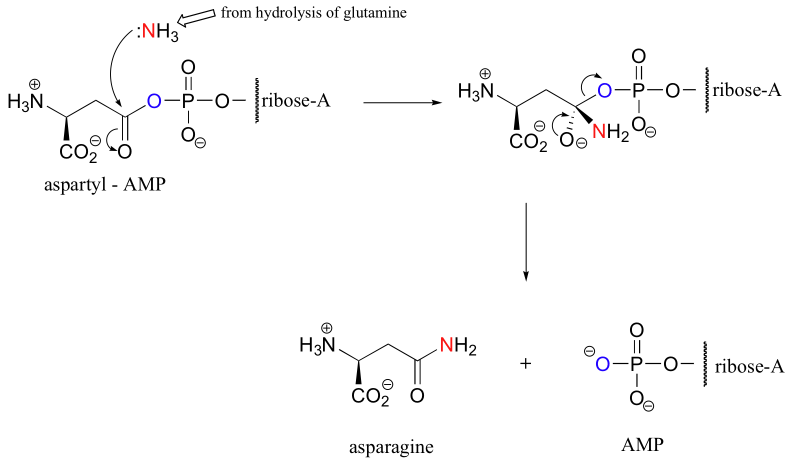


Once again, ATP provides the energy for driving the uphill reaction. This time, however, the activated carboxylate takes the form of an acyl adenosine (mono)phosphate. All that has happened is that the carboxylate oxygen has attacked the a-phosphate of ATP rather than the g-phosphate.

The reactive acyl-AMP version of aspartate is now ready to be converted to an amide (asparagine) via nucleophilic attack by ammonia. In the case of glutamine synthase, the source of ammonia was free ammonium ion in solution. In the case of asparagine synthase, the NH_3 is derived from the hydrolysis of glutamine (this is simply another acyl substitution reaction):

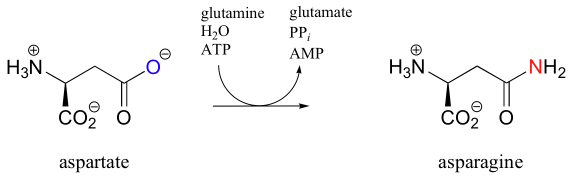


The hydrolysis reaction is happening in the same enzyme active site – as the NH_3 is expelled in the hydrolysis of glutamine, it immediately turns around and acts as the nucleophile in the conversion of aspartyl-AMP to asparagine:



Keep in mind that the same enzyme is also binding ATP and using it to activate aspartate – this is a busy construction zone!

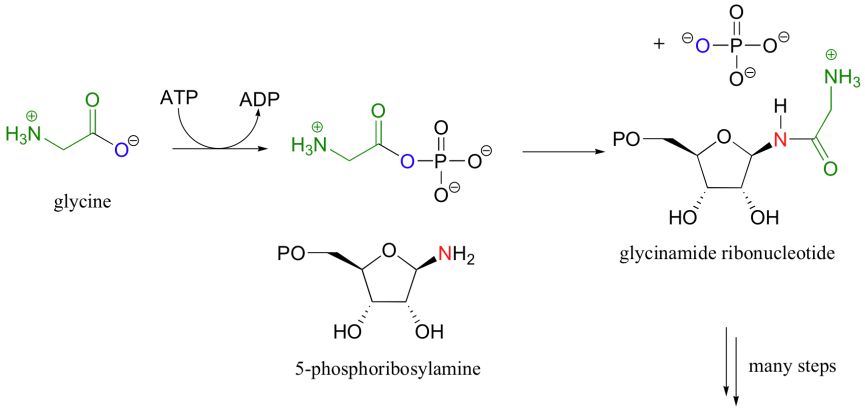
Overall, this reaction can be written in condensed form as:

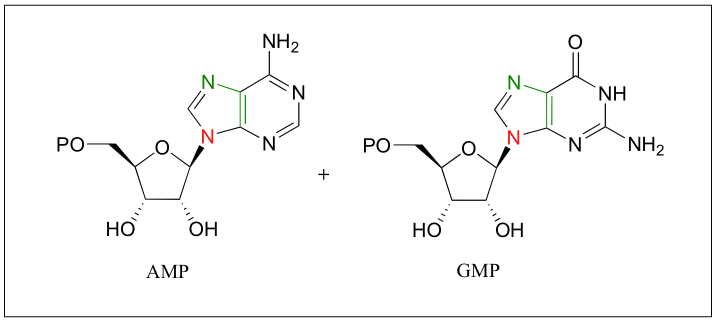


The use of glutamine as a ‘carrier’ for ammonia is a fairly common strategy in metabolic pathways. This strategy makes sense, as it allows cells to maintain a constant source of NH_3 for reactions that require it, without the need for high solution concentrations of free ammonia.

Glycinamide ribonucleotide synthetase

One of the early steps in the construction of purine bases (the adenine and guanine bases in DNA and RNA) involves an acyl substitution reaction with an acyl phosphate intermediate. In this case, the attacking nucleophile is not ammonia but a primary amine. The strategy, however, is similar to that of glutamine synthase. The carboxylate group on glycine is converted to an acyl phosphate, at the cost of one ATP molecule. The acyl group is then transferred to 5-phosphoribosylamine, resulting in an amide product.



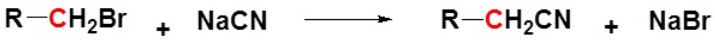


Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

20.9: Nitriles

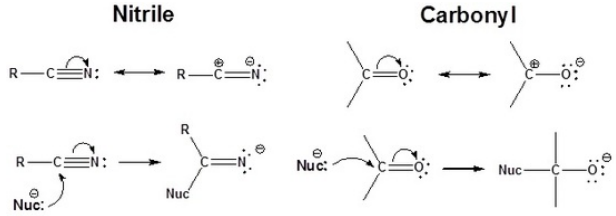
Synthesis of Nitriles

Nitriles are formed by an S_N2 reaction between a bromide and sodium cyanide



Reactivity of Nitriles

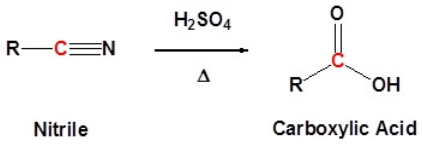
The carbon in a nitrile is electrophilic because a resonance structure can be drawn which places a positive charge on it. Because of this the triple bond of a nitrile accepts a nucleophile in a manner similar to a carbonyl.



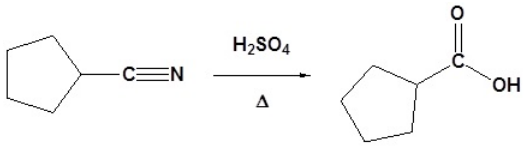
Hydrolysis of Nitriles

Nitriles can be converted to carboxylic acid with heating in sulfuric acid. During the reaction an amide intermediate is formed.

General Reaction



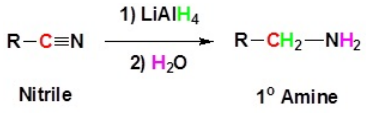
Example



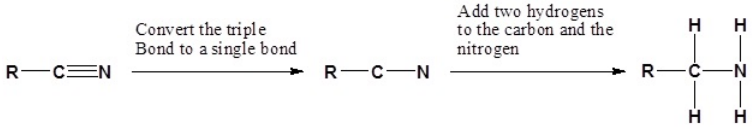
Reduction of Nitriles

Nitriles can be converted to 1° amines by reaction with $LiAlH_4$. During this reaction the hydride nucleophile attacks the electrophilic carbon in the nitrile to form an imine anion. Once stabilized by a Lewis acid-base complexation the imine salt can accept a second hydride to form a dianion. The dianion can then be converted to an amine by addition of water.

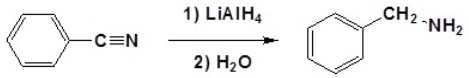
General Reaction



Going from reactants to products simplified

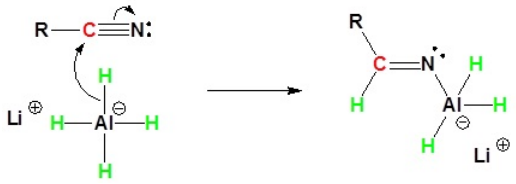


Example

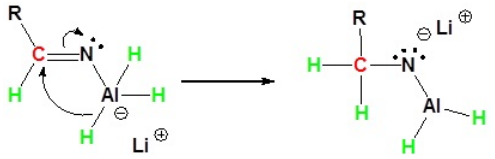


Mechanism

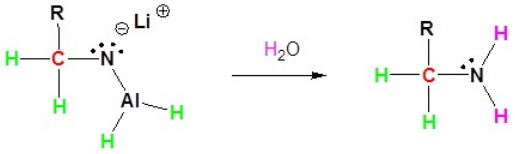
1) Nucleophilic Attack by the Hydride



2) Second nucleophilic attack by the hydride.



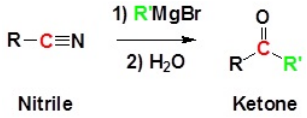
3) Protonation by addition of water to give an amine



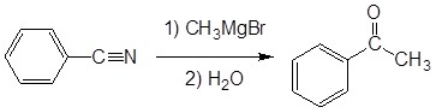
Addition of Grignard Reagents

Grignard reagents can attack the electophillic carbon in a nitrile to form an imine salt. This salt can then be hydrolyzed to become a ketone.

General Reaction

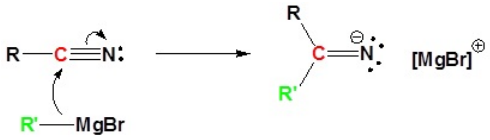


Example

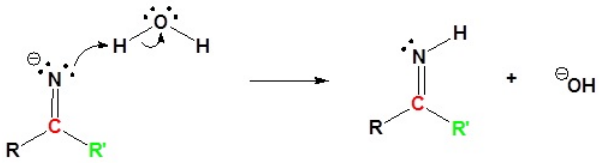


Mechanism

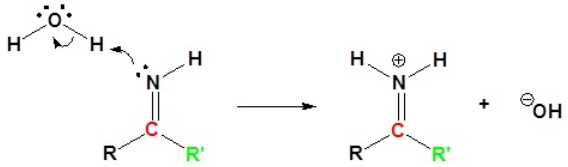
1) Nucleophilic Attack by the Grignard Reagent



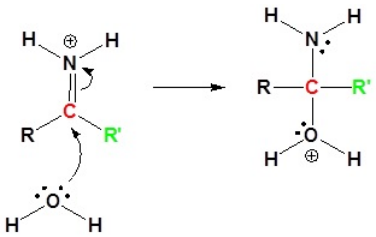
2) Protonation



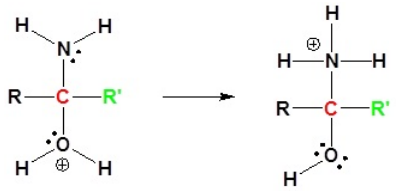
3) Protonation



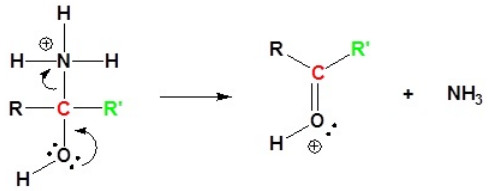
4) Nucleophilic attack by water



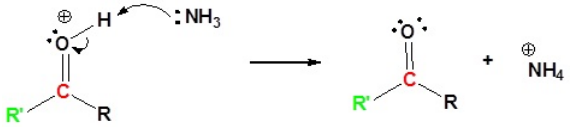
5) Proton Transfer



6) Leaving group removal



7) Deprotonation



Contributors

- Prof. Steven Farmer (Sonoma State University)

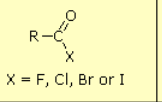
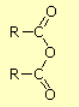
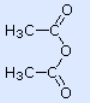
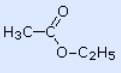
20.10: Introduction

Background and Properties

The important classes of organic compounds known as alcohols, phenols, ethers, amines and halides consist of alkyl and/or aryl groups bonded to hydroxyl, alkoxyl, amino and halo substituents respectively. If these same functional groups are attached to an **acyl group** (RCO–) their properties are substantially changed, and they are designated as **carboxylic acid derivatives**. Carboxylic acids have a hydroxyl group bonded to an acyl group, and their functional derivatives are prepared by replacement of the hydroxyl group with substituents, such as halo, alkoxyl, amino and acyloxy. Some examples of these functional derivatives were displayed earlier.

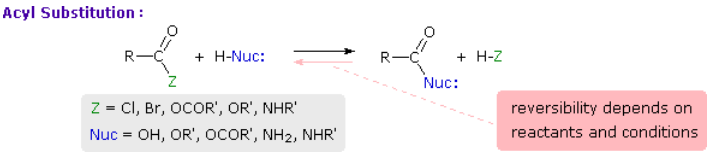
The following table lists some representative derivatives and their boiling points. An aldehyde and ketone of equivalent molecular weight are also listed for comparison. Boiling points are given for 760 torr (atmospheric pressure), and those listed as a range are estimated from values obtained at lower pressures. As noted earlier, the relatively high boiling point of carboxylic acids is due to extensive hydrogen bonded dimerization. Similar hydrogen bonding occurs between molecules of 1º and 2º-amides (amides having at least one N–H bond), and the first three compounds in the table serve as hydrogen bonding examples.

Other functional group combinations with the carbonyl group can be prepared from carboxylic acids, and are usually treated as related derivatives. Five common classes of these **carboxylic acid derivatives** are listed in the following table. Although nitriles do not have a carbonyl group, they are included here because the functional carbon atoms all have the same oxidation state. The top row (yellow shaded) shows the general formula for each class, and the bottom row (light blue) gives a specific example of each. As in the case of amines, amides are classified as 1º, 2º or 3º, depending on the number of alkyl groups bonded to the nitrogen.

acyl halide	anhydride	ester	amide	nitrile
 X = F, Cl, Br or I			 R′ = H or alkyl	
 propanoyl chloride	 acetic anhydride	 ethyl acetate	 formamide	acetonitrile

Acyl Group Substitution

This is probably the single most important reaction of carboxylic acid derivatives. The overall transformation is defined by the following equation, and may be classified either as **nucleophilic substitution at an acyl group** or as **acylation of a nucleophile**. For certain nucleophilic reagents the reaction may assume other names as well. If Nuc-H is water the reaction is often called **hydrolysis**, if Nuc–H is an alcohol the reaction is called **alcoholysis**, and for ammonia and amines it is called **aminolysis**.

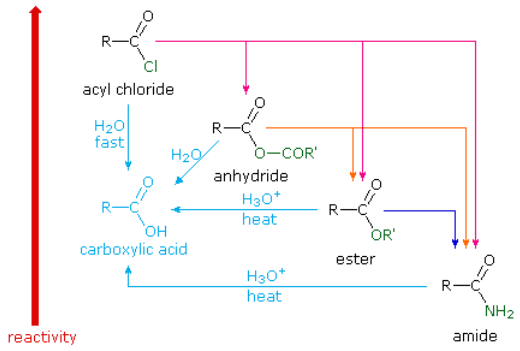


Different carboxylic acid derivatives have very different reactivities, acyl chlorides and bromides being the most reactive and amides the least reactive, as noted in the following qualitatively ordered list. The change in reactivity is dramatic. In homogeneous solvent systems, reaction of acyl chlorides with water occurs rapidly, and does not require heating or catalysts. Amides, on the other hand, react with water only in the presence of strong acid or base catalysts and external heating.

Reactivity: acyl halides > anhydrides >> esters ≈ acids >> amides

Because of these differences, the conversion of one type of acid derivative into another is generally restricted to those outlined in the following diagram. Methods for converting carboxylic acids into these derivatives were shown in a previous section, but the amide and anhydride preparations were not general and required strong heating. A better and more general anhydride synthesis can be achieved from acyl chlorides, and amides are easily made from any of the more reactive derivatives. Specific examples of these conversions will be displayed by clicking on the product formula. The carboxylic acids themselves are not an essential part of this

diagram, although all the derivatives shown can be hydrolyzed to the carboxylic acid state (light blue formulas and reaction arrows). Base catalyzed hydrolysis produces carboxylate salts.

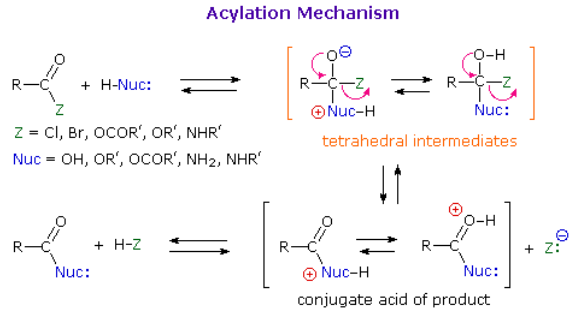


Original Diagram

Before proceeding further, it is important to review the general mechanism by means of which all these acyl transfer or **acylation reactions** take place. Indeed, an alert reader may well be puzzled by the facility of these nucleophilic substitution reactions. After all, it was previously noted that halogens bonded to sp^2 or sp hybridized carbon atoms do not usually undergo substitution reactions with nucleophilic reagents. Furthermore, such substitution reactions of alcohols and ethers are rare, except in the presence of strong mineral acids. Clearly, the mechanism by which acylation reactions occur must be different from the S_N1 and S_N2 procedures described earlier.

In any substitution reaction two things must happen. The bond from the substrate to the leaving group must be broken, and a bond to the replacement group must be formed. The timing of these events may vary with the reacting system. In nucleophilic substitution reactions of alkyl compounds examples of bond-breaking preceding bond-making (the S_N1 mechanism), and of bond-breaking and bond-making occurring simultaneously (the S_N2 mechanism) were observed. On the other hand, for most cases of electrophilic aromatic substitution bond-making preceded bond-breaking.

As illustrated in the following diagram, acylation reactions generally take place by an **addition-elimination process** in which a nucleophilic reactant bonds to the electrophilic carbonyl carbon atom to create a tetrahedral intermediate. This tetrahedral intermediate then undergoes an elimination to yield the products. In this two-stage mechanism bond formation occurs before bond cleavage, and the carbonyl carbon atom undergoes a hybridization change from sp^2 to sp^3 and back again. The facility with which nucleophilic reagents add to a carbonyl group was noted earlier for aldehydes and ketones.



Mechanism Toggle

Acid and base-catalyzed variations of this mechanism will be displayed in turn as the "Mechanism Toggle" button is clicked. Also, a specific example of acyl chloride formation from the reaction of a carboxylic acid with thionyl chloride will be shown. The number of individual steps in these mechanisms vary, but the essential characteristic of the overall transformation is that of **addition followed by elimination**. Acid catalysts act to increase the electrophilicity of the acyl reactant; whereas, base catalysts act on the nucleophilic reactant to increase its reactivity. In principle all steps are reversible, but in practice many reactions of this kind are irreversible unless changes in the reactants and conditions are made. The acid-catalyzed formation of esters from carboxylic acids and alcohols, described earlier, is a good example of a reversible acylation reaction, the products being determined by the

addition or removal of water from the system. The reaction of an acyl chloride with an alcohol also gives an ester, but this conversion cannot be reversed by adding HCl to the reaction mixture.

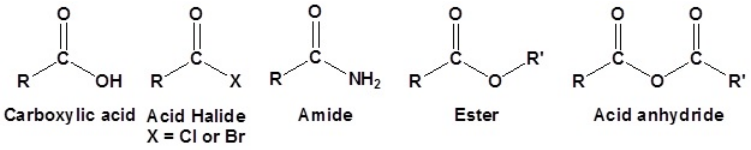
Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

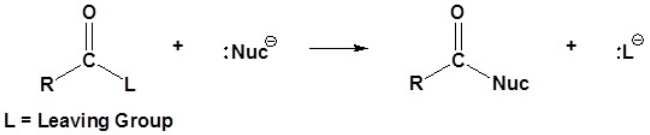
20.11: Structure and Bonding

Introduction

Carboxylic acid derivatives are functional groups whose chemistry is closely related. The main difference is the presence of an electronegative substituent that can act as a leaving group during a nucleophile substitution reaction. Although there are many types of carboxylic acid derivatives known, this article focuses on four: acid halides, acid anhydrides, esters, and amides.

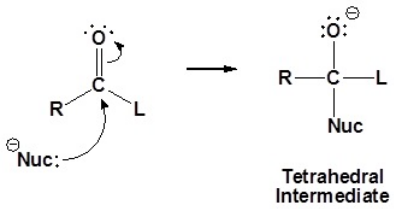


General reaction

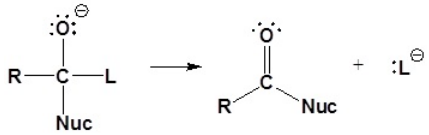


General mechanism

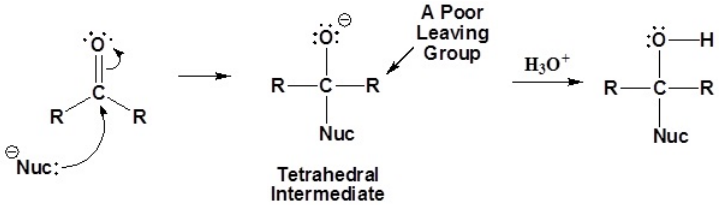
1) Nucleophilic attack on the carbonyl



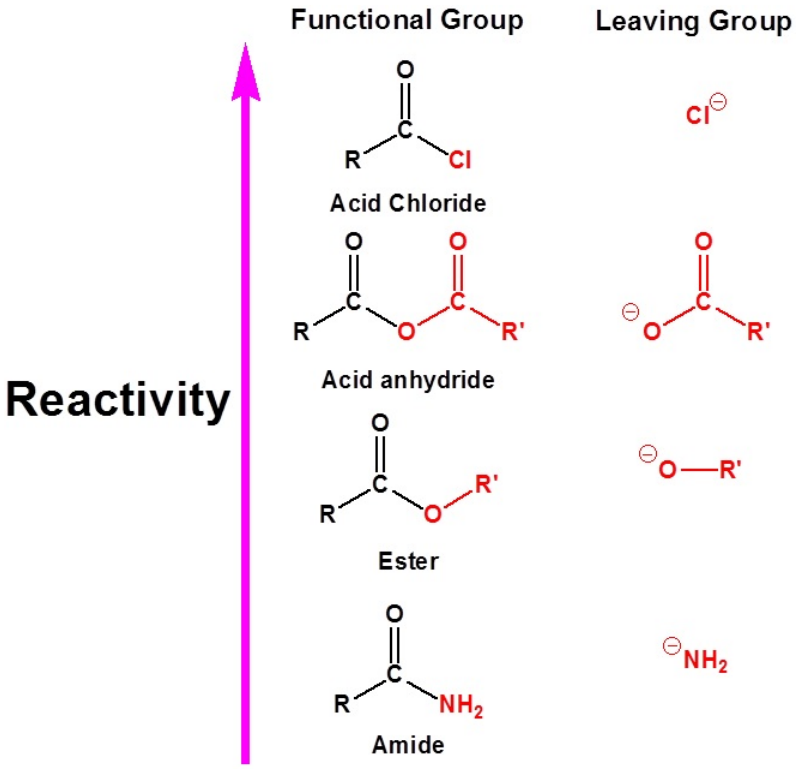
2) Leaving group is removed



Although aldehydes and ketones also contain carbonyls, their chemistry is distinctly different because they do not contain suitable leaving groups. Once a tetrahedral intermediate is formed, aldehydes and ketones cannot reform their carbonyls. Because of this, aldehydes and ketones typically undergo nucleophilic additions and not substitutions.



The relative reactivity of carboxylic acid derivatives toward nucleophile substitutions is related to the electronegative leaving group's ability to activate the carbonyl. The more electronegative leaving groups withdraw electron density from the carbonyl, thereby increasing its electrophilicity.



Contributors

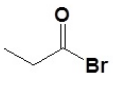
- Prof. Steven Farmer (Sonoma State University)

20.12: Nomenclature

Nomenclature of acid halides

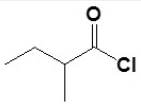
The nomenclature of acid halides starts with the name of the corresponding carboxylic acid. The **–ic acid** ending is removed and replaced with the ending **-yl** followed by the name of the halogen with an **–ide** ending. This is true for both common and IUPAC nomenclature. The carbonyl carbon is given the #1 location number. It is not necessary to include the location number in the name because it is assumed that the functional group will be on the end of the parent chain.

Example 1:



Propanoyl bromide

(Propionyl bromide)



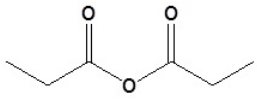
2-Methylbutanoyl chloride

(2-Methylbutyryl chloride)

The acid anhydride functional group results when two carboxylic acids combine and lose water (anhydride = without water). Symmetrical acid anhydrides are named like carboxylic acids except the ending **-acid** is replaced with **-anhydride**. This is true for both the IUPAC and Common nomenclature.

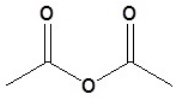
Nomenclature of Anhydrides

Symmetrical anhydrides



Propanoic anhydride

(Propionic anhydride)

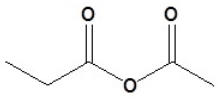


Ethanoic anhydride

(Acetic anhydride)

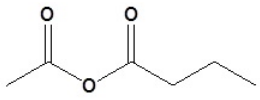
Unsymmetrical acid anhydrides

Unsymmetrical acid anhydrides are named by first naming each component carboxylic acid alphabetically arranged (without the word acid) followed by spaces and then the word anhydride.



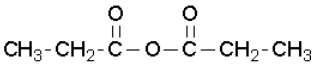
Ethanoic propanoic anhydride

(Acetic propionic anhydride)

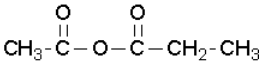


Butanoic ethanoic anhydride

(Acetic butyic anhydride)



propanoic anhydride



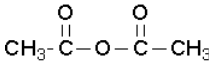
ethanoic propanoic anhydride

Try to name the following compound

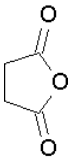
Try to draw a structure for the following compound

- 1,2-benzenedicarboxylic anhydride J

Common names that you should know



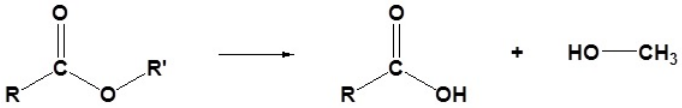
acetic anhydride (Try to name this anhydride by the proper name. J)



succinic anhydride (Try to name this anhydride by the proper name. J)

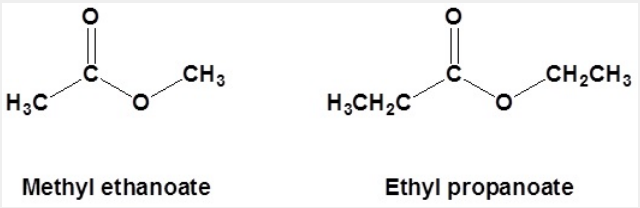
Nomenclature of Esters

Esters are made from a carboxylic acid and an alcohol.



Esters are named as if the alkyl chain from the alcohol is a substituent. No number is assigned to this alkyl chain. This is followed by the name of the parent chain form the carboxylic acid part of the ester with an **–e** remove and replaced with the ending **–oate**.

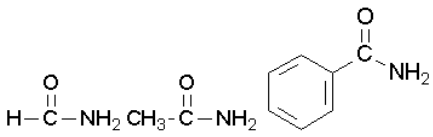
Example 1:



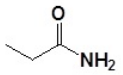
Nomenclature of amides

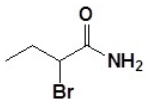
Primary amides

Primary amides are named by changing the name of the acid by dropping the -oic acid or -ic acid endings and adding -amide. The carbonyl carbon is given the #1 location number. It is not necessary to include the location number in the name because it is assumed that the functional group will be on the end of the parent chain.



methanamide or formamide (left), ethanamide or acetamide (center) , benzamide (right)



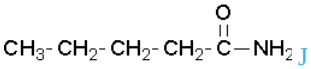


Propanamide 2-Bromobutanamide

Try to draw a structure for the following compound

- 3-chlorobenzamide J

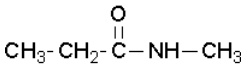
Try to name the following compound



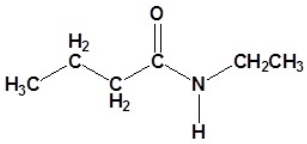
J

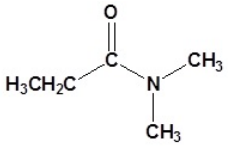
Secondary amides

Secondary amides are named by using an upper case N to designate that the alkyl group is on the nitrogen atom. Alkyl groups attached to the nitrogen are named as substituents. The letter N is used to indicate they are attached to the nitrogen. Tertiary amides are named in the same way.



N-methylpropanamide



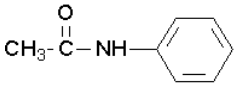


N-Ethylbutanamide N,N-Dimethylpropanamide

Try to draw a structure for the following compound

- N,N-dimethylformamide J

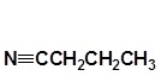
Try to name the following compound

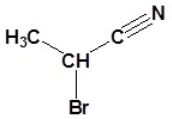


J

Name the parent alkane (include the carbon atom of the nitrile as part of the parent) followed with the word -nitrile. The carbon in the nitrile is given the #1 location position. It is not necessary to include the location number in the name because it is assumed that the functional group will be on the end of the parent chain.

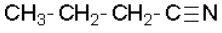
Nomenclature of nitriles





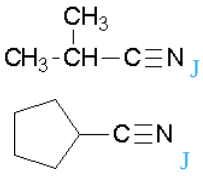
Butane nitrile 2-Bromopropane nitrile

Cycloalkanes are followed by the word -carbonitrile. The substituent name is cyano.



- 1-butanenitrile or 1-cyanopropane

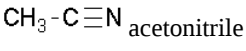
Try to name the following compounds using these conventions

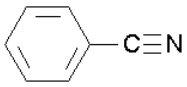


Try to draw structures for the following compounds

- butanedinitrile
- 2-methycyclohexanecarbonitrile

Some common names that you should know are...


acetonitrile


benzonitrile

Try to draw a structure for the following compound

- 2-methoxybenzonitrile

Contributors

- Prof. Steven Farmer (Sonoma State University)

Richard Banks (Boise State University)

20.13: Physical Properties

Physical Properties of Some Carboxylic Acid Derivatives

Formula	IUPAC Name	Molecular Weight	Boiling Point	Water Solubility
$CH_3(CH_2)_2CO_2H$	butanoic acid	88	164 ºC	very soluble
$CH_3(CH_2)_2CONH_2$	butanamide	87	216-220 ºC	soluble
$CH_3CH_2CONHCH_3$	N-methylpropanamide	87	205 -210 ºC	soluble
$CH_3CON(CH_3)_2$	N,N-dimethylethanamide	87	166 ºC	very soluble
$HCON(CH_3)CH_2CH_3$	N-ethyl, N-methylmethanamide	87	170-180 ºC	very soluble
$CH_3(CH_2)_3CN$	pentanenitrile	83	141 ºC	slightly soluble
CH_3CO_2CHO	ethanoic methanoic anhydride	88	105-112 ºC	reacts with water
$CH_3CH_2CO_2CH_3$	methyl propanoate	88	80 ºC	slightly soluble
$CH_3CO_2C_2H_5$	ethyl ethanoate	88	77 ºC	moderately soluble
CH_3CH_2COCl	propanoyl chloride	92.5	80 ºC	reacts with water
$CH_3(CH_2)_3CHO$	pentanal	86	103 ºC	slightly soluble
$CH_3(CH_2)_2COCH_3$	2-pentanone	86	102 ºC	slightly soluble

The last nine entries in the above table cannot function as hydrogen bond donors, so hydrogen bonded dimers and aggregates are not possible. The relatively high boiling points of equivalent 3º-amides and nitriles are probably due to the high polarity of these functions. Indeed, if hydrogen bonding is not present, the boiling points of comparable sized compounds correlate reasonably well with their dipole moments.

Contributors

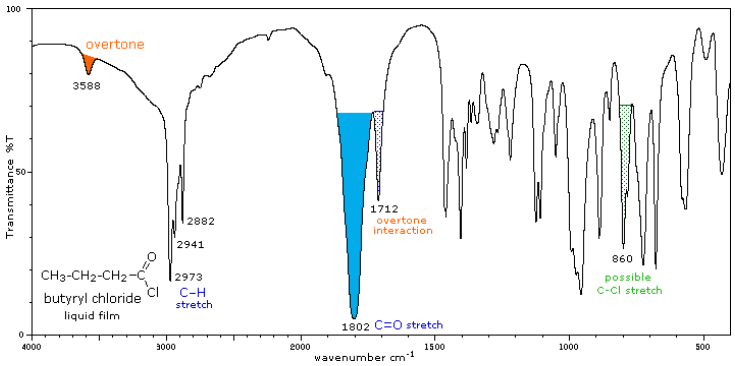
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

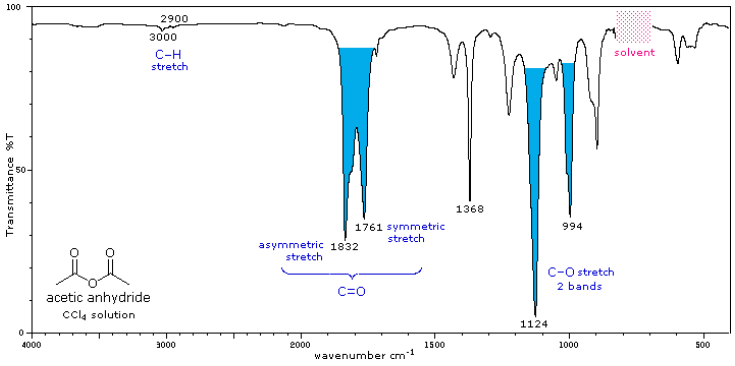
20.14: Spectroscopic Properties

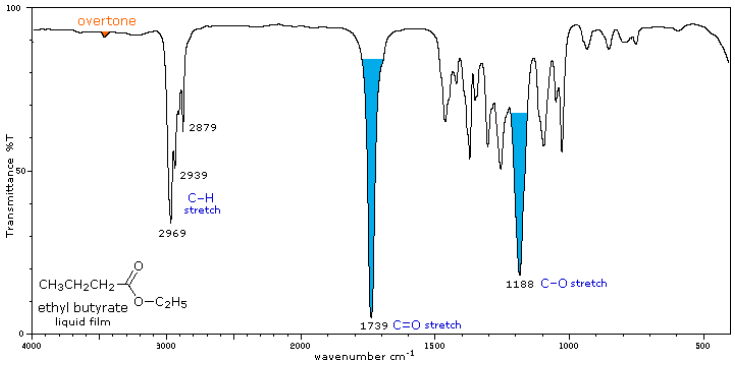
The influence of heteroatom substituents on the reactivity of carbonyl functions toward nucleophiles was discussed earlier with respect to carboxylic acid derivatives. A useful relationship exists between the reactivity of these derivatives and their carbonyl stretching frequencies. Thus, the very reactive acyl halides and anhydrides absorb at frequencies significantly higher than ketones, whereas the relatively unreactive amides absorb at lower frequencies. These characteristics are listed below.

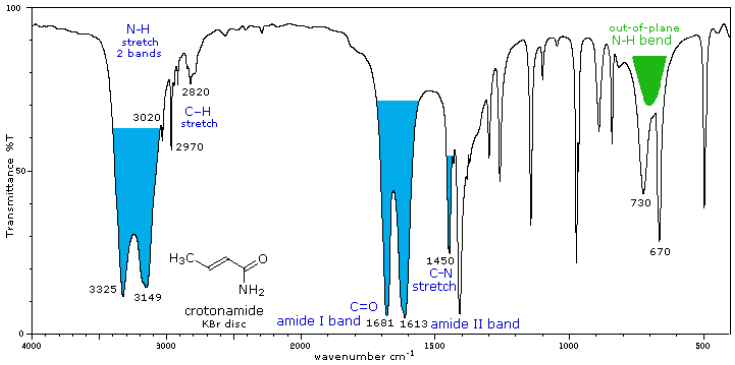
Infrared spectra of many carboxylic acid derivatives will be displayed in the figure below the table by clicking the appropriate buttons presented there.

Carbonyl Derivative	Carbonyl Absorption	Comments
Acyl Halides (RCOX) X = F X = Cl X = Br	**C=O stretch** 1860 ± 20 cm^{-1} 1800 ± 15 1800 ± 15	Conjugation lowers the C=O frequencies reported here, as with aldehydes & ketones. In acyl chlorides a lower intensity shoulder or peak near 1740 cm^{-1} is due to an overtone interaction.
Acid Anhydride, $(RCO)_2O$ acyclic 6-membered ring 5-membered ring	**C=O stretch** (2 bands) 1750 & 1820 cm^{-1} 1750 &1820 1785 & 1865	Conjugation lowers the C=O frequencies reported here, as with aldehydes & ketones. The two stretching bands are separated by 60 ± 30 cm^{-1}, and for acyclic anhydrides the higher frequency (asymmetric stretching) band is stronger than the lower frequency (symmetric) absorption. Cyclic anhydrides also display two carbonyl stretching absorptions, but the lower frequency band is the strongest. One or two -CO-O-CO- stretching bands are observed in the 1000 to 1300 cm^{-1} region.
Esters & Lactones (RCOOR') esters 6-membered lactone 5-membered lactone 4-membered lactone	**C=O stretch** 1740 cm ± 10 cm^{-1} 1740 cm ± 10 1765 cm± 5 1840 cm ± 5	Conjugation lowers the C=O frequencies reported here, as with aldehydes & ketones Strong CO-O stretching absorptions (one ot two) are found from 1150 to 1250 cm^{-1}
Amides & Lactams $(RCONR_2)$ 1° & 2°-amides 3°-amides 6-membered lactams 5-membered lactams 4-membered lactams	**C=O bands** 1510 to 1700 cm^{-1} (2 bands) 1650± 15 (one band) 1670 ± 10 (one band) 1700 ± 15 1745 ± 15	The effect of conjugation is much less than for aldehydes & ketones. The higher frequency absorption (1665± 30) is called the **Amide I band**. The lower frequency **Amide II band** (1620± 30 in 1° amides & 1530± 30 in 2° amides) is largely due to N-H bending trans to the carbonyl oxygen. In concentrated samples this absorption is often obscured by the stronger amide I absorption. Hydrogen bonded association shifts some of these absorptions, as well as the prominent N-H stretching absorptions. **N-H stretch**: 3170 to 3500 cm^{-1}. Two bands for 1°-amides, one for 2°-amides.









NMR Spectra

Protons on carbons adjacent to carbonyls absorb at ~2.0-2.5 ppm.

The N-H protons attached to primary and secondary amines absorb at ~7.5-8.5.

The carbonyl carbon in carboxylic acid derivatives show up at ~ 160-180 ppm.

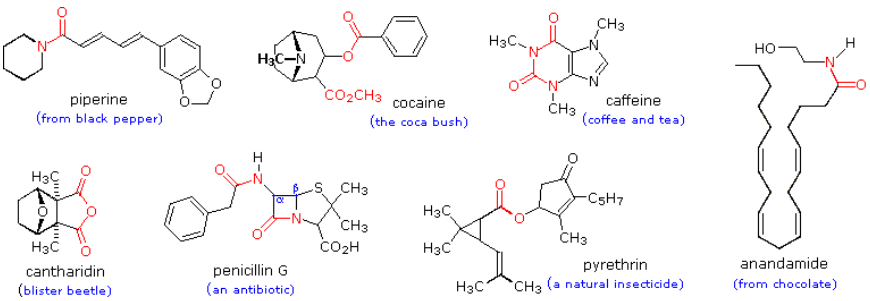
The carbon in a nitrile appear ~ 115-120 ppm in their ^{13}C NMR spectrum. This is because of their *sp* hybridization.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

20.15: Interesting Esters and Amides

Functional groups of this kind are found in many kinds of natural products. Some examples are shown below with the functional group colored red. Most of the functions are amides or esters, cantharidin being a rare example of a natural anhydride. Cyclic esters are called **lactones**, and cyclic amides are referred to as **lactams**. Penicillin G has two amide functions, one of which is a β-lactam. The Greek letter locates the nitrogen relative to the carbonyl group of the amide.



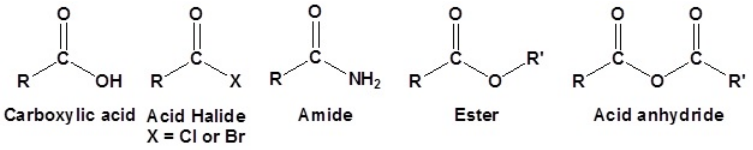
Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

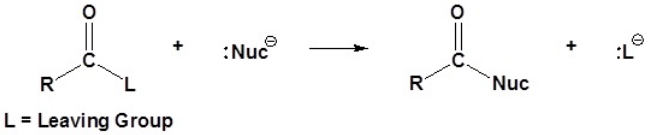
20.16: Introduction to Nucleophilic Acyl Substitution

Introduction

Carboxylic acid derivatives are functional groups whose chemistry is closely related. The main difference is the presence of an electronegative substituent that can act as a leaving group during a nucleophile substitution reaction. Although there are many types of carboxylic acid derivatives known, this article focuses on four: acid halides, acid anhydrides, esters, and amides.

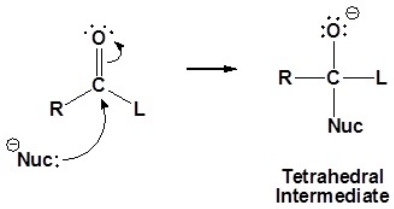


General reaction

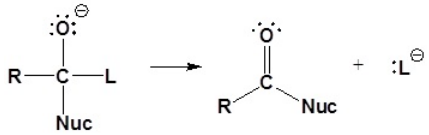


General mechanism

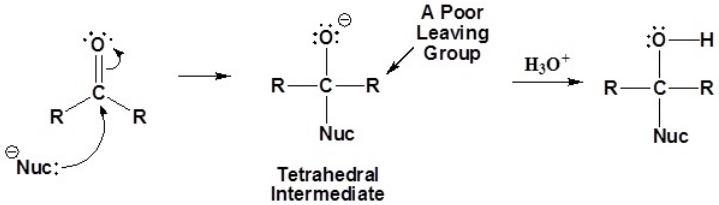
1) Nucleophilic attack on the carbonyl



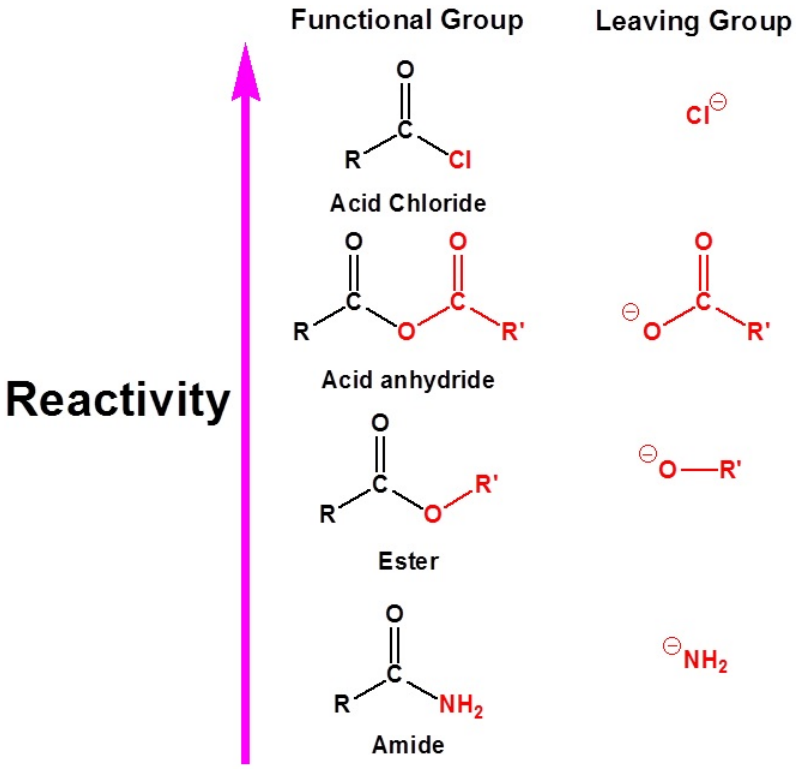
2) Leaving group is removed



Although aldehydes and ketones also contain carbonyls, their chemistry is distinctly different because they do not contain suitable leaving groups. Once a tetrahedral intermediate is formed, aldehydes and ketones cannot reform their carbonyls. Because of this, aldehydes and ketones typically undergo nucleophilic additions and not substitutions.



The relative reactivity of carboxylic acid derivatives toward nucleophile substitutions is related to the electronegative leaving group's ability to activate the carbonyl. The more electronegative leaving groups withdraw electron density from the carbonyl, thereby increasing its electrophilicity.



Contributors

- Prof. Steven Farmer (Sonoma State University)

20.16.1: 22.8 Reactions of Acid Chlorides

Your page has been created!

Remove this content and add your own.

Edit page

Click the Edit page button in your user bar. You will see a suggested structure for your content. Add your content and hit Save.

Tips:

Drag and drop

Drag one or more image files from your computer and drop them onto your browser window to add them to your page.

Classifications

Tags are used to link pages to one another along common themes. Tags are also used as markers for the dynamic organization of content in the CXone Expert framework.

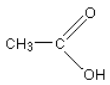
Working with templates

CXone Expert templates help guide and organize your documentation, making it flow easier and more uniformly. Edit existing templates or create your own.

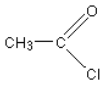
Visit for all help topics.

20.17: Reactions of Acid Chlorides

Acyl chlorides (also known as acid chlorides) are one of a number of types of compounds known as "acid derivatives". This is ethanoic acid:



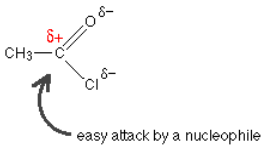
If you remove the -OH group and replace it by a -Cl, you have produced an acyl chloride.



This molecule is known as ethanoyl chloride and for the rest of this topic will be taken as typical of acyl chlorides in general. Acyl chlorides are extremely reactive. They are open to attack by nucleophiles - with the overall result being a replacement of the chlorine by something else.

Why are acyl chlorides attacked by nucleophiles?

The carbon atom in the -COCl group has both an oxygen atom and a chlorine atom attached to it. Both of these are very electronegative. They both pull electrons towards themselves, leaving the carbon atom quite positively charged.



The Overall Reaction

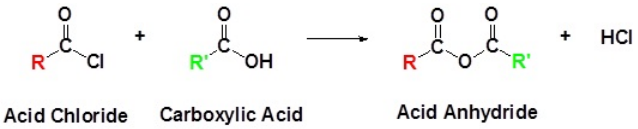
We are going to generalize this for the moment by writing the reacting molecule as "Nu-H". Nu is the bit of the molecule which contains the nucleophilic oxygen or nitrogen atom. The attached hydrogen turns out to be essential to the reaction. The general equation for the reaction is:

In each case, the net effect is that you replace the -Cl by -Nu, and hydrogen chloride is formed as well.

Since the initial attack is by a nucleophile, and the overall result is substitution, it would seem reasonable to describe the reaction as nucleophilic substitution. However, the reaction happens in two distinct stages. The first involves an addition reaction, which is followed by an elimination reaction where HCl is produced. So the mechanism is also known as nucleophilic addition / eliminatio

Acid chlorides react with carboxylic acids to form anhydrides.

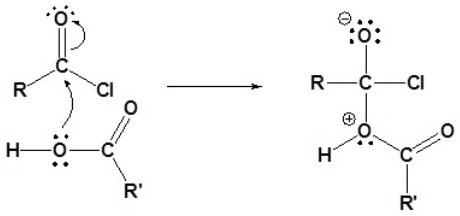
General Reaction



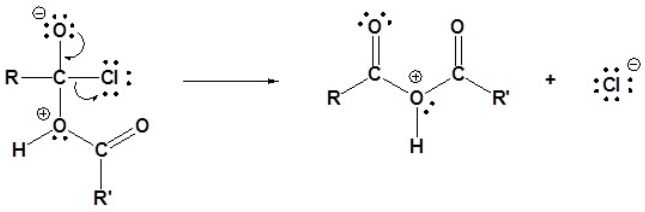
Example 1:

Mechanism

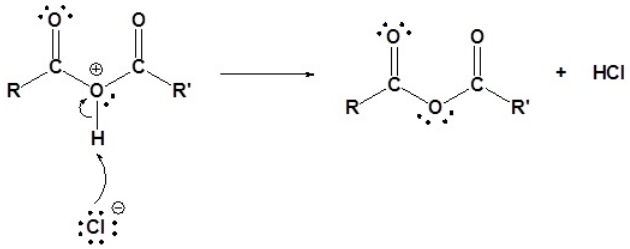
1) Nucleophilic attack by the alcohol



2) Leaving group is removed



3) Deprotonation

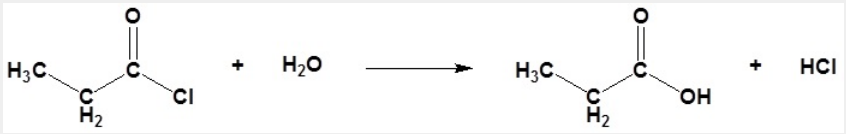


Acid chlorides react with water to form carboxylic acids.

General reaction

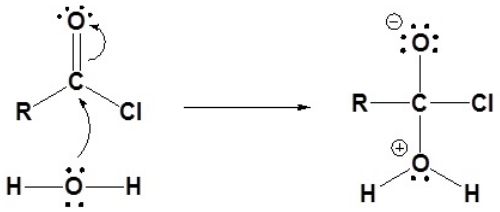
Acid Chloride Carboxylic Acid

Example 1:

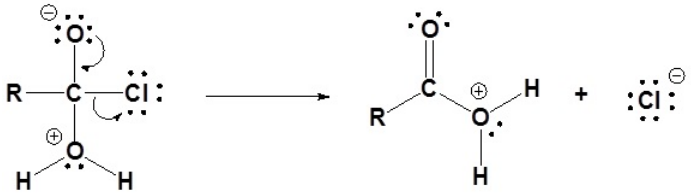


Mechanism

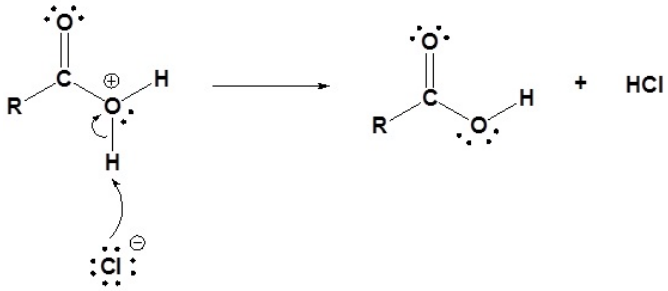
1) Nucleophilic attack by water



2) Leaving group is removed

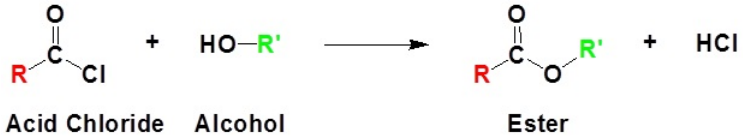


3) Deprotonation



Acid chlorides react with alcohols to form esters

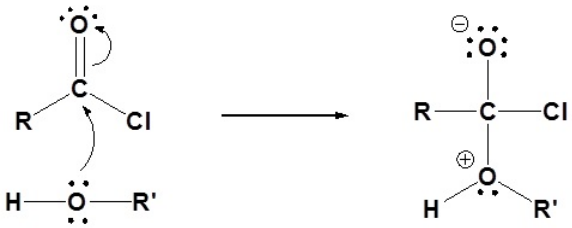
General Reaction



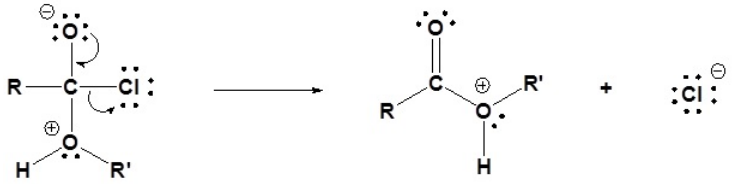
Example 1:

Mechanism

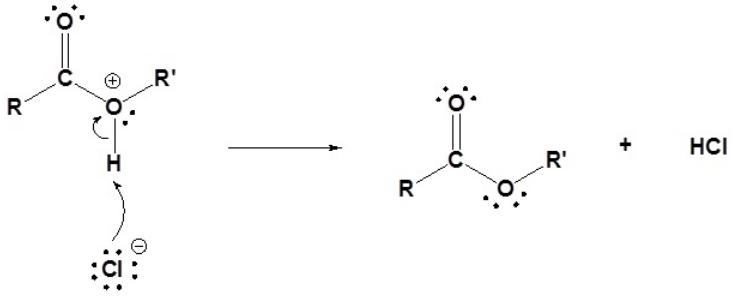
1) Nucleophilic attack by the alcohol



2) Leaving group is removed

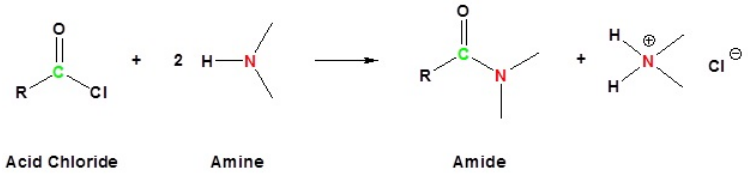


3) Deprotonation

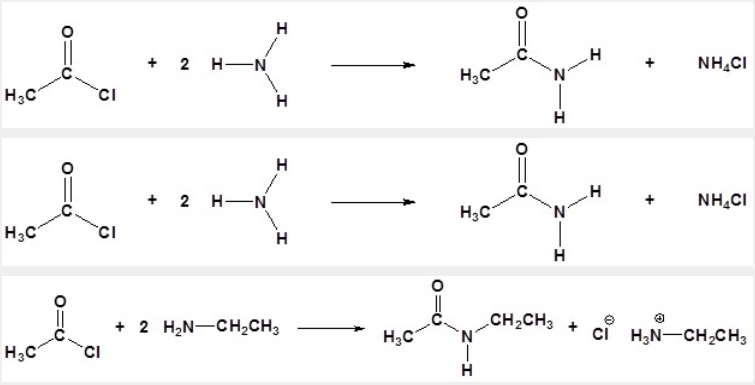


Acid chlorides react with ammonia, 1º amines and 2º amines to form amides.

General Reaction

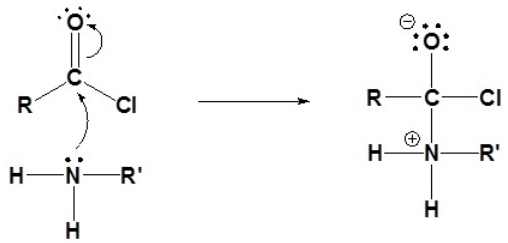


Examples:

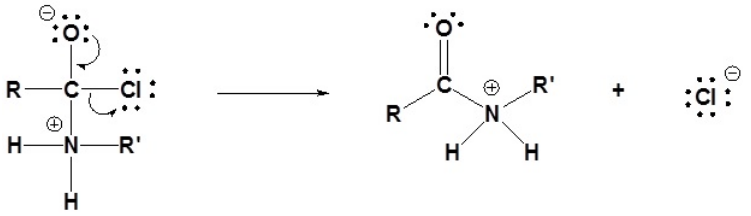


Mechanism

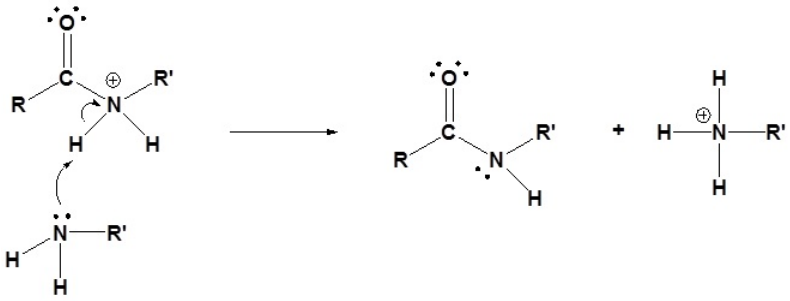
1) Nucleophilic attack by the amine



2) Leaving group is removed



3) Deprotonation



Contributors

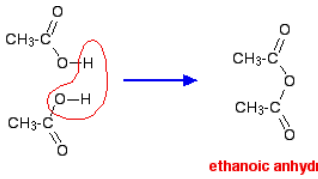
- Prof. Steven Farmer (Sonoma State University)
- Jim Clark (Chemguide.co.uk)

20.18: Reactions of Anhydrides

This page explains what acid anhydrides are and looks at their simple physical properties such as boiling points. It introduces their chemical reactivity in a general way. A carboxylic acid such as ethanoic acid has the structure:

ethanoic acid

If you took two ethanoic acid molecules and removed a molecule of water between them you would get the acid anhydride, ethanoic anhydride (old name: acetic anhydride).

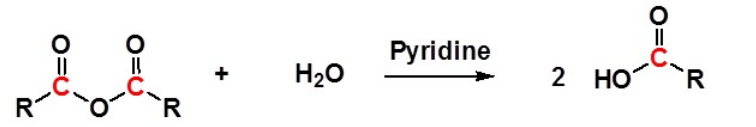


ethanoic anhydride

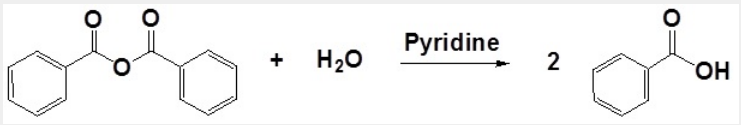
You can actually make ethanoic anhydride by dehydrating ethanoic acid, but it is normally made in a more efficient, round-about way

Acid Anhydrides react with water to form carboxylic acids

General Reaction

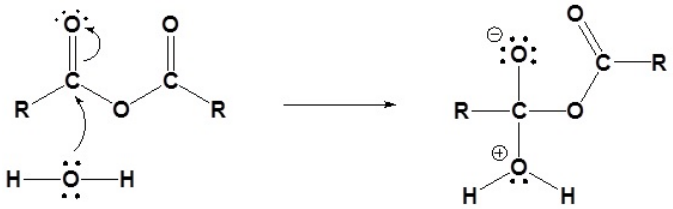


Example 1:

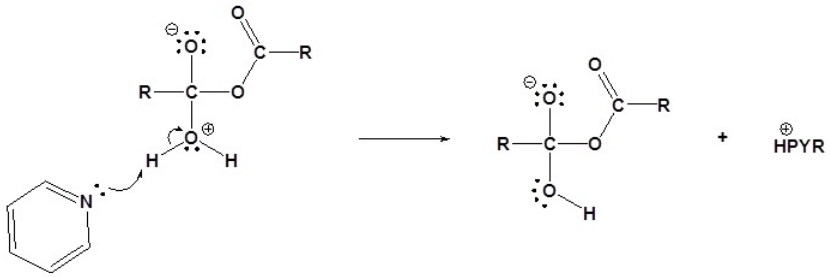


Mechanism

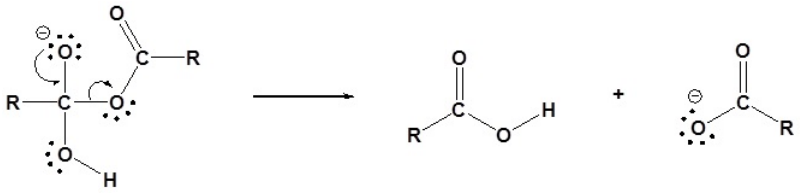
1) Nucleophilic Attack by the water molcule



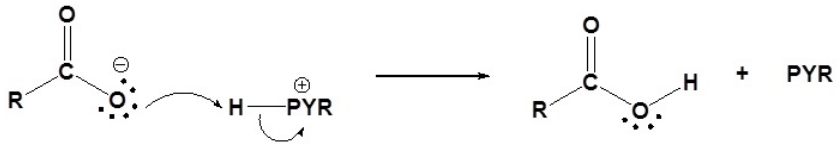
2) Deprotonation by pyridine



3) Leaving group removal

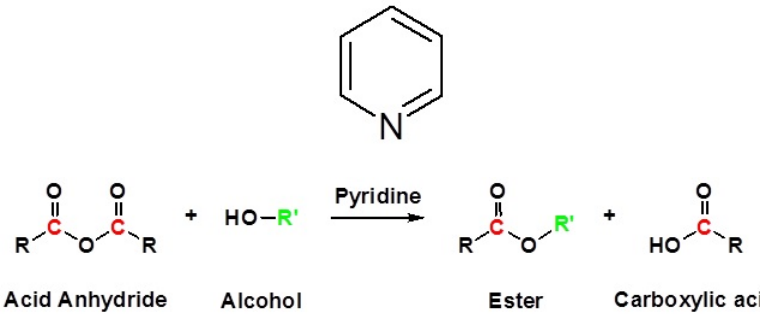


4) Protonation of the carboxylate

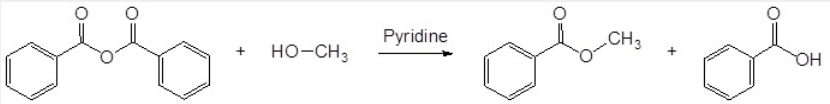


Acid Anhydrides react with alcohols to form esters

Reactions of anhydrides use Pyridine as a solvent

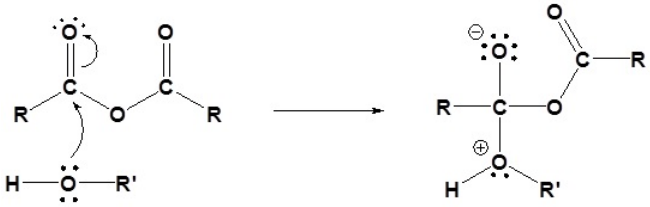


Example 1:

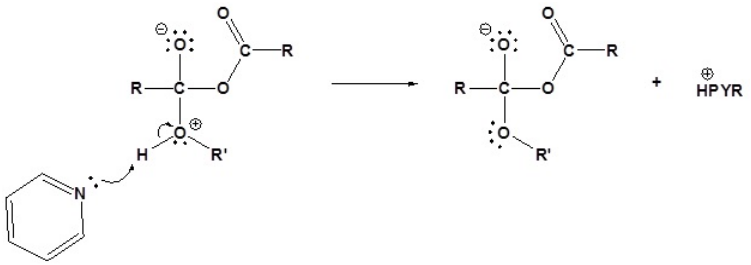


Mechanism

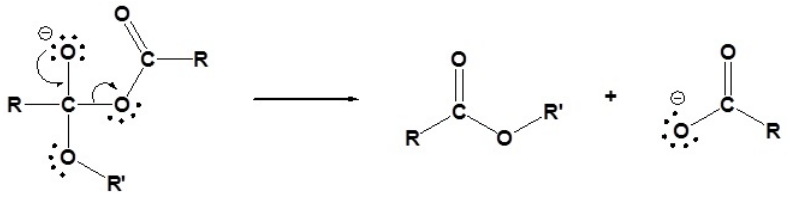
1) Nucleophilic Attack by the Alcohol



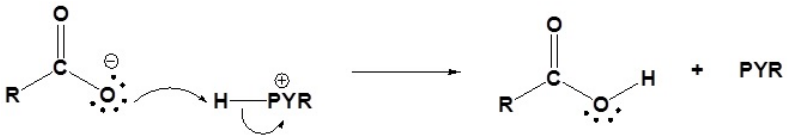
2) Deprotonation by pyridine



3) Leaving group removal

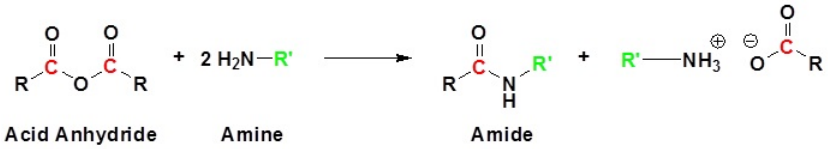


4) Protonation of the carboxylate



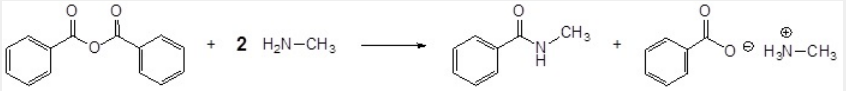
Acid Anhydrides react with amines to form amides

General Reaction



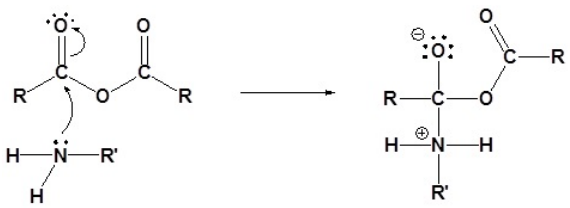
Acid Anhydride Amine Amide

Example 1:

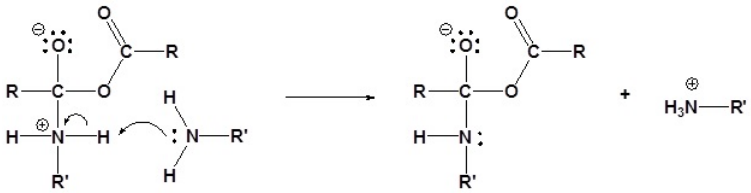


Mechanism

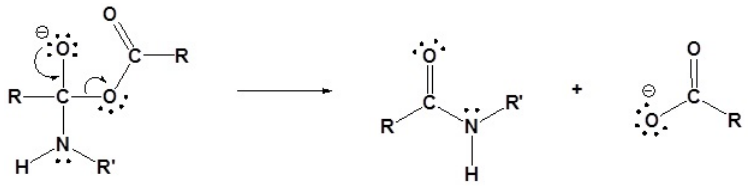
1) Nucleophilic Attack by the Amine



2) Deprotonation by the amine



3) Leaving group removal



Contributors

- Prof. Steven Farmer (Sonoma State University)
- Jim Clark (Chemguide.co.uk)

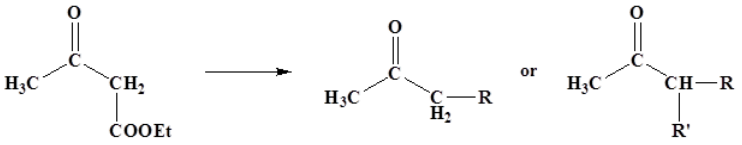
CHAPTER OVERVIEW

21: Substitution Reactions of Carbonyl Compounds at the Alpha Carbon

---

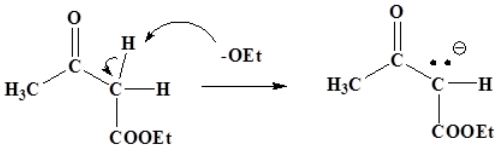
21.1: Acetoacetic Ester Synthesis

The acetoacetic ester synthesis allows for the conversion of ethyl acetoacetate into a methyl ketone with one or two alkyl groups on the alpha carbon.

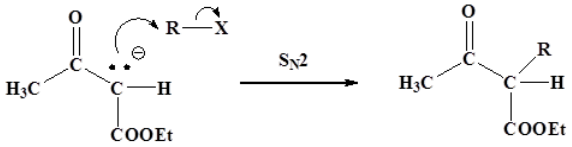


Steps

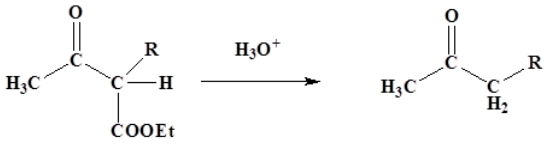
1) Deprotonation with ethoxide



2) Alkylation via and SN2 Reaction

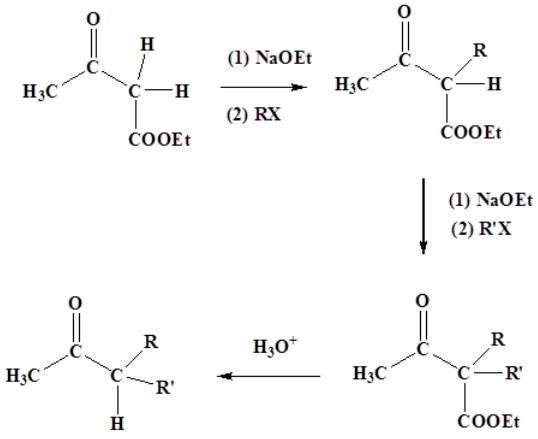


3) Hydrolysis and decarboxylation



Addition of a second alky group

After the first step and additional alkyl group can be added prior to the decarboxylation step. Overall this allows for the addition of two different alkyl groups.



Contributors

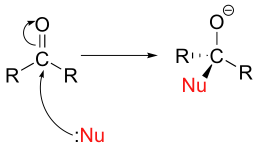
- Prof. Steven Farmer (Sonoma State University)

21.2: Introduction

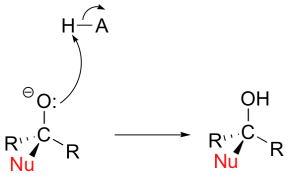
Thus far two general reactions have been observed with carbonyls

Nucleophilic Addition to Aldehydes and Ketones

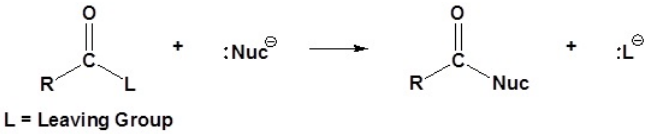
The result of carbonyl bond polarization, however it is depicted, is straightforward to predict. The carbon, because it is electron-poor, is an electrophile: it is a great target for attack by an electron-rich nucleophilic group. Because the oxygen end of the carbonyl double bond bears a partial negative charge, anything that can help to stabilize this charge by accepting some of the electron density will increase the bond's polarity and make the carbon more electrophilic. Very often a general acid group serves this purpose, donating a proton to the carbonyl oxygen.



After the carbonyl is attacked by the nucleophile, the negatively charged oxygen has the capacity to act as a nucleophile. However, most commonly the oxygen acts instead as a base, abstracting a proton from a nearby acid group in the solvent or enzyme active site.



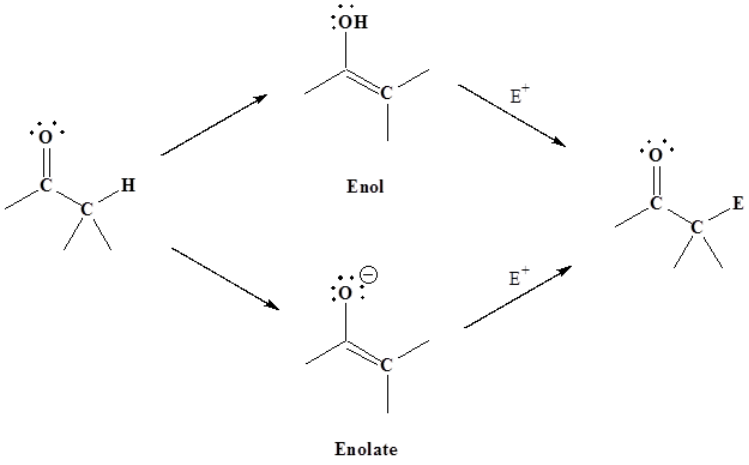
Nucleophilic Substitution of RCOZ (Z = Leaving Group)



A new carbonyl reaction

Reactions at The Alpha Carbon

Now we will investigate reactions which occur a the carbon alpha to the carbonyl groups. These reactions involve two new neucleophilic species the enol and the enolate.



Note! The electrophile replaces the hydrogen on the alpha carbon.

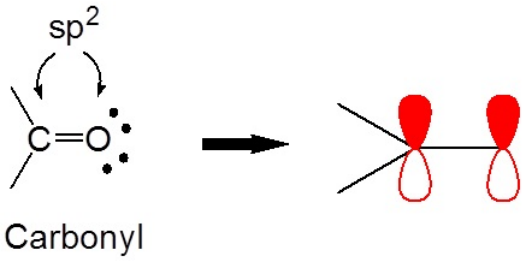
Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- Prof. Steven Farmer (Sonoma State University)

21.3: Enols

Acidity of Alpha Hydrogens

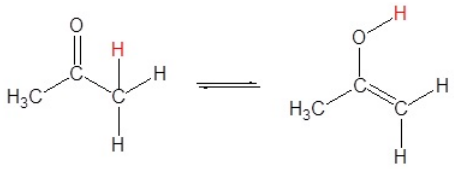
Functional groups, such as aldehydes, ketones and esters, contain a carbonyl group which is made up of a sp^2 hybridized carbon and oxygen. Because they are sp^2 hybridized the carbon and oxygen both have unhybridized p orbitals which can overlap to form the C=O π bond.



Carbonyl

Keto-enol Tautomerism

Because of the acidity of α hydrogens carbonyls undergo keto-enol tautomerism. Tautomers are rapidly interconverted constitutional isomers, usually distinguished by a different bonding location for a labile hydrogen atom and a differently located double bond. The equilibrium between tautomers is not only rapid under normal conditions, but it often strongly favors one of the isomers (acetone, for example, is 99.999% keto tautomer). Even in such one-sided equilibria, evidence for the presence of the minor tautomer comes from the chemical behavior of the compound. Tautomeric equilibria are catalyzed by traces of acids or bases that are generally present in most chemical samples.



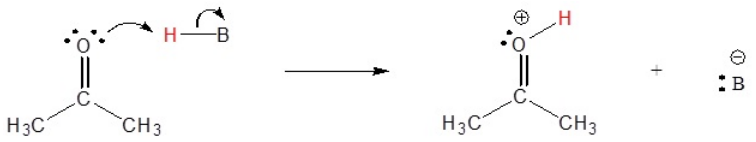
Keto Tautomer ~99.999%

Enol Tautomer ~0.001%

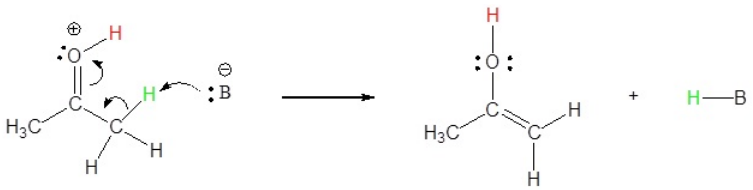
Mechanism for Enol Formation

Acid conditions

1) Protonation of the Carbonyl

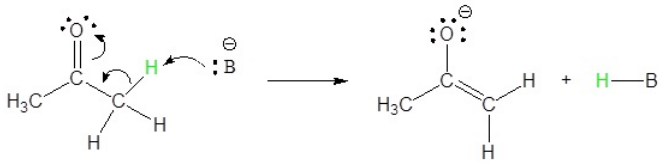


2) Enol formation

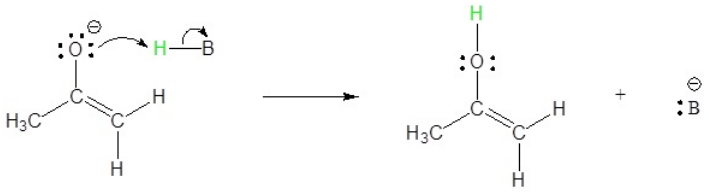


Basic conditions

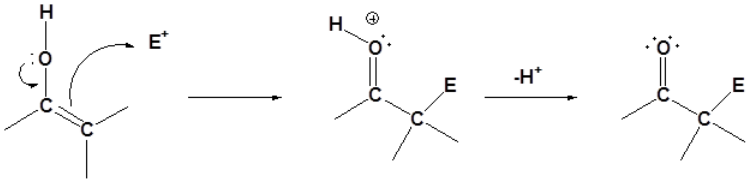
1) Enolate formation



2) Protonation



How Enols React

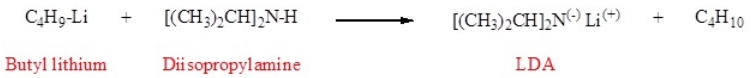


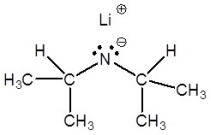
Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)

21.4: Enolates

For alkylation reactions of enolate anions to be useful, these intermediates must be generated in high concentration in the absence of other strong nucleophiles and bases. The aqueous base conditions used for the aldol condensation are not suitable because the enolate anions of simple carbonyl compounds are formed in very low concentration, and hydroxide or alkoxide bases induce competing S_N2 and E2 reactions of alkyl halides. It is necessary, therefore, to achieve complete conversion of aldehyde or ketone reactants to their enolate conjugate bases by treatment with a very strong base ($pK_a > 25$) in a non-hydroxylic solvent before any alkyl halides are added to the reaction system. Some bases that have been used for enolate anion formation are: NaH (sodium hydride, $pK_a > 45$), $NaNH_2$ (sodium amide, $pK_a = 34$), and $LiN[CH(CH_3)_2]_2$ (lithium diisopropylamide, LDA, pK_a 36). Ether solvents like tetrahydrofuran (THF) are commonly used for enolate anion formation. With the exception of sodium hydride and sodium amide, most of these bases are soluble in THF. Certain other strong bases, such as alkyl lithium and Grignard reagents, cannot be used to make enolate anions because they rapidly and irreversibly add to carbonyl groups. Nevertheless, these very strong bases are useful in making soluble amide bases. In the preparation of lithium diisopropylamide (LDA), for example, the only other product is the gaseous alkane butane.



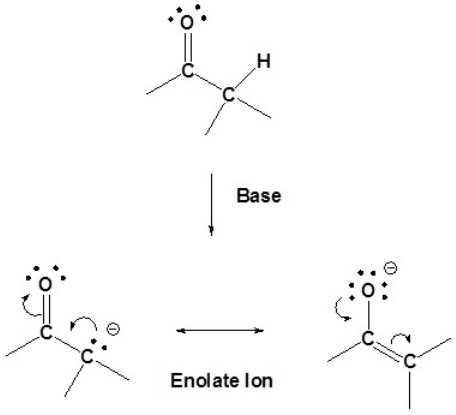


LDA

Sodium Amide

Because of its solubility in THF, LDA is a widely used base for enolate anion formation. In this application, one equivalent of diisopropylamine is produced along with the lithium enolate, but this normally does not interfere with the enolate reactions and is easily removed from the products by washing with aqueous acid. Although the reaction of carbonyl compounds with sodium hydride is heterogeneous and slow, sodium enolates are formed with the loss of hydrogen, and no other organic compounds are produced.

The presence of these overlapping p orbitals gives α hydrogens (Hydrogens on carbons adjacent to carbonyls) special properties. In particular, α hydrogens are weakly acidic because the conjugate base, called an enolate, is stabilized though conjugation with the π orbitals of the carbonyl. The effect of the carbonyl is seen when comparing the pK_a for the α hydrogens of aldehydes (~16-18), ketones (~19-21), and esters (~23-25) to the pK_a of an alkane (~50).



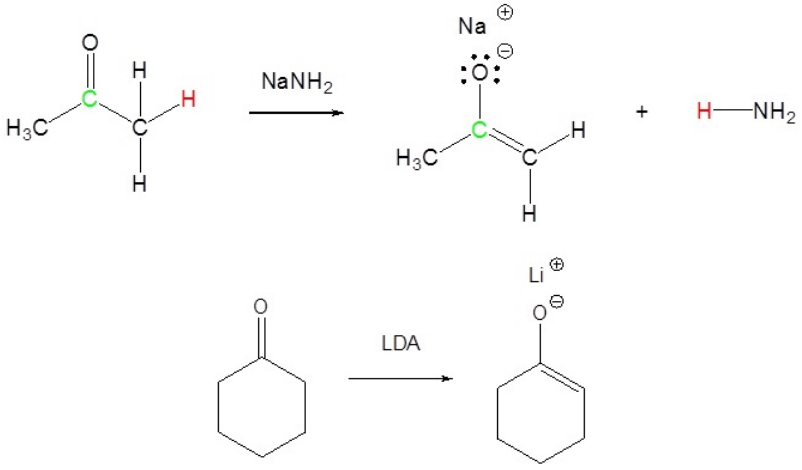
Of the two resonance structures of the enolate ion the one which places the negative charge on the oxygen is the most stable. This is because the negative change will be better stabilized by the greater electronegativity of the oxygen.

Acidity of α-Hydrogens in Some Activated Compounds

Compound	$RCH_2–NO_2$	$RCH_2–COR$	$RCH_2–C\equiv N$	$RCH_2–SO_2R$

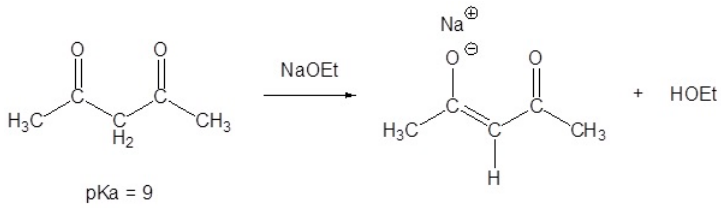
pK_a	9	20	25	25

Examples



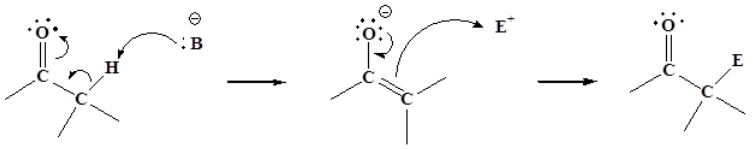
If the formed enolate is stabilized by more than one carbonyl it is possible to use a weaker base such as sodium ethoxide.

$NaOCH_2CH_3 = Na^+ {}^-OCH_2CH_3 = NaOEt$



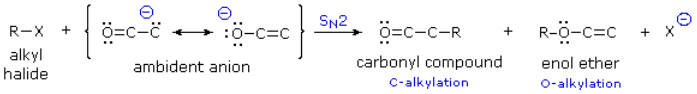
Because of the acidity of α hydrogens, carbonyls undergo keto-enol tautomerism. Tautomers are rapidly interconverted constitutional isomers, usually distinguished by a different bonding location for a labile hydrogen atom and a differently located double bond. The equilibrium between tautomers is not only rapid under normal conditions, but it often strongly favors one of the isomers (acetone, for example, is 99.999% keto tautomer). Even in such one-sided equilibria, evidence for the presence of the minor tautomer comes from the chemical behavior of the compound. Tautomeric equilibria are catalyzed by traces of acids or bases that are generally present in most chemical samples.

General Reaction of Enolates



The Ambident Character of Enolate Anions

Since the negative charge of an enolate anion is delocalized over the alpha-carbon and the oxygen, as shown earlier, electrophiles may bond to either atom. Reactants having two or more reactive sites are called **ambident**, so this term is properly applied to enolate anions. Modestly electrophilic reactants such as alkyl halides are not sufficiently reactive to combine with neutral enol tautomers, but the increased nucleophilicity of the enolate anion conjugate base permits such reactions to take place. Because alkylations are usually irreversible, their products should reflect the inherent (kinetic) reactivity of the different nucleophilic sites.



If an alkyl halide undergoes an S_N2 reaction at the carbon atom of an enolate anion the product is an alkylated aldehyde or ketone. On the other hand, if the S_N2 reaction occurs at oxygen the product is an ether derivative of the enol tautomer; such compounds are stable in the absence of acid and may be isolated and characterized. These alkylations (shown above) are irreversible under the conditions normally used for S_N2 reactions, so the product composition should provide a measure of the relative rates of substitution at carbon versus oxygen. It has been found that this competition is sensitive to a number of factors, including negative charge density, solvation, cation coordination and product stability.

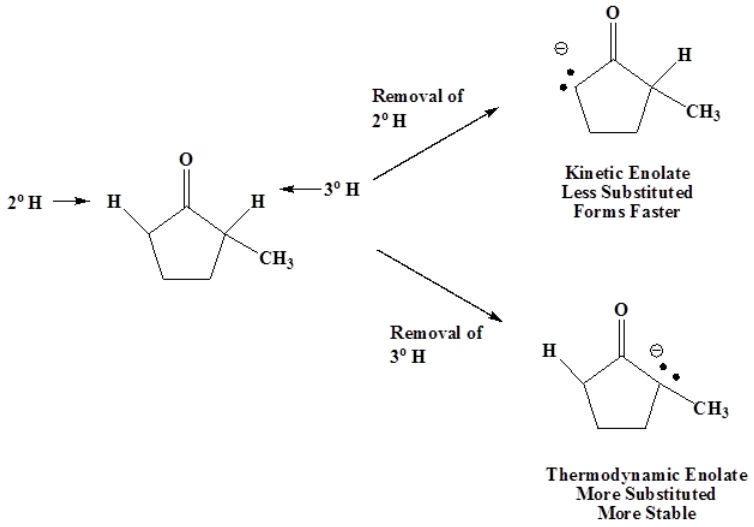
Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)

21.5: Enolates of Unsymmetrical Carbonyl Compounds

Enolate of Unsymmetrical Carbonyl Compounds

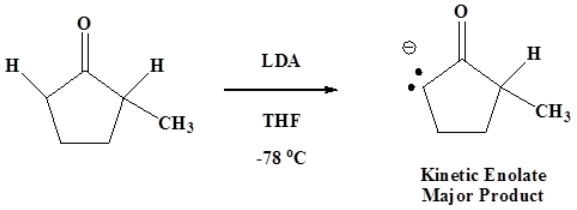
Now let's consider what happens when an unsymmetrical carbonyl is treated with a base. In the case displayed below there are two possible enolates which can form. The removal of the 2o hydrogen forms the kinetic enolate and is formed faster because it is less substituted and thereby less sterically hindered. The removal of the 3o hydrogen forms the thermodynamic enolate which is more stable because it is more substituted.



Kinetic Enolates

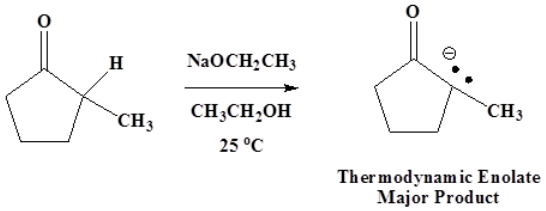
Kinetic enolates are formed when a strong bulky base like LDA is used. The bulky base finds the 2o hydrogen less sterically hindered and preferable removes it.

Low temperature are typically used when forming the kinetic enolate to prevent equilibration to the more stable thermodynamic enolate. Typically a temperature of -78 oC is used.



Thermodynamic Enolates

The thermodynamic enolate is favored by conditions which allow for equilibration. The thermodynamic enolate is usually formed by using a strong base at room temperature. At equilibrium the lower energy of the thermodynamic enolate is preferred, so that the more stable, more stubstituted enolate is formed.



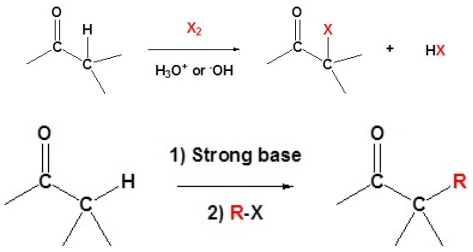
Contributors

- Prof. Steven Farmer (Sonoma State University)

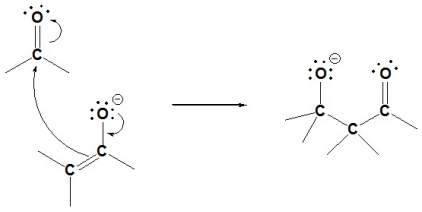
21.6: Racemization at the α Carbon

21.7: A Preview of Reactions at the α Carbon

Enolates can react with electrophiles to produce substitution products



Enolates can attack the eletrophilic carboyl carbon



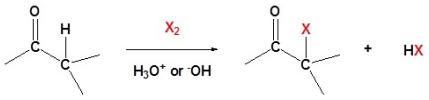
Contributors

- Prof. Steven Farmer (Sonoma State University)

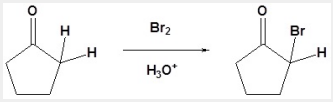
21.8: Halogenation at the α Carbon

A carbonyl containing compound with α hydrogens can undergo a substitution reaction with halogens. This reaction comes about because of the tendency of carbonyl compounds to form enolates in basic condition and enols in acidic condition. In these cases even weak bases, such as the hydroxide anion, is sufficient enough to cause the reaction to occur because it is not necessary for a complete conversion to the enolate. For this reaction Cl_2, Br_2 or I_2 can be used as the halogens.

General reaction



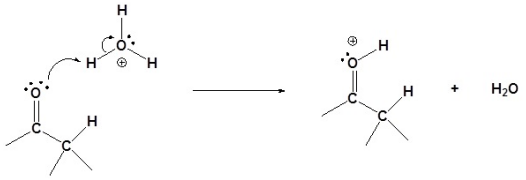
Example



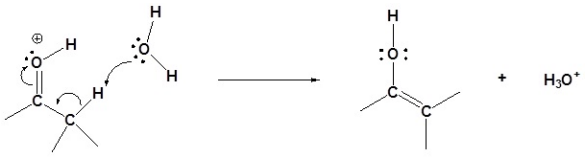
Acid Catalyzed Mechanism

Under acidic conditions the reaction occurs thought the formation of an enol which then reacts with the halogen.

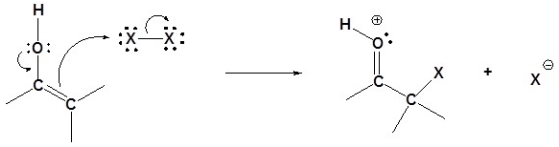
1) Protonation of the carbonyl



2) Enol formation



3) S_N2 attack

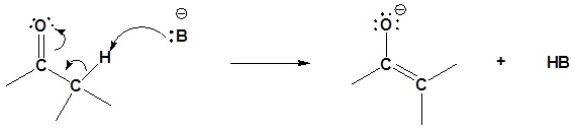


4) Deprotonation

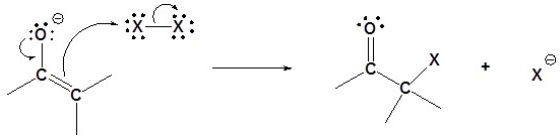
Base Catalyzed Mechanism

Under basic conditions the enolate forms and then reacts with the halogen. Note! This is base promoted and not base catalyzed because an entire equivalent of base is required.

1) Enolate formation

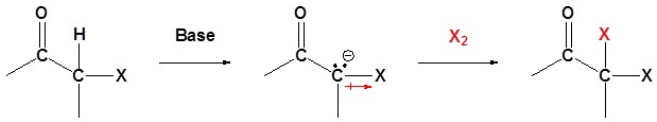


2) S_N2 attack



Overreaction during base promoted α halogenation

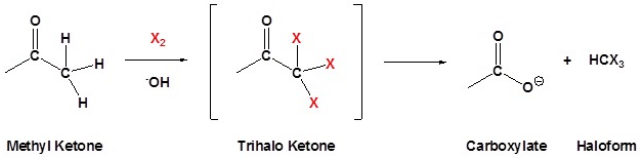
The fact that an electronegative halogen is placed on an α carbon means that the product of a base promoted α halogenation is actually more reactive than the starting material. The electron withdrawing effect of the halogen makes the α carbon even more acidic and therefor promotes further reaction. Because of this multiple halogenations can occur. This effect is exploited in the haloform reaction discussed later. If a monohalo product is required then acidic conditions are usually used.



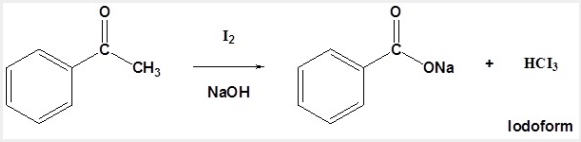
The Haloform Reaction

Methyl ketones typically undergo halogenation three times to give a trihalo ketone due to the increased reactivity of the halogenated product as discussed above. This trihalomethyl group is an effective leaving group due to the three electron withdrawing halogens and can be cleaved by a hydroxide anion to effect the haloform reaction. The product of this reaction is a carboxylate and a haloform molecule ($CHCl_3$, $CHBr_3$, CHI_3). Overall the haloform reaction represents an effective method for the conversion of methyl ketones to carboxylic acids. Typically, this reaction is performed using iodine because the subsequent iodoform (CHI_3) is a bright yellow solid which is easily filtered off.

General reaction

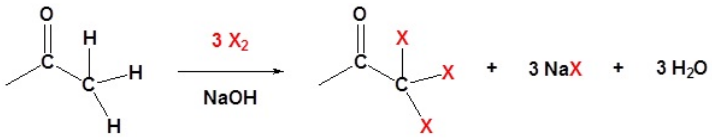


Example: The Haloform Reaction

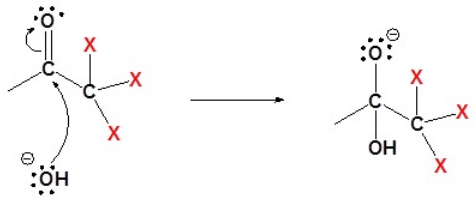


Mechanism

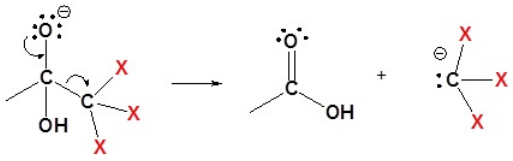
1) Formation of the trihalo species



2) Nulceophilic attack on the carbonyl carbon



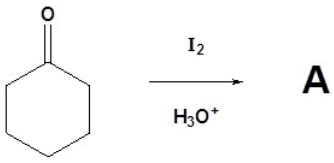
3) Removal of the leaving group



4) Deprotonation

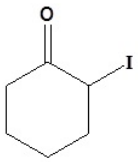
Problems

1) Please draw the products of the following reactions



Answers

1)



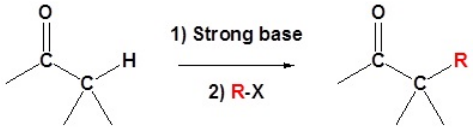
A

Contributors

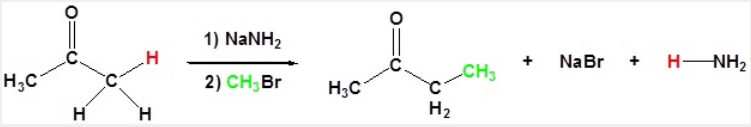
- Prof. Steven Farmer (Sonoma State University)

21.9: Direct Enolate Alkylation

Enolates can act as a nucleophile in S_N2 type reactions. Overall an α hydrogen is replaced with an alkyl group. This reaction is one of the more important for enolates because a carbon-carbon bond is formed. These alkylations are affected by the same limitations as S_N2 reactions previously discussed. A good leaving group, Chloride, Bromide, Iodide, Tosylate, should be used. Also, secondary and tertiary leaving groups should not be used because of poor reactivity and possible competition with elimination reactions. Lastly, it is important to use a strong base, such as LDA or sodium amide, for this reaction. Using a weaker base such as hydroxide or an alkoxide leaves the possibility of multiple alkylation's occurring.

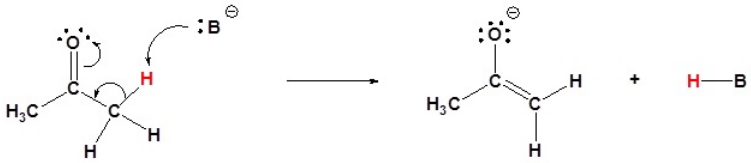


Example 1: Alpha Alkylation

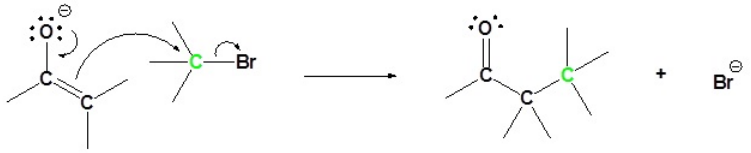


Mechanism

1) Enolate formation



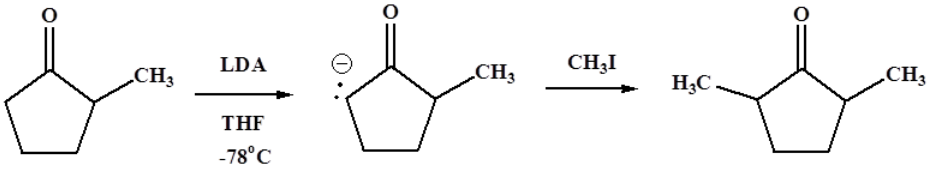
2) S_n2 attack



Alkylation of Unsymmetrical Ketones

Unsymmetrical ketones can be regioselctively alkylated to form one major product depending on the reagents.

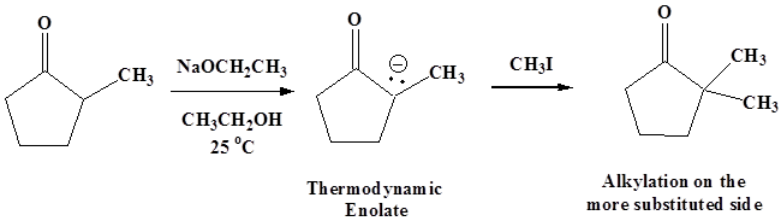
Treatment with LDA in THF at -78°C tends to form the less substituted kinetic enolate.



Kinetic Enolate

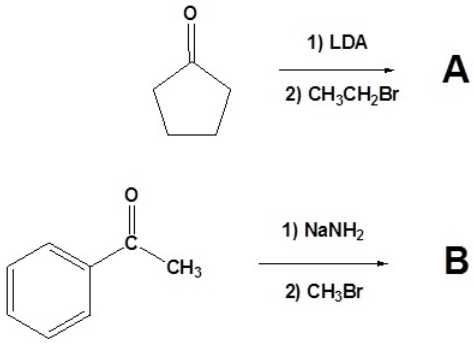
Alkylation on the less substituted side

Using sodium ethoxide in ethanol at room temperature forms the more substituted thermodynamic enolate.



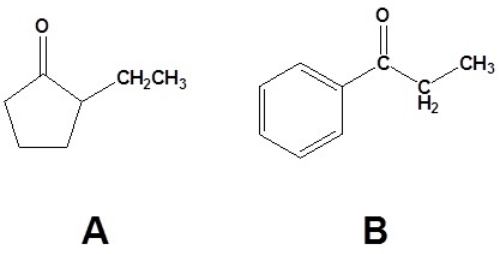
Problems

1) Please write the structure of the product for the following reactions.



Answers

1)

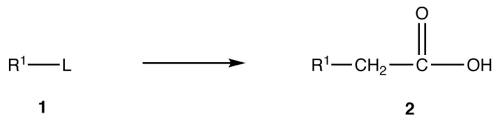


Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)

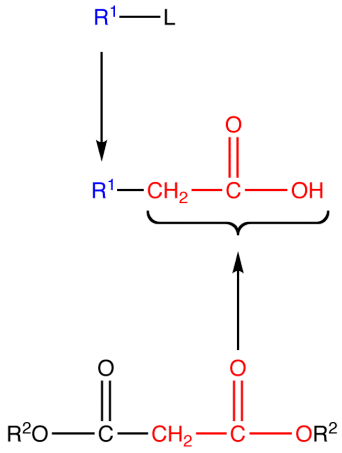
21.10: Malonic Ester Synthesis

Malonic ester is a reagent specifically used in a reaction which converts alkyl halides to carboxylic acids called the Malonic Ester Synthesis. Malonic ester synthesis is a synthetic procedure used to convert a compound that has the general structural formula 1 into a carboxylic acid that has the general structural formula 2.



- R^1 = alkyl group
- L = leaving group

The group —CH_2CO_2H in 2 is contributed by a malonic ester, hence the term malonic ester synthesis.



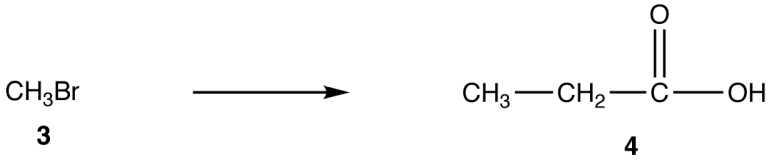
- R^2 = alkyl, aryl

Mechanism

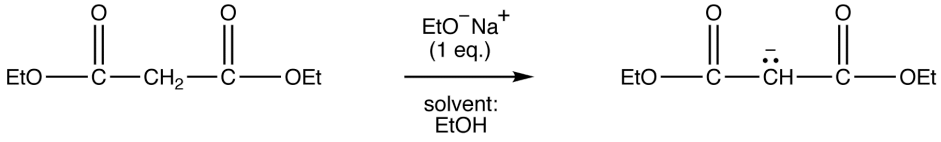
Malonic ester synthesis consists of four consecutive reactions that can be carried out in the same pot.

- reaction 1: acid-base reaction
- reaction 2: nucleophilic substitution
- reaction 3: ester hydrolysis (using saponification)
- reaction 4: decarboxylation

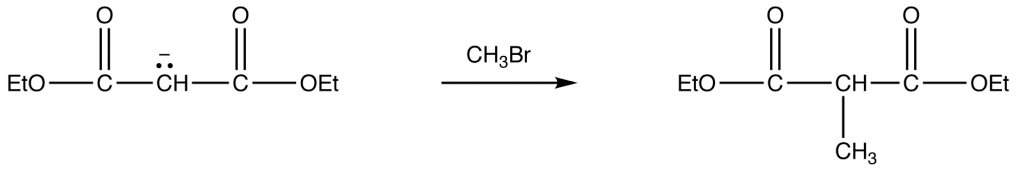
eg:



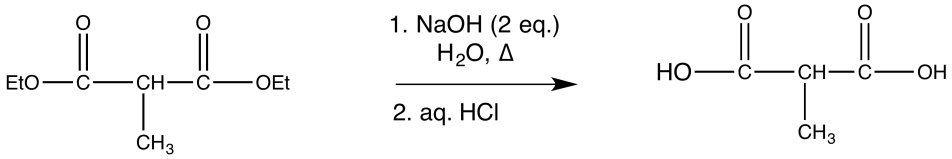
reaction 1:



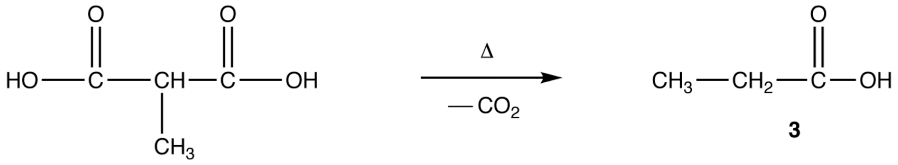
reaction 2:



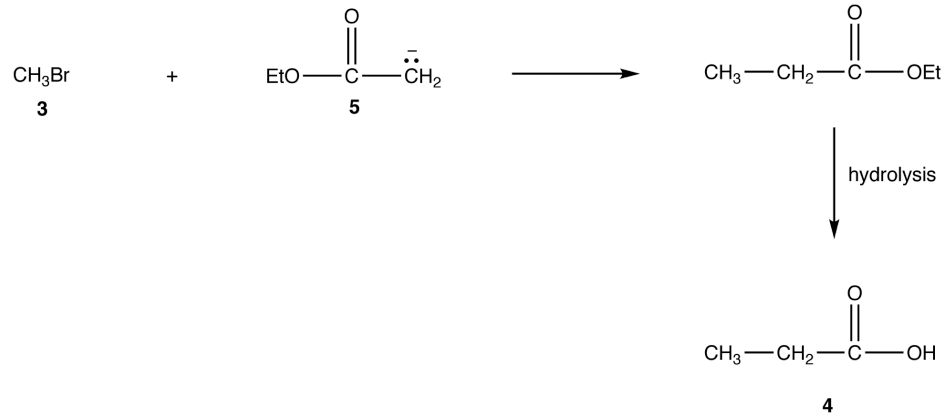
reaction 3:



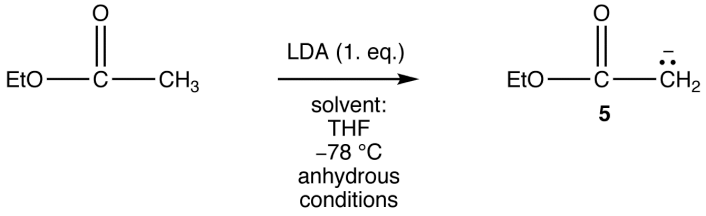
reaction 4:



A more direct method to convert **3** into **4** is the reaction of **3** with the enolate ion **(5)** of ethyl acetate followed by hydrolysis of the resultant ester.

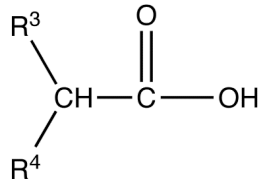


However, the generation of **5** from ethyl acetate quantitatively in high yield is not an easy task because the reaction requires a very strong base, such as LDA, and must be carried out at very low temperature under strictly anhydrous conditions.



Malonic ester synthesis provides a more convenient alternative to convert **3** to **4**.

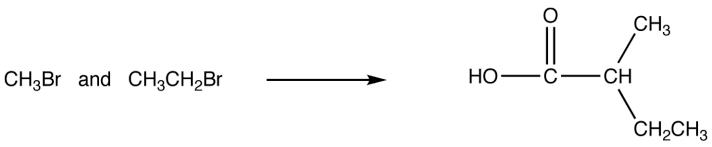
Malonic ester synthesis can be adapted to synthesize compounds that have the general structural formula **6**.



6

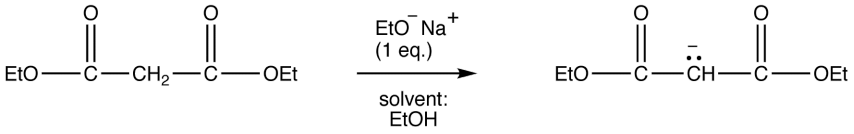
R^3, R^4 = identical or different alkyl groups

eg:

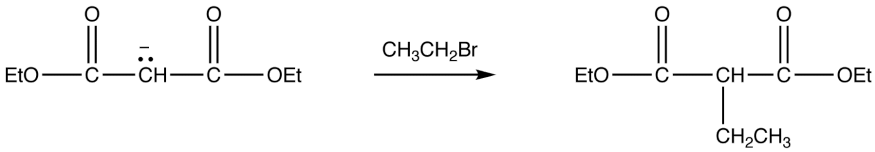


7

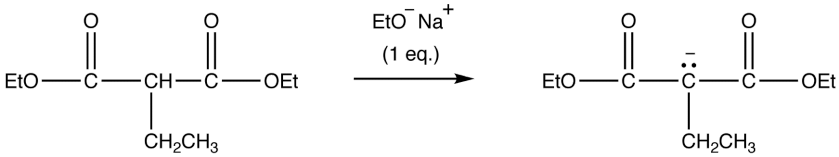
reaction 1:



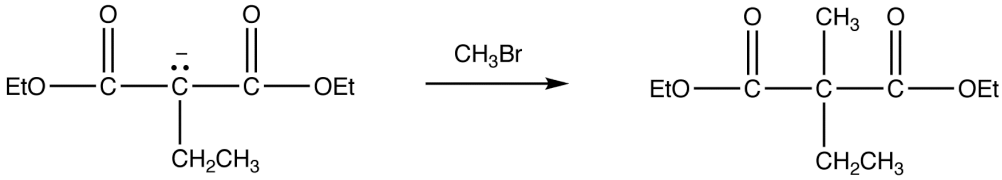
reaction 2:



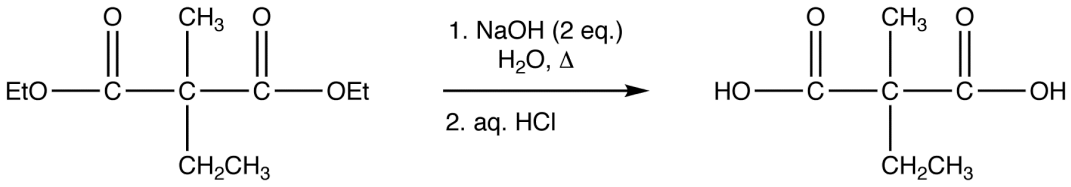
reaction 1 (repeat):



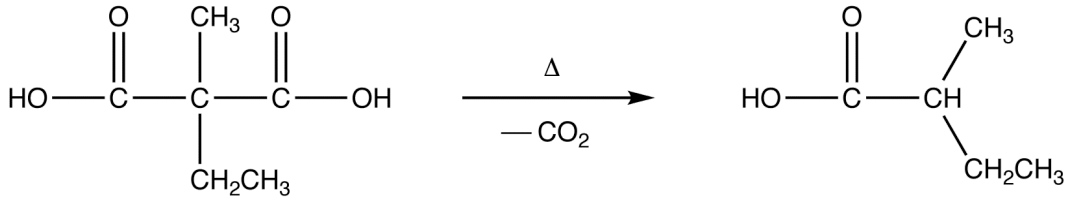
reaction 2 (repeat):



reaction 3:

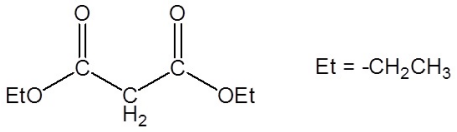


reaction 4:



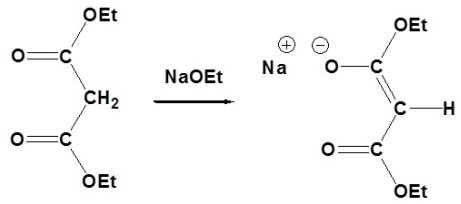
7

Malonic Ester Synthesis



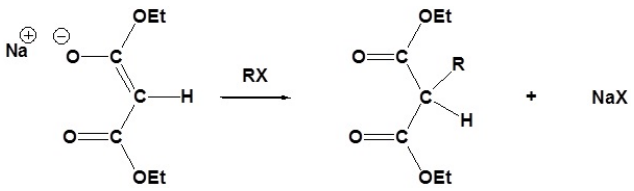
Malonic Ester

Due to the fact that Malonic ester's α hydrogens are adjacent to two carbonyls, they can be deprotonated by sodium ethoxide (NaOEt) to form Sodio Malonic Ester.

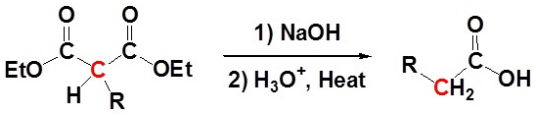


Malonic Ester **Sodio Malonic Ester**

Because Sodio Malonic Ester is an enolate, it can then be alkylated with alkyl halides.

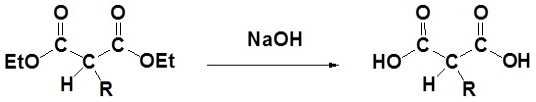


After alkylation the product can be converted to a dicarboxylic acid through saponification and subsequently one of the carboxylic acids can be removed through a decarboxylation step.

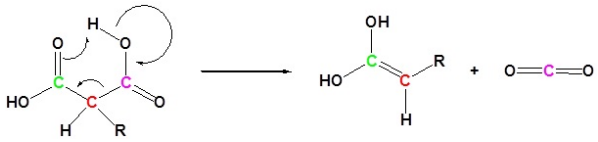


Mechanism

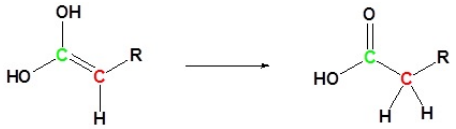
1) Saponification



2) Decarboxylation



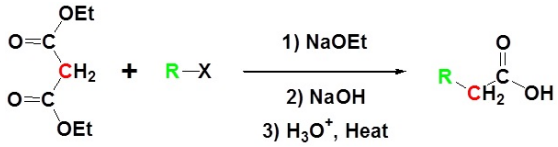
3) Tautomerization



All of the steps together form the Malonic ester synthesis.

$$RX \rightarrow RCH_2CO_2H \tag{21.10.1}$$

Example



- Bernard E. Hoogenboom , Phillip J. Ihrig , Arne N. Langsjoen , Carol J. Linn and Stephen D. Mulder, The malonic ester synthesis in the undergraduate laboratory, *J. Chem. Educ.*, 1991, 68 (8), p 689

Contributors

- Prof. Steven Farmer (Sonoma State University)
- ◦ Gamini Gunawardena from the OChemPal site (Utah Valley University)

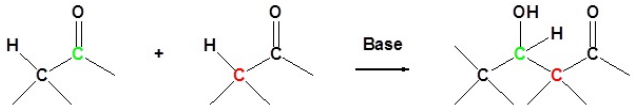
CHAPTER OVERVIEW

22: Carbonyl Condensation Reactions

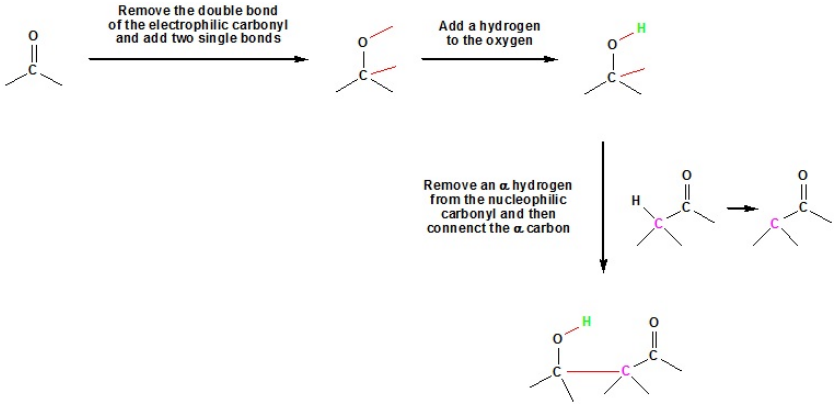
22.1: The Aldol Reaction

A useful carbon-carbon bond-forming reaction known as the **Aldol Reaction** is yet another example of electrophilic substitution at the alpha carbon in enolate anions. The fundamental transformation in this reaction is a dimerization of an aldehyde (or ketone) to a beta-hydroxy aldehyde (or ketone) by alpha C–H addition of one reactant molecule to the carbonyl group of a second reactant molecule. Due to the carbanion like nature of enolates they can add to carbonyls in a similar manner as Grignard reagents. For this reaction to occur at least one of the reactants must have α hydrogens.

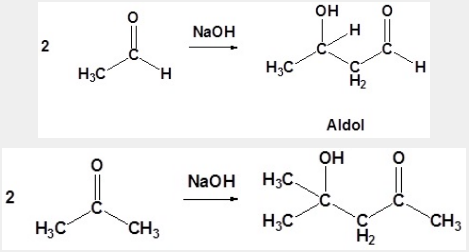
General Aldol reaction



Going from reactants to products simply

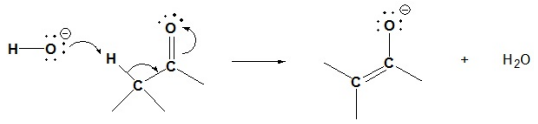


Example 1: Aldol Reactions

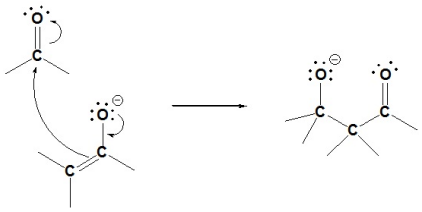


Aldol Reaction Mechanism

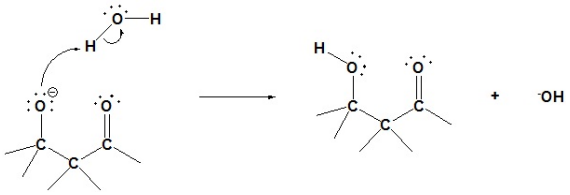
Step 1: Enolate formation



Step 2: Nucleophilic attack by the enolate



Step 3: Protonation



Aldol Condensation: the dehydration of Aldol products to synthesize α, β unsaturated carbonyl (enones)

The products of aldol reactions often undergo a subsequent elimination of water, made up of an alpha-hydrogen and the beta-hydroxyl group. The product of this *β*-**elimination** reaction is an α,β-unsaturated aldehyde or ketone. Base-catalyzed elimination occurs with heating. The additional stability provided by the conjugated carbonyl system of the product makes some aldol reactions thermodynamically and mixtures of stereoisomers (E & Z) are obtained from some reactions. Reactions in which a larger molecule is formed from smaller components, with the elimination of a very small by-product such as water, are termed **Condensations**. Hence, the following examples are properly referred to as **aldol condensations**. Overall the general reaction involves a dehydration of an aldol product to form an alkene:

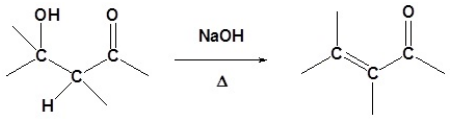


***Figure**: General reaction for an aldol condensation*

Going from reactants to products simply

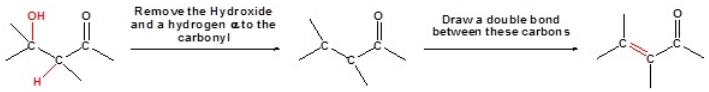
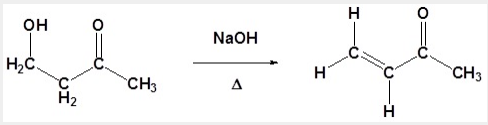


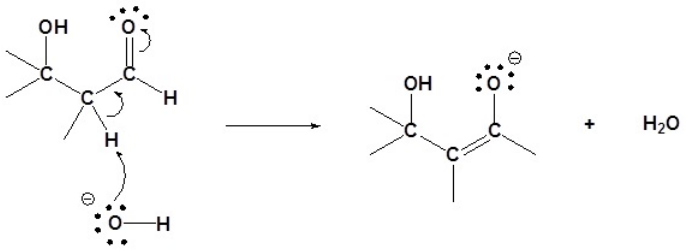
***Figure**: The aldol condensatio* example

Example 2: Aldol Condensation

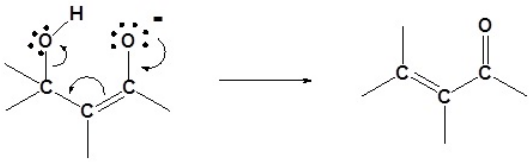


Aldol Condensation Mechanism

1) Form enolate

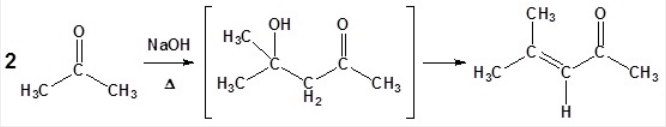


2) Form enone



When performing both reactions together always consider the aldol product first then convert to the enone. Note! The double bond always forms in conjugation with the carbonyl.

Example



Contributors

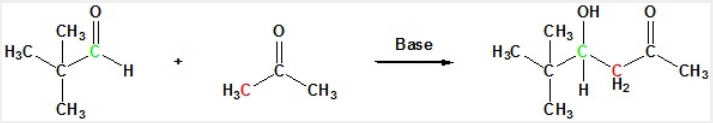
- Prof. Steven Farmer (Sonoma State University)

22.2: Crossed Aldol Reactions

Mixed Aldol Reaction and Condensations

The previous examples of aldol reactions and condensations used a common reactant as both the enolic donor and the electrophilic acceptor. The product in such cases is always a dimer of the reactant carbonyl compound. Aldol condensations between different carbonyl reactants are called **crossed** or **mixed** reactions, and under certain conditions such crossed aldol condensations can be effective.

Example 3: Mixed Aldol Reaction



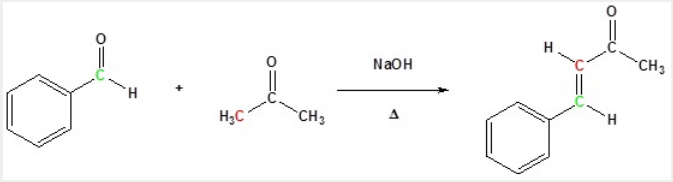
The success of these mixed aldol reactions is due to two factors. First, aldehydes are more reactive acceptor electrophiles than ketones, and formaldehyde is more reactive than other aldehydes. Second, aldehydes lacking alpha-hydrogens can only function as acceptor reactants, and this reduces the number of possible products by half. Mixed aldols in which both reactants can serve as donors and acceptors generally give complex mixtures of both dimeric (homo) aldols and crossed aldols. Because of this most mixed aldol reactions are usually not performed unless one reactant has no alpha hydrogens.

The following abbreviated formulas illustrate the possible products in such a case, red letters representing the acceptor component and blue the donor. If all the reactions occurred at the same rate, equal quantities of the four products would be obtained. Separation and purification of the components of such a mixture would be difficult.

$$\mathbf{A}\mathbf{A}CH_2CHO + \mathbf{B}CH_2CHO + NaOH \rightarrow A\text{–}A + B\text{–}B + A\text{–}B + B\text{–}A$$

The aldol condensation of ketones with aryl aldehydes to form α,β-unsaturated derivatives is called the **Claisen-Schmidt** reaction.

Example 4: Claisen-Schmidt Reaction

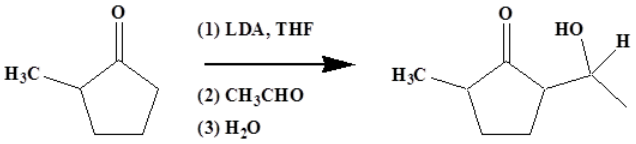


Contributors

- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

22.3: Directed Aldol Reactions

Directed aldol reactions are a variation of the crossed aldol reaction. The enolate is prepared with one carbonyl compound using LDA. This causes the other carbonyl compound to be the electrophile. Even though both components have alpha hydrogens only one acts as an enolate because it is formed with LDA. Then an unsymmetrical ketone is use the LDA will selectively form the less substituted enolate.



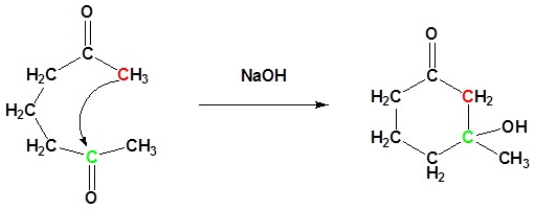
Contributors

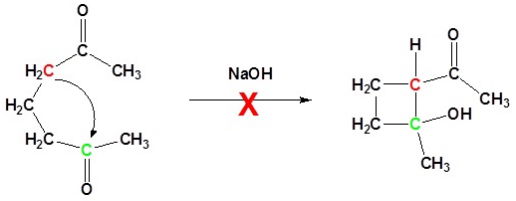
- Prof. Steven Farmer (Sonoma State University)

22.4: Intramolecular Aldol Reactions

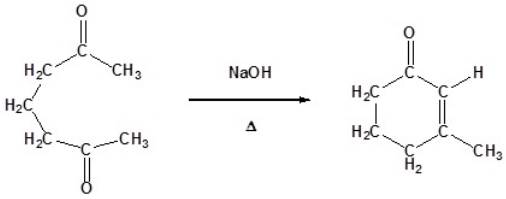
Intramolecular aldol reaction

Molecules which contain two carbonyl functionalities have the possibility of forming a ring through an intramolecular aldol reaction. In most cases two sets of α hydrogens need to be considered. As with most ring forming reaction five and six membered rings are preferred.





As with other aldol reaction the addition of heat causes an aldol condensation to occur.



Contributors

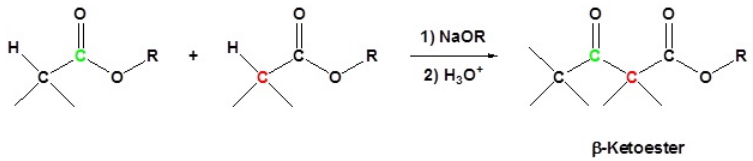
- Prof. Steven Farmer (Sonoma State University)

22.5: The Claisen Reaction

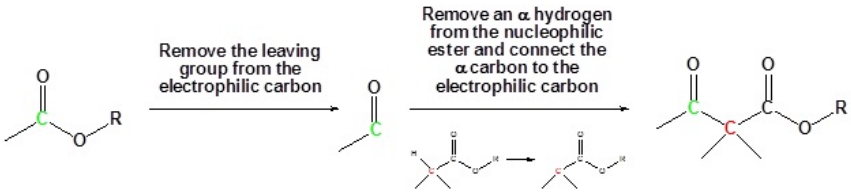
Because esters can contain α hydrogens they can undergo a condensation reaction similar to the aldol reaction called a **Claisen Condensation**. In a fashion similar to the aldol, one ester acts as a nucleophile while a second ester acts as the electrophile. During the reaction a new carbon-carbon bond is formed. The product is a β-keto ester. A major difference with the aldol reaction is the fact that hydroxide cannot be used as a base because it could possibly react with the ester. Instead, an alkoxide version of the alcohol used to synthesize the ester is used to prevent transesterification side products.

Claisen Condensation

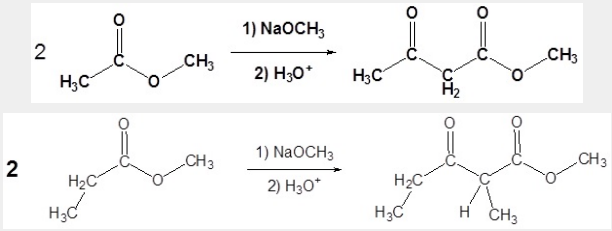
Basic reaction



Going from reactants to products simply



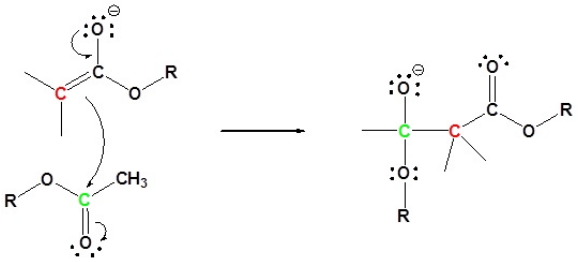
Example 1: Claisen Condensation



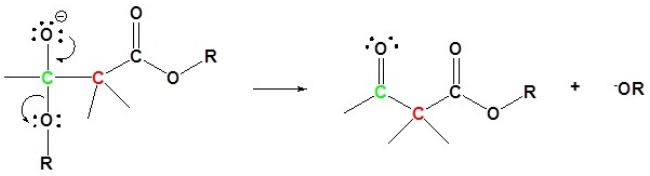
Claisen Condensation Mechanism

1) Enolate formation

2) Nucleophilic attack



3) Removal of leaving group



Contributor

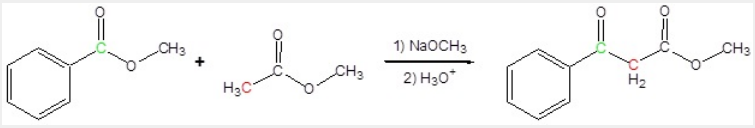
- Prof. Steven Farmer (Sonoma State University)

22.6: The Crossed Claisen and Related Reactions

Crossed Claisen Condensation

Claisen condensations between different ester reactants are called **Crossed Claisen** reactions. Crossed Claisen reactions in which both reactants can serve as donors and acceptors generally give complex mixtures. Because of this most Crossed Claisen reactions are usually not performed unless one reactant has no alpha hydrogens.

Example 3: Crossed Claisen Condensation



Contributors

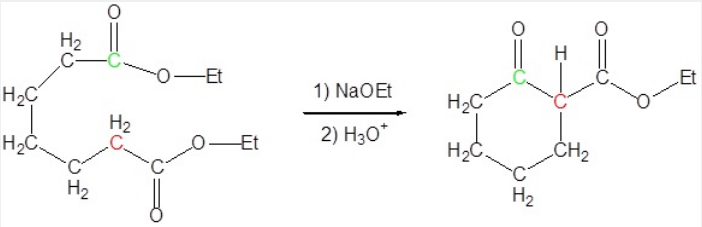
- Prof. Steven Farmer (Sonoma State University)

22.7: The Dieckmann Reaction

Dieckmann Condensation

A diester can undergo an intramolecular reaction called a Dieckmann condensation.

Example 2: Dieckman Condensation

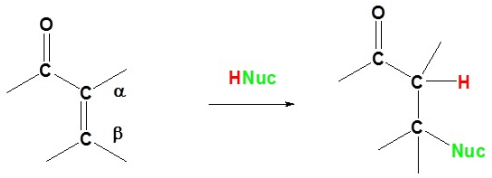


Contributors

- Prof. Steven Farmer (Sonoma State University)

22.8: The Michael Reaction

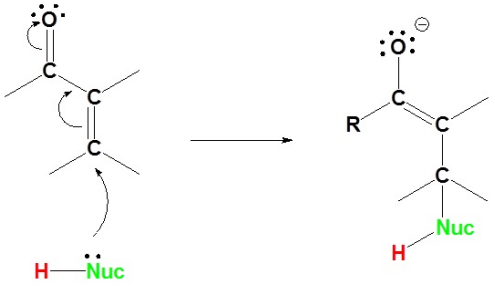
Basic reaction of 1,4 addition



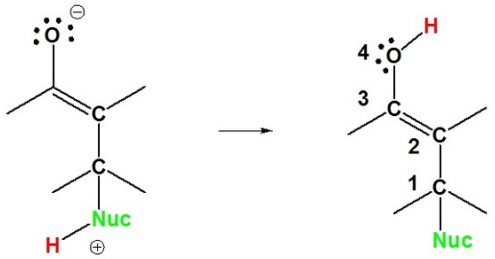
In 1,4 addition the Nucleophile is added to the carbon β to the carbonyl while the hydrogen is added to the carbon α to the carbonyl.

Mechanism for 1,4 addition

1) Nucleophilic attack on the carbon β to the carbonyl

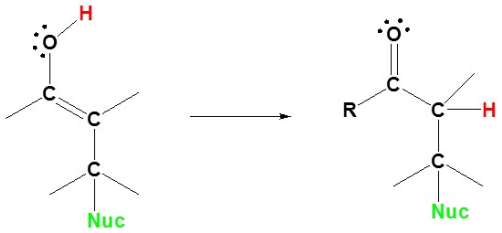


2) Proton Transfer



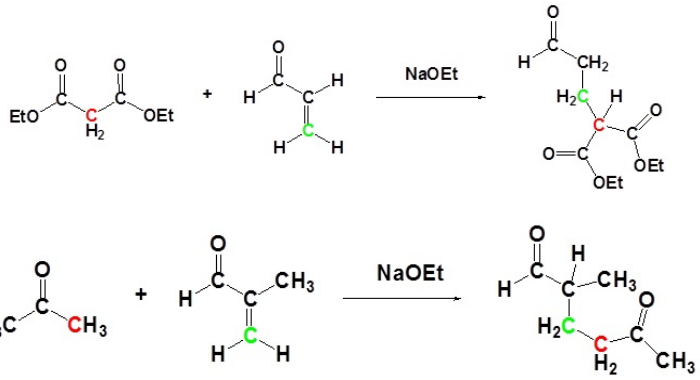
Here we can see why this addition is called 1,4. The nucleophile bonds to the carbon in the one position and the hydrogen adds to the oxygen in the four position.

3) Tautomerization



Enolates undergo 1,4 addition to α, β-unsaturated carbonyl compounds is a process called a Michael addition. The reaction is named after American chemist Arthur Michael (1853-1942).

Examples of Michael Additions



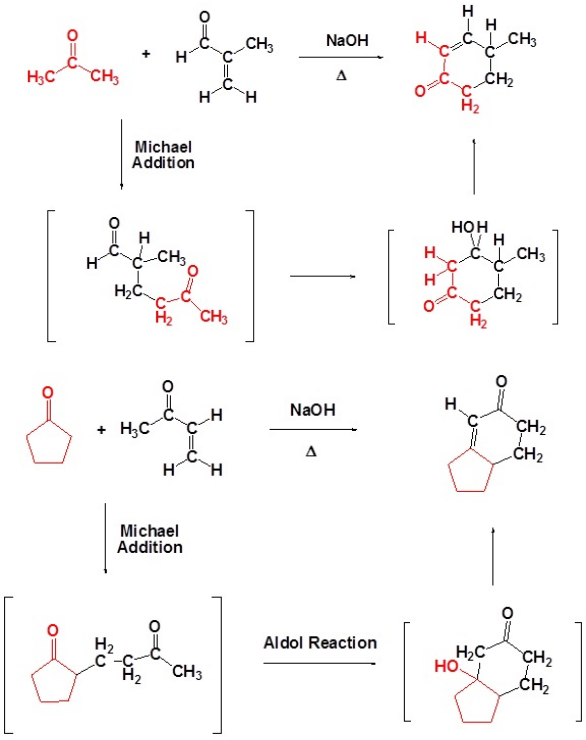
Contributors

- Prof. Steven Farmer (Sonoma State University)

22.9: The Robinson Annulation

Many times the product of a Michael addition produces a dicarbonyl which can then undergo an intramolecular aldol reaction. These two processes together in one reaction creates two new carbon-carbon bonds and also creates a ring. Ring-forming reactions are called annulations after the Latin work for ring annulus. The reaction is named after English chemist Sir Robert Robinson (1886-1975) who developed it. He received the Nobel prize in chemistry in 1947. Remember that during annulations five and six membered rings are preferred.

Examples of Robinson Annulations



Contributors

- Prof. Steven Farmer (Sonoma State University)

CHAPTER OVERVIEW

23: Amines

Topic hierarchy

23.1: Relative Basicity of Amines and Other Compounds

Basicity of nitrogen groups

In this section we consider the relative basicity of several nitrogen-containing functional groups: amines, amides, anilines, imines, and nitriles.

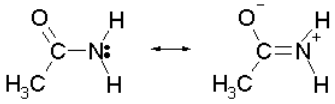
When evaluating the basicity of a nitrogen-containing organic functional group, the central question we need to ask ourselves is: how reactive (and thus how basic) is the lone pair on the nitrogen? In other words, how much does that lone pair want to break away from the nitrogen nucleus and form a new bond with a hydrogen?

Comparing the basicity of alkyl amines to ammonia

Because alkyl groups donate electrons to the more electronegative nitrogen. The inductive effect makes the electron density on the alkylamine's nitrogen greater than the nitrogen of ammonium. Correspondingly, primary, secondary, and tertiary alkyl amines are more basic than ammonia.

Comparing the basicity of alkylamines to amides

With an alkyl amine the lone pair electron is localized on the nitrogen. However, the lone pair electron on an amide are delocalized between the nitrogen and the oxygen through resonance. This makes amides much less basic compared to alkylamines.



In fact,when and amide is reacted with an acid, the protonation occurs at the carbonyl oxygen and not the nitrogen. This is becase the cation resulting from oxygen protonation is resonance stabilised. The cation resulting for the protonation of nitrogen is not resonance stabilized.

Basicity of aniline

Aniline is substantially less basic than methylamine, as is evident by looking at the pK_a values for their respective ammonium conjugate acids (remember that the lower the pKa of the conjugate acid, the weaker the base).

This difference is basicity can be explained by the observation that, in aniline, the basic lone pair on the nitrogen is to some extent tied up in – and stabilized by – the aromatic p system.

This effect is accentuated by the addition of an electron-withdrawing group such as a carbonyl, and reversed to some extent by the addition of an electron-donating group such as methoxide.

In the case of 4-methoxy aniline (the molecule on the left side of the figure above), the lone pair on the methoxy group donates electron density to the aromatic system, and a resonance contributor can be drawn in which a negative charge is placed on the carbon adjacent to the nitrogen, which makes the lone pair of the nitrogen more reactive. In effect, the methoxy group is 'pushing' electron density towards the nitrogen. Conversely, the aldehyde group on the right-side molecule is 'pulling' electron density away from the nitrogen, decreasing its basicity.

At this point, you should draw resonance structures to convince yourself that these resonance effects are possible when the substituent in question (methoxy or carbonyl) is located at the *ortho* or *para* position, but not at the *meta* position.an imine functional group is characterized by an sp^2-hybridized nitrogen double-bonded to a carbon. Imines are somewhat basic, with pK_a values for the protonated forms ranging around 7. Notice that this is significantly less basic than amine groups (eg. $pK_a = 10.6$ for methylammonium), in which the nitrogen is sp^3-hybridized. This phenomenon can be explained using orbital theory and the inductive effect: the sp^2 orbitals of an imine nitrogen are one part *s* and two parts *p*, meaning that they have about 67% *s* character. The sp^3 orbitals of an amine nitrogen, conversely, are only 25% *s* character (one part *s*, three parts *p*). Because the *s* atomic orbital holds electrons in a spherical shape, closer to the nucleus than a *p* orbital, sp^2hybridization implies greater electronegative than sp^3 hybridization. Finally, recall the inductive effect from section 7.3C: more electronegative atoms absorb electron density more easily, and thus are more acidic. Moral of the story: protonated imine nitrogens are more acidic than protonated amines, thus imines are less basic than amines.

Basicity of heterocyclic amines

When a nitrogen atom is incorporated directly into an aromatic ring, its basicity depends on the bonding context. In a pyridine ring, for example, the nitrogen lone pair occupies an sp^2-hybrid orbital, and is *not* part of the aromatic sextet - it is essentially an imine nitrogen. Its electron pair is available for forming a bond to a proton, and thus the pyridine nitrogen atom is somewhat basic.

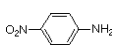
In a pyrrole ring, in contrast, the nitrogen lone pair *is* part of the aromatic sextet. This means that these electrons are very stable right where they are (in the aromatic system), and are much less available for bonding to a proton (and if they *do* pick up a proton, the aromic system is destroyed). For these reasons, pyrrole nitrogens are not strongly basic.

The aniline, pyridine, and pyrrole examples are good models for predicting the reactivity of nitrogen atoms in more complex ring systems (a huge diversity of which are found in nature). The tryptophan side chain, for example, contains a non-basic 'pyrrole-like' nitrogen, while adenine (a DNA/RNA base) contains all three types.

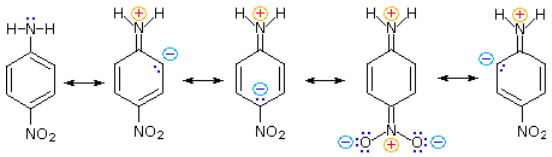
The lone pair electrons on the nitrogen of a **nitrile** are contained in a *sp* hybrid orbital. The 50% *s* character of an *sp* hybrid orbital means that the electrons are close to the nucleus and therefore not significantly basic.

A review of basic acid-base concepts should be helpful to the following discussion. Like ammonia, most amines are Brønsted and Lewis bases, but their base strength can be changed enormously by substituents. It is common to compare basicity's quantitatively by using the pK_a's of their conjugate acids rather than their pK_b's. Since $pK_a + pK_b = 14$, **the higher the pK_a the stronger the base**, in contrast to the usual inverse relationship of pK_a with acidity. Most simple alkyl amines have pK_a's in the range 9.5 to 11.0, and their water solutions are basic (have a pH of 11 to 12, depending on concentration). The first four compounds in the following table, including ammonia, fall into that category.

The last five compounds (colored cells) are significantly weaker bases as a consequence of three factors. The first of these is the hybridization of the nitrogen. In pyridine the nitrogen is sp^2 hybridized, and in nitriles (last entry) an sp hybrid nitrogen is part of the triple bond. In each of these compounds (shaded red) the non-bonding electron pair is localized on the nitrogen atom, but increasing s-character brings it closer to the nitrogen nucleus, reducing its tendency to bond to a proton.

Compound				NH_3						$CH_3C{\equiv}N$
pK_a	11.0	10.7	10.7	9.3	5.2	4.6	1.0	0.0	-1.0	-10.0

Secondly, aniline and p-nitroaniline (first two green shaded structures) are weaker bases due to delocalization of the nitrogen non-bonding electron pair into the aromatic ring (and the nitro substituent). This is the same delocalization that results in activation of a benzene ring toward electrophilic substitution. The following resonance equations, which are similar to those used to explain the enhanced acidity of ortho and para-nitrophenols illustrate electron pair delocalization in p-nitroaniline. Indeed, aniline is a weaker base than cyclohexyl amine by roughly a million fold, the same factor by which phenol is a stronger acid than cyclohexanol. This electron pair delocalization is accompanied by a degree of rehybridization of the amino nitrogen atom, but the electron pair delocalization is probably the major factor in the reduced basicity of these compounds. A similar electron pair delocalization is responsible for the very low basicity (and nucleophilic reactivity) of amide nitrogen atoms (last green shaded structure). This feature was instrumental in moderating the influence of amine substituents on aromatic ring substitution, and will be discussed further in the section devoted to carboxylic acid derivatives.



Reduced Basicity of *para*-Nitroaniline due to Electron Pair Delocalization

Conjugated amine groups influence the basicity of an existing amine. Although 4-dimethylaminopyridine (DMAP) might appear to be a base similar in strength to pyridine or N,N-dimethylaniline, it is actually more than ten thousand times stronger, thanks to charge delocalization in its conjugate acid. The structure in the gray box shows the locations over which positive charge (colored red) is delocalized in the conjugate acid. This compound is often used as a catalyst for acyl transfer reactions.
Finally, the very low basicity of pyrrole (shaded blue) reflects the exceptional delocalization of the nitrogen electron pair associated

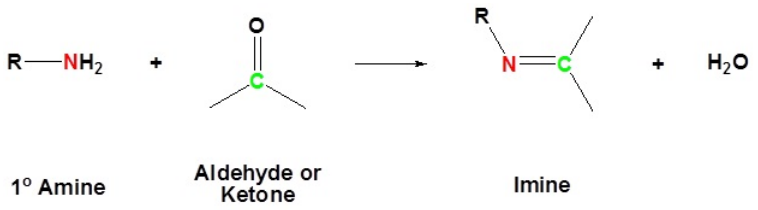
with its incorporation in an aromatic ring. Indole (pK_a = -2) and imidazole (pK_a = 7.0), see above, also have similar heterocyclic aromatic rings. Imidazole is over a million times more basic than pyrrole because the sp^2 nitrogen that is part of one double bond is structurally similar to pyridine, and has a comparable basicity.

Contributors

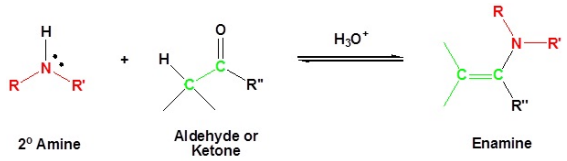
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

23.2: Amines as Nucleophiles

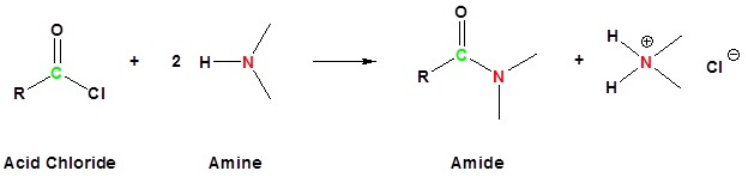
The reaction of aldehydes and ketones with ammonia or 1º-amines forms imine derivatives, also known as Schiff bases (compounds having a C=N function). Water is eliminated in the reaction, which is acid-catalyzed and reversible in the same sense as acetal formation. The pH for reactions which form imine compounds must be carefully controlled. The rate at which these imine compounds are formed is generally greatest near a pH of 5, and drops at higher and lower pH's. At high pH there will not be enough acid to protonate the OH in the intermediate to allow for removal as H_2O. At low pH most of the amine reactant will be tied up as its ammonium conjugate acid and will become non-nucleophilic.



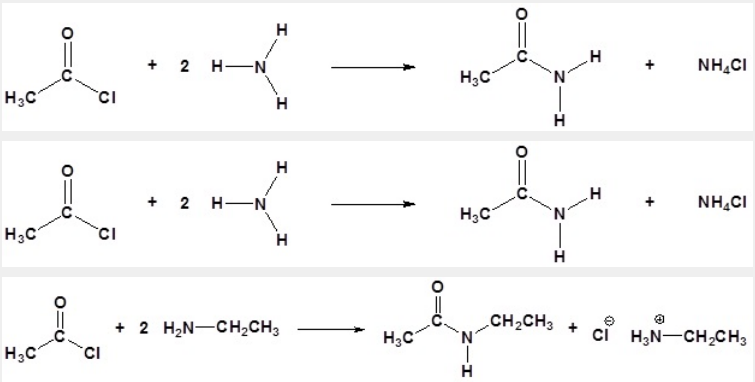
Most aldehydes and ketones react with 2º-amines to give products known as **enamines**. It should be noted that, like acetal formation, these are acid-catalyzed reversible reactions in which water is lost. Consequently, enamines are easily converted back to their carbonyl precursors by acid-catalyzed hydrolysis.



Acid chlorides react with ammonia, 1º amines and 2º amines to form amides.



Examples:



Contributors

- Prof. Steven Farmer (Sonoma State University)

23.3: Hofmann Elimination

Amine functions seldom serve as leaving groups in nucleophilic substitution or base-catalyzed elimination reactions. Indeed, they are even less effective in this role than are hydroxyl and alkoxyl groups. In the case of alcohols and ethers, a useful technique for enhancing the reactivity of the oxygen function was to modify the leaving group ($OH^{(-)}$ or $OR^{(-)}$) to improve its stability as an anion (or equivalent). This stability is conveniently estimated from the strength of the corresponding conjugate acids.

As noted earlier, 1º and 2º-amines are much weaker acids than alcohols, so it is not surprising that it is difficult to force the nitrogen function to assume the role of a nucleophilic leaving group. For example, heating an amine with HBr or HI does not normally convert it to the corresponding alkyl halide, as in the case of alcohols and ethers. In this context we note that the acidity of the putative ammonium leaving group is at least ten powers of ten less than that of an analogous oxonium species. The loss of nitrogen from diazonium intermediates is a notable exception in this comparison, due to the extreme stability of this leaving group (the conjugate acid of N_2 would be an extraordinarily strong acid).

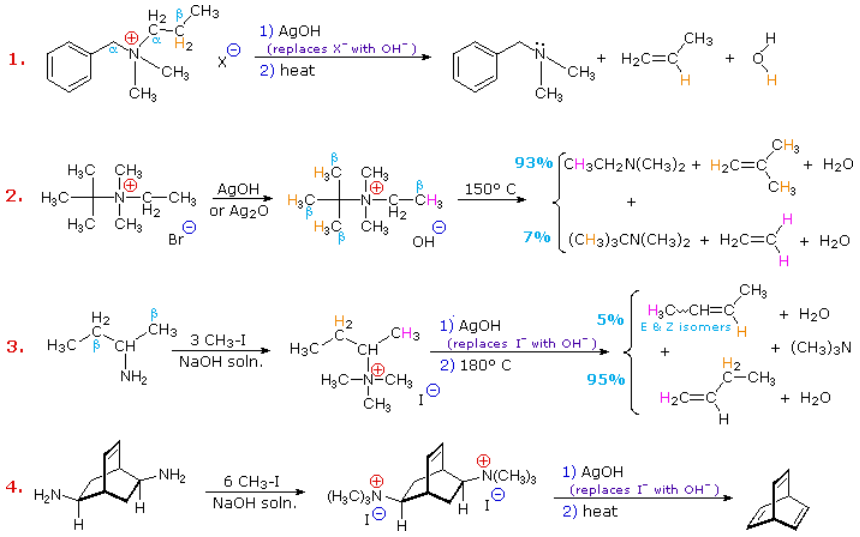
One group of amine derivatives that have proven useful in S_N2 and E2 reactions is that composed of the tetraalkyl (4º-) ammonium salts. Most applications involving this class of compounds are eliminations, but a few examples of S_N2 substitution have been reported.

$C_6H_5–N(CH_3)_3^{(+)}\ Br^{(-)} + R\text{-}S^{(-)}\ Na^{(+)}$	acetone & heat ⟶	$R\text{-}S\text{-}CH_3 + C_6H_5–N(CH_3)_2 + NaBr$

$(CH_3)_4N^{(+)}\ OH^{(-)}$	heat ⟶	$CH_3–OH + (CH_3)_3N$

Hofmann Elimination

Elimination reactions of 4º-ammonium salts are termed **Hofmann eliminations**. Since the counter anion in most 4º-ammonium salts is halide, this is often replaced by the more basic hydroxide ion through reaction with silver hydroxide (or silver oxide). The resulting hydroxide salt must then be heated (100 - 200 ºC) to effect the E2-like elimination of a 3º-amine. Example #1 below shows a typical Hofmann elimination. Obviously, for an elimination to occur one of the alkyl substituents on nitrogen must have one or more beta-hydrogens, as noted earlier in examining elimination reactions of alkyl halides.



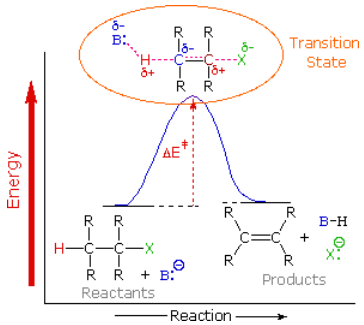
In example #2 above, two of the alkyl substituents on nitrogen have beta-hydrogens, all of which are on methyl groups (colored orange & magenta). The chief product from the elimination is the alkene having the more highly substituted double bond, reflecting not only the 3:1 numerical advantage of those beta-hydrogens, but also the greater stability of the double bond.

Example #3 illustrates two important features of the Hofmann elimination:

1. Simple amines are easily converted to the necessary 4º-ammonium salts by exhaustive alkylation, usually with methyl iodide (methyl has no beta-hydrogens and cannot compete in the elimination reaction). Exhaustive methylation is shown again in example #4.
2. When a given alkyl group has two different sets of beta-hydrogens available to the elimination process (colored orange & magenta here), the major product is often the alkene isomer having the less substituted double bond.

The tendency of Hofmann eliminations to give the less-substituted double bond isomer is commonly referred to as the **Hofmann Rule**, and contrasts strikingly with the Zaitsev Rule formulated for dehydrohalogenations and dehydrations. In cases where other activating groups, such as phenyl or carbonyl, are present, the Hofmann Rule may not apply. Thus, if 2-amino-1-phenylpropane is treated in the manner of example #3, the product consists largely of 1-phenylpropene (E & Z-isomers).

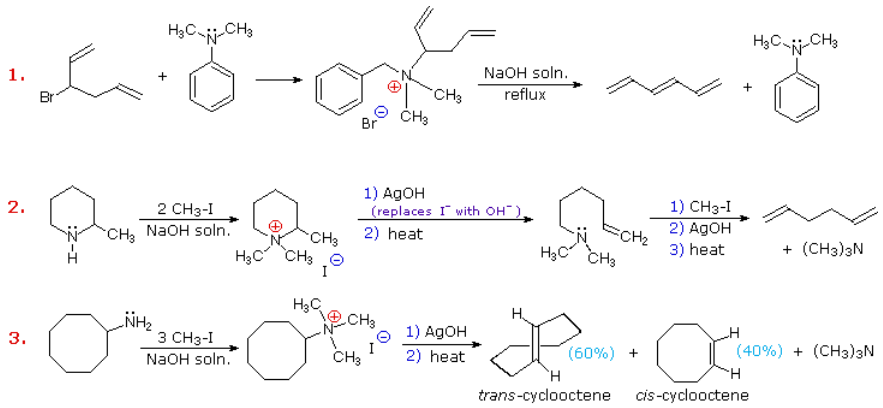
To understand why the base-induced elimination of 4º-ammonium salts behaves differently from that of alkyl halides it is necessary to reexamine the nature of the E2 transition state, first described for dehydrohalogenation. The energy diagram shown earlier for a single-step bimolecular E2 mechanism is repeated below.



The E2 transition state is less well defined than is that of S_N2 reactions. More bonds are being broken and formed, with the possibility of a continuum of states in which the extent of C–H and C–X bond-breaking and C=C bond-making varies. For example, if the bond to the leaving group (X) is substantially broken relative to the other bond changes, the transition state approaches that for an E1 reaction (initial ionization followed by a fast second step). At the other extreme, if the acidity of the beta-hydrogens is enhanced, then substantial breaking of C–H may occur before the other bonds begin to be affected. For most simple alkyl halides it was proper to envision a balanced transition state, in which there was a synchronous change in all the bonds. Such a model was consistent with the **Zaitsev Rule**.

When the leaving group X carries a positive charge, as do the 4º-ammonium compounds discussed here, the inductive influence of this charge will increase the acidity of both the alpha and the beta-hydrogens. Furthermore, the 4º-ammonium substituent is much larger than a halide or hydroxyl group and may perturb the conformations available to substituted beta-carbons. It seems that a combination of these factors acts to favor base attack at the least substituted (least hindered and most acidic) set of beta-hydrogens. The favored anti orientation of the leaving group and beta-hydrogen, noted for dehydrohalogenation, is found for many Hofmann eliminations; but syn-elimination is also common, possibly because the attraction of opposite charges orients the hydroxide base near the 4º-ammonium leaving group.

Three additional examples of the Hofmann elimination are shown in the following diagram. Example #1 is interesting in two respects. First, it generates a 4º-ammonium halide salt in a manner different from exhaustive methylation. Second, this salt is not converted to its hydroxide analog prior to elimination. A concentrated aqueous solution of the halide salt is simply dropped into a refluxing sodium hydroxide solution, and the volatile hydrocarbon product is isolated by distillation.



Example #2 illustrates an important aspect of the Hofmann elimination. If the nitrogen atom is part of a ring, then a single application of this elimination procedure does not remove the nitrogen as a separate 3º-amine product. In order to sever the nitrogen function from the molecule, a second Hofmann elimination must be carried out. Indeed, if the nitrogen atom was a member of two rings (fused or spiro), then three repetitions of the Hofmann elimination would be required to sever the nitrogen from the remaining molecular framework.

Example #3 is noteworthy because the less stable trans-cyclooctene is the chief product, accompanied by the cis-isomer. An anti-E2-transition state would necessarily give the cis-cycloalkene, so the trans-isomer must be generated by a syn-elimination. The cis-cyclooctene produced in this reaction could also be formed by a syn-elimination. Cyclooctane is a conformationally complex structure. Several puckered conformations that avoid angle strain are possible, and one of the most stable of these is shown on the right. Some eclipsed bonds occur in all these conformers, and transannular hydrogen crowding is unavoidable. Since the trimethylammonium substituent is large (about the size of tert-butyl) it will probably assume an equatorial-like orientation to avoid steric crowding. An anti-E2 transition state is likely to require an axial-like orientation of this bulky group, making this an unfavorable path.

Contributors

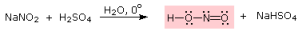
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

23.4: Reaction of Amines with Nitrous Acid

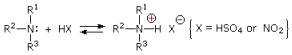
Nitrous acid (HNO_2 or $HONO$) reacts with aliphatic amines in a fashion that provides a useful test for distinguishing primary, secondary and tertiary amines.

- 1°-Amines + HONO (cold acidic solution) → Nitrogen Gas Evolution from a Clear Solution
- 2°-Amines + HONO (cold acidic solution) → An Insoluble Oil (N-Nitrosamine)
- 3°-Amines + HONO (cold acidic solution) → A Clear Solution (Ammonium Salt Formation)

Nitrous acid is a Brønsted acid of moderate strength (pK_a = 3.3). Because it is unstable, it is prepared immediately before use in the following manner:

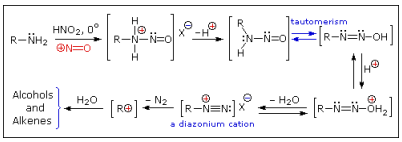


Under the acidic conditions of this reaction, all amines undergo reversible salt formation:

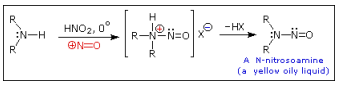


This happens with 3º-amines, and the salts are usually soluble in water. The reactions of nitrous acid with 1°- and 2°- aliphatic amines may be explained by considering their behavior with the nitrosonium cation, $NO^{(+)}$, an electrophilic species present in acidic nitrous acid solutions.

Primary Amines

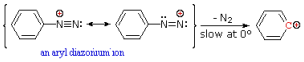


Secondary Amines



The distinct behavior of 1º, 2º & 3º-aliphatic amines is an instructive challenge to our understanding of their chemistry, but is of little importance as a synthetic tool. The S_N1 product mixtures from 1º-amines are difficult to control, and rearrangement is common when branched primary alkyl groups are involved. The N-nitrosamines formed from 2º-amines are carcinogenic, and are not generally useful as intermediates for subsequent reactions.

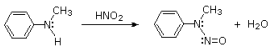
Aryl Amines



Aqueous solutions of these diazonium ions have sufficient stability at 0º to 10 ºC that they may be used as intermediates in a variety of nucleophilic substitution reactions. For example, if water is the only nucleophile available for reaction, phenols are formed in good yield.

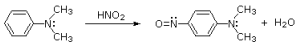
2º-Aryl Amines:

2º-Aryl amines give N-nitrosamine derivatives on reaction with nitrous acid, and thus behave identically to their aliphatic counterparts.



3º-Aryl Amines:

Depending on ring substitution, 3º-Aryl amines may undergo aromatic ring nitrosation at sites ortho or para to the amine substituent. The nitrosonium cation is not sufficiently electrophilic to react with benzene itself, or even toluene, but highly activated aromatic rings such as amines and phenols are capable of substitution. Of course, the rate of reaction of $NO^{(+)}$ directly at nitrogen is greater than that of ring substitution, as shown in the previous example. Once nitrosated, the activating character of the amine nitrogen is greatly diminished; and N-nitrosoaniline derivatives, or indeed any amide derivatives, do not undergo ring nitrosation.

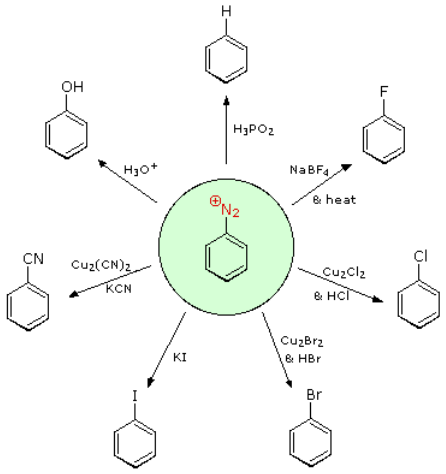


Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

23.5: Substitution Reactions of Aryl Diazonium Salts

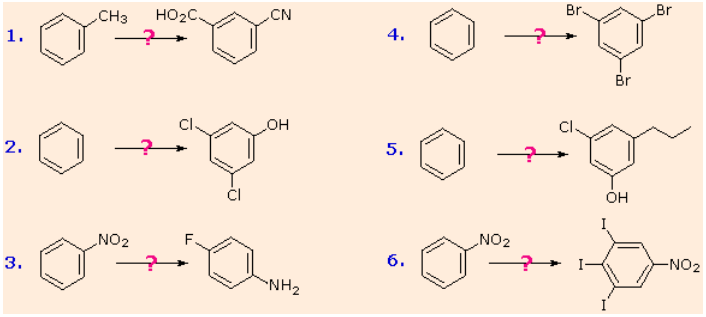
Aryl diazonium salts are important intermediates. They are prepared in cold (0 º to 10 ºC) aqueous solution, and generally react with nucleophiles with loss of nitrogen. Some of the more commonly used substitution reactions are shown in the following diagram. Since the leaving group (N_2) is thermodynamically very stable, these reactions are energetically favored. Those substitution reactions that are catalyzed by cuprous salts are known as **Sandmeyer reactions**. Fluoride substitution occurs on treatment with $BF_4^{(-)}$, a reaction known as the **Schiemann reaction**. Stable diazonium tetrafluoroborate salts may be isolated, and on heating these lose nitrogen to give an arylfluoride product. The top reaction with hypophosphorus acid, H_3PO_2, is noteworthy because it achieves the reductive removal of an amino (or nitro) group. Unlike the nucleophilic substitution reactions, this reduction probably proceeds by a radical mechanism.



These aryl diazonium substitution reactions significantly expand the tactics available for the synthesis of polysubstituted benzene derivatives. Consider the following options:

I. The usual precursor to an aryl amine is the corresponding nitro compound. A nitro substituent deactivates an aromatic ring and directs electrophilic substitution to meta locations.
II. Reduction of a nitro group to an amine may be achieved in several ways. The resulting amine substituent strongly activates an aromatic ring and directs electrophilic substitution to ortho & para locations.
III. The activating character of an amine substituent may be attenuated by formation of an amide derivative (reversible), or even changed to deactivating and meta-directing by formation of a quaternary-ammonium salt (irreversible).
IV. Conversion of an aryl amine to a diazonium ion intermediate allows it to be replaced by a variety of different groups (including hydrogen), which may in turn be used in subsequent reactions.

The following examples illustrate some combined applications of these options to specific cases. You should try to conceive a plausible reaction sequence for each. Once you have done so, you may check suggested answers by clicking on the question mark for each.



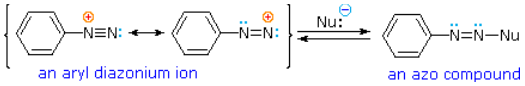
Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

23.6: Coupling Reactions of Aryl Diazonium Salts

Bonding to Nitrogen

A resonance description of diazonium ions shows that the positive charge is delocalized over the two nitrogen atoms. It is not possible for nucleophiles to bond to the inner nitrogen, but bonding (or coupling) of negative nucleophiles to the terminal nitrogen gives neutral azo compounds. As shown in the following equation, this coupling to the terminal nitrogen should be relatively fast and reversible. The azo products may exist as E / Z stereoisomers. In practice it is found that the E-isomer predominates at equilibrium.



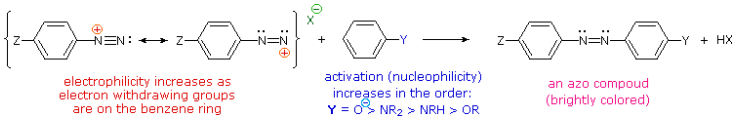
Unless these azo products are trapped or stabilized in some manner, reversal to the diazonium ion and slow nucleophilic substitution at carbon (with irreversible nitrogen loss) will be the ultimate course of reaction, as described in the previous section. For example, if phenyldiazonium bisufate is added rapidly to a cold solution of sodium hydroxide a relatively stable solution of sodium phenyldiazoate (the conjugate base of the initially formed diazoic acid) is obtained. Lowering the pH of this solution regenerates phenyldiazoic acid (pK_a ca. 7), which disassociates back to the diazonium ion and eventually undergoes substitution, generating phenol.

$C_6H_5N_2^{(+)}$ $HSO_4^{(-)}$ + NaOH	(cold solution)	$C_6H_5N_2$–OH + NaOH (cold)	⟶	$C_6H_5N_2$–$O^{(-)}$ $Na^{(+)}$
phenyldiazonium bisulfate		phenyldiazoic acid		sodium phenyldiazoate

Aryl diazonium salts may be reduced to the corresponding hydrazines by mild reducing agents such as sodium bisulfite, stannous chloride or zinc dust. The bisulfite reduction may proceed by an initial sulfur-nitrogen coupling, as shown in the following equation.

Ar-$N_2^{(+)}$ $X^{(-)}$	$NaHSO_3$ ⟶	Ar-N=N-SO_3H	$NaHSO_3$ ⟶	Ar-NH-NH-SO_3H	H_2O ⟶	Ar-NH-NH_2 + H_2SO_4

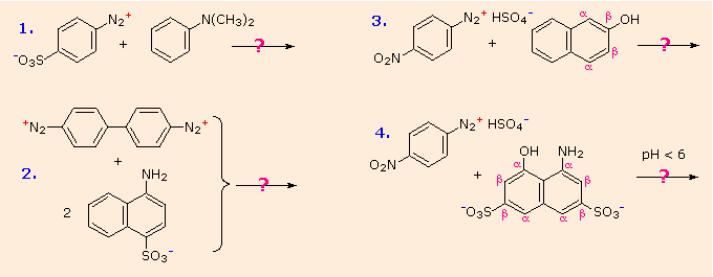
The most important application of diazo coupling reactions is electrophilic aromatic substitution of activated benzene derivatives by diazonium electrophiles. The products of such reactions are highly colored aromatic azo compounds that find use as synthetic dyestuffs, commonly referred to as azo dyes. Azobenzene (Y=Z=H) is light orange; however, the color of other azo compounds may range from red to deep blue depending on the nature of the aromatic rings and the substituents they carry. Azo compounds may exist as cis/trans isomer pairs, but most of the well-characterized and stable compounds are trans.



Some examples of azo coupling reactions are shown below. A few simple rules are helpful in predicting the course of such reactions:

I. At acid pH (< 6) an amino group is a stronger activating substituent than a hydroxyl group (i.e. a phenol). At alkaline pH (> 7.5) phenolic functions are stronger activators, due to increased phenoxide base concentration.
II. Coupling to an activated benzene ring occurs preferentially para to the activating group if that location is free. Otherwise ortho-coupling will occur.
III. Naphthalene normally undergoes electrophilic substitution at an alpha-location more rapidly than at beta-sites; however, ortho-coupling is preferred. See the diagram for examples of α / β notation in naphthalenes.

You should try to conceive a plausible product structure for each of the following couplings.



Contributors

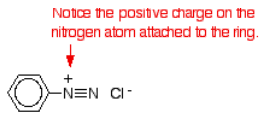
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

23.7: Application- Synthetic Dyes

This page looks at some typical reactions of diazonium ions, including examples of both substitution reactions and coupling reactions. If you have come straight to this page from a search engine and want to know about the preparation of the diazonium ions, you will find a link at the bottom of the page.

Substitution reactions of diazonium ions

Diazonium ions are present in solutions such as benzenediazonium chloride solution. They contain an $-N_2^+$ group. In the case of benzenediazonium chloride, this is attached to a benzene ring. Benzenediazonium chloride looks like this:

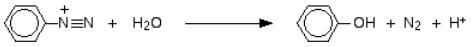


benzenediazonium chloride

In this set of reactions of the diazonium ion, the $-N_2^+$ group is replaced by something else. The nitrogen is released as nitrogen gas.

Substitution by an -OH group

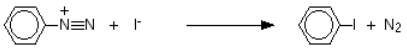
To get this reaction, all you need to do is warm the benzenediazonium chloride solution. The diazonium ion reacts with the water in the solution and phenol is formed - either in solution or as a black oily liquid (depending on how much is formed). Nitrogen gas is evolved.



This is the same reaction that you get if you react phenylamine with nitrous acid in the warm. The diazonium ion is formed first and then immediately reacts with the water in the solution to give phenol.

Substitution by an iodine atom

This is a good example of the use of diazonium salts to substitute things into a benzene ring which are otherwise quite difficult to attach. (That's equally true of the previous reaction, by the way.) If you add potassium iodide solution to the benzenediazonium chloride solution in the cold, nitrogen gas is given off, and you get oily droplets of iodobenzene formed. There is a simple reaction between the diazonium ions and the iodide ions from the potassium iodide solution.



Coupling reactions of diazonium ions

In the substitution reactions above, the nitrogen in the diazonium ion is lost. In the rest of the reactions on this page, the nitrogen is retained and used to make a bridge between two benzene rings.

The reaction with phenol

Phenol is dissolved in sodium hydroxide solution to give a solution of sodium phenoxide.

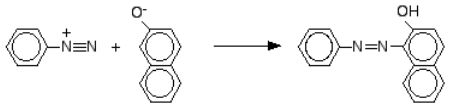
sodium phenoxide

The solution is cooled in ice, and cold benzenediazonium chloride solution is added. There is a reaction between the diazonium ion and the phenoxide ion and a yellow-orange solution or precipitate is formed. The product is one of the simplest of what are known as *azo compounds*, in which two benzene rings are linked by a nitrogen bridge.

The reaction with naphthalen-2-ol

Naphthalen-2-ol is also known as 2-naphthol or beta-naphthol. It contains an -OH group attached to a naphthalene molecule rather than to a simple benzene ring. Naphthalene has two benzene rings fused together.

The reaction is done under exactly the same conditions as with phenol. The naphthalen-2-ol is dissolved in sodium hydroxide solution to produce an ion just like the phenol one. This solution is cooled and mixed with the benzenediazonium chloride solution. An intense orange-red precipitate is formed - another azo compound.



The reaction with phenylamine (aniline)

Some liquid phenylamine is added to a cold solution of benzenediazonium chloride, and the mixture is shaken vigorously. A yellow solid is produced.

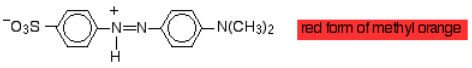
These strongly colored azo compounds are frequently used as dyes known as azo dyes. The one made from phenylamine (aniline) is known as "aniline yellow" (amongst many other things - see note above). Azo compounds account for more than half of modern dyes.

The use of an azo dye as an indicator - methyl orange

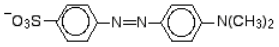
Azo compounds contain a highly delocalised system of electrons which takes in both benzene rings and the two nitrogen atoms bridging the rings. The delocalisation can also extend to things attached to the benzene rings as well.

If white light falls on one of these molecules, some wavelengths are absorbed by these delocalised electrons. The color you see is the result of the non-absorbed wavelengths. The groups which contribute to the delocalisation (and so to the absorption of light) are known as a chromophore.

Modifying the groups present in the molecule can have an effect on the light absorbed, and so on the color you see. You can take advantage of this in indicators. Methyl orange is an azo dye which exists in two forms depending on the pH:



red form of methyl orange



yellow form of methyl orange

As the hydrogen ion is lost or gained there is a shift in the exact nature of the delocalization in the molecule, and that causes a shift in the wavelength of light absorbed. Obviously that means that you see a different color.

When you add acid to methyl orange, a hydrogen ion attaches to give the red form. Methyl orange is red in acidic solutions (in fact solutions of pH less than 3.1). If you add an alkali, hydrogen ions are removed and you get the yellow form. Methyl orange is yellow at pH's greater than 4.4. In between, at some point there will be equal amounts of the red and yellow forms and so methyl orange looks orange.

Contributors

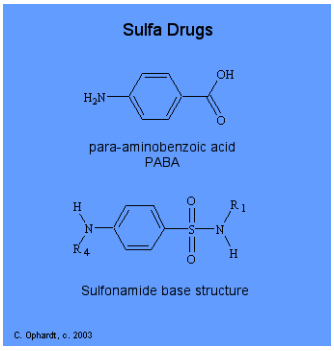
- Jim Clark (Chemguide.co.uk)

23.8: Application- Sulfa Drugs

Sulfonamides are synthetic antimicrobial agents with a wide spectrum encompassing most gram-positive and many gram-negative organisms. These drugs were the first efficient treatment to be employed systematically for the prevention and cure of bacterial infections.

Introduction

Their use introduced and substantiated the concept of metabolic antagonism. Sulfonamides, as antimetabolites, compete with para-aminobenzoic acid (PABA) for incorporation into folic acid. The action of sulfonamides illustrates the principle of selective toxicity where some difference between mammal cells and bacterial cells is exploited. All cells require folic acid for growth. Folic acid (as a vitamin is in food) diffuses or is transported into human cells. However, folic acid cannot cross bacterial cell walls by diffusion or active transport. For this reason bacteria must synthesize folic acid from p-aminobenzoic acid. Sulfonamides or sulfa drugs have the following general structures as shown below.



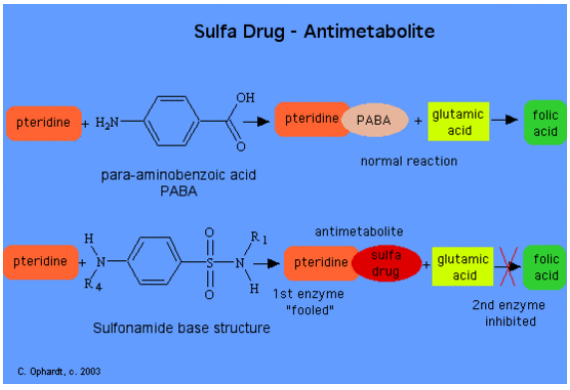
Sulfanilamide which was the first compound used of this type has H's at R1 and R4. To date about 15,000 sulfonamide derivatives, analogues, and related compounds have been synthesized. This has lead to the discovery of many useful drugs which are effective for diuretics, antimalerial and leprosy agents, and antithyroid agents. The basic structure of sulfonamide cannot be modified if it is to be an effective competitive "mimic" for p-aminobenzoic acid. Essential structural features are the benzene ring with two substituents para to each other; an amino group in the fourth position; and the singly substituted 1-sulfonamido group.

Mechanism for Action

Normally folic acid is synthesized in two steps in bacteria by the top reaction on the left. If A sulfa drug is used, the first enzyme is not to specific and can use the sulfonamide in the first reaction. This reaction produces the product containing pteridine and the sulfa drug. The next and final step is the reaction PABA + with glutamic acid to make folic acid. If the sulfa drug has been substituted for the PABA, then the final enzyme is inhibited and no folic acid is produced.

Recent studies indicate that substituents on the N(1) nitrogen may play the role of competing for a site on the enzyme surface reserved for the glutamate residue in p-aminobenzoic acid-glutamate through one of the following two ways:

1. Direct competition in the linking of PABA-glutamate with the pteridine derivative.
2. Indirect interference with the coupling of glutamate to dihydropteroic acid.



Questions

1. In your own words explain how the sulfa drug works including enzyme inhibition, folic acid, and antimetabolite.

Contributors

Charles Ophardt (Professor Emeritus, Elmhurst College); Virtual Chembook

23.9: Introduction

Amines are derivatives of ammonia in which one or more of the hydrogens has been replaced by an alkyl or aryl group.

The basic properties of amines

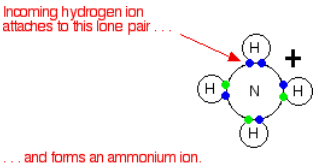
We are going to have to use two different definitions of the term "base" in this page. A base is

- a substance which combines with hydrogen ions. This is the Bronsted-Lowry theory.
- an electron pair donor. This is the Lewis theory.

The easiest way of looking at the basic properties of amines is to think of an amine as a modified ammonia molecule. In an amine, one or more of the hydrogen atoms in ammonia has been replaced by a hydrocarbon group. Replacing the hydrogens still leaves the lone pair on the nitrogen unchanged - and it is the lone pair on the nitrogen that gives ammonia its basic properties. Amines will therefore behave much the same as ammonia in all cases where the lone pair is involved.

The reactions of amines with acids

These are most easily considered using the Bronsted-Lowry theory of acids and bases - the base is a hydrogen ion acceptor. We'll do a straight comparison between amines and the familiar ammonia reactions. Ammonia reacts with acids to produce ammonium ions. The ammonia molecule picks up a hydrogen ion from the acid and attaches it to the lone pair on the nitrogen.



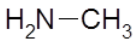
If the reaction is in solution in water (using a dilute acid), the ammonia takes a hydrogen ion (a proton) from a hydroxonium ion. (Remember that hydrogen ions present in solutions of acids in water are carried on water molecules as hydroxonium ions, H_3O^+.)

If the acid was hydrochloric acid, for example, you would end up with a solution containing ammonium chloride - the chloride ions, of course, coming from the hydrochloric acid. You could also write this last equation as:

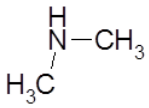
. . . but if you do it this way, you must include the state symbols. If you write H^+ on its own, it implies an unattached hydrogen ion - a proton. Such things don't exist on their own in solution in water. If the reaction is happening in the gas state, the ammonia accepts a proton directly from the hydrogen chloride:

This time you produce clouds of white solid ammonium chloride.

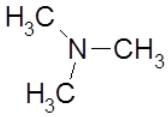
The designation 1º, 2º and 3º is determined by the number of alkyl groups attached to the nitrogen.



Primary amine 1°



Secondary amine 2°



Tertiary 3°

Contributors

- Jim Clark (Chemguide.co.uk)
- Prof. Steven Farmer (Sonoma State University)

23.9.1: 25.2 Structure and Bonding

Your page has been created!

Remove this content and add your own.

- Edit page

  Click the Edit page button in your user bar. You will see a suggested structure for your content. Add your content and hit Save.

Tips:

- Drag and drop

  Drag one or more image files from your computer and drop them onto your browser window to add them to your page.

- Classifications

  Tags are used to link pages to one another along common themes. Tags are also used as markers for the dynamic organization of content in the CXone Expert framework.

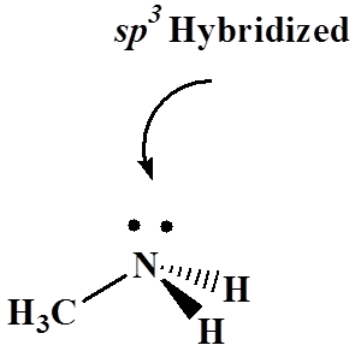
- Working with templates

  CXone Expert templates help guide and organize your documentation, making it flow easier and more uniformly. Edit existing templates or create your own.

- Visit for all help topics.

23.10: Structure and Bonding

Amines typically have three bonds and one pair of lone pair electrons. This makes the nitrogen sp3 hybridized, trigonal pyramidal, with a bond angle of roughly 109.5°.



Stereogenic Nitrogen

Single-bonded nitrogen is pyramidal in shape, with the non-bonding electron pair pointing to the unoccupied corner of a tetrahedral region. Since the nitrogen in these compounds is bonded to three different groups, its configuration is chiral. The non-identical mirror-image configurations are illustrated in the following diagram (the remainder of the molecule is represented by R, and the electron pair is colored yellow). If these configurations were stable, there would be four additional stereoisomers of ephedrine and pseudoephedrine. However, pyramidal nitrogen is normally not configurationally stable. It rapidly inverts its configuration (equilibrium arrows) by passing through a planar, sp2-hybridized transition state, leading to a mixture of interconverting R and S configurations. If the nitrogen atom were the only chiral center in the molecule, a 50:50 (racemic) mixture of R and S configurations would exist at equilibrium. If other chiral centers are present, as in the ephedrin isomers, a mixture of diastereomers will result. The take-home message is that nitrogen does not contribute to isolable stereoisomers.

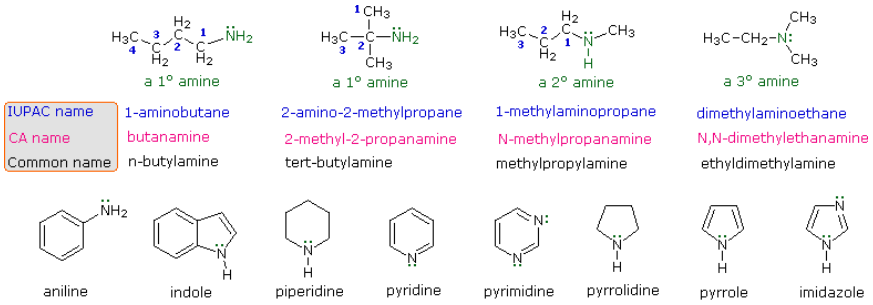
Contributors

- Jim Clark (Chemguide.co.uk)
- Prof. Steven Farmer (Sonoma State University)

23.11: Nomenclature

In the IUPAC system of nomenclature, functional groups are normally designated in one of two ways. The presence of the function may be indicated by a characteristic suffix and a location number. This is common for the carbon-carbon double and triple bonds which have the respective suffixes **ene** and **yne**. Halogens, on the other hand, do not have a suffix and are named as substituents, for example: $(CH_3)_2C{=}CHCHClCH_3$ is 4-chloro-2-methyl-2-pentene. If you are uncertain about the IUPAC rules for nomenclature you should review them now.

Amines are derivatives of ammonia in which one or more of the hydrogens has been replaced by an alkyl or aryl group. The nomenclature of amines is complicated by the fact that several different nomenclature systems exist, and there is no clear preference for one over the others. Furthermore, the terms primary (1º), secondary (2º) & tertiary (3º) are used to classify amines in a completely different manner than they were used for alcohols or alkyl halides. **When applied to amines these terms refer to the number of alkyl (or aryl) substituents bonded to the nitrogen atom**, whereas in other cases they refer to the nature of an alkyl group. The four compounds shown in the top row of the following diagram are all $C_4H_{11}N$ isomers. The first two are classified as 1º-amines, since only one alkyl group is bonded to the nitrogen; however, the alkyl group is primary in the first example and tertiary in the second. The third and fourth compounds in the row are 2º and 3º-amines respectively. A nitrogen bonded to four alkyl groups will necessarily be positively charged, and is called a 4º-ammonium cation. For example, $(CH_3)_4N^{(+)}$ $Br^{(-)}$ is tetramethylammonium bromide.



- The IUPAC names are listed first and colored blue. This system names amine functions as substituents on the largest alkyl group. The simple -NH substituent found in 1º-amines is called an **amino group**. For 2º and 3º-amines a compound prefix (e.g. dimethylamino in the fourth example) includes the names of all but the root alkyl group.
- The Chemical Abstract Service has adopted a nomenclature system in which the suffix **-amine** is attached to the root alkyl name. For 1º-amines such as butanamine (first example) this is analogous to IUPAC alcohol nomenclature (-ol suffix). The additional nitrogen substituents in 2º and 3º-amines are designated by the prefix **N-** before the group name. These CA names are colored magenta in the diagram.
- Finally, a common system for simple amines names each alkyl substituent on nitrogen in alphabetical order, followed by the suffix **-amine**. These are the names given in the last row (colored black).

Many aromatic and heterocyclic amines are known by unique common names, the origins of which are often unknown to the chemists that use them frequently. Since these names are not based on a rational system, it is necessary to memorize them. There is a systematic nomenclature of heterocyclic compounds, but it will not be discussed here.

Contributors

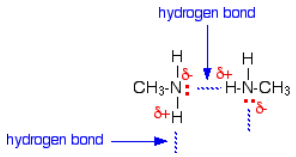
Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

23.12: Physical Properties

Boiling Point and Water Solubility

It is instructive to compare the boiling points and water solubility of amines with those of corresponding alcohols and ethers. The dominant factor here is hydrogen bonding, and the first table below documents the powerful intermolecular attraction that results from -O-H---O- hydrogen bonding in alcohols (light blue columns). Corresponding -N-H---N- hydrogen bonding is weaker, as the lower boiling points of similarly sized amines (light green columns) demonstrate. Alkanes provide reference compounds in which hydrogen bonding is not possible, and the increase in boiling point for equivalent 1º-amines is roughly half the increase observed for equivalent alcohols.



Compound	CH_3CH_3	CH_3OH	CH_3NH_2	$CH_3CH_2CH_3$	CH_3CH_2OH	$CH_3CH_2NH_2$
Mol.Wt.	30	32	31	44	46	45
Boiling Point ºC	-88.6º	65º	-6.0º	-42º	78.5º	16.6º

The second table illustrates differences associated with isomeric 1º, 2º & 3º-amines, as well as the influence of chain branching. Since 1º-amines have two hydrogens available for hydrogen bonding, we expect them to have higher boiling points than isomeric 2º-amines, which in turn should boil higher than isomeric 3º-amines (no hydrogen bonding). Indeed, 3º-amines have boiling points similar to equivalent sized ethers; and in all but the smallest compounds, corresponding ethers, 3º-amines and alkanes have similar boiling points. In the examples shown here, it is further demonstrated that chain branching reduces boiling points by 10 to 15 ºC.

Compound	$CH_3(CH_2)_2CH_3$	$CH_3(CH_2)_2OH$	$CH_3(CH_2)_2NH_2$	$CH_3CH_2NHCH_3$	$(CH_3)_3CH$	$(CH_3)_2CHOH$	$(CH_3)_2CHNH_2$	$(CH_3)_3N$
Mol.Wt.	58	60	59	59	58	60	59	59
Boiling Point ºC	-0.5º	97º	48º	37º	-12º	82º	34º	3º

The water solubility of 1º and 2º-amines is similar to that of comparable alcohols. As expected, the water solubility of 3º-amines and ethers is also similar. These comparisons, however, are valid only for pure compounds in neutral water. The basicity of amines (next section) allows them to be dissolved in dilute mineral acid solutions, and this property facilitates their separation from neutral compounds such as alcohols and hydrocarbons by partitioning between the phases of non-miscible solvents.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

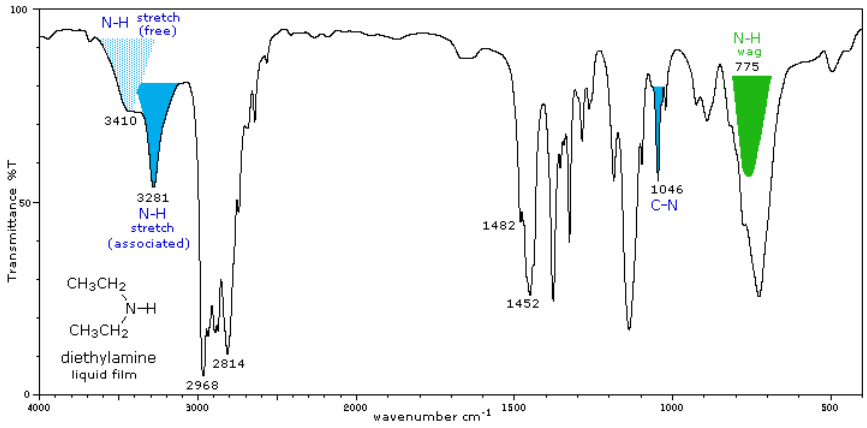
23.13: Spectroscopic Properties

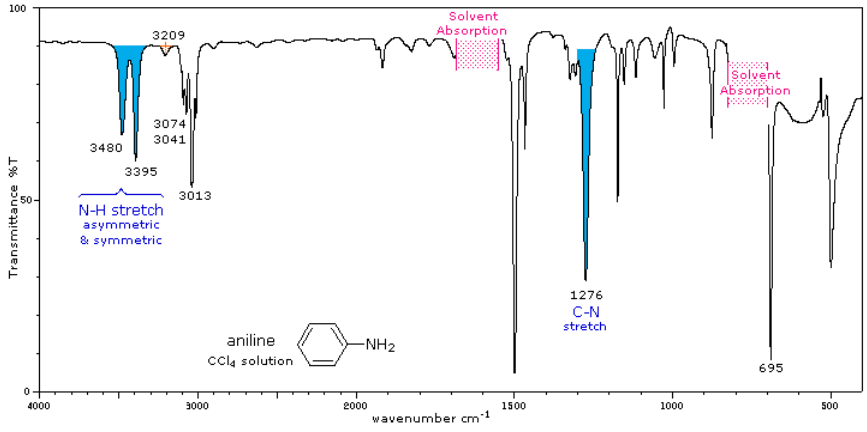
IR

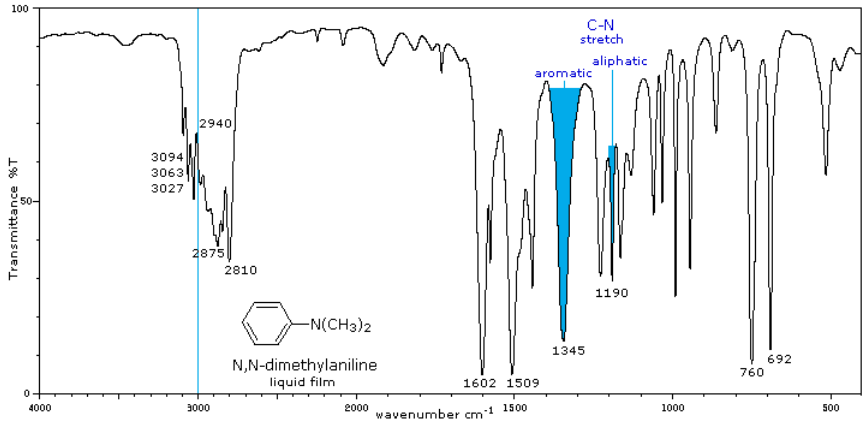
The infrared spectrum of aniline is shown beneath the following table. Some of the characteristic absorptions for C-H stretching and aromatic ring substitution are also marked, but not colored.

Amine Class	Stretching Vibrations	Bending Vibrations
Primary (1°)	The N-H stretching absorption is less sensitive to hydrogen bonding than are O-H absorptions. In the gas phase and in dilute CCl_4 solution free N-H absorption is observed in the 3400 to 3500 cm^{-1} region. Primary aliphatic amines display two well-defined peaks due to asymmetric (higher frequency) and symmetric N-H stretching, separated by 80 to 100 cm^{-1}. In aromatic amines these absorptions are usually 40 to 70 cm^{-1} higher in frequency. A smaller absorption near 3200 cm^{-1} (shaded orange in the spectra) is considered to be the result of interaction between an overtone of the 1600 cm^{-1} band with the symmetric N-H stretching band. C-N stretching absorptions are found at 1200 to 1350 cm^{-1} for aromatic amines, and at 1000 to 1250 cm^{-1} for aliphatic amines.	Strong in-plane NH_2 scissoring absorptions at 1550 to 1650 cm^{-1}, and out-of-plane wagging at 650 to 900 cm^{-1} (usually broad) are characteristic of 1°-amines.
Secondary (2°)	Secondary amines exhibit only one absorption near 3420 cm^{-1}. Hydrogen bonding in concentrated liquids shifts these absorptions to lower frequencies by about 100 cm^{-1}. Again, this absorption appears at slightly higher frequency when the nitrogen atom is bonded to an aromatic ring. The C-N absorptions are found in the same range, 1200 to 1350 cm^{-1}(aromatic) and 1000 to 1250 cm^{-1} (aliphatic) as for 1°-amines.	A weak N-H bending absorption is sometimes visible at 1500 to 1600 cm^{-1}. A broad wagging absorption at 650 to 900 cm^{-1} may be discerned in liquid film samples.

Tertiary (3°)	No N-H absorptions. The C-N absorptions are found in the same range, 1200 to 1350 cm^{-1} (aromatic) and 1000 to 1250 cm^{-1} (aliphatic) as for 1°-amines.	Aside from the C-N stretch noted on the left, these compounds have spectra characteristic of their alkyl and aryl substituents.







NMR

The hydrogens attached to an amine show up ~ 0.5-5.0 ppm. The location is dependent on the amount of hydrogen bonding and the sample's concentration.

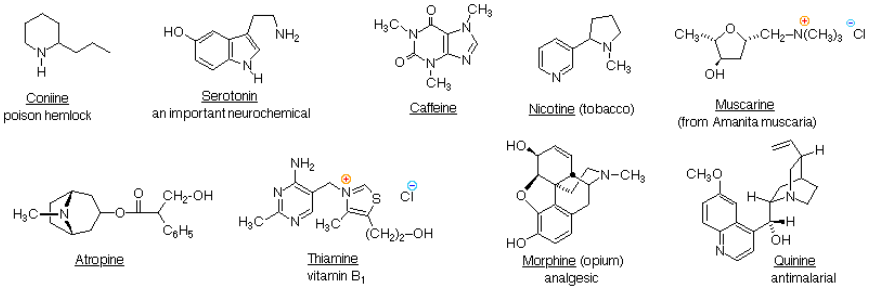
The hydrogens on carbons directly bonded to an amine typically appear ~2.3-3.0 ppm.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

23.14: Interesting and Useful Amines

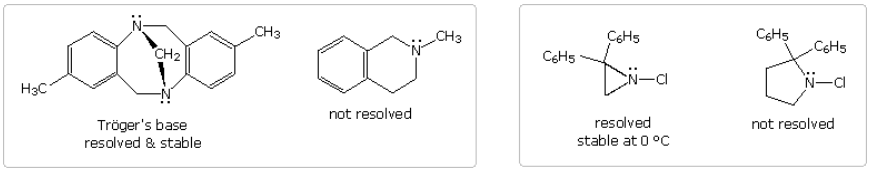
Nature abounds with nitrogen compounds, many of which occur in plants and are referred to as **alkaloids**. Structural formulas for some representative alkaloids and other nitrogen containing natural products are displayed below, and we can recognize many of the basic structural features listed above in their formulas. Thus, Serotonin and Thiamine are 1º-amines, Coniine is a 2º-amine, Atropine, Morphine and Quinine are 3º-amines, and Muscarine is a 4º-ammonium salt.



The reader should be able to recognize indole, imidazole, piperidine, pyridine, pyrimidine & pyrrolidine moieties among these structures. These will be identified by pressing the "Show Structures" button under the diagram.

Nitrogen atoms that are part of aromatic rings , such as pyridine, pyrrole & imidazole, have planar configurations (sp^2 hybridization), and are not stereogenic centers. Nitrogen atoms bonded to carbonyl groups, as in caffeine, also tend to be planar. In contrast, atropine, coniine, morphine, nicotine and quinine have stereogenic pyramidal nitrogen atoms in their structural formulas (think of the non-bonding electron pair as a fourth substituent on a sp^3 hybridized nitrogen). In quinine this nitrogen is restricted to one configuration by the bridged ring system. The other stereogenic nitrogens are free to assume two pyramidal configurations, but these are in rapid equilibrium so that distinct stereoisomers reflecting these sites cannot be easily isolated.

It should be noted that structural factors may serve to permit the resolution of pyramidal chiral amines. Two examples of such 3º-amines, compared with similar non-resolvable analogs, are shown in the following diagram. The two nitrogen atoms in Trögers base are the only stereogenic centers in the molecule. Because of the molecule's bridged structure, the nitrogens have the same configuration and cannot undergo inversion. The chloro aziridine can invert, but requires a higher activation energy to do so, compared with larger heterocyclic amines. It has in fact been resolved, and pure enantiomers isolated. An increase in angle strain in the sp^2-hybridized planar transition state is responsible for the greater stability of the pyramidal configuration. The rough estimate of angle strain is made using a C-N-C angle of 60º as an arbitrary value for the three-membered heterocycle.



Of course, quaternary ammonium salts, such as that in muscarine, have a tetrahedral configuration that is incapable of inversion. With four different substituents, such a nitrogen would be a stable stereogenic center.

Amines as Antidepressants

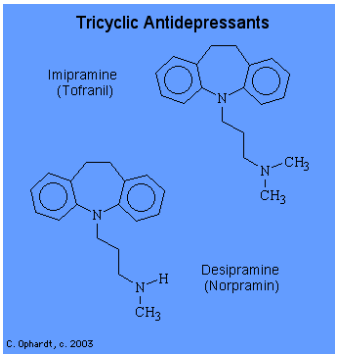
Antidepressant drugs act by one or more of the following stimulation type mechanisms:

1. Increase release of norepinephrine:Amphetamines and electroconvulsive therapy act by this mechanism. Amphetamines mimic norepinephrine.
2. Prevent inactivation of norepinephrine:Monoamine oxidase (MAO) inhibitors are thought to act as antidepressant agents in part by preventing the breakdown and inactivation of norepinephrine.
3. Prevent the re uptake of norepinephrine:The action of norepinephrine at the receptor site is terminated by the re uptake of norepinephrine by the neuron from which it was originally released.

Tricyclic Antidepressants

The tricyclic antidepressants are the most effective drugs presently available for the treatment of depression. These act by increasing the release of norepinephrine. Amphetamine and cocaine can also act in this manner. Imipramine, amitriptylin, and other closely related drugs are among the drugs currently most widely used for the treatment of major depression.

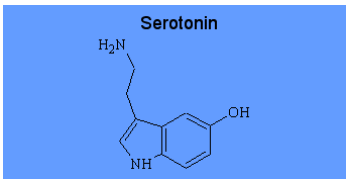
- imipramine (Tofranil)
- desipramine (Norpramin)



The activity of the tricyclic drugs depends on the central ring of seven or eight atoms which confers an angled or twisted conformation. The side chain must have at least 2 carbons although 3 appear to be better. The amine group may be either tertiary or secondary. All tricyclic antidepressants block the re-uptake of norepinephrine at nerve terminals. However, the potency and selectivity for the inhibition of the uptake of norepinephrine, serotonin, and dopamine vary greatly among the agents. The tertiary amine tricyclics seem to inhibit the serotonin uptake pump, whereas the secondary amine ones seem better in switching off the NE pump. For instance, imipramine is a potent and selective blocker of serotonin transport, while desipramine inhibits the uptake of norepinephrine.

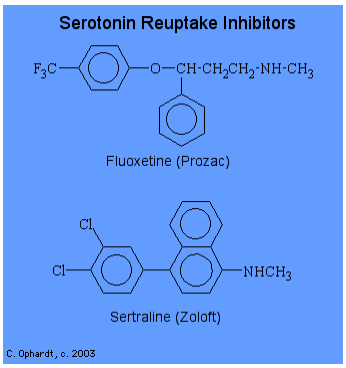
Serotonin

Serotonin (5-hydroxytryptamine or 5-HT) is a monoamine neurotransmitter found in cardiovascular tissue, in endothelial cells, in blood cells, and in the central nervous system. The role of serotonin in neurological function is diverse, and there is little doubt that serotonin is an important CNS neurotransmitter. Although some of the serotonin is metabolized by monoamine oxidase, most of the serotonin released into the post-synaptic space is removed by the neuron through a re uptake mechanism inhibited by the tricyclic antidepressants and the newer, more selective antidepressant re uptake inhibitors such as fluoxetine and sertraline.



Selective Serotonin Reuptake Inhibitors

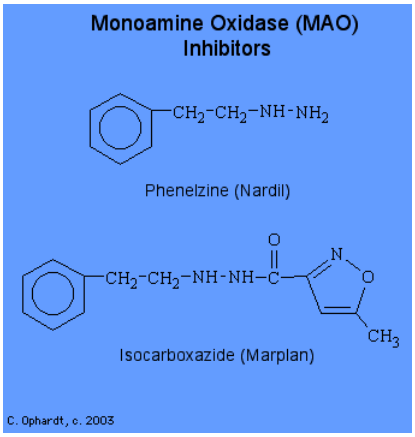
In recent years, selective serotonin reuptake inhibitors have been introduced for the treatment of depression. Prozac is the most famous drug in this class. Clomiprimine, fluoxetine (Prozac), sertraline and paroxetine selectively block the re uptake of serotonin, thereby increasing the levels of serotonin in the central nervous system. Note the similarities and differences between the tricyclic antidepressants and the selective serotonin re uptake inhibitors. Clomipramine has been useful in the treatment of obsessive-compulsive disorders.



Monoamine Oxidase Inhibitors

Monoamine oxidase (MAO) causes the oxidative deamination of norephinephrine, serotonin, and other amines. This oxidation is the method of reducing the concentration of the neurotransmitter after it has sent the signal at the receptor site. A drug which inhibits this enzyme has the effect of **increasing the concentration of the norepinephrine which in turn causes a stimulation effect.** Most MAO inhibitors are hydrazine derivatives. Hydrazine is highly reactive and may form a strong covalent bond with MAO with consequent inhibition for up to 5 days.

These drugs are less effective and produce more side effects than the tricyclic antidepressants. For example, they lower blood pressure and were at one time used to treat hypertension. Their use in psychiatry has also become very limited as the tricyclic antidepressants have come to dominate the treatment of depression and allied conditions. Thus, MAOIs are used most often when tricyclic antidepressants give unsatisfactory results.



Phenelzine is the hydrazine analog of phenylethylamine, a substrate of MAO. This and several other MAOIs, such as isocarboxazide, are structurally related to amphetamine and were synthesized in an attempt to enhance central stimulant properties.

- phenelzine (Nardil)
- isocarboxazid (Marplan)

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Jim Clark (Chemguide.co.uk)

23.15: Preparation of Amines

This page summarises the reactions of amines as nucleophiles. This includes their reactions with halogenoalkanes (haloalkanes or alkyl halides), with acyl chlorides (acid chlorides) and with acid anhydrides.

Amines by direct nucleophilic substitution

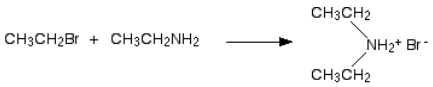
A nucleophile is something which is attracted to, and then attacks, a positive or slightly positive part of another molecule or ion. All amines contain an active lone pair of electrons on the very electronegative nitrogen atom. It is these electrons which are attracted to positive parts of other molecules or ions.

The reactions of primary amines with halogenoalkanes

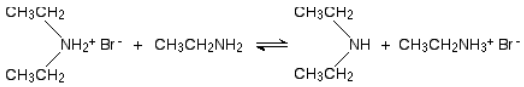
You get a complicated series of reactions on heating to give a mixture of products - probably one of the most confusing sets of reactions you will meet at this level. The products of the reactions include secondary and tertiary amines and their salts, and quaternary ammonium salts.

Making secondary amines and their salts

In the first stage of the reaction, you get the salt of a secondary amine formed. For example if you started with ethylamine and bromoethane, you would get diethylammonium bromide



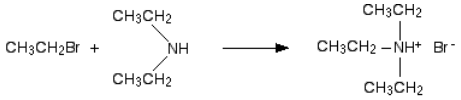
In the presence of excess ethylamine in the mixture, there is the possibility of a reversible reaction. The ethylamine removes a hydrogen from the diethylammonium ion to give free diethylamine - a secondary amine.



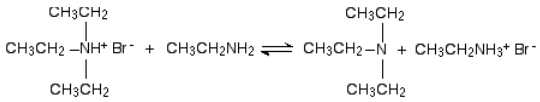
Making tertiary amines and their salts

But it doesn't stop here! The diethylamine also reacts with bromoethane - in the same two stages as before. This is where the reaction would start if you reacted a secondary amine with a halogenoalkane.

In the first stage, you get triethylammonium bromide.



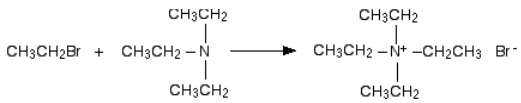
There is again the possibility of a reversible reaction between this salt and excess ethylamine in the mixture.



The ethylamine removes a hydrogen ion from the triethylammonium ion to leave a tertiary amine - triethylamine.

Making a quaternary ammonium salt

The final stage! The triethylamine reacts with bromoethane to give tetraethylammonium bromide - a quaternary ammonium salt (one in which all four hydrogens have been replaced by alkyl groups).



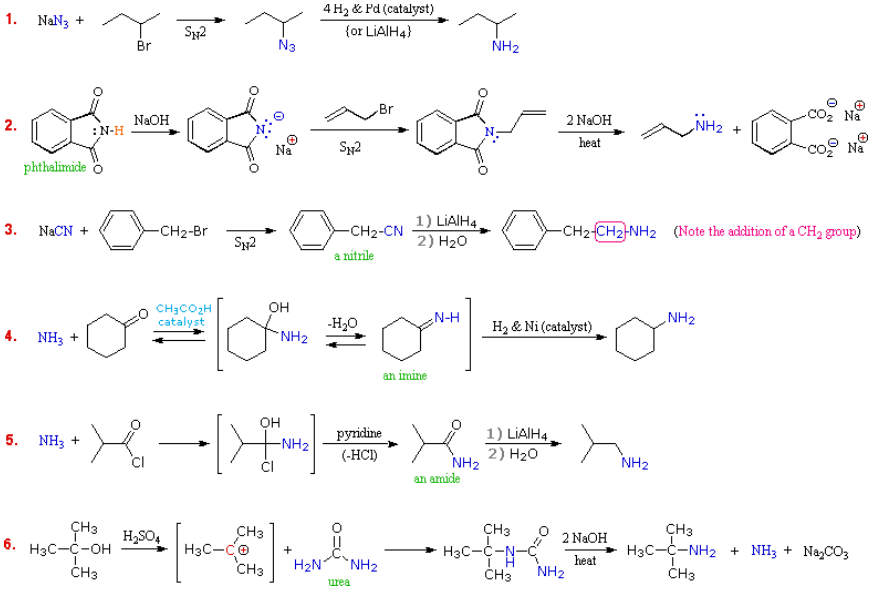
This time there isn't any hydrogen left on the nitrogen to be removed. The reaction stops here.

Preparation of Primary Amines

Although direct alkylation of ammonia by alkyl halides leads to 1º-amines, alternative procedures are preferred in many cases. These methods require two steps, but they provide pure product, usually in good yield. The general strategy is to first form a carbon-nitrogen bond by reacting a nitrogen nucleophile with a carbon electrophile. The following table lists several general examples of this strategy in the rough order of decreasing nucleophilicity of the nitrogen reagent. In the second step, extraneous nitrogen substituents that may have facilitated this bonding are removed to give the amine product.

Nitrogen Reactant	Carbon Reactant	1st Reaction Type	Initial Product	2nd Reaction Conditions	2nd Reaction Type	Final Product
$N_3^{(-)}$	RCH_2-X or R_2CH-X	S_N2	RCH_2-N_3 or R_2CH-N_3	$LiAlH_4$ or 4 H_2 & Pd	Hydrogenolysis	RCH_2-NH_2 or R_2CH-NH_2
$C_6H_5SO_2NH^{(-)}$	RCH_2-X or R_2CH-X	S_N2	RCH_2-$NHSO_2C_6H_5$ or R_2CH-$NHSO_2C_6H_5$	Na in NH_3 (liq)	Hydrogenolysis	RCH_2-NH_2 or R_2CH-NH_2
$CN^{(-)}$	RCH_2-X or R_2CH-X	S_N2	RCH_2-CN or R_2CH-CN	$LiAlH_4$	Reduction	RCH_2-CH_2NH_2 or R_2CH-CH_2NH_2
NH_3	RCH=O or R_2C=O	Addition / Elimination	RCH=NH or R_2C=NH	H_2 & Ni or $NaBH_3CN$	Reduction	RCH_2-NH_2 or R_2CH-NH_2
NH_3	RCOX	Addition / Elimination	RCO-NH_2	$LiAlH_4$	Reduction	RCH_2-NH_2
NH_2CONH_2 (urea)	$R_3C^{(+)}$	S_N1	R_3C-$NHCONH_2$	NaOH soln.	Hydrolysis	R_3C-NH_2

A specific example of each general class is provided in the diagram below. In the first two, an anionic nitrogen species undergoes an S_N2 reaction with a modestly electrophilic alkyl halide reactant. For example #2 an acidic phthalimide derivative of ammonia has been substituted for the sulfonamide analog listed in the table. The principle is the same for the two cases, as will be noted later. Example #3 is similar in nature, but extends the carbon system by a methylene group (CH_2). In all three of these methods 3º-alkyl halides cannot be used because the major reaction path is an E2 elimination.



The methods illustrated by examples #4 and #5 proceed by attack of ammonia, or equivalent nitrogen nucleophiles, at the electrophilic carbon of a carbonyl group. A full discussion of carbonyl chemistry is presented later, but for present purposes it is sufficient to recognize that the C=O double bond is polarized so that the carbon atom is electrophilic. Nucleophile addition to aldehydes and ketones is often catalyzed by acids. Acid halides and anhydrides are even more electrophilic, and do not normally

require catalysts to react with nucleophiles. The reaction of ammonia with aldehydes or ketones occurs by a reversible addition-elimination pathway to give **imines** (compounds having a C=N function). These intermediates are not usually isolated, but are reduced as they are formed (i.e. *in situ*). Acid chlorides react with ammonia to give amides, also by an addition-elimination path, and these are reduced to amines by $LiAlH_4$.

The 6th example is a specialized procedure for bonding an amino group to a 3º-alkyl group (none of the previous methods accomplishes this). Since a carbocation is the electrophilic species, rather poorly nucleophilic nitrogen reactants can be used. Urea, the diamide of carbonic acid, fits this requirement nicely. The resulting 3º-alkyl-substituted urea is then hydrolyzed to give the amine.

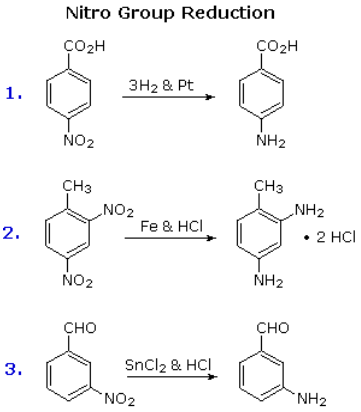
One important method of preparing 1º-amines, especially aryl amines, uses a reverse strategy. Here a strongly electrophilic nitrogen species ($NO_2^{(+)}$) bonds to a nucleophilic carbon compound. This nitration reaction gives a nitro group that can be reduced to a 1º-amine by any of several reduction procedures.

The Hofmann rearrangement of 1º-amides provides an additional synthesis of 1º-amines. To learn about this useful procedure Click Here.

Reduction of Other Functional Groups that Contain Nitrogen

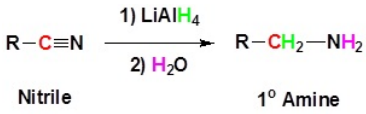
Reduction of Nitro Groups

Several methods for reducing nitro groups to amines are known. These include catalytic hydrogenation (H_2 + catalyst), zinc or tin in dilute mineral acid, and sodium sulfide in ammonium hydroxide solution. The procedures described above are sufficient for most case

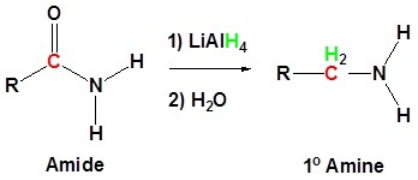


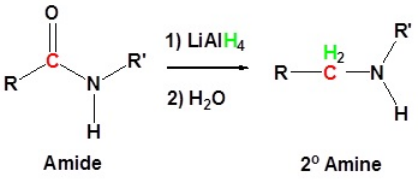
Nitriles can be converted to 1° amines by reaction with $LiAlH_4$

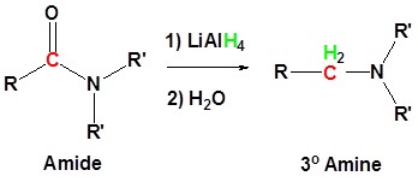
During this reaction the hydride nucleophile attacks the electrophilic carbon in the nitrile to form an imine anion. Once stabilized by a Lewis acid-base complexation the imine salt can accept a second hydride to form a dianion. The dianion can then be converted to an amine by addition of water.



Amides can be converted to 1°, 2° or 3° amines using $LiAlH_4$

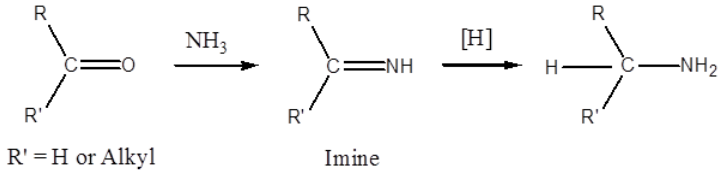


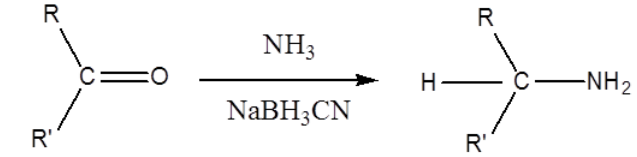


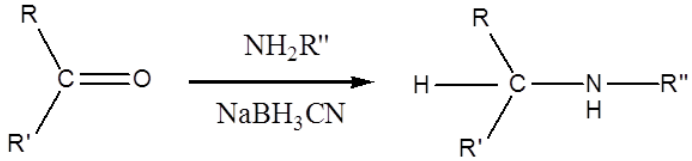


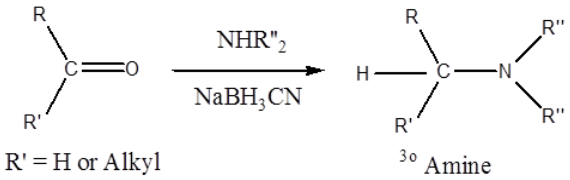
Reductive amination

Aldehydes and ketones can be converted into 1°, 2° and 3° amines using reductive amination. The reaction takes place in two parts. The first step is the nucleophiic addition of the carbonyl group to form an imine. The second step is the reduction of the imine to an amine using an reducing agent. A reducing agent commonly used for this reaction is sodium cyanoborohydride ($NaBH_3CN$).









Contributors

- Jim Clark (Chemguide.co.uk)

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)

23.16: Reactions of Amines—General Features

The basic properties of amines

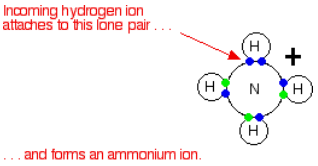
We are going to have to use two different definitions of the term "base" in this page. A base is

- a substance which combines with hydrogen ions. This is the Bronsted-Lowry theory.
- an electron pair donor. This is the Lewis theory.

The easiest way of looking at the basic properties of amines is to think of an amine as a modified ammonia molecule. In an amine, one or more of the hydrogen atoms in ammonia has been replaced by a hydrocarbon group. Replacing the hydrogens still leaves the lone pair on the nitrogen unchanged - and it is the lone pair on the nitrogen that gives ammonia its basic properties. Amines will therefore behave much the same as ammonia in all cases where the lone pair is involved.

The reactions of amines with acids

These are most easily considered using the Bronsted-Lowry theory of acids and bases - the base is a hydrogen ion acceptor. We'll do a straight comparison between amines and the familiar ammonia reactions. Ammonia reacts with acids to produce ammonium ions. The ammonia molecule picks up a hydrogen ion from the acid and attaches it to the lone pair on the nitrogen.



If the reaction is in solution in water (using a dilute acid), the ammonia takes a hydrogen ion (a proton) from a hydroxonium ion. (Remember that hydrogen ions present in solutions of acids in water are carried on water molecules as hydroxonium ions, H_3O^+.)

If the acid was hydrochloric acid, for example, you would end up with a solution containing ammonium chloride - the chloride ions, of course, coming from the hydrochloric acid. You could also write this last equation as:

. . . but if you do it this way, you must include the state symbols. If you write H^+ on its own, it implies an unattached hydrogen ion - a proton. Such things don't exist on their own in solution in water. If the reaction is happening in the gas state, the ammonia accepts a proton directly from the hydrogen chloride:

This time you produce clouds of white solid ammonium chloride

Electrophilic Substitution at Nitrogen

Ammonia and many amines are not only bases in the Brønsted sense, they are also nucleophiles that bond to and form products with a variety of electrophiles. A general equation for such **electrophilic substitution of nitrogen** is:

$$2\ R_2\ddot{N}H + E^{(+)} \rightleftharpoons R_2NHE^{(+)} \rightleftharpoons R_2\ddot{N}E + H^{(+)}\ \text{(bonded to a base)}$$

A list of some electrophiles that are known to react with amines is shown here. In each case the electrophilic atom or site is colored red.

Electrophile	$RCH_2–X$	$RCH_2–OSO_2R$	$R_2C=O$	$R(C=O)X$	$RSO_2–Cl$	$HO–N=O$

Name	Alkyl Halide	Alkyl Sulfonate	Aldehyde or Ketone	Acid Halide or Anhydride	Sulfonyl Chloride	Nitrous Acid

Contributors

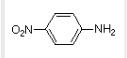
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Jim Clark (Chemguide.co.uk)

23.17: Amines as Bases

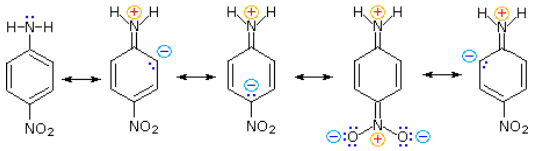
Basicity of Amines

A review of basic acid-base concepts should be helpful to the following discussion. Like ammonia, most amines are Brønsted and Lewis bases, but their base strength can be changed enormously by substituents. It is common to compare basicity's quantitatively by using the pK_a's of their conjugate acids rather than their pK_b's. Since $pK_a + pK_b = 14$, **the higher the pK_a the stronger the base**, in contrast to the usual inverse relationship of pK_a with acidity. Most simple alkyl amines have pK_a's in the range 9.5 to 11.0, and their water solutions are basic (have a pH of 11 to 12, depending on concentration). The first four compounds in the following table, including ammonia, fall into that category.

The last five compounds (colored cells) are significantly weaker bases as a consequence of three factors. The first of these is the hybridization of the nitrogen. In pyridine the nitrogen is sp^2 hybridized, and in nitriles (last entry) an sp hybrid nitrogen is part of the triple bond. In each of these compounds (shaded red) the non-bonding electron pair is localized on the nitrogen atom, but increasing s-character brings it closer to the nitrogen nucleus, reducing its tendency to bond to a proton.

Compound				NH_3						$CH_3C{\equiv}N$
pK_a	11.0	10.7	10.7	9.3	5.2	4.6	1.0	0.0	-1.0	-10.0

Secondly, aniline and p-nitroaniline (first two green shaded structures) are weaker bases due to delocalization of the nitrogen non-bonding electron pair into the aromatic ring (and the nitro substituent). This is the same delocalization that results in activation of a benzene ring toward electrophilic substitution. The following resonance equations, which are similar to those used to explain the enhanced acidity of ortho and para-nitrophenols illustrate electron pair delocalization in p-nitroaniline. Indeed, aniline is a weaker base than cyclohexyl amine by roughly a million fold, the same factor by which phenol is a stronger acid than cyclohexanol. This electron pair delocalization is accompanied by a degree of rehybridization of the amino nitrogen atom, but the electron pair delocalization is probably the major factor in the reduced basicity of these compounds. A similar electron pair delocalization is responsible for the very low basicity (and nucleophilic reactivity) of amide nitrogen atoms (last green shaded structure). This feature was instrumental in moderating the influence of amine substituents on aromatic ring substitution, and will be discussed further in the section devoted to carboxylic acid derivatives.

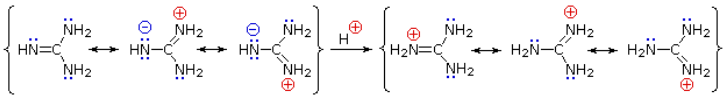


Reduced Basicity of *para*-Nitroaniline due to Electron Pair Delocalization

Conjugated amine groups influence the basicity of an existing amine. Although 4-dimethylaminopyridine (DMAP) might appear to be a base similar in strength to pyridine or N,N-dimethylaniline, it is actually more than ten thousand times stronger, thanks to charge delocalization in its conjugate acid. The structure in the gray box shows the locations over which positive charge (colored red) is delocalized in the conjugate acid. This compound is often used as a catalyst for acyl transfer reactions.

Finally, the very low basicity of pyrrole (shaded blue) reflects the exceptional delocalization of the nitrogen electron pair associated with its incorporation in an aromatic ring. Indole (pK_a = -2) and imidazole (pK_a = 7.0), see above, also have similar heterocyclic aromatic rings. Imidazole is over a million times more basic than pyrrole because the sp^2 nitrogen that is part of one double bond is structurally similar to pyridine, and has a comparable basicity.

Although resonance delocalization generally reduces the basicity of amines, a dramatic example of the reverse effect is found in the compound guanidine (pK_a = 13.6). Here, as shown below, resonance stabilization of the base is small, due to charge separation, while the conjugate acid is stabilized strongly by charge delocalization. Consequently, aqueous solutions of guanidine are nearly as basic as are solutions of sodium hydroxide.



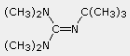
The relationship of amine basicity to the acidity of the corresponding conjugate acids may be summarized in a fashion analogous to that noted earlier for acids:

Strong bases have weak conjugate acids, and weak bases have strong conjugate acids.

Important Reagent Bases

Edit section

The significance of all these acid-base relationships to practical organic chemistry lies in the need for organic bases of varying strength, as reagents tailored to the requirements of specific reactions. The common base sodium hydroxide is not soluble in many organic solvents, and is therefore not widely used as a reagent in organic reactions. Most base reagents are alkoxide salts, amines or amide salts. Since alcohols are much stronger acids than amines, their conjugate bases are weaker than amide bases, and fill the gap in base strength between amines and amide salts. In the following table, pK_a again refers to the conjugate acid of the base drawn above it.

Base Name	Pyridine	Triethyl Amine	Hünig's Base	Barton's Base	Potassium t-Butoxide	Sodium HMDS	LDA
Formula		$(C_2H_5)_3N$			$(CH_3)_3CO^{(-)}\ K^{(+)}$	$[(CH_3)_3Si]_2N^{(-)}\ Na^{(+)}$	$[(CH_3)_2CH]_2N^{(-)}\ L$
pK_a	5.3	10.7	11.4	14	19	26	35.7

Pyridine is commonly used as an acid scavenger in reactions that produce mineral acid co-products. Its basicity and nucleophilicity may be modified by steric hindrance, as in the case of 2,6-dimethylpyridine (pK_a=6.7), or resonance stabilization, as in the case of 4-dimethylaminopyridine (pK_a=9.7). Hünig's base is relatively non-nucleophilic (due to steric hindrance), and like DBU is often used as the base in E2 elimination reactions conducted in non-polar solvents. Barton's base is a strong, poorly-nucleophilic, neutral base that serves in cases where electrophilic substitution of DBU or other amine bases is a problem. The alkoxides are stronger bases that are often used in the corresponding alcohol as solvent, or for greater reactivity in DMSO. Finally, the two amide bases see widespread use in generating enolate bases from carbonyl compounds and other weak carbon acids.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

CHAPTER OVERVIEW

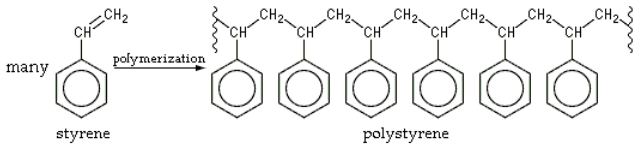
24: Synthetic Polymers

Topic hierarchy

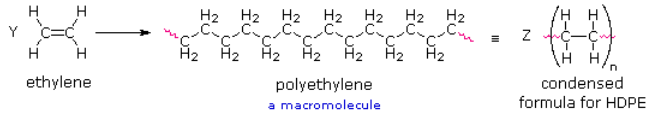
24.1: Introduction

Polymers are long chain, giant organic molecules are assembled from many smaller molecules called **monomers**. Polymers consist of many repeating monomer units in long chains, sometimes with *branching* or *cross-linking* between the chains. A polymer is analogous to a necklace made from many small beads (monomers). A chemical reaction forming polymers from monomers is called **polymerization**, of which there are many types. A common name for many synthetic polymer materials is plastic, which comes from the Greek word "plastikos", suitable for molding or shaping.

In the following illustrated example, many monomers called styrene are polymerized into a long chain polymer called polystyrene. The squiggly lines indicate that the polymer molecule extends further at both the left and right ends. In fact, polymer molecules are often hundreds or thousands of monomer units long.



The repeating structural unit of most simple polymers not only reflects the monomer(s) from which the polymers are constructed, but also provides a concise means for drawing structures to represent these macromolecules. For polyethylene, arguably the simplest polymer, this is demonstrated by the following equation. Here ethylene (ethene) is the monomer, and the corresponding linear polymer is called high-density polyethylene (HDPE). HDPE is composed of macromolecules in which n ranges from 10,000 to 100,000 (molecular weight 2×10^5 to 3×10^6).



If Y and Z represent moles of monomer and polymer respectively, Z is approximately 10^{-5} Y. This polymer is called polyethylene rather than polymethylene, $(-CH_2-)_n$, because ethylene is a stable compound (methylene is not), and it also serves as the synthetic precursor of the polymer. The two open bonds remaining at the ends of the long chain of carbons (colored magenta) are normally not specified, because the atoms or groups found there depend on the chemical process used for polymerization. The synthetic methods used to prepare this and other polymers will be described later in this chapter

Introduction

Many objects in daily use from packing, wrapping, and building materials include half of all polymers synthesized. Other uses include textiles, many electronic appliance casings, CD's, automobile parts, and many others are made from polymers. A quarter of the solid waste from homes is plastic materials - some of which may be recycled as shown in the table below.

Some products, such as adhesives, are made to include monomers which can be polymerized by the user in their application.

Polyurethane Foam

Types of Polymers

There are many types of polymers including synthetic and natural polymers.

Natural biopolymers

- Polypeptides in proteins - silk, collagen, keratin.
- Polysaccharides (Carbohydrate chains) - cellulose, starch, glycogen
- Nucleic acids - DNA and RNA

Synthetic polymers

- Plastics
- Elastomers - solids with rubber-like qualities
  - Rubber (carbon backbone often from hydrocarbon monomers)
  - silicones (backbone of alternating silicon and oxygen atoms).
- Fibers
- Solid materials of intermediate characteristics
- Gels or viscous liquids

Classification of Polymers

- Homopolymers: These consist of chains with identical bonding linkages to each monomer unit. This usually implies that the polymer is made from all identical monomer molecules. These may be represented as : -[A-A-A-A-A-A]- Homopolymers are commonly named by placing the prefix poly in front of the constituent monomer name. For example, polystyrene is the name for the polymer made from the monomer styrene (vinylbenzene).
- Copolymers: These consist of chains with two or more linkages usually implying two or more different types of monomer units. These may be represented as : -[A-B-A-B-A-B]-

Polymers classified by mode of polymerization

- Addition Polymers: The monomer molecules bond to each other without the loss of any other atoms. Addition polymers from alkene monomers or substituted alkene monomers are the biggest groups of polymers in this class. Ring opening polymerization can occur without the loss of any small molecules.
- Condensation Polymers: Usually two different monomer combine with the loss of a small molecule, usually water. Most polyesters and polyamides (nylon) are in this class of polymers. Polyurethane Foam in graphic above.

Polymers classified by Physical Response to Heating

Thermoplastics

Plastics that soften when heated and become firm again when cooled. This is the more popular type of plastic because the heating and cooling may be repeated and the thermoplastic may be reformed.

Thermosets

These are plastics that soften when heated and can be molded, but harden permanently. They will decompose when reheated. An example is Bakelite, which is used in toasters, handles for pots and pans, dishes, electrical outlets and billiard balls.

Contributors

- Charles Ophardt, Professor Emeritus, Elmhurst College; Virtual Chembook
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

24.2: Chain-Growth Polymers—Addition Polymers

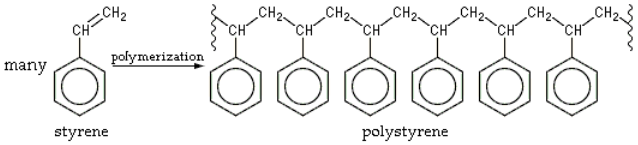
Polymers are long chain giant organic molecules are assembled from many smaller molecules called **monomers**. **Polymers** consist of many repeating monomer units in long chains. A polymer is analogous to a necklace made from many small beads (monomers). Many monomers are alkenes or other molecules with double bonds which react by **addition** to their unsaturated double bonds.

Introduction

The electrons in the double bond are used to bond two monomer molecules together. This is represented by the red arrows moving from one molecule to the space between two molecules where a new bond is to form. The formation of polyethylene from ethylene (ethene) may be illustrated in the graphic on the left as follows. In the complete polymer, all of the double bonds have been turned into single bonds. No atoms have been lost and you can see that the monomers have just been joined in the process of addition. A simple representation is -[A-A-A-A-A]-. Polyethylene is used in plastic bags, bottles, toys, and electrical insulation.

- **LDPE - Low Density Polyethylene:** The first commercial polyethylene process used peroxide catalysts at a temperature of 500 C and 1000 atmospheres of pressure. This yields a transparent polymer with highly branched chains which do not pack together well and is low in density. LDPE makes a flexible plastic. Today most LDPE is used for blow-molding of films for packaging and trash bags and flexible snap-on lids. LDPE is recyclable plastic #4.
- **HDPE - High Density Polyethylene:** An alternate method is to use Ziegler-Natta aluminum titanium catalysts to make HDPE which has very little branching, allows the strands to pack closely, and thus is high density. It is three times stronger than LDPE and more opaque. About 45% of the HDPE is blow molded into milk and disposable consumer bottles. HDPE is also used for crinkly plastic bags to pack groceries at grocery stores. HDPE is recyclable plastic #2.

Other Addition Polymers

- **PVC** (polyvinyl chloride), which is found in plastic wrap, simulated leather, water pipes, and garden hoses, is formed from vinyl chloride ($H_2C=CHCl$). The reaction is shown in the graphic on the left. Notice how every other carbon must have a chlorine attached.
- **Polypropylene:** The reaction to make polypropylene ($H_2C=CHCH_3$) is illustrated in the middle reaction of the graphic. Notice that the polymer bonds are always through the carbons of the double bond. Carbon #3 already has saturated bonds and cannot participate in any new bonds. A methyl group is on every other carbon.
- **Polystyrene:** The reaction is the same for polystrene where every other carbon has a benzene ring attached. Polystyrene (PS) is recyclable plastic #6. In the following illustrated example, many styrene monomers are polymerized into a long chain polystyrene molecule. The squiggly lines indicate that the polystyrene molecule extends further at both the left and right ends.
- 

- Blowing fine gas bubbles into liquid polystyrene and letting it solidify produces *expanded polystyrene*, called *Styrofoam* by the Dow Chemical Company.
- **Polystyrene with DVB:** Cross-linking between polymer chains can be introduced into polystyrene by copolymerizing with ***p*-divinylbenzene** (**DVB**). DVB has vinyl groups ($-CH=CH_2$) at each end of its molecule, each of which can be polymerized into a polymer chain like any other vinyl group on a styrene monomer.

Other addition polymers

Table 1: Links to various polymers with Chime molecule - Macrogalleria at U. Southern Mississippi

Monomer	Polymer Name	Trade Name	Uses
$F_2C=CF_2$	polytetrafluoroethylene	Teflon	Non-stick coating for cooking utensils, chemically-resistant specialty plastic parts, Gore-Tex
$H_2C=CCl_2$	polyvinylidene dichloride	Saran	Clinging food wrap

Monomer	Polymer Name	Trade Name	Uses
$H_2C=CH(CN)$	polyacrylonitrile	Orlon, Acrilan, Creslan	Fibers for textiles, carpets, upholstery
$H_2C=CH(OCOCH_3)$	polyvinyl acetate		Elmer's glue - Silly Putty Demo
$H_2C=CH(OH)$	polyvinyl alcohol		Ghostbusters Demo
$H_2C=C(CH_3)COOCH_3$	polymethyl methacrylate	Plexiglass, Lucite	Stiff, clear, plastic sheets, blocks, tubing, and other shapes

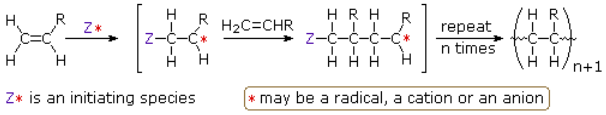
Addition polymers from conjugated dienes

Polymers from conjugated dienes usually give elastomer polymers having rubber-like properties.

Table 2. Addition homopolymers from conjugated dienes

Monomer	Polymer name	Trade name	Uses
$H_2C=CH\text{-}C(CH_3)=CH_2$	polyisoprene	natural or some synthetic rubber	applications similar to natural rubber
$H_2C=CH\text{-}CH=CH_2$	polybutadiene	polybutadiene synthetic rubber	select synthetic rubber applications
$H_2C=CH\text{-}CCl=CH_2$	polychloroprene	Neoprene	chemically-resistant rubber

All the monomers from which addition polymers are made are alkenes or functionally substituted alkenes. The most common and thermodynamically favored chemical transformations of alkenes are addition reactions. Many of these addition reactions are known to proceed in a stepwise fashion by way of reactive intermediates, and this is the mechanism followed by most polymerizations. A general diagram illustrating this assembly of linear macromolecules, which supports the name chain growth polymers, is presented here. Since a pi-bond in the monomer is converted to a sigma-bond in the polymer, the polymerization reaction is usually exothermic by 8 to 20 kcal/mol. Indeed, cases of explosively uncontrolled polymerizations have been reported.

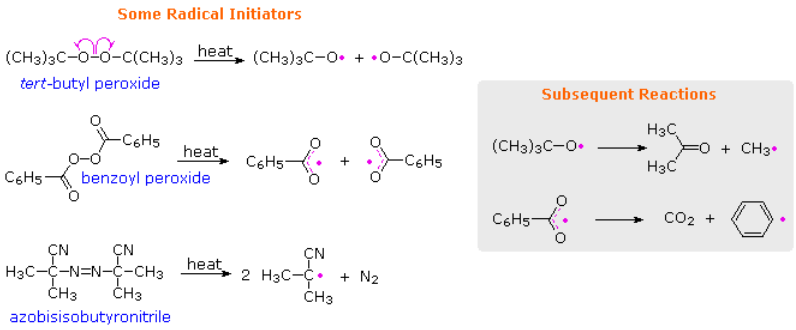


It is useful to distinguish four polymerization procedures fitting this general description.

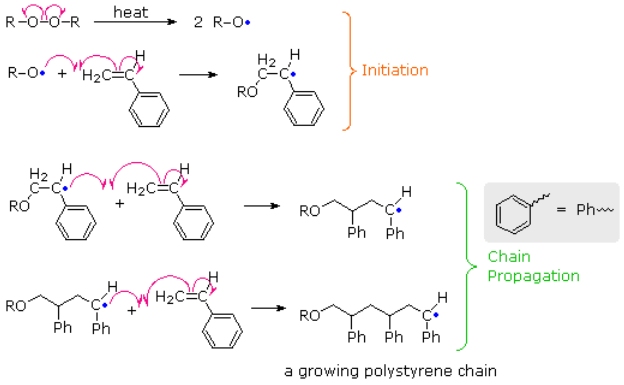
• Radical Polymerization The initiator is a radical, and the propagating site of reactivity (*) is a carbon radical.
• Cationic Polymerization The initiator is an acid, and the propagating site of reactivity (*) is a carbocation.
• Anionic Polymerization The initiator is a nucleophile, and the propagating site of reactivity (*) is a carbanion.
• Coordination Catalytic Polymerization The initiator is a transition metal complex, and the propagating site of reactivity (*) is a terminal catalytic complex.

Radical Chain-Growth Polymerization

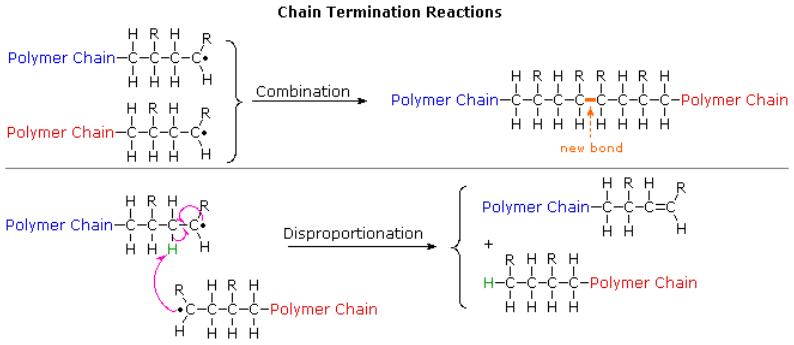
Virtually all of the monomers described above are subject to radical polymerization. Since this can be initiated by traces of oxygen or other minor impurities, pure samples of these compounds are often "stabilized" by small amounts of radical inhibitors to avoid unwanted reaction. When radical polymerization is desired, it must be started by using a radical initiator, such as a peroxide or certain azo compounds. The formulas of some common initiators, and equations showing the formation of radical species from these initiators are presented below.



By using small amounts of initiators, a wide variety of monomers can be polymerized. One example of this radical polymerization is the conversion of styrene to polystyrene, shown in the following diagram. The first two equations illustrate the initiation process, and the last two equations are examples of chain propagation. Each monomer unit adds to the growing chain in a manner that generates the most stable radical. Since carbon radicals are stabilized by substituents of many kinds, the preference for head-to-tail regioselectivity in most addition polymerizations is understandable. Because radicals are tolerant of many functional groups and solvents (including water), radical polymerizations are widely used in the chemical industry.



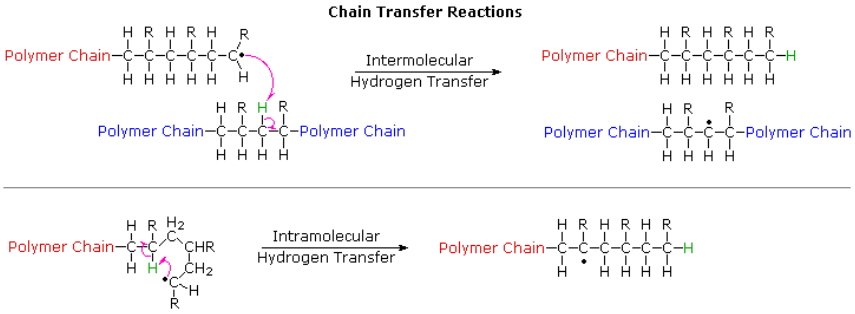
In principle, once started a radical polymerization might be expected to continue unchecked, producing a few extremely long chain polymers. In practice, larger numbers of moderately sized chains are formed, indicating that chain-terminating reactions must be taking place. The most common termination processes are Radical Combination and Disproportionation. These reactions are illustrated by the following equations. The growing polymer chains are colored blue and red, and the hydrogen atom transferred in disproportionation is colored green. Note that in both types of termination two reactive radical sites are removed by simultaneous conversion to stable product(s). Since the concentration of radical species in a polymerization reaction is small relative to other reactants (e.g. monomers, solvents and terminated chains), the rate at which these radical-radical termination reactions occurs is very small, and most growing chains achieve moderate length before termination.



The relative importance of these terminations varies with the nature of the monomer undergoing polymerization. For acrylonitrile and styrene combination is the major process. However, methyl methacrylate and vinyl acetate are terminated chiefly by disproportionation.

Another reaction that diverts radical chain-growth polymerizations from producing linear macromolecules is called chain transfer. As the name implies, this reaction moves a carbon radical from one location to another by an intermolecular or intramolecular

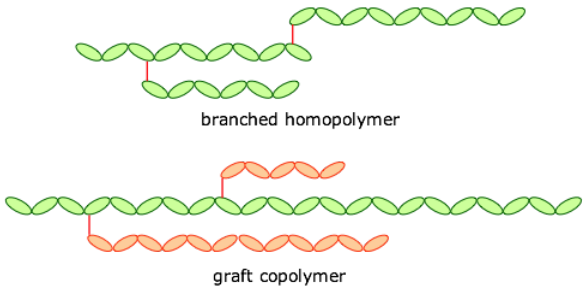
hydrogen atom transfer (colored green). These possibilities are demonstrated by the following equations



Chain transfer reactions are especially prevalent in the high pressure radical polymerization of ethylene, which is the method used to make LDPE (low density polyethylene). The 1º-radical at the end of a growing chain is converted to a more stable 2º-radical by hydrogen atom transfer. Further polymerization at the new radical site generates a side chain radical, and this may in turn lead to creation of other side chains by chain transfer reactions. As a result, the morphology of LDPE is an amorphous network of highly branched macromolecules.

Chain topology

Polymers may also be classified as straight-chained or branched, leading to forms such as these:

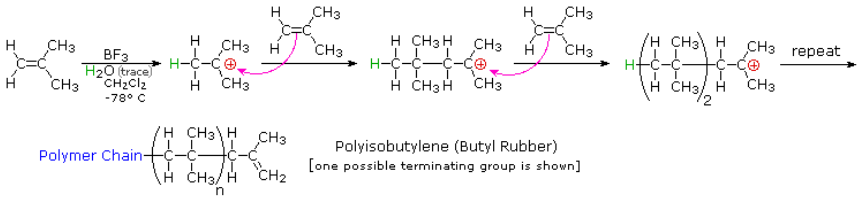


The monomers can be joined end-to-end, and they can also be *cross-linked* to provide a harder material:

If the cross-links are fairly long and flexible, adjacent chains can move with respect to each other, producing an *elastic* polymer or

Cationic Chain-Growth Polymerization

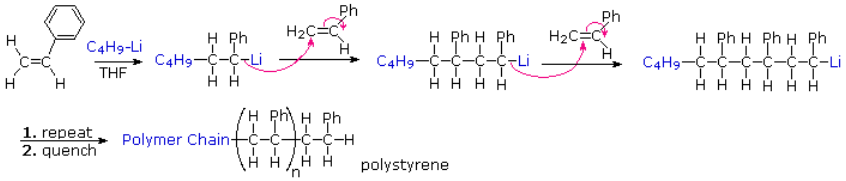
Polymerization of isobutylene (2-methylpropene) by traces of strong acids is an example of cationic polymerization. The polyisobutylene product is a soft rubbery solid, Tg = _70º C, which is used for inner tubes. This process is similar to radical polymerization, as demonstrated by the following equations. Chain growth ceases when the terminal carbocation combines with a nucleophile or loses a proton, giving a terminal alkene (as shown here).



Monomers bearing cation stabilizing groups, such as alkyl, phenyl or vinyl can be polymerized by cationic processes. These are normally initiated at low temperature in methylene chloride solution. Strong acids, such as HClO4 , or Lewis acids containing traces of water (as shown above) serve as initiating reagents. At low temperatures, chain transfer reactions are rare in such polymerizations, so the resulting polymers are cleanly linear (unbranched).

Anionic Chain-Growth Polymerization

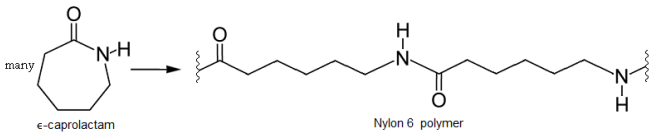
Treatment of a cold THF solution of styrene with 0.001 equivalents of n-butyllithium causes an immediate polymerization. This is an example of anionic polymerization, the course of which is described by the following equations. Chain growth may be terminated by water or carbon dioxide, and chain transfer seldom occurs. Only monomers having anion stabilizing substituents, such as phenyl, cyano or carbonyl are good substrates for this polymerization technique. Many of the resulting polymers are largely isotactic in configuration, and have high degrees of crystallinity.



Species that have been used to initiate anionic polymerization include alkali metals, alkali amides, alkyl lithiums and various electron sources. A practical application of anionic polymerization occurs in the use of superglue. This material is methyl 2-cyanoacrylate, CH2=C(CN)CO2CH3. When exposed to water, amines or other nucleophiles, a rapid polymerization of this monomer takes place.

Ring opening polymerization

In this kind of polymerization, molecular rings are opened in the formation of a polymer. Here epsilon-caprolactam, a 6-carbon cyclic monomer, undergoes ring opening to form a Nylon 6 homopolymer, which is somewhat similar to but not the same as Nylon 6,6 alternating copolymer.



Addition Copolymerization

Most direct copolymerizations of equimolar mixtures of different monomers give statistical copolymers, or if one monomer is much more reactive a nearly homopolymer of that monomer. The copolymerization of styrene with methyl methacrylate, for example, proceeds differently depending on the mechanism. Radical polymerization gives a statistical copolymer. However, the product of cationic polymerization is largely polystyrene, and anionic polymerization favors formation of poly(methyl methacrylate). In cases where the relative reactivities are different, the copolymer composition can sometimes be controlled by continuous introduction of a biased mixture of monomers into the reaction.

Formation of alternating copolymers is favored when the monomers have different polar substituents (e.g. one electron withdrawing and the other electron donating), and both have similar reactivities toward radicals. For example, styrene and acrylonitrile copolymerize in a largely alternating fashion.

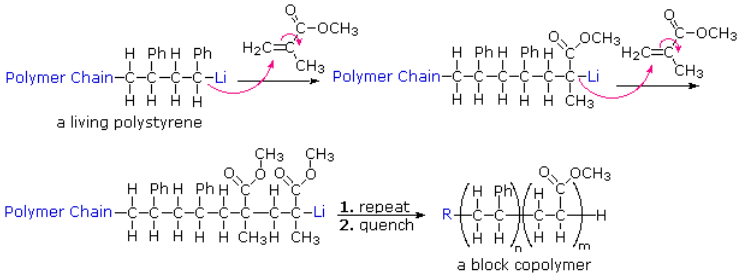
Some Useful Copolymers

Monomer A	Monomer B	Copolymer	Uses
$H_2C=CHCl$	$H_2C=CCl_2$	Saran	films & fibers
$H_2C=CHC_6H_5$	$H_2C=C-CH=CH_2$	SBR styrene butadiene rubber	tires
$H_2C=CHCN$	$H_2C=C-CH=CH_2$	Nitrile Rubber	adhesives hoses
$H_2C=C(CH_3)_2$	$H_2C=C-CH=CH_2$	Butyl Rubber	inner tubes
$F_2C=CF(CF_3)$	$H_2C=CHF$	Viton	gaskets

A terpolymer of acrylonitrile, butadiene and styrene, called ABS rubber, is used for high-impact containers, pipes and gaskets.

Block Copolymerization

Several different techniques for preparing block copolymers have been developed, many of which use condensation reactions (next section). At this point, our discussion will be limited to an application of anionic polymerization. In the anionic polymerization of styrene described above, a reactive site remains at the end of the chain until it is quenched. The unquenched polymer has been termed a living polymer, and if additional styrene or a different suitable monomer is added a block polymer will form. This is illustrated for methyl methacrylate in the following diagram.



Contributors

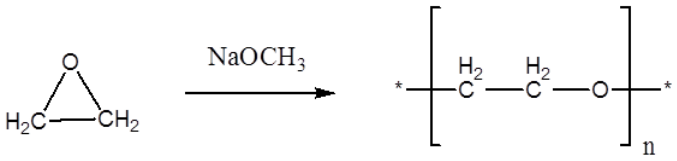
Charles Ophardt (Professor Emeritus, Elmhurst College); Virtual Chembook

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

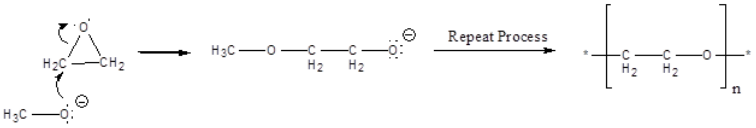
24.3: Anionic Polymerization of Epoxides

Another type of anionic polymerization involves an epoxide and forms a polyether. The strained three-memebered epoxide ring is easily opened by nuleophiles, typically a hydroxide or an alkoxy group. Note! This polymerization is different to the other chain-growth polymerizations discussed because the process forms a C-O bond in the polymer chain.

Reaction



Mechanism

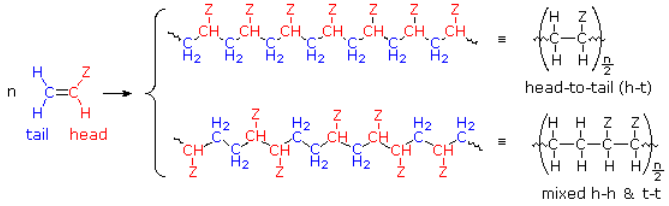


Contributors

- Prof. Steven Farmer (Sonoma State University)

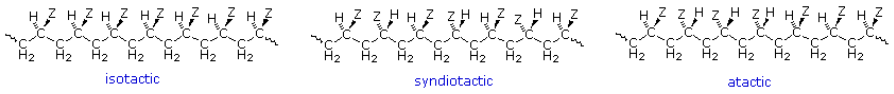
24.4: Ziegler–Natta Catalysts and Polymer Stereochemistry

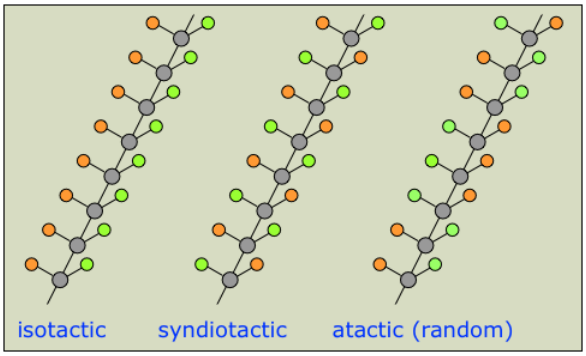
Symmetrical monomers such as ethylene and tetrafluoroethylene can join together in only one way. Monosubstituted monomers, on the other hand, may join together in two organized ways, described in the following diagram, or in a third random manner. Most monomers of this kind, including propylene, vinyl chloride, styrene, acrylonitrile and acrylic esters, prefer to join in a head-to-tail fashion, with some randomness occurring from time to time. The reasons for this regioselectivity will be discussed in the synthetic methods section.



Regioisomeric Polymers from Substituted Monomers

If the polymer chain is drawn in a zig-zag fashion, as shown above, each of the substituent groups (Z) will necessarily be located above or below the plane defined by the carbon chain. Consequently we can identify three configurational isomers of such polymers. If all the substituents lie on one side of the chain the configuration is called isotactic. If the substituents alternate from one side to another in a regular manner the configuration is termed syndiotactic. Finally, a random arrangement of substituent groups is referred to as atactic. Examples of these configurations are shown here.





Many common and useful polymers, such as polystyrene, polyacrylonitrile and poly(vinyl chloride) are atactic as normally prepared. Customized catalysts that effect stereoregular polymerization of polypropylene and some other monomers have been developed, and the improved properties associated with the increased crystallinity of these products has made this an important field of investigation. The following values of Tg have been reported.

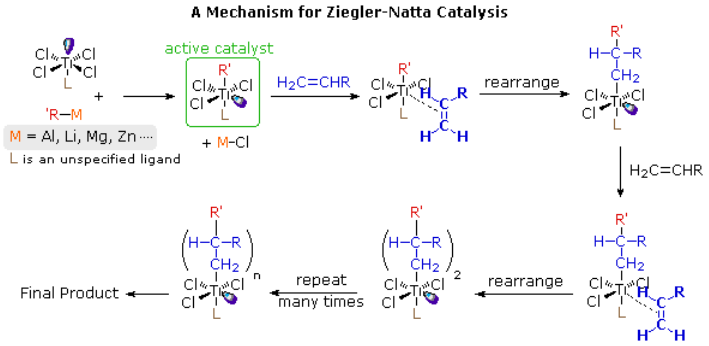
Polymer	T_g atactic	T_g isotactic	T_g syndiotactic
PP	–20 ºC	0 ºC	–8 ºC
PMMA	100 ºC	130 ºC	120 ºC

The properties of a given polymer will vary considerably with its tacticity. Thus, atactic polypropylene is useless as a solid construction material, and is employed mainly as a component of adhesives or as a soft matrix for composite materials. In contrast, isotactic polypropylene is a high-melting solid (ca. 170 ºC) which can be molded or machined into structural components.

Ziegler-Natta Catalytic Polymerization

An efficient and stereospecific catalytic polymerization procedure was developed by Karl Ziegler (Germany) and Giulio Natta (Italy) in the 1950's. Their findings permitted, for the first time, the synthesis of unbranched, high molecular weight polyethylene (HDPE), laboratory synthesis of natural rubber from isoprene, and configurational control of polymers from terminal alkenes like propene (e.g. pure isotactic and syndiotactic polymers). In the case of ethylene, rapid polymerization occurred at atmospheric pressure and moderate to low temperature, giving a stronger (more crystalline) product (HDPE) than that from radical polymerization (LDPE). For this important discovery these chemists received the 1963 Nobel Prize in chemistry.

Ziegler-Natta catalysts are prepared by reacting certain transition metal halides with organometallic reagents such as alkyl aluminum, lithium and zinc reagents. The catalyst formed by reaction of triethylaluminum with titanium tetrachloride has been widely studied, but other metals (e.g. V & Zr) have also proven effective. The following diagram presents one mechanism for this useful reaction. Others have been suggested, with changes to accommodate the heterogeneity or homogeneity of the catalyst. Polymerization of propylene through action of the titanium catalyst gives an isotactic product; whereas, a vanadium based catalyst gives a syndiotactic product.



Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

24.5: Natural and Synthetic Rubbers

Rubber is an example of an elastomer type polymer, where the polymer has the ability to return to its original shape after being stretched or deformed. The rubber polymer is coiled when in the resting state. The elastic properties arise from the its ability to stretch the chains apart, but when the tension is released the chains snap back to the original position. The majority of rubber polymer molecules contain at least some units derived from conjugated diene monomers (see Polymerization of Conjugated Dienes). Such conjugated diene monomers have a constructive backbone of at least four carbon atoms with a double-single-double bond reactive core (C=C-C=C). Most if not practically all such dienes undergo 1,4-addition to the polymer chain, where 1 and 4 refer to the 1st and 4th carbons of the backbone unit, which become single-bonded to the rest of the polymer chain. The diene's double bonds turn into single bonds, and the single bond between them turns into a Z or E configured double bond, depending on the polymerization conditions. The unit's backbone thus becomes like this (-C-C=C-C-). Rubber gets its elasticity when the formed double bond gets the Z configuration. For 1,3-butadiene, Z is equivalent to a *cis* and E is equivalent to a *trans* configuration.

Natural Rubber

Natural rubber is an addition polymer that is obtained as a milky white fluid known as latex from a tropical rubber tree. Natural rubber is from the monomer isoprene (2-methyl-1,3-butadiene), which is a conjugated diene hydrocarbon as mentioned above. In natural rubber, most of the double fonds formed in the polymer chain have the Z configuration, resulting in natural rubber's elastomer qualities.

Charles Goodyear accidentally discovered that by mixing sulfur and rubber, the properties of the rubber improved in being tougher, resistant to heat and cold, and increased in elasticity. This process was later called vulcanization after the Roman god of fire. Vulcanization causes shorter chains to cross link through the sulfur to longer chains. The development of vulcanized rubber for automobile tires greatly aided this industry.

Synthetic Rubber

Important conjugated dienes used in synthetic rubbers include isoprene (2-methyl-1,3-butadiene), 1,3-butadiene, and chloroprene (2-chloro-1,3-butadiene). Polymerized 1,3-butadiene is mostly referred to simply as polybutadiene. Polymerized chloroprene was developed by DuPont and given the trade name *Neoprene*.

In a number of cases, monomers which are not dienes are also used for certain types of synthetic rubber, often copolymerized with dienes. Some of the most commercially important addition polymers are the copolymers. These are polymers made by polymerizing a mixture of two or more monomers. An example is *styrene-butadiene rubber* (SBR) - which is a copolymer of 1,3-butadiene and styrene which is mixed in a 3 to 1 ratio, respectively.

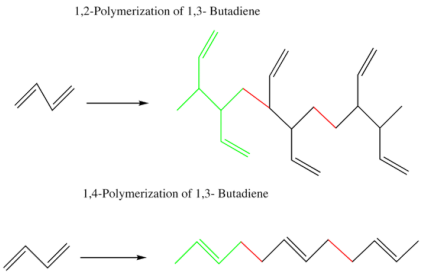
SBR rubber was developed during World War II when important supplies of natural rubber were cut off. SBR is more resistant to abrasion and oxidation than natural rubber and can also be vulcanized. More than 40% of the synthetic rubber production is SBR and is used in tire production. A tiny amount is used for bubble-gum in the unvulcanized form.

Nitrile rubber is copolymerized from butadiene and acrylonitrile (H_2C=CH-CN). *Butyl rubber* is copolymerized from isobutylene [which is methylpropene $H_2C=C(CH_3)_2$] and a small percentage of isoprene. *Silicone rubber* and other compounds, chemically called *polysiloxanes*, are not from conjugated dienes but have repeating units like -O-SiR_2- where R is some organic radical group like methyl. There is a separate page on Silicone Polymers.

Conjugated dienes (alkenes with two double bonds and a single bond in between) can be polymerized to form important compounds like rubber. This takes place, in different forms, both in nature and in the laboratory. Interactions between double bonds on multiple chains leads to cross-linkage which creates elasticity within the compound.

Polymerization of 1,3-Butadiene

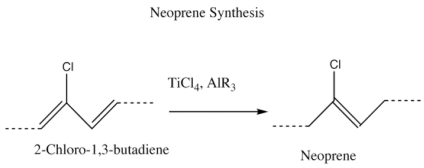
For rubber compounds to be synthesized, 1,3-butadiene must be polymerized. Below is a simple illustration of how this compound is formed into a chain. The 1,4 polymerization is much more useful to polymerization reactions.



Above, the green structures represent the base units of the polymers that are synthesized and the red represents the bonds between these units which form these polymers. Whether the 1,3 product or the 1,4 product is formed depends on whether the reaction is thermally or kinetically controlled.

Synthetic Rubber

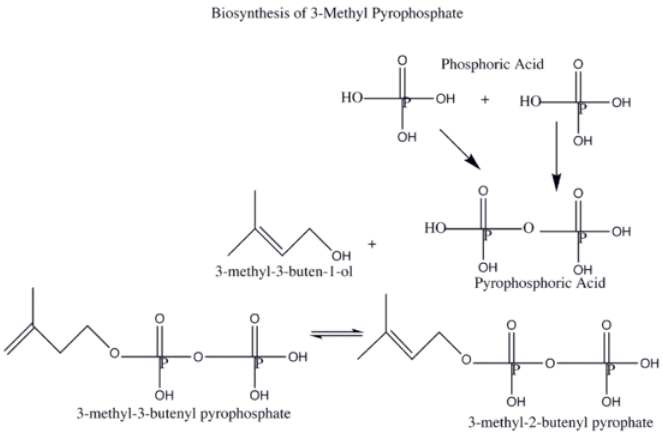
The most important synthetic rubber is Neoprene which is produced by the polymerization of 2-chloro-1,3-butadiene.



In this illustration, the dashed lines represent repetition of the same base units, so both the products and reactants are polymers. The reaction proceeds with a mechanism similar to the Friedel-Crafts mechanism. Cross-linkage between the chlorine atom of one chain and the double bond of another contributes to the overall elasticity of neoprene. This cross-linkage occurs as the chains lie next to each other at random angles, and the attractions between double bonds prevent them from sliding back and forth.

Natural Rubber

The synthesis of rubber in nature in somewhat similar the artificial synthesis of rubber except that it takes place within a plant. Instead of the 2-chloro-1,3-butadiene used in the synthesis of neoprene, natural rubber is synthesized from 2-methyl-1,3-butadiene. As an electrophile, the plant synthesizes the pyrophosphate 3-methyl-3-butenyl pyrophosphate is from phosphoric acid and 3-methyl-3-buten-1-ol. This pyrophosphate then catalyzes the reaction that leads to natural rubber.



The 3-methyl-3-butenyl pyrophosphate (OPP) is then used in the polymerization of natural rubber as it pulls electrons off 2-methyl-1,3-butadiene (see questions section for this process.)

Outside links

- "Dienes," http://en.wikipedia.org/wiki/Diene
- "Rubber," http://en.wikipedia.org/wiki/Rubber
- "Neoprene," http://en.wikipedia.org/wiki/Neoprene

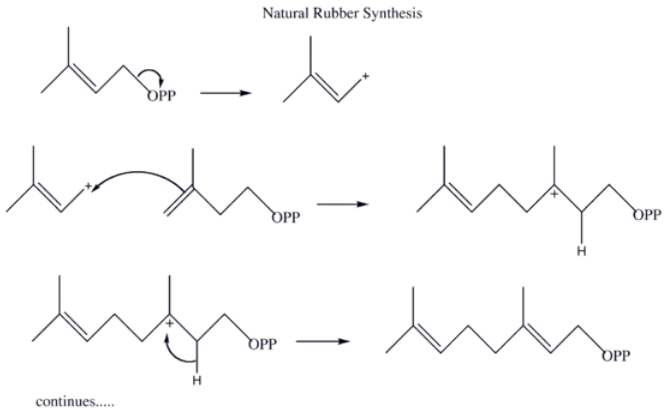
References

1. Vollhardt, Peter, and Neil E. Schore. Organic Chemistry: Structure and Function. New York: W. H. Freeman & Company, 2007.
2. Buehr, Walter. Rubber: Natural and Synthetic. Morrow, 1964.

Problem

Draw out the mechanism for the natural synthesis of rubber from 3-methyl-3-butenyl pyrophosphate and 2-methyl-1,3-butadiene. Show the movement of electrons with arrows.

Answer



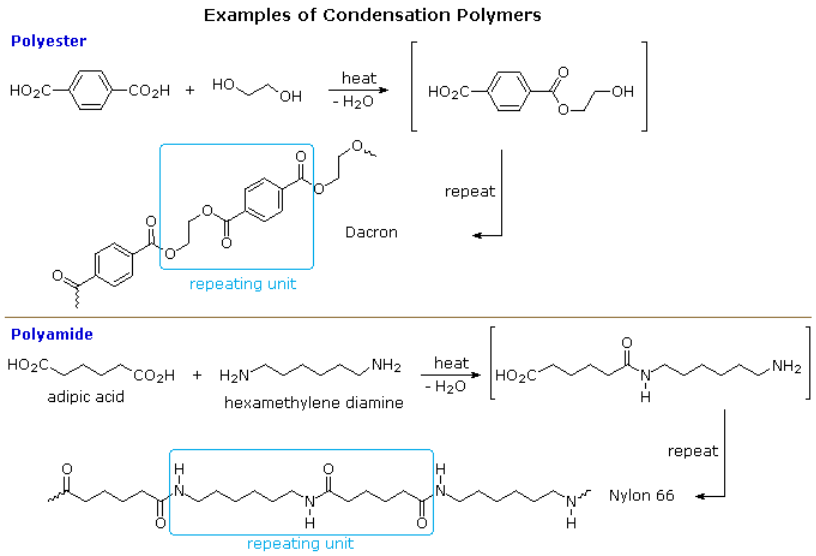
Contributors

- Charles Ophardt, Professor Emeritus, Elmhurst College; Virtual Chembook
- User:H Padleckas

24.6: Step-Growth Polymers—Condensation Polymers

A large number of important and useful polymeric materials are not formed by chain-growth processes involving reactive species such as radicals, but proceed instead by conventional functional group transformations of polyfunctional reactants. These polymerizations often (but not always) occur with loss of a small byproduct, such as water, and generally (but not always) combine two different components in an alternating structure. The polyester Dacron and the polyamide Nylon 66, shown here, are two examples of synthetic condensation polymers, also known as step-growth polymers. In contrast to chain-growth polymers, most of which grow by carbon-carbon bond formation, step-growth polymers generally grow by carbon-heteroatom bond formation (C-O & C-N in Dacron & Nylon respectively). Although polymers of this kind might be considered to be alternating copolymers, the repeating monomeric unit is usually defined as a combined moiety.

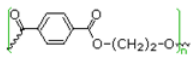
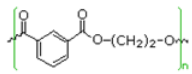
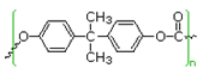
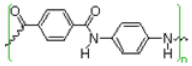
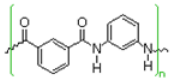
Examples of naturally occurring condensation polymers are cellulose, the polypeptide chains of proteins, and poly(β-hydroxybutyric acid), a polyester synthesized in large quantity by certain soil and water bacteria. Formulas for these will be displayed below by clicking on the diagram.



Characteristics of Condensation Polymers

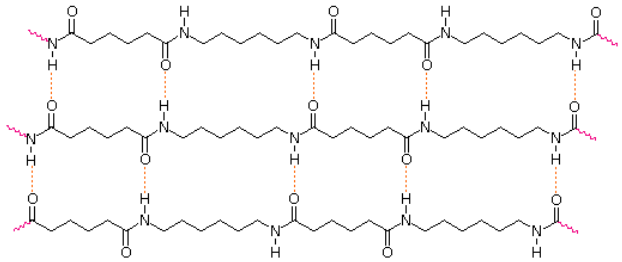
Condensation polymers form more slowly than addition polymers, often requiring heat, and they are generally lower in molecular weight. The terminal functional groups on a chain remain active, so that groups of shorter chains combine into longer chains in the late stages of polymerization. The presence of polar functional groups on the chains often enhances chain-chain attractions, particularly if these involve hydrogen bonding, and thereby crystallinity and tensile strength. The following examples of condensation polymers are illustrative.

Note that for commercial synthesis the carboxylic acid components may actually be employed in the form of derivatives such as simple esters. Also, the polymerization reactions for Nylon 6 and Spandex do not proceed by elimination of water or other small molecules. Nevertheless, the polymer clearly forms by a step-growth process. Some Condensation Polymers

Formula	Type	Components	T_g ºC	T_m ºC
~[CO(CH$_2$)$_4$CO-OCH$_2$CH$_2$O]$_n$~	**polyester**	HO$_2$C-(CH$_2$)$_4$-CO$_2$H HO-CH$_2$CH$_2$-OH	< 0	50
	**polyester** Dacron, Mylar	para HO$_2$C-C$_6$H$_4$-CO$_2$H HO-CH$_2$CH$_2$-OH	70	265
	**polyester**	meta HO$_2$C-C$_6$H$_4$-CO$_2$H HO-CH$_2$CH$_2$-OH	50	240
	**polycarbonate** Lexan	(HO-C$_6$H$_4$-)$_2$C(CH$_3$)$_2$ (Bisphenol A) X$_2$C=O (X = OCH$_3$ or Cl)	150	267
~[CO(CH$_2$)$_4$CO-NH(CH$_2$)$_6$NH]$_n$~	**polyamide** Nylon 66	HO$_2$C-(CH$_2$)$_4$-CO$_2$H H$_2$N-(CH$_2$)$_6$-NH$_2$	45	265
~[CO(CH$_2$)$_5$NH]$_n$~	**polyamide** Nylon 6 Perlon		53	223
	**polyamide** Kevlar	para HO$_2$C-C$_6$H$_4$-CO$_2$H para H$_2$N-C$_6$H$_4$-NH$_2$	---	500
	**polyamide** Nomex	meta HO$_2$C-C$_6$H$_4$-CO$_2$H meta H$_2$N-C$_6$H$_4$-NH$_2$	273	390

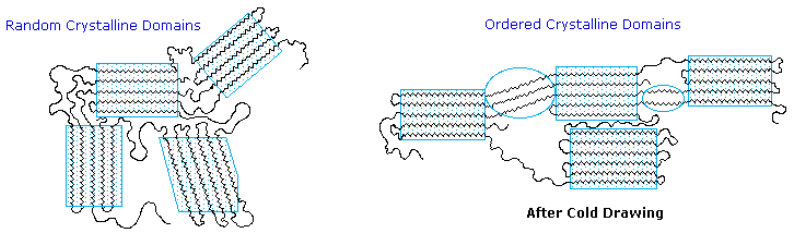
The difference in Tg and Tm between the first polyester (completely aliphatic) and the two nylon polyamides (5th & 6th entries) shows the effect of intra-chain hydrogen bonding on crystallinity. The replacement of flexible alkylidene links with rigid benzene rings also stiffens the polymer chain, leading to increased crystalline character, as demonstrated for polyesters (entries 1, 2 &3) and polyamides (entries 5, 6, 7 & 8). The high Tg and Tm values for the amorphous polymer Lexan are consistent with its brilliant transparency and glass-like rigidity. Kevlar and Nomex are extremely tough and resistant materials, which find use in bullet-proof vests and fire resistant clothing.

Interchain Hydrogen Bonding Enhances Crystallinity

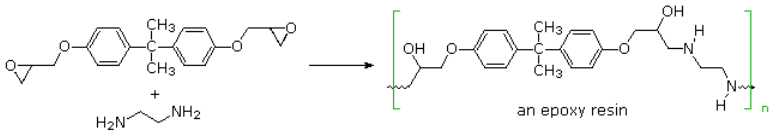


Many polymers, both addition and condensation, are used as fibers The chief methods of spinning synthetic polymers into fibers are from melts or viscous solutions. Polyesters, polyamides and polyolefins are usually spun from melts, provided the Tm is not too high. Polyacrylates suffer thermal degradation and are therefore spun from solution in a volatile solvent. Cold-drawing is an important physical treatment that improves the strength and appearance of these polymer fibers. At temperatures above T_g, a thicker than desired fiber can be forcibly stretched to many times its length; and in so doing the polymer chains become untangled, and tend to align in a parallel fashion. This cold-drawing procedure organizes randomly oriented crystalline domains, and also aligns amorphous domains so they become more crystalline. In these cases, the physically oriented morphology is stabilized and retained in the final product. This contrasts with elastomeric polymers, for which the stretched or aligned morphology is unstable relative to the amorphous random coil morphology.

This cold-drawing treatment may also be used to treat polymer films (e.g. Mylar & Saran) as well as fibers.

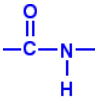


Step-growth polymerization is also used for preparing a class of adhesives and amorphous solids called epoxy resins. Here the covalent bonding occurs by an S_N2 reaction between a nucleophile, usually an amine, and a terminal epoxide. In the following example, the same bisphenol A intermediate used as a monomer for Lexan serves as a difunctional scaffold to which the epoxide rings are attached. Bisphenol A is prepared by the acid-catalyzed condensation of acetone with phenol.



What are polyamides?

Polyamides are polymers where the repeating units are held together by amide links. An amide group has the formula - $CONH_2$. An amide link has this structure:



In an amide itself, of course, the bond on the right is attached to a hydrogen atom.

Nylon

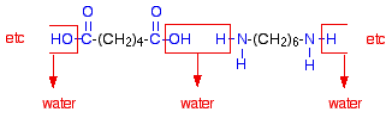
In nylon, the repeating units contain chains of carbon atoms. (That is different from Kevlar, where the repeating units contain benzene rings - see below.) There are various different types of nylon depending on the nature of those chains.

Nylon-6,6

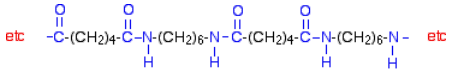
Nylon-6,6 is made from two monomers each of which contain 6 carbon atoms - hence its name. One of the monomers is a 6 carbon acid with a -COOH group at each end - hexanedioic acid. The other monomer is a 6 carbon chain with an amino group, $-NH_2$, at each end. This is 1,6-diaminohexane (also known as hexane-1,6-diamine).

When these two compounds polymerise, the amine and acid groups combine, each time with the loss of a molecule of water. This is known as condensation polymerization. Condensation polymerization is the formation of a polymer involving the loss of a small molecule. In this case, the molecule is water, but in other cases different small molecules might be lost.

The diagram shows the loss of water between two of the monomers:

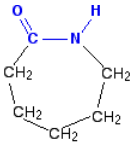


This keeps on happening, and so you get a chain which looks like this:



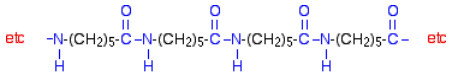
Nylon-6

Iit is possible to get a polyamide from a single monomer. Nylon-6 is made from a monomer called caprolactam.



caprolactam

Notice that this already contains an amide link. When this molecule polymerizes, the ring opens, and the molecules join up in a continuous chain.



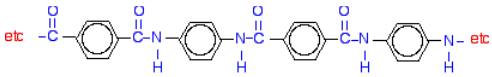
Kevlar

Kevlar is similar in structure to nylon-6,6 except that instead of the amide links joining chains of carbon atoms together, they join benzene rings. The two monomers are benzene-1,4-dicarboxylic acid and 1,4-diaminobenzene.

benzene-1,4-dicarboxylic acid

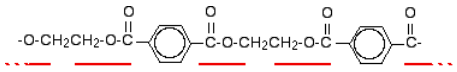
1,4-diaminobenzene

If you line these up and remove water between the -COOH and -NH_2 groups in the same way as we did with nylon-6,6, you get the structure of Kevlar:



What is a polyester?

A polyester is a polymer (a chain of repeating units) where the individual units are held together by ester linkages.



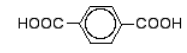
ester linkages

The diagram shows a very small bit of the polymer chain and looks pretty complicated. But it is not very difficult to work out - and that's the best thing to do: work it out, not try to remember it. You will see how to do that in a moment.

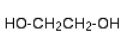
The usual name of this common polyester is poly(ethylene terephthalate). The everyday name depends on whether it is being used as a fibre or as a material for making things like bottles for soft drinks. When it is being used as a fiber to make clothes, it is often just called *polyester*. It may sometimes be known by a brand name like *Terylene*. When it is being used to make bottles, for example, it is usually called *PET*.

Making polyesters as an example of condensation polymerisation

In condensation polymerisation, when the monomers join together a small molecule gets lost. That's different from addition polymerisation which produces polymers like poly(ethene) - in that case, nothing is lost when the monomers join together. A polyester is made by a reaction involving an acid with two -COOH groups, and an alcohol with two -OH groups. In the common polyester drawn below.



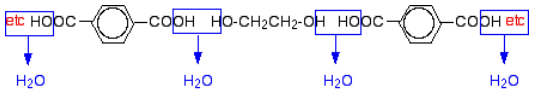
benzene-1,4-dicarboxylic acid



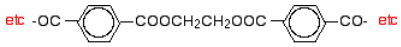
ethane-1,2-diol

Figure: The acid is benzene-1,4-dicarboxylic acid (old name: terephthalic acid) and the alcohol is ethane-1,2-diol (old name: ethylene glycol).

Now imagine lining these up alternately and making esters with each acid group and each alcohol group, losing a molecule of water every time an ester linkage is made.



That would produce the chain shown above (although this time written without separating out the carbon-oxygen double bond - write it whichever way you like).



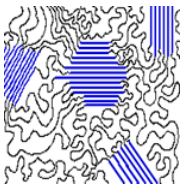
Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Jim Clark (Chemguide.co.uk)

24.7: Polymer Structure and Properties

A comparison of the properties of polyethylene (both LDPE & HDPE) with the natural polymers rubber and cellulose is instructive. As noted above, synthetic HDPE macromolecules have masses ranging from 105 to 106 amu (LDPE molecules are more than a hundred times smaller). Rubber and cellulose molecules have similar mass ranges, but fewer monomer units because of the monomer's larger size. The physical properties of these three polymeric substances differ from each other, and of course from their monomers.

- HDPE is a rigid translucent solid which softens on heating above 100º C, and can be fashioned into various forms including films. It is not as easily stretched and deformed as is LDPE. HDPE is insoluble in water and most organic solvents, although some swelling may occur on immersion in the latter. HDPE is an excellent electrical insulator.
- LDPE is a soft translucent solid which deforms badly above 75º C. Films made from LDPE stretch easily and are commonly used for wrapping. LDPE is insoluble in water, but softens and swells on exposure to hydrocarbon solvents. Both LDPE and HDPE become brittle at very low temperatures (below -80º C). Ethylene, the common monomer for these polymers, is a low boiling (-104º C) gas.
- Natural (latex) rubber is an opaque, soft, easily deformable solid that becomes sticky when heated (above. 60º C), and brittle when cooled below -50º C. It swells to more than double its size in nonpolar organic solvents like toluene, eventually dissolving, but is impermeable to water. The C5H8 monomer isoprene is a volatile liquid (b.p. 34º C).
- Pure cellulose, in the form of cotton, is a soft flexible fiber, essentially unchanged by variations in temperature ranging from -70 to 80º C. Cotton absorbs water readily, but is unaffected by immersion in toluene or most other organic solvents. Cellulose fibers may be bent and twisted, but do not stretch much before breaking. The monomer of cellulose is the $C_6H_{12}O_6$ aldohexose D-glucose. Glucose is a water soluble solid melting below 150º C.



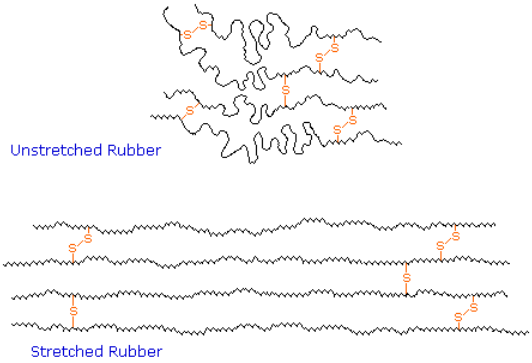
To account for the differences noted here we need to consider the nature of the aggregate macromolecular structure, or morphology, of each substance. Because polymer molecules are so large, they generally pack together in a non-uniform fashion, with ordered or crystalline-like regions mixed together with disordered or amorphous domains. In some cases the entire solid may be amorphous, composed entirely of coiled and tangled macromolecular chains. Crystallinity occurs when linear polymer chains are structurally oriented in a uniform three-dimensional matrix. In the diagram on the right, crystalline domains are colored blue.
Increased crystallinity is associated with an increase in rigidity, tensile strength and opacity (due to light scattering). Amorphous polymers are usually less rigid, weaker and more easily deformed. They are often transparent.

Three factors that influence the degree of crystallinity are:
i) Chain length
ii) Chain branching
iii) Interchain bonding

The importance of the first two factors is nicely illustrated by the differences between LDPE and HDPE. As noted earlier, HDPE is composed of very long unbranched hydrocarbon chains. These pack together easily in crystalline domains that alternate with amorphous segments, and the resulting material, while relatively strong and stiff, retains a degree of flexibility. In contrast, LDPE is composed of smaller and more highly branched chains which do not easily adopt crystalline structures. This material is therefore softer, weaker, less dense and more easily deformed than HDPE. As a rule, mechanical properties such as ductility, tensile strength, and hardness rise and eventually level off with increasing chain length.

The nature of cellulose supports the above analysis and demonstrates the importance of the third factor (iii). To begin with, cellulose chains easily adopt a stable rod-like conformation. These molecules align themselves side by side into fibers that are stabilized by inter-chain hydrogen bonding between the three hydroxyl groups on each monomer unit. Consequently, crystallinity is high and the cellulose molecules do not move or slip relative to each other. The high concentration of hydroxyl groups also accounts for the facile absorption of water that is characteristic of cotton.

Natural rubber is a completely amorphous polymer. Unfortunately, the potentially useful properties of raw latex rubber are limited by temperature dependence; however, these properties can be modified by chemical change. The cis-double bonds in the hydrocarbon chain provide planar segments that stiffen, but do not straighten the chain. If these rigid segments are completely removed by hydrogenation (H2 & Pt catalyst), the chains lose all constrainment, and the product is a low melting paraffin-like semisolid of little value. If instead, the chains of rubber molecules are slightly cross-linked by sulfur atoms, a process called vulcanization which was discovered by Charles Goodyear in 1839, the desirable elastomeric properties of rubber are substantially improved. At 2 to 3% crosslinking a useful soft rubber, that no longer suffers stickiness and brittleness problems on heating and cooling, is obtained. At 25 to 35% crosslinking a rigid hard rubber product is formed. The following illustration shows a cross-linked section of amorphous rubber. By clicking on the diagram it will change to a display of the corresponding stretched section. The more highly-ordered chains in the stretched conformation are entropically unstable and return to their original coiled state when allowed to relax



Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

24.8: Green Polymer Synthesis

24.9: Polymer Recycling and Disposal

Most plastics crumble into ever-tinier fragments as they are exposed to sunlight and the elements. Except for the small amount that's been incinerated–and it's a very small amount–every bit of plastic ever made still exists, unless the material's molecular structure is designed to favor biodegradation. Unfortunately, cleaning up the garbage patch is not a realistic option, and unless we change our disposal and recycling habits, it will undoubtedly get bigger. One sensible solution would require manufacturers to use natural biodegradable packaging materials whenever possible, and consumers to conscientiously dispose of their plastic waste. Thus, instead of consigning all plastic trash to a land fill, some of it may provide energy by direct combustion, and some converted for reuse as a substitute for virgin plastics. The latter is particularly attractive since a majority of plastics are made from petroleum, a diminishing resource with a volatile price.

The energy potential of plastic waste is relatively significant, ranging from 10.2 to 30.7MJ kg Ã, suggesting application as an energy source and temperature stabilizer in municipal incinerators, thermal power plants and cement kilns. The use of plastic waste as a fuel source would be an effective means of reducing landfill requirements while recovering energy. This, however, depends on using appropriate materials. Inadequate control of combustion, especially for plastics containing chlorine, fluorine and bromine, constitutes a risk of emitting toxic pollutants.

Whether used as fuels or a source of recycled plastic, plastic waste must be separated into different categories. To this end, an identification coding system was developed by the Society of the Plastics Industry (SPI) in 1988, and is used internationally. This code, shown on the right, is a set of symbols placed on plastics to identify the polymer type, for the purpose of allowing efficient separation of different polymer types for recycling. The abbreviations of the code are explained in the following table.

PETE	HDPE	V	LDPE
polyethylene terephthalate	high density polyethylene	polyvinyl chloride	low density polyethylene
PP	**PS**	**OTHER**	
polypropylene	polystyrene	polyesters, acrylics polyamides, teflon etc.	

Despite use of the recycling symbol in the coding of plastics, there is consumer confusion about which plastics are readily recyclable. In most communities throughout the United States, PETE and HDPE are the only plastics collected in municipal recycling programs. However, some regions are expanding the range of plastics collected as markets become available. (Los Angeles, for example, recycles all clean plastics numbered 1 through 7) In theory, most plastics are recyclable and some types can be used in combination with others. In many instances, however, there is an incompatibility between different types that necessitates their effective separation. Since the plastics utilized in a given manufacturing sector (e.g. electronics, automotive, etc.) is generally limited to a few types, effective recycling is often best achieved with targeted waste streams.

Recycled Plastics

Recycle Code	Abbreviation and Chemical Name of Plastic	Types of Uses and Examples
1	PET - polyethylene terephthalate	Many types of clear plastic consumer bottles, including clear, 2-liter beverage bottles
2	HDPE - High density polyethylene	Milk jugs, detergent bottles, some water bottles, some grocery plastic bags
3	PVC - Polyvinyl chloride	Plastic drain pipe, shower curtains, some water bottles

4	LDPE - Low density polyethylene	Plastic garbage and other bags, garment bags, snap-on lids such as coffee can lids
5	PP - Polypropylene	Many translucent (or opaque) plastic containers; containers for some products such as yogurt, soft butter, or margarine; aerosol can tops; rigid bottle caps; candy wrappers; bottoms of bottles
6	PS - Polystyrene	Hard clear plastic cups, foam cups, eating utensils, deli food containers, toy model kits, some packing popcorn
7	Other	Polycarbonate is a common type, Biodegradable, Some packing popcorn

Index

Glossary

Sample Word 1 | Sample Definition 1

Detailed Licensing

Overview

Title: Map: Organic Chemistry (Smith)

Webpages: 368

Applicable Restrictions: Noncommercial

All licenses found:

- CC BY-NC-SA 4.0: 97.3% (358 pages)
- Undeclared: 2.4% (9 pages)
- CC BY-NC-SA 3.0: 0.3% (1 page)

By Page