ORGANIC CHEMISTRY II

Layne Morsch et al.
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Organic Chemistry Vol II

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CHAPTER OVERVIEW

12: STRUCTURE DETERMINATION - MASS SPECTROMETRY AND INFRARED SPECTROSCOPY

LEARNING OBJECTIVES

After you have completed Chapter 12, you should be able to

1. fulfillall of the detailed objectives listed under each individual section.
2. solve road-map problems that include mass spectral data, infrared data, or both.
3. define, and use in context, the key terms introduced.

The processes of identifying and characterizing organic compounds are of great importance to the working organic chemist. With the use of modern instrumental techniques, these tasks can now be accomplished much more readily than in the past. In this chapter, you will learn about two spectroscopic techniques (mass spectroscopy and infrared spectroscopy) that are used to identify organic compounds.

12.0: INTRODUCTION

OBJECTIVE

After completing this section, you should be able to recognize the various spectroscopic techniques used to identify and characterize organic compounds.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- spectroscopy

STUDY NOTES

The term spectroscopy is used to describe a number of techniques used by chemists to obtain information about the structure and bonding of chemical compounds. Four types of spectroscopy are described in the course:

1. mass spectroscopy (also called mass spectrometry, Chapter 12).
2. infrared spectroscopy (often simply called IR, Chapter 12).
3. nuclear magnetic resonance spectroscopy (usually referred to as NMR, Chapter 13).
4. ultraviolet spectroscopy (abbreviated UV, Chapter 14).

Of these four techniques, we shall spend the least time on ultraviolet spectroscopy, as it is much less powerful than the other three. If you do any reading on chemistry outside of the course materials, you will almost certainly see references to other spectroscopic techniques, such as Raman spectroscopy, electron spin resonance (ESR) spectroscopy, and atomic absorption (AA) spectroscopy. Even a description of these techniques and the information they can provide is beyond the scope of this course.

12.1: MASS SPECTROMETRY OF SMALL MOLECULES - MAGNETIC-SECTOR INSTRUMENTS

OBJECTIVES

After completing this section, you should be able to

1. describe, briefly, how a mass spectrometer works.
2. sketch a simple diagram to show the essential features of a mass spectrometer.
3. identify peaks in a simple mass spectrum, and explain how they arise.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- base peak
- parent peak (molecular ion peak)
- cation radical
- relative abundance
- mass spectrometer
- mass spectroscopy
- mass spectrum
- molecular ion (M+·)
- mass-to-charge ratio (*m/z*)

STUDY NOTES

You may remember from general first-year chemistry how mass spectroscopy has been used to establish the atomic mass and abundance of isotopes.

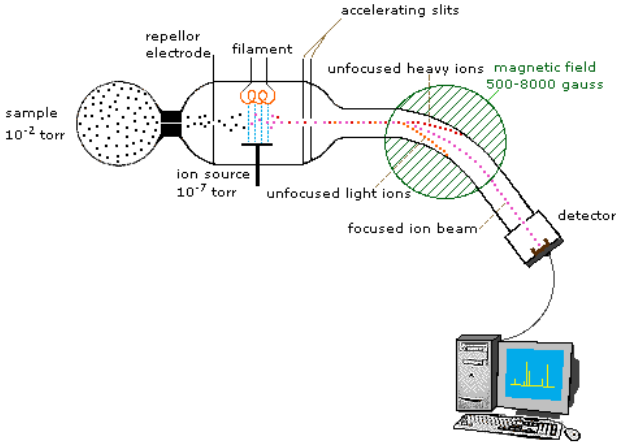
Mass spectrometers are large and expensive, and usually operated only by fully trained personnel, so you may not have the opportunity to use such an instrument as part of this course. Research chemists often rely quite heavily on mass spectra to assist them in the identification of compounds, and you will be required to interpret simple mass spectra both in assignments and on examinations. Note that in most attempts to identify an unknown compound, chemists do not rely exclusively on the results obtained from a single spectroscopic technique. A combination of chemical and physical properties and spectral evidence is usually employed.

THE MASS SPECTROMETER

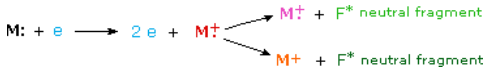
In order to measure the characteristics of individual molecules, a mass spectrometer converts them to ions so that they can be moved about and manipulated by external electric and magnetic fields. The three essential functions of a mass spectrometer, and the associated components, are:

1. A small sample is ionized, usually to cations by loss of an electron. **The Ion Source**
2. The ions are sorted and separated according to their mass and charge. **The Mass Analyzer**
3. The separated ions are then measured, and the results displayed on a chart. **The Detector**

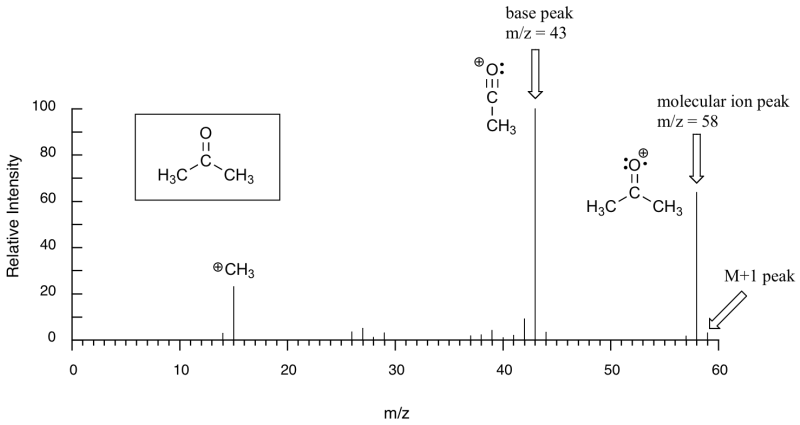
Because ions are very reactive and short-lived, their formation and manipulation must be conducted in a vacuum. Atmospheric pressure is around 760 torr (mm of mercury). The pressure under which ions may be handled is roughly 10^{-5} to 10^{-8} torr (less than a billionth of an atmosphere). Each of the three tasks listed above may be accomplished in different ways. In one common procedure, ionization is effected by a high energy beam of electrons, and ion separation is achieved by accelerating and focusing the ions in a beam, which is then bent by an external magnetic field. The ions are then detected electronically and the resulting information is stored and analyzed in a computer. A mass spectrometer operating in this fashion is outlined in the following diagram. The heart of the spectrometer is the **ion source**. Here molecules of the sample (black dots) are bombarded by electrons (light blue lines) issuing from a heated filament. This is called an **EI** (electron-ionization) source. Gases and volatile liquid samples are allowed to leak into the ion source from a reservoir (as shown). Non-volatile solids and liquids may be introduced directly. Cations formed by the electron bombardment (red dots) are pushed away by a charged repellor plate (anions are attracted to it), and accelerated toward other electrodes, having slits through which the ions pass as a beam. Some of these ions fragment into smaller cations and neutral fragments. A perpendicular magnetic field deflects the ion beam in an arc whose radius is inversely proportional to the mass of each ion. Lighter ions are deflected more than heavier ions. By varying the strength of the magnetic field, ions of different mass can be focused progressively on a detector fixed at the end of a curved tube (also under a high vacuum).



When a high energy electron collides with a molecule it often ionizes it by knocking away one of the molecular electrons (either bonding or non-bonding). This leaves behind a **molecular ion** (colored red in the following diagram). Residual energy from the collision may cause the molecular ion to fragment into neutral pieces (colored green) and smaller **fragment ions** (colored pink and orange). The molecular ion is a radical cation, but the fragment ions may either be radical cations (pink) or carbocations (orange), depending on the nature of the neutral fragment. An animated display of this ionization process will appear if you click on the ion source of the mass spectrometer diagram.



Below is typical output for an electron-ionization MS experiment (MS data below is derived from the Spectral Database for Organic Compounds, a free, web-based service provided by AIST in Japan.



The sample is acetone. On the horizontal axis is the value for m/z, which is the mass to charge ratio (as we stated above, the charge z is almost always +1, so in practice this is the same as mass). On the vertical axis is the relative abundance of each ion detected. On this scale, the most abundant ion, called the **base peak**, is set to 100%, and all other peaks are recorded relative to this value. For acetone, the base peak corresponds to a fragment with m/z = 43 - . The molecular weight of acetone is 58, so we can identify the peak at m/z = 58 as that corresponding to the **molecular ion peak**, or **parent peak**. Notice that there is a small peak at m/z = 59: this is referred to as the **M+1 peak**. How can there be an ion that has a greater mass than the molecular ion? Simple: a small fraction - about 1.1% - of all carbon atoms in nature are actually the ^{13}C rather than the ^{12}C isotope. The ^{13}C isotope is, of course, heavier than ^{12}C by 1 mass unit. In addition, about 0.015% of all hydrogen atoms are actually deuterium, the ^{2}H isotope. So the M+1 peak represents those few acetone molecules in the sample which contained either a ^{13}C or ^{2}H.

12.2: INTERPRETING MASS SPECTRA

OBJECTIVES

After completing this section, you should be able to

1. suggest possible molecular formulas for a compound, given the *m/z* value for the molecular ion, or a mass spectrum from which this value can be obtained.
2. predict the relative heights of the M+·, (M + 1)+·, etc., peaks in the mass spectrum of a compound, given the natural abundance of the isotopes of carbon and the other elements present in the compound.
3. interpret the fragmentation pattern of the mass spectrum of a relatively simple, known compound (e.g., hexane).
4. use the fragmentation pattern in a given mass spectrum to assist in the identification of a relatively simple, unknown compound (e.g., an unknown alkane).

STUDY NOTES

When interpreting fragmentation patterns, you may find it helpful to know that, as you might expect, the weakest carbon-carbon bonds are the ones most likely to break. You might wish to refer to the table of bond dissociation energies when attempting problems involving the interpretation of mass spectra.

This page looks at how fragmentation patterns are formed when organic molecules are fed into a mass spectrometer, and how you can get information from the mass spectrum.

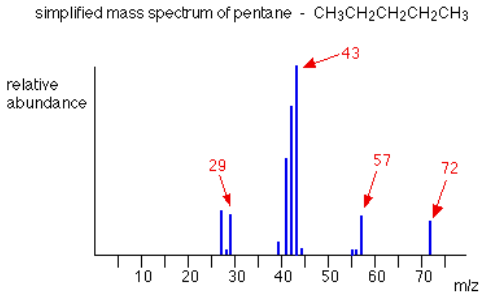
THE ORIGIN OF FRAGMENTATION PATTERNS

When the vaporized organic sample passes into the ionization chamber of a mass spectrometer, it is bombarded by a stream of electrons. These electrons have a high enough energy to knock an electron off an organic molecule to form a positive ion. This ion is called the **molecular ion - or sometimes the parent ion** and is often given the symbol M^+ or $M^{+\bullet}$. The dot in this second version represents the fact that somewhere in the ion there will be a single unpaired electron. That's one half of what was originally a pair of electrons - the other half is the electron which was removed in the ionization process.

The molecular ions are energetically unstable, and some of them will break up into smaller pieces. The simplest case is that a molecular ion breaks into two parts - one of which is another positive ion, and the other is an uncharged free radical.

The uncharged free radical will **not** produce a line on the mass spectrum. Only charged particles will be accelerated, deflected and detected by the mass spectrometer. These uncharged particles will simply get lost in the machine - eventually, they get removed by the vacuum pump.

The ion, X^+, will travel through the mass spectrometer just like any other positive ion - and will produce a line on the stick diagram. All sorts of fragmentations of the original molecular ion are possible - and that means that you will get a whole host of lines in the mass spectrum. For example, the mass spectrum of pentane looks like this:



NOTE

The pattern of lines in the mass spectrum of an *organic compound* tells you something quite different from the pattern of lines in the mass spectrum of an *element*. With an element, each line represents a different isotope of that element. With a compound, each line represents a different fragment produced when the molecular ion breaks up.

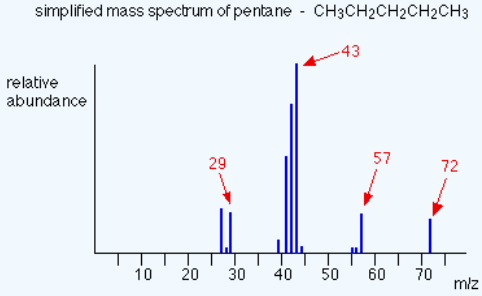
In the stick diagram showing the mass spectrum of pentane, the line produced by the heaviest ion passing through the machine (at m/z = 72) is due to the molecular ion. The tallest line in the stick diagram (in this case at m/z = 43) is called the **base peak**. This is usually given an arbitrary height of 100, and the height of everything else is measured relative to this. The base peak is the tallest peak because it represents the commonest fragment ion to be formed - either because there are several ways in which it could be produced during fragmentation of the parent ion, or because it is a particularly stable ion.

USING FRAGMENTATION PATTERNS

This section will ignore the information you can get from the molecular ion (or ions). That is covered in three other pages which you can get at via the mass spectrometry menu. You will find a link at the bottom of the page.

EXAMPLE 12.2.1: PENTANE

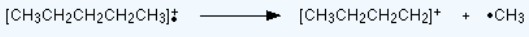
Let's have another look at the mass spectrum for pentane:



What causes the line at m/z = 57?

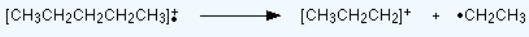
How many carbon atoms are there in this ion? There cannot be 5 because 5 x 12 = 60. What about 4? 4 x 12 = 48. That leaves 9 to make up a total of 57. How about $C_4H_9^+$ then?

$C_4H_9^+$ would be $[CH_3CH_2CH_2CH_2]^+$, and this would be produced by the following fragmentation:

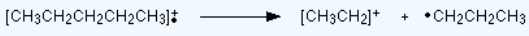


The methyl radical produced will simply get lost in the machine.

The line at m/z = 43 can be worked out similarly. If you play around with the numbers, you will find that this corresponds to a break producing a 3-carbon ion:



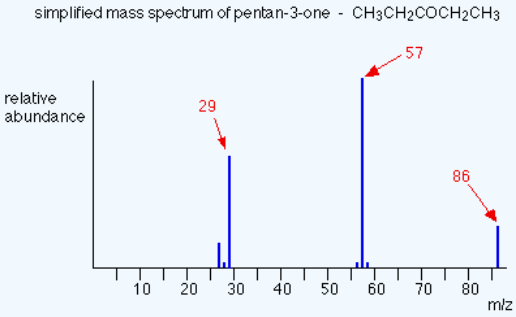
The line at m/z = 29 is typical of an ethyl ion, $[CH_3CH_2]^+$:



The other lines in the mass spectrum are more difficult to explain. For example, lines with m/z values 1 or 2 less than one of the easy lines are often due to loss of one or more hydrogen atoms during the fragmentation process.

EXAMPLE 12.2.2: PENTAN-3-ONE

This time the base peak (the tallest peak - and so the commonest fragment ion) is at m/z = 57. But this is not produced by the same ion as the same m/z value peak in pentane.



If you remember, the m/z = 57 peak in pentane was produced by $[CH_3CH_2CH_2CH_2]^+$. If you look at the structure of pentan-3-one, it's impossible to get that particular fragment from it.

Work along the molecule mentally chopping bits off until you come up with something that adds up to 57. With a small amount of patience, you'll eventually find $[CH_3CH_2CO]^+$ - which is produced by this fragmentation:

You would get exactly the same products whichever side of the CO group you split the molecular ion. The m/z = 29 peak is produced by the ethyl ion - which once again could be formed by splitting the molecular ion either side of the CO group.

PEAK HEIGHTS AND STABILITY

The more stable an ion is, the more likely it is to form. The more of a particular sort of ion that's formed, the higher its peak height will be. We'll look at two common examples of this.

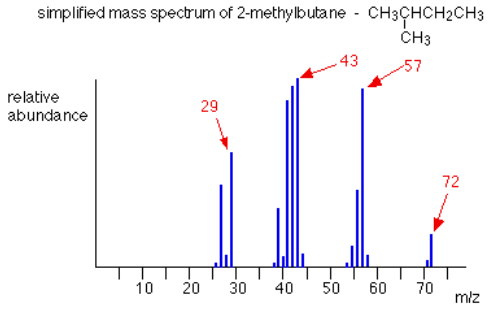
CARBOCATIONS (CARBONIUM IONS)

Summarizing the most important conclusion from the page on carbocations:

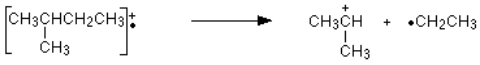
Order of stability of carbocations

primary < secondary < tertiary

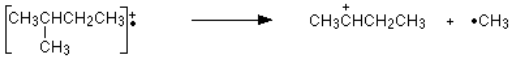
Applying the logic of this to fragmentation patterns, it means that a split which produces a secondary carbocation is going to be more successful than one producing a primary one. A split producing a tertiary carbocation will be more successful still. Let's look at the mass spectrum of 2-methylbutane. 2-methylbutane is an isomer of pentane - isomers are molecules with the same molecular formula, but a different spatial arrangement of the atoms.



Look first at the very strong peak at m/z = 43. This is caused by a different ion than the corresponding peak in the pentane mass spectrum. This peak in 2-methylbutane is caused by:



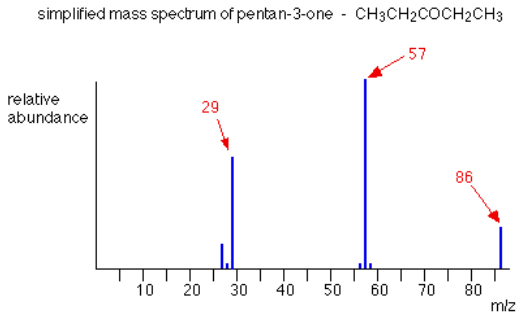
The ion formed is a secondary carbocation - it has two alkyl groups attached to the carbon with the positive charge. As such, it is relatively stable. The peak at m/z = 57 is much taller than the corresponding line in pentane. Again a secondary carbocation is formed - this time, by:



You would get the same ion, of course, if the left-hand CH_3 group broke off instead of the bottom one as we've drawn it. In these two spectra, this is probably the most dramatic example of the extra stability of a secondary carbocation.

ACYLIUM IONS, $[RCO]^+$

Ions with the positive charge on the carbon of a carbonyl group, C=O, are also relatively stable. This is fairly clearly seen in the mass spectra of ketones like pentan-3-one.



The base peak, at m/z=57, is due to the $[CH_3CH_2CO]^+$ ion. We've already discussed the fragmentation that produces this.

NOTE

The more stable an ion is, the more likely it is to form. The more of a particular ion that is formed, the higher will be its peak height.

USING MASS SPECTRA TO DISTINGUISH BETWEEN COMPOUNDS

Suppose you had to suggest a way of distinguishing between pentan-2-one and pentan-3-one using their mass spectra.

pentan-2-one	$CH_3COCH_2CH_2CH_3$
pentan-3-one	$CH_3CH_2COCH_2CH_3$

Each of these is likely to split to produce ions with a positive charge on the CO group. In the pentan-2-one case, there are two different ions like this:

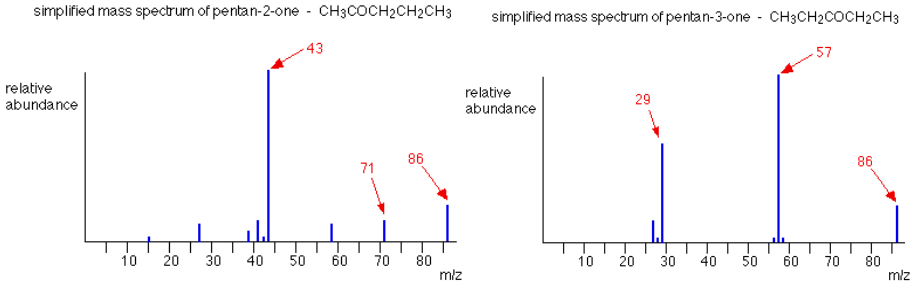
- $[CH_3CO]^+$
- $[COCH_2CH_2CH_3]^+$

That would give you strong lines at m/z = 43 and 71. With pentan-3-one, you would only get one ion of this kind:

- $[CH_3CH_2CO]^+$

In that case, you would get a strong line at 57. You don't need to worry about the other lines in the spectra - the 43, 57 and 71 lines give you plenty of difference between the two. The 43 and 71 lines are missing from the pentan-3-one spectrum, and the 57 line is missing from the pentan-2-one one.

The two mass spectra look like this:



As you've seen, the mass spectrum of even very similar organic compounds will be quite different because of the different fragmentation patterns that can occur. Provided you have a computer data base of mass spectra, any unknown spectrum can be computer analyzed and simply matched against the data base.

EXERCISES

QUESTIONS

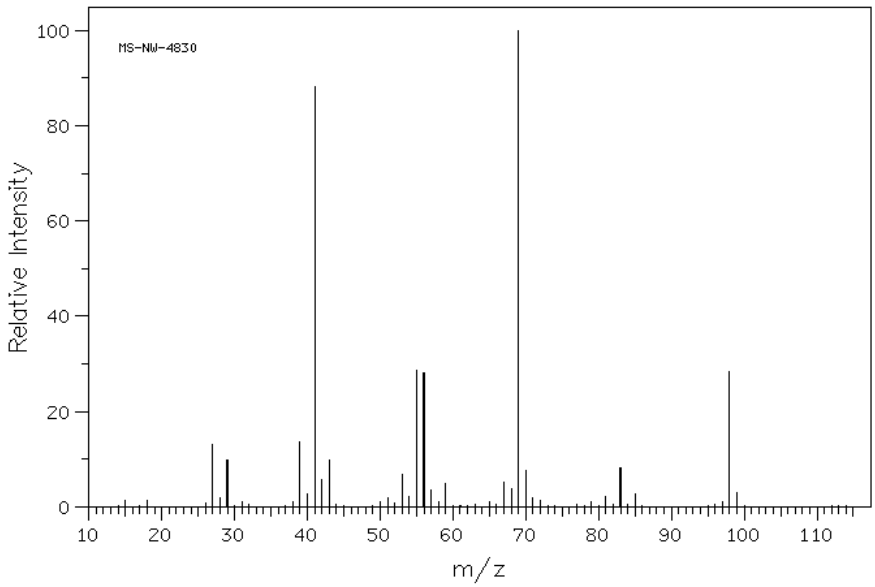
Q12.2.1

Caffeine has a mass of 194.19 amu, determined by mass spectrometry, and contains C, N, H, O. What is a molecular formula for this molecule?

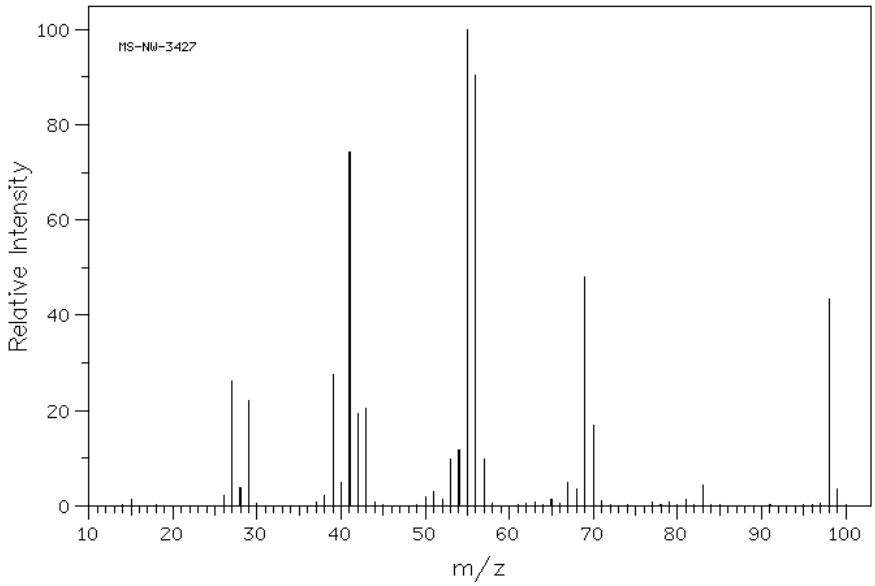
Q12.2.2

The following are the spectra for 2-methyl-2-hexene and 2-heptene, which spectra belongs to the correct molecule. Explain.

A:



B:



Source: SDBSWeb : http://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, 2 December 2016)

SOLUTIONS

S12.2.1

$C_8H_{10}N_4O_2$

C = 12 × 8 = 96

N = 14 × 4 = 56

H = 1 × 10 = 10

O = 2 × 16 = 32

96+56+10+32 = 194 g/mol

S12.2.2

The (A) spectrum is 2-methyl-2-hexene and the (B) spectrum is 2-heptene. Looking at (A) the peak at 68 *m/z* is the fractioned molecule with just the tri-substituted alkene present. While (B) has a strong peak around the 56 *m/z*, which in this case is the di-substituted alkene left behind from the linear heptene.

12.3: MASS SPECTROMETRY OF SOME COMMON FUNCTIONAL GROUPS

OBJECTIVE

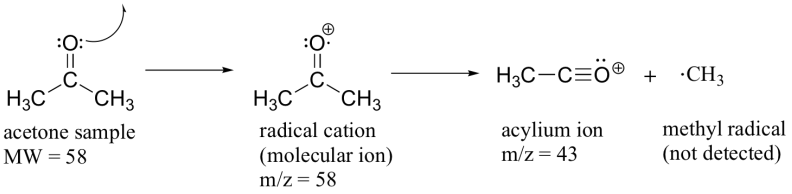
After completing this section, you should be able to predict the expected fragmentation for common functional groups, such as alcohols, amines, and carbonyl compounds.

KEY TERMS

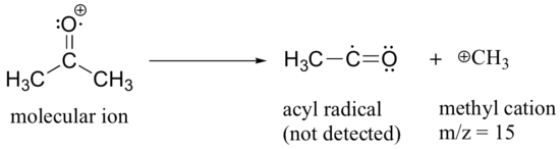
Make certain that you can define, and use in context, the key terms below.

- alpha (α) cleavage
- McLafferty rearrangement

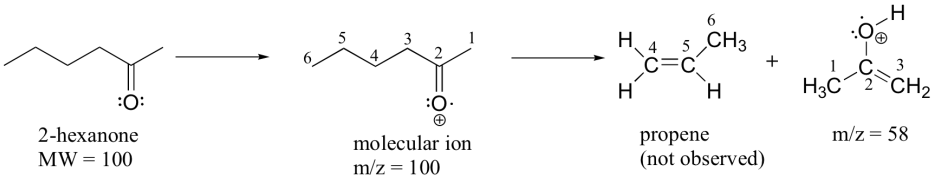
Much of the utility in electron-ionization MS comes from the fact that the radical cations generated in the electron-bombardment process tend to fragment in predictable ways. Detailed analysis of the typical fragmentation patterns of different functional groups is beyond the scope of this text, but it is worthwhile to see a few representative examples, even if we don't attempt to understand the exact process by which the fragmentation occurs. We saw, for example, that the base peak in the mass spectrum of acetone is m/z = 43. This is the result of cleavage at the 'alpha' position - in other words, at the carbon-carbon bond adjacent to the carbonyl. Alpha cleavage results in the formation of an acylium ion (which accounts for the base peak at m/z = 43) and a methyl radical, which is neutral and therefore not detected.



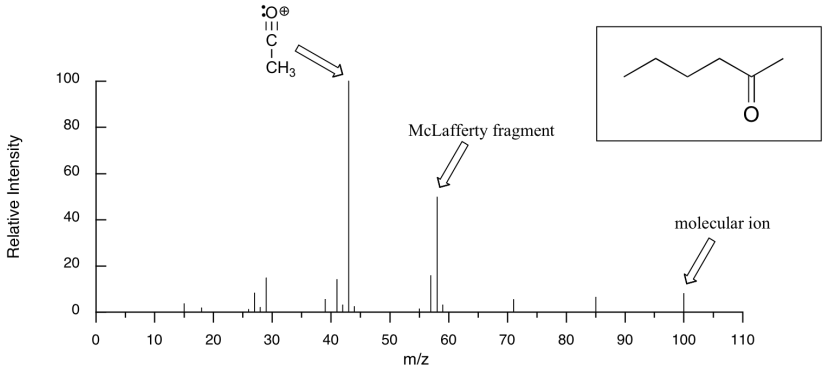
After the parent peak and the base peak, the next largest peak, at a relative abundance of 23%, is at m/z = 15. This, as you might expect, is the result of formation of a methyl cation, in addition to an acyl radical (which is neutral and not detected).



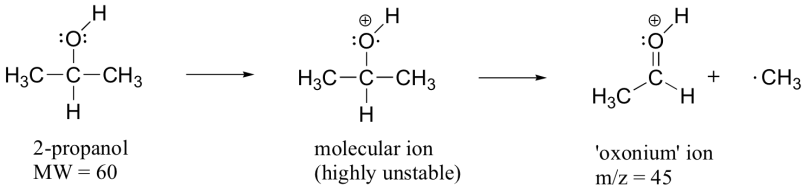
A common fragmentation pattern for larger carbonyl compounds is called the **McLafferty rearrangement**:

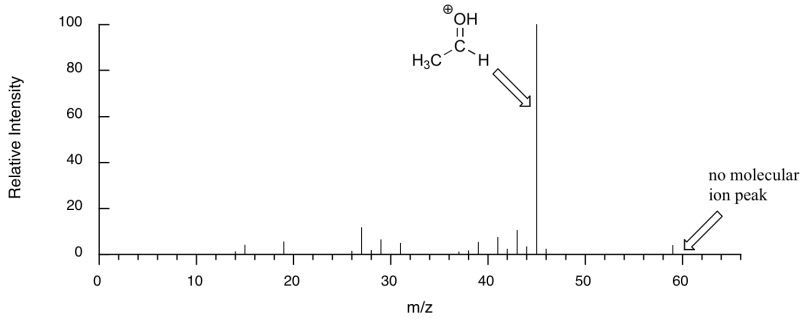


The mass spectrum of 2-hexanone shows a 'McLafferty fragment' at m/z = 58, while the propene fragment is not observed because it is a neutral species (remember, only cationic fragments are observed in MS). The base peak in this spectrum is again an acylium ion.



When alcohols are subjected to electron ionization MS, the molecular ion is highly unstable and thus a parent peak is often not detected. Often the base peak is from an ‘oxonium’ ion.





Other functional groups have predictable fragmentation patterns as well. By carefully analyzing the fragmentation information that a mass spectrum provides, a knowledgeable spectrometrist can often ‘put the puzzle together’ and make some very confident predictions about the structure of the starting sample.

Click here for examples of compounds listed by functional group, which demonstrate patterns which can be seen in mass spectra of compounds ionized by electron impact ionization.

✔ EXAMPLE 12.3.1

The mass spectrum of an aldehyde gives prominent peaks at *m/z* = 59 (12%, highest value of *m/z* in the spectrum), 58 (85%), and 29 (100%), as well as others. Propose a structure, and identify the three species whose *m/z* values were listed.

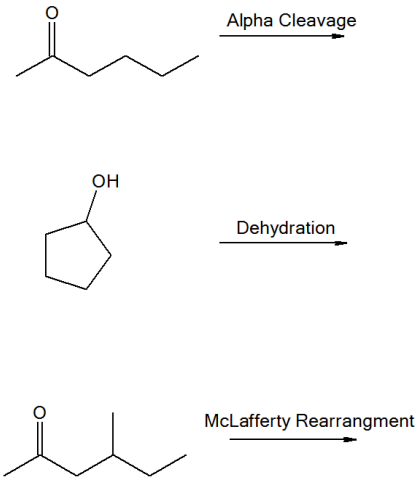
Solution

EXERCISES

QUESTIONS

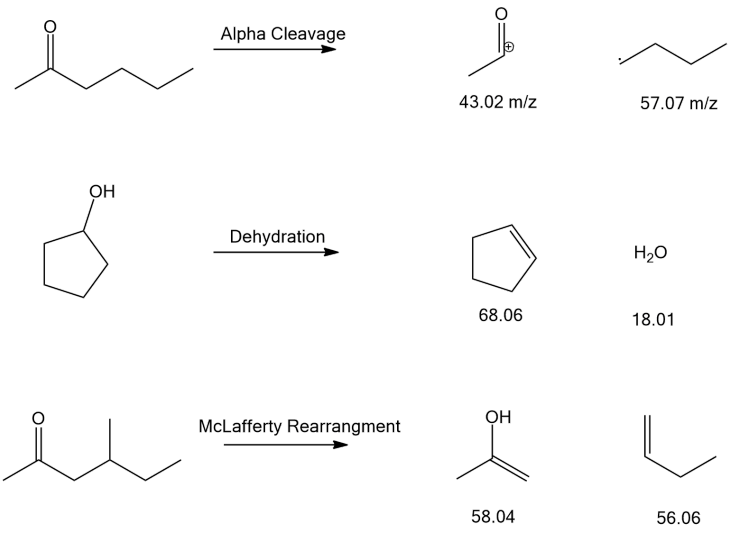
Q12.3.1

What are the masses of all the components in the following fragmentations?



SOLUTIONS

S12.3.1



12.4: MASS SPECTROMETRY IN BIOLOGICAL - TIME-OF-FLIGHT (TOF) INSTRUMENTS

OBJECTIVE

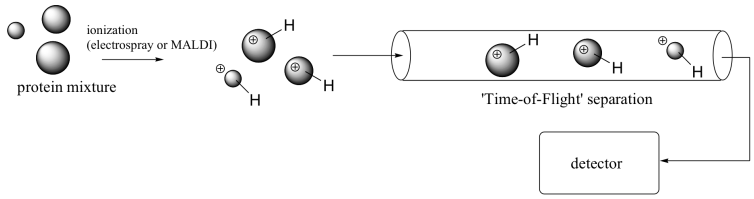
This section is intended only to demonstrate that mass spectrometry can be useful for the investigation of some very large molecules present in biological systems.

MASS SPECTROMETRY OF PROTEINS - APPLICATIONS IN PROTEOMICS

Mass spectrometry has become in recent years an increasingly important tool in the field of **proteomics**. Traditionally, protein biochemists tend to study the structure and function of individual proteins. Proteomics researchers, in contrast, want to learn more about how large numbers of proteins in a living system interact with each other, and how they respond to changes in the state of the organism. One very important subfield of proteomics is the search for protein **biomarkers** for human disease. These can be proteins which are present in greater quantities in a sick person than in a healthy person, and their detection and identification can provide medical researchers with valuable information about possible causes or treatments. Detection in a healthy person of a known biomarker for a disease such as diabetes or cancer could also provide doctors with an early warning that the patient may be especially susceptible, so that preventive measures could be taken to prevent or delay onset of the disease.

New developments in MS technology have made it easier to detect and identify proteins that are present in very small quantities in biological samples. Mass spectrometrists who study proteins often use instrumentation that is somewhat different from the electron-ionization, magnetic deflection system described earlier. When proteins are being analyzed, the object is often to ionize the proteins *without* causing fragmentation, so 'softer' ionization methods are required. In one such method, called **electrospray ionization**, the protein sample, in solution, is sprayed into a tube and the molecules are induced by an electric field to pick up extra protons from the solvent. Another common 'soft ionization' method is 'matrix-assisted laser desorption ionization' (**MALDI**). Here, the protein sample is adsorbed onto a solid matrix, and protonation is achieved with a laser.

Typically, both electrospray ionization and MALDI are used in conjunction with a time-of-flight (TOF) mass analyzer component.



The ionized proteins are accelerated by an electrode through a column, and separation is achieved because lighter ions travel at greater velocity than heavier ions with the same overall charge. In this way, the many proteins in a complex biological sample (such as blood plasma, urine, etc.) can be separated and their individual masses determined very accurately. Modern protein MS is extremely sensitive – very recently, scientists were even able to obtain a mass spectrum of *Tyrannosaurus rex* protein from fossilized bone! (Science **2007**, 316, 277).

In one recent study, MALDI-TOF mass spectrometry was used to compare fluid samples from lung transplant recipients who had suffered from tissue rejection to control samples from recipients who had not suffered rejection. Three peptides (short proteins) were found to be present at elevated levels specifically in the tissue rejection samples. It is hoped that these peptides might serve as biomarkers to identify patients who are at increased risk of rejecting their transplanted lungs (Proteomics **2005**, 5, 1705).

12.5: SPECTROSCOPY AND THE ELECTROMAGNETIC SPECTRUM

OBJECTIVES

After completing this section, you should be able to

1. write a brief paragraph discussing the nature of electromagnetic radiation.
2. write the equations that relate energy to frequency, frequency to wavelength and energy to wavelength, and perform calculations using these relationships.
3. describe, in general terms, how absorption spectra are obtained.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- electromagnetic radiation
- electromagnetic spectrum
- hertz (Hz)
- infrared spectroscopy
- photon
- quantum

STUDY NOTES

From your studies in general chemistry or physics, you should be familiar with the idea that electromagnetic radiation is a form of energy that possesses wave character and travels through space at a speed of $3.00 \times 10^8 m \cdot s^{-1}$. However, such radiation also displays some of the properties of particles, and on occasion it is more convenient to think of electromagnetic radiation as consisting of a stream of particles called *photons*.

In spectroscopy, the frequency of the electromagnetic radiation being used is usually expressed in *hertz* (*Hz*), that is, cycles per second. Note that $1\ Hz = s^{-1}$.

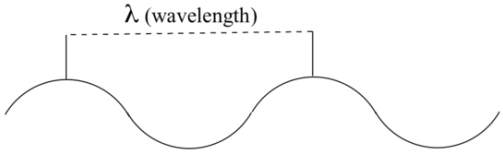
A *quantum* is a small, definite quantity of electromagnetic radiation whose energy is directly proportional to its frequency. (The plural is "quanta.") If you wish, you can read about the properties of electromagnetic radiation and the relationships among wavelength, frequency and energy, or refer to your general chemistry textbook if you still have it.

Note also that in SI units, Planck's constant is $6.626 \times 10^{-34} J \cdot s$.

THE ELECTROMAGNETIC SPECTRUM

Electromagnetic radiation, as you may recall from a previous chemistry or physics class, is composed of electrical and magnetic waves which oscillate on perpendicular planes. Visible light is electromagnetic radiation. So are the gamma rays that are emitted by spent nuclear fuel, the x-rays that a doctor uses to visualize your bones, the ultraviolet light that causes a painful sunburn when you forget to apply sun block, the infrared light that the army uses in night-vision goggles, the microwaves that you use to heat up your frozen burritos, and the radio-frequency waves that bring music to anybody who is old-fashioned enough to still listen to FM or AM radio.

Just like ocean waves, electromagnetic waves travel in a defined direction. While the speed of ocean waves can vary, however, the speed of electromagnetic waves – commonly referred to as the speed of light – is essentially a constant, approximately 300 million meters per second. This is true whether we are talking about gamma radiation or visible light. Obviously, there is a big difference between these two types of waves – we are surrounded by the latter for more than half of our time on earth, whereas we hopefully never become exposed to the former to any significant degree. The different properties of the various types of electromagnetic radiation are due to differences in their wavelengths, and the corresponding differences in their energies: *shorter wavelengths correspond to higher energy.*



High-energy radiation (such as gamma- and x-rays) is composed of very short waves – as short as 10^{-16} meter from crest to crest. Longer waves are far less energetic, and thus are less dangerous to living things. Visible light waves are in the range of 400 – 700 nm (nanometers, or 10^{-9} m), while radio waves can be several hundred meters in length.

The notion that electromagnetic radiation contains a quantifiable amount of energy can perhaps be better understood if we talk about light as a stream of *particles*, called **photons**, rather than as a wave. (Recall the concept known as 'wave-particle duality': at the quantum level, wave behavior and particle behavior become indistinguishable, and very small particles have an observable 'wavelength'). If we describe light as a stream of photons, the energy of a particular wavelength can be expressed as:

$$E = \frac{hc}{\lambda} \tag{12.5.1}$$

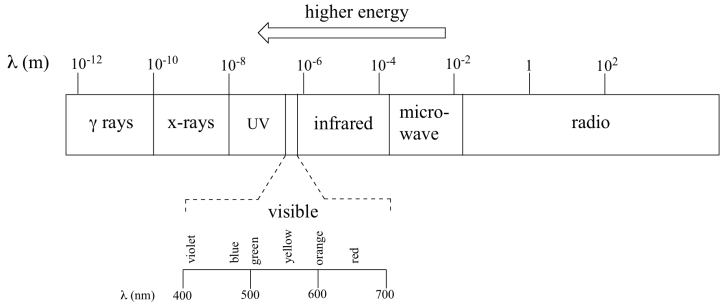
where E is energy in kcal/mol, **λ** (the Greek letter *lambda*) is wavelength in meters, *c* is 3.00 x 10^8 m/s (the speed of light), and *h* is 6.626 × 10^{-34} J · s, a number known as Planck's constant.

Because electromagnetic radiation travels at a constant speed, each wavelength corresponds to a given frequency, which is the number of times per second that a crest passes a given point. Longer waves have lower frequencies, and shorter waves have higher frequencies. Frequency is commonly reported in hertz (Hz), meaning 'cycles per second', or 'waves per second'. The standard unit for frequency is s^{-1}.

When talking about electromagnetic waves, we can refer either to wavelength or to frequency - the two values are interconverted using the simple expression:

$$\lambda\nu = c \tag{12.5.2}$$

where **ν** (the Greek letter '*nu*') is frequency in s^{-1}. Visible red light with a wavelength of 700 nm, for example, has a frequency of 2.84 x 10^{-19} J per photon or 171 kJ per mole of photons (remember Avogadro's number = 6.02 × 10^{23} mol^{-1}). The full range of electromagnetic radiation wavelengths is referred to as the **electromagnetic spectrum**.



Notice in the figure above that visible light takes up just a narrow band of the full spectrum. White light from the sun or a light bulb is a mixture of all of the visible wavelengths. You see the visible region of the electromagnetic spectrum divided into its different wavelengths every time you see a rainbow: violet light has the shortest wavelength, and red light has the longest.

EXAMPLE 12.5.1

Visible light has a wavelength range of about 400-700 nm. What is the corresponding frequency range? What is the corresponding energy range, in kcal/mol of photons?

Answer

Using λν = *c*, we first rearrange to ν = *c*/λ to solve for frequency.

For light with a wavelength of 400 nm, the frequency is 7.50 × 10^{14} Hz:

$$\nu = \frac{3 \times 10^8 \text{ m s}^{-1}}{400 \times 10^{-9} \text{ m}} = 7.50 \times 10^{14} \text{ s}^{-1}$$

In the same way, we calculate that light with a wavelength of 700 nm has a frequency of 4.29 × 10^{14} Hz.

To calculate corresponding energies using *hc*/λ. We find for light at 400 nm:

$$E = \frac{(6.626 \times 10^{-34}\ \text{J s mol}^{-1})(3.00 \times 10^{8}\ \text{m s}^{-1})}{400 \times 10^{-9}\ \text{m}}$$

$$= 4.97 \times 10^{-19}\ \text{J per photon}$$

$$E\ (\text{one mole}) = E \times N$$

$$= (4.97 \times 10^{-19}\ \text{J})(6.02 \times 10^{23}\ \text{mol}^{-1})$$

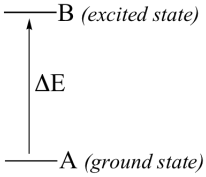
$$= 299\ \text{kJ mol}^{-1}$$

Using the same equation, we find that light at 700 nm corresponds to 171 kJ mol^{-1}.

MOLECULAR SPECTROSCOPY – THE BASIC IDEA

In a spectroscopy experiment, electromagnetic radiation of a specified range of wavelengths is allowed to pass through a sample containing a compound of interest. The sample molecules absorb energy from some of the wavelengths, and as a result jump from a low energy 'ground state' to some higher energy 'excited state'. Other wavelengths are *not* absorbed by the sample molecule, so they pass on through. A detector on the other side of the sample records which wavelengths were absorbed, and to what extent they were absorbed.

Here is the key to molecular spectroscopy: *a given molecule will specifically absorb only those wavelengths which have energies that correspond to the energy difference of the transition that is occurring.* Thus, if the transition involves the molecule jumping from ground state A to excited state B, with an energy difference of **Δ**E, the molecule will specifically absorb radiation with wavelength that corresponds to **Δ**E, while allowing other wavelengths to pass through unabsorbed.



By observing which wavelengths a molecule absorbs, and to what extent it absorbs them, we can gain information about the nature of the energetic transitions that a molecule is able to undergo, and thus information about its structure.

These generalized ideas may all sound quite confusing at this point, but things will become much clearer as we begin to discuss specific examples.

EXERCISES

QUESTIONS

Q12.5.1

Which of the following frequencies/wavelengths are higher energy

A. $\lambda = 2.0 \times 10^{-6}$ m or $\lambda = 3.0 \times 10^{-9}$ m

B. $\upsilon = 3.0 \times 10^{9}$ Hz or $\upsilon = 3.0 \times 10^{-6}$ Hz

Q12.5.2

Calculate the energies for the following;

A. Gamma Ray $\lambda = 4.0 \times 10^{-11}$ m

B. X-Ray $\lambda = 4.0 \times 10^{-9}$ m

C. UV light $\upsilon = 5.0 \times 10^{15}$ Hz

D. Infrared Radiation $\lambda = 3.0 \times 10^{-5}$ m

E. Microwave Radiation $\upsilon = 3.0 \times 10^{11}$ Hz

SOLUTIONS

S12.5.1

A. $\lambda = 3.0 \times 10^{-9}$ m

B. $\upsilon = 3.0 \times 10^{9}$ Hz

S12.5.2

A. 4.965×10^{-15} J

B. 4.965×10^{-17} J

C. 3.31×10^{-18} J

D. 6.62×10^{-21} J

E. 1.99×10^{-22} J

12.6: INFRARED SPECTROSCOPY

OBJECTIVES

After completing this section, you should be able to

1. identify (by wavelength, wavenumber, or both) the region of the electromagnetic spectrum which is used in infrared (IR) spectroscopy.
2. interconvert between wavelength and wavenumber.
3. discuss, in general terms, the effect that the absorption of infrared radiation can have on a molecule.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- infrared spectrum
- wavenumber (reciprocal centimetres)

STUDY NOTES

Notice that the scale at the bottom of the infrared spectrum for 2-hexanone shown is calibrated in wavenumbers (cm^{-1}). A wavenumber is the reciprocal of a wavelength (1/λ); thus, a wavenumber of 1600 cm^{-1} corresponds to a wavelength of

$$\frac{1}{1600\,\mathrm{cm}^{-1}} = 6.25 \times 10^{-4}\mathrm{cm\ or} 6.25\,\mu\,\mathrm{m}$$

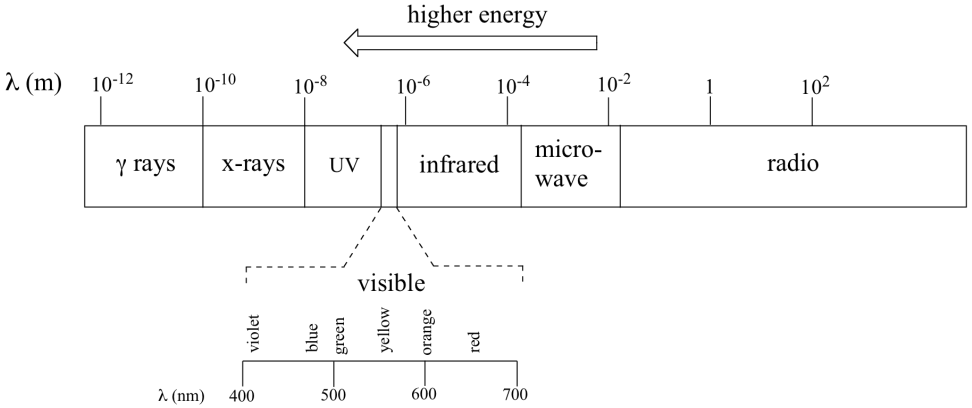
Organic chemists find it more convenient to deal with wavenumbers rather than wavelengths when discussing infrared spectra.

You will obtain infrared spectra for a number of the compounds you will synthesize in the laboratory component of this course.

The inverted peaks observed in the spectra correspond to molecular stretching and bending vibrations that only occur at certain quantized frequencies. When infrared radiation matching these frequencies falls on the molecule, the molecule absorbs energy and becomes excited. Eventually the molecule returns to its original (ground) state, and the energy which was absorbed is released as heat.

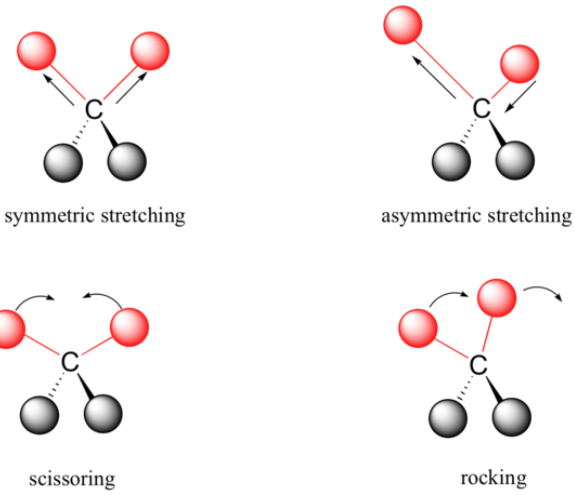
INFRARED SPECTROSCOPY

The full range of electromagnetic radiation wavelengths is referred to as the **electromagnetic spectrum**.



Notice in the figure above that infrared light is lower energy than visible light. The wavelengths of infrared radiation are between 0.8 and 250 μm. The units that are typically used for infrared spectroscopy are wavenumbers (which is cm^{-1}). IR spectroscopy analyzes radiation between 40 to 13,000 cm^{-1}. But what type of excitation is occurring when infrared radiation is absorbed by a molecule?

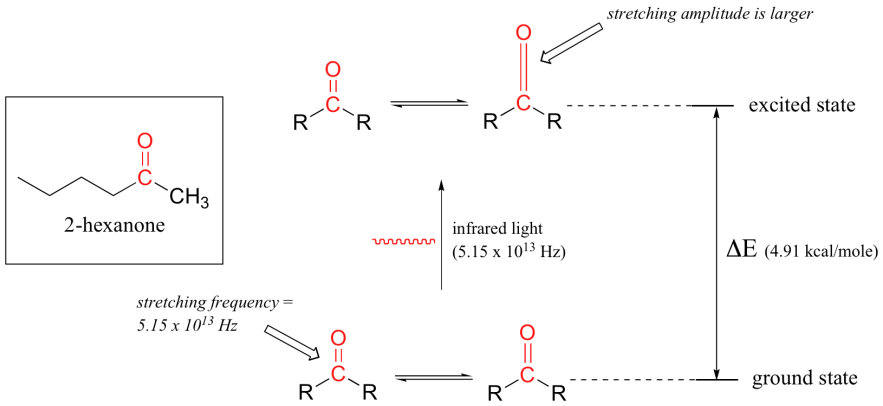
Covalent bonds in organic molecules are not rigid sticks – rather, they behave more like springs. At room temperature, organic molecules are always in motion, as their bonds stretch, bend, and twist. These complex vibrations can be broken down mathematically into individual **vibrational modes**, a few of which are illustrated below.



The energy of molecular vibration is *quantized* rather than continuous, meaning that a molecule can only stretch and bend at certain 'allowed' frequencies. If a molecule is exposed to electromagnetic radiation that matches the frequency of one of its vibrational modes, it will in most cases absorb energy from the radiation and jump to a higher vibrational energy state - what this means is that the *amplitude* of the vibration will increase, but the vibrational *frequency* will remain the same. The difference in energy between the two vibrational states is equal to the energy associated with the wavelength of radiation that was absorbed. It turns out that it is the *infrared* region of the electromagnetic spectrum which contains frequencies corresponding to the vibrational frequencies of organic bonds.

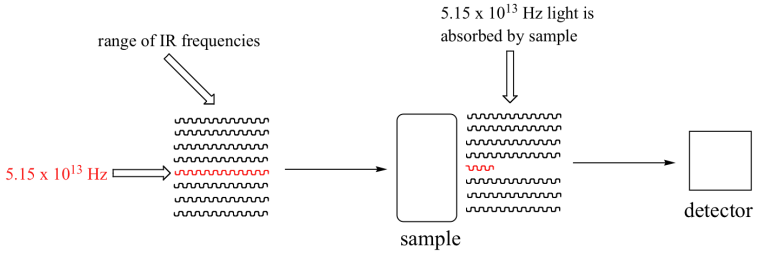
Let's take 2-hexanone as an example. Picture the carbonyl bond of the ketone group as a spring. This spring is constantly bouncing back and forth, stretching and compressing, pushing the carbon and oxygen atoms further apart and then pulling them together. This is the **stretching mode** of the carbonyl bond. In the space of one second, the spring 'bounces' back and forth 5.15 x 10^{13} times - in other words, the ground-state frequency of carbonyl stretching for a the ketone group is about 5.15 x 10^{13} Hz.

If our ketone sample is irradiated with infrared light, the carbonyl bond will specifically absorb light with this same frequency, which by equations 4.1 and 4.2 corresponds to a wavelength of 5.83 x 10^{-6} m and an energy of 4.91 kcal/mol. When the carbonyl bond absorbs this energy, it jumps up to an excited vibrational state.



The value of **ΔE** - the energy difference between the low energy (ground) and high energy (excited) vibrational states - is equal to 4.91 kcal/mol, the same as the energy associated with the absorbed light frequency. The molecule does not remain in its excited vibrational state for very long, but quickly releases energy to the surrounding environment in form of heat, and returns to the ground state.

With an instrument called an infrared spectrophotometer, we can 'see' this vibrational transition. In the spectrophotometer, infrared light with frequencies ranging from about 10^{13} to 10^{14} Hz is passed though our sample of cyclohexane. Most frequencies pass right through the sample and are recorded by a detector on the other side.



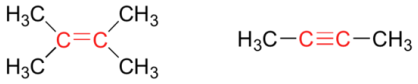
Our 5.15 x 10^{13} Hz carbonyl stretching frequency, however, is absorbed by the 2-hexanone sample, and so the detector records that the intensity of this frequency, after having passed through the sample, is something less than 100% of its initial intensity.

The vibrations of a 2-hexanone molecule are not, of course, limited to the simple stretching of the carbonyl bond. The various carbon-carbon bonds also stretch and bend, as do the carbon-hydrogen bonds, and all of these vibrational modes also absorb different frequencies of infrared light.

The power of infrared spectroscopy arises from the observation that *different functional groups have different characteristic absorption frequencies*. The carbonyl bond in a ketone, as we saw with our 2-hexanone example, typically absorbs in the range of 5.11 - 5.18 x 10^{13} Hz, depending on the molecule. The carbon-carbon triple bond of an alkyne, on the other hand, absorbs in the range 6.30 - 6.80 x 10^{13} Hz. The technique is therefore very useful as a means of identifying which functional groups are present in a molecule of interest. If we pass infrared light through an unknown sample and find that it absorbs in the carbonyl frequency range but not in the alkyne range, we can infer that the molecule contains a carbonyl group but not an alkyne.

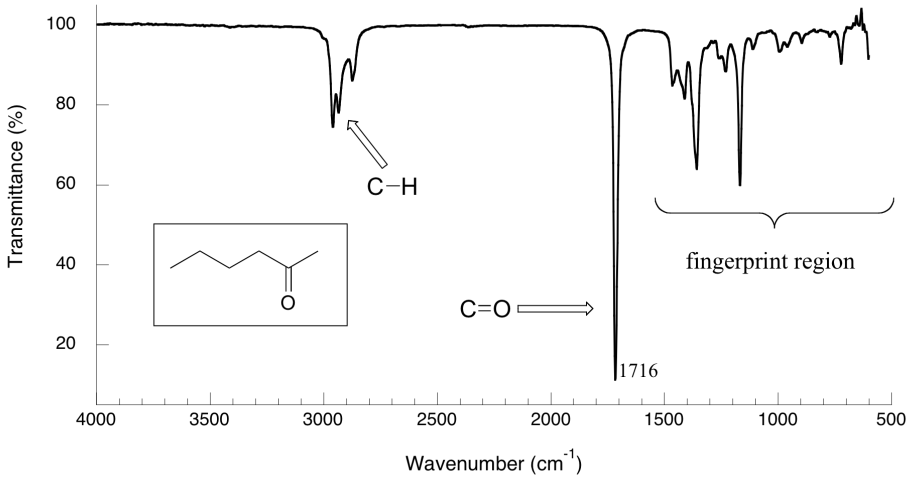
Some bonds absorb infrared light more strongly than others, and some bonds do not absorb at all. *In order for a vibrational mode to absorb infrared light, it must result in a periodic change in the dipole moment of the molecule*. Such vibrations are said to be **infrared active**. In general, the greater the polarity of the bond, the stronger its IR absorption. The carbonyl bond is very polar, and absorbs very strongly. The carbon-carbon triple bond in most alkynes, in contrast, is much less polar, and thus a stretching vibration does not result in a large change in the overall dipole moment of the molecule. Alkyne groups absorb rather weakly compared to carbonyls.

Some kinds of vibrations are **infrared inactive**. The stretching vibrations of completely symmetrical double and triple bonds, for example, do not result in a change in dipole moment, and therefore do not result in any absorption of light (but other bonds and vibrational modes in these molecules *do* absorb IR light).



infrared-inactive double and triple bonds

Now, let's look at some actual output from IR spectroscopy experiments. Below is the IR spectrum for 2-hexanone.



There are a number of things that need to be explained in order for you to understand what it is that we are looking at. On the horizontal axis we see IR wavelengths expressed in terms of a unit called **wavenumber** (cm^{-1}), which tells us how many waves fit into one centimeter. On

the vertical axis we see '**% transmittance**', which tells us how strongly light was absorbed at each frequency (100% transmittance means no absorption occurred at that frequency). The solid line traces the values of % transmittance for every wavelength – the 'peaks' (which are actually pointing down) show regions of strong absorption. For some reason, it is typical in IR spectroscopy to report wavenumber values rather than wavelength (in meters) or frequency (in Hz). The 'upside down' vertical axis, with absorbance peaks pointing down rather than up, is also a curious convention in IR spectroscopy. We wouldn't want to make things too easy for you!

12.7: INTERPRETING INFRARED SPECTRA

OBJECTIVES

After completing this section, you should be able to

1. describe how the so-called “fingerprint region” of an infrared spectrum can assist in the identification of an unknown compound.
2. identify the functional group or groups present in a compound, given a list of the most prominent absorptions in the infrared spectrum and a table of characteristic absorption frequencies.
3. identify the broad regions of the infrared spectrum in which occur absorptions caused by
   a. N−H, C−H, and O−H
   b. C≡C and C≡N
   c. C=O, C=N$, and$C=C

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- fingerprint region

STUDY NOTES

When answering assignment questions, you may use this IR table to find the characteristic infrared absorptions of the various functional groups. However, you should be able to indicate in broad terms where certain characteristic absorptions occur. You can achieve this objective by memorizing the following table.

Region of Spectrum (cm^{-1})	Absorption
2500-4000	$\ce{\sf{N−H}}$, $\ce{\sf{O−H}}$, $\ce{\sf{C−H}}$
2000-2500	$\ce{\sf{C#C}}$, $\ce{\sf{C#N}}$
1500-2000	$\ce{\sf{C=O}}$, $\ce{\sf{C=N}}$, $\ce{\sf{C=C}}$
below 1500	Fingerprint region

THE ORIGIN OF GROUP FREQUENCIES

An important observation made by early researchers is that many functional group absorb infrared radiation at about the same wavenumber, regardless of the structure of the rest of the molecule. For example, C-H stretching vibrations usually appear between 3200 and 2800cm^{-1} and carbonyl(C=O) stretching vibrations usually appear between 1800 and 1600cm^{-1}. This makes these bands diagnostic markers for the presence of a functional group in a sample. These types of infrared bands are called group frequencies because they tell us about the presence or absence of specific functional groups in a sample.

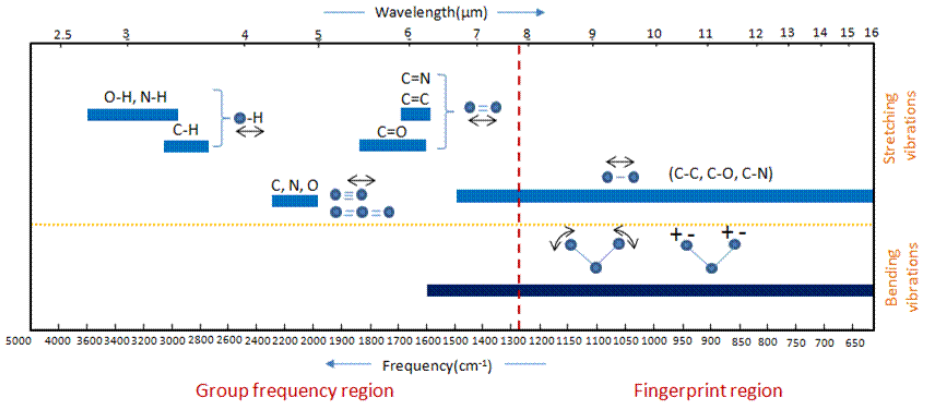
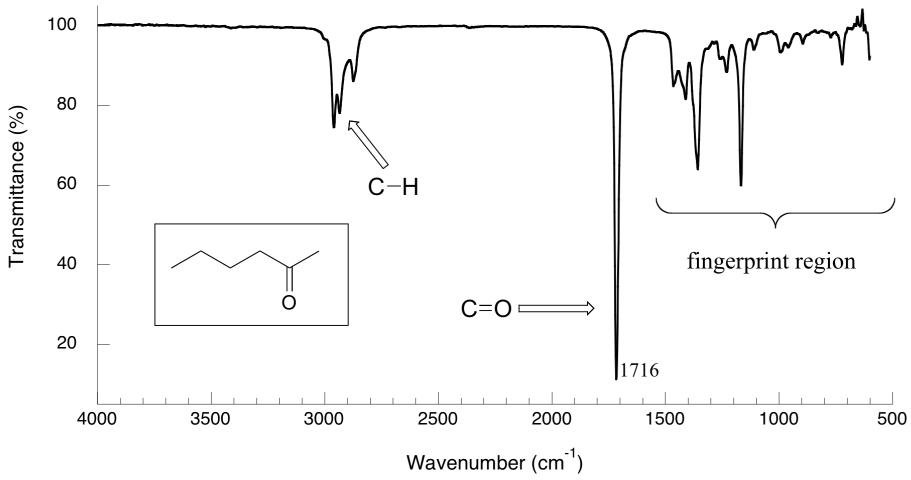


Figure 2. Group frequency and fingerprint regions of the mid-infrared spectrum

The region of the infrared spectrum from 1200 to 700 cm^{-1} is called the fingerprint region. This region is notable for the large number of infrared bands that are found there. Many different vibrations, including C-O, C-C and C-N single bond stretches, C-H bending vibrations, and some bands due to benzene rings are found in this region. The fingerprint region is often the most complex and confusing region to

interpret, and is usually the last section of a spectrum to be interpreted. However, the utility of the fingerprint region is that the many bands there provide a fingerprint for a molecule.

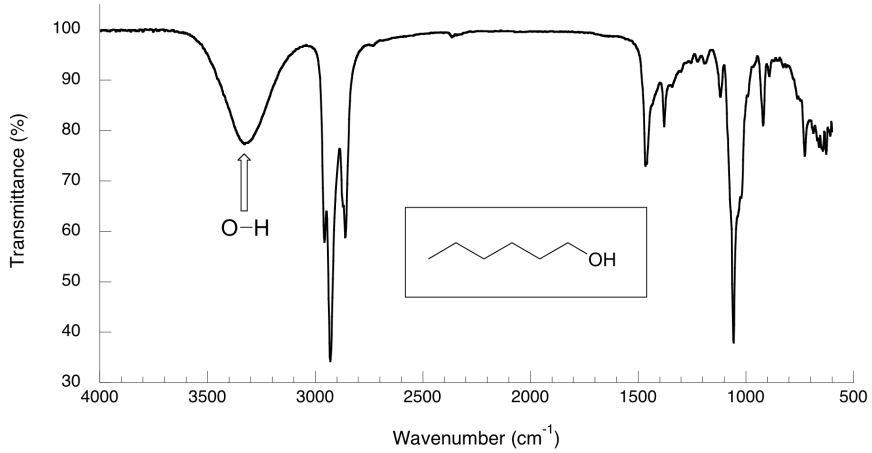


The key absorption peak in this spectrum is that from the carbonyl double bond, at 1716 cm^{-1} (corresponding to a wavelength of 5.86 mm, a frequency of 5.15 x 10^{13} Hz, and a **ΔE** value of 4.91 kcal/mol). Notice how strong this peak is, relative to the others on the spectrum: *a strong peak in the 1650-1750 cm^{-1} region is a dead giveaway for the presence of a carbonyl group*. Within that range, carboxylic acids, esters, ketones, and aldehydes tend to absorb in the shorter wavelength end (1700-1750 cm-1), while conjugated unsaturated ketones and amides tend to absorb on the longer wavelength end (1650-1700 cm^{-1}).

The jagged peak at approximately 2900-3000 cm^{-1} is characteristic of tetrahedral carbon-hydrogen bonds. This peak is not terribly useful, as just about every organic molecule that you will have occasion to analyze has these bonds. Nevertheless, it can serve as a familiar reference point to orient yourself in a spectrum.

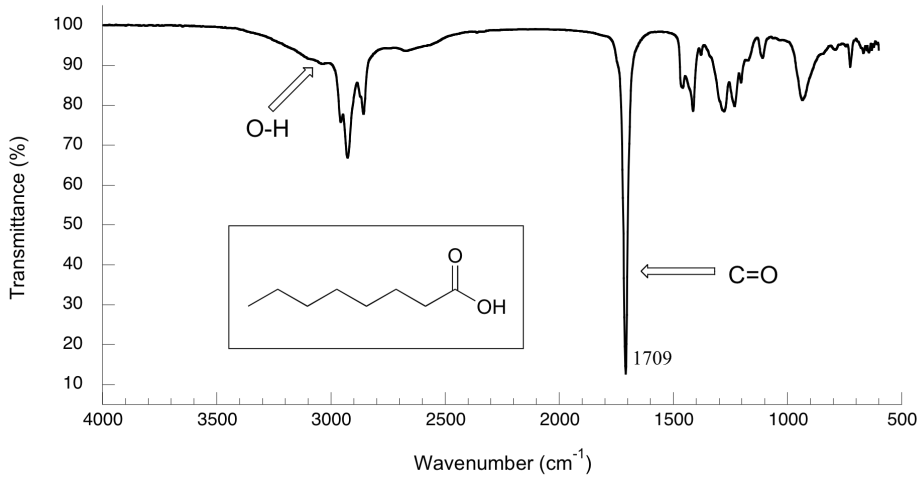
You will notice that there are many additional peaks in this spectrum in the longer-wavelength 400 -1400 cm^{-1} region. This part of the spectrum is called the **fingerprint region**. While it is usually very difficult to pick out any specific functional group identifications from this region, it does, nevertheless, contain valuable information. The reason for this is suggested by the name: just like a human fingerprint, the pattern of absorbance peaks in the fingerprint region is unique to every molecule, meaning that the data from an unknown sample can be compared to the IR spectra of known standards in order to make a positive identification. In the mid-1990's, for example, several paintings were identified as forgeries because scientists were able to identify the IR footprint region of red and yellow pigment compounds that would not have been available to the artist who supposedly created the painting (for more details see Chemical and Engineering News, Sept 10, 2007, p. 28).

Now, let's take a look at the IR spectrum for 1-hexanol.



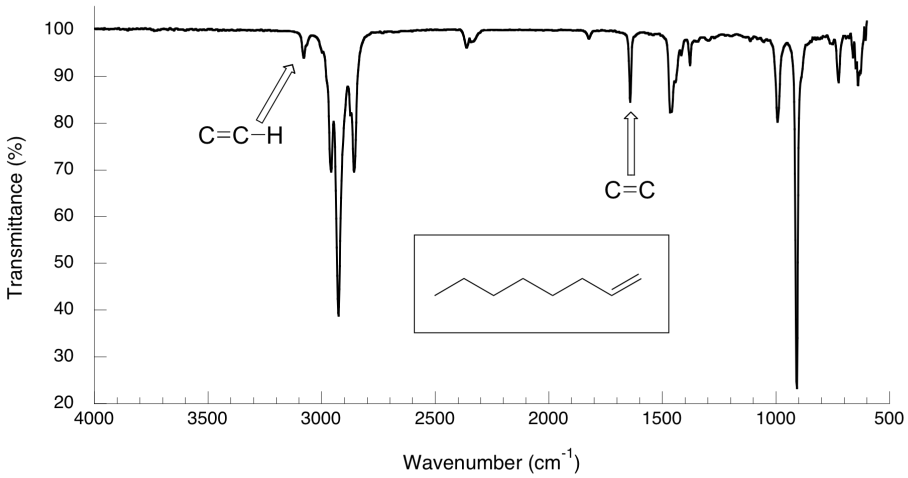
As you can see, the carbonyl peak is gone, and in its place is a very broad 'mountain' centered at about 3400 cm^{-1}. This signal is characteristic of the O-H stretching mode of alcohols, and is a dead giveaway for the presence of an alcohol group. The breadth of this signal is a consequence of hydrogen bonding between molecules.

In the spectrum of octanoic acid we see, as expected, the characteristic carbonyl peak, this time at 1709 cm^{-1}.



We also see a low, broad absorbance band that looks like an alcohol, except that it is displaced slightly to the right (long-wavelength) side of the spectrum, causing it to overlap to some degree with the C-H region. This is the characteristic carboxylic acid O-H single bond stretching absorbance.

The spectrum for 1-octene shows two peaks that are characteristic of alkenes: the one at 1642 cm^{-1} is due to stretching of the carbon-carbon double bond, and the one at 3079 cm-1 is due to stretching of the s bond between the alkene carbons and their attached hydrogens.



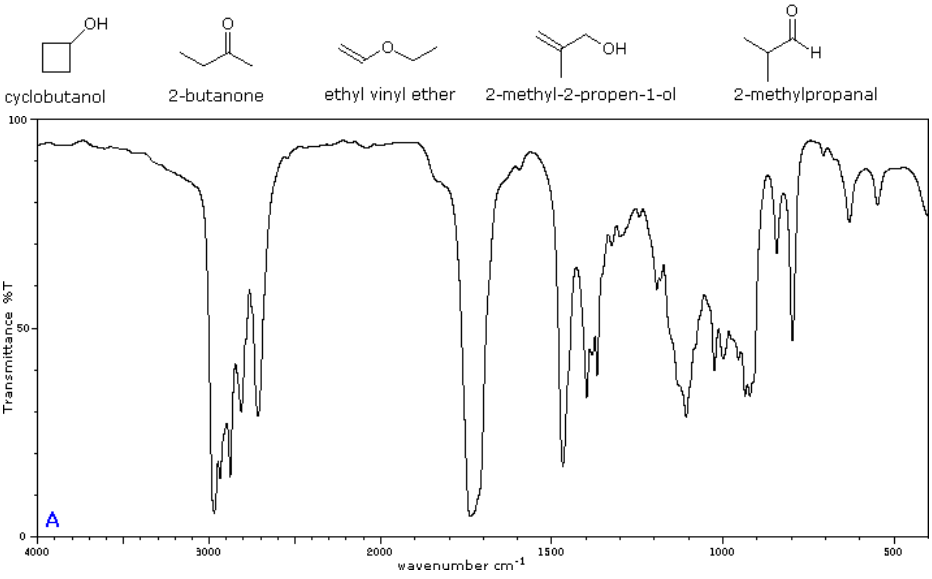
Alkynes have characteristic IR absorbance peaks in the range of 2100-2250 cm^{-1} due to stretching of the carbon-carbon triple bond, and terminal alkenes can be identified by their absorbance at about 3300 cm-1, due to stretching of the bond between the sp-hybridized carbon and the terminal hydrogen.

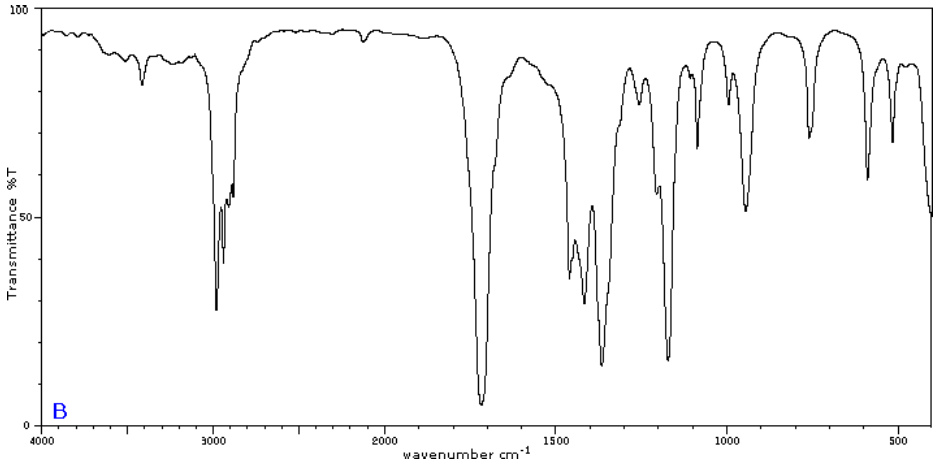
It is possible to identify other functional groups such as amines and ethers, but the characteristic peaks for these groups are considerably more subtle and/or variable, and often are overlapped with peaks from the fingerprint region. For this reason, we will limit our discussion here to the most easily recognized functional groups, which are summarized in this table.

As you can imagine, obtaining an IR spectrum for a compound will not allow us to figure out the complete structure of even a simple molecule, unless we happen to have a reference spectrum for comparison. In conjunction with other analytical methods, however, IR spectroscopy can prove to be a very valuable tool, given the information it provides about the presence or absence of key functional groups. IR can also be a quick and convenient way for a chemist to check to see if a reaction has proceeded as planned. If we were to run a reaction in which we wished to convert cyclohexanone to cyclohexanol, for example, a quick comparison of the IR spectra of starting compound and product would tell us if we had successfully converted the ketone group to an alcohol.

MORE EXAMPLES OF IR SPECTRA

To illustrate the usefulness of infrared absorption spectra, examples for five C_4H_8O isomers are presented below their corresponding structural formulas. Try to associate each spectrum with one of the isomers in the row above it.




100
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Transmittance %T
B
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3000
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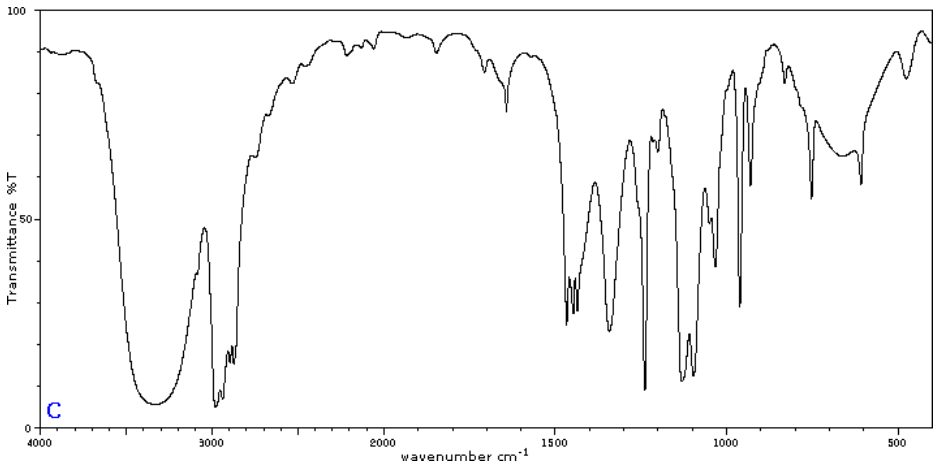
500
wavenumber cm-1


100
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C
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2000
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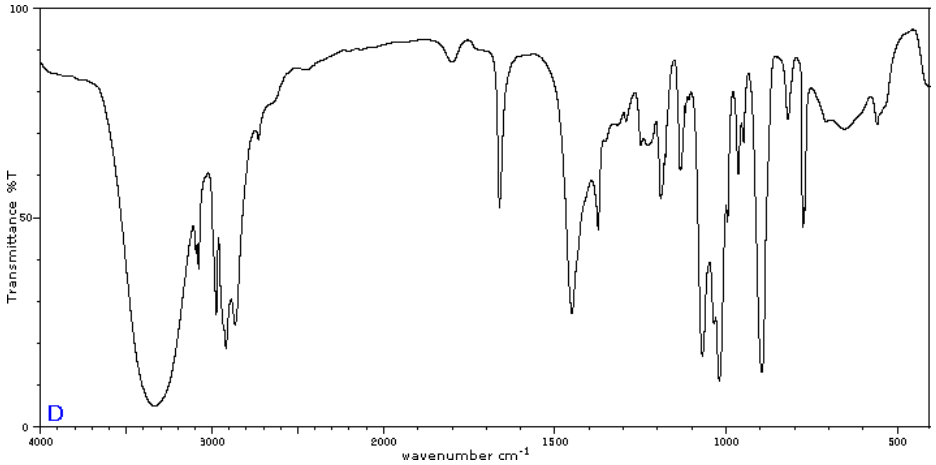
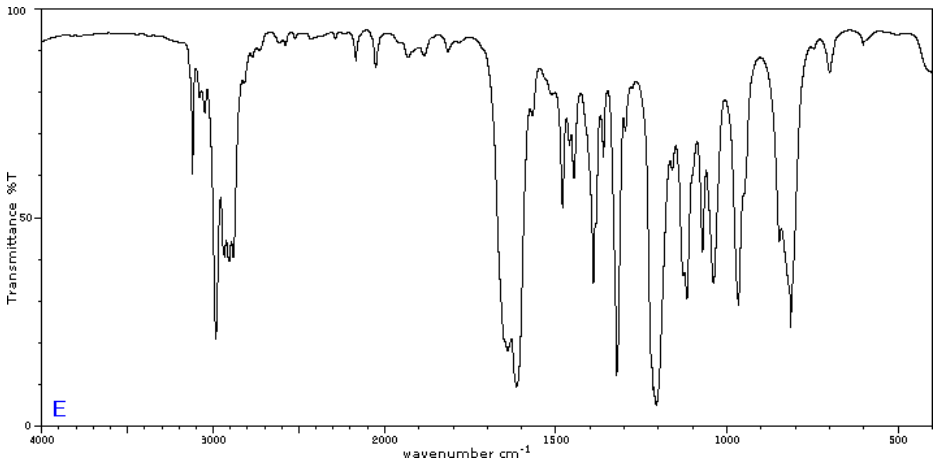
500
wavenumber cm-1





EXERCISES

QUESTIONS

Q12.7.1

What functional groups give the following signals in an IR spectrum?

A) 1700 cm^{-1}

B) 1550 cm^{-1}

C) 1700 cm^{-1} and 2510-3000 cm^{-1}

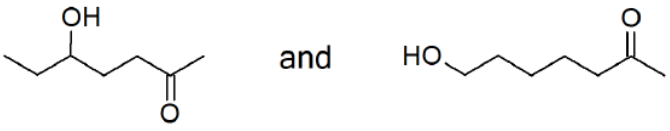
Q12.7.2

How can you distinguish the following pairs of compounds through IR analysis?

A) CH_3OH (Methanol) and $CH_3CH_2OCH_2CH_3$ (Diethylether)

B) Cyclopentane and 1-pentene.

C)



(i) (ii)

SOLUTIONS

S12.7.1

S12.7.2

A) A OH peak will be present around 3300 cm^{-1} for methanol and will be absent in the ether.

B) 1-pentene will have a alkene peak around 1650 cm^{-1} for the C=C and there will be another peak around 3100 cm^{-1} for the sp^2 C-H group on the alkene

C) Cannot distinguish these two isomers. They both have the same functional groups and therefore would have the same peaks on an IR spectra.

12.8: INFRARED SPECTRA OF SOME COMMON FUNCTIONAL GROUPS

OBJECTIVE

After completing this section, you should be able to use an infrared spectrum to determine the presence of functional groups, such as alcohols, amines and carbonyl groups, in an unknown compound, given a list of infrared absorption frequencies.

STUDY NOTES

In Chapter 12.7 you should have learned, in broad terms, where a few key absorptions occur. Otherwise, to find the characteristic infrared absorptions of the various functional groups, refer to this IR table.

SPECTRAL INTERPRETATION BY APPLICATION OF GROUP FREQUENCIES

One of the most common application of infrared spectroscopy is to the identification of organic compounds. The major classes of organic molecules are shown in this category and also linked on the bottom page for the number of collections of spectral information regarding organic molecules.

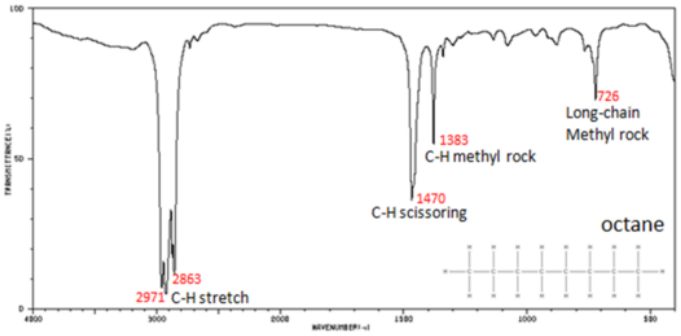
HYDROCARBONS

Hydrocarbons compounds contain only C-H and C-C bonds, but there is plenty of information to be obtained from the infrared spectra arising from C-H stretching and C-H bending.

In alkanes, which have very few bands, each band in the spectrum can be assigned:

- C–H stretch from 3000–2850 cm^{-1}
- C–H bend or scissoring from 1470-1450 cm^{-1}
- C–H rock, methyl from 1370-1350 cm^{-1}
- C–H rock, methyl, seen only in long chain alkanes, from 725-720 cm^{-1}

Figure 12.8.1 shows the IR spectrum of octane. Since most organic compounds have these features, these C-H vibrations are usually not noted when interpreting a routine IR spectrum. Note that the change in dipole moment with respect to distance for the C-H stretching is greater than that for others shown, which is why the C-H stretch band is the more intense.



12.8.1: Infrared Spectrum of Octane

In alkenes compounds, each band in the spectrum can be assigned:

- C=C stretch from 1680-1640 cm^{-1}
- =C–H stretch from 3100-3000 cm^{-1}
- =C–H bend from 1000-650 cm^{-1}

Figure 12.8.2 shows the IR spectrum of 1-octene. As alkanes compounds, these bands are not specific and are generally not noted because they are present in almost all organic molecules.

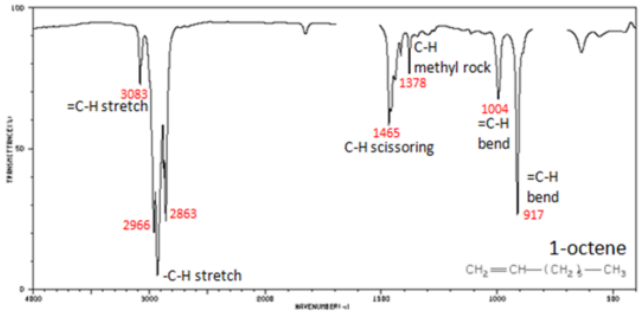


Figure 12.8.2: Infrared Spectrum of 1-Octene

In alkynes, each band in the spectrum can be assigned:

- –C≡C– stretch from 2260-2100 cm^{-1}
- –C≡C–H: C–H stretch from 3330-3270 cm^{-1}
- –C≡C–H: C–H bend from 700-610 cm^{-1}

The spectrum of 1-hexyne, a terminal alkyne, is shown below.

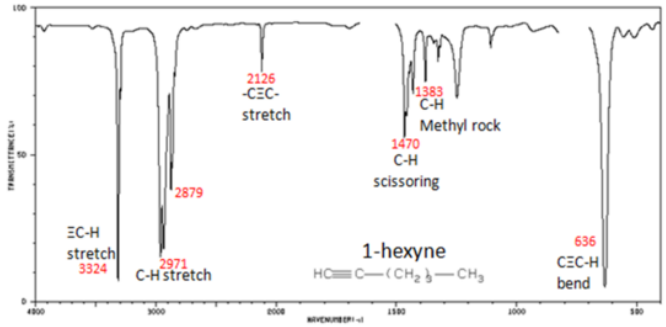


Figure 12.8.3: Infrared Spectrum of 1-Hexyne

In aromatic compounds, each band in the spectrum can be assigned:

- C–H stretch from 3100-3000 cm^{-1}
- overtones, weak, from 2000-1665 cm^{-1}
- C–C stretch (in-ring) from 1600-1585 cm^{-1}
- C–C stretch (in-ring) from 1500-1400 cm^{-1}
- C–H "oop" from 900-675 cm^{-1}

Note that this is at slightly higher frequency than is the –C–H stretch in alkanes. This is a very useful tool for interpreting IR spectra. Only alkenes and aromatics show a C–H stretch slightly higher than 3000 cm^{-1}. Figure 12.8.4 shows the spectrum of toluene.

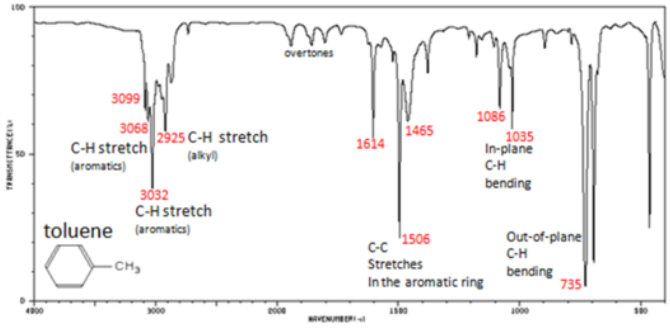


Figure 12.8.4: Infrared Spectrum of Toluene

FUNCTIONAL GROUPS CONTAINING THE C-O BOND

Alcohols have IR absorptions associated with both the O-H and the C-O stretching vibrations.

- O–H stretch, hydrogen bonded 3500-3200 cm^{-1}
- C–O stretch 1260-1050 cm^{-1} (s)

Figure 12.8.5 shows the spectrum of ethanol. Note the very broad, strong band of the O–H stretch.

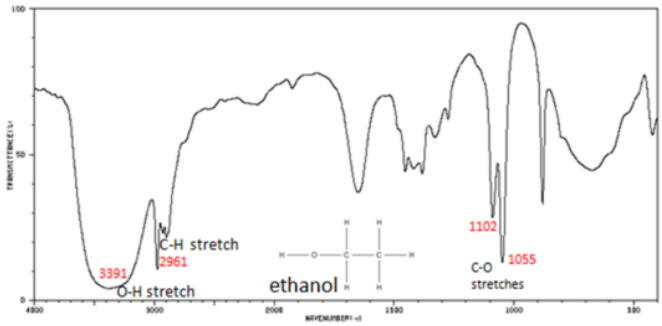


Figure 12.8.5: Infrared Spectrum of Ethanol

The carbonyl stretching vibration band C=O of saturated aliphatic ketones appears:

- C=O stretch - aliphatic ketones 1715 cm^{-1}
- α, β -unsaturated ketones 1685-1666 cm^{-1}

Figure 12.8.6 shows the spectrum of 2-butanone. This is a saturated ketone, and the C=O band appears at 1715.

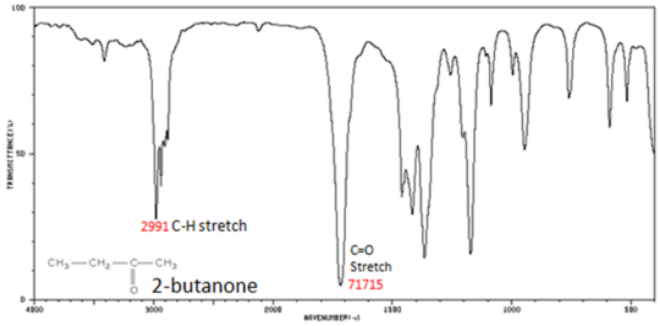


Figure 12.8.6: Infrared Spectrum of 2-Butanone

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}
  - α, β -unsaturated aldehydes 1710-1685 cm^{-1}

Figure 12.8.7 shows the spectrum of butyraldehyde.

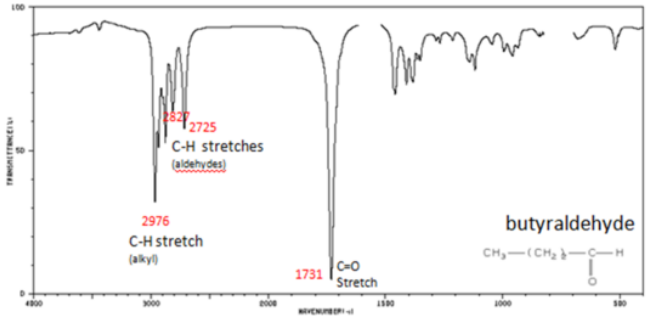


Figure 12.8.7: Infrared Spectrum of Butyraldehyde

The carbonyl stretch C=O of esters appears:

- C=O stretch
  - aliphatic from 1750-1735 cm^{-1}
  - α, β -unsaturated from 1730-1715 cm^{-1}

- C–O stretch from 1300-1000 cm^{-1}

Figure 12.8.8: shows the spectrum of ethyl benzoate.

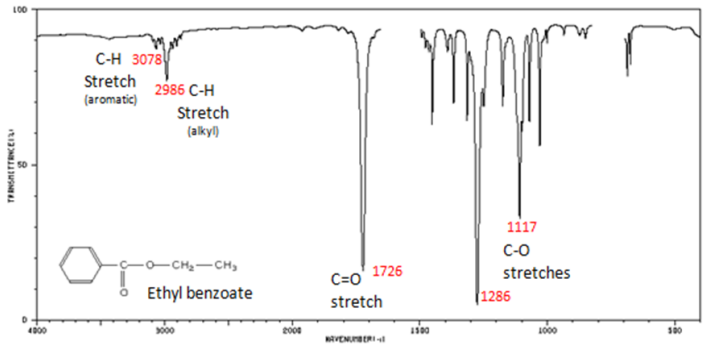


Figure 12.8.8: Infrared Spectrum of Ethyl benzoate

The carbonyl stretch C=O of a carboxylic acid appears as an intense band from 1760-1690 cm^{-1}. The exact position of this broad band depends on whether the carboxylic acid is saturated or unsaturated, dimerized, or has internal hydrogen bonding.

- O–H stretch from 3300-2500 cm^{-1}
- C=O stretch from 1760-1690 cm^{-1}
- C–O stretch from 1320-1210 cm^{-1}
- O–H bend from 1440-1395 and 950-910 cm^{-1}

Figure 12.8.9: shows the spectrum of hexanoic acid.

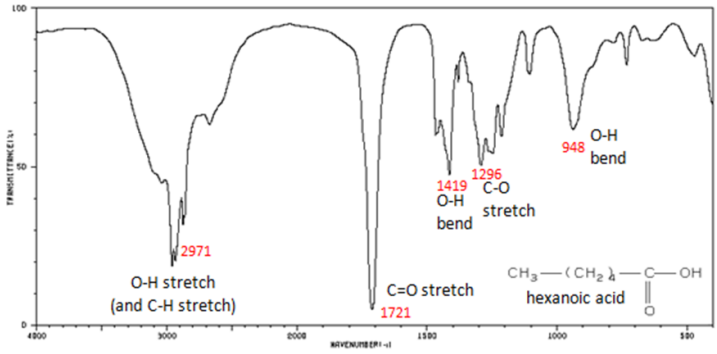


Figure 12.8.9: Infrared Spectrum of Hexanoic acid

ORGANIC NITROGEN COMPOUNDS

- N–O asymmetric stretch from 1550-1475 cm^{-1}
- N–O symmetric stretch from 1360-1290 cm^{-1}

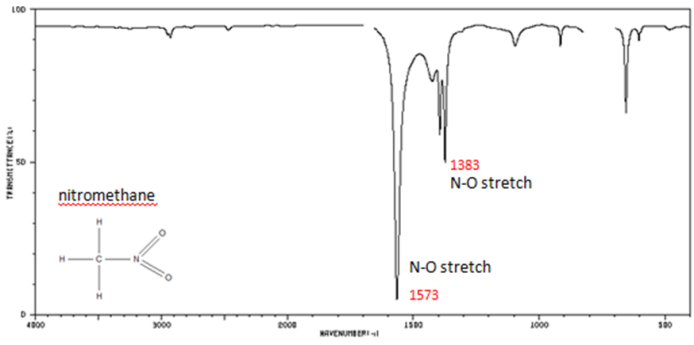


Figure 12.8.10: Infrared Spectrum of Nitomethane

ORGANIC COMPOUNDS CONTAINING HALOGENS

Alkyl halides are compounds that have a C–X bond, where X is a halogen: bromine, chlorine, fluorene, or iodine.

- C–H wag (-CH_2X) from 1300-1150 cm^{-1}
- C–X stretches (general) from 850-515 cm^{-1}
  - C–Cl stretch 850-550 cm^{-1}
  - C–Br stretch 690-515 cm^{-1}

The spectrum of 1-chloro-2-methylpropane are shown below.

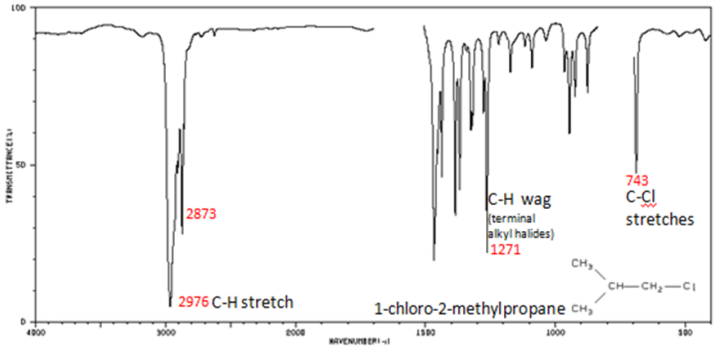


Figure 12.8.11: Infrared Spectrum of 1-chloro-2-methylpropane

For more Infrared spectra Spectral database of organic molecules is introduced to use free database. Also, the infrared spectroscopy correlation table is linked on bottom of page to find other assigned IR peaks.

? EXERCISE 12.8.1

Caffeine has a mass of 194.19 amu, determined by mass spectrometry, and contains C, N, H, O. What is a molecular formula for this molecule?

Answer

$C_8H_{10}N_4O_2$

C = 12 × 8 = 96

N = 14 × 4 = 56

H = 1 × 10 = 10

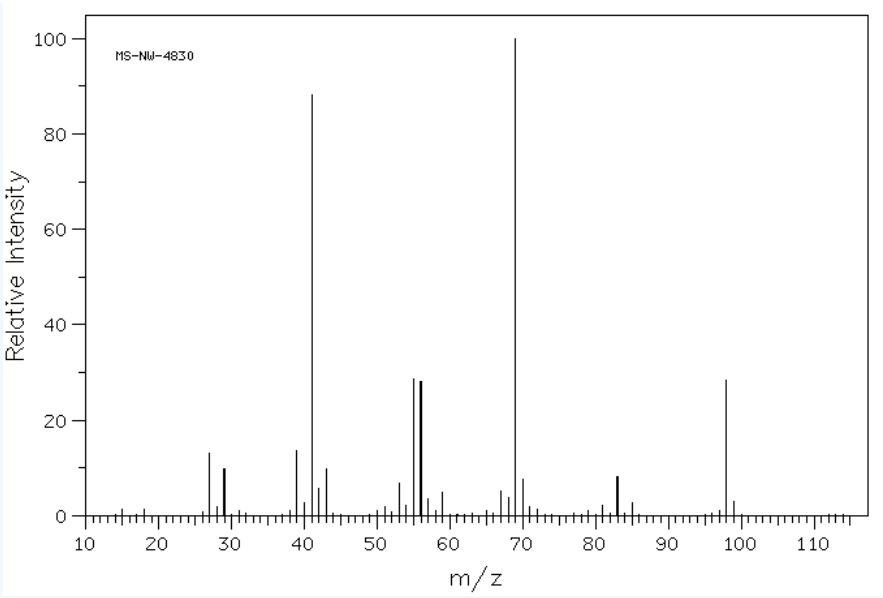
O = 2 × 16 = 32

96+56+10+32 = 194 g/mol

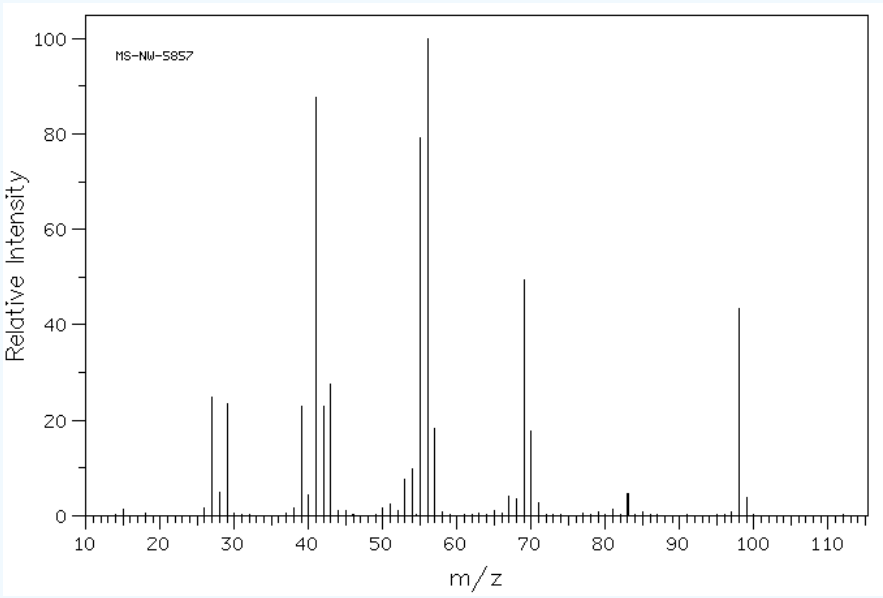
? EXERCISE 12.8.2

The following are the spectra for 2-methyl-2-hexene and 2-heptene, which spectra belongs to the correct molecule. Explain.

A:



B:



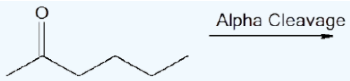
Source: SDBSWeb : http://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, 2 December 2016)

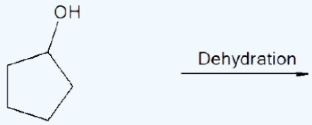
Answer

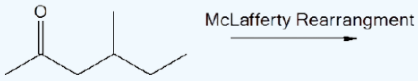
The (A) spectrum is 2-methyl-2-hexene and the (B) spectrum is 2-heptene. Looking at (A) the peak at 68 *m/z* is the fractioned molecule with just the tri-substituted alkene present. While (B) has a strong peak around the 56 *m/z*, which in this case is the di-substituted alkene left behind from the linear heptene.

? EXERCISE 12.8.3

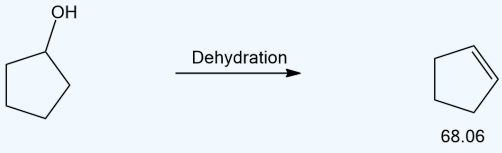
What are the masses of all the components in the following fragmentations?







Answer



EXERCISE 12.8.4

Which of the following frequencies/wavelengths are higher energy

a. $\lambda = 2.0 \times 10^{-6}$ m or $\lambda = 3.0 \times 10^{-9}$ m
b. $\upsilon = 3.0 \times 10^{9}$ Hz or $\upsilon = 3.0 \times 10^{-6}$ Hz

Answer

a. $\lambda = 3.0 \times 10^{-9}$ m
b. $\upsilon = 3.0 \times 10^{9}$ Hz

EXERCISE 12.8.5

Calculate the energies for the following;

a. Gamma Ray $\lambda = 4.0 \times 10^{-11}$ m
b. X-Ray $\lambda = 4.0 \times 10^{-9}$ m
c. UV light $\upsilon = 5.0 \times 10^{15}$ Hz
d. Infrared Radiation $\lambda = 3.0 \times 10^{-5}$ m
e. Microwave Radiation $\upsilon = 3.0 \times 10^{11}$ Hz

Answer

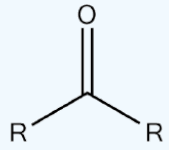
a. 4.965×10^{-15} J
b. 4.965×10^{-17} J
c. 3.31×10^{-18} J
d. 6.62×10^{-21} J
e. 1.99×10^{-22} J

EXERCISE 12.8.6

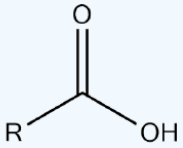
What functional groups give the following signals in an IR spectrum?

a. 1700 cm^{-1}
b. 1550 cm^{-1}
c. 1700 cm^{-1} and 2510-3000 cm^{-1}

Answer

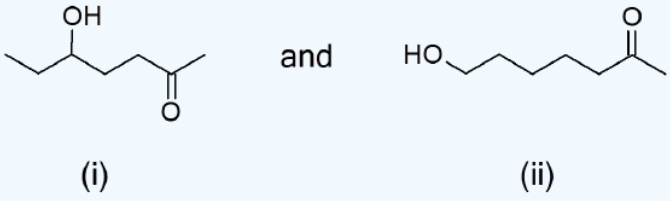
A)  Carbonyl

B) Nitro

C)  Carboxylic Acid

EXERCISE 12.8.7

How can you distinguish the following pairs of compounds through IR analysis?

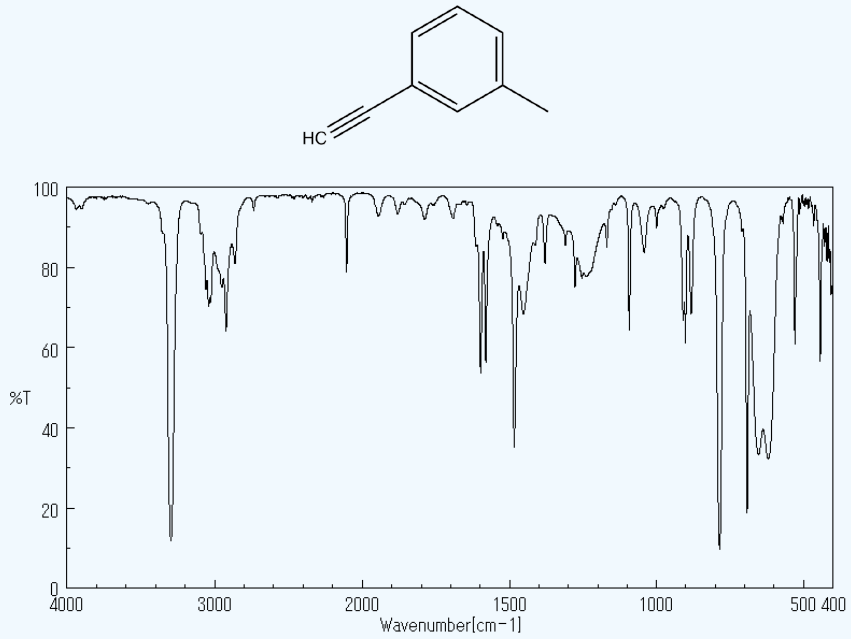
a. CH_3OH (Methanol) and $CH_3CH_2OCH_2CH_3$ (Diethylether)
b. Cyclopentane and 1-pentene.
c. 

Answer

a. A OH peak will be present around 3300 cm^{-1} for methanol and will be absent in the ether.
b. 1-pentene will have a alkene peak around 1650 cm^{-1} for the C=C and there will be another peak around 3100 cm^{-1} for the sp^2 C-H group on the alkene
c. Cannot distinguish these two isomers. They both have the same functional groups and therefore would have the same peaks on an IR spectra.

EXERCISE 12.8.8

The following spectra is for the accompanying compound. What are the peaks that you can I identify in the spectrum?



Source: SDBSWeb : http://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, 2 December 2016)

Answer

Frequency (cm^{-1}) Functional Groups

3200 C≡C-H

2900-3000 C-C-H, C=C-H

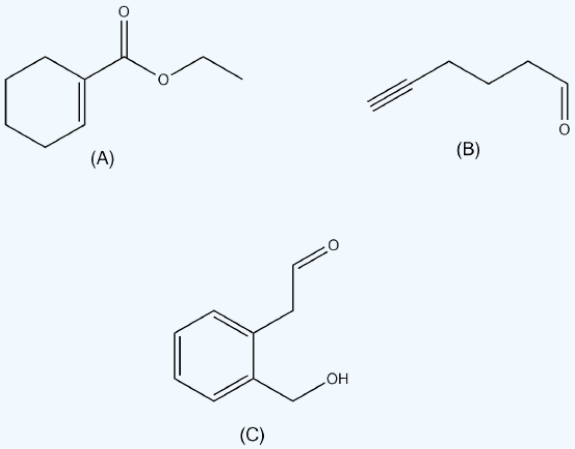
2100 C≡C

1610 C=C

(There is also an aromatic undertone region between 2000-1600 which describes the substitution on the phenyl ring.)

EXERCISE 12.8.9

What absorptions would the following compounds have in an IR spectra?



Answer

A)

Frequency (cm-1) Functional Group

2900-3000 C-C-H, C=C-H

1710 C=O

1610 C=C

1100 C-O

B)

Frequency (cm-1) Functional Group

3200 C≡C-H

2900-3000 C-C-H, C=C-H

2100 C≡C

1710 C=O

C)

Frequency (cm-1) Functional Group

3300 (broad) O-H

2900-3000 C-C-H, C=C-H

2000-1800 Aromatic Overtones

1710 C=O

1610 C=C

12.S: STRUCTURE DETERMINATION - MASS SPECTROMETRY AND INFRARED SPECTROSCOPY (SUMMARY)

CONCEPTS & VOCABULARY

12.1 Introduction

- Spectroscopy describes several techniques used by chemists to understand chemical structures and bonds.

12.2 Mass Spectrometry of Small Molecules - Magnetic Sector Instruments

- Mass spectrometers consist of an **ion source**, **mass analyzer** and dectector.
- There are several common **ion sources** including **electron ionization** and **chemical ionization**.
- Upon ionization, a molecular ion is formed (the molecule after losing a single electron) which will break into smaller pieces (fragments).
- Fragments that are charged will appear in the mass spectrum and are helpful in identifying the parent molecule.
- The most abundant ion in a mass spectrum is called the **base peak**.
- The ion with the same mass as the parent molecule is called the **molecular ion**.
- Isotopes of carbon and hydrogen lead to common M+1 peaks.
- The x-axis of a mass spectrum is **m/z -** the mass to charge ratio, which in practice equals the mass of the ion.

12.3 Interpreting Mass Spectra

- Uncharged particles do not appear in mass spectra.
- The y-axis of a mass spectrum is the relative abundance, with the base peak set at 100 as the most abundant ion.
- Abundance of ions is related to their stability.

12.4 Mass Spectrometry of Some Common Functional Groups

12.5 Mass Spectrometry in Biological - Time-of-flight (TOF) Instruments

12.6 Spectroscopy and the Electromagnetic Spectrum

- Electromagnetic radiation is composed of waves where shorter wavelengths correspond to higher energy radiation.
- Electromagnetic radiation can also be thought of as a stream of particles called **photons**.
- The electromagnetic spectrum is made up of many types of radiation including infrared, ultraviolet, and visible lights as well as x-rays, gamma rays, microwaves, and radio waves.
- Molecular spectroscopy works by exposing a chemical sample to electromagnetic radiation. It will only absorb radiation with energy that corresponds to some excited state, while all other energies will pass through unabsorbed.

12.7 Infrared Spectroscopy

- When infrared radiation is absorbed, molecules will move to a higher vibrational energy state.
- Examples of molecular vibrations include bending and stretching of bonds. These vibrations can be symmetric or asymmetric.
- In general, more polar bonds have stronger IR absorption.
- IR spectra typically use wavenumbers (cm^{-1}) as units for the x-axis.
- The y-axis for IR spectra is usually % transmittance, with 100% at the top of the spectrum and absorbances looking like valleys (or downward peaks).

12.8 Interpreting Infrared Spectra

- Functional groups have standard regions within the IR spectrum where they absorb.
- The general regions include hydrogen bonding (O-H and N-H), carbon-hydrogen bonds, triple bonds, carbonyls, alkenes, and fingerprint region.

12.9 Infrared Spectra of Some Common Functional Groups

SKILLS TO MASTER

- Skill 12.1 Determine specific atoms from mass spectra based on molecular ion and M+2 peaks (N, Cl, Br).
- Skill 12.2 Interpret mass spectra fragments - recognizing common fragments.
- Skill 12.3 Interpret infrared spectra to determine functional groups that are present or absent.

MEMORIZATION TASKS (MT)

- MT 12.1 Memorize common mass spectra fragments.
- MT 12.2 Memorize common functional group regions in infrared spectroscopy.

CHAPTER OVERVIEW

13: STRUCTURE DETERMINATION - NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

LEARNING OBJECTIVES

- fulfillall of the detailed objectives listed under each individual section.
- solve road-map problems which may require the interpretation of ^{1}H NMR spectra in addition to other spectral data.
- define, and use in context, the key terms introduced.

In Chapter 12, you learned how an organic chemist could use two spectroscopic techniques, mass spectroscopy and infrared spectroscopy, to assist in determining the structure of an unknown compound. This chapter introduces a third technique, nuclear magnetic resonance (NMR). The two most common forms of NMR spectroscopy, ^{1}H NMR and ^{13}C NMR, will be discussed, the former in much more detail than the latter. Nuclear magnetic resonance spectroscopy is a very powerful tool, particularly when used in combination with other spectroscopic techniques.

13.0: NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

OBJECTIVES

After completing this section, you should be able to

1. discuss the principles of NMR spectroscopy.
2. identify the two magnetic nuclei that are most important to an organic chemist.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- resonance

STUDY NOTES

Notice that the word “resonance” has a different meaning when we are discussing nuclear magnetic resonance spectroscopy than it does when discussing molecular structures.

INTRODUCTION

Some types of atomic nuclei act as though they spin on their axis similar to the Earth. Since they are positively charged they generate an electromagnetic field just as the Earth does. So, in effect, they will act as tiny bar magnetics. Not all nuclei act this way, but fortunately both ^{1}H and ^{13}C do have nuclear spins and will respond to this technique.

NMR Spectrometer

In the absence of an external magnetic field the direction of the spin of the nuclei will be randomly oriented (see figure below left). However, when a sample of these nuclei is place in an external magnetic field, the nuclear spins will adopt specific orientations much as a compass needle responses to the Earth’s magnetic field and aligns with it. Two possible orientations are possible, with the external field (*i.e.* parallel to and in the same direction as the external field) or against the field (*i.e.* antiparallel to the external field) - see Figure 13.0.1.

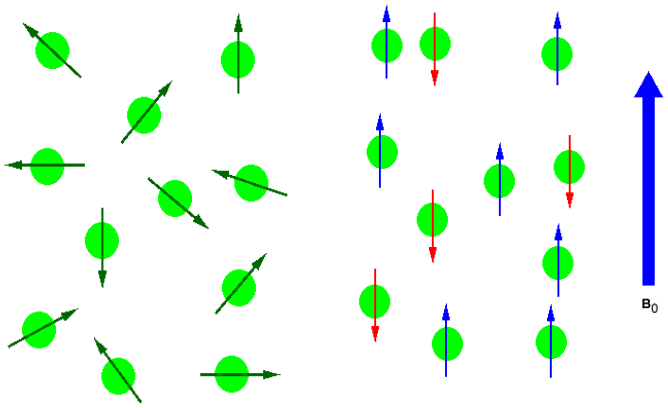
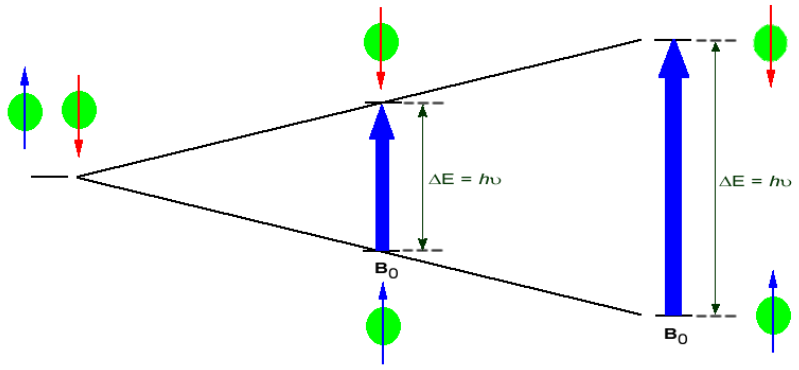


Figure 13.0.1: (Left) Random nuclear spin without an external magnetic field. (Right) Ordered nuclear spin in an external magnetic field

If the ordered nuclei are now subjected to EM radiation of the proper frequency the nuclei aligned with the field will absorb energy and "spin-flip" to align themselves against the field, a higher energy state. When this spin-flip occurs the nuclei are said to be in "resonance" with the field, hence the name for the technique, **N**uclear **M**agentic **R**esonance or NMR.

The amount of energy, and hence the exact frequency of EM radiation required for resonance to occur is dependent on both the strength of the magnetic field applied and the type of the nuclei being studied. As the strength of the magnetic field increases the energy difference between the two spin states increases and a higher frequency (more energy) EM radiation needs to be applied to achieve a spin-flip (see image below).



Superconducting magnets can be used to produce very strong magnetic field, on the order of 21 tesla (T). Lower field strengths can also be used, in the range of 4 - 7 T. At these levels the energy required to bring the nuclei into resonance is in the MHz range and corresponds to radio wavelength energies, *i.e.* at a field strength of 4.7 T 200 MHz bring ^{1}H nuclei into resonance and 50 MHz bring ^{13}C into resonance. This is considerably less energy then is required for IR spectroscopy, ~10^{-4} kJ/mol versus ~5 - ~50 kJ/mol.

^{1}H and ^{13}C are not unique in their ability to undergo NMR. All nuclei with an odd number of protons (^{1}H, ^{2}H, ^{14}N, ^{19}F, ^{31}P ...) or nuclei with an odd number of neutrons (*i.e.* ^{13}C) show the magnetic properties required for NMR. Only nuclei with even number of both protons and neutrons (^{12}C and ^{16}O) do not have the required magnetic properties.

? EXERCISE 13.0.1

If in a field strength of 4.7 T, H^1 requires 200 MHz of energy to maintain resonance. If atom X requires 150 MHz, calculate the amount of energy required to spin flip atom X's nucleus. Is this amount greater than the energy required for hydrogen?

Answer

$E = h\upsilon$

$E = (6.62 \times 10^{-34})(150\ \text{MHz})$

$E = 9.93 \times 10^{-26}$ J

The energy is equal to 9.93x10^{-26} J. This value is smaller than the energy required for hydrogen (1.324×10^{-25} J).

EXERCISE 13.0.1

Calculate the energy required to spin flip at 400 MHz. Does changing the frequency to 500 MHz decrease or increase the energy required? What about 300 MHz.

Answer

$E = h\upsilon$

$E = (6.62 \times 10^{-34})(400\ \text{MHz})$

$E = 2.648 \times 10^{-25}\ \text{J}$

The energy would increase if the frequency would increase to 500 MHz, and decrease if the frequency would decrease to 300 MHz.

13.1: THE NATURE OF NMR ABSORPTIONS

OBJECTIVES

After completing this section, you should be able to

1. explain, in general terms, the origin of shielding effects in NMR spectroscopy.
2. explain the number of peaks occurring in the ^{1}H or ^{13}C NMR spectrum of a simple compound, such as methyl acetate.
3. describe, and sketch a diagram of, a simple NMR spectrometer.
4. explain the difference in time scales of NMR and infrared spectroscopy.
5. predict the number of peaks expected in the ^{1}H or ^{13}C NMR spectrum of a given compound.

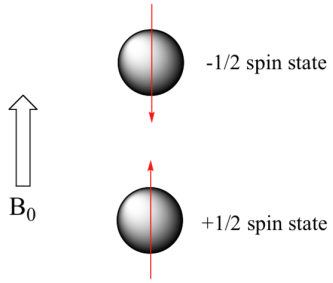
STUDY NOTES

Before you go on, make sure that you understand that each signal in the ^{1}H NMR spectrum shown for methyl acetate is due to a different proton environment. The three protons on the same methyl group are equivalent and appear in the spectrum as one signal. However, the two methyl groups are in two different environments (one is more deshielded) and so we see two signals in the whole spectrum (aside from the TMS reference peak).

Methyl acetate has a very simple ^{1}H NMR spectrum, because there is no proton-proton coupling, and therefore no splitting of the signals. In later sections, we discuss splitting patterns in ^{1}H NMR spectra and how they help a chemist determine the structure of organic compounds.

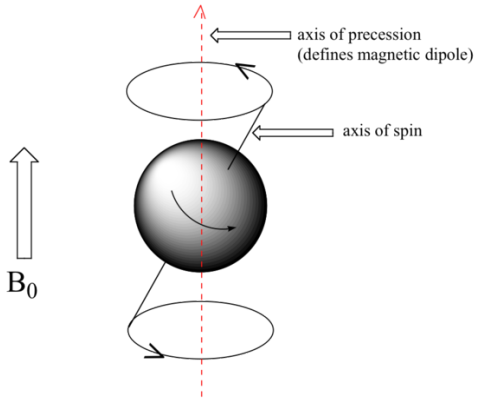
NUCLEAR PRECESSION, SPIN STATES, AND THE RESONANCE CONDITION

When a sample of an organic compound is sitting in a flask on a laboratory benchtop, the magnetic moments of its hydrogen atoms are randomly oriented. When the same sample is placed within the field of a very strong magnet in an NMR instrument (this field is referred to by NMR spectroscopists as the **applied field**, abbreviated $\mathbf{B_0}$) each hydrogen will assume one of two possible **spin states**. In what is referred to as the +½ spin state, the hydrogen's magnetic moment is aligned *with* the direction of B_0, while in the -½ spin state it is aligned *opposed to* the direction of B_0.



Because the +½ spin state is slightly lower in energy, in a large population of organic molecules slightly more than half of the hydrogen atoms will occupy this state, while slightly less than half will occupy the –½ state. *The difference in energy between the two spin states increases with increasing strength of B_0.*This last statement is in italics because it is one of the key ideas in NMR spectroscopy, as we shall soon see.

At this point, we need to look a little more closely at how a proton spins in an applied magnetic field. You may recall playing with spinning tops as a child. When a top slows down a little and the spin axis is no longer completely vertical, it begins to exhibit **precessional motion**, as the spin axis rotates slowly around the vertical. In the same way, hydrogen atoms spinning in an applied magnetic field also exhibit precessional motion about a vertical axis. It is this axis (which is either parallel or antiparallel to B_0) that defines the proton's magnetic moment. In the figure below, the proton is in the +1/2 spin state.

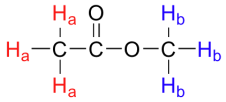


The **frequency of precession** (also called the **Larmour frequency,** abbreviated ω_L) is simply the number of times per second that the proton precesses in a complete circle. A proton`s precessional frequency increases with the strength of B_0.

If a proton that is precessing in an applied magnetic field is exposed to electromagnetic radiation of a frequency ν that matches its precessional frequency ω_L, we have a condition called **resonance**. *In the resonance condition, a proton in the lower-energy +½ spin state (aligned with B_0) will transition (flip) to the higher energy –½ spin state (opposed to B_0). In doing so, it will absorb radiation at this resonance frequency* $\nu = \omega_L$. This frequency, as you might have already guessed, corresponds to the energy difference between the proton's two spin states. With the strong magnetic fields generated by the superconducting magnets used in modern NMR instruments, the resonance frequency for protons falls within the radio-wave range, anywhere from 100 MHz to 800 MHz depending on the strength of the magnet.

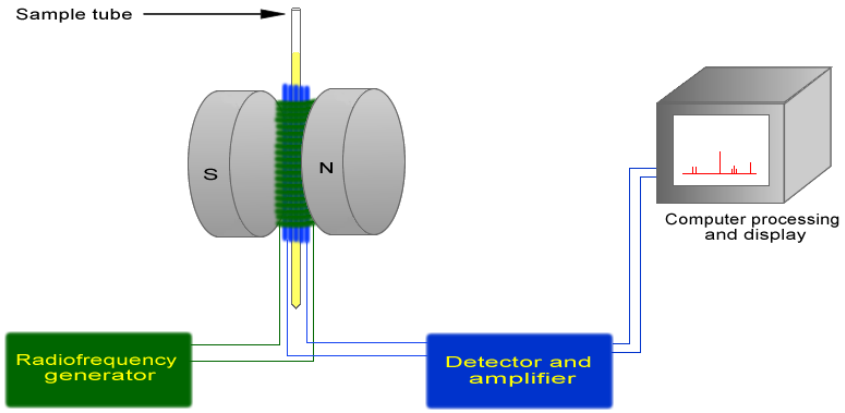
THE BASICS OF AN NMR EXPERIMENT

So far, you may have the impression that all ^1H nuclei in a molecule would absorb the same frequency. However, this would be of little use to organic chemists if that were the case. It turns out that not all ^1H nuclei absorb the same frequency and this is the same for all other NMR active nuclei. It turns out that chemically nonequivalent protons (or other nuclei) have different resonance frequencies in the same applied magnetic field. Nonequivalent protons are in different chemical environments. This allows NMR spectroscopy to provide us with useful information about the structure of an organic molecule. A full explanation of how a modern NMR instrument functions is beyond the scope of this text, but here is what happens. First, a sample compound (we'll use methyl acetate) is placed inside a very strong applied magnetic field (B_0). There are two types of protons in methyl acetate. H_a are bonded to a C that is then bonded to a carbonyl, whereas H_b are bonded to a carbon that is then bonded to an oxygen atom. This difference in bonding leads to different types of environments for H_a and H_b. All the H_a protons are the same since they all have the same type of bonding and will be in the same chemical environment and the same is true for H_b.



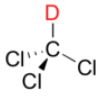
methyl acetate

The basic arrangement of an NMR spectrometer is displayed below. A sample (in a small glass tube, where the methyl acetate is in solution) is placed between the poles of a strong magnet. A radio frequency generator pulses the sample and excites the nuclei causing a spin-flip. The spin flip is detected by the detector and the signal sent to a computer where it is processed.

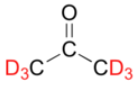


In the magnet, all of the protons begin to precess: the H_a protons at precessional frequency ω_a, the H_b protons at ω_b. At first, the magnetic moments of (slightly more than) half of the protons are aligned with B_0, and half (slightly less than half) are aligned against B_0. Then, the sample is hit with electromagnetic radiation in the radio frequency range. The two specific frequencies which match ω_a and ω_b (i.e. the resonance frequencies) cause those H_a and H_b protons which are aligned *with* B_0 to 'flip' so that they are now aligned *against* B_0. In doing so, the protons absorb radiation at the two resonance frequencies. The NMR instrument records which frequencies were absorbed, as well as the intensity of each absorbance.

In most cases, a sample being analyzed by NMR is in solution. If we used a common laboratory solvent (diethyl ether, acetone, dichloromethane, ethanol, water, etc.) to dissolve our NMR sample, however, we run into a problem – there many more solvent protons in solution than there are sample protons, therefore the signals from the sample protons will be overwhelmed. To get around this problem, we use special NMR solvents in which all protons have been replaced by deuterium. Recall that deuterium is NMR-active, but its resonance frequency is very different from that of protons, and thus it is `invisible` in ^{1}H-NMR. Some common NMR solvents are shown below. There are multiple deuterated solvents since molecules have different solubilities, so one molecule may dissolve in deuterated chloroform while others may not.



deuterated chloroform ($CDCl_3$)

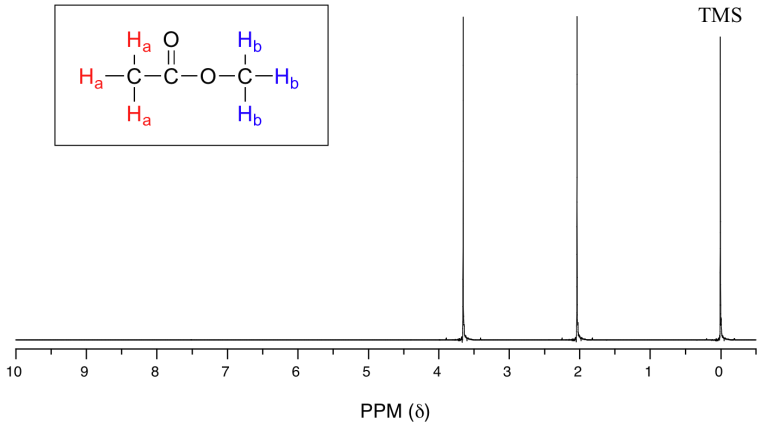


d_6-acetone

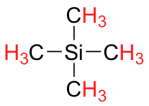
D_2O

THE CHEMICAL SHIFT

Let's look at an actual ^{1}H-NMR plot for methyl acetate. Just as in IR and UV-vis spectroscopy, the vertical axis corresponds to intensity of absorbance, the horizontal axis to frequency (typically the vertical axis is not shown in an NMR spectrum).



We see three absorbance signals: two of these correspond to H_a and H_b, while the peak at the far right of the spectrum corresponds to the 12 chemically equivalent protons in tetramethylsilane (TMS), a standard reference compound that was added to our sample.



tetramethylsilane (TMS)

You may be wondering about a few things at this point - why is TMS necessary, and what is the meaning of the `ppm (δ)` label on the horizontal axis? Shouldn't the frequency units be in Hz? Keep in mind that NMR instruments of many different applied field strengths are used in organic chemistry laboratories, and that the proton's resonance frequency range depends on the strength of the applied field. The spectrum above was generated on an instrument with an applied field of approximately 7.1 Tesla, at which strength protons resonate in the neighborhood of 300 million Hz (chemists refer to this as a 300 MHz instrument). If our colleague in another lab takes the NMR spectrum of the same molecule using an instrument with a 2.4 Tesla magnet, the protons will resonate at around 100 million Hz (so we'd call this a 100 MHz instrument). It would be inconvenient and confusing to always have to convert NMR data according to the field strength of the instrument used. Therefore, chemists report resonance frequencies not as absolute values in Hz, but rather as values *relative to a common standard*, generally the signal generated by the protons in TMS. This is where the ppm – parts per million – term comes in. Regardless of

the magnetic field strength of the instrument being used, the resonance frequency of the 12 equivalent protons in TMS is defined as a zero point. The resonance frequencies of protons in the sample molecule are then reported in terms of how much higher they are, in ppm, relative to the TMS signal (almost all protons in organic molecules have a higher resonance frequency than those in TMS, for reasons we shall explore quite soon).

The two proton groups in our methyl acetate sample are recorded as resonating at frequencies 2.05 and 3.67 ppm higher than TMS. One-millionth (1.0 ppm) of 300 MHz is 300 Hz. Thus 2.05 ppm, on this instrument, corresponds to 615 Hz, and 3.67 ppm corresponds to 1101 Hz. If the TMS protons observed by our 7.1 Tesla instrument resonate at exactly 300,000,000 Hz, this means that the protons in our ethyl acetate samples are resonating at 300,000,615 and 300,001,101 Hz, respectively. Likewise, if the TMS protons in our colleague's 2.4 Tesla instrument resonate at exactly 100 MHz, the methyl acetate protons in her sample resonate at 100,000,205 and 100,000,367 Hz (on the 100 MHz instrument, 1.0 ppm corresponds to 100 Hz). The absolute frequency values in each case are not very useful – they will vary according to the instrument used – but the *difference* in resonance frequency from the TMS standard, expressed in parts per million, should be the same regardless of the instrument.

Expressed this way, the resonance frequency for a given proton in a molecule is called its **chemical shift**. A frequently used symbolic designation for chemical shift in ppm is the lower-case Greek letter *delta* (δ). Most protons in organic compounds have chemical shift values between 0 and 12 ppm from TMS, although values below zero and above 12 are occasionally observed. By convention, the left-hand side of an NMR spectrum (higher chemical shift) is called **downfield**, and the right-hand direction is called **upfield**.

In our methyl acetate example we included for illustrative purposes a small amount of TMS standard directly in the sample, as was the common procedure for determining the zero point with older NMR instruments. That practice is generally no longer necessary, as modern NMR instruments are designed to use the deuterium signal from the solvent as a standard reference point, then to extrapolate the 0 ppm baseline that corresponds to the TMS proton signal (in an applied field of 7.1 Tesla, the deuterium atom in $CDCl_3$ resonates at 32 MHz, compared to 300 MHz for the protons in TMS). In the remaining NMR spectra that we will see in this text we will not see an actual TMS signal, but we can always assume that the 0 ppm point corresponds to where the TMS protons *would* resonate if they were present.

EXAMPLE

A proton has a chemical shift (relative to TMS) of 4.56 ppm.

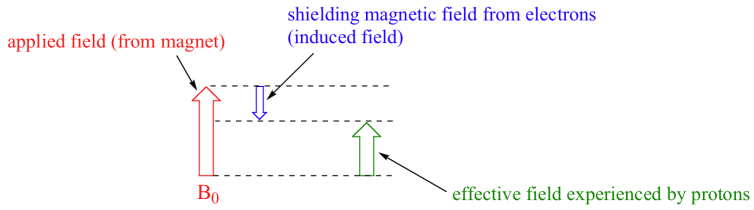
a. a) What is its chemical shift, expressed in Hz, in a 300 MHz instrument? On a 200 MHz instrument?
b. b) What is its resonance frequency, expressed in Hz, in a 300 MHz instrument? On a 200 MHz instrument?

(Assume that in these instruments, the TMS protons resonate at exactly 300 or 200 MHz, respectively)

Solution

DIAMAGNETIC SHIELDING AND DESHIELDING

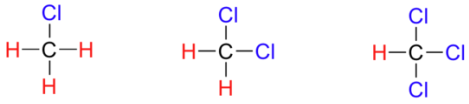
We come now to the question of *why* nonequivalent protons have different chemical shifts. The chemical shift of a given proton is determined primarily by its immediate electronic environment. Consider the methane molecule (CH_4), in which the protons have a chemical shift of 0.23 ppm. The valence electrons around the methyl carbon, when subjected to B_0, are induced to circulate and thus generate their own very small magnetic field that *opposes* B_0. This **induced field**, to a small but significant degree, *shields* the nearby protons from experiencing the full force of B_0, an effect known as **local diamagnetic shielding**. The methane protons therefore do not experience the full force of B_0 - what they experience is called B_{eff}, or the **effective field**, which is slightly *weaker* than B_0.



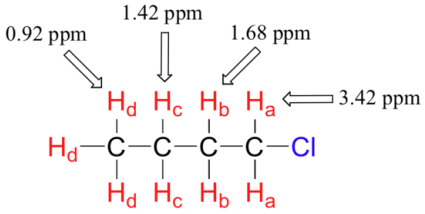
Therefore, their resonance frequency is slightly lower than what it would be if they did not have electrons nearby to shield them.

Now consider methyl fluoride, CH_3F, in which the protons have a chemical shift of 4.26 ppm, significantly higher than that of methane. This is caused by something called the **deshielding effect**. Because fluorine is more electronegative than carbon, it pulls valence electrons away from the carbon, effectively *decreasing* the electron density around each of the protons. For the protons, lower electron density means less diamagnetic shielding, which in turn means a greater overall exposure to B_0, a stronger B_{eff}, and a higher resonance frequency. Put another way, the fluorine, by pulling electron density away from the protons, is *deshielding* them, leaving them more exposed to B_0. As the electronegativity of the substituent increases, so does the extent of deshielding, and so does the chemical shift. This is evident when we look at the chemical shifts of methane and three halomethane compounds (remember that electronegativity increases as we move up a column in the periodic table).

To a large extent, then, we can predict trends in chemical shift by considering how much deshielding is taking place near a proton. The chemical shift of trichloromethane is, as expected, higher than that of dichloromethane, which is in turn higher than that of chloromethane.



The deshielding effect of an electronegative substituent diminishes sharply with increasing distance:



The presence of an electronegative oxygen, nitrogen, sulfur, or sp^2-hybridized carbon also tends to shift the NMR signals of nearby protons slightly downfield:

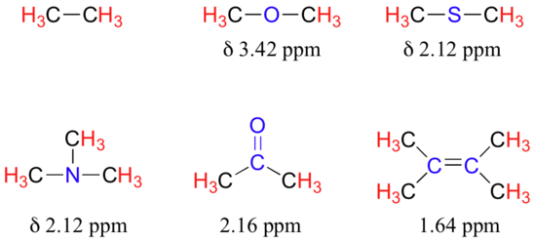
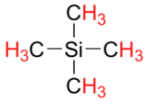


Table 2 lists typical chemical shift values for protons in different chemical environments.

Armed with this information, we can finally assign the two peaks in the the ^{1}H-NMR spectrum of methyl acetate that we saw a few pages back. The signal at 3.65 ppm corresponds to the methyl ester protons (H_b), which are deshielded by the adjacent oxygen atom. The upfield signal at 2.05 ppm corresponds to the acetate protons (H_a), which is deshielded - but to a lesser extent - by the adjacent carbonyl group.

Finally, a note on the use of TMS as a standard in NMR spectroscopy: one of the main reasons why the TMS proton signal was chosen as a zero-point is that the TMS protons are highly shielded: silicon is slightly *less* electronegative than carbon, and therefore *donates* some additional shielding electron density. Very few organic molecules contain protons with chemical shifts that are negative relative to TMS.



13.2: THE CHEMICAL SHIFT

OBJECTIVES

After completing this section, you should be able to

1. describe the delta scale used in NMR spectroscopy.
2. perform calculations based on the relationship between the delta value (in ppm), the observed chemical shift (in Hz), and the operating frequency of an NMR spectrometer (in Hz).

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- chemical shift
- delta scale
- upfield/downfield

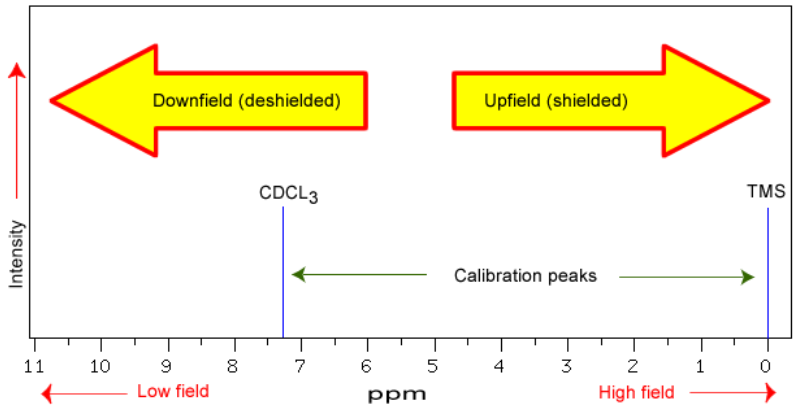
STUDY NOTES

Although the calculations described in this section will help you understand the principles of NMR, it is the actual delta values, not the calculations, which are of greatest importance to the beginning organic chemist. Thus, we shall try to focus on the interpretation of NMR spectra, not the mathematical aspects of the technique.

In Section 13.9 we discuss ^{1}H NMR chemical shifts in more detail. Although you will eventually be expected to associate the approximate region of a ^{1}H NMR spectrum with a particular type of proton, you are expected to use a general table of ^{1}H NMR chemical shifts such as the one shown in Section 13.9.

CHEMICAL SHIFTS

The NMR spectra is displayed as a plot of the applied radio frequency versus the absorption. The applied frequency increases from left to right, thus the left side of the plot is the low field, downfield or deshielded side and the right side of the plot is the high field, upfield or shielded side (see the figure below). The concept of shielding will be explained shortly.



The position on the plot at which the nuclei absorbs is called the **chemical shift**. Since this has an arbitrary value a standard reference point must be used. The two most common standards are TMS (tetramethylsilane, $(Si(CH_3)_4)$ which has been assigned a chemical shift of zero, and $CDCl_3$ (deuterochloroform) which has a chemical shift of 7.26 for ^{1}H NMR and 77 for ^{13}C NMR. The scale is commonly expressed as parts per million (ppm) which is independent of the spectrometer frequency. The scale is the **delta (δ) scale**.

$$\delta = \frac{\text{frequency of signal} - \text{frequency of standard}}{\text{spectrometerfrequency}} \times 10^{6}$$

The range at which most NMR absorptions occur is quite narrow. Almost all ^{1}H absorptions occur downfield within 10 ppm of TMS. For ^{13}C NMR almost all absorptions occurs within 220 ppm downfield of the C atom in TMS.

SHIELDING IN NMR

Structural features of the molecule will have an effect on the exact magnitude of the magnetic field experienced by a particular nucleus. This means that H atoms which have different chemical environments will have different chemical shifts. This is what makes NMR so useful for structure determination in organic chemistry. There are three main features that will affect the shielding of the nucleus, electronegativity, magnetic anisotropy of π systems and hydrogen bonding.

ELECTRONEGATIVITY

The electrons that surround the nucleus are in motion so they created their own electromagnetic field. This field opposes the the applied magnetic field and so reduces the field experienced by the nucleus. Thus the electrons are said to **shield** the nucleus. Since the magnetic field experienced at the nucleus defines the energy difference between spin states it also defines what the chemical shift will be for that nucleus. Electron with-drawing groups can decrease the electron density at the nucleus, deshielding the nucleus and result in a larger chemical shift. Compare the data in the table below.

Compound, CH_3X	CH_3F	CH_3OH	CH_3Cl	CH_3Br	CH_3I	CH_4	$(CH_3)_4Si$
Electronegativity of X	4.0	3.5	3.1	2.8	2.5	2.1	1.8
Chemical shift δ (ppm)	4.26	3.4	3.05	2.68	2.16	0.23	0

As can be seen from the data, as the electronegativity of X increases the chemical shift, δ increases. This is an effect of the halide atom pulling the electron density away from the methyl group. This exposes the nuclei of both the C and H atoms, "deshielding" the nuclei and shifting the peak downfield.

The effects are cumulative so the presence of more electron withdrawing groups will produce a greater deshielding and therefore a larger chemical shift, *i.e.*

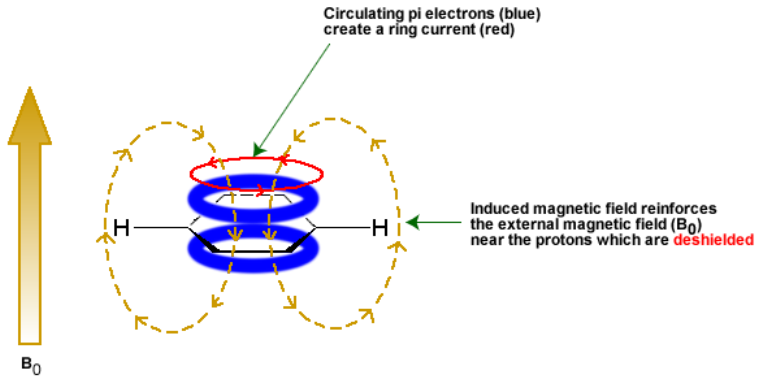
Compound	CH_4	CH_3Cl	CH_2Cl_2	$CHCl_3$
δ (ppm)	0.23	3.05	5.30	7.27

These **inductive effects** are not only felt by the immediately adjacent atoms, but the deshielding can occur further down the chain, *i.e.*

NMR signal	$-CH_2-CH_2-CH_2Br$
δ (ppm)	1.25 1.69 3.30

MAGNETIC ANISOTROPY: Π ELECTRON EFFECTS

The π electrons in a compound, when placed in a magnetic field, will move and generate their own magnetic field. The new magnetic field will have an effect on the shielding of atoms within the field. The best example of this is benzene (see the figure below).

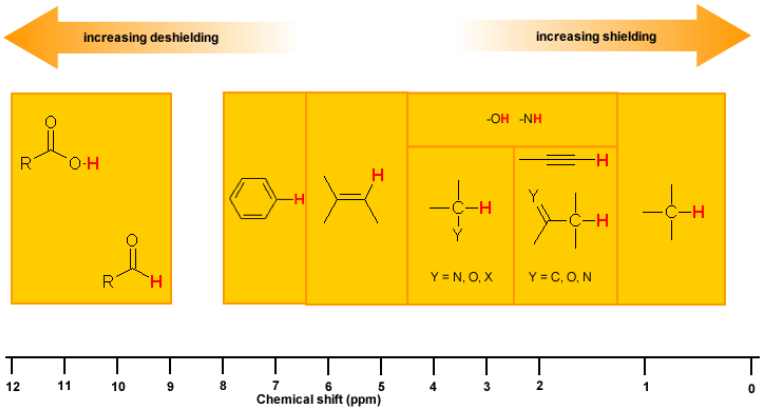


This effect is common for any atoms near a π bond, *i.e.*

Proton Type	Effect	Chemical shift (ppm)
C_6H_5-H	highly deshielded	6.5 - 8
C=C-H	deshielded	4.5 - 6
C≡C-H	shielded*	~2.5
O=C-H	very highly deshielded	9 - 10
* the acetylene H is shielded due to its location relative to the π system		

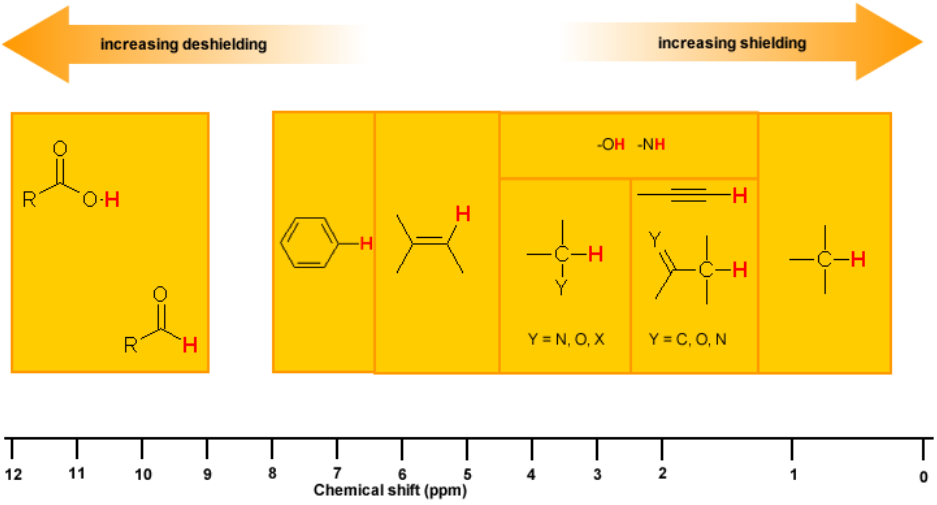
HYDROGEN BONDING

Protons that are involved in hydrogen bonding (*i.e.*-OH or -NH) are usually observed over a wide range of chemical shifts. This is due to the deshielding that occurs in the hydrogen bond. Since hydrogen bonds are dynamic, constantly forming, breaking and forming again, there will be a wide range of hydrogen bonds strengths and consequently a wide range of deshielding. This as well as solvation effects, acidity, concentration and temperature make it very difficult to predict the chemical shifts for these atoms.



Experimentally -OH and -NH can be identified by carrying out a simple D_2O exchange experiment since these protons are exchangeable.

- run the normal H-NMR experiment on your sample
- add a few drops of D_2O
- re-run the H-NMR experiment
- compare the two spectra and look for peaks that have "disappeared"



EXERCISE

QUESTIONS

Q13.3.1

The following peaks were from a H^1 NMR spectra from a 400 MHz spectrometer. Convert to δ units

A. $CHCl_3$ 1451 Hz

B. CH_3Cl 610 Hz

C. CH_3OH 693 Hz

D. CH_2Cl_2 1060 Hz

Q13.3.2

Butan-2-one shows a chemical shift around 2.1 on a 300 MHz spectrometer in the H^1 NMR spectrum.

A. How far downfield is this peak from TMS in Hz?

B. If the spectrum was done with a 400 MHz instrument, would a different chemical shift be seen?

C. On this new 400 MHz spectrum, what would be the difference in Hz from the chemical shift and TMS?

SOLUTIONS

S13.3.1

A. 3.627 ppm

B. 1.525 ppm

C. 1.732 ppm

D. 2.65 ppm

S13.3.2

A. Since TMS is at 0 δ = 0 Hz for reference, the difference between the two would be 630 Hz

B. No not a different chemical shift, but a different frequency would be seen, 840 Hz

C. 840 Hz

13.3: CHEMICAL SHIFTS IN ^{1}H NMR SPECTROSCOPY

OBJECTIVES

After completing this section, you should be able to

1. state the approximate chemical shift (δ) for the following types of protons:
   a. aromatic.
   b. vinylic.
   c. those bonded to carbon atoms which are in turn bonded to a highly electronegative element.
   d. those bonded to carbons which are next to unsaturated centres.
   e. those bonded to carbons which are part of a saturated system.
2. predict the approximate chemical shifts of each of the protons in an organic compound, given its structure and a table of chemical shift correlations.

STUDY NOTES

You should not attempt to memorize the chemical shifts listed in the table of this section, although it is probable that you will need to refer to it quite frequently throughout the remainder of this course. To fulfill Objective 1, above, you should be familiar with the information presented in the figure of chemical shift ranges for organic compounds. If you have an approximate idea of the chemical shifts of some of the most common types of protons, you will find the interpretation of ^{1}H NMR spectra less arduous than it might otherwise be. Notice that we shall not try to understand why aromatic protons are deshielded or why alkynyl protons are not deshielded as much as vinylic protons. These phenomena can be explained, but the focus is on the interpretation of ^{1}H NMR spectra, not on the underlying theory.

^{1}H NMR CHEMICAL SHIFTS

Chemical shifts in NMR (Nuclear Magnetic Resonance) spectroscopy refer to the phenomenon where the resonant frequency of a nucleus in a magnetic field is influenced by its chemical environment. This effect arises from the shielding or deshielding of the nucleus by the surrounding electron cloud. When a nucleus experiences different local electron densities due to nearby atoms or functional groups, its resonant frequency is altered relative to a reference standard, usually tetramethylsilane in organic solvents. This alteration is expressed in parts per million (ppm) and is known as the chemical shift. Tetramethylsilane [TMS;$(CH_3)_4Si$] is generally used for standard to determine chemical shift of compounds: δ_{TMS}=0 ppm. In other words, frequencies for chemicals are measured for a ^{1}H nucleus of a sample from the ^{1}H or resonance of TMS. It is important to understand trend of chemical shift in terms of NMR interpretation. The proton NMR chemical shift is affect by nearness to electronegative atoms (O, N, halogen.) and unsaturated groups (C=C,C=O, aromatic). Electronegative groups move to the down field (left; increase in ppm). Unsaturated groups shift to downfield (left) when affecting nucleus is in the plane of the unsaturation, but reverse shift takes place in the regions above and below this plane. ^{1}H chemical shift play a role in identifying many functional groups. Figure 1. indicates important example to figure out the functional groups.

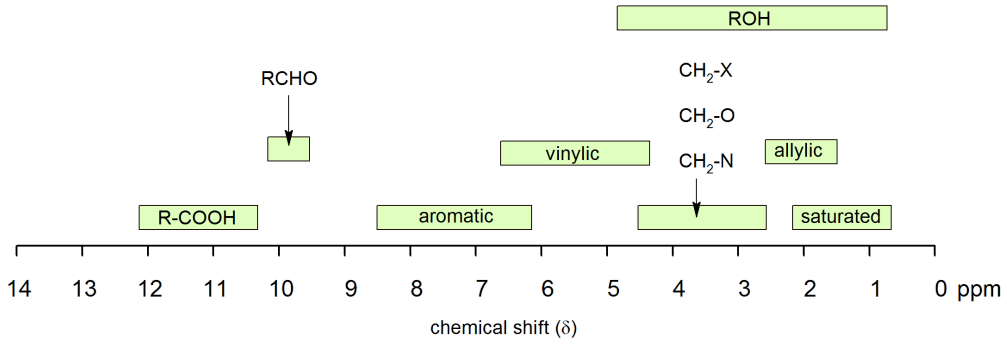
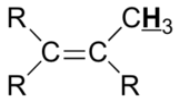
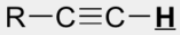
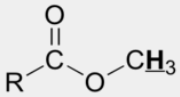
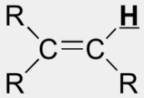
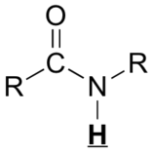
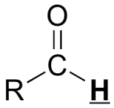
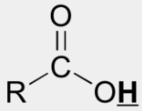


Figure 1. 1H chemical shift ranges for organic compounds

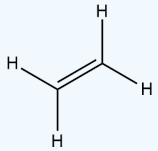
Chemical shift values are in parts per million (ppm) relative to tetramethylsilane.

Table 13.3.1: Common Chemical Shift values

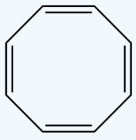
Hydrogen type	Chemical shift (ppm)
$RC\underline{H}_3$	0.9 - 1.0
$RC\underline{H}_2R$	1.2 - 1.7
$R_3C\underline{H}$	1.5 – 2.0
	2.0 – 2.3
	1.5 – 1.8
$RN\underline{H}_2$	1 - 3
$ArC\underline{H}_3$	2.2 – 2.4
	2.3 – 3.0
$ROC\underline{H}_3$	3.7 – 3.9
	3.7 – 3.9
$RO\underline{H}$	1 - 5
	3.7 – 6.5
	5 - 9
$Ar\underline{H}$	6.0 – 8.7
	9.5 – 10.0
	10 - 13

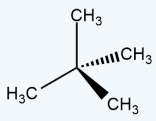
EXERCISE 13.3.1

The following have one H^1 NMR peak. In each case predict approximately where this peak would be in a spectra.

A) 

B) 

C) 

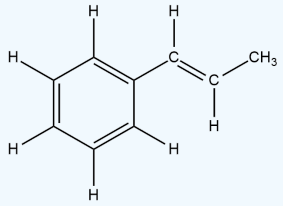
D) 

Answer

A. 5.20 δ; B. 1.50 δ; C. 6.40 δ; D. 1.00 δ

EXERCISE 13.3.2

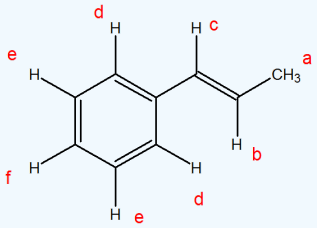
Identify the different equivalent protons in the following molecule and predict their expected chemical shift.



Answer

There are 6 different protons in this molecule

The shifts are (close) to the following: (a) 2 δ; (b) 6 δ; (c) 6.5 δ; (d) 7 δ; (e) 7.5 δ; (f) 7 δ



13.4: INTEGRATION OF ^{1}H NMR ABSORPTIONS - PROTON COUNTING

OBJECTIVES

After completing this section, you should be able to

- explain what information can be obtained from an integrated ^{1}H NMR spectrum, and use this information in the interpretation of such a spectrum.
- use an integrated ^{1}H NMR spectrum to determine the ratio of the different types of protons present in an organic compound.

STUDY NOTES

The concept of peak integration is that the area of a given peak in a ^{1}H NMR spectrum is proportional to the number of (equivalent) protons giving rise to the peak. Thus, a peak which is caused by a single, unique proton has an area which measures one third of the area of a peak resulting from a methyl (CH_3) group in the same spectrum.

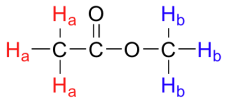
In practice, we do not have to measure these areas ourselves: it is all done electronically by the spectrometer, and an integration curve is superimposed on the rest of the spectrum. The integration curve appears as a series of steps, with the height of each step being proportional to the area of the corresponding absorption peak, and consequently, to the number of protons responsible for the absorption.

As it can be difficult to decide precisely where to start and stop when measuring integrations, you should not expect your ratios to be exact whole numbers.

Signal integration in NMR (Nuclear Magnetic Resonance) spectroscopy is crucial for quantifying the relative number of nuclei contributing to each signal in the spectrum. This process involves measuring the area under each peak in the NMR spectrum, which directly correlates to the abundance of the corresponding nuclei in the sample.

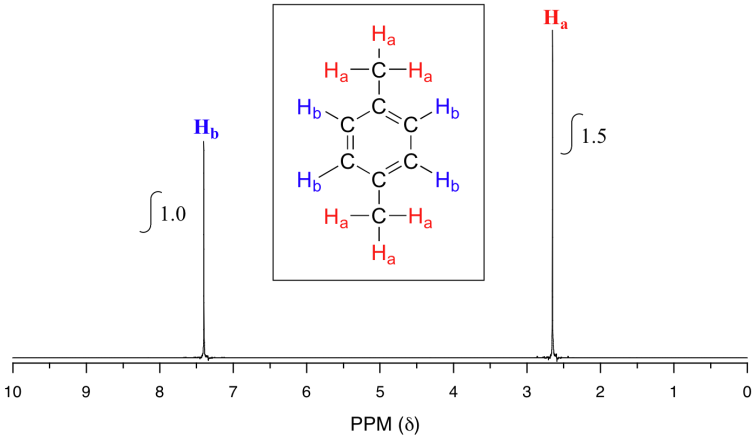
SIGNAL INTEGRATION

The computer in an NMR instrument can be instructed to automatically integrate the area under a signal or group of signals. This is very useful, because *in ^{1}H-NMR spectroscopy the area under a signal is proportional to the number of hydrogens to which the peak corresponds*. In the previous example of methyl acetate from Section 13.2, for example, the Ha and H_b peaks would integrate to approximately the same area, because they both correspond to a set of three equivalent protons.



methyl acetate

Now, take a look next at the spectrum of *para*-xylene (IUPAC name 1,4-dimethylbenzene):



This molecule has two sets of protons: the six methyl (H_a) protons and the four aromatic (H_b) protons. When we instruct the instrument to integrate the areas under the two signals, we find that the area under the peak at 2.6 ppm is 1.5 times greater than the area under the peak at

7.4 ppm, which is the case with 6 methyl protons and 4 aromatic protons. This (along with the actual chemical shift values, which we'll discuss soon) tells us which set of protons corresponds to which NMR signal.

The integration function can also be used to determine the relative amounts of two or more compounds in a *mixed* sample. If we have a sample that is a 50:50 (mole/mole) mixture of benzene and acetone, for example, the acetone signal should integrate to the same value as the benzene sample, because both signals represent six equivalent protons. If we have a 50:50 mixture of acetone and cyclopentane, on the other hand, the ratio of the acetone peak area to the cylopentane peak area will be 3:5 (or 6:10), because the cyclopentane signal represents ten protons.

EXAMPLE 13.4.1

You take a ^{1}H-NMR spectrum of a mixed sample of acetone ($CH_3(CO)CH_3$) and dichloromethane (CH_2Cl_2). The integral ratio of the two signals (acetone : dichloromethane) is 2.3 to 1. What is the molar ratio of the two compounds in the sample?

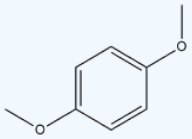
EXAMPLE 13.4.2

You take the ^{1}H-NMR spectrum of a mixed sample of 36% *para*-xylene and 64% acetone in $CDCl_3$ solvent (structures are shown earlier in this chapter). How many peaks do you expect to see? What is the expected ratio of integration values for these peaks? (set the acetone peak integration equal to 1.0)

Solutions

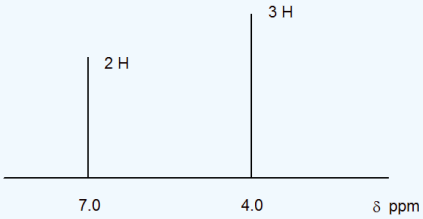
EXERCISE 13.4.1

Predict how many signals the following molecule would have? Sketch the spectra and estimate the integration of the peaks.



Answer

There will be two peaks. Ideal general spectrum shown with integration.



13.5: SPIN-SPIN SPLITTING IN ^{1}H NMR SPECTRA

OBJECTIVES

After completing this section, you should be able to

1. explain the spin-spin splitting pattern observed in the ^{1}H NMR spectrum of a simple organic compound, such as chloroethane or 2-bromopropane.
2. interpret the splitting pattern of a given ^{1}H NMR spectrum.
3. determine the structure of a relatively simple organic compound, given its ^{1}H NMR spectrum and other relevant information.
4. use coupling constants to determine which groups of protons are coupling with one another in a ^{1}H NMR spectrum.
5. predict the splitting pattern which should be observed in the ^{1}H NMR spectrum of a given organic compound.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- coupling constant
- multiplet
- quartet
- triplet
- doublet

STUDY NOTES

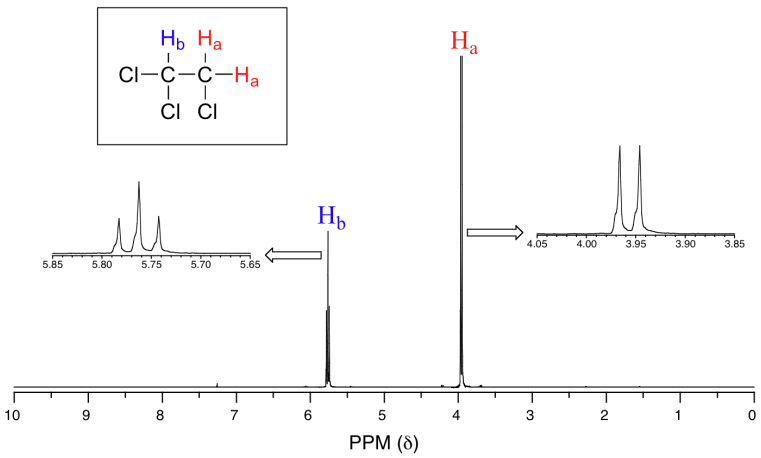
From what we have learned about ^{1}H NMR spectra so far, we might predict that the spectrum of 1,1,2-trichloroethane, $CHCl_2CH_2Cl$, would consist of two peaks—one, at about 2.5-4.0 δ, expected for CH_2-halogen compounds and one shifted downfield because of the presence of an additional electronegative chlorine atom on the second carbon. However, when we look at the spectrum it appears to be much more complex. True, we see absorptions in the regions we predicted, but these absorptions appear as a group of two peaks (a *doublet*) and a group of three peaks (a *triplet*). This complication, which may be disturbing to a student who longs for the simple life, is in fact very useful to the organic chemist, and adds greatly to the power of NMR spectroscopy as a tool for the elucidation of chemical structures. The split peaks (*multiplets*) arise because the magnetic field experienced by the protons of one group is influenced by the spin arrangements of the protons in an adjacent group.

Spin-spin coupling is often one of the more challenging topics for organic chemistry students to master. Remember the $n + 1$ rule and the associated coupling patterns.

THE SOURCE OF SPIN-SPIN COUPLING

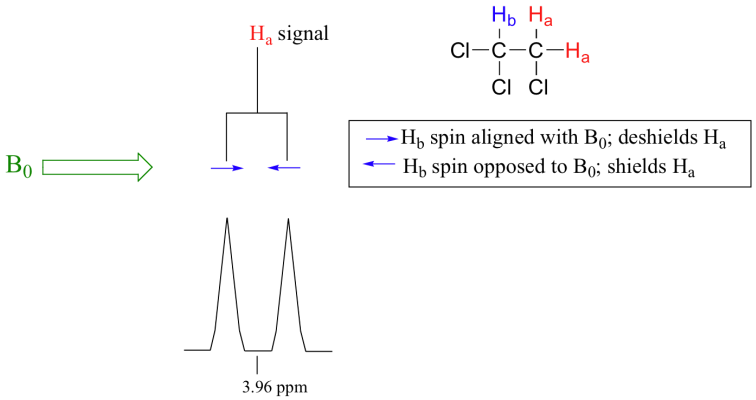
The ^{1}H-NMR spectra that we have seen so far (of methyl acetate and *para*-xylene) are somewhat unusual in the sense that in both of these molecules, each set of protons generates a single NMR signal. In fact, the ^{1}H-NMR spectra of most organic molecules contain proton signals that are 'split' into two or more sub-peaks. Rather than being a complication, however, this splitting behavior actually provides us with more information about our sample molecule.

Consider the spectrum for 1,1,2-trichloroethane. In this and in many spectra to follow, we show enlargements of individual signals so that the signal splitting patterns are recognizable.

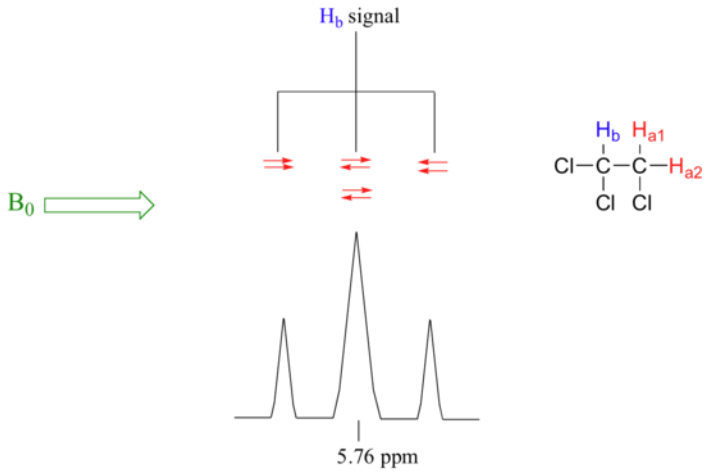


The signal at 3.96 ppm, corresponding to the two H_a protons, is split into two subpeaks of equal height (and area) – this is referred to as a **doublet**. The H_b signal at 5.76 ppm, on the other hand, is split into three sub-peaks, with the middle peak higher than the two outside peaks - if we were to integrate each subpeak, we would see that the area under the middle peak is twice that of each of the outside peaks. This is called a **triplet**.

The source of signal splitting is a phenomenon called **spin-spin coupling**, a term that describes the magnetic interactions between neighboring, non-equivalent NMR-active nuclei. In our 1,1,2 trichloromethane example, the H_a and H_b protons are spin-coupled to each other. Here's how it works, looking first at the H_a signal: in addition to being shielded by nearby valence electrons, each of the H_a protons is also influenced by the small magnetic field generated by H_b next door (remember, each spinning proton is like a tiny magnet). The magnetic moment of H_b will be aligned *with* B_0 in (slightly more than) half of the molecules in the sample, while in the remaining half of the molecules it will be opposed to B_0. The B_{eff} 'felt' by H_a is a slightly weaker if H_b is aligned against B_0, or slightly stronger if H_b is aligned with B_0. In other words, in half of the molecules H_a is *shielded* by H_b (thus the NMR signal is shifted slightly upfield) and in the other half H_a is *deshielded* by H_b(and the NMR signal shifted slightly downfield). What would otherwise be a single H_a peak has been split into two sub-peaks (a doublet), one upfield and one downfield of the original signal. These ideas an be illustrated by a **splitting diagram**, as shown below.

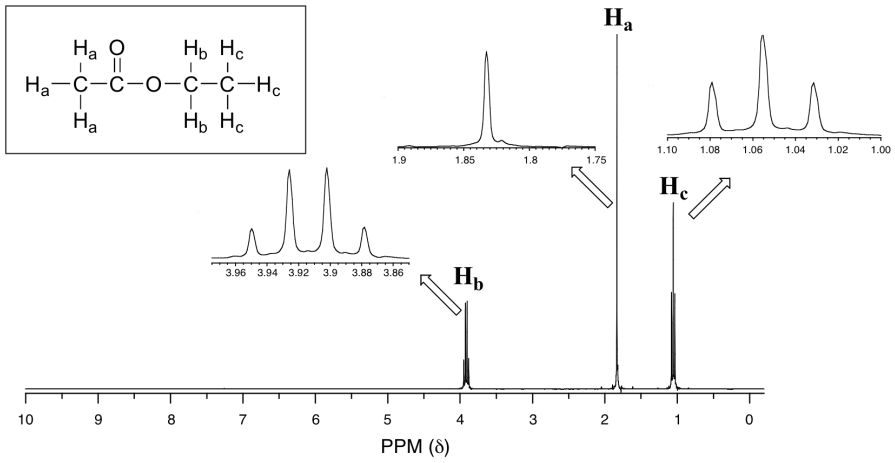


Now, let's think about the $H_b$signal. The magnetic environment experienced by H_b is influenced by the fields of both neighboring H_a protons, which we will call H_{a1} and H_{a2}. There are four possibilities here, each of which is equally probable. First, the magnetic fields of both H_{a1} and H_{a2} could be aligned with B_0, which would deshield H_b, shifting its NMR signal slightly downfield. Second, both the H_{a1} and H_{a2} magnetic fields could be aligned opposed to B_0, which would shield H_b, shifting its resonance signal slightly upfield. Third and fourth, H_{a1} could be with B_0 and H_{a2} opposed, or H_{a1}opposed to B_0 and H_{a2} with B_0. In each of the last two cases, the shielding effect of one H_a proton would cancel the deshielding effect of the other, and the chemical shift of H_b would be unchanged.



So in the end, the signal for H_b is a **triplet**, with the middle peak twice as large as the two outer peaks because there are *two* ways that H_{a1} and H_{a2} can cancel each other out.

Now, consider the spectrum for ethyl acetate:



We see an unsplit '**singlet**' peak at 1.833 ppm that corresponds to the acetyl (H_a) hydrogens – this is similar to the signal for the acetate hydrogens in methyl acetate that we considered earlier. This signal is unsplit because there are no adjacent hydrogens on the molecule. The signal at 1.055 ppm for the H_c hydrogens is split into a triplet by the two H_b hydrogens next door. The explanation here is the same as the explanation for the triplet peak we saw previously for 1,1,2-trichloroethane.

The $H_b$hydrogens give rise to a **quartet** signal at 3.915 ppm – notice that the two middle peaks are taller then the two outside peaks. This splitting pattern results from the spin-coupling effect of the *three* H_c hydrogens next door, and can be explained by an analysis similar to that which we used to explain the doublet and triplet patterns.

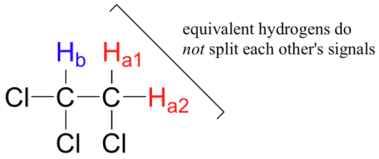
EXAMPLE 13.11.1

a. Explain, using left and right arrows to illustrate the possible combinations of nuclear spin states for the H_c hydrogens, why the H_b signal in ethyl acetate is split into a quartet.
b. The integration ratio of doublets is 1:1, and of triplets is 1:2:1. What is the integration ratio of the H_b quartet in ethyl acetate? (Hint – use the illustration that you drew in part a to answer this question.)

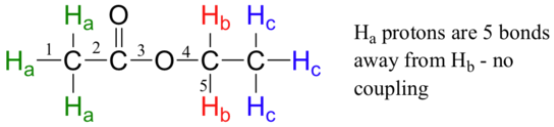
Solution

By now, you probably have recognized the pattern which is usually referred to as the ***n* + 1 rule**: if a set of hydrogens has *n* neighboring, non-equivalent hydrogens, it will be split into *n* + 1 subpeaks. Thus the two H_b hydrogens in ethyl acetate split the H_c signal into a triplet, and the three H_c hydrogens split the H_b signal into a quartet. This is very useful information if we are trying to determine the structure of an unknown molecule: if we see a triplet signal, we know that the corresponding hydrogen or set of hydrogens has two `neighbors`. When we begin to determine structures of unknown compounds using ^{1}H-NMR spectral data, it will become more apparent how this kind of information can be used.

Three important points need to be emphasized here. First, signal splitting only occurs between non-equivalent hydrogens – in other words, H_{a1} in 1,1,2-trichloroethane is *not* split by H_{a2}, and vice-versa.

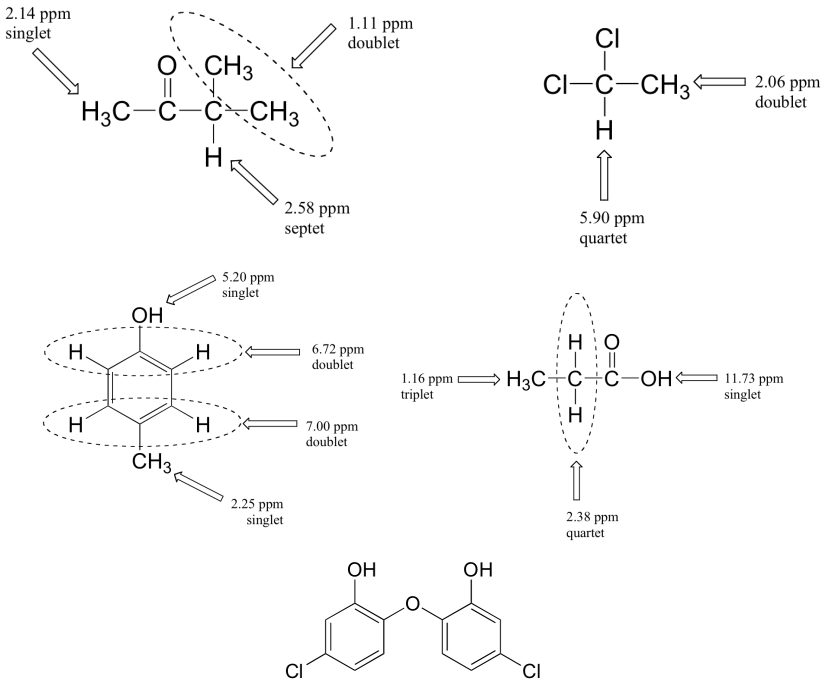


Second, splitting occurs primarily between hydrogens that are separated by three bonds. This is why the H_a hydrogens in ethyl acetate form a singlet– the nearest hydrogen neighbors are five bonds away, too far for coupling to occur.



Occasionally we will see four-bond and even 5-bond splitting, but in these cases the magnetic influence of one set of hydrogens on the other set is much more subtle than what we typically see in three-bond splitting (more details about how we quantify coupling interactions is provided in section 5.5B). Finally, splitting is most noticeable with hydrogens bonded to carbon. Hydrogens that are bonded to heteroatoms (alcohol or amino hydrogens, for example) are coupled weakly - or not at all - to their neighbors. This has to do with the fact that these protons exchange rapidly with solvent or other sample molecules.

Below are a few more examples of chemical shift and splitting pattern information for some relatively simple organic molecules.



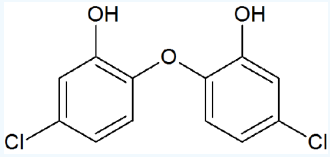
MULTIPLICITY IN PROTON NMR

The number of lines in a peak is always one more (n+1) than the number of hydrogens on the neighboring carbon. This table summarizes coupling patterns that arise when protons have different numbers of neighbors.

# of lines	ratio of lines	term for peak	# of neighbors
1	-	singlet	0
2	1:1	doublet	1
3	1:2:1	triplet	2
4	1:3:3:1	quartet	3
5	1:4:6:4:1	quintet	4
6	1:5:10:10:5:1	sextet	5
7	1:6:15:20:15:6:1	septet	6
8	1:7:21:35:35:21:7:1	octet	7
9	1:8:28:56:70:56:28:8:1	nonet	8

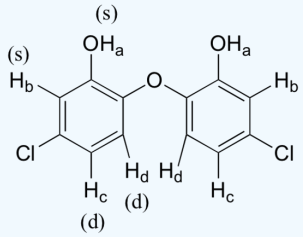
EXAMPLE 13.11.2

How many proton signals would you expect to see in the ^{1}H-NMR spectrum of the structure shown? For each of the proton signals, predict the splitting pattern. Assume that you see only 3-bond coupling.



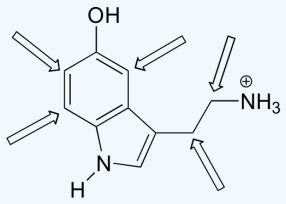
Answer

Because of the symmetry in the molecule, there are only four proton signals. Predicted splitting is indicated.



EXAMPLE 13.11.3

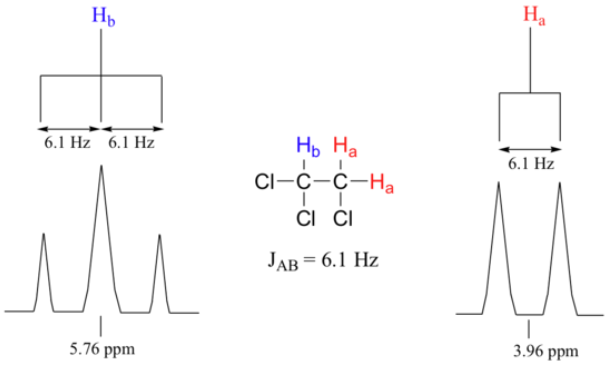
Predict the splitting pattern for the ^{1}H-NMR signals corresponding to the protons at the locations indicated by arrows (the structure is that of the neurotransmitter serotonin).



Solutions

COUPLING CONSTANTS

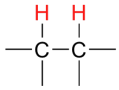
Chemists quantify the spin-spin coupling effect using something called the **coupling constant**, which is abbreviated with the capital letter *J*. The coupling constant is simply the difference, expressed in Hz, between two adjacent sub-peaks in a split signal. For our doublet in the 1,1,2-trichloroethane spectrum, for example, the two subpeaks are separated by 6.1 Hz, and thus we write $^3J_{a\text{-}b}$ = 6.1 Hz.



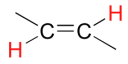
The superscript 3 tells us that this is a three-bond coupling interaction, and the a-b subscript tells us that we are talking about coupling between H_a and H_b. Unlike the chemical shift value, *the coupling constant, expressed in Hz, is the same regardless of the applied field strength of the NMR magnet*. This is because the strength of the magnetic moment of a neighboring proton, which is the source of the spin-spin coupling phenomenon, does *not* depend on the applied field strength.

When we look closely at the triplet signal in 1,1,2-trichloroethane, we see that the coupling constant - the `gap` between subpeaks - is 6.1 Hz, the same as for the doublet. This is an important concept! The coupling constant $^3J_{a\text{-}b}$ quantifies the magnetic interaction between the H_a and H_b hydrogen sets, and *this interaction is of the same magnitude in either direction*. In other words, H_a influences H_b to the same extent that H_b influences H_a. When looking at more complex NMR spectra, this idea of **reciprocal coupling constants** can be very helpful in identifying the coupling relationships between proton sets.

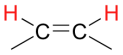
Coupling constants between proton sets on neighboring sp^3-hybridized carbons is typically in the region of 6-8 Hz. With protons bound to sp^2-hybridized carbons, coupling constants can range from 0 Hz (no coupling at all) to 18 Hz, depending on the bonding arrangement.



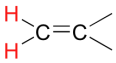
^3J = 6-8 Hz



vinylic *trans*:
^3J = 11-18 Hz

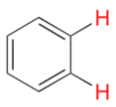


vinylic *cis*:
^3J = 6-15 Hz

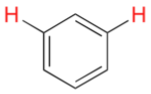


vinylic *gem*:
^2J = 0-5 Hz

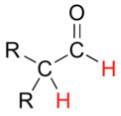
For vinylic hydrogens in a *trans* configuration, we see coupling constants in the range of ^3J = 11-18 Hz, while *cis* hydrogens couple in the ^3J = 6-15 Hz range. The 2-bond coupling between hydrogens bound to the same alkene carbon (referred to as geminal hydrogens) is very fine, generally 5 Hz or lower. *Ortho* hydrogens on a benzene ring couple at 6-10 Hz, while 4-bond coupling of up to 4 Hz is sometimes seen between *meta* hydrogens.



ortho-benzylic:
^3J = 6-10 Hz



meta-benzylic:
^4J = 0-4 Hz



aldehyde:
^3J = 2-3 Hz

Fine (2-3 Hz) coupling is often seen between an aldehyde proton and a three-bond neighbor. Table 4 lists typical constant values.

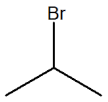
EXERCISE

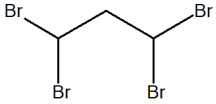
Note: Remember, chemically equivalent protons do not couple with one another to give spin-spin splitting.

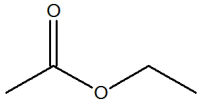
QUESTIONS

Q13.11.1

Predict the splitting patterns of the following molecules:

A) 

B) 

C) 

Q13.11.2

Draw the following according to the criteria given.

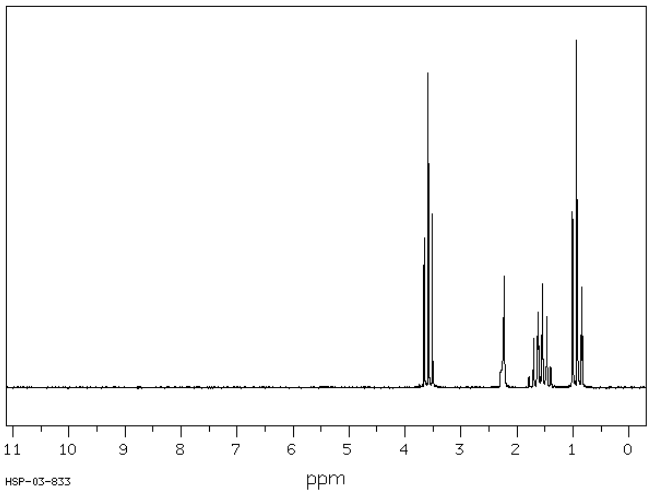
A. C_3H_5O; two triplet, 1 doublet

B. $C_4H_8O_2$; three singlets

C. C_5H_{12}; one singlet

Q13.11.3

The following spectrum is for C_3H_8O. Determine the structure.



A triplet; B singlet; C sextet; D triplet

Source: SDBSWeb : http://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, 3 December 2016)

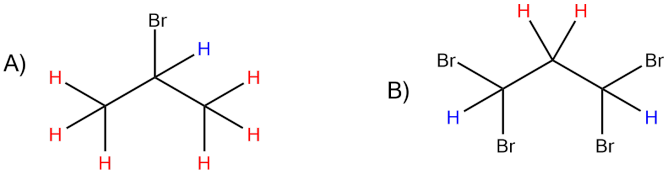
SOLUTIONS

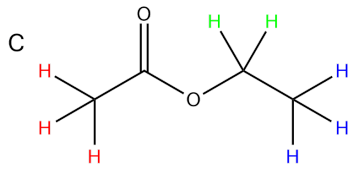
S13.11.1

A. H: Doublet. H: Septet

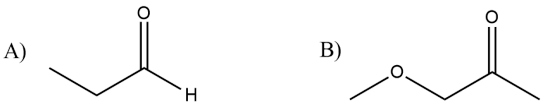
B. H: Doublet, H: Triplet

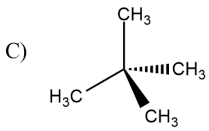
C. H: Singlet, H: Quartet, H: Triplet





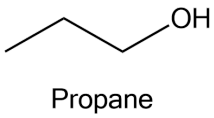
S13.11.2





These are just some drawings, more may be possible.

S13.11.3



13.6: ^{1}H NMR SPECTROSCOPY AND PROTON EQUIVALENCE

OBJECTIVES

After completing this section, you should be able to

- identify those protons which are equivalent in a given chemical structure.
- use the ^{1}H NMR spectrum of a simple organic compound to determine the number of equivalent sets of protons present.

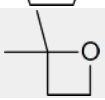
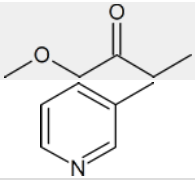
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

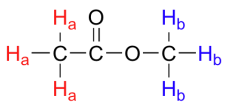
- diastereotopic
- enantiotopic
- homotopic

STUDY NOTES

It is important at this stage to be able to identify equivalent protons in any organic compound given the structure of that compound. Once you know the number of different groups of equivalent protons in a compound, you can predict the number (before coupling) and relative strength of signals. Look at the following examples and make sure you understand how the number and intensity ratio of signals are derived from the structure shown.

Structure	Number of Signals	Ratio of Signals	
$CH_3OCH_2CH_2Br$	3	A : B : C	3 : 2 : 2
	1		
	3	A : B : C	2 : 2 : 6 (or 1 : 1 : 3)
	3	A : B : C	2 : 4 : 2 (or 1 : 2 : 1)
	4	A : B : C : D	3 : 2 : 2 : 3
	5	A : B : C : D : E	3 : 1 : 1 : 1 : 1

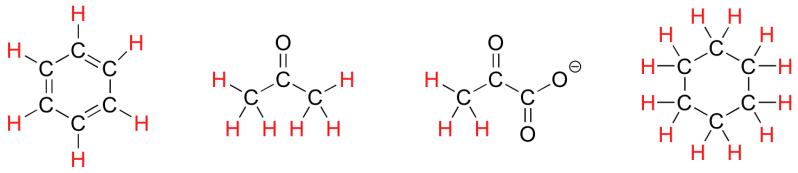
Proton equivalence in proton NMR refers to the concept that not all hydrogen atoms in a molecule produce distinct signals in the NMR spectrum. Instead, chemically equivalent protons, meaning those that occupy identical environments within a molecule, yield the same NMR signal. This concept is essential for interpreting NMR spectra accurately. Chemical equivalence is determined by the molecular structure and symmetry of a molecule. If all protons in all organic molecules had the same resonance frequency in an external magnetic field of a given strength, the information in the previous paragraph would be interesting from a theoretical standpoint, but would not be terribly useful to organic chemists. Fortunately for us, however, resonance frequencies are not uniform for all protons in a molecule. *In an external magnetic field of a given strength, protons in different locations in a molecule have different resonance frequencies, because they are in non-identical electronic environments.* In methyl acetate, for example, there are two 'sets' of protons. The three protons labeled H_a have a different - and easily distinguishable – resonance frequency than the three H_b protons, because the two sets of protons are in non-identical environments: they are, in other words, chemically nonequivalent.



On the other hand, the three H_a protons are all in the same electronic environment, and are chemically equivalent to one another. They have identical resonance frequencies. The same can be said for the three H_b protons. These protons are considered to be homotopic. Homotopic

protons are chemically identical, so electronically equivalent, thus show up as identical NMR absorptions.

The ability to recognize chemical equivalency and nonequivalency among atoms in a molecule will be central to understanding NMR. In each of the molecules below, all protons are chemically equivalent, and therefore will have the same resonance frequency in an NMR experiment.



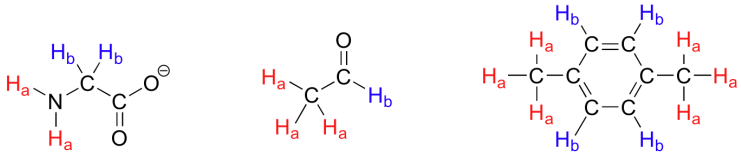
benzene acetone pyruvate cyclohexane

You might expect that the equatorial and axial hydrogens in cyclohexane would be non-equivalent, and would have different resonance frequencies. In fact, an axial hydrogen *is* in a different electronic environment than an equatorial hydrogen. Remember, though, that the molecule rotates rapidly between its two chair conformations, meaning that any given hydrogen is rapidly moving back and forth between equatorial and axial positions. It turns out that, except at extremely low temperatures, this rotational motion occurs on a time scale that is much faster than the time scale of an NMR experiment.

ring-flip process is *fast* compared to the NMR time-scale

In this sense, NMR is like a camera that takes photographs of a rapidly moving object with a slow shutter speed - the result is a blurred image. In NMR terms, this means that all 12 protons in cyclohexane are equivalent.

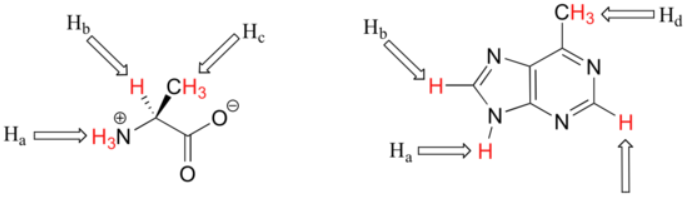
Each the molecules in the next figure contains *two* sets of protons, just like our previous example of methyl acetate, and again in each case the resonance frequency of the H_a protons will be different from that of the H_b protons.



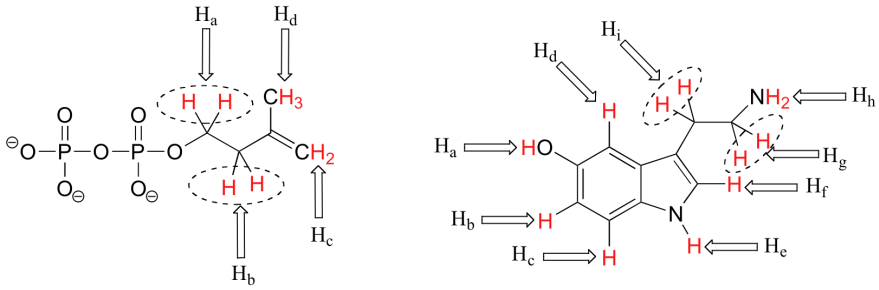
glycine acetaldehyde *para*-xylene

Notice how the symmetry of *para*-xylene results in there being only two different sets of protons.

Most organic molecules have several sets of protons in different chemical environments, and each set, in theory, will have a different resonance frequency in ^{1}H-NMR spectroscopy.

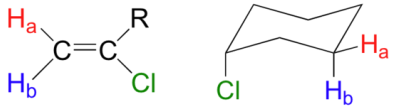


alanine (an amino acid) adenine (a DNA/RNA base)

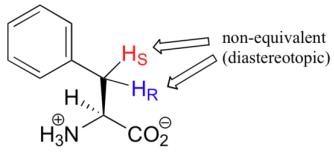


isopentenyl diphosphate (a lipid building block) seratonin (a neurotransmitter)

When stereochemistry is taken into account, the issue of equivalence vs nonequivalence in NMR starts to get a little more complicated. It should be fairly intuitive that hydrogens on different sides of asymmetric ring structures and double bonds are in different electronic environments, and thus are non-equivalent and have different resonance frequencies. In the alkene and cyclohexene structures below, for example, H_a is *trans* to the chlorine substituent, while H_b is *cis* to chlorine.

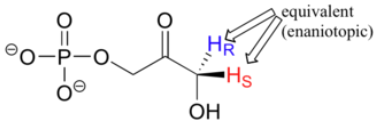


What is not so intuitive is that diastereotopic hydrogens (section 3.10) on chiral molecules are also non-equivalent:

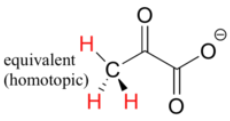


phenylalanine

However, enantiotopic and homotopic hydrogens are chemically equivalent. To determine if protons are homotopic or enantiotopic, you can do a thought experiment by replacing one H with X followed by the other H by X. In pyruvate below, if you replace any of the Hs with an X, then you would get the same molecule. These protons are homotopic. In dihydroxyacetone phosphate, this is not quite the case. If you exchange H_R for X, then you would create a stereocenter with R configuration. If you exchange H_S for X, then you would create a stereocenter with S configuration. The two "new molecules" would have the relationship of being enantiomers. Therefore H_R and H_S are enantiotopic protons. The only way these protons will show up different under NMR experimental conditions would be if you used a solvent that was chiral. Since most common solvents are all achiral, the enantiotopic protons are NMR equivalent and will show up as if they were the same proton.



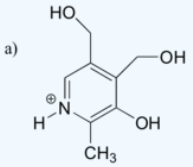
dihydroxyacetone phosphate



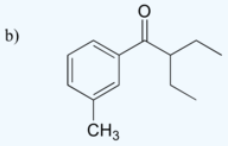
pyruvate

EXAMPLE 13.6.1

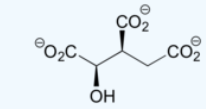
How many different sets of protons do the following molecules contain? (count diastereotopic protons as non-equivalent).



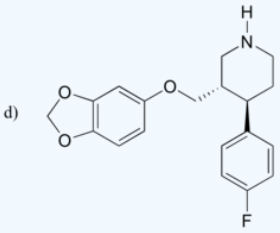
pyridoxine
(vitamin B_6)



DEET
(an insect repellent)



isocitrate
(a citric acid cycle intermediate)



paroxetine
(an antianxietry drug, trade name Paxil)

Solution

EXERCISE 13.6.1

How many non-equivalent hydrogen are in the following molecules; how many different signals will you see in a H^1 NMR spectrum.

a. $CH_3CH_2CH_2Br$
b. $CH_3OCH_2C(CH_3)_3$
c. Ethyl Benzene
d. 2-methyl-1-hexene

Answer

A. 3; B. 3; C. 5; D. 7

13.7: MORE COMPLEX SPIN-SPIN SPLITTING PATTERNS

OBJECTIVES

After completing this section, you should be able to

- explain how multiple coupling can give rise to complex-looking ^{1}H NMR spectra.
- predict the splitting pattern expected in the ^{1}H NMR spectrum of an organic compound in which multiple coupling is possible.
- interpret ^{1}H NMR spectra in which multiple coupling is evident.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

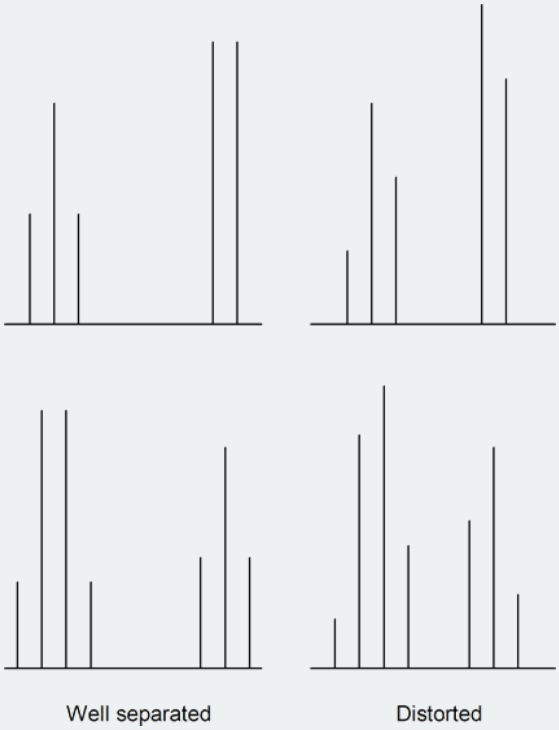
- tree diagram

STUDY NOTES

We saw the effects of spin-spin coupling on the appearance of a ^{1}H NMR signal. These effects can be further complicated when that signal is coupled to several different protons. For example, $BrCH_2CH_2CH_2Cl$ would produce three signals. The hydrogens at C_1 and C_3 would each be triplets because of coupling to the two hydrogens on C_2. However, the hydrogen on C_2 "sees" two different sets of neighboring hydrogens, and would therefore produce a triplet of triplets.

Another effect that can complicate a spectrum is the "closeness" of signals. If signals accidently overlap they can be difficult to identify. In the example above, we expected a triplet of triplets. However, if the coupling is identical (or almost identical) between the hydrogens on C_2 and the hydrogens on both C_1 and C_3, one would observe a quintet in the ^{1}H NMR spectrum. [You can try this yourself by drawing a tree diagram of a triplet of triplets assuming, first, different coupling constants, and then, identical coupling constants.] Keep this point in mind when interpreting real ^{1}H NMR spectra.

Also, when multiplets are well separated, they form patterns. However, when multiplets approach each other in the spectrum they sometimes become distorted. Usually, the inner peaks become larger than the outer peaks. Note the following examples:



Aromatic ring protons quite commonly have overlapping signals and multiplet distortions. Sometimes you cannot distinguish between individual signals, and one or more messy multiplets often appear in the aromatic region.

It is much easier to rationalize the observed ^{1}H NMR spectrum of a known compound than it is to determine the structure of an unknown compound from its ^{1}H NMR spectrum. However, rationalizations can be a useful learning technique as you try to improve your proficiency in spectral interpretation. Remember that when a chemist tries to interpret the ^{1}H NMR spectrum of an unknown compound, he or she usually has additional information available to make the task easier. For example, the chemist will almost certainly have an infrared spectrum of the compound and possibly a mass spectrum too. Details of how the compound was synthesized may be available, together with some indication of its chemical properties, its physical properties, or both.

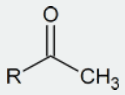
In examinations, you will be given a range of information (IR, MS, UV data and empirical formulae) to aid you with your structural determination using ^{1}H NMR spectroscopy. For example, you may be asked to determine the structure of $C_6H_{12}O$ given the following spectra:

Infrared spectrum: 3000 cm^{-1} and 1720 cm^{-1} absorptions are both strong

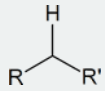
^{1}H NMR

δ (ppm)	Protons	Multiplicity
0.87	6	doublet
1.72	1	broad multiplet
2.00	3	singlet
2.18	2	doublet

To answer this question, you note that the infrared spectrum of $C_6H_{12}O$ shows $C-H$ stretching (3000 cm^{-1}) and $C-O$ stretching (1720 cm^{-1}). Now you have to piece together the information from the ^{1}H NMR spectrum. Notice the singlet with three protons at 2.00 ppm. This signal indicates a methyl group that is not coupled to other protons. It could possibly mean the presence of a methyl ketone functional group.

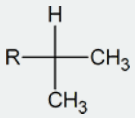


The signal at 1.72 ppm is a broad multiplet, suggesting that a carbon with a single proton is beside carbons with several different protons.



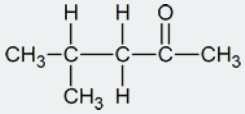
The doublet signal at 2.18 ppm implies that a $-CH_2^-$ group is attached to a carbon having only one proton.

The six protons showing a doublet at 0.87 ppm indicate two equivalent methyl groups attached to a carbon with one proton.



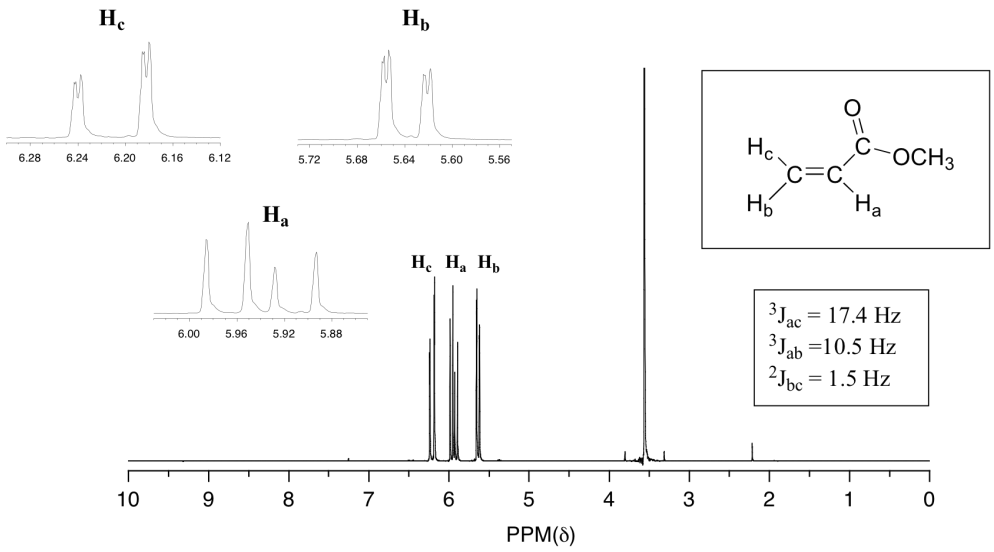
Whenever you see a signal in the 0.7-1.3 ppm range that is a multiplet of three protons (3, 6, 9) it is most likely caused by equivalent methyl groups.

Using trial and error, and with the above observations, you should come up with the correct structure.

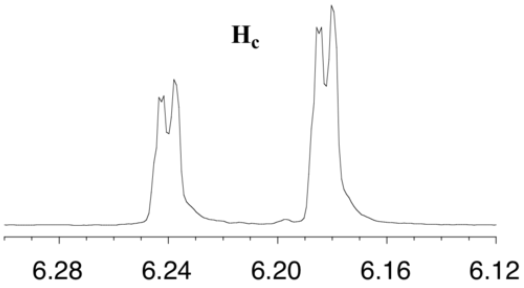


COMPLEX COUPLING

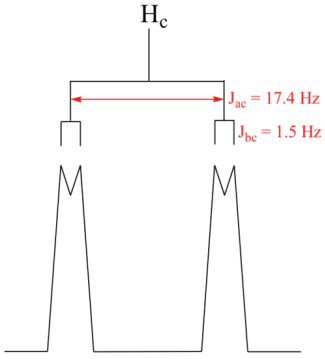
In all of the examples of spin-spin coupling that we have seen so far, the observed splitting has resulted from the coupling of one set of hydrogens to *just one* neighboring set of hydrogens. When a set of hydrogens is coupled to *two or more* sets of nonequivalent neighbors, the result is a phenomenon called **complex coupling**. A good illustration is provided by the ^{1}H-NMR spectrum of methyl acrylate:



First, let's first consider the H_c signal, which is centered at 6.21 ppm. Here is a closer look:

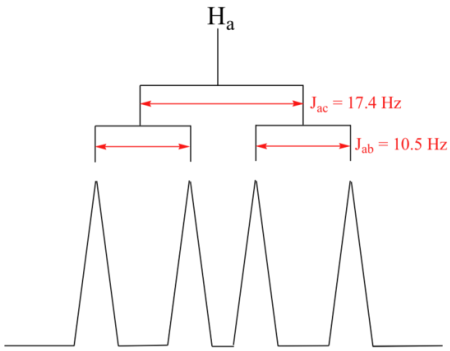


With this enlargement, it becomes evident that the Hc signal is actually composed of four sub-peaks. Why is this? H_c is coupled to both H_a and H_b , but with *two different coupling constants*. Once again, a splitting diagram (or tree diagram) can help us to understand what we are seeing. H_a is *trans* to H_c across the double bond, and splits the H_c signal into a doublet with a coupling constant of $^3J_{ac}$ = 17.4 Hz. In addition, each of these H_c doublet sub-peaks is split again by H_b (*geminal* coupling) into two more doublets, each with a much smaller coupling constant of $^2J_{bc}$ = 1.5 Hz.

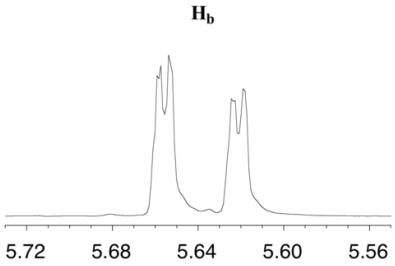


The result of this `double splitting` is a pattern referred to as a **doublet of doublets**, abbreviated `**dd**`.

The signal for H_a at 5.95 ppm is also a doublet of doublets, with coupling constants $^3J_{ac}$= 17.4 Hz and $^3J_{ab}$ = 10.5 Hz.



The signal for H_b at 5.64 ppm is split into a doublet by H_a, a *cis* coupling with $^3J_{ab}$ = 10.4 Hz. Each of the resulting sub-peaks is split again by H_c, with the same *geminal* coupling constant $^2J_{bc}$ = 1.5 Hz that we saw previously when we looked at the H_c signal. The overall result is again a doublet of doublets, this time with the two `sub-doublets` spaced slightly closer due to the smaller coupling constant for the *cis* interaction. Here is a blow-up of the actual $H_b$signal:



EXAMPLE 13.7.1

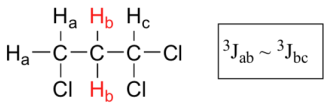
Construct a splitting diagram for the H_b signal in the ^{1}H-NMR spectrum of methyl acrylate. Show the chemical shift value for each sub-peak, expressed in Hz (assume that the resonance frequency of TMS is exactly 300 MHz).

Solution

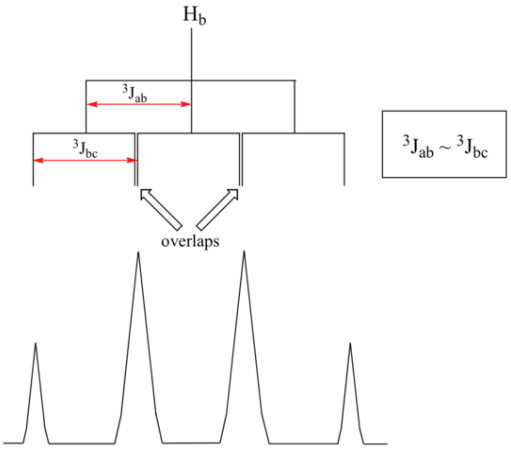
NOTE

When constructing a splitting diagram to analyze complex coupling patterns, it is usually easier to show the larger splitting first, followed by the finer splitting (although the reverse would give the same end result).

When a proton is coupled to two different neighboring proton sets with identical or very close coupling constants, the splitting pattern that emerges often appears to follow the simple `$n$ + 1 rule` of non-complex splitting. In the spectrum of 1,1,3-trichloropropane, for example, we would expect the signal for H_b to be split into a triplet by H_a, and again into doublets by H_c, resulting in a 'triplet of doublets'.

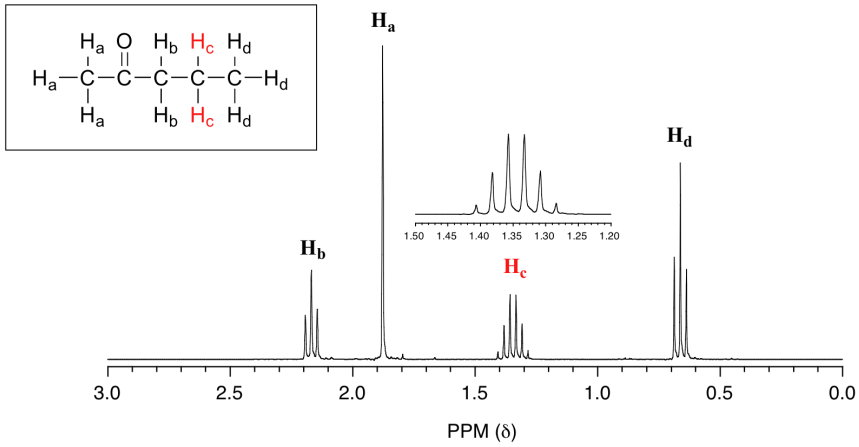


H_a and H_c are not equivalent (their chemical shifts are different), but it turns out that $^3J_{ab}$ is very close to $^3J_{bc}$. If we perform a splitting diagram analysis for H_b, we see that, due to the overlap of sub-peaks, the signal appears to be a quartet, and for all intents and purposes follows the n + 1 rule.



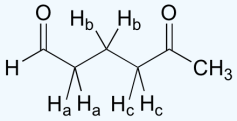
triplet of doublets becomes a quartet when coupling constants are close

For similar reasons, the H_c peak in the spectrum of 2-pentanone appears as a sextet, split by the five combined H_b and H_d protons. Technically, this 'sextet' could be considered to be a 'triplet of quartets' with overlapping sub-peaks.



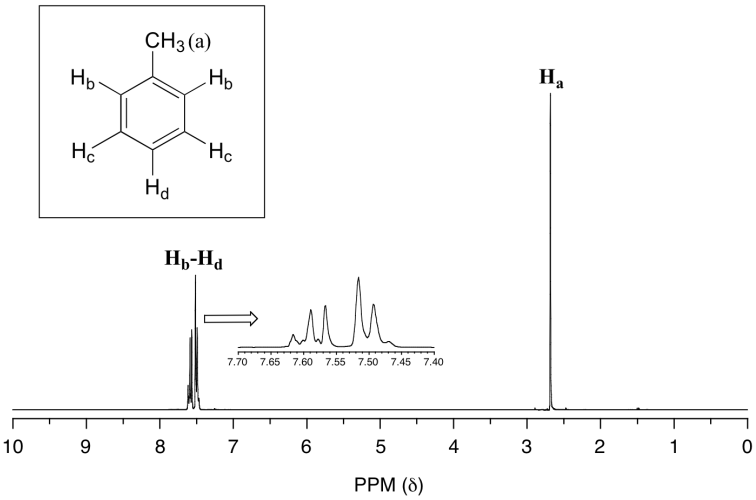
EXAMPLE 13.7.2

What splitting pattern would you expect for the signal corresponding to H_b in the molecule below? Assume that $J_{ab} \sim J_{bc}$. Draw a splitting diagram for this signal, and determine the relative integration values of each subpeak.



Solution

In many cases, it is difficult to fully analyze a complex splitting pattern. In the spectrum of toluene, for example, if we consider only 3-bond coupling we would expect the signal for H_b to be a doublet, H_d a triplet, and H_c a triplet.



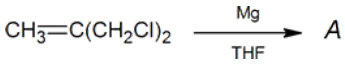
In practice, however, all three aromatic proton groups have very similar chemical shifts and their signals overlap substantially, making such detailed analysis difficult. In this case, we would refer to the aromatic part of the spectrum as a **multiplet**.

When we start trying to analyze complex splitting patterns in larger molecules, we gain an appreciation for why scientists are willing to pay large sums of money (hundreds of thousands of dollars) for higher-field NMR instruments. Quite simply, the stronger our magnet is, the more resolution we get in our spectrum. In a 100 MHz instrument (with a magnet of approximately 2.4 Tesla field strength), the 12 ppm frequency 'window' in which we can observe proton signals is 1200 Hz wide. In a 500 MHz (~12 Tesla) instrument, however, the window is 6000 Hz - five times wider. In this sense, NMR instruments are like digital cameras and HDTVs: better resolution means more information and clearer pictures (and higher price tags!)

EXERCISES

1. Given the information below, draw the structures of compounds *A* through *D*.

   a. An unknown compound *A* was prepared as follows:

   Mass spectrum:

   base peak *m*/*e* = 39

   parent peak *m*/*e* = 54

   ^{1}H NMR spectrum:

δ (ppm)	Relative Area	Multiplicity
1.0	2	triplet
5.4	1	quintet

   b. Unknown compound *B* has the molecular formula $C_7H_6O_2$.

   Infrared spectrum:

   3200 cm^{-1} (broad) and 1747 cm^{-1} (strong) absorptions

   ^{1}H NMR spectrum:

δ (ppm)	Protons
6.9	2
7.4	2
9.8	1
10.9	1

   Hint: Aromatic ring currents deshield all proton signals just outside the ring.

   c. Unknown compound *C* shows no evidence of unsaturation and contains only carbon and hydrogen.

   Mass spectrum:

   parent peak *m*/*e* = 68

^{1}H NMR spectrum:

δ (ppm)	Relative Area	Multiplicity
1.84	3	triplet
2.45	1	septet

Hint: Think three dimensionally!

d. Unknown compound *D* ($C_{15}H_{14}O$) has the following spectral properties.

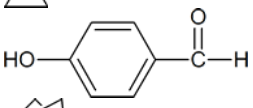
Infrared spectrum:

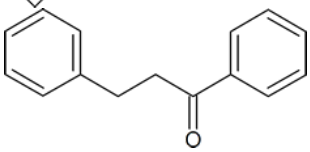
3010 cm^{-1} (medium)
1715 cm^{-1} (strong)
1610 cm^{-1} (strong)
1500 cm^{-1} (strong)

^{1}H NMR spectrum:

δ (ppm)	Relative Area	Multiplicity
3.00	2	triplet
3.07	2	triplet
7.1-7.9	10	Multiplets

Answers

1. a. 
   b. 

   c. 
   d. 

13.8: USES OF ^{1}H NMR SPECTROSCOPY

OBJECTIVE

After completing this section, you should be able to use data from ^{1}H NMR spectra to distinguish between two (or more) possible structures for an unknown organic compound.

There will be cases in which you already know what the structure might be. In these cases:

- You should draw attention to pieces of data that most strongly support your expected structure. This approach will demonstrate evaluative understanding of the data; that means you can look at data and decide what parts are more crucial than others.
- You should also draw attention to negative results: that is, peaks that might be there if this spectrum matched another, possible structure, but that are in fact missing.

One of the most complicated problems to deal with is the analysis of a mixture. This situation is not uncommon when students run reactions in lab and analyse the data.

- Sometimes the spectra show a little starting material mixed in with the product.
- Sometimes solvents show up in the spectrum.
- As you might expect, the minor component usually shows up as smaller peaks in the spectrum. If there are fewer molecules present, then there are usually fewer protons to absorb in the spectrum.
- In this case, you should probably make two completely separate sets of data tables for your analysis, one for each compound, or else one for the main compound and one for impurities.

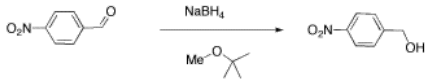
Remember that integration ratios are really only meaningful within a single compound. If your NMR sample contains some benzene (C_6H_6) and some acetone (CH_3COCH_3), and there is a peak at 7.15 that integrates to 1 proton and a peak at 2.10 ppm integrating to 6 protons, it might mean there are 6 protons in acetone and 1 in benzene, but you can tell that isn't true by looking at the structure. There must be six times as many acetone molecules as benzene molecules in the sample.

There are six protons in the benzene, and they should all show up near 7 ppm. There are six protons in acetone, and they should all show up near 2 ppm. Assuming that small integral of 1H for the benzene is really supposed to be 6H, then the large integral of 6H for the acetone must also represent six times as many hydrogens, too. It would be 36 H. There are only six hydrogens in acetone, so it must represent six times as many acetone molecules as there are benzenes.

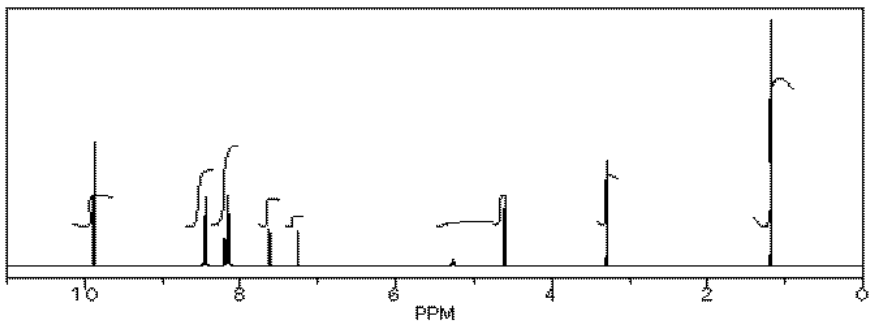
Similarly, if you have decided that you can identify two sets of peaks in the ^{1}H spectrum, analysing them in different tables makes it easy to keep the integration analysis completely separate too ; 1 H in one table will not be the same size integral as 1 H in the other table unless the concentrations of the two compounds in the sample are the same.

However, comparing the ratio of two integrals for two different compounds can give you the ratio of the two compounds in solution, just as we could determine the ratio of benzene to acetone in the mixture described above.

We will look at two examples of sample mixtures that could arise in lab. Results like these are pretty common events in the labIn the first example, a student tried to carry out the following reaction, a borohydride reduction of an aldehyde. The borohydride should give a hydride anion to the C=O carbon; washing with water should then supply a proton to the oxygen, giving an alcohol.

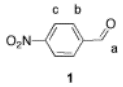
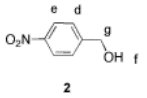
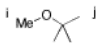


Her reaction produced the following spectrum.



(simulated data)

From this data, she produced the table below.

	shift	integration	int(n)	internal ratio	multiplicity	part structure	assignment
a	9.9 ppm	11 mm	2H	1H	singlet		
b	8.5 ppm	23 mm	4H	2H	doublet		 1
c	8.1 ppm	(20 mm?)	4H	2H	doublet		
d	8.2 ppm	(10 mm?)	2H	2H	doublet		
e	7.6 ppm	9 mm	2H	2H	doublet		 2
f	5.3 ppm	2 mm	0.4H	<1H	singlet	OH	
g	4.7 ppm	12 mm	2H	2H	singlet		
h	7.2 ppm	4 mm	0.8H	1H	singlet	$CHCl_3$	
i	3.3 ppm	8 mm	1.5H	3H	singlet		
j	1.2 ppm	24 mm	4.5H	9H	singlet		
			23.4H total				

Ratio of reactant **1** to product **2** is 2:1 based on peaks at 9.9 and 4.7 ppm (2H / 1H) : (2H / 2H); the reaction is 33% complete [2 / (2+1)]

Ratio of product **2** to TBME is 2:1 based on peaks at 4.7 and 3.3 ppm (2H / 2H) : (1.5H / 3H); the ratio of **1**:**2**:TBME is 2:1:0.5, so the sample is 57% **1** [2/(2+1+0.5)], 29% **2** and 14% TBME.

Notice how she calculated that ratio. She found a peak in molecule 1, the aldehyde, that she was pretty sure corresponded to the aldehydic hydrogen, the H attached to the C=O; in other words, the CH=O. She found another peak from molecule 2, the alcohol, that she was pretty sure represented the two hydrogens on the carbon attached to oxygen, the CH_2-O.

The integrals for those two peaks are equal. They are both 2H in her table. However, she notes that within each molecule, the first integral really represents 1H and the second represents 2H. That means there must be twice as many of molecule 1 as there are molecule 2. That way, there would be 2 x CH=O, and its integral would be the same as the 1 x CH_2-O in the other molecule.

One way to approach this kind of problem is to:

- choose one peak from each of the two compounds you want to compare.
- decide how many hydrogens each peak is supposed to represent in a molecule. Is it supposed to be a CH_2, a CH, a CH_3?
- divide the integral value for that peak by that number of hydrogens it is supposed to represent in a molecule.
- compare the two answers (integral A / ideal # H) vs (integral B / ideal # H).
- the ratio of those two answers is the ratio of the two molecules in the sample.

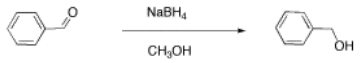
So there is twice as much aldehyde as alcohol in the mixture. In terms of these two compounds alone, she has 33% alcohol and 66% aldehyde. That's (1/(1+2)) x100% for the alcohol, and (2/(1+2)) x100% for the aldehyde. That calculation just represents the amount of individual component divided by the total of the components she wants to compare.

There are a number of things to take note of here.

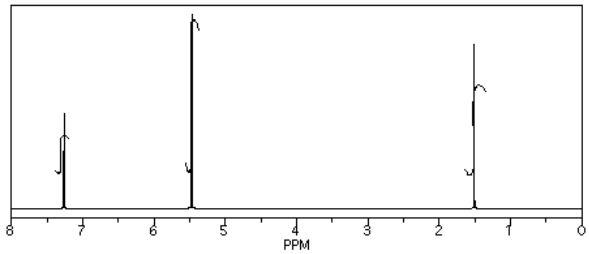
- Her reaction really didn't work very well. She still has majority starting material, not product.
- She will get a good grade on this lab. Although the experiment didn't work well, she has good data, and she has analyzed it very clearly.
- She has separated her data table into different sections for different compounds. Sometimes that makes it easier to analyze things.
- She has noted the actual integral data (she may have measured the integral with a ruler) and also converted it into a more convenient ratio, based on the integral for a peak that she felt certain about.
- She went one step further, and indicated the internal integration ratio within each individual compound.
- She calculated the % completion of the reaction using the integral data for the reactant and product, and she made clear what part of the data she used for that calculation. A similar procedure could be done if a student were just trying to separate two components in a mixture rather than carry out a reaction.
- She also calculated the overall purity of the mixture, including a solvent impurity that she failed to remove.

- However, $CHCl_3$ is not included in her analysis of purity. $CHCl_3$ really isn't part of her sample; it was just present in the NMR solvent, so it doesn't represent anything in the material she ended up with at the end of lab.

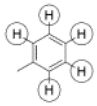
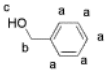
Another student carried out a similar reaction, shown below. He also finished the reaction by washing with water, but because methanol is soluble in water, he had to extract his product out of the water. He chose to use dichloromethane for that purpose.



He obtained the following data.



From this data, he constructed the following table.

	shift	integration	int(n)	multiplicity	partial structure	assignment
a	7.3 ppm	16 mm	5H	singlet		
b	5.4 ppm	64 mm	2H	singlet		
c	1.6 ppm	37 mm	1H	singlet	OH	

There are some things to learn about this table, too.

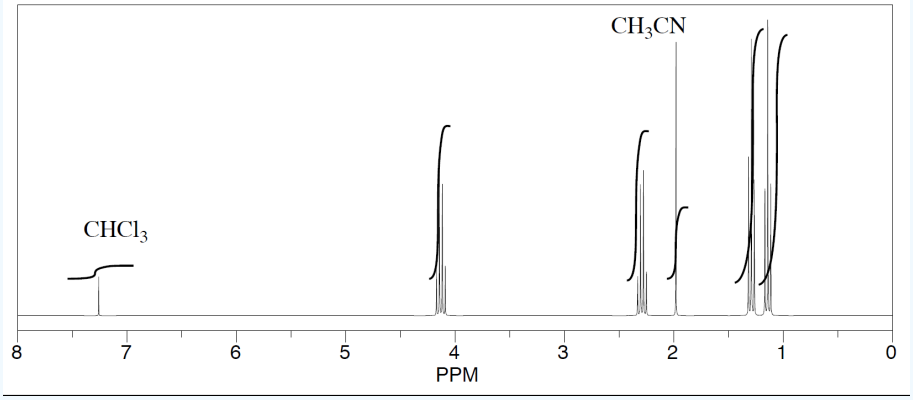
- Does the integration ratio really match the integral data? Or is this just wishful thinking?
- This table might reflect what he wants to see in the data. But what else could be in the data?
- $CHCl_3$ is often seen in NMR spectra if $CDCl_3$ is used for the NMR sample. It's there, at 7.2 ppm.
- "Leftover" or residual solvent is very common in real lab data. There it is, CH_2Cl_2 from the extraction, at 5.4 ppm.
- What about water? Sometimes people don't dry their solutions properly before evaporating the solvent. There is probably water around 1.5 to 1.6 ppm here.

This student might not get a very good grade; the sample does not even show up in the spectrum, so he lost it somewhere. But his analysis is also poor, so he will really get a terrible grade.

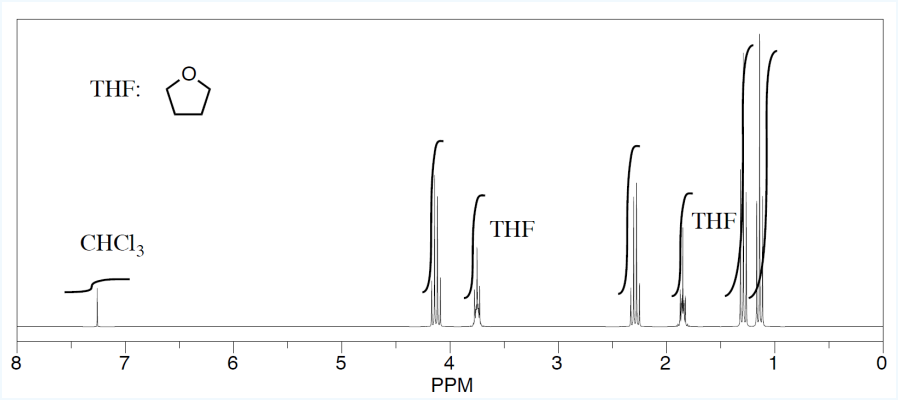
EXAMPLE 13.8.1

Three students performed a synthesis of a fragrant ester, ethyl propanoate, $CH_3CH_2CO_2CH_2CH_3$. During their reactions, they each used a different solvent. The students were able to see peaks in the NMR spectrum for ethyl propanoate, as well as peaks for chloroform ($CHCl_3$, in the $CDCl_3$ they used to make their NMR samples).

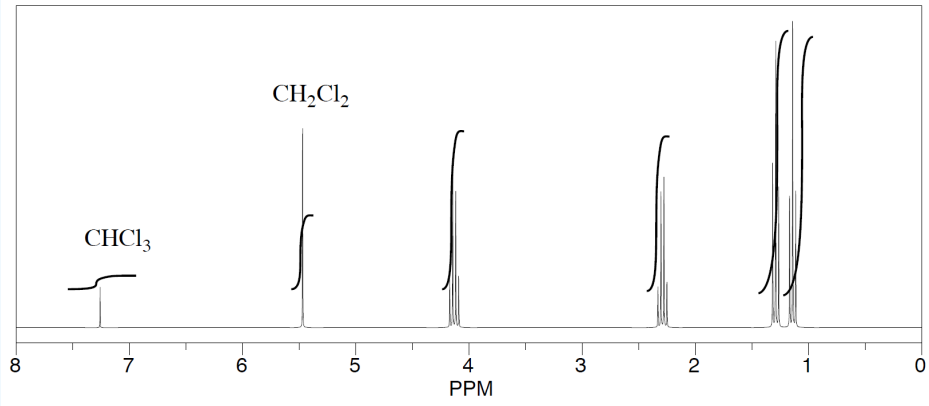
First student's spectrum:



Second student's spectrum:



Third student's spectrum:

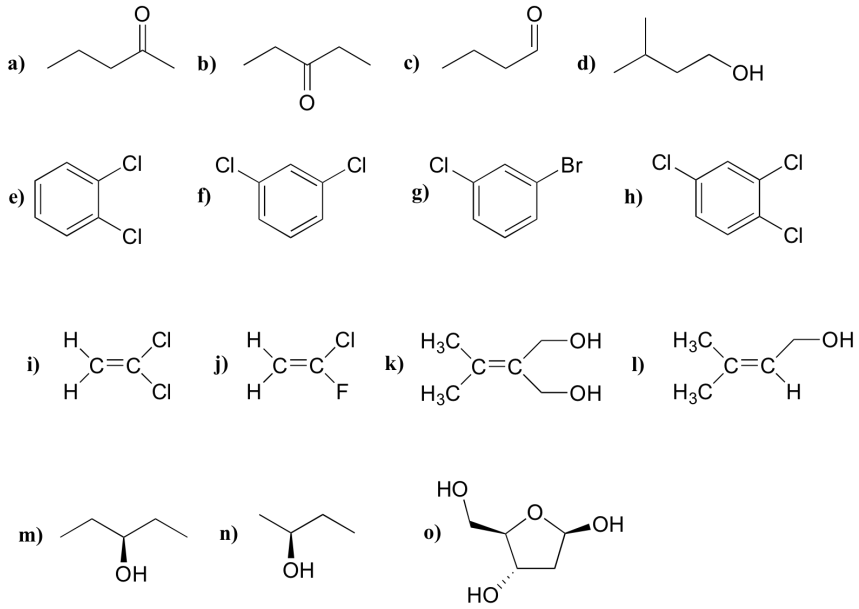


They were also able to determine that they had some leftover solvent in their samples by consulting a useful table of solvent impurities in NMR (which they found in Goldberg et. al., Organometallics 2010, 29, 2176-2179).

1. What is the ratio of leftover solvent to ethyl propanoate in each sample?
2. What is the percent of each sample that is leftover solvent

ADDITIONAL NMR EXAMPLES

For each molecule, predict the number of signals in the ^{1}H-NMR and the ^{13}C-NMR spectra (do not count split peaks - eg. a quartet counts as only one signal). Assume that diastereotopic groups are non-equivalent.

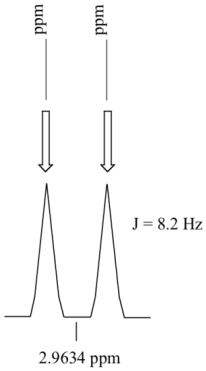


P5.2: For each of the 20 common amino acids, predict the number of signals in the proton-decoupled ^{13}C-NMR spectrum.

P5.3: Calculate the chemical shift value (expressed in Hz, to one decimal place) of each sub-peak on the ^{1}H-NMR doublet signal below. Do this for:

a) a spectrum obtained on a 300 MHz instrument

b) a spectrum obtained on a 100 MHz instrument

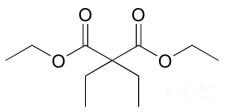


P5.4: Consider a quartet signal in an ^{1}H-NMR spectrum obtained on a 300 MHz instrument. The chemical shift is recorded as 1.7562 ppm, and the coupling constant is J = 7.6 Hz. What is the chemical shift, expressed to the nearest 0.1 Hz, of the furthest downfield sub-peak in the quartet? What is the resonance frequency (again expressed in Hz) of this sub-peak?)

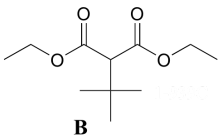
P5.5: One easily recognizable splitting pattern for the aromatic proton signals from disubstituted benzene structures is a pair of doublets. Does this pattern indicate *ortho*, *meta*, or *para* substitution?

P5.6 : Match spectra below to their corresponding structures A-F.

Structures:



A



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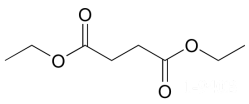

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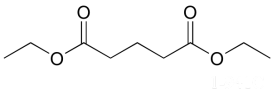

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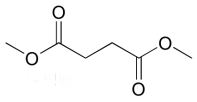
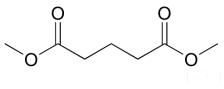


E



F

Spectrum 1

δ	splitting	integration
4.13	q	2
2.45	t	2
1.94	quintet	1
1.27	t	3

Spectrum 2

δ	splitting	integration
3.68	s	3
2.99	t	2
1.95	quintet	1

Spectrum 3

δ	splitting	integration
4.14	q	1
2.62	s	1
1.26	t	1.5

Spectrum 4

δ	splitting	integration
4.14	q	4
3.22	s	1
1.27	t	6
1.13	s	9

Spectrum 5

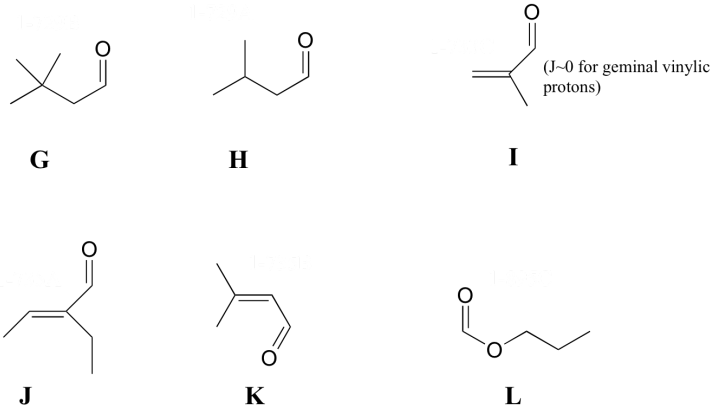
δ	splitting	integration
4.18	q	1
1.92	q	1
1.23	t	1.5
0.81	t	1.5

Spectrum 6

δ	splitting	integration
3.69	s	1.5
2.63	s	1

P5.7: Match spectra 7-12 below to their corresponding structures G-L .

Structures:



G **H** **I**

J **K** **L**

Spectrum 7:

δ	splitting	integration
9.96	d	1
5.88	d	1
2.17	s	3
1.98	s	3

Spectrum 8:

δ	splitting	integration
9.36	s	1
6.55	q	1
2.26	q	2
1.99	d	3
0.96	t	3

Spectrum 9:

δ	splitting	integration
9.57	s	1
6.30	s	1
6.00	s	1
1.84	s	3

Spectrum 10:

δ	splitting	integration
9.83	t	1
2.27	d	2
1.07	s	9

Spectrum 11:

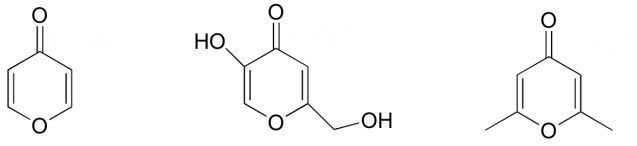
δ	splitting	integration
9.75	t	1
2.30	dd	2
2.21	m	1
0.98	d	6

Spectrum 12:

δ	splitting	integration
8.08	s	1
4.13	t	2
1.70	m	2
0.96	t	3

P5.8: Match the ^{1}H-NMR spectra 13-18 below to their corresponding structures M-R .

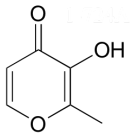
Structures:



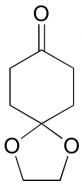
M

N

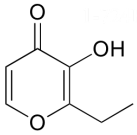
O



P



Q



R

Spectrum 13:

δ	splitting	integration
8.15	d	1
6.33	d	1

Spectrum 14: 1-723C (structure O)

δ	splitting	integration
6.05	s	1
2.24	s	3

Spectrum 15:

δ	splitting	integration
8.57	s (b)	1
7.89	d	1
6.30	d	1
2.28	s	3

Spectrum 16:

δ	splitting	integration
9.05	s (b)	1
8.03	s	1
6.34	s	1
5.68	s (b)	1
4.31	s	2

Spectrum 17:

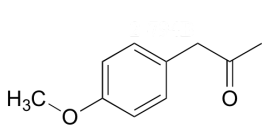
δ	splitting	integration
7.76	d	1
7.57	s (b)	1
6.44	d	1
2.78	q	2
1.25	t	3

Spectrum 18:

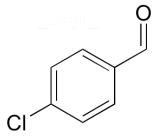
δ	splitting	integration
4.03	s	1
2.51	t	1
2.02	t	1

P5.9: Match the ^{1}H-NMR spectra 19-24 below to their corresponding structures S-X.

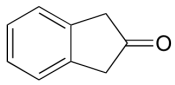
Structures:



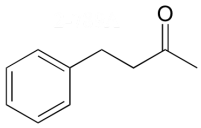
S



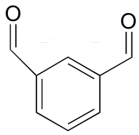
T



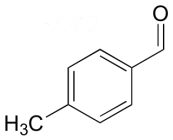
U



V



W



X

Spectrum 19:

δ	splitting	integration
9.94	s	1
7.77	d	2
7.31	d	2
2.43	s	3

Spectrum 20:

δ	splitting	integration
10.14	s	2
8.38	s	1
8.17	d	2
7.75	t	1

Spectrum 21:

δ	splitting	integration
9.98	s	1
7.81	d	2
7.50	d	2

Spectrum 22:

δ	splitting	integration
7.15-7.29	m	2.5
2.86	t	1
2.73	t	1
2.12	s	1.5

Spectrum 23:

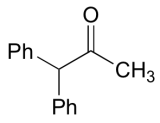
δ	splitting	integration
7.10	d	1
6.86	d	1
3.78	s	1.5
3.61	s	1
2.12	s	1.5

Spectrum 24:

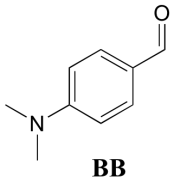
δ	splitting	integration
7.23-7.30	m	1
3.53	s	1

P5.10: Match the ^{1}H-NMR spectra 25-30 below to their corresponding structures AA-FF.

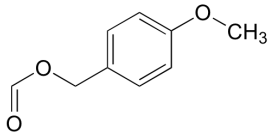
Structures:



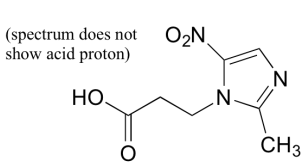
AA



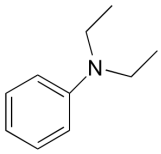
BB



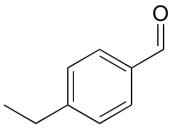
CC



DD



EE



FF

Spectrum 25:

δ	splitting	integration
9.96	s	1
7.79	d	2
7.33	d	2
2.72	q	2
1.24	t	3

Spectrum 26:

δ	splitting	integration
9.73	s	1
7.71	d	2
6.68	d	2
3.06	s	6

Spectrum 27:

δ	splitting	integration
7.20-7.35	m	10
5.12	s	1
2.22	s	3

Spectrum 28:

δ	splitting	integration
8.08	s	1
7.29	d	2
6.87	d	2
5.11	s	2
3.78	s	3

Spectrum 29:

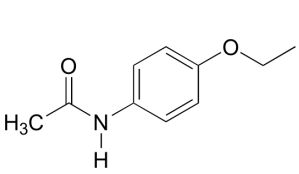
δ	splitting	integration
7.18	d	1
6.65	m	1.5
3.2	q	2
1.13	t	3

Spectrum 30:

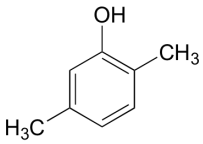
δ	splitting	integration
8.32	s	1
4.19	t	2
2.83	t	2
2.40	s	3

P5.11: Match the ^{1}H-NMR spectra 31-36 below to their corresponding structures GG-LL

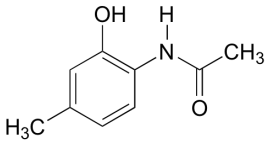
Structures:



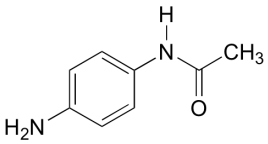
GG



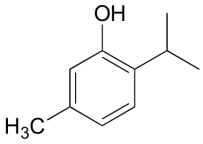
HH



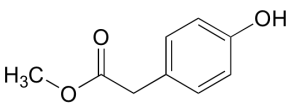
II



JJ



KK



LL

Spectrum 31:

δ	splitting	integration
6.98	d	1
6.64	d	1
6.54	s	1
4.95	s	1
2.23	s	3
2.17	s	3

Spectrum 32:

δ	splitting	integration
7.08	d	1
6.72	d	1
6.53	s	1
4.81	s	1
3.15	7-tet	1
2.24	s	3
1.22	d	6

Spectrum 33:

δ	splitting	integration
7.08	d	2
6.71	d	2
6.54	s	1
3.69	s	3
3.54	s	2

Spectrum 34:

δ	splitting	integration
9.63	s	1
7.45	d	2
6.77	d	2
3.95	q	2
2.05	s	3
1.33	t	3

Spectrum 35:

δ	splitting	integration
9.49	s	1
7.20	d	2
6.49	d	2
4.82	s	2
1.963	s	3

Spectrum 36:

δ	splitting	integration
9.58	s(b)	1
9.31	s	1
7.36	d	1
6.67	s	1
6.55	d	1
2.21	s	3
2.11	s	3

P5.12: Use the NMR data given to deduce structures.

a) Molecular formula: C_5H_8O

^{1}H-NMR:

δ	splitting	integration
9.56	s	1
6.25	d (J~1 Hz)	1
5.99	d (J~1 Hz)	1
2.27	q	2
1.18	t	3

^{13}C-NMR

δ	DEPT
194.60	CH
151.77	C
132.99	CH_2
20.91	CH_2
11.92	CH_3

b) Molecular formula: $C_7H_{14}O_2$

^{1}H-NMR:

δ	splitting	integration
3.85	d	2
2.32	q	2
1.93	m	1
1.14	t	3
0.94	d	6

^{13}C-NMR

δ	DEPT
174.47	C
70.41	CH_2
27.77	CH
27.64	CH_2
19.09	CH_3
9.21	CH_3

c) Molecular formula: $C_5H_{12}O$

^{1}H-NMR:

δ	splitting	integration
3.38	s	2H
2.17	s	1H
0.91	s	9H

^{13}C-NMR

δ	DEPT
73.35	CH_2
32.61	C
26.04	CH_3

d) Molecular formula: $C_{10}H_{12}O$

^{1}H-NMR:

δ	splitting	integration
7.18-7.35	m	2.5
3.66	s	1
2.44	q	1
1.01	t	1.5

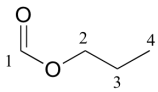
^{13}C-NMR

δ	DEPT
208.79	C
134.43	C
129.31	CH
128.61	CH
126.86	CH
49.77	CH_2
35.16	CH_2
7.75	CH_3

P5.13:

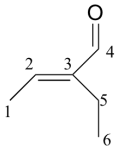
^{13}C-NMR data is given for the molecules shown below. Complete the peak assignment column of each NMR data table.

a)



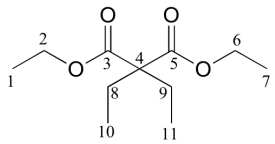
δ	DEPT	carbon #
161.12	CH	
65.54	CH_2	
21.98	CH_2	
10.31	CH_3	

b)



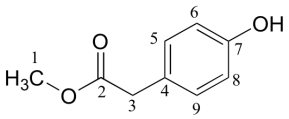
δ	DEPT	carbon #
194.72	C	
149.10	C	
146.33	CH	
16.93	CH_2	
14.47	CH_3	
12.93	CH_3	

c)



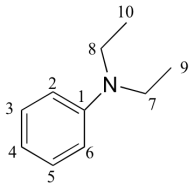
δ	DEPT	carbon #
171.76	C	
60.87	CH_2	
58.36	C	
24.66	CH_2	
14.14	CH_3	
8.35	CH_3	

d)



δ	DEPT	carbon #
173.45	C	
155.01	C	
130.34	CH	
125.34	C	
115.56	CH	
52.27	CH_3	
40.27	CH_2	

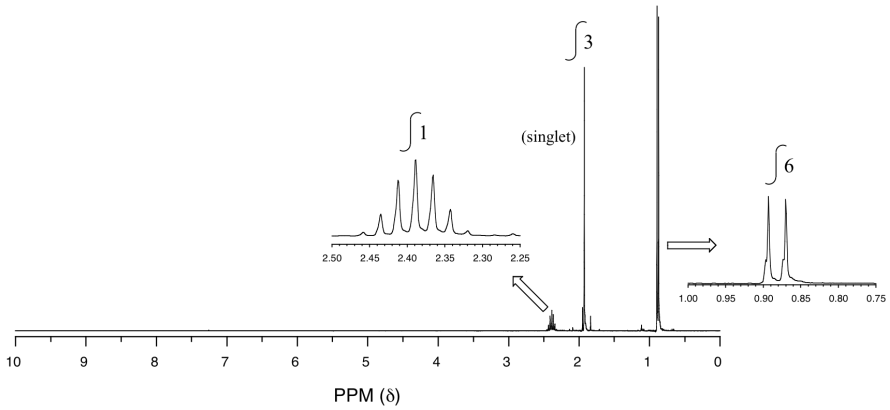
e)



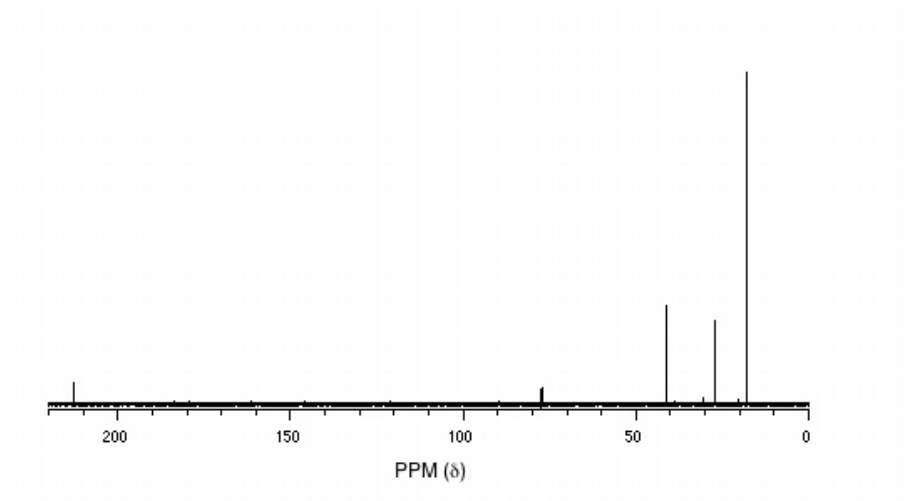
δ	DEPT	carbon #
147.79	C	
129.18	CH	
115.36	CH	
111.89	CH	
44.29	CH_2	
12.57	CH_3	

P5.14: You obtain the following data for an unknown sample. Deduce its structure.

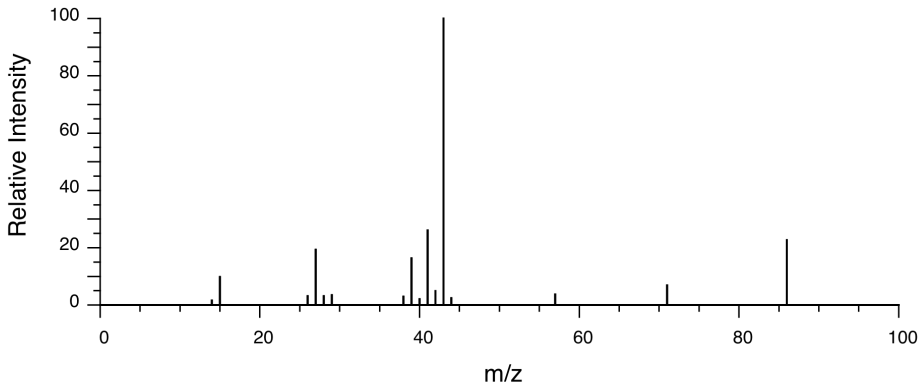
^{1}H-NMR:



^{13}C-NMR:



Mass Spectrometry:



P5.15: You take a ^{1}H-NMR spectrum of a sample that comes from a bottle of 1-bromopropane. However, you suspect that the bottle might be contaminated with 2-bromopropane. The NMR spectrum shows the following peaks:

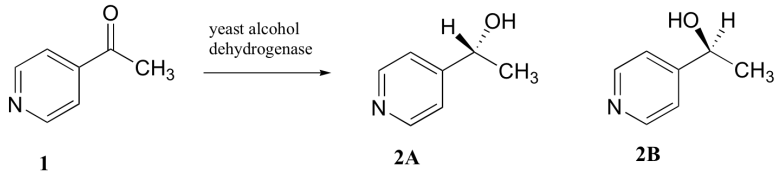
δ	splitting	integration
4.3	septet	0.0735
3.4	triplet	0.661
1.9	sextet	0.665
1.7	doublet	0.441
1.0	triplet	1.00

How badly is the bottle contaminated? Specifically, what percent of the molecules in the bottle are 2-bromopropane?

Challenge problems

C5.1: All of the ^{13}C-NMR spectra shown in this chapter include a signal due to $CDCl_3$, the solvent used in each case. Explain the splitting pattern for this signal.

C5.2: Researchers wanted to investigate a reaction which can be catalyzed by the enzyme alcohol dehydrogenase in yeast. They treated 4'-acylpyridine (1) with living yeast, and isolated the alcohol product(s) (some combination of 2A and 2B).

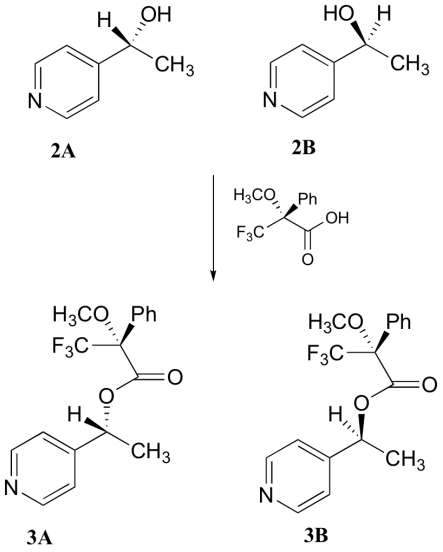


1 2A 2B

a) Will the products 2A and 2B have identical or different ^{1}H-NMR spectra? Explain.

b) Suggest a ^{1}H-NMR experiment that could be used to determine what percent of starting material (1) got turned into product (2A and 2B).

c) With purified 2A/2B, the researchers carried out the subsequent reaction shown below to make 3A and 3B, known as 'Mosher's esters'. Do 3A and 3B have identical or different ^{1}H-NMR spectra? Explain.



2A 2B 3A 3B

d) Explain, very specifically, how the researchers could use ^{1}H-NMR to determine the relative amounts of 2A and 2B formed in the reaction catalyzed by yeast enzyme.

13.9: ^{13}C NMR SPECTROSCOPY - SIGNAL AVERAGING AND FT-NMR

OBJECTIVES

After completing this section, you should be able to

- Understand why the nuclei C NMR looks at is ^{13}C and not ^{12}C.
- Know why more scans are needed in ^{13}C NMR than ^{1}H NMR.

Most of what we have learned about ^{1}H-NMR spectroscopy also applies to ^{13}C-NMR, although there are several important differences.

SIGNAL STRENGTH IN ^{13}C-NMR SPECTROSCOPY

The ^{12}C isotope of carbon - which accounts for more than 98% of the carbons in organic molecules - does not have a nuclear magnetic moment, and thus is NMR-inactive. Fortunately for organic chemists, however, the ^{13}C isotope, which accounts for 1.1% of the remaining carbon atoms in nature, has a magnetic moment just like protons.

The magnetic moment of a ^{13}C nucleus is much weaker than that of a proton, meaning that NMR signals from ^{13}C nuclei are inherently much weaker than proton signals. This, combined with the low natural abundance of ^{13}C, means that it is much more difficult to observe carbon signals and there is a much lower signal-to-noise ratio than in ^{1}H NMR. Therefore, more concentrated samples are required to generate a useful spectrum, and often the data from hundreds of scans must be averaged in order to bring the signal-to-noise ratio down to acceptable levels. This type of **signal averaging** works since background noise in a spectrum is typically random while the signal caused by the ^{13}C nuclei is not. Therefore if the spectra from multiple scans is averaged, the noise gets closer to 0 while the signal stays the same, increasing the signal-to-noise ratio.

FOURIER TRANSFORM (FT) NMR

Earlier versions of NMR instruments used variable magnetic fields which required recording of each signal in the spectrum sequentially which is called continuous wave (CW) NMR. The **Fourier Transform** allows recording of all signals simultaneously by introducing a short pulse of all RF frequencies that cause resonance for a given nucleus. This complex signal is then manipulated through complex mathematical processing that creates an NMR spectrum that looks similar to a CW spectrum, but in much less time.

13.10: CHARACTERISTICS OF ^{13}C NMR SPECTROSCOPY

OBJECTIVES

After completing this section, you should be able to

- Determine the number of distinct C atoms in a molecule.
- Use the chemical shifts table to determine functional groups present in a molecule.
- Assign a chemical shift to each carbon in a given molecule.

THE BASICS OF ^{13}C-NMR SPECTROSCOPY

Unlike ^{1}H-NMR signals, the area under a ^{13}C-NMR signal cannot be used to determine the number of carbons to which it corresponds. This is because the signals for some types of carbons are inherently weaker than for other types – peaks corresponding to carbonyl carbons, for example, are much smaller than those for methyl or methylene (CH_2) peaks. Peak integration is generally not useful in ^{13}C-NMR spectroscopy, except when investigating molecules that have been enriched with ^{13}C isotope.

The resonance frequencies of ^{13}C nuclei are lower than those of protons in the same applied field - in a 7.05 Tesla instrument, protons resonate at about 300 MHz, while carbons resonate at about 75 MHz. This is fortunate, as it allows us to look at ^{13}C signals using a completely separate 'window' of radio frequencies. This means you will only see the ^{13}C nuclei in a ^{13}C NMR experiment like in the ^{1}H NMR experiments we just looked at, we only saw hydrogens. Just like in ^{1}H-NMR, the standard used in ^{13}C-NMR experiments to define the 0 ppm point is tetramethylsilane (TMS), although of course in ^{13}C-NMR it is the signal from the four equivalent *carbons* in TMS that serves as the standard. Chemical shifts for ^{13}C nuclei in organic molecules are spread out over a much wider range than for protons – up to 200 ppm for ^{13}C compared to 12 ppm for protons (see Table 3 for a list of typical ^{13}C-NMR chemical shifts). This is also fortunate, because it means that the signal from each carbon in a compound can almost always be seen as a distinct peak, without the overlapping that often plagues ^{1}H-NMR spectra. The chemical shift of a ^{13}C nucleus is influenced by essentially the same factors that influence a proton's chemical shift: bonds to electronegative atoms and diamagnetic anisotropy effects tend to shift signals downfield (higher resonance frequency). In addition, sp^2 hybridization results in a large downfield shift. The ^{13}C-NMR signals for carbonyl carbons are generally the furthest downfield (170-220 ppm), due to both sp^2 hybridization and to the double bond to oxygen.

EXAMPLE 13.10.1

a. How many sets of non-equivalent carbons are there in each of the molecules shown in exercise 5.1?
b. How many sets of non-equivalent carbons are there in:

- toluene
- 2-pentanone
- para-xylene
- triclosan

(all structures are shown earlier in this chapter)

Solution

a

a) 8 signals (each carbon is different)

b) 11 signals (the two enantiotopic CH_2CH_3 groups are NMR-equivalent)

c) 6 signals (each carbon is different)

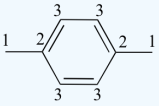
d) 16 signals (the fluorobenzene group only contributes 4 signals due to symmetry)

b

a) 5 signals

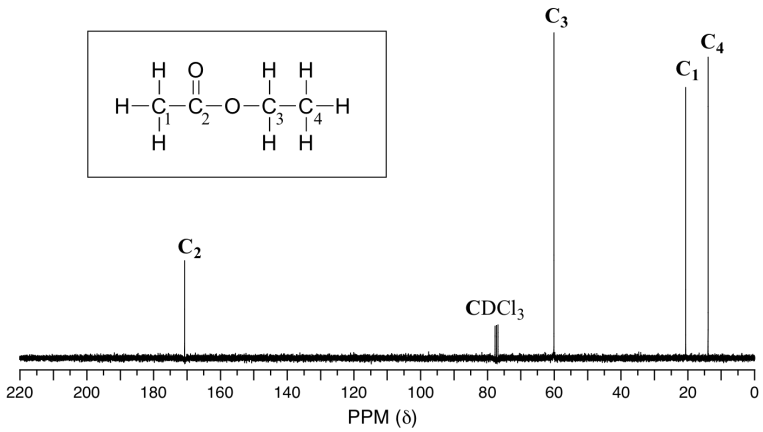
b) 5 signals

c) 3 signals

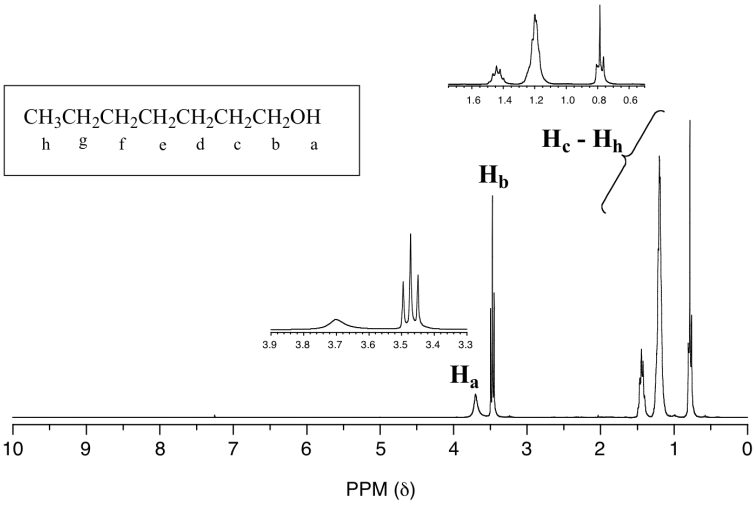


d) 6 signals

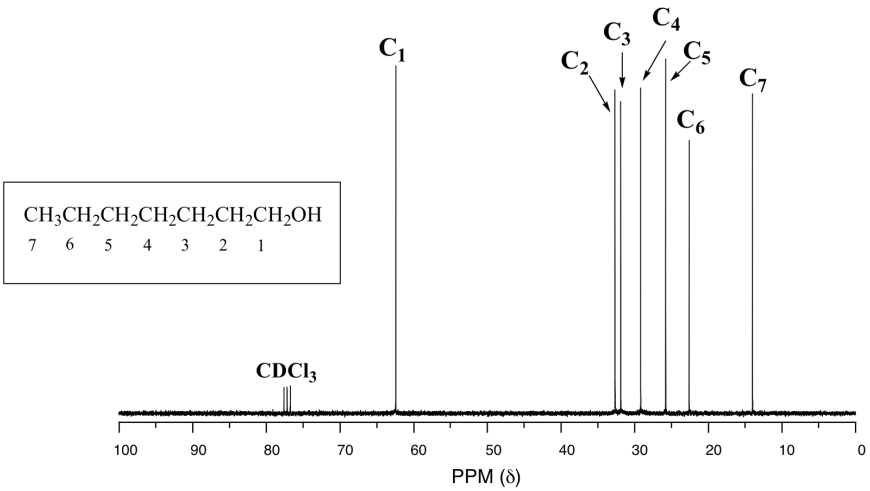
Because of the low natural abundance of ^{13}C nuclei, it is very unlikely to find two ^{13}C atoms near each other in the same molecule, and thus *we do not see spin-spin coupling between neighboring carbons in a ^{13}C-NMR spectrum*. There is, however, **heteronuclear coupling** between ^{13}C carbons and the hydrogens to which they are bound. Carbon-proton coupling constants are very large, on the order of 100 – 250 Hz. For clarity, chemists generally use a technique called **broadband decoupling**, which essentially 'turns off' C-H coupling, resulting in a spectrum in which all carbon signals are singlets. Below is the proton-decoupled^{13}C-NMR spectrum of ethyl acetate, showing the expected four signals, one for each of the carbons.



One of the greatest advantages of ^{13}C-NMR compared to ^{1}H-NMR is the breadth of the spectrum - recall that carbons resonate from 0-220 ppm relative to the TMS standard, as opposed to only 0-12 ppm for protons. Because of this, ^{13}C signals rarely overlap, and we can almost always distinguish separate peaks for each carbon, even in a relatively large compound containing carbons in very similar environments. In the proton spectrum of 1-heptanol, for example, only the signals for the alcohol proton (H_a) and the two protons on the adjacent carbon (H_b) are easily analyzed. The other proton signals overlap, making analysis difficult.



In the ^{13}C spectrum of the same molecule, however, we can easily distinguish each carbon signal, and we know from this data that our sample has seven non-equivalent carbons. (Notice also that, as we would expect, the chemical shifts of the carbons get progressively smaller as they get farther away from the deshielding oxygen.)



This property of ^{13}C-NMR makes it very helpful in the elucidation of larger, more complex structures.

^{13}C NMR CHEMICAL SHIFTS

The Carbon NMR is used for determining functional groups using characteristic shift values. ^{13}C chemical shifts are greatly affected by electronegative effects. If a H atom in an alkane is replaced by substituent X, electronegative atoms (O, N, halogen), ^{13}C signals for nearby carbons shift downfield (left; increase in ppm) with the effect diminishing with distance from the electron withdrawing group. Figure 13.11.1 shows typical ^{13}C chemical shift regions of the major chemical class.

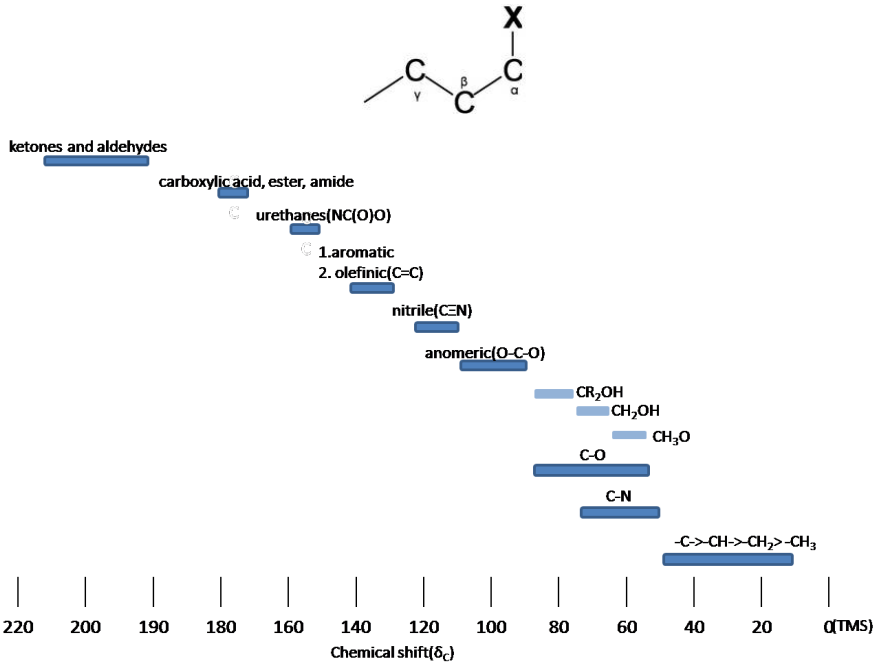


Figure 13.10.1: ^{13}C Chemical shift range for organic compound

SPIN-SPIN SPLITTING

Comparing the ^{1}H NMR, there is a big difference thing in the ^{13}C NMR. The ^{13}C-^{13}Cspin-spin splitting rarely exit between adjacent carbons because ^{13}C is naturally lower abundant (1.1%)

- **^{13}C-^{1}H Spin coupling**: ^{13}C-^{1}H Spin coupling provides useful information about the number of protons attached a carbon atom. In case of one bond coupling ($^{1}J_{CH}$), -CH, -CH_2, and CH_3 have respectively doublet, triplet, quartets for the ^{13}C resonances in the spectrum. However, ^{13}C-^{1}H Spin coupling has an disadvantage for ^{13}C spectrum interpretation. ^{13}C-^{1}H Spin coupling is hard to analyze and reveal structure due to a forest of overlapping peaks that result from 100% abundance of ^{1}H.
- **Decoupling**: Decoupling is the process of removing ^{13}C-^{1}H coupling interaction to simplify a spectrum and identify which pair of nuclei is involved in the J coupling. The decoupling ^{13}C spectra shows only one peak(singlet) for each unique carbon in

the molecule (Fig 13.11.2). Decoupling is performed by irradiating at the frequency of one proton with continuous low-power RF.

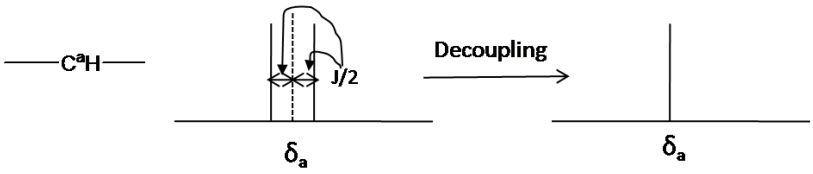


Figure 13.10.2 Decoupling in the ^{13}C NMR

SUMMARY

^{13}C NMR (Carbon-13 Nuclear Magnetic Resonance) Spectroscopy is a powerful analytical technique used to study the structure and connectivity of organic molecules. Unlike proton NMR, which detects hydrogen nuclei, ^{13}C NMR specifically targets the carbon nuclei within a molecule. In ^{13}C NMR spectroscopy, carbon atoms resonate at characteristic frequencies based on their local chemical environment, which is influenced by neighboring atoms and functional groups. These resonances appear as peaks in the NMR spectrum, providing valuable information about the types of carbon atoms present and their surroundings. By analyzing the chemical shifts, intensities, and coupling patterns of these peaks, chemists can deduce crucial structural details such as the number and types of carbon atoms, their connectivity, and the presence of certain functional groups. This information is essential for determining the molecular structure and understanding chemical properties and reactivities.

13.11: DEPT ^{13}C NMR SPECTROSCOPY

OBJECTIVES

After completing this section, you should be able to

- Understand why the peaks do not have splitting like in ^{1}H NMR.
- Using DEPT, distinguish whether a methyl (CH_3), methylene (CH_2), methine (CH) or quarternary C is present in the molecule and how many.
- Propose a structure based on ^{13}C spectral data.

DEPT (Distortionless Enhancement by Polarization Transfer) ^{13}C NMR Spectroscopy is a powerful technique used in organic chemistry to elucidate the structure of organic molecules. Unlike traditional ^{13}C NMR spectroscopy, which provides only basic information about carbon environments, DEPT enhances signals from specific types of carbon atoms, allowing for more detailed analysis. DEPT works by selectively enhancing signals from three types of carbon atoms: methyl (CH_3), methylene (CH_2), and quaternary carbons (C with no attached hydrogens). This enhancement is achieved through a series of pulse sequences that manipulate the nuclear spins of carbon atoms, resulting in distinct peaks in the NMR spectrum corresponding to each carbon type.

DEPT experiments are used for distinguishing between a CH_3 group (methyl), a CH_2 group (methylene), and a CH group (methine). The proton pulse is set at 45°, 90°, or 135° in the three separate experiments. The different pulses depend on the number of protons attached to a carbon atom. Figure 13.11.1 is an example about DEPT spectrum of n-isobutlybutrate.

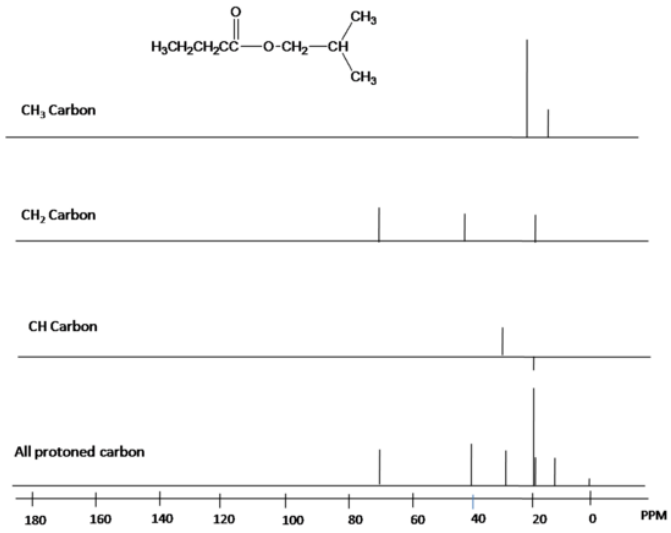


Figure 13.11.1: DEPT spectrum of n-isobutlybutrate.

While broadband decoupling results in a much simpler spectrum, useful information about the presence of neighboring protons is lost. However, another modern NMR technique called DEPT (Distortionless Enhancement by Polarization Transfer) allows us to determine how many hydrogens are bound to each carbon. For example, a DEPT experiment tells us that the signal at 171 ppm in the ethyl acetate spectrum is a quaternary carbon (no hydrogens bound, in this case a carbonyl carbon), that the 61 ppm signal is from a methylene (CH_2) carbon, and that the 21 ppm and 14 ppm signals are both methyl (CH_3) carbons. The details of the DEPT experiment are beyond the scope of this text, but DEPT information will often be provided along with ^{13}C spectral data in examples and problems.

Below are two more examples of ^{13}C NMR spectra of simple organic molecules, along with the type of substitution for that carbon which was obtained from a DEPT experiment.

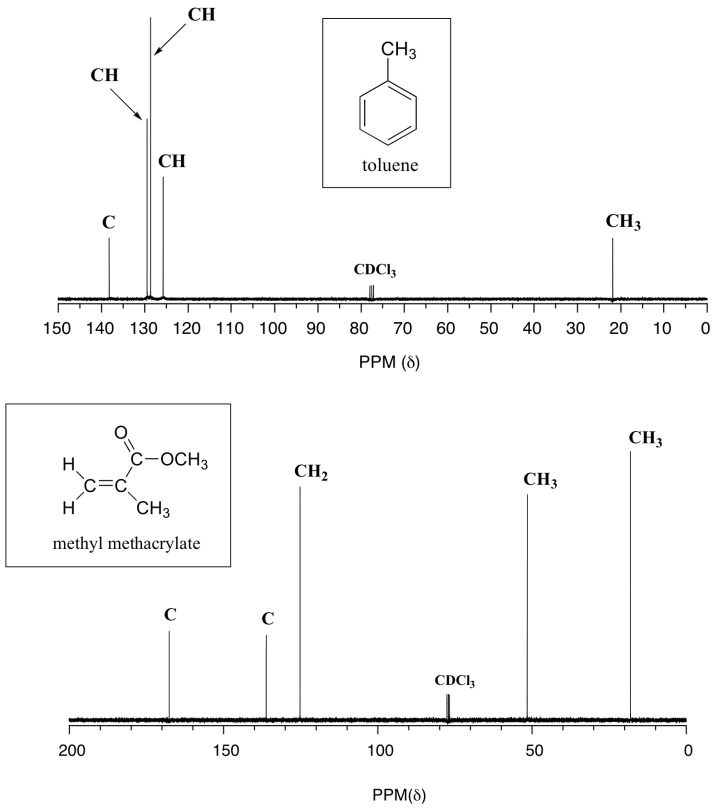
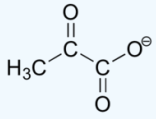


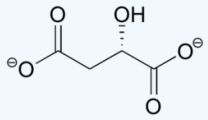
Figure 13.11.2 ^{13}C NMR spectra of toluene (left) and meth methacrylate (right)

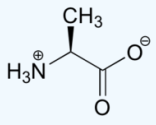
EXERCISE 13.11.1

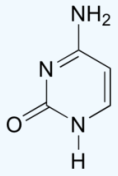
^{13}C-NMR (and DEPT) data for some common biomolecules are shown below (data are from the Aldrich Library of ^{1}H and ^{13}C NMR). Match the NMR data to the correct structure, and make complete peak assignments.

- spectrum a: 168.10 ppm (C), 159.91 ppm (C), 144.05 ppm (CH), 95.79 ppm (CH)
- spectrum b: 207.85 ppm (C), 172.69 ppm (C), 29.29 ppm (CH_3)
- spectrum c: 178.54 ppm (C), 53.25 ppm (CH), 18.95 ppm (CH_3)
- spectrum d: 183.81 ppm (C), 182. 63 ppm (C), 73.06 ppm (CH), 45.35 ppm (CH_2)

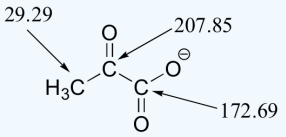

pyruvate


(S)-malate

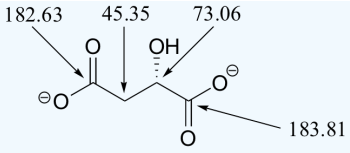

alanine


cytosine

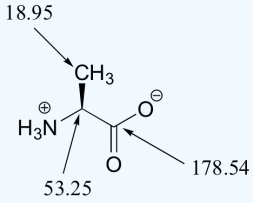
Answer



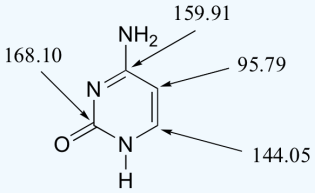
pyruvate: spectrum b



(S)-malate: spectrum d



alanine (spectrum c)



cytosine (spectrum a)

13.12: USES OF ^{13}C NMR SPECTROSCOPY

OBJECTIVES

After completing this section, you should be able to use data from ^{13}C NMR spectra to distinguish between two (or more) possible structures for an unknown organic compound.

FEATURES OF A ^{13}C NMR SPECTRUM

Butane shows two different peaks in the ^{13}C NMR spectrum, below. Note that: the chemical shifts of these peaks are not very different from methane. The carbons in butane are in a similar environment to the one in methane.

- there are two distinct carbons in butane: the methyl, or CH_3, carbon, and the methylene, or CH_2, carbon.
- the methyl carbon absorbs slightly upfield, or at lower shift, around 10 ppm.
- the methylene carbon absorbs at slightly downfield, or at higher shift, around 20 ppm.
- other factors being equal, methylene carbons show up at slightly higher shift than methyl carbons.

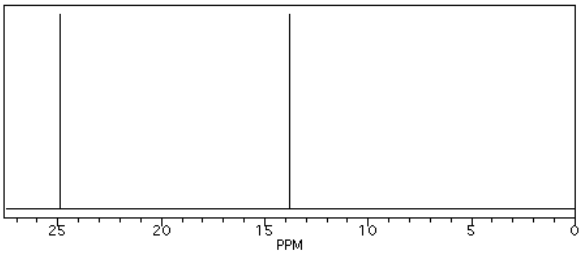


Figure 13.12.1 *Simulated ^{13}C NMR spectrum of butane (showing only the upfield portion of the spectrum).*

In the ^{13}C NMR spectrum of pentane (below), you can see three different peaks, even though pentane just contains methyl carbons and methylene carbons like butane. As far as the NMR spectrometer is concerned, pentane contains three different kinds of carbon, in three different environments. That result comes from symmetry.

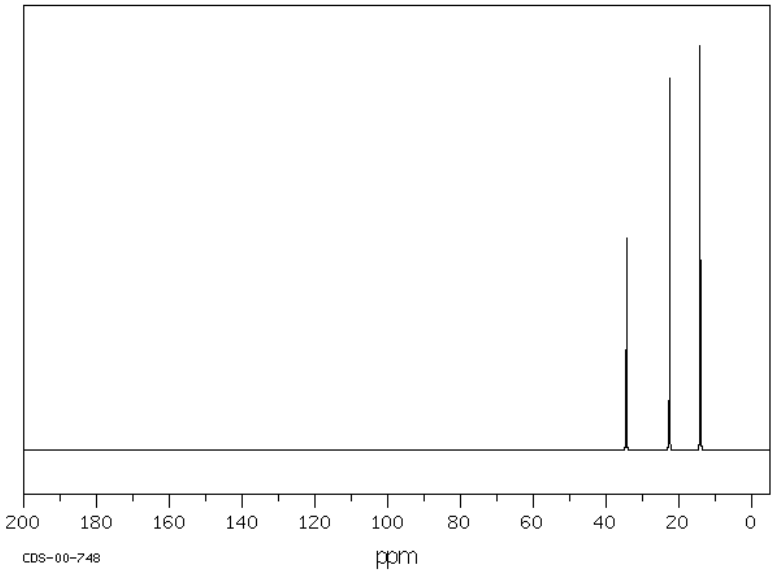


Figure 13.12.2 *^{13}C NMR spectrum of pentane. Source: SDBSWeb : http://riodb01.ibase.aist.go.jp/sdbs/ (National Institute of Advanced Industrial Science and Technology of Japan, 15 August 2008)*

Symmetry is an important factor in spectroscopy. Nature says:

- atoms that are symmetry-inequivalent can absorb at different shifts.
- atoms that are symmetry-equivalent must absorb at the same shift.

To learn about symmetry, take a model of pentane and do the following:

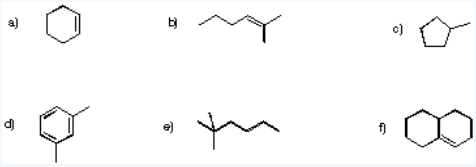
- make sure the model is twisted into the most symmetric shape possible: a nice "W".

- choose one of the methyl carbons to focus on.
- rotate the model 180 degrees so that you are looking at the same "W" but from the other side.
- note that the methyl you were focusing on has simply switched places with the other methyl group. These two carbons are symmetry-equivalent via two-fold rotation.

By the same process, you can see that the second and fourth carbons along the chain are also symmetry-equivalent. However, the middle carbon is not; it never switches places with the other carbons if you rotate the model. There are three different sets of inequivalent carbons; these three groups are not the same as each other according to symmetry.

EXAMPLE 13.12.1

Determine how many inequivalent carbons there are in each of the following compounds. How many peaks do you expect in each ^{13}C NMR spectrum?



Practically speaking, there is only so much room in the spectrum from one end to the other. At some point, peaks can get so crowded together that you can't distinguish one from another. You might expect to see ten different peaks in eicosane, a twenty-carbon alkane chain, but when you look at the spectrum you can only see seven different peaks. That may be frustrating, because the experiment does not seem to agree with your expectation. However, you will be using a number of methods together to minimize the problem of misleading data.

Solution

a) Three inequivalent carbons/three peaks. There is a plane of symmetry that bisects the cyclohexene horizontally. The three different carbons are one of the alkene (C1), the CH_2 next to alkene (C3) and C4.

b) Six inequivalent carbons/six peaks. The two methyl groups attached to the alkene are identical.

c) Four inequivalent carbons/four peaks. This molecule has a plane of symmetry through the molecule, including the methyl group. The two carbons adjacent to the methyl group are equivalent (C2 and C5). C3 and C4 are also equivalent.

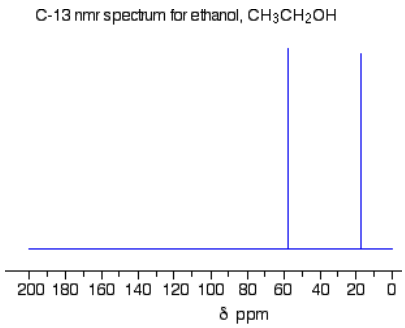
d) Five inequivalent carbons/five peaks. This molecule has a plane of symmetry that passes through the ring carbon between the two methyl groups. The two methyl carbons are identical. The two ring carbons with the methyl groups attached are identical (C1 and C3). C4 and C6 are also equivalent.

e) Six inequivalent carbons/six peaks. The three methyl groups at the end of the molecule are equivalent.

f) Ten inequivalent carbons/ten peaks. There is no symmetry for the carbons in this molecule.

THE ^{13}C NMR SPECTRUM FOR ETHANOL

This is a simple example of a ^{13}C NMR spectrum. Don't worry about the scale for now - we'll look at that in a minute.



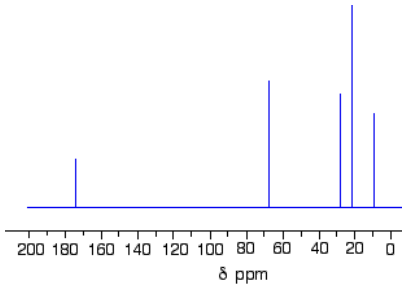
NOTE

Note: The NMR spectra on this page have been produced from graphs taken from the Spectral Data Base System for Organic Compounds (SDBS) at the National Institute of Materials and Chemical Research in Japan.

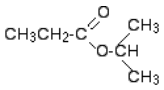
There are two peaks because there are two different environments for the carbons. The carbon in the CH_3 group is attached to 3 hydrogens and a carbon. The carbon in the CH_2 group is attached to 2 hydrogens, a carbon and an oxygen. The two lines are in different places in the NMR spectrum because they need different external magnetic fields to bring them in to resonance at a particular radio frequency.

THE ^{13}C NMR SPECTRUM FOR A MORE COMPLICATED COMPOUND

This is the ^{13}C NMR spectrum for 1-methylethyl propanoate (also known as isopropyl propanoate or isopropyl propionate).



This time there are 5 lines in the spectrum. That means that there must be 5 different environments for the carbon atoms in the compound. Is that reasonable from the structure?



If you count the carbon atoms, there are 6 of them. So why only 5 lines? In this case, two of the carbons are in exactly the same environment. They are attached to exactly the same things. Look at the two CH_3 groups on the right-hand side of the molecule.

You might reasonably ask why the carbon in the CH_3 on the left is not also in the same environment. Just like the ones on the right, the carbon is attached to 3 hydrogens and another carbon. But the similarity is not exact - you have to chase the similarity along the rest of the molecule as well to be sure.

The carbon in the left-hand CH_3 group is attached to a carbon atom which in turn is attached to a carbon with two oxygens on it - and so on down the molecule. That's not exactly the same environment as the carbons in the right-hand CH_3 groups. They are attached to a carbon which is attached to a single oxygen - and so on down the molecule. We'll look at this spectrum again in detail on the next page - and look at some more similar examples as well. This all gets easier the more examples you look at.

For now, all you need to realize is that each line in a ^{13}C NMR spectrum recognizes a carbon atom in one particular environment in the compound. If two (or more) carbon atoms in a compound have exactly the same environment, they will be represented by a single line.

NOTE

You might wonder why all this works, since only about 1% of carbon atoms are ^{13}C. These are the only ones picked up by this form of NMR. If you had a single molecule of ethanol, then the chances are only about 1 in 50 of there being one ^{13}C atom in it, and only about 1 in 10,000 of both being ^{13}C.

But you have got to remember that you will be working with a sample containing huge numbers of molecules. The instrument can pick up the magnetic effect of the ^{13}C nuclei in the carbon of the CH_3 group and the carbon of the CH_2 group even if they are in separate molecules. There's no need for them to be in the same one.

13.S: STRUCTURE DETERMINATION - NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY (SUMMARY)

CONCEPTS & VOCABULARY

13.1 Nuclear Magnetic Resonance Spectroscopy

- An applied magnetic field orients nuclei from random to aligned with or against the field. The nuclei absorb EM radiation of a frequency with energy that matches this energy gap.

13.2 The Nature of NMR Absorptions

- Nuclei in an applied field can align with the magnetic field (+1/2) or against the magnetic field (-1/2). The difference in the energy of these two states is the resonant frequency of that atom.
- To allow comparison between NMR spectra from instruments of differing field strength, the x-axis is reported as chemical shift, rather than frequency.
- **Chemical shift** is defined as the frequency of absorbance (in Hz) divided by the resonant frequency of the instrument (in MHz), thus the units are PPM (parts per million).
- Tetramethylsilane is used as a standard reference with its **chemical shift** set to 0 PPM (since these protons are highly shielded).
- Higher **chemical shifts** are called downfield, while lower shifts are called upfield.
- Nearby electrons shield the nuclei from the induced magnetic field, thus reducing their chemical shift. Atoms of higher electronegativity pull some of this electron density away from the nuclei causing increased **chemical shift**. This is called **deshielding**.

13.3 The Chemical Shift

- Pi electrons in a compound generate their own magnetic field that influences shielding of nearby atoms. This is most clearly exemplified by benzene protons that are highly deshielded (chemical shifts of 6.5-8 PPM).
- Protons that are involved in hydrogen bonding have variable chemical shifts and often do not absorb at one specific frequency, leading to broader peaks.

13.4 Chemical Shifts in ^{1}H NMR Spectroscopy

- Chemical shifts of protons are shifted upfield (higher ppm) by electronegative groups attached to the same carbon (and to a lesser effect when attached to nearby carbons).
- Aromatic protons appear between 6.5 and 8 ppm.
- Chemical shifts of O-H and N-H bonds vary with temperature and concentration.

13.5 Integration of ^{1}H NMR Absorptions - Proton Counting

- The are under a ^{1}H NMR signal is proportional to the number of hydrogens that caused the signal.

13.6 Spin-Spin Splitting in ^{1}H NMR Spectra

- ^{1}H signals are split into multiple peaks by neighboring H atoms whose spins can add to or subtract from the magnetic field.
- Spin-spin coupling yields n+1 peaks where n is the number of neighboring protons.
- Multiplets formed from spin-spin splitting follow specific symmetry based on the number of neighboring protons.
- The distance between peaks in a signal are called coupling constants.

13.7 ^{1}H NMR Spectroscopy and Proton Equivalence

- Equivalent protons (protons in identical electrical environments) only give 1 signal.
- To determine the number of ^{1}H NMR signals expected, symmetry of a molecule needs to be examined to find equivalent protons.
- Protons with different stereochemistry are not equivalent.
- Protons on chiral molecules that are diastereotopic (would create a diastereomer if replaced) are not equivalent.

13.8 More Complex Spin-Spin Splitting Patterns

- ^{1}H NMR signals can overlap making interpretation more difficult.
- Signals can distort where the peaks are not completely symmetrical in shape.
- When neighboring protons are nonequivalent, the coupling constant can be different leading to complex sets of peaks.
- Some complex multiplets can be identified such as a doublet of doublets, but others cannot and are referred to as multiplets.

13.9 Uses of ^{1}H NMR Spectroscopy

- ^{1}H NMR can help identify components of a mixture or determine which product was formed in a reaction.

13.10 ^{13}C NMR Spectroscopy - Signal Averaging and FT-NMR

- NMR signals for ^{13}C NMR are much weaker than for ^{1}H, requiring higher sample concentration and averaging of many scans (hundreds or even thousands).
- **Signal averaging** increases signal-to-noise ratio when running multiple scans in NMR.
- **Fourier Transform** NMR allows the entire spectrum to be acquired at once, rather than one frequency at a time.

13.11 Characteristics of ^{13}C NMR Spectroscopy

- Chemical shifts for ^{13}C NMR are spread over a wider range of frequencies (0-200 ppm).
- Carbons with sp^2 hybridization are shifted far downfield
- Since it is exceptionally rare to have two ^{13}C atoms adjacent to one another, there is no spin-spin coupling in ^{13}C NMR.
- Coupling constants between carbons and hydrogens are large and make interpretation of ^{13}C NMR spectra difficult, so most spectra are run using broadband decoupling. This leads to all signals in ^{13}C NMR appearing as singlets.

13.12 DEPT ^{13}C NMR Spectroscopy

- ^{13}C NMR DEPT experiments are used to identify the number of attached hydrogens each carbon has.

13.13 Uses of ^{13}C NMR Spectroscopy

SKILLS TO MASTER

- Skill 13.1 Interpretation of ^{1}H NMR Spectra.
- Skill 13.2 Interpretation of ^{13}C NMR Spectra.

MEMORIZATION TASKS (MT)

MT 13.1 Memorize chemical shifts patterns in ^{1}H NMR.

MT 13.2 Memorize spin-spin splitting patterns

MT 13.3 Memorize chemical shift patterns in ^{13}C NMR.

CHAPTER OVERVIEW

14: CONJUGATED COMPOUNDS AND ULTRAVIOLET SPECTROSCOPY

LEARNING OBJECTIVES

After you have completed Chapter 14, you should be able to

1. fulfillall of the detailed objectives listed under each individual section.
2. use the reactions discussed, along with those from previous chapters, when designing multi-step syntheses.
3. use the reactions and concepts discussed to solve road-map problems.
4. use ultraviolet-spectral data, in conjunction with other spectral data, to elucidate the structure of an unknown compound.
5. define, and use in context, the key terms introduced.

You have already studied the chemistry of compounds that contain one carbon-carbon double bond. In this chapter, you will focus your attention on compounds that contain two or more such bonds. In particular you will study the properties of those compounds that contain two carbon-carbon double bonds which are separated by one carbon-carbon single bond. These compounds are called “conjugated dienes.”

To understand the properties exhibited by conjugated dienes, you must first examine their bonding in terms of the molecular orbital theory introduced in Section 1.11. Then, you must learn how the products of a reaction are dependent on both thermodynamic and kinetic considerations. Which of these two factors is the most important can sometimes determine which of two possible products will predominate when a reaction is carried out under specific conditions. Although we shall not make extensive use of ultraviolet spectroscopy, this technique can often provide important information when conjugated compounds are being investigated. In general, ultraviolet spectroscopy is less useful than the other spectroscopic techniques introduced earlier.

14.0: INTRODUCTION

OBJECTIVE

After completing this section, you should be able to determine whether or not a molecule contains a conjugated system, given its Kekulé, condensed or shorthand formula.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

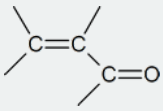
- conjugated diene
- conjugated double bonds
- diene
- enone
- polyene

STUDY NOTES

Conjugated double bonds are double bonds which are separated by one carbon-carbon single bond. Thus the double bonds in butadiene, $\ce{\sf{CH2=CH-CH=CH2}}$, are conjugated, and this compound is an example of a *conjugated diene*.

Just as the term *diene*indicates the presence of two carbon-carbon double bonds in a compound, so the term *polyene* is used to describe compounds containing many carbon-carbon double bonds.

An *enone* is a compound containing a carbon-carbon double bond (ene) and a carbonyl group (one). A conjugated enone contains the structural unit:



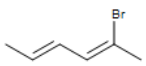
CONJUGATED DIENES

A diene is a hydrocarbon chain that has two double bonds that may or may not be adjacent to each other. This section focuses on the delocalization of π systems by comparing two neighboring double bonds. The arrangements of these double bonds can have varying affects on the compounds reactivity and stability.

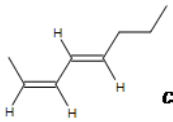
NAMING DIENES

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:

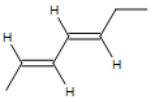


2-Bromo-2,4-hexadiene



***cis*-2-*trans*-4-octadiene**

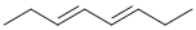
1,3-cyclopentadiene



***trans*-2,4-heptadiene**

CONJUGATED VS. NONCONJUGATED VS. CUMULATED DIENES

Conjugated dienes are two double bonds separated by a single bond

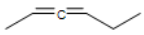


3,5-octadiene

Nonconjugated (Isolated) dienes are two double bonds are separated by more than one single bond.

2,5-heptadiene

Cumulated dienes (allenes) are two double bond connected to a carbon atom.



2,3-hexadiene

The reactivity of these molecules is substantially different from that of alkenes which have isolated C=C. These molecules are thus considered a different class of organic molecule. Conjugated dienes, especially butadiene, are very important materials in the production of rubber, and thus for the tires of our cars.

14.1: STABILITY OF CONJUGATED DIENES- MOLECULAR ORBITAL THEORY

OBJECTIVES

After completing this section, you should be able to

1. write a reaction sequence to show a convenient method for preparing a given conjugated diene from an alkene, allyl halide, alkyl dihalide or alcohol (diol).
2. identify the reagents needed to prepare a given diene from one of the starting materials listed in Objective 1, above.
3. compare the stabilities of conjugated and non-conjugated dienes, using evidence obtained from hydrogenation experiments.
4. discuss the bonding in a conjugated diene, such as 1,3-butadiene, in terms of the hybridization of the carbon atoms involved.
5. discuss the bonding in 1,3-butadiene in terms of the molecular orbital theory, and draw a molecular orbital for this and similar compounds.

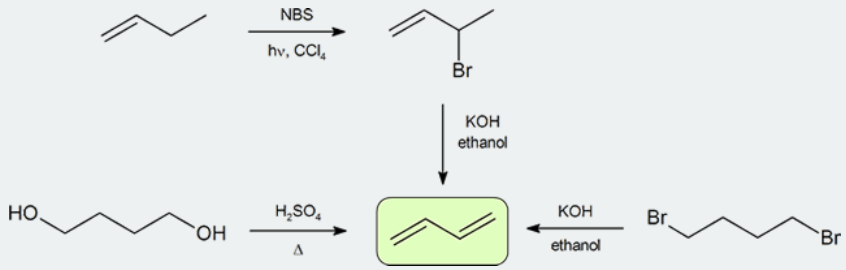
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- delocalized electrons
- node

STUDY NOTES

The two most frequent ways to synthesize conjugated dienes are dehydration of alcohols and dehydrohalogenation of organohalides, which were introduced in the preparation of alkenes (Section 8.1). The following scheme illustrates some of the routes to preparing a conjugated diene.



The formation of synthetic polymers from dienes such as 1,3-butadiene and isoprene is discussed in Section 14.6. Synthetic polymers are large molecules made up of smaller repeating units. You are probably somewhat familiar with a number of these polymers; for example, polyethylene, polypropylene, polystyrene and poly(vinyl chloride).

As the hydrogenation of 1,3-butadiene releases less than the predicted amount of energy, the energy content of 1,3-butadiene must be lower than we might have expected. In other words, 1,3-butadiene is more stable than its formula suggests.

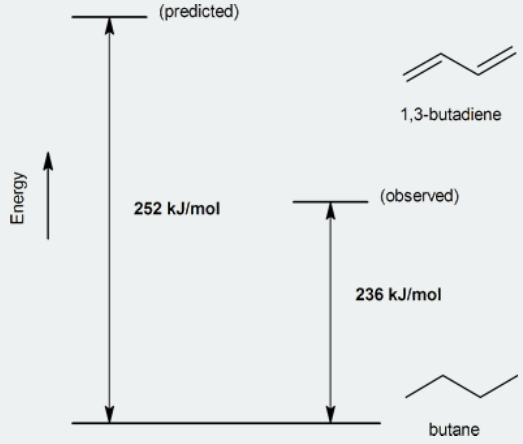


Figure 14.1: Energy diagram for the hydrogenation of 1,3-butadiene (not to scale).

Some university-level general chemistry courses do not introduce the subject of molecular orbitals. If you have taken such a course, or forgotten what is meant by the term "molecular orbital," combine a review of Section 1.11 with your study of this section.

CONJUGATED VS. NON-CONJUGATED DIENES

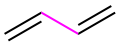
Dienes are compounds which contain two double bonds. These dienes can be non-conjugated (the two double bonds are separated by at least one sp^3 hybridized atom. Conjugated dienes have the two double bonds separated by a single bond. Conjugated dienes have properties and reactivity which are distinctly different than non-conjugated dienes. Determining if double bonds are conjugated represents an important skill in organic chemistry.

3,5-Octadiene
(Conjugated)

2,5-Octadiene
(Non-Conjugated)

1,3-Cyclohexadiene
(Conjugated)

1,4-Cyclohexadiene
(Non-Conjugated)

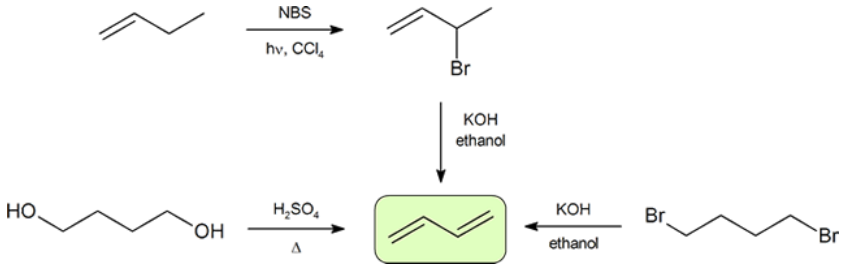


1,3-Butadiene
(Conjugated)

1,4-Pentadiene
(Non-Conjugated)

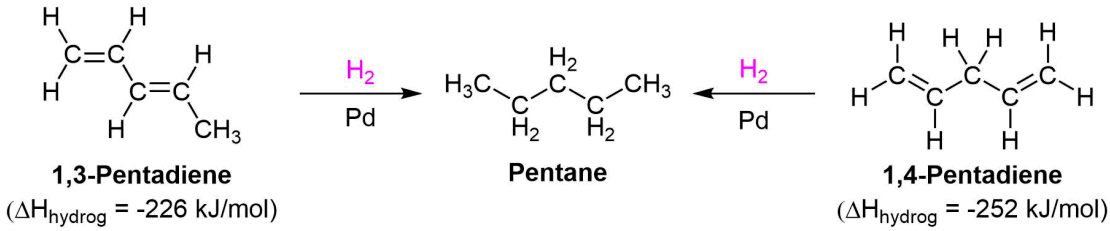
SYNTHESIS OF DIENES

Conjugated dienes can be prepared using many of the methods used for the preparation of alkenes previously discussed (**Sections 11-7, 11-8, 11-9, and 11-10**). A convenient method starts with the free radical halogenation of the allylic carbon of an alkene using NBS. The resulting halide can then be reacted with a strong base to result in E2 elimination and create a diene product. The compound, 1,3-butadiene, is the simplest conjugated diene and has an important use in the synthesis of polymers which will be discussed in Section 14.6. Many simple dienes, such as 1,3-butadiene and isoprene, can be prepared industrially by the double dehydration of alcohols and the double dehydrohalogenation of organohalides.

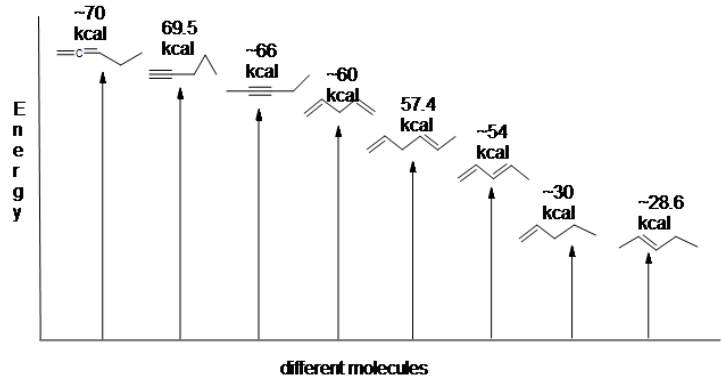


STABILITY OF CONJUGATED DIENES

Conjugated dienes are known to be more stable than non-conjugated dienes as shown by their experimentally determined heats of hydrogenation. In **Section 7-6**, it was shown that as alkenes become more stable, they contain less energy, and therefore release less heat during hydrogenation. Experiments have shown that conjugated dienes have a lower heat of hydrogenation (-226 kJ/mol) than non-conjugated dienes (-251 kJ/mol). Using the differences in heats of hydrogenation the stabilization energy in conjugated dienes can be estimate to be roughly 25 kJ/mol.

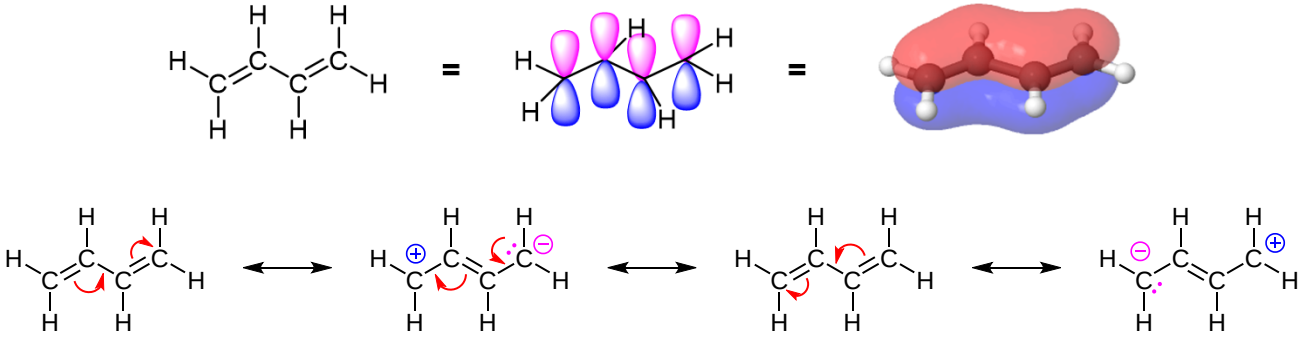


Here is an energy diagram comparing different types of bonds with their heats of hydrogenation to show relative stability of each molecule:

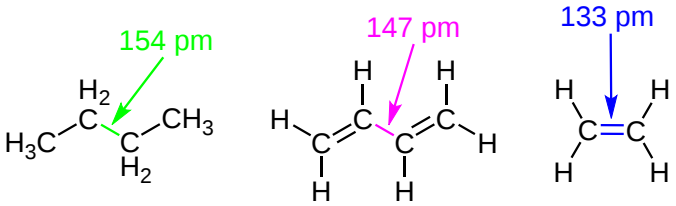


The stabilization of dienes by conjugation is less dramatic than the aromatic stabilization of benzene. Nevertheless, similar resonance and molecular orbital descriptions of conjugation may be written.

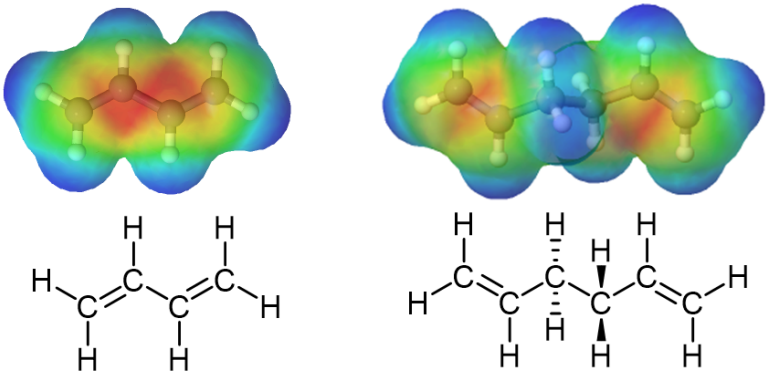
Each alkene carbon in 1,3 dienes are sp^2 hybridized and therefore have one unhybridized *p* orbital. The four *p* orbitals in 1,3-butadiene overlap to form a conjugated system which can be represented by the resonance forms shown below. This delocalization of charges stabilizes conjugated diene making them more stable than non-conjugated dienes.



Evidence of conjugation in 1,3 dienes is seen in the single bond being stronger and shorter (147 pm) than an ordinary alkane C-C bond (154 pm). The resonance hybrid of a 1,3-butadiene shows this bond to contain significant double bond character with its bond length being roughly the average of a single and double bond.



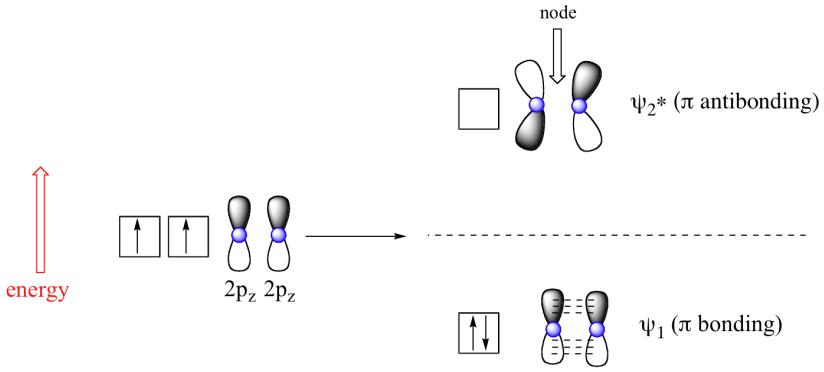
The delocalized electron density of a 1,3 diene can be seen when viewing an electrostatic potential maps. In conjugated dienes, it is observed that the pi electron density overlap (shown in red) is closer together and delocalized in conjugated dienes, while in non-conjugated dienes the pi electron density is located completely on the double bonds.



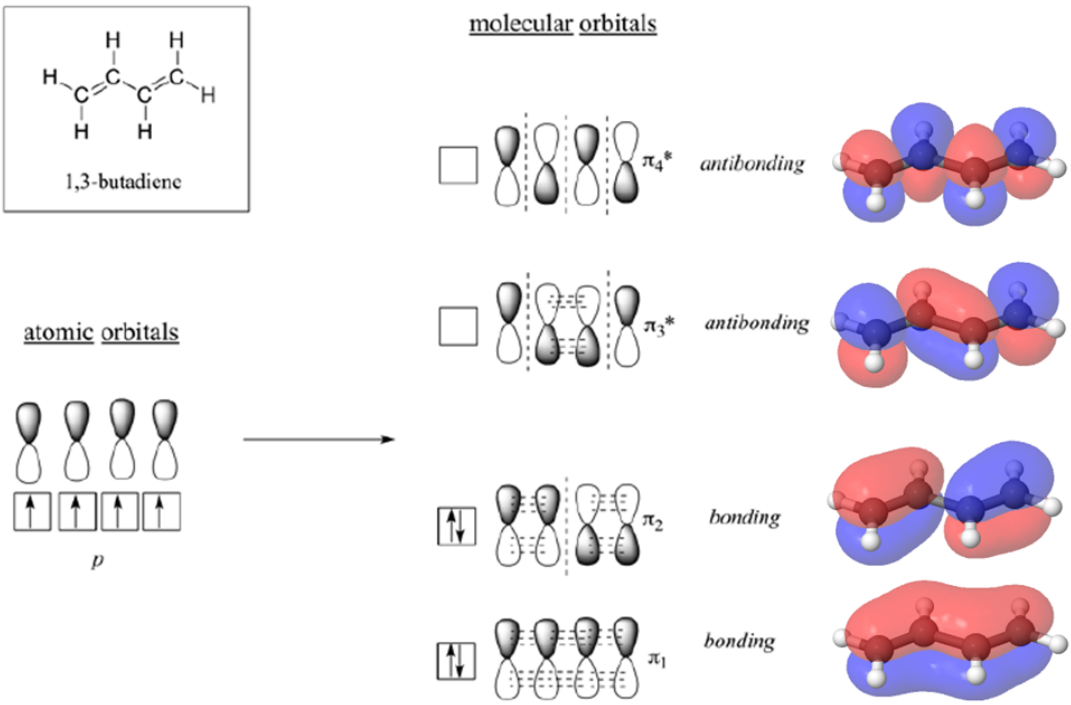
Conjugated **Non-Conjugated**

MOLECULAR ORBITALS OF 1,3 DIENES

According to MO theory discussed in section 1-11, when a double bond is non-conjugated, the two atomic $2p_z$ orbitals combine to form two **pi (π) molecular orbitals**, one a low-energy π bonding orbital and one a high-energy **π-star (π*) anti-bonding molecular orbital**. These are sometimes denoted, in MO diagrams like the one below, with the Greek letter psi (Ψ) instead of π. In the bonding Ψ_1 orbital, the two (+) lobes of the $2p_z$ orbitals interact constructively with each other, as do the two (-) lobes. Therefore, there is increased electron density between the nuclei in the molecular orbital – this is why it is a bonding orbital. In the higher-energy anti-bonding Ψ_2* orbital, the (+) lobes of one $2p_z$ orbital interacts destructively with the (-) lobe of the second $2p_z$ orbital, leading to a node between the two nuclei and overall repulsion. By the *aufbau* principle, the two electrons from the two atomic orbitals will be paired in the lower-energy $\Psi_1$orbital when the molecule is in the ground state.



With a conjugated diene, such as 1,3-butadiene, the four *2p* atomic orbitals combine to form four pi molecular orbitals of increasing energy. Two bonding pi orbitals and two anti-bonding pi* orbitals. The combination of four pi molecular orbitals allow for the formation of a bonding molecular orbital that is lower in energy than those created by an unconjugated alkene. The 4 pi electrons of 1,3-butadiene completely fill the bonding molecular orbitals giving is the additional stability associated with conjugated double bonds.



14.2: ELECTROPHILIC ADDITIONS TO CONJUGATED DIENES- ALLYLIC CARBOCATIONS

OBJECTIVES

After completing this section, you should be able to

1. write an equation for the addition of one or two mole equivalents of a halogen or a hydrogen halide to a nonconjugated diene.
2. write an equation for the addition of one or two mole equivalents of a halogen or a hydrogen halide to a conjugated diene.
3. write the mechanism for the addition of one mole equivalent of hydrogen halide to a conjugated diene, and hence account for the formation of 1,2- and 1,4-addition products.
4. explain the stability of allylic carbocations in terms of resonance.
5. draw the resonance contributors for a given allylic carbocation.
6. predict the products formed from the reaction of a given conjugated diene with one mole equivalent of halogen or hydrogen halide.
7. predict which of the possible 1,2- and 1,4-addition products is likely to predominate when one mole equivalent of a hydrogen halide is reacted with a given conjugated diene.
8. use the concept of carbocation stability to explain the ratio of the products obtained when a given conjugated diene is reacted with one mole equivalent of hydrogen halide.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

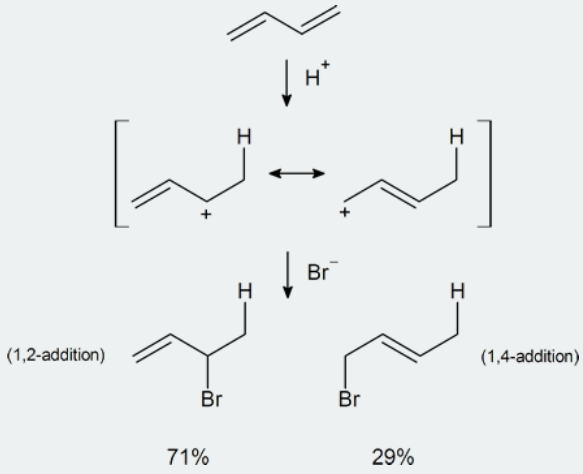
- 1,2-addition
- 1,4-addition

STUDY NOTES

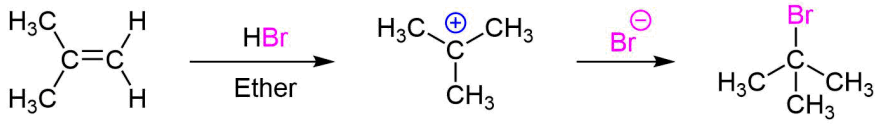
Notice that the numbers used in the expressions 1,2-addition and 1,4-addition do *not* refer to the positions of the carbon atoms in the diene molecule. Here, 1,2 indicates two neighbouring carbon atoms, while 1,4 indicates two carbon atoms which are separated in the carbon chain by two additional carbon atoms. Thus in 1,2- and 1,4-additions to 2,4-hexadiene, the additions actually occur at carbons 2 and 3, and 2 and 5, respectively.

The term “monoadduct” should be interpreted as meaning the product or products formed when one mole of reagent adds to one mole of substrate. In the objectives above, this process is referred to as the addition of one mole equivalent (or one mol equiv).

In Section 7.9 we saw that electrophilic addition to a simple alkene would follow Markovnikov’s rule, where the stability of the carbocation intermediate would increase: primary < secondary < tertiary. With conjugated dienes the allylic carbocation intermediately generated has different resonance forms. The following scheme represents the mechanism for the addition of HBr to 1,3-butadiene (at 0°C). Note the resonance contributors for the allylic carbocation intermediate and that the product resulting from the secondary cation is generated in higher yield than from the primary cation as you might expect from our discussions until now. However, in the next section you will see that the resulting product ratio can be drastically affected by a number of reaction conditions, including temperature.

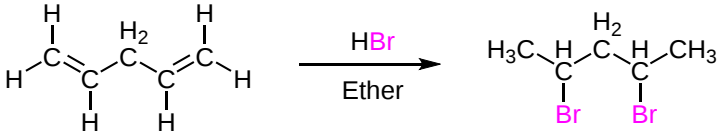


In Section 7.9 we saw that electrophilic addition to a simple alkene would follow Markovnikov's rule. Markovnikov's rule states that for the electrophilic addition of HX, the carbocation intermediate forms on the double bond carbon with the greatest number of alkyl substitutents. Because the stability of carbocation intermediates increases as it number of alky groups increases (primary < secondary < tertiary), this regioselectivity is provided by preferably forming a more stable carbocation intermediate during the reaction. During the electrophilic addition of HBr to 2-methylpropene, the more stable tertiary carbocation intermediate is preferably formed which yields the Markovnikov addition product 2-bromo-2-methylpropane. Formation of 1-bromo-2-methylpropane does not occur because it would require the formation of a less stable primary carbocation intermediate.



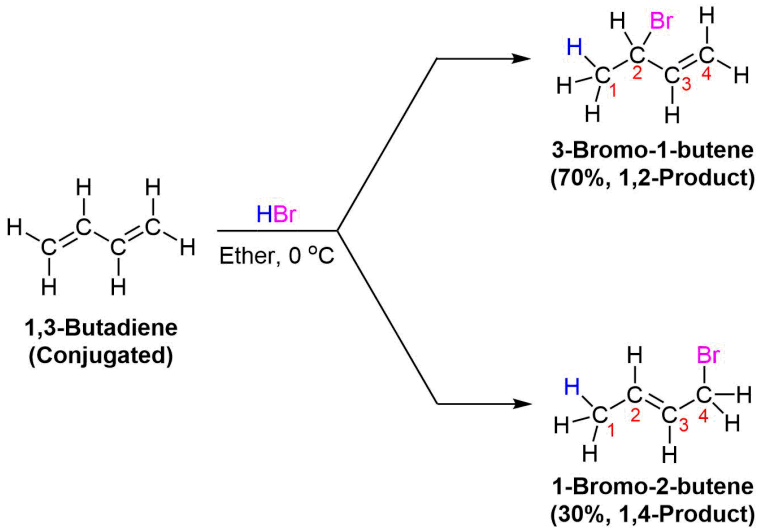
2-Methylpropene | **Tertiary Carbocation** | **2-Bromo-2-Methylpropane (Markovnikov addition product)**

When an electrophilic addition is performed on a non-conjugated diene, the double bonds react in much the same manner as individual alkenes. During the addition of two equivalents of HBr to 1,4-pentadiene, a non-conjugated diene, Markovnikov's rule is still followed producing 2,4-dibromopentane as the product.



1,4-Pentadiene (Non-conjugated) | **2,4-Dibromopentane (Markovnikov addition product)**

Conjugated dienes undergo the usual reactions of alkenes, such as catalytic hydrogenation, radical additions, and electrophilic additions more readily than most alkenes or dienes that have isolated double bonds. During the electrophilic addition of one equivalent of HX to a conjugated diene, the expected Markovnikov addition product is formed during a process called **1,2-addition**. In addition, an unexpected product is formed from **1,4-addition**, i.e. the halogen bonds at the terminal carbon atoms of a conjugated diene and the remaining double bond shifts to the 2,3-location. Note, the numbers (1 and 4) refer to which of the four carbons making up the conjugated diene the H and Br are bonded to in the products and are not used for the compounds IUPAC nomenclature. Although there are various methods for effecting the relative ratio of 1,2 and 1,4 addition products during the electrophilic addition to a conjugated diene, a mixture of these products is almost always produced. When one equivalent HBr undergoes electrophilic addition to 1,3-butadiene, 1,2 addition provides the expected Markovnikov product 3-bromo-1-butene in a 70% yield. This process is called a 1,2 addition because the hydrogen from HBr (labeled blue) bonds to the first carbon of the diene and the bromine from HBr bonds to the second carbon of the diene. The compound 1-bromo-2-butene is also produced in a 30% yield during the reaction as product of 1,4 addition. Here the hydrogen of HBr bonds to the first carbon of the diene and the Br bonds to the fourth carbon of the diene.



1,3-Butadiene (Conjugated)

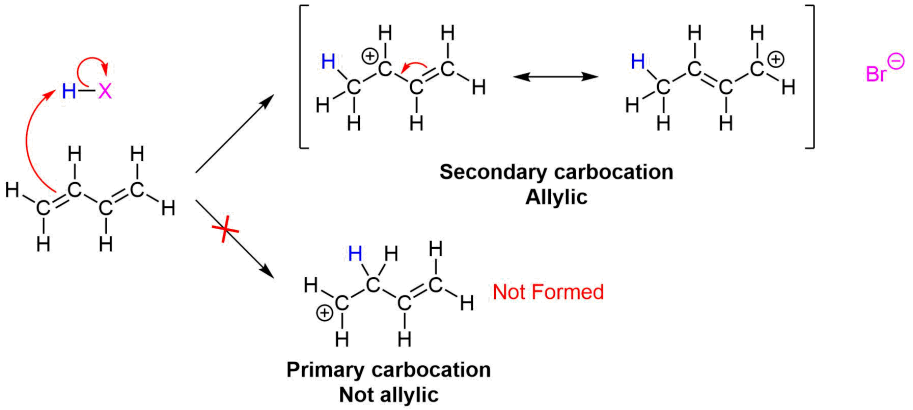
3-Bromo-1-butene (70%, 1,2-Product)

1-Bromo-2-butene (30%, 1,4-Product)

THE MECHANISM FOR ELECTROPHILIC ADDITION OF HBR TO A CONJUGATED DIENE

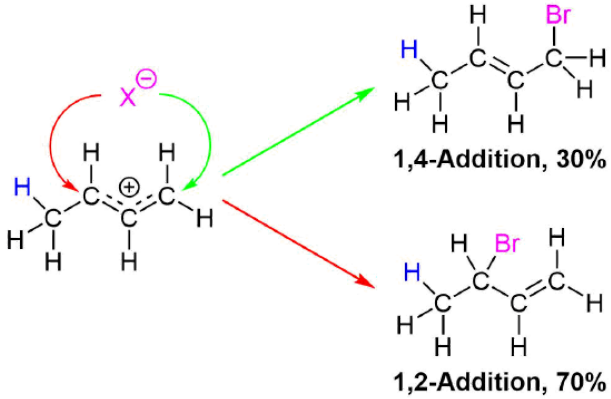
Regardless if the 1,2 or 1,4 addition product is formed, the first step of the mechanism is the protonation of one of the double bonds. In the same manner as the electrophilic addition of HX to an alkene, the protonation occurs regioselectively to give the more stable carbocation. In the case of a conjugated diene, the more stable cation is not only secondary, but also *allylic*, and therefore enjoys the stabilization created from the positive charge being distributed over two carbons by resonance. The resonance hybrid of the allylic carbocation intermediate can be depicted by two resonance forms (shown below) both of which have a full positive charge.

STEP 1)



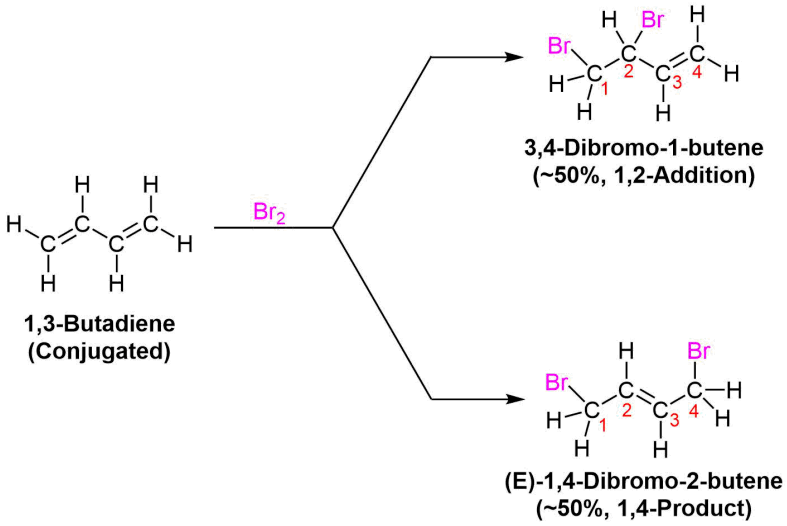
Step 2)

This allylic carbocation, more properly denoted as the resonance hybrid shown below, has two carbons which have significant positive charge. The halide ion can attack either carbon. Attacking the central carbon, adjacent to the site of protonation, leads to the the 1,2-addition product. Attacking the terminal carbon, distant from the site of protonation, leads to the 1,4 addition product.



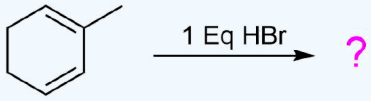
OTHER ELECTROPHILIC ADDITIONS

Formation of both 1,2- and 1,4-addition products occurs not only with hydrogen halides, but also with other electrophiles such as the halogens (X_2). The electrophilic 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 1,2 addition product) and 1,4-dibromo-2-butene (the 1,4 addition product) is obtained. The double bond of the 1,4 addition product is primarily formed as the (E) isomer.



WORKED EXAMPLE 14.2.1

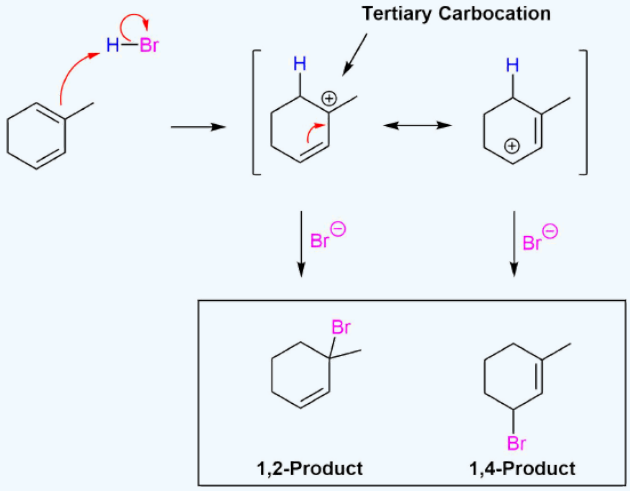
Give the expected products from the following reaction. Show both 1,2 and 1,4 addition products.



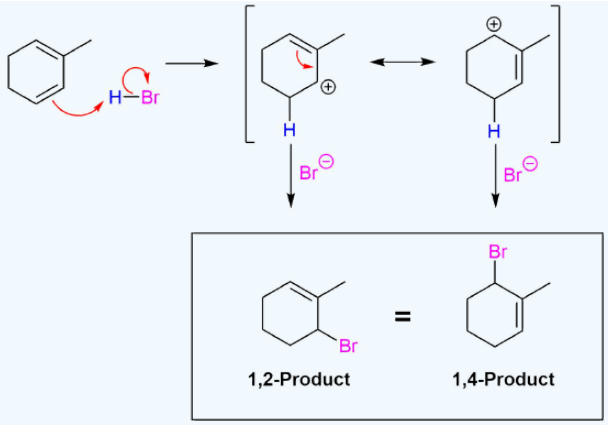
Solution

For this example the two double bonds in the diene are not equivalent and must be considered separately. Each double bond of the reactant has the possibility of forming a 1,2 and a 1,4 addition product so the reaction has the possibility of forming four product. Protonate each double bond separately and draw out the resonance forms of the allylic carbocation intermediate created. Then react each resonance form with Br- to create the two possible products. Repeat this process with the second double bond to create the four possible product. Lastly, look for symmetry in the products to see if any are same molecule. Also, consider the stability of each carbocation created during this process. The most stable carbocation will generally product the favored product of the reaction.

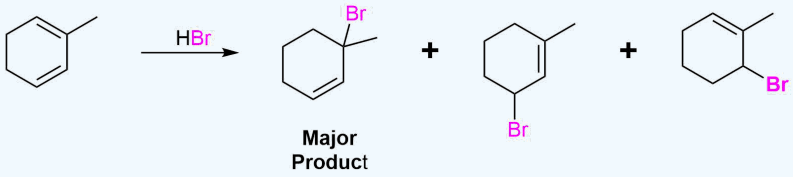
Addition to the first double bond creates a resonance form with a tertiary carbocation intermediate. Due to the stability of the tertiary carbocation this product will most likely go one to be the preferred product of this reaction.



Addition to the second double bond creates a symmetrical compound so only one product is formed.



Over the reaction proposed would be expected to form three products.

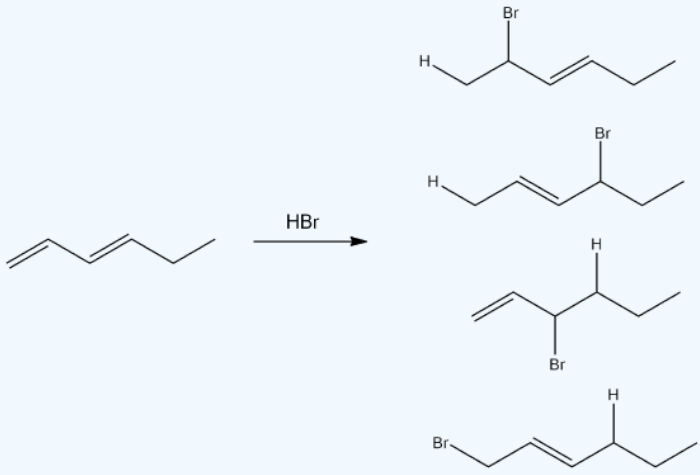


EXERCISE 14.2.1

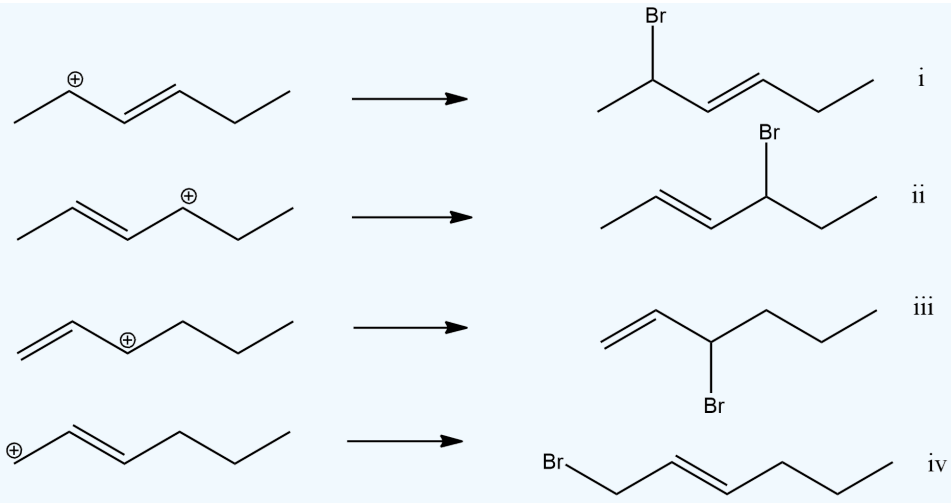
1. Give the 1,2 and the 1,4 products of the addition of one equivalent of HBr to 1,3-hexa-diene.
2. Look at the previous addition reaction of HBr with a diene. Consider the transition states, predict which of them would be the major products and which will be the minor.
3. Write out the products of 1,2 addition and 1,4- addition of HBr to 1,3-cyclohexadiene.
4. What is unusual about the products of 1,2- and 1,4- addition of HX to an unsubstituted cyclic 1,3-diene?
5. Write out the products of 1,2 addition and 1,4- addition of Br2 to 1,3-cyclohexadiene.

Answer

1)



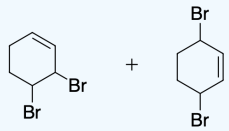
2) The products i-iii all show a secondary cation intermediate which is more stable than primary. Therefore those would be major products and the iv product would be the minor product.



3) The same product will result from 1,2 and 1,4 addition.

4) Addition of the HX to unsubstituted cycloalka-1,3-dienes in either 1,2- or 1,4- manner gives the same product because of symmetry.

5) Both 1,2 and 1,4 products will form.



14.3: KINETIC VS. THERMODYNAMIC CONTROL OF REACTIONS

OBJECTIVES

After completing this section, you should be able to

1. explain the difference between thermodynamic and kinetic control of a chemical reaction; for example, the reaction of a conjugated diene with one equivalent of hydrogen halide.
2. draw a reaction energy diagram for a reaction which can result in both a thermodynamically controlled product and a kinetically controlled product.
3. explain how reaction conditions can determine the product ratio in a reaction in which there is competition between thermodynamic and kinetic control.

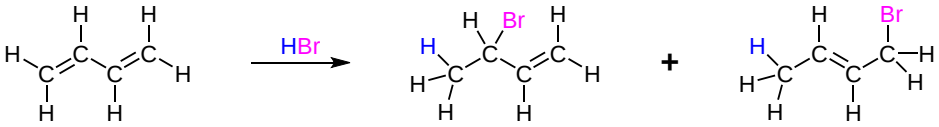
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- kinetic control
- thermodynamic control

Like non-conjugated dienes, conjugated dienes are subject to attack by electrophiles. In fact, conjugated dienes experience relatively greater kinetic reactivity when reacted with electrophiles than non-conjugated dienes do. The reaction mechanism is similar to other electrophilic addition reactions to alkenes (Section 7.9). During the electrophilic addition of HBr to a 1,3-butadiene, However, there are two possible outcomes once the carbocation intermediate is formed. The allyl carbocation is stabilized by resonance structures that vary in the position of the carbocation. This allows the bromide ion to add to either of these carbons resulting in the formation 1,2 and 1,4 addition products. When this reaction is run at a temperature of 0 ^{o}C or lower, the 1,2 addition product dominates. However, if the same reaction is run at 40 ^{o}C the 1,4 addition product dominates.

The reaction of one equivalent of hydrogen bromide with 1,3-butadiene yields different product ratios under different reaction conditions and is a classic example of the concept of **thermodynamic** versus **kinetic** control of a reaction.



1,3-Butadiene **1,2-Addition Product** **1,4-Addition Product**

At -80 ^{o}C:	80%	20%	**Kinetic Control**
At 0 ^{o}C:	70%	30%	**Kinetic Control**
At 40 ^{o}C:	15%	85%	**Thermodynamic Control**
At 60 ^{o}C:	10%	90%	**Thermodynamic Control**

At lower temperatures the formation of the 1,2 and 1,4 addition products are irreversible and thus do not reach equilibrium. When a reaction is irreversible the major product is determined by the relative reaction rates and not by thermodynamic stability. Of the two products, the formation of the 1,2 addition product has a higher rate of reaction and forms faster making it the major product. The reaction product which forms with a higher rate of reaction is called the **Kinetic Product** and when the kinetic product dominates, the reaction is said to be under **Kinetic Control**.

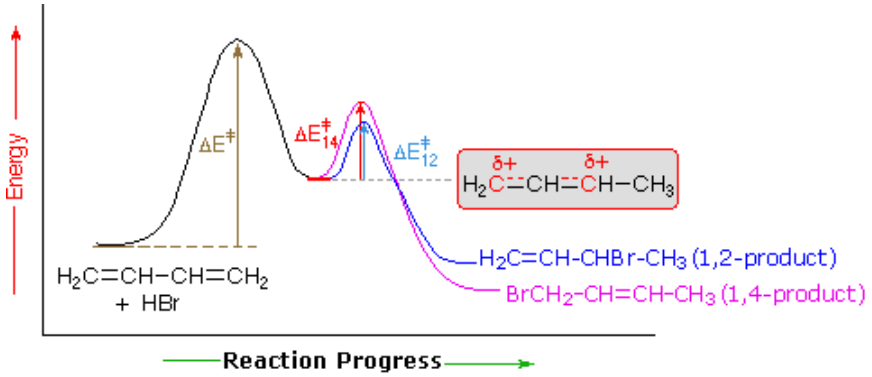
At higher temperatures the reaction to form both products becomes reversible and a reaction equilibrium is reached. When a reaction is reversible the major product is determined by thermodynamic stability. The 1,4 addition product is more stable and becomes the major product under these reaction conditions. The more stable product is called the **Thermodynamic Product** and when the thermodynamic product dominates, the reaction is said to be under **Thermodynamic Control**.

The 1,4 addition product is more stable because it has an internal, disubstituted double bond, and we know that as a general rule that the thermodynamic stability of an alkene increases with increasing substitution. So, when compared to the terminal, monosubstituted alkene of the 1,2 addition product, the 1,4 addition product is expected to be more stable.

> *A simple definition is that the kinetic product is the product that is formed faster, and the thermodynamic product is the product that is more stable. This is precisely what is happening here. The kinetic product is 3-bromobut-1-ene, and the thermodynamic product is 1-bromobut-2-ene (specifically, the trans isomer).*

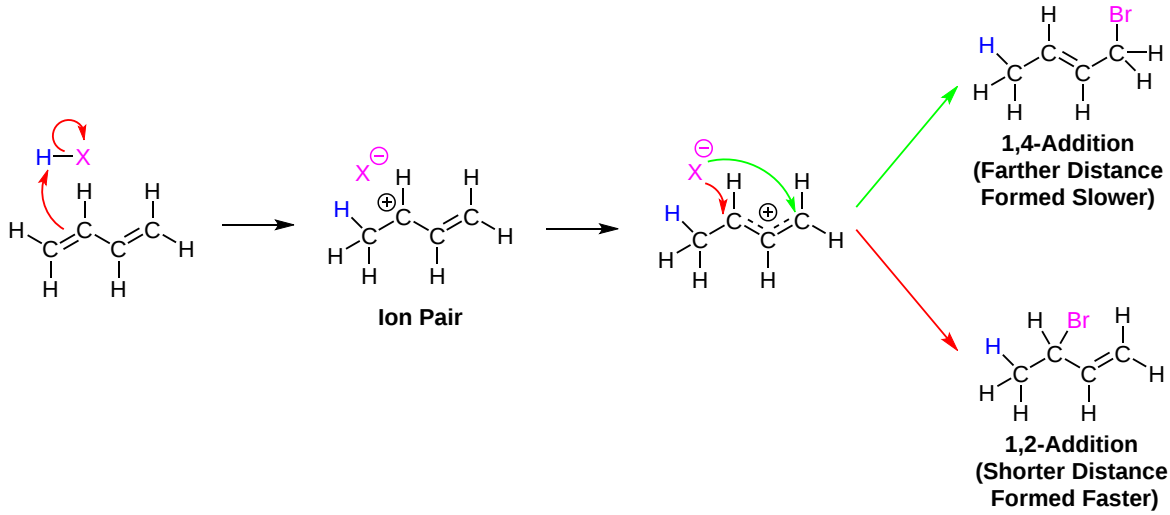
An explanation for the temperature influence is shown in the following energy diagram for the addition of HBr to 1,3-butadiene. The initial step in which a proton bonds to carbon #1 is the **rate determining step**, as indicated by the large activation energy (light gray arrow). The second faster step is the **product determining step**, and there are two reaction paths (colored blue for 1,2-addition and magenta for 1,4-addition).

At elevated temperatures, the products are more likely to have enough energy to overcome the reverse activation barrier for the second step allowing regeneration of the carbocation intermediate. Under these conditions, this step of the mechanism will be reversible and an equilibrium will be established. Since the system is no longer limited by temperature, the system will minimize its Gibbs free energy, which is the thermodynamic criterion for chemical equilibrium. This places the reaction under *thermodynamic control* and the most thermodynamically stable molecule, the 1,4 addition product, will be predominantly formed.



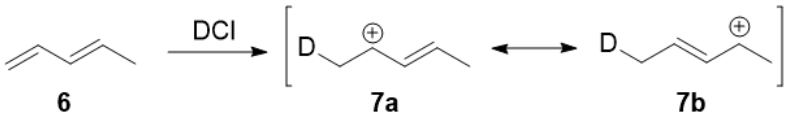
If the reaction temperature is kept sufficiently *low*, the products will not have enough energy to overcome the reverse activation barrier to regenerate the carbocation intermediate making this step of the mechanism effectively irreversible. This reaction is under kinetic control meaning the product which forms faster, the kinetic product, will predominate.

Of the two reaction pathways, the 1,2-addition has a smaller activation energy and would be expected to have a higher reaction rate than the 1,4-addition. The high reaction rate for 1,2-addition can be attributed to the formation of an ion pair during the reaction mechanism. This means that, after a double bond is protonated, the halide counterion remains in close proximity to the carbocation generated. Immediately following dissociation of HX, the chloride ion is going to be much closer to C−2 than it is to C−4, and therefore attack at C−2 is much faster. This ion pair mechanism is a pre-exponential constant effects that is attributed to the proximity and frequency of collision rather than a activation barrier effect.

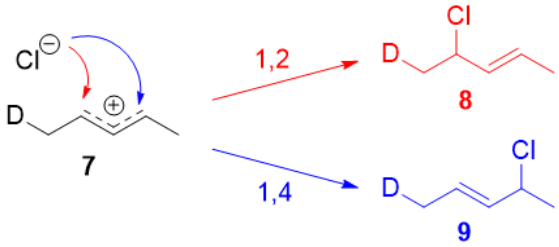


EXPERIMENTAL EVIDENCE FOR THE ION-PAIR MECHANISM

In 1979, Nordlander *et al.* carried out a similar investigation on the addition of DCl (deuterated hydrochloric acid) to a different substrate, 1,3-pentadiene. This experiment was ingenious, because it was designed to proceed via an almost symmetrical intermediate:



Resonance forms **7a** and **7b** are both allylic and secondary. There is a very minor difference in their stabilities arising from the different hyperconjugative ability of C-D *vs* C-H bonds, but in any case, it is not very large. Therefore, if we adopt the explanation in the previous section, one would expect there not to be any major *kinetic* pathway, and both 1,2- and 1,4-addition products (**8** and **9**) would theoretically be formed roughly equally.



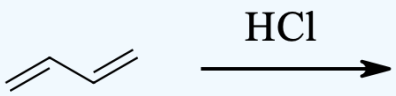
Instead, it was found that the 1,2-addition product was favored over the 1,4-addition product. For example, at -78ºC in the absence of solvent, there was a roughly (75:25) ratio of 1,2- to 1,4-addition products. Clearly, there is a factor that favors 1,2-addition that does not depend on the electrophilicity of the carbon being attacked! The authors attributed this effect to an *ion pair* mechanism. This means that, after the double bond is protonated (deuterated in this case), the chloride counterion remains in close proximity to the carbocation generated. Immediately following dissociation of DCl, the chloride ion is going to be much closer to *C-2* than it is to *C-4*, and therefore attack at *C-2* is much faster. In fact, normal electrophilic addition of HX to conjugated alkenes in polar solvents can also proceed via similar ion pair mechanisms. This is reflected by the greater proportion of *syn* addition products to such substrates.

? EXERCISE 14.3.1

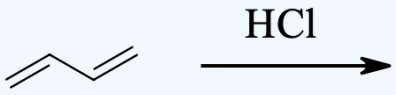
1) Why is the 1,4-addition product the thermodynamically more stable product?

2) Addition of 1 equivalent of bromine to 2,4-hexadiene at 0 degrees C gives 4,5-dibromo-2-hexene plus an isomer. What is the structure of that isomer?

3) The kinetically controlled product in the below reaction is:



4) For the reaction above, which product is the result of 1,4-addition?



5) What would be the major product of the addition of HBr to 2,3-dimethyl-1,3-cyclohexadiene under thermodynamic conditions?

6) Consider the reaction with 1,3-buta-diene reacting with HCl. Propose a mechanism for the reaction. Also, Predict why the 1,4 adduct is the major product in this reaction compared to the 1,2.

Answer

1) The 1,4- product is more thermodynamically stable because there are two alkyl groups on each side of the double bond and more substituted alkenes are more stable.

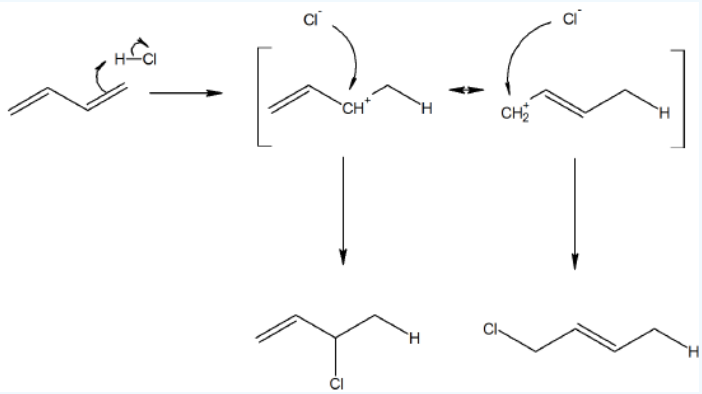
2) 2,5-Dibromo-3-hexene

3) 3-Chloro-1-butene

4) 1-Chloro-2-butene

5)

6)



Even though the cation would prefer to be in a secondary position in the transition state, the final product is less stable with a terminal alkene. Therefore the major product will be the 1,4 adduct.

14.4: THE DIELS-ALDER CYCLOADDITION REACTION

OBJECTIVES

After completing this section, you should be able to

1. write an equation to represent a typical Diels-Alder reaction.
2. draw the structure of the product formed when a given conjugated diene reacts with a given dienophile in a Diels-Alder reaction.
3. identify the diene and dienophile that must be used to prepare a given compound by a Diels-Alder reaction.
4. explain the general mechanism of the Diels-Alder reaction, without necessarily being able to describe it in detail.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- Diels-Alder cycloaddition
- pericyclic reaction

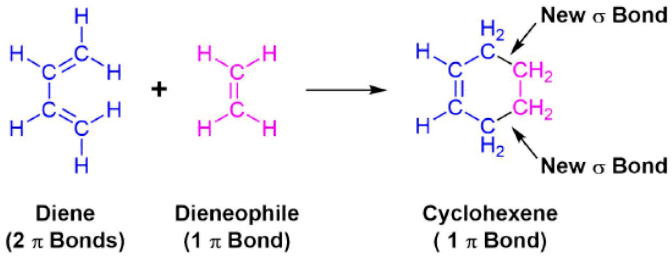
STUDY NOTES

The Diels-Alder reaction is an example of an organic chemical reaction which does not proceed by either a polar or a free radical pathway, but rather a pericyclic reaction.

Although we do not expect you to be able to provide a detailed account of the mechanism of this reaction, you should learn enough about the Diels-Alder reaction to fulfillthe objectives stated above. You will find it useful to contrast the mechanism of the Diels-Alder reaction with the polar and radical mechanisms studied earlier.

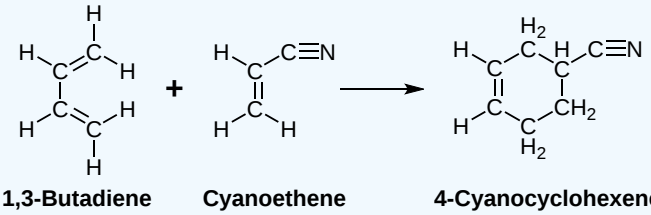
The unique character of conjugated dienes manifests itself dramatically in the **Diels-Alder Cycloaddition Reaction**. The Diels-Alder reaction is an important and widely used synthetic method for making six-membered rings. In the Diels-Alder reaction, a conjugated diene, simply referred to as the **diene**, reacts with a double or triple bond co-reactant called the **dienophile**, because it combines with (has an affinity for) the diene. During the reaction, two pi-bonds are converted to two sigma-bonds. The Diels-Alder cycloaddition is classified as a pericyclic process. Pericyclic reactions involve the redistribution of bonding electrons in a single step mechanism and will be discussed in greater detail in **Chapter 30**. In particular, the Diels-alder reaction is called a [4+2] process because the diene has four pi-electrons that shift position in the reaction and the dienophile has two.

GENERAL REACTION



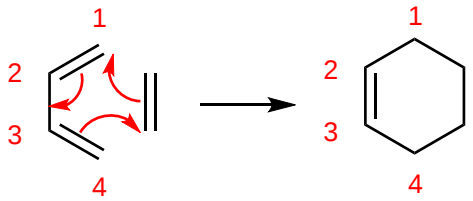
An example of the Diels-Alder reaction is the cycloaddition of 1,3-butadiene to cyanoethene (acrylonitrile) to form 4-cyanocyclohexene.

EXAMPLE 14.4.1

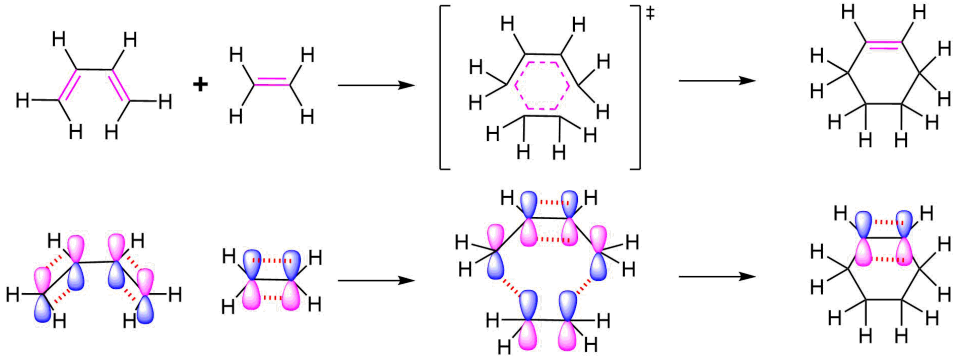


MECHANISM

All of the electron rearrangements of the Diels-Alder reaction take place once in a single mechanistic step. During this step carbons 1 and 4 of the diene and both alkene carbons of the dienophile, rehybridize from sp^2 to sp^3 and electrons rearrange to create two new sigma bonds in the cyclic product. Carbons 2 and 3 of the diene remain sp^2 hybridized and form a new pi bond in the product.

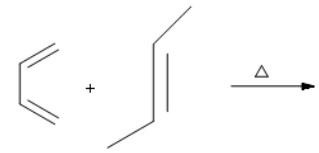


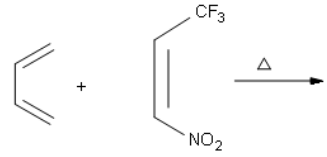
The mechanism occurs through a cyclic transition state in which there is head-on overlap of two p orbitals on carbons 1 and 4 of the diene with the two p orbitals from the alkene of the dienophile to form two new sigma bonds in the cyclohexene product. The remaining two p orbitals from the diene overlap to form the new pi bond.

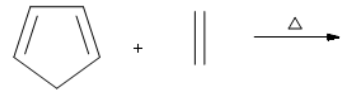


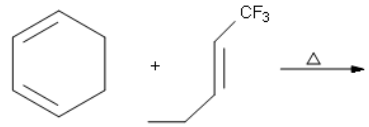
PROBLEMS

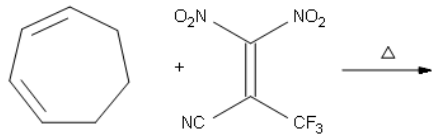
1. 

2. 

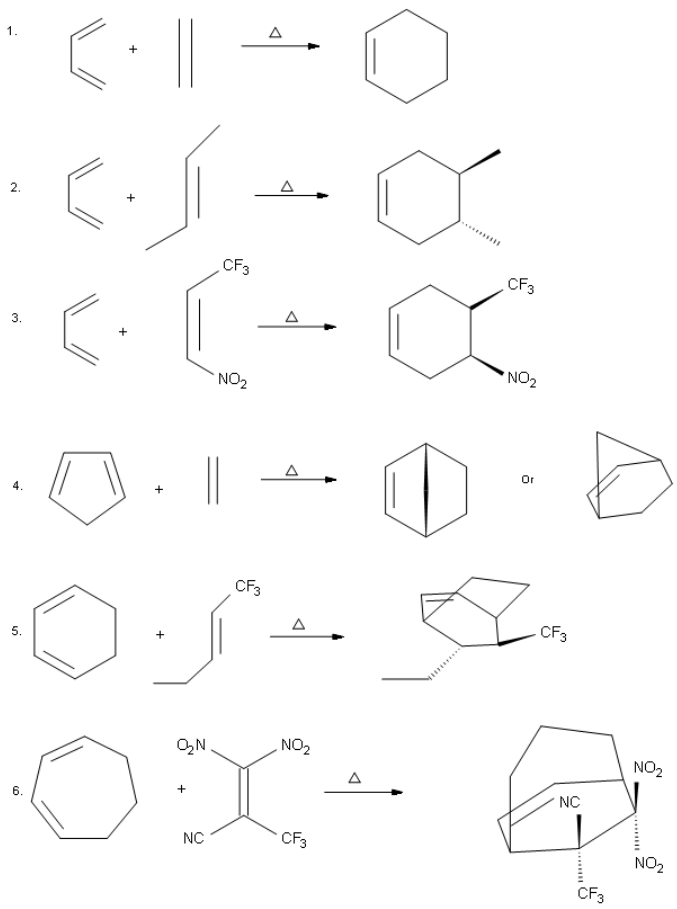
3. 

4. 

5. 

6. 

ANSWERS



14.5: CHARACTERISTICS OF THE DIELS-ALDER REACTION

OBJECTIVES

After completing this section, you should be able to

1. determine whether or not a given compound would behave as a reactive dienophile in a Diels-Alder reaction.
2. predict the stereochemistry of the product obtained from the reaction of a given diene with a given dienophile.
3. recognize that in order to undergo a Diels-Alder reaction, a diene must be able to assume ans-cis geometry, and determine whether or not a given diene can assume this geometry.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- dienophile
- dimerization

STUDY NOTES

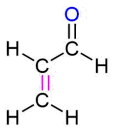
Make sure that you understand that the *s*-cis and *s*-trans forms of a diene such as 1,3-butadiene are conformers, not isomers. Note that some textbooks can confuse the issue further by referring to a compound such as (2Z, 4Z)-hexadiene as cis, cis-2,4-hexadiene, and saying that the most stable form of this compound is its *s*-trans conformer!

In fulfilling Objective 2, above, you must recognize that the Diels-Alder reaction is stereospecific.

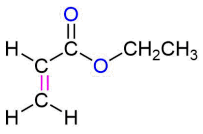
Finally, note reaction **B** in the reading shows 1,3-cyclopentadiene reacting with another molecule of 1,3-cyclopentadiene. When the same compound acts as both diene and dienophile in a Diels-Alder reaction to couple it is a dimerization.

THE DIENOPHILE

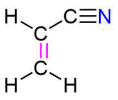
In general, Diels-Alder reactions proceed fastest with electron-withdrawing groups on the dienophile (diene lover). Ethylene reacts slowly while **propenal, ethyl propenoate, and other molecules shown below** are highly reactive in a Diels-Alder reaction.



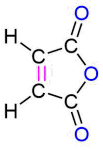
Prepenal (Acrolein)



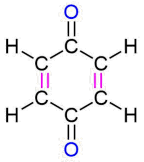
Ethyl propenoate (Ethyl acrylate)



Propenenitrile (Acrylonitrile)

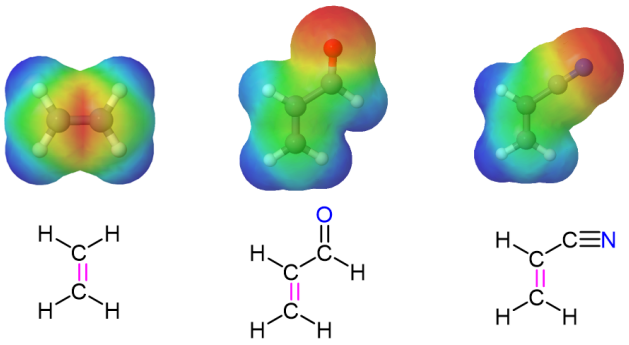


Maleic anhydride



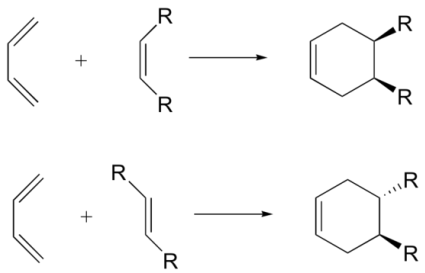
Benzoquinone

In much the same manner as electron-withdrawing substituents on a benzene ring, these are typically a double or triple bond in conjugation with the double bond in the dienophile. A resonance form can be drawn which places a positive charge in the dienophile double bond. This results in the double bond being less electron rich (greater electron density shown in Red/Orange) than ethylene. Electrostatic potential maps show that the electron-withdrawing groups pull electron density away from the double bond.

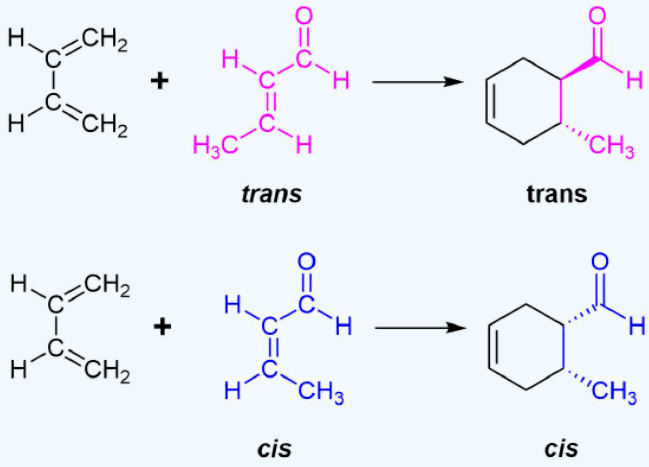


STEREOCHEMISTRY OF DIELS-ALDER (DIENOPHILE)

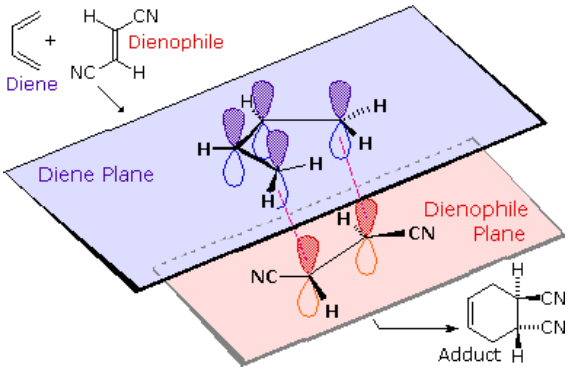
The Diels-Alder reaction is enormously useful for synthetic organic chemists, not only because ring-forming reactions are useful in general but also because in many cases multiple new stereocenters are formed, and the reaction is inherently stereospecific. During a Diels-Alder reaction the stereochemistry of the dienophile is retained in the product. A *cis* dienophile will generate a cyclohexene ring with *cis (syn)* substitution on the two carbons from the dienophile. Likewise a *trans* dienophile will generate a cyclohexene ring with *trans (anti)* substitution on these two carbon.



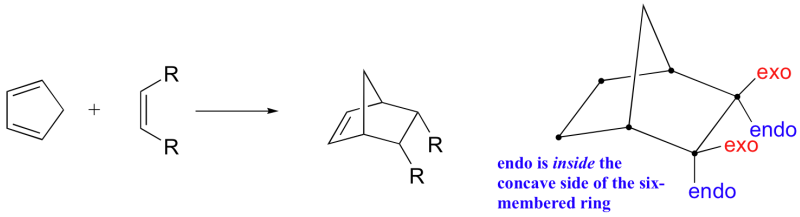
EXAMPLE 14.5.1



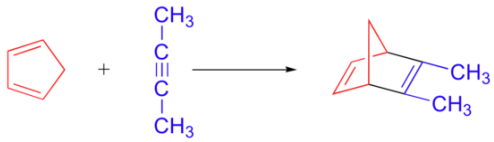
The retention of stereochemistry is due to the planar nature of both reactants and that the forming process is **suprafacial** (i.e. to or from the same face of each plane). This stereospecificity also confirms the concerted nature of the Diels-Alder mechanism. The drawing below illustrates this fact 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.



Another facet of the stereochemical retention of the dienophile is that only the endo product, rather than the alternative exo product, is formed. The words *endo* and *exo* are used to indicate relative stereochemistry when referring to bicyclic structures like substituted norbornanes. 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. Diels-Alder reactions with cyclic dienes favor the formation of bicyclic structures in which substituents are in the **endo position**. Preference of the endo position is also a facet of the suprafacial nature of the Diels-Alder reaction. The orbital overlap required for the reaction is greater when the dienophile lies directly underneath the diene.

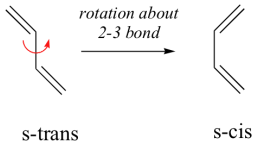


Alkynes can also serve as dienophiles in Diels-Alder reactions:

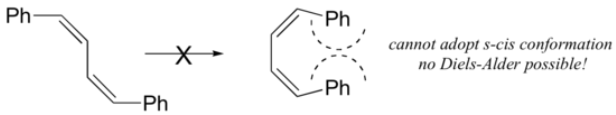


THE DIENE

In general, Diels-Alder reactions proceed fastest with electron-donating groups on the diene (eg. alkyl groups). The Diels-Alder reaction is a single step process, so the diene component must adopt an s-cis conformation 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.



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.

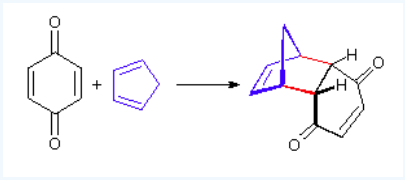


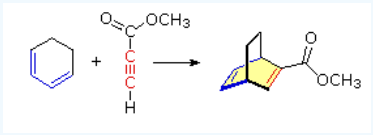
Cyclic dienes, on the other hand, are 'locked' in the s-cis conformation, and are especially reactive. The result of a Diels-Alder reaction involving a cyclic diene is a **bicyclic** structure:

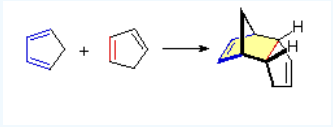
STEREOCHEMISTRY OF DIELS-ALDER (DIENE)

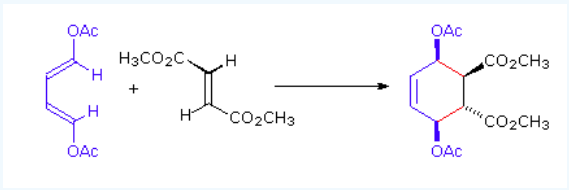
The 1 and 4 Carbons in the diene have the possibility of forming two new stereocenters in the cyclohexene product. Similarly to the effects of dienophile stereochemistry, the positioning of substituents on the 1 and 4 carbons in the diene determine the stereochemistry in the product. The diene substituents can be thought of as being either cis (both facing in or both facing out) or trans and the stereochemistry is retained to form a cis or trans cyclohexene product.

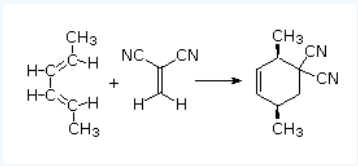
EXAMPLES 14.5.1

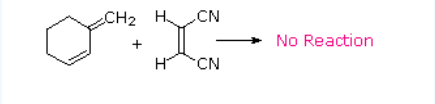








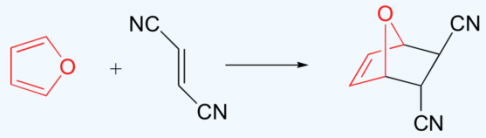




THE ESSENTIAL CHARACTERISTICS OF THE DIELS-ALDER CYCLOADDITION REACTION:

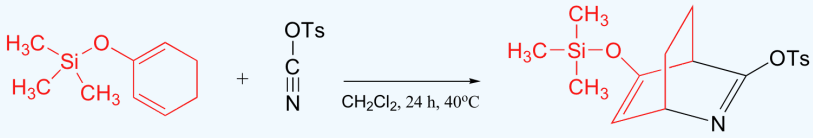
i. The reaction always creates a new six-membered ring.
ii. The diene component must be able to assume an s-cis conformation.
iii. Electron withdrawing groups on the dienophile facilitate reaction.
iv. Electron donating groups on the diene facilitate reaction.
v. Steric hindrance at the bonding sites may inhibit or prevent reaction.
vi. The reaction is stereospecific with respect to substituent configuration in both the dienophile and the diene.

EXAMPLES 14.5.2



J. Med. Chem. **2008,** *51*, 424 link

Org. Lett. **2001,** *3*, 1559 link

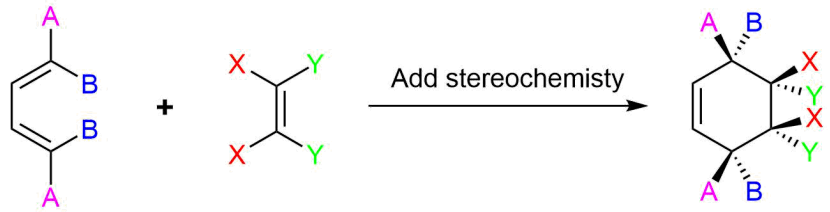


J. Org. Chem. **2003,** *68*, 8256 link

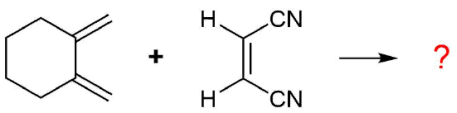
PREDICTING THE PRODUCT OF A DIELS-ALDER REACTION

Start by rotating the diene until it is in the s-cis conformation then point it towards the double bond of the dienophile. Remove the double bonds present in the diene and dieneophile. Connect carbons 1 and 4 of the the diene to a carbon in the dienophile double bond using a sigma bond to create a six-membered ring. Create a double bond between carbons 2 and 3 of diene.

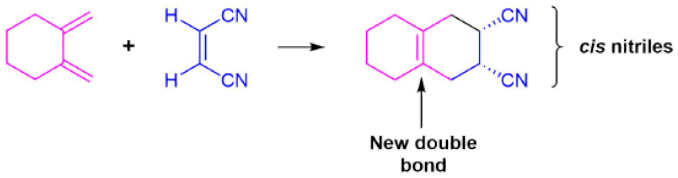
Determine if any substituents attached to either the double bond of the dieneophile or carbons 1 and 4 of the diene have a *cis*/*trans* conformation. If so make sure the substituents have the same configuration in the cycloalkene product.



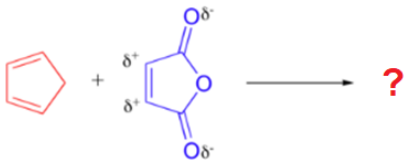
Predict the product of the following reaction:



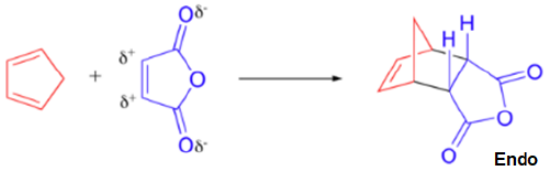
The diene is locked into an s-cis configuration which will promote the reaction. The ring portion of the diene will act as electron donating groups which will also promote the reaction. Because the diene already contained a ring the product will be bicyclic. The dienophile has two nitriles attached to it both of which are electron withdrawing. Since the two nitriles in the dieneophile are *cis* to each other the the two nitriles will be cis to each other in the product.



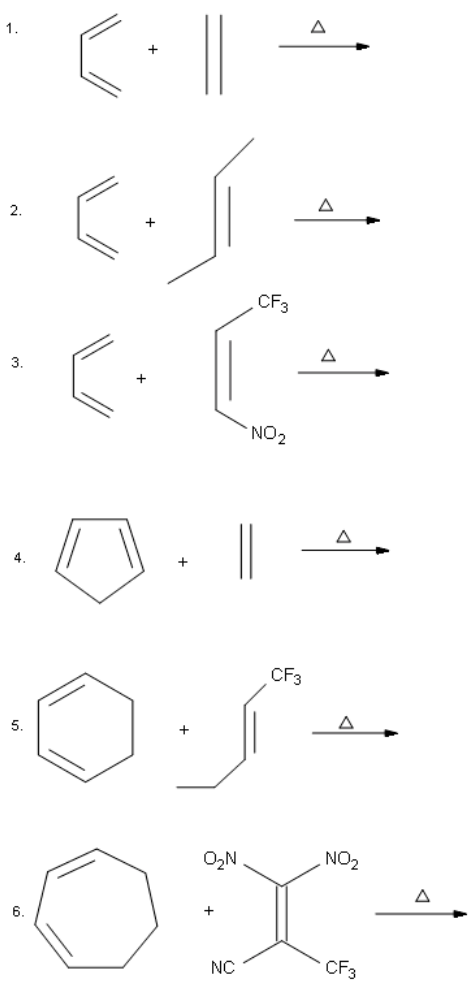
Predict the product of the following reaction:



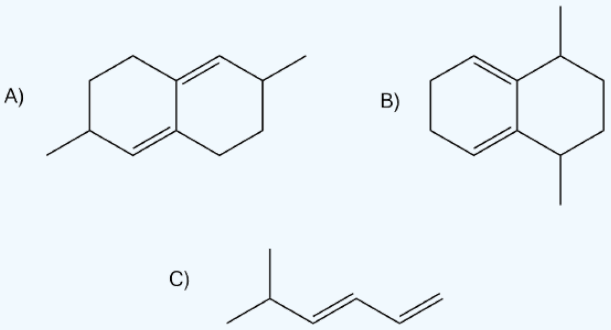
A particularly rapid Diels-Alder reaction takes place between cyclopentadiene and maleic anhydride. Cyclopentadiene is held in the required s-cis configuration so it will make a good diene for a Diels-Alder reaction. Maleic anhydride is also a very good dienophile, because the electron-withdrawing effect 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. Since it is part of a ring, the double bond of maleic anhydride is in a cis configuration so the cyclohexene ring will also have a cis configuration. Lastly, the product will prefer the endo position.



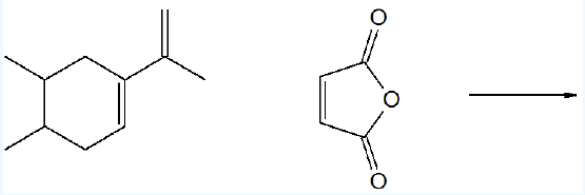
? EXERCISE 14.5.1



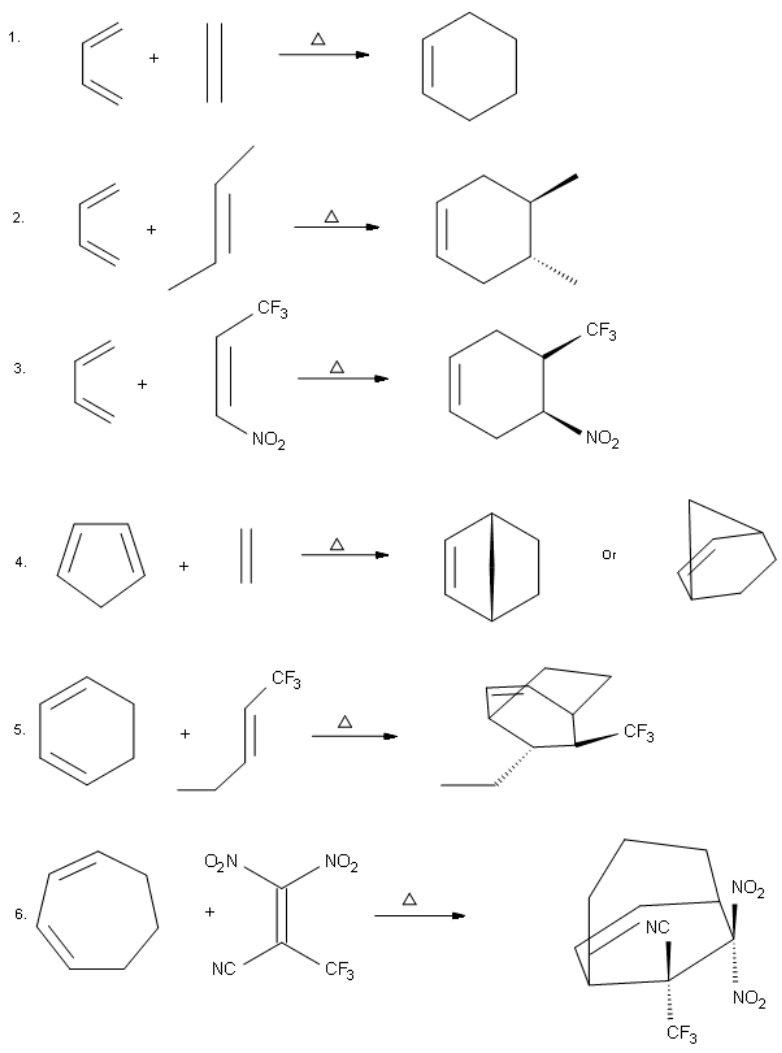
7) Of the following dienes, which are S-trans and which are s-cis? Of those that are s-trans, are they able to rotate to become s-cis?



8) Predict the product of the following reaction.



Answer



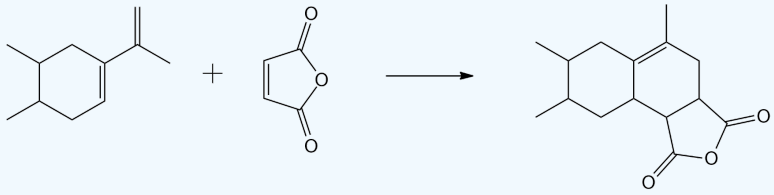
7)

A) s-trans, unable to rotate to become s-cis

B) s-cis

C) s-trans, can rotate to become s-cis.

8)



14.6: DIENE POLYMERS- NATURAL AND SYNTHETIC RUBBERS

OBJECTIVES

After completing this section, you should be able to

1. show that the polymerization of a diene, such as 1,3-butadiene or isoprene (2-methyl-1,3-butadiene), can result in the formation of either a cis or trans polymer.
2. draw the structure of natural rubber.
3. explain, briefly, the process of vulcanization.

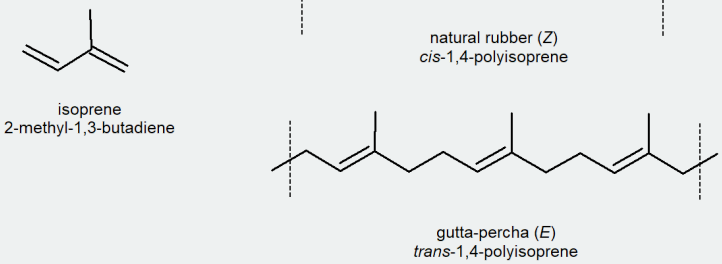
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- cross-link
- vulcanization

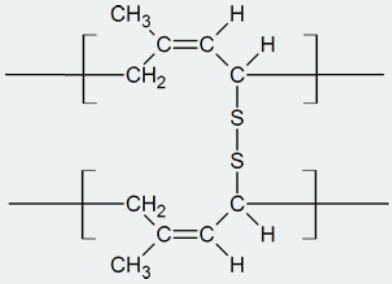
STUDY NOTES

Natural rubber is formed from the isoprene monomer and has *Z* stereochemistry. The *E* polymer gutta-percha also occurs naturally, but is more brittle than rubber. Uses of this thermoplastic include dentistry, electrical insulators and the covering on golf balls.



Before 1839, the uses of natural rubber were somewhat limited. It became sticky in summer, hardened and cracked in winter, and was susceptible to attack by a variety of solvents. Charles Goodyear became interested in rubber in 1831, and bought the Eagle India Rubber Company of Woburn, Massachusetts, in 1838. In January of 1839, Goodyear accidentally placed a sample of rubber that had been mixed with sulfur and lead(II) oxide on a hot stove; the result was a product similar to charred leather, which did not melt below 138°C. Goodyear was granted a U.S. patent for his process (called vulcanization) in June of 1844. The story of vulcanization is an example of how major scientific and technological advances are often brought about as a result of an accidental discovery.

Notice that in the vulcanization process, the sulfur bridges are attached to allylic carbon atoms which connect the long *Z* polymer chains of rubber.



Vulcanized rubber

The amount of sulfur used in the vulcanization process will depend on the rigidity required in the product. For example, about 5% sulfur is used when producing rubber for rubber bands; about 30% sulfur is used when making rubber for use in battery casings. There are several characteristics of dienes and rubbers that you should recognize. First, be aware of the similarity between the polymerization of a diene and the 1,4-addition reactions of dienes. Second, recognize the similarity between a vulcanized rubber and a peptide

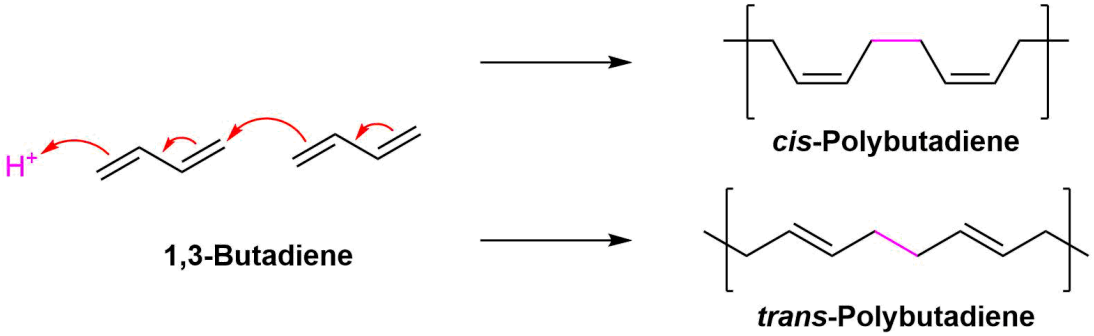
containing cysteine cross-links. Third, be aware that as natural rubber contains double bonds, it will display some of the properties of simple alkenes.

The 1,4 polymerization of 1,3-butadiene shown in the reading produces the *trans* form of polybutadiene. However, it should be noted that the *cis* form shown here can also be formed.

cis- polbutadiene

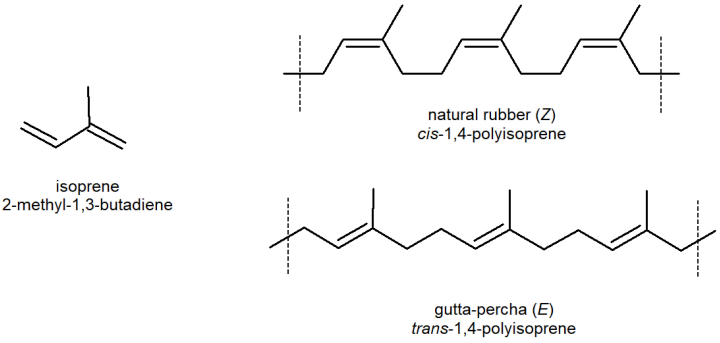
POLYMERIZATION OF 1,3-BUTADIENE

Conjugated dienes can be polymerized much like alkenes **(**Section 8-10**)** to form important compounds like rubber. Diene polymers are more structurally complex and have the possibility of forming different isomers. The polymerization of conjugated dienes are commonly initiated by ether a radical or an acid. Interactions between double bonds on multiple chains leads to cross-linkage which creates elasticity within the compound. The polymerization takes place by a type of 1,4 addition to 1,3-butadiene which leads to the possibility of forming cis (*Z*) or trans (*E*) double bonds in the polymer product.

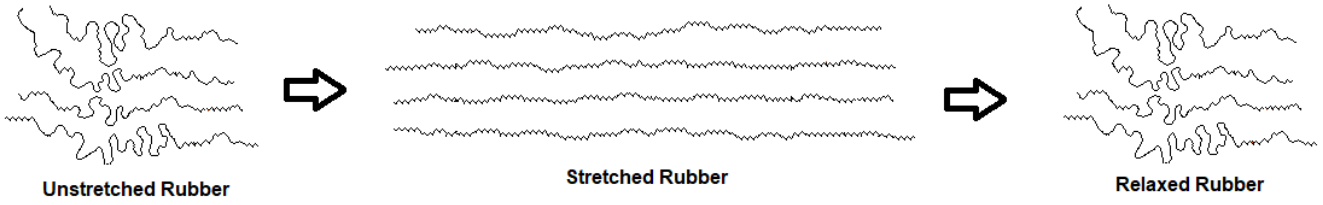


NATURAL RUBBER

Rubber is undoubtedly the best known and most widely used compound of this kind. Natural rubber is an addition polymer that is obtained as a milky white colloidal suspension known as latex with the major source being a tropical rubber tree (*Hevea brasiliensis*). Natural rubber is from the monomer isoprene (2-methyl-1,3-butadiene), which is a conjugated diene hydrocarbon as mentioned above. The double bonds in rubber all have a Z-configuration, which causes this macromolecule to adopt a kinked or coiled conformation. This is reflected in the physical properties of rubber. Despite its high molecular weight (about one million), crude latex rubber is a soft, sticky, elastic substance. Chemical modification of this material is normal for commercial applications. Gutta-percha (structure below) is a naturally occurring E-isomer of rubber. Here the hydrocarbon chains adopt a uniform zig-zag or rod like conformation, which produces a more rigid and tough substance. Uses of gutta-percha include electrical insulation and the covering of golf balls.

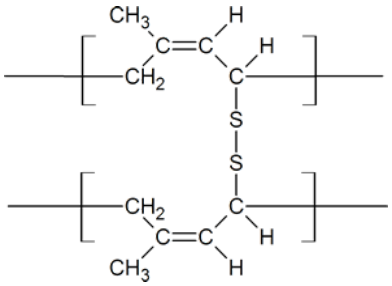


Due to rubber being an amorphous polymer, its coiled polymer chains can be straightened by stretching. The more highly-ordered chains in the stretched conformation are entropically unstable and return to their original coiled state when allowed to relax.

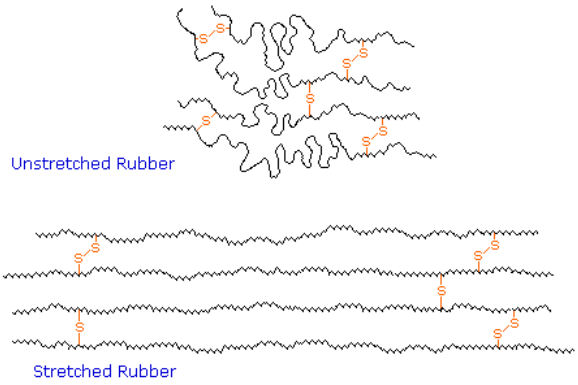


VULCANIZATION

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. Sulfur vulcanization is a chemical process for converting natural rubber or related polymers into more durable materials by heating them with sulfur or other equivalent curatives. Sulfur forms cross-links (bridges) between sections of polymer chains which results in increased rigidity and durability, as well as other changes in the mechanical and electronic properties of the material. A vast array of products are made with vulcanized rubber, including tires, shoe soles, hoses, and conveyor belts.



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 section of amorphous rubber cross-linked with sulfur by the vulcanization process.



SYNTHETIC RUBBER

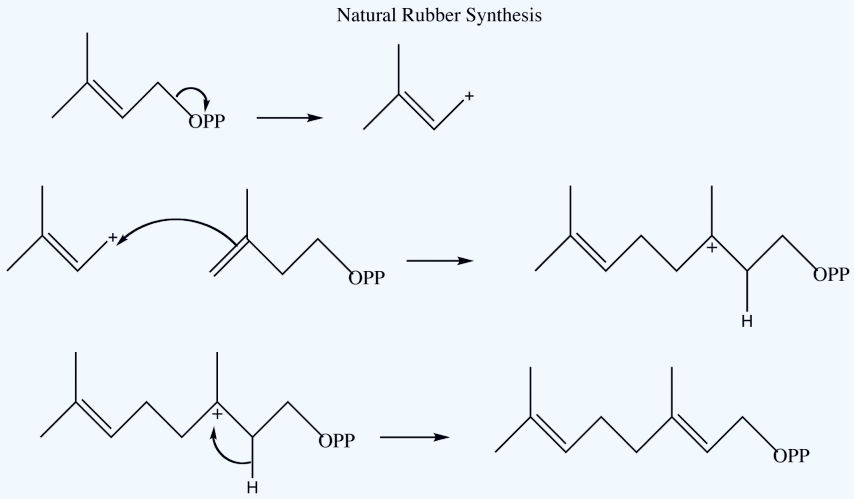
Neoprene (also **polychloroprene** or **pc-rubber**) is a family of synthetic rubbers that are produced by polymerization of 2-chloro-1,3-butadiene (chloroprene). Neoprene exhibits good chemical stability and maintains flexibility over a wide temperature range. Neoprene is sold either as solid rubber or in latex form and is used in a wide variety of applications, such as laptop sleeves, orthopaedic braces (wrist, knee, etc.), electrical insulation, liquid and sheet applied elastomeric membranes or flashings, and automotive fan belts.

EXERCISE 14.6.1

a. 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
b. Draw a segment for the polymer that may be made from 2-*tert*-butyl-1,3-butadiene.
c. Propose the mechanism for the acid catalyzed polymerization of 2-methyl-1,3-butadiene.

Answer

1)



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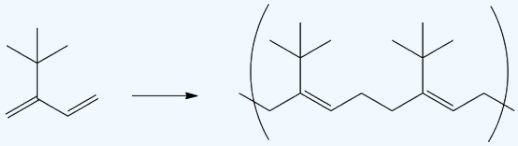
2)



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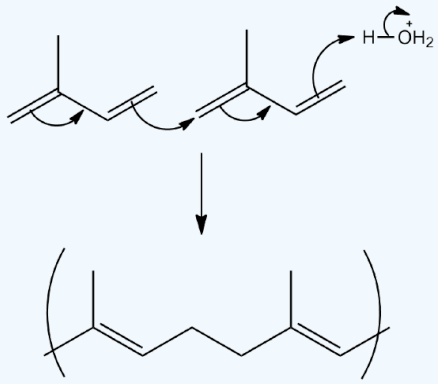


14.7: STRUCTURE DETERMINATION IN CONJUGATED SYSTEMS - ULTRAVIOLET SPECTROSCOPY

OBJECTIVES

After completing this section, you should be able to

1. identify the ultraviolet region of the electromagnetic spectrum which is of most use to organic chemists.
2. interpret the ultraviolet spectrum of 1,3-butadiene in terms of the molecular orbitals involved.
3. describe in general terms how the ultraviolet spectrum of a compound differs from its infrared and NMR spectra.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- ultraviolet (UV) spectroscopy
- Molar absorptivity

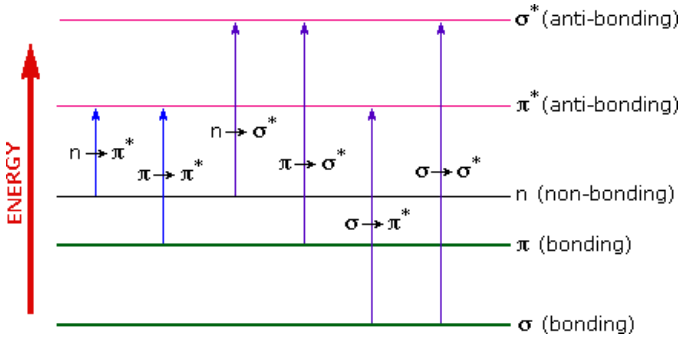
STUDY NOTES

Ultraviolet spectroscopy provides much less information about the structure of molecules than do the spectroscopic techniques studied earlier (infrared spectroscopy, mass spectroscopy, and NMR spectroscopy). Thus, your study of this technique will be restricted to a brief overview. You should, however, note that for an organic chemist, the most useful ultraviolet region of the electromagnetic spectrum is that in which the radiation has a wavelength of between 200 and 400 nm.

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. Ultraviolet-visible absorption spectroscopy provides much less information about the structure of molecules than do the spectroscopic techniques studied earlier (infrared spectroscopy, mass spectroscopy, and NMR spectroscopy) and mainly provides information about conjugated pi systems. For an organic chemist the most useful ultraviolet region of the electromagnetic spectrum involves radiation with a wavelength between 200 and 400 nm. UV/Vis absorption spectra also involve radiation from the visible region of the electromagnetic spectrum with wavelengths between 400 and 800 nm.

A diagram highlighting the various kinds of electronic excitation that may occur in organic molecules is shown below. Of the six transitions outlined, only the two lowest energy ones, n to pi* and pi to pi* (colored blue) are achieved by the energies available in the 200 to 800 nm range of a UV/VIs spectrum. These energies are sufficient to promote or excite a molecular electron to a higher energy orbital in many conjugated compounds.

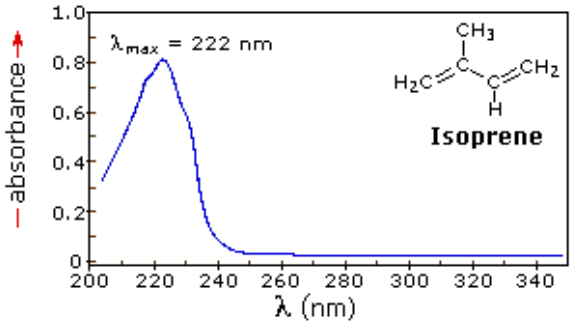


When sample molecules are exposed to light having an energy that matches a possible electronic transition within the molecule, some of the light energy will be absorbed as the electron is promoted to a higher energy orbital. A UV/Vis spectrometer records the wavelengths at which absorption occurs, together with the degree of absorption at each wavelength. A**bsorbance**, abbreviated 'A', is a unitless number which contains the same information as the 'percent transmittance' number used in IR spectroscopy. To calculate absorbance at a given wavelength, the computer in the spectrophotometer simply takes the intensity of light at that wavelength *before* it passes through the sample (I_0), divides this value by the intensity of the same wavelength *after* it passes through the sample (I), then takes the $\log_{10}$ of that number:

$$A = \log\left(\frac{I_0}{I}\right)$$

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. Notice that the convention in UV-vis spectroscopy is to show the baseline at the bottom of the graph with the peaks pointing up. Wavelength values on the x-axis are generally measured in nanometers (nm) rather than in cm^{-1} as is the convention in IR spectroscopy.

Typically, there are two things that are noted and recorded from a UV-Vis spectrum. The first is λ_{max}, which is the wavelength at maximal light absorbance. As you can see, isoprene has λ_{max} = 222 nm. The second valuable piece of data is the absorbance at the λ_{max}. In the isoprene spectrum the absorbance at the value λ_{max} of 222 nm is about 0.8.



MOLAR ABSORPTIVITY

Molar absorptivity (*epsilon*) is a physical constant, characteristic of the particular substance being observed and thus characteristic of the particular electron system in the molecule. Molar absorptivities may be very large for strongly absorbing chromophores (>100,000) and very small if absorption is weak (10 to 100). The magnitude of *epsilon* reflects both the size of the chromophore and the probability that light of a given wavelength will be absorbed when it strikes the chromophore. Molar absorptivity (ϵ) is defined via Beer's law as:

$$\epsilon = \frac{A}{c\,l}$$

where

- A is the sample absorbance
- c is the sample concentration in moles/liter
- l is the length of light path through the sample in cm

If the isoprene spectrum show above was obtained from a dilute hexane solution (c = 4 * 10^{-5} moles per liter) in a 1 cm sample cuvette, a simple calculation using the above formula indicates a molar absorptivity of 20,000 at the maximum absorption wavelength, symbolized as λ_{max}.

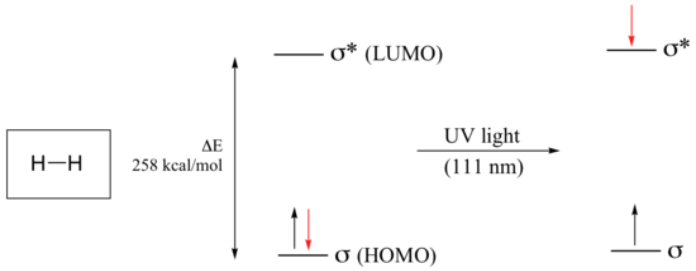
The only molecular moieties likely to absorb light in the 200 to 800 nm region are functional groups that contain pi-electrons and hetero atoms having non-bonding valence-shell electron pairs. Such light absorbing groups are referred to as **chromophores**. A list of some simple chromophores and their light absorption characteristics are provided below. The oxygen non-bonding electrons in alcohols and ethers do not give rise to absorption above 160 nm. Consequently, pure alcohol and ether solvents may be used for spectroscopic studies.

Chromophore	Example	Excitation	λmax, nm	ε @ λmax	Solvent
C=C	Ethene	π → π*	171	15,000	hexane
C≡C	1-Hexyne	π → π*	180	10,000	hexane
C=O	Ethanal	n → π*	290	15	hexane
		π → π*	180	10,000	hexane
N=O	Nitromethane	n → π*	275	17	ethanol
		π → π*	200	5,000	ethanol
C-X X=Br	Methyl bromide	n → σ*	205	200	hexane
X=I	Methyl Iodide	n → σ*	255	360	hexane

ELECTRONIC TRANSITIONS (CAUSE OF UV-VISIBLE ABSORPTION)

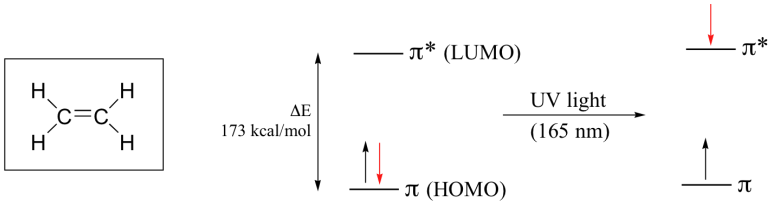
As previously noted, electronic transitions in organic molecules lead to UV and visible absorption. As a rule, energetically favored electron promotion will be from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO), and the resulting species is called an **excited state.** The molecular orbital picture for the hydrogen molecule (H_2) 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).

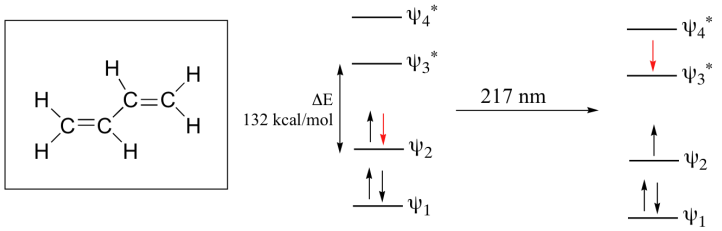


If the molecule is exposed to light of a wavelength with energy equal to ΔE, the HOMO-LUMO energy gap, this wavelength will be absorbed and the energy used to bump one of the electrons from the HOMO to the LUMO – in other words, from the σ to the σ* orbital. This is referred to as a **σ - σ* transition**. 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.

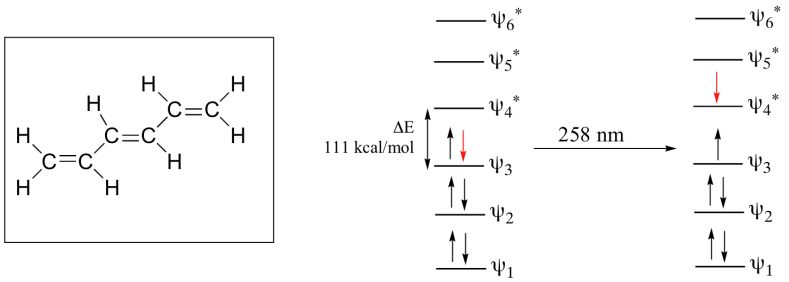


The electronic transitions of both molecular hydrogen and ethene are too energetic to be accurately recorded. Where electronic transition becomes useful to most organic and biological chemists is in the study of molecules with conjugated pi systems. In these groups, the energy gap for π -π* transitions is smaller than for isolated double bonds, and thus the wavelength absorbed is longer. The MO diagram for 1,3-butadiene, the simplest conjugated system. 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 pi bonding, while the upper two are pi antibonding.



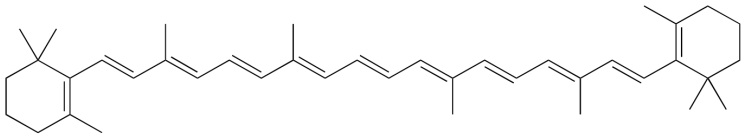
Comparing this MO picture to that of ethene, our isolated pi-bond example, we see that the HOMO-LUMO energy gap is indeed smaller for the conjugated system. 1,3-butadiene absorbs UV light with a wavelength of 217 nm.

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 **Δ**E of 111 kcal/mol.



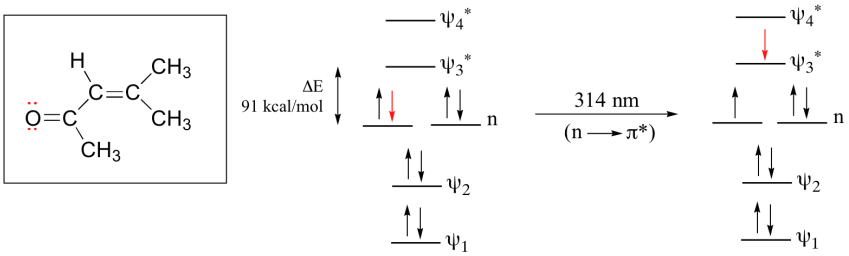
In molecules with extended pi systems, the HOMO-LUMO energy gap becomes so small that absorption occurs in the visible rather then the UV region of the electromagnetic spectrum. Beta-carotene, with its system of 11 conjugated double bonds, absorbs light with wavelengths

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

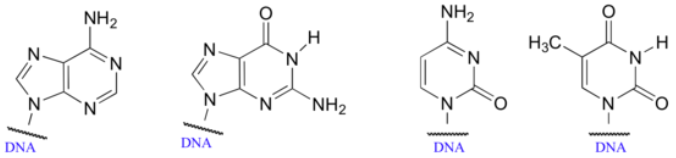
The conjugated pi system in 4-methyl-3-penten-2-one gives rise to a strong UV absorbance at 236 nm due to a π - π* transition. However, this molecule also absorbs at 314 nm. This second absorbance is due to the transition of a non-bonding (lone pair) electron on the oxygen up to a π* antibonding MO:



This is referred to as an $n-\pi^*$ transition. The nonbonding (n) MO's are higher in energy than the highest bonding p orbitals, so the energy gap for an $n-\pi^*$ transition is smaller that that of a $\pi-\pi^*$ transition – and thus the $n-\pi^*$ peak is at a longer wavelength. In general, $n-\pi^*$ transitions are weaker (less light absorbed) than those due to $\pi-\pi^*$ transitions.

USE OF UV/VIS SPECTROSCOPY IN BIOLOGICAL SYSTEMS

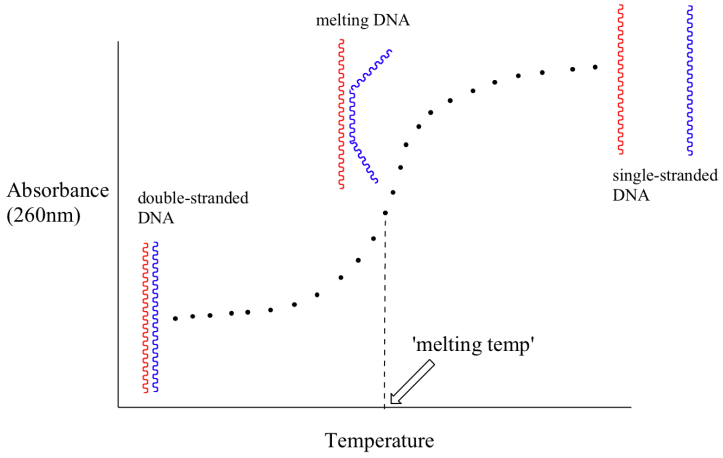
The bases of DNA and RNA are good chromophores:



Adenine Guanine Cytosine Thymine

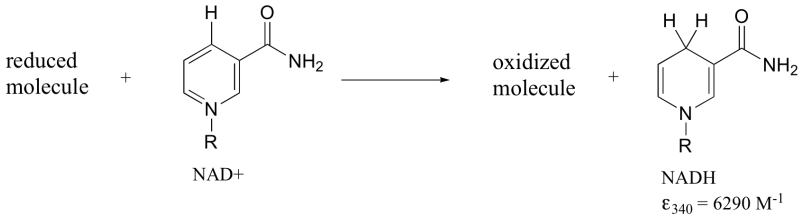
Biochemists and molecular biologists often determine the concentration of a DNA sample by assuming an average value of ε = 0.020 ng^{-1}×mL for double-stranded DNA at its λ_{max} of 260 nm (notice that concentration in this application is expressed in mass/volume rather than molarity: ng/mL is often a convenient unit for DNA concentration when doing molecular biology).

Because the extinction coefficient of double stranded DNA is slightly lower than that of single stranded DNA, we can use UV spectroscopy to monitor a process known as DNA melting. If a short stretch of double stranded DNA is gradually heated up, it will begin to 'melt', or break apart, as the temperature increases (recall that two strands of DNA are held together by a specific pattern of hydrogen bonds formed by 'base-pairing').

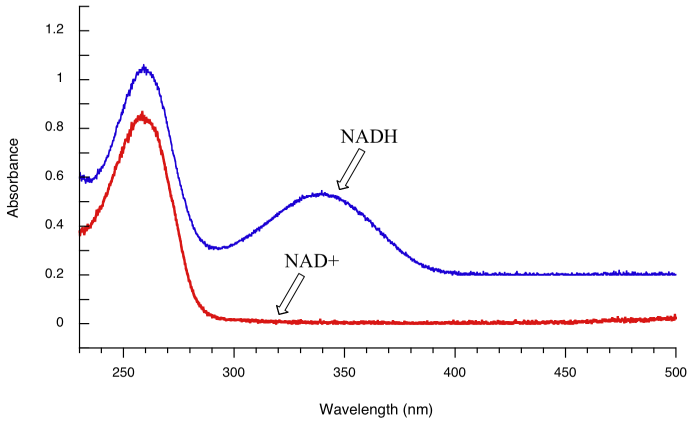


As melting proceeds, the absorbance value for the sample increases, eventually reaching a high plateau as all of the double-stranded DNA breaks apart, or 'melts'. The mid-point of this process, called the 'melting temperature', provides a good indication of how tightly the two strands of DNA are able to bind to each other.

Later we will see how the Beer - Lambert Law and UV spectroscopy provides us with a convenient way to follow the progress of many different enzymatic redox (oxidation-reduction) reactions. In biochemistry, oxidation of an organic molecule often occurs concurrently with reduction of nicotinamide adenine dinucleotide (NAD^+, the compound whose spectrum we saw earlier in this section) to NADH:

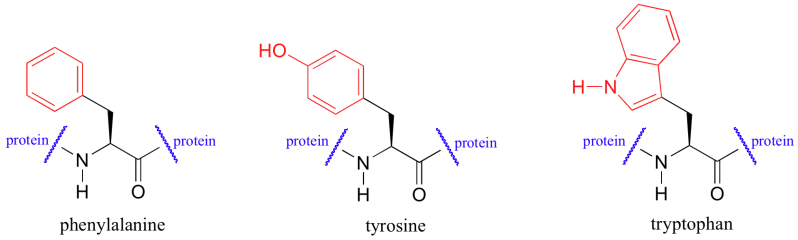


Both NAD^+ and NADH absorb at 260 nm. However NADH, unlike NAD^+, has a second absorbance band with λ_{max} = 340 nm and ε = 6290 $L*mol^{-1}*cm^{-1}$. The figure below shows the spectra of both compounds superimposed, with the NADH spectrum offset slightly on the y-axis:



By monitoring the absorbance of a reaction mixture at 340 nm, we can 'watch' NADH being formed as the reaction proceeds, and calculate the rate of the reaction.

UV spectroscopy is also very useful in the study of proteins. Proteins absorb light in the UV range due to the presence of the aromatic amino acids tryptophan, phenylalanine, and tyrosine, all of which are chromophores.

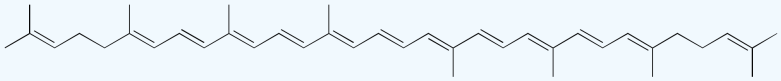


Biochemists frequently use UV spectroscopy to study conformational changes in proteins - how they change shape in response to different conditions. When a protein undergoes a conformational shift (partial unfolding, for example), the resulting change in the environment around an aromatic amino acid chromophore can cause its UV spectrum to be altered.

? EXERCISE 14.7.1

1. 50 microliters of an aqueous sample of double stranded DNA is dissolved in 950 microliters of water. This diluted solution has a maximal absorbance of 0.326 at 260 nm. What is the concentration of the original (more concentrated) DNA sample, expressed in micrograms per microliter?
2. What is the energy range for 300 nm to 500 nm in the ultraviolet spectrum? How does this compare to energy values from NMR and IR spectroscopy?

3. Identify all isolated and conjugated pi bonds in lycopene, the red-colored compound in tomatoes. How many pi electrons are contained in the conjugated pi system?



lycopene

Answer

1) Using ε = A/c, we plug in our values for ε and A and find that c = 3.27 x 10^{-5}M, or 32.7 mM.

2)

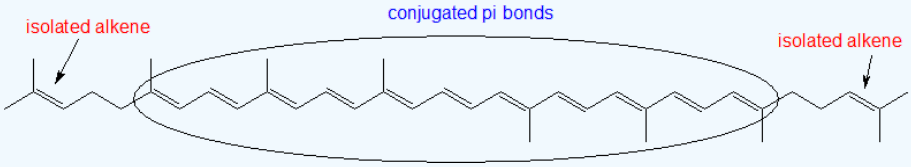
$E = hc/\lambda$

$E = (6.62 \times 10^{-34}\ \text{Js})(3.00 \times 10^{8}\ \text{m/s})/(3.00 \times 10^{-7}\ \text{m})$

$E = 6.62 \times 10^{-19}\ \text{J}$

The range of 3.972×10^{-19} to 6.62×10^{-19} joules. This energy range is greater in energy than the in NMR and IR.

3)



14.8: INTERPRETING ULTRAVIOLET SPECTRA- THE EFFECT OF CONJUGATION

OBJECTIVE

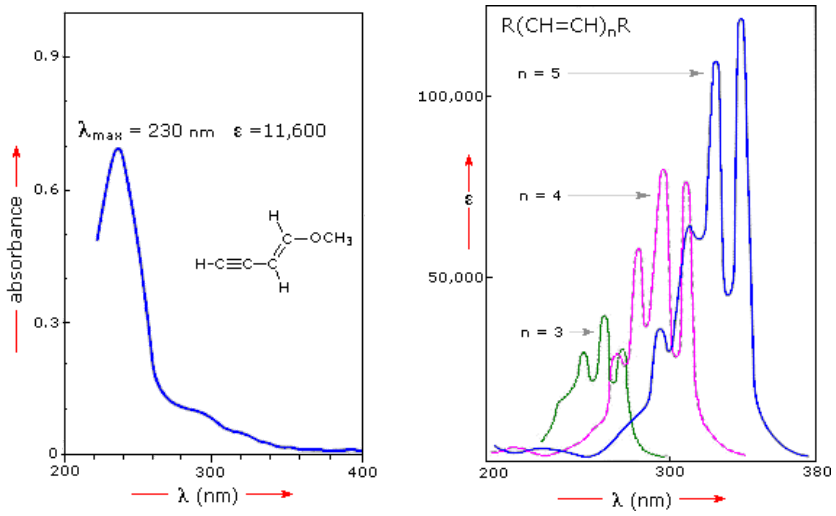
After completing this section, you should be able to use data from ultraviolet spectra to assist in the elucidation of unknown molecular structures.

STUDY NOTES

It is important that you recognize that the ultraviolet absorption maximum of a conjugated molecule is dependent upon the extent of conjugation in the molecule.

THE IMPORTANCE OF CONJUGATION

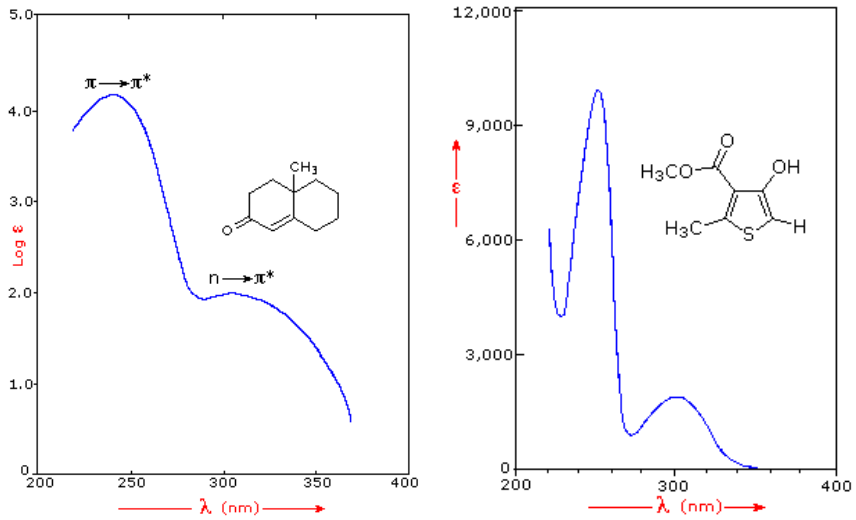
A comparison of the UV/Vis absorption spectrum of 1-butene, λ_{max} = 176 nm, with that of 1,3-butadiene, λ_{max} = 292 nm, clearly demonstrates that the effect of increasing conjugation is to shift toward longer wavelength (lower frequency, lower energy) absorptions. Further evidence of this effect is shown below. The spectrum on the left illustrates that conjugation of double and triple bonds also shifts the absorption maximum to longer wavelengths. From the polyene spectra displayed in the right it is clear that each additional double bond in the conjugated pi-electron system increases the absorption maximum about 30 nm. Also, the molar absorptivity (ε) roughly doubles with each new conjugated double bond. Spectroscopists use the terms defined in the table below when describing shifts in absorption. Thus, extending conjugation generally results in bathochromic and hyperchromic shifts in absorption.



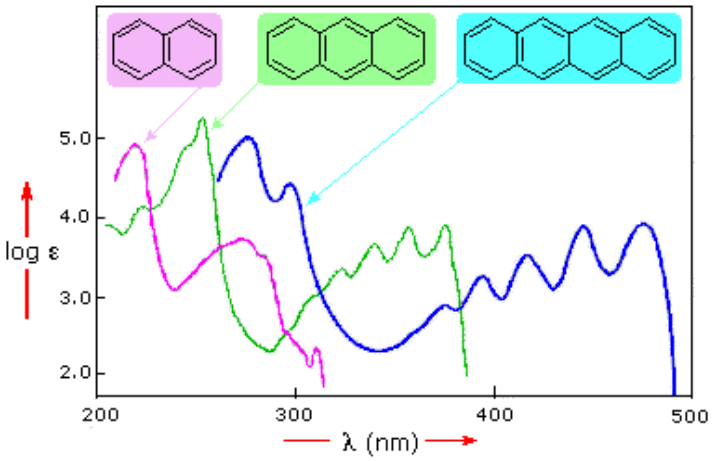
Terminology for Absorption Shifts

Nature of Shift	Descriptive Term
To Longer Wavelength	Bathochromic
To Shorter Wavelength	Hypsochromic
To Greater Absorbance	Hyperchromic
To Lower Absorbance	Hypochromic

Many other kinds of conjugated pi-electron systems act as chromophores and absorb light in the 200 to 800 nm region. These include unsaturated aldehydes and ketones and aromatic ring compounds. A few examples are displayed below. The spectrum of the unsaturated ketone (on the left) illustrates the advantage of a logarithmic display of molar absorptivity. The $\pi \rightarrow \pi^*$ absorption located at 242 nm is very strong, with an ε = 18,000. The weak $n \rightarrow \pi^*$ absorption near 300 nm has an ε = 100.

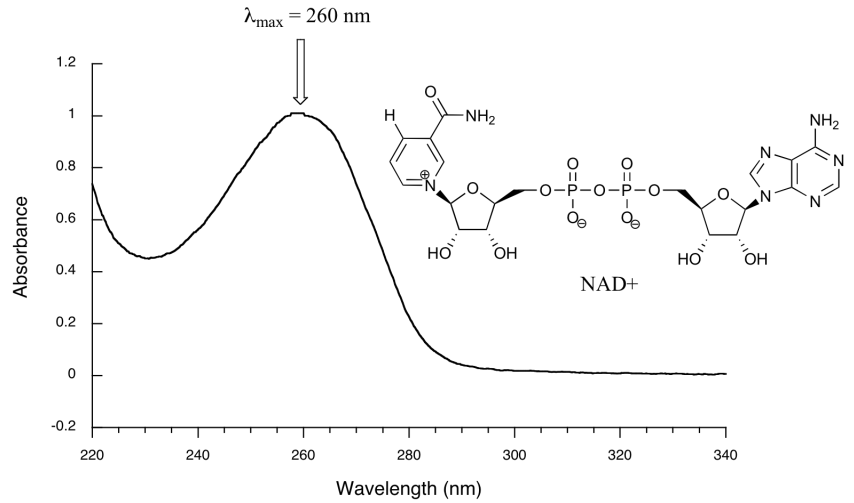


Benzene exhibits very strong light absorption near 180 nm (ε > 65,000) , weaker absorption at 200 nm (ε = 8,000) and a group of much weaker bands at 254 nm (ε = 240). Only the last group of absorptions are completely displayed because of the 200 nm cut-off characteristic of most spectrophotometers. The added conjugation in naphthalene, anthracene and tetracene causes bathochromic shifts of these absorption bands, as displayed in the chart below. All the absorptions do not shift by the same amount, so for anthracene (green shaded box) and tetracene (blue shaded box) the weak absorption is obscured by stronger bands that have experienced a greater red shift. As might be expected from their spectra, naphthalene and anthracene are colorless (with their absorptions in the UV range), but tetracene is orange (since its absorptions move into the visible range).

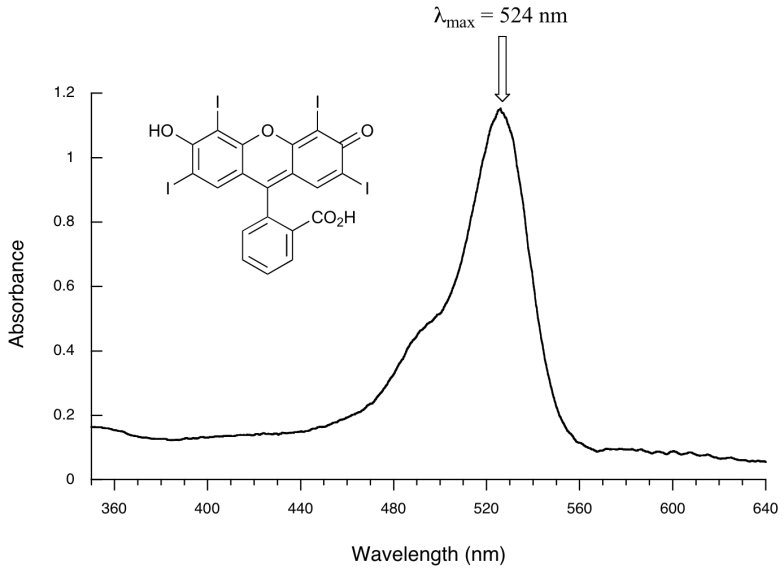


LOOKING AT UV-VIS SPECTRA

Below is the absorbance spectrum of an important biological molecule called nicotinamide adenine dinucleotide, abbreviated NAD^+. This compound absorbs light in the UV range due to the presence of conjugated pi-bonding systems.



Below is the absorbance spectrum of the common food coloring Red #3. The extended system of conjugated pi bonds causes the molecule to absorb light in the visible range. Because the λ_{max} of 524 nm falls within the green region of the spectrum, the compound appears red to our eyes (recalling the color wheel from Section 14.7).



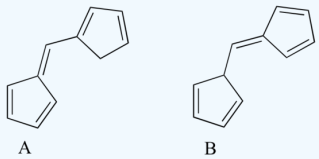
EXAMPLE 14.8.2

How large is the π - π* transition in 4-methyl-3-penten-2-one?

Solution

EXAMPLE 14.8.3

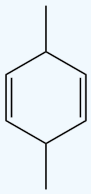
Which of the following molecules would you expect absorb at a longer wavelength in the UV region of the electromagnetic spectrum? Explain your answer.

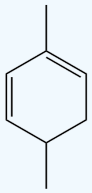


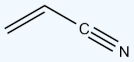
Solution

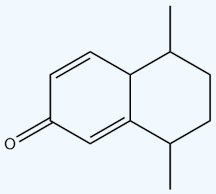
EXERCISE 14.8.1

Which of the following would show UV absorptions in the 200-300 nm range?

A) 

B) 

C) 

D) 

Answer

B and D would be in that range.

14.9: CONJUGATION, COLOR, AND THE CHEMISTRY OF VISION

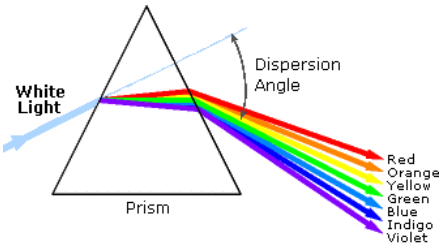
OBJECTIVES

After completing this section, you should be able to

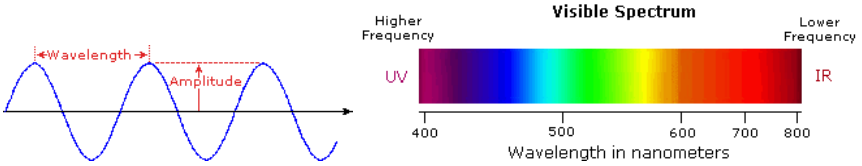
1. explain why some organic compounds have different colors based on compound structure and our perception of light.
2. state the relationship between frequency of light absorbed and the extent of conjugation in an extended pi electron system.

INTRODUCTION

An obvious difference between certain compounds is their color. Thus, quinone is yellow; chlorophyll is green; and aspirin is colorless. In this respect the human eye is functioning as a spectrometer analyzing the light reflected from the surface of a solid or passing through a liquid. Although we see sunlight (or white light) as uniform or homogeneous in color, it is actually composed of a broad range of radiation wavelengths in the ultraviolet (UV), visible and infrared (IR) portions of the spectrum. As shown on the image below, the component colors of the visible portion can be separated by passing sunlight through a prism, which acts to bend the light in differing degrees according to wavelength.

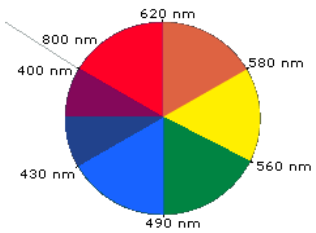


Visible wavelengths cover a range from approximately 400 to 800 nm. The longest visible wavelength is red and the shortest is violet. The wavelengths of what we perceive as particular colors in the visible portion of the spectrum are displayed and listed below.



- **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

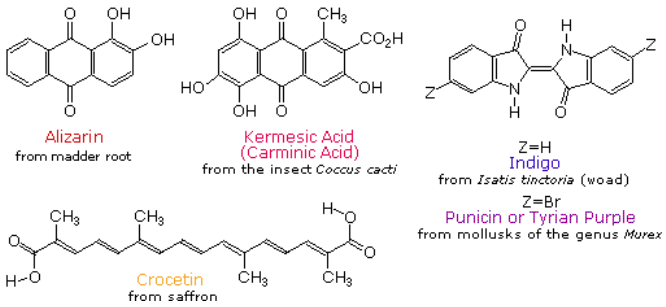
When white light passes through or is reflected by a colored substance, a characteristic portion of the mixed wavelengths is absorbed. The remaining light will then assume the complementary color to the wavelength(s) absorbed. This relationship is demonstrated by the color wheel shown below. Here, complementary colors are diametrically opposite each other. Thus, absorption of violet (400-440 nm) light renders a substance yellow, and absorption of 490-560 nm (green) light makes it red. Green is unique in that it can be created by absorption close to 400 nm as well as absorption near 800 nm.



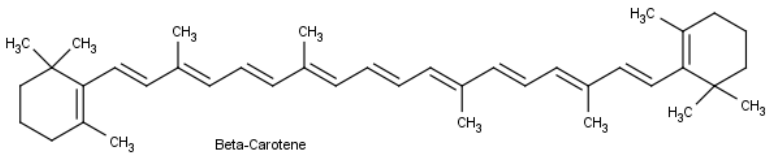
Early humans valued colored pigments, and used them for decorative purposes. Many of these were inorganic minerals, but several important organic dyes were also known. These included the crimson pigment, kermesic acid, the blue dye, indigo, and the yellow saffron

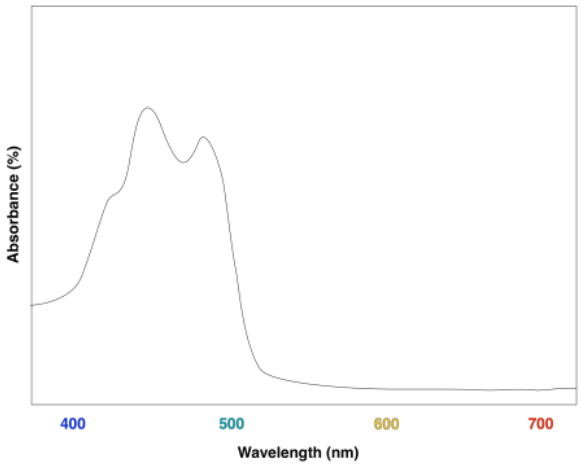
pigment, crocetin. A rare dibromo-indigo derivative, punicin, was used to color the robes of the royal and wealthy. A common feature of all these colored compounds, displayed below, is a system of **extensively conjugated π-electrons**.

Some Natural Organic Pigments

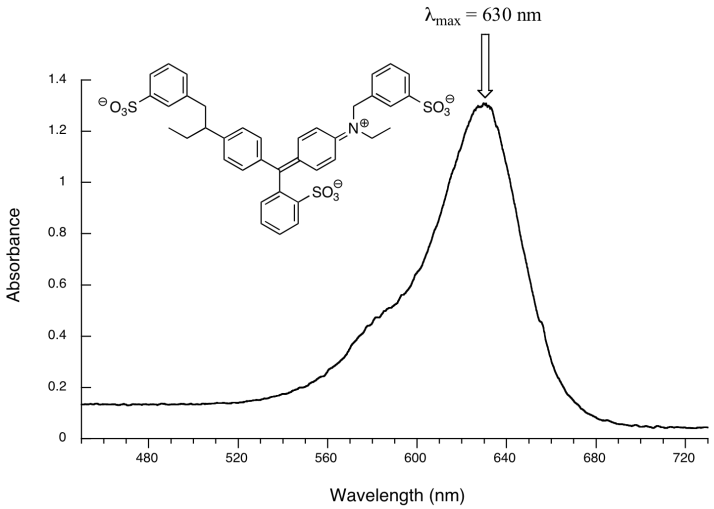


By understanding visible light, complementary colors, and adsorption the color of organic compounds can be understood. Beta-carotene, a compound found in carrots, is a deep orange color. Beta-carotene has 11 conjugated double bonds which places its λ_{max} at 455 nm which is within the blue region of the visible spectrum. The Beta-carotene compound absorbs blue from white light so it appears orange which is the the complementary color of blue.





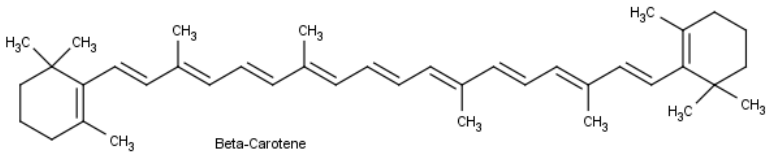
Another example is seen in the absorption spectrum of another food coloring, Blue #1:

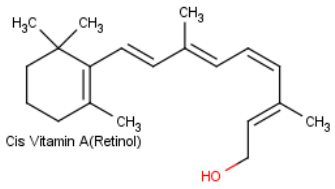


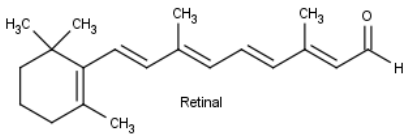
Blue #1 absorbs at a λ_{max} at 630 nm which is the color red in the visible spectrum. Blue is the complementary color of red.

MECHANISM OF VISION

Conjugation is also important in light sensitive compounds used for vision. Beta carotene, found in carrots and other natural products is cleaved into the liver and converted into Vitamin A, also known as retinol. Vitamin A is critical for vision because it is needed by the retina of eye. Retinol can be oxidized to an aldehyde called retinal which is also important for vision.



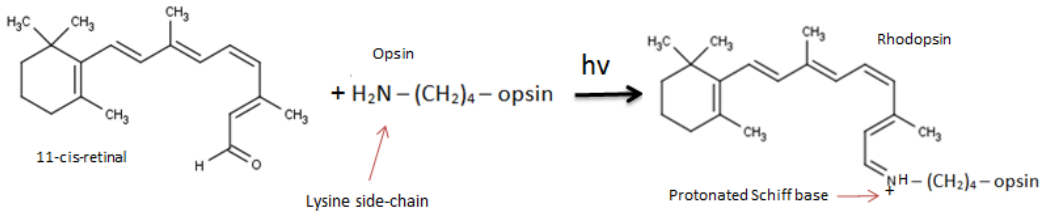




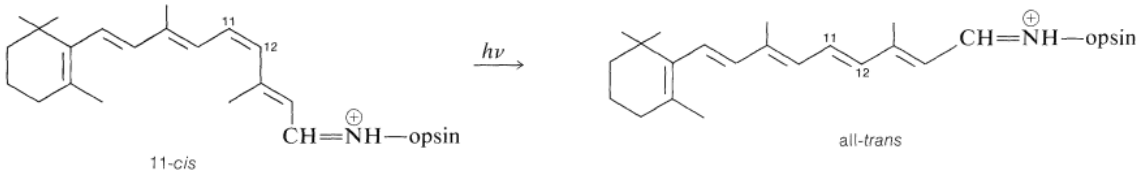
The eye is an extraordinarily sensitive instrument. Although its wavelength response is restricted to 400-800 nm, but its degree of sensitivity is such that a fully dark-adapted eye can clearly detect objects in light so dim as to correspond to a light input over the retina of only about 10,000 quanta per second - one light quantum per three minutes per receptor cell in the retina!

The retina is made up of two kinds of light-sensitive (photoreceptor) cells, known as rods and cones. The rods are the more sensitive and are responsible for vision in dim light. The cones are much fewer in number than the rods and provide detail and color vision in good light. The part of the retina that corresponds to the center of the visual field contains only cones. A red pigment called **rhodopsin** is the photosensitive substance in the rod cells of the retina. It absorbs most strongly in the blue-green region of the visible spectrum (λ_{max} = 500nm) and is essentially unaffected by the far-red end of the spectrum. Cone vision appears to involve a different pigment called **iodopsin**, which absorbs farther toward the red than does rhodopsin.

Rhodopsin, is made up of a protein (opsin) and retinal. Opsin does not absorb visible light, but when it is bonded with 11-cis-retinal to from rhodopsin, the new molecule has a very broad absorption band in the visible region of the spectrum. Rhodopsin is formed by an an imine (Schiff base) functional group formed between the aldehyde group of the retinal and the side-chain amino function of a lysine unit of opsin.

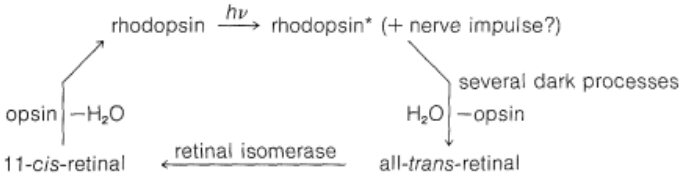


Opsin itself is colorless, whereas 11-cis-retinal absorbs strongly at 370 nm. The combination of opsin with 11-cis-retinal produces a remarkable shift of λ_{max} to longer wavelengths (430 nm to 620 nm, depending on the species). Light striking the retina changes the color of rhodopsin from red to yellow. The primary photochemical event in this process was established by G. Wald (Nobel Laureate in Physiology and Medicine, 1967), who showed that light absorption led to a change of configuration about the C_{11}-C_{12} double bond of the retinal moiety fo rhodopsin from *cis* to *trans* to form a compound called metarhodopsin II. The new form of trans-retinal does not fit as well into the opsin protein, and so a series of geometry changes in the protein begins. As the protein changes its geometry, it initiates a cascade of biochemical reactions that result in changes in charge so that a large potential difference builds up across the neuron membranes. This potential difference is passed along to an adjoining nerve cell as an electrical impulse. The nerve cell carries this impulse to the brain, where the visual information is interpreted.



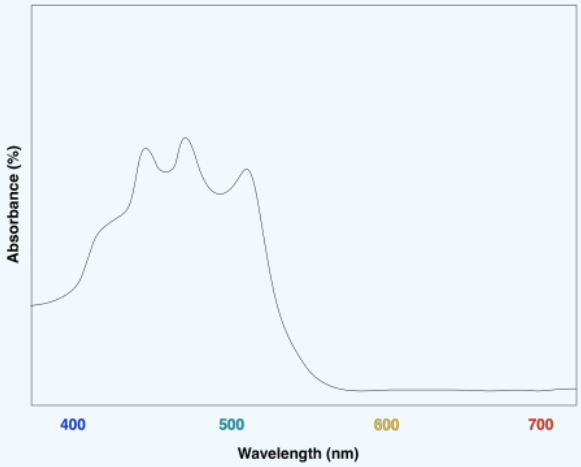
Rhodopsin **Metarhodopsin II**

Metarhodopsin II can then be recycled back to rhodopsin by first cleaving to form all-*trans*-retinal and the isomerization back to 11-*cis*-retinal by the enzyme retinal isomerase. Finally, 11-*cis*-retinal is once again coupled with opsin to form rhodopsin.



? EXERCISE 14.9.1

Lycopene is conjugated compound found in tomatoes. What colors correspond to the UV-Vis absorption maxima of lycopene? What color do we see when we look at lycopene?



Answer

The absorption maxima of lycopene are regions of blue and green in the visible spectrum. Lycopene would be expected to appears orange and red.

EXERCISE 14.9.2

Asprin has a λ_{max} of 220 nm. Briefly explain why Asprin appears white.

Answer

Asprin absorbs in the ultraviolet portion of the electromagnetic spectrum. Asprin cannot remove any colors from white light by absorption so the compound itself appears white. Many compounds with a relatively small amount of conjugation appear white because they only absorb in the ultraviolet and not the visible region.

14.S: CONJUGATED COMPOUNDS AND ULTRAVIOLET SPECTROSCOPY (SUMMARY)

CONCEPTS & VOCABULARY

14.0 Introduction

- Dienes that consist of two double bonds separated by a single bond are conjugated.
- Dienes that have the double bonds separated by more than one single bond are isolated (non-conjugated)

14.1 Stability of Conjugated Dienes - Molecular Orbital Theory

- Conjugated dienes are more stable than non-conjugated dienes.
- Electrons in conjugated dienes are delocalized due to overlap of all 4 p-orbitals.
- Molecular orbitals show stability of dienes and allylic carbocations.

14.2 Electrophilic Additions to Conjugated Dienes - Allylic Carbocations

- Addition to conjugated dienes occur at multiple positions due to resonance of the allyl carbocation intermediate called 1,2 and 1,4 addition.

14.3 Kinetic vs. Thermodynamic Control of Reactions

- Lower transition states lead to kinetic products.
- More stable products lead to thermodynamic products.
- Kinetic reaction conditions favor 1,2 addition to conjugated dienes.
- Thermodynamic reaction conditions favor 1,4 addition to conjugated dienes.
- For some reactions, the kinetic and thermodynamic products are the same molecule.

14.4 The Diels-Alder Cycloaddition Reaction

- Cycloaddition reactions involve concerted bonding of two independent pi-electron systems for form a new ring.
- The Diels-Alder reaction is a widely used [4+2] cycloaddition that froms two new sigma bonds.

14.5 Characteristics of the Diels-Alder Reaction

- The Diels-Alder reaction is stereospecific with cis dienophiles yielding *cis* substitution and *trans* dienophiles generate trans substitution.
- The diene in a Diels-Alder reaction must be able to adopt an s-cis conformation.
- Diels-Alder reactions with cyclic dienes favor endo substituents.

14.6 Diene Polymers - Natural and Synthetic Rubbers

- Dienes can form polymers including natural examples such as rubber which is formed from isoprene monomers.

14.7 Ultraviolet Spectroscopy

- When UV and visible light is absorbed, electrons are excited from a bonding or non-bonding orbital to a nearby anti-bonding orbital.
- Colored organic molecules all include extensive conjugated pi electron systems.
- UV absorbance is higher energy than visible light, allowing for excitation of electrons without the low energy pi-bonding to pi anti-bonding transitions available in highly conjugated molecules.
- Chromophores are molecules or structural features that absorb light in the UV-Visible range.

14.8 Interpreting Ultraviolet Spectra: The Effect of Conjugation

- Conjugated pi systems lowers the energy gap for π -π^* transitions causing the molecule to absorb light of a longer wavelength.
- Many molecules absorb in the UV spectrum. As the energy gap becomes smaller, these absorbances move into the visible spectrum, starting with violet light which makes the resulting molecules appear yellow.

14.9 Conjugation, Color, and the Chemistry of Vision

- Absorption of light causes chemical changes in the rods and cones in eyes leading to visual sensations.

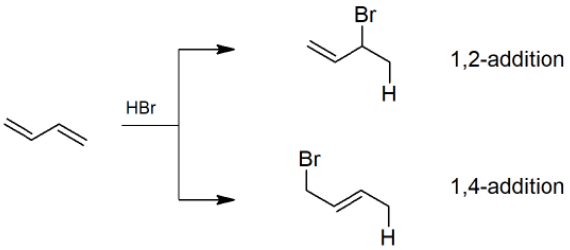
SKILLS TO MASTER

- Skill 14.1 Differentiate between conjugated and isolated dienes.
- Skill 14.2 Explain stability of conjugated dienes using Molecular Orbital Theory.
- Skill 14.3 Draw mechanisms for 1,2 and 1,4 addition to conjugated dienes.
- Skill 14.4 Predict kinetic and thermodynamic products of addition reactions to conjugated dienes.
- Skill 14.5 Explain kinetic and thermodynamic control of reactions.
- Skill 14.6 Identify dienes and dienophiles for Diels-Alder Cycloaddition reactions.

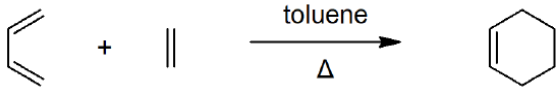
- Skill 14.7 Determine products of Diels-Alder Cycloaddition, including stereochemistry and endo/exo.
- Skill 14.8 Draw mechanisms for Diels-Alder Cycloaddition.
- Skill 14.9 Apply reactions of conjugated dienes to polymerization and natural rubber formation.
- Skill 14.10 Explain the electronic transitions that occur with absorption of UV-Visible light.
- Skill 14.11 Explain the effects of conjugation on wavelength of light absorbed in π -π* transitions.

SUMMARY OF REACTIONS

Electrophilic Addition



Diels−Alder Cycloaddition



CHAPTER OVERVIEW

15: BENZENE AND AROMATICITY

LEARNING OBJECTIVES

After you have completed Chapter 15, you should be able to

1. fulfillall of the detailed objectives listed under each individual section.
2. use the information presented in this chapter, along with material from earlier chapters, to solve problems, particularly road-map problems and those requiring an understanding of spectroscopy.
3. explain the concept of aromaticity and the stability of aromatic compounds.
4. define, and use in context, the key terms introduced.

In Chapter 3, we identified an aromatic compound as being a compound which contains a benzene ring (or phenyl group). It is now time to define aromaticity in a more sophisticated manner. In this chapter, we discuss the stability of benzene and other aromatic compounds, explaining it in terms of resonance and molecular orbital theory. You will study the nomenclature of aromatic compounds and the Hückel ($4n + 2$) rule for predicting aromaticity. The chapter concludes with a brief summary of the spectroscopic properties of arenes.

15.0: INTRODUCTION

OBJECTIVES

After completing this section, you should be able to

1. explain what is meant by the term “aromatic compound.”
2. identify the aromatic portions present in naturally occurring compounds, given the necessary structures.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- aromatic

STUDY NOTES

At this point in the course, we shall use the term *aromatic* to describe those compounds which contain a benzene ring. A broader definition of aromaticity will be given in Section 15.3.

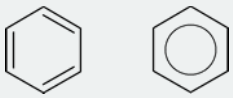
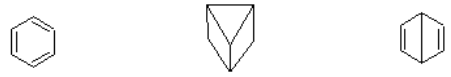


Figure 15.0.1: Two common ways of representing a benzene ring

THE 100 YEAR MYSTERY OF BENZENE

It took humans over 100 years to determine and confirm the structure of benzene. Why did it take so long? Why was there such a curiosity? The 1:1 ratio of carbon to hydrogen in the empirical formula and low chemical reactivity of benzene were a paradox to chemists in the early 1800's.In 1825, Michael Faraday isolated an oily residue of gas lamps. Faraday called this liquid "bicarburet of hydrogen" and measured the boiling point to be 80°C. Additionally, Faraday determined the empirical formula to be CH. About nine years later, Eilhard Mitscherlich synthesized the same compound from benzoic acid and lime (CaO).

During the mid to late 1800's, several possible structures (shown below) were proposed for benzene.



It was not until the 1930's that Kekule's structure was confirmed by X-ray and electron diffraction. During the end of Kekule's career he revealed that the structure came to him in a vision after enjoying a glass or two of wine by the fire in his favorite chair. His inspiration for the structure of benzene was derived from an ouroboros in the flames.

Benzene, C_6H_6, is the simplest member of a large family of hydrocarbons, called aromatic hydrocarbons. These compounds contain ring structures and exhibit bonding that must be described using the resonance hybrid concept of valence bond theory or the delocalization concept of molecular orbital theory. (To review these concepts, refer to the earlier chapters on chemical bonding). The resonance structures for benzene, C_6H_6, are:

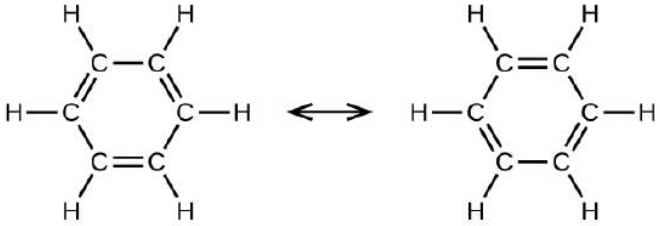


Figure 15.0.1.

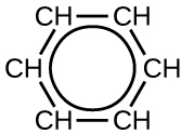
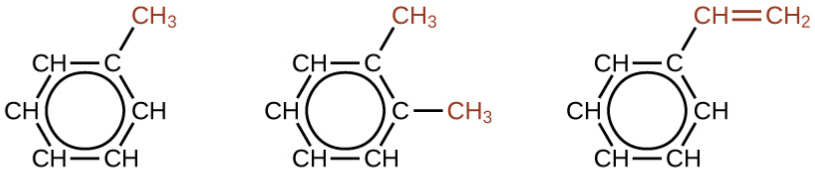


Figure 15.0.1: This condensed formula shows the unique bonding structure of benzene.

There are many derivatives of benzene. The hydrogen atoms can be replaced by many different substituents. Aromatic compounds more readily undergo substitution reactions than addition reactions; replacement of one of the hydrogen atoms with another substituent will leave the delocalized double bonds intact. The following are typical examples of substituted benzene derivatives:

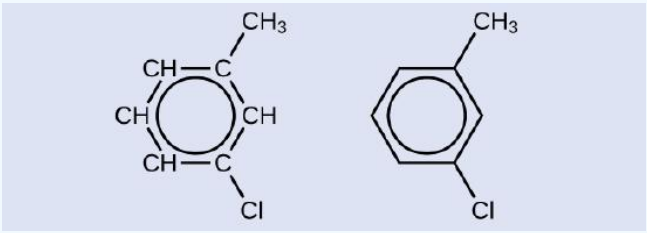


toluene xylene styrene

Toluene and xylene are important solvents and raw materials in the chemical industry. Styrene is used to produce the polymer polystyrene.

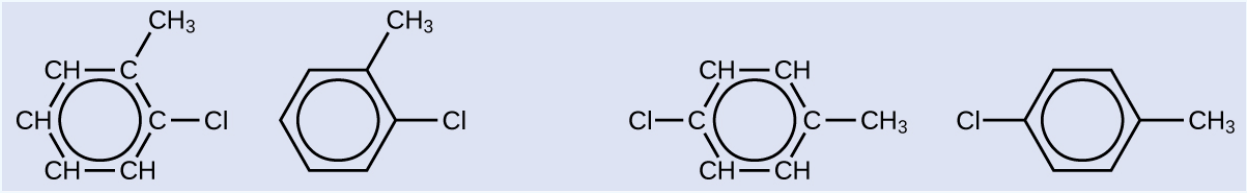
STRUCTURE OF AROMATIC HYDROCARBONS

One possible isomer created by a substitution reaction that replaces a hydrogen atom attached to the aromatic ring of toluene with a chlorine atom is shown here. Draw two other possible isomers in which the chlorine atom replaces a different hydrogen atom attached to the aromatic ring:



Solution

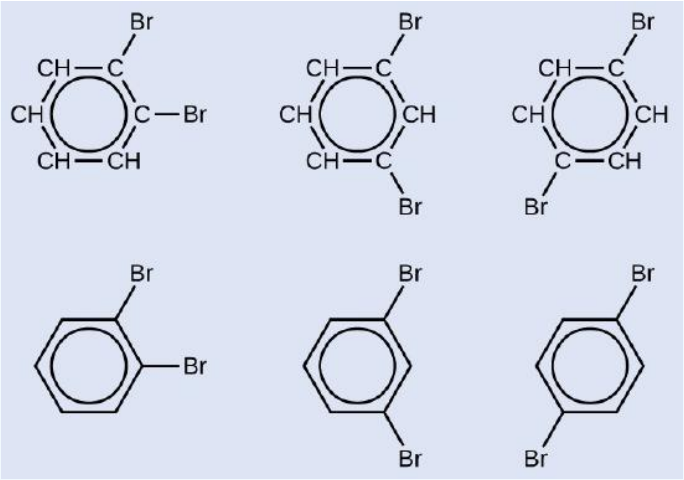
Since the six-carbon ring with alternating double bonds is necessary for the molecule to be classified as aromatic, appropriate isomers can be produced only by changing the positions of the chloro-substituent relative to the methyl-substituent:



EXERCISE 15.0.1

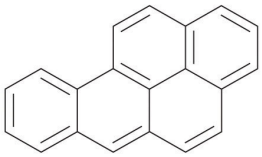
Draw three isomers of a six-membered aromatic ring compound substituted with two bromines.

Answer



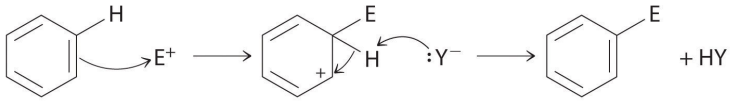
Most arenes that contain a single six-membered ring are volatile liquids, such as benzene and the xylenes, although some arenes with substituents on the ring are solids at room temperature. In the gas phase, the dipole moment of benzene is zero, but the presence of electronegative or electropositive substituents can result in a net dipole moment that increases intermolecular attractive forces and raises the melting and boiling points. For example, 1,4-dichlorobenzene, a compound used as an alternative to naphthalene in the production of mothballs, has a melting point of 52.7°C, which is considerably greater than the melting point of benzene (5.5°C).

Certain aromatic hydrocarbons, such as benzene and benz[a]pyrene, are potent liver toxins and carcinogens. In 1775, a British physician, Percival Pott, described the high incidence of cancer of the scrotum among small boys used as chimney sweeps and attributed it to their exposure to soot. His conclusions were correct: benz[a]pyrene, a component of chimney soot, charcoal-grilled meats, and cigarette smoke, was the first chemical carcinogen to be identified.



Benz[a]pyrene

Although arenes are usually drawn with three C=C bonds, benzene is about 150 kJ/mol more stable than would be expected if it contained three double bonds. This increased stability is due to the delocalization of the π electron density over all the atoms of the ring. Compared with alkenes, arenes are poor nucleophiles. Consequently, they do not undergo addition reactions like alkenes; instead, they undergo a variety of electrophilic aromatic substitution reactions that involve the replacement of –H on the arene by a group –E, such as $–NO_2$, $–SO_3H$, a halogen, or an alkyl group, in a two-step process. The first step involves addition of the electrophile (E) to the π system of benzene, forming a carbocation. In the second step, a proton is lost from the adjacent carbon on the ring:



The carbocation formed in the first step is stabilized by resonance.

> *Arenes undergo substitution reactions rather than elimination because of increased stability arising from delocalization of their π electron density.*

Many substituted arenes have potent biological activity. Some examples include common drugs and antibiotics such as aspirin and ibuprofen, illicit drugs such as amphetamines and peyote, the amino acid phenylalanine, and hormones such as adrenaline.

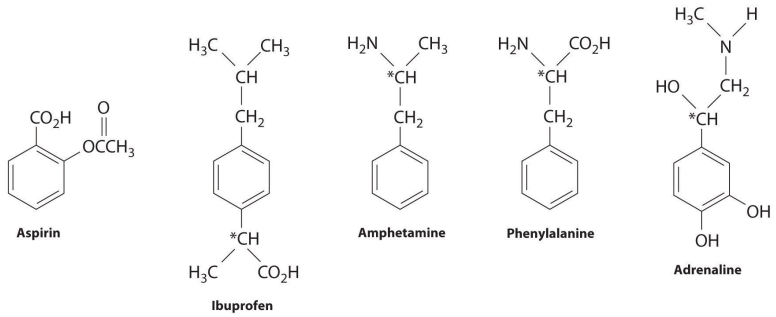


Figure 15.0.2: *Biologically Active Substituted Arenes*

Aspirin (antifever activity), ibuprofen (antifever and anti-inflammatory activity), and amphetamine (stimulant) have pharmacological effects. Phenylalanine is an amino acid. Adrenaline is a hormone that elicits the “fight or flight” response to stress. Chiral centers are indicated with an asterisk.

15.1: NAMING AROMATIC COMPOUNDS

OBJECTIVES

After completing this section, you should be able to

1. draw the structure of each of the common aromatic compounds in Figure 16 (Common benzene derived compounds with various substituents), given their IUPAC-accepted trivial names.
2. write the IUPAC-accepted trivial name for each of the compounds in Figure 16, given the appropriate Kekulé, condensed or shorthand structure.
3. identify the ortho, meta and para positions in a monosubstituted benzene ring.
4. use the ortho/meta/para system to name simple disubstituted aromatic compounds.
5. draw the structure of a simple disubstituted aromatic compound, given its name according to the ortho/meta/para system.
6. provide the IUPAC name of a given aromatic compound containing any number of the following substituents: alkyl, alkenyl or alkynyl groups; halogens; nitro groups; carboxyl groups; amino groups; hydroxyl groups.
7. draw the structure of an aromatic compound containing any number of the substituents listed in Objective 6, above, given the IUPAC name.
8. provide the IUPAC name of a given aromatic compound in which the phenyl group is regarded as a substituent.
9. draw the Kekulé, condensed or shorthand structure of an aromatic compound in which the phenyl group is regarded as a substituent, given its IUPAC name.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- arene
- benzyl group
- phenyl group

STUDY NOTES

You should already know the names and structures of several of the hydrocarbons shown in Figure 15.1. A compound containing a benzene ring which has one or more alkyl substituents is called an arene.

A phenyl group consists of a benzene ring with one of its hydrogens removed.

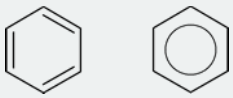


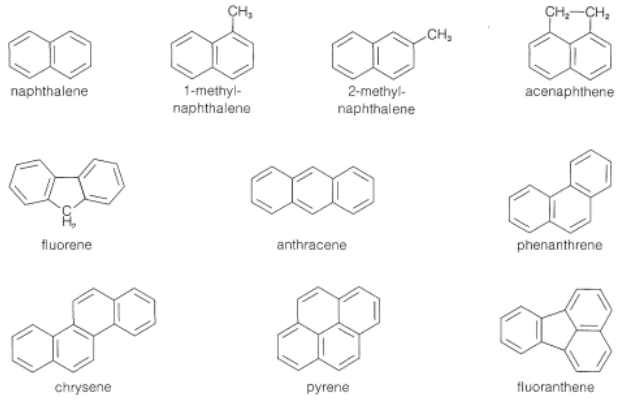
Figure 15.1.1: Two ways of representing a phenyl group

You should memorize the structures and formulas shown in Figure 16. You will meet these compounds frequently throughout the remainder of this course.

Note that the ortho/meta/para system cannot be used when more than two substituents are present in the benzene ring. The “numbering system” can be used instead of the ortho/meta/para system in most cases when only two substituents are present.

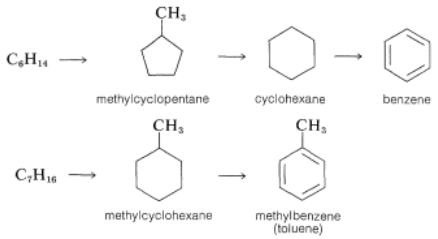
SOURCES OF AROMATIC COMPOUNDS

Initially aromatic compounds were isolated from coal tar. Coal tar, which is a distillate obtained when heating coal at 1000 ^{o}C in the absence of air, is a source of an amazing number of aromatic compounds. Many simple aromatic compounds, some of which includes nitrogen, oxygen, and sulfur, as well as hydrocarbons are obtained.



Some of the Aromatic Compounds Obtained from Coal Tar

Prior to World War II, coal tar was the only important source of aromatic hydrocarbons, but during the war the demand for benzene and toluene, a precursor to the explosive TNT, rose so sharply that other sources had to be found. Today, most of the benzene and almost all of the toluene produced in the United States are derived from petroleum. Although petroleum does contain some aromatic compound, it primarily made up of alkanes of various chain lengths. Aromatic compounds are synthesized from petroleum the by a process referred to in the petroleum industry as catalytic re-forming or hydroforming. This involves heating a C6-C10 alkane fraction of petroleum with hydrogen in the presence of a catalyst to modify the molecular structure of its components. Some amazing transformations take place, and the C6-C7 alkanes can be converted to cycloalkanes, which, in turn, are converted to arenes. Benzene, and methylbenzene (toluene) are produced primarily in this way.



NOMENCLATURE OF MONO-SUBSTITUTED BENZENES

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. Common names are often used in the nomenclature of aromatic compounds. IUPAC still allows for some of the more widely used common name to be used. A partial list of these common name is shown in Figure 15.1.2 and there are numerous others. These common names take the place of the benzene base name. Methylbenzene is commonly known with the base name toluene, hydroxyphenol is known as phenol etc. It is very important to be able to identify these structures as they will be utilized in the nomenclature of more complex compounds.

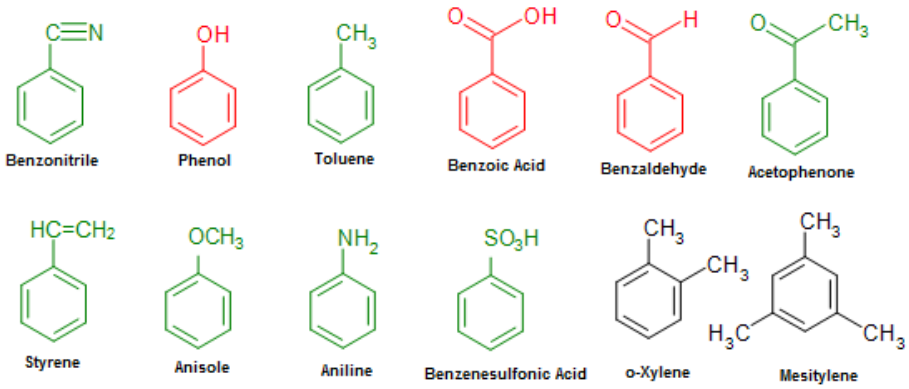
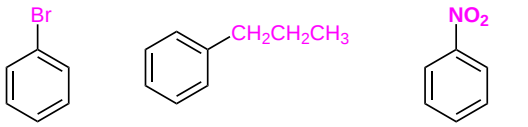


Figure 15.1.2: Common Names for Mono-Substituted Benzenes

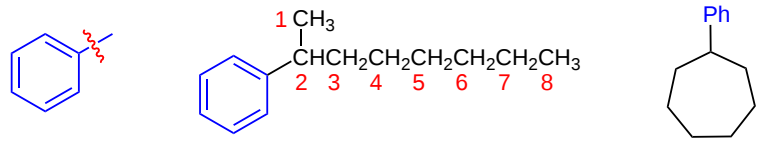
Mono-substituted benzene rings, with a substituent not on the list above, are named with benzene being the parent name. These compounds are named as such: *Name of the substituent + Benzene.*



Bromobenzene **Propyl**benzene **Nitro**benzene

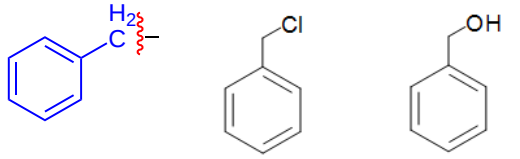
THE USE OF PHENYL AND BENZYL IN NOMENCLATURE

If the alkyl group attached to the benzene contains seven or more carbons the compounds is named as a phenyl substituted alkane. The name phenyl (C_6H_5-)is often abbreviated (Ph) and comes from the Greek word **pheno** which means "I bear light". This name commemorates the fact that benzene was first isolated by Michael Faraday in 1825 from the residue left in London street lamps which burned coal gas. If the alkyl substituent is smaller than the benzene ring (six or fewer carbons), the compound is named as an alkyl-substituted benzene following the rules listed above.



Phenyl group **2-Phenyl**octane **Phenyl**cycloheptane

The benzyl group (abbv. Bn), similar to the phenyl group and 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.

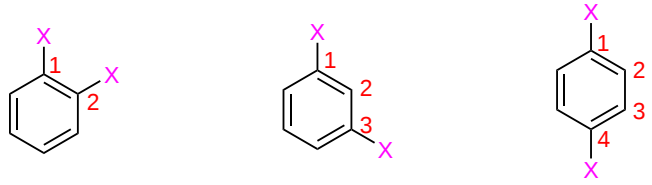


Benzyl group **Benzyl Chloride** **Benzyl Alcohol**

NOMENCLATURE OF DISUBSTITUTED BENZENES

With disubstituted benzenes there are three distinct positional isomers which can occur and must be identified in the compounds name. Although numbering can be used to indicate the position of the two subsituents it is much more common for the compounds to be named using prefixes. These prefixes are italicized and are often abbreviated with a single letter. 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)

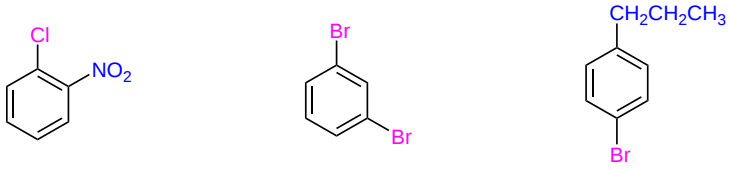


***ortho*-Disubstituted (1,2)** ***meta*-Disubstituted (1,3)** **para-Disubstituted (1,4)**

Figure 15.1.2. If any do appear then the compound is not named as a benzene but with a different parent name. These compounds are named as such: *Position prefix-Name of the substituent + Name of parent chain.*

ortho-Chlorophenol **meta-Nitrobenzoic acid** **para-Xylene**

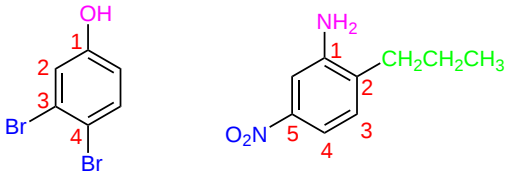
Figure 15.1.2 the compound is named as such: *Position prefix-Names of the substituents in alphabetical order + benzene.* Remember if two of the same substituent appears then the prefix *di-* is used before the substituent's name.



ortho-Chloronitrobenzene **meta-Dibromobenzene** **para-Bromopropylbenzene**

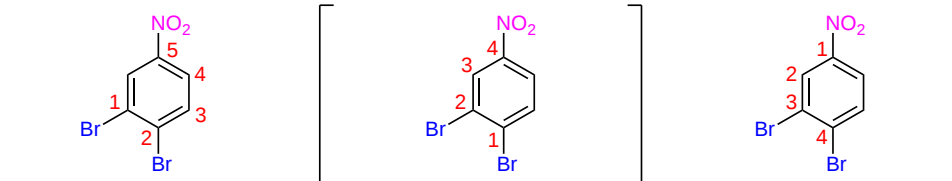
NOMENCLATURE OF BENZENES WITH THREE OR MORE SUBSTITUENTS

When three or more substituents are present the ortho, meta, para positional prefixes become inadequate and a numbering system for the ring must be applied. Here again it is important to check if any of the substituents are listed in **Figure 15.1.2 .** If a substituent from **Figure 15.1.2** is present it is given the parent name in the nomenclature. Also, this substituent is given position one in the numbering system. The other substituents are numbered such that they get the lowest possible sum. In the compound's name the subsituents are given their position number and listed alphabetically. Remember that di-, tri, tetra- prefixes are still used to indicate multiple of the same substituent being present but are ignored for alphabetical listing.



3,4-Dibromophenol **5-Nitro-2-propylaniline**

Figure 15.1.2, the benzene ring is name in the same fashion as cycloalkanes. The lowest possible number is given to the substituents present. This is best done by arbitrarily giving a substituent position one and then numbering the rest of the substituents. Then this process is repeated with the other substituents. Which ever iteration provides the lowest overall sum of numbers will be used in the compound's name. The substituents are assigned a location number, listed alphabetically and the suffix *-benzene* is added.



1,2-Dibromo-5-nitrobenzene **1,2-Dibromo-4-nitrobenzene** **3,4-Dibromo-1-nitrobenzene**

This numbering provides the lowest numbers to the substituents

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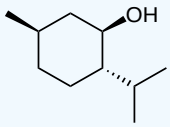
EXERCISES

EXERCISE 15.1.1



(True/False) The compound above contains a benzene ring and thus is aromatic.

Answer

False, this compound does not contain a benzene ring in its structure.

EXERCISE 15.1.2

Benzene unusual stability is caused by how many conjugated pi bonds in its cyclic ring? ____

Answer

3

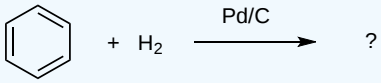
EXERCISE 15.1.3

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?

Answer

No, a substance that is fragrant does not imply a benzene ring is in its structure. See camphor example (figure 1)

EXERCISE 15.1.4



Answer

No reaction, benzene requires a special catalyst to be hydrogenated due to its unusual stability given by its three conjugated pi bonds.

EXERCISE 15.1.5

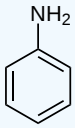
At normal conditions, benzene has ___ resonance structures.

Answer

2

EXERCISE 15.1.6

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

Answer

b, d

EXERCISE 15.1.7

Convert 1,4-dimethylbenzene into its common name.

Answer

p-Xylene

EXERCISE 15.1.8

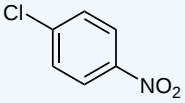
TNT's common name is: _____

Answer

2,4,6-trinitrotoluene

EXERCISE 15.1.9

Name the following compound using OMP nomenclature:



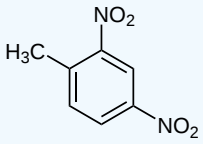
Answer

p-chloronitrobenzene

EXERCISE 15.1.10

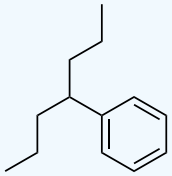
Draw the structure of 2,4-dinitrotoluene.

Answer



EXERCISE 15.1.11

Name the following compound:

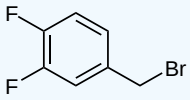


Answer

4-phenylheptane

EXAMPLE 15.1.12

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

Solution

a

EXERCISE 15.1.13

(True/False) Benzyl chloride can be abbreviated Bz-Cl.

Answer

False, the correct abbreviation for the benzyl group is Bn, not Bz. The correct abbreviation for Benzyl chloride is Bn-Cl.

EXERCISE 15.1.14

Benzoic Acid has what R group attached to its phenyl functional group?

Answer

COOH

EXERCISE 15.1.15

(True/False) A single aromatic compound can have multiple names indicating its structure.

Answer

True. TNT, for example, has the common name 2,4,6-trinitrotoluene and its systematic name is 2-methyl-1,3,5-trinitrobenzene.

EXERCISE 15.1.16

List the corresponding positions for the OMP system (o-, m-, p-).

Answer

Ortho - 1,2 ; Meta - 1,3 ; Para - 1,4

EXERCISE 15.1.17

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

Answer

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.

EXERCISE 15.1.18

Which of the following statements is **false** for the compound, phenol?

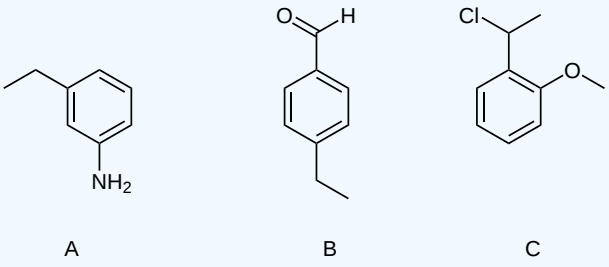
a. Phenol is a benzene derived compound.
b. Phenol can be made by attaching an -OH group to a phenyl group.
c. Phenol is highly toxic to the body even in small doses.
d. Phenol can be used as a catalyst in the hydrogenation of benzene into cyclohexane.
e. Phenol is used as an antiseptic in minute doses.
f. Phenol is amongst one of the three common names retained in the IUPAC nomenclature.

Answer

d

EXERCISE 15.1.19

State wither the following is para, meta, or ortho substituted.



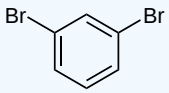
A B C

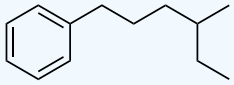
Answer

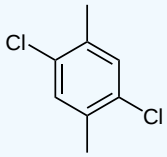
A – meta; B – para; C – ortho

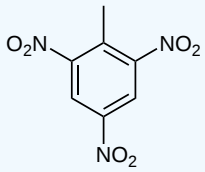
EXERCISE 15.1.20

Name the following compounds.

A) 

B) 

C) 

D) 

Answer

a. 1,3-Dibromobenzene

b. 1-phenyl-4-methylhexane

c. 1,4-Dichloro-2,5-dimethylbenzene

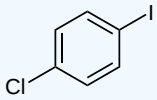
d. 2-methyl-1,3,5-trinitrobenzene. (Also known as trinitrotoluene, or TNT)

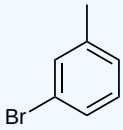
EXERCISE 15.1.21

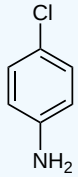
Draw the following structures

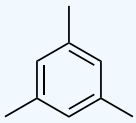
a. p-chloroiodobenzene
b. m-bromotoluene
c. p-chloroaniline
d. 1,3,5-trimethylbenzene

Answer

A) 

C) 

B) 

D) 

15.2: STRUCTURE AND STABILITY OF BENZENE

OBJECTIVES

After completing this section, you should be able to

1. compare the reactivity of a typical alkene with that of benzene.
2. Use the heat of hydrogenation data to show that benzene is more stable than might be expected for “cyclohexatriene.”
3. state the length of the carbon-carbon bonds in benzene, and compare this length with those of bonds found in other hydrocarbons.
4. describe the geometry of the benzene molecule.
5. describe the structure of benzene in terms of resonance.
6. describe the structure of benzene in terms of molecular orbital theory.
7. draw a molecular orbital diagram for benzene.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- degenerate

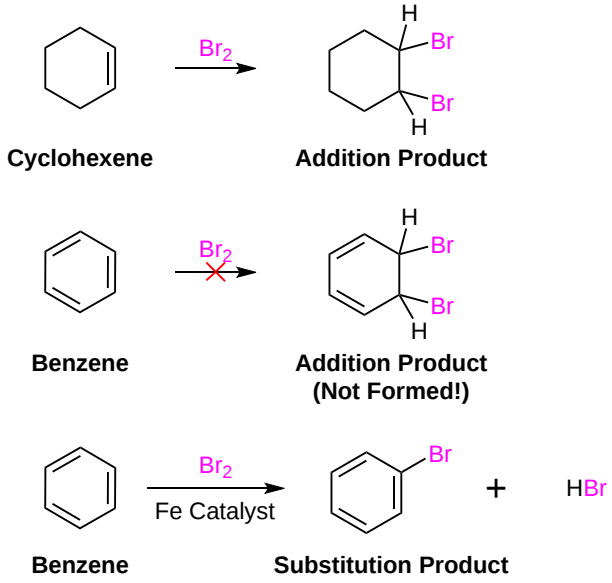
STUDY NOTES

You may wish to review Sections 1.5 and 14.1 before you begin to study this section.

Note that the figure showing the molecular orbitals of benzene has two bonding (π_2 and π_3) and two anti-bonding (π^* and π_5^*) orbital pairs at the same energy levels. Orbitals with the same energy are described as degenerate orbitals.

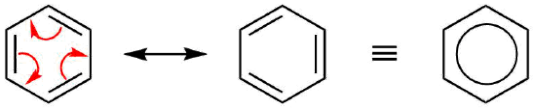
STRUCTURE OF BENZENE

When benzene (C_6H_6) was first discovered its low hydrogen to carbon ratio (1:1) led chemists to believe it contained double or triple bonds. Since double and triple bonds rapidly add bromine (Br_2), this reaction was applied to benzene. Surprisingly, benzene was entirely unreactive toward bromine. In addition, if benzene is forced to react with bromine through the addition of a catalyst, it undergoes **substitution reactions** rather than the addition reactions that are typical of alkenes. These experiments suggested that the six-carbon benzene core is unusually stable to chemical modification.

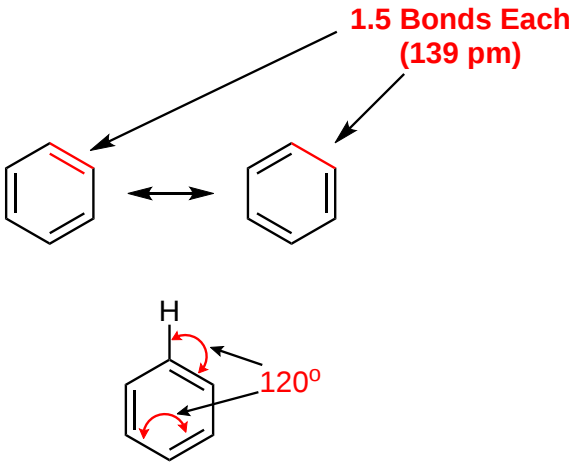


The conceptual contradiction presented by a high degree of unsaturation (low H:C ratio) and high chemical stability for benzene and related compounds remained an unsolved puzzle for many years. Eventually, the presently accepted structure of benzene as a hexagonal, planar ring of carbons with alternating single and double bonds was adopted, and the exceptional chemical stability of this system was attributed to special resonance stabilization of the conjugated cyclic triene. No single structure provides an accurate representation of benzene as it is a combination of two structurally and energetically equivalent resonance forms representing the continuous cyclic conjugation of the double

bonds. In the past, the benzene resonance hybrid was represented by a hexagon with a circle in the center to represent the benzene's pi-electron delocalization. This method has largely been abandoned because it does not show the pi electrons contained in benzene. Currently, the structure of benzene is usually represented by drawing one resonance form with the understanding that it does not completely represent the true structure of benzene.

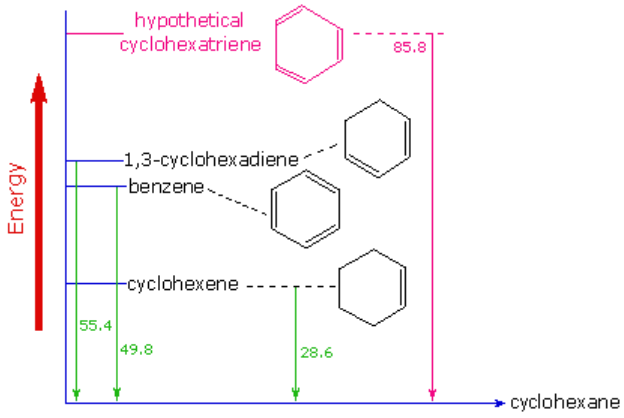


The six-membered ring in benzene is a perfect hexagon with all carbon-carbon bonds having an identical length of 139 pm[1]. The 139 pm bond length is roughly in between those of a C=C double bond (134 pm) and a C-C single (154 pm) which agrees with the benzene ring being a resonance hybrid made up of 1.5 C-C bonds. Each carbon in the benzene ring is sp^2 hybridized which makes all the C-C-C and H-C-C bond angles in benzene 120^o and makes the overall molecule planar.



THE HIGH STABILITY OF BENZENE

In previous polyalkene, examples the electron delocalization described by resonance enhanced the stability of the molecule. However, benzene's stability goes beyond this. 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 called **aromaticity** and molecules with aromaticity are called aromatic compounds. Benzene is the most common aromatic compound but there are many others. Aromatic stabilization explains benzene's lack of reactivity compared to typical alkenes.

ATOMIC ORBITALS OF BENZENE

Also, each of benzene's six carbon atoms are sp^2 hybridized and have an unhybrized p orbital perpendicular to plane of the ring. Because each of the six carbon atoms and their corresponding p orbitals are equivalent, it is impossible for them to only overlap with one adjacent p orbital to create three defined double bonds. Instead each p orbital overlaps equally with both adjacent orbitals creating a cyclic overlap involving all six p orbitals. This allows the p orbitals to be delocalized in molecular orbitals that extend all the way around the ring allowing for more overlap than would be obtained from the linear 1,3,5-hexatriene equivalent.

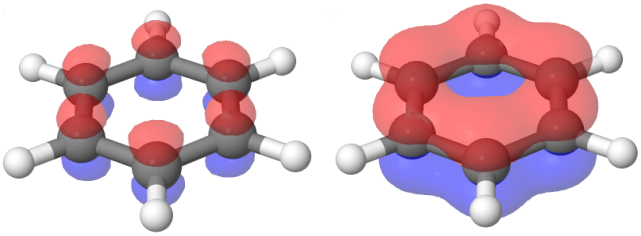


Figure 15.2.1: Each carbon in the benzene ring is sp2 hybrized with a p orbital perpendicular to the ring plane (Left) Being planar and cyclic allows benzene's p orbitals to undergo cyclic overlap (Right)

For this to happen, of course, the ring must be planar – otherwise the *p* orbitals couldn't overlap properly and benzene is known to be a flat molecule. An electrostatic potential map of benzene, shown below, shows that the pi electrons are evenly distributed around the ring and that every carbon equivalent.

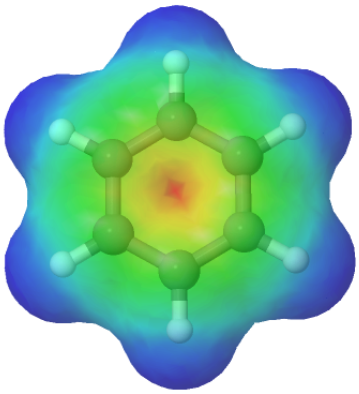
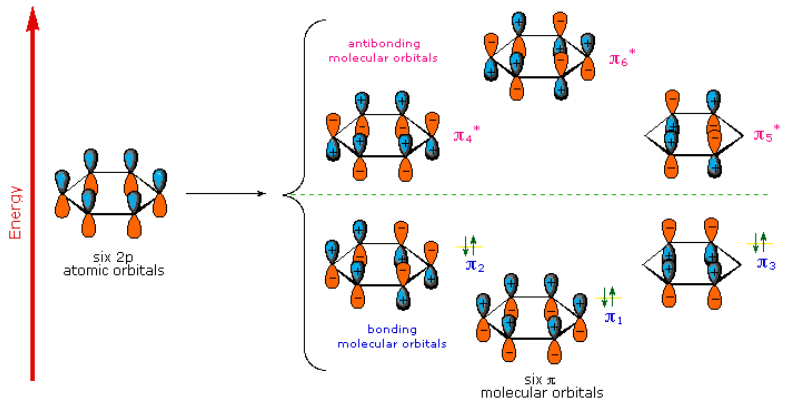


Figure 15.2.2: An electrostatic potential map of benzene

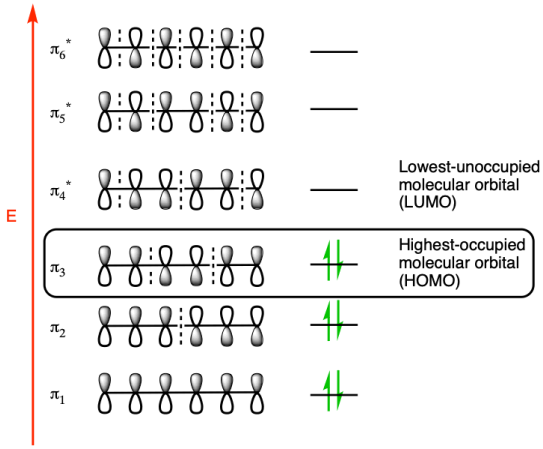
THE MOLECULAR ORBITALS OF BENZENE

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.



To better see source of the stabilizing aromaticity effect created by the cyclic p orbitals of benzene, the molecular orbitals of 1,3,5-hexatriene must be investigated. The molecule 1,3,5-hexatriene contains six p orbitals which all overlap but in a linear fashion. As with benzene, this overlap creates 3 stabilized bonding molecular which are completely filled with six p electron. As expected, the conjugation creates a marked increase of stability in 1,3,5-hexatriene but not as much as in benzene.

The Pi Molecular Orbitals Of 1,3,5 Hexatriene



The main difference in stability can be seen when comparing the lowest energy molecular orbital of 1,3,5-hexatriene and benzene: pi_1. In pi_1 molecular orbital of 1,3,5-hexatriene there are 5 stabilizing bonding interactions where there are 6 stabilizing bonding interactions in the pi_1 of benzene. The sixth bonding interaction is made possible by benzene's p orbitals being in a ring. Because benzene's pi_1 molecular orbital has more stabilizing bonding interactions it is lower in energy than the pi_1 molecular orbital of 1,3,5-hexatriene. This gives benzene the additional aromatic stability not seen in the acyclic 1,3,5-hexatriene.

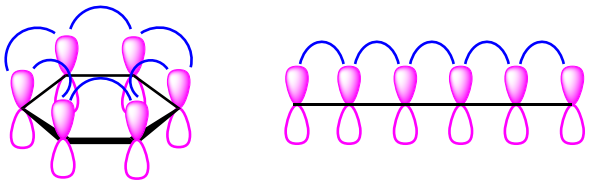
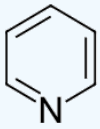


Figure 15.2.3: The pi_1 molecular orbital of benzene (Left) has 6 stabilizing bonding interaction where 1,3,5-hexatriene's (Right) only has 5.

EXERCISES

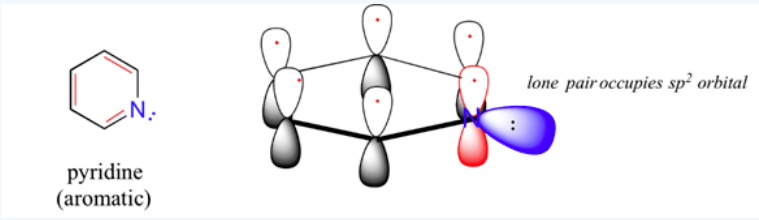
EXERCISE 15.2.1

The molecule, pyridine, is planar with bond angles of 120°. Pyridine has many other characteristics similar to benzene. Draw a diagram showing the p orbitals in pyridine and use it to explain its similarity to benzene.



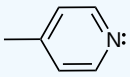
Answer

The nitrogen and each carbon in the pyridine ring is sp^2 hybridized. In the bonding picture for pyridine, the nitrogen is sp^2-hybridized, with two of the three sp^2 orbitals forming sigma overlaps with the sp^2 orbitals of neighboring carbon atoms, and the third nitrogen sp^2 orbital containing the lone pair electrons. The unhybridized p orbital contains a single electron, which is part of the 6 pi-electron system delocalized around the ring. Pyridine is most likely aromatic which gives it its planar shape and 120° bond angles.

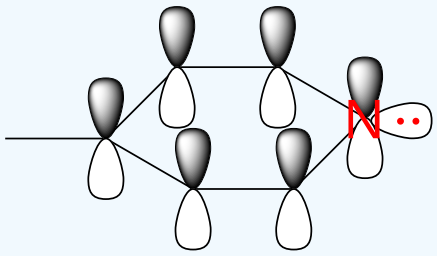


EXERCISE 15.2.2

The molecule shown, *p*-methylpyridine, has similar properties to benzene (flat, 120° bond angles). Draw the pi-orbitals for this compound.



Answer



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15.3: AROMATICITY AND THE HÜCKEL 4N + 2 RULE

OBJECTIVES

After completing this section, you should be able to

1. define aromaticity in terms of the Hückel $4n + 2$ rule.
2. use the Hückel $4n + 2$ rule to determine whether or not a given polyunsaturated cyclic hydrocarbon should exhibit aromatic properties.
3. describe the difference in properties between an aromatic hydrocarbon, such as benzene, and a non-aromatic polyunsaturated cyclic hydrocarbon, such as cyclobutadiene or cyclooctatetraene.
4. draw molecular orbital diagrams for aromatic species, such as benzene, the cyclopentadienyl anion and pyridine, and compare these diagrams with those obtained for non-aromatic species, such as cyclobutadiene and the cyclopentadienyl cation.

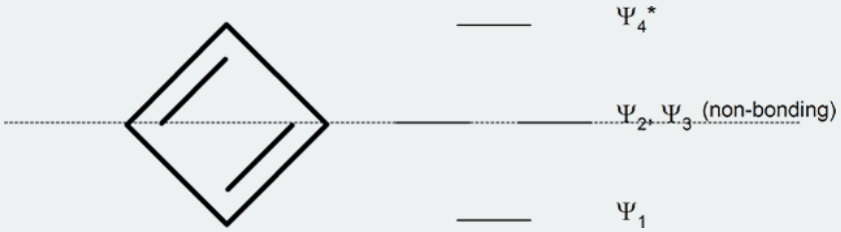
STUDY NOTES

The following mnemonic device will help you establish the approximate energy levels for the molecular orbitals of various organic ring systems.

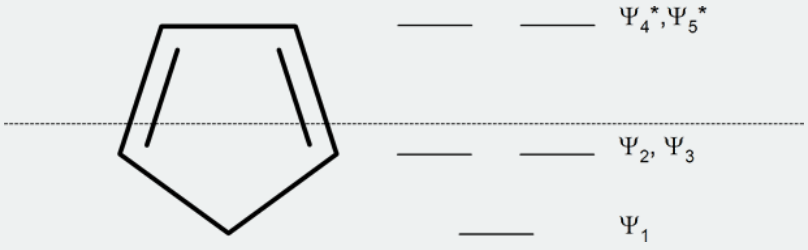
Whatever the size of the ring, place one point of the ring down to the bottom. The corners of the ring, where the carbons are located, will roughly approximate the location and pattern of the molecular orbital energy levels. Cut the ring exactly in half. The energy levels in the top half will be anti-bonding (Ψ^*) orbitals and those in the bottom will be bonding (Ψ) orbitals. If the carbons fall directly in the centre of the ring (e.g., four-membered rings) the energy levels there are non-bonding.

cyclopropenyl ring (three-membered ring)

cyclobutadienyl ring (four-membered ring)



cyclopentadienyl ring (five-membered ring)



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

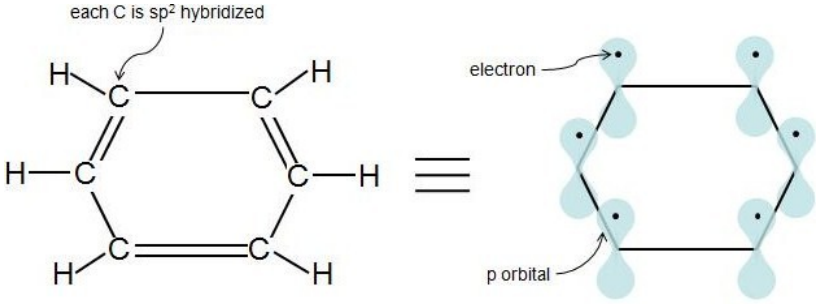
When deciding if a compound is aromatic, go through the following checklist. If the compound does not meet all the following criteria, it is likely not aromatic.

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 π electrons (n=0 or any positive integer)

COUNTING Π ELECTRONS?

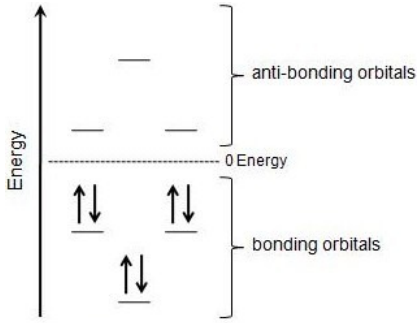
Perhaps the toughest part of Hückel's Rule is figuring out which electrons in the compound are actually π electrons. Once this is figured out, the rule is quite straightforward. Pi electrons lie in the p orbitals and sp^2 hybridized atoms have 1 of these p orbitals each. When looking at a C=C double bond we know that there is one sigma bond and one pi bond. The pi bond is formed by the overlap of 1 p orbital from each carbon in the double bond. Each p orbital contains one electron so when the two p orbitals overlap the two electrons become a pi bond and are thus called pi electrons. Because aromaticity deals directly with double bonds and conjugation it is simpler to just count the number pi electrons in a compound. Each double bond (π bond) always contributes 2 π electrons. Benzene has 3 double bonds, so it has 6 π electrons.



benzene has 6 π electrons

WHY 4N+2 Π ELECTRONS?

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:

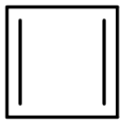
$$4n+2=6 \tag{15.3.1}$$
$$4n=4 \tag{15.3.2}$$
$$n=1 \tag{15.3.3}$$

For benzene, we find that $n=1$, which is a positive integer, so the rule is met.

With Hückel's theory we can assume that if a molecule meets the other criteria for aromaticity and also has 2, 6, 10, 14, 18 ect. pi electrons it will most likely be aromatic.

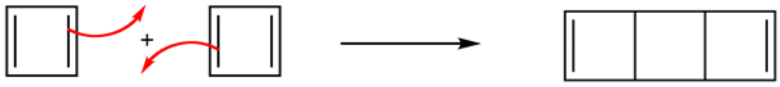
ANTIAROMATICITY

More than 100 years ago, chemists recognized the possible existence of other conjugated cyclic polyalkenes, which at least superficially would be expected to have properties like benzene. The most interesting of these are cyclobutadiene, whose shape and alignment of p orbitals suggested it should have substantial electron-delocalization energies.



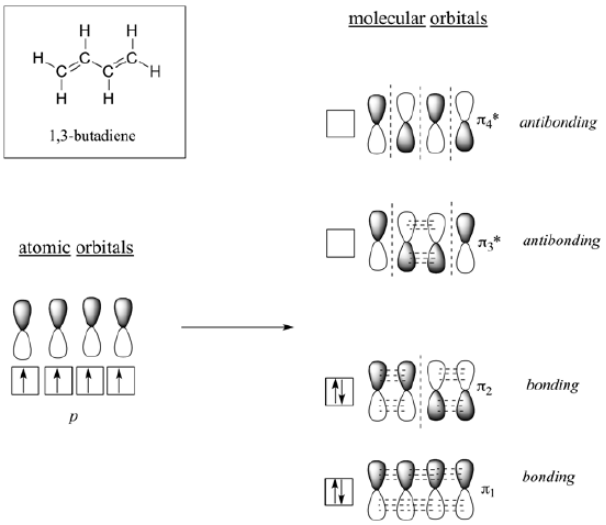
Cyclobutadiene

However, cyclobutadiene was found to be an extremely unstable molecules. In fact, cyclobutadiene is even more reactive than most alkenes. The synthesis of cyclobutadiene eluded chemists for almost 100 years. As more work was done, it became increasingly clear that the molecule, when formed in reactions, was immediately converted to something else. Finally, cyclobutadiene was captured in an essentially rigid matrix of argon at 8K. On warming to even 35K , it dimerizes through a Diels Alder reaction to yield a tricyclicdiene.



Due to the square ring, cyclobutadiene was expected to have some degree of destabilization associated with ring strain. However, estimations of the strain energies, though substantial, did not account for cyclobutadiene's high degree of instability. Also, why was it not being stabilized through cyclic conjugation in the same way as benzene. The answer can be seen in the molecular orbitals.

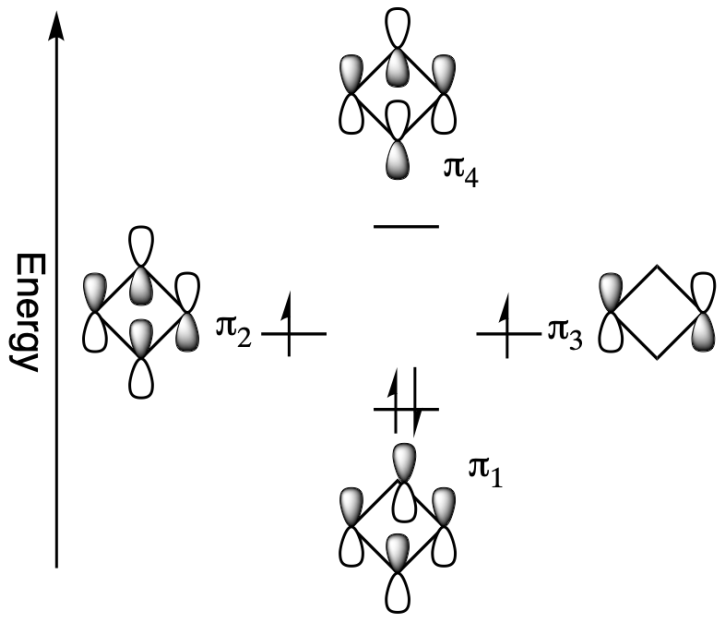
We considering the molecular orbitals diagram of the analogous 1,3-butadiene, the four *2p* atomic orbitals combine to form four pi molecular orbitals of increasing energy. Two bonding pi orbitals and two antibonding pi* orbitals. The 4 pi electrons of 1,3-butadiene completely fill the bonding molecular orbitals giving is the additional stability associated with conjugated double bonds.



However, when placed into a ring the molecular orbitals undergo a significant change. The four p orbitals of cyclobutadiene combine to form the following 4 molecular orbitals:

- a bonding molecular orbital which is lower in energy than the atomic orbitals
- two degenerate non-bonding molecular orbitals which are of equivalent energy to the atomic orbitals
- one antibonding molecular orbital which is higher in energy

The non-bonding orbitals represent that there is no direct interaction between adjacent atoms. When adding cyclobutadiene's 4 pi electrons to the molecular orbital diagram, the bonding orbital is filled and both non-bonding orbitals are singly occupied. If cyclobutadiene's double bonds were delocalized, all the pi electrons would be in low energy bonding orbitals. However, only two of the pi electrons are in bonding orbitals; the other two are non-bonding. In addition, the molecular orbital diagram shows that two of the electrons are unpaired, a situation called a triplet state, which usually makes organic molecules very reactive. For cyclobutadiene cyclic conjugation has made the molecule less stable. This unexpected instability in 4n π-electron cyclic conjugated compounds is termed **antiaromaticity** and the compounds are called antiaromatic.

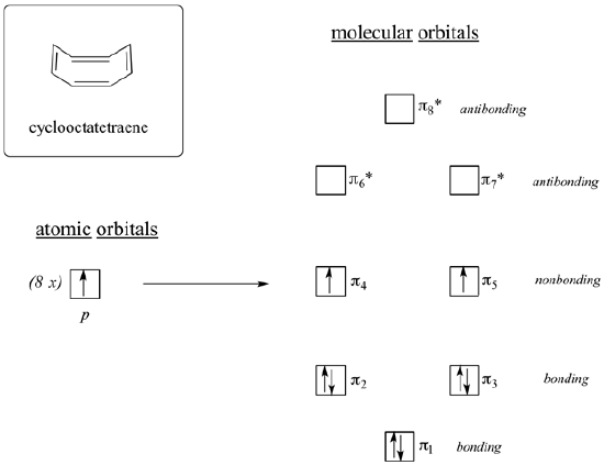


Antiaromaticity gives cyclobutadiene some interesting structural features. Cyclobutadiene's single and double bonds have different bond lengths, 158 pm and 135 pm respectively which give it a rectangular shape. If the double bonds were conjugated, there would only be one average bond length, like benzene, and shape would be square. In fact, cyclobutadiene's double bonds are not conjugated but locked into position.

Just like 4n + 2 rule with aromaticity, compounds which are flat, cyclic, have a p orbital at every member of the ring, and 4n pi electrons should be antiaromatic. Another potentially antiaromatic molecule is 1,3,5,7-cyclooctatetraene.

Cyclooctatetraene was first synthesized in 1911 by a German chemist, R. Willstatter (Nobel Prize 1915), who reported an extraordinary thirteen-step synthesis of cyclooctatetraene from a rare alkaloid called pseudopelletierine isolated from the bark of pomegranate trees. However, during the Second World War, the German chemist W. Reppe found that cyclooctatetraene can be made in reasonable yields by the tetramerization of ethyne under the influence of a nickel cyanide catalyst:

If cyclooctatetraene was flat it would have all the requirements to be antiaromatic. It is cyclic, has a p orbital in every member of the ring, and has 8 pi electrons. When looking at the molecular orbital diagram of cyclooctatetraene we see it shares certain characteristics in common with cyclobutadiene. Two of the molecular orbitals are degenerate non-bonding orbitals. When the molecular orbitals are fill with cyclooctatetraene's 8 pi electrons the last two electrons are unpaired in the two nonbonding orbitals creating a triplet state. Based off the molecular orbital diagram cyclooctatetraene should be antiaromatic.

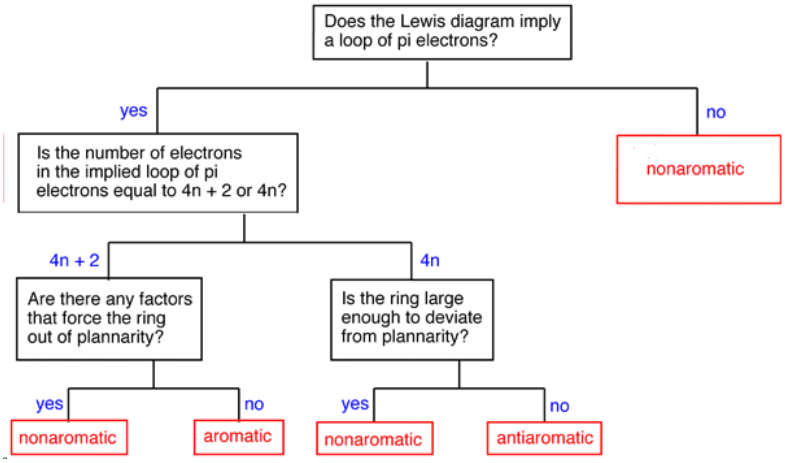


However, cyclooctatetraene is easily prepared and relatively stable. Also, it undergoes addition reactions typical of alkenes. In reality, cyclooctatetraene is not flat but has a tub-like shape. By assuming this shape, the p orbtials between double bond are out of alignment for

overlap. Because the double bonds are not conjugated, cyclooctatetraene escapes the destabilizing effects of antiaromaticity. This makes its its pi bonds react like 'normal' alkenes. Because cyclooctatetraene is not flat nor conjugated it is properly defined as non-aromatic. In general, if an antiaromatic compound has the ability to form a non-planar shape it will do so to avoid destabilization by becoming non-aromatic.

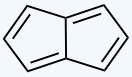
DETERMINING IF A COMPOUND IS AROMATIC, ANTIAROMATIC, OR NONAROMATIC

To make this determination it is important to first as if the compound has the possibility of cyclic conjugation. This requires that the compound be cyclic and have a p orbital at every atom in the ring. If the compound does not have both of these criteria it cannot be aromatic or antiaromatic and must therefore be nonaromatic. Next the number of pi electrons in the ring is determined to see if it follows the count of aromaticity (4n + 2) or antiaromaticity (4n). Before making the final determination, it is vital to know the actual geometry of the molecule. Despite the number of pi electrons, a compound cannot be aromatic or antiaromatic if its geometry is not planar to allow for p orbital overlap.

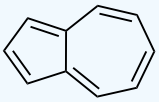


EXAMPLE 15.3.1

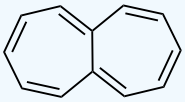
Cyclopentadiene (planar)
4 p Electrons
Nonaromatic



Pentalene (planar)
8 p Electrons
Antiaromatic



Azulene (planar)
10 p Electrons
Aromatic



Heptalene (planar)
12 p Electrons
Antiaromatic

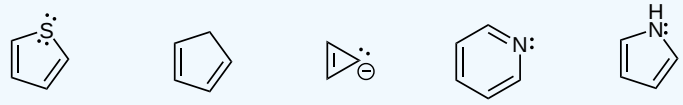
A COMMON MISCONCEPTION

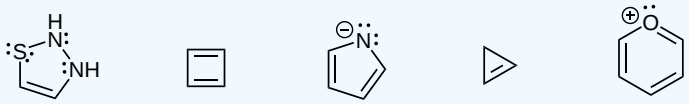
A very common misconception is that hybridization can be used to predict the geometry, or that hybridization somehow involves an energy cost associated with 'promoting' electrons into the hybrid orbitals. **This is entirely wrong.** Hybridization is always determined by geometry. You can only assign hybridization states to an atom if you already know its geometry, based on some experimental or theoretical evidence. The geometry of the oxygen in furan is trigonal planar and therefore the hybridization must be sp^2.

The *specific* rule is that if you have an sp^2 conjugated system, the lone pair will be involved ***if it makes the system more stable.*** In this case, conferring Hückel 4n+2 aromaticity. For furan with *two* lone pairs on the oxygen atom, if we count electrons from the carbon atoms, we have 4 (one per carbon). So adding two electrons from one of the lone pairs will give 6 = 4(1)+2, so Hückel rule is applicable and furan is aromatic.

EXERCISE 15.3.1

Using the criteria for aromaticity, determine if the following molecules are aromatic:





Answer

a) Aromatic - only 1 of S's lone pairs counts as π electrons, so there are 6 π electrons, n=1

b) Not aromatic - not fully conjugated, top C is sp^3 hybridized

c) Not aromatic - top C is sp^2 hybridized, but there are 4 π electrons, n=1/2

d) 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

e) Aromatic - there are 6 π electrons, n=1

f) 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

g) Not aromatic - there are 4 π electrons, n=1/2

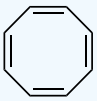
h) Aromatic - only 1 of N's lone pairs counts as π electrons, so there are 6 π electrons, n=1

i) Not aromatic - not fully conjugated, top C is sp^3 hybridized

j) 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

? EXERCISE 15.3.2

To be aromatic, a molecule must be planar conjugated, and obey the 4n+2 rule. The following is the following molecule aromatic?



Answer

No, it is not. It does not obey the 4n+2 rule. Also it is not planar.

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.

15.4: AROMATIC IONS

OBJECTIVES

After completing this section, you should be able to

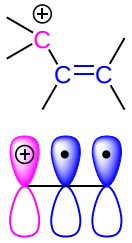
1. use the Hückel 4*n* + 2 rule to explain the stability of the cyclopentadienyl anion, the cycloheptatrienyl cation and similar species.
2. use the Hückel 4*n* + 2 rule to determine whether or not a given unsaturated cyclic hydrocarbon anion or cation is aromatic.
3. draw the resonance contributors for the cyclopentadienyl anion, cation and radical, and similar species.

AROMATIC IONS

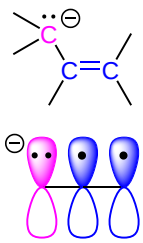
As previously, noted a ring must be fully conjugated to have the potential to be aromatic. This means that every atom in the ring must have a *p* orbital which can overlap with adjacent *p* orbitals. Until now the atoms providing the *p* orbitals have been neutral sp^2 hybridized carbons, however it is also possible for sp^2 hybridized carbons to have a charge. There are several examples of cationic and anionic compounds with unexpected stabilities that suggest that they are aromatic. It is important to understand how charged carbons in these compounds will affect the determination of aromaticity.

There are two main situations which need to be considered: The conjugation of a carbocation and the conjugation of a carbanion. A carbocation carbon is surrounded by three electron groups giving it sp^2 hybridization. The remaining unhybridized *p* orbital holds the carbocation's positive charge and is vacant of pi electrons. Although a carbocation is capable of extending conjugation it does not add to the compound's pi electron count.

A carbanion carbon is surrounded by four electron groups and would normally be sp^3 hybridized. However, to obtain the stabilizing effects of conjugation, carbanion carbons can becomes sp^2 hybridized putting the set of lone pair electrons into the unhybridized *p* orbital. Because the carbanion's *p* orbital contains two electrons in the form of a set of lone pair electrons, it increases a compound's pi electron count by 2.



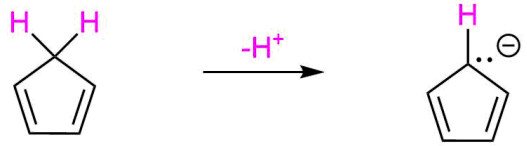
2 p Electrons Total
The carbocation adds
0 p Electrons



4 p Electrons Total
The carbanion adds
2 p Electrons

CYCLOPENTADIENE ION

One of the most well know examples of an aromatic ion is the 1,3-cyclopentadiene ion. 1,3-Cyclopentadiene is nonaromatic due to the presence of an intervening sp^3 hybridized -CH_2- carbon atom which prevents pi electrons from delocalizing about the entire ring. Also, it only has 4 pi electrons which does not follow Hückel's 4n + 2 rule. However, if a proton is removed form the CH_2 group to form the cyclopentadienyl anion, the carbon atom becomes sp^2 hybridized and the two electrons of the resulting lone pair occupy the newly produced *p* orbital. This increases the number of pi electrons in the cyclopentadienyl anion to 6 which follows the 4n +2 rule. Moreover, this new *p* orbital overlaps with the *p* orbitals already present allowing for cyclic delocalization of pi electrons about the entire ring.

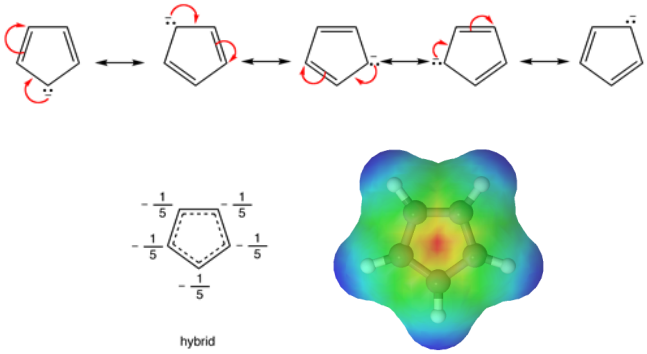


1,3-Cyclopentadiene
Nonaromatic
4 π electrons

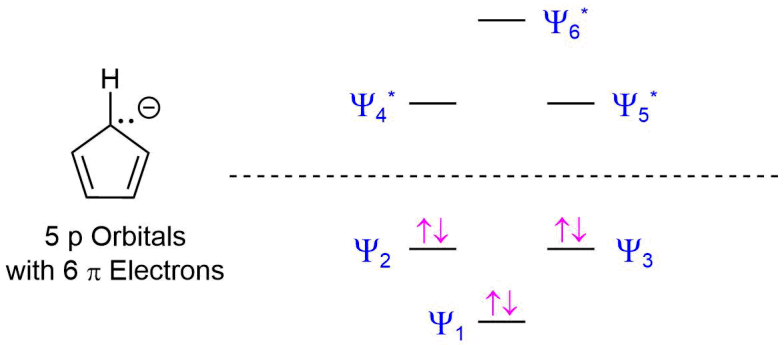
Cyclopentadienyl Anion
Aromatic
6 π electrons

The lone pair electrons and the negative charge are conjugated about the entire ring making each carbon in the cyclopentadienyl anion equivalent with 1/5 the negative charge. The resonance hybrid can be shown by drawing a series of five resonance form. Also, the

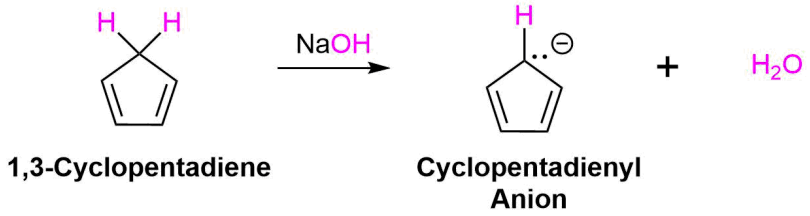
electrostatic potential map of the cyclopentadienyl anion show the negative charge, seen in red/yellow is distributed over the entire ring. The fact that the red/yellow color is held in the center of the ring indicates that the extra electrons of the ion are involved in the aromatic p-electron system.



The reason why the 4n +2 rule still works for a 5 p orbital ring system can be seen by looking the molecular orbital diagram of the cyclopentadienyl anion. As discussed in **Section 15.3**, the molecular orbital diagram of a 5 p orbital system is made up of 3 bonding MO's and 2 antibonding MO's. The 6 pi electrons gained by forming an anion is enough to completely fill the bonding MO's in the diagram giving the cyclopentadienyl anion aromaticity.



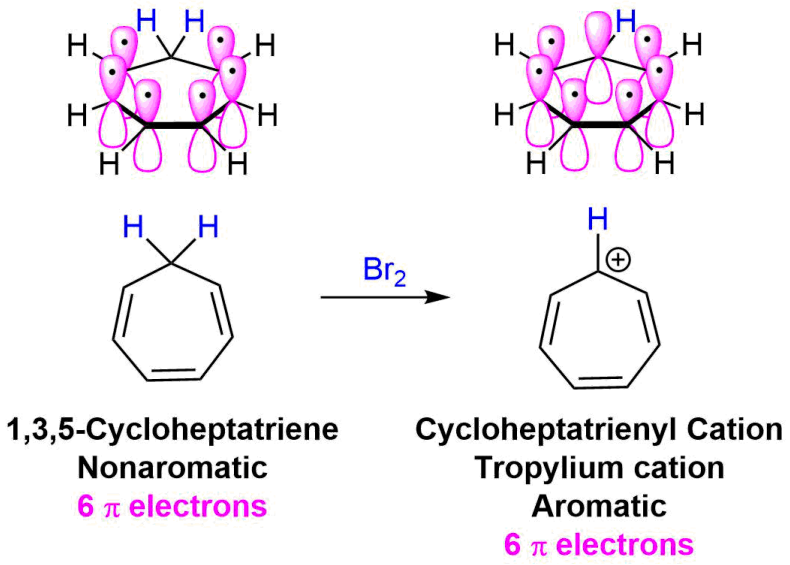
One of the effects of the aromaticity of the cyclopentadienyl anion is that the acidity of 1,3-cyclopentadiene is unusually strong. As previously discussed, stabilizing the conjugate base increases the acidity of the corresponding acid. In this case, the conjugate base of 1,3-cyclopentadiene, the cyclopentadienyl anion, is stabilized through aromaticity. This makes 1,3-cyclopentadiene one of the most acidic hydrocarbons known with a pK_a of 16. This is almost 10^{30} times more acidic than cyclopentane. Because of its acidity, cyclopentadiene can be deprotonated by moderately strong bases such as NaOH.



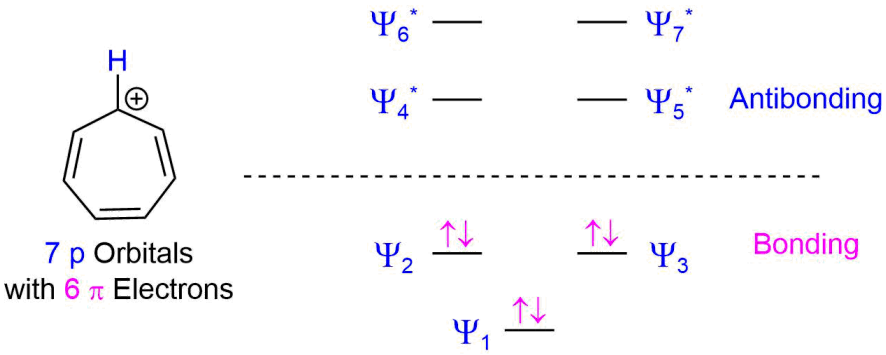
TROPYLIUM ION

The molecule 1,3,5-cycloheptatriene has six pi electrons but is nonaromatic due the presence of an sp^3 hybridized -CH_2- group which prevents cyclic delocalization. When 1,3,5-cycloheptatriene is reacted with a reagent that can remove a hydride ion ($H:^-$), the 1,3,5-cycloheptatrienyl cation, which is commonly known as the tropylium cation, is formed with unexpected ease. Despite the presence of an electron deficient carbocation, the tropylium cation, is unusually stable and can be isolated as a salt.

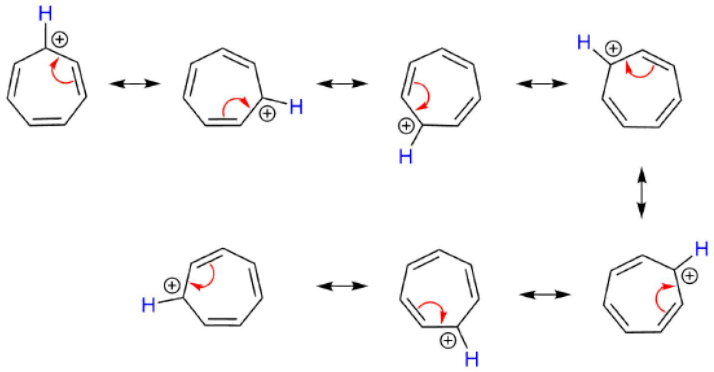
Removal of a hydride from the -CH_2- group in 1,3,5-cycloheptatriene creates an sp^2 hybridized carbocation with a vacant *p* orbital. The new *p* orbital allows for cyclic conjugation to occur among the seven *p* orbitals in the tropylium cation. The vacant *p* orbital does not change the pi electron count so the tropylium cation has 6 pi electrons which obeys the 4n + 2 rule for aromaticity.

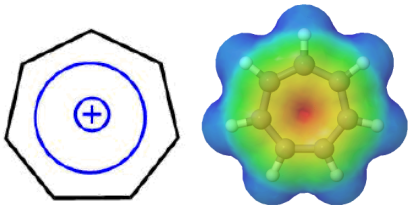


The molecular orbital diagram for the 7 *p* orbitals in the tropylium cation has three bonding MO's and 4 antibonding MO's. The tropylium cation's 6 pi electrons completely fill the bonding molecular orbitals which is consistent with the tropylium cation being aromatic and therefore unusually stable.



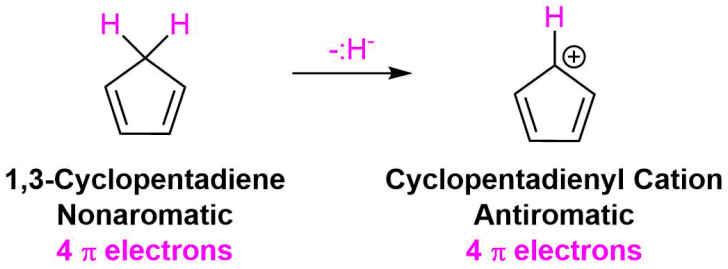
As predicted with aromaticity, the positive charge is completely conjugated about the entire ring giving each carbon +1/7 charge. The true resonance hybrid can be depicted by drawing a series of seven resonance form. Also, the electrostatic potential map of the tropylium cation shows the positive charge is evenly distributed over the entire ring. The equivalency of the carbons in the seven membered ring is experimentally supported by an ^{1}H NMR spectrum of the tropylium cation which contains one peak showing that all seven protons are equivalent.



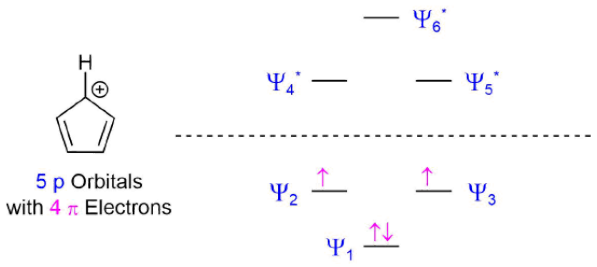


ANTIAROMATIC IONS

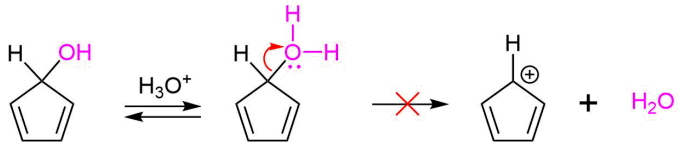
In a similar fashion, cyclically conjugated ions with 4n pi electrons can be predicted to be antiaromatic and therefore highly unstable. An excellent example is the cyclopentadienyl cation. Above, the cyclopentadienyl anion was shown to be aromatic, however, the formation of a carbocation produces a different result. Although the vacant *p* orbital provided by the carbocation allows for cyclic conjugation to occur the compound only has 4 pi electrons.



After placing these 4 pi electrons into the molecular orbital for a cyclic 5 *p* orbital species the bonding molecular orbitals remain unfilled. Two of the pi electrons are unpaired in degenerate molecular orbitals creating the highly unstable triplet state. As predicted by Hückel's Rule, the cyclopentadienyl cation has 4n pi electrons and should be anitaromatic and very unstable.



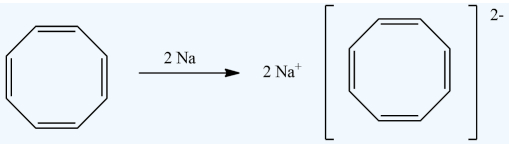
Although there is some discussion as to whether the cyclopentadienyl cation is truly antiaromatic, there is experimental evidence which shows it is usually unstable. In particular, the compound 2,4-cyclopentadien-1-ol is usually resistant to S_N1 reactions with acid halides. The carbocation intermediate created during the mechanism of this reaction would be expected to easily form due to the resonance stabilization provided by the two double bonds. Because the carbocation intermediate is antiaromatic it does not form so the reaction does not occur.



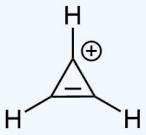
? EXERCISE 15.4.1

1) Are all bonds equivalent cyclopentadienyl anion? How many lines (signals) would you expect to see in a H^1 and C^{13} NMR spectrum?

2) The following reaction occurs readily. Propose a reason why this occurs?



3) Is the cyclopropenium ion aromatic? Use the 4n + 2 rule and the MO diagram for a 3 p orbital ring system to explain your answer.



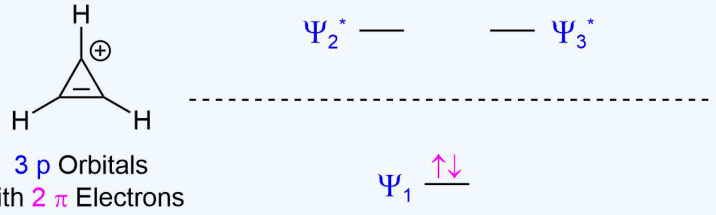
Cyclopropenium Ion

Answer

1) Due to the cyclopentadienyl anion being fully conjugated a protons and carbons are equivalent. Both the ^{1}H and ^{13}C NMR spectrum would only have one signal.

2) The addition of two electrons gives the ring system 10 pi electrons which follows the 4n+2 rule making the dianion aromatic. When looking at the MO diagram for an 8 p orbital ring system, 10 pi electrons completely fills the three bonding MO's and the two nonbonding MO's allowing for aromaticity.

3) The cyclopropenium ion has 2 pi electrons which follows the 4n + 2 rule when n = 0. When considering the molecular orbital diagram for a 3 p orbital ring system the is one bonding MO and two antibonding MO's. The two pi electrons completely fill the bonding MO allowing for aromaticity.



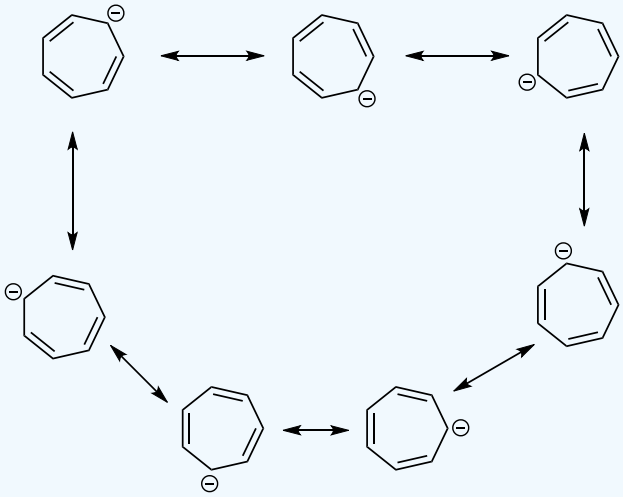
EXERCISES

? EXERCISE 15.4.2

Draw the resonance structures for cycloheptatriene anion. Are all bonds equivalent? How many lines (signals) would you see in a H^{1} NMR? C^{13} NMR?

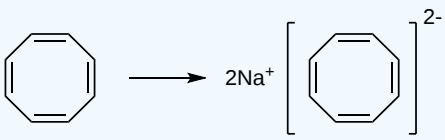
Answer

All protons and carbons are the same, so therefore each spectrum will only have one signal each in the proton NMR and carbon NMR.



EXERCISE 15.4.3

The following reaction occurs readily. Propose a reason why this occurs?



Answer

The ring becomes aromatic with the addition of two electrons. Thereby obeying the 4n+2 rule.

15.5: AROMATIC HETEROCYCLES - PYRIDINE AND PYRROLE

OBJECTIVES

After completing this section, you should be able to

1. draw the structure of the common aromatic heterocycles pyridine and pyrrole.
2. use the Hückel $4n + 2$ rule to explain the aromaticity of each of pyridine and pyrrole.
3. draw a diagram to show the orbitals involved in forming the conjugated six-pi-electron systems present in aromatic heterocycles such as pyridine, pyrrole, etc.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

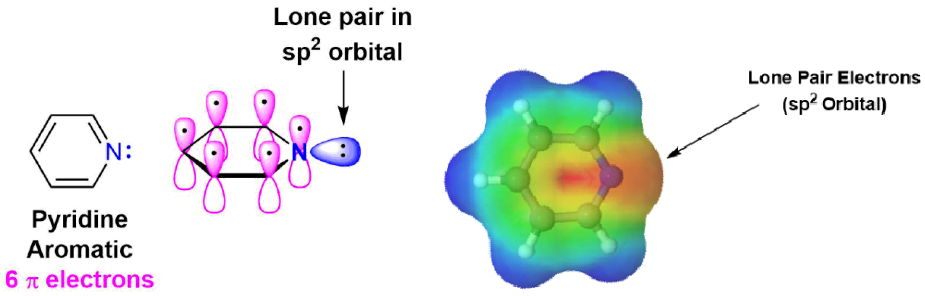
- carbocycles
- heterocycles

AROMATIC HETEROCYCLES

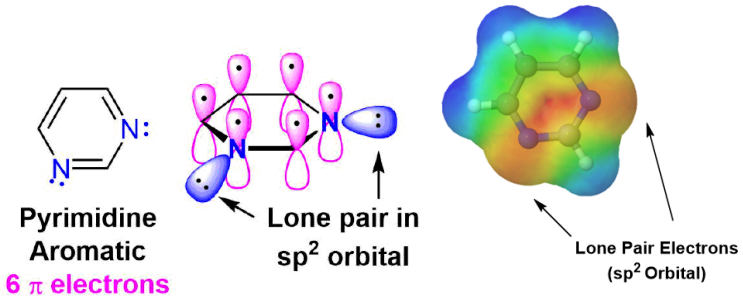
Many cyclic compounds have an element other than carbon present in the ring. Cyclic compounds that include one or more elements other than carbon are called a heterocycle. The most common heterocyclic compounds contain carbon along with nitrogen, oxygen, or sulfur. Because some heterocyclic compounds are aromatic, it is important to discuss how the inclusion of non-carbon atoms affects the determination of aromaticity. The reactivity and general physical properties of aromatic nitrogen heterocycles will be discussed in greater detail in Section 24.9.

PYRIDINE & PYRIMIDINE

Pyridine is an example of a six-membered aromatic heterocycle and has an electronic structure similar to benzene. In the bonding picture of pyridine the five carbons and single nitrogen are all sp^2 hybridized. All six of these atoms have a p orbital perpendicular to the plane of the ring and each contains one pi electron which allows the ring to be fully conjugated. This makes the pi electron count for pyridine 6 pi electrons. In much the same fashion as benzene, the 6 pi electrons follow the 4n + 2 rule and completely fill the bonding molecular orbitals which fulfills the electronic requirement for aromaticity. The lone pair electrons on pyridine's nitrogen are contained in a sp^2 orbital that lies in the same plane as the ring and does not overlap with the p orbitals of the ring. The lone pair electrons are not part of the aromatic system and do not affect the p electron count. Pyridine's electrostatic potential map shows that the lone pair electrons, shown in a yellow/red color, are locked onto the nitrogen and not distributed around the ring.

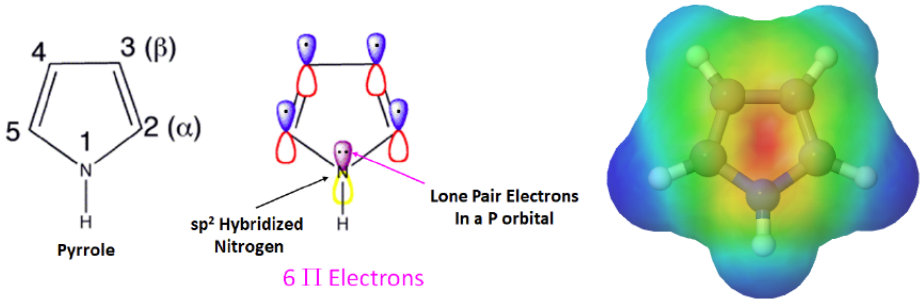


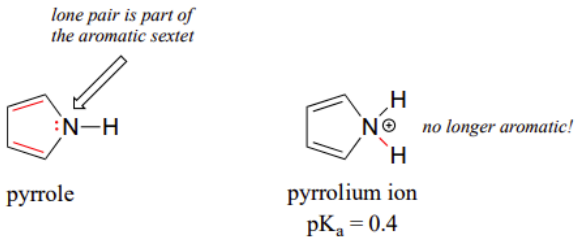
Pyrimidine is an another six-membered aromatic heterocycle that is analogous to pyridine. Pyrimidine has four carbons atoms and two nitrogen atoms that are sp^2 hybridized. Each of these atoms contributes a p orbital and a pi election allowing pyrimidine to be fully conjugated and aromatic. Both of the nitrogens in pyrimidine have lone pair electrons contained in a sp^2 orbitals and are not involved in the aromatic system. An electrostatic potential map of pyrimidine shows that neither set of lone pair electrons is distributed around the ring.



PYRROLE

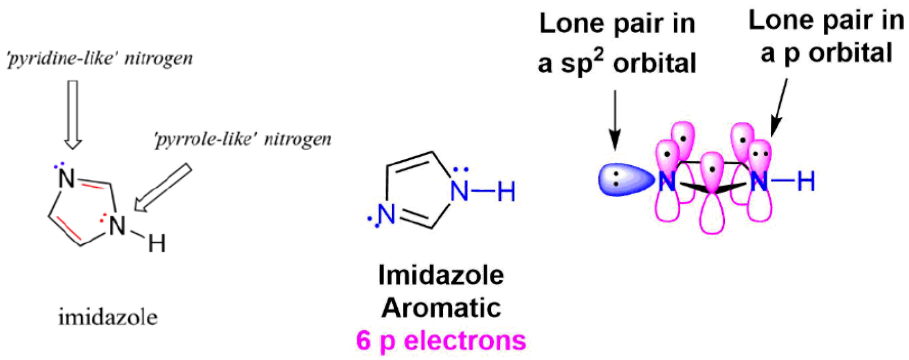
Pyrrole is a five-membered heterocyclic ring which has 5 p orbitals and six pi electrons contributing to its aromaticity. Each carbon in pyrrole contributes one p orbital and pi electron. The nitrogen in pyrrole contributes two pi electrons by becoming sp^2 hybridized and placing its lone pair electrons into a p orbital. The electrostatic potential map of pyrrole show the nitrogen's lone pair electrons are distributed in the ring. Because the nitrogen lone pair *is* part of the aromatic sextet the electrons are very stable and are much less available for bonding to a proton (and if they *do* pick up a proton, the molecule loses aromaticity). Pyrrole is a very weak base: the conjugate acid, the pyrrolium ion, is a strong acid with a pK_a of 0.4.

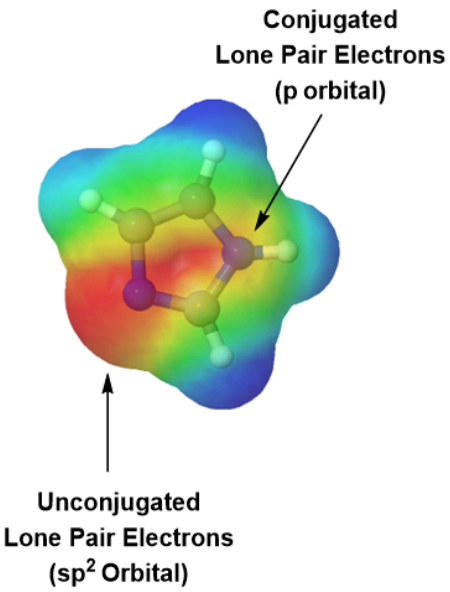




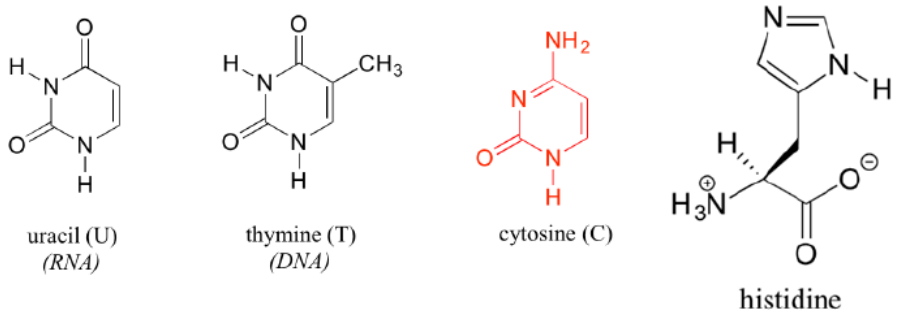
IMIDAZOLE

Imidazole is another five-membered heterocyclic ring which has 6 pi electrons and is aromatic. Both of the nitrogen atoms are sp^2 hybridized. One nitrogen is pyridine-like because it is part of a double bond and adds one pi electron to the aromatic pi ring. The other nitrogen is not part of a double bond making it pyrrole-like allowing it to contribute 2 pi electrons from it lone pair electrons. When looking at the electrostatic potential map of imidazole, the lone pair electrons on the pyrrole-like nitrogen are distributed around the ring while the lone pair electrons on the pyridine-like nitrogen are non-conjugated and locked into place.





Pyrimidine and imidazole rings are particularly important in biological chemistry. Pyrimidine, for instance, is the parent ring system in cytosine, thymine, and uracil, three of the five heterocyclic amine bases found in nucleic acids. An aromatic imidazole ring is present in histidine, one of the amino acids found in proteins.



? WORKED EXAMPLE 15.5.1

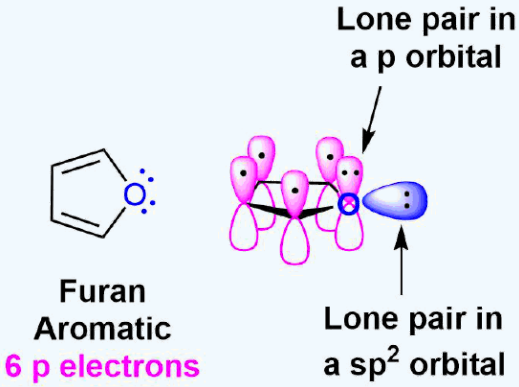
Determine if furan is aromatic. Draw an orbital diagram to support your answer.

Furan

Answer

For a molecule to be aromatic it must: Be cyclic, be planar, be fully conjugated, and have 4n+2 π electrons.

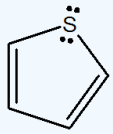
Furan is obviously cyclic and can be assumed to be planar due to the constrains of having a five membered ring with two double bonds. To be fully conjugated each atom in the ring must have a p orbital. Although the oxygen has 4 electron groups and appears to be sp^3 hybridized, it will become sp^2 hybridized to gain the stability of conjugation. Becoming sp^2 hybridized allows the oxygen atom to put a set of lone pair electrons into a p orbital allowing it to be part of the cyclic conjugation. These two pi electrons along with the 4 pi electrons provided by the two double bonds gives furan 6 pi electrons total. This follows the 4n + 2 rule making furan aromatic.



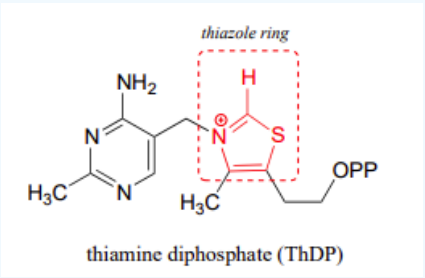
EXERCISES

? EXERCISE 15.5.1

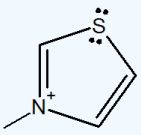
1) Draw the orbitals of thiophene to show that it is aromatic.



2) The thiazolium ring is a five-membered sulfur containing aromatic ring system which is found in biological systems, such as thiamine diphosphate (ThDP). Describe how thiazolium ring is aromatic.

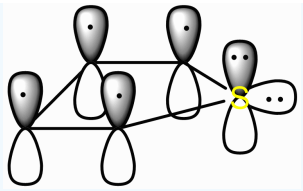


thiamine diphosphate (ThDP)

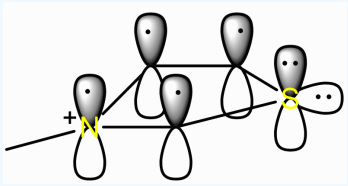


Answer

1) This drawing shows thiophene has 6 electrons in the pi-orbital.



2) Similar to the last question, the drawing shows that there is only 6 electrons in the pi-system.

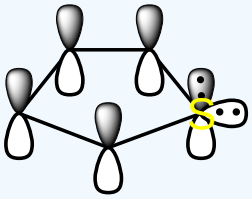


EXERCISE 15.5.2

Draw the orbitals of thiophene to show that is aromatic.

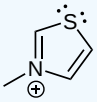
Answer

This drawing shows it has 6 electrons in the pi-orbital.



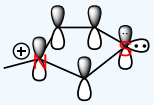
EXERCISE 15.5.3

The following ring is called a thiazolium ring. Describe how it is aromatic.



Answer

Similar to the last question, the drawing shows that there is only 6 electrons in the pi-system.



15.6: POLYCYCLIC AROMATIC COMPOUNDS

OBJECTIVES

After completing this section, you should be able to draw the resonance contributors for polycyclic aromatic compounds, such as naphthalene, anthracene, etc.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- polycyclic aromatic compounds

STUDY NOTES

As their name indicates, *polycyclic aromatic hydrocarbons* are aromatic hydrocarbons which contain more than one benzenoid (i.e., benzene-like) ring. This section deals only with those compounds in which the benzenoid rings are fused together; in other words, compounds in which at least one carbon-carbon bond is common to two aromatic rings. Another type of polycyclic aromatic hydrocarbon contains two or more benzenoid rings joined by a carbon-carbon single bond. The simplest compound of this type is biphenyl, the compound from which PCBs (polychlorinated biphenyls) are derived.

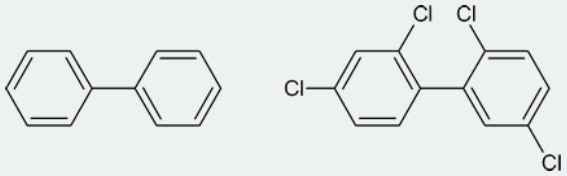


Figure 15.3: Structures of biphenyl and a typical PCB

POLYCYCLIC AROMATIC COMPOUNDS

Hückel's 4n +2 rule for aromaticity does not only apply to mono-cyclic compounds. 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 (in the structure below, note that the top right and center right rings are not attached to one another). This helical configuration renders the hexahelicene molecule chiral, and it has been resolved into stable enantiomers.

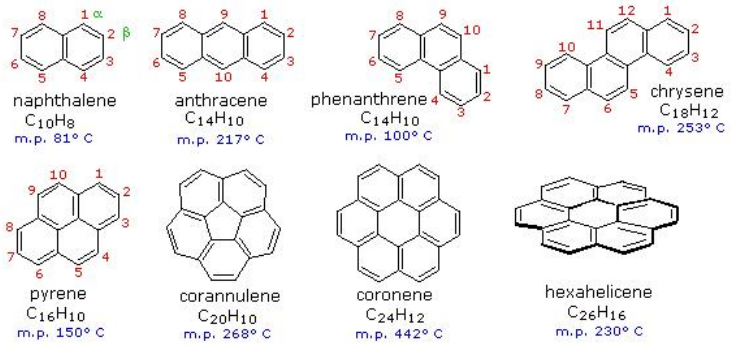
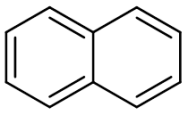
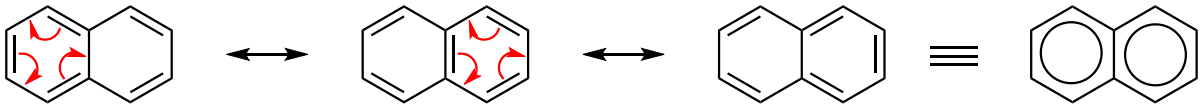


***Figure 2**: Examples of Polycyclic Aromatic Hydrocarbons (PAHs).*

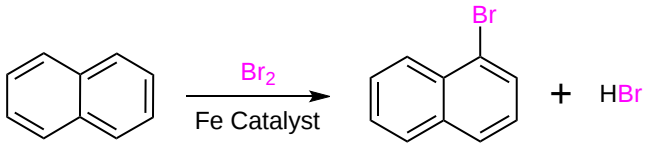
Probably the most well know polycyclic aromatic compound which only contains carbon is naphthalene ($C_{10}H_8$). Naphthalene shares many of the same characteristic as benzene. Naphthalene is cyclic and known to be flat. Each carbon in naphthalene is sp^2 hybridized so it is completely conjugated. The true structure of naphthalene is a combination of three resonance hybrids.



Naphthalene

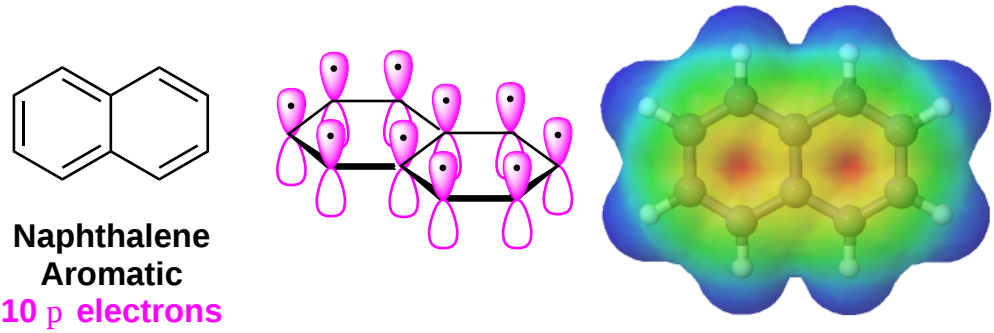


Heat of hydrogenation experiments with naphthalene shows an unusual "aromatic" stabilization energy. Also, naphthalene prefers to react with electrophiles to give substitution products rather than the typical double bond addition products.



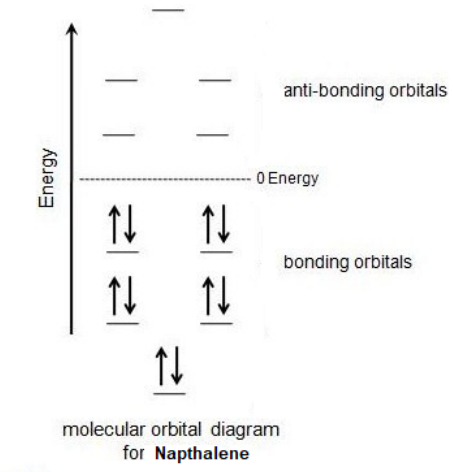
Naphthalene **1-Bromonaphthalene Substitution Product**

Every carbon in naphthalene is sp^2 hybridized so there is conjugated p orbital overlap over the entire ring system. The electrostatic potential map shows that pi electrons in naphthalene are evenly distributed making each carbon equivalent.



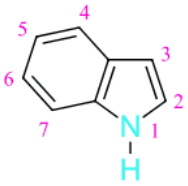
Naphthalene
Aromatic
10 p electrons

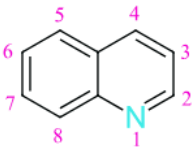
Lastly, naphthalene has 10 pi electrons which fulfills Hückel's rule. The importance of the 4n + 2 rule can be seen when considering the molecular orbital diagram of naphthalene. Naphthalene has 10 p orbitals which is 4 more than benzene. In the molecular orbital diagram of naphthalene, the 4 additional p orbitals become 2 bonding orbitals and two anti-bonding orbitals. The two additional bonding orbitals require 4 additional pi electrons to be filled so naphthalene needs 10 pi electrons in total to fill all of the bonding molecular orbitals.

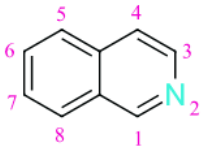


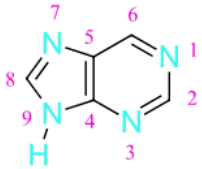
POLYCYCLIC AROMATIC HETEROCYCLES

There is a wide variety of polycyclic aromatic heterocycles, many of which contain nitrogen, oxygen, or sulfur. Some of the biologically important structures, are the nitrogen containing polycyclic aromatic heterocycles indole, quinoline, isoquinoline, and purine which are all polycyclic aromatic heterocycles commonly found in nature. Notice that these compound all have 10 pi electrons.

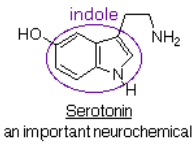

Indole


Quinoline

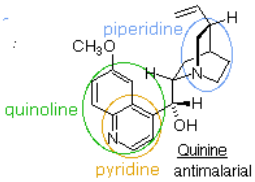

Isoquinoline


Purine

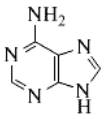
Indole, quinoline, and isoquinoline all contain a hetrocyclic ring fused to benzene. Purine is made up to two heterocyclic rings, imidazole and pyrimidine, fused together. Quinoline is found in the antimalarial drug quinine. Indole is found in the neurotransmitter serotonin. The purine ring structure is found in adenine and guanine, two important parts of DNA and in the stimulant caffeine.

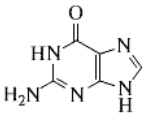


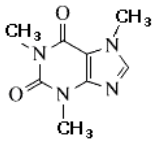
Serotonin
an important neurochemical



Quinine
pyridine
antimalarial


adenine

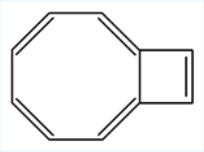

guanine


caffeine

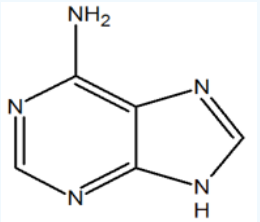
EXERCISES

EXERCISE 15.6.1

1) The following molecule is an isomer of naphthalene. Is it aromatic? Draw a resonance structure for it.

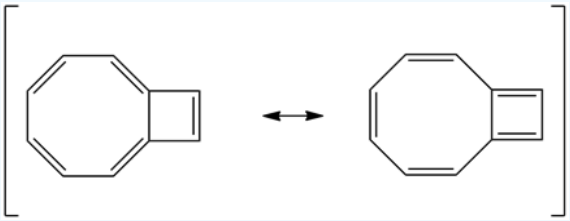


2) The following molecule is adenine. It has a purine core. Of the nitrogen in the core, how many electrons are donated into the pi system?

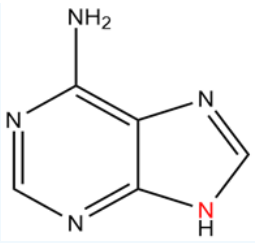


Answer

1) It has 10 pi electrons which follows the 4n+2 rule making it aromatic.

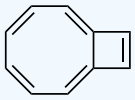


2) There is only one nitrogen of the core that contributes a set of lone pair electrons as 2 pi electrons (in red). All of the other nitrogens are sp2 hybrized and contribute 1 pi electron each. In total, the core is aromatic with 10 electrons in the pi-system.



EXERCISE 15.6.2

This is an isomer of naphthalene. Is it aromatic? Draw a resonance structure for it.

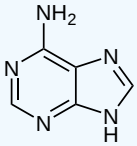


Answer

Yes, it is aromatic. 4n+2 pi-electrons.

EXERCISE 15.6.3

The following molecule is adenine. It has a purine core. Of the nitrogen in the core, how many electrons are donated into the pi system?



Answer

There is only one nitrogen of the core that contributes to the pi-system (in red). With this one lone pair the core is aromatic with 10 electrons in the pi-system.

15.7: SPECTROSCOPY OF AROMATIC COMPOUNDS

OBJECTIVES

After completing this section, you should be able to

1. determine whether an unknown compound contains an aromatic ring by inspection of its infrared spectrum, given a table of characteristic infrared absorptions.
2. state the approximate chemical shift of aryl protons in a proton NMR spectrum.
3. explain why signals resulting from the presence of aryl protons are found downfield from those caused by vinylic protons in a proton NMR spectrum.
4. propose possible structures for an unknown aromatic compound, given its proton NMR spectrum, other spectroscopic data (such as a ^{13}C NMR or infrared spectrum), or both.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- ring current

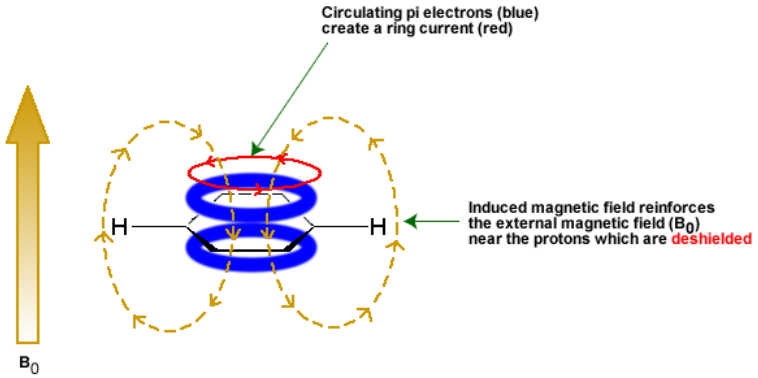
STUDY NOTES

It is not necessary that you memorize detailed spectroscopic data. In the laboratory, on assignments and when writing examinations, you will be provided with a table of characteristic infrared absorptions to assist you in interpreting infrared spectra.

The important points to note about the proton NMR of aromatic compounds are the approximate chemical shifts of such protons and the complex splitting pattern that is sometimes observed. You are advised not to spend too long trying to understand why the signal for an aryl proton is found downfield from the signal for a vinylic proton. In general, we want you to be able to interpret NMR spectra, and leave the underlying theory for subsequent chemistry courses.

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 p electrons is delocalized around the ring. When the molecule is exposed to B_0, these p electrons 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 p electrons 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 outside the ring in the figure above, we feel a magnetic field pointing in a northerly direction. If we are inside the ring, however, we feel a field pointing to the south.

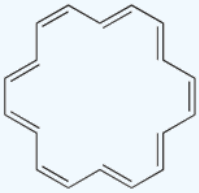
In the induced field generated by the aromatic ring current, the benzylic protons are outside the ring – this means that the induced current in this region of space is oriented in the *same* direction as B_0.

In total, the benzylic protons are subjected to three magnetic fields: the applied field (B_0) and the induced field from the electrons 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 de-shielded. Their chemical shift is far downfield, in the 6.5-8 ppm region.

The presence of anisotropy effects is often used to indicate aromaticity in a molecule. An example is the nonaromatic 8 pi electron cyclooctatetraene. In order to avoid anti-aromatic destabilization, the molecule takes a non-planar conformation which prevents conjugation and ring currents. Consequently, the molecule's protons absorbed at 5.8 ppm which is within the alkene region of ^{1}H NMR.

? EXERCISE 15.7.1

The ^{1}H-NMR spectrum of [18] annulene has two peaks, at 8.9 ppm and -1.8 ppm (upfield of TMS!) with an integration ratio of 2:1. Explain the unusual chemical shift of the latter peak.



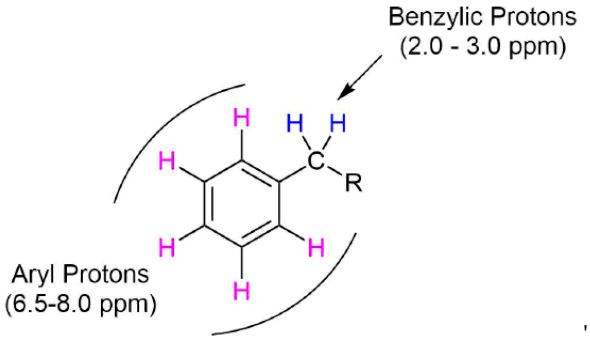
[18] annulene

Answer

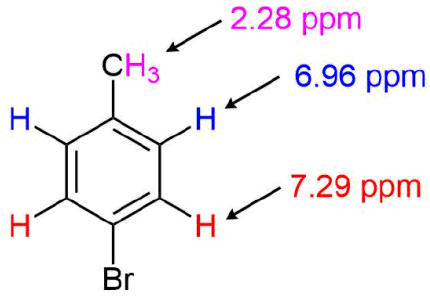
The molecule contains two groups of equivalent protons: the twelve pointing to the outside of the ring, and the six pointing into the center of the ring. The molecule is aromatic, as evidenced by the chemical shift of the 'outside' protons' (and the fact that there are 18 p electrons - a Hückel number). The inside protons are *shielded* by the induced field of the aromatic ring current, because *inside the ring this field points in the opposite direction of B_0*. This is the source of the unusually low (negative relative to TMS) chemical shift for these protons.

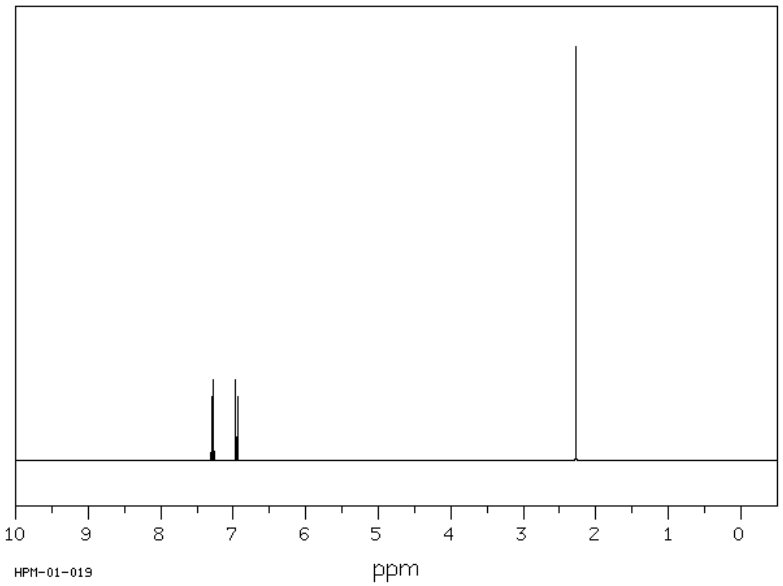
CHARACTERISTIC ^{1}H NMR ABSORPTIONS OF AROMATIC COMPOUNDS

Protons directly attached to an aromatic ring, commonly called aryl protons, show up about 6.5-8.0 PPM. This range is typically called the aromatic region of an ^{1}H NMR spectrum. Protons on carbons directly bonded to an aromatic ring, called benzylic protons, show up about 2.0-3.0 PPM.



For the ^{1}H NMR spectrum of p-bromotoluene, the absorption for the benzylic protons appears as a strong singlet at 2.28 ppm. Due to the molecule's symmetry, the aryl protons appear as two doublets at 6.96 & 7.29 ppm.





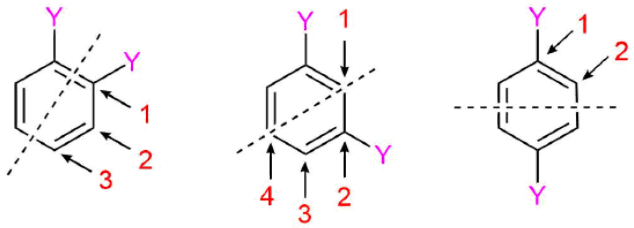
CHARACTERISTIC ^{13}C NMR ABSORPTIONS OF AROMATIC COMPOUNDS

Carbons in an aromatic ring absorb in the range of 120-150 ppm in a ^{13}C NMR spectrum. This is virtually the same range as nonaromatic alkenes (110-150 ppm) so peaks in this region are not definitive proof of a molecule's aromaticity.

Due to the decoupling in ^{13}C NMR, the number of absorptions due to aromatic carbons can easily be observed. This can be used to determine the relative positions (*ortho*, *meta*, or *para*) for di-substituted benzenes. Peak assignments can be simplified by noting that ^{13}C peaks tend to be larger if two carbons contribute to the absorption.

SYMMETRICAL DI-SUBSTITUTED BENZENES

Benzenes substituted with two identical groups have a relatively high amount of symmetry. In all three configurations, there is a plane of symmetry which reduces the number of distinct aryl carbon absorptions to less than six. The *ortho* configuration has a plane of symmetry which mirrors each carbon in the benzene ring causing only three ^{13}C aryl absorptions to occur. The *meta* configuration's plane of symmetry mirrors two carbons of the benzene ring allowing for four aryl absorptions to occur. The *para* configuration actually has two planes of symmetry (one vertical and one horizontal on the structure below) through the benzene ring, which only allows two distinct aryl absorptions to occur.



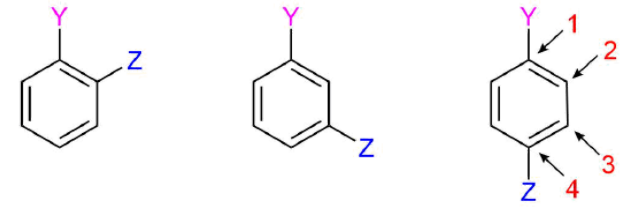
Ortho
Three ^{13}C
Arene Peaks

Meta
Four ^{13}C
Arene Peaks

Para
Two ^{13}C
Arene Peaks

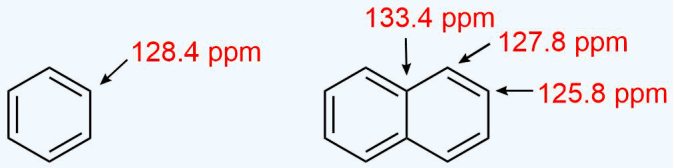
ASYMMETRICAL DI-SUBSTITUTED BENZENES

The lack of a plane of symmetry in asymmetrical di-substituted benzenes makes each carbon in the *ortho* and *meta* configuration unique. Consequently, their ^{13}C NMR spectra show six arene absorptions. However, the *para* configuration has a plane of symmetry drawn through the two substituents which mirrors two carbons of the benzene ring causing only 4 arene absorptions to appear.

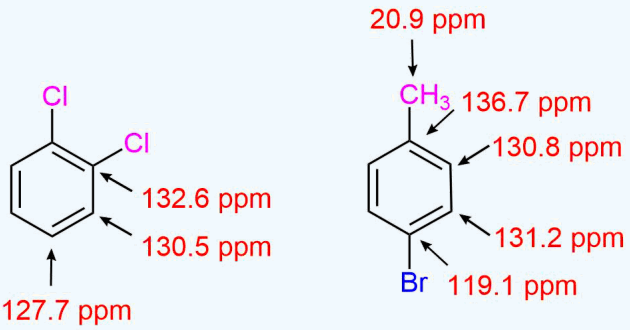


Ortho	Meta	Para
No Symmetry	No Symmetry	Four ^{13}C
Six ^{13}C	Six ^{13}C	Arene Peaks
Arene Peaks	Arene Peaks	

EXAMPLE 15.7.1



Benzene **Naphthalene**



***o*-Dichlorobenzne** ***p*-Bromotoluene**

CHARATERISTIC IR ABSORPTION OF BENZENE DERIVATIVES

Arenes have absorption bands in the 650-900 cm^{-1} region due to bending of the C–H bond out of the plane of the ring. The exact placement of these absorptions can indicate the pattern of substitution on a benzene ring. However, this is beyond the scope of introductory organic chemistry. Arenes also possess a characteristic absorption at about 3030-3100 cm^{-1} as a result of the aromatic C–H stretch. It is somewhat higher than the alkyl C–H stretch (2850–2960 cm^{-1}), but falls in the same region as olefinic compounds. Two bands (1500 and 1660 cm^{-1}) caused by C=C in plane vibrations are the most useful for characterization as they are intense and are likely observed.

In aromatic compounds, each band in the spectrum can be assigned:

- C–H stretch from 3100-3000 cm^{-1}
- overtones, weak, from 2000-1665 cm^{-1}
- C–C stretch (in-ring) from 1600-1585 cm^{-1}
- C–C stretch (in-ring) from 1500-1400 cm^{-1}
- C–H "oop" from 900-675 cm^{-1}

Note that this is at slightly higher frequency than is the –C–H stretch in alkanes. This is a very useful tool for interpreting IR spectra. Only alkenes and aromatics show a C–H stretch slightly higher than 3000 cm^{-1}.

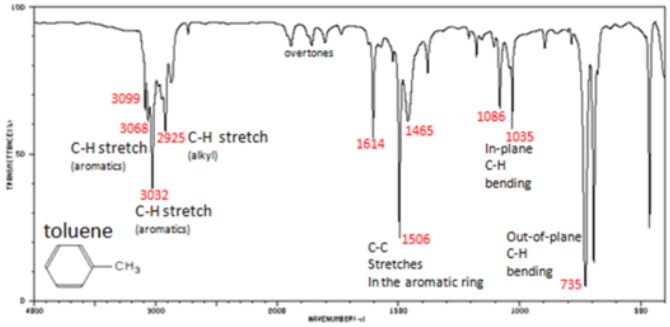
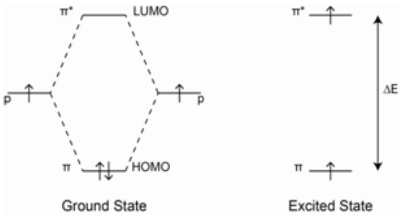


Figure 6. Infrared Spectrum of Toluene

ULTRAVIOLET SPECTROSCOPY

The presence of conjugated π bonds makes aromatic rings detectable in a UV/Vis spectrum. Benzene primarily absorbs through a be a π-π* transition over the range from 160-208 nm with a λ_{max} value of about 178 nm.



Benzene shows a less intense absorption in 230-276 nm range. These absorptions are due to vibrational fine structure often displayed by rigid molecules such as benzene and other aromatic compounds.

15.S: BENZENE AND AROMATICITY (SUMMARY)

CONCEPTS & VOCABULARY

15.0 Introduction

- Aromatic compounds contain ring structures with a special type of resonance delocalization.
- Aromatic compounds can be drawn with alternating single and double bonds, each atom in the ring must have a p-orbital available.

15.1 Naming Aromatic Compounds

- Disubstituted benzene derivatives are often named using ortho (1,2), meta (1,3) and para (1,4).
- There are common benzene derivative names that are used by IUPAC such as toluene, phenol, benzoic acid and benzaldehyde.
- A benzene group that is named as a substituent is called phenyl.
- A benzene with a CH_2 as a substituent group is called benzyl.

15.2 Structure and Stability of Benzene

- Benzene does not undergo the same reactions that alkenes do, due to its aromatic stability.
- Aromatic molecules must have all ring atoms in the same plane to allow delocalization of the pi electrons.
- Heats of hydrogenation can be used to show the special stability of benzene compared to what would be expected for a theoretical cyclohexatriene molecule.

15.3 Aromaticity and the Hückel 4n + 2 Rule

- The four criteria for aromaticity are that the molecule must:
  - be cyclic
  - be planar
  - be fully conjugated
  - have 4n+2 π Electrons
- Ionic molecules and heterocyclic molecules can also be aromatic if they meet the four criteria.

15.4 Aromatic Ions

- Carbanions and carbocations that meet the rules for aromaticity are also aromatic.

15.5 Aromatic Heterocycles: Pyridine and Pyrrole

- Heterocycles that meet the rules for aromaticty are also aromatic.
- If a lone pair of electrons on a ring atom can result in 4n+2 π Electrons, they will be in a p-orbital. If not, they will remain in hybrid orbitals.

15.6 Polycyclic Aromatic Compounds

- Benzene rings can be fused together to give larger aromatic compounds with mutliple rings called polycyclic aromatic compounds (or polycyclic aromatic hydrocarbons).

15.7 Spectroscopy of Aromatic Compounds

- Aromatic compounds can be identified by common infrared absorptions in the 3000-3100 cm^{-1} and 1500-1600 cm^{-1}.
- In ^1H NMR, aromatic hydrogens appear in the 6.5-8 ppm region.

SKILLS TO MASTER

- Skill 15.1 Using IUPAC rules to name substituted benzene molecules.
- Skill 15.2 Use heats of hydrogenation to explain aromatic stabilization.
- Skill 15.3 Draw molecular orbital diagram for benzene (all 6 MO's).
- Skill 15.4 Use the criteria for aromaticity to determine if a molecule is aromatic or not.
- Skill 15.5 Determine whether lone pairs of electrons for ions and heterocycles will be in p orbitals or hybrid orbitals.
- Skill 15.6 Identify aromatic absorbances in infrared spectroscopy.
- Skill 15.7 Identify aromatic resonances in ^1H NMR spectroscopy.

CHAPTER OVERVIEW

16: CHEMISTRY OF BENZENE - ELECTROPHILIC AROMATIC SUBSTITUTION

LEARNING OBJECTIVES

When you have completed Chapter 16, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. solve road-map problems that require an understanding of the chemistry discussed in this chapter and those that preceded it.
3. design multistep syntheses using the reactions discussed in this and the preceding chapters. In particular you should be prepared to show how an aromatic compound containing two or more substituents could be synthesized, taking care to introduce the substituents into the ring in the correct order.
4. define, and use in context, the key terms introduced.

In the preceding chapter, you studied the concept of aromaticity and spent considerable time on the theoretical aspects of the chemistry of aromatic compounds. In this chapter, you will begin to study the chemical reactions of aromatic compounds, focusing in particular on electrophilic aromatic substitution, and to a lesser extent on nucleophilic aromatic substitution. We will discuss, in detail, the mechanism of electrophilic substitution, paying particular attention to the factors that determine both the rate and position of substitution in those aromatic compounds which already have one or more substituents present in the aromatic ring. When we discuss nucleophilic aromatic substitution, you will see that it can be achieved by two different mechanisms, one of which involves the formation of an unusual looking intermediate, benzyne.

You will also see how alkyl and acyl groups can be introduced on to an aromatic ring; how, once introduced, alkyl groups can be converted to carboxyl groups; and how bromine can be introduced to the alkyl side chain of alkylbenzene. The latter reaction is particularly useful because the benzylic bromide so produced undergoes the reactions of a typical alkyl bromide, thus providing us with a synthetic route to a large variety of compounds.

16.0: INTRODUCTION

OBJECTIVE

After completing this section, you should be able to identify electrophilic substitution as the single most important reaction of aromatic compounds.

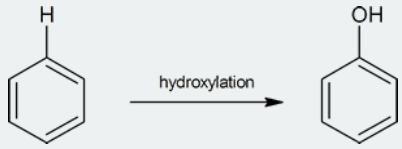
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- acylation
- alkylation
- electrophilic substitution
- halogenation
- hydroxylation
- nitration
- sulfonation

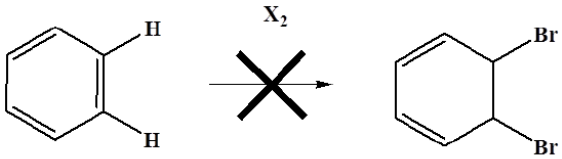
STUDY NOTES

In this chapter, you will study all of the reactions shown in the Reaction Type table. In addition to these five reaction types, we also add a sixth common electrophilic substitution known as hydroxylation.



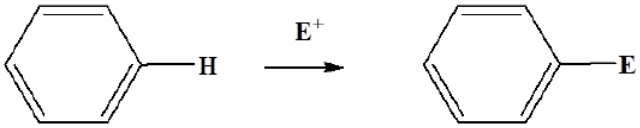
It is important that you recognize the similarities between these reactions to minimize the amount you must memorize.

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

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	$RCO^{(+)}$

16.1: ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS - BROMINATION

OBJECTIVES

After completing this section, you should be able to

1. write the detailed mechanism for the reaction of bromine with benzene in the presence of a suitable catalyst.
2. draw the resonance contributors for the carbocation which is formed during the reaction of bromine with benzene.
3. compare the reaction which takes place between bromine and benzene and the reaction which takes place between bromine and an alkene.
4. draw an energy diagram for the reaction of bromine with benzene.
5. identify the reagents required to bring about aromatic bromination.
6. write an equation to represent aromatic bromination.

STUDY NOTES

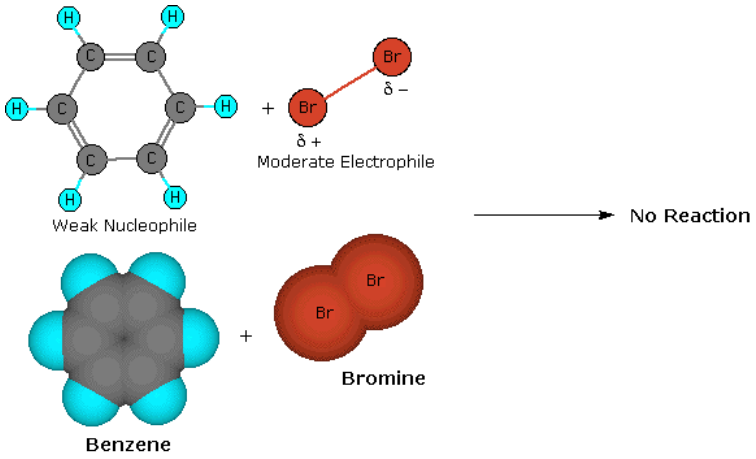
The Mechanism for Electrophilic Substitution Reactions of Benzene is the key to understanding electrophilic aromatic substitution. You will see similar equations written for nitration, sulphonation, acylation, etc., with the major difference being the identity of the electrophile in each case.

Note that the carbocation intermediate formed has a number of resonance forms. Also, you may wish to review Section 8.2 to meet Objective 3.

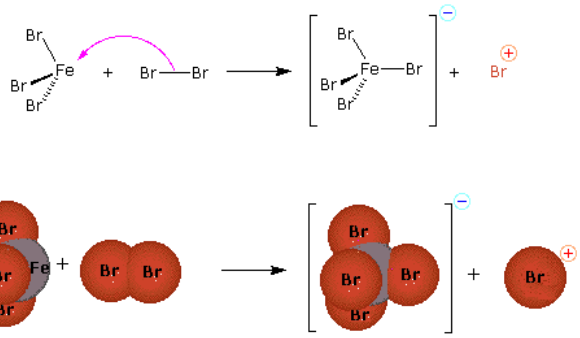
Halogenation is an example of electrophillic aromatic substitution. In electrophilic aromatic substitutions, a benzene is attacked by an electrophile which results in substition of hydrogens. However, halogens are not electrophillic enough to break the aromaticity of benzenes, which require a catalyst to activate.

A 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 **arenium 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.

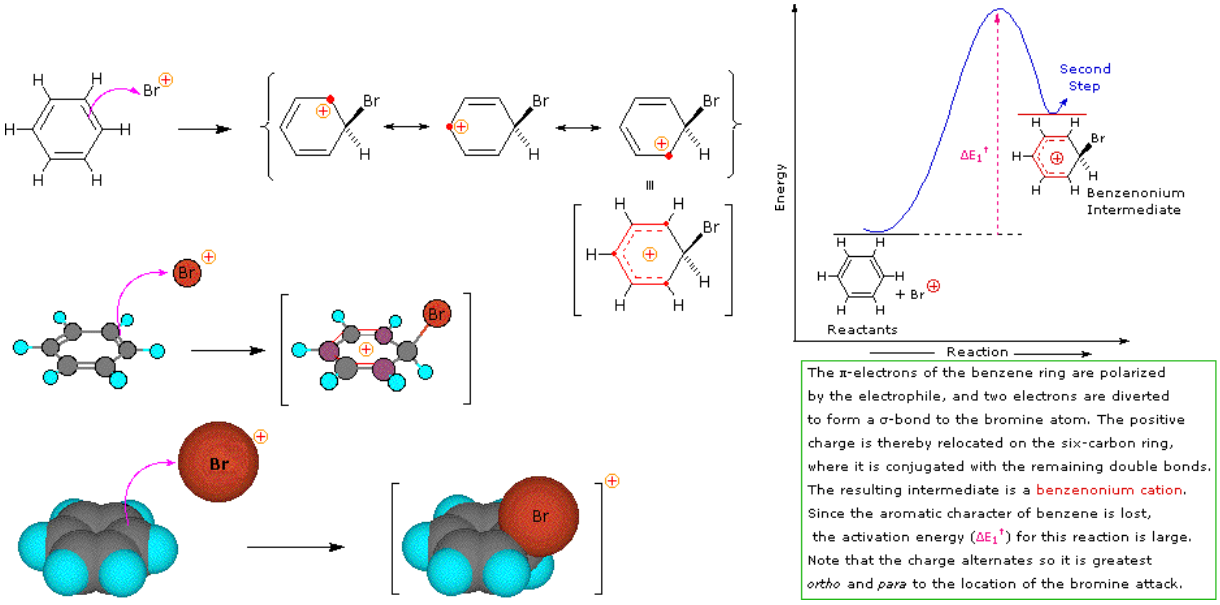


The bromine molecule is polarized so that one end is electrophilic and the other nucleophilic. Although the electrophilic end reacts easily with simple alkenes and dienes, it fails to react with the more stable and weaker nucleophilic π-electron system of benzene.

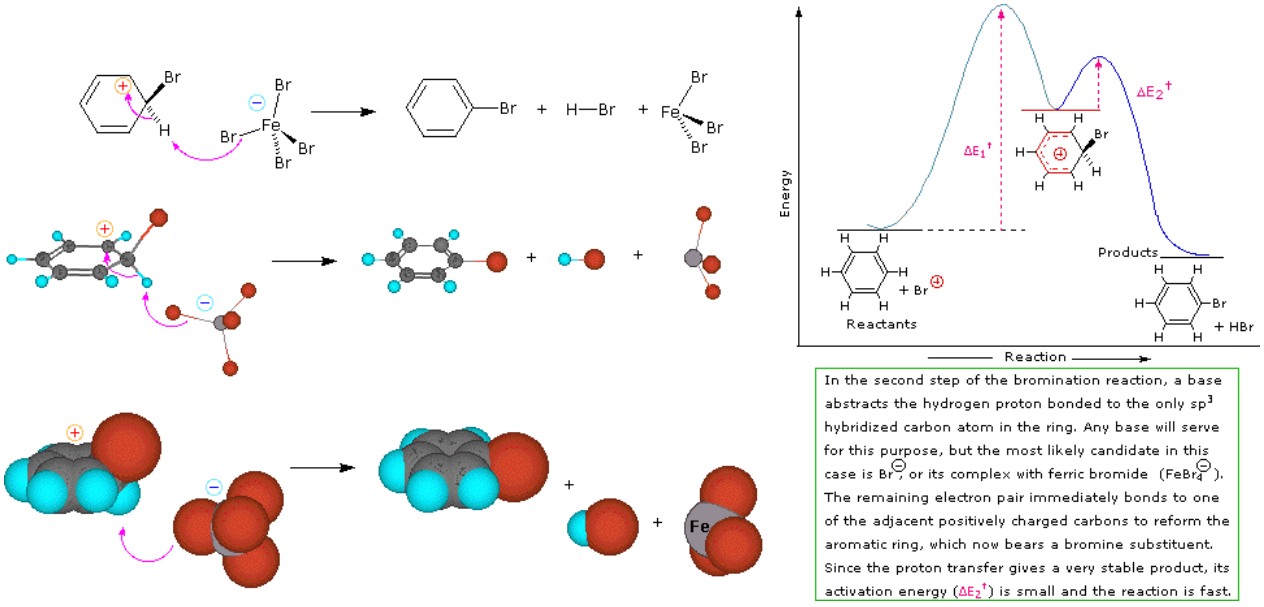


Ferric bromide and other Lewis acids enhance the electrophilic strength of bromine by forming a complex anion, in this case $FeBr_4^{\ominus}$. At the same time, this complexation creates the strongly electrophilic bromine cation, which reacts with nucleophiles.

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:

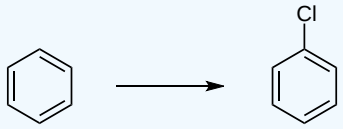
1. The cation may bond to a nucleophile to give a substitution or addition product.
2. The cation may transfer a proton to a base, giving a double bond product.
3. The cation may rearrange to a more stable carbocation, and then react by mode #1 or #2.

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 arenium 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).

EXERCISES

? EXERCISE 16.1.1

What reagents would you need to get the given product?

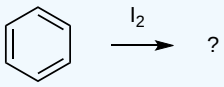


Answer

Cl_2 and $AlCl_3$ or Cl_2 and $FeCl_3$

? EXERCISE 16.1.2

What product would result from the given reagents?

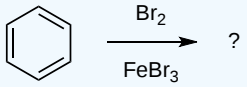


Answer

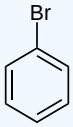
No Reaction

EXERCISE 16.1.3

What is the major product given the reagents below?



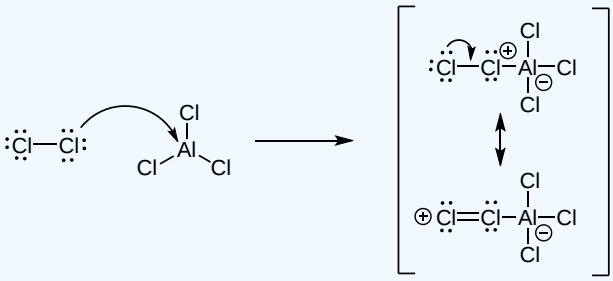
Answer



EXERCISE 16.1.4

Draw the formation of Cl^+ from $AlCl_3$ and Cl_2.

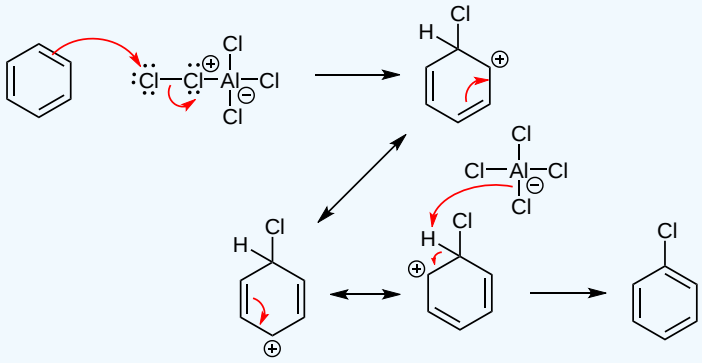
Answer



EXERCISE 16.1.5

Draw the mechanism of the reaction between Cl^+ and a benzene.

Answer



16.2: OTHER AROMATIC SUBSTITUTIONS

OBJECTIVES

After completing this section, you should be able to

1. write a balanced equation for the halogenation (F, Cl, Br, I) of benzene in the presence of a suitable catalyst or promoter.
2. draw the resonance contributors for the carbocation which is formed during the reaction of chlorine or bromine with benzene.
3. write the equation for the nitration and sulfonation of benzene.
4. write the detailed mechanism for the nitration and sulfonation of benzene.
5. write the equation for the reduction of an aromatic nitro compound to an amine.
6. identify aromatic sulfonation as being a reversible process, and describe the conditions under which the forward and reverse reactions are favoured.
7. write the equation for the desulfonation of an aromatic sulfonic acid.
8. identify aromatic sulfonic acids as being key intermediates in the manufacture of sulfa drugs.

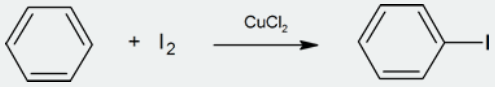
KEY TERMS

Make certain that you can define, and use in context, the key term below.

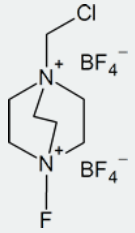
- nitronium ion, (NO^{+2})

STUDY NOTES

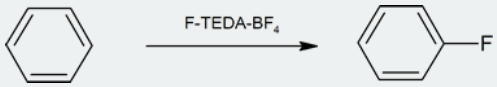
You should be careful to remember that iodine and fluorine cannot be introduced into an aromatic ring by the method used for bromine and chlorine. On its own, iodine is unreactive with aromatic rings, but one method for aromatic iodination is treatment in the presence of a copper salt such as copper(II)chloride where I2 is oxidized to the more electrophilic species I^+.



In contrast, fluorine is too reactive, so it cannot be used directly for aromatic flourination. However, fluorinating agents like 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate (also known as F-TEDA-BF_4) sold commercially as Sectfluor® offer convenient sources of "F^+" for this type of reaction.



F-TEDA-BF_4

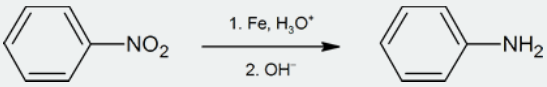


The overall equation for the formation of nitronium ions by the action of sulfuric acid on nitric acid is

$\ce{\sf{HNO3 + 2H2SO4 <=> H3O+ + NO2+ + HSO4- }}$

The ability of compounds such as nitronium tetrafluoroborate to bring about the nitration of aromatic compounds is good evidence in support of the proposed mechanism.

The nitration of an aromatic ring is an important synthetic pathway to generating arylamines. The reaction below shows one common method of reducing the nitro group. (Amines are examined in more detail in Chapter 24.)

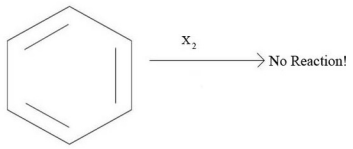


HALOGENATION OF BENZENE

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.

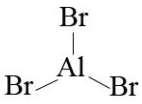
ACTIVATION OF HALOGEN

(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)

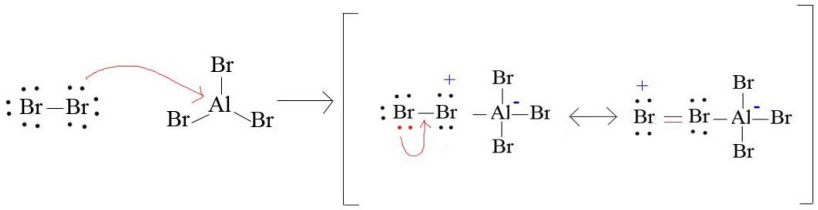


Hence, Halogen needs the help and aid of Lewis Acidic Catalysts to activate it to become a very strong electrophile. Examples of these activated halogens are Ferric Hallides (FeX_3) Aluminum Halides (AlX_3) where X= Br or Cl. In the following examples, the halogen we will look at is Bromine.

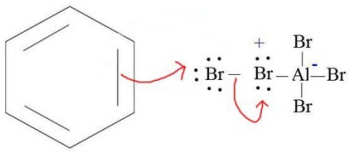
In the example of bromine, in order to make bromine electrophillic enough to react with benzene, we use the aid of an aluminum halide such as aluminum bromide.

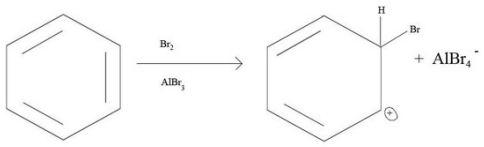


With aluminum bromide as a Lewis acid, we can mix Br_2 with $AlBr_3$ to give us Br^+. The presence of Br^+ is a much better electrophile than Br_2 alone. Bromination is acheived with the help of $AlBr_3$ (Lewis acid catalysts) as it polarizes the Br-Br bond. The polarization causes polarization causes 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.

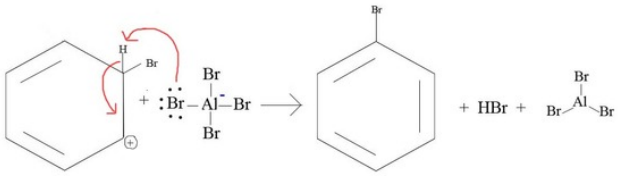


As the bromine has now become more electrophillic after activation of a catalyst, an electrophillic attack by the benzene occurs at the terminal bromine of Br-Br-$AlBr_3$. This allows the other bromine atom to leave with the $AlBr_3$ as a good leaving group, $AlBr_4$-.





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.

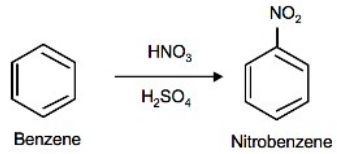
DISSOCIATION ENERGIES OF HALOGENS AND ITS EFFECT ON HALOGENATION OF BENZENES

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.

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.

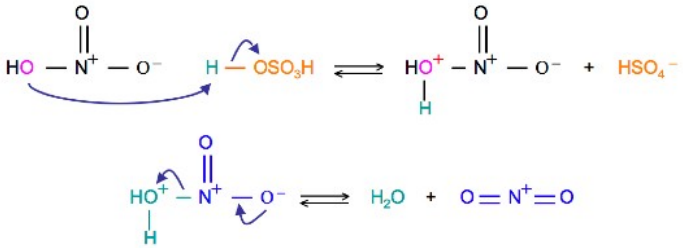
NITRATION OF BENZENE

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.



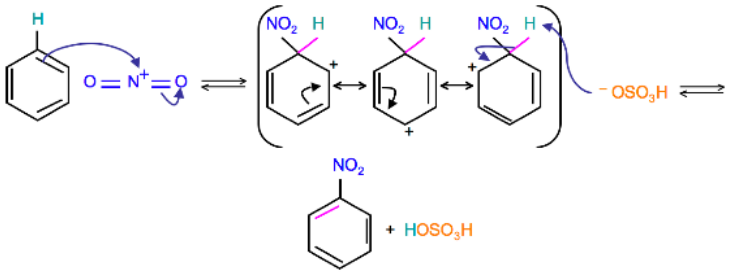
SULFURIC ACID ACTIVATION OF NITRIC ACID

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.

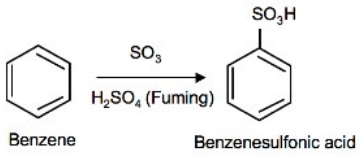
MECHANISM



(Resonance forms of the intermediate can be seen in the generalized electrophilic aromatic substitution)

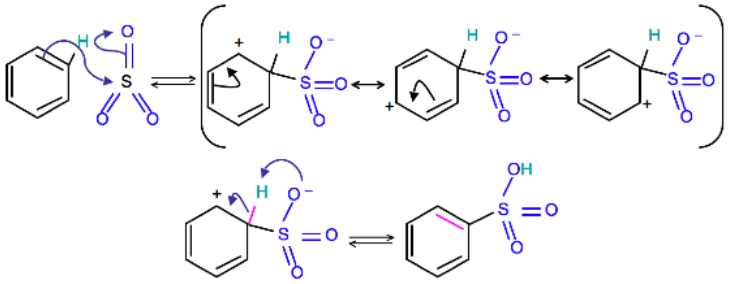
SULFONATION OF BENZENE

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.



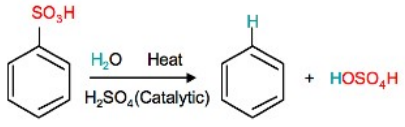
MECHANISM

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

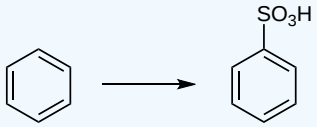
Nitration is used to add nitrogen to a benzene ring, which can be used further in substitution reactions. The nitro group acts as a ring deactivator. Having nitrogen present in a ring is very useful because it can be used as a directing group as well as a masked amino group. The products of aromatic 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.

EXERCISES

EXERCISE 16.2.1

1. What is/are the required reagent(s)for the following reaction:

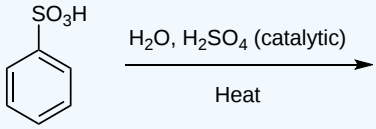


Answer

SO_3 and H_2SO_4 (fuming)

EXERCISE 16.2.2

What is the product of the following reaction:



Answer

EXERCISE 16.2.3

Why is it important that the nitration of benzene by nitric acid occurs in sulfuric acid?

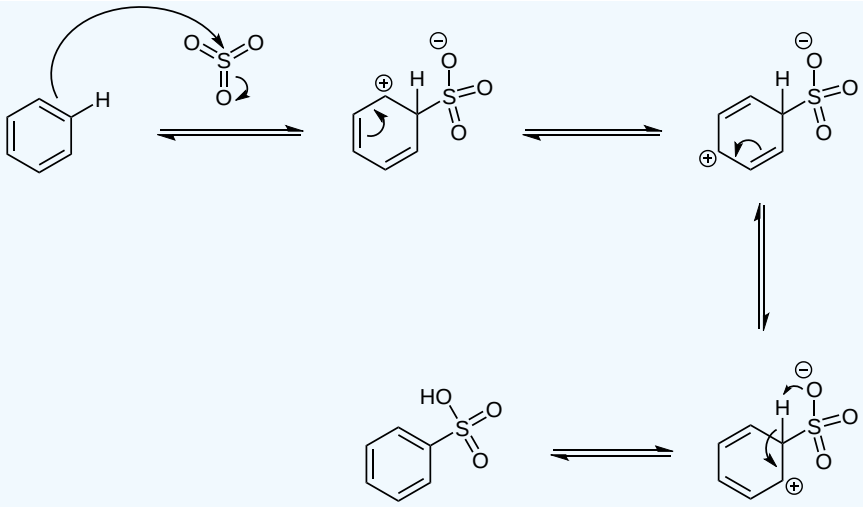
Answer

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.

EXERCISE 16.2.4

Write a detailed mechanism for the sulfonation of benzene, including all resonance forms.

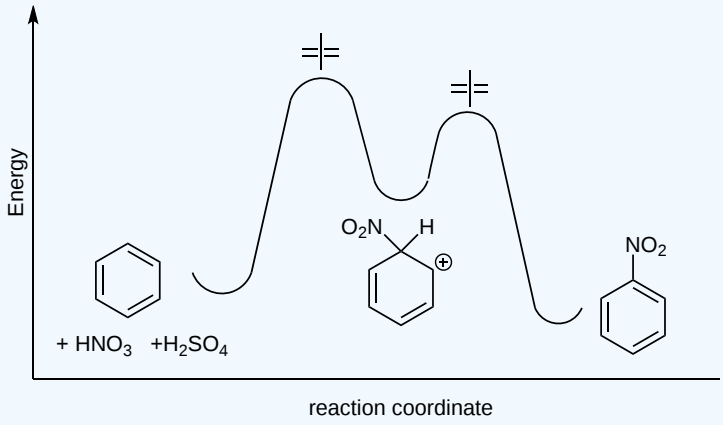
Answer



EXERCISE 16.2.5

Draw an energy diagram for the nitration of benzene. Draw the intermediates, starting materials, and products. Label the transition states.

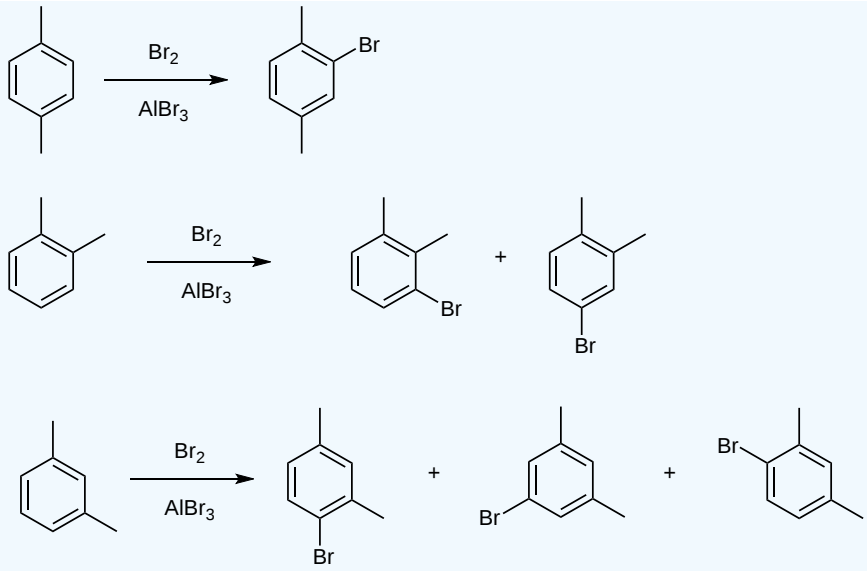
Answer



EXERCISE 16.2.6

In each case, how many products would be possible for the bromination of *p*-xylene, *o*-xylene, and *m*-xylene?

Answer

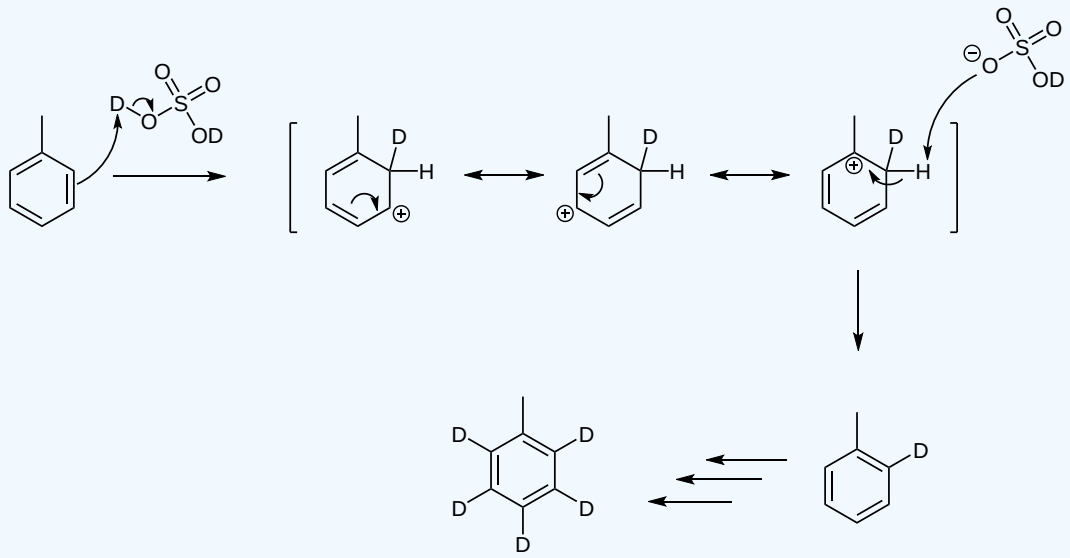


EXERCISE 16.2.7

If toluene is treated with D_2SO_4 all the hydrogen's are replaced with deuterium. Explain.

Answer

The deuterium is added to the ring. When the ring "re-aromatizes" the base scavenges the hydrogen before the deuterium and therefore is left on the ring. Continues for the rest of the hydrogen on the ring.



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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.

16.3: ALKYLATION AND ACYLATION OF AROMATIC RINGS - THE FRIEDEL-CRAFTS REACTION

OBJECTIVES

After completing this section, you should be able to

- write the equation for the preparation of an alkylbenzene by a Friedel-Crafts alkylation reaction.
- identify the product formed from the Friedel-Crafts alkylation of a given aromatic compound.
- identify the aromatic compound needed to prepare a given arene by a Friedel-Crafts alkylation.
- identify the alkyl halide and catalyst needed to form a specified arene from a given aromatic compound.
- write the detailed mechanism for the Friedel-Crafts alkylation reaction, and identify the similarities between this reaction and those electrophilic aromatic substitution reactions you studied in Sections 16.1 and 16.2.
- show how alkyl halides and acylhalides can be used as alkylating agents in Friedel-Crafts alkylation reactions.
- discuss the limitations of the Friedel-Crafts alkylation reaction, paying particular attention to the structure of the alkyl halide, the structure of the aromatic substrate and the problem of polyalkylation.
- write an equation for a typical Friedel-Crafts acylation.
- write the detailed mechanism of the Friedel-Crafts acylation reaction.
- identify the product formed by the Friedel-Crafts acylation of a given aromatic compound.
- identify the aromatic compound, and the reagent and catalyst needed to prepare a given ketone through a Friedel-Crafts acylation reaction.
- Explain the following laws within the Ideal Gas Law

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- acyl group
- Friedel-Crafts acylation reaction
- Friedel-Crafts alkylation reaction
- polyalkylation

STUDY NOTES

A Friedel-Crafts alkylation reaction is an electrophilic aromatic substitution reaction in which a carbocation is attacked by a pi bond from an aromatic ring with the net result that one of the aromatic protons is replaced by an alkyl group. If you prefer, you may regard these reactions as involving an attack by an aromatic ring on a carbocation. The latter approach is the one used in the textbook, but the former approach is probably more common.

When more than one alkyl group is introduced into an aromatic ring during the course of a Friedel-Crafts alkylation reaction, polyalkylation is said to have occurred.

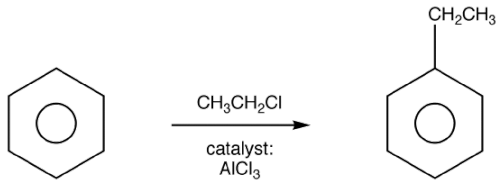
The four limitations on the use of Friedel-Crafts alkylations are as follows:

1. vinyl and aryl halides cannot be used to form carbocations.
2. the aromatic substrate must not contain a strongly deactivating group, or groups, such as NH_2, NHR or NR_2, which form complexes with the Lewis acid catalyst and in so doing become strongly deactivating.
3. polyalkylation, which can be overcome by using a large excess of the aromatic substrate.
4. carbocation rearrangements may occur in any reaction that involves a carbocation.

The reaction of an aromatic substrate with an acid chloride (or acid anhydride) in the presence of an aluminum chloride catalyst is used to introduce an acyl group (C=O) into the aromatic ring through an electrophilic aromatic substitution mechanism. Such reactions are Friedel-Crafts acylation reactions.

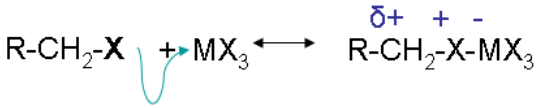
FRIEDEL-CRAFTS ALKYLATION

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 effectiveness.



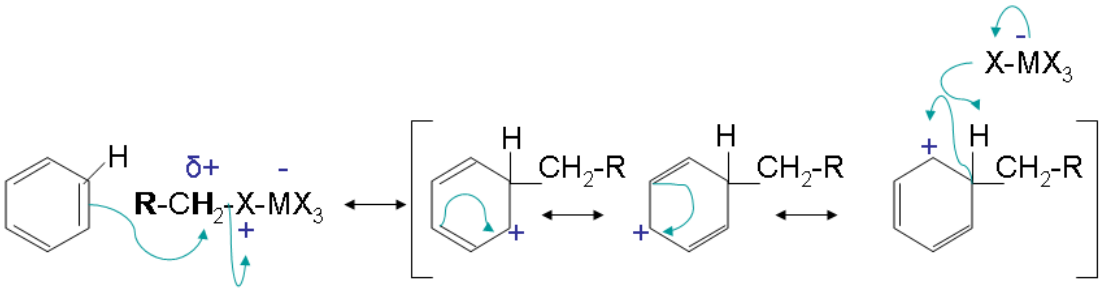
The mechanism takes place as follows:

Step 1:



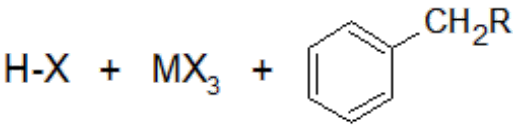
Step one creates a carbocation that acts as the electrophile in the reaction. This steps activates the haloalkane. Secondary and tertiary halides only form the free carbocation in this step.

Steps 2 and 3:



Step 2 has an electron pair from the aromatic ring attack the carbocation forming a new C-C bond. The arenium ion intermediate results with stabilization from multiple resonance forms. The loss of a proton then gives the neutral alkylated substitution product.

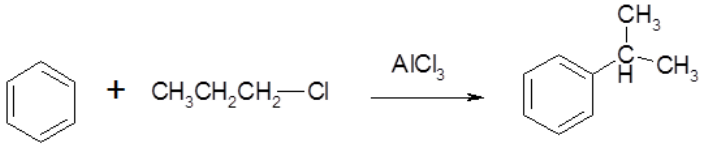
Final Products



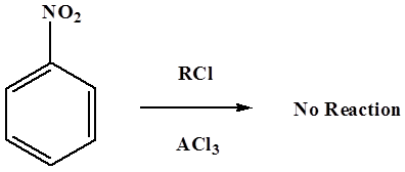
The reactivity of haloalkanes increases as you move up the periodic table and increase polarity. This means that an RF haloalkane is most reactive followed by RCl then RBr and finally RI. This means that the Lewis acids used as catalysts in Friedel-Crafts Alkylation reactions tend have similar halogen 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

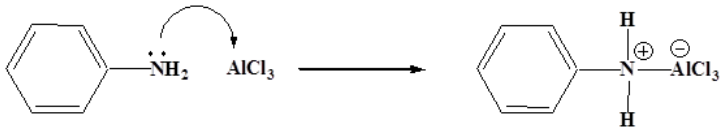
There are possibilities of carbocation rearrangements when you are trying to add a carbon chain greater than two carbons. The rearrangements occur due to hydride shifts and methyl shifts. For example, the product of a Friedel-Crafts Alkylation will show an iso rearrangement when adding a three carbon chain as a substituent. 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.

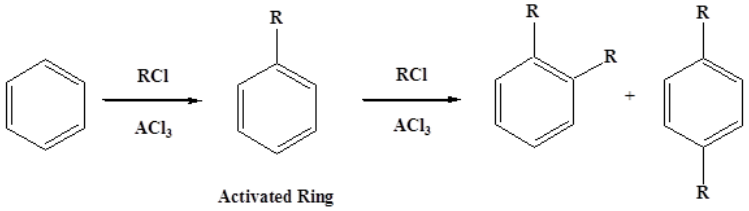


Friedel-Crafts reactions cannot be preformed then the aromatic ring contains a NH_2, NHR, or NR_2 substituent. The lone pair electrons on the amines react with the Lewis acid $AlCl_3$. This places a positive charge next to the benzene ring, which is so strongly activating that the Friedel-Crafts reaction cannot occur.



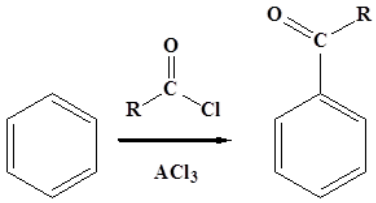
The positive charge strongly deactivates the benzene ring

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

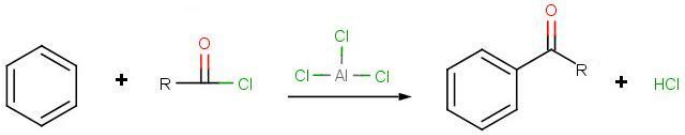
This problem does not occur during Friedel-Crafts Acylation because an acyl group is deactivating, thus prevents further acylations.



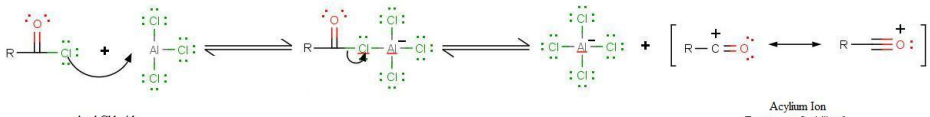
Dectivated Ring

FRIEDEL-CRAFTS ACYLATION

The goal of the reaction is the following:



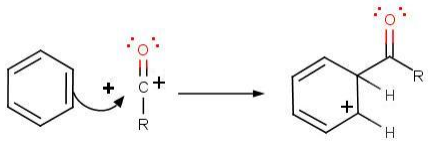
The very first step involves the formation of the acylium ion which will later react with benzene:



Acyl Chloride

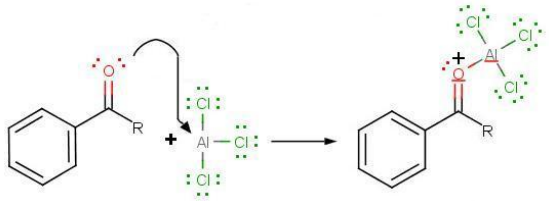
Acylium Ion (Resonance Stabilized)

The second step involves the attack of the acylium ion on benzene as a new electrophile to form one complex:

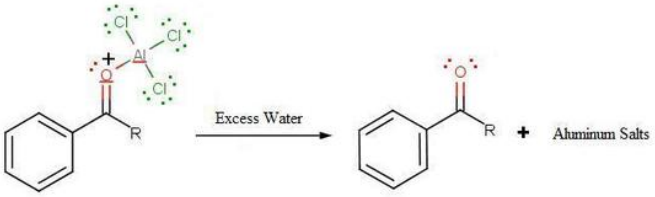


The third step involves the departure of the proton to reform aromaticity:

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:

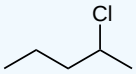
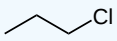


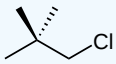
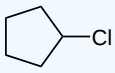
Because the acylium ion (as was shown in step one) is stabilized by resonance, no rearrangement occurs (unlike in Friedel-Crafts Alkylation reactions - see Limitation 1 above). Also, because of of the deactivation of the product, it is no longer susceptible to electrophilic attack and hence, no longer goes into further reactions (Limitation 3 above from Friedel-Crafts Alkylation reactions). However, as not all is perfect, Limitation 2 still prevails where Friedel-Crafts Acylation fails with strong deactivating rings.

EXERCISES

? EXERCISE 16.3.1

Which of the following will NOT undergo a rearrangement in a Friedel-Crafts reaction?

A) CH_3Cl B)  C) 

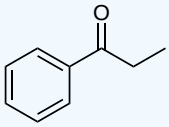
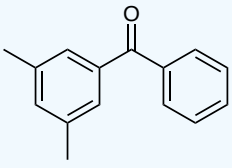
D)  E) 

Answer

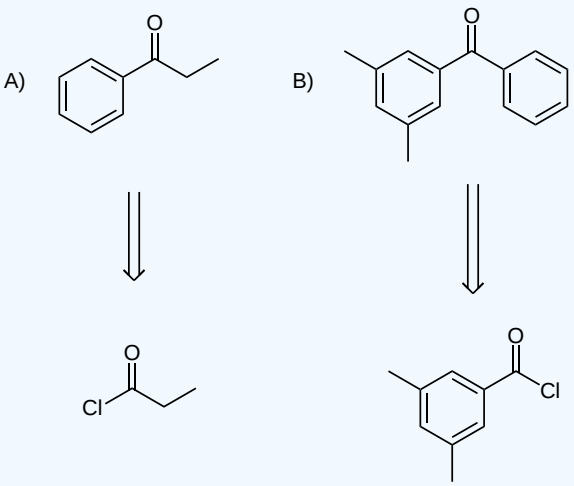
A and E will not undergo a rearrangement.

? EXERCISE 16.3.2

Suggest an acyl chloride that was used to make the following compounds:

A)  B) 

Answer



16.4: SUBSTITUENT EFFECTS IN SUBSTITUTED AROMATIC RINGS

OBJECTIVES

After completing this section, you should be able to

1. describe the two ways in which a substituent influences the electrophilic substitution of a monosubstituted aromatic compound.
2. classify each of the following substituents as being either activating or deactivating with respect to electrophilic aromatic substitution: $-NH_2$, $-OH$, $-NHR$, $-NR_2$, $-OR$, $-NHCOR$, alkyl (R), phenyl, R_3N^+, $-NO_2$, $-CN$, $-COR$, $-CO_2H$, $-CO_2R$, $-CHO$, halogens.
3. list a given series of substituents (selected from those given in Objective 2) in order of increasing or decreasing ability to activate or deactivate an aromatic ring with respect to electrophilic substitution.
4. explain, in general terms, the factors that determine whether a given substituent will activate or deactivate an aromatic ring with respect to electrophilic substitution.
5. list a given series of aromatic compounds in order of increasing or decreasing reactivity with respect to electrophilic substitution.
6. explain the inductive effects displayed by substituents such as nitro, carboxyl, alkyl and the halogens during electrophilic aromatic substitution reactions.
7. explain the resonance effects displayed by substituents such as nitro, carbonyl-containing, hydroxy, alkoxy and amino groups during electrophilic aromatic substitution reactions.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

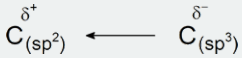
- inductive effect
- resonance effect

STUDY NOTES

On reading Objective 2 students may exclaim “How am I ever going to memorize all of this!”—or words to that effect. The answer is that if you are trying to memorize such things, you are taking the wrong approach to organic chemistry. What you should be doing is trying to understand the factors that determine whether a given substituent will activate or deactivate a benzene ring with respect to electrophilic substitution.

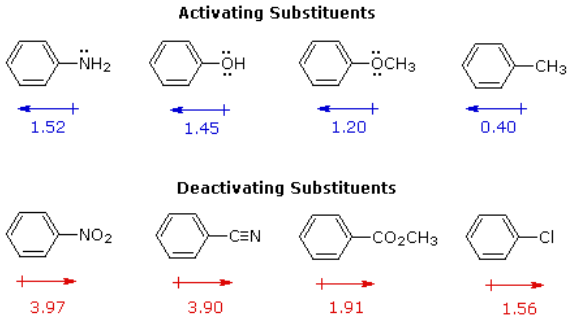
You may wish to review earlier material on to the inductive effect. If so, refer to Sections 2.1, 7.9 (paying particular attention to the “Study Notes”) and 14.5.

Note that one argument sometimes used to explain the ability of alkyl groups to donate electrons inductively to an aromatic ring is that sp^2-hybridized carbon atoms are more electronegative than sp^3-hybridized carbon atoms. Thus, a sigma bond between sp^2- and sp^3-carbon is slightly polarized, as follows:



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).

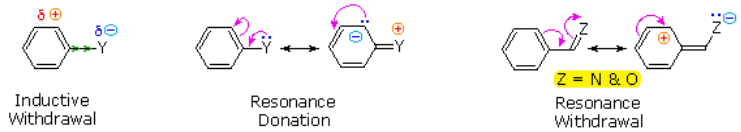


The influence a substituent exerts on the reactivity of a benzene ring may be explained by the interaction of two effects:

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.

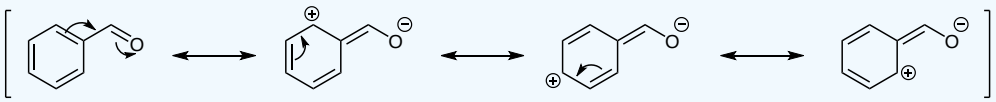


EXERCISES

? EXERCISE 16.4.1

Draw the resonance structures for benzaldehyde to show the electron-withdrawing group.

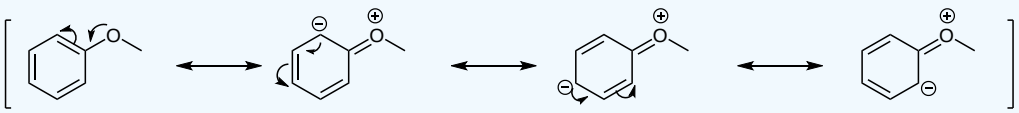
Answer



? EXERCISE 16.4.2

Draw the resonance structures for methoxybenzene to show the electron-donating group.

Answer



16.5: AN EXPLANATION OF SUBSTITUENT EFFECTS

OBJECTIVES

After completing this section, you should be able to

1. draw the resonance contributors for the carbocation intermediate formed during the reaction of a given monosubstituted benzene derivative with any of the electrophiles discussed in this chapter.
2. classify each of the substituents listed in Objective 2 of Section 16.4 as being either meta or ortho/para directing.
3. classify each of the substituents listed in Objective 2 of Section 16.4 as being ortho/para directing activators, ortho/para directing deactivators, or meta directing deactivators.
4. predict the product or products formed from the reaction of a given monosubstituted benzene derivative with each of the electrophiles discussed in this chapter.
5. explain, by drawing the resonance contributors for the intermediate carbocation, why the electrophilic substitution of an alkyl benzene results in a mixture of mainly ortho- and para- substituted products.
6. explain why the electrophilic substitution of phenols, amines and their derivatives proceeds more rapidly than the electrophilic substitution of benzene itself.
7. explain, by drawing the resonance contributors for the intermediate carbocation, why meta substitution predominates in electrophilic aromatic substitution reactions carried out on benzene derivatives containing one of the substituents R_3N^+, NO_2, CO_2H, CN, CO_2R, COR or CHO.
8. explain why electrophilic aromatic substitution of benzene derivatives containing one of the substituents listed in Objective 7, above, proceeds more slowly than the electrophilic substitution of benzene itself.
9. explain, by drawing the resonance contributors for the intermediate carbocation, why the electrophilic aromatic substitution of halobenzenes produces a mixture of mainly ortho- and para-substituted products.
10. explain why the electrophilic aromatic substitution of halobenzenes proceeds more slowly than does the electrophilic substitution of benzene itself.
11. use the principles developed in this chapter to predict in which of the three categories listed in Objective 3, above, a previously unencountered substituent should be placed.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- steric effect
- steric hindrance

STUDY NOTES

As you saw in Section 16.4, a substituent on a benzene ring can be an activator or a deactivator. At the same time, a substituent can also be a meta director or an ortho/para director. Of the four possible combinations, only three are known—there are no meta directing activators.

If you look at the data for the nitration of toluene, you will see that the yield of *o*-nitrotoluene is 63% and that of *p*-nitrotoluene is 34%. Statistically, we should expect to obtain twice as much ortho product as para product, because the former is produced by attack at either of two carbon atoms whereas the latter is produced by attack at only one carbon atom (see Figure below).

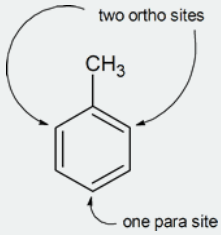


Figure 16.5.1: Proportions of *o*-nitrotoluene and *p*-nitrotoluene produced by the nitration of toluene

In this instance, the observed ortho/para ratio is almost 2:1, as we might expect. However, if we study the ortho/para ratio found in the nitration of a number of other arenes, we see that this is not always the case. Note that the data for the nitration of toluene given in the table below differ from those presented elsewhere. The variation may result from a difference in temperature, reaction conditions or reagent, and emphasizes the point that it is the trends which are important, not the numbers themselves.

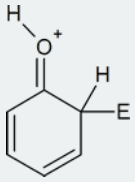
Substrate	% ortho	% para	ortho/para ratio
toluene	58	37	1.57:1
ethylbenzene	45	49	0.92:1
isopropylbenzene	30	62	0.48:1
tert-butylbenzene	16	73	0.22:1

[**Source:** These data were taken from the audiocassette *Some Organic Reaction Pathways*, by Peter Sykes. London: Educational Techniques Subject Group, The Chemical Society, 1975.]

Table 16.5.1**:** Nitration of arenes

The table above shows us that as the size of the alkyl substituent already present in the ring increases, attack at the ortho position becomes more difficult, and the percentage of ortho isomers in the mixture of products decreases. This is an example of a *steric effect*—an effect caused by the size of the substituent—and we would say that as the size of the alkyl group increases, attack at the ortho position becomes less favorable as a result of *steric hindrance*. Note that the size of the electrophile can also be a factor in determining the ortho/para ratio: the larger the electrophile, the less able it is to attack at the ortho position, particularly if the substituent already present in the ring is itself quite bulky.

When drawing the resonance contributors to the carbocation formed during an electrophilic aromatic substitution, bear in mind that those of the type



are particularly important, because in such structures each atom possesses a complete octet of electrons.

Note that, as do the hydroxyl and amino groups, the halogens have an inductive electron-withdrawing effect and a resonance electron-releasing effect on a benzene ring. The difference in behavior during electrophilic substitutions arises because, with the hydroxyl and amino groups, the resonance effect is much greater than the inductive effect, whereas with the halogens, there is a much finer balance. In the case of the latter, the inductive effect reduces the overall reactivity, but the resonance effect means that this reduction is felt less at the ortho and para positions than at the meta position.

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:

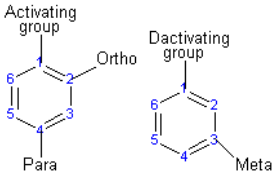
$$F > Cl > Br > I$$

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 electronegative 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 substitutes for the hydrogen that is on carbon 2 or carbon 4. The deactivating group directs the reaction to the meta position, which means the electrophile substitutes for the

hydrogen that is on carbon 3 with the exception of the halogens which are deactivating groups but direct the ortho or para substitution.

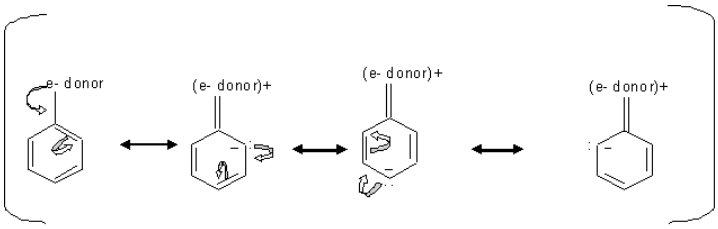


SUBSTITUENTS DETERMINE THE REACTION DIRECTION BY RESONANCE OR INDUCTIVE EFFECT

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 substituents such as -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.

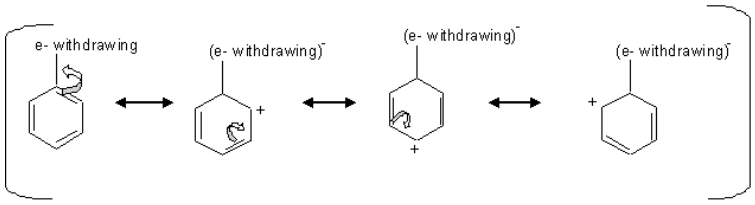


By looking at the mechanism above, we can see how electron donating groups direct electrophilic substitution to the ortho and para positions. Since the extra electron density is localized on the ortho and para carbons, these carbons are more likely to react with the electrophile.

Inductive effects of alkyl groups activate 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 electron density away from the ring.



The mechanism above shows that when electron density is withdrawn from the ring, that leaves the carbons at the ortho, para positions with a parital 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 to 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.

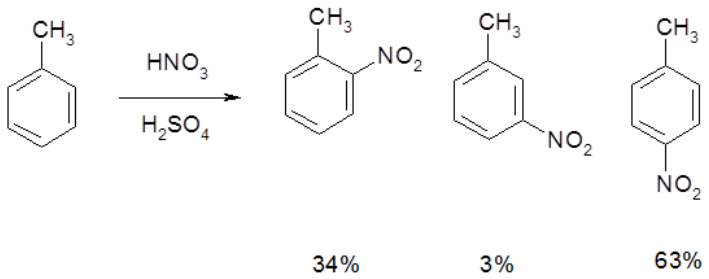
SUBSTITUENTS DETERMINE THE REACTIVITY OF RINGS

The reaction of a substituted ring with an activating group is faster than the same reaction wtih benzene. On the other hand, a substituted ring with a deactivated group reacts slower than benzene.

Activating groups speed up reaction with electrophiles due to increased electron density on the ring. This stabilizes the intermediate carbocation, which decreases the activation energy for the reaction. On the other hand, deactivating groups withdraw electron density away

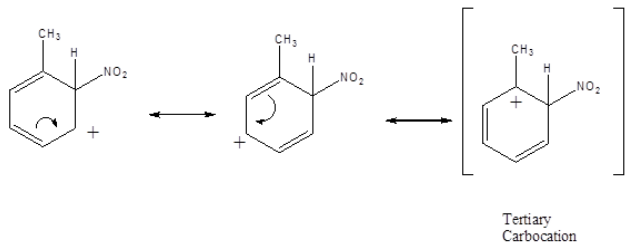
from the carbocation formed in the intermediate step, increasing the activation energy, which slows down the reaction.

THE CH_3 GROUP IS AN ORTHO, PARA DIRECTOR



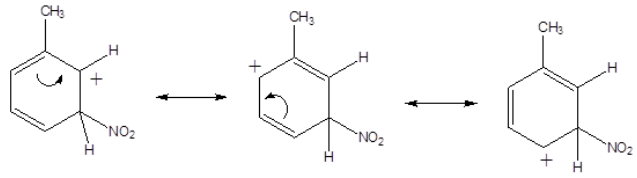
Alkyl groups are inductively donating, therefore are activators. This resulsts in o/p attack to form a tertiary arenium carbocation which speeds up the reaction.

Ortho Attack

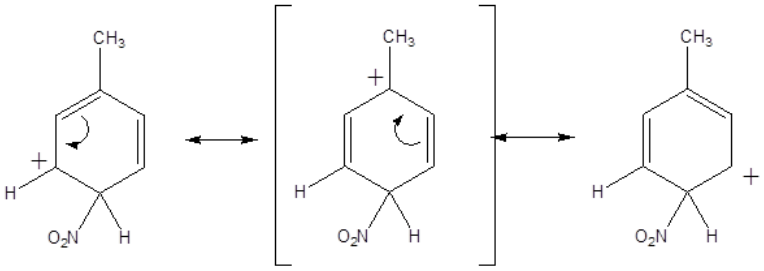


Tertiary Carbocation

Meta Attack

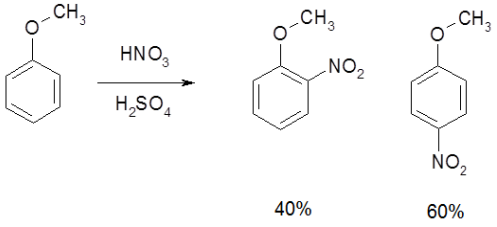


Para Attack



Tertiary Carbocation

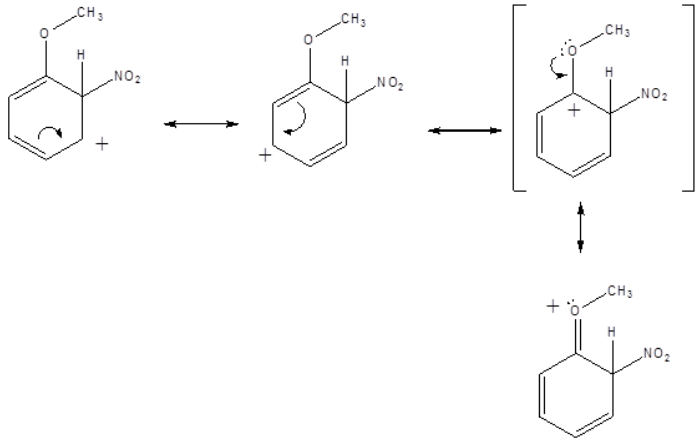
THE O-CH_3 GROUP IS AN ORTHO, PARA DIRECTOR



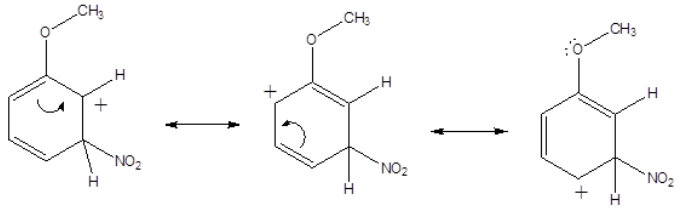
The methoxy group is an example of groups that are ortho, para directors by having and oxygen or nitrogen adjacent to the aromatic ring. This same activation is present with alcohols, amines, esters and amides (with the oxygen or nitrogen attached to the ring, not the carbonyl).

Groups with an oxygen or nitrogen attached to the aromatic ring are ortho and para directors since the O or N can push electrons into the ring, making the ortho and para positions more reactive and stabilizing the arenium ion that forms. This causes the ortho and para products to form faster than meta. Generally, the para product is preferred because of steric effects.

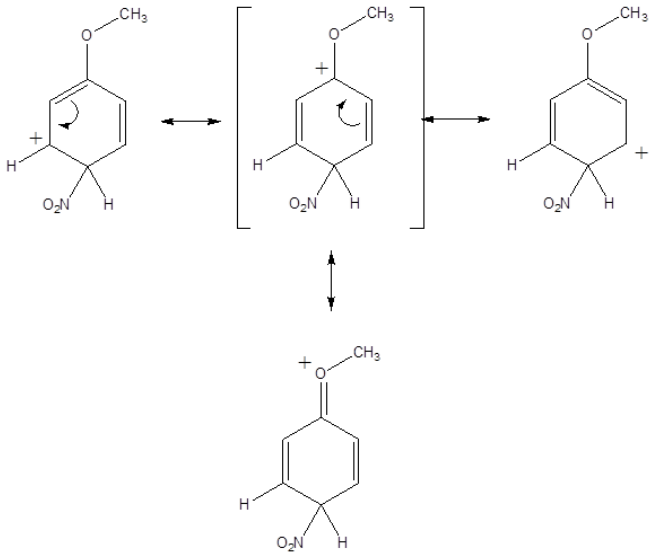
Ortho Attack



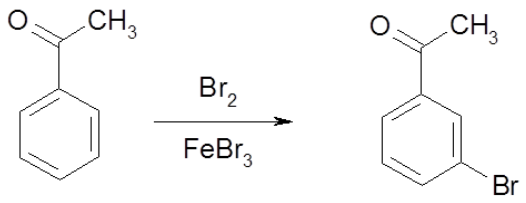
Meta Attack



Para Attack



ACYL GROUPS ARE META DIRECTORS

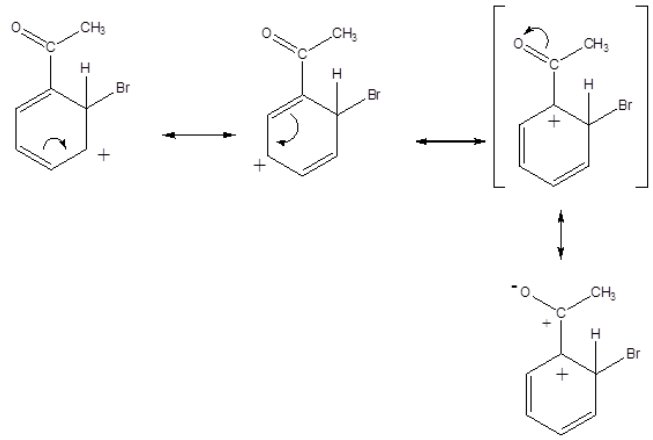


72%

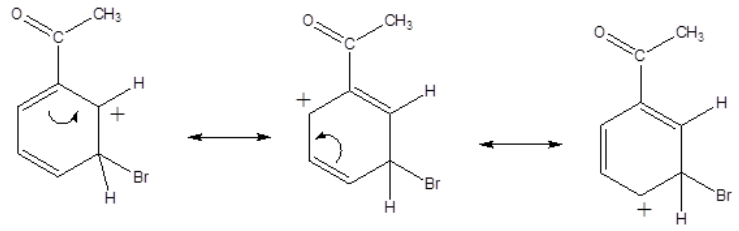
Ketones are an example of groups that deactivate an aromatic ring through resonance. Similar deactivation also occurs with ammonium ions, nitro groups, aldehydes, nitriles, sulfonic acids, and groups with a carbonyl attached to the ring (amides, esters, carboxylic acids, and anhydrides).

Acyl groups are resonance deactivators. Ortho and para attack produces a resonance structure which places the arenium cation next to an 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 destabilizing resonance structure.

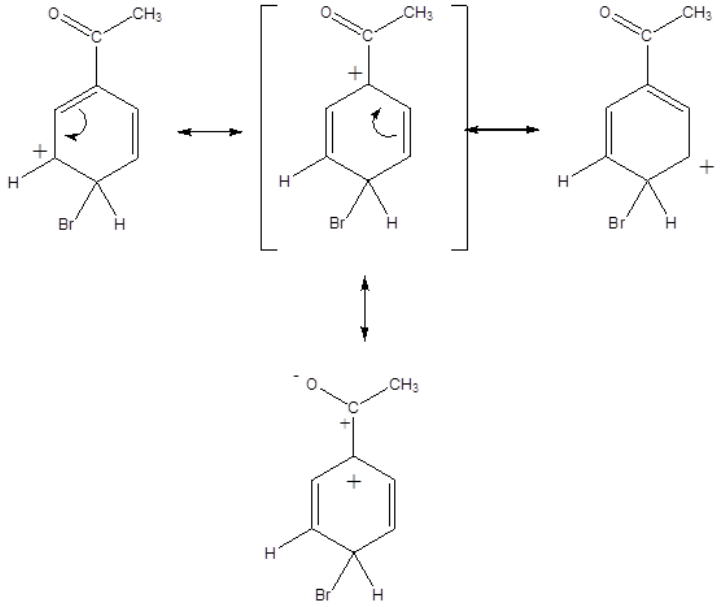
Ortho Attack



Meta Attack



Para Attack



HALOGENS

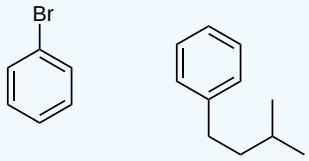
Halogens are an interesting hybrid case. They are ortho, para directors, but deactivators. Overall, they remove electron density from the ring, making it less reactive. However, due to their resonance donation to the ring, if it does react, it reacts primarily at ortho and para positions.

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.

? EXERCISE 16.5.1

Predict the pattern of the electrophilic substitution on these rings:



Answer

The first substitution is going to be ortho and/or para substitution since we have a halogen subtituent. The second substitution is going to be ortho and/or para substitution also since we have an alkyl substituent.

? EXERCISE 16.5.2

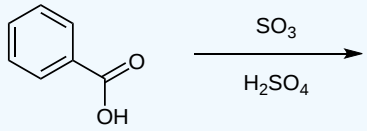
Which nitration product is going to form faster: nitration of aniline or nitration of nitrobenzene?

Answer

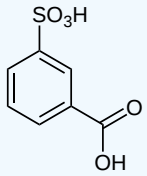
The nitration of aniline is going to be faster than the nitration of nitrobenzene, since the aniline is a ring with NH_2 substituent and nitrobenzene is a ring with NO_2 substituent. As described above NH_2 is an activating group which speeds up the reaction and NO_2 is a deactivating group that slows down the reaction.

EXERCISE 16.5.3

Predict the product of the following sulfonation reaction:



Answer



EXERCISE 16.5.4

Classify these two groups as activating or deactivating groups:

A. alcohol

B. ester

Answer

A. alcohol is an activating group.

B. Esters can be either. If the oxygen atom is next to the ring, esters are activating. However if the carbonyl is next to the ring, the ester is a deactivating group.

EXERCISE 16.5.5

Does a chloride substituent activate or deactivate an aromatic ring?

Answer

Chloride deactivate an aromatic ring due to the inductive effect.

EXERCISE 16.5.6

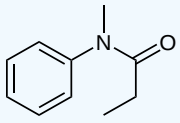
(Trichloromethyl)benzene has a strong concentration of electrons at the methyl substituent. Comparing this toluene, which is more reactive toward electrophilic substitution?

Answer

The trichloromethyl group is an electron donor into the benzene ring, therefore making it more stable and therefore more reactive compared to electrophilic substitution.

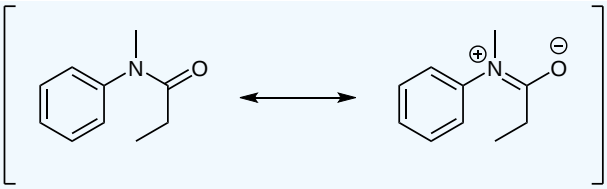
EXERCISE 16.5.7

The following compound is less reactive towards electrophilic substitution than aniline? Explain.



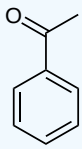
Answer

As seen in resonance the electron density is also localized off of the ring, thereby deactivating it compared to aniline.

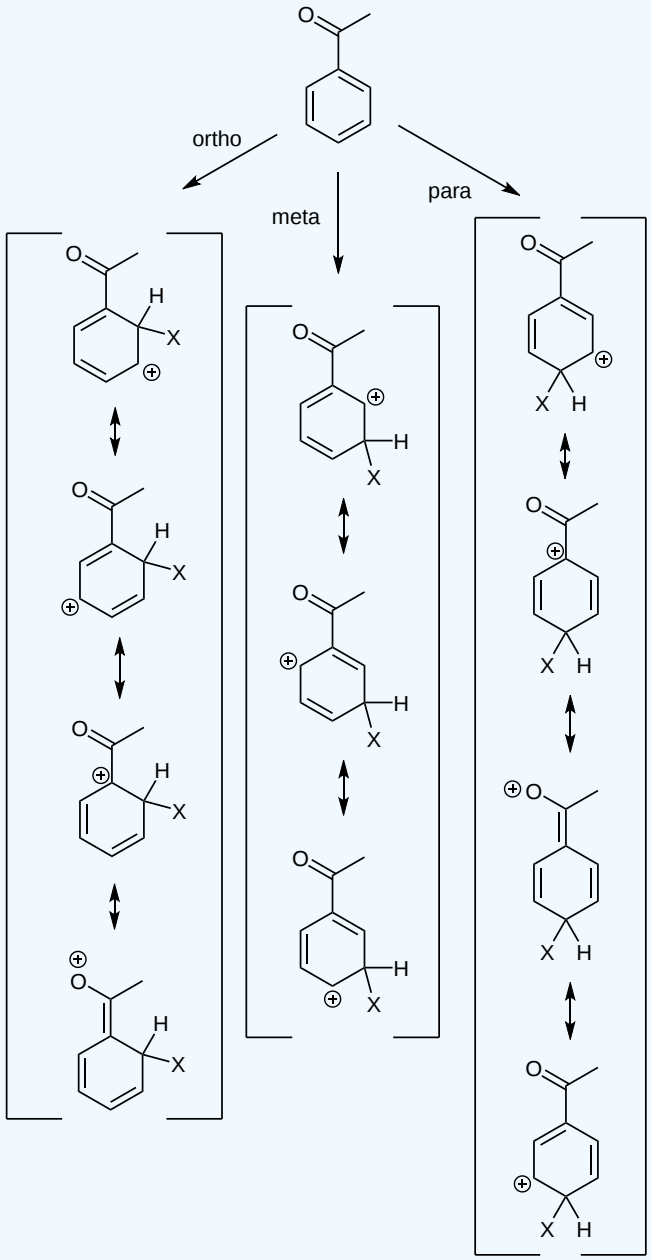


EXERCISE 16.5.8

Consider the intermediates of the following molecule during an electrophilic substitution. Draw resonance structures for ortho, meta, and para attacks.



Answer



16.6: TRISUBSTITUTED BENZENES - ADDITIVITY OF EFFECTS

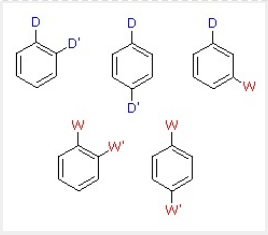
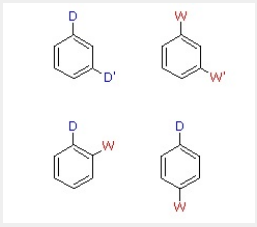
OBJECTIVES

After completing this section, you should be able to

1. predict the position or positions at which electrophilic substitution will occur when a third substituent is introduced into a disubstituted benzene ring.
2. explain the observed substitution pattern when a third substituent is introduced into a disubstituted benzene ring.

ORIENTATIONAL INTERACTION OF SUBSTITUENTS

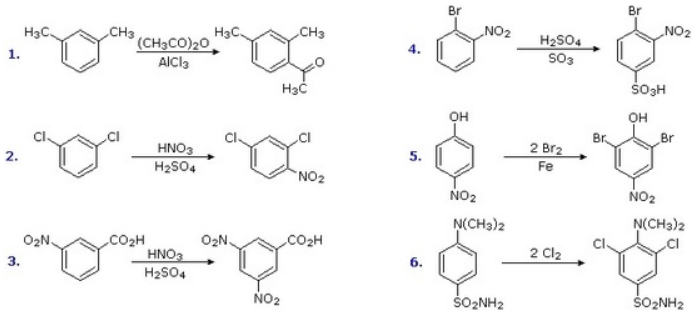
When a benzene ring has two substituent groups, each exerts an influence on subsequent substitution reactions. The activation or deactivation of the ring can be predicted more or less by the sum of the individual effects of these substituents. The site at which a new substituent is introduced depends 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

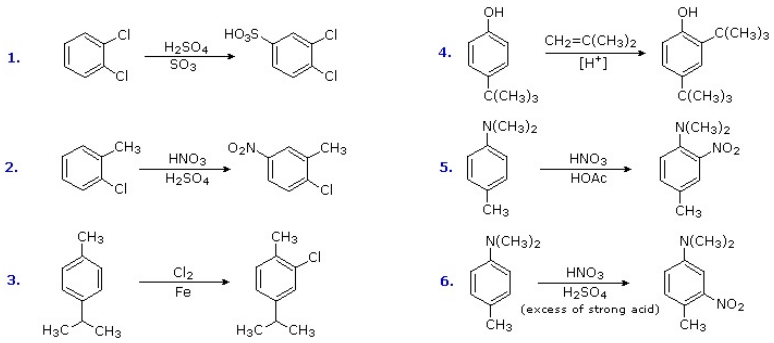
The products from substitution reactions of compounds having a reinforcing orientation of substituents are easier to predict than those having antagonistic substituents. For example, the six equations shown below are all examples of reinforcing or cooperative directing effects operating in the expected 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 6.

ANTAGONISTIC OR NON-COOPERATIVE SUBSTITUTIONS

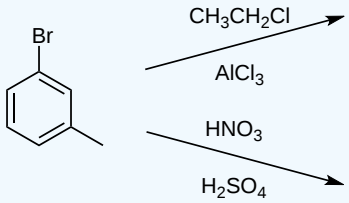
Substitution reactions of compounds having an antagonistic orientation of substituents require a more careful analysis. If the substituents are identical, as in example 1 below, the symmetry of the molecule will again simplify the decision. When one substituent has a pair of non-bonding electrons available 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.

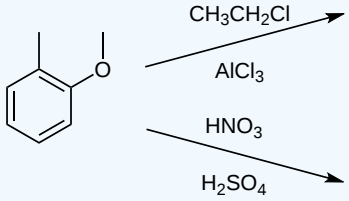


EXERCISES

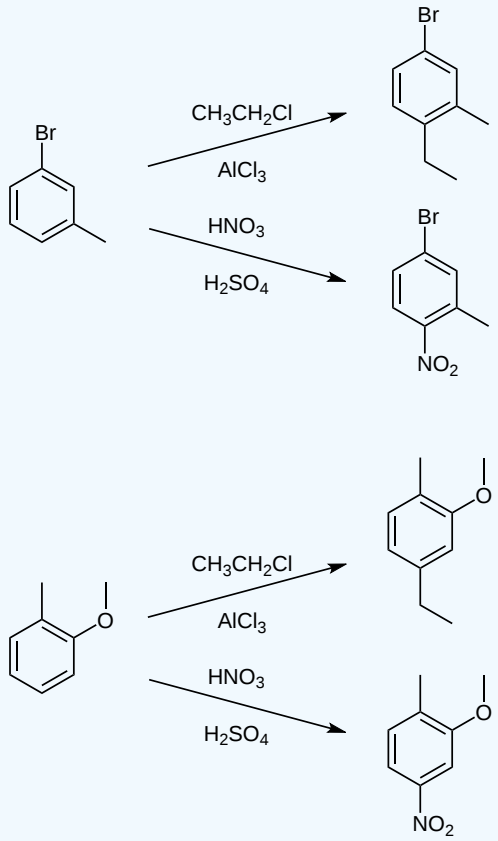
? EXERCISE 16.6.1

Predict the products of the following reactions:





Answer



16.7: NUCLEOPHILIC AROMATIC SUBSTITUTION

OBJECTIVES

After completing this section, you should be able to

1. identify the conditions necessary for an aryl halide to undergo nucleophilic aromatic substitution, and give an example of such a reaction.
2. write the detailed mechanism for a nucleophilic aromatic substitution reaction.
3. compare the mechanism of a nucleophilic aromatic substitution reaction and the S_N1 and S_N2 mechanisms discussed earlier.
4. identify the product formed when a given nucleophile reacts with a given aryl halide in a nucleophilic aromatic substitution reaction.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- Meisenheimer complex
- nucleophilic aromatic substitution

STUDY NOTES

A *nucleophilic aromatic substitution reaction* is a reaction in which one of the substituents in an aromatic ring is replaced by a nucleophile.

A *Meisenheimer complex* is a negatively charged intermediate formed by the attack of a nucleophile upon one of the aromatic-ring carbons during the course of a nucleophilic aromatic substitution reaction. A typical Meisenheimer complex is shown in the reaction scheme below. Notice how this particular complex can be formed from two different starting materials by using a different nucleophile in each case.

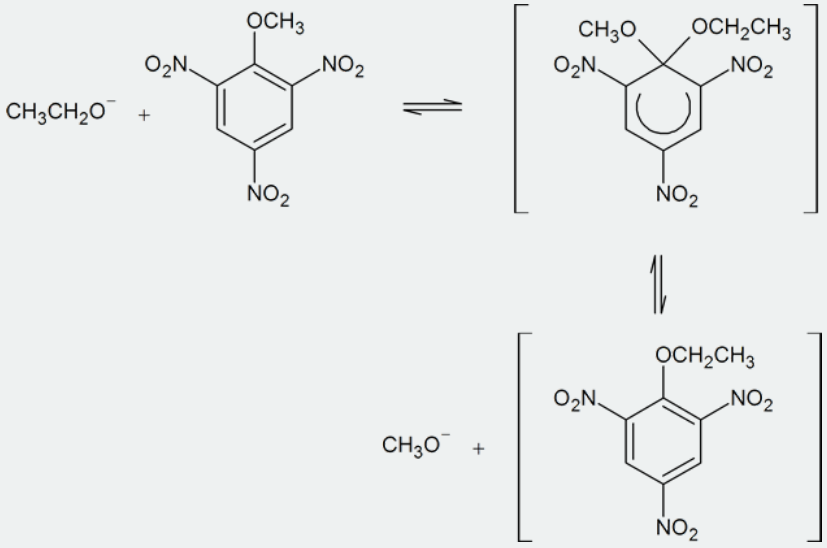


Figure 16.7.1: The formation of a typical Meisenheimer complex

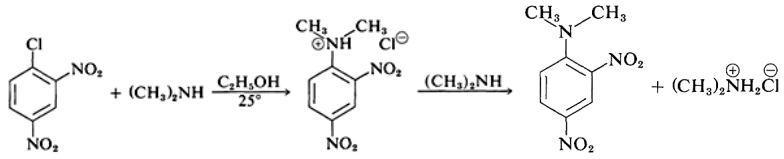
A NUCLEOPHILIC AROMATIC DISPLACEMENT REACTIONS OF ARYL HALIDES

The carbon-halogen bonds of aryl halides are like those of alkenyl halides in being much stronger than those of alkyl halides. The simple aryl halides generally are resistant to attack by nucleophiles in either S_N1 or S_N2 reactions. However, this low reactivity can be changed dramatically by changes in the reaction conditions and the structure of the aryl halide. In fact, nucleophilic displacement becomes quite rapid

a. when the aryl halide is activated by substitution with strongly electron-attracting groups such as NO_2, and
b. when very strongly basic nucleophilic reagents are used.

ADDITION-ELIMINATION MECHANISM OF NUCLEOPHILIC SUBSTITUTION OF ARYL HALIDES

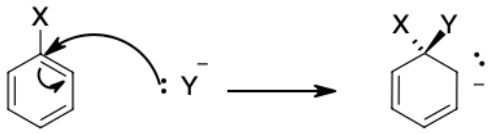
Although the simple aryl halides are inert to the usual nucleophilic reagents, considerable activation is produced by strongly electron-attracting substituents provided these are located in either the ortho or para positions, or both. For example, the displacement of chloride ion from 1-chloro-2,4-dinitrobenzene by dimethylamine occurs readily in ethanol solution at room temperature. Under the same conditions chlorobenzene completely fails to react; thus the activating influence of the two nitro groups amounts to a factor of at least 108:



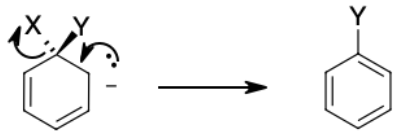
A related reaction is that of 2,4-dinitrofluorobenzene with the amino groups of peptides and proteins, and this reaction provides a means for analysis of the N-terminal amino acids in polypeptide chains.

In general, the reactions of activated aryl halides closely resemble the S_N2-displacement reactions of aliphatic halides. The same nucleophilic reagents are effective (e.g., $CH_3O^{\ominus}$, $HO^{\ominus}$, and RNH_2); the reactions are second order overall (first order in halide and first order in nucleophile); and for a given halide the more nucleophilic the attacking reagent, the faster the reaction. However, there must be more than a subtle difference in mechanism because an aryl halide is unable, to pass through the same type of transition state as an alkyl halide in S_N2 displacements.

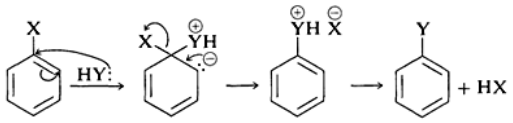
The generally accepted mechanism of nucleophilic aromatic substitution of aryl halides carrying activating groups involves two steps. The first step involves attack of the nucleophile $Y:^{\ominus}$ at the carbon bearing the halogen substituent to form an intermediate carbanion. The aromatic system is destroyed on forming the anion, and the carbon at the reaction site changes from planar (sp^2 bonds) to tetrahedral (sp^3 bonds).



In the second step, loss of an anion, $X^{\ominus}$ or $Y^{\ominus}$, regenerates an aromatic system, and, if $X^{\ominus}$ is lost, the overall reaction is nucleophilic displacement of X by Y.

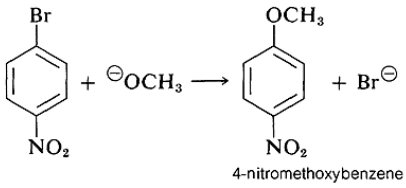


In the case of a neutral nucleophilic reagent, Y or HY, the reaction sequence would be the same except for the necessary adjustments in the charge of the intermediate:



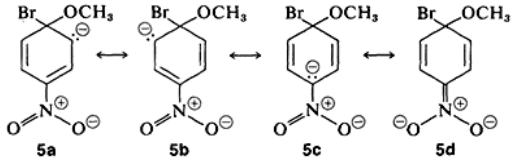
Why is this reaction pathway generally unfavorable for the simple aryl halides? The answer is that the intermediate is too high in energy to be formed at any practical rate. Not only has it lost the aromatic stabilization of the benzene ring, but its formation results in transfer of a negative charge to the ring carbons, which themselves are not very electronegative.

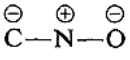
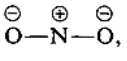
However, when strongly electron-attracting groups are located on the ring at the ortho-para positions, the intermediate anion is stabilized by delocalization of electrons from the ring carbons to more favorable locations on the substituent groups. As an example, consider the displacement of bromine by methoxid (OCH_3) in the reaction of 4-bromonitrobenzene and methoxide ion:

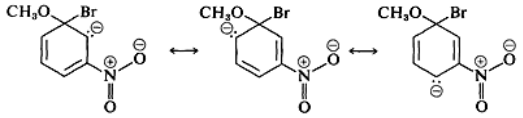


4-nitromethoxybenzene

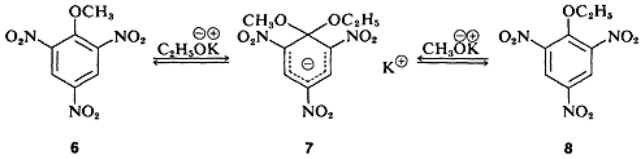
The anionic intermediate formed by addition of methoxide ion to the aryl halide can be described by the valence-bond structures 5a-5d. Of these structures 5d is especially important because in it the charge is transferred from the ring carbons to the oxygen of the nitro substituent:



Substituents in the meta positions have much less effect on the reactivity of an aryl halide because delocalization of electrons to the substituent is not possible. No formulas can be written analogous to 5c and 5d in which the negative charges are both on atoms next to positive nitrogen,  and  ,



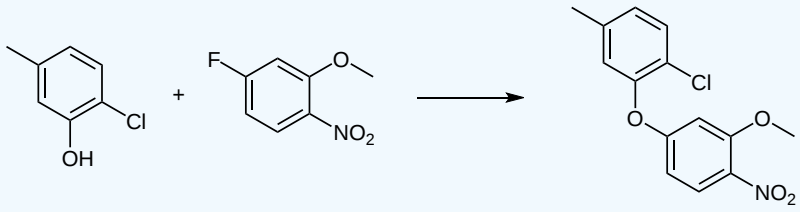
In a few instances, stable compounds resembling the postulated reaction intermediate have been isolated. One classic example is the complex 7 (isolated by J. Meisenheimer), which is the product of the reaction of either the methyl aryl ether 6 with potassium ethoxide, or the ethyl aryl ether 8 and potassium methoxide:



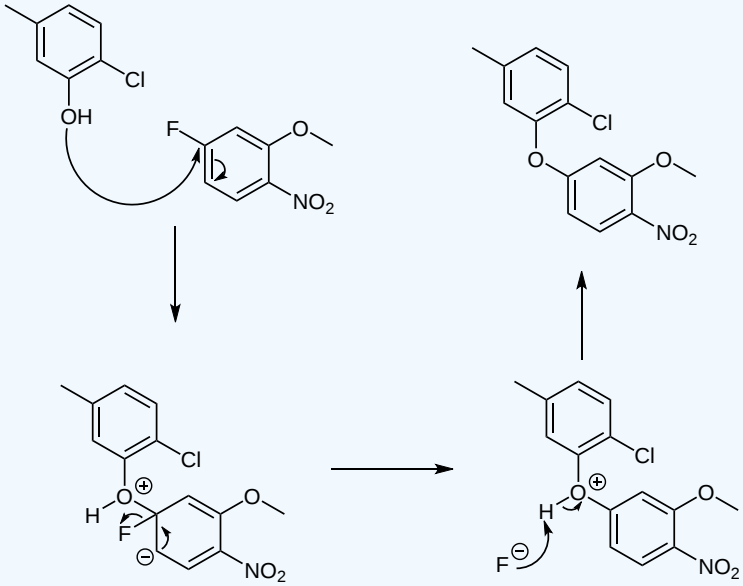
EXERCISES

? EXERCISE 16.7.1

Propose a mechanism for the following reaction:



Answer



16.8: BENZYNE

OBJECTIVES

After completing this section, you should be able to

1. identify the reagents and conditions required to produce phenol from chlorobenzene on an industrial scale.
2. write the mechanism for the conversion of an alkyl halide to a phenol through a benzyne intermediate.
3. discuss the experimental evidence which supports the existence of benzyne intermediates.
4. discuss the bonding in benzyne, and hence account for its high reactivity.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- benzyne
- elimination-addition mechanism

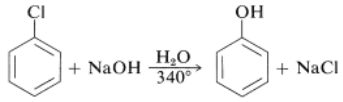
STUDY NOTES

An elimination-addition mechanism involves the elimination of the elements of a small molecule from a substrate to produce a highly reactive intermediate, which then undergoes an addition reaction.

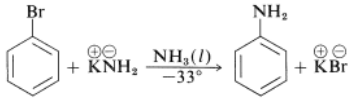
The elimination-addition mechanism of nucleophilic aromatic substitution involves the remarkable intermediate called benzyne or arynes.

ELIMINATION-ADDITION MECHANISM OF NUCLEOPHILIC AROMATIC SUBSTITUTION. ARYNES

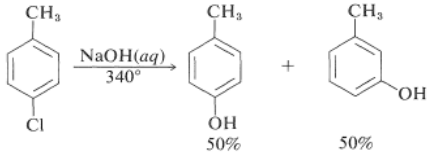
The reactivities of aryl halides, such as the halobenzenes, are exceedingly low toward nucleophilic reagents that normally effect substitution with alkyl halides and activated aryl halides. Substitutions do occur under forcing conditions of either high temperatures or very strong bases. For example, chlorobenzene reacts with sodium hydroxide solution at temperatures around 340^{o} and this reaction was once an important commercial process for the production of benzenol (phenol):



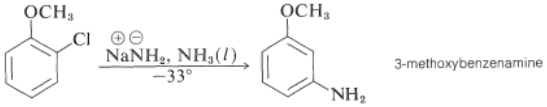
In addition, aryl chlorides, bromides, and iodides can be converted to areneamines $\mathrm{ArNH_2}$ by the conjugate bases of amines. In fact, the reaction of potassium amide with bromobenzene is extremely rapid, even at temperatures as low as -33^{o} with liquid ammonia as solvent:



However, substitution reactions of this type differ from the previously discussed substitutions of activated aryl halides in that rearrangement often occurs. That is, *the entering group does not always occupy the same position on the ring as that vacated by the halogen substituent*. For example, the hydrolysis of 4-chloromethylbenzene at 340^{o} gives an equimolar mixture of 3- and 4-methylbenzenols:

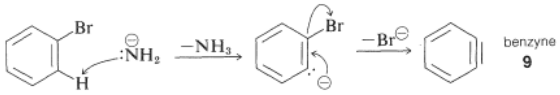


Even more striking is the exclusive formation of 3-methoxybenzenamine in the amination of 2-chloromethoxybenzene. Notice that this result is a violation of the principle of least structural change:



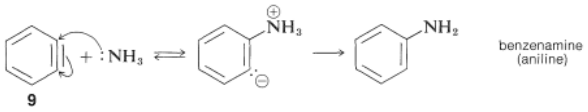
The mechanism of this type of reaction has been studied extensively, and much evidence has accumulated in support of a stepwise process, which proceeds first by base-catalyzed *elimination* of hydrogen halide (HX) from the aryl halide - as illustrated below for the amination of bromobenzene:

Elimination

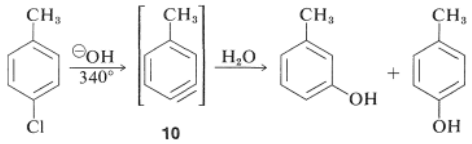


The product of the elimination reaction is a highly reactive intermediate 9 called **benzyne**, or **dehydrobenzene**, which differs from benzene in having two less hydrogen and an extra bond between two ortho carbons. Benzyne reacts rapidly with any available nucleophile, in this case the solvent, ammonia, to give an addition product:

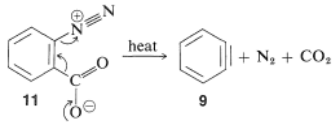
Addition



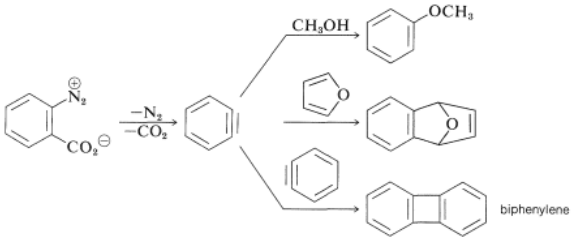
The rearrangements in these reactions result from the attack of the nucleophile at one or the other of the carbons of the extra bond in the intermediate. With benzyne the symmetry is such that no rearrangement would be detected. With substituted benzynes isomeric products may result. Thus 4-methylbenzyne, 10, from the reaction of hydroxide ion with 4-chloro-1-methylbenzene gives both 3- and 4-methylbenzenols:



In the foregoing benzyne reactions the base that produces the benzyne in the elimination step is derived from the nucleophile that adds in the addition step. This need not always be so, depending on the reaction conditions. In fact, the synthetic utility of aryne reactions depends in large part of the success with which the aryne can be generated by one reagent but captured by another. One such method will be discussed in Section 14-10C and involves organometallic compounds derived from aryl halides. Another method is to generate the aryne by thermal decomposition of a 1,2-disubstituted arene compound such as 11, in which both substituents are leaving groups - one leaving with an electron pair, the other leaving without:



When 11 decomposes in the presence of an added nucleophile, the benzyne intermediate is trapped by the nucleophile as it is formed. Or, if a conjugated diene is present, benzyne will react with it by a [4 + 2] cycloaddition. In the absence of other compounds with which it can react, benzyne will undergo [2 + 2] cycloaddition to itself:

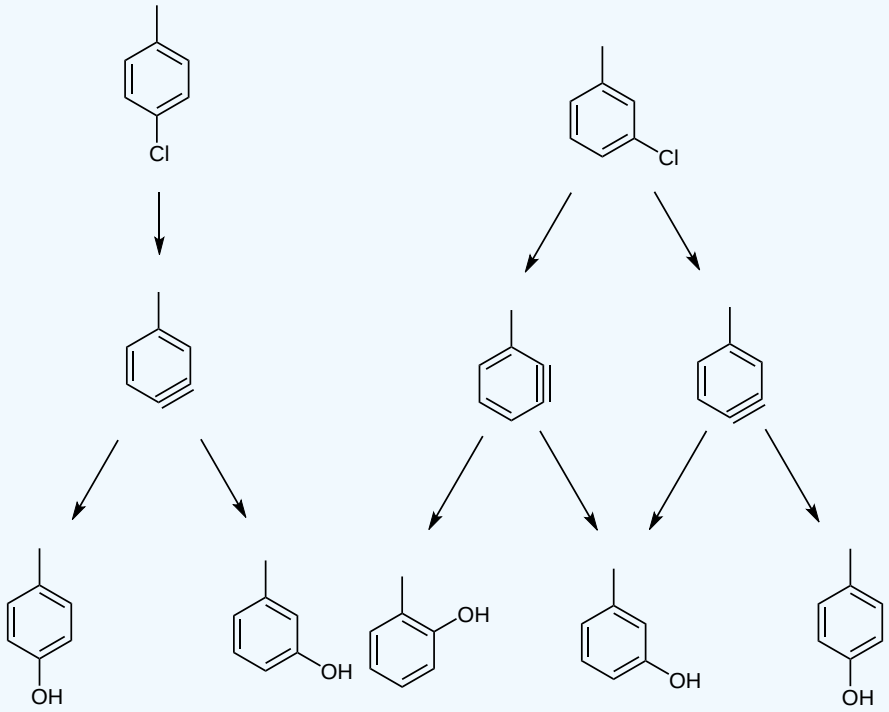


? EXERCISE 16.8.1

When *p*-chlorotoluene is reacted with NaOH, two products are seen. While when *m*-chlorotoluene is reacted with NaOH, three products are seen. Explain this.

Answer

You need to look at the benzyne intermediates. The para substituted only allows for two products, while the para produces two different alkynes which give three different products.



16.9: OXIDATION OF AROMATIC COMPOUNDS

OBJECTIVES

After completing this section, you should be able to

- write an equation to describe the oxidation of an alkylbenzene to a carboxylic acid.
- identify the reagents required to oxidize a given alkylbenzene to a carboxylic acid.
- identify the product formed from the side-chain oxidation of a given alkylbenzene.
- identify the aromatic compound needed to produce a given carboxylic acid through side-chain oxidation.
- write the equation for the bromination of an alkylbenzene side chain.
- identify the reagents and conditions necessary to bring about bromination in the side chain of an alkylbenzene.
- identify the product formed when a given alkylbenzene undergoes side-chain bromination.
- identify the alkylbenzene needed to prepare a given benzylic bromide by radical substitution.
- write the mechanism for the radical substitution at the benzylic position of an alkylbenzene.
- explain the stability of benzylic radicals in terms of resonance, and draw the resonance contributors of a given benzyl radical.
- explain, and illustrate with appropriate examples, the importance of benzylic bromides as intermediates in organic syntheses.
- arrange a given series of radicals (including benzylic type radicals) in order of increasing or decreasing stability. (Review Section 10.3 if necessary.)

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- benzylic oxidation
- benzylic position
- side-chain oxidation

STUDY NOTES

As you can see from the examples, no matter what the length of the alkyl group in the arene substrate, the product is always a one-carbon carboxyl group. Thus, the benzylic carbon atom has been oxidized and the term *benzylic oxidation* is appropriate. The term *side-chain oxidation* is also commonly used.

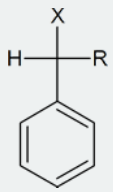
In alkylbenzenes, the carbon atom which is attached to the aromatic ring is particularly reactive. Reactions taking place at this carbon atom are said to occur at the *benzylic position*.

You may wish to review Section 10.3 to remind yourself about allylic bromination using N-bromosuccinimide.

Benzylic halides undergo the typical reactions of alkyl halides; thus, you can expect to see such compounds used frequently in multistep syntheses.

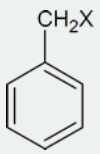
Note that we have adopted the terminology given below.

Any compound of the type



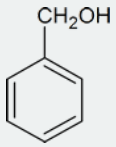
(where X = halogen) will be referred to as a “benzylic halide.”

Compounds of the type



are actually called benzyl chloride, benzyl bromide, etc.

The compound



is called benzyl alcohol.

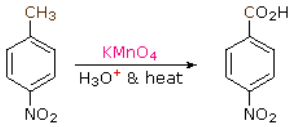
OXIDATION OF ALKYL SIDE-CHAINS

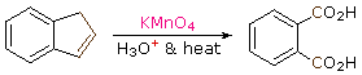
The benzylic hydrogens of alkyl substituents on a benzene ring are activated toward free radical attack, as noted earlier. Furthermore, S_N1 S_N2 and E1 reactions of benzylic halides, show enhanced reactivity, due to the adjacent aromatic ring. The possibility that these observations reflect a general 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 permanganate 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.

$$C_6H_5-CH_2CH_2CH_2CH_3 + KMnO_4 + H_3O^+ + \text{heat} \longrightarrow C_6H_5-CO_2H + CO_2$$

$$p-(CH_3)_3C-C_6H_4-CH_3 + KMnO_4 + H_3O_6+ + \text{heat} \longrightarrow p-(CH_3)_3C-C_6H_4-CO_2H$$

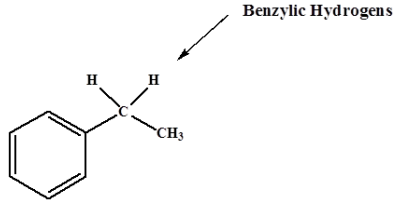
These equations are not balanced. The permanganate oxidant is reduced, usually to Mn(IV) or Mn(II). Two other examples of this reaction are given below, and illustrate its usefulness in preparing substituted benzoic acids.



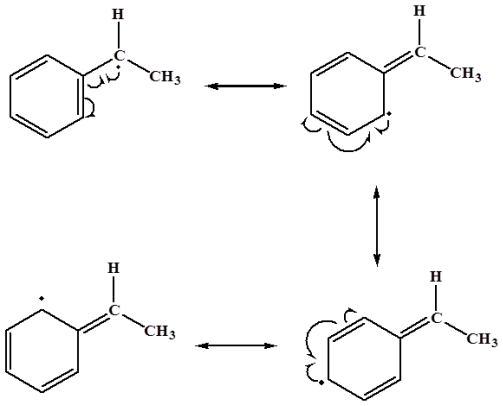


BROMINATION OF THE BENZYLIC CARBON

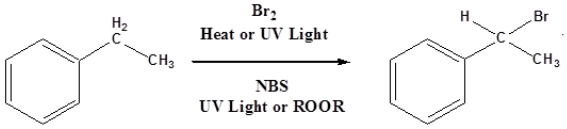
The benzylic C-H bonds weaker than most sp^3 hybridized C-H. This is because the radical formed from homolysis is resonance stabilized.



Resonance stabilization of the benzylic radical

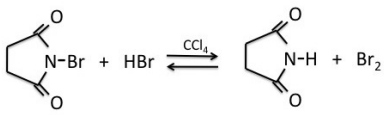


Because of the weak C-H bonds, benzylic hydrogens can form benzylic halides under radical conditions.



NBS AS A BROMINE SOURCE

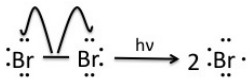
NBS (N-bromosuccinimide) is the most commonly used reagent to produce low concentrations of bromine. When suspended in tetrachloride (CCl_4), NBS reacts with trace amounts of HBr to produce a low enough concentration of bromine to facilitate the allylic bromination reaction.



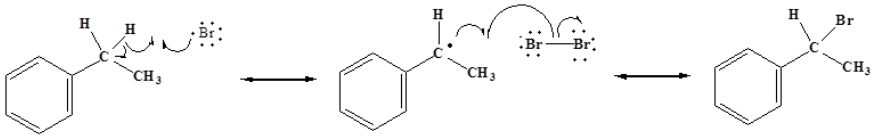
ALLYLIC BROMINATION MECHANISM

Step 1: Initiation

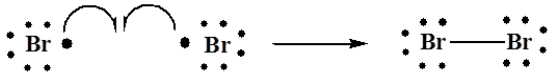
Once the pre-initiation step involving NBS produces small quantities of Br_2, the bromine molecules are homolytically cleaved by light to produce bromine radicals.



Step 2 and 3: Propagation

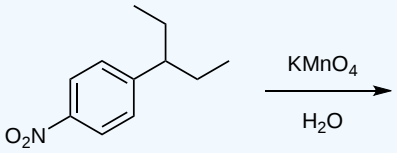


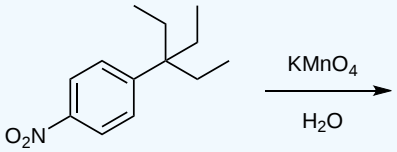
Step 4: Termination



? EXERCISE 16.9.1

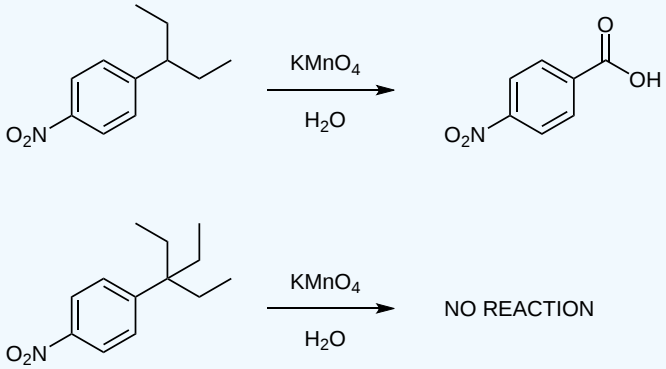
Predict the products of the following two reactions.





Answer

The second one leads to no reaction because it requires a hydrogen just off the phenyl ring.



EXERCISE 16.9.2

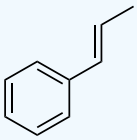
Consider a benzyl radical. Would it be more stable than an alkyl radical? Explain.

Answer

Yes it would be more stable than an alkyl radical. The benzyl radical is stabilized through several resonance structures where the radical is moved through the ring via the pi system there.

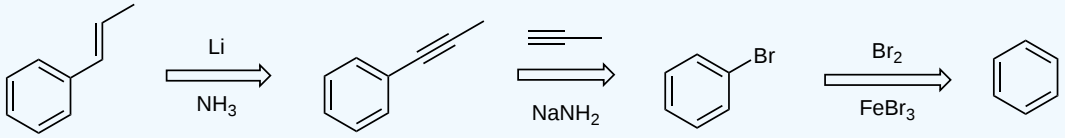
EXERCISE 16.9.3

How would you make the following molecule?



Answer

The following is just one possibility.



16.10: REDUCTION OF AROMATIC COMPOUNDS

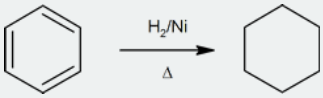
OBJECTIVES

After completing this section, you should be able to

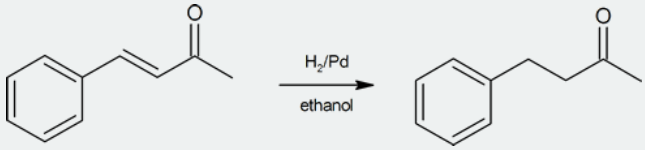
- write an equation to represent the reduction of a substituted benzene to a substituted cyclohexane.
- identify the catalyst and reagents used to reduce aromatic rings.
- compare the ease of reduction of alkenes with the difficulty in reducing benzene rings, and show how this difference in reactivity can be used in organic synthesis.
- write an equation to illustrate the reduction of an aromatic ketone to an arene.
- explain why Friedel-Crafts acylation, followed by reduction, provides a better route to primary alkylbenzenes than does direct alkylation.
- show how a specified alkylbenzene may be prepared by a Friedel-Crafts acylation, followed by reduction. Specify all reagents, the structure of the intermediate ketone, and the necessary starting material.

STUDY NOTES

Catalytic hydrogenation of aromatic rings requires forcing conditions (high heat and hydrogen pressure).

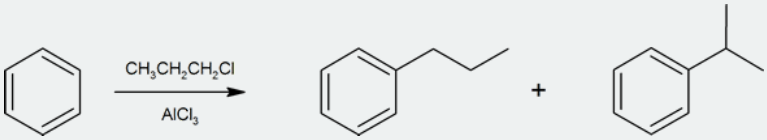


Under milder conditions it is possible to reduce the double-bond of an alkene without reducing the aromatic ring.

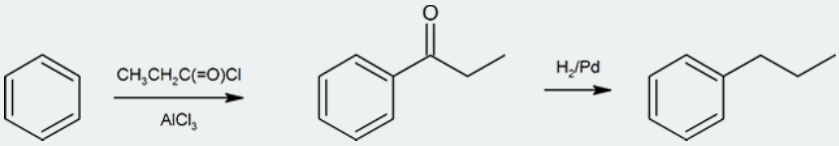


Notice in the above equation that H_2/Pd does not reduce the keto-carbonyl group. Remember, however, that H_2/Pd will reduce a keto-carbonyl group when it is directly attached to an aromatic ring (see equations 4 and 5 under Carbonyl Reductions).

This reduction of the (C=O) group next to an aromatic ring is an important synthetic tool. Recall the Friedel-Crafts alkylation from Section 16.3. When attaching larger alkyl groups to arenes there is a possibility of rearrangement of the alkyl group structure.

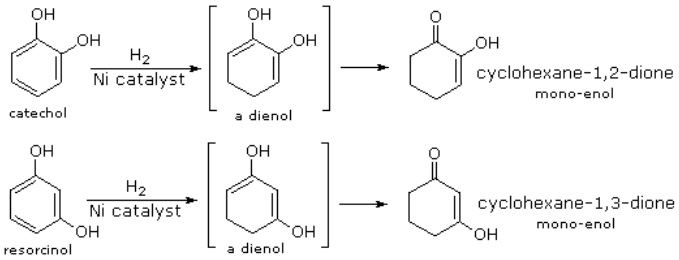


To generate the target compound (in this case *n*-propylbenzene) in a more controlled fashion, one can simply use the equivalent Friedel-Crafts acylation and then reduce the keto-carbonyl group next to the ring as a final step.

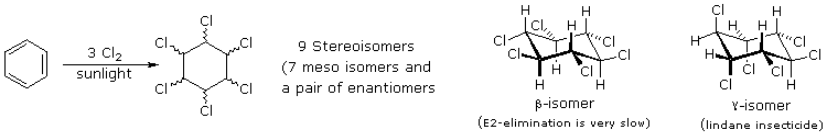


AROMATIC REDUCTION REACTIONS

Although it does so less readily than simple alkenes or dienes, benzene adds hydrogen at high pressure in the presence of Pt, Pd or Ni catalysts. The product is cyclohexane and the heat of reaction provides evidence of benzene's thermodynamic stability. Substituted benzene rings may also be reduced in this fashion, and hydroxy-substituted compounds, such as phenol, catechol and resorcinol, give carbonyl products resulting from the fast ketonization of intermediate enols. Nickel catalysts are often used for this purpose, as noted in the following equations.

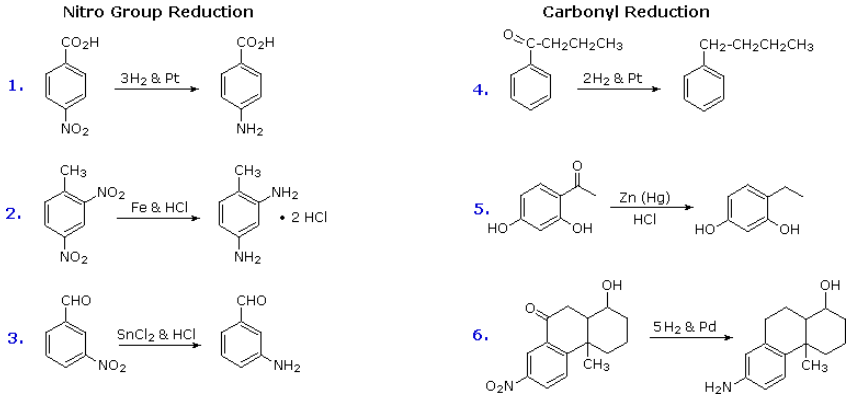


Benzene is more susceptible to radical addition reactions than to electrophilic addition. We have already noted that benzene does not react with chlorine or bromine in the absence of a catalyst and heat. In strong sunlight or with radical initiators benzene adds these halogens to give hexahalocyclohexanes. It is worth noting that these same conditions effect radical substitution of cyclohexane, the key factors in this change of behavior are the pi-bonds array in benzene, which permit addition, and the weaker C-H bonds in cyclohexane. The addition of chlorine is shown below on the left; two of the seven meso-stereoisomers are displayed to the right.



REDUCTION OF NITRO GROUPS AND ARYL KETONES

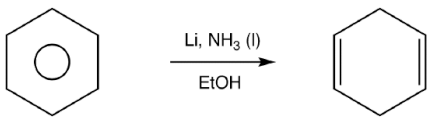
Electrophilic nitration and Friedel-Crafts acylation reactions introduce deactivating, meta-directing substituents on an aromatic ring. The attached atoms are in a high oxidation state, and their reduction converts these electron withdrawing functions into electron donating amino and alkyl groups. Reduction is easily achieved either by catalytic hydrogenation (H_2 + 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).



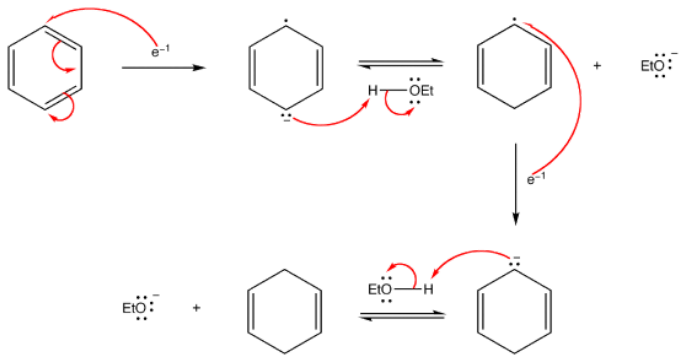
Several alternative methods for reducing nitro groups to amines are known. These include zinc or tin in dilute mineral acid, and sodium sulfide in ammonium hydroxide solution. The procedures described above are sufficient for most cases.

THE BIRCH REDUCTION

Another way of adding hydrogen to the benzene ring is by treatment with the electron rich solution of alkali metals, usually lithium or sodium, in liquid ammonia. See examples of this reaction, which is called the **Birch Reduction.** The Birch reduction is the dissolving-metal reduction of aromatic rings in the presence of an alcohol.



MECHANISM:

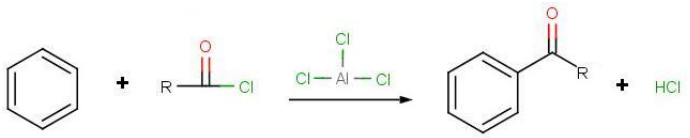


LIMITATIONS OF FRIEDEL-CRAFTS ALKYLATION

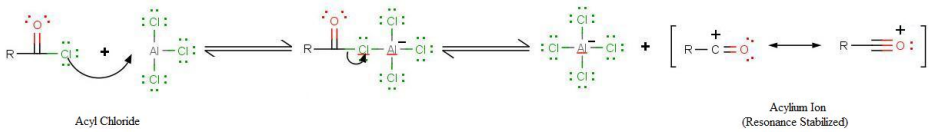
1. Carbocation Rearrangement - Only certain alkylbenzenes can be made due to the tendency of cations to rearrange.
2. **Compound Limitations** - Friedel-Crafts fails when used with compounds such as nitrobenzene and other strong deactivating systems.
3. **Polyalkylation** - Products of Friedel-Crafts 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.

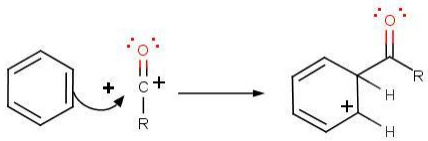
The goal of the reaction is the following:



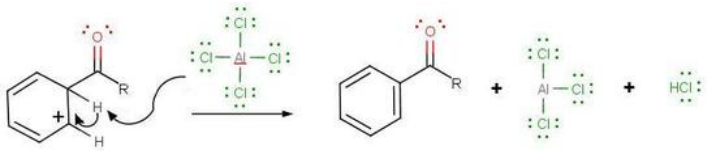
The very first step involves the formation of the acylium ion which will later react with benzene:



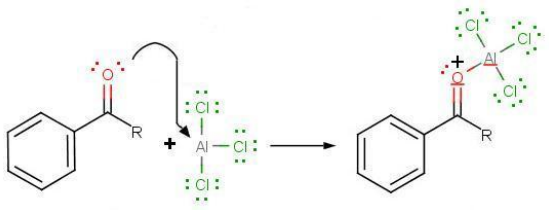
The second step involves the attack of the acylium ion on benzene as a new electrophile to form one complex:



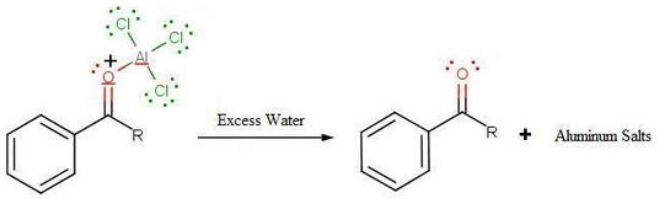
The third step involves the departure of the proton in order for aromaticity to return to benzene:



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:



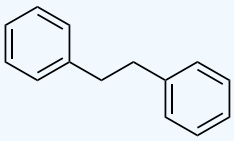
The final step involves the addition of water to liberate the final product as the acylbenzene:



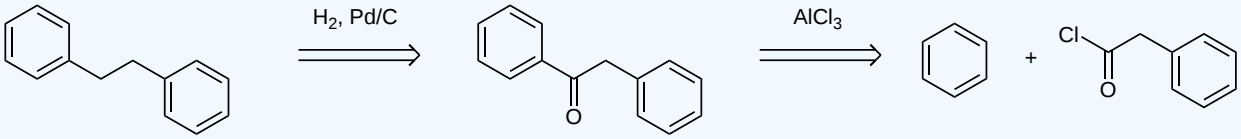
Because the acylium ion (as was shown in step one) is stabilized by resonance, no rearrangement occurs (Limitation 1). Also, because of of the deactivation of the product, it is no longer susceptible to electrophilic attack and hence, is no longer susceptible to electrophilic attack and hence, no longer 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.

? EXERCISE 16.10.1

How would you make the following from benzene and an acid chloride?



Answer



16.11: SYNTHESIS OF POLYSUBSTITUTED BENZENES

OBJECTIVES

After completing this section, you should be able to

- Design a multistep synthesis which may involve reactions in the alkyl side chain of an alkylbenzene and the electrophilic substitution reactions discussed in this chapter. You should pay particular attention to
  - carrying out the reactions in the correct order.
  - using the most appropriate reagents and conditions.
  - the limitations of certain types of reactions.
- Analyze a proposed multistep synthesis involving aromatic substitution to determine its feasibility, point out any errors in the proposal and identify possible problem areas.

STUDY NOTES

As you can see, designing a multistep synthesis requires an analytical mind and an ability to think logically, as well as a knowledge of organic reactions. The best way to become an expert in designing such syntheses is to get lots of practice by doing plenty of problems.

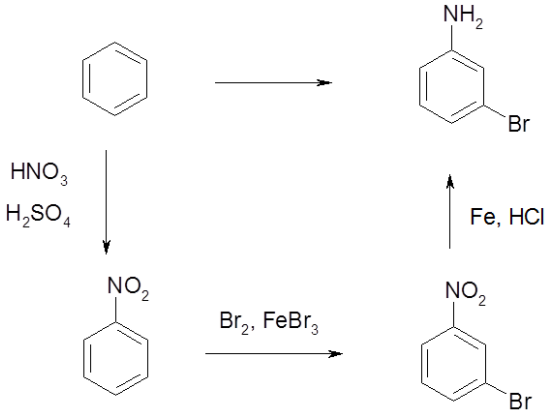
The ability to plan a successful multi step synthesis of complex molecules is one of the goals of organic chemists. It requires a working knowledge of the uses and limitations of many organic reactions - not only which reactions to use, but when. A few examples follow:

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.

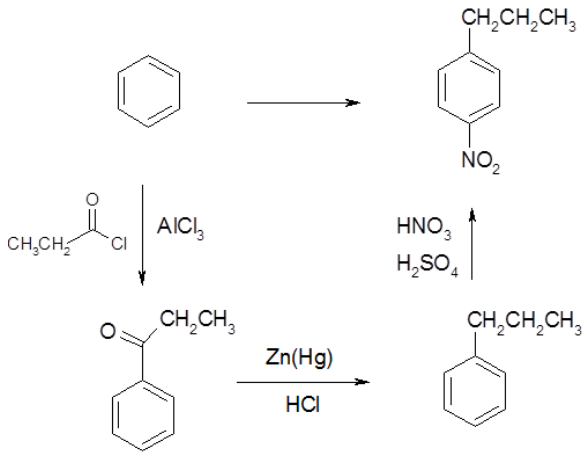


FROM BENZENE MAKE *P*-NITROPROPYLBENZENE :

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. Remember 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.



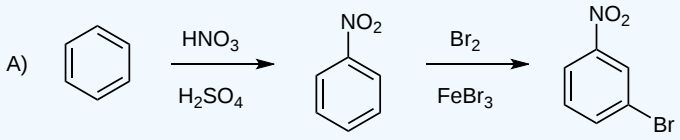
EXERCISE 16.11.1

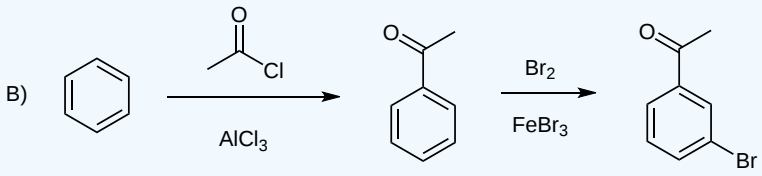
How would make the following compounds from benzene?

a. *m*-bromonitrobenzene
b. *m*-bromoethylbenzene

Answer

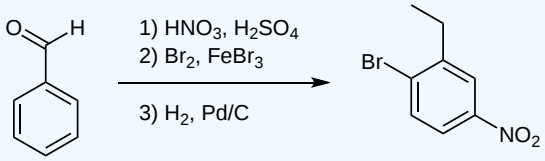
Only one possible synthesis is shown for each compound. There are multiple possibilities.





EXERCISE 16.11.2

There is something wrong with the following reaction, what is it?



Answer

The bromine should be in the meta position. Right now it is in the ortho position, from perhaps having the ethyl group present first and then the having it substituted there. BUT the ethyl group is last to form, and the aldehyde and nitro groups would both encourage a meta substitution.

16.S: CHEMISTRY OF BENZENE - ELECTROPHILIC AROMATIC SUBSTITUTION (SUMMARY)

CONCEPTS & VOCABULARY

16.0 Introduction

- Aromatic compounds don't typically undergo addition reactions.
- Aromatic compounds typically undergo substitution reactions.

16.1 Electrophilic Aromatic Substitution Reactions: Bromination

- Aromatic molecules only react with strong electrophiles.
- The first step in many electrophilic aromatic substitution mechanisms is activation or formation of the electrophile.
- The electrophilic aromatic substitution mechanism occurs in two steps. The first is addition of the electrophile to the ring and the second is elimination of a hydrogen from the ring to re-form the pi bond and restore aromaticity.
- In bromination of an aromatic ring, molecular bromine (Br_2) is reacted with iron tribromide ($FeBr_3$) to form the strongly electrophilic bromine cation and $FeBr_4$. Following this, the aromatic ring is reacted with the bromine cation and adds to the ring to form a benzenonium cation. This molecule then reacts with one of the bromine atoms from $FeBr_4$ to lose a hydrogen forming the product and HBr as well as reforming the iron tribromide.

16.2 Other Aromatic Substitutions

- Aluminum bromide ($AlBr_3$) can be used in place of $FeBr_3$ to create the bromine cation. Also the chlorides of alumnium and iron can also be used to create a chlorine cation which will also undergo electrophilic aromatic substitution.
- Reacting nitric acid and sulfuric acid forms nitronium (NO_2^+), which will react with aromatics for form nitro compounds.
- Sulfonation of aromatics can be accomplished by reacting with sulfur trioxide and sulfuric acid to yield sulfonic acids.

16.3 Alkylation and Acylation of Aromatic Rings - The Friedel-Crafts Reaction

- Friedel-Crafts reactions incorporate activation of alkyl and acyl halides by reacting them with a Lewis Acid catalyst, $AlCl_3$.
- Friedel-Crafts alkylations allow for adding alkyl chains to aromatic rings.
- After activation with aluminum chloride, alkyl carbocations can undergo rearrangement if it leads to a more stable intermediate.
- Friedel-Crafts acylations add alkyl ketones to aromatic rings.

16.4 Substituent Effects in Substituted Aromatic Rings

- Aromatic inductive effects are caused by differences in electronegativity between atoms bonded to the ring and the ring carbons.
- Most common heteroatoms (N, O, halogens) donate electron density toward the ring inductively.
- Aromatic resonance effects are caused by conjugation of substituents with the pi bonds of the ring.
- Substituents that increase the electron density of the ring activate the ring (make more reactive) toward electrophilic substitution.
- Substituents that decrease the electron density of the ring deactivate the ring (make less reactive) toward electrophilic substitution.

16.4b An Explanation of Substituent Effects

- Steric effects can increase para substitution as ortho/para directors become larger.
- Activating groups are ortho/para (o, p) directors.
- Deactivating groups are meta directors.
- Alkyl groups inductively donate electron density to the ring making them o, p directors.
- Groups with an O or N attached to the aromatic ring are activators and o, p directors due to resonance.
- Groups with a pi bond attached to the aromatic ring are deactivators and m directors due to resonance.
- Halogens are o, p directors, but are deactivators.

16.5 Trisubstituted Benzenes: Additivity of Effects

- When there is more than one group attached to an aromatic ring, these groups may reinforce directing effects (cooperative) or have opposing directing effects (non-cooperative).

16.6 Nucleophilic Aromatic Substitution

- Highly activated aromatic rings can react with strong nucleophiles through a substitution mechanism.
- The mechanism typically begins with addition of a nucleophile followed by elimination of a leaving group.

16.7 Benzyne

- Under highly reactive conditions, a mechanism that begins with elimination for form a benzyne molecule intermediate followed by addition of a nucleophile resulting in nucleophilic aromatic substitution.

16.8 Oxidation of Aromatic Compounds

- Alkyl side-chains can be oxidized to benzoic acid (or a benzoic acid derivative if there are other groups present on the ring) by potassium permanganate ($KMnO_4$) as long as the benzylic carbon has at least one hydrogen attached.
- Radical halogenation will occur at the benzylic carbon, due to stabilization of radical intermediates.

16.9 Reduction of Aromatic Compounds

- Catalytic hydrogenation (H_2 and a catalyst) can be used to reduce many aromatic side-chains.
- Nitro groups can be selectively reduced to amines with $SnCl_2$ and HCl or with Fe and HCl.
- Carbonyls adjacent to the ring can be reduced by either Clemmensen reduction (Zn(Hg) and HCl.
- Birch reductions can reduce aromatic rings.

16.10 Synthesis of Polysubstituted Benzenes

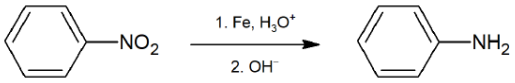
- Multistep synthesis requires a combination of forward (from the starting material) and backward (from the target compound) thinking.

SKILLS TO MASTER

- Skill 16.1 Write detailed electrophilic aromatic substitution mechanisms (halogentation, nitration, sulfonation, Friedel-Crafts alkyation and acylation).
- Skill 16.2 Write detailed mechanisms for formation of reactive electrophiles.
- Skill 16.3 Predict and explain rearrangements that can occur during Friedel-Crafts alkylation.
- Skill 16.4 Explain activation and deactivation of aromatic rings toward electrophilic aromatic substitution.
- Skill 16.5 Explain ortho, para vs. meta directing during electrophilic aromatic substitution reactions.
- Skill 16.6 Combine activation and deactivation and directing effects to predict products of reactions of substituted aromatic molecules.
- Skill 16.7 Write detailed nucleophilic aromatic substitution mechanisms through addition-elimination.
- Skill 16.8 Write detailed nucleophilic aromatic substitution mechanisms through benzyne elimination-addition.
- Skill 16.9 Draw products of oxidation of aromatic molecules.
- Skill 16.10 Draw products of reduction of aromatic side-chains.
- Skill 16.11 Draw mechanisms for reduction of aromatic rings.
- Skill 16.12 Solve multistep synthesis problems incorporating directing effects and side-chain reactions.

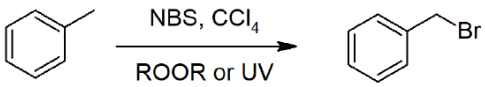
SUMMARY OF REACTIONS

Reduction of Nitro Group



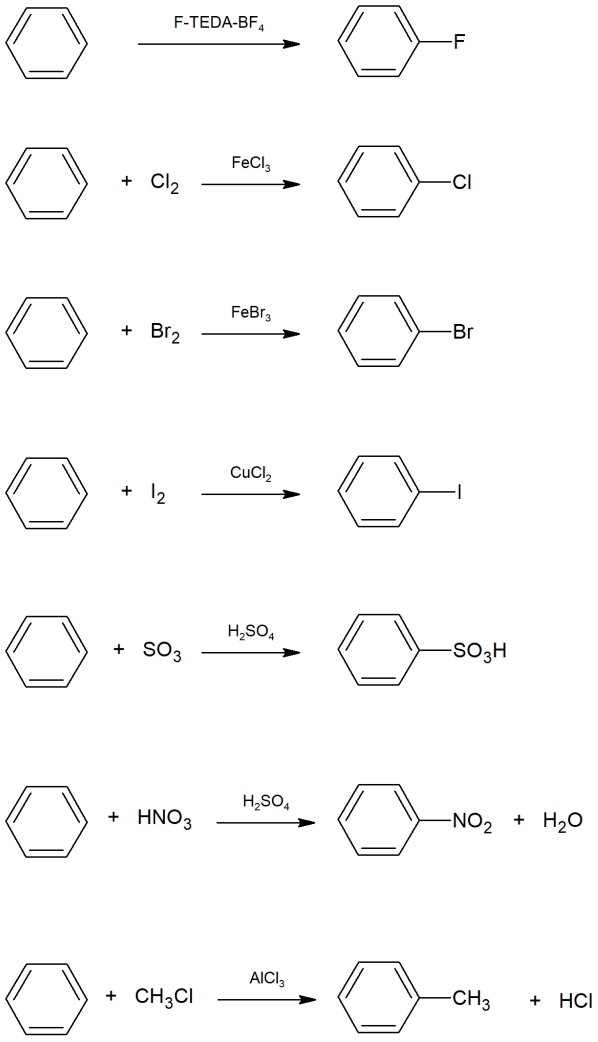
Oxidation of Alkylbenzene

Benzylic Bromination of Alkylbenzene

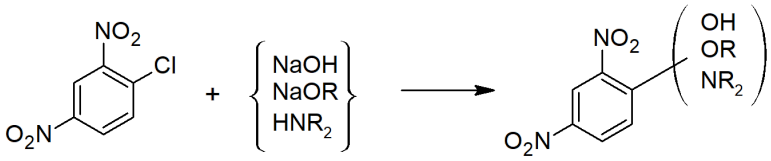


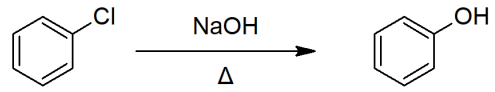
Reduction of Aromatic Compounds

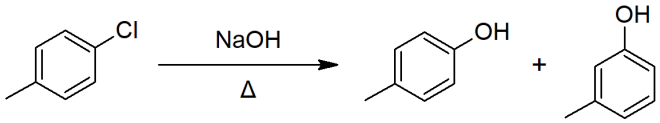
Electrophilic Aromatic Substitution

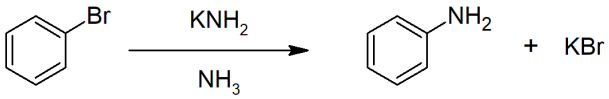


Nucleophilic Aromatic Substitution









CHAPTER OVERVIEW

17: ALCOHOLS AND PHENOLS

LEARNING OBJECTIVES

When you have completed Chapter 17, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. design a multi-step synthesis using any of the reactions introduced in this chapter, together with any number of the reactions discussed in *Chemistry 350*.
3. solve "road-map" problems that require a knowledge of the chemistry of alcohols and phenols, in addition to the chemistry of the other classes of compounds discussed in *Chemistry 350*.
4. define, and use in context, the key terms introduced in this chapter.

In this chapter, we examine the chemistry of the alcohol family of compounds. Alcohols can undergo a wide variety of reactions, and because of this reactivity and because they can be prepared in a number of different ways, alcohols occupy an important position in organic chemistry.

The discussion begins with an outline of the nomenclature of alcohols and phenols. We review the physical properties of these compounds, and discuss methods used to obtain the lower members of the series on an industrial scale. A detailed discussion of the laboratory preparation of alcohols follows, with particular emphasis on those methods that involve either the reduction of a carbonyl compound or the use of a Grignard reagent.

Certain reactions of alcohols were discussed in previous chapters. In this chapter, we concentrate on the oxidation of alcohols to carbonyl compounds. We also introduce the concept of protecting a sensitive functional group during an organic synthesis. The discussion then turns to the uses of phenols, their preparation and their chemical reactivity.

Infrared, nuclear magnetic resonance and mass spectroscopy each can provide valuable information about alcohols and phenols, and we illustrate the application of these techniques to the identification of unknown alcohols and phenols with a number of examples.

17.0: INTRODUCTION TO ALCOHOLS AND PHENOLS

OBJECTIVES

After completing this section, you should be able to

1. describe the structural differences among alcohols, phenols and enols.
2. write equations describing the industrial preparation of the two simplest alcohols: methanol and ethanol.

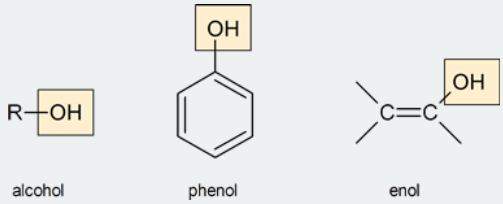
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- alcohol
- enol
- phenol

STUDY NOTES

Alcohols and phenols are organic compounds with at least one hydroxyl group attached to a saturated or an aryl carbon, respectively. Enols are a related third class of compounds, with the hydroxyl group attached to a vinylic carbon. We will discuss enols in more detail in Chapter 22.



The reading correctly points out the toxicity of methanol, and describes the adverse effects of its consumption. These effects have not been exaggerated; you may recall reading about the deaths of six residents of Peerless Lake, Alberta, in 1986, brought about by drinking photocopier fluid which contained methanol (or methyl hydrate as it is often called in press reports). In 2000, more than 100 people died in El Salvador after black marketeers sold discarded liquor bottles that had been refilled with a methanol mixture. Indeed the problem has repeated itself globally and so often that in 2014 the World Health Organization released an information note warning of methanol poisoning outbreaks which “occur when methanol is added to illicitly- or informally-produced alcoholic drinks.”

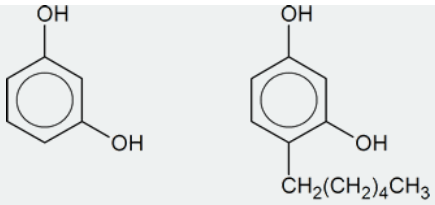
Almost everyone is aware that the alcohol present in alcoholic beverages is ethanol (also called ethyl alcohol or grain alcohol). However, many people do not realize that in its pure state, or in solutions of high concentration, this substance is poisonous. In the laboratory one may find containers labelled “absolute ethanol,” “95% ethanol” and “denatured ethanol.” The acquisition of ethanol by laboratories, and its subsequent disposal, is carefully monitored by provincial authorities. On no account should one consider drinking laboratory ethanol, even after it has been diluted to a concentration equivalent to that found in beer. Denatured alcohol is ethanol to which appropriate quantities of poisonous or nauseating substances (such as methanol) have been added.

A third commonly encountered alcohol, isopropyl alcohol (“rubbing alcohol” or 2-propanol), is also toxic. It has the ability to kill germs and has a temporary lubricating effect during the rubbing process. Unlike methanol, 2-propanol is not absorbed through the skin; therefore it poses less of a health hazard.

The use of alcohols as fuels is well established. In 2010, the Canadian federal government joined several of the provinces in requiring that all gasoline must include an average of five per cent ethanol. Some gasoline producers, notably Husky/Mohawk, average ten per cent ethanol content in their products. Some especially modified vehicles can use fuel that consists of 85 per cent ethanol (E85).

A phenol is an organic compound in which a hydroxyl group is directly bonded to one of the carbon atoms of an aromatic ring.

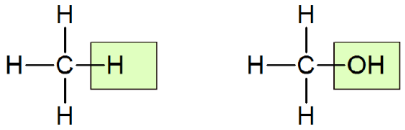
Until the late nineteenth century, a person undergoing surgery had to face the fact that he or she might suffer the consequences of what we now know to be bacterial infection, contracted during the course of the operation. The physicians of the time did not know that bacteria existed, and had no way to counter the problems that bacteria caused. In 1867, Joseph Lister, who had learned of the existence of bacteria as a result of research done by Louis Pasteur, began using solutions of phenol to clean wounds and surgical instruments. The phenol solution was an effective antiseptic, killing bacteria, and as a result, a patient’s chances of surviving surgery improved greatly. Phenol itself was rather strong for these purposes—it burns healthy tissue—and substitutes were eventually found. One such substitute, used today in throat lozenges and mouthwashes, is 4-*n*-hexylresorcinol.



resorcinol 4-*n*-hexylresorcinol

ALCOHOLS

Molecules of alcohols contain one or more hydroxyl groups (OH groups) substituted for hydrogen atoms along the carbon chain. The structure of the simplest alcohol, methanol (methyl alcohol), can be derived from that of methane by putting an OH in place of one of the H's:



methane methanol

The name, too, is derived from the name methane by replacing the final *e* with *ol* (for alcoh*ol*). The general formula for an alcohol may be written as R—OH, where R represents the hydrocarbon (alkane) portion of the molecule and is called an **alkyl group**. In methanol, R is the methyl group CH_3.

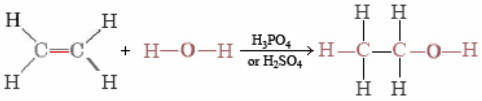
Methanol is also called wood alcohol because it can be obtained by heating wood in the absence of air, a process called **destructive distillation**. Methanol vapor given off when the wood is heated can be condensed to a liquid by cooling below its boiling point of 65°C. The effect of polarity and especially hydrogen bonding due to the OH group is evident when this is compared with the temperature of –85°C at which ethane, C_2H_6, boils. Both molecules contain 18 electrons and are nearly the same size, and so London forces should be about the same, but the OH group in one methanol molecule can form strong hydrogen bonds with an OH in another molecule. Methanol is an important industrial chemical—nearly 3×10^{10} kg was produced worldwide in 2003[1]. Some was made by destructive distillation, but most was synthesized from hydrogen and carbon monoxide:

$$2\,H_2(g) + CO(g) \longrightarrow CH_3OH(l)$$

This reaction is carried out at pressures several hundred times normal atmospheric pressure, using metal oxides as catalysts. Methanol is mainly used to make other compounds from which plastics are manufactured, but some is consumed as fuel in jet engines and racing cars. Methanol is also a component of nonpermanent antifreeze and automobile windshield-washer solvent.

The second member of the alcohol family is ethanol (ethyl alcohol)— the substance we commonly call *alcohol*. Ethanol is also known as grain alcohol because it is obtained when grain or sugar ferments. **Fermentation** refers to a chemical reaction which is speeded up by enzymes and occurs in the absence of air. (Enzymes, catalysts which occur naturally in yeasts and other living organisms, are discussed in more detail elsewhere.)

Ethanol can also be synthesized by adding H_2O to ethene, obtained during petroleum refining:



This is a typical example of an **addition reaction**. The H and OH from H_2O are added to the ethene molecule and held there by electrons made available when one-half of the double bond breaks.

Ethanol is used as a solvent, in some special fuels, in antifreeze, and to manufacture a number of other chemicals. You are probably most familiar with it as a component of alcoholic beverages. Ethanol makes up 3 to 6 percent of beer, 12 to 15 percent of most wines, and 49 to 59 percent of distilled liquor. (The "proof" of an alcoholic beverage is just twice the percentage of ethanol.) Alcohol's intoxicating effects are well known, and it is a mild depressant. Prolonged overuse can lead to liver damage. Methanol also produces intoxication but is much more poisonous than ethanol—it can cause blindness and death. Denatured alcohol is ethanol to which methanol or some other poison has been added, making it unfit for human consumption. Most of the ethanol not used in alcoholic beverages is denatured because in that form its sale is taxed at a much lower rate.

PHENOLS

Compounds in which a hydroxyl group is bonded to an aromatic ring are called phenols. The chemical behavior of phenols is different in some respects from that of the alcohols, so it is sensible to treat them as a similar but characteristically distinct group. A corresponding difference in reactivity was observed in comparing aryl halides, such as bromobenzene, with alkyl halides, such as butyl bromide and tert-butyl chloride. Thus, nucleophilic substitution and elimination reactions were common for alkyl halides, but rare with aryl halides. This distinction carries over when comparing alcohols and phenols, so for all practical purposes substitution and/or elimination of the phenolic hydroxyl group does not occur.

17.1: NAMING ALCOHOLS AND PHENOLS

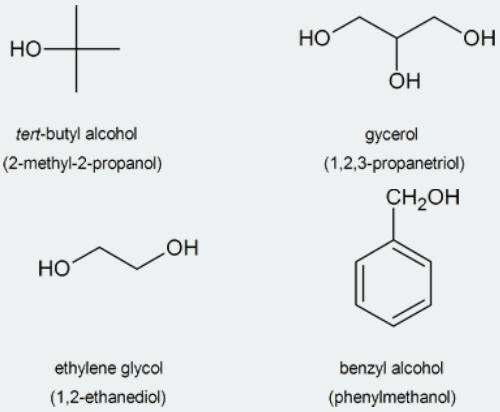
OBJECTIVES

After completing this section, you should be able to

1. identify an alcohol as being primary, secondary or tertiary, given its structure, its IUPAC name or its trivial name.
2. write the IUPAC name of an alcohol or phenol given its Kekulé, condensed or shorthand structure.
3. draw the structure of an alcohol or phenol given its IUPAC name.
4. identify a number of commonly occurring alcohols (e.g., benzyl alcohol, *tert*-butyl alcohol) by their trivial names.

STUDY NOTES

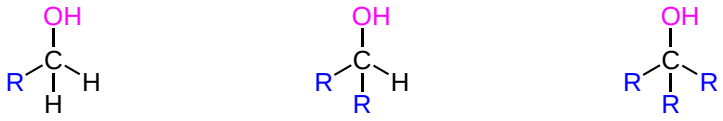
The following are common names of some alcohols (with IUPAC name).



tert-butyl alcohol (2-methyl-2-propanol) | gycerol (1,2,3-propanetriol) | ethylene glycol (1,2-ethanediol) | benzyl alcohol (phenylmethanol)

ALCOHOL CLASSIFICATIONS

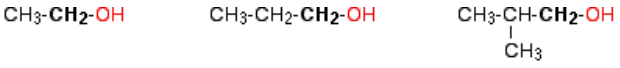
Alcohols can be classified as primary (**1º**), secondary (**2º**), or tertiary (**3º**) depending on the number of alkyl substituents attached to the carbon bonded to the O-H group.



Primary (1º) Alcohol **Secondary (2º) Alcohol** **Tertiary (3º) Alcohol**

PRIMARY ALCOHOLS

In a primary (1°) alcohol, the carbon which carries the -OH group is only attached to one alkyl group. Some examples of primary alcohols include:

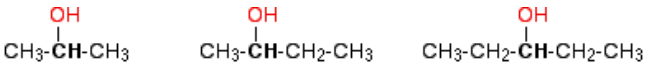


ethanol | propan-1-ol | 2-methylpropan-1-ol

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 -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 carbon with the -OH group on it.

SECONDARY ALCOHOLS

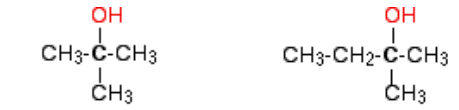
In a secondary (2°) alcohol, the carbon with the -OH group attached is joined directly to two alkyl groups, which may be the same or different. Examples:



propan-2-ol butan-2-ol pentan-3-ol

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 same or different. Examples:



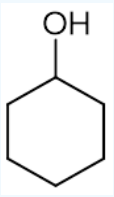
2-methylpropan-2-ol 2-methylbutan-2-ol

? EXERCISE 17.1.1

Indicate if the following molecules are 1°, 2°, or 3° alcohols:

1)

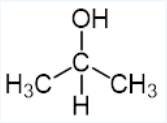
a)



b) $(CH_3)_3COH$

c) $CH_3CH_2CH_2OH$

d)



Answer

1)

a) Secondary

b) Tertiary

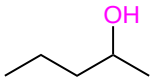
c) Primary

d) Secondary

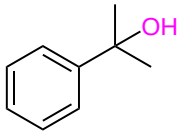
NAMING ALCOHOLS

The IUPAC naming of alcohols is based off the name of the parent alkane chain:

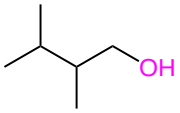
1. The longest chain containing the hydroxyl group (OH) is considered the parent chain. Remove the final **-e** from the parent alkane chain name and add the suffix **-ol**.
2. Number the parent alkane chain such that the hydroxyl group get the lowest possible number. Older IUPAC rules origianlly place the hydroxyl group number before the name of the parent chain. However, the newer rules places the number before the **-ol** suffix.
3. Number the substituents according to their position on the parent chain. Then list the substituents in alphabetical order.



2-Pentanol
(New: Pentan-2-ol)



2-Phenyl-2-propanol
(New: 2-Phenylpropan-2-ol)

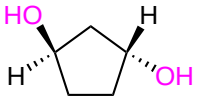


2,3-Dimethyl-1-butanol
(New: 2,3-Dimethylbutan-1-ol)

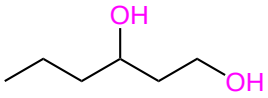
4. When naming a cyclic structure with a hydroxyl group, the -OH is assumed to be on the first carbon.

5. When multiple alcohols are present use **di, tri,** et.c before the **ol,** after the parent name. Also, when a prefix is used the **-e** is not removed from the parent chain name ex. 2,3-hexanediol

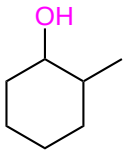
6. When an alkene and alcohol are present in a molecule it is named as follows **(location of the alkene)-(prefix for the parent chain + en)-(location of the hydroxyl)-ol**



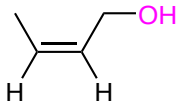
trans-1,3-Cyclopentanediol
(trans-Cyclopentane-1,3-diol)



1,3-Hexanediol
(Hexane-1,3-diol)



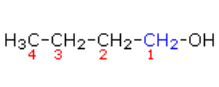
2-Methylcyclohexanol



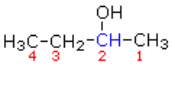
(Z)-2-Buten-1-ol

COMMON NAMES OF ALCOHOLS

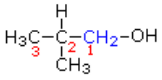
The common system of naming is often used when the alcohol only contains a few carbons. As discussed in **Section 3-3**, the common system names alcohols as if the hydroxyl group (-OH) is attached to a single substituent with the word alcohol added at the end **(Name of the substituent + Alcohol)**. Also, some simple alcohols are given their own generic name such ethylene glycol or glycerol.



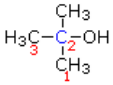
1-butanol
(butyl alcohol)



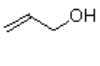
2-butanol
(*sec*-butyl alcohol)



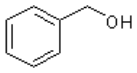
2-methyl-1-propanol
(isobutyl alcohol)



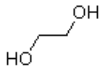
2-methyl-2-propanol
(*tert*-butyl alcohol)



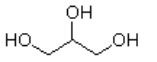
2-propen-1-ol
(allyl alcohol)



phenylmethanol
(benzyl alcohol)



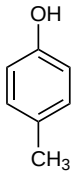
1,2-ethanediol
(ethylene glycol)



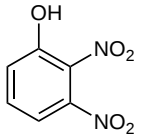
1,2,3-propanetriol
(glycerol)

NAMING PHENOLS

Phenols are named using the rules for aromatic compounds discussed in **Section 15-1**. Note that *-phenol is used* as the ending rather than *-benzene*.



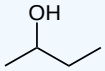
p-methylphenol

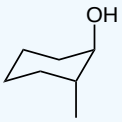


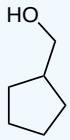
2,3-dinitrophenol

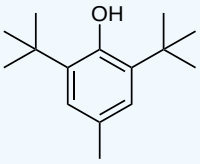
EXERCISE 17.1.1

Give IUPAC names for the following structures.

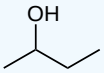




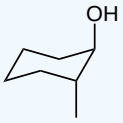




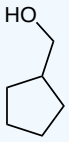
Answer



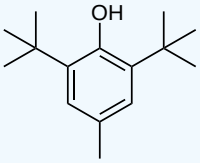
butan-2-ol



(1*R*, 2*R*)-2-mthylcyclohexan-1-ol



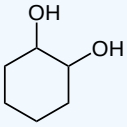
cyclopentylmethanol

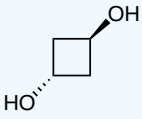


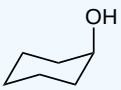
2,6-di-tert-butyl-4-methylphenol

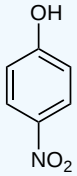
EXERCISE 17.1.2

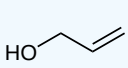
Name the following structures.



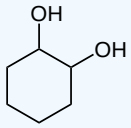




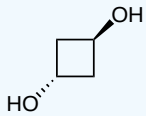




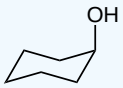
Answer



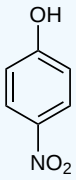
cyclohexane-1,2,-diol



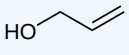
trans-cyclobutane-1,3-diol



cyclohexanol



4-nitrophenol



prop-2-en-1-ol

cycloproanol

EXERCISE 17.1.3

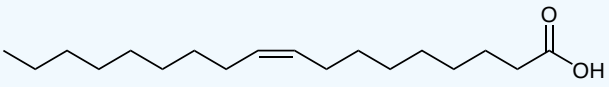
Draw and name all the alcohol isomers of C_3H_9O

Answer

Add texts here. Do not delete this text first.

EXERCISE 17.1.4

Oleic acid, a commonly occurring fatty acid in vegetable oils, has the following structure. Name the compound, making sure to give the correct alkene geometry.

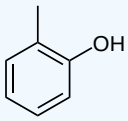


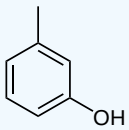
Answer

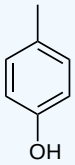
(9Z)-Octadec-9-enoic acid

EXERCISE 17.1.5

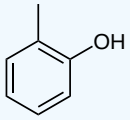
Creosols are naturally occurring compounds used building blocks for many molecules, they occur as three different isomers. Name each of the following isomers.



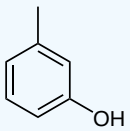




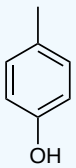
Answer



2-methylphenol



3-methylphenol



4-methylphenol

17.2: PROPERTIES OF ALCOHOLS AND PHENOLS

OBJECTIVES

After completing this section, you should be able to

1. explain why the boiling points of alcohols and phenols are much higher than those of alkanes, ethers, etc., of similar molecular mass.
2. discuss the factors that are believed to determine the acidity of alcohols and phenols.
3. list a given series of alcohols or phenols in order of increasing or decreasing acidity.
4. explain the difference in acidity between two given alcohols or phenols.
5. explain why phenols are more acidic than alcohols.
6. explain, in terms of inductive and resonance effects, why a given substituted phenol is more or less acidic than phenol itself.
7. write equations for the reactions of given alcohols and phenols with strong bases, such as sodium hydride and sodium amide.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

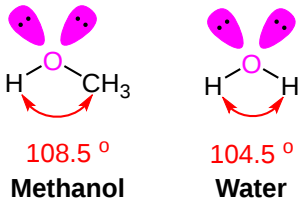
- acid ionization constant (K_a)
- alkoxide ion (RO^-)
- phenoxide ion (ArO^-)

STUDY NOTES

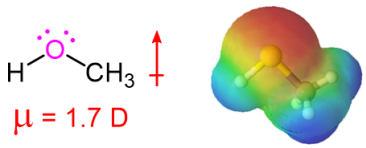
You may wish to review the concept of hydrogen bonding, which should have been discussed in your first-year general chemistry course.

BOILING POINTS OF ALCOHOLS

The oxygen in alcohols and phenols is sp^3 hybridized which gives the roughly the same tetrahedral geometry as water. The bond angle of methanol (108.5 ^{o}) is slightly less than the tetrahedral value mainly due to the presence of its lone pair electrons.



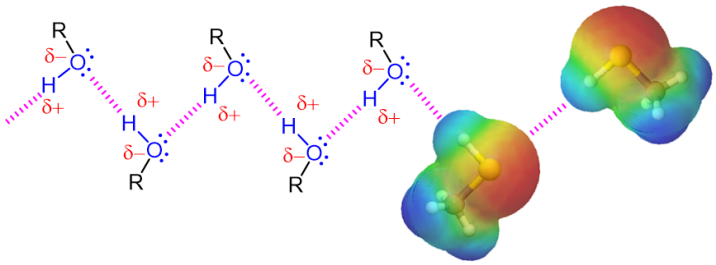
The presence of a highly electronegative oxygen confers a measure of polar character to alcohols. Much of the electron density of an alcohol is drawn towards the oxygen, giving alcohols a relatively high dipole momeny (1.7 D for Methanol).



The Dipole Moment of Methanol

Alcohols contain an extremely polar covalent O-H bond. The electrons in this bond are strongly drawn towards the oxygen giving it a partial negative charge (delta-) while the electrons are drawn away from the hydrogen giving is a partial positive charge (delta+). The polar character of this bond leads to an interaction between alcohol molecules where the positively polarized hydrogen of one alcohol molecule is attracted to the lone pair electrons on the electronegative oxygen atom of a different alcohol molecule. This creates a type of intramolecular attraction is called “hydrogen bonding.” Although the strength of such attractions are much less than most conventional chemical bonds, they are still significant (about 5 to 10 kcal per bond). For an alcohol to vaporize, these intramolecular hydrogen bonding attractions must be broken making alcohols substantially less volatile, have higher boiling points, and greater water solubility than molecules with a similar

molecular weight (Table 17.2.1). An example of this is seen when comparing 1-propanol (MW = 60.1), Chloroethane (MW = 64.5), and butane (MW = 58.1) which have boiling points of 94.7 ºC, 12.3 ºC, and -1 ºC respectively.



A Representation of Hydrogen Bonding in Alcohols

This table shows that alcohols (in blue) have higher boiling points than haloalkanes and alkanes with the equivalent molecular weight. It also shows that the boiling points of alcohols increase with the number of carbon atoms.

Table 17.2.1: Physical Properties of Selected Alcohols, Haloalkanes, and Alkanes

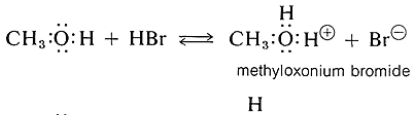
Compound	IUPAC Name	Molecular Weight (g/mol)	Melting Point (ºC)	Boiling Point (ºC)
CH_3OH	Methanol	32.0	-97.8	65.0
CH_3Cl	Chloromethane	50.5	-97.7	-24.2
CH_3CH_2OH	Ethanol	46.1	-114.7	78.5
$CH_3CH_2CH_2CH_3$	Butane	58.1	-140.	-1
$CH_3CH_2CH_2OH$	1-Propanol	60.1	-126.5	97.4
CH_3CH_2Cl	Chloroethane	64.5	-136.4	12.3
$CH_3CH_2CH_2CH_2CH_3$	Pentane	72.2	-130	36.3
$CH_3CH_2CH_2CH_2OH$	1-Butanol	74.1	-89.5	117.3
$CH_3(CH_2)_4OH$	1-Pentanol	88.1	-79	138

SOLUBILITY OF ALCOHOLS IN WATER

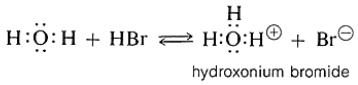
Alcohols and water have the ability to form hydrogen bonds with one another which tends to make the two liquids miscible. Small alcohols are completely soluble in water; mixing the two in any proportion generates a single solution. However, solubility decreases as the length of the hydrocarbon chain 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.

BASIC PROPERTIES OF ALCOHOLS

Alcohols are weak bases similar in strength to water and can accept protons from strong acids to form the conjugate acid called oxonium ions (ROH_2^+). An example is the reaction of methanol with hydrogen bromide to give methyloxonium bromide, which is analogous to the formation of hydroxonium bromide from the reaction of hydrogen bromide and water:



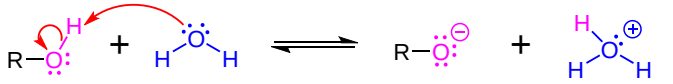
methyloxonium bromide



hydroxonium bromide

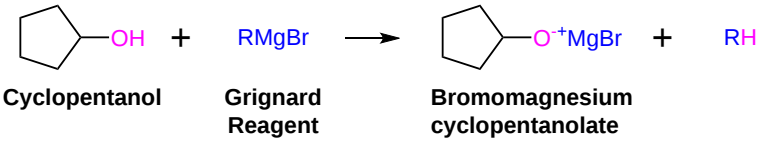
ACIDIC PROPERTIES OF ALCOHOLS

Alcohols, like water, are both weak bases and weak acids. In aqueous solutions, alcohols dissociate slightly by donating a hydrogen to water. This creates the alcohol's conjugate base, called an alkoxide ion (RO^-), along with hydronium (H_3O^+). The acid ionization constant (K_a) of ethanol is about 10^{-18}, which is slightly less than that of water. Alcohols, such as ethanol, can be deprotonated to form its conjugate base by reaction with a stronger base, such as sodium amide ($NaNH_2$), sodium hydride (NaH), or Grignard reagents (RMgBr). Alkoxides can also be formed using sodium or potassium metal which reacts vigorously but controllably with alcohols.

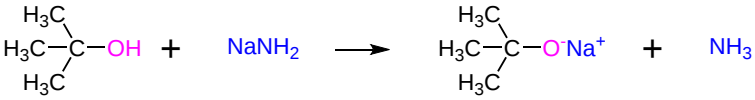


Alcohol **Alkoxide** **Hydronium**

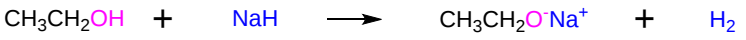
Once created, alkoxides act as bases and are often used as reagents in organic chemistry. Alkoxide's systematic names are based of the corresponding alcohol with the suffix *-ate* added. For example, ethanol becomes ethanolate. They are named systematically by adding the *-ate* suffix to the name of the alcohol. Methanol becomes methanolate, for instance. Common names are often used for small alkoxides. Common names are generated as: (Name of the positive counter ion) (Prefix for the parent chain + oxide). Example: ethanol becomes ethoxide.



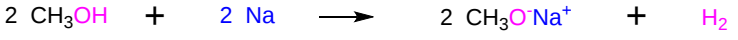
Cyclopentanol | **Grignard Reagent** | **Bromomagnesium cyclopentanolate**



***tert*-Butyl Alcohol (2-Methyl-2-propanol)** | **Sodium Amide** | **Sodium *tert*-Butoxide (Sodium 2-Methyl-2-proanolate)**



Ethanol | **Sodium Hydride** | **Sodum Ethoxide (Sodium ethanolate)**



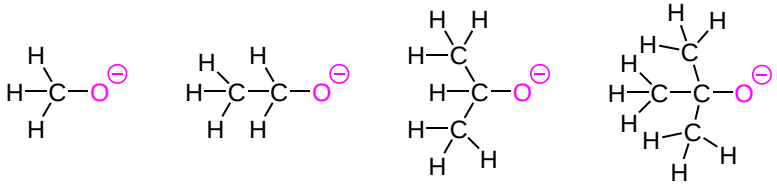
Methanol | **Sodium** | **Sodium methoxide (Sodium methanolate)**

As discussed in **Section 2.8**, the strength of an acid in water can be expressed either by its K_a or its pK_a. Compounds with a lower K_a and a higher pK_a are considered less acidic than compound with a higher K_a and a lower pK_a.

$$K_a = \frac{[A^-][H_3O^+]}{[HA]} \tag{17.2.1}$$

$$pK_a = -\log K_a$$

In general, alcohols in aqueous solution are slightly less acidic than water. The order of acidity of various liquid alcohols generally is water > primary > secondary > tertiary ROH. By this we mean that the pK_a is increased as R is changed from primary to secondary to tertiary; therefore, *tert*-butyl alcohol is less acidic than ethanol. This trend is explained by the importance of solvation in equilibrium. In solution, the larger alkoxide ions, are less well solvated than the smaller ions, because fewer solvent molecules can be accommodated around the negatively charged oxygen in the larger ions. Acidity of alcohols therefore decreases as the size of the conjugate base increases. This trend can be clearly seen when comparing alkoxide size to the pKa of the corresponding alcohol listed in Table 17.2.2.



Methoxide | **Ethoxide** | **Isopropoxide** | ***tert*-Butoxide**

$$ROH + OH^- \rightleftharpoons RO^- + HOH$$

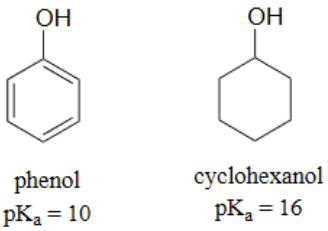
Table 17.2.2: The pKa's of various alcohols

R	Name	pK_{a1}
H	water	14.0
CH_3	methanol	15.5
CH_3CH_2	ethanol	15.9
$(CH_3)_2CH$	propan-2-ol (isopropyl alcohol)	16.5
$(CH_3)_3C$	2-methylpropan-2-ol (*tert*-butanol)	17
C_6H_5 (phenyl)	phenol	9.95

The addition of an electron-withdrawing group, such as an electronegative halogen, can increase the acid strength of an alcohol by stabilizing its alkoxide conjugate base through induction (**Section 2.10**). The electron-withdrawing group helps to spread out the electron density of the alkoxide's negative charge, which has a stabilizing effect. The inductive effect is cumulative such that the acid strength of an alcohol becomes stronger (Lower pK_a) as the number of halogens increases. The presence of nine fluorines in nonafluoro-*tert*-butyl alcohol decreases its pK_a to 5.4 which is significantly more acidic than *tert*-butyl alcohol (pK_a = 18). The electron-withdrawing effect of the fluorines is clearly seen when comparing the electrostatic potential maps of the corresponding alkoxides. In *tert*-butoxide the molecule's electron density is firmly centered around the oxygen as shown by the orange/yellow color. In nonafluoro-*tert*-butoxide the molecule's electron density is almost completely removed from the oxygen and shifted to the fluorines.

ACIDITY OF PHENOL

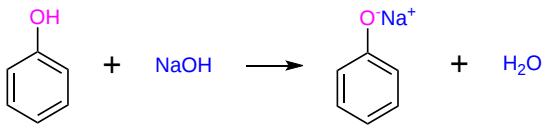
Another method for increasing acidity is through stabilizing a conjugate base through resonance effects. An excellent example of this effect is shown through phenol being roughly a million times more acidic than cyclohexanol.



phenol
$pK_a = 10$

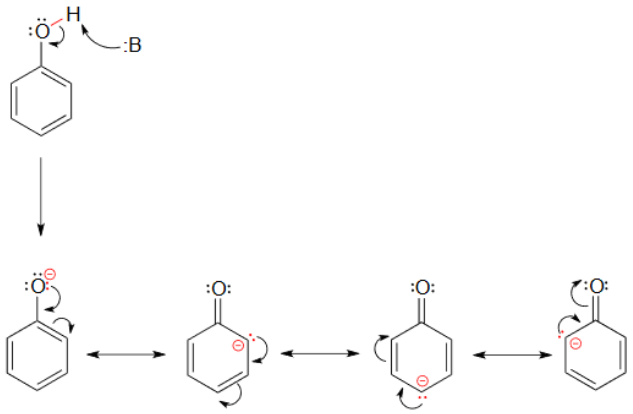
cyclohexanol
$pK_a = 16$

Phenol is acidic enough to be deprotonated by weaker bases, such as sodium hydroxide (NaOH), to form the phenoxide ion.



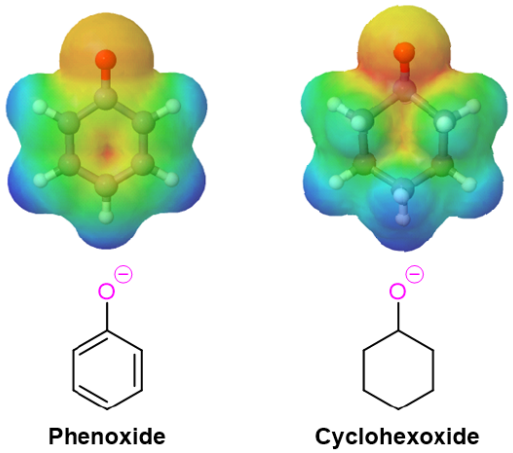
Phenol **Sodium Phenoxide**

The increased acidity of phenol is caused by the negative charge and a set of lone pair electrons from the phenoxide's oxygen atom being delocalized by resonance to three different carbons on the aromatic ring. As a result, the negative charge is no longer entirely localized on the oxygen, but is spread throughout the whole ion allowing it to be highly stabilized.



Although these are all minor resonance contributors (negative charge is placed on a carbon rather than the more electronegative oxygen), they nonetheless have a significant effect on the acidity of the phenolic proton. Essentially, the benzene ring is acting as an electron-withdrawing group by resonance.

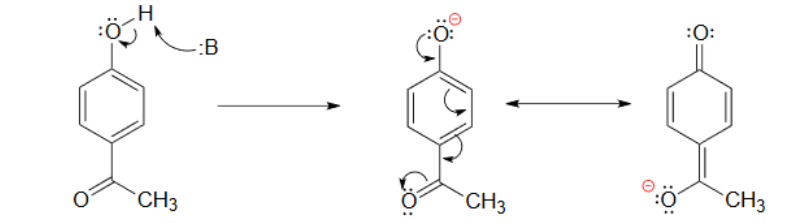
The electrostatic potential maps below compare the phenoxide ion to an unconjugated alkoxide. The negative charge of the phenoxide ion, show as a yellow/orange color, is delocalized from oxygen into the aromatic ring (seen by the growing red color in the phenoxide ring).



Phenoxide **Cyclohexoxide**

ACIDITY OF SUBSTITUTED PHENOLS

Phenolic acidity is further enhanced by the presence of an additional electron-withdrawing substituent, such as a nitro or carbonyl, on the aromatic ring. For the conjugate base of the phenol derivative below, an additional resonance contributor can be drawn in which the negative formal charge is placed on the carbonyl oxygen.



para-hydroxyacetophenone
(pKa = 4.2)

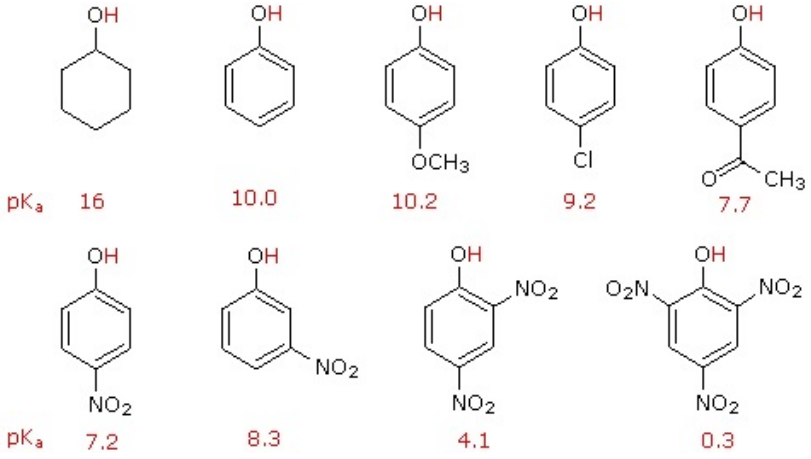
negative charge can be delocalized to a second oxygen

Now the negative charge on the conjugate base can be spread out over two oxygens (in addition to three aromatic carbons). The phenol acid therefore has a pK_a similar to that of a carboxylic acid, where the negative charge on the conjugate base is also delocalized to two oxygen

atoms. The ketone group on the aromatic ring is acting as an electron withdrawing group and 'pulling' electron density towards itself, through both inductive and resonance effects.

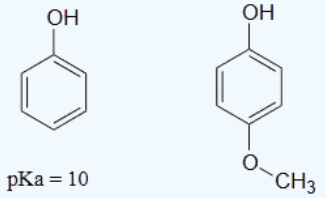
It is noteworthy that the influence of a nitro substituent is over ten times stronger in the *para*-location than it is meta, despite the fact that the latter position is closer to the hydroxyl group. This occurs since nitro groups at the meta position cannot accept the negative charge through resonance. Furthermore additional nitro groups have an additive influence if they are positioned *ortho* or *para* locations to the hydroxide. The trinitro compound shown at the lower right is a very strong acid called picric acid.

Lastly, if an electron donating group is attached to aromatic ring, as in *p*-methoxyphenol, the phenoxide ion is destabilized which causes a decrease in acidity in the corresponding phenol.



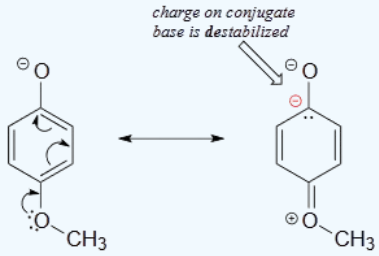
WORKED EXAMPLE 17.2.1

Using resonance structures, please explain why 4-methoxyphenol is less acidic than phenol.



Answer

The methoxy group is an electron-donating group by resonance. A resonance contributor can be drawn in which a formal negative charge is placed on the carbon adjacent to the negatively-charged phenolate oxygen.

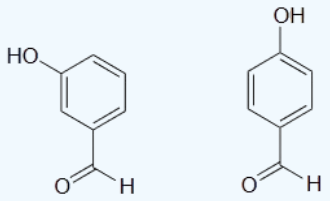


Because of like-charge repulsion, this destabilizes the negative charge on the phenolate oxygen, making the corresponding phenol less acidic.

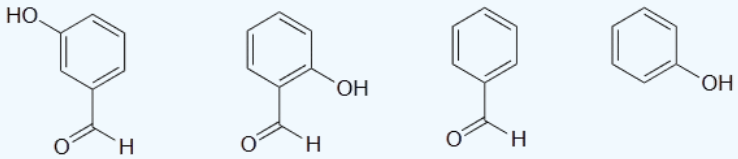
EXERCISE 17.2.1

1.

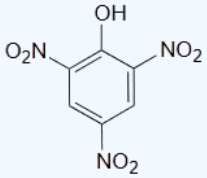
The position of the electron-withdrawing substituent relative to the phenol hydroxyl is very important in terms of its effect on acidity. Which of the two substituted phenols below is more acidic? Use resonance drawings to explain your answer.



2) Rank the four compounds below from most acidic to least.



3) Use a resonance argument to explain why picric acid has such a low pKa.



picric acid
pKa = 0.25

4) Predict which compound of each pair is more soluble in water and explain your reasoning.

a. Butan-1-ol or pentan-1-ol
b. Phenol or cyclohexanol
c. Octan-1,3-diol or octan-1-ol
d. 1-Chlorohexane or hexan-1-ol

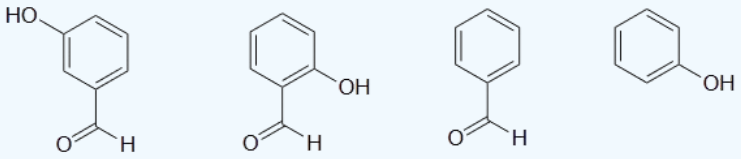
5) Predict which compound has the higher boiling point and explain your reasoning.

a. Water or ethanol
b. Butan-1-ol or octan-1-ol
c. Hexan-2-ol or hexan-2-one

Answer

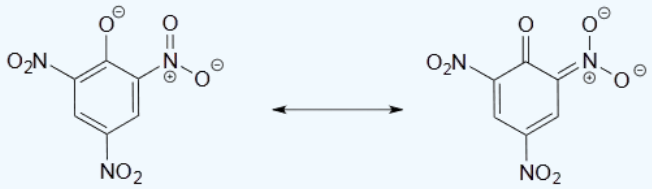
1) The para-subsituted phenol is more acidic, because the negative charge on the conjugate base can be delocalized to the aldehyde oxygen. This is not possible when the aldehyde group is in the meta position

2) Compound B is the strongest acid due to electron-withdrawing resonance effects-the negative charge on the conjugate base can be delocalized to the aldehyde oxygen. Compound A is the 2nd strongest acid -while the negative charge on the conjugate base cannot be delocalized to the aldehyde oxygen due to the *meta*-position, the aldehyde none the less has a stabilizing, electron-withdrawing inductive effect. Compound D is ranked #3 -it is phenol, and does not have any electron-withdrawing substituents on the ring as do B and A. Compound C is the least acidic -neither the phenyl group nor the aldehyde are even slightly acidic.



A B C D

3) The negative charge on the conjugate base of picric acid can be delocalized to oxygen atoms on all threeof the nitro groups. One such resonance contributor is shown below. This extensive delocalization means that the conjugate base is very stable, and the conjugate acid is thus a very strong acid.



4)

a. Butan-1-ol is more soluble in water because it has a smaller hydrophobic region compared to pentan-1-ol, allowing butan-1-ol to interact with water better.
b. Phenol is more soluble in water than cyclohexanol because of the more polar character of its ring. phenol is able to interact with water better than cyclohexanol due to the conjugated pi-system of electrons in its ring, which which gives it a more ionic character.
c. Octan-1,3-diol is more soluble in water as it has two hydroxy groups, allowing it to form more hydrogen bonds and interact with water better than octan-1-ol.
d. Hexan-1-ol is more soluble in water as it can hydrogen bond compared to alkyl halides, such as 1-chlorohexane, which are insoluble in water.

5)

a. Water has a higher boiling point compared to ethanol as it participates in more hydrogen bonding with other water molecules, thus requiring more energy to break the intermolecular attractions between water molecules.
b. Octan-1-ol has the higher boiling point compared to butan-1-ol. Both alcohols can H-bond, however the longer hydrophobic carbon chain tail of octan-1-ol experiences more van der Waal interactions compared to the shorter hydrophobic region of butan-1-ol leading to a higher boiling point.
c. Since hexan-1-ol can H-bond, it has a higher boiling point than hexan-2-one, which cannot H-bond.

17.3: PREPARATION OF ALCOHOLS- A REVIEW

OBJECTIVES

After completing this section, you should be able to describe in detail the methods of preparing alcohols and diols, which you encountered in previous chapters.

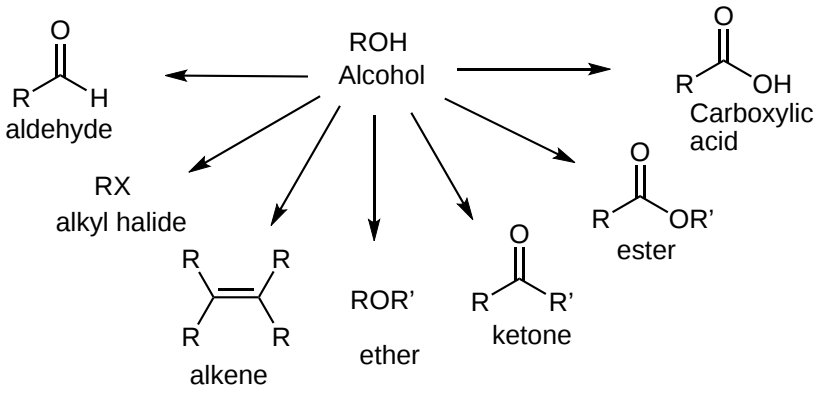
STUDY NOTES

If necessary, you should review Sections 8.4 and 8.5 describing direct hydration of alkenes, and Section 8.7 describing preparation of cis and trans diols from alkenes. Section 8.7 also gives more details on the formation of the respective osmate and epoxide intermediates of these reactions.

INTRODUCTION

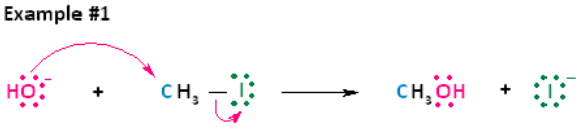
Alcohols are considered on of the more important functional groups in organic chemistry. They can be prepared from compounds containing a wide assortment of functional groups. Also, the can be used to create compounds with a wide variety of functional groups such as: alkenes, ketones, carboxylic acids, and others. Many functional group conversions can be accomplished through the preparation of an alcohol giving them an important central position in organic synthesis. ex. Alkene → Alcohol → Ketone.

Many methods for the preparation of alcohols have been discussed in previous chapter of this textbook and will be review in this section.



ALCOHOLS FROM SUBSTITUTION REACTIONS

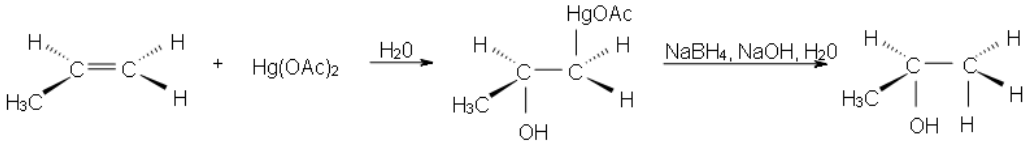
Methyl and primary alkyl halides can be converted to alcohols by using an S_N2 reaction with OH^- as a nucleophile (Section 11.5). Also, secondary and tertiary alkyl halides can be converted to alcohols by an S_N1 reaction using water as the nucleophile (and it can even be the solvent). Recall that S_N1 reactions are promoted in polar, protic solvents (Section 11.7).



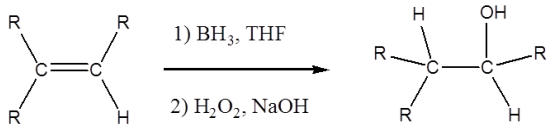
The Synthesis of Methanol Using an S_N2 Reaction

ALCOHOLS FROM ALKENES

Oxymercuration - demercurationis a special electrophilic addition (Section 8.5). It is anti-stereospecific and regioselective. This reaction involves mercury undergoing electrophilic addition to the alkene double bond forming a *Mercurinium Ion Bridge*. A water molecule then attacks the most substituted carbon to open the mercurium ion bridge, followed by proton transfer to form a hydroxyl group (-OH). The organomercury intermediate is then reduced by sodium borohydride. Notice that overall, the oxymercuration - demercuration mechanism follows Markovnikov's Regioselectivity with the OH group attached to the most substituted carbon and the H is attached to the least substituted carbon. Also, the H and OH species will be anti to each other in the product.

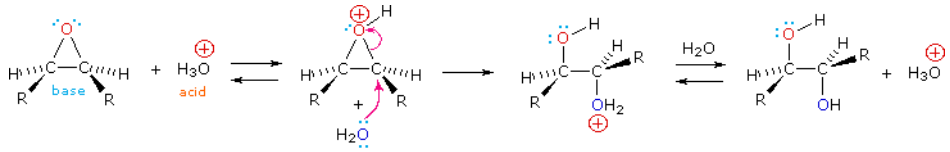


Hydroboration-Oxidation is a two step pathway used to produce alcohols (Section 8.6). It is syn-stereospecific and regioselective. The reaction proceeds in an Anti-Markovnikov manner, where the hydrogen (from BH_3 or BHR_2) attaches to the more substituted carbon and the boron attaches to the least substituted carbon in the alkene double bond. The organoborane intermediate is then converted to an alcohol by reaction with hydrogen peroxide (H_2O_2) and sodium hydroxide (NaOH). The hydroboration mechanism has the elements of both hydrogenation and electrophilic addition and it is a stereospecific ***(syn addition)***, meaning that the addition of the H and OH species takes place on the same face of the double bond leading to their ***cis*** configuration in the product. Because the BH_3 can attack either face of the alkene, this reaction can product a racemic mixture of enantiomers in the product.

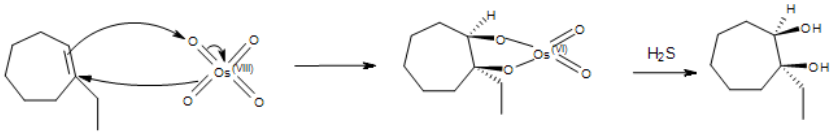


DIOLS FROM ALKENES

Epoxides may be cleaved by aqueous acid to give anti-1,2-diols which are also called glycols. Proton transfer from the acid catalyst generates the conjugate acid of the epoxide, which is attacked by a water nucleophile. Because the nucleophilic attach utilizes an S_N2 mechanism the result is an anti-stereospecific configuration of the diol product. The water nucleophile prefers to attack the more substituted carbon on the epoxide which allows for regioselectivity in the reaction.



Osmium tetroxide oxidizes alkenes to give 1,2-diols through syn addition. The reaction with OsO_4 is a concerted process that creates a cyclic intermediate with no rearrangements. The intermediate osmium compound is reduced to the diol product by reduction with H_2S or $NaHSO_4$ with H_2O.



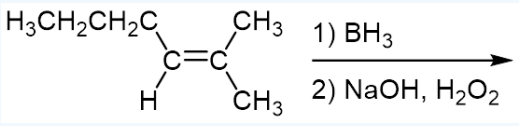
Electrophilic Attack **Intermediate** **Reduced Glycol**

This *syn*-dihydroxylation complements the epoxide-hydrolysis sequence which creates an *anti*-dihydroxylation product. This reaction lack regioselectivity so an alkene reacts with osmium tetroxide there is a possibility of a reaction producing a racemic mixture as the product. In general for this reaction, cis alkenes produce a meso product while trans alkenes produce a racemic mixture as the product.

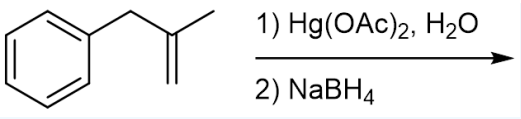
? EXERCISE 17.3.1

1) Predict the products of the following reactions:

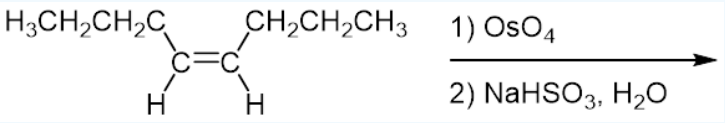
a)



b)



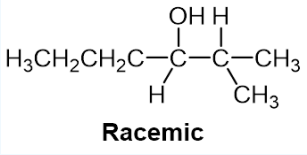
c)



Answer

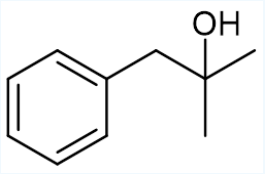
1)

a)

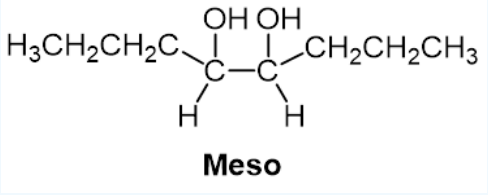


Racemic

b)



c)



Meso

17.4: ALCOHOLS FROM CARBONYL COMPOUNDS- REDUCTION

OBJECTIVES

After completing this section, you should be able to

1. determine whether a given reaction should be classified as an oxidation or a reduction.
2. write an equation to represent the reduction of an aldehyde or ketone using sodium borohydride or lithium aluminum hydride.
   a. discuss the relative advantages and disadvantages of using sodium borohydride or lithium aluminum hydride to reduce aldehydes or ketones to alcohols.
   b. identify the product formed from the reduction of a given aldehyde or ketone.
   c. identify the aldehyde or ketone that should be used to produce a given alcohol in a reduction reaction.
   d. identify the best reagent to carry out the reduction of a given aldehyde or ketone.
3. write an equation to represent the reduction of an ester or a carboxylic acid to an alcohol.
   a. identify the product formed from the reduction of a given ester or carboxylic acid.
   b. identify the esters or carboxylic acids that could be reduced to form a given alcohol.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- (organic) oxidation
- (organic) reduction

STUDY NOTES

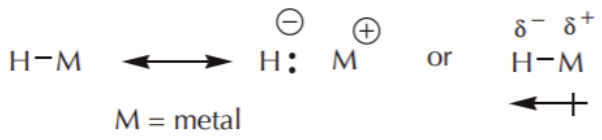
In your course in first-year general chemistry, you probably discussed oxidation-reduction reactions in terms of the transfer of electrons and changes in oxidation numbers (oxidation states). In organic chemistry, it is often more convenient to regard reduction as the gain of hydrogen or loss of oxygen, and oxidation as the gain of oxygen or the loss of hydrogen. There is no contradiction in using these various definitions. For example, when hydrogen is added across the double bond of ethene to reduce it to ethane, the oxidation number of the doubly bonded carbon atoms decreases from −II to −III. Similarly, when 2-propanol

is oxidized to acetone

hydrogen is removed from the compound and the oxidation number of the central carbon atom increases from 0 to +II. If necessary, review the concept of oxidation number.

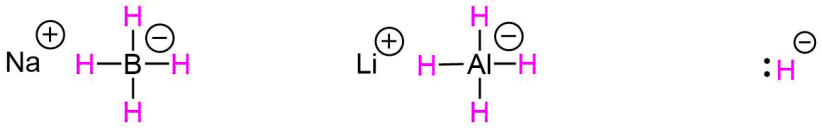
REDUCTION OF ALDEHYDES AND KETONES

Like carbon, hydrogen can be used as a nucleophile if it is bonded to a metal in such a way that the electron density balance favors the hydrogen side. A hydrogen atom that carries a net negative charge and bears a pair of unshared electrons is called a **hydride ion (:H).** How much of the negative charge density resides on hydrogen depends on the difference in electronegativity between hydrogen and the metal it's bonded to.



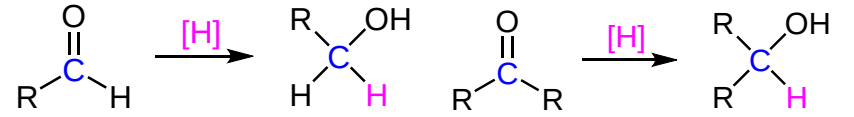
The most common sources of the hydride nucleophile are lithium aluminum hydride ($LiAlH_4$) and sodium borohydride ($NaBH_4$). Note! The hydride anion is not present during this reaction; rather, these reagents serve as a source of hydride due to the presence of a polar metal-

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.



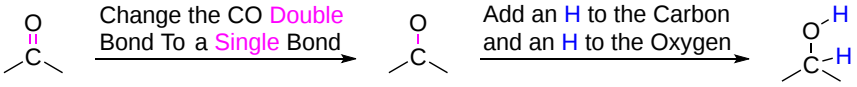
Sodium Borohydride **Lithium Aluminum Hydride** **Hydride Nucleophile**

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. These reactions will be discussed in more detail in **Chapter 19**.



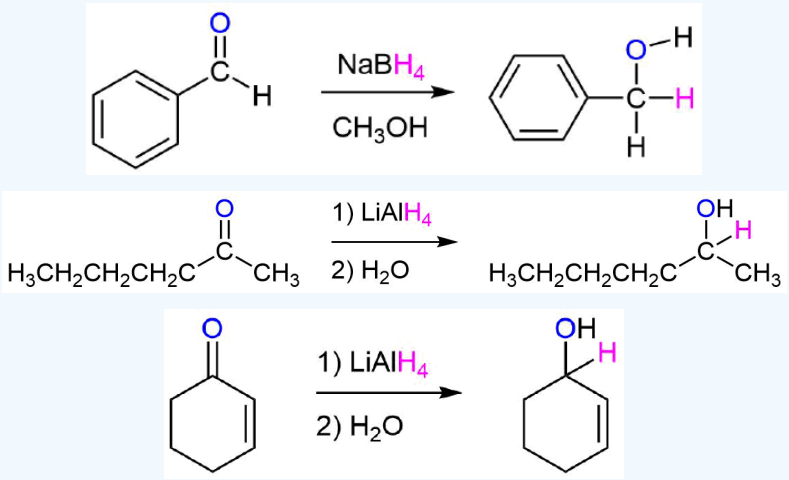
Aldehyde **1° Alcohol** **Ketone** **2° Alcohol**

PREDICTING THE PRODUCT OF A HYDRIDE ADDITION TO A CARBONYL



During the reduction the C=O double bond in the reactant and forms a C-O single bond in the product. The breaking of the C=O double bond allows for the formation of two single bonds in the product. One will be attached to the oxygen and one to the carbon which originally in the carbonyl. Both of these single bonds will be attached to an "H" in the product formed.

EXAMPLE 17.4.1

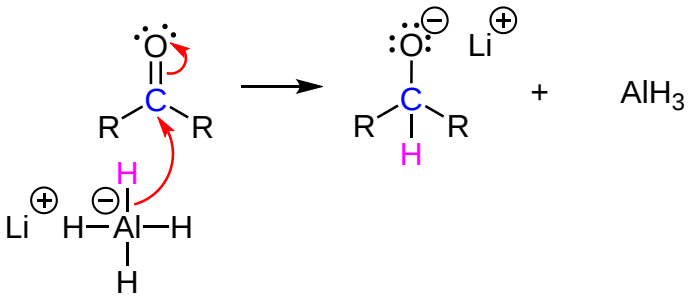


MECHANISM

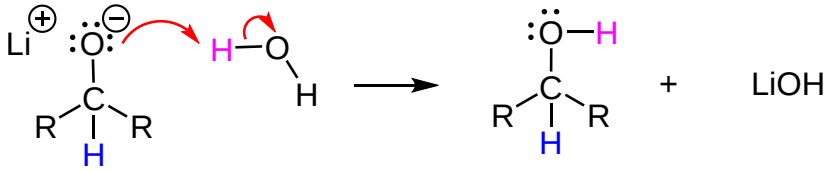
Both $NaBH_4$ and $LiAlH_4$ act as if they were a source of the hydride anion nucleophile. They hydride anion undergoes nucleophilic addition to the carbonyl carbon to form a C-H single bond and forming a tetrahedral alkoxide ion intermediate. The alkoxide ion is subsequently converted to an alcohol by reaction with a proton source. In the $LiAlH_4$ reduction, the resulting alkoxide salts are insoluble and need to be hydrolyzed (with care) before the alcohol product can be isolated. In the borohydride reduction the hydroxylic solvent system achieves this hydrolysis automatically. The lithium, sodium, boron and aluminum end up as soluble inorganic salts.

Note! The reaction and the corresponding mechanism of hydride reductions of carbonyls is fairly complicated. The following mechanism has been simplified for easier understanding..

1) Nucleophilic attack to form a tetrahedral alkoxide intermediate



2) Protonation to form an alcohol



In metal hydride 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.

BIOLOGICAL REDUCTION

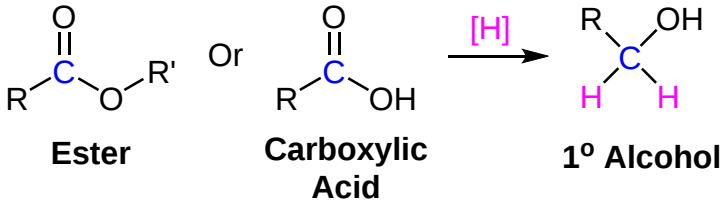
Aldehydes, ketones and alcohols are very common features in biological molecules. Converting between these compounds is a frequent event in many biological pathways. However, semi-anionic compounds like sodium borohydride don't exist in the cell. Instead, a number of biological hydride donors play a similar role.

NADH is a common biological reducing agent. NADH is an acronym for nicotinamide adenine dinucleotide hydride. Instead 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^+. However, NAD^+ is stabilized by the fact that its nicotinamide ring is aromatic; it was not aromatic in NADH.

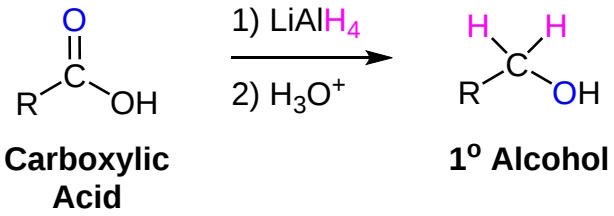
CONADH2.png

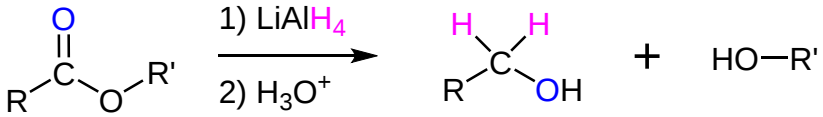
REDUCTION OF CARBOXYLIC ACIDS AND ESTERS

Carboxylic acids and esters can be converted to 1^o alcohols using Lithium aluminum hydride ($LiAlH_4$).



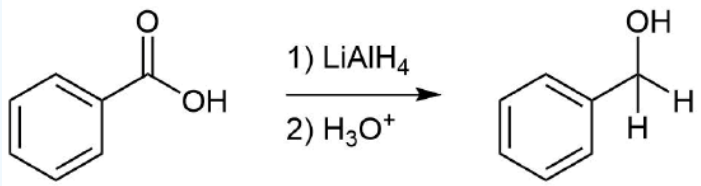
Note that $NaBH_4$ is not strong enough to convert carboxylic acids or esters to alcohols. Notice that during these reaction two hydrogen atoms are added the to carbonyl carbon whereas only one hydrogen atom was added during aldehyde and ketone reductions. These reactions will be discussed in more detail in **Chapter 21**.

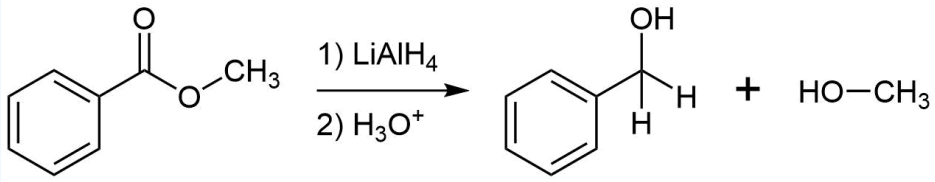




Ester **1° Alcohol**

EXAMPLE 17.4.2

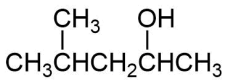




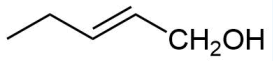
WORKED EXAMPLE

How would you prepare the following molecules using a hydride reduction?

a)



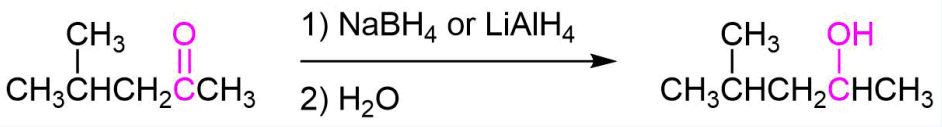
b)



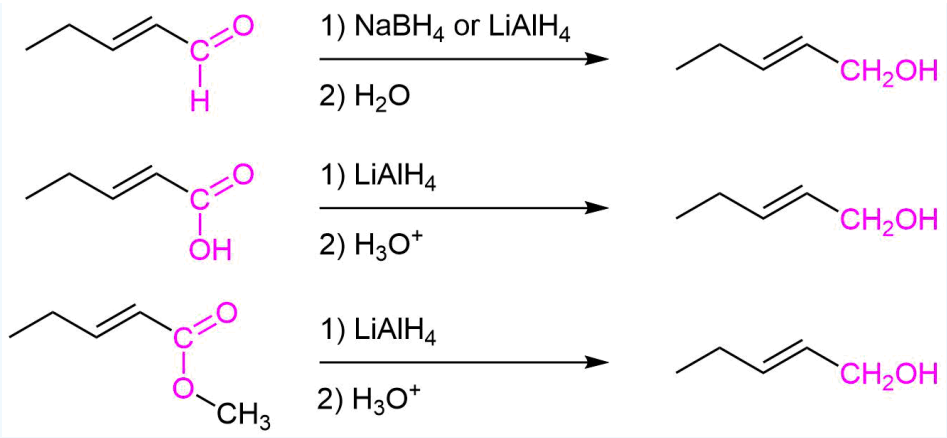
Answer

Analysis: The first step is to note if the target molecule is a 1° or 2° alcohol. Primary alcohols can be made by the hydride reduction of an aldehyde, carboxylic acid, or ester while secondary alcohols are made by the reduction of ketones. A 3° alcohol cannot be made by a hydride reduction. Also, it is important to remember than aldehydes and ketones can be reduced by both $NaBH^4$ and $LiAlH_4$ whereas carboxylic acids and ester can only be reduced by $LiAlH_4$.

a) Because the target molecule is a secondary alcohol the starting material must be a ketone.



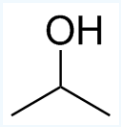
b) Because the target molecule is a primary alcohol the starting material could be an aldehyde, a carboxylic acid, or an ester.

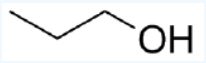


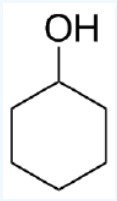
EXERCISES

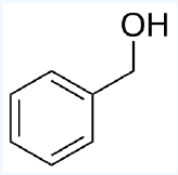
EXERCISE 17.4.1

1) Give the aldehyde, ketone, or carboxylic acid (there can be multiple answers) that could be reduced to form the following alcohols.

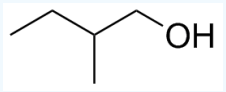
a) 

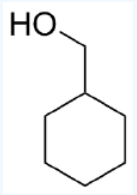
b) 

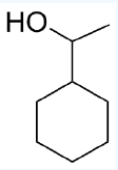
c) 

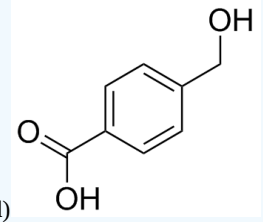
d) 

2) Given the following alcohol, draw the structure from which it could be derived using only $NaBH_4$

a) 

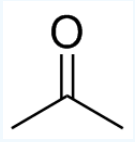
b) 

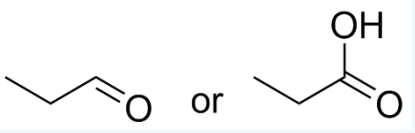
c) 

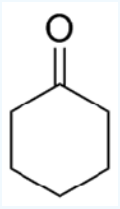
d) 

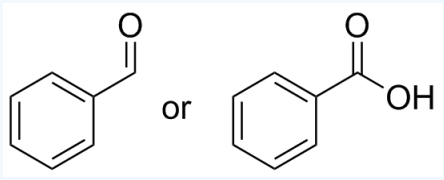
Answer

1)

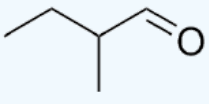
a) 

b) 

c) 

d) 

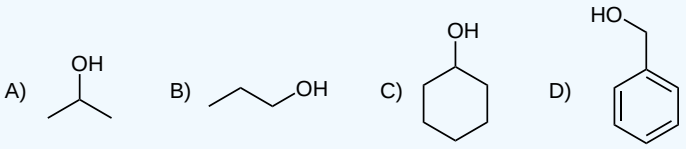
2) Note, $NaBH_4$ is only a strong enough reducing agent to reduce ketones and aldehydes.

a) 

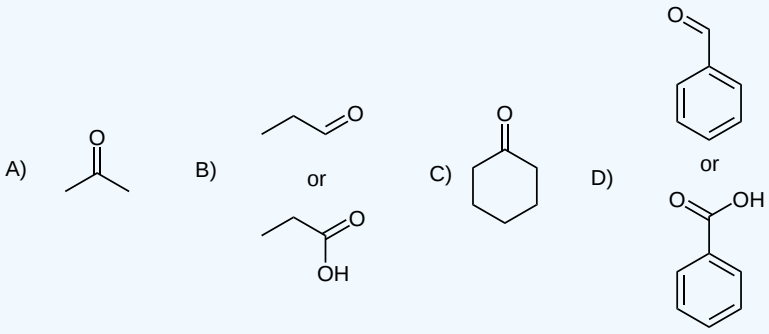
b)

EXERCISE 17.4.2

Give the aldehyde, ketone, or carboxylic acid (there can be multiple answers) that could be reduced to form the following alcohols.

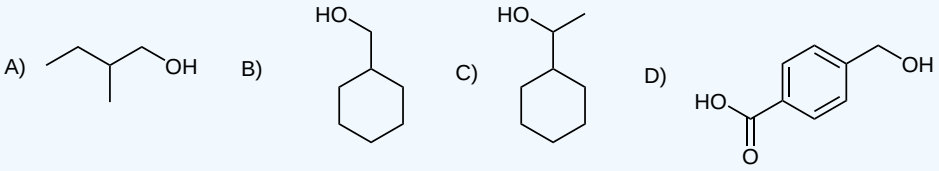


Answer



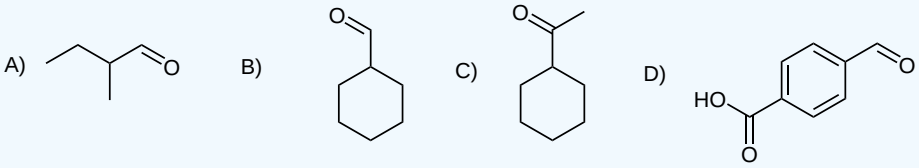
EXERCISE 17.4.3

Given the following alcohol, draw the structure from which it could be derived using only $NaBH_4$.



Answer

Note: $NaBH_4$ is only a strong enough reducing agent to reduce ketones and aldehydes.



17.5: ALCOHOLS FROM CARBONYL COMPOUNDS - GRIGNARD REAGENTS

OBJECTIVES

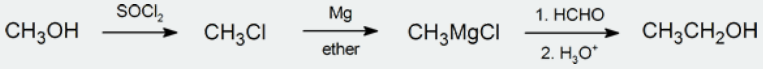
After completing this section, you should be able to

1. write an equation to illustrate the formation of a Grignard reagent.
2. write a general equation to represent the reaction of an aldehyde or ketone with a Grignard reagent.
3. write the detailed mechanism for the reaction of an aldehyde or ketone with a Grignard reagent.
4. identify the product formed from the reaction of a given aldehyde or ketone with a given Grignard reagent.
5. identify the carbonyl compound, the Grignard reagent, or both, needed to prepare a given alcohol.
6. write the equation to describe the reaction of an ester with a Grignard reagent.
7. identify the product formed from the reaction of a given ester with a given Grignard reagent.
8. discuss the limitations of Grignard reagent formation, and determine whether a given compound can be used to form such a reagent.

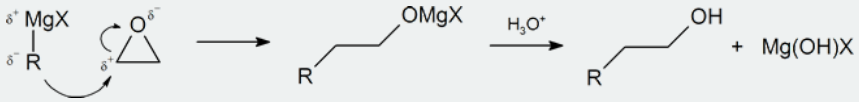
STUDY NOTES

Before you begin this section, you may wish to review Section 10.8 which discusses the formation of Grignard reagents. Link to section 10.8

Grignard reagents are among the most frequently used reagents in organic synthesis. They react with a wide variety of substrates; however, in this section, we are concerned only with those reactions that produce alcohols. Notice that in a reaction involving a Grignard reagent, not only does the functional group get changed, but the number of carbon atoms present also changes. This fact provides us with a useful method for ascending a homologous series. For example:



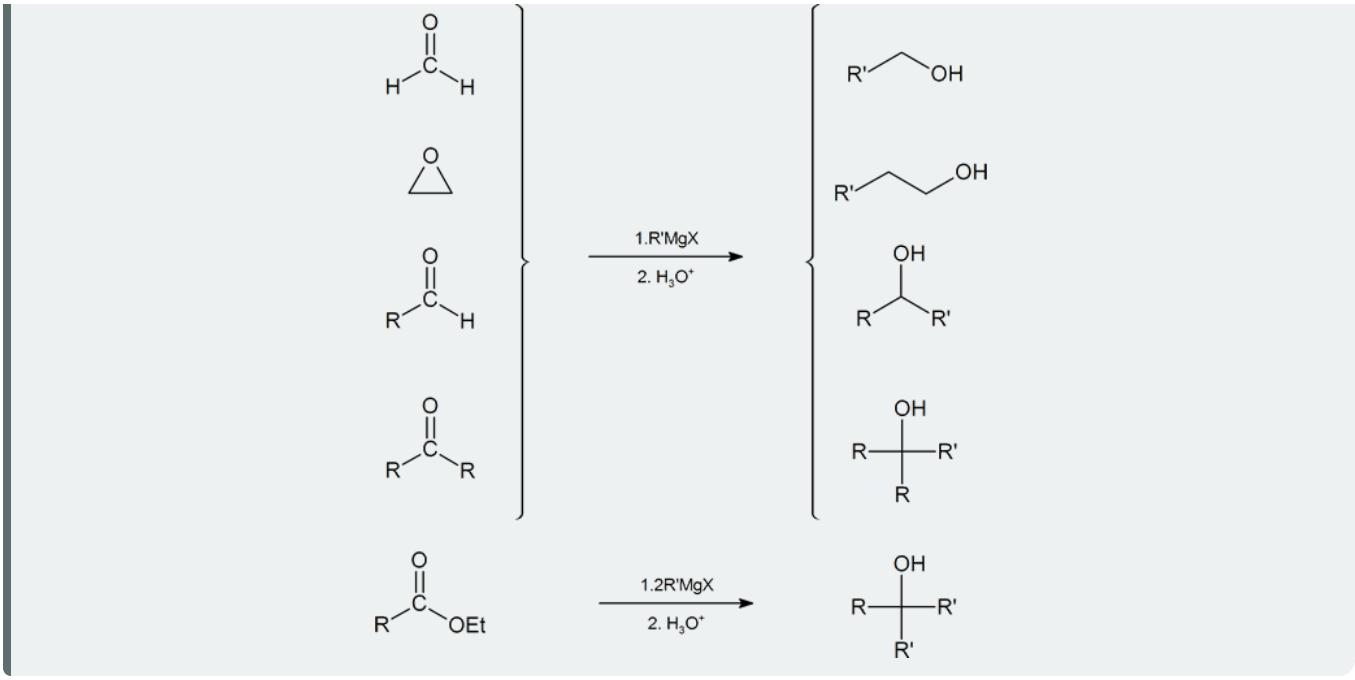
One important route for producing an alcohol from a Grignard reagent has been omitted from the discussion in the reading. It involves the reaction of the Grignard reagent with ethylene oxide to produce a primary alcohol containing two more carbon atoms than the original Grignard reagent.



As mentioned in the reading, both organolithium and Grignard reagents are good nucleophiles. They also act as strong bases in the presence of acidic protons such as $-CO_2H$, $-OH$, $-SH$, $-NH$ and terminal alkyne groups. Not only do acidic protons interfere with the nucleophilic attack on the carbonyl of these organometallic reagents, if the starting materials possess any acidic protons, reagents cannot be generated in the first place. They are also the reason these reactions must be carried out in a water-free environment.

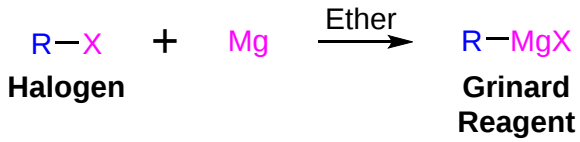
Another limitation of preparing Grignard and organolithium reagents is that they cannot already contain a carbonyl group (or other electrophilic multiple bonds like C=N, nitriles, N=O, S=O) because it would simply react with itself.

A summary of the methods used to prepare alcohols from Grignard reagents is provided below.



FORMATION OF GRIGNARD REAGENTS

Grignard reagents (RMgX) can be prepared through the reaction of halogens with magnesium metal (Section 10-6). Grignard reagents are a source of carbanion nucleophiles (R:$^{-}$ $^{+}$MgX) which add to carbonyl compounds to yield alcohols. 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. This complex helps stabilize the organometallic and increases its ability to react.



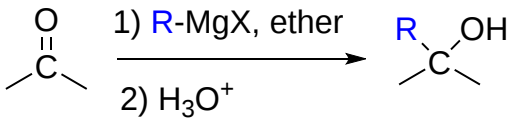
R = 1^{o}, 2^{o}, or 3^{o} alkyl, aryl, or vinylic groups

X = Cl, Br, or I

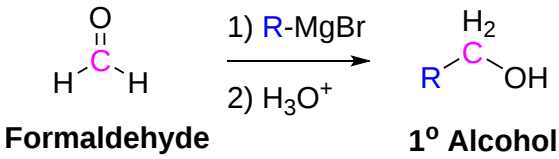
REACTION OF GRIGNARD REAGENTS WITH CARBONYLS

Because organometallic reagents react as their corresponding carbanion, they are excellent nucleophiles. Aldehydes, ketones, and other carbonyl containing compounds will undergo nucleophilic addition with Grignard reagents. The nucleophilic carbon in the organometallic reagents forms a C-C single bond with the electrophilic carbonyl carbon. An alkoxide ion intermediate is formed which becomes an alcohol with subsequent protonation by an acid. The type of alcohol produced depends on the number of alkyl substituents attached to the electrophilic carbonyl carbon. Reacting a Grignard reagent with formaldehyde (H_2C=O) produces 1^{o} alcohols, aldehydes produce 2^{o} alcohols, and ketones produce 3^{o} alcohols. These reactions will be discussed in greater detail in **Section 19.7**.

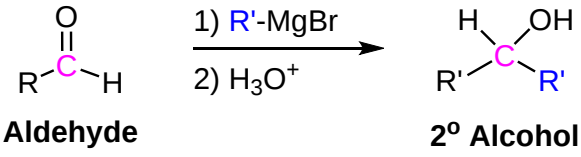
GENERAL REACTION



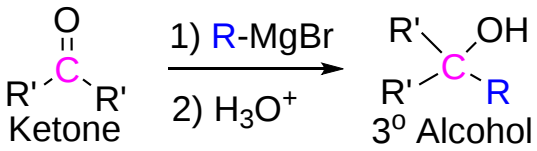
ADDITION TO FORMALDEHYDE GIVES 1^{O} ALCOHOLS



ADDITION TO ALDEHYDES GIVES 2° ALCOHOLS

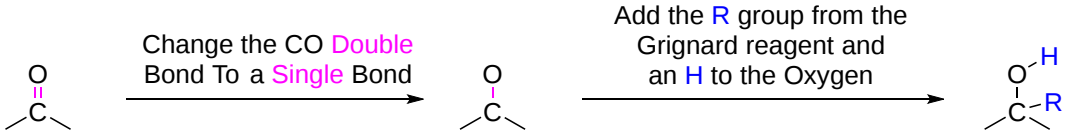


ADDITION TO KETONES GIVES 3° ALCOHOLS

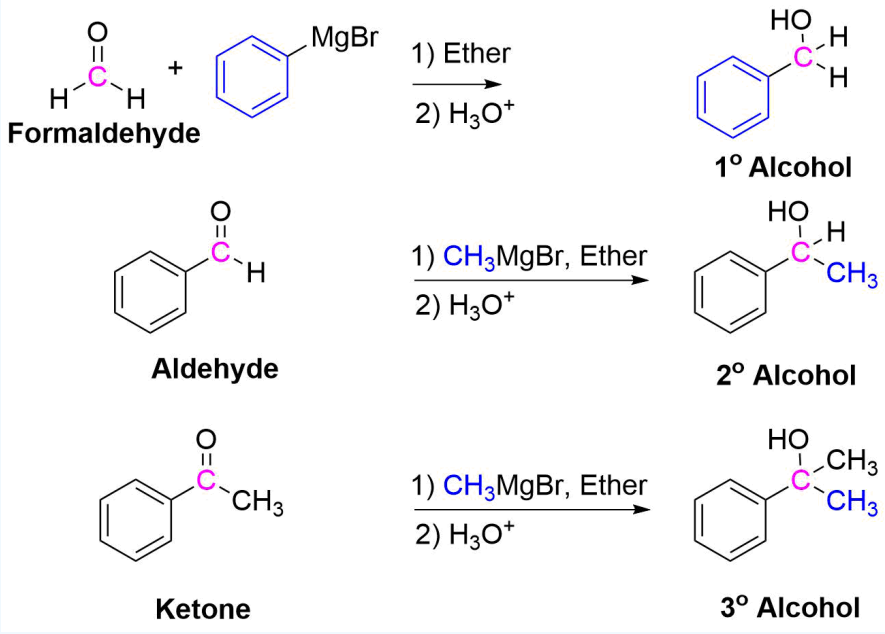


PREDICTING THE PRODUCT OF THE ADDITION OF GRIGNARD REAGENT TO CARBONYL

During the reaction, the C=O double bond in the reactant forms a C-O single bond in the product. The breaking of the C=O double bond allows for the formation of two single bonds in the product. One will be attached to the oxygen and one to the carbon which was originally in the carbonyl. The carbon will gain whatever R group was contained in the Grignard reagent and the oxygen will gain a hydrogen.



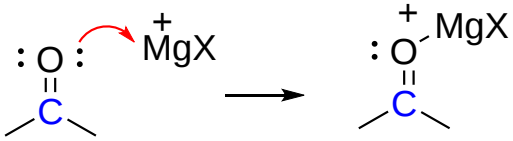
EXAMPLE 17.5.1



MECHANISM FOR THE ADDITION OF GRIGNARD REAGENTS TO CARBONYLS

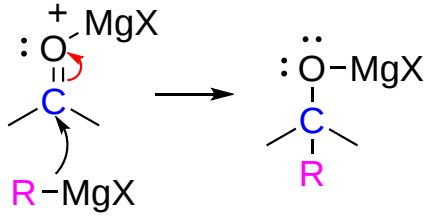
The mechanism starts with the formation of a acid-base complex between $^{+}$MgX and the carbonyl oxygen. The $^{+}$MgBr of the Grignard reagent acts as a Lewis acid and accepts a set of lone pair electrons from the carbonyl oxygen. This gives the oxygen a positive charge which correspondingly increases the partial positive charge on the carbonyl carbon increasing its susceptibility to nucleophilic attack.

Step 1: Lewis acid-base formation



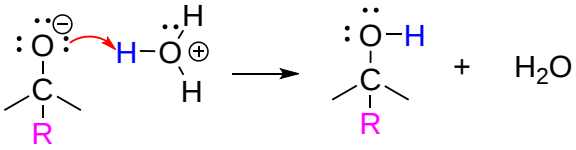
Step 2: Nucleophilic attack

The carbanion nucleophile from the Grignard reagent adds to the electrophilic carbon of the acid-base complex forming a C-C bond. The two electrons of the C=O are pushed toward the carbonyl oxygen atom forming a tetrahedral Magnesium alkoxide intermediate.



Step 3: Protonation

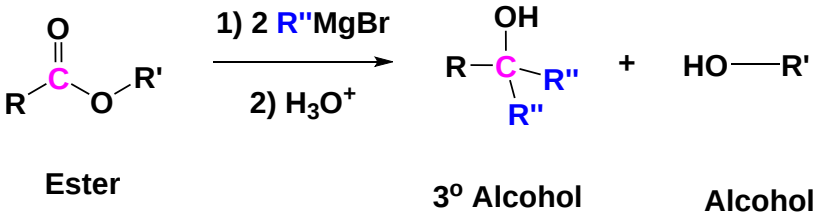
The alkoxide intermediate is converted to an alcohol through addition of a acidic aqueous solution. The $^{+}$MgX ion is also converted to HOMgX.'



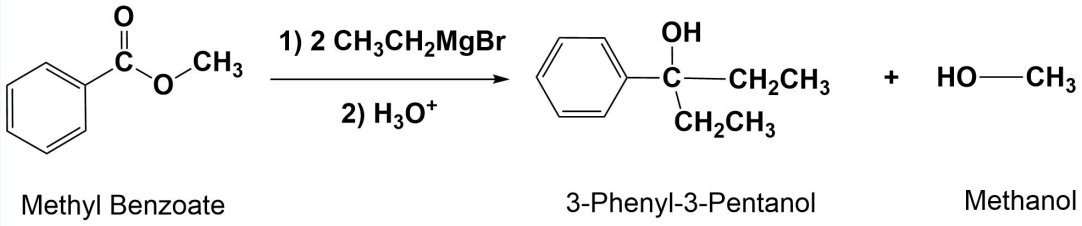
GRIGNARD REAGENTS CONVERT ESTERS TO 3^{O} ALCOHOLS

With esters, after the first Grignard reaction, the carbonyl reforms creating a ketone which can then react with a second molecule of the Grignard. In effect, the Grignard reagent adds twice. This reaction will be discussed in greater detail in **Section 21.6**.

GENERAL REACTION

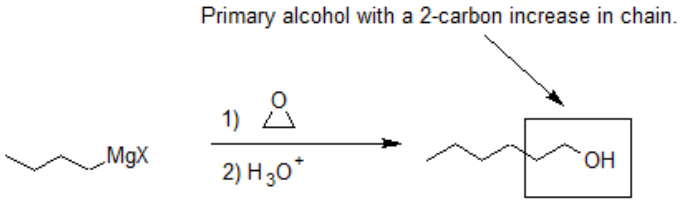


EXAMPLE 17.5.2

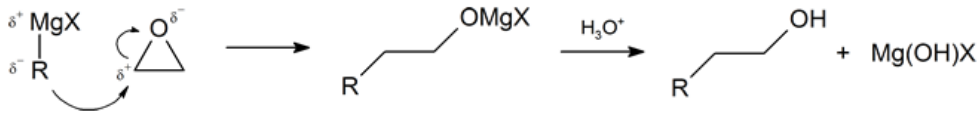


GRIGNARD REAGENTS CONVERT EPOXIDES TO 1O ALCOHOLS

Another important route for producing an alcohol from a Grignard reagent involves the reaction of the Grignard reagent with ethylene oxide to produce a primary alcohol containing two more carbon atoms than the original Grignard reagent. This reaction will be discussed in greater detail in **Section 18.6**.

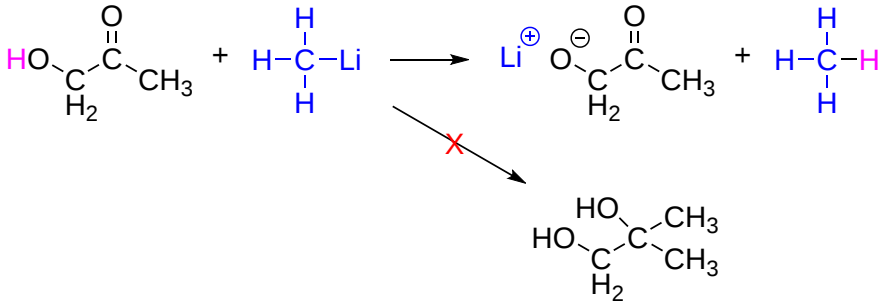


The first step of the mechanism is shown below. With the second step following the protonation step common to the other reaction pathways studied in this section.



LIMITATION OF ORGANOMETALLIC REAGENTS

Grignard and organolithium reagents are powerful bases. Because of this they cannot be prepared using halogen compounds which contain an additional functional group that has acidic hydrogens. If there are acidic hydrogens present, the organometallic reagent 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 (ROH), carboxylic acids (RCO_2H), thiols (RSH), and terminal alkynes (RCCH). Additionally, amides ($RCONH_2$) and amines (RNH_2) that have NH bonds cannot be used with organometallic reagents.

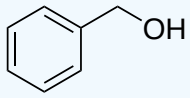


PLANNING AN ALCOHOL SYNTHESIS USING A GRIGNARD REACTION

The nucleophilic addition of a Grignard reagent to a carbonyl is a powerful tool in organic synthesis because if forms a C-C bond. Also, there is often more than one way to make a given target molecule. Primary alcohols have one C-C bond which can retrosynthetically cleaved. Secondary alcohols have two and tertiary alcohols have three.

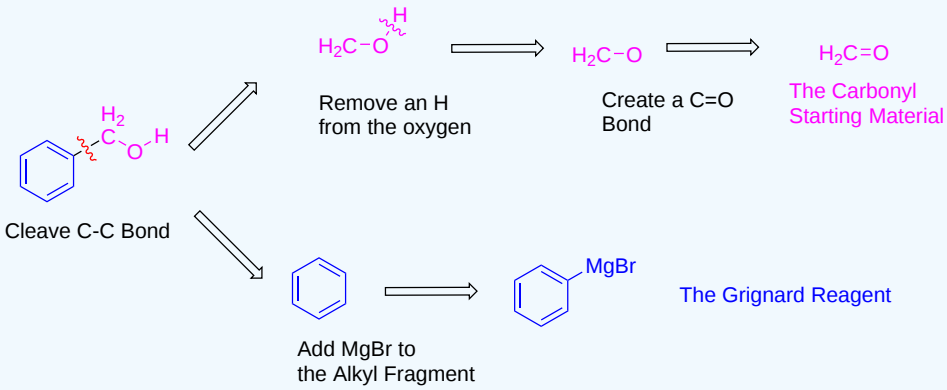
? WORKED EXAMPLE 17.5.1

What reagents are required to make the following molecule using a Grignard Reaction?



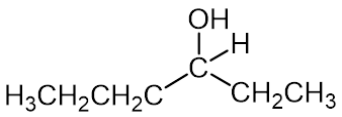
Answer

Analysis: Because the target molecule is a 1o alcohol there is only one C-C bond which can be cleaved to generate possible starting materials. The only possible reagents which would provide the target molecule would be formaldehyde and phenylmagnesium bromide.



WORKED EXAMPLE 17.5.2

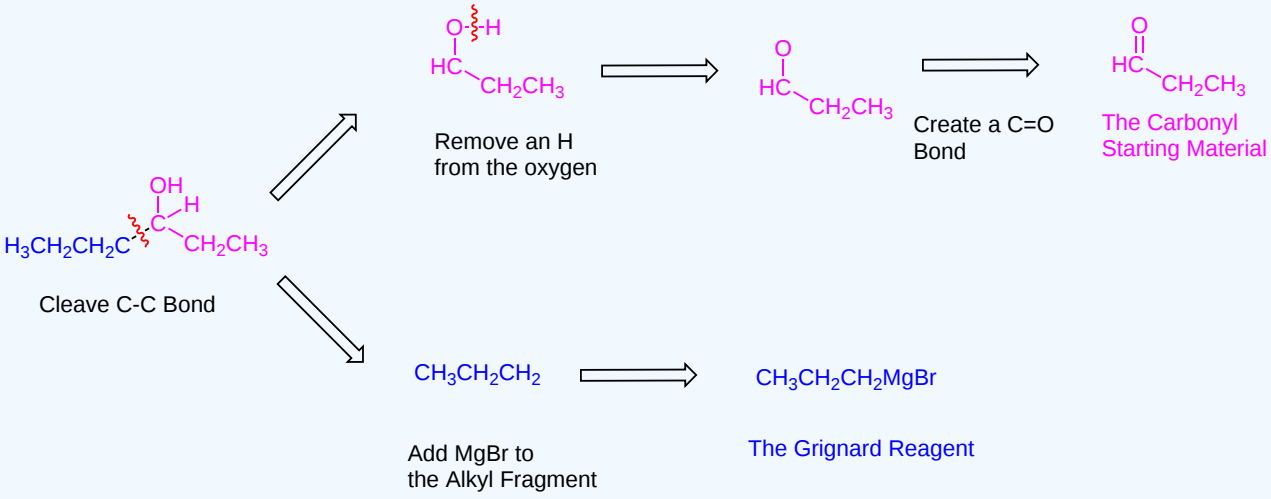
What reagents are required to make the following molecule using a Grignard Reaction?



Answer

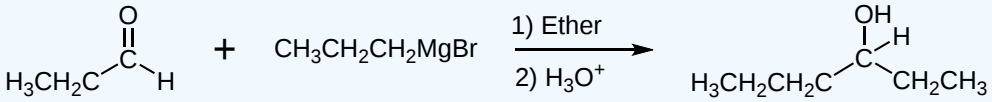
Analysis: Because the target molecule is an asymmetrical 2º alcohol there are two different C-C bond cleavage points. Each of these will provide a unique set of reagents which should be considered in terms of their reactivity and availability.

Pathway 1)

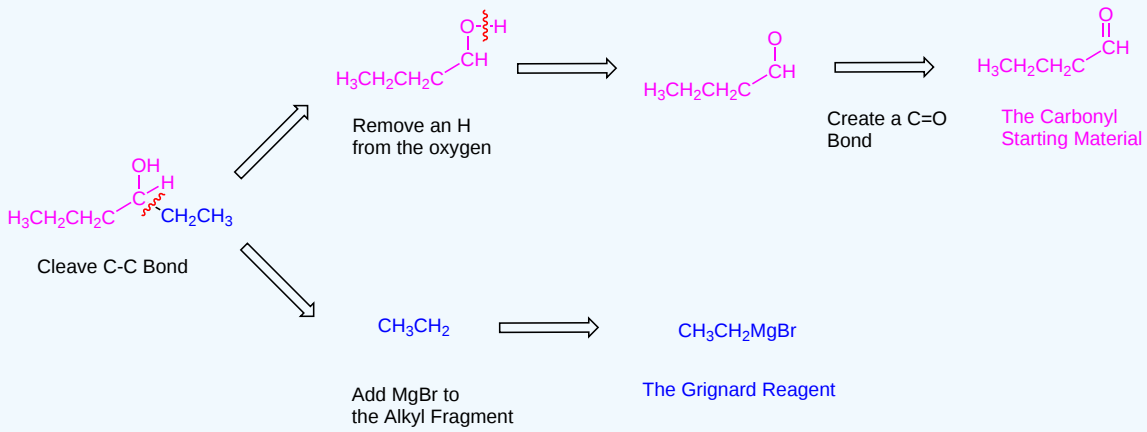


Pathway 1 synthesis)

Pathway 1 shows that propanal and propylmagnesium bromide can be reacted to create the target molecule.

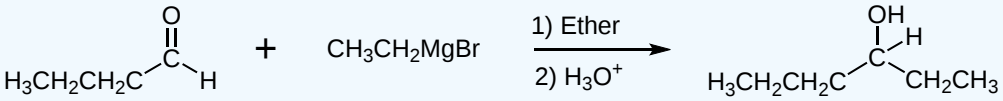


Pathway 2)



Pathway 2 synthesis)

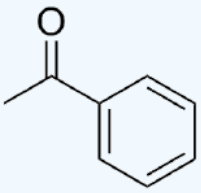
Pathway 2 shows that butanal and ethylmagnesium bromide can be reacted to create the target molecule.



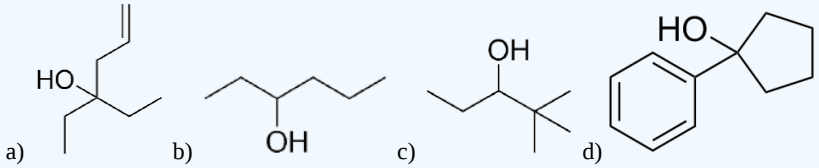
EXERCISES

EXERCISE 17.5.1

1) If allylmagnesium chloride were added to a solution of the following compound and then worked-up with acid, the product would contain a chiral center. Would the product be a racemic mixture or an enatiomerically pure product? Draw both enantiomers.



2) What combination of carbonyl compound and grignard (use MgBr) reagent would yield the following alcohols (after workup)?

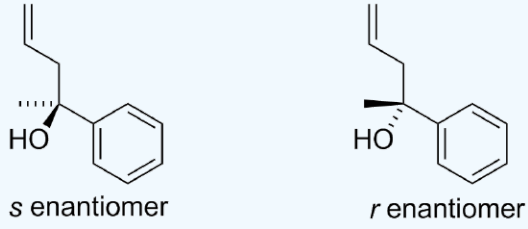


3) If the following compounds were reacted with methylmagnesium bromide what would be the products?

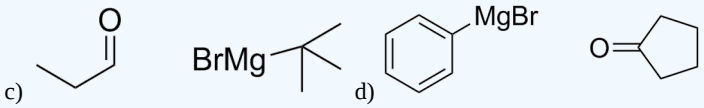
a) Cyclohexanone b) Acetophenone c) 2-Hexanone

Answer

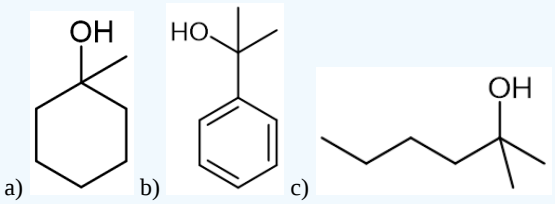
1) The result would be a racemic mixture of the following.



2)

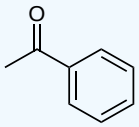


3)



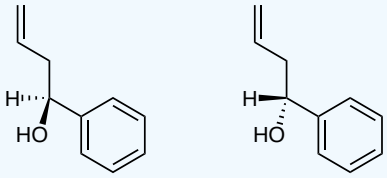
EXERCISE 17.5.2

If allylmagnesium chloride were added to a solution of the following compound and then worked-up with acid, the product would contain a chiral center. Would the product be a racemic mixture or an enatiomerically pure product? Draw both enantiomers.



Answer

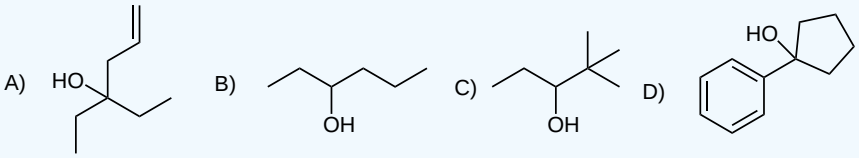
The result would be a racemic mixture of the following.



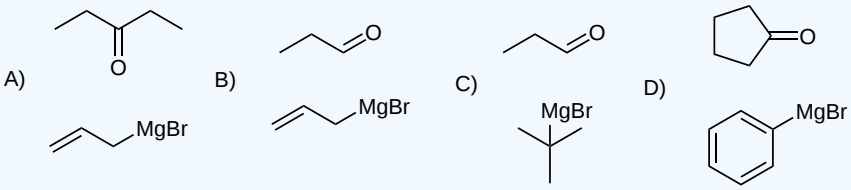
(*S*)-enantiomer (*R*)-enantiomer

EXERCISE 17.5.3

What combination of carbonyl compound and grignard (use MgBr) reagent would yield the following alcohols (after workup)?

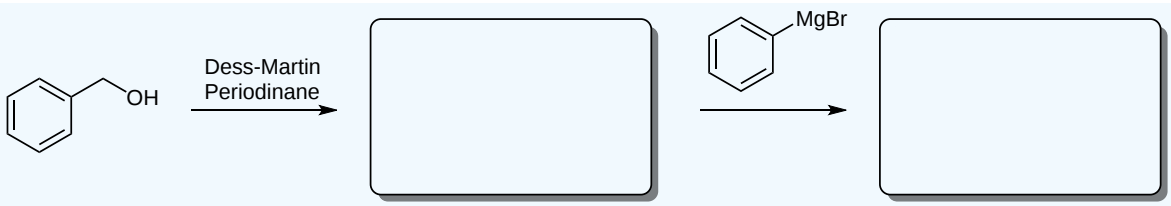


Answer

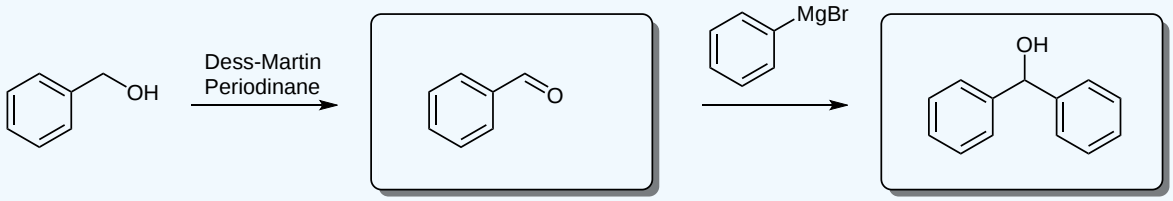


EXERCISE 17.5.4

Fill in the blanks of the following reaction scheme.



Answer



17.6: REACTIONS OF ALCOHOLS

OBJECTIVES

After completing this section, you should be able to

1. discuss the reactions of alcohols that have been introduced in previous units. These reactions include
   a. conversion of alcohols into alkyl halides.
   b. conversion of alcohols into tosylates.
   c. dehydration of alcohols to yield alkenes.
   d. conversion of alcohols into esters.

STUDY NOTES

As you read through Section 17.6 you should be prepared to turn back to those earlier sections in which some of the reactions of alcohols were discussed:

- dehydration to alkenes—Section 8.1.
- conversion to alkyl halides—Section 10.5.

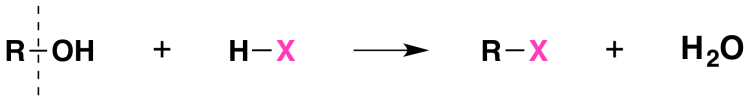
You may also wish to review the discussion of acidity constants, which can be found in Section 2.8.

Remember that when an alcohol reacts with tosyl chloride to form a tosylate, it is the O-H bond of the alcohol that is broken, not the C-O bond. This means that the absolute configuration of the carbon atom attached to the hydroxyl group remains unchanged throughout the reaction. The reading illustrates how this fact can be exploited to control the stereochemistry in an organic synthesis.

Finally, the reading shows the production of an ester from an alcohol and and an acid chloride. In Section 21.3 we will discuss the Fischer esterification, a famous reaction that uses an alcohol and a carboxylic acid to form the ester.

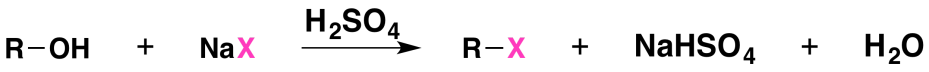
CONVERSION OF ALCOHOLS INTO ALKYL HALIDES

When alcohols react with a hydrogen halide, a substitution takes place producing an alkyl halide and water:



- 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).

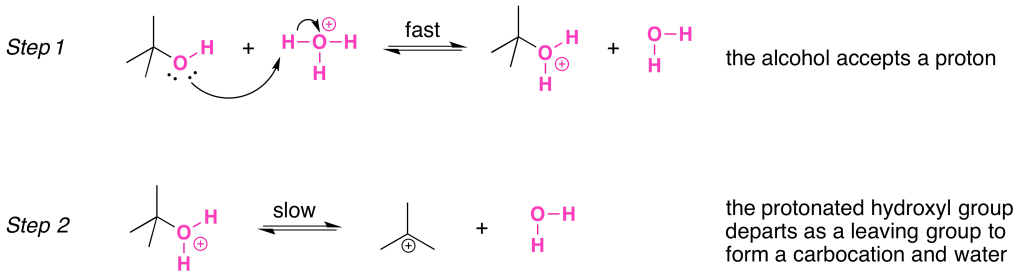
The reaction is acid catalyzed. Alcohols react with the strongly acidic hydrogen halides HCl, HBr, and HI, but they do not react with nonacidic NaCl, NaBr, or NaI. Primary and secondary alcohols can be converted to alkyl chlorides and bromides by allowing them to react with a mixture of a sodium halide and sulfuric acid:



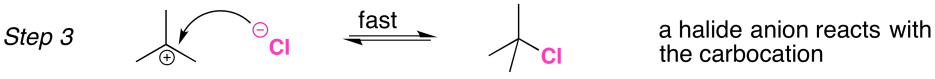
MECHANISMS OF THE REACTIONS OF ALCOHOLS WITH HX

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 a leaving group.

The S_N1 mechanism is illustrated by the reaction of 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.

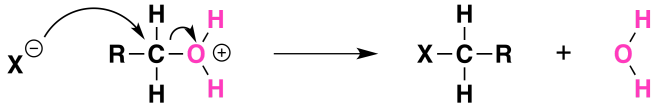


In step 3, the carbocation reacts with a nucleophile (a halide ion) to complete the substitution.

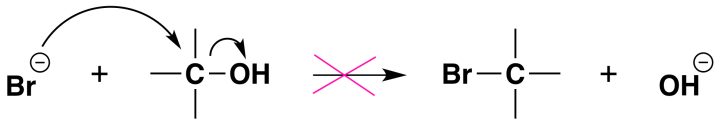


When we convert an alcohol to an alkyl halide, we carry out the reaction in the presence of acid and in the presence of halide ions, and not at elevated temperature. Halide ions are good nucleophiles (they are much stronger nucleophiles than water), and since halide ions are present in high concentration, 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.

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:



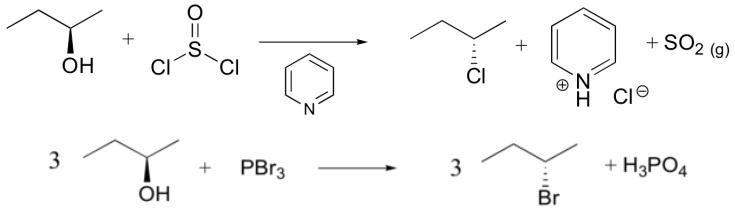
Again, acid is required. Although halide ions (particularly iodide and bromide ions) are strong nucleophiles, they are not strong enough to carry out substitution reactions with alcohols themselves. Direct displacement of the hydroxyl group does not occur because the leaving group would have to be a strongly basic hydroxide ion:



CONVERSION OF ALCOHOLS INTO ALKYL HALIDES USING $SOCL_2$ OR PBR_3

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:

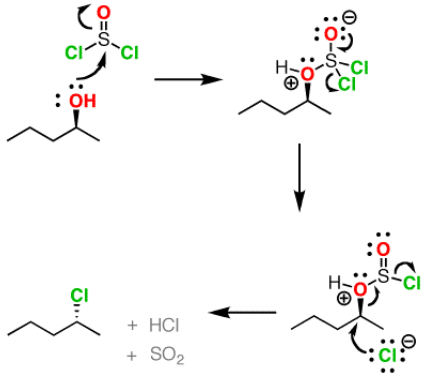


MECHANISMS

Both of these reagents form an alkyl halide through an S_N2 mechanism. The mechanism for both reactions start by making the alcohol's -OH a better leaving group through conversion to an intermediate. Thionyl chloride creates an intermediate chlorosulfite ($-OSOCl_2$) compound and phosphorus tribromide makes an intermediate dibromophosphite ($-OPBr_2$) compound. These intermediate compounds can subsequently be eliminated as a leaving group during an S_N2 reaction with the corresponding nucleophilic halide ion. Since these reactions proceeds through a backside attack, there is inversion of configuration at the carbon.

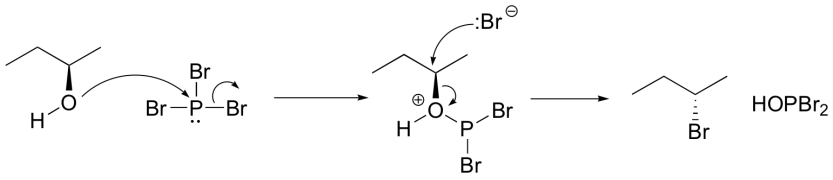
THIONYL CHLORIDE

Notice that during the reaction with thonyl chloride hydrochloric acid (HCl) and sulfurdioxide (SO_2) are produced as byproducts.



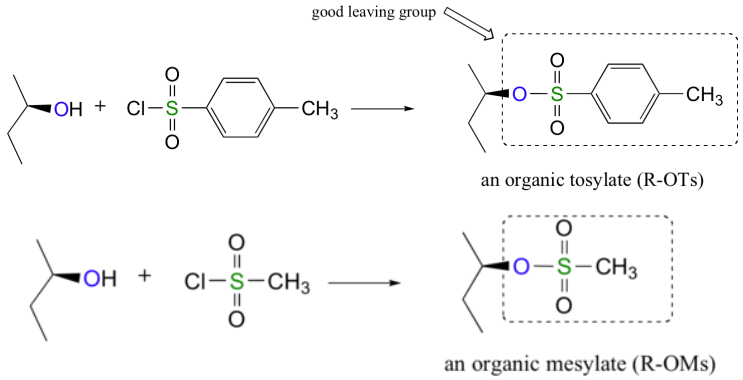
PHOSPHORUSTRIBROMIDE

During this reaction $HOPBr_2$ is made as biproducts.

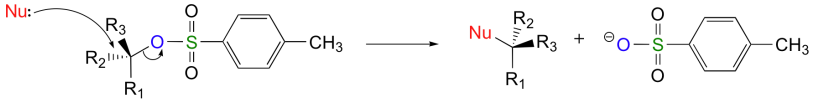


CONVERSION OF ALCOHOLS INTO TOSYLATES

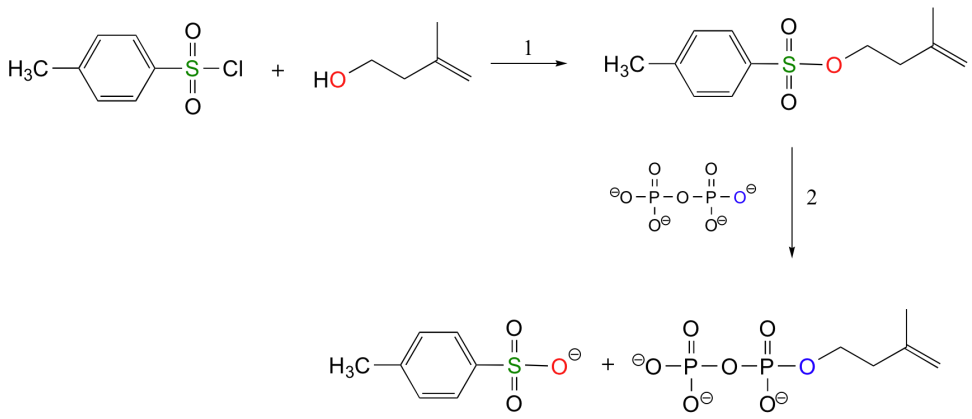
Alternatively, we can transform an alcohol group into sulfonic ester using *para*-toluene sulfonyl chloride (Ts-Cl) or methanesulfonyl chloride (Ms-Cl), creating what is termed an organic **tosylate** or **mesylate.** Notice that unlike the halogenation reactions above, the C-O bond of the alcohol is not broken during the conversion to a tosylate or mesylate so the reaction proceeds with retention of configuration at the electrophilic carbon.



Tosylate and mesylate groups are excellent leaving groups in nucleophilic substitution reactions, due to resonance delocalization of the developing negative charge on the leaving oxygen. They behave much line alkyl halides and can undergo S_N2 and S_N1 reaction depending on the conditions.



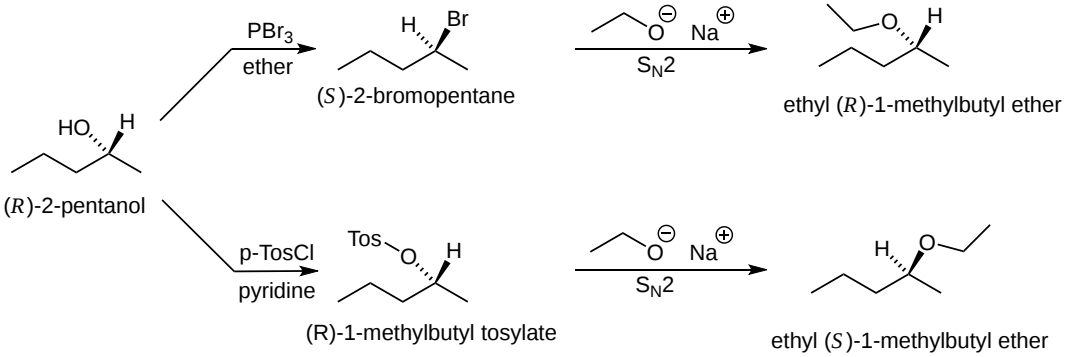
The laboratory synthesis of isopentenyl diphosphate - the 'building block' molecule used by nature for the construction of isoprenoid molecules such as cholesterol and b-carotene - was accomplished by first converting the alcohol into an organic tosylate (step 1), then displacing the tosylate group with an inorganic pyrophosphate nucleophile (step 2) (*J. Org. Chem* **1986**, *51*, 4768).



USING SULFONATE ESTERS FOR STEREOCHEMICAL CONTROL

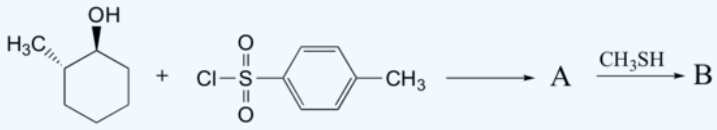
Tosylate and mesylate group's retention of conversion during formation makes them an important source of stereochemical control in organic synthesis. In the conversion of an alcohol to a halide for a subsequent S_N2 substitution there are two inversions of configuration. One during the conversion of the alcohol to a halide and the second during the S_N2 substitution reaction. Overall, these reaction steps produce a product with the same stereochemistry as the alcohol starting material.

When a tosylate or a mesylate are used for a similar conversion there is only one inversion of configuration. During the conversion of an alcohol to a tosylate the configuration of the alcohol strarting material is retained. This means that the tosylate will have the same stereochemical configuration as the alcohol starting material. The subsequent S_N2 reaction with the tosylate causes an inversion of configuration which provides a product of opposite stereochemistry as the alcohol starting material. The figure below outlines the relative stereochemistry of a series of reactions which summarize these points.

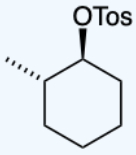


EXAMPLE 17.6.2

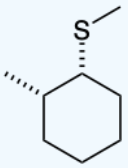
Predict the structures of A and B in the following reaction:



A. The tosylate is formed with retained stereochemistry.

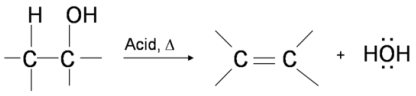


B. The thioether is formed with inverted stereochemistry.



DEHYDRATION OF ALCOHOLS TO YIELD ALKENES

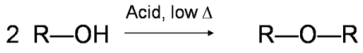
One way to synthesize alkenes is by dehydration of alcohols, a process in which alcohols undergo E1 or E2 mechanisms to lose water and form a double bond. The dehydration reaction of alcohols to generate alkene proceeds by heating the alcohols in the presence of a strong acid, such as sulfuric or phosphoric 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).

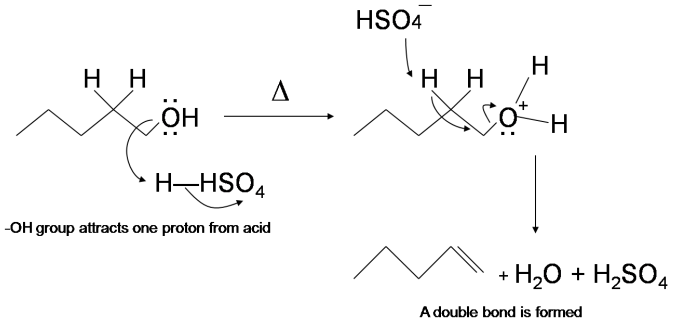


MECHANISM FOR THE DEHYDRATION OF ALCOHOL INTO ALKENE

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. First, the hydoxyl oxygen becomes protonated by reagent acid (sulfuric acid H_2SO_4), forming an alkyloxonium ion leaving group. Next, in a concerted process, then the conjugate base of the reagent acid (HSO_4^-) removes an adjacent hydrogen, the alkyloxonium ion is removed as a leaving group, and alkene double bond is formed. Remember that this reaction follows Zaitsev's rule which states that the most stable alkene will be the major product. In this reaction there is only one possible alkene product.

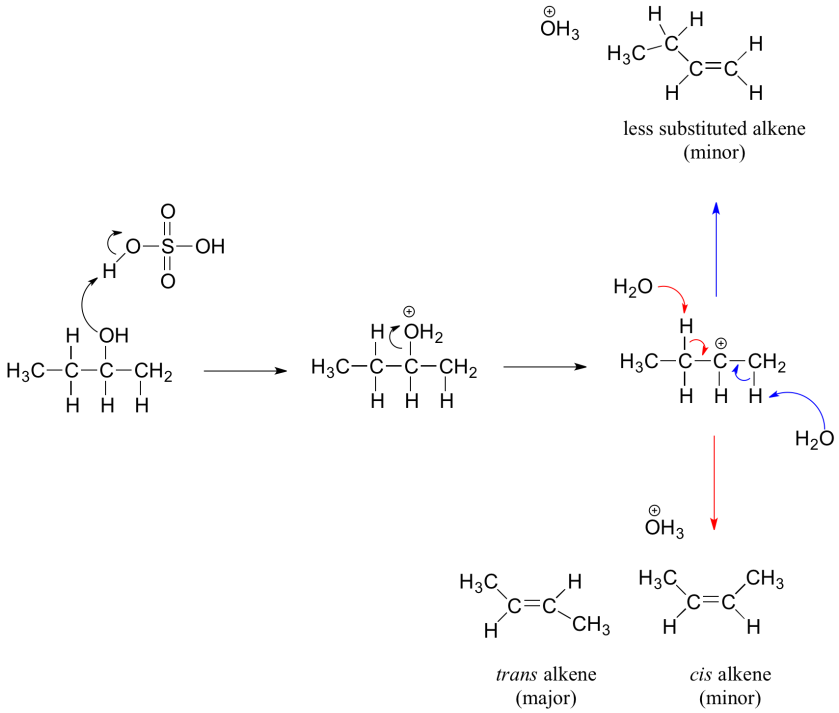


E1 MECHANISM FOR THE DEHYDRATION OF ALCOHOLS INTO ALKENES

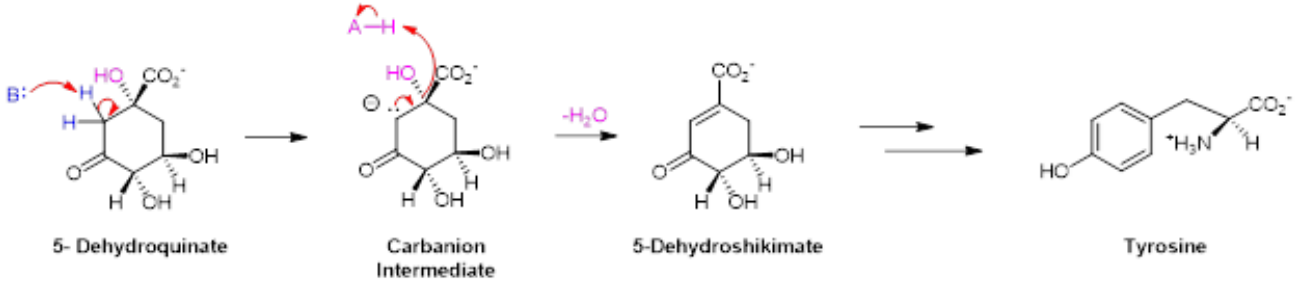
Secondary and tertiary alcohols dehydrate through the E1 mechanism. Similarly to the reaction above, secondary and tertiary –OH protonate to form alkyloxonium ions. However, in this case the ion leaves first to form a carbocation a reaction intermediate. The eliminated water molecule (which is a stronger 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 alkene formed depends on which adjacent 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. This reaction also follows Zaitsev's rule which states that the most stable alkene will be the major product.

As a general rule that more substituted alkenes are more stable than less substituted alkenes. Also, *trans* alkenes are more stable than *cis* alkenes. Therefore, the *trans* isomer of the 2-butene product is expected to be the major product of this reaction.

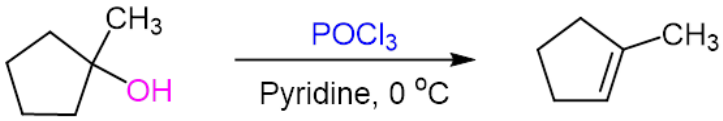


Similar biological dehydrations are fairly common. These reaction usually occur by an E1cB mechanism where the OH leaving group is two carbons away from a carbonyl group. An example is the dehydration of 5-dehydroquinate to form 5-dehydroshikimate as part of aromatic amino acid biosynthesis of tyrosine. Initially a biological deprotonates the carbon adjacent to the carbonyl group. The resulting carbanion intermediate forms a double bond by eliminating an OH group. This OH group is protonated by an acid and form water.



CONVERSION OF ALCOHOLS INTO ALKENES USING $POCl_3$

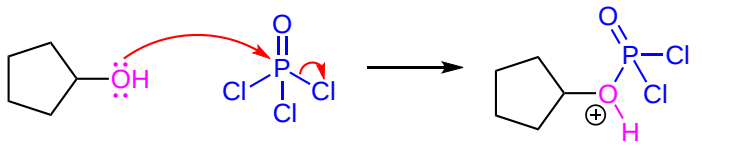
The E2 elimination of 2° and 3°-alcohols under mild, basic conditions may be accomplished by treatment with phosphorous oxychloride ($POCl_3$) in pyridine. Pryidine is typically used as the reaction solvent and acts as the base which removes an adjacent proton in the E2 mechanism.



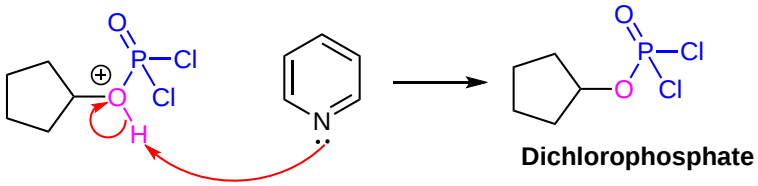
MECHANISM

The reaction starts with the reactant alcohol undergoing a substitution reaction with $POCl_3$ to form a dichlorophospate intermediate. Next pyridine removes an adjacent proton and the dichlorophospate group is eliminated as a leaving group to form a double bond by an E2 mechanism.

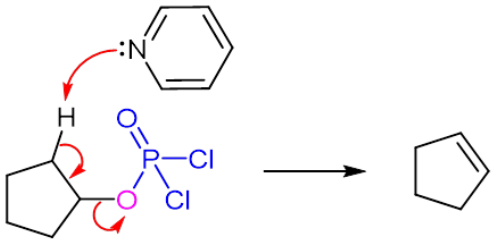
1) Formation of a dichlorphosphonium intermediate.



2) Deprotonation of the dichlorophosphonium intermediate to form a dichlorophosphate.

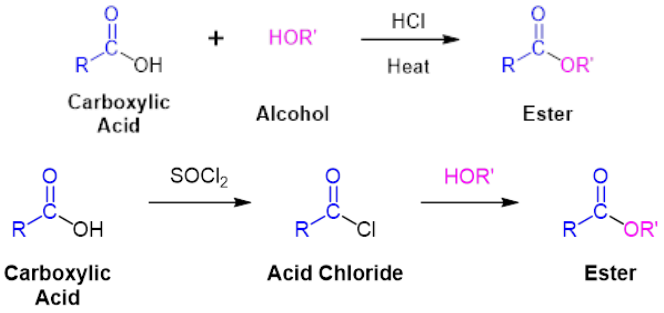


2) E2 elimination

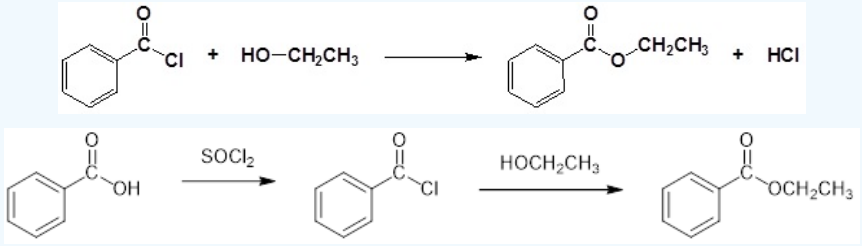


CONVERSION OF ALCOHOLS INTO ESTERS

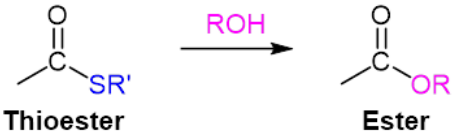
Alcohols can be converted into esters through reaction with carboxylic acids using a strong acid as a catalyst. Often this transformation is performed by increasing the reactivity of the carboxylic acid by first converting it into a carboxylic acid chloride functional group by reacting with thionyl chloride ($SOCl_2$). The acid chloride can then be reacted with an alcohol to create an ester. These reactions will be discussed in greater detail in **Chapter 21**.

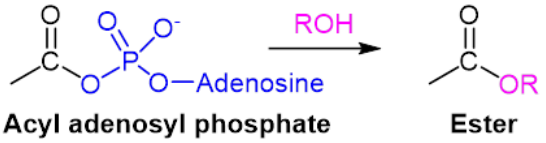


EXAMPLE 17.6.3



In biological systems, ester formation occurs through a similar process except thioester or acyl adenosyl phosphates are used instead of carboxylic acid chlorides. These reaction will be discussed in more detail in **Chapter 21**.





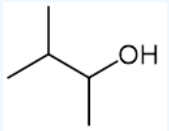
EXERCISES

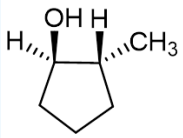
EXERCISE 17.6.1

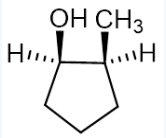
1) Draw the expected product of the reaction of cylohexanol with the following reagents.

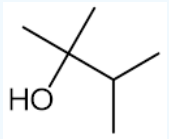
(a) $SOCl_2$ (b) PBr_3

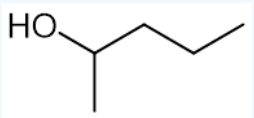
2) Draw the expected product of the treatment of the following compounds with $OPCl_3$ in pyridine.

a) 

b) 

c) 

d) 

e) 

Answer

1) a) Chlorocyclohexane b) Bromocyclohexane

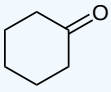
2) a) 2-Methyl-2-butene b) 3-Methylcyclopentene c) 1-Methylcyclopentene d) 2,3-Dimethyl-2-butene e) 2-Methyl-2-butene

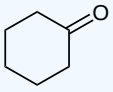
EXERCISE 17.6.2

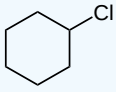
Draw the expected product of the reaction of cylohexanol with the following reagents.

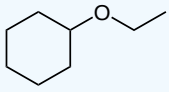
(A) CrO_3, H_2SO_4, H_2O (B) Dess-Martin Periodinane (C) $SOCl_2$ (D) NaH and 1-bromoethane (E) PBr_3

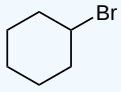
Answer

A) 

B) 

C) 

D) 

E) 

EXERCISE 17.6.3

Starting with cyclohexanol, describe how you would prepare the following?

(A) cyclohexyl acetate (B) 1-allylcyclohexan-1-ol (C) cyclohexene (D) ethoxycyclohexane

Answer

A) This can be seen as a transesterification, acid and some other ester would be needed to form cyclohexylacetate

B) First, oxidize the alcohol to a ketone, take for example Dess-Martin Periodinane, then use an allyl grignard to form 1-allylcyclohexan-1-ol

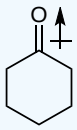
C) Alcohols can dehydrate to form alkenes under acidic conditions, so using anhydrous acid and heat would yield cyclohexene

D) The alcohol can also be a nucleophile, perform a halogen substitution, using 1-X ethane, to yield ethoxycyclohexane

EXERCISE 17.6.4

In cyclohexanone, a ketone, indicate the polarity of the bond between oxygen and carbon.

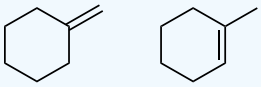
Answer



Oxygen is more electronegative than carbon creating the polar bond. This is the basis for the carbon's electrophilicity.

EXERCISE 17.6.5

In the dehydration of 1-methylcyclohexanol, which product is favored?

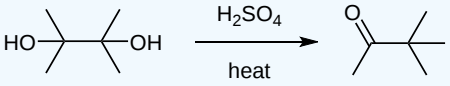


Answer

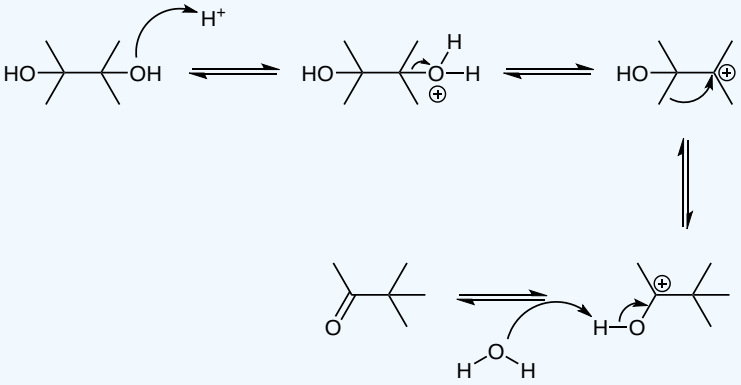
The more substituted alkene is favored, as more substituted alkenes are relatively lower in energy.

EXERCISE 17.6.6

In the dehydration of this diol the resulting product is a ketone. Draw the mechanism of its formation. (Hint: a rearrangement occurs.)

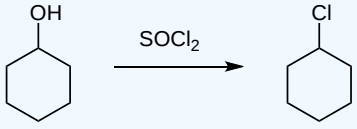


Answer

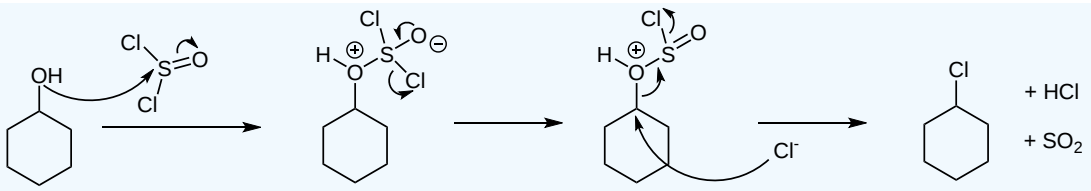


EXERCISE 17.6.7

Draw the mechanism of the reaction of thinoylchloride with cyclohexanol, given below.

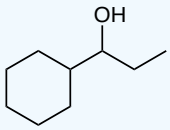


Answer



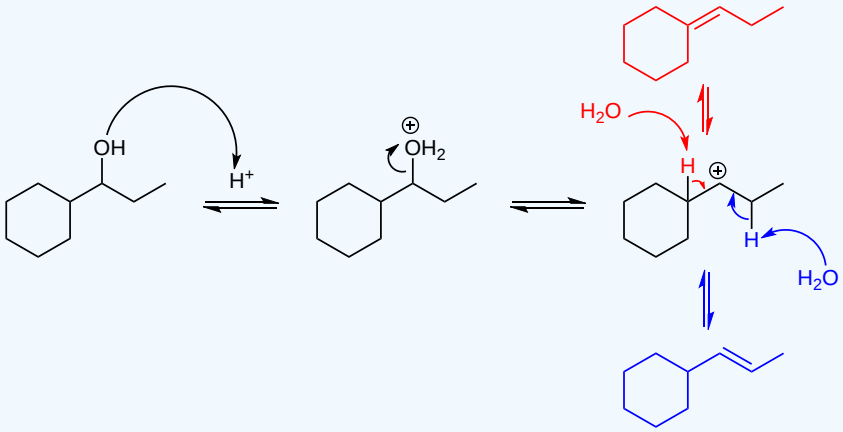
EXERCISE 17.6.8

Draw an arrow pushing mechanism for the acid catalyzed dehydration of the following alcohol, make sure to draw both potential mechanisms. Assume no rearrangement for the first two product mechanisms. Which of these two would likely be the major product? If there was a rearrangement, draw the expected major product.

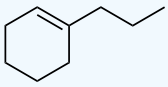


Answer

The major product of this mechanism would be the more highly substituted alkene, or the product formed from the red arrows.

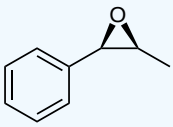


Note the secondary carbocation adjacent a tertiary carbon center, if there were a hydride transfer (rearrangement) to form a tertiary carbocation the following would be the major product. The minor product being the same product as the one formed from the red arrows.



EXERCISE 17.6.9

The following epoxide can be transformed into an alcohol using a grignard reagent, take for example allylmagnesium chloride. Draw the product of the treatment of this epoxide with this grignard after being worked up with H_2O. Note the stereochemistry and also remember that benzyllic carbons are good S_N2 electrophiles.



Answer

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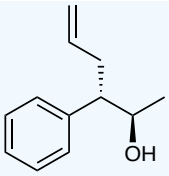
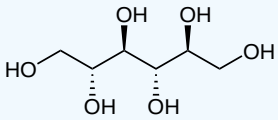


? EXERCISE 17.6.10

As seen in the previous example, there are many examples of chiral compounds containing alcohols. One common example of these are sugars, is the given the following sugar, allitol, also chiral?



Answer

This compound actually has a plane of symmetry, the plane parallel to the carbon chain/backbone. So, it is not chiral, also called a meso compound.

17.7: OXIDATION OF ALCOHOLS

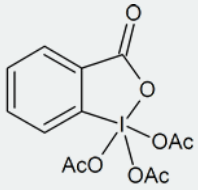
OBJECTIVES

After completing this section, you should be able to

1. write an equation to represent the oxidation of an alcohol.
2. identify the reagents that may be used to oxidize a given alcohol.
3. identify the specific reagent that is used to oxidize primary alcohols to aldehydes rather than to carboxylic acids.
4. identify the product formed from the oxidation of a given alcohol with a specified oxidizing agent.
5. identify the alcohol needed to prepare a given aldehyde, ketone or carboxylic acid by simple oxidation.
6. write a mechanism for the oxidation of an alcohol using a chromium(VI) reagent.

STUDY NOTES

The reading mentions that pyridinium chlorochromate (PCC) is a milder version of chromic acid that is suitable for converting a primary alcohol into an aldehyde without oxidizing it all the way to a carboxylic acid. This reagent is being replaced in laboratories by **Dess-Martin periodinane (DMP)**, which has several practical advantages over PCC, such as producing higher yields and requiring less rigorous reaction conditions. DMP is named after Daniel Dess and James Martin, who developed it in 1983.



Dess–Martin periodinane (DMP)

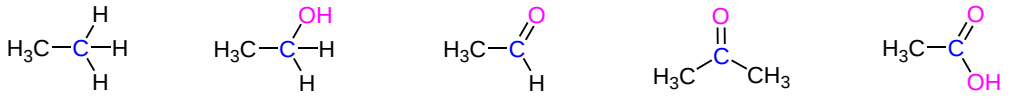
OXIDATION STATES OF CARBON

The general idea of oxidation and reduction reactions learned in general chemistry is that when a compound or atom is oxidized it loses electrons, and when it is reduced it gains electrons. In order, to keep track of electrons in organic molecules a oxidation state formalism is used. Oxidation states to not represent the actual charge but it will allow the number of electrons being gained or lost by a particular atom during a reaction.

To calculate the oxidation state of a carbon atom the following rules are used:

1. A C-C bond does not affect the oxidation state of a carbon. So a carbon attached to 4 carbons has an oxidation state of zero.
2. Every C-H bond will **decrease** the oxidation state of the carbon by 1.
3. Each C-X bond will **increase** the oxidation state of the carbon by 1. Where X is an electronegative, such as nitrogen, oxygen, sulfur, or a halogen.

When looking at the oxidation states of carbon in the common functional groups shown below it can be said that carbon loses electron density as it becomes more oxidized.

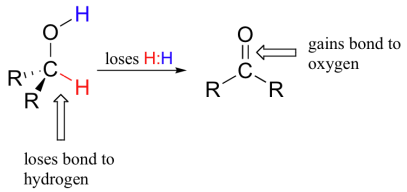


	Ethane	Ethanol	Ethanal	Propanone	Ethanoic Acid
Oxidation State:	**3(-1) + O = -3**	**2(-1) +1 +0 = -1**	**2(+1) -1 +0 = +1**	**2(+1) + 2(0) = +2**	**3(+1) +0 = +3**

Most Reduced ⟹ **Most Oxidized**

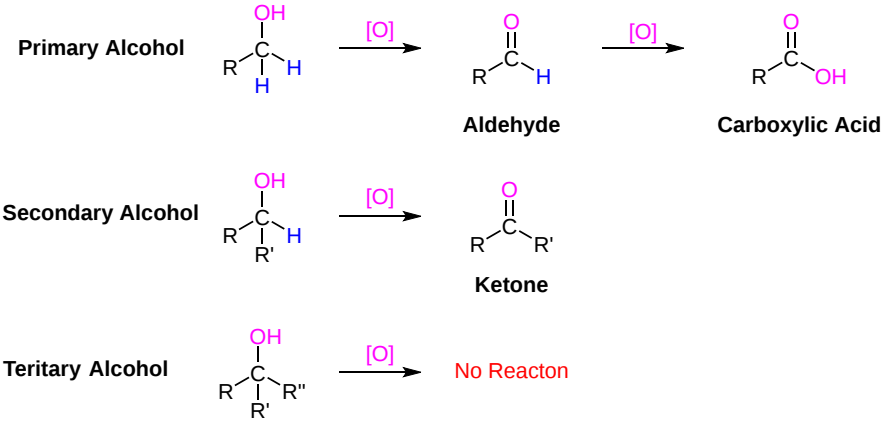
For this section, a simpler way to consider this process is to say that when a carbon atom in an organic compound loses a bond to hydrogen and gains a new bond to a oxygen it has been oxidized. A very commonly example is the oxidation of an alcohol to a ketone or aldehyde. Notice that during this process the carbon atom loses a hydrogen and gains a bond to oxygen.

Dehydrogenation (oxidation) of an alcohol



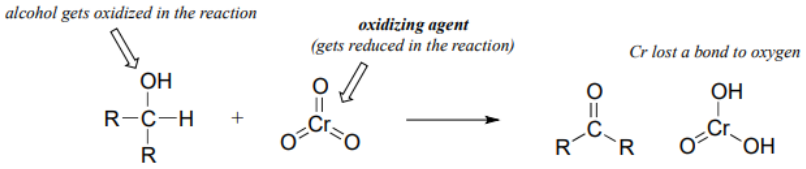
OXIDATION OF ALCOHOLS

On of the most important reactions of alcohols is their oxidation to carbonyl containing compounds such as aldehyde, ketones, and carboxylic acid. Typically primary alcohols, depending on the reagent used, produce aldehydes or carboxylic acids during oxidations. Secondary alcohols are oxidized to produce ketones, and tertiary alcohols are usually not affected by oxidations.



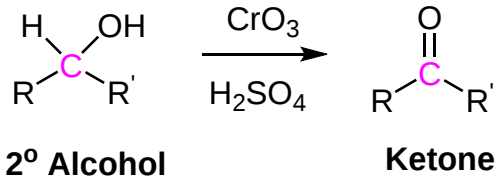
ALCOHOL OXIDIZING AGENTS

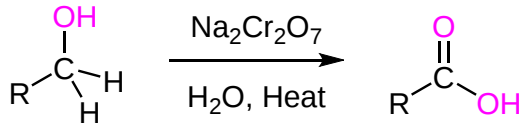
Oxidation and reduction reactions always occurs in tandem: when one compound is oxidized, another compound must be reduced. For an alcohol to be oxidized in a reaction there must also be a compound being reduced. This reduced compound is also called the oxidizing agent. For example, chromium trioxide (CrO_3) is a common oxidizing agent used by organic chemists to oxidize a secondary alcohol to a ketone. During this reaction CrO_3 is being reduced to form H_2CrO_3. 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.



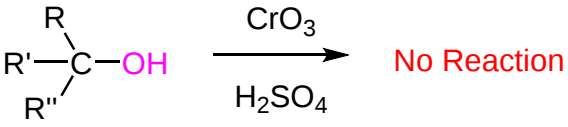
There is a wide selection of oxidizing agents available for use in the organic chemistry laboratory, each with its own particular properties and uses. In addition to CrO_3, other commonly used oxidizing agents include potassium permanganate ($KMnO_4$) and sodium dichromate ($Na_2Cr_2O_7$). Any of these reagents can be used to oxidize secondary alcohols to form ketones and primary alcohols to form carboxylic acids. Tertiary alcohols remain unreactive to oxidation.

GENERAL REACTIONS



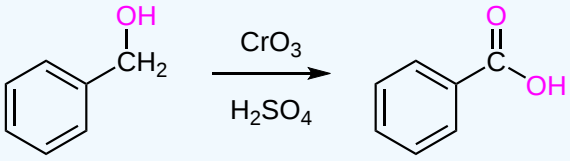


1º Alcohol **Carboylic Acid**

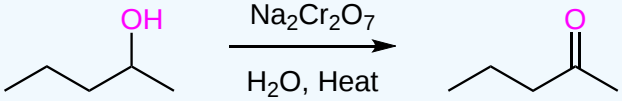


3º Alcohol

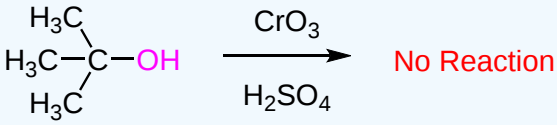
EXAMPLE 17.7.1



Oxidation of Benzyl Alcohol to Benzoic Acid

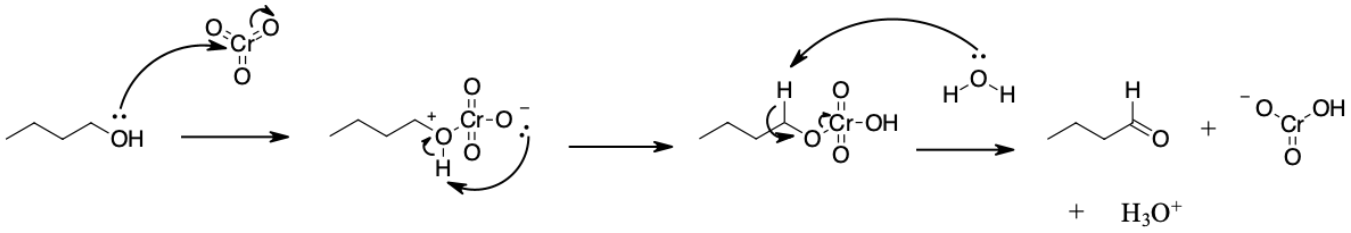


Oxidation of 2-Pentanol to 2-Pentanone



MECHANISM

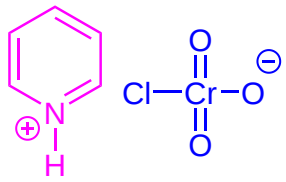
During this reaction mechanism the chromium atom is being reduced from Cr(VI) in the CrO_3 starting material to Cr(IV) in the H_2CrO_3 product. Also, notice the the C=O bond is formed in the third step of the mechanism through an E2 reaction. Although E2 reaction are generally know for forming C=C double bonds thought the elimination of a halide leaving group, in this case they are use to generate a C=O through the elimination of a reduced metal as a leaving group.



EXAMPLES

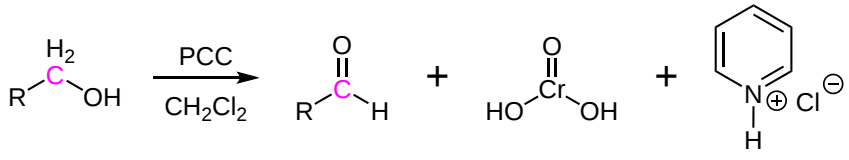
OXIDATION OF 1º ALCOHOLS WITH PCC TO FORM ALDEHYDES

Pyridinium chlorochromate (PCC) is a milder version of chromic acid. PCC oxidizes 1º alcohols one rung up the oxidation ladder, turning primary alcohols into aldehydes and secondary alcohols into ketones. Unlike chromic acid, PCC will not oxidize aldehydes to carboxylic acids. Cr(IV) as well as pyridinium chloride are produced as byproducts of this reaction.

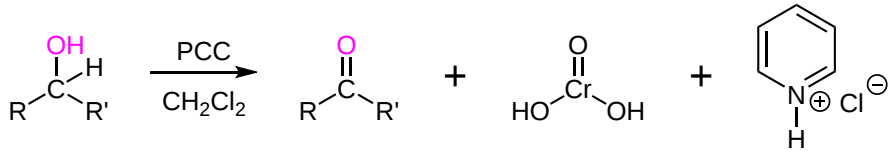


Pyridinium chlorochromate (PCC)

GENERAL REACTIONS

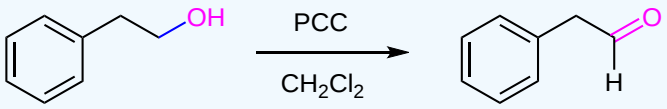


1^o Alcohol **Aldehyde** **Cr(IV)** **Pyridinium Chloride**

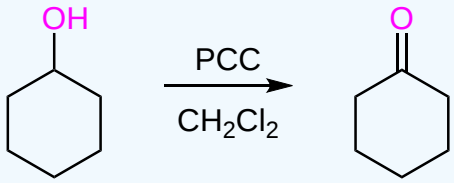


2^o Alcohol **Ketone** **Cr(IV)** **Pyridinium Chloride**

? EXAMPLE 17.7.2



Oxidation of 2-Phenylethanol to Phenylacetaldehyde

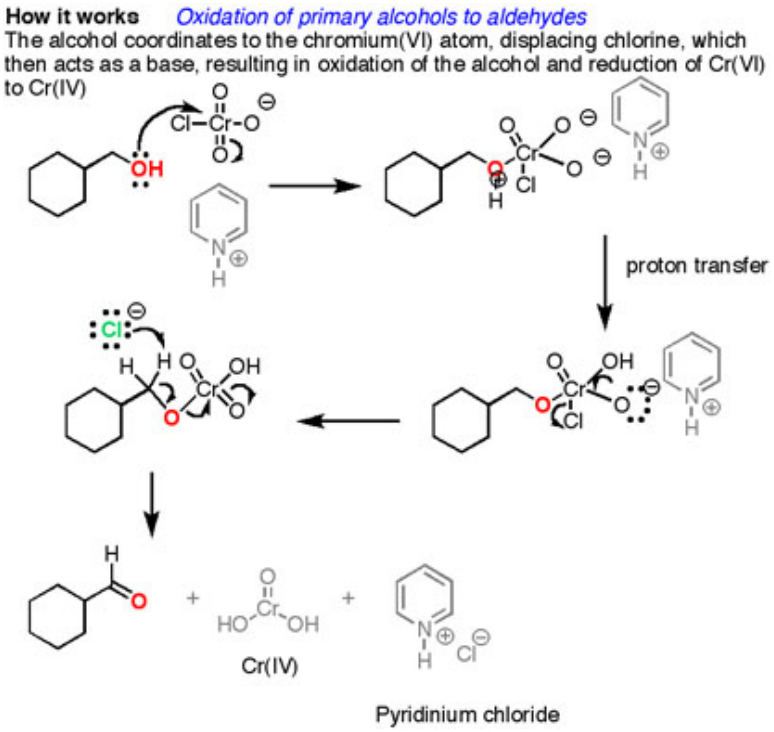


Oxidation of Cyclohexanol to Cyclohexanone

MECHANISM

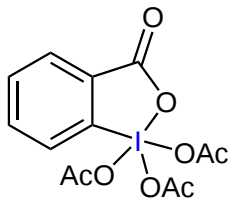
The first step of the mechanism is attack of alcohol oxygen on the chromium atom to form the Cr-O bond. Secondly, a proton on the (now positive) OH is transferred to one of the oxygens of the chromium, possibly through the intermediacy of the pyridinium salt. A chloride ion is then displaced, in a reaction 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. 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. In an E2 reaction, the electrons from the C-H bond move to form the C=O bond, and in the process break the O-Cr bond. During this step Cr(VI) gains two electrons to become Cr(IV) (drawn here as $O{=}Cr(OH)_2$).



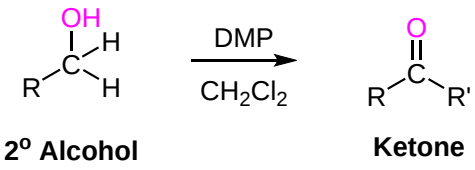
OXIDATION OF 1^{O} ALCOHOLS WITH DESS-MARTIN PERIODINANE (DMP) TO FORM ALDEHYDES

PCC is being replaced in laboratories by **Dess-Martin periodinane (DMP)** in dichloromethane solvent, which has several practical advantages over PCC, such as producing higher yields and requiring less rigorous conditions (lower reaction temperature and a nonacidic medium). DMP is named after Daniel Dess and James Martin, who developed it in 1983.

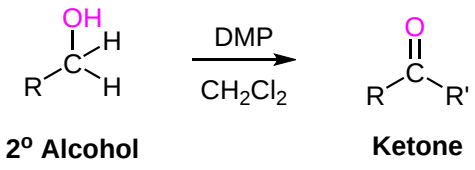


Dess-Martin periodinane (DMP)

GENERAL REACTIONS

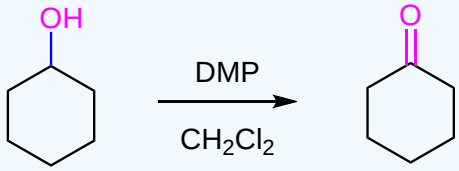


2^{o} Alcohol **Ketone**

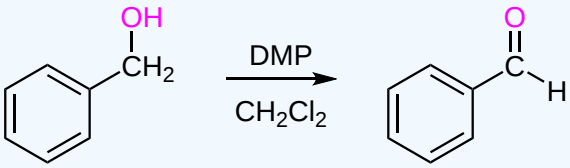


2^{o} Alcohol **Ketone**

✔ EXAMPLE 17.7.3



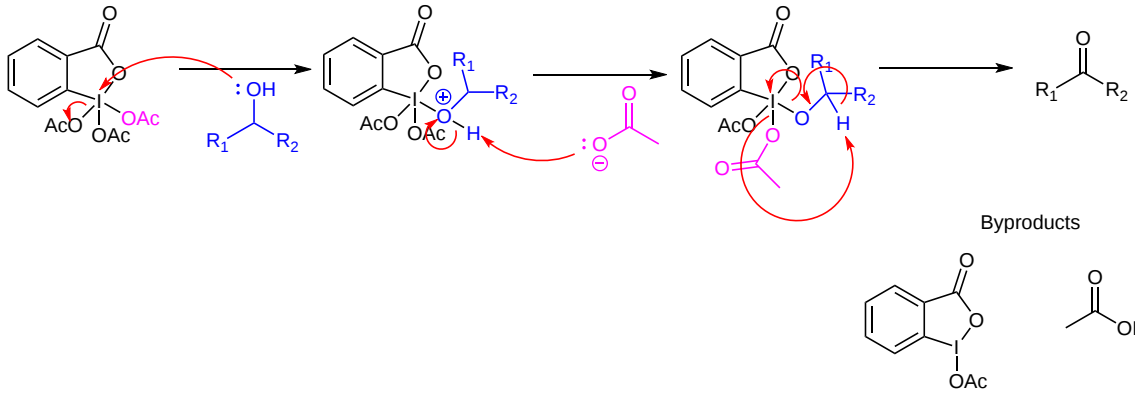
Oxidation of Cyclohexanol to Cyclohexanone



Oxidation of Benzyl Alcohol to Benzaldehyde

MECHANISM

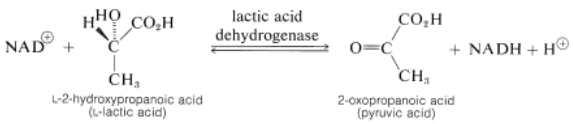
The first step of the mechanism involves the reactant alcohol attacking the Iodine (V) atom and eliminating an acetate (Ac^-) leaving group to form a periodinate intermediate. The next step is a concerted E2-like reaction where a hydrogen is removed from the alcohol, the C=O bond is formed, an acetate group is eliminated from the iodine atom, and the iodine (V) atom gains two electrons to be reduced to iodine (III).

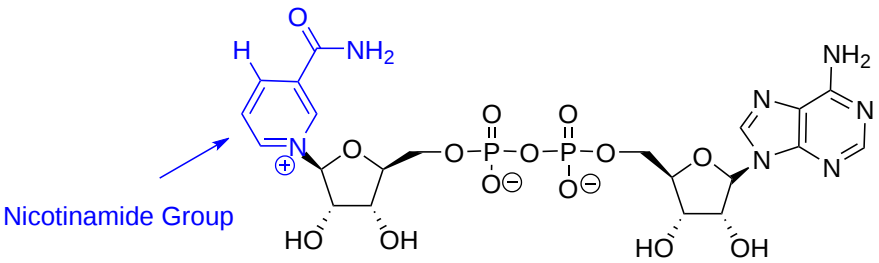


BIOLOGICAL ALCOHOL OXIDATIONS

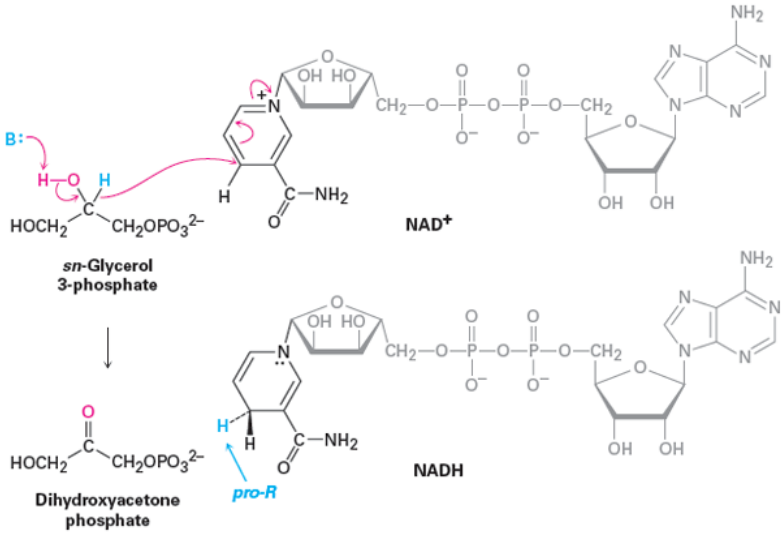
There are many biological oxidations that convert a primary or secondary alcohol to a carbonyl compound. These reactions cannot possibly involve the extreme pH conditions and vigorous inorganic oxidants used in typical laboratory oxidations. Rather, they occur at nearly neutral pH values and they all require enzymes as catalysts, which for these reactions usually are called *dehydrogenases*. An important group of biological oxidizing agents includes the pyridine nucleotides, of which nicotinamide adenine dinucleotide (NAD^+) is an example. This very complex molecule functions to accept hydride ($H:^-$) or the equivalent ($H^+ + 2e^-$) from the α carbon of an alcohol. The reduced form of NAD^+ is abbreviated as NADH and the $H:^-$ is added at the 4-position of the pyridine ring. It is important to note that the hydride adds exclusively to the *Re* face of the pyridine ring giving NADH a *pro*-R stereochemistry.

An example of the remarkable specificity of this kind of redox system. One of the last steps in the metabolic breakdown of glucose is the reduction of 2-oxopropanoic (pyruvic) acid to L-2-hydroxypropanoic (lactic) acid. The reverse process is oxidation of L-lactic acid. The enzyme *lactic acid dehydrogenase* catalyses this reaction, and it functions only with the L-enantiomer of lactic acid. During this reaction a base removes the alcohol hydrogen. The resulting alkoxide ion then forms the C=O bond causing a hydride ion to transfer to NAD^+.



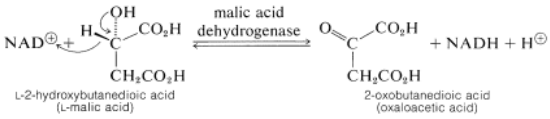


The Structure of NAD+



From an outside source. Convert mechanism to use lactic acid.

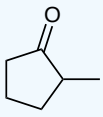
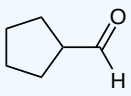
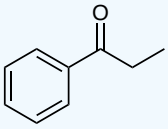
Another example is provided by one of the steps in metabolism by way of the Krebs citric acid cycle, is the oxidation of L-2-hydroxy-butanedioic (L-malic) acid to 2-oxobutanedioic (oxaloacetic) acid. This enzyme functions only with L-malic acid:



EXERCISES

? EXERCISE 17.7.1

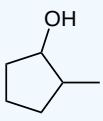
Draw the alcohol that the following ketones/aldehydes would have resulted from if oxidized. What oxidant could be used?

a)  b)  c) 

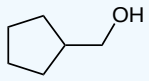
Answer

1)

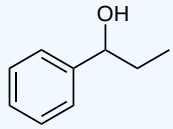
a) Any oxidant capable of oxidizing an alcohol to a ketone would work, such as the Jones reagent (CrO_3, H_2SO_4, H_2O), PCC, or Dess-Martin periodinane.



b) Since this is a primary alcohol, there are some precautions necessary to avoid formation of the carboxyllic acid. Milder oxidants such as the Dess-Martin periodinane, and also PCC (there is no water to form the carboxyllic acid) would work



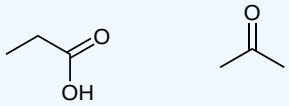
c) Any oxidant capable of oxidizing an alcohol to a ketone would work, such as the Jones reagent (CrO_3, H_2SO_4, H_2O), PCC, or Dess-Martin periodinane.



? EXERCISE 17.7.2

Show the products of the oxidation of 1-propanol and 2-propanol with chromic acid in aqueous solution.

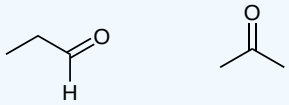
Answer



? EXERCISE 17.7.3

Show the products of the oxidation of 1-propanol and 2-propanol with Dess-Martin periodinane.

Answer



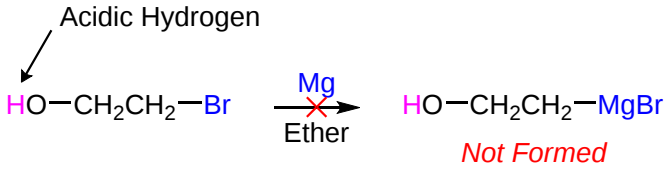
17.8: PROTECTION OF ALCOHOLS

OBJECTIVES

After completing this section, you should be able to

1. explain what is meant by “protecting” a functional group during an organic synthesis.
2. describe one common method for protecting the hydroxy group of an alcohol, and give an example of its use (e.g., in the preparation of a Grignard reagent).

Often during the synthesis of complex molecules one functional group in a molecule interferes with an intended reaction on a second functional group on the same molecule. An excellent example is the fact that a Grignard reagent can't be prepared from halo alcohol because the C-Mg bond is not compatible with the acidic -OH group.



When situations like this occurs chemists circumvent the problem by changing the interfering functional group into one that does not interfere with the intended reaction. Chemists call this process protection of a functional group. Functional group protection involves three steps:

1. Blocking the interfering functionality by introducing a protecting group.
2. Performing the intended reaction.
3. Removing the protecting group and reforming the original functional group.

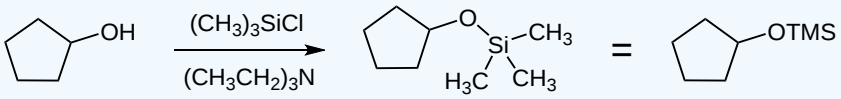
PROTECTING ALCOHOLS THROUGH THE FORMATION OF TRIALKYLSILYL ETHERS

There are several methods for protecting an alcohol, however, the most common is the reaction with a chlorotrialkylsilane, Cl-SiR_3 This reactions forms a trialkylsilyl ether, R'O-SiR_3. One of the most common reagents is chlorotrimethylsilane [$(CH_3)_3SiCl$] which is often used in conjunction with a base, such as triethylamine. The base helps to form the alkoxide anion and remove the HCl produced by the reaction. The produced trimethylsilyl ether is commonly abbreviated -OTMS. This silyl ether no longer has the fairly acidic OH proton as the alcohol group has been changed (protected).

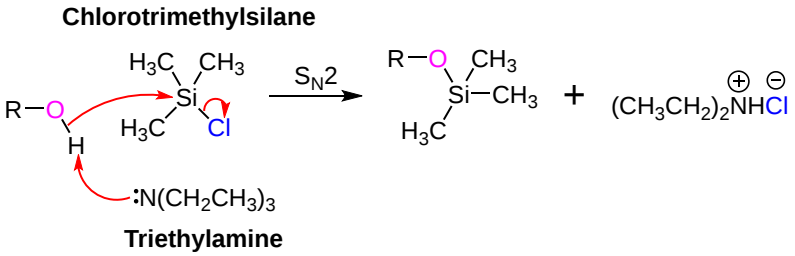
GENERAL REACTION

Alcohol **Trimethylsilyl ether (TMS)**

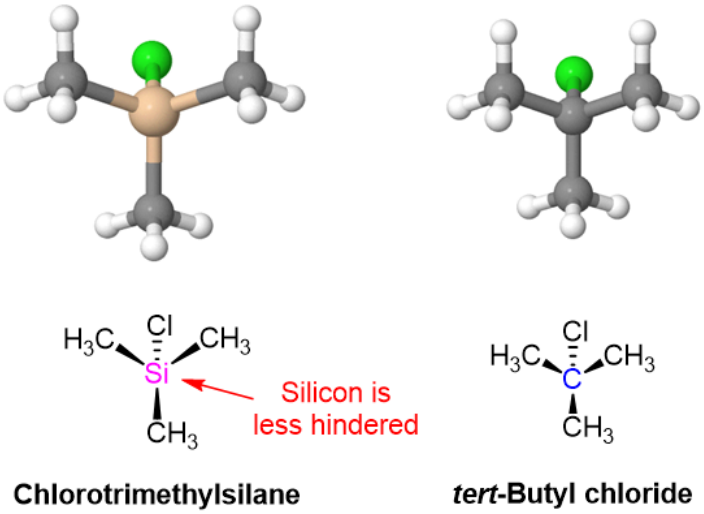
EXAMPLE 17.8.1



MECHANISM

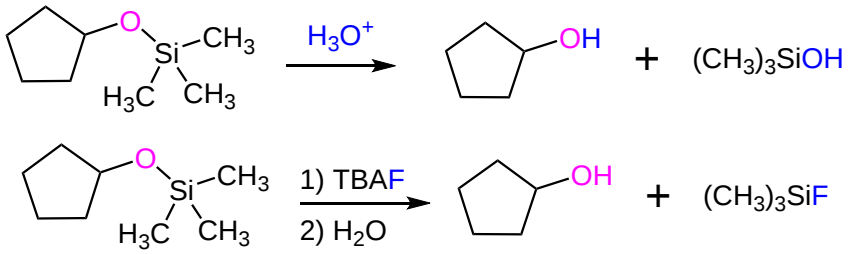


Notice this reaction occurs through an S_N2-like mechanism with the alcohol attacking a trialkyl-substitued silicon atom. Normally, an S_N2 reaction would not be viable for the analogous *tert*-butyl chloride due to the steric hindrance of the tertiary electrophilic carbon. Being a third-row atom, silicon is larger and forms longer bonds that carbon. The Si-C bonds of chlorotrimethylsilane are 195 pm compared to the 154 pm C-C bonds or *tert*-butylchloride. The three methyl groups attached to silicon are more spread out and offer less steric hindrance so the S_N2-like reaction can occur.



DEPROTECTION

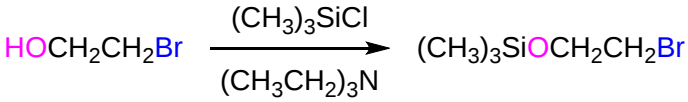
Trimethylsilyl ethers, like most other ethers, are relatively unreactive towards many reagents such as oxidizing agents, reducing agents, or Grignard reagents. However, the TMS ether protecting group can be removed by reaction with an aqueous acid or the fluoride ion (F^-) to regenerate the alcohol. Common sources of the fluoride ion are lithium fluoride (LiF) and tetrabutylammoniumfluoride (TBAF) [$(CH_3CH_2CH_2CH_2)_4NF$]. This step is commonly referred to as a **deprotection**.



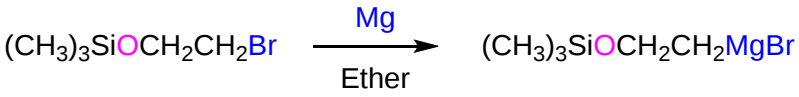
UTILIZING A PROTECTING GROUP FOR A GRIGNARD REACTION

The problem posed at the beginning of this section can be solved through the use of a TMS protecting group. Once the alcohol is converted into a TMS ether the acidic hydrogen will no longer be present and a Grignard reagent can be formed.

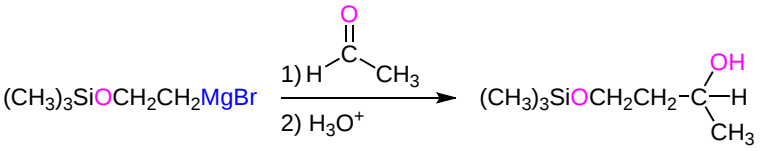
1) Protection of the Alcohol



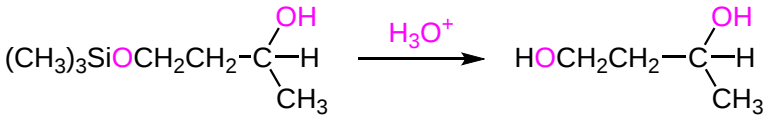
2) Form the Grignard Reagent



3) Perform the Grignard Reaction



4) Deprotection

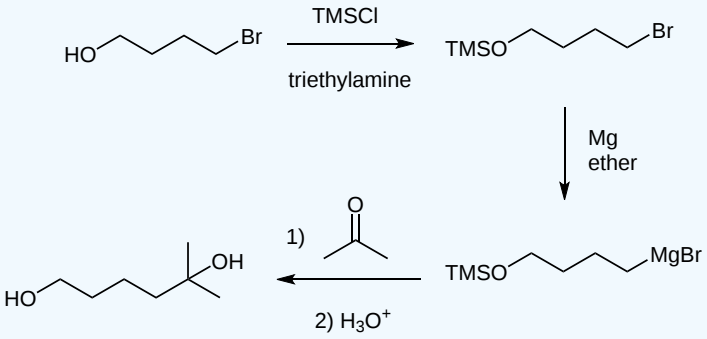


EXERCISES

? EXERCISE 17.8.1

Propose a multiple-step synthesis to transform 4-bromo-1-butanol into 2-methylhexane-2,6-diol.

Answer



CONTRIBUTORS AND ATTRIBUTIONS

-
- Layne Morsch (University of Illinois Springfield)
- James Kabrhel (University of Wisconsin - Green Bay, Sheboygan Campus)

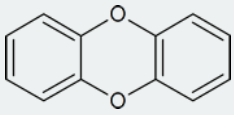
17.9: PHENOLS AND THEIR USES

OBJECTIVES

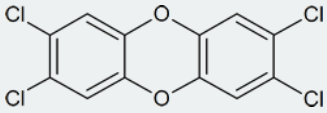
After completing this section, you should be able to describe two methods that can be used to obtain phenol on an industrial scale.

STUDY NOTES

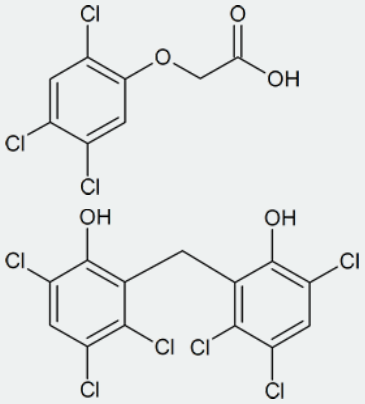
One substance that has become symbolic of the struggle between industrial development and environmental protection is dioxin. The name dioxin is used to refer to a family of compounds having a basic structure in which two benzene rings are joined by two oxygen atoms:



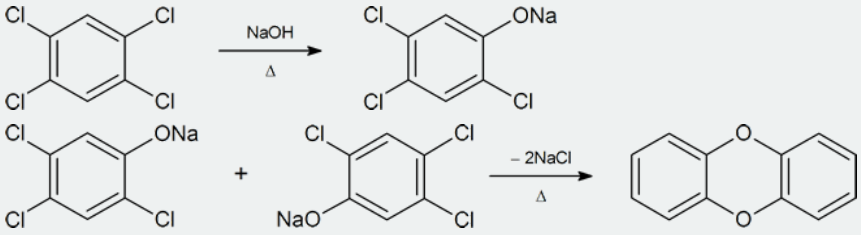
However, media references to dioxin are usually in connection with 2,3,7,8-tetrachlorodibenzo- *p*-dioxin, or TCDD:



TCDD is a by-product formed in the manufacture of trichlorophenol, an intermediate in the production of the herbicide 2,4,5-T (one of the ingredients of the infamous Agent Orange), in the manufacture of hexachlorophene, by pulp and paper mills that use chlorine to produce white paper, and as a result of the incineration of municipal refuse.



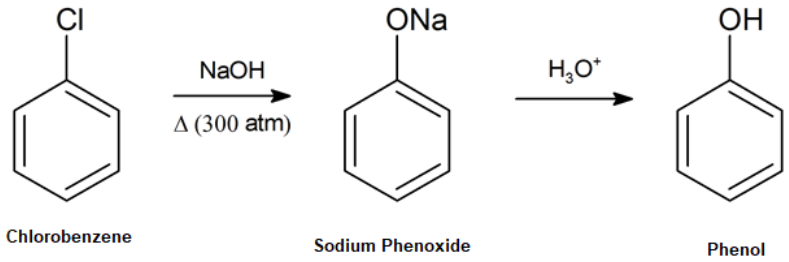
The equation given below shows how 2,3,7,8-tetrachlorodibenzo- *p*-dioxin is formed during the manufacture of 2,4,5-trichlorophenol, an intermediate produced in the synthesis of 2,4,5-T. The process involves the reaction of 1,2,4,5-tetrachlorobenzene with base at a temperature of about 160°C.



The possible hazards presented by dioxin first became apparent in 1957, when some German workers involved in the manufacture of 2,4,5-T developed chloracne—a skin condition resembling acne. The precise toxicological effects of dioxin on humans is open to debate, but as little as 0.6 mg per kg of body weight will kill 50% of guinea pigs injected with TCDD within a specified time.

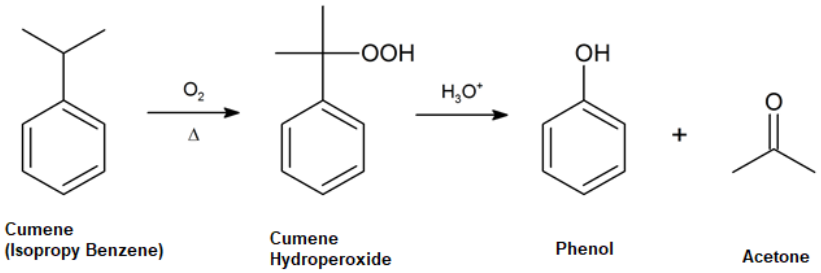
DOW'S PROCESS

An early commercial preparation of phenol in the late 19th and early 20th century was by the hydrolysis of chlorobenzene with strong base to produce a sodium phenoxide intermediate, which affords phenol upon acidification.



CUMENE PROCESS

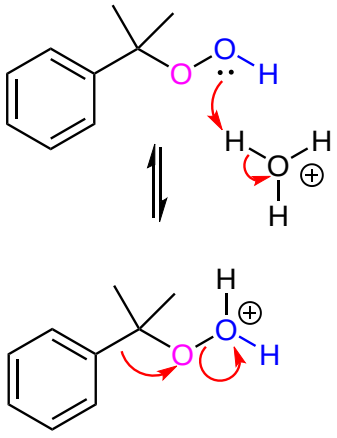
Developed in the 1940s and currently responsible for most industrial phenol production this process involves isopropylbenzene—commonly known as cumene. Treatment of cumene with oxygen in air generates 2-hydroperoxypropan-2-ylbenzene (cumene hydroperoxide) through a radical pathway. When hydrolyzed in acidic medium the peroxide intermediate produces phenol and acetone, which are both valuable chemical products.



MECHANISM

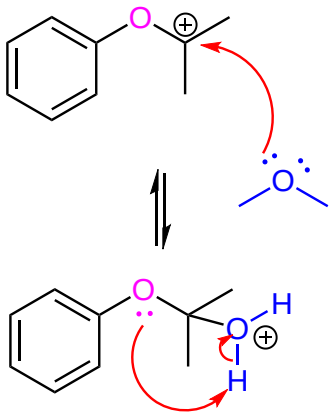
PROTONATION AND WATER LOSS

Initially cumene react with oxygen (O_2) to form cumene hydroperoxide. The -OH oxygen of the peroxide is protonated creating a good leaving group. This is following by a rearrangement where the phenyl group shifts form a carbon to an oxygen with the simultaneous loss of water.



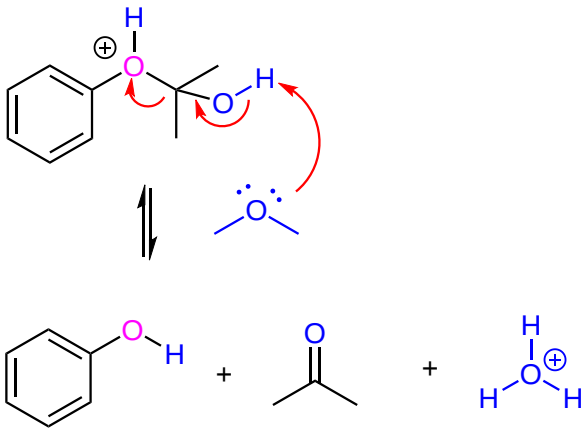
ADDITION OF WATER AND PROTON TRANSFER

The resulting carbocation intermediate is attacked by a nucleophilic water to form a protonated hemiacetal. A hemiacetal is a compound with an ether group (-OR) and a hydroxide group (-OH) bonded to the same carbon atom. A proton transfer occurs with the oxygen near the ring taking the extra hydrogen.



ELIMINATION

An E2 reaction occurs which forms the C=O bond in the product acetone, and eliminating phenol as the other product.

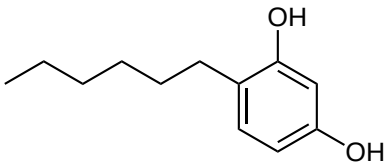


TO YOUR HEALTH: PHENOLS AND US

Phenols are widely used as antiseptics (substances that kill microorganisms on living tissue) and as disinfectants (substances intended to kill microorganisms on inanimate objects such as furniture or floors). The first widely used antiseptic was phenol. Joseph Lister used it for antiseptic surgery in 1867. Phenol is toxic to humans, however, and can cause severe burns when applied to the skin. In the bloodstream, it is a systemic poison—that is, one that is carried to and affects all parts of the body. Its severe side effects led to searches for safer antiseptics, a number of which have been found.

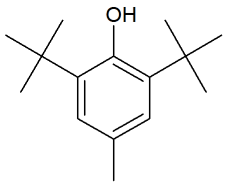
An operation in 1753, painted by Gaspare Traversi, of a surgery before antiseptics were used.

One safer phenolic antiseptic is 4-hexylresorcinol (4-hexyl-1,3-dihydroxybenzene; resorcinol is the common name for 1,3-dihydroxybenzene, and 4-hexylresorcinol has a hexyl group on the fourth carbon atom of the resorcinol ring). It is much more powerful than phenol as a germicide and has fewer undesirable side effects. Indeed, it is safe enough to be used as the active ingredient in some mouthwashes and throat lozenges.

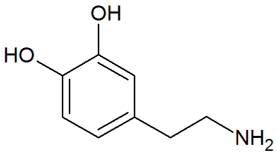


The compound 4-hexylresorcinol is mild enough to be used as the active ingredient in antiseptic preparations for use on the skin.

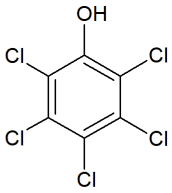
In addition to acting as an antiseptic, phenol is also a useful precursor in many chemical syntheses to produce pharmaceuticals, food preservatives, polymers, resins and adhesives. Phenolics are also present in a number of biological systems and natural products such as neurotransmitters, flavoring agents, and vitamins to name a few.



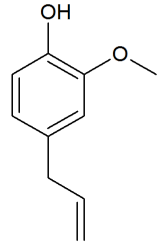
butylated hydroxytoluene
BHT (food preservative)



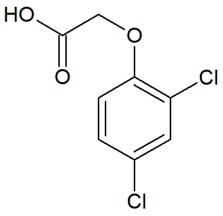
dopamine (neurotransmitter)



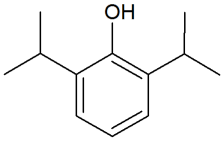
pentachlorophenol (wood preservative)



eugenal (perfume)



2,4-dichlorophenoxyacetic acid
2,4-D (herbicide)



propofol (pharmaceutical)

BISPHENOL A

In the United States, single-serve bottled water is the fastest growing beverage of choice. However, drinking tap water creates less pollution and uses less energy and natural resources than transporting and manufacturing plastic water bottles. Unlike soda and other carbonated beverages, there is no deposit on water bottles and therefore fewer are recycled by consumers. Nationally, only 10% of plastic water bottles are recycled creating large quantities of waste. Many water bottles consist of a polycarbonate plastic made with Bisphenol A (BPA).

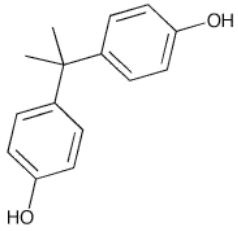


Figure 1: *Bisphenol A*

BPA was first synthesized by Thomas Zincke of the University of Marburg, Germany in 1905. Zincke did not propose uses for BPA however scientists discovered the many uses of BPA in 1953. Polycarbonate plastics became a commonly used commercial product in the 1950's.

BPA was created from a condensation reaction of phenol and acetone with hydrogen chloride, an acid catalyst, and a promoter such as methyl mercaptan. Once formed by this reaction, BPA is washed with water, neutralized with calcium hydroxide and distilled under vacuum. BPA can also be purified further by distillation and extractive crystallisation. Higher purity BPA is used to make polycarbonate plastics while the lower purity BPA is used to make Epoxy Resin. BPA's IUPAC name is 4,4'-dihydroxy-2,2,-diphenylpropane. It's chemical formula is $C_{15}H_{16}O_2$. The production of BPA produces H_2O (see image below) and therefore requires a condensation reaction for production.

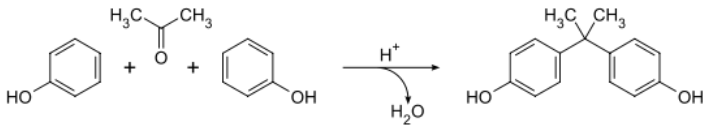


Figure 2 *The production of BPA*

A concern with the use of BPA in water bottles is the potential for leaching into the water which is then consumed. When BPA is present in the human body, it mimics the hormone estrogen and is capable of binding to estrogen receptors. In doing so, it changes the genes in the body that are expressed which triggers changes in hormone concentration, enzyme function and protein synthesis.

Using plastic water bottles that contain BPA is damaging both to the environment and human health. A greener alternative to the use of plastic water bottles is filtered tap water carried in refillable stainless steel containers.

CONTRIBUTORS AND ATTRIBUTIONS

-
-
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- Layne Morsch (University of Illinois Springfield)

17.10: REACTIONS OF PHENOLS

OBJECTIVES

After completing this section, you should be able to

1. explain why phenols and phenoxide ions are very reactive towards electrophilic aromatic substitution (see Section 16.4 of the textbook).
2. write an equation to illustrate the oxidation of a phenol or an arylamine to a quinone, and identify the reagents used to oxidize phenols.
3. write an equation to illustrate the reduction of a quinone to a hydroquinone, and identify the reagents used to reduce quinones.
4. describe, briefly, the biological importance of the redox properties of quinones.

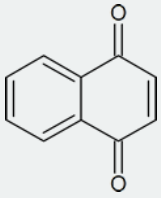
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

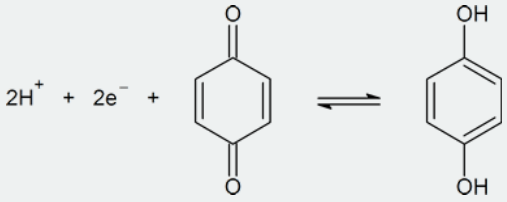
- hydroquinone
- quinone
- ubiquinone

STUDY NOTES

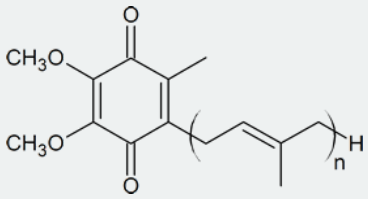
"Quinone" is a term used to describe cyclohexadiendiones in general, and *p*-benzoquinone in particular. In addition to benzene, other aromatic systems also give rise to quinones; for example, 1,4-naphthoquinone



"Hydroquinones" are produced by the reduction of quinones according to the following half-reaction:

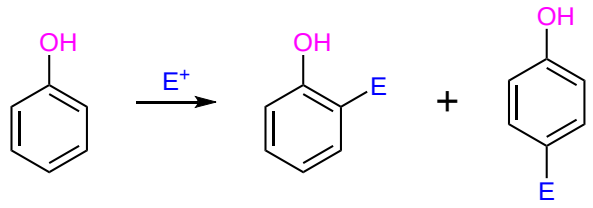


"Ubiquinones" are naturally occurring quinones whose role is to transfer a pair of electrons from one substance to another in enzyme-catalyzed reactions. Ubiquinones are also called coenzymes Q.



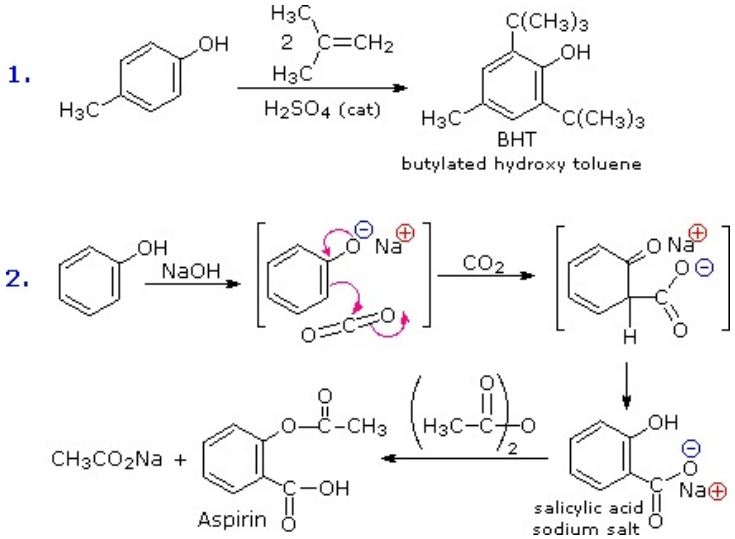
ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS

The hydroxyl subsistent of phenol is *ortho* and *para* directing and makes the aromatic ring strongly activated towards electrophilic aromatic substitution reaction (Section 16-4). In fact, phenols are strongly activating that often times electrophilic addition is difficult to limit to a single addition.



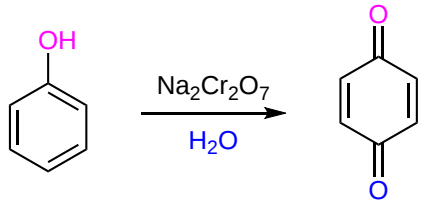
The ease with which the aromatic ring of phenols and phenol ethers undergoes electrophilic substitution is shown in the two examples in the diagram below. The first shows the Friedel-Crafts synthesis of the food preservative BHT from *para*-cresol. In this example, an electrophilic is added to both of the *ortho* positions to the alcohol of *para*-cresol.

The second example is interesting in that it further demonstrates the delocalization of charge that occurs in the phenolate anion. Carbon dioxide is a weak electrophile and normally does not react with aromatic compounds; however, the negative charge concentration on the phenolate ring enables the carboxylation reaction shown in the second step. The sodium salt of salicylic acid is the major product, and the preference for *ortho* substitution may reflect the influence of the sodium cation. This is called the **Kolbe-Schmidt reaction**, and it has served in the preparation of aspirin, as the last step illustrates.



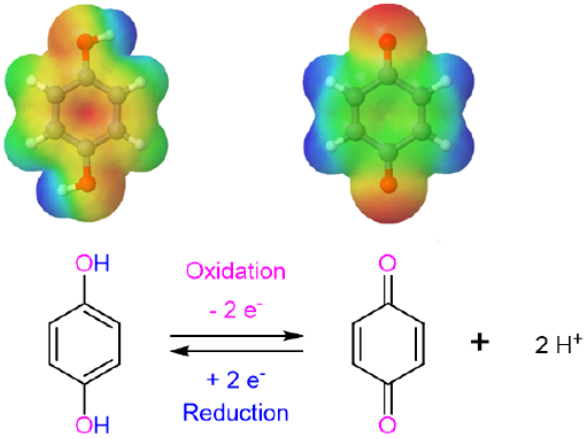
OXIDATION OF PHENOLS: QUINONES

Phenols are rather easily oxidized despite the absence of a hydrogen atom on the hydroxyl bearing carbon. Among the colored products from the oxidation of phenol by chromic acid is the dicarbonyl compound **para-benzoquinone** (also known as 1,4-benzoquinone).



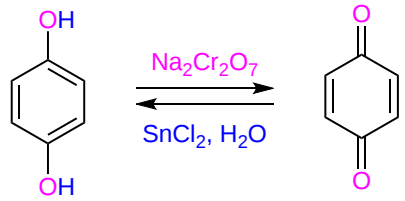
Phenol ***para*-Benzoquinone**

Quinones are an important class of compounds because of their redox equilibrium with their dihydroxybenzene analogs. The difference in electron density is seen in the electron potential map of hydroquinone and *para*-benzoquinone. The reduced compound, hyrodoquinone, has a greater electron density in the ring seen as a yellow/red color. The oxidized compound, *para*-benzoquinone, has significantly less electron density around the ring shown by the presence of green and blue colors.

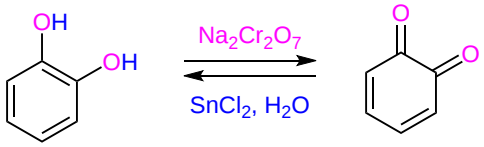


Hydroquinone (Reduced Form) **_para_-Benzoquinone (Oxidized Form)**

Dihydroxybenzenes can easily be oxidzed to the corresponding quinones by a wide variety of oxidizing agents including: sodium dichromate ($Na_2Cr_2O_7$), chromium trioxide (CrO_3), and potassium nitrosodisulfonate [$(KSO_3)_2NO$] called **Fremy's salt**. Likewise, quinone can be easily reduced back to hydroquinones using reagents such as stannous chloride ($SnCl_2$) or sodium borohydride ($NaBH_4$).



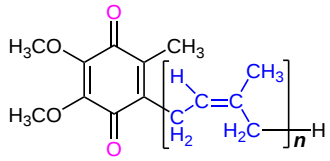
Hydroquinone (1,4-Dihydroxybenzene) **_para_-Benzoquinone**



Catechol (1,2-Dihydroxybenzene) **_ortho_-Benzoquinone**

UBIQUINONES

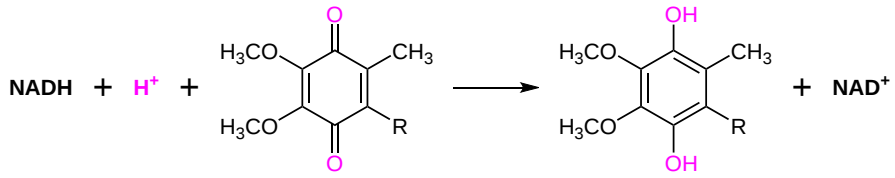
The redox abilities of quinones are utilized as biological oxidizing agents in the mitochondria of cells of aerobic organism. These quinone containing compounds called ubiquinones or coenzymes Q are a coenzyme family that is ubiquitous in all animals and bacteria which is the source of their name.



Ubiquinones (n = 1-10)

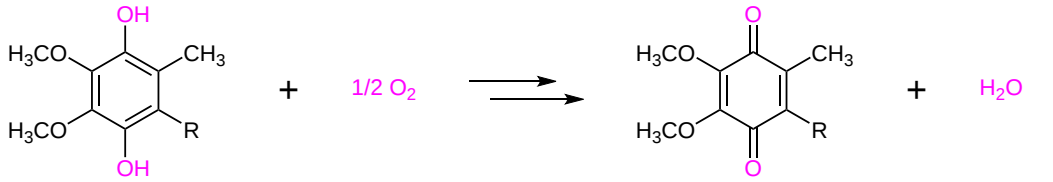
During the production of energy in cells, the redox capabilities of ubiquinones is utilized to mediate the electron-transfer process in which electrons are transferred from the biological reducing agent NADH to molecular oxygen. This process occurs in a series of steps. Initially, a ubiquinone reduced to its corresponding dihydroxy benzene in order to oxidize NADH to NAD^+. Later, the dihydroxy benzene is oxidized back to its ubiquinone form allowing for oxygen (O_2) to be reduced to water. When looking at the overall process NADH is oxidized to NAD^+ and oxygen is reduced to water. The ubiquinone only acts as an intermediate and is unchanged during this process.

STEP 1



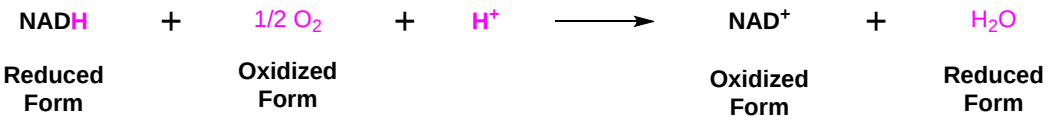
Reduced Form | Oxidized Form | Reduced Form | Oxidized Form

STEP 2



Reduced Form | Oxidized Form | Oxidized Form | Reduced Form

OVERALL PROCESS

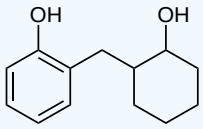


Reduced Form | Oxidized Form | Oxidized Form | Reduced Form

EXERCISES

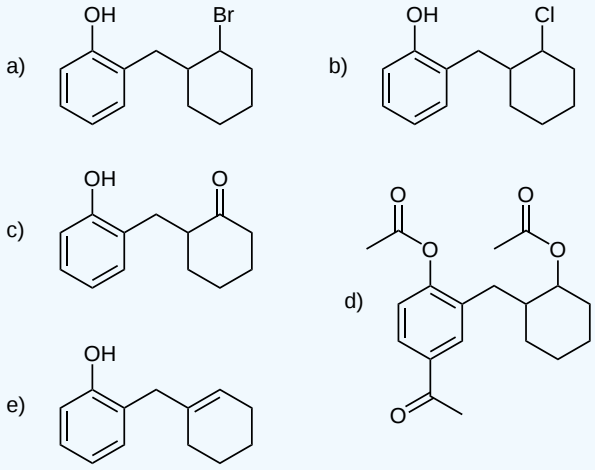
? EXERCISE 17.10.1

Predict the major product if the following reagents/reagents were used. No reaction is also a possible answer.



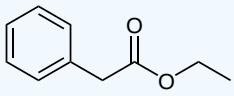
a. 1 equivalent of PBr_3
b. 1 equivalent of $SOCl_2$
c. Dess–Martin periodinane
d. 3 equivalents of acetyl chloride and $AlCl_3$ as a catalyst
e. Heat and H_2SO_4 (assume the phenol does not act as a nucleophile in this case)

Answer



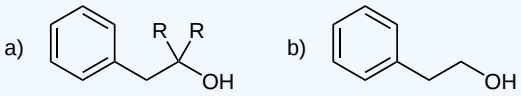
EXERCISE 17.10.2

Predict the major product if the following reagents/conditions were used. No reaction is also a possible answer.



a. 2 equivalents of RMgBr and H_3O^+ work-up
b. $LiAlH_4$ and H_3O^+ work-up
c. $NaBH_4$ and H_3O^+ work-up

Answer



CONTRIBUTORS AND ATTRIBUTIONS

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-
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- James Kabrhel (University of Wisconsin - Green Bay, Sheboygan Campus)

17.11: SPECTROSCOPY OF ALCOHOLS AND PHENOLS

OBJECTIVES

After completing this section, you should be able to

1. identify the two most prominent absorptions seen in the infrared spectra of alcohols and phenols.
2. describe the characteristic feature of the proton NMR spectra of alcohols and phenols.
    a. explain how deuterium oxide (D_2O) can be used to assist in the identification of the signal caused by the presence of the O-H proton in the ^1H NMR spectrum of an alcohol.
    b. predict the general form (i.e., number of peaks, approximate chemical shifts, and splitting pattern) of the proton NMR of a given alcohol or phenol.
3. describe the two most common initial fragmentations in the mass spectra of alcohols.
4. use spectral data (infrared, NMR, mass spectroscopy) to assist in the identification of an unknown alcohol or phenols. You may use tables of characteristic absorptions as an aid to accomplishing this objective.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- alpha cleavage
- dehydration

STUDY NOTES

The ^1H NMR chemical shifts for phenols are not particularly distinctive. However, one expects the $-OH$ signal to be in the 4–7 ppm range, while the aromatic protons (see Section 15.7) are expected to be found at 7–8 ppm.

In a mass spectrometer, alcohols fragment in two characteristic ways: alpha cleavage and dehydration. From the equation showing H-Y elimination, you can see that the dehydration of an alcohol in a mass spectrometer is essentially the same as the dehydration of an alcohol in a normal chemical reaction. “Alpha cleavage” refers to the breaking of the bond between the oxygen-bearing carbon atom and one of the neighboring carbons.

INFRARED SPECTROSCOPY

The IR spectrum of aliphatic alcohols have a distinctive O-H stretch in the range of 3300 to 3400 cm^{-1}. This peak tends to be very strong and very broad. This exact position of the peak is dependent on the amount of hydrogen bonding in the alcohol. In addition alcohol have a strong C-O stretch near 1000 cm^{-1}. In the IR spectra of 1-butanol, show below, the O-H stretch appears at 3300 cm^{-1} and the C-O stretch appears at 1073 cm^{-1}.

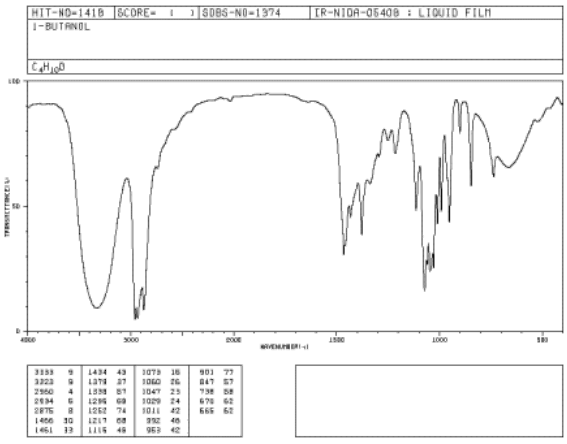
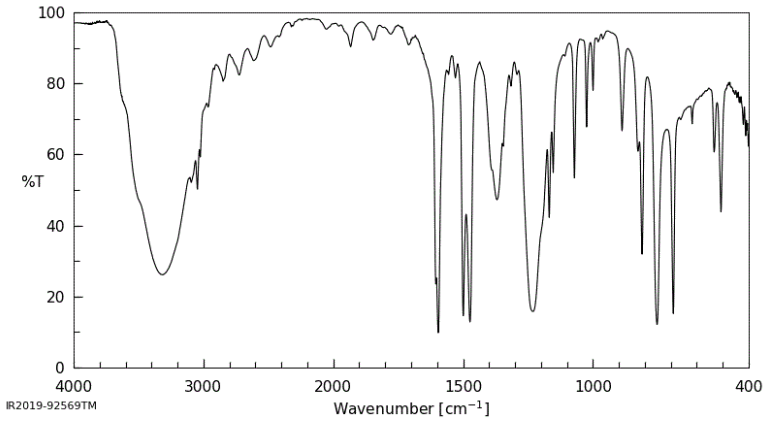


Figure IR8. IR spectrum of 1-butanol. Source: SDBSWeb : http://riodb01.ibase.aist.go.jp/sdbs/ (National Institute of Advanced Industrial Science and Technology of Japan, 14 July 2008)

Peak shapes are sometimes very useful in recognizing what kind of bond is present. The rounded shape of most O-H stretching modes occurs because of hydrogen bonding between different hydroxy groups. Because protons are shared to varying extent with neighboring

oxygens, the covalent O-H bonds in a sample of alcohol all vibrate at slightly different frequencies and show up at slightly different positions in the IR spectrum. Instead of seeing one sharp peak, you see a broad set of multiple overlapping peaks. The broadness of the O-H peak makes it very easy to distinguish in an IR spectrum.

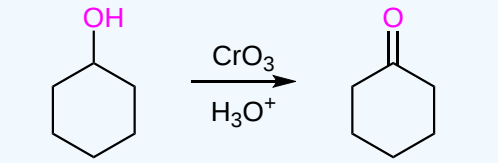
The IR spectrum of phenols the O-H stretch appears at roughly 3500 cm^{-1}. In addition, the IR spectra will show the bands typical for aromatic compounds in the region of 1500-1600 cm^{-1}.



The IR Spectrum of Phenol

? EXERCISE 17.11.1

Assume that you have just converted cyclohexanol into cyclohexanone. How would you use IR spectroscopy to tell if the conversion was successful? What changes would you expect to see between the starting material and the product?



Cyclohexanol **Cyclohexanone**

Answer

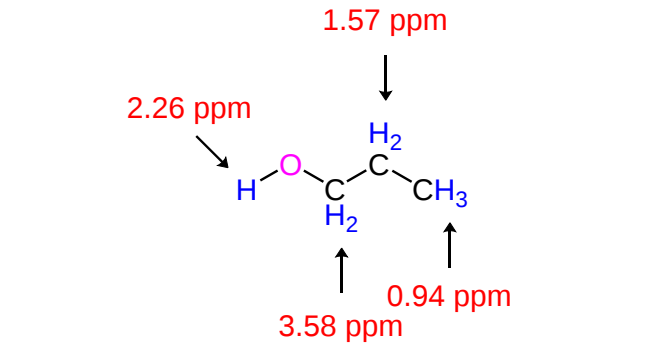
The cyclohexanol starting material would have a distinctive O-H stretch between 3300 and 3400 cm^{-1}. If the conversion were successful this peak would not be present in the product. Also, the IR spectrum of the product would have a strong C=O stretch between 1700 and 1800 cm^{-1}.

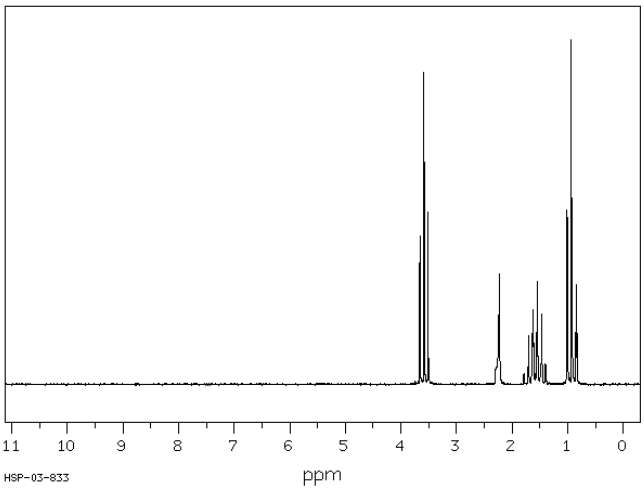
^{1}H NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

ALCOHOLS

- Protons on carbon adjacent to the alcohol oxygen show up in the region of 3.4-4.5 ppm. The electronegativity of the alcohol oxygen de-shields these protons causing them to appear downfield when compared to alkane protons.
- Protons directly attached to the alcohol oxygen often appear in the region of 2.0 to 2.5 ppm. These peaks tend to appear as short, broad singlets. The position of the -OH peak can vary depending on the conditions, such as the NMR solvent used, the concentration of the alcohol, the purity of the alcohol, temperature, and if any water is present in the sample.

Notice that the alcohol proton is not involved in spin-spin splitting. This is usually true unless the alcohol is exceptionally pure. Most samples of alcohols contain minute amounts of acidic impurities which catalyze the exchange of protons causing the splitting effects to be removed. This is why alcohol protons typically appears as a singlet in NMR spectrum. The ^{1}H NMR spectrum of propanol shows the -CH_2- attached to the alcohol as a triplet at 3.58 ppm. This shows that the signal is being split by the adjacent -CH_2- group and not the alcohol -OH. The signal for the proton attached to the oxygen appears as a singlet at 2.26 ppm. If this signal was involved in spin-spin splitting with the adjacent -CH_2- group it would appear as a triplet.

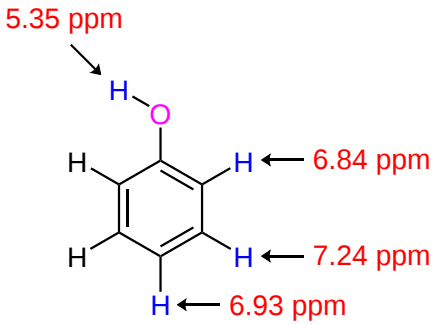


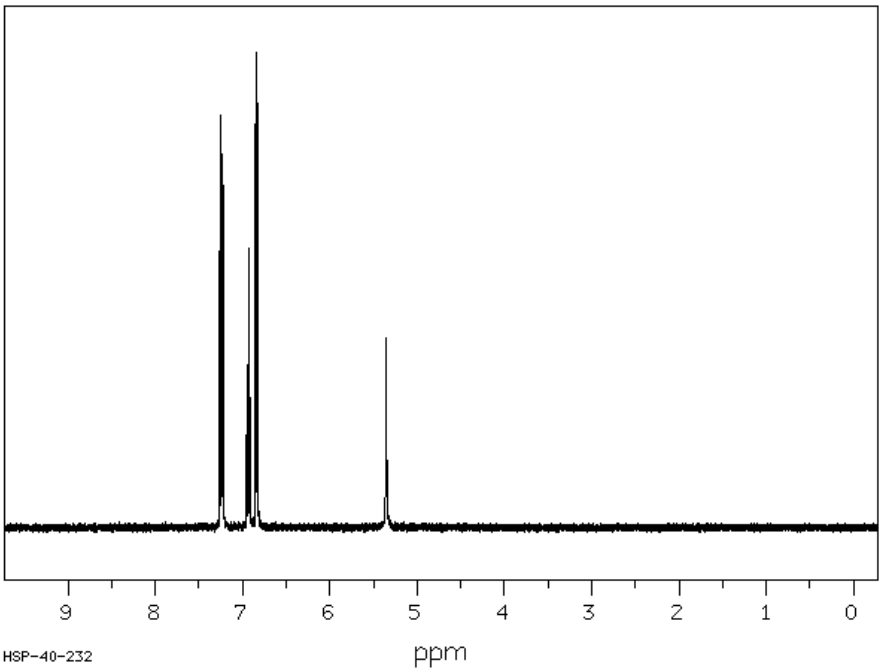


Source: SDBSWeb : http://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, 28 June 2017

PHENOL

- Protons attached to the aromatic ring in phenols show up near the aromatic region of an NMR spectrum (7-8 ppm). These peaks will have splitting typical for aromatic protons.
- The protons directly attached to the alcohol oxygen of phenols appear in the region of 3 to 8 ppm. These peaks tend to appear as short, broad singlets similarly to other alcohols.

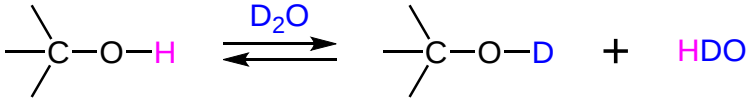




DETERMINING THE POSITION OF AN -OH PEAK IN ^{1}H NMR

The position of the -OH absorption for alcohols and phenols can be easily determined through the addition a few drops of deuterium oxide, D_2O to the NMR sample tube.

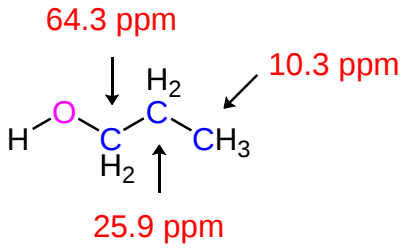
After addition, the OH proton will be rapidly exchanged for a deuterium. Because deuterium atoms do not produce peaks in a typical NMR spectrum the original -OH peak will disappear. This technique is sometimes called a **"D_2O shake"** due to the mixing required after D_2O has been added to the NMR sample tube.

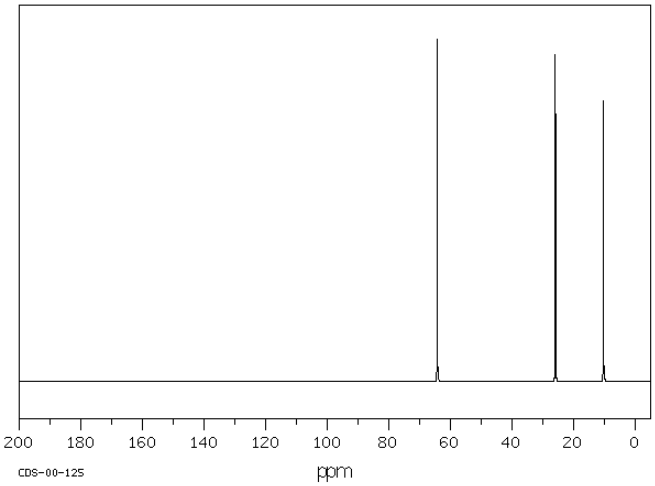


^{13}C NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

ALCOHOLS

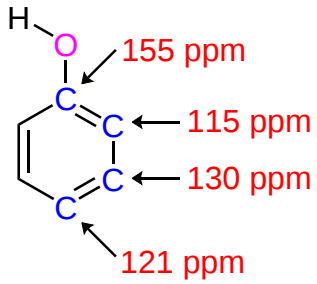
- Carbons adjacent to the alcohol oxygen show up in the distinctive region of 50-65 ppm in ^{13}C NMR spectrum.

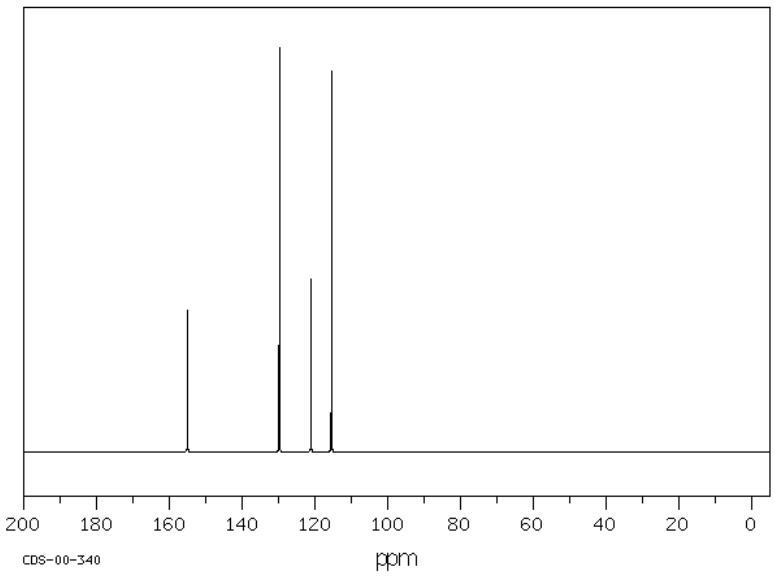




PHENOLS

- Due to the electronegative oxygen, the aromatic carbon attached to the -OH group is shifted downfield to 155 ppm.
- The other carbons in the phenol ring appear in the region typical for aromatic carbons of 125-150 ppm.





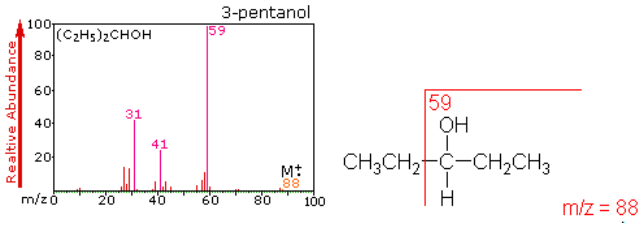
MASS SPECTRA

ALCOHOLS

An alcohol's molecular ion is small or non-existent. Alpha-cleavage of the C-C bond next to the oxygen usually occurs. A loss of H_2O may occur as in the spectra below.

3-Pentanol ($C_5H_{12}O$) with MW = 88.15

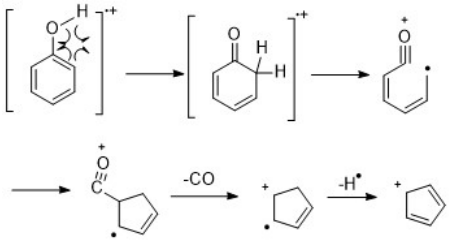
3-Pentanol shows three significant fragment ions. Alpha-fragmentation (loss of an ethyl radical) forms the m/z=59 base peak. Loss of water from this gives a m/z=41 fragment, and loss of ethene from m/z=59 gives a m/z=31 fragment.



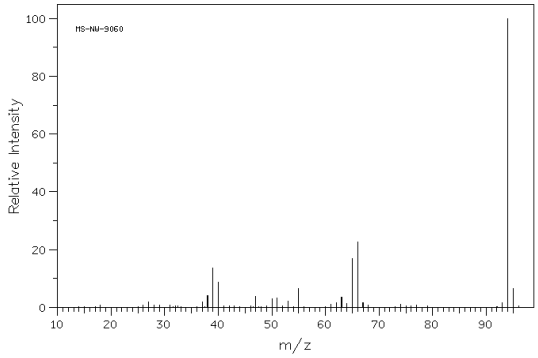
PHENOL

Phenol (C_6H_6O) with MW = 94.11

Phenol exhibit a strong molecular ion peak. The presence of an aromatic ring and an OH gives phenol a unique fragmentation pattern. In particular loss of CO (M – 28) and loss of a formyl radical (HCO·, M – 29) are common observed.

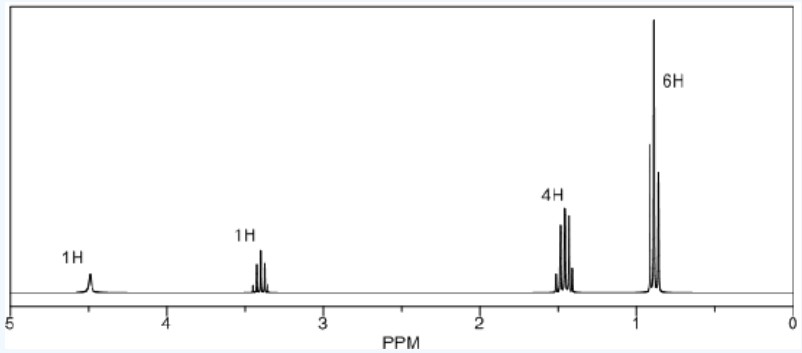


From an outside source



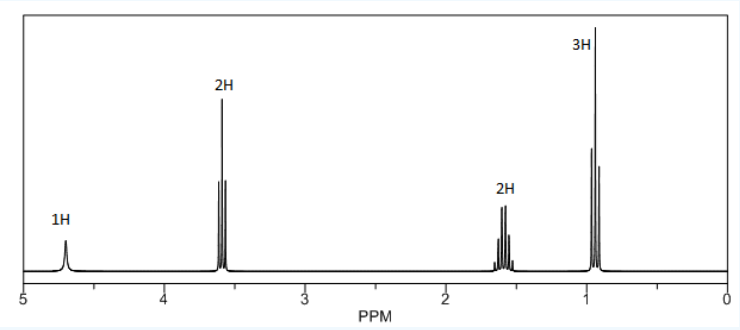
EXERCISE 17.11.1

1) From mass spectroscopy analysis it was determined that a compound has the general formula $C_5H_{12}O$. Given the following ^1H NMR spectrum, draw the structure. The integration values of each group of signals is given on the spectrum.



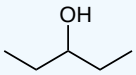
2) How would you expect the NMR spectrum show in question one to change if D_2O was added to the NMR sample tube.

3) From mass spectroscopy analysis it was determined that a compound has the general formula $C3H_8O$. Given the following ^1H NMR spectrum, draw the structure. The integration values of each group of signals is given on the spectrum.



Answer

1) 3-Pentanol



EXERCISE 17.11.2

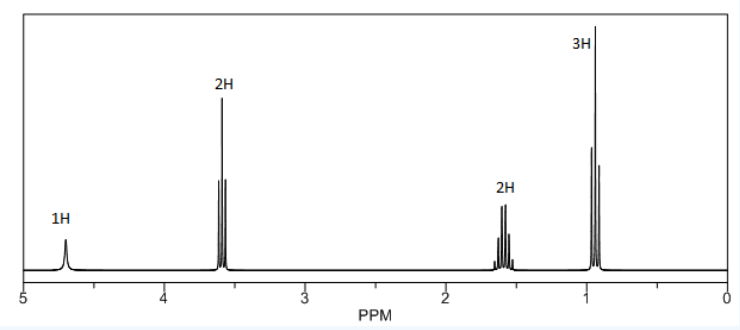
How would you expect the NMR spectrum shown in Exercise 1 to change if D_2O was added to the NMR sample tube.

Answer

The -OH peak at 4.5 ppm would dissappear due to dueterium exchange.

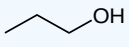
EXERCISE 17.11.3

From mass spectroscopy analysis it was determined that a compound has the general formula $C3H_8O$. Given the following ^1H NMR spectrum, draw the structure. The integration values of each group of signals is given on the spectrum.



Answer

1-Propanol



CONTRIBUTORS AND ATTRIBUTIONS

-
-
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- James Kabrhel (University of Wisconsin - Green Bay, Sheboygan Campus)

17.S: ALCOHOLS AND PHENOLS (SUMMARY)

CONCEPTS & VOCABULARY

17.0 Introduction

- Alcohols have hydroxide groups (OH) bonded to an sp^3 carbon.
- Enols have a hydroxide bonded to an sp^2 carbon that is not part of an aromatic ring, a vinyl carbon.
- Phenols have a hydroxide bonded to an sp^2 carbon that is part of an aromatic ring, an aryl carbon.

17.1 Naming Alcohols and Phenols

- Alcohols can be described as methyl, primary, secondary or tertiary, based on the number of alkyl groups attached to the carbon bonded to OH.
- Alcohols are named following IUPAC rules, by dropping the -e of an alkane and replacing with -ol.

17.2 Properties of Alcohols and Phenols

- Alcohols, enols and phenols all have significantly higher boiling points than alkanes, due to hydrogen bonding.
- Small alcohols are soluble in water.
- Alcohols are amphoteric, they act as an acid when reacting with bases and as a base when reacting with acids.
- Phenols are more acidic than alcohols due to resonance delocalization of the negative charge in the phenoxide conjugate base.
- Substituent groups on an aromatic ring that withdraw electron density increase the acidity of phenols, while substituent groups that donate electron density decrease acidity of phenols.

17.3 Preparation of Alcohols: A Review

- Alcohols can be prepared from alkyl halides by reacting with hydroxide.
- Alcohols can be prepared from alkenes by reaction with acid/water or oxymercuration to form the more substituted alcohol.
- Alcohols can be prepared from alkenes by hydroboration/oxidation to form the less substituted alcohol.
- Diols can be prepared from alkenes by first forming an epoxide, then ring opening the epoxide to form an anti-diol.
- Diols can be prepared from alkenes by reacting with osmium tetraoxide, then reducing off the osmium to form syn-diols.

17.4 Alcohols from Carbonyl Compounds: Reduction

- Organic reduction can be defined by increasing the number of bonds to hydrogen.
- Aldehydes and ketones can be reduced to alcohols with several different hydride donor reagents.
- NADH is an example of a biological reducing agent, which donates a hydride to carbonyl groups, reducing them to an alcohol.
- Carboxylic acids and esters can be reduced to alcohols with a strong reducing agent such as lithium aluminum hydride $LiAlH_4$.

17.5 Alcohols from Carbonyl Compounds: Grignard Reaction

- One of the most important organometallic groups of molecules are Grignard reagents, which are alkyl magnesium halides.
- Grignard reagents, like other organometallic compounds, include a nucleophilic alkyl group that can react with many different electrophiles.
- Grignard reagents will add to aldehydes and ketones forming alcohol products.
- Grignard reagents will add twice to ester molecules, forming alcohol products.
- Grignard reagents are strong bases, therefore the will not undergo nucleophilic addition reactions with molecules that have protons that are even slightly acidic such as: alcohols, carboxylic acids, alkynes, and amines or amides that have an N-H bond.

17.6 Reactions of Alcohols

- Alcohols can be converted into alkyl halides directly by reaction with strong hydrogen halides. This works best for 3º alcohols.
- Conversion of 1º and 2º alcohols into alkyl halides commonly use thionyl chloride ($SOCl_2$) or phosphorus tribromide (PBr_3).
- To activate an alcohol in order to make the hydroxide a good leaving group, tosylates (toluenesulfonates) and mesylates (methanesulfonates) can be formed.
- Alcohols can be dehydrated by heating in strong acid solution to form an alkene.
- Alcohols react with acid chlorides to form esters.

17.7 Oxidation of Alcohols

- Primary and secondary alcohols can be oxidized with various chromium reagents, while tertiary alcohols are not.
- Secondary alcohols are oxidized to ketones.
- Primary alcohols are oxidized to carboxylic acids using chromium trioxide or dichromate compounds.
- Primary alcohols can be stopped in their oxidation at aldehydes by reacting with pyridinium chlorochromate or Dess-Martin periodinane.

17.8 Protection of Alcohols

- Protection of a functional group is useful when that functional group may interfere with an intended reaction.
- Protection converts a functional group into a non-interfering derivative molecule through a reaction that can be easily reversed to remove the protecting group.
- Protection consists of a series of reactions that include protect, perform intended reactions, and deprotect.
- Alcohols can be protected as silyl ethers by reacting with chlorotrialkyl silanes.

17.9 Phenols and Their Uses

- Phenols can be prepared from chlorobenzene or isopropylbenzene.
- Phenol and phenol derivatives (such as resorcinol) are used as germicides and antiseptics.
- Bisphenol A (BPA) has controversially been used to create polycarbonate plastics such as water bottles.

17.10 Reactions of Phenols

- Phenols can react with strong electrophiles (such as in Friedel-Crafts reactions).
- Phenols react with strong oxidizing agents including Jones reagent or silver oxide to form quinones.

17.11 Spectroscopy of Alcohols and Phenols

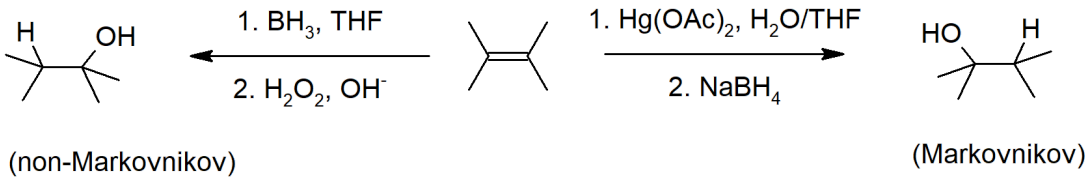
- Alcohols are among the most identifiable functional groups in infrared spectroscopy due to the strong, wide absorbance around 3400 cm^{-1}.
- Alcohol peaks are much more difficult to recognize in ^1H NMR, since OH hydrogens are relatively reactive and can exchange with hydrogens from the solvent, they are often weak absorptions without strong, sharp peaks.
- Hydroxide protons are not split in ^1H NMR.
- Loss of hydroxide in mass spectroscopy can lead to loss of a fragment with 17 m/z.

SKILLS TO MASTER

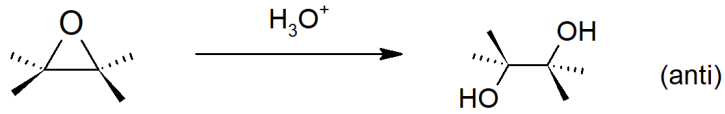
- Skill 17.1 Identify types of alcohols.
- Skill 17.2 Name molecules with hydroxide groups using IUPAC rules.
- Skill 17.3 Describe properties related to intermolecular forces (including hydrogen bonding).
- Skill 17.4 Explain acid-base properties of alcohols and phenols.
- Skill 17.5 Describe how additional functional groups affect the acidity of phenols.
- Skill 17.6 Draw mechanisms to form alcohols from alkyl halides.
- Skill 17.7 Draw mechanisms to form alcohols from alkenes.
- Skill 17.8 Draw mechanisms to form alcohols by reduction reactions.
- Skill 17.9 Draw mechanisms to form alcohols by reaction of carbonyl compounds with Grignard reagents (and other organometallics).
- Skill 17.10 Draw mechanisms for conversion of alcohols to alkyl halides.
- Skill 17.11 Draw mechanisms for conversion of alcohols to tosylates.
- Skill 17.12 Draw mechanisms for dehydration of alcohols to alkenes.
- Skill 17.13 Draw mechanisms for conversion of alcohols to esters.
- Skill 17.14 Draw mechanisms for oxidation of alcohols to aldehydes, ketones, and carboxylic acids.
- Skill 17.15 Write out syntheses that incorporate protection and deprotection of alcohols.
- Skill 17.16 Identify presence of alcohols by IR, NMR and MS.

SUMMARY OF REACTIONS

Alcohol Preparation (Hydrolysis)



(non-Markovnikov) (Markovnikov)



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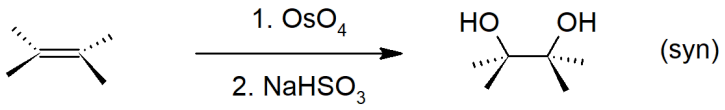

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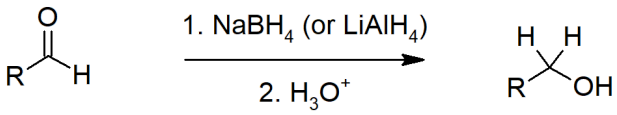
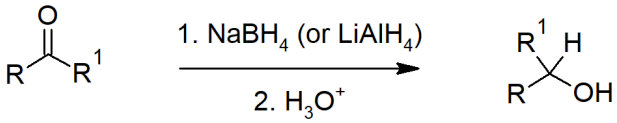
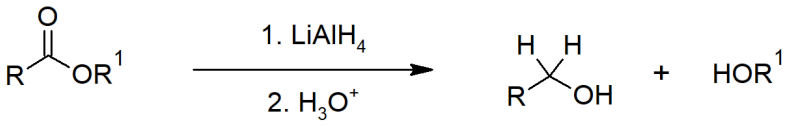
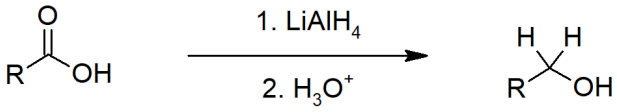
Alcohol Preparation (Reducing the Carbonyl)

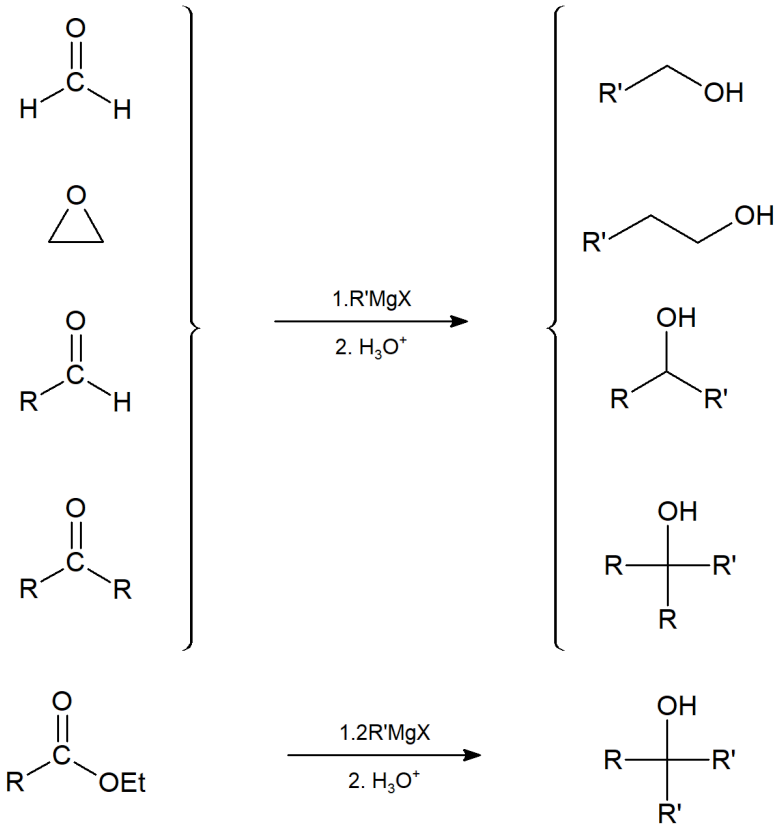




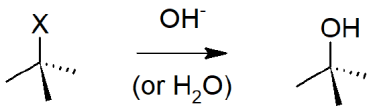




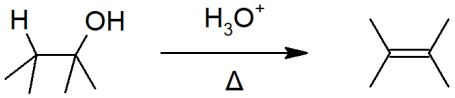
Alcohol Preparation (Grignard Additions)

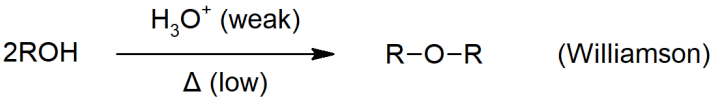


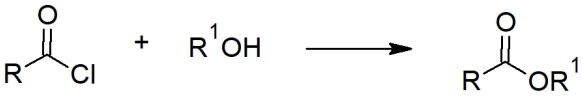
Alcohol Preparation (from Organohalide)

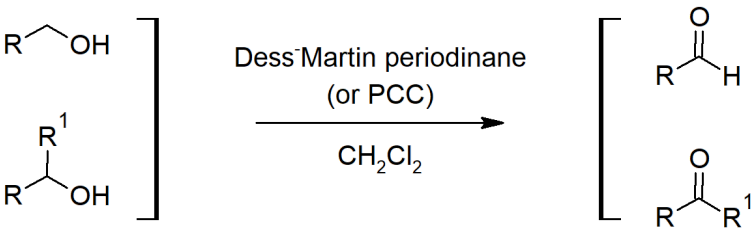


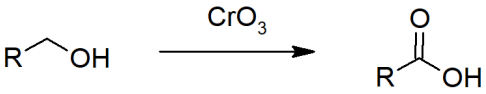
Alcohol Reactions



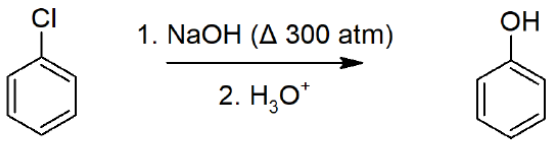


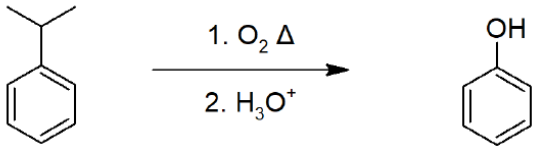






Phenol Preparation





CONTRIBUTORS AND ATTRIBUTIONS

- Layne Morsch (University of Illinois Springfield)
-

CHAPTER OVERVIEW

18: ETHERS AND EPOXIDES; THIOLS AND SULFIDES

We shall begin in a very traditional manner, with a discussion of the nomenclature of ethers. We will then describe how ethers may be prepared in the laboratory, and discuss the relative inertness of these compounds. A discussion of the chemistry of cyclic ethers follows, with particular emphasis on the preparation and reactions of epoxides (cyclic ethers containing a three-membered ring). We will then introduce crown ethers—compounds that consist of large rings containing several oxygen atoms and the spectroscopic properties of ethers. The unit will close with a description of the chemistry of thiols and sulfides, the sulfur-containing analogues of alcohols and ethers.

LEARNING OBJECTIVES

- fulfill all of the detailed objectives listed under each individual section.
- design a multi-step synthesis using one or more of the reactions introduced in this chapter, along with any number of the reactions you have studied to date.
- solve “road-map” problems that may require a knowledge of the chemistry of ethers, epoxides, thiols and sulfides, in addition to any of the material you have studied up to this point in organic chemistry.
- define, and use in context, the key terms introduced in this chapter.

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18.0: INTRODUCTION

OBJECTIVES

After completing this section, you should be able to use the terms “ether,” “diethyl ether ” and “ethyl ether ” appropriately in context.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

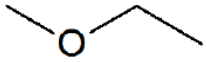
- ether ($R-O-R'$)
- sulfide ($R-S-R'$)
- thiol ($R-S-H$)

STUDY NOTES

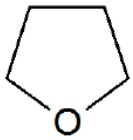
As defined in the textbook, an “ether” is a substance with the general formula ($R-O-R'$) where R and R' are alkyl, aryl, vinyl or allyl groups. However, the word “ether” is also commonly used to refer to the specific compound, $CH_3-CH_2-O-CH_2-CH_3$, which is correctly called “diethyl ether.” Further confusion can arise because some chemists refer to “diethyl ether ” as “ethyl ether.” In this course, “ether ” will be used to refer to the class of compounds with the structure ($R-O-R'$); diethyl ether will refer to the compound, $CH_3-CH_2-O-CH_2-CH_3$; and “ethyl ether ” will not be used.

ETHERS AND EPOXIDES

While the general formula for ethers is R-O-R′, keep in mind that there also cyclic ethers like tetrahydrofuran (a common organic solvent) or even epoxides which you first encounter in Section 8.7 in synthesizing diols from alkenes.



ethyl methyl ether

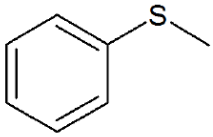


tetrahydrofuran

THIOLS AND SULFIDES

Thiols (thio alcohols or mercaptans) and sulfides (thioethers) are the sulfur analogues of alcohols and ethers and have the general formulas of R-S-H and R-S-R′, respectively.

ethanethiol



methyl phenyl sulfide

CONTRIBUTORS AND ATTRIBUTIONS

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18.1: NAMES AND PROPERTIES OF ETHERS

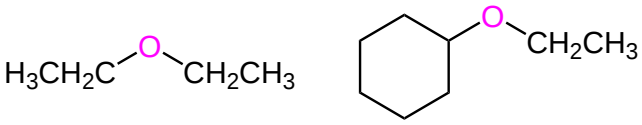
OBJECTIVES

After completing this section, you should be able to

1. write two acceptable names for a simple dialkyl ether, given its Kekulé, shorthand or condensed structure.
2. name a complicated ether by the IUPAC system, given its Kekulé, shorthand or condensed structure.
3. draw the Kekulé, condensed or shorthand structure of an ether, given an acceptable name.
4. explain why the boiling point of an ether is generally higher than that of an alkane of similar molecular mass.

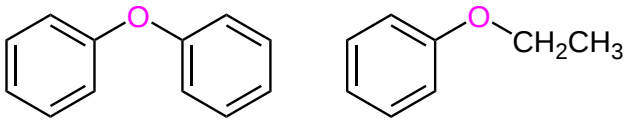
STRUCTURE OF ETHERS

Ethers are a class of organic compounds that contain an sp^3 hybridized oxygen between two alkyl groups and have the formula R-O-R'. These compounds are used in dyes, perfumes, oils, waxes and other industrial uses. Aliphatic ethers have no aryl groups directly attached to the ether oxygen.



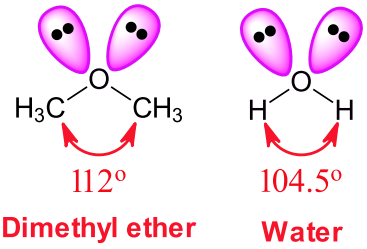
Examples of Aliphatic Ethers

Aromatic ethers have at least one aryl ring directly attached to the ether oxygen. In aryl ethers, the lone pair electrons on oxygen are conjugated with the aromatic ring which significantly changes the properties of the ether.

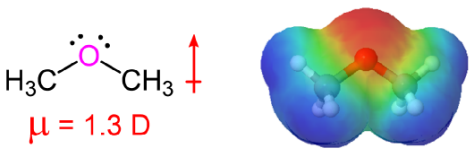


Example of Aromatic Ethers

The sp^3 hybridization of oxygen gives ethers roughly the same geometry as alcohols and water. The R-O-R' bond angle is close to what is expected in a tetrahedral geometry. The bond angle of dimethyl ether is 112º which is larger than the H-O-H bond angle in water (104.5º) due to the steric repulsion of the methyl groups.



The presence of an electronegative oxygen atom gives ethers a small dipole moment with the electron density primarily on oxygen (red and orange in the electrostatic potential map).



COMPARISONS OF PHYSICAL PROPERTIES OF ALCOHOLS AND ETHERS

Ethers, unlike alcohols, have no hydrogen atom on the oxygen atom (that is, no OH group). Therefore, there is no intermolecular hydrogen bonding between ether molecules, which makes their boiling points much lower than an alcohol with similar mass. Despite the presence of a small dipole moment, ethers have boiling points that are about the same as alkanes of comparable molar mass. (Table 18.1.1).

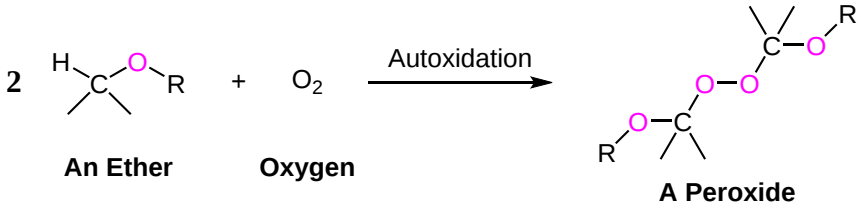
Table 18.1.1 : Comparison of Boiling Points of Alkanes, Alcohols, and Ethers

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

Ether molecules do have an oxygen atom, however, and engage in hydrogen bonding with water molecules. Consequently, an ether has about the same solubility in water as the alcohol that is isomeric with it. For example, dimethyl ether and ethanol (both having the molecular formula C_2H_6O) are completely soluble in water, whereas diethyl ether and 1-butanol (both $C_4H_{10}O$) are barely soluble in water (8 g/100 mL of water).

PEROXIDE FORMATION

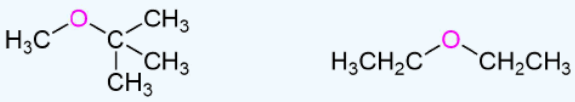
Many ethers can react with oxygen to form explosive peroxide compounds n a free radical process called autoxidation. For this reason ethers should not be stored for long periods of time and should not be stored in glass bottles. The danger is particularly acute when ether solutions are distilled to near dryness. The hydroperoxides can become more concentrated during a distillation because they tend to have a slightly higher boiling point than the corresponding ether. Before performing an ether distillation great care should be taken to test for the presence of peroxides.



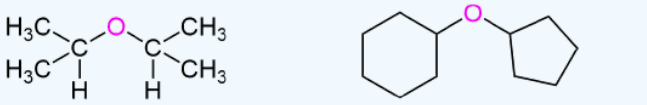
NAMING ETHERS

When no other functional group is present, simple ethers are often given common functional class names. Both alkyl groups attached to the oxygen atom are named as substituents (in alphabetical order) and then the word *ether* is added. The common names for alkyl substituents discussed in **Section 3.3** are often used.

EXAMPLE 18.1.1



Methyl *tert*-butyl ether — Diethyl ether



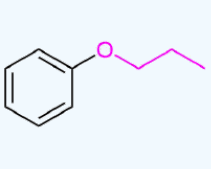
Diisopropyl ether — Cyclohexyl cyclopentyl ether

IUPAC nomenclature for ethers should be used for complicated ethers, compounds with more than one ether linkage, and compounds where other functional groups are present with an ether. In these cases, an RO group of the ether is named as an alkoxy substituent. Common alkoxy substituents are given names derived from their alkyl component. The suffix *-yl* is replaced with *-oxy*. (Table 18.1.2):

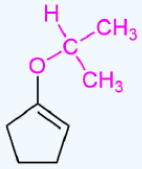
Table 18.1.2 : Common Alkyl and Alkoxy Groups

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

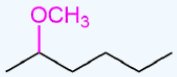
EXAMPLE 18.1.2



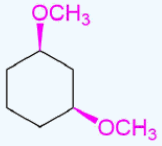
Propoxybenzene



1-Isopropoxycyclopentene



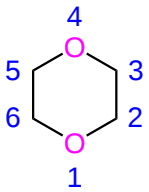
2-Methoxyhexane



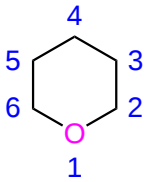
Cis-1,3-Dimethoxycyclohexane

CYCLIC ETHERS

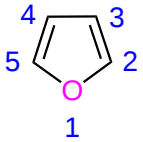
Cyclic ethers are a type of heterocycle with one or more oxygens located in the ring. Many cyclic ethers have common names and are often used as solvents due to their inert nature. These ring structures are also found in many biological molecules such as sugars and DNA. The rings are numbered so that an oxygen gets position 1.



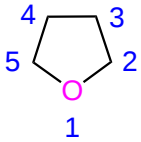
Dioxane



Tetrahydropyran

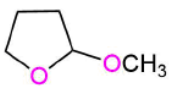


Furan

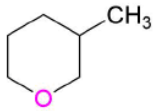


Tetrahydrofuran

EXAMPLE 18.1.3



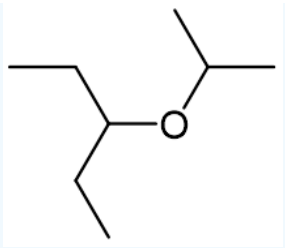
2-Methoxytetrahydrofuran



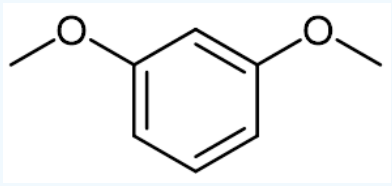
3-Methyltetrahydropyran

EXERCISE 18.1.1

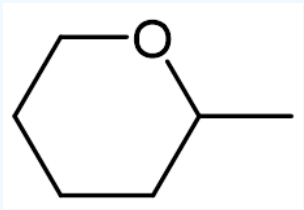
Name the following ethers:



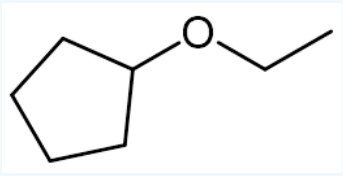
b)



c)



d)



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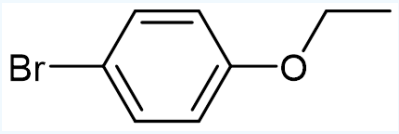
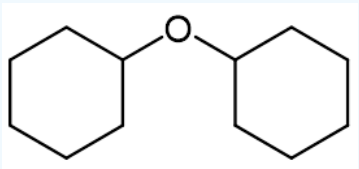
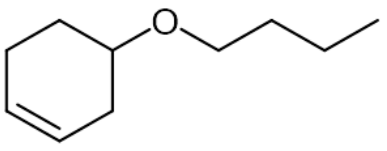


f)



g)



Answers

a) 3-Isopropoxypentane

b) 1,3-Dimethoxybenzene

c) 2-Methyltetrahydropyran

d) Cyclopentyl ethyl ether

e) 4-Bromo-1-ethoxybenzene

f) Dicyclohexyl ether

g) 4-Butoxycyclohexene

18.2: PREPARING ETHERS

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate the industrial preparation of simple symmetrical ethers.
2. write an equation to illustrate the Williamson synthesis of ethers.
   a. identify the ether obtained from the reaction of a given alkyl halide with a given alkoxide ion.
   b. identify the reagents needed to prepare a given ether through a Williamson synthesis.
   c. identify the limitations of the Williamson synthesis, and make the appropriate choices when deciding how best to synthesize a given ether.
   d. write an equation to describe the formation of an alkoxide from an alcohol.
   e. identify silver(I) oxide as a reagent which can be used in a Williamson synthesis.
3. write an equation to show how an ether can be prepared by the alkoxymercuration-demercuration of an alkene.
   a. identify the product formed from the alkoxymercuration-demercuration of a given alkene.
   b. identify the alkene, the reagents, or both, needed to prepare a given ether by the alkoxymercuration-demercuration process.
   c. write the detailed mechanism of the reaction between an alkene, an alcohol and mercury(II) trifluoroacetate.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- alkoxymercuration
- oxymercuration
- Williamson ether synthesis

STUDY NOTES

We studied oxymercuration as a method of converting an alkene to an alcohol in Section 8.5. “Alkoxymercuration” is a very similar process, except that we are now converting an alkene into an ether. The two processes are compared below.

Description	oxymercuration	alkoxymercuration
we react an	alkene	alkene
with	water	an alcohol
in the presence of	$Hg(O_2CCH_3)_2$	$Hg(O_2CCF_3)_2$
followed by treatment with	$NaBH_4$	$NaBH_4$
to produce an	alcohol	ether

Review the mechanism of the oxymercuration reaction in Section 8.5, paying particular attention to the regiochemistry and the stereochemistry of the reaction. The mechanism is identical to alkoxymercuration.

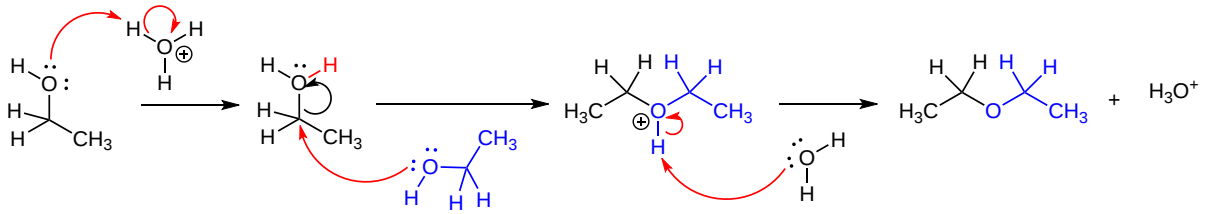
ETHER FORMATION THOUGH DEHYDRATION

Acid-catalyzed dehydration of small 1º-alcohols constitutes a specialized industrial method of preparing symmetrical ethers. This reaction **cannot** be employed to prepare unsymmetrical ethers because a mixture of products is likely to be obtained. Also, 2º and 3º alcohols cannot be used for this reaction because they dehydrate to form alkenes by an E1 mechanism (**Section 17-6**).

$$2\,CH_3CH_2-OH + H_2SO_4 \xrightarrow{130\ ^oC} CH_3CH_2-O-CH_2CH_3 + H_2O \tag{18.2.1}$$

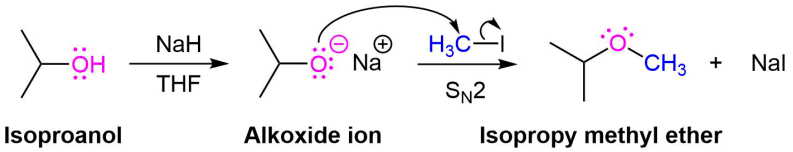
MECHANISM

In the first step of the reaction mechanism, one alcohol is protonated to become a good leaving group. In the second step, a second alcohol displaces water from the protonated alcohol during an S_N2 reaction yielding a protonated ether. In the final step, this intermediate is deprotonated to yield the symmetrical ether.



WILLIAMSON ETHER SYNTHESIS

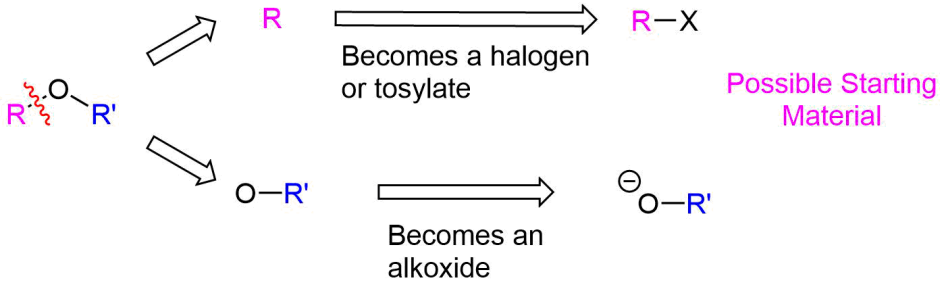
One important procedure, known as the **Williamson Ether Synthesis**, proceeds by an S_N2 reaction of an alkoxide nucleophile with a primary alkyl halide or tosylate. As previously discussed in **Section 17-2**, alkoxides are commonly created by deprotonating an alcohol with a strong base, such as sodium hydride (NaH). Simple alcohols can be used a solvent during a Williamson ether synthesis and with their alkoxide created through the addition of sodium metal ($Na_{(s)}$).



PLANNING A WILLIAMSON ETHER SYNTHESIS

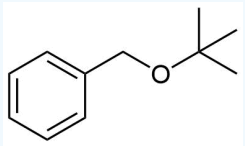
The Williamson ether synthesis has the same limitations as other S_N2 reactions, as discussed in **Section 11-3**. Since alkoxide anions are strong bases, utilizing 2º or 3º halogen leaving groups could possibly produce an E2 elimination product. When considering the synthesis of an unsymmetrical ether, there are two different combinations of reactants possible and each should be carefully considered. In general, the pathway which utilizes the least sterically hindered halogen will be preferred.

The key bond cleavage in the target molecule involves a C-O bond. Because unsymmetrical ethers have two unique C-O bonds, each can be broken to provide a unique set of reactants. After cleavage, the fragment with the oxygen will become an alkoxide. The other fragment will become a halogen or tosylate.



? WORKED EXAMPLE 18.2.1

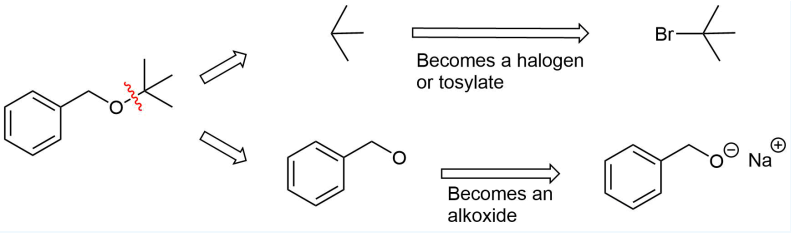
How would you prepare the following molecule using a Williamson Ether Synthesis?



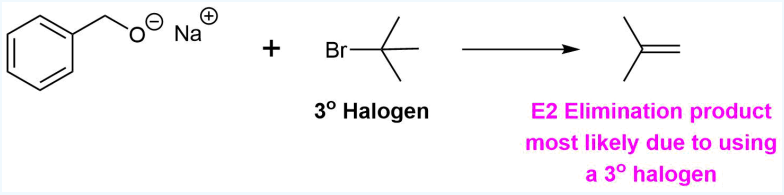
Answer

Analysis: The ether is asymmetrical so each of the C-O bonds can be broken to create a different set of possible reactants. After cleavage of the C-O bond, pathway 1 shows a 3º halogen as the starting material. This reaction will most likely not be effective due to alkoxides reacting with 3º halogens to preferable form an alkenes by E2 elimination. Pathway 2 shows a 1º halogen as a starting material which is favorable for S_N2 reactions.

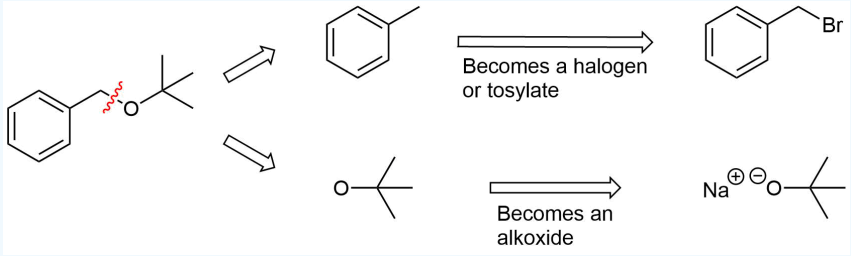
Pathway 1



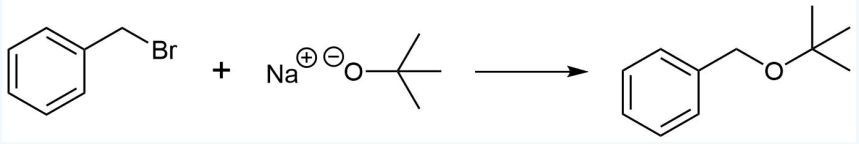
Solution 1



Pathway 2

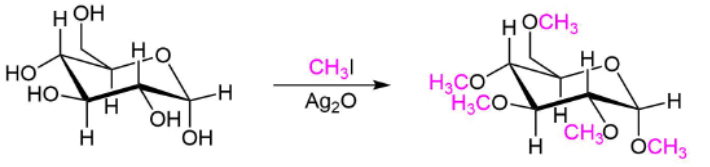


Solution 2



ETHER SYNTHESIS USING SILVER OXIDE

A variation of the Williamson ether synthesis uses silver oxide (Ag_2O) in the place of the strong base. The conditions of this variation are milder than the typical Willamson synthesis because a strong base and the formation of an alkoxide intermediate are not necessary. This reaction is particually useful when converting the -OH groups on a sugar into ethers.

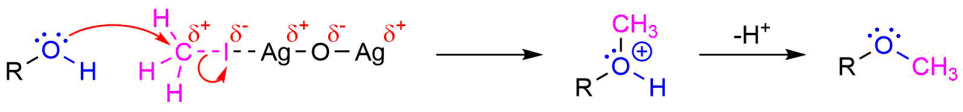


α-D-Glucopyranose

Methyl 2,3,4,6-tetra-*O*-methyl-α-D-Glucopyranoside

MECHANISM

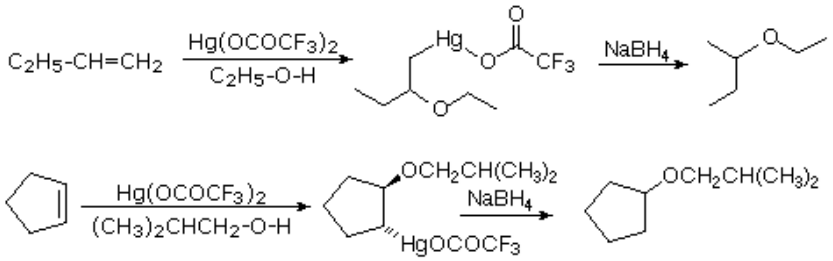
During this reaction a partial positively charged silver in Ag_2O gives draws electron density from the iodine in CH_3I. This correspondingly removes electron density from the adjacent carbon increasing its partial positive charge which increases its electrophlicity. This allows the alcohol to act as a nucleophile in the subsequent S_N2 reaction.



Alcohol **Polarized C-I Bond** **Ether**

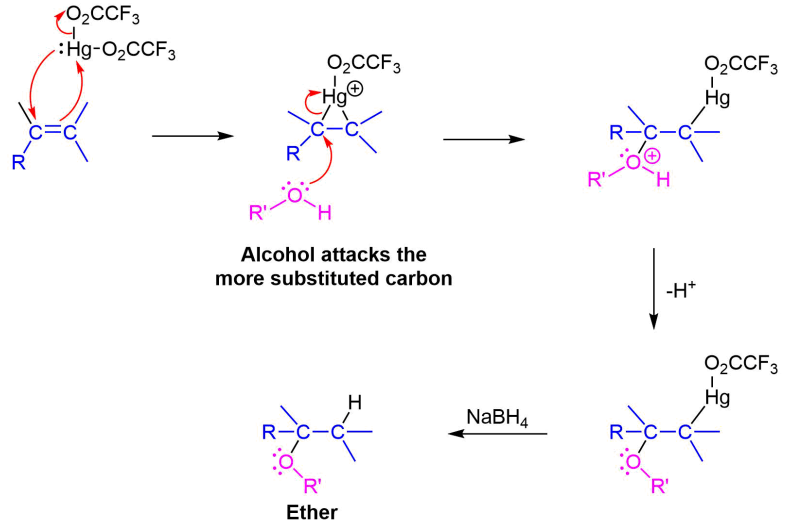
ETHER SYNTHESIS USING ALKOXYMERCURATION

Alkoxymercuration, is patterned after the oxymercuration reaction discussed in Section 8-4. Reaction of an alkene with an alcohol in the presence of a trifluoroacetate mercury (II) salt [$(CF_3CO_2)_2Hg$] prodcues an alkoxymercuration product. Demercuration using sodium borohydride ($NaBH_4$) yields an ether product. Overall, this reaction allows for the Markovnikov addition of an alcohol to an alkene to create an ether. Note that the alcohol reactant is used as the solvent, and a trifluoroacetate mercury (II) salt is used in preference to the mercuric acetate (trifluoroacetate anion is a poorer nucleophile than acetate). Most 1^o, 2^o, 3^o alcohols can be successfully used for this reaction.



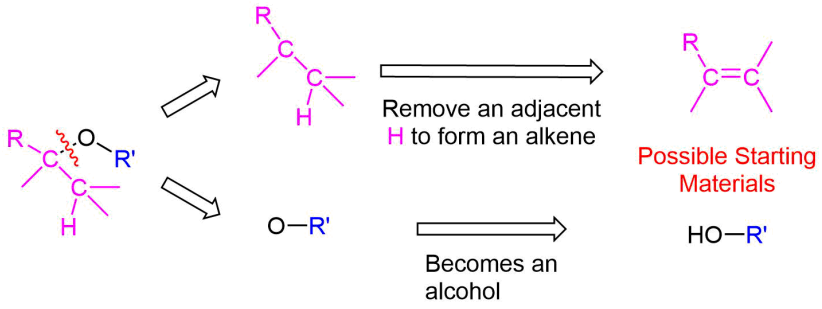
MECHANISM

The mechanism of alkoxymercuration is similar to that of oxymercuration, with electrophillic addition of the mercuric species to the alkene. The alcohol nucleophile attacks the more substituted carbon of the three-membered ring via a S_N2 reaction. Finally, sodium borohydride ($NaBH_4$) provides a reductive demercuration to form the ether product.



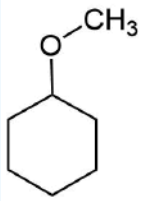
PLANNING THE SYNTHESIS OF AN ETHER USING ALKOXYMERCURATION

The key bond cleavage in the target molecule involves a C-O bond. Because unsymmetrical ethers have two unique C-O bonds, each can be broken to provide a unique set of reactants. After cleavage, the fragment with the oxygen will become an alcohol. The alkyl fragment will lose a hydrogen from a adjacent carbon to form an alkene. The main point to consider when choosing a possible synthesis pathways is the ability of the alkyl fragment to form an alkene.



WORKED EXAMPLE 18.2.2

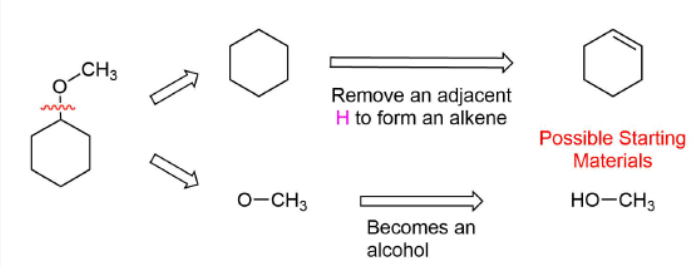
How would you prepare the following molecule using a alkoxymercuration?



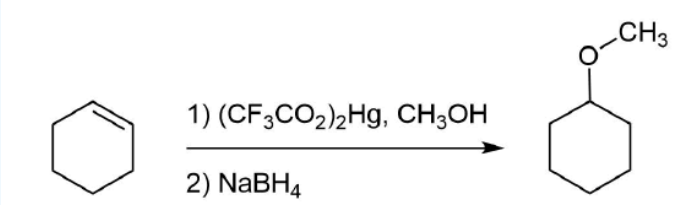
Answer

Analysis: The ether is symmetrical so each C-O bond of the ether can be cleaved to produce a set of starting materials for consideration. Pathway one shows a set of starting material which should work well for this reaction. The alcohol, methanol, can easily be used as a solvent. Although the alkene does not have a defined more and less substituted side, its symmetry will prevent a mixture of product from forming. The fragmentation for pathway 2 shows starting material which are not viable for this reaction. The alkyl fragment only has one carbon which cannot be used to form an alkene starting material. This means pathway 2 is not a viable method for the synthesis of the target molecule.

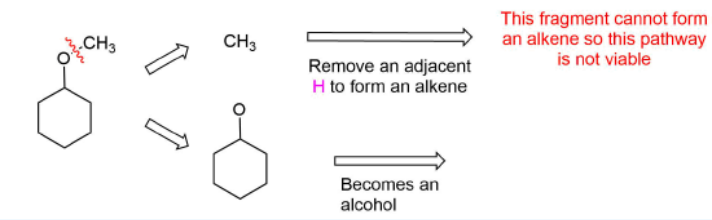
Pathway 1



Solution 1



Pathway 2



EXERCISE 18.2.1

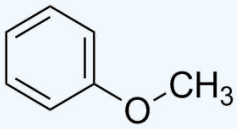
When preparing ethers using the Williamson ether synthesis, what factors are important when considering the nucleophile and the electrophile?

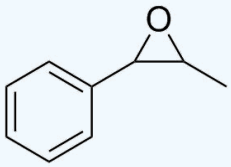
Answer

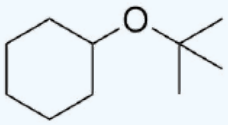
The nucleophile ideally should be very basic, yet not sterically hindered. This will minimize any elimination reactions from occurring. The electrophile should have the characteristics of a good S_N2 electrophile, preferably primary to minimize any elimination reactions from occurring.

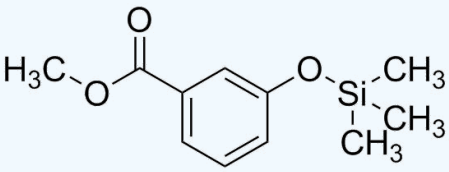
EXERCISE 18.2.2

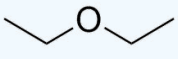
How would you synthesize the following ethers? Keep in mind there are multiple ways. The Williamson ether synthesis, alkoxymercuration of alkenes, and also the acid catalyzed substitution.

(a) 

(b) 

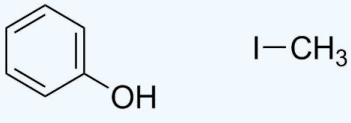
(c) 

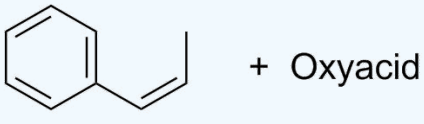
(d) 

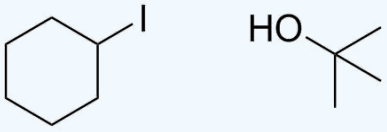
(e) 

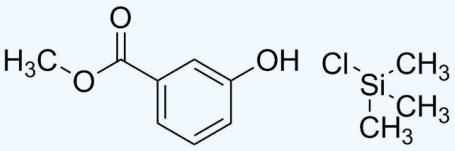
Answer

The Williamson ether syntheses require added catalytic base. Also, most of the halides can be interchanged, say for example for a -Br or a -Cl. Although, typically -I is the best leaving group.

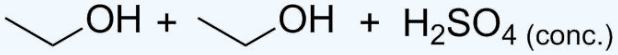
(a) 

(b) 

(c) 

(d) 

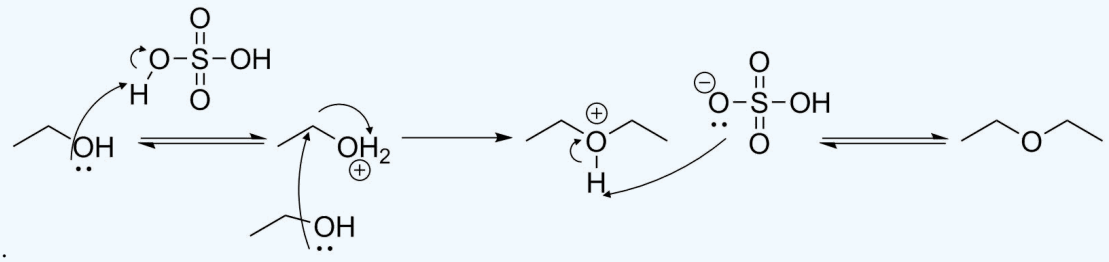
Note, there is only one ether (also called a silyl ether, and often used as an alcohol protecting group.) The other group is an ester.

(e) 

EXERCISE 18.2.3

Draw the electron arrow pushing mechanism for the formation of diethyl ether in the previous problem.

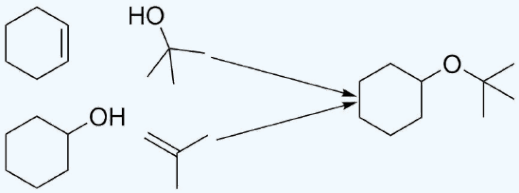
Answer



EXERCISE 18.2.4

t-butoxycyclohexane can be prepared two different ways from an alkene and an alcohol, draw both possible reactions.

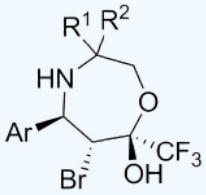
Answer



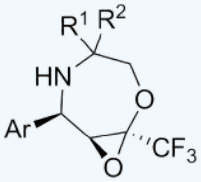
While both are possible, the top route is likely easier because both starting materials are a liquid.

EXERCISE 18.2.5

Epoxides are often formed intramolecularly. Take for example this large ring, in a publication from 2016 [*J. Org. Chem.*, **2016**, *81 (20)*, pp 10029–10034]. If subjected to base, what epoxide would be formed? (Include stereochemistry)



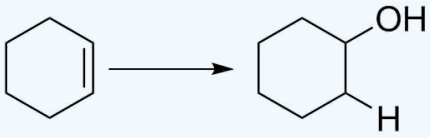
Answer



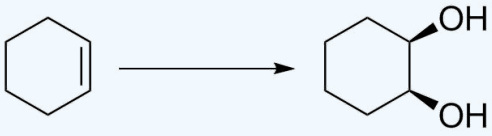
EXERCISE 18.2.6

What reagents would you use to perform the following transformations?

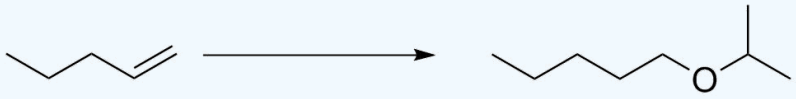
(a)



(b)

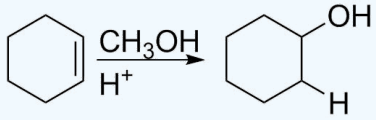


(c)

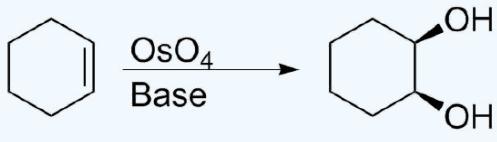


Answer

(a)

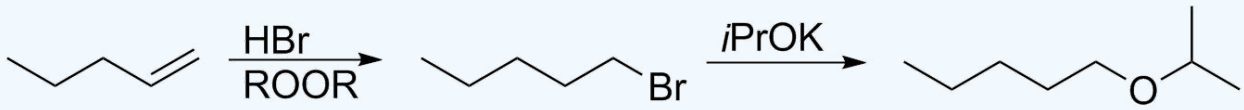


(b)



Note the cis addition

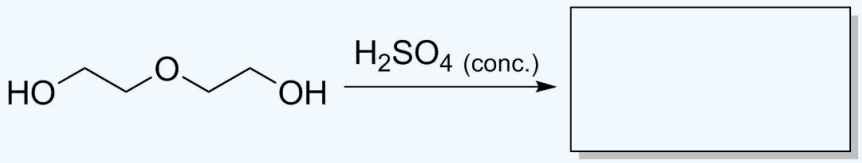
(c)



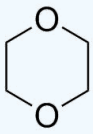
An oxidation to an alcohol through hydroboration, and subsequent substitution with 2-bromopropane could also work, but this route provides the least likelihood of an elimination reaction occurring.

? EXERCISE 18.2.7

Predict the product of the following.



Answer



The result is the production of dioxane, a common solvent.

18.3: REACTIONS OF ETHERS - ACIDIC CLEAVAGE

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate the acidic cleavage of an ether.
2. identify the products formed when a given ether is cleaved by a strong acid.
3. identify the reagent needed to bring about cleavage of a given ether.
4. deduce the structure of an unknown ether, given the products of acidic cleavage of the ether.
5. write the detailed mechanism for the acidic cleavage of a given ether.

STUDY NOTES

There are a number of points in this section that require additional explanations.

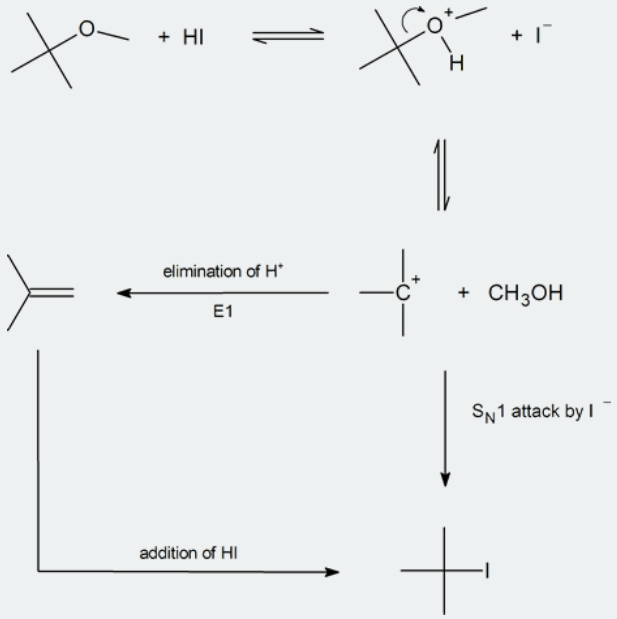
First, if an excess of HI (or HBr) is used in the cleavage reaction, the alcohol formed is converted by a nucleophilic substitution reaction to the appropriate alkyl halide:

$$ROH + HI \rightarrow RI + H_2O$$

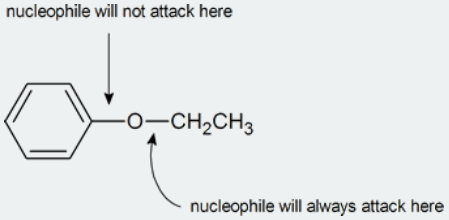
In view of this substitution, some textbooks simplify the overall cleavage process as:

$$R{-}O{-}R' + 2\,HI \rightarrow RI + R'I + H_2O$$

Second, we should consider in detail how certain ethers (those containing tertiary alkyl, benzyl or allyl groups) cleave by an S_N1 mechanism:



Finally, notice that an aryl alkyl ether will always produce a phenol and an alkyl halide, never an aryl halide and an alcohol. This is because we rarely see a nucleophile attacking an aromatic ring carbon in preference to an aliphatic carbon:

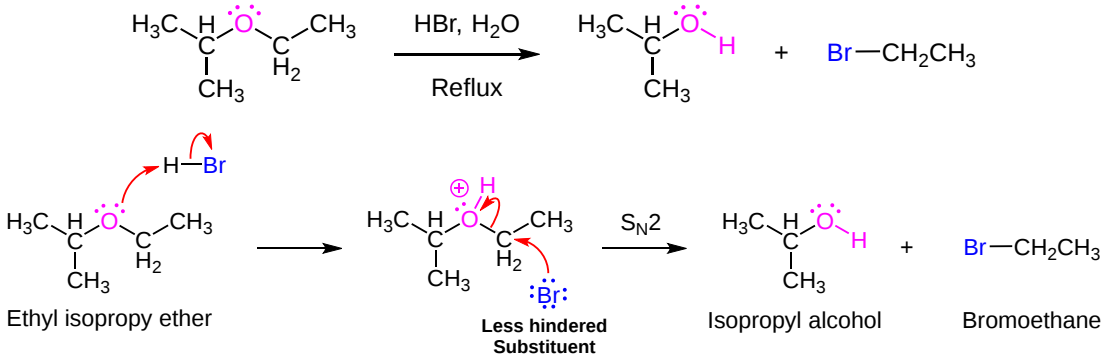


As phenols do not undergo nucleophilic substitution reactions, even if an excess of HX is used, the products from the cleavage of an aryl alkyl ether are a phenol and an alkyl halide. Diaryl ethers are not cleaved by acids.

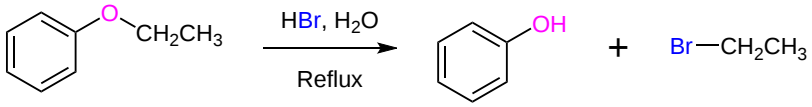
Ethers are known to be unreactive towards most reagents which makes them excellent reaction solvents. The most common reaction of ethers is cleavage of the C–O bond by using strong acids. During acidic cleavage the ether oxygen is protonated to form a good leaving groups which can be eliminated as part of an S_N2, S_N1, or E1 reaction mechanism. The mechanistic pathway is primarily determined by the strong acid used and the type of substituents attached to the ether.

ACIDIC CLEAVAGE OF ETHERS

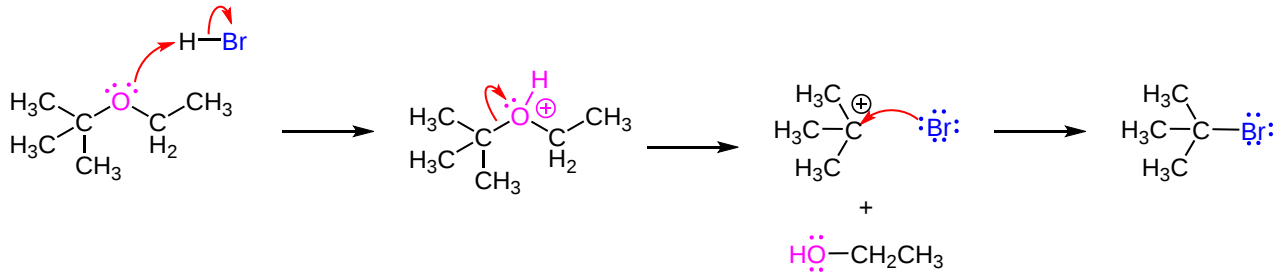
Aqueous solutions of HBr or HI (but not HCl) tend to cleave ethers into alcohol and an alkyl halide product by either an S_N2 or S_N1 mechanism. If the ether is attached to only primary, secondary, or methyl alkyl groups, a selective cleavage will typically take place using an S_N2 mechanism. First, the strong acid protonates the ether oxygen. Then resulting halide conjugate base attacks the protonated ether at the less sterically hindered alkyl substituent forming a halogen product. The ether's more sterically hindered alkyl substituent is ejected as a leaving group and forms an alcohol product. The example below show that when ethyl isopropyl ether is cleaved with hydrobromic acid the products isopropyl alcohol and bromoethane are produced. The bromide nucleophile preferably attacks the ether's ethyl substituent because it is less hindered (1°) than the isopropyl substituent (2°).



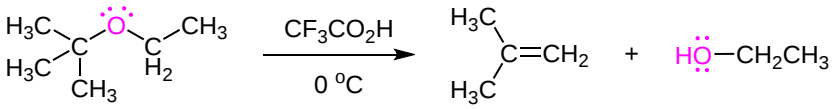
It is important to note that a phenyl substituent on an ether is not capable of participating in the S_N2 reaction of an acidic cleavage. If a phenyl group is present it will become a phenol in the product due to the halide nucleophile preferably attacking the other alkyl substituent.



When using HBr or HI, the acidic cleavage of ethers with tertiary, benzylic, or allylic substituents tend to occur by an S_N1 mechanism. The ability of these substituents to produce relatively stable carbocations promotes the S_N1 mechanism. The change in mechanism causes the tertiary, benzylic, or allyic group to preferably become the halogen product of the acidic cleavage. This makes the ether's other alkyl substituent become the alcohol product.

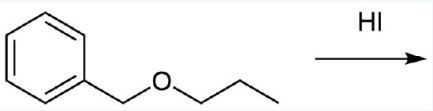


When using a strong acid whose conjugate base is a poor nucleophile, such as trifluoroacetic acid (CF_3CO_2H), for the the acidic cleavage of an ether with a tertiary alkyl substituent, the mechanism will often be E1. In this case the tertiary alkyl substituent will lose an adjacent hydrogen to form an alkene product. The ether's other alkyl substituent will form an alcohol product.



WORKED EXAMPLE 18.3.1

Predict the products of the following reaction:



Answer

Analysis: When considering the acidic cleavage of ethers it is important to realize that S_N2, S_N1, or E1 reactions are possible depending on the conditions. First, identify if the ether has a substituent which can easily form a carbocation: tertiary, benzylic, or allylic substituents. If none of these substituents are present the reaction will most likely be S_N2. However, if one of the substituents is present the reaction will most likely be S_N1 or E1. Next, identify if the reaction conditions will allow for an E1 reaction. These are the presence of a tertiary alkyl substituent on the ether along with the use of a strong acid which has a poor nucleophile as a conjugate base. If this set of conditions is not present the reaction will most likely be S_N1.

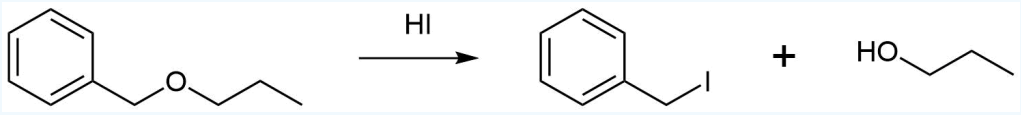
For a S_N2 reaction: The less hindered alkyl substituent of the ether will become a halogen. The other alkyl substituent will become an alcohol.

For a S_N1 reaction: The substituent which easily forms a carbocation will become a halogen and the other alkyl substituent will become an alcohol.

For an E1 reaction: The tertiary alkyl substutent will form an alkene and the other alkyl substiutent will become an alcohol.

For the reaction proposed above, the reactant contains a benzylic substituent so the reaction will most likely be S_N1. Consequently, the benzylic substituent will become and Iodide product and the propyl substituent will become an alcohol.

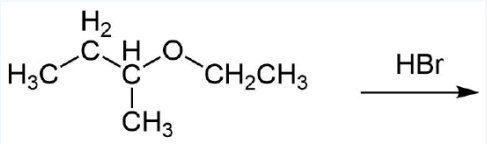
Solution



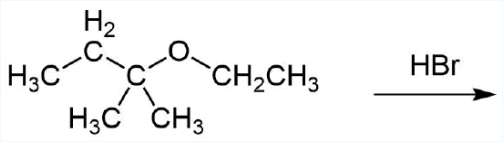
EXERCISES 18.3.1

1) Predict the product of the following reactions:

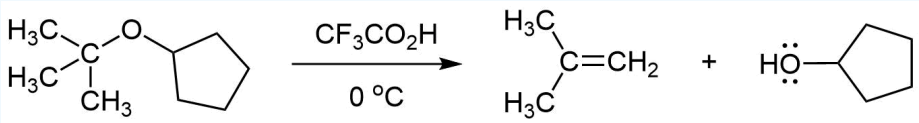
a)



b)



2) Please draw the mechanism for the following reaction:

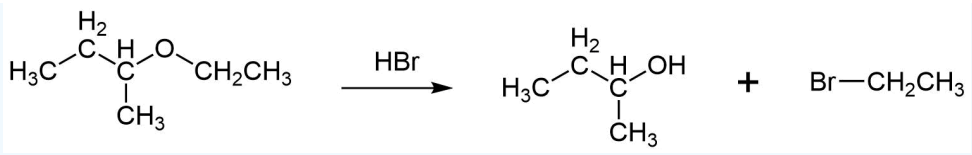


3) Why is HCl less effective at cleaving ethers than HBr or HI?

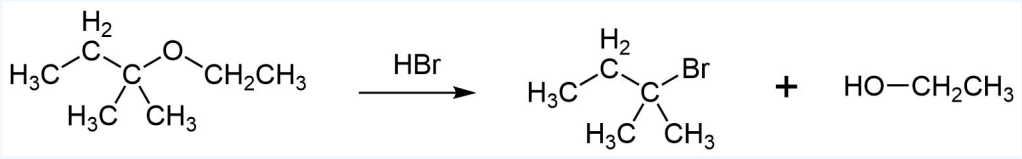
Answer

1)

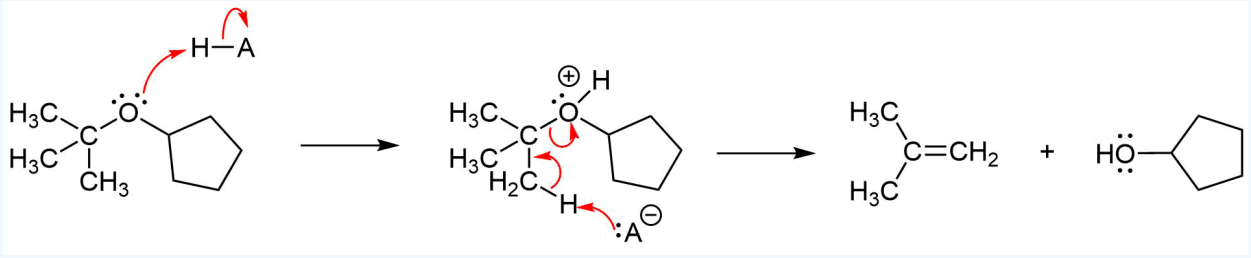
a)



b)



2)



3) HCl's conjugate base Cl^- is a poor nucleophile when compared to Br^- and I^-. The chloride anion is not a strong enough nucleophile to promote the acidic cleavage of ethers.

18.4: REACTIONS OF ETHERS - CLAISEN REARRANGEMENT

OBJECTIVES

After completing this section, you should be able to

1. write an equation to represent the Claisen rearrangement of allyl phenyl ester.
2. account for the formation of a specific product from a Claisen rearrangement, without giving mechanistic details.

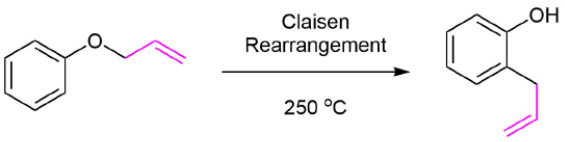
KEY TERMS

Make certain that you can define, and use in context, the key term below.

- Claisen rearrangement

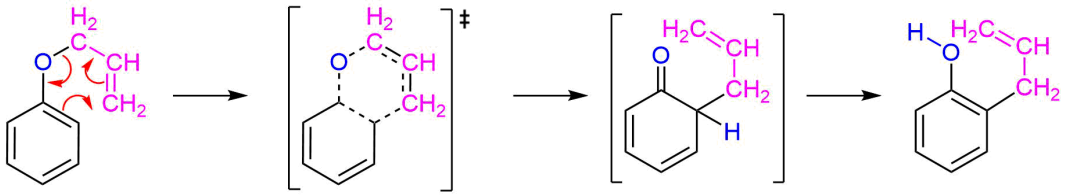
CLAISEN REARRANGEMENTS

The Claisen rearrangement is a key organic reaction that involves the thermal rearrangement of allyl vinyl ethers to form β-aryl allyl ethers. This reaction is specific to ally aryl ethers and allyl vinyl ethers. Heating an allyl aryl ether to 250 ºC causes an intramolecular rearrangement to produce an *o*-allylphenol.



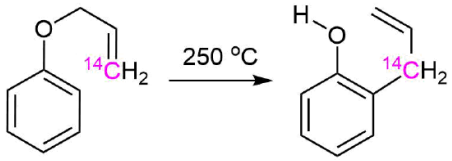
Allyl phenyl ether **o-Allylphenol**

The Claisen rearrangement takes place through a concerted mechanism in which a C-C bond forms between the C3 of the allyl group and the ortho position of the benzene ring at the same time that the C-O bond of the ether breaks. This rearrangement initially produces the non-aromatic 6-allyl-2,4- cyclohexadienone intermediate which quickly undergoes a proton shift to reform the aromatic ring in the *o*-allylphenol product. Claisen rearrangement occurs in a six-membered, cyclic transition state involving the concerted movement of six bonding electrons in the first step. The presence of six electrons in a ring suggests that the transition state may have aromatic characteristics. The Claisen rearrangement is part of a broader class of reactions called sigmatropic rearrangements which will be discussed in more detail in **Section 30-8**.



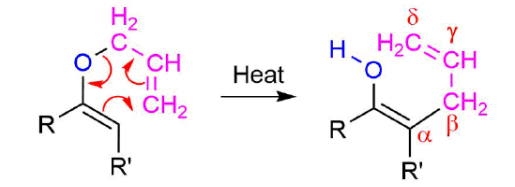
Transition State **Intermediate**

Evidence for this mechanism was provided by performing the rearrangement with allyl group with a ^{14}C label at C3. The product of this reaction was shown to have the ^{14}C labeled carbon exclusively bonded to the ring.

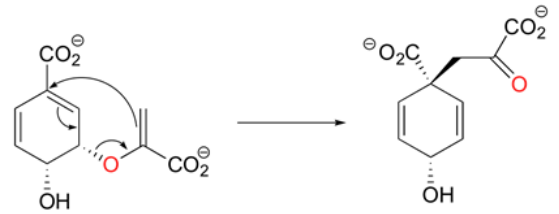


Only Product

Allyl vinyl ethers can also undergo a Claisen rearrangement when heated to form gamma, delta -unsaturated ketones or aldehydes.



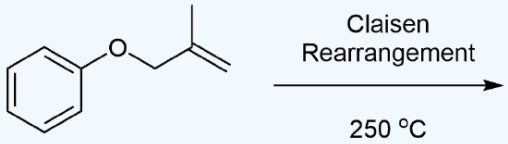
Claisen rearrangements are rare in biological chemistry. One example is the chorismate mutase catalyzed Claisen rearrangement of chorismate (a allylic vinyl ether) to form prephenate. Prephenate is a precursor in the biosynthetic pathway of aromatic amino acids phenylalanine and tyrosine.



EXERCISE 18.4.1

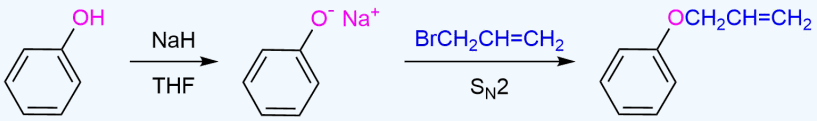
1) Show how you could synthesize allyl phenyl ether from allyl bromide and phenol.

2) What would be the expected product of the following Claisen rearrangement?

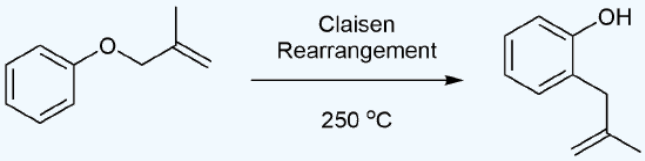


Answer

1)



2)



18.5: CYCLIC ETHERS - EPOXIDES

OBJECTIVES

After completing this section, you should be able to

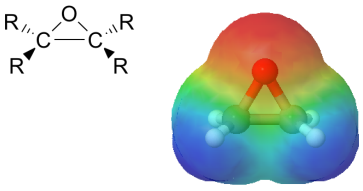
- write an equation to describe the industrial preparation of ethylene oxide.
- list two important industrial uses of ethylene oxide.
- write an equation to describe the normal laboratory preparation of an epoxide.
- identify the epoxide produced from the reaction of a given alkene with a peroxyacid.
- identify the alkene, the reagent, or both, needed to prepare a given epoxide.
- write an equation to describe the preparation of an epoxide from an alkene via a halohydrin.

KEY TERMS

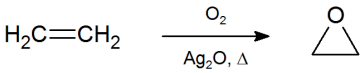
Make certain that you can define, and use in context, the key term below.

- epoxide (oxirane)

Epoxides (also known as **oxiranes**) are three-membered ring structures in which one of the vertices is an oxygen and the other two are carbons. Epoxides behave differently than other ethers due to the strain created by the three-membered ring.



The most important and simplest epoxide is ethylene oxide which is prepared on an industrial scale by catalytic oxidation of ethylene by air. Ethylene oxide is used as an important chemical feedstock in the manufacturing of ethylene glycol, which is used as antifreeze, liquid coolant and solvent. In turn, ethylene glycol is used in the production of polyester and polyethylene terephthalate (PET) the raw material for plastic bottles.

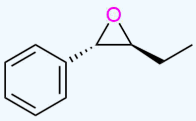


NOMENCLATURE OF EPOXIDES

The name ethylene oxide is not systematic but common. Epoxides are systematically named as an oxirane ring system much like the other cyclic ethers discussed in Section 18.1. The oxygen is numbered in the 1 position.

Oxirane

EXAMPLE 18.5.1



***trans*-2-Ethyl-3-phenyloxirane**

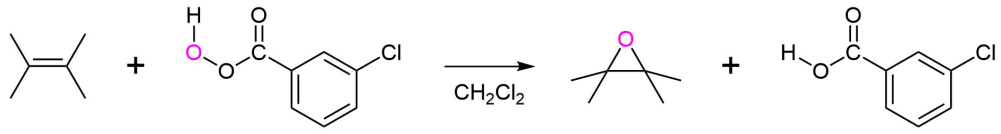
***cis*-2,3-Dimethyloxirane**

2,2-Dimethyloxirane

SYNTHESIS OF EPOXIDES

As discussed in Section 8-7, epoxides are typically prepared by the reaction of an alkene and a peroxycarboxylic acid (RCO_3H), such as *meta*-chloroperbenzoic acid (MCPBA). The peroxycarboxylic acid has the unique property of having an electropositive oxygen atom on the CO_3H 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 CO_3H group becomes CO_2H.

General Reaction

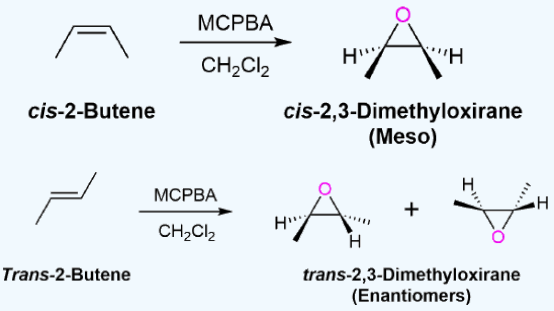


Alkene | ***meta*-Chloroperoxy-benzoic acid (MCPBA)** | **Epoxide** | ***meta*-Chloro-benzoic acid**

Stereochemical Consideration

The oxygen addition to the alkene is a syn addition and is stereospecific. The substituents of a *cis*-alkene will appear in the *cis* configuration on the epoxide ring. Likewise, Substituents of a *trans*-alkene will appear in the *trans* configuration on the epoxide ring. During this reaction the sp^2 hybridized carbons of the alkene are converted to sp^3 hybridized carbons in the epoxide. Thus, there is the possibility of two new chiral carbons forming in the epoxide product. In most cases, epoxidation of an alkene will product a mixture of enantiomers in the product, due to the electrophilic oxygen being able to attack from above or below the plane of the alkene. One major exception is the epoxidation of symmetrical cis-alkene which produces a meso compound product.

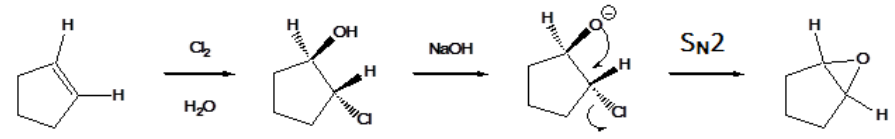
EXAMPLE 18.5.2



***cis*-2-Butene** | ***cis*-2,3-Dimethyloxirane (Meso)**

***Trans*-2-Butene** | ***trans*-2,3-Dimethyloxirane (Enantiomers)**

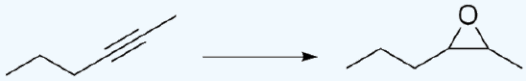
Treatment of an alkene with X_2 & H_2O creates a halohydrin (Section 8-3). When a halohydrin is treated with a base the alcohol is deprotonated to from an alkoxide. This causes an intramolecular Williamson ether synthesis to produce an epoxide along with the elimination of HX. Note, that this reaction generally forms a mixture of enantiomeric products unless a meso compound is produced.



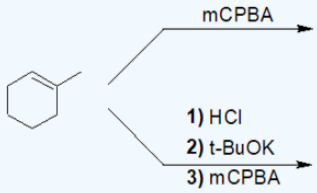
Alkene | Halohydrin | Epoxide

EXERCISE 18.5.1

1) What reagents would you use to perform the following transformation?



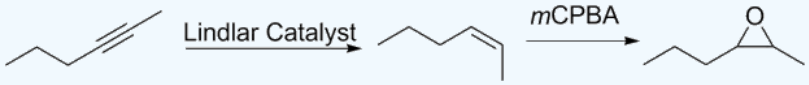
2) Predict the products of the following reactions:



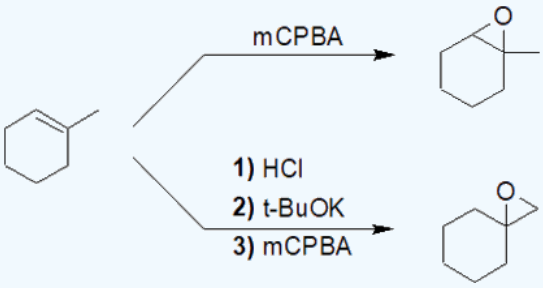
3) Predict the product of the following reaction. Be sure to include proper stereochemistry.

Answer

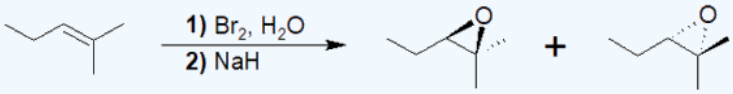
1) Lindlar's catalyst reduces alkynes to cis/Z alkenes. This stereochemistry is retained after epoxidation.



2)



3)



18.6: REACTIONS OF EPOXIDES - RING-OPENING

OBJECTIVES

After completing this section, you should be able to

1. write an equation to describe the opening of an epoxide ring under mildly acidic conditions.
   a. identify the product formed from the hydrolysis of an epoxide.
   b. write the mechanism for the opening of an epoxide ring by an aqueous acid, paying particular attention to the stereochemistry of the product.
   c. identify the product formed when an epoxide ring is opened by a hydrogen halide under anhydrous conditions.
2. predict the major product from the acidic cleavage of a given unsymmetrical epoxide.
3. write an equation to illustrate the cleavage of an epoxide ring by a base.
   a. identify the product formed from the reaction of a given epoxide with given base.
   b. explain why epoxides are susceptible to cleavage by bases, whereas other cyclic ethers are not.

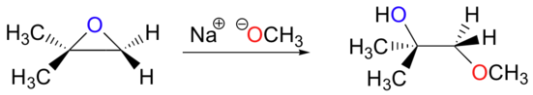
STUDY NOTES

In the discussion on base-catalyzed epoxide opening, the mechanism is essentially S_N2. While oxygen is a poor leaving group, the ring strain of the epoxide really helps to drive this reaction to completion. Indeed, larger cyclic ethers would not be susceptible to either acid-catalyzed or base-catalyzed cleavage under the same conditions because the ring strain is not as great as in the three-membered epoxide ring.

EPOXIDE RING-OPENING BY ALCOHOLYSIS

The ring-opening reactions of epoxides provide a nice overview of many of the concepts discussed in earlier chapters of this book. 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 alcoholysis 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:

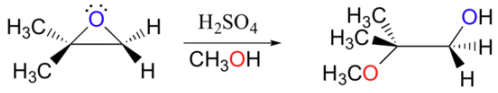
basic ring-opening:



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:

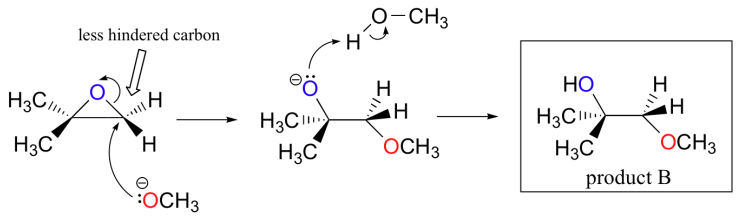


product **A**

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).

BASIC EPOXIDE RING-OPENING BY ALCOHOLYSIS

In the basic, S_N2 reaction, 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 (**Section 11-3**), and thus the ring is unlikely to open without a 'push' from the nucleophile.

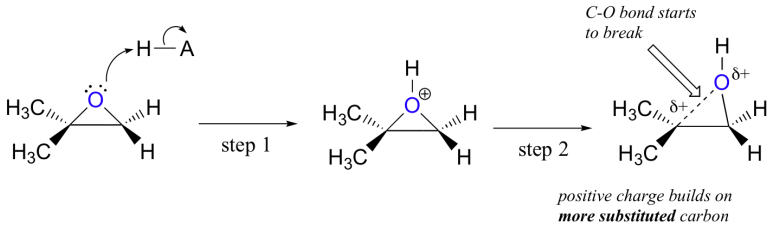


The nucleophile itself is potent: a deprotonated, negatively charged methoxide ion. When a nucleophilic substitution reaction involves a poor leaving group and a powerful nucleophile, it is very likely to proceed by an S_N2 mechanism.

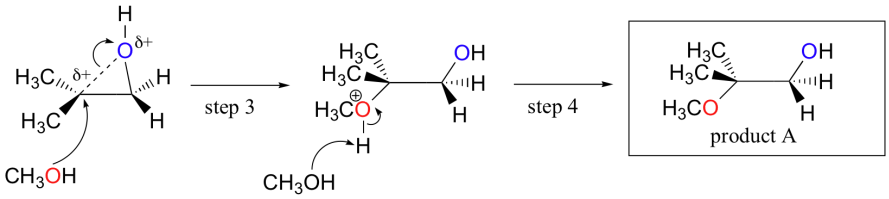
There are two electrophilic carbons in the epoxide, but the best target for the nucleophile in an S_N2 reaction is the carbon that is *least hindered*. This accounts for the observed regiochemical outcome. Like in other S_N2 reactions, nucleophilic attack takes place from the backside, resulting in inversion at the electrophilic carbon.

ACID-CATALYZED EPOXIDE RING-OPENING BY ALCOHOLYSIS

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 that alkyl substituents can donate electron density through hyper conjugation and stabilize a positive charge on a carbon.



Unlike in an S_N1 reaction, the nucleophile attacks the electrophilic carbon (step 3) before a complete carbocation intermediate has a chance to form.

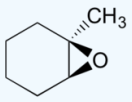


Attack takes place preferentially from the backside (like in an S_N2 reaction) because the carbon-oxygen bond is still to some degree in place, and the oxygen blocks attack from the front side. Notice, however, how the regiochemical outcome is different from the base-catalyzed reaction: in the acid-catalyzed process, the nucleophile attacks the more substituted carbon because it is this carbon that holds a greater degree of positive charge.

EXAMPLE 18.6.1

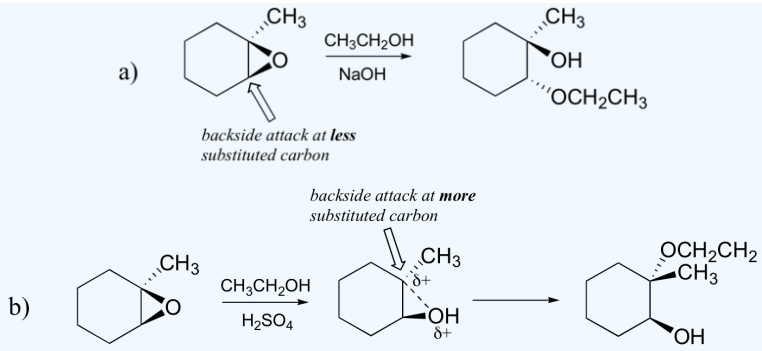
Predict the major product(s) of the ring opening reaction that occurs when the epoxide shown below is treated with:

a. ethanol and a small amount of sodium hydroxide
b. ethanol and a small amount of sulfuric acid



Hint: be sure to consider both regiochemistry **and** stereochemistry!

Answer



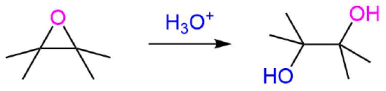
EPOXIDE RING-OPENING BY HYDROLYSIS

Epoxides may be cleaved by hydrolysis to give ***trans*-1,2-diols** (1,2 diols are also called **vicinal diols or vicinal glycols)**. The reaction can be preformed under acidic or basic conditions which will provide the same regioselectivity previously discussed.

ACID CATALYZED HYDROLYSIS

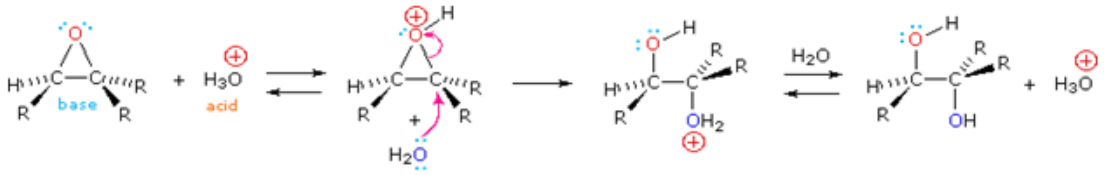
Under aqueous acidic conditions the epoxide oxygen is protonated and is subsequently attacked by a nucleophilic water. After deprotonation to reform the acid catalyst a 1,2-diol product is formed. If the epoxide is asymmetric, the incoming water nucleophile will preferably attack the more substituted epoxide carbon. The epoxide ring is opened by an S_N2 like mechanism so the two -OH groups will be *trans* to each other in the product.

GENERAL REACTION



Epoxide **1,2-Diol**

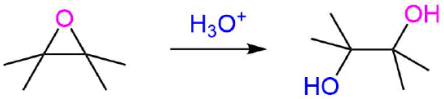
MECHANISM



BASIC HYDROLYSIS

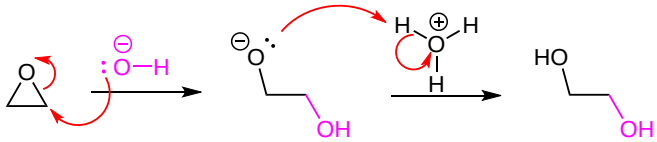
Under aqueous basic conditions the epoxide is opened by the attack of hydroxide nucleophile during an S_N2 reaction. The epoxide oxygen forms an alkoxide which is subsequently protonated by water forming the 1,2-diol product. If the epoxide is asymmetric the incoming hydroxide nucleophile will preferable attack the less substituted epoxide carbon. Because the reaction takes place by an S_N2 mechanism the two -OH groups in the product will be *trans* to each other.

GENERAL REACTION



Epoxide **1,2-Diol**

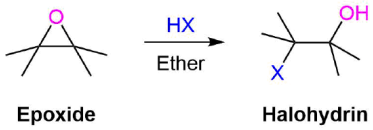
MECHANISM



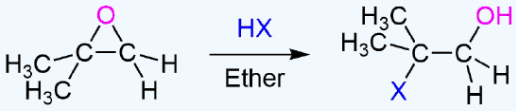
EPOXIDE RING-OPENING BY HX

Epoxides can also be opened by anhydrous acids (HX) to form a trans halohydrin. When both the epoxide carbons are either primary or secondary the halogen anion will attack the less substituted carbon through an S_N2 like reaction. However, if one of the epoxide carbons is tertiary, the halogen anion will primarily attack the tertiary carbon in an S_N1 like reaction.

GENERAL REACTION

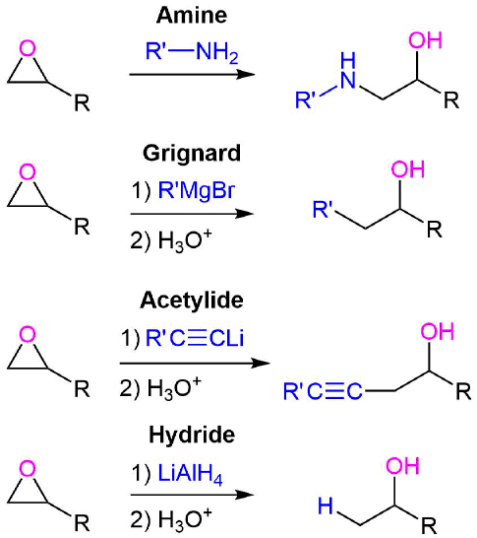


EXAMPLE 18.6.2

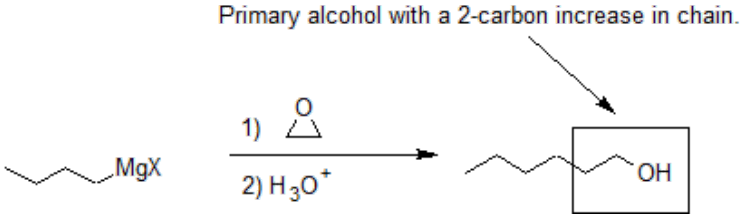


EPOXIDE RING-OPENING BY OTHER BASIC NUCLEOPHILES

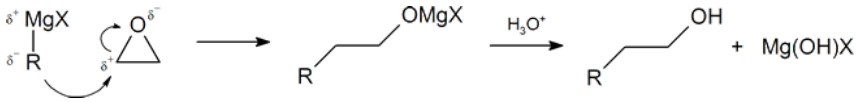
A wide variety of basic nucleophiles can be used for the ring opening of an epoxide including, amines, hydrides, Grignard reagents, acetylide anions, and hydride. These ring openings generally take place by an S_N2 mechanism.



Reacting Grignard reagents with ethylene oxide is a particularly useful reaction because it produces a primary alcohol containing two more carbon atoms than the original Grignard reagent.

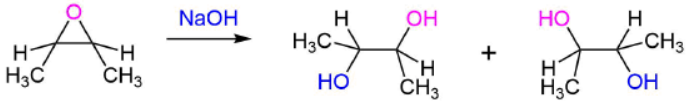


This reaction follows the same S_N2 mechanism as the opening of epoxide rings under basic conditions since Grignard reagents are both strong nucleophiles and strong bases. The first step of the mechanism of this reaction involves the S_N2 attack of the Grignard reaction to open the epoxide to form an alkoxide. The second step of the mechanism involves the protonation of the alkoxide to form an alcohol.



ADDITIONAL STEREOCHEMICAL CONSIDERATIONS OF RING-OPENING

During the ring-opening of an asymmetrical epoxide, the regiochemical control of the reaction usually allows for one stereoisomer to be produced. However, if the epoxide is symmetrical, each epoxide carbon has roughly the same ability to accept the incoming nucleophile. When this occurs the product typically contains a mixture of enantiomers.

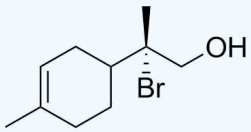


EXERCISES

EXERCISE 18.6.1

Given the following, predict the product assuming only the epoxide is affected. (Remember to show stereochemistry)

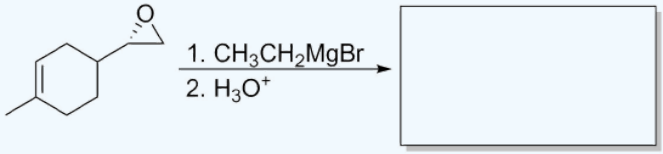
Answer



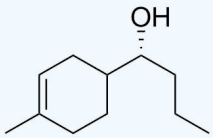
Note that the stereochemistry has been inverted

EXERCISE 18.6.2

Predict the product of the following, similar to above but a different nucleophile is used and not in acidic conditions. (Remember stereochemistry)

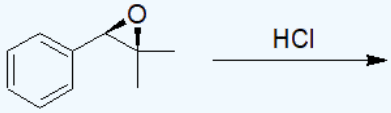


Answer

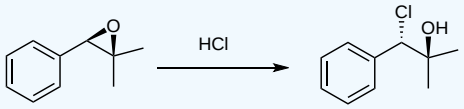


EXERCISE 18.6.3

Provide the structure of the product of the following reaction. Be sure to include proper stereochemistry.



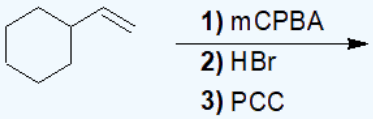
Answer



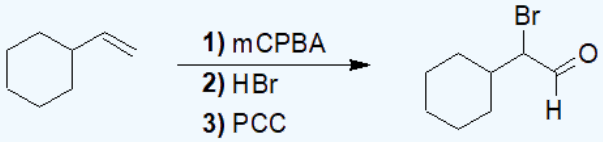
The ring side of the protonated epoxide intermediate will better stabilize a partial positive charge, so would be the more likely carbon for the chloride ion to attack.

EXERCISE 18.6.4

Predict the product of the following reaction.

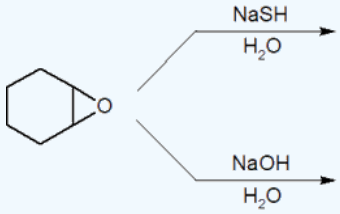


Answer

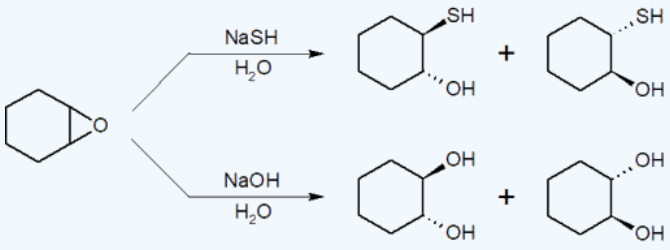


EXERCISE 18.6.5

Provide the final products of the following reactions.



Answer



18.7: CROWN ETHERS

OBJECTIVES

After completing this section, you should be able to

1. write the normally accepted name for a crown ether, given its structure.
2. draw the structure of a crown ether, given its normally accepted name.
3. describe, briefly, the uses of crown ethers.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

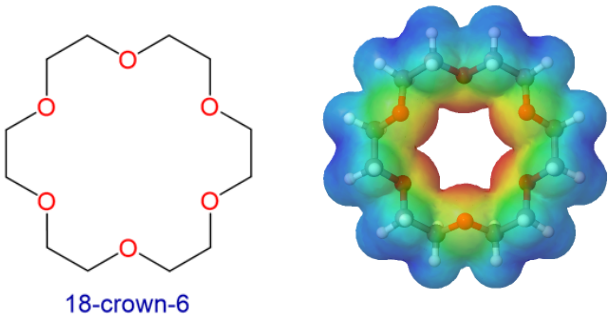
- crown ether

STUDY NOTES

A “crown ether ” is a cyclic ether containing several (i.e., 4, 5, 6 or more) oxygen atoms. As we have indicated in the objectives above, a detailed knowledge of these compounds is not required in this course.

CROWN ETHERS

Crown ethers are cyclic polyethers with four or more oxygen atoms each separated by two or three carbon atoms. Crown ethers have the general formula of $(OCH_2CH_2)_n$ or $(OCH_2CH_2CH_2)_n$ and are named using both the total number of atoms in the ring and the number of oxygen atoms. Thus 18-crown-6 is an 18-membered ring with six oxygen atoms. All crown ethers have a cavity in the center this is lined with oxygen atoms and can accommodate a alkali metal ion, such as K^+. The cation is stabilized by interacting with lone pairs of electrons on the surrounding oxygen atoms. The negative character of center cavity of 18-crown-6 can be seen by looking at its electrostatic potential map shown below. The presence of high electron density is shown by a red color.



Crown ethers are useful for dissolving ionic substances in organic solvents, such as $KMnO_4$ dissolving in toluene, by sequestering the cations inside a hydrophilic cavity, whereas the outer shell, consisting of C–H bonds, is hydrophobic.

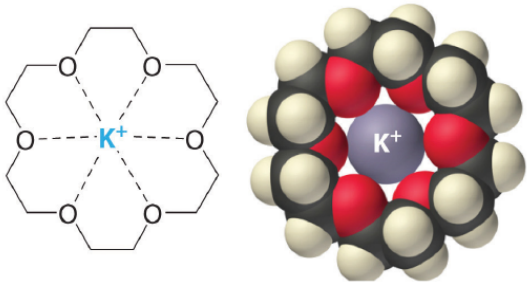
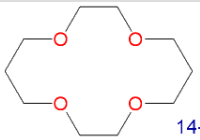
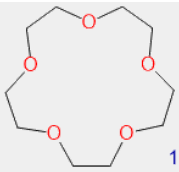
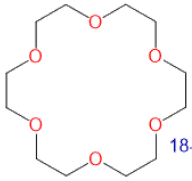
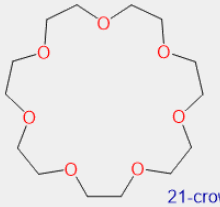


Figure 18.7.1: Potassium complex of the crown ether 18-crown-6. (CC BY-SA-NC 3.0; Anonymous via LibreTexts)

The availability of crown ethers with cavities of different sizes allows specific cations to be solvated with a high degree of selectivity. Crown ethers prefer to bind alkali metal cations with sizes that match that of their binding cavity. For instance, as shown in Table 18.7.1, 14-crown-4 preferentially binds to Li^+, 15-crown-5 preferentially binds to Na^+, 18-crown-6 preferentially binds to K^+, and 21-crown-7 preferentially binds to Cs^+.

Table 18.7.1: Crown ethers preferentially bind cations with sizes that match the cavity size of their crown-shaped conformers.

Crown Ether	Cavity Diameter (A˚)	Preferred Cation	Cation Diameter (A˚)
 14-crown-4	1.2-1.5	Li^+	1.36
 15-crown-5	1.7-2.2	Na^+	1.94
 18-crown-6	2.6-3.2	K^+	2.66
 21-crown-7	3.4-4.3	Cs^+	3.34

CRYPTANDS

Cryptands (from the Greek *kryptós*, meaning “hidden”) are variations of crown ethers comprised of two nitrogens connected by three polyether strands. A common nomenclature is used where the numbers preceding the word cryptan indicate the number of oxygen atoms in each strand of the molecule.

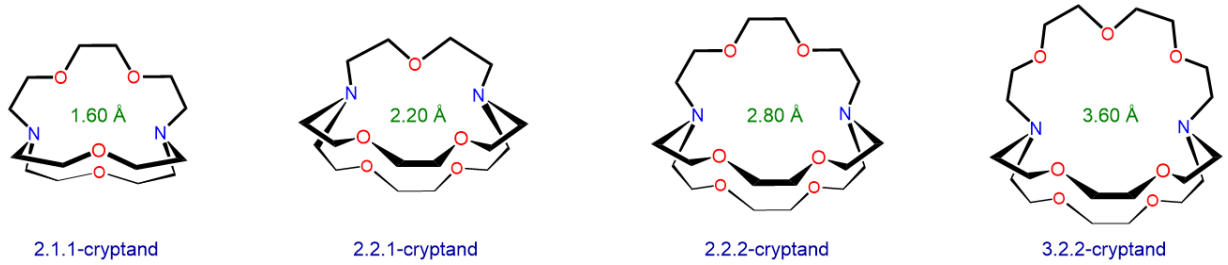


Figure 18.7.2: Structures and approximate binding cavity diameters for several cryptands.

Like crown ethers, cryptands are compounds that contains a central cavity that can completely surround a cation with lone pair electrons from oxygen and nitrogen atoms. Also, cryptands can be used to prepare solutions of ionic compounds in solvents that are otherwise too nonpolar to dissolve them. Similar to crown ethers, cryptands prefer to bind with alkali metal cations whose diameter matches the size of their binding cavity.

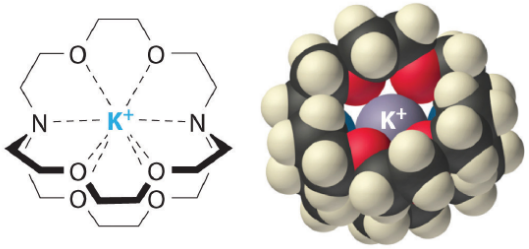


Figure 18.7.3: Potassium complex of 2,2,2-cryptand. (CC BY-SA-NC 3.0; Anonymous via LibreTexts)

EXERCISE 18.7.1

Cryptand ligands also preferentially bind alkali metal ions with sizes that match the size of their binding cavities. The structure and approximate cavity sizes of several cryptands are shown above. Use the information in Table 18.7.1 to predict which alkali metal ion each cryptand will preferentially bind.

Answer

The cryptands might be expected to selectively bind the largest ion which fits within the cavity. Predicted selectivity of crown ethers for alkali metal cations based on the hypothesis that they will selectively bind the largest ion which fits their binding cavity are listed below.

Cryptand	Cavity Diameter of (Å)	Preferred Cation	Cation Diameter (Å)
2.1.1-cryptand	1.60	Li^+	1.36
2.2.1-cryptand	2.20	Na^+	1.96
2.2.2-cryptand	2.80	K^+	2.66
3.2.2-cryptand	3.60	Cs^+	3.34

18.8: THIOLS AND SULFIDES

OBJECTIVES

After completing this section, you should be able to

1. a. write the IUPAC name of a thiol, given its Kekulé, condensed or shorthand structure.
   b. draw the structure of a thiol, given its IUPAC name.
   c. write an equation to represent the formation of a thiol by the reaction of hydrosulfide anion with an alkyl halide.
   d. write an equation to illustrate the preparation of a thiol by the reaction of thiourea with an alkyl halide.
2. write an equation to show the interconversion between thiols and disulfides.
3. a. write the name of a sulfide, given its structure.
   b. draw the structure of a sulfide, given its name.
   c. write an equation showing how a sulfide may be prepared by the reaction of a thiolate anion on an alkyl halide.
   d. identify the product from the reaction of a given alkyl halide with a given thiolate anion.
   e. identify the reagents necessary to prepare a given sulfide.
   f. write an equation to illustrate the formation of a trialkylsulfonium salt from a sulfide and an alkyl halide.

KEY TERMS

Note: All of these terms are defined in the "Study Notes," below.

- disulfide
- mercapto group
- (organic) sulfide
- sulfone
- sulfoxide
- thiol
- thiolate anion
- trialkylsulfonium ion (trialkylsulfonium salt)

STUDY NOTES

The chemistry of sulfur-containing organic compounds is often omitted from introductory organic chemistry courses. However, we have included a short section on these compounds, not for the sake of increasing the amount of material to be digested, but because much of the chemistry of these substances can be predicted from a knowledge of their oxygen-containing analogues.

A thiol is a compound which contains an SH functional group. The SH group itself is called a mercapto group. A disulfide is a compound containing an S-S linkage.

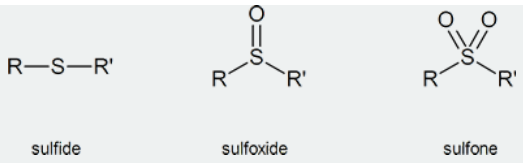
(Organic) sulfides have the structure R-S-R′, and are therefore the sulfur analogues of ethers. The nomenclature of sulfides can be easily understood if one understands the nomenclature of the corresponding ethers. Notice that the term "thio" is also used in inorganic chemistry. For example, SO_4^{2-} is the sulfate ion; while $S_2O_3^{2-}$, in which one of the oxygen atoms of a sulfate ion has been replaced by a sulfur atom, is called thiosulfate. Thiolate anions, RS^-, are analogous to alkoxy anions, RO^-. Thiolate anions are better nucleophiles than are alkoxy anions.

If you have trouble understanding why trialkylsulfonium ions are formed, think of them as being somewhat similar to the hydronium ions that are formed by protonating water:

hydronium ion trialkylsulfonium ion

Later we shall see examples of tetraalkylammonium ions, R_4N^+, which again may be regarded as being similar to hydronium ions.

Sulfoxides and sulfones are obtained by oxidizing organic sulfides. You need not memorize the methods used to carry out these oxidations.



sulfide sulfoxide sulfone

Table 18.1, below, provides a quick comparison of oxygen-containing and sulfur-containing organic compounds.

Table 18.8.1: Comparison of compounds containing oxygen and sulfur

Oxygen-containing Compound	Sulfur Analogue
ether, R-O-R′	sulfide, R-S-R′
alkoxy anion, RO^-	thiolate anion, RS^-
alcohol, ROH	thiol, RSH
hydroxy group, OH^-	mercapto group, SH^-
peroxide, R-O-O-R′	disulfide, R-S-S-R′

Note that when we name thiols, we include the “e” of the alkane name. Thus, CH_3CH_2SH is called “ethanethiol,” not “ethanthiol.”

Thiols and sulfides are the "sulfur equivalent" of alcohols and ethers. You can replace the oxygen atom of an alcohol with a sulfur atom to make a thiol; similarly, you can replace the oxygen atom in an ether with S to make the corresponding alkyl sulfide. This is because thiols contain the C-S-H functional group, while sulfides contain the C-S-C group.

OXIDATION STATES OF SULFUR COMPOUNDS

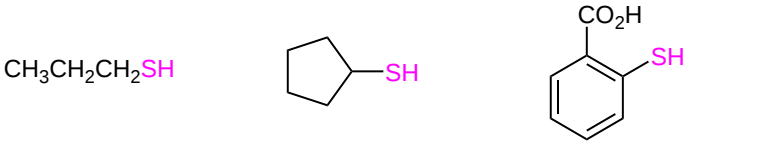
Oxygen assumes only two oxidation states in its organic compounds (–1 in peroxides and –2 in other compounds). Sulfur, on the other hand, is found in oxidation states ranging from –2 to +6, as shown in the following table (some simple inorganic compounds are displayed in orange).

Sulfur Oxidation States in Organic Compounds

-2	-1	0	+2	+4	+6
H_2S R–S–H thiols R–S–R sulfides R–S(+)–R R sulfonium ions	R–S–S–R disulfides	S elemental R–S(=O)–R sulfoxides R–S–OH sulfenic acids	R–S(=O)(=O)–R sulfones R–S(=O)–OH sulfinic acids	SO_2 R–S(=O)(=O)–OH sulfonic acids R–O–S(=O)–O–R sulfite esters	SO_3 R–O–S(=O)(=O)–O–R sulfate esters

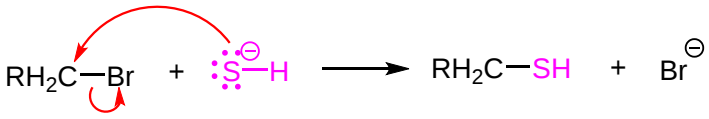
THIOLS

Thiols are often called “mercaptans,” a reference to the Latin term mercurium captans (capturing mercury), since the -SH group forms strong bonds with mercury and its ions. Thiols are analogous to alcohols. Thiols are weakly acidic (pK_a ~ 10) and are much stronger acids than alcohols (pKa ~ 16). However, thiols usually do not form hydrogen bonds due to the sulfur atom not have sufficient electronegativity. Thiols named using the same rules as alcohols except the parent chain is named as alkane with the suffix -thiol added. As a substituent the -SH group is called a **mercapto** group.



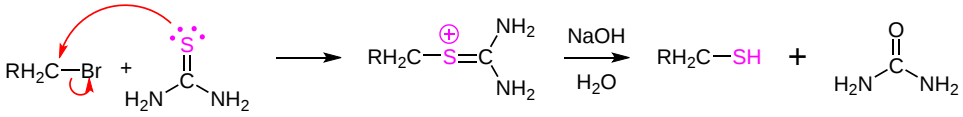
Propanethiol **Cyclopentanethiol** ***o*-Mercaptobenzoic acid**

Thiols are usually prepared by using the hydrosulfide anion (-SH) as a nucleophile in an S_N2 reaction with alkyl halides.



Hydrosulfide ion **Thiol**

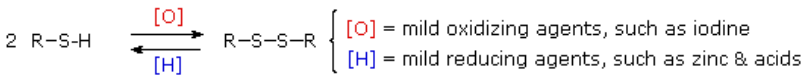
One problem with this reaction is that the thiol product can deprotonate and undergo a second S_N2 reaction with an additional alkyl halide to produce a sulfide side product. This problem can be solved by using thiourea, $(NH_2)_2C{=}S$, as the nucleophile. The S_N2 reaction first produces an alkyl isothiourea salt as an intermediate. This salt is then hydrolyzed to form the thiol by a reaction with aqueous base.



Thiourea **Thiol** **Urea**

DISULFIDES

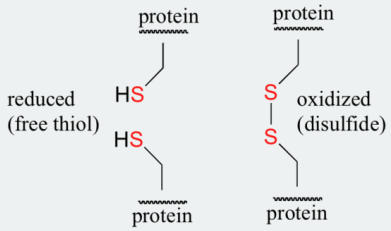
Thiols (R-S-H) can be oxidized to form disulfides (R-S-S-R') through reaction with Br_2 or I_2. Note, an equivalent oxidation of alcohols (R-O-H) to peroxides (R-O-O-R') is not normally observed. The reasons for this different behavior becomes clear when looking at bond strengths. The S–S single bond in disulfides is nearly twice as strong as the O–O bond in peroxides. Also, the O–H bond in alcohols is more than 25 kcal/mole stronger than the S–H bond in thiols. Thus, thermodynamics favors disulfide formation over peroxide. Disulfides can easily be reduced back to a thiols through reaction with zinc and acid.



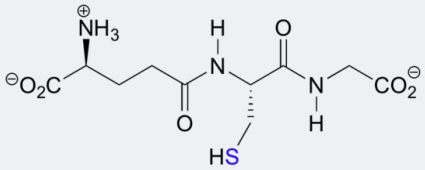
Thiol **Disulfide**

DISULFIDE BRIDGES IN PROTEINS

Disulfide (sulfur-sulfur) linkages between two cysteine residues are an integral component of the three-dimensional structure of many proteins. The interconversion between thiols and disulfide groups is a redox reaction: the thiol is the reduced state, and the disulfide is the oxidized state.

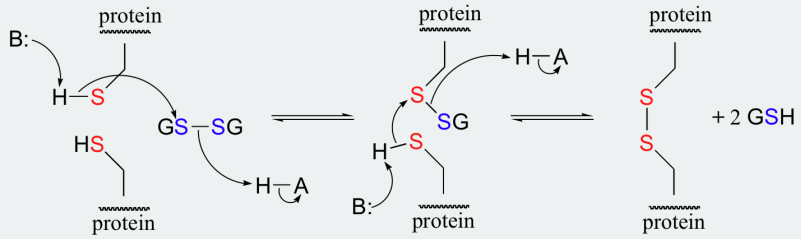


Notice that in the oxidized (disulfide) state, each sulfur atom has lost a bond to hydrogen and gained a bond to a sulfur - this is why the disulfide state is considered to be oxidized relative to the thiol state. The redox agent that mediates the formation and degradation of disulfide bridges in most proteins is glutathione, a versatile coenzyme. Recall that the important functional group in glutathione is the thiol, highlighted in blue in the figure below. In its reduced (free thiol) form, glutathione is abbreviated 'GSH'.



Glutathione (GSH)

In its oxidized form, glutathione exists as a dimer of two molecules linked by a disulfide group, and is abbreviated 'GSSG'. A new disulfide in a protein forms via a 'disulfide exchange' reaction with GSSG, a process that can be described as a combination of two S_N2-like attacks. The end result is that a new cysteine-cysteine disulfide forms at the expense of the disulfide in GSSG.



In its reduced (thiol) state, glutathione can reduce disulfides bridges in proteins through the reverse of the above reaction.

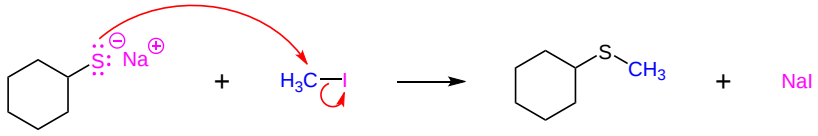
SULFIDES

Sulfides are named using the same rules as ethers except *sulfide* is used in the place of *ether*. For more complex substances, alkylthio is used in place of alkoxy.

Diethyl sulfide **Ethyl phenyl sulfide** **3-(Methylthio)cyclopentene**

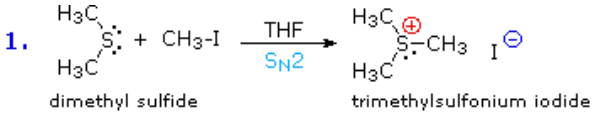
Sulfur analogs of ethers are called **sulfides**. Sulfides are less common than thiols as naturally occurring compounds. However, sulfides—especially disulfides (C-S-S-C)—have important biological functions, mainly in reducing agents (antioxidants).

Since thiols are weakly acidic their conjugate bases, called thiolate ions, can be easily formed through reaction with a strong base such as NaH. Thiolates have proven to be excellent nucleophiles and easily undergo S_N2 reactions with primary and secondary alkyl halides to form sulfides. The reaction is analogous to the Williamson ether synthesis previously discussed in this chapter (**Section 18-2**)



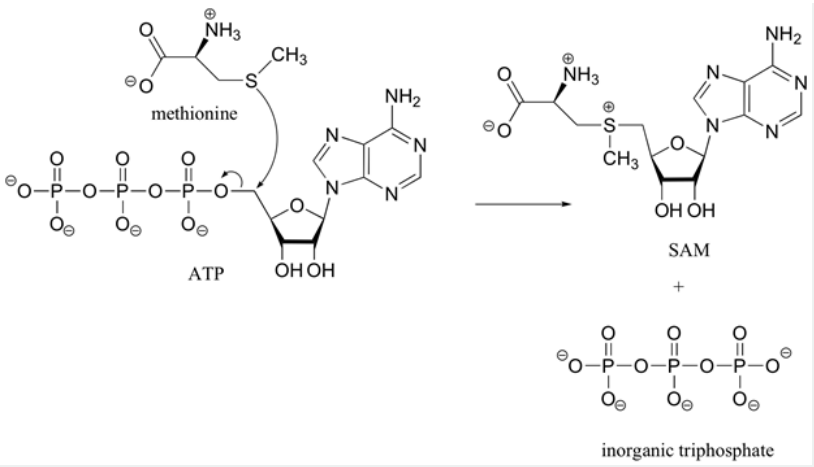
Cyclohexanethiolate **Cyclohexyl methyl sulfide**

The chemical behavior of sulfides contrasts with that of ethers in some important ways. Because sulfur's valence electrons involve 3P orbitals they are further away and less tightly held than the valence electrons on oxygen which involve 2P orbitals. This makes the nucleophilicity of sulfur atoms much greater than that of oxygen, leading to a number of interesting and useful electrophilic substitutions of sulfur that are not normally observed for oxygen. For instance, sulfides, unlike ethers, easily react with primary alkyl halides through an S_N2 mechanism to give ternary sulfonium ions (R_3S^+) in the same manner that 3°-amines can be alkylated to form quaternary ammonium salts. Although equivalent oxonium salts of ethers are known, they are only prepared under extreme conditions, and are exceptionally reactive.

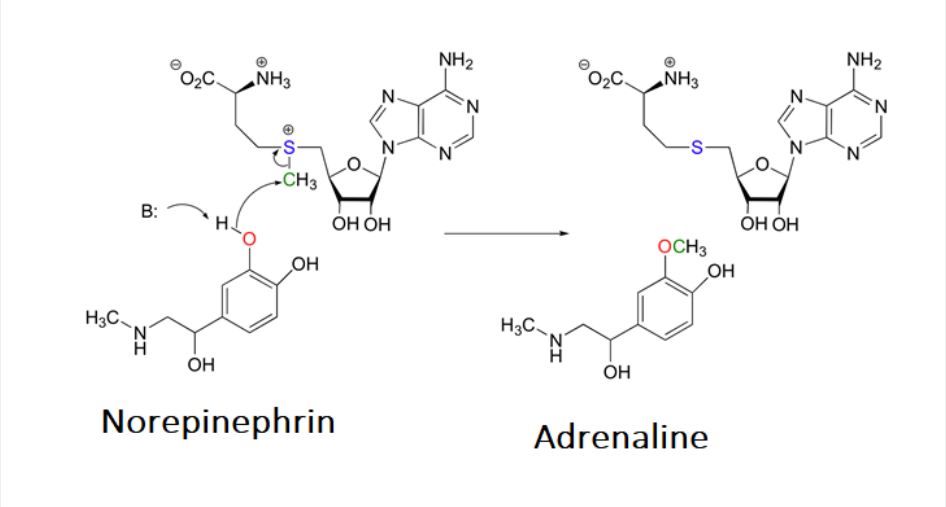


BIOLOGICAL SULFONIUM ION FORMATION

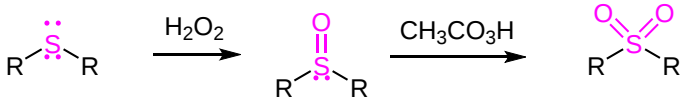
In biological systems the sulfonium ion, *S*-adenosylmethionine (SAM), is formed by a S_N2 reaction between the nucleophilic sulfur atom of the amino acid methionine and the electrophilic methene (CH_2) carbon of adenosine triphosphate (ATP). This reaction is unusually in that the triphosphate ion is removed from ATP as a leaving group. In most cases biological nucleophiles attack an electrophilic phosphorus on ATP causing a diphosphate ion to be removed as the leaving group.



The sulfonium ion in SAM is an effective methylating agent. Through an S_N2 reaction, biological nucleophiles can attack the electrophilic methyl group bonded to the positively charged sulfonium ion and cause the removal of a neutral sulfide as a leaving group. An example of this reaction is the catechol-O-methyltransferase catalyzed O-methylation of norepinephrin by SAM to produce adrenaline.

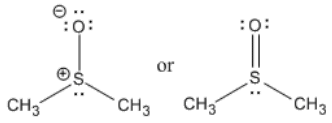


Sulfides can be easily oxidized. Reacting a sulfide with hydrogen peroxide, H_2O_2, as room temperature produces a sulfoxide (R_2SO). The oxidation can be continued by reaction with a peroxyacid, such as peracetic acid (CH_3CO_3H), to produce the sulfone (R_2SO_2).



Sulfide **Sulfoxide** **Sulfone**

A common example of a sulfoxide is the solvent dimethyl sulfoxide (DMSO). DMSO is considered a polar aprotic solvent.

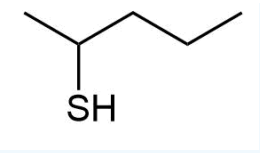


DMSO is a very polar, aprotic solvent

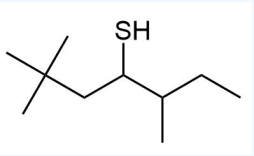
EXERCISE 18.8.1

Give IUPAC names the following compounds:

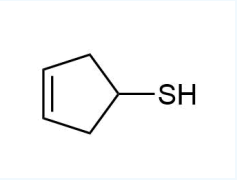
a)



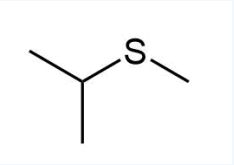
b)



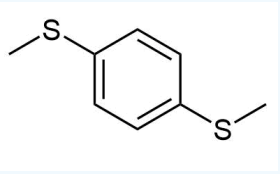
c)



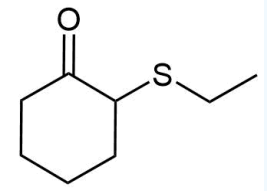
d)



e)



f)



Answer

a) 2-Pentanethiol

b) 2,2,5-Trimethyl-4-heptanethiol

c) 3-Cyclopentene-1-thiol

d) Methyl isopropyl sulfide

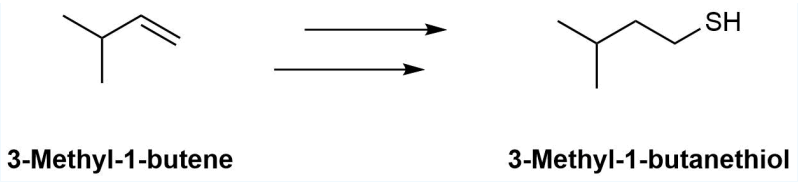
e) *p*-Di(methylthio)benzene

f) 2-(Ethylthio)cyclohexanone

? EXERCISE 18.8.2

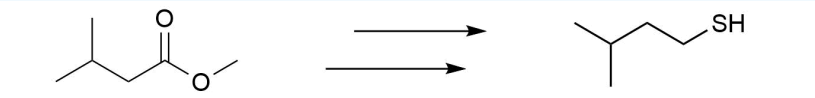
The molecule 3-methyl-1-butanethiol has been shown to be one of the components of skunk spray. How would make the following conversions?

a)



3-Methyl-1-butene 3-Methyl-1-butanethiol

b)



Methyl 3-methylbutyrate 3-Methyl-1-butanethiol

Answers

a) 1) HBr & Peroxides, 2) $(NH_2)_2C=S$, 3) NaOH & H_2O

b) 1) $LiAlH_4$, 2) PBr_3, 3) $(NH_2)_2C=S$, 4) NaOH & H_2O

18.9: SPECTROSCOPY OF ETHERS

OBJECTIVES

After completing this section, you should be able to

1. use the ^{1}H NMR spectrum of an unknown ether or epoxide to determine its identity.
2. identify the approximate chemical shift expected for protons attached to the carbon atoms that are bonded to oxygen in an ether or an epoxide.

INFRARED SPECTROSCOPY

Ethers and epoxides typically have a strong C-O stretch between 1000 and 1300 1/cm. Because this absorption appears in the fingerprint region of the IR is can be difficult to assign. In addition to the C-O peak, it is helpful to note if an IR spectrum has no C=O or O-H stretch peaks to confirms it is not aldehyde, ketone, or alcohol.

If you look at an IR spectrum of dibutyl ether, you will see:

- there are the usual sp^3 C-H stretching and CH_2 bending modes at 2900 and 1500 cm^{-1}.
- there is a strong peak near 1100 cm^{-1}. This peak is due to the C-O stretching vibration.

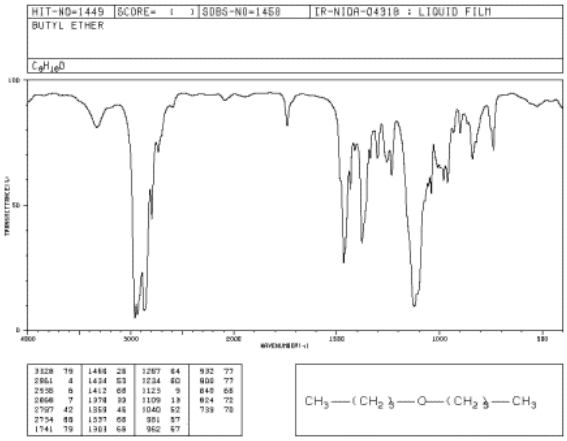
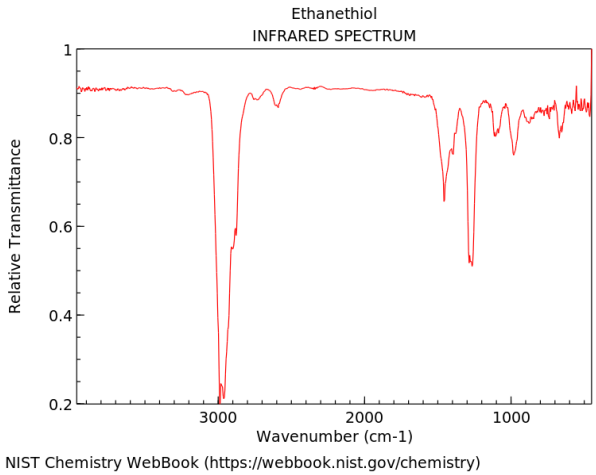


Figure IR7. *IR spectrum of dibutyl ether. Source: SDBSWeb: http://riodb01.ibase.aist.go.jp/sdbs/ (National Institute of Advanced Industrial Science and Technology of Japan, 14 July 2008)*

Although thios and sulfides do have a weak C-S stretch between 710 and 570 1/cm, the absorption is very difficult to assign. In addition thios have a weak S-H stretch at 2600-2550 1/cm.

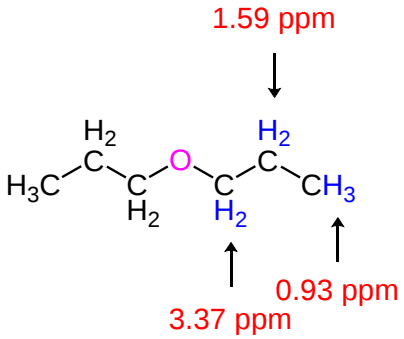


^{1}H NMR SPECTROSCOPY

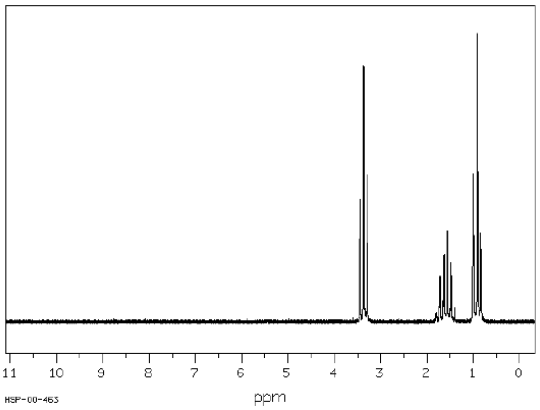
- Hydrogens on carbon adjacent to the ether show up in the region of 3.4-4.5 ppm.

- Similar peaks in epoxides are shifted to a slightly higher field than other ethers. Hydrogens on carbons in and epoxide appear in the region of 2.5 to 3.5 ppm.
- Hydrogens on carbons adjacent to the sulfur in sulfides and thiols appear in the region of 2.0 to 2.5 ppm.
- The SH hydrogen of a thiol typically appears in the region of 1.3-1.5 ppm.

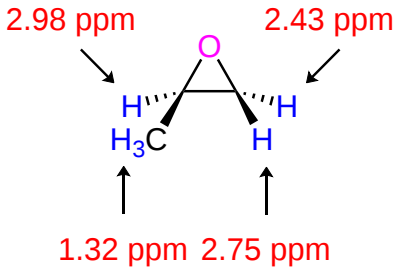
The ^{1}H NMR spectrum of dipropyl ether shows three signals with the triplet at 3.37 ppm assigned to the -CH_2- beside the ether and the other two signals upfield (1.59 and 0.93 ppm). Notice the protons closer to the electron withdrawing oxygen atom are further downfield indicating some deshielding. Protons at (A) and (C) are each coupled to two equivalent (B) protons. So, each of these signals appears as a triplet. The (B) protons in turn are coupled to a set of two and three equivalent protons and appears as a sextet. Source: SDBSWeb : http://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, 28 June 2017).



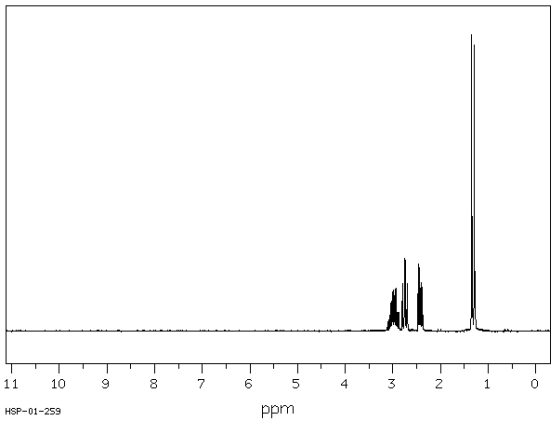
Dipropyl ether



Source: SDBSWeb : http://sdbs.db.aist.go.jp

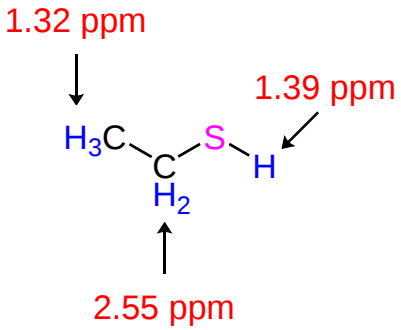


2-Methyloxirane

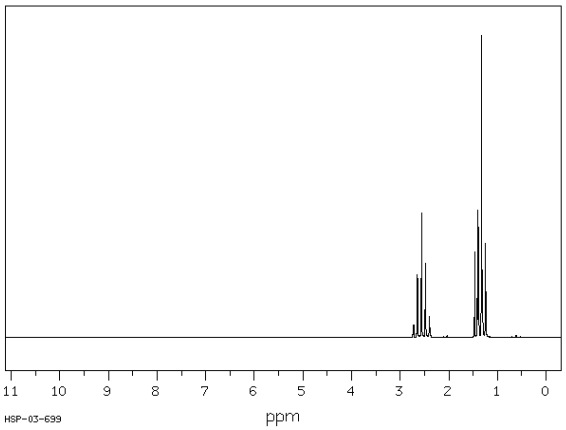


Source: SDBSWeb : http://sdbs.db.aist.go.jp

The methylene protons of this epoxide are diastereotopic and appear as two separate peak. When looking at the 3D structure of 2-methyloxirane it is clear that each methylene hydrogen is distinctly different. Also, hydrogens attached to the carbons in eposxides tend to display complex splitting patterns (Sections **13-7 and 13-8**).



Ethanethiol

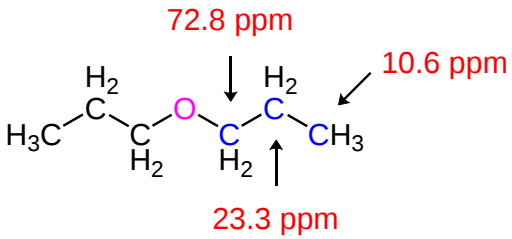


Source: SDBSWeb : http://sdbs.db.aist.go.jp

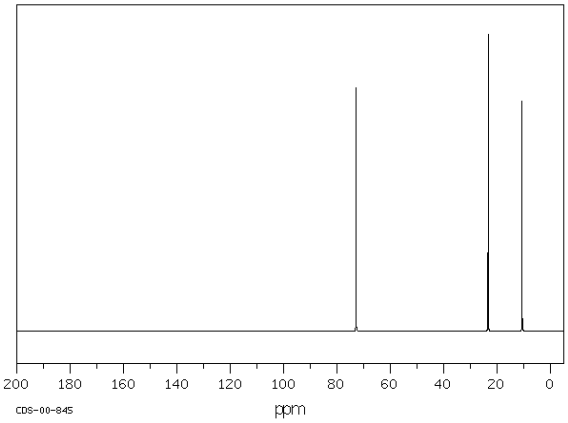
Note that in this ^{1}H NMR spectra the SH proton is actively involved in splitting. The SH proton peak at 1.39 ppm is split into a triplet and the methylene peak at 2.55 ppm is split into a quintet.

^{13}C NMR SPECTRA

- Carbons adjacent to the ether appear in the region of 50-80 ppm.
- Carbons that are part of the epoxide appear in the region of 40-60 ppm.
- Carbons adjacent to the sulfur in sulfides and thiols appear in the region of 20-40 ppm.



Dipropyl ether



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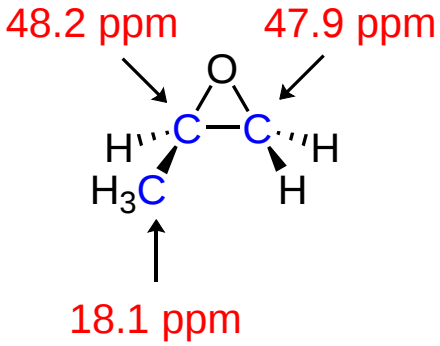
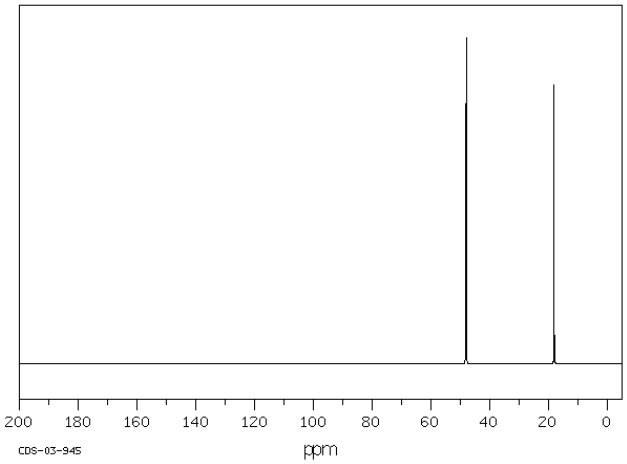
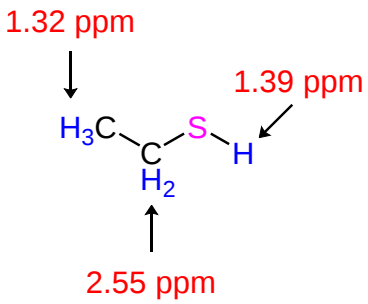


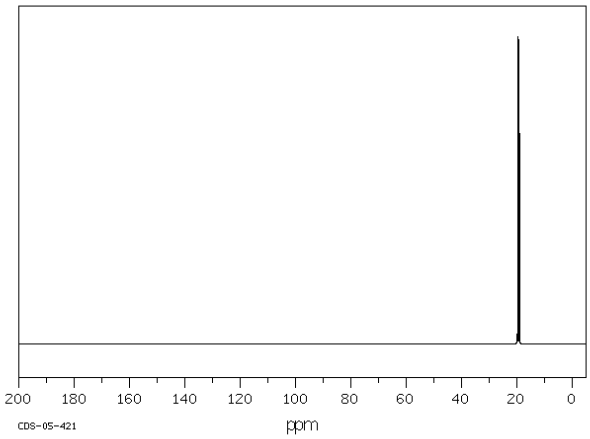
2-Methyloxirane



Source: SDBSWeb : http://sdbs.db.aist.go.jp



Ethanethiol



Source: SDBSWeb : http://sdbs.db.aist.go.jp

MASS SPECTRA

Ethers, sulfides, and epoxides all have similar fragmentation patterns in mass spectra with a few subtle variations.

ETHERS

- The M^+ is typically weak or absent
- They primarily undergo alpha-cleavage to produce $[H_2C{=}O\text{-}R]^+$
- They can also undergo an inductive cleavage to produce R^+

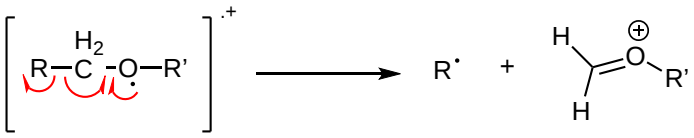
EPOXIDES

- The M^+ is typically weak or absent
- They primarily undergo alpha-cleavage to produce an alkyl radical

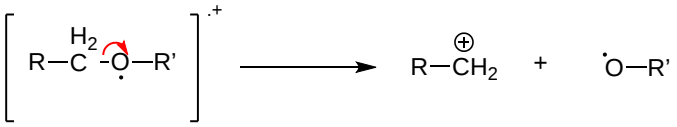
SULFIDES

- The M^+ is typically stronger than the corresponding ether
- They primarily undergo alpha-cleavage to produce an alkyl radical
- They can also undergo an inductive cleavage to produce R^+

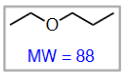
FRAGMENTATION PATTERNS



alpha-cleavage

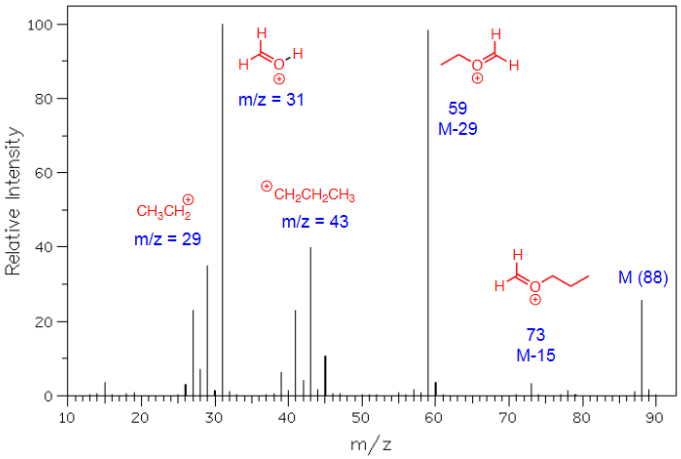


inductive cleavage

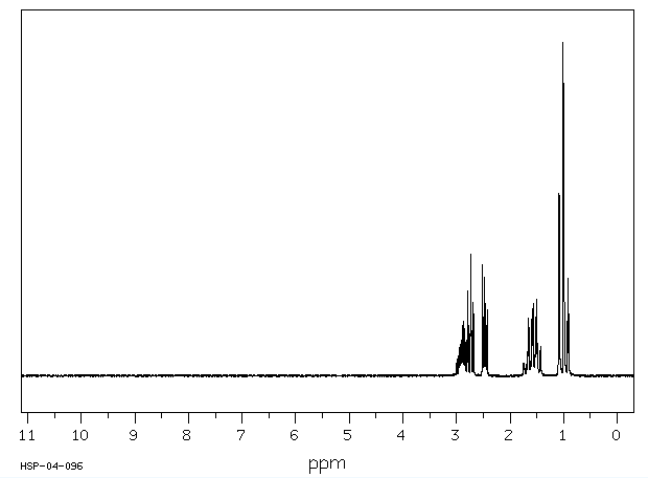


Ethers

ethyl propyl ether



EXERCISE 18.9.1



Source: SDBSWeb : http://sdbs.db.aist.go.jp

Answer

2-Ethyloxirane

18.10: INTERCHAPTER - A PREVIEW OF CARBONYL CHEMISTRY

So far, in our survey of the oxygen-containing organic compounds, we have studied the chemistry of ethers and alcohols. Now we turn our attention to a much larger group of compounds—those containing a carbonyl group:

The variety of carbonyl compounds is so wide, and their chemistry so extensive, that we shall need the next five chapters to discuss them thoroughly. One advantage of this course is that we have divided up the discussion of carbonyl compounds so that this large amount of factual material can be studied in small, readily digestible blocks.

The purpose of this chapter is to provide a general outline of what is to follow in the next five chapters: the various types of carbonyl compounds are introduced, the nature of the carbonyl group is explained, and the four most common mechanisms by which carbonyl groups react are described in general terms.

CHAPTER OBJECTIVES

When you have completed this chapter, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. identify the various types of carbonyl compounds.
3. write the mechanism of each of the four general types of reactions discussed in the chapter.
4. define, and use in context, the key terms introduced in this chapter.

INTRODUCTION

OBJECTIVES

After completing this section, you should be able to give examples of the wide variety of biologically important, pharmaceutical and industrial compounds that contain one or more carbonyl groups.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- carbonyl group

STUDY NOTES

A “carbonyl group” consists of an sp^2-hybridized carbon atom that is joined to an oxygen atom by a double bond.

NATURAL OCCURRENCE OF 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.

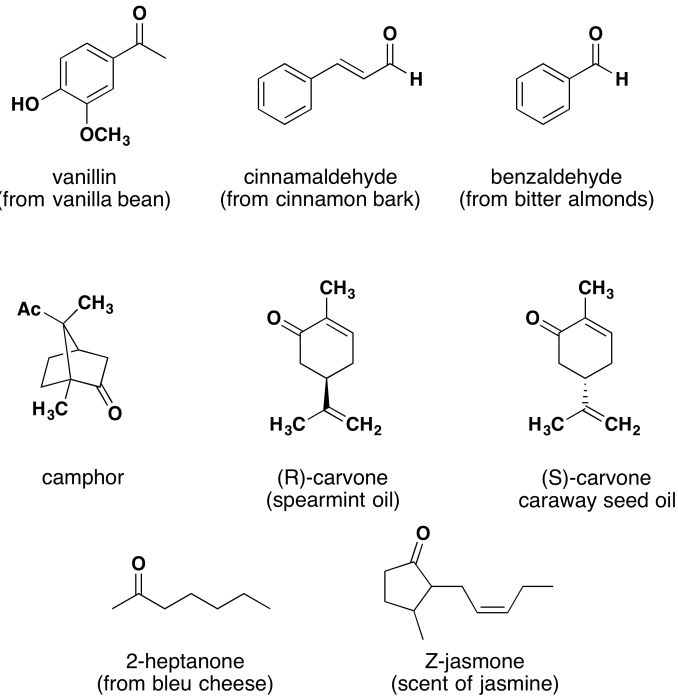


Figure 1. Aldehyde and ketone containing molecules isolated from plant sources.

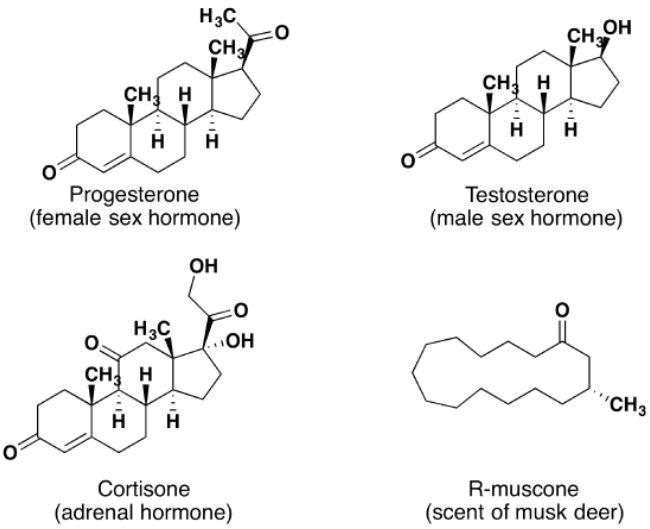


Figure 2. Aldehyde and ketone containing molecules isolated from animal sources.

I KINDS OF CARBONYL COMPOUNDS

OBJECTIVES

After completing this section, you should be able to

1. identify the following types of compounds as containing carbonyl groups: aldehydes, ketones, carboxylic acids, acid chlorides, acid anhydrides, esters, lactones, amides and lactams.
2. identify the important difference between aldehydes and ketones, and the other types of compounds listed under Objective 1, above.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- acyl fragment or acyl group

STUDY NOTES

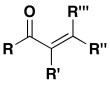
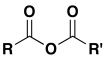
The idea of an “acyl group”

is not really new. Recall that in Chapter 16 we discussed the introduction of acyl groups into benzene rings by means of the Friedel-Crafts acylation reaction.

Note the use of the word “moiety” as an alternative to “group” or “fragment.”

Study the different types of carbonyl compounds listed in the table so that you can immediately recognize to which type a given compound belongs.

SOME CARBONYL COMPOUNDS

Compound	Aldehyde	Ketone	Formaldehyde	Carboxylic Acid	Ester	Amide	Enone	Acyl Halide	Acid Anhydride
Structure									
General Formula	RCHO	RCOR'	CH_2O	RCOOH	RCOOR'	RCONR'R''	RC(O)C(R')CR''R'''	RCOX	$(RCO)_2O$

One should also add to this list lactones (cyclic esters) and lactams (cyclic amides).

II NATURE OF THE CARBONYL GROUP

OBJECTIVES

After completing this section, you should be able to describe the electronic structure, polarity, and geometry of the carbonyl group.

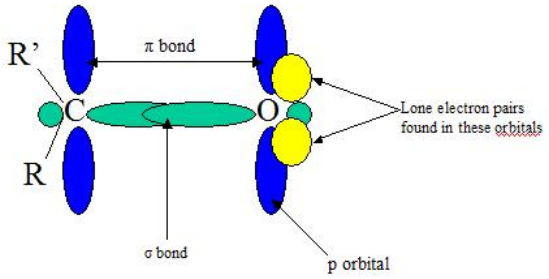
A carbonyl group is a chemically organic functional group composed of a carbon atom double-bonded to an oxygen atom --> [**C=O**] The simplest carbonyl groups are aldehydes and ketones usually attached to another carbon compound. These structures can be found in many aromatic compounds contributing to smell and taste.

INTRODUCTION

Before going into anything in depth be sure to understand that the **C=O** entity itself is known as the "Carbonyl group" while the members of this group are called "carbonyl compounds" --> **X**-C=O. The carbon and oxygen are usually sp^2 hybridized and planar.

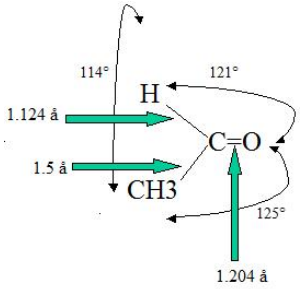
CARBONYL GROUP DOUBLE BONDS

The double bonds in alkenes and double bonds in carbonyl groups are VERY different in terms of reactivity. The C=C is *less* reactive due to C=O electronegativity attributed to the oxygen and its two lone pairs of electrons. One pair of the oxygen lone pairs are located in 2s while the other pair are in 2p orbital where its axis is directed perpendicular to the direction of the pi orbitals. The Carbonyl groups properties are directly tied to its electronic structure as well as geometric positioning. For example, the electronegativity of oxygen also polarizes the pi bond allowing the single bonded substituent connected to become electron withdrawing.



**Note: Both the pi bonds are in phase (top and botom blue ovals)*

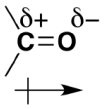
The double bond lengths of a carbonyl group is about 1.2 angstroms and the strength is about 176-179 kcal/mol). It is possible to correlate the length of a carbonyl bond with its polarity; the longer the bond meaing the lower the polarity. For example, the bond length in C=O is larger in acetaldehyde than in formaldehyde (this of course takes into account the inductive effect of CH_3 in the compound).



POLARIZATION

As discussed before, we understand that oxygen has two lone pairs of electrons hanging around. These electrons make the oxygen more electronegative than carbon. The carbon is then partially postive (electrophillic) and the oxygen partially negative (nucleophillic). The polarizability is denoted by a lowercase delta and a positive or negative superscript depending. For example, carbon would have d+ and oxygen delta^(-). The polarization of carbonyl groups also effects the boiling point of aldehydes and ketones to be higher than those of hydrocarbons in the same amount. The larger the carbonyl compound the less soluble it is in water. If the compound exceeds six carbons it then becomes insoluble.

**For more information about carbonyl solubility, look in the "outside links" section*



**Amides are the most stable of the carbonyl couplings due to the high-resonance stabilization between nitrogen-carbon and carbon-oxygen.*

III GENERAL REACTIONS OF CARBONYL COMPOUNDS

OBJECTIVES

After completing this section, you should be able to

1. list the four general reaction mechanisms that dominate the chemistry of carbonyl compounds.
2. discuss nucleophilic addition reactions of aldehydes and ketones (Chapter 19).
    a. write a general mechanism for nucleophilic addition to a carbonyl compound.
    b. write a detailed mechanism for the addition of a given nucleophile (e.g., a Grignard reagent) to an aldehyde or ketone.
3. discuss nucleophilic acyl substitution reactions of carboxylic acid derivatives (Chapter 21).
    a. write a general mechanism to illustrate nucleophilic acyl substitution reactions.
    b. write a detailed mechanism for the reaction of a given carbonyl-containing compound with a given nucleophile through a nucleophilic acyl substitution.
4. discuss alpha substitution reactions (Chapter 22).
    a. write a general mechanism to illustrate alpha-substitution of a carbonyl compound through the formation of an enol or enolate anion.
    b. explain the stability and ease of formation of enolate anions.
    c. write the detailed mechanism for the formation of an alpha-substituted carbonyl compound from the overall reaction of a carbonyl compound with a primary alkyl halide.
5. discuss carbonyl condensation reactions (Chapter 23).
    a. write a general mechanism to illustrate the condensation reaction that can occur between two molecules of a carbonyl compound; for example, the reaction of two molecules of acetaldehyde to form one molecule of aldol.

KEY TERMS

Note: All of these terms are defined in the “Study Notes,” below.

- aldol reaction
- alkylation
- alpha substitution
- carbonyl condensation
- enol
- enolate anion
- nucleophilic acyl substitution
- nucleophilic addition reaction

STUDY NOTES

A “nucleophilic addition reaction” (of a carbonyl compound) involves the initial attack of a nucleophile on the slightly positive carbonyl-carbon atom to form a tetrahedral intermediate.

In a “nucleophilic acyl substitution reaction,” a nucleophile attacks the carbonyl carbon of a carboxylic acid derivative

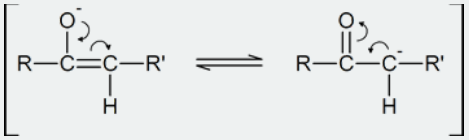
and initially produces a tetrahedral intermediate. The intermediate then reacts by expelling the leaving group, X, thereby forming a new carboxylic acid derivative.

In an “alpha substitution reaction” of a carbonyl compound, one of the hydrogen atoms attached to a carbon atom adjacent to the carbonyl group is removed and replaced by some other group.

Alpha substitution reactions of carbonyl compounds involve the “enol” form of the compound. Keto-enol tautomerism was briefly introduced in Section 9.4. Review this section if necessary.

keto form enol form

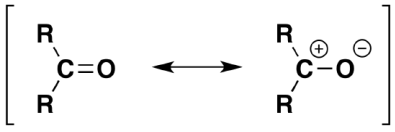
As you can see from the above diagram, the enol form has a hydroxyl group attached to one of the sp^2 hybridized carbon atoms of a carbon-carbon double bond. Removal of the proton from the hydroxyl group produces a resonance-stabilized “enolate anion”:



A “carbonyl condensation reaction” is one in which two carbonyl- containing molecules condense together (i.e., join together), often with the elimination of water. The reaction involves the formation of an enolate anion from one carbonyl-containing molecule, followed by the subsequent nucleophilic attack by this enolate anion on the carbonyl carbon atom of the second molecule.

NUCLEOPHILIC ADDITION TO A 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.



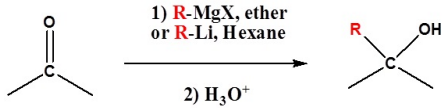
**Remember: due to the electronegative nature of oxygen the carbon is partially positive and oxygen is partially negative*

1 2 3

1. The Nucleophile (Nu) attacks the positively charged carbon and pushes one of the double bond electrons onto oxygen to give it a negative charge.
2. The Nucleophile is now a part of the carbon structure with a negatively charged oxygen and a Na^+ "floating" around.
3. The negatively charged oxygen attacks the proton (H^+) to give the resulting product above.

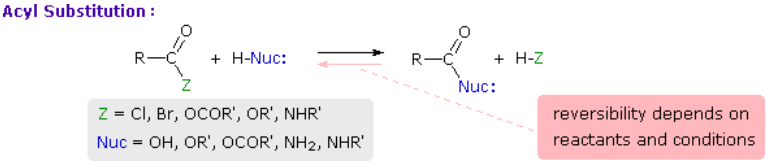
An Organometallic Example

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.

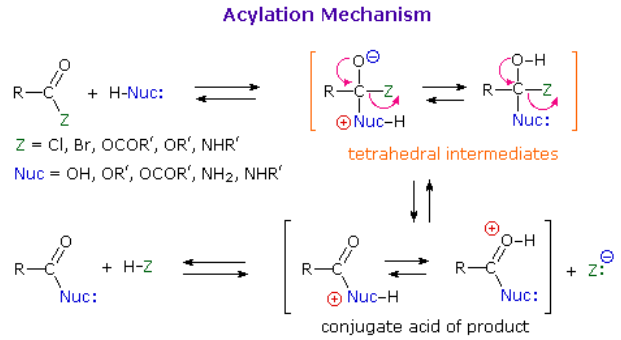


NUCLEOPHILIC ACYL SUBSTITUTION

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**.



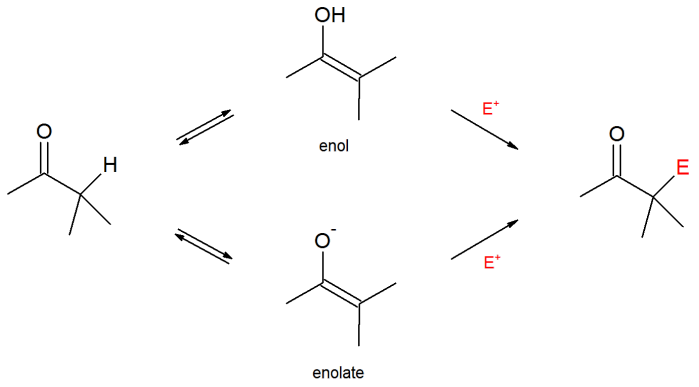
As illustrated in the following diagram, acylation reactions generally take place by an **addition-elimination process** in which a nucleophilic reactant bonds to the electrophilic carbonyl carbon atom to create a tetrahedral intermediate. This tetrahedral intermediate then undergoes an elimination to 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

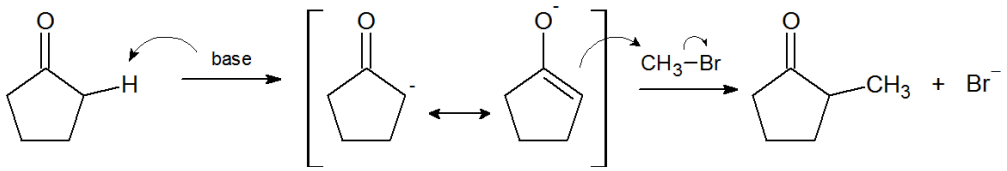
ALPHA-SUBSTITUTION REACTIONS

Now we will investigate reactions which occur a the carbon alpha to the carbonyl groups. These reactions involve two new nucleophilic species the enol and the enolate.



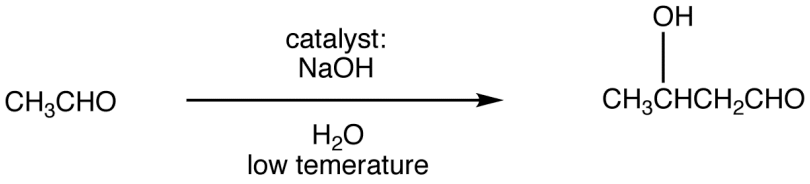
Note! The electrophile replaces the hydrogen on the alpha carbon.

The following is a specific example of this type of reaction. Here we methylate the carbon alpha to the carbonyl group through an enolate intermediate. The hydrogen on the alpha carbon is acidic because of the presence of the C=O group and is therefore preferentially abstracted by the base.



CARBONYL CONDENSATION REACTIONS

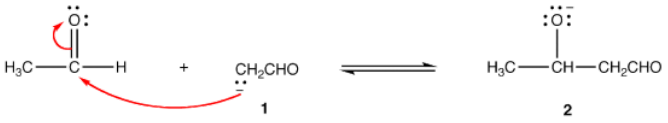
Enolizable aldehydes and enolizable ketones, in the presence of an acid or base catalyst usually in aqueous medium at low temperature, undergo a reaction, giving an aldol as the major product. This reaction is known as aldol reaction. The base-catalyzed aldol reaction, in which the catalyst is usually the hydroxide ion, is more common. Careful control of reaction temperature is critical because high temperatures promote aldol condensation. The optimum temperature depends on the nature of the aldehyde or ketone. Typically, heating the reaction mixture results in aldol condensation. For example:



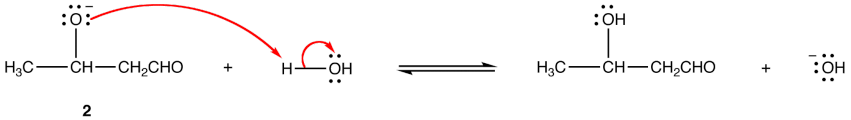
Mechanism:

Step 1: The hydroxide ion deprotanates the aldehyde reversibly.

Step 2: Enolate ion 1 adds to the unreacted aldehyde.



Step 3: Alkoxide ion 2 is protonated by water.



Since all three steps are reversible, the overall reaction is reversible and its equilibrium constant depends on the nature of the aldehyde or ketone. The reactions of aldehydes in which the α-carbon is a secondary carbon usually have large equilibrium constants; those of other

aldehydes and ketones have small equilibrium constants. These observations suggest that the equilibrium constant of aldol reaction is sensitive to steric hindrance at the carbonyl carbon in the aldehyde or ketone.

18.S: ETHERS AND EPOXIDES; THIOLS AND SULFIDES (SUMMARY)

CONCEPTS & VOCABULARY

18.0 Introduction

- Ethers are molecules containing oxygen which is bonded to two carbon groups.
- Thiols are sulfur analogues of alcohols with an SH group instead of OH.
- Sulfides are sulfur analogues of ethers with sulfur bonded to two carbon groups instead of oxygen.

18.1 Names and Properties of Ethers

- Ether groups are named as alkoxy groups.
- Ethers do not have intramolecular hydrogen bonding (unlike alcohols), therefore ethers have significantly reduced intermolecular forces causing boiling points that are much lower than similar sized alcohols.

18.2 Preparing Ethers

- Alkoxymercuration can be used to prepare an ether from an alkene.

18.3 Reactions of Ethers: Acidic Cleavage

- The carbon-oxygen bonds of ethers can be cleaved with strong acids through either nucleophilic substitution or elimination reactions.

18.4 Reactions of Ethers: Claisen Rearrangement

- The Claisen rearrangement is a [3, 3] sigmatropic rearrangement reaction that converts aryl or enol ethers into carbonyl compounds (though the aromatic version rearranges into a phenol to re-establish aromaticity.

18.5 Cyclic Ethers: Epoxides

- Epoxides, also called oxiranes, have a three-membered ring structure with one oxygen and two carbon atoms.
- Epoxides can be formed from alkenes by reaction with peroxy acids (MCPBA for example).
- Epoxides can be formed from halohydrin molecules by reaction with a base, which causes an intramolecular Williamson ether synthesis.

18.6 Reactions of Epoxides: Ring Opening

- When epoxides are ring opened under basic conditions, they follow S_N2 mechanism leading to the nucleophile adding to the less substituted side of the epoxide.
- When epoxides are ring opened under acidic conditions, they follow S_N1 mechanism leading to the nucleophile adding to the more substituted side of the epoxide.
- When epoxides are ring opened in aqueous reactions, the result is an anti-diol.
- Halo acids can be added to epoxides to form anti-halohydrins.

18.7 Crown Ethers

- Crown ethers are cyclic ethers containing several oxygen atoms.
- Crown ethers are named by the number of total atoms in the ring, followed by the word crown and finally the number of oxygen atoms (18-crown-6 for example).

18.8 Thiols and Sulfides

- Thiols can be prepared from alkyl halides through reaction with hydrosulfide ion (SH^-) or through a more complicated series of reactions including thiourea.
- Thiols can be oxidized with mild oxidizing agents to form disulfides.
- Disulfide bridges link cysteine residues in protein structures.
- Sulfides are sulfur analogues of ether, though are much better nucleophiles with sulfur in place of oxygen.

18.9 Spectroscopy of Ethers

- Ethers show standard C-H stretches and bends in IR along with a strong C-O stretch around 1000 cm^{-1}.
- In ^1H NMR, hydrogens on carbons adjacent to the oxygen typically appear between 3.4-4.5 ppm.
- Hydrogens on carbons of an epoxide ring typically appear between 2.5-3.5 ppm in ^1H NMR.

18.10 Interchapter: A Preview of Carbonyl Chemistry

- Carbonyl groups are one of the most important features in organic chemistry and consist of a sp^2 carbon double-bonded to oxygen.
- Carbonyl groups are present in ~10 different functional groups.
- Carbonyl groups are polarized with a partial positive charge on carbon and partial negative charge on oxygen. This makes the carbon atom an electrophile, while the oxygen can act as a nucleophile.

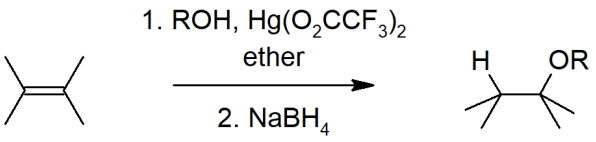
- Carbonyl groups can react through several mechanisms including nucleophilic addition and nucleophilic acyl substitution, alpha substitution and condensation.

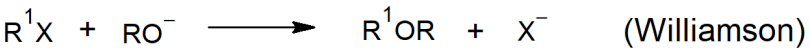
SKILLS TO MASTER

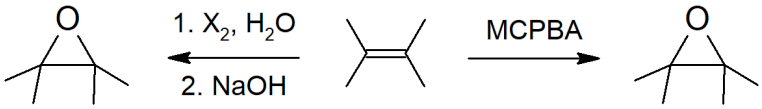
- Skill 18.1 Name ethers using common naming and IUPAC.
- Skill 18.2 Write reaction equations for preparation of ethers.
- Skill 18.3 Write mechanisms for reactions of ethers with strong halogen acids.
- Skill 18.4 Draw mechanisms for Cope and Claisen rearrangements.
- Skill 18.5 Draw mechanisms for ring-opening epoxides under acidic and basic conditions.
- Skill 18.6 Draw and name crown ethers.
- Skill 18.7 Explain how disulfide bridges contribute to protein structure.
- Skill 18.8 Give an example of S-adenosyl methionine activity in biological systems.
- Skill 18.9 Use IR and NMR spectra to identify ethers.

SUMMARY OF REACTIONS

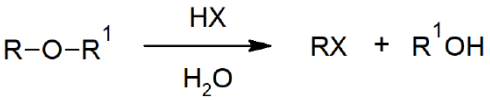
Ether and Epoxide Preparation

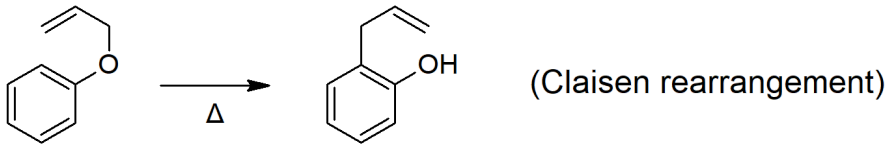


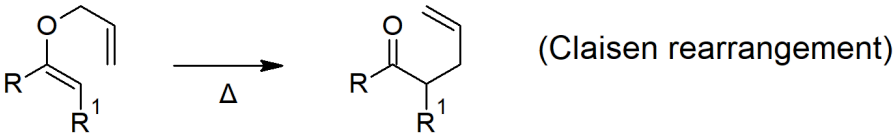




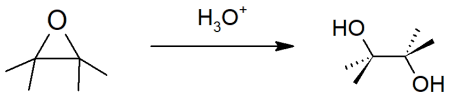
Ether Reactions

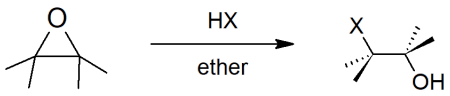


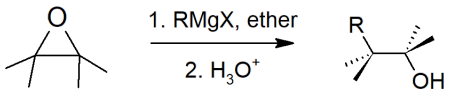


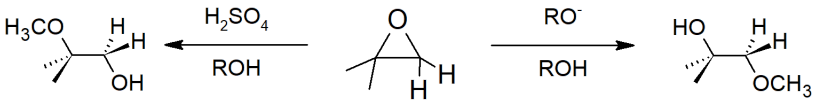


Epoxide Reactions

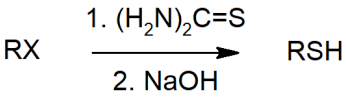


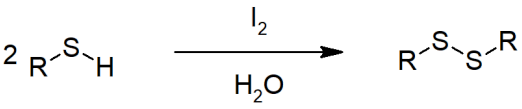


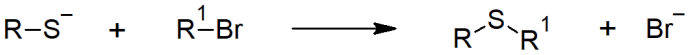


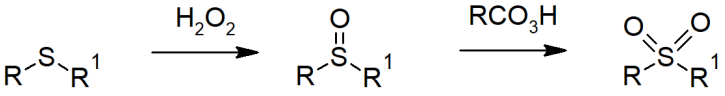


Sulfur Compound Reactions









CHAPTER OVERVIEW

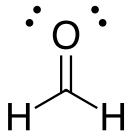
19: ALDEHYDES AND KETONES- NUCLEOPHILIC ADDITION REACTIONS

19.0: CHAPTER OBJECTIVES AND PREVIEW OF CARBONYL CHEMISTRY

OBJECTIVES

- fulfill all of the detailed objectives listed under each individual section.
- design a multi-step synthesis in which you may have to use any of the reactions discussed in this chapter together with any number of reactions from previous chapters.
- solve “road-map” problems that require a knowledge of the chemistry of aldehydes and ketones.
- use evidence from any combination of infrared spectroscopy, nuclear magnetic resonance spectroscopy, mass spectroscopy and chemical reactions to determine the structure of an unknown aldehyde or ketone.
- define, and use in context, the key terms introduced in this chapter.

In 1969 the molecule formaldehyde was discovered to be the first polyatomic organic molecule present in interstellar space by the National Radio Astronomy Observatory. The reactivity of formaldehyde gives it a wide variety of uses from embalming fluid to finger nail polish. Formaldehyde contain a C=O bond called a carbonyl, which is fundamental to study of organic chemistry. In this chapter we will begin a multi-chapter discussion on the chemistry of the carbonyl bond starting with aldehyde and ketone functional groups.



formaldehyde

In Chapter 19, we make a comprehensive study of the chemistry of aldehydes and ketones. Aldehydes and ketones are discussed together because their chemistry is very similar. However, as you work through the chapter, be sure to look for specific instances where the chemistry of these two classes of compounds differs.

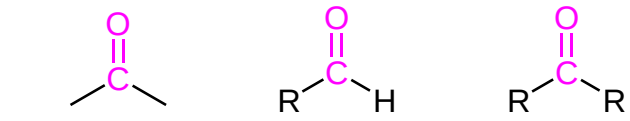
As usual, we begin the chapter with a discussion of nomenclature. This introduction is followed by descriptions of the methods used to prepare aldehydes and ketones in the laboratory. You will notice that a number of these reactions have already appeared in previous units. Note that an important difference between aldehydes and ketones is the resistance of ketones to oxidation.

A large part of this chapter is concerned with the addition of various nucleophiles to the carbonyl group of aldehydes and ketones. In particular, we discuss the addition of a variety of nitrogen-containing compounds, alcohols and phosphorus ylides. Many of these reactions are important to chemists concerned primarily with the synthesis of new organic compounds.

We also describe the Cannizzaro reaction and conjugate addition to α, β-unsaturated carbonyl compounds. We mention the occurrence of nucleophilic addition reactions in biological systems, and conclude the unit with a look at the use of spectroscopic techniques in the analysis of aldehydes and ketones.

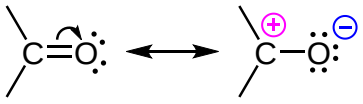
PREVIEW OF CARBONYL CHEMISTRY

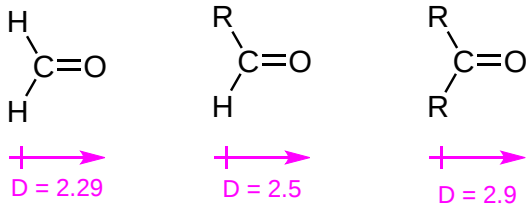
Aldehydes and ketones are organic compounds which incorporate a carbonyl functional group, C=O. The carbon atom of this group has two remaining bonds that may be occupied by hydrogen, alkyl or aryl substituents. If at least one of these substituents is hydrogen, the compound is an aldehyde. If both are carbons, the compound is a ketone.



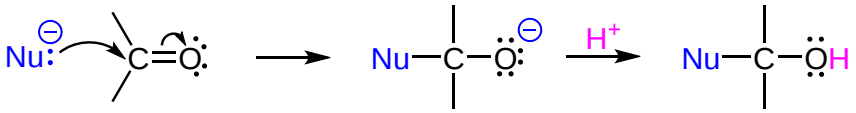
Carbonyl Group Aldehyde Ketone

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 below illustrate this polarity, and the relative dipole moments of formaldehyde, other aldehydes and ketones.





This polarity causes the carbonyl carbon to be partially positive (electrophillic) and the oxygen partially negative (nucleophillic). The C=O bond is prone to nucleophillic attack because or carbon's positive charge and oxygen's negative charge. In general, nucleophiles attack the electrophilic carbon and become a part of the structure while the oxygen is protonated forming a hydroxyl group.



Aldehydes and ketones are widespread in nature and are often combined with other functional groups. Examples of naturally occurring molecules which contain an 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.

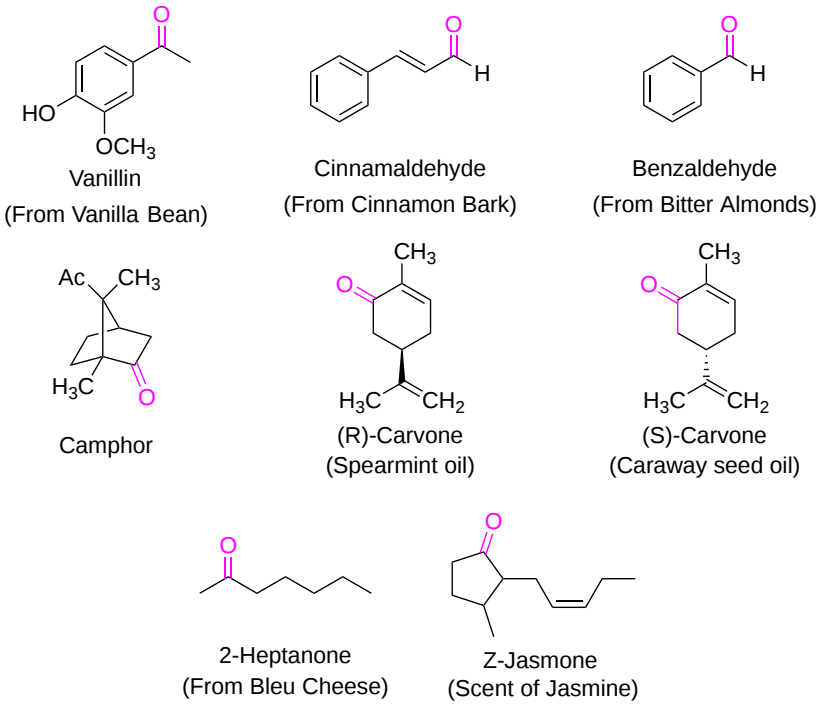


Figure 1. Aldehyde and ketone containing molecules isolated from plant sources.

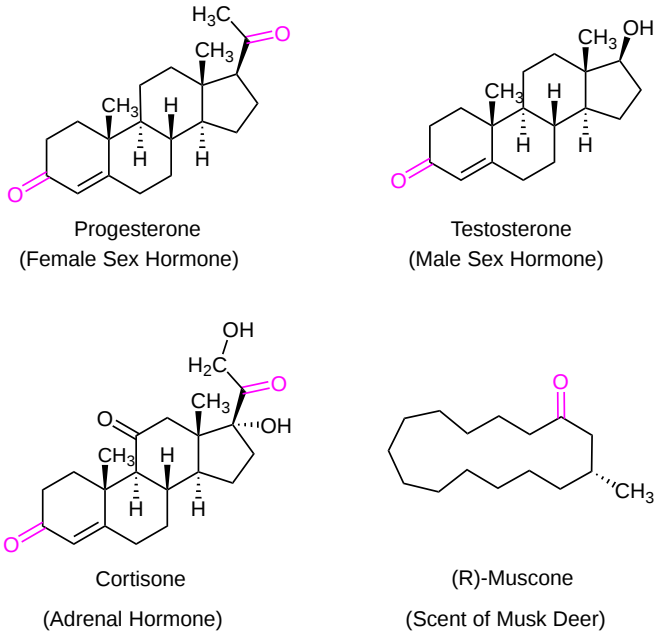


Figure 2. Aldehyde and ketone containing molecules isolated from animal sources.

CONTRIBUTORS AND ATTRIBUTIONS

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
-
- Layne Morsch (University of Illinois Springfield)

19.1: NAMING ALDEHYDES AND KETONES

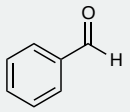
OBJECTIVES

After completing this section, you should be able to

- provide the IUPAC name of an aldehyde or ketone, given its Kekulé, condensed, or skeletal structure.
- draw the structure of an aldehyde or ketone, given its IUPAC name.
- draw the structure of the following aldehydes and ketones, given their common names: formaldehyde, acetaldehyde, benzaldehyde, acetone, acetophenone, benzophenone.

STUDY NOTES

We will only use those common names listed under Objective 3, above. We will use systematic names in all other cases. For example, the systematic name of the compound shown below is benzenecarbaldehyde, but it has the common name of benzaldehyde.



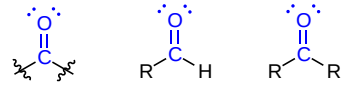
benenecarbaldehyde
(benzaldehyde)

When naming unsaturated aldehydes and ketones, you must give the carbonyl group "priority" over the double bond when you are deciding which end of the carbon chain to begin numbering The carbonyl-carbon of an aldehyde will always be at the end of the carbon chain in an acyclic compound; and therefore numbering always starts at this carbon. It is for this reason, too, that the number "1" is not required when naming a compound such as 2-ethyl-4-methylpentanal.

The 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 TO NAMING CARBONYLS

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**.

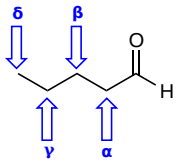


carbonyl group | aldehyde | ketone

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.



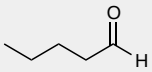
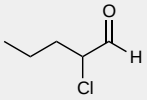
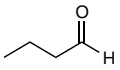
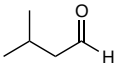
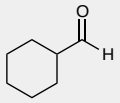
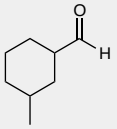
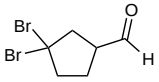
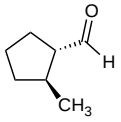
If the aldehyde group (-CHO) is attached to a ring the suffix ***–carbaldehyde*** is added to the name of the ring. The carbon attached to this group will get the #1 location number in naming the ring.

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 19.1.1

The IUPAC system names are given on top while the common name is given on the bottom in parentheses.

 methanal (formaldehyde)	 ethanal (acetaldehyde)
 pentanal (valeraldehyde)	 2-chloropentanal (α-chlorovaleraldehyde)
 butanal (butyraldehyde)	 3-methylbutanal (isovaleraldehyde)
 cyclohexanecarbaldehyde	 3-methylcyclohexanecarbaldehyde
 3,3-dibromocyclopentanecarbaldehyde	 *trans*-2-methylcyclopentanecarbaldehyde

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.

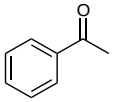
SUMMARY OF KETONE NOMENCLATURE RULES

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 simple ketones are known by their common names. Such as *propanone* which is commonly referred to as *acetone*.

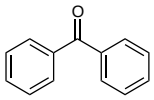
✔ EXAMPLE 19.1.2

The IUPAC system names are given on top while the common name is given on the bottom in parentheses.

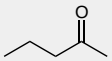
propanone
(acetone)



acetophenone
(methyl phenyl ketone)

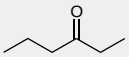


benzophenone
(diphenyl ketone)



2-pentanone
(methyl propyl ketone)

3-methyl-2-butanone
(methyl isopropyl ketone)

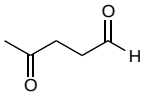


3-hexanone
(ethyl propyl ketone)

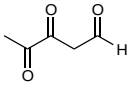
NAMING ALDEHYDES AND KETONES IN THE SAME MOLECULE

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.

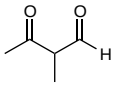
EXAMPLE 19.1.3



4-oxopentanal



3,4-dioxopentanal

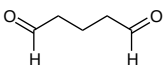


2-methyl-3-oxobutanal

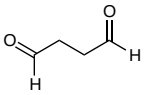
NAMING DIALDEHYDES AND DIKETONES

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 19.1.4



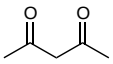
pentanedial



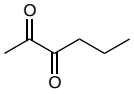
butanedial

For diketones both carbonyls require a location number. The ending **-dione** is added to the end of the parent chain.

EXAMPLE 19.1.5



2,4-pentanedione



2,3-hexanedione

NAMING CYCLIC KETONES AND DIKETONES

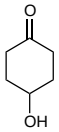
In cyclic ketones the carbonyl group is assigned location position #1, and this number is not included in the name, unless more than one carbonyl group is present. The rest of the ring is numbered to give substituents the lowest possible location numbers. Remember the prefix **cyclo** is included before 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.

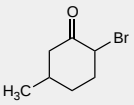
With cycloalkanes which contain two ketones both carbonyls need to be given a location numbers. Also, an **–e** is not removed from the end but the suffix **–dione** is added.

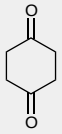
EXAMPLE 19.1.6


cyclopentanone


2-bromocyclopentanone


4-hydroxycyclohexanone


2-bromo-5-methylcyclohexanone

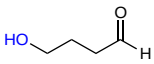

1,4-cyclohexanedione

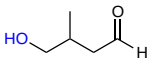

1,2-cyclopentanedione

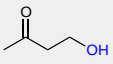
NAMING CARBONYLS AND HYDROXYLS IN THE SAME MOLECULE

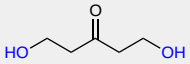
When an aldehyde or ketone is present in a molecule which also contains an alcohol functional group the carbonyl is given nomenclature priority by the IUPAC system. This means that the carbonyl is given the lowest possible location number and the appropriate nomenclature suffix is included. In the case of alcohols the **OH** is named as a **hydroxyl** substituent. However, the **l** in hydroxyl is generally removed.

EXAMPLE 19.1.7


4-hydroxybutanal


4-hydroxy-3-methylbutanal


4-hydroxy-2-butanone


1,5-dihydroxy-3-pentanone

NAMING CARBONYLS AND ALKENES IN THE SAME MOLECULE

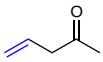
When an aldehyde or ketone is present in a molecule which also contains an alkene functional group the carbonyl is given nomenclature priority by the IUPAC system. This means that the carbonyl is given the lowest possible location number and the appropriate nomenclature suffix is included.

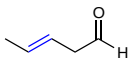
When carbonyls are included with an alkene the following order is followed:

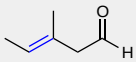
(Location number of the alkene)-(Prefix name for the longest carbon chain minus the **-ane** ending)-(an **-en** ending to indicate the presence of an alkene)-(the location number of the carbonyl if a ketone is present)-(either an **–one** or and **-anal** ending).

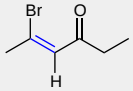
Remember that the carbonyl has priority so it should get the lowest possible location number. Also, remember that cis/tran or E/Z nomenclature for the alkene needs to be included if necessary.

EXAMPLE 19.1.8


4-penten-2-one


trans-3-pentenal

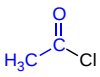

(*E*)-3-methyl-3-pentenal


(*Z*)-5-bromo-4-hexen-3-one

ALDEHYDES AND KETONES AS FRAGMENTS

- **Alkanoyl** is the common name of the R-C=O fragment, though the older naming, *acyl*, is still widely used.
- **Formyl** is the common name of the H-C=O fragment.
- **Acetyl** is the common name of the CH_3-C=O- fragment.

EXAMPLE 19.1.9



acetyl chloride

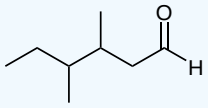
acetylaldehyde

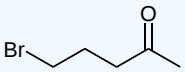
formyl fluoride

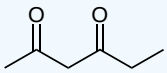
EXERCISES

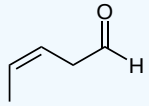
EXERCISE 19.1.1

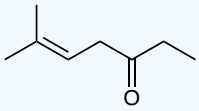
Give the IUPAC name for each compound:

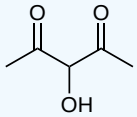
a) 

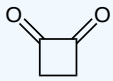
b) 

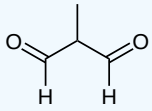
c) 

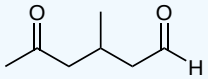
d) 

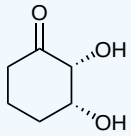
e) 

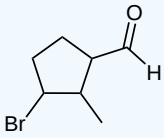
f) 

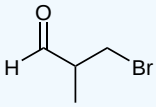
g) 

h) 

i) 

j) 

k) 

l) 

Answer

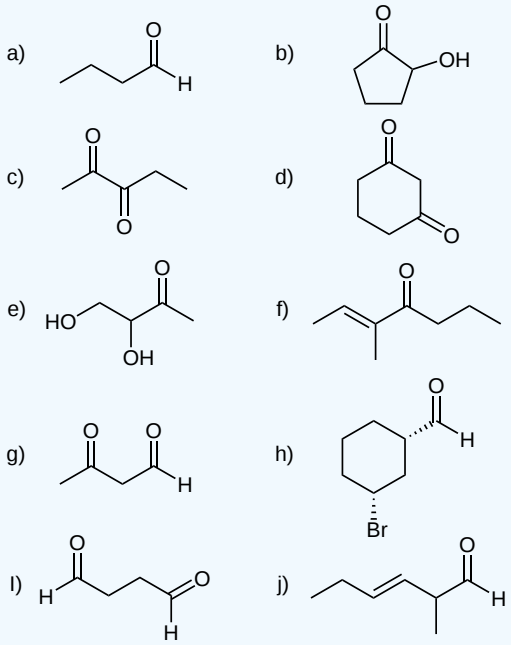
a. 3,4-dimethylhexanal
b. 5-bromo-2-pentanone
c. 2,4-hexanedione
d. *cis*-3-pentenal
e. 6-methyl-5-hepten-3-one
f. 3-hydroxy-2,4-pentanedione
g. 1,2-cyclobutanedione
h. 2-methyl-propanedial
i. 3-methyl-5-oxo-hexanal
j. *cis*-2,3-dihydroxycyclohexanone
k. 3-bromo-2-methylcyclopentanecarboaldehyde
l. 3-bromo-2-methylpropanal

EXERCISE 19.1.2

Give the structure corresponding to each IUPAC name:

a. butanal
b. 2-hydroxycyclopentanone
c. 2,3-pentanedione
d. 1,3-cyclohexanedione
e. 3,4-dihydoxy-2-butanone
f. 3-methyl-2-hepten-4-one
g. 3-oxobutanal
h. *cis*-3-bromocyclohexanecarboaldehyde
i. butanedial
j. *trans*-2-methyl-3-hexenal

Answer



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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.

19.2: PREPARING ALDEHYDES AND KETONES

OBJECTIVES

After completing this section, you should be able to

1. describe in detail the methods for preparing aldehydes discussed in earlier units (i.e., the oxidation of primary alcohols and the cleavage of alkenes).
2. write an equation to describe the reduction of an ester to an aldehyde.
   a. identify the product formed when a given ester is reduced with diisobutylaluminum hydride.
   b. identify the reagents and conditions used in the reduction of an ester to an aldehyde.
   c. identify the disadvantages of using diisobutylaluminum hydride to reduce an ester to an aldehyde.
3. describe in detail the methods for preparing ketones discussed in earlier units (i.e., the oxidation of secondary alcohols, the ozonolysis of alkenes, Friedel-Crafts acylation, and the hydration of terminal alkynes).
   a. write an equation to illustrate the formation of a ketone through the reaction of an acid chloride with a dialkylcopper lithium reagent.
   b. identify the ketone produced from the reaction of a given acid chloride with a specified dialkylcopper lithium reagent.
   c. identify the acid chloride, the dialkylcopper lithium reagent, or both, needed to prepare a specific ketone.

STUDY NOTES

You may wish to review the sections in which we discuss the oxidation of alcohols (17.7) and the cleavage of alkenes (8.8). A third method of preparing aldehydes is to reduce a carboxylic acid derivative; for example, to reduce an ester with diisobutylaluminum hydride (DIBAL-H).

There are essentially five methods of preparing ketones in the laboratory. Four of them have been discussed in earlier sections:

1. the oxidation of a secondary alcohol—Section 17.7.
2. the ozonolysis of an alkene—Section 8.8.
3. Friedel-Crafts acylation—Section 16.3.
4. the hydration of a terminal alkyne—Section 9.5.

The "new" method we introduce in this section involves the reaction of an acid chloride with a diorganocopper reagent. The latter substances were discussed in Section 10.9, which you might now wish to review.

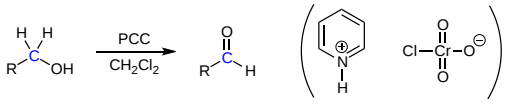
Aldehydes and ketones can be prepared using a wide variety of reactions. Although these reactions are discussed in greater detail in other sections, they are listed here as a summary and to help with planning multistep synthetic pathways. Please use the appropriate links to see more details about the reactions.

FORMATION OF ALDEHYDES

OXIDATION OF 1^{O} ALCOHOLS TO FORM ALDEHYDES (SECTION 17.7)

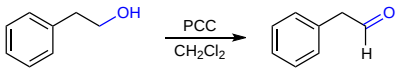
PCC

Pyridinium chlorochromate (PCC) is a milder version of chromic acid. 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.



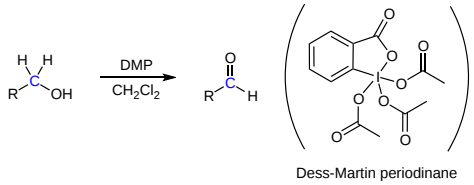
pyridinium chlorochromate (PCC)

Example oxidation of a primary alcohol to an aldehyde

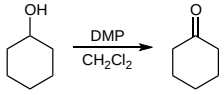


DESS-MARTIN PERIODINANE (DMP)

PCC is being replaced in laboratories by Dess-Martin periodinane (DMP), which has several practical advantages over PCC, such as producing higher yields and requiring less rigorous reaction conditions. DMP is named after Daniel Dess and James Martin, who developed it in 1983. Similar to PCC, it oxidizes primary alcohols to aldehydes without continuing the oxidation to a carboxylic acid. It can also be used to oxidize secondary alcohols to ketones.

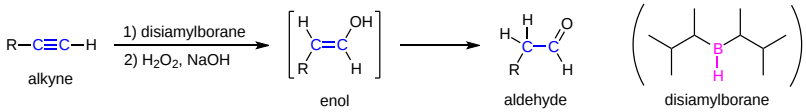


Example oxidation of an alcohol to a ketone using DMP

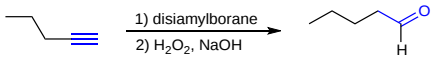


HYDRATION OF AN ALKYNES TO FORM ALDEHYDES (SECTION 9.5)

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. This can be accomplished by hydroboration-oxidation reactions.

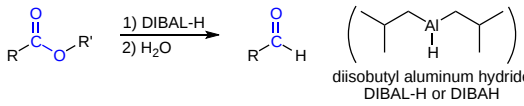


Example reaction of a terminal alkyne with disiamylborane followed by oxidation with hydrogen peroxide and hydroxide converting 1-pentyne to pentanal.



HYDRIDE REDUCTION OF ESTERS TO FORM ALDEHYDES (SECTION 21.8)

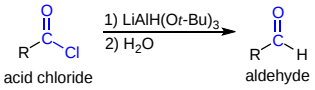
Various hydride sources allow for the partial reduction of some carboxylic acid derivatives to form aldehydes. These reactions are usually carried out at low temperatures (-78 ^{o}C) to prevent over reaction with the aldehyde product.



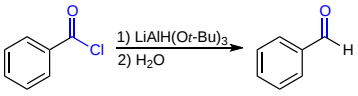
DIBAL-H reduction of methyl benzoate to benzaldehyde

HYDRIDE REDUCTION OF ACID CHLORIDES TO FORM ALDEHYDES (SECTIONS 21.6)

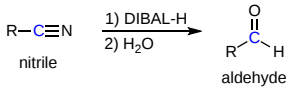
Reduction of acid chlorides to aldehydes requires hydride reagents with reduced reactivity as lithium aluminum hydride will continue reducing to the primary alcohol.



Example reduction of an acid halide to form an aldehyde



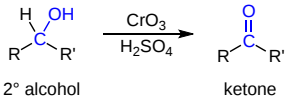
HYDRIDE REDUCTION OF A NITRILE TO FORM ALDEHYDES



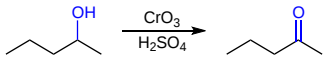
FORMATION OF KETONES

OXIDATION OF 2^{O} ALCOHOLS TO FORM KETONES (SECTION 17.7)

Oxidation of 2^{o} alcohols to form ketones typically uses Jones reagent (CrO_3 in H_2SO_4) but many other oxidizing agents can be used.

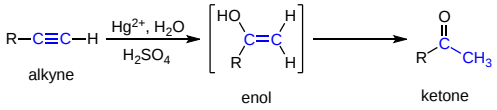


Example oxidation of a secondary alcohol to a ketone

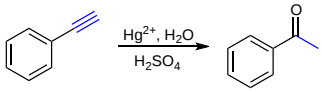


HYDRATION OF ALKYNES TO FORM KETONES (SECTION 9.4)

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.

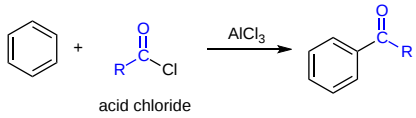


Example reaction of an alkyne with Hg^{2+}, H_2O, and H_2SO_4 to give a ketone

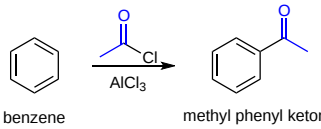


FRIEDEL-CRAFTS ACYLATION TO FORM A KETONE (SECTION 16.3)

Aromatic ketones can synthesized through Friedel–Crafts acylation of an aromatic ring with an acid chloride. Aluminum chloride ($AlCl_3$) is used as a Lewis acid catalyst.

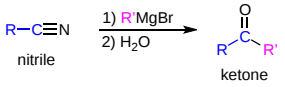


Example of Friedel-Crafts acylation to form a ketone from benzene.

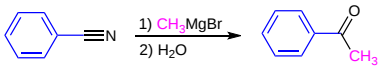


REACTION OF GRIGNARD REAGENTS WITH NITRILES TO FORM KETONES (SECTION 20.7)

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.

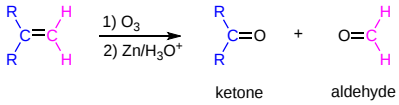


Example of Grignard addition to a nitrile to give a ketone.

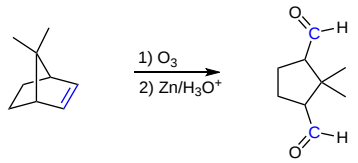


ALKENES CAN BE CLEAVED USING OZONE (O_3) TO FORM ALDEHYDES AND/OR KETONES (SECTION 8.8)

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.

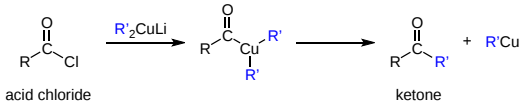


Example ozonolysis of an alkene to form aldehydes.

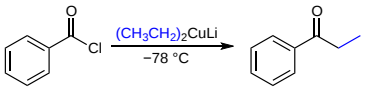


ORGANOCUPRATE REAGENTS CONVERT ACID CHLORIDES TO KETONES (SECTION 21.4)

An important reaction exhibited by lithium alkylcopper reagents (Gilman Reagents), is the nucleophilic addition to acid chlorides. Gilman reagents are a source of carbanion like nucleophiles similar to Grignard and Organolithium reagents. However, the reactivity of organocuprate reagents is slightly different and this difference is exploited to allow for a single nucleophilic addition to form a ketone.



Example of organocuprate addition to an acid chloride to generate a ketone.



? EXERCISE 19.2.1

What reagents would be required to prepare hexanal from the following starting materials?

a. $CH_3CH_2CH_2CH_2CH_2CH_2OH$
b. $CH_3CH_2CH_2CH_2CH_2CH{=}CH_2$
c. $CH_3CH_2CH_2CH_2CO_2CH_3$
d. $CH_3CH_2CH_2CH{=}CH_2$

Answer

a. Dess–Martin periodinane or PCC in CH_2Cl_2
b. 1. O_3, 2. Zn/H_3O^+
c. 1. DIBAH 2. H_2O
d. 1. BH_3 2. $H_2O_2/NaOH$; 2. Dess–Martin periodinane or PCC

19.3: OXIDATION OF ALDEHYDES AND KETONES

OBJECTIVES

After completing this section, you should be able to

- write an equation for the oxidation of an aldehyde using
  - CrO_3/sulphuric acid.
  - Tollens reagent.
- explain the difference in structure which makes aldehydes susceptible to oxidation and ketones difficult to oxidize.
- identify the carboxylic acid produced when a given aldehyde is oxidized.
- identify the aldehyde, the oxidizing agent, or both, needed to prepare a given carboxylic acid.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- Tollens reagent

STUDY NOTES

An important difference between aldehydes and ketones is the ease with which the latter can be oxidized. Tollen's reagent is a classical organic laboratory technique to test for the presence of an aldehyde. The reagent consists of silver(I) ions dissolved in dilute ammonia. When the aldehyde is oxidized, the silver(I) ions are reduced to silver metal. When the reaction is carried out in a test-tube, the metallic silver is deposited on the walls of the tube, giving it a mirrorlike appearance. This characteristic accounts for the term "silver mirror test" which is applied when this reaction is used to distinguish between aldehydes and ketones—the latter, of course, do not react.

WHY DO ALDEHYDES AND KETONES BEHAVE DIFFERENTLY?

Aldehydes have a proton attached to the carbonyl carbon which can be abstracted, allowing them to be easily oxidized to form carboxylic acids. The lack of this hydrogen, makes ketones generally inert to these oxidation conditions. Nevertheless, ketones can be oxidized but only under extreme conditions.

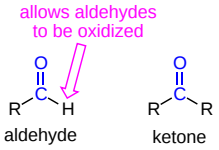


Figure 19.3.1: This characteristic accounts for the term "silver mirror test" which is applied when this reaction is used to distinguish between aldehydes and ketones—the latter, of course, do not react.

A significant distinction between aldehydes and ketones lies in their susceptibility to oxidation, with aldehydes being more easily oxidized than ketones. One of the classic methods for identifying aldehydes in the laboratory is through the use of **Tollen's reagent** which consists of silver(I) ions dissolved in dilute ammonia. When an aldehyde is present, it undergoes oxidation, causing the silver(I) ions to be reduced to metallic silver. This reduction results in the deposition of silver on the surface of the test tube, forming a reflective, mirror-like coating. This reaction is commonly referred to as the "silver mirror test," and it serves as a reliable way to distinguish aldehydes from ketones. Ketones, in contrast, do not react with Tollen's reagent, making this test specific for aldehydes.

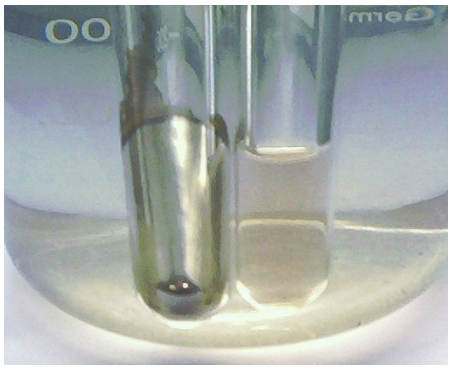
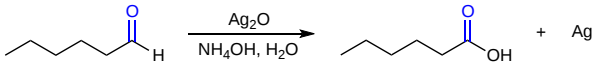


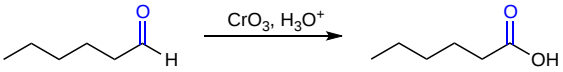
Figure 19.3.2: Tollens test for Aldehyde. The left side is positive (silver mirror) and the right side is negative.



Oxidation of hexanal to form hexanoic acid using Tollens Reagent

OXIDATION OF ALDEHYDES

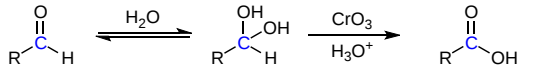
There are a wide variety of reagents which can cause the oxidation of aldehydes to carboxylic acids. The most common reagent for this conversion is CrO_3 in aqueous acid also called **Jones Reagent**. This reaction generally gives good yields at room temperature.



Example of the oxidation of hexanal to form hexanoic acid using Jones Reagent

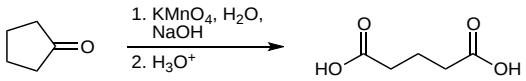
MECHANISM

The oxidation of aldehydes occur through the reversible nucleophilic addition of water to the carbonyl to form a gem-diol functional group. This addition reaction is discussed in greater detail in Section 19.5. One of the OH groups of the *gem*-diol is oxidized to create a carbonyl (C=O) thereby forming a carboxylic acid.



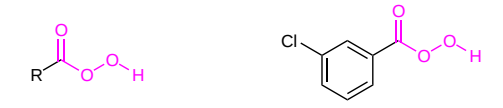
OXIDATION OF KETONES AND BAEYER-VILLIGER OXIDATION

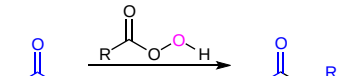
Because ketones do not have hydrogen atom attached to their carbonyl, they are resistant to oxidation. Only very strong oxidizing agents such as potassium manganate(VII) (potassium permanganate) solution oxidize ketones. However, this type of powerful oxidation occurs with cleavage, breaking carbon-carbon bonds and forming two carboxylic acids. Because of this destructive nature this reaction is rarely used.



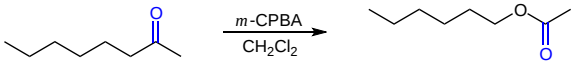
Oxidation of cyclopentanone to form pentanedioic acid

Peroxycarboxylic acids, such as **meta-chloroperoxybenzoic acid (mCPBA)**, are capable of oxidizing ketones to esters in a reaction known as the **Baeyer-Villiger oxidation**. Baeyer-Villiger oxidation has considerable synthetic utility because ketones normally are difficult to oxidize without degrading the structure to smaller fragments.

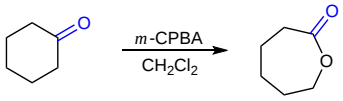




Baeyer-Villiger oxidations can be used with both straight chain ketones and cyclic ketones as shown in the following examples.



Baeyer-Villiger Oxidation of 2-octanone to form hexyl ethanoate

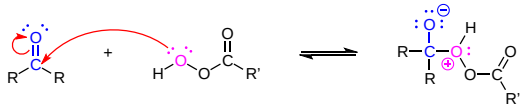


Baeyer-Villiger Oxidation of cyclohexanone to 6-hexanolactone

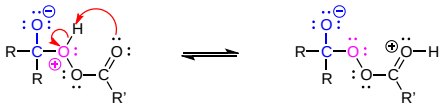
MECHANISM

The mechanism of the Baeyer-Villiger oxidation has been studied extensively and is of interest because it involves a rearrangement step in which a substituent group (R) moves from a carbon to an oxygen. In the first step, one oxygen from the peroxy carboxylic acid adds to the carbonyl group of the ketone. The adduct has multiple oxygen atoms on which protons can reside. An intramolecular proton transfer followed by protonation allows for generation of the Criegee intermediate. Migration of an alkyl group and elimination of a carboxylic acid, R^1CO_2H, then occur in the fourth step. This generates a protonated form of the ester product, which is deprotonated in the final step of the mechanism.

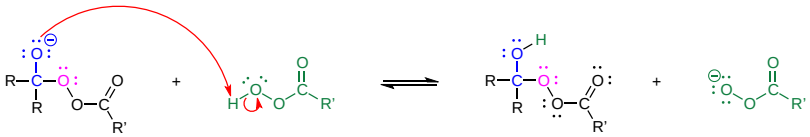
STEP 1: NUCLEOPHILIC ATTACK ON THE CARBONYL



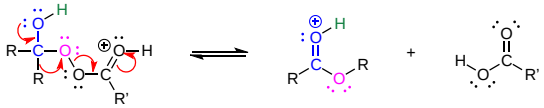
STEP 2: INTRAMOLECULAR PROTON TRANSFER



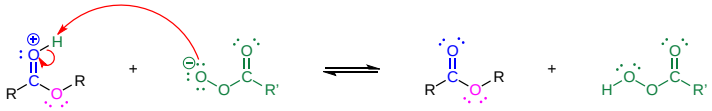
STEP 3: PROTONATION OF THE ALKOXIDE



STEP 4: MIGRATION OF AN ALKYL GROUP



STEP 5: DEPROTONATION



19.4: NUCLEOPHILIC ADDITION REACTIONS OF ALDEHYDES AND KETONES

OBJECTIVES

After completing this section, you should be able to

- give a general description of the nucleophilic addition reactions of aldehydes and ketones, identifying the two possible courses (or variations) that such reactions can take after the initial attack by the nucleophile.
- explain why, in general, aldehydes undergo nucleophilic addition reactions more readily than do ketones, and determine which of two given aldehydes or ketones will react most readily in such reactions.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

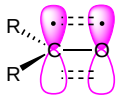
- nucleophilic addition reaction

STUDY NOTES

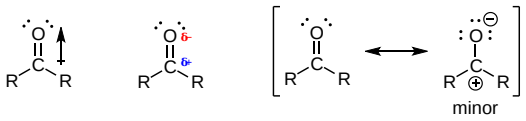
We have already discussed electrophilic addition reactions at some length; in this section nucleophilic addition reactions will be presented. Nucleophilic addition reactions involve the initial attack of a nucleophile on the slightly positive carbon center of the carbonyl group.

INTRODUCTION

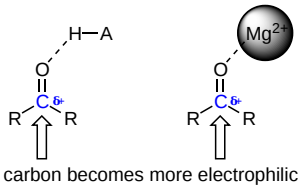
Before we consider in detail the reactivity of aldehydes and ketones, we need to look back and remind ourselves of what the bonding picture looks like in a carbonyl. Carbonyl carbons are sp^2 hybridized, with the three sp^2 orbitals forming three sigma bonds by overlapping with orbitals from the R groups (carbons or hydrogens) and an sp^2 hybrid orbital from oxygen. Due to the sp^2 orbitals, these three bonds adopt trigonal planar geometry seen in carbonyls. The carbonyl carbon's remaining unhybridized 2p orbital is perpendicular to this plane, and forms a 'side-by-side' pi bond by overlapping with a 2p orbital from the carbonyl oxygen.



The carbon-oxygen double bond is polar since 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 (pointing toward the more electronegative atom), or by showing the oxygen as holding a partial negative charge and the carbonyl carbon with 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 pi bond 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.



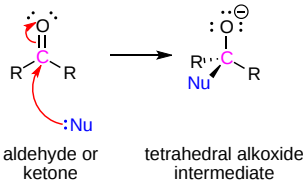
The result of carbonyl bond polarization, however it is depicted, is straightforward to predict. The carbon, because it is electron-poor, is an electrophile: it is a great target for attack by an electron-rich nucleophilic group. Because the oxygen end of the carbonyl double bond bears a partial negative 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 (Mg^{2+}), is located near the carbonyl oxygen.



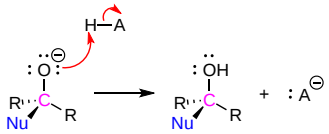
NUCLEOPHILIC ADDITION TO A CARBONYL

Most important reactions involving carbonyl groups characteristically have a nucleophilic addition as part of their mechanism. The generic mechanism for the nucleophilic addition of a negatively charged nucleophile to a carbonyl is shown below.

In the first step of the nucleophilc addition mechanism, the nucleophile forms a bond with the the electrophilic C=O carbon atom. This causes the rehybridization of the carbonyl carbon from sp^2 to sp^3. These reactions differ from nucleophilic substitution reactions since neither aldehydes nor ketones have a leaving group. Instead electrons in the pi bond are pushed up to the electronegative oxygen atom forming a tetrahedral alkoxide intermediate.

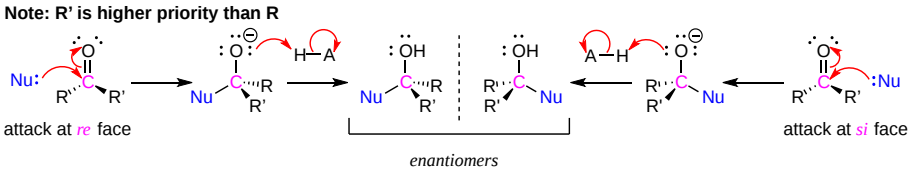


In the second step of the mechanism, the alkoxide is protonated by the addition of an acid to form an alcohol.



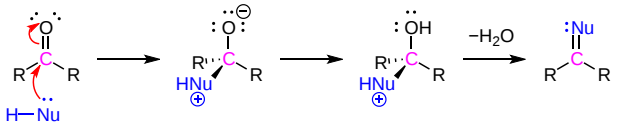
STEREOCHEMISTRY OF NUCLEOPHILIC ADDITION TO A CARBONYL

When the two groups adjacent to a carbonyl are not the same, we can distinguish between the **re** and **si** 'faces' of the planar structure. The concept of a trigonal planar group having two distinct faces comes into play when we consider the stereochemical outcome of a nucleophilic addition reaction. Notice that in the course of a carbonyl addition reaction, the hybridization of the carbonyl carbon changes from sp^2 to sp^3, meaning that the bond geometry changes from trigonal planar to tetrahedral. If the two R groups are not equivalent, then a chiral center is created upon addition of the nucleophile. The configuration of the new chiral center depends upon which side of the carbonyl plane the nucleophile attacks from. Reactions of this type often result in a 50:50 racemic mixture of stereoisomers, but it is also possible that one stereoisomer may be more abundant, depending on the structure of the reactants and the conditions under which the reaction takes place.



NUCLEOPHILIC ADDITION OF A NEUTRAL NUCLEOPHILE

Neutral nucleophiles can also undergo nucleophilic addition to carbonyls. The mechanism is slightly different than with a negatively charged nucleophile. The presence of an additional hydrogen atom in the nucleophile allows for the the carbonyl oxygen to be completely removed as water and a C=Nu bond to be formed.



RELATIVE REACTIVITY OF ALDEHYDES AND KETONES TO NUCLEOPHILIC ADDITION

In general, aldehydes are more reactive than ketones because they have a greater polarization of the carbonyl bond. The primary carbocation formed in the polarizing resonance structure of an aldehyde (shown below) is less stable and therefore more reactive than the secondary carbocation formed in a similar resonance structure formed by a ketone. The stability difference in these resonance structures is due to the extra alkyl group present in the ketone. Alky groups stabilize carbocations through induction as discussed in Section 7.11.

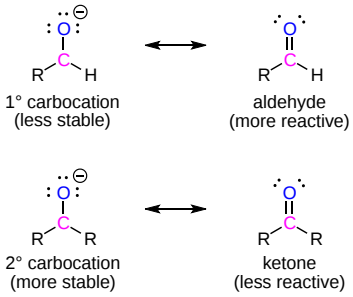


Figure 19.4.1). The carbonyl carbon of formaldehyde is more positive (more blue) and therefore more reactive towards nucleophlic addition than the carbonyl carbon in acetone which is less positive (more green). As discussed above, electron-attracting groups can further increase its positive character of a carbonyl carbon and thereby facilitate nucleophilic addition.

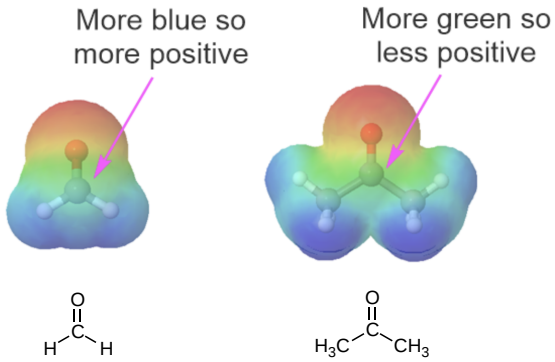


Figure 19.4.1: The Electrostatic Potential Map of Formaldehyde (Left) and Acetone (Right)

Another reason aldehydes tend to me more reactive to nucleophilic addition than ketones is steric hindrance. Ketones have two alkyl groups attached to their carbonyl carbon while aldehydes only have one. This means nucleophiles have a less sterically hindered path when attacking the carbonyl carbon of an aldehyde. Also, the transition state of the rate determining step for formation of the tetrahedral intermediate is less sterically crowded, lower in energy, and more kinetically favorable for an aldehyde than a ketone. The difference in sterics in the carbonyl carbon of an aldehyde and a ketone is easily seen when comparing the space filling models of acetaldehyde and acetone (Figure 19.4.2).

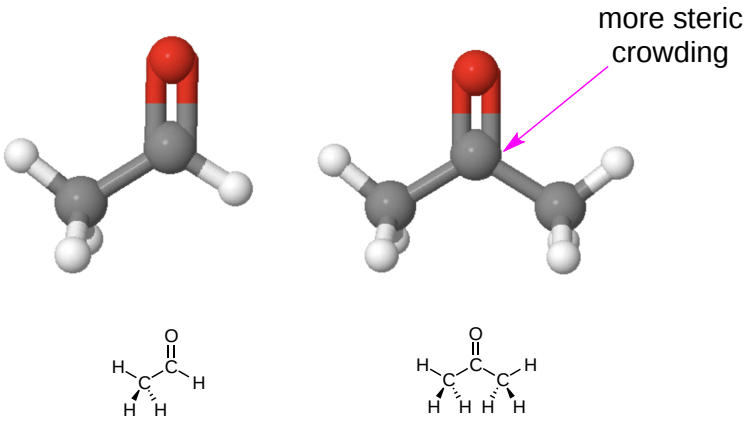
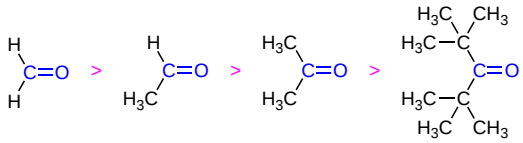


Figure 19.4.2: The Relative Steric Crowding of Acetaldehyde (Left) and Acetone (Right)

In fact, reactivity of a carbonyl toward nucleophilic addition decreases with increasing bulkiness of carbonyl substituents, as seen in the following series.



EXERCISE 19.4.1

Benzaldehyde is less reactive to nucleophilic addition reactions than aliphatic aldehydes. Explain.

Answer

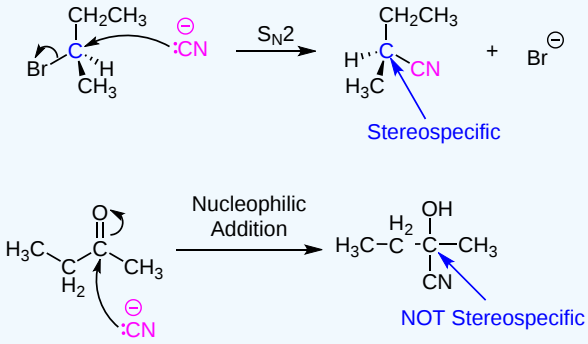
Aromatic rings act as an electron-donating group due to resonance effect. Electron donating groups make the carbonyl group in benzaldehyde less electrophilic.

EXERCISE 19.4.2

Compare the mechanisms of an S_N2 reaction between 2-bromobutane and cyanide and the tetrahedral complex formation between 2-butanone and cyanide.

Answer

In the S_N2 reaction the cyanide nucleophilic must undergo back side attack. This causes an inversion of stereochemistry and creates a product which is stereospecific. The carbonyl used in the nucleophilic addition is trigonal planar. This means the cyanide nucleophile can attack from either plane. This tends to create a racemic mixture of enantiomers.



19.5: NUCLEOPHILIC ADDITION OF WATER- HYDRATION

OBJECTIVES

After completing this section, you should be able to

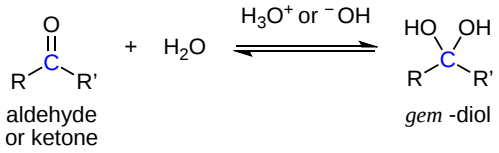
- write the step-wise mechanism for the base-catalyzed hydration of an aldehyde or ketone.
- write the step-wise mechanism for the acid-catalyzed hydration of an aldehyde or ketone.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- geminal (gem) diol

It has been demonstrated that water, in the presence of an acid or a base, adds rapidly to the carbonyl group of aldehydes and ketones establishing a reversible equilibrium with a **hydrate** (geminal-diol, *gem*-diol, or 1,1-diol). The term hydrate implies the addition of water. The word germinal or abbreviation gem comes from the Latin word for twin, *geminus*.



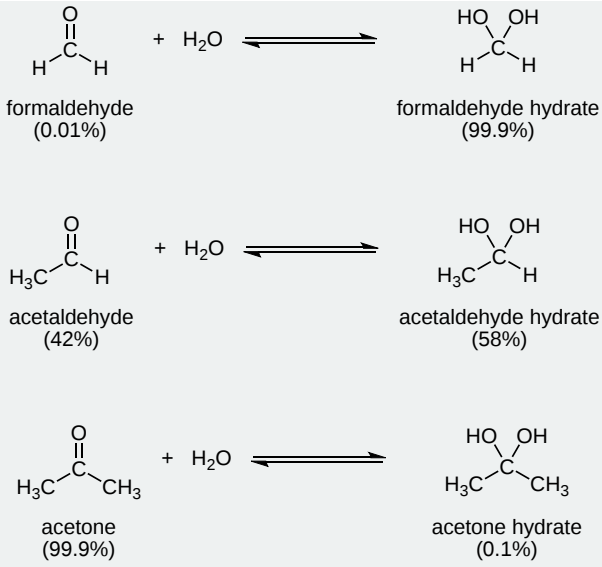
aldehyde or ketone — *gem* -diol

FACTORS AFFECTING THE HYDRATE EQUILIBRIUM

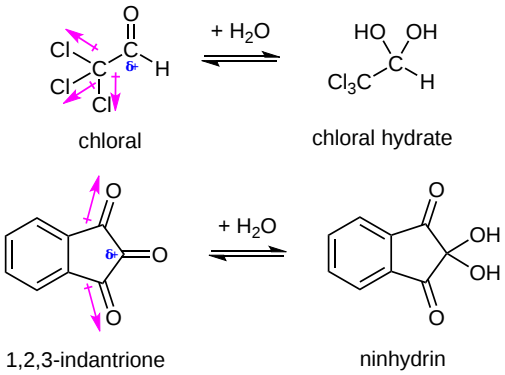
The equilibrium for hydrate formation depends both on steric and electrical factors of the carbonyl as discussed in the previous section. In most cases the resulting *gem*-diol is unstable relative to the reactants and cannot be isolated. Exceptions to this rule exist, one being formaldehyde where the small size of the hydrogen substituents relative to aldehydes and ketones favor hydrate formation. 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.

~100% *gem* -diol — <1% *gem* -diol

EQUILIBRIUM DISTRIBUTION OF COMMON ALDEHYDES AND KETONES WITH THEIR HYDRATE FORMS

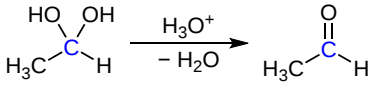


Likewise, the addition of strong electron-withdrawing groups destabilizes the carbonyl and tends to form stable hydrates. Two examples of this are chloral, and 1,2,3-indantrione. It should be noted that chloral hydrate is a sedative and has been added to alcoholic beverages to make a “knock-out” drink also called a Mickey Finn. Also, ninhydrin is commonly used by forensic investigators to reveal fingerprints.



REVERSIBILITY OF HYDRATE FORMATION

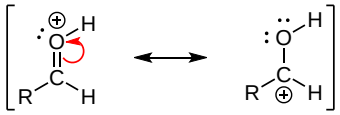
Isolation of hydrates is difficult because the reaction is reversible. Removal of water from the hydrate can cause the conversion of a gem-diol back to the corresponding carbonyl.



ACID OR BASE CATALYZED HYDRATE FORMATION

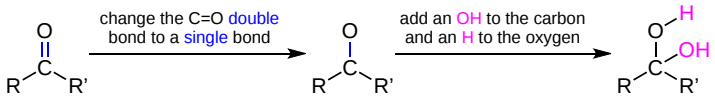
The nucleophilic addition of water to a carbonyl to form a hydrate is usually slow under neutral condition (pH = 7). The rate can be significantly increased through the addition of an acid or base as a catalyst.

The addition of an acid or base changes the mechanism and promote the nucleophilic addition of water to a carbonyl to form a hydrate. Basic conditions speed up the reaction because hydroxide is a better nucleophile than water. Acidic conditions speed up the reaction because the carbonyl becomes protonated. Protonation increases the polarity of the carbonyl bond which increase the partial positive charge on the carbon making it more electrophilic.

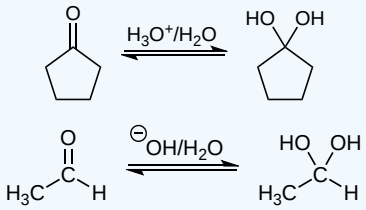


PREDICTING THE PRODUCT OF A HYDRATION

Overall, the C=O of the carbonyl in the starting material is removed and replaced by two single bonds both of which are attached to the original carbonyl carbon. Both of these single bonds are attached to OH groups in the product.



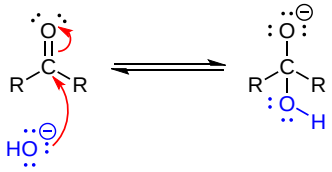
EXAMPLE 19.5.1



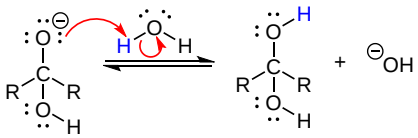
MECHANISM OF ACID OR BASE CATALYZED HYDRATE FORMATION

HYDRATE FORMATION UNDER BASIC CONDITIONS

Step 1: Basic conditions means there is a significant amount of hydroxide present. Hydroxide is a better nucleophile than water which speeds up the reaction. The negatively charged hydroxide forms a single bond with the electrophilic carbonyl carbon. This pushes the two electrons of the pi bond onto the electronegative oxygen forming an alkoxide ion intermediate.

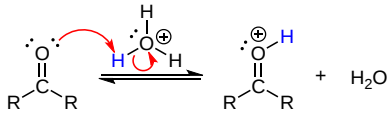


Step 2: Water acts as an acid and protonates the alkoxide ion to form a neutral hydrate while also regenerating hydroxide. The fact that hydroxide is not being used during the reaction is consistent with it acting as a catalyst.

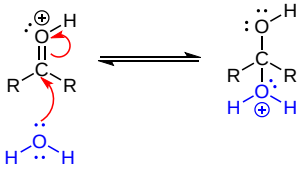


HYDRATE FORMATION UNDER ACIDIC CONDITIONS

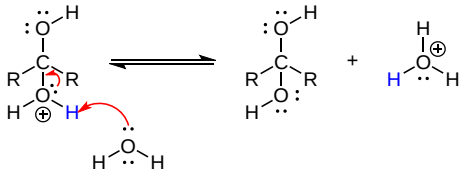
Step 1: Acidic conditions means there is a significant amount of hydronium present. Hydronium protonates the carbonyl oxygen thereby making the carbonyl carbon more electrophilic. After protonation the oxygen becomes positively charged.



Step 2: Under acidic conditions the most nucleophilic species is water. Water forms a single bond with the electrophilic carbon. This pushes the two electrons in the carbonyl pi bond onto the electronegative oxygen. The oxygen from the carbonyl becomes neutral while the oxygen from the water nucleophile become positively charged.

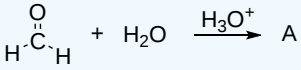


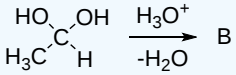
Step 3: Water acts as a base and deprotonates the intermediate to produce the neutrally charged hydrate while regenerating hydronium. The fact that hydronium is not being used during the reaction is consistent with it acting as a catalyst.

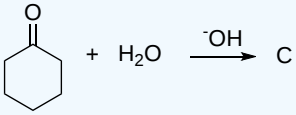


EXERCISE 19.5.1

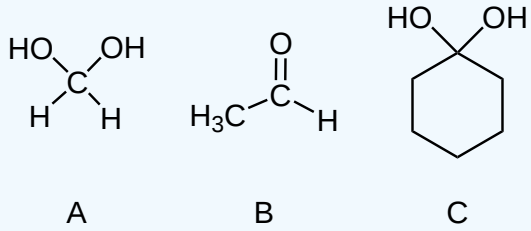
Draw the expected products of the following reactions.







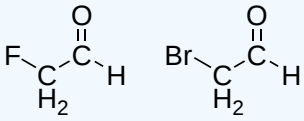
Answer



A B C

EXERCISE 19.5.2

Of the following pairs of molecules which would you expect to form a larger percentage of *gem*-diol at equilibrium? Please explain your answer.

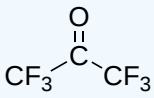


Answer

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.

EXERCISE 19.5.3

Would you expect the following molecule to form appreciable amount of *gem*-diol in water? Please explain your answer.



Answer

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 the alkyl group is dominated by the presence of six highly electronegative fluorines turning these into electron withdrawing groups.

19.6: NUCLEOPHILIC ADDITION OF HCN- CYANOHYDRIN FORMATION

OBJECTIVES

After completing this section, you should be able to

1. write an equation to describe the formation of a cyanohydrin from an aldehyde or ketone.
2. identify the cyanohydrin formed from the reaction of a given aldehyde or ketone with hydrogen cyanide.
3. identify the aldehyde or ketone, the reagents, or both, needed to prepare a given cyanohydrin.
4. write the detailed mechanism for the addition of hydrogen cyanide to an aldehyde or ketone.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- cyanohydrin

STUDY NOTES

For successful cyanohydrin formation it is important to have free cyanide ions available to react with the ketone or aldehyde. This can be achieved by using a salt (e.g. KCN or NaCN) or a silylated (e.g. Me_3SiCN) form of cyanide under acidic conditions or by using HCN with some base added to produce the needed CN^- nucleophile.

Hydrogen cyanide (HC≡N), adds reversibly to aldehydes and many ketones forming hydroxyalkanenitrile adducts commonly known and as **cyanohydrins**. Cyanohydrins have the structural formula of $R_2C(OH)CN$. The “R” on the formula represents an alkyl group, aryl group, or hydrogen.

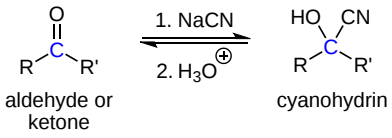
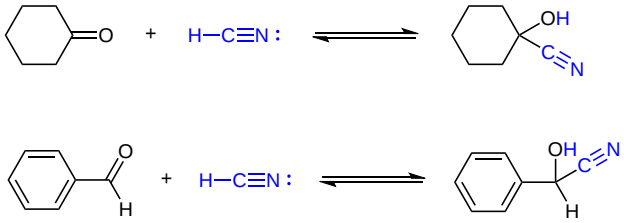


Figure 19.6.1: General Reaction of Cyanohydrin Formation

An important feature of cyanohydrin formation is that it requires a basic catalyst. Since hydrogen cyanide itself is a weak acid (pK_a = 9.25), the best results occur when a small amount of a strong base activates hydrogen cyanide by converting it to **cyanide ion (⁻C≡N)**, which can function as a carbon nucleophile. In the absence of base, the reaction does not proceed, or is at best very slow. Cyanohydrin formation is weakly exothermic, and is favored for aldehydes, and unhindered cyclic and methyl ketones.



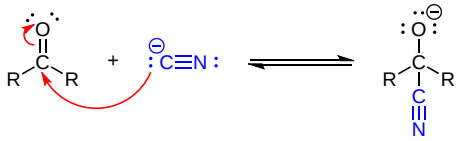
Examples of Cyanohydrin Formation

Hydrogen cyanide (HCN) is hazardous to handle because it is highly toxic. Therefore in many syntheses of cyanohydrins, HCN is created *in situ* by adding a strong acid to a mixture of sodium cyanide and the carbonyl compound, so that hydrogen cyanide is generated *in situ*. The amount of acid added should be insufficient to consume all the cyanide ion, therefore sufficiently alkaline conditions are maintained for rapid addition.

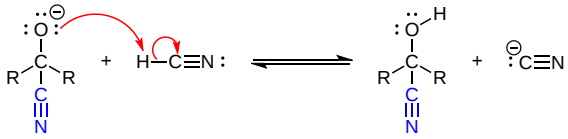
MECHANISM OF CYANOHYDRIN FORMATION

In the first step of the mechanism, the cyanide ion acts as a nucleophile and forms a C-C bond with the electrophillic carbonyl carbon. The two electrons in the carbonyl pi bond are pushed on to the electronegative oxygen forming a tetrahedral alkoxide ion intermediate. In the second step, the alkoxide ion is protonated by HCN which regenerates the cyanide ion.

STEP 1: NUCLEOPHILIC ATTACK

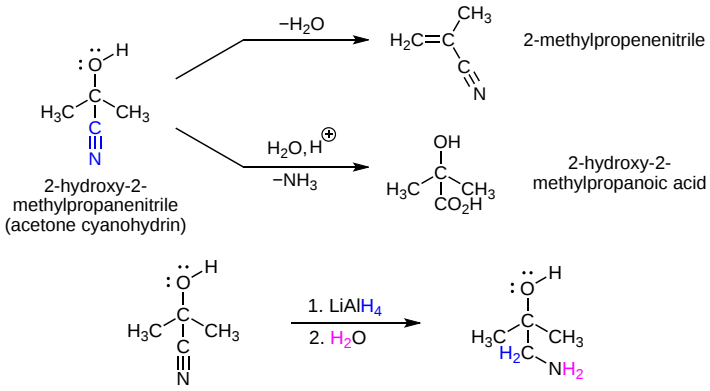


STEP 2: PROTONATION



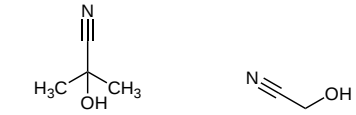
FURTHER CHEMISTRY OF CYANOHYDRINS

Cyanohydrin functional groups often prove useful because of the further chemistry that can be carried out due to the presence of a hydroxyl and a nitrile functionality. In particular, dehydration can convert the hydroxyl group into an alkene (Section 17.6). The nitrile can be converted into a carboxylic acid function group through reaction with a hot acidic aqueous solution (Section 20.7). Also, the nitrile can be reduced by the addition of $LiAlH_4$ to form a primary amine.



OTHER CYANOHYDRINS

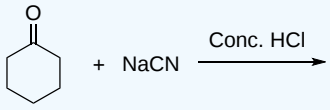
Other interesting cyanohydrins are: **acetone cyanohydrin**, and **glycolonitrile**.



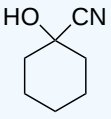
Acetone cyanohydrin has the structure, $(CH_3)_2C(OH)CN$, and is used in the production of methyl methacrylate (also known as acrylic). Glycolonitrile is an organic compound with the structural formula of $HOCH_2CN$, which is the simplest cyanohydrin that is derived by formaldehydes.

? EXERCISE 19.6.1

Complete the following reaction for cyanohydrins.

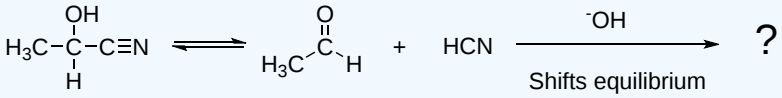


Answer

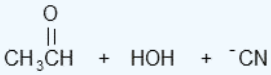


EXERCISE 19.6.2

Complete the following reaction for cyanohydrins.



Answer



EXERCISE 19.6.3

True or False: For a cyanohydrin to form, a *fast addition* of strong acid to cyanide salt is carried out to convert the salt into HCN.

Answer

False, slow addition

EXERCISE 19.6.4

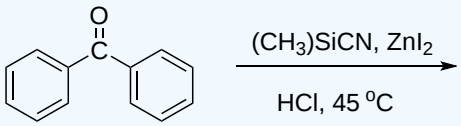
True or False: Cyanohydrin reactions are *irreversible*.

Answer

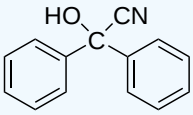
False, reversible

EXERCISE 19.6.5

What is the product for the overall reaction?



Answer



19.7: NUCLEOPHILIC ADDITION OF HYDRIDE AND GRIGNARD REAGENTS - ALCOHOL FORMATION

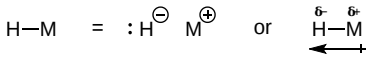
OBJECTIVES

After completing this section, you should be able to

1. write the equation to describe the nucleophilic addition reaction between a Grignard reagent and a carbonyl group.
2. write the general mechanism of nucleophilic addition of the "hydride ion" in the reduction of a carbonyl group.

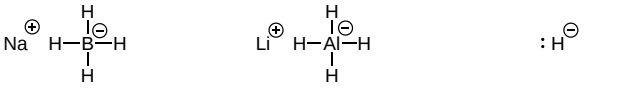
REDUCTION OF CARBONYLS TO ALCOHOLS USING METAL HYDRIDES

Like carbon, hydrogen can be used as a nucleophile if it is bonded to a metal in such a way that the electron density balance favors the hydrogen side. A hydrogen atom that carries a net negative charge and bears a pair of unshared electrons is called a **hydride ion.** How much negative charge density resides on hydrogen depends on the difference in electronegativity between hydrogen and the metal it's bonded to.



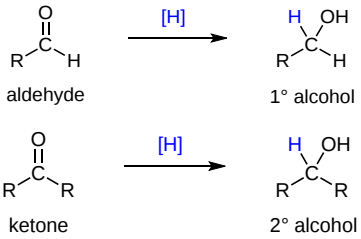
(M = metal)

The most common sources of the hydride anion (:H) 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. Also, each are capable of delivering up to 4 hydride equivalents. The reaction equation of hydride reductions are not typically balanced (*i.e.* it does not specify the stoichiometry of the reagent). 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.



GENERAL REACTION

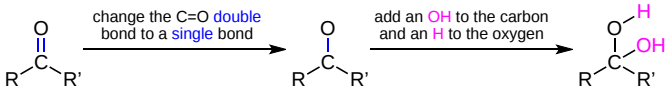
Nucleophilic addition of a hydride anion (:H) to an aldehyde or a ketone gives a tetrahedral alkoxide anion intermediate, which on protonation yields the corresponding alcohol. Aldehydes produce 1°-alcohols and ketones produce 2°-alcohols. Both $LiAlH_4$ and $NaBH_4$ are capable of reducing aldehydes and ketones to the corresponding alcohol.



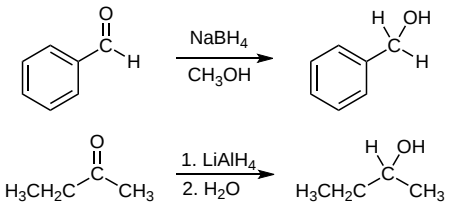
In metal hydrides reductions, the resulting alkoxide salts are insoluble and need to be hydrolyzed (with care) before the alcohol product can be isolated. In the sodium borohydride reduction the methanol solvent system achieves this hydrolysis automatically. In the lithium aluminum hydride reduction 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.

PREDICTING THE PRODUCT OF A HYDRIDE ADDITION TO A CARBONYL

During the reduction, the C=O double bond in the reactant becomes a C-O single bond in the product. The breaking of the C=O double bond allows for the formation of two new single bonds in the product. One will be attached to the oxygen (O-H) and one to the carbon (C-H).



EXAMPLE

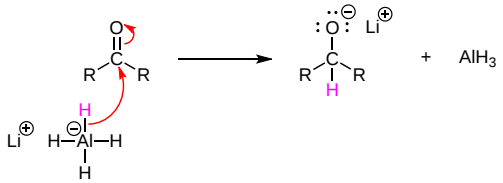


MECHANISM FOR THE REDUCTION OF CARBONYLS USING LIALH$_4$

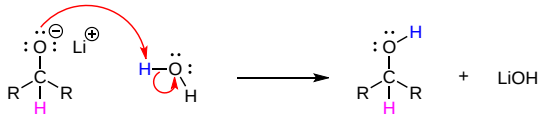
Both $NaBH_4$ and $LiAlH_4$ act as if they were a source of hydride. The hydride anion undergoes nucleophilic addition to the carbonyl carbon to form a C-H single bond and forming a tetrahedral alkoxide ion intermediate. The alkoxide ion is subsequently converted to an alcohol by reaction with a proton source (such as water). In the $LiAlH_4$ reduction, the resulting alkoxide salts are insoluble and need to be hydrolyzed (with care) before the alcohol product can be isolated. In the borohydride reduction the hydroxylic solvent system achieves this hydrolysis automatically. The lithium, sodium, boron and aluminum end up as soluble inorganic salts.

Note! The reaction and the corresponding mechanism of hydride reductions of carbonyls is fairly complicated. The following mechanism has been simplified for easier understanding.

Step 1: Nucleophilic attack to form a tetrahedral alkoxide intermediate



Step 2: Protonation to form an alcohol



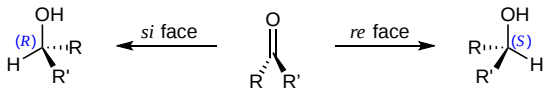
PROPERTIES OF HYDRIDE SOURCES

Two practical sources of hydride-like reactivity are the complex metal hydrides lithium aluminum hydride (LiAlH4) and sodium borohydride (NaBH4). 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.

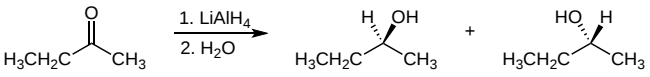
Reagent	Preferred Solvents	Functions Reduced	Reaction Work-up
Sodium Borohydride $NaBH_4$	ethanol; aqueous ethanol 15% NaOH; diglyme avoid strong acids	aldehydes to 1º-alcohols ketones to 2º-alcohols inert to most other functional groups	**1)** simple neutralization **2)** extraction of product
Lithium Aluminum Hydride $LiAlH_4$	ether; THF avoid alcohols and amines avoid halogenated compounds avoid strong acids	aldehydes to 1º-alcohols ketones to 2º-alcohols carboxylic acids to 1º-alcohols esters to alcohols epoxides to alcohols nitriles & amides to amines halides & tosylates to alkanes most functional groups react	**1)** careful addition of water **2)** remove aluminum salts **3)** extraction of product

LIMITATIONS OF HYDRIDE REDUCTIONS

A hydride addition to an asymmetric ketone has the possibility of forming a chiral carbon that is not stereospecific. Attack by the hydride can occur from either the *re* or the *si* face of an asymmetrical carbonyl, leading to a mixture of the (*S*) and (*R*) alcohols. These reactions can be made to have stereochemical control by using several different methods including stereospecific reagents, sterics, and by the affect of an enzyme during a biological reduction.



EXAMPLE

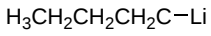


2-butanone (*S*)-2-butanol (*R*)-2-butanol

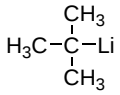
ORGANOMETALLIC REACTIONS

Lithium and magnesium metals reduce the carbon-halogen bonds of alkyl halides to form **organolithium reagents** and **Grignard reagents** respectively. In both cases, the carbon bonds to the metal and has characteristics similar to a carbanion ($R:^-$) nucleophile. Some common organometallic reagents are shown below:

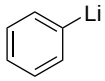
Methyl Lithium



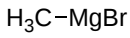
Butyl Lithium



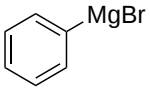
t-Butyl Lithium



Phenyl Lithium



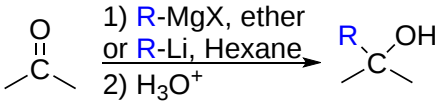
Methyl Magnesium Bromide



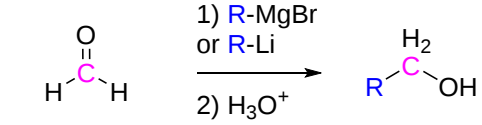
Phenylmagnesium Bromide

Because organometallic reagents react as their corresponding carbanion, they are excellent nucleophiles. Aldehydes and ketones will undergo nucleophilic addition with organolithium and Grignard reagent nucleophiles. The nucleophilic carbon in the organometallic reagents forms a C-C single bond with the electrophilic carbonyl carbon. An alkoxide ion intermediate is formed which becomes an alcohol with subsequent protonation with an acid. Both Grignard and organolithium reagents will perform these reactions.

GENERAL REACTION

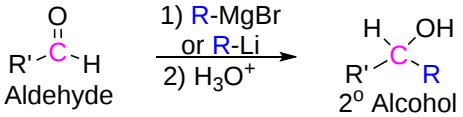


ADDITION TO FORMALDEHYDE GIVES 1^O ALCOHOLS

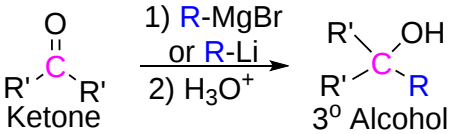


Formaldehyde 1^o Alcohol

ADDITION TO ALDEHYDES GIVES 2^O ALCOHOLS



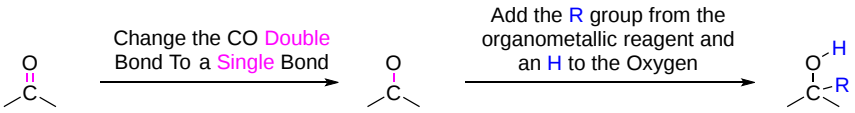
ADDITION TO KETONES GIVES 3^O ALCOHOLS



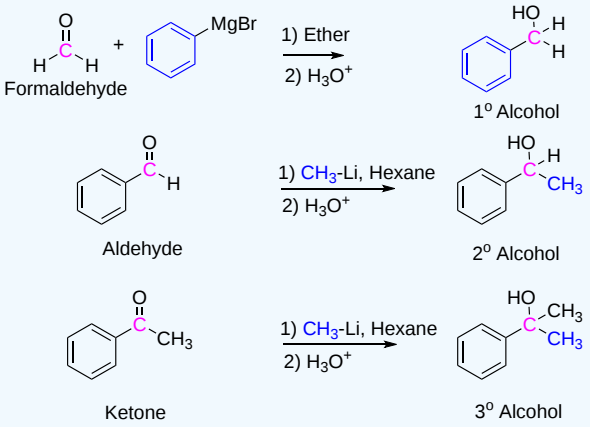
PREDICTING THE PRODUCT OF ADDITION OF ORGANOMETALLIC REAGENTS TO ALDEHYDES AND KETONES

During the reaction, the C=O double bond in the reactant forms a C-O single bond in the product. The breaking of the C=O double bond allows for the formation of two single bonds in the product. One will be attached to the oxygen and one to the carbon which was originally

in the carbonyl. The carbon will gain whatever R group was part of the organometallic reagent and the oxygen will gain a "H".



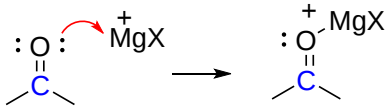
EXAMPLE 19.7.2



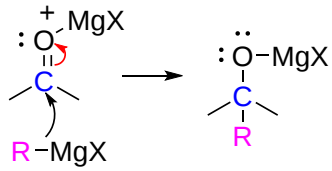
MECHANISM FOR THE ADDITION OF GRIGNARD REAGENTS TO CARBONYLS

The mechanism starts with the formation of a acid-base complex between $^{+}$MgX and the carbonyl oxygen. The $^{+}$MgBr of the Grignard reagent acts as a Lewis acid and accepts a lone pair of electrons from the carbonyl oxygen. This gives the oxygen a positive charge which correspondingly increases the partial positive charge on the carbonyl carbon increasing it susceptibility to nucleophilic attack. The carbanion nucleophile from the Grignard reagent adds to the electrophilic carbon of the acid-base complex forming a C-C bond. The two electrons of the C=O are pushed toward the carbonyl oxygen atom forming a tetrahedral magnesium alkoxide intermediate. The alkoxide intermediate is converted to an alcohol through addition of a acidic aqueous solution. The $^{+}$MgX ion is also converted to HOMgX.

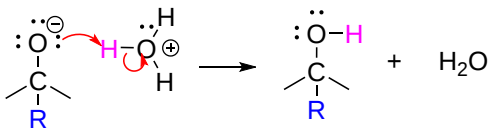
STEP 1: LEWIS ACID-BASE FORMATION



STEP 2: NUCLEOPHILIC ATTACK

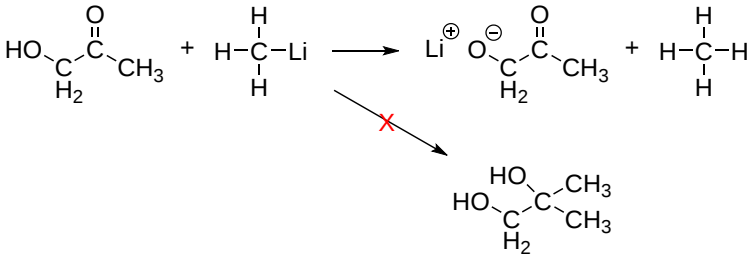


STEP 3: PROTONATION



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 with organometallic reagents includes: alcohols, amides, 1° amines, 2° amines, carboxylic acids, and terminal alkynes.

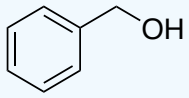


PLANNING AN ALCOHOL SYNTHESIS USING A GRIGNARD REACTION

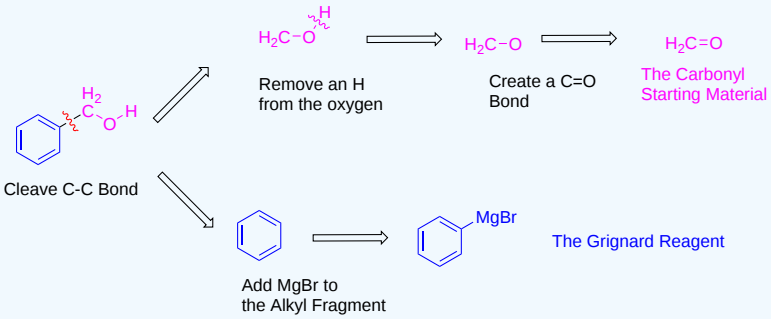
The nucleophilic addition of a Grignard reagent to a carbonyl is a powerful tool in organic synthesis because if forms a C-C bond. Also, there is often more than one way to make a given target molecule. Primary alcohols have one C-C bond which can be retrosynthetically cleaved. Secondary alcohols have two and tertiary alcohols have three.

EXAMPLE 19.7.2

What reagents are required to make the following molecule using a Grignard Reaction?

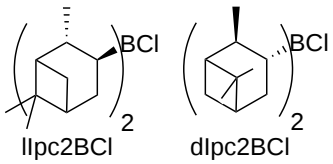


Solution



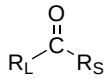
SOMETHING EXTRA

As previously mentioned, a hydride reduction using $LiAlH_4$ or $NaBH_4$ has the possibility of forming R or S stereoisomers of a chiral carbon in the product. An important area of organic synthesis is developing stereoselective methods which yield only one of the possible R and S stereocenters. Stereoselective hydride reductions can be accomplished by using the reagent **Diisopinocampheylchloroborane (Ipc_2BCl).** The two versions of this reagent, (+)-Ipc_2BCl & (−)-Ipc_2BCl, allow for either an R or S stereocenter to be created during the hydride reduction. Ipc_2BCl was first reported in 1961 by Zweifel and Brown and is considered a pioneering work in stereoselective synthesis using boranes. Herbert Charles Brown (1912-2004) was an American chemist who received the Nobel Prize in Chemistry in 1979 for his work with organoboranes.

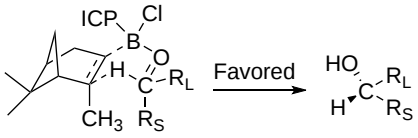


Ipc_2BCl allows for stereoselectivity by changing the mechanism of the hydride reduction and introducing sterics to the reaction. Asymmertric carbonyls which have a sterically large substituent (R_L) and a sterically small substituent (R_S) will have a preferred orientation during this reaction causing a particular stereoisomer to be formed.

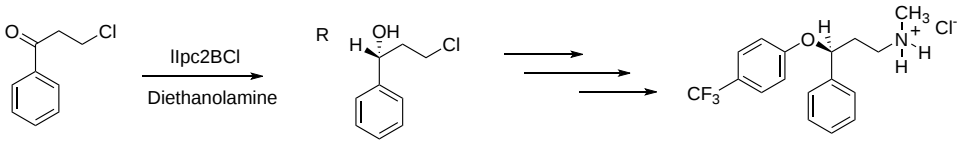
Asymmetric Carbonyl



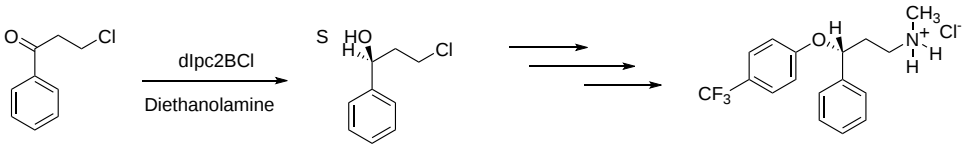
RL = Sterically Large Substituent
RS = Sterically Small Substituent



Stereochemical control during a synthesis is important because a particular stereoisomer is usually the target molecular. This is particularly true in the synthesis of pharmaceuticals were one stereoisomer often has different biological properties and another. An example of this is the drug Fluoxetine (Prozac) which was shown to have superior biological properties when the R isomer of its single chiral carbon was tested. Fluoxetine is an antidepressant given FDA approval in 1987. in 2010, over 24.4 million prescriptions for fluoxetine were filled in the United States alone. Currently, there are many different synthesis pathways to Fluoxetine. A fragment of one pathway is shown below which uses the two Ipc_2BCl versions to synthesis both the R and S enantiomers of Fluoxetine.

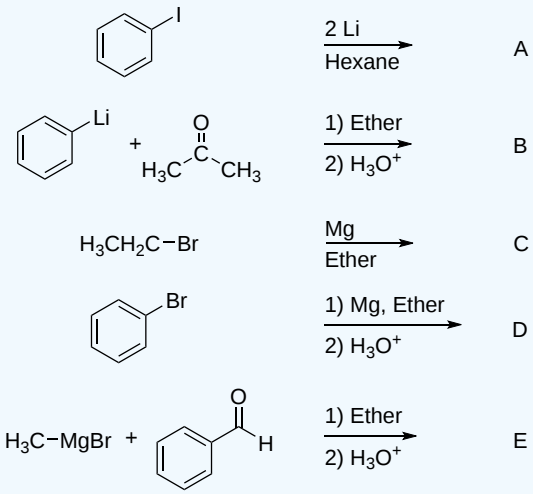


Fluoxetin Hydrochloride
(Prozac)

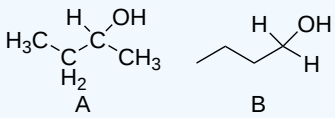


EXERCISE 19.7.1

Please draw the products of the following reactions:

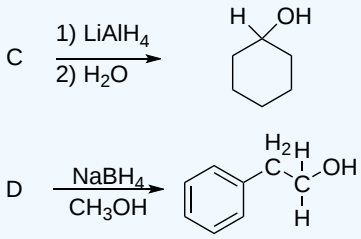


Answer

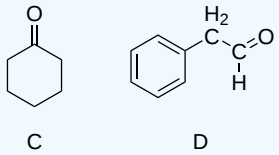


EXERCISE 19.7.2

Draw the structure of the molecule which must be reacted to produce the product.

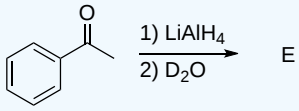


Answer

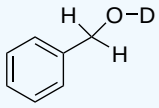


EXERCISE 19.7.3

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.

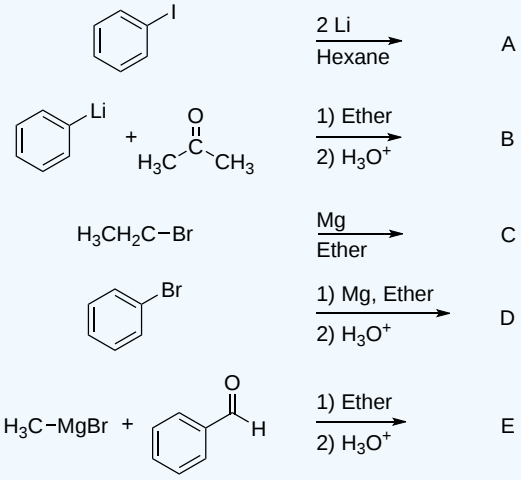


Answer

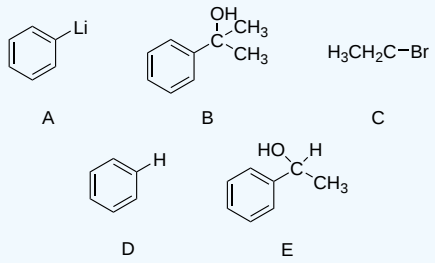


EXERCISE 19.7.4

Please write the product of the following reactions.

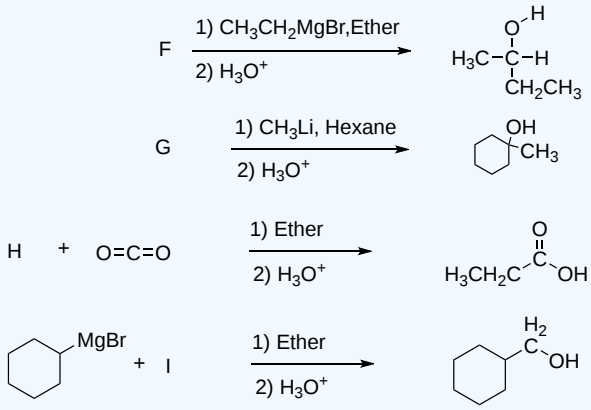


Answer

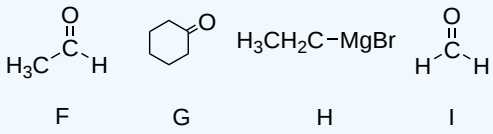


EXERCISE 19.7.5

Please indicate the starting material required to produce the product.

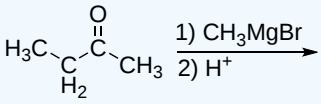


Answer



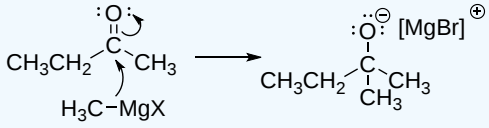
EXERCISE 19.7.6

Give a detailed mechanism and the final product of this reaction

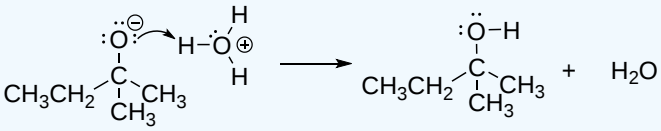


Answer

Step 1: Nucleophilic attack

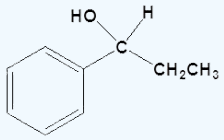


Step 2: Protonation

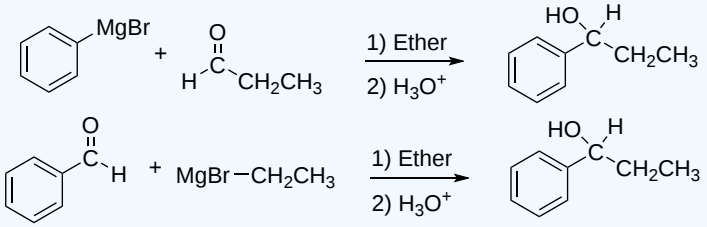


EXERCISE 19.7.7

How two sets of reactants which could be used to synthesize the following molecule using a Grignard reaction.



Answer



19.8: NUCLEOPHILIC ADDITION OF AMINES - IMINE AND ENAMINE FORMATION

OBJECTIVES

After completing this section, you should be able to

- write equations to describe the reactions that occur between aldehydes or ketones and primary or secondary amines.
- identify the product formed from the reaction of a given aldehyde or ketone with a given primary or secondary amine.
- identify the aldehyde or ketone, the amine, or both, required in the synthesis of a given imine or enamine.
- write the detailed mechanism for the reaction of an aldehyde or ketone with a primary amine.
- write the detailed mechanism for the reaction of an aldehyde or ketone with a secondary amine.
- explain why the rate of a reaction between an aldehyde or ketone and a primary or secondary amine is dependent on pH.

KEY TERMS

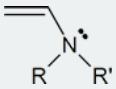
Make certain that you can define, and use in context, the key terms below.

- 2,4-dinitrophenylhydrozone
- enamine
- imine

STUDY NOTES

An imine is a compound that contains the structural unit

An enamine is a compound that contains the structural unit



Both of these types of compound can be prepared through the reaction of an aldehyde or ketone with an amine.

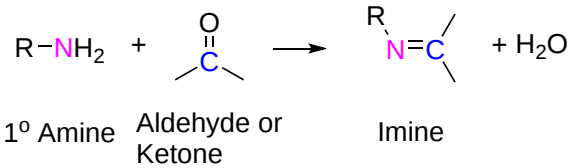
You may have the opportunity to observe the reaction of an aldehyde and ketone with 2,4-dinitrophenylhydrazine (Brady's reagent) to form a 2,4-dinitrophenylhydrozone in the laboratory. This is a classical organic chemistry test to confirm the presence of a carbonyl group. The reaction produces very colorful and bright precipitates of yellow, orange and red.

If you can understand why the two reactions of imine and enamine formation are essentially identical, and can write a detailed mechanism for each one, you are well on the way to mastering organic chemistry. If you understand how and why these reactions occur, you can keep the amount of material that you need to memorize to a minimum.

The nucleophilic addition of amines involves reacting primary or secondary amines with carbonyl compounds like aldehydes or ketones. This forms imines (with primary amines) or enamines (with secondary amines) along with water as a byproduct. These reactions are crucial in organic synthesis for building carbon-nitrogen bonds and creating various functional groups.

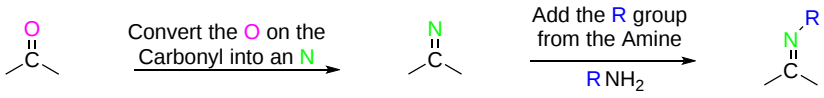
REACTION WITH PRIMARY AMINES TO FORM IMINES

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.

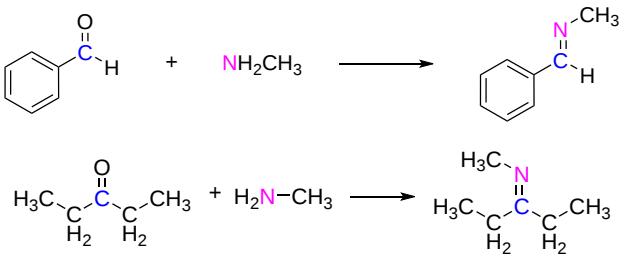


PREDICTING THE PRODUCTS OF AN IMINE FORMING REACTION

During imine formation, the carbonyl oxygen is completely removed. The nitrogen of the 1° amine reactant replaces the carbonyl oxygen to form the imine C=N bond. During the process the nitrogen of the 1° amine loses both of its hydrogens.



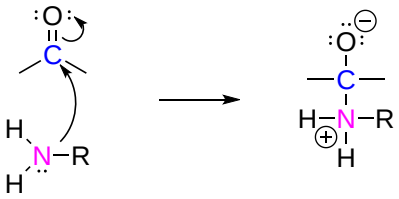
EXAMPLES OF IMINE FORMING REACTIONS



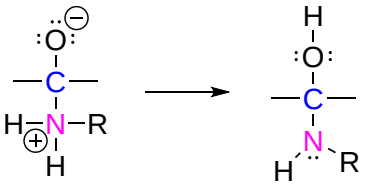
MECHANISM OF IMINE FORMATION

Imine formation is a reversible process that starts with the nucleophilic addition of a primary amine to the carbonyl group of an aldehyde or ketone. Next, a proton transfer forms a neutral amino alcohol called a carbinolamine. Acid protonation of the carbinolamine oxygen converts it into a better leaving group which is subsequently eliminated as water producing an iminium ion. Deprotonation of nitrogen gives the final imine product.

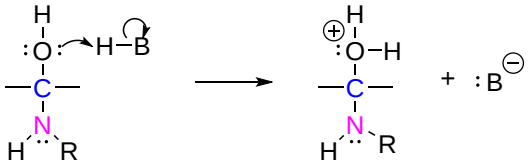
STEP 1: NUCLEOPHILIC ADDITION



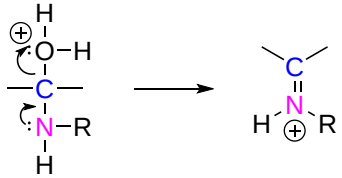
STEP 2: PROTON TRANSFER



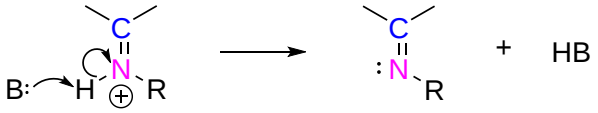
STEP 3: PROTONATION



STEP 4: WATER IS ELIMINATED TO FORM AN IMINIUM ION

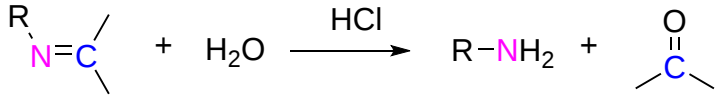


STEP 5: DEPROTONATION



REVERSIBILITY OF IMINE FORMING REACTIONS

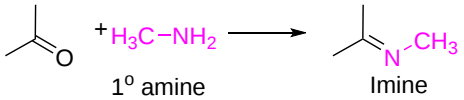
Imines can be hydrolyzed back to the corresponding 1^o amine under acidic conditions.

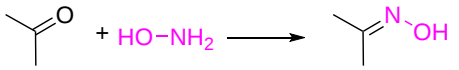


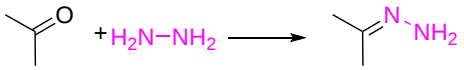
REACTIONS INVOLVING OTHER REAGENTS OF THE TYPE Y-NH_2

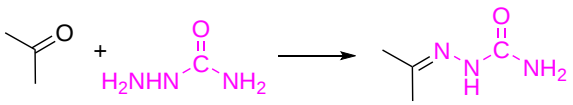
A wide variety of substances with $-NH_2$ groups can react with aldehydes and ketones by an addition-elimination sequence to yield compounds with a carbon-nitrogen double bond. Imines are sometimes difficult to isolate and purify due to their sensitivity to hydrolysis. Consequently, other reagents of 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 below, 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 Section 19.9.

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 three nitrogen groups ($–NH_2$) only one of them is a reactive amine. The other two are similar to amides and are deactivated by resonance with the adjacent carbonyl group.

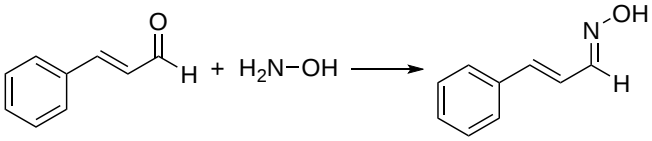




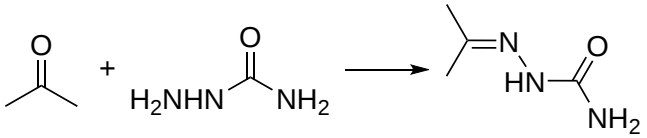




EXAMPLE



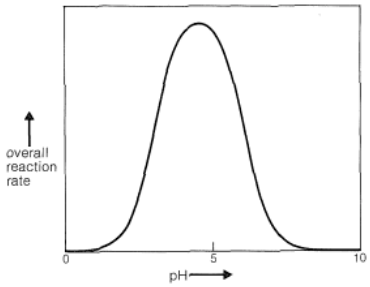
Cinnamaldehyde reacting with hydroxylamine to form cinnamaldehyde oxime



Acetone reacting with semicarbazide to form acetone semicarbazide

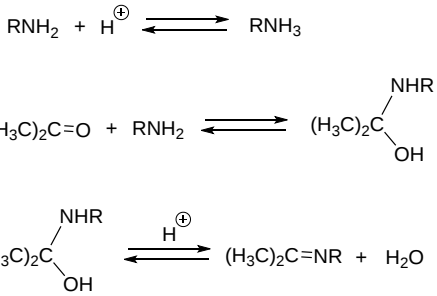
THE PH DEPENDENCE OF IMINE FORMING REACTIONS

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.



Schematic variation of the rate of condensation of RNH_2 with a carbonyl compound as a function of pH.

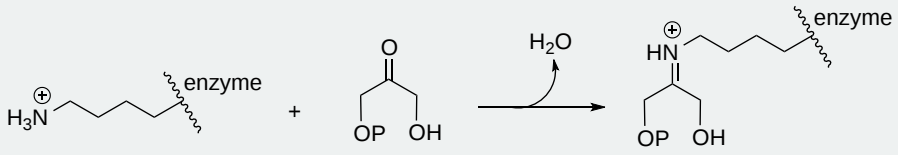
Clearly, if the unshared electron pair on the nitrogen of RNH_2 is combined with a proton it cannot attack the carbonyl carbon to give the aminoalkanol produced during the mechanism. So at high acid concentration (low pH) we expect the rate and the equilibrium for the overall reaction to be unfavorable.



Dehydration of the aminoalkanol is acid catalyzed; this reaction normally is fast at pH values smaller than 3-4. As the pH is increased above 4, the dehydration step in the mechanism decreases in rate because it requires an acid catalyst. At pH 6 dehydration is the slow step of the mechanism, and at higher pH values it finally becomes too slow to give a useful overall rate of reaction.

BIOLOGICAL IMINE FORMING REACTIONS

Imine intermediates are common in biological pathways. Carbon-carbon bond forming enzymes called aldolases often form a protonated iminium link between a carbonyl carbon on a substrate and the $-NH_3^+$ from a lysine amino acid found in the active site of the enzyme. The reaction below shows an aldolase reaction from the Calvin Cycle where the carbonyl containing substrate is dihydroxyacetone. The Calvin Cycle is involved in the biochemical processes of carbon fixation and the production of sugars in plants.

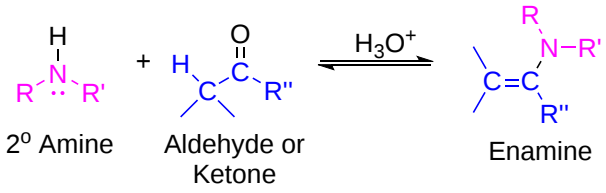


Protonated Amine From Lysine | **Dihydroxyacetone** | **A Protonated Iminium Linkage**

After the carbon-carbon bond forming part of an aldolase reaction is completed, the iminium linkage is hydrolyzed, freeing the product so that it can diffuse out of the active site and allow another catalytic cycle to begin.

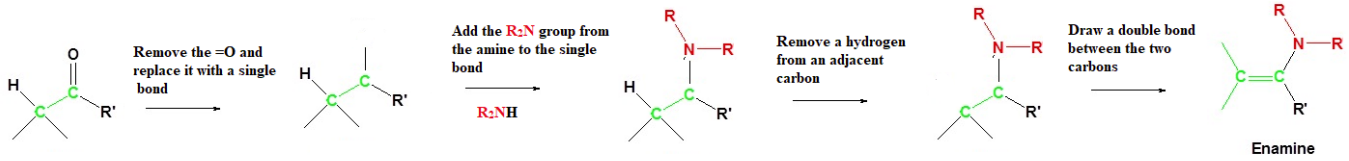
REACTION WITH SECONDARY AMINES TO FORM ENAMINES

Most aldehydes and ketones react with 2°-amines to give products known as **enamines** (alkene + amine). It should be noted that, like acetal formation, these are acid-catalyzed reversible reactions in which water is lost. Secondary amines form a distinctly different functional group after nucleophilic addition because they lack the second hydrogen on nitrogen required for imine formation. During this reaction a hydrogen is removed from an adjacent carbon forming a C=C bond.

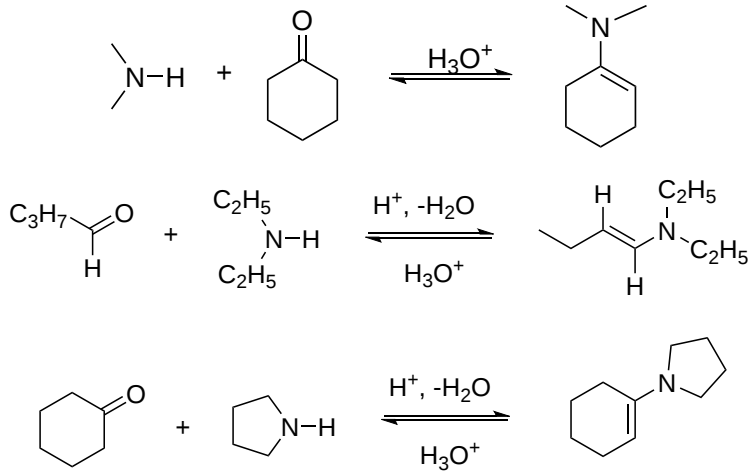


PREDICTING THE PRODUCTS OF AN ENAMINE FORMING REACTION

During enamine formation the carbonyl oxygen is completely removed. The nitrogen of the amine reactant replaces the oxygen to form a N-C bond. During the process the amine loses its lone hydrogen. A hydrogen is removed from a carbon adjacent to the original carbonyl carbon forming a C=C between them.

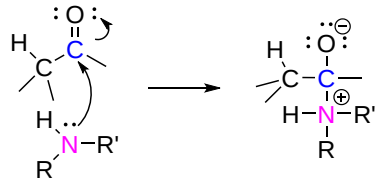


EXAMPLE

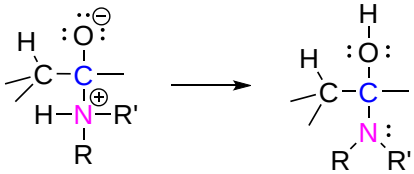


MECHANISM

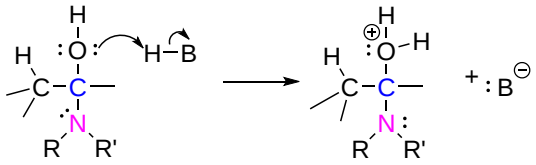
STEP 1: THE SECONDARY AMINE UNDERGOES NUCLEOPHILIC ADDITION TO FORM A NEUTRAL TETRAHEDRAL INTERMEDIATE



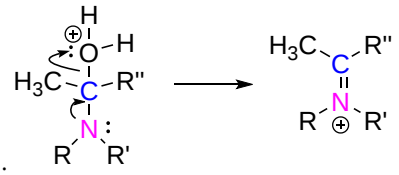
STEP 2: A PROTON IS TRANSFERRED FROM THE AMMONIUM ION MOIETY OF THE TETRAHEDRAL INTERMEDIATE TO THE ALKOXIDE ION MOIETY. THIS FORMS A NEUTRAL FUNCTIONAL GROUP CALLED A CARBINOLAMINE



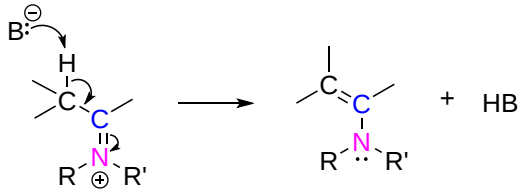
STEP 3: THE OH GROUP ON THE CARBINOLAMINE IS PROTONATED BY HYDRONIUM TURNING IT INTO A GOOD LEAVING GROUP



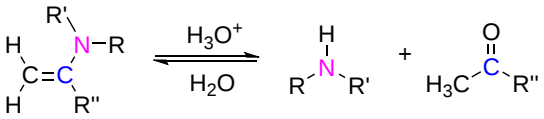
STEP 4: THE LONE PAIR ELECTRONS ON THE NITROGEN FORM THE C=N DOUBLE BOND CAUSING WATER TO BE ELIMINATED. THIS FORMS AN IMINIUM ION



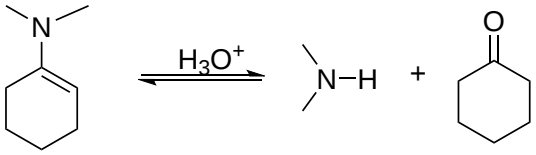
Step 5: Water (or a base) removes a hydrogen from an adjacent carbon to form an alkene bond. This pushes two electrons from the C=N double bond onto the positively charged nitrogen creating the neutral enamine product and hydronium (or BH).



REVERSIBILITY OF ENAMINES

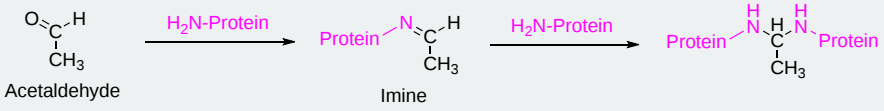


EXAMPLE



SOMETHING EXTRA: HOW DOES ALCOHOL CAUSE CIRRHOSIS AND LIVER CANCER?

One of the most insidious aspects of alcohol abuse is the fact that it will allow a user to continue, sometimes for decades, while it slowly destroys their body. Our bodies are actually designed to handle limited amounts of alcohol. Human metabolism includes enzymes that can convert alcohol into harmless metabolites in three steps. In the first step, an enzyme called alcohol dehydrogenase (ADH) acts as a catalyst for the conversion of alcohol to the toxic intermediate acetaldehyde.

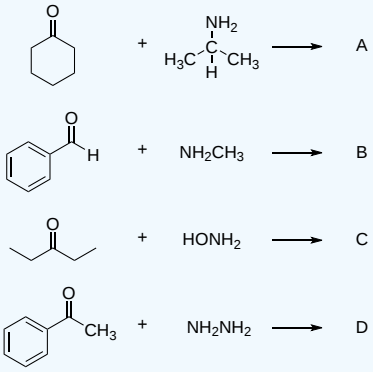


How acetaldehyde forms a protein adduct

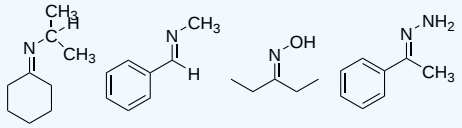
Forming adducts with DNA changes its structure and increases the chances of irregular replication, which is the starting point of cancer. Our bodies have processes that can repair or replace damaged proteins and DNA, but if enough build up they can lead to cirrhosis, liver cancer, liver failure, and death. Alcohol accounts for 28% of all liver-disease-related deaths in the U.S., and is also responsible for a little over 3% of all cancer deaths that occur globally. Hepatocellular carcinoma (liver cancer) is the fifth most common type of cancer, with an estimated 500,000 new cases being diagnosed every year worldwide. Because this type of cancer is usually discovered late, the prognosis is poor, with a median survival time of 1-2 months.

EXAMPLE 19.8.1

Please draw the products of the following reactions.



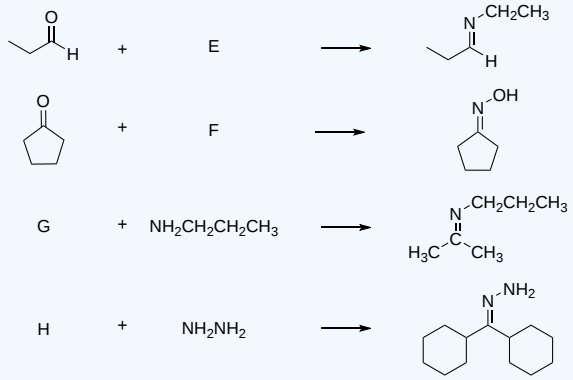
Solution



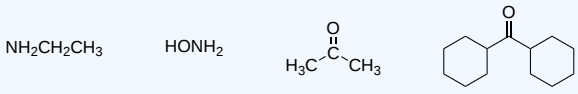
A B C D

EXAMPLE 19.8.2

Please draw the structure of the reactant needed to produce the indicated product.



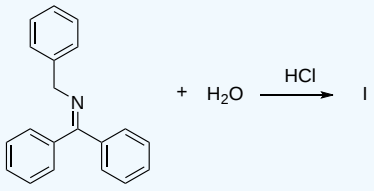
Solution



E F G H

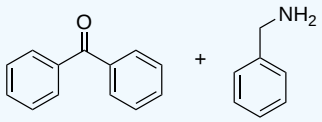
EXAMPLE 19.8.3

Please draw the products of the following reactions.



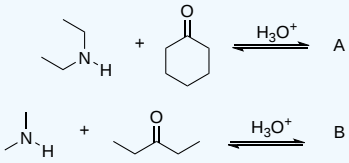
Solution

I

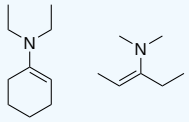


EXAMPLE 19.8.4

Please draw the products for the following reactions.



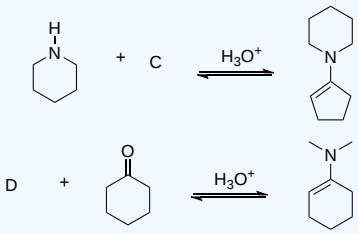
Solution



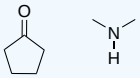
A B

EXAMPLE 19.8.5

Please give the structure of the reactant needed to product the following product



Solution



C D

19.9: NUCLEOPHILIC ADDITION OF HYDRAZINE - THE WOLFF-KISHNER REACTION

OBJECTIVES

After completing this section, you should be able to

- write an equation to illustrate the Wolff-Kishner reduction of an aldehyde or ketone.
- identify the product formed from the Wolff-Kishner reduction of a given aldehyde or ketone.

KEY TERMS

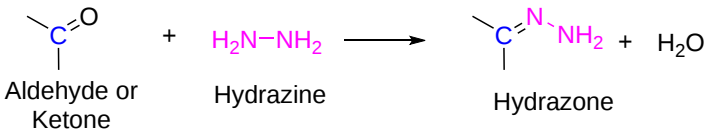
Make certain that you can define, and use in context, the key term below.

- Wolff-Kishner reduction

STUDY NOTES

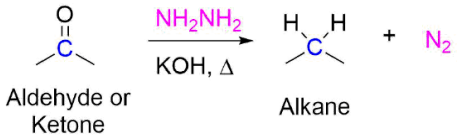
After studying this section, you can add yet another method of reducing organic compounds to your growing list of reduction reactions.

Aldehydes and ketones can be converted to a hydrazone derivative by reaction with hydrazine (H_2NNH_2). Hydrazone formation is a variation of the imine forming reaction discussed in the previous section.



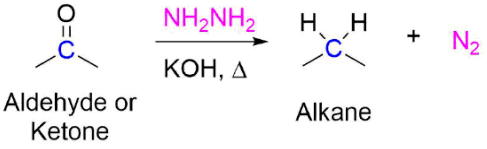
REACTION WITH A BASE AND HEAT CONVERTS A HYDRAZONE TO AN ALKANE

Hydrazones can be further converted to the corresponding alkane by reaction with a base, usually KOH, and heat. Typically a high boiling point solvent, such as ethylene glycol, is used to provide the high temperatures needed for this reaction to occur. In the examples below the symbol "Δ" represents the addition of heat to a reaction. During this reaction nitrogen gas, which contains a very stable N-N triple bond, is produced.

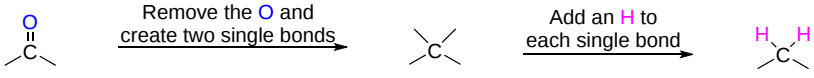


BOTH REACTIONS TOGETHER PRODUCE THE WOLFF-KISHNER REDUCTION

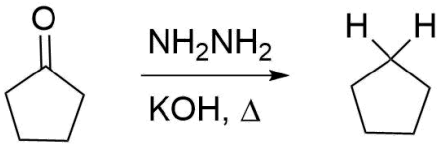
These two steps previously discussed can be combined to provide a general reaction for the conversion of aldehydes and ketones to alkanes called the Wolff-Kishner Reduction. Overall, the Wolff-Kishner reduction removes the carbonyl oxygen in the form of water by forming an intermediate hydrazone. The hydrazone then undergoes loss of N_2 gas along with protonation to give the alkane reaction product. Note that the Clemmensen reduction accomplishes the same transformation of a carbonyl to an alkane under acidic conditions.



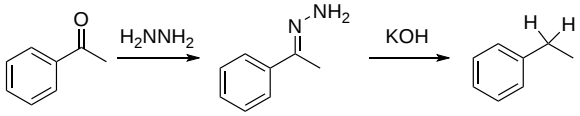
PREDICTING THE PRODUCTS OF A WOLFF-KISHNER REDUCTION



EXAMPLES



Conversion of Cyclopentanone to cyclopentane

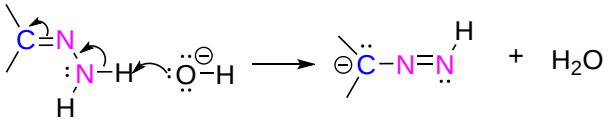


Conversation of Acetophenone to Ethylbenzne

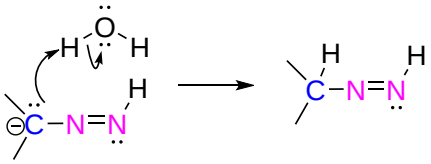
MECHANISM OF THE WOLFF-KISHNER REDUCTION

Hydrazine reacts with a carbonyl to form a hydrazone using a mechanism similar to that of an imine formation discussed in the previous section. The weakly acidic N-H bond is deprotonated to form the hydrazone anion. The hydrazone anion has a resonance structure that places a double bond between the nitrogens and a negative charge on carbon. The hydrazone anion is then protonated to form a neutral intermediate. A second weakly acidic N-H bond is deprotonated which causes the formation of N_2 gas and a carbanion. In the final step the carbanion is protonated to form an alkane product.

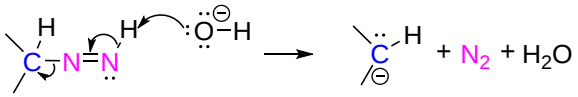
STEP 1: DEPROTONATION



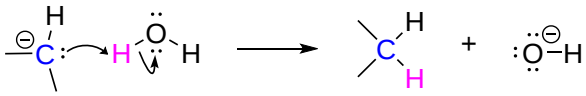
STEP 2: PROTONATION



STEP 3: SECOND DEPROTONATION

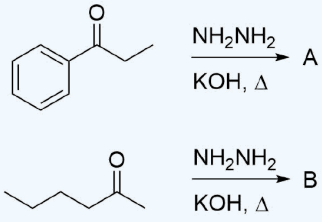


STEP 4: THE CARBANION IS PROTONATED TO FORM THE ALKANE PRODUCT.

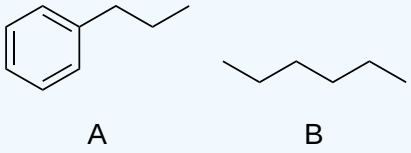


? EXERCISE 19.9.1

Please draw the products of the following reactions.



Answer



19.10: NUCLEOPHILIC ADDITION OF ALCOHOLS- ACETAL FORMATION

OBJECTIVES

After completing this section, you should be able to

- write an equation to illustrate the formation of acetals.
- identify the acetal formed from the reaction of a given aldehyde or ketone with a given alcohol.
- identify the carbonyl compound, the alcohol, or both, needed to form a given acetal.
- write a detailed mechanism for the reaction which occurs between an aldehyde or a ketone and an alcohol.
- explain how an acid catalyst makes aldehydes and ketones more susceptible to attack by alcohols.
- illustrate how the reversibility of the reaction between an aldehyde or a ketone and an alcohol can be used to protect a carbonyl group during an organic synthesis.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

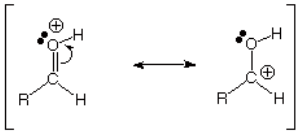
- acetal
- hemiacetal

STUDY NOTES

This section presents a second example of the use of a protecting group. [The first was in the discussion of alcohols, Section 17.8.] Because of the reactivity of hydroxy groups and carbonyl groups, we often need to protect such groups during organic syntheses. When you are designing multi-step syntheses as part of an assignment or examination question, you must always keep in mind the possibility that you may need to protect such groups to carry out the desired sequence of reactions successfully.

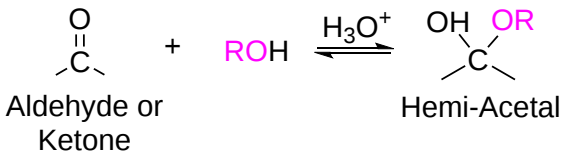
It has been demonstrated in Section 19.5 that water adds rapidly to the carbonyl function of aldehydes and ketones to form geminal-diols. In a similar reaction, one equivalent of an alcohol, in the presence of an acid catalyst, adds reversibly to aldehydes and ketones to form a hydroxy ether called a **hemiacetal** (R_2COHOR') (h*emi*, Greek, half). This reaction can continue by adding another equivalent of an alcohol to form a diether called an **acetal** $R_2C(OR')_2$. Hemiacetals and acetals are important functional groups because they appear in the structures of many sugars.

An acid catalyst must be used during this reaction because alcohols are weak nucleophiles and would add very slowly under neutral conditions. Under acidic conditions, the oxygen of the carbonyl becomes protonated, increasing the electrophilicity of the carbonyl carbon, speeding up the reaction.

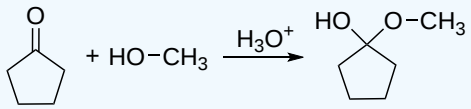


Also, it is common to actively remove the water created with the formation of an acetal by using molecular sieves or a **Dean-Stark trap**. This step is important, since acetal formation is reversible, and the removal of water pushes the equilibrium to the right by Le Chatelier's principal. Indeed, once pure hemiacetals or acetals are obtained, they may be hydrolyzed back to their starting components by treatment with aqueous acid and an excess of water.

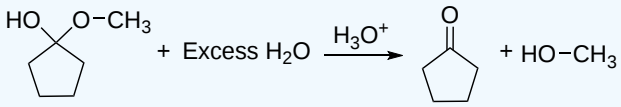
FORMATION OF HEMIACETALS



EXAMPLE 19.10.1: FORMATION OF A HEMIACETAL

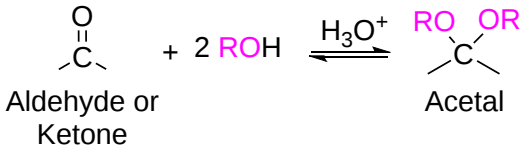


EXAMPLE 19.10.2: HEMIACETAL HYDROLYSIS REVERTING TO THE KETONE



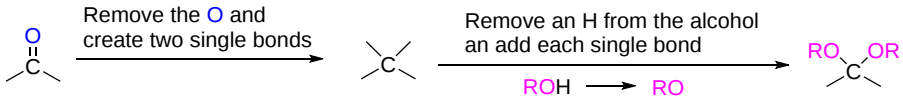
FORMATION OF ACETALS

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.

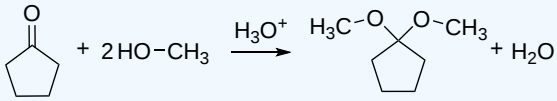


PREDICTING THE PRODUCT OF A ACETAL FORMATION

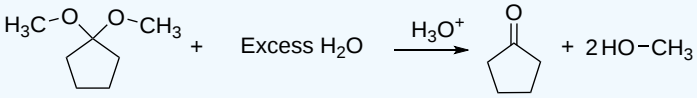
Overall, the carbonyl in the reactant is removed and replaced by two single bonds between oxygen and the original carbonyl carbon. Both of these single bonds are attached O-R groups produced after the reagent alcohol has lost a hydrogen.



EXAMPLE 19.10.3: FORMATION OF ACETALS



EXAMPLE 19.10.4: ACETAL HYDROLYSIS REVERTING TO THE KETONE

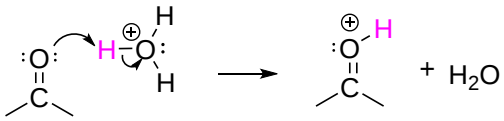


MECHANISM FOR HEMIACETAL AND ACETAL FORMATION

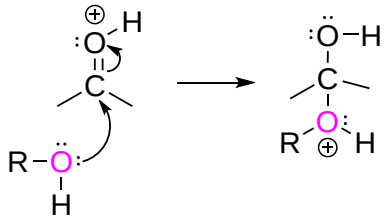
After protonation, an alcohol undergoes nucleophilic addition to the carbonyl group initially forming a hemiacetal upon deprotonation. Further protonation of the OH group in the hemiacetal allows for the elimination of water to form an oxonium ion. A second alcohol nucleophile adds to the oxonium ion to produce a protonated acetal. After deprotonation, the product acetal is formed.

The mechanism shown here applies to both acetal and hemiacetal formation.

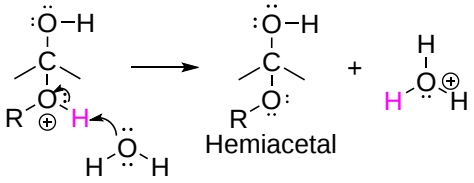
STEP 1: THE ACID CATALYST PROTONATES THE CARBONYL OXYGEN, MAKING THE CARBONYL CARBON MORE ELECTROPHILIC.



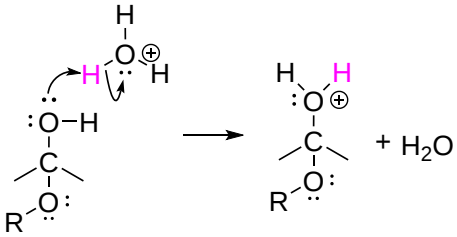
STEP 2: AN ALCOHOL UNDERGOES NUCLEOPHILIC ADDITION TO THE CARBONYL PRODUCING A PROTONATED HEMIACETAL.



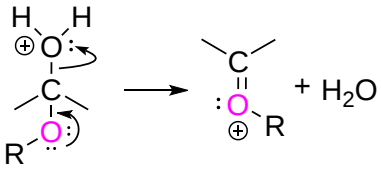
STEP 3: WATER ACTS AS BASE TO CAUSE A DEPROTONATION CREATING A HEMIACETAL AND HYDRONIUM.



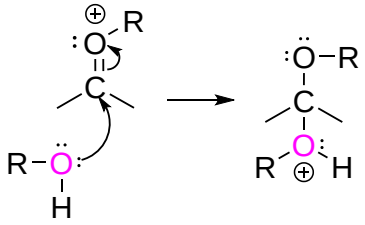
STEP 4: THE OH GROUP OF THE HEMIACETAL IS PROTONATED MAKING IT INTO A GOOD LEAVING GROUP.



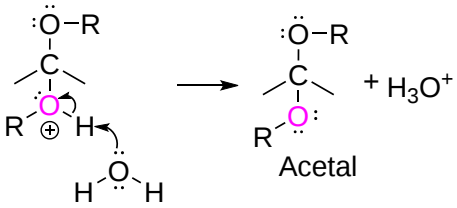
STEP 5: LONE PAIR ELECTRONS ON THE ETHER OXYGEN REFORMS THE C=O BOND CAUSING THE ELIMINATION OF WATER AND PRODUCING AN OXONIUM ION.



STEP 6: A SECOND ALCOHOL UNDERGOES NUCLEOPHILIC ADDITION TO OXONIUM ION PRODUCING A PROTONATED ACETAL.

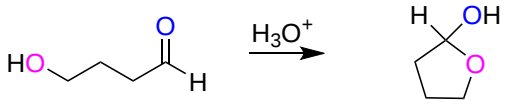


STEP 7: WATER ACTS AS A BASE AND CAUSES A DEPROTONATION, CREATING THE PRODUCT ACETAL AND HYDRONIUM.



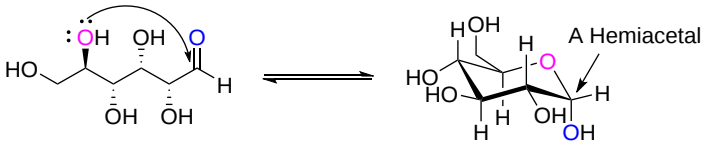
BIOLOGICAL ACETAL AND HEMIACETAL FORMATION

Molecules which have both an alcohol and a carbonyl can undergo an intramolecular reaction to form a cyclic hemiacetal.



Cyclic Hemiacetal

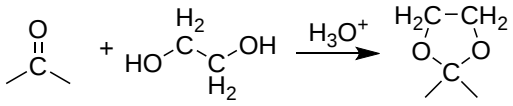
Because sugars often contain alcohol and carbonyl functional groups, intramolecular hemiacetal formation is common in carbohydrate chemistry as we will see in Section 25.7. For example, the common sugar glucose exists in the cylcic manner more than 99% of the time in a mixture of aqueous solution.



Conversion of D-Glucose to Beta-D-Glucopyranose (Cyclic Hemiacetal)

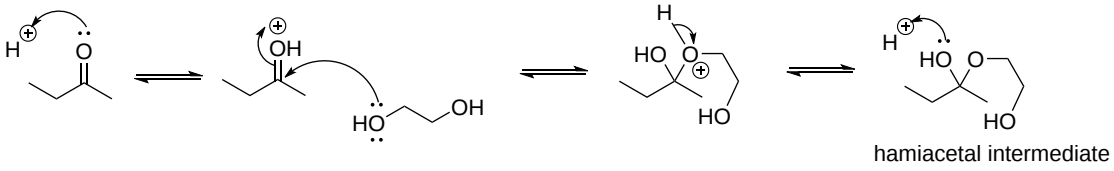
ACETALS AS PROTECTING GROUPS

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 reagents ($LiAlH_4$ & $NaBH_4$), and organometallic reagents (RMgX & RLi). 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. To accomplish this, it is common to use a diol such as ethylene glycol(rather than two equivalents of a simple alcohol) to form a cyclic acetal ring commonly called a dioxolane.

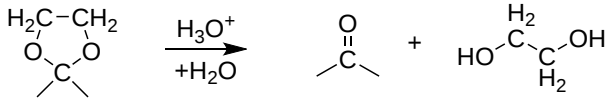


Ethylene Glycol Cyclic Acetal

Because both OH groups are part of the same molecule, the second nucleophilic addtion in the formation of the acetal is intramolecular and forms a ring. Cyclic acetals are more stable towards hydrolysis than acyclic ones and are also kinetically favored because the intramolecular ring-closing reaction is fast.



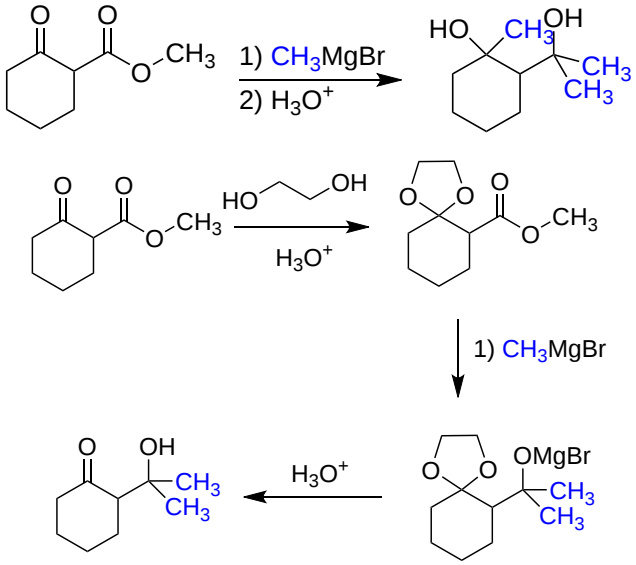
Once the addition reaction is accomplished (or whatever reaction required protecting the carbonyl), the reversibility of acetal formation can be used to reform the original carbonyl.



Cyclic Acetal Ethylene Glycol

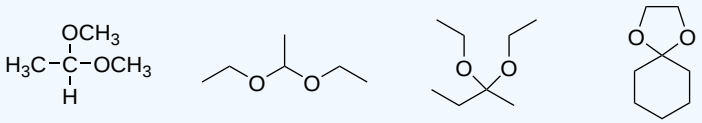
In the following example we would like a Grignard reagent to react with the ester and not the ketone. This cannot be done without a protecting group because Grignard reagents react with both esters and ketones with the ketone typically more reactive than the ester. This

reaction sequence uses ethylene glycol to form the cyclic acetal protecting group for the ketone followed by reaction of the ester with a Grignard reagent. Once this reaction is complete, the acetal is hydrolyzed back to the ketone in the same step that reprotonates the alcohol (while eliminating the MgBr).

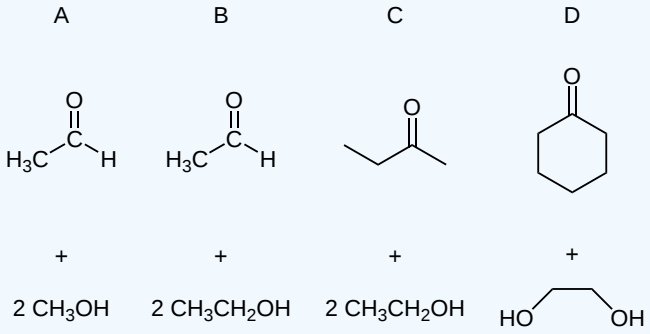


EXERCISE 19.10.1

For each acetal/ketal A-D in the figure below, specify the required aldehyde/ketone and alcohol starting materials.

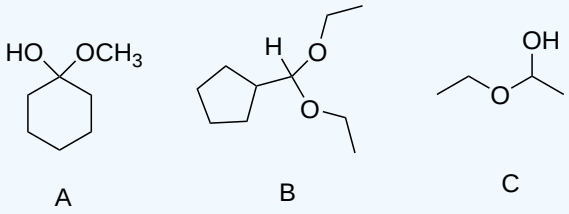


Answer

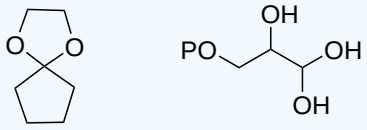


EXERCISE 19.10.2

Categorize each of the following molecules as a hemiacetal, acetal, hydrate of an aldehyde, or hydrate of a ketone.



A B C



D E

Answer

A - hemiacetal, B - acetal, C - hemiacetal, D - acetal, E - hydrate of an aldehyde

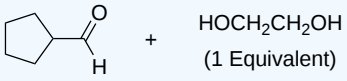
EXERCISE 19.10.3

Specify the acetal that would form from a reaction between the given starting compounds.

a.

(2 Equivalents)

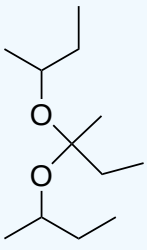
b.



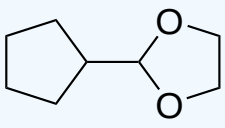
(1 Equivalent)

Answer

a.



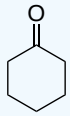
b.

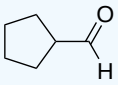


EXERCISE 19.10.4

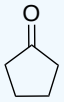
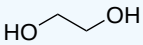
Specify the aldehyde/ketone and alcohol combination that would be required to form the compounds in exercise 2.

Answer

A  + CH_3OH (1 Eq.)

B  + CH_3CH_2OH (2 Eq.)

C  + CH_3CH_2OH (1 Eq.)

C  +  (1Eq.)

19.11: NUCLEOPHILIC ADDITION OF PHOSPHORUS YLIDES - THE WITTIG REACTION

OBJECTIVES

After completing this section, you should be able to

- write an equation to illustrate the formation of an ylide (phosphorane).
- write an equation to illustrate the reaction that takes place between an ylide and an aldehyde or ketone.
- identify the alkene which results from the reaction of a given ylide with a given aldehyde or ketone.
- identify the aldehyde or ketone, the ylide, or both, needed to prepare a given alkene by a Wittig reaction.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- betaine
- Wittig reaction
- ylide (phosphorane)

STUDY NOTES

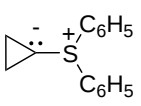
The name triphenylphosphine is derived as follows: the compound PH_3 is called phosphine; replacing the three hydrogen atoms with phenyl groups therefore gives us triphenylphosphine.

Note the following series of IUPAC-accepted trivial names:

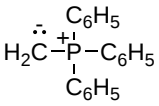
- NH_3—ammonia
- PH_3—phosphine
- AsH_3—arsine

PHOSPHORUS YLIDES

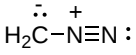
An **ylide,** is defined as a compound with positive and negative charges on adjacent atoms and an overall neutral charge. There are multiple types of ylides but for the Wittig reaction an **organophosphorus ylide**, also called a **Wittig Reagent**, will be used.



Sulfur Ylide



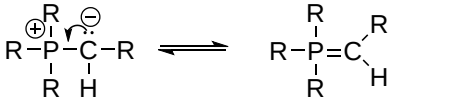
Phosphorus Ylide



Nitrogen Ylide

Although many Wittig reagents are commercially available, it is often necessary to create them synthetically. Wittig reagents can be synthesized from an **alkylphosphonium salt** created using an S_N2 reaction between an alkyl halide and a nucleophilic trialkyl phosphine. Because trialkyl phosphines typically make good nucleophiles, the S_N2 reactions usually occur with high yields. The subsequent alkylphosphonium salt has an increased acidity (pKa ~22) and can be deprotonated using strong bases, such as *n*-butyllithium, sodium amide, sodium hydride, and alkoxides to create the neutral Wittig reagent. The increased acidity of the alkylphosphonium salt is due to the stabilizing inductive and resonance effects provided by the phosphorus adjacent to the carbanion conjugate base.

The ability of phosphorus to hold more than eight valence electrons allows for a resonance structure to be drawn forming a double bonded structure call a **phosphorane**. Although Wittig reagents are commonly drawn in the phosphorane form, the ylide form is often used because it shows the nucleophilic carbanion.

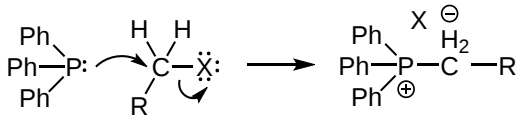


Ylide Form Phosphorane Form

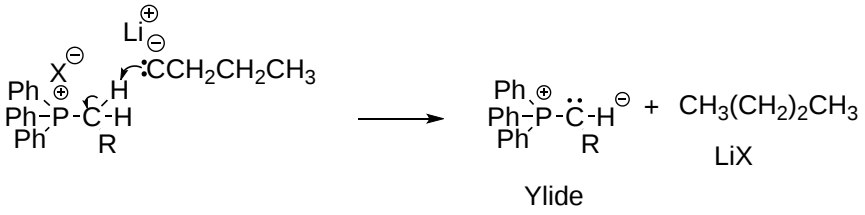
MECHANISM OF YLIDE FORMATION

The lone pair electrons on the phosphine attack the electrophilic carbon of an alkyl halide as part of a S_N2 reaction. This forms a P-C bond while ejecting the halogen leaving group to create an alkylphosphonium salt. A strong base, such as *n*-butyllithium, deprotonates the acidic hydrogen of the alkylphosphonium salt to create an ylide Wittig reagent.

STEP 1: S_N2 REACTION

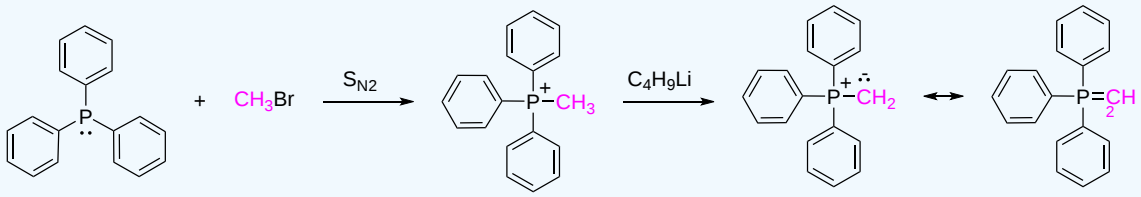


STEP 2: DEPROTONATION



EXAMPLE 19.11.1

A common Wittig reagent is **methylenetriphenylphosphorane** ($Ph_3P{=}CH_2$) which is synthesized by reacting **Triphenyl phosphine** with methylbromide followed by deprotonation with *n*-butyllithium.



YLIDES IN SYNTHESIS

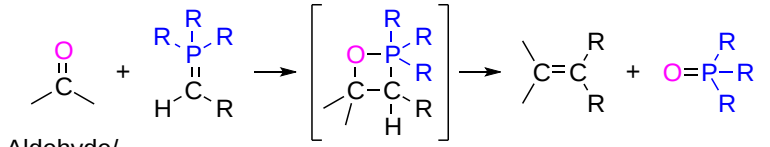
Because an S_N2 reaction is used in the synthesis of ylides, methyl and primary halides perform the best. Secondary halides can also be used but the yields are generally lower. This should be considered when planning out a synthetic pathway which involves a synthesized Wittig reagent.

The ylides are typically strong bases and are protonated by water, alcohols, and other acidic hydrogens. Contact with water causes phosphorous ylides to decompose in to hydrocarbons and phosphine oxides, as shown below.

THE WITTIG REACTION

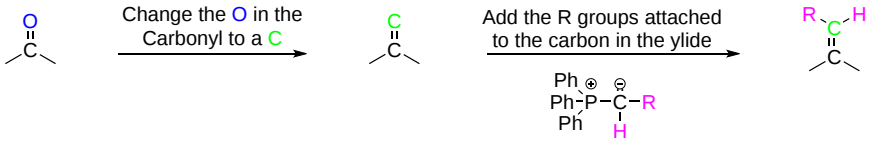
Alkylidenephosphorane ylides (Wittig Reagents) react with aldehydes or ketones through nucleophilic addition, to give substituted alkenes in a reaction called the **Wittig reaction**. This reaction was developed in 1954 by George Wittig who was awarded the Nobel Prize for this work in 1979. Because of its reliability and wide applicability, the Wittig reaction has become a standard tool used in organic synthesis for the preparation of alkenes.

In the Wittig reaction, an **ylide** (typically triphenylphosphorus ylide), adds to an aldehyde or ketone to yield a four-membered heterocyclic intermediate called an **oxaphosphetane**. The oxaphosphetane intermediate spontaneously decomposes to produce an alkene plus a **phosphine oxide**. Cleavage of the oxaphosphetane to alkene and phosphine oxide products is exothermic and irreversible.

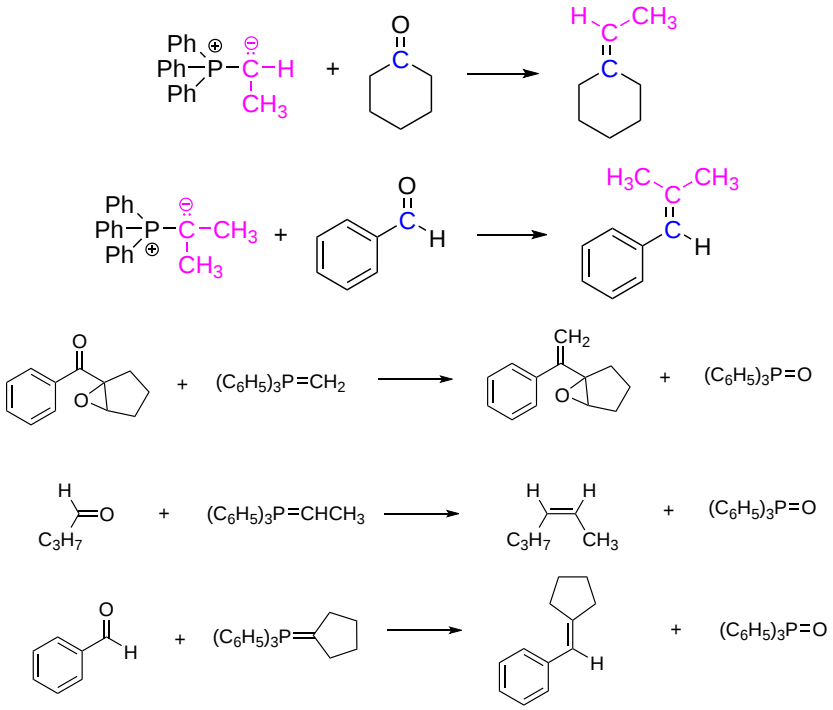


PREDICTING THE PRODUCT OF A WITTIG REACTION

Overall the carbonyl oxygen of an aldehyde or ketone is replaced by the nucleophilic, carbanion present in the ylide while still maintaining the double bond. First, convert the oxygen in the starting material into a carbon while maintaining the double bond. This carbon represents the nucleophilic carbon in the ylide. Then look at the ylide reactant and observe the two groups attached to the nucleophilic carbon. Then transfer these to the bare carbon in the double bond. There may be some possibility of creating E/Z isomers and this will be discussed later.



EXAMPLES OF THE WITTIG REACTION

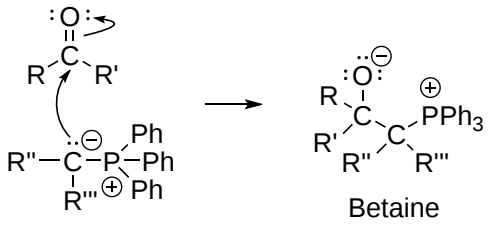


MECHANISM OF THE WITTIG REACTION

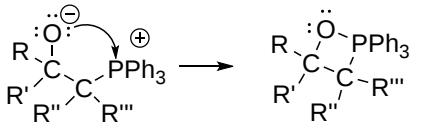
The initial mechanistic step to form the oxaphosphetane intermediate appears to take place by different pathways which is dependent on the structure of the reactants and the exact experimental conditions. One pathway involves a [2+2] cycloaddition between the ylide and carbonyl to directly form the oxaphosphetane. Cyloadditions, such as this, will be discussed in more detail in section 30.5.

In another postulated mechanism, the ylide undergoes nucleophilic addition to the carbonyl group, forming the initial carbon-carbon bond and creating a dipolar charge-separated intermediate species called a **betaine**. The betaine subsequently undergoes ring closure to form the four-membered oxaphosphetane structure. In the final step of the mechanism, the oxaphosphetane undergoes intramolecular elimination to give an alkene and a triphenylphosphine oxide.

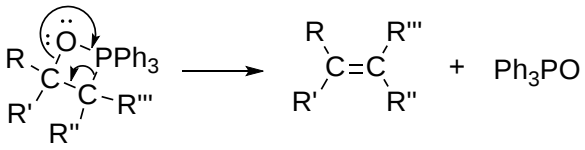
STEP 1: NUCLEOPHILLIC ATTACK ON THE CARBONYL DOUBLE BOND



STEP 2: FORMATION OF THE 4-MEMBERED OXAPHOSPHETANE RING

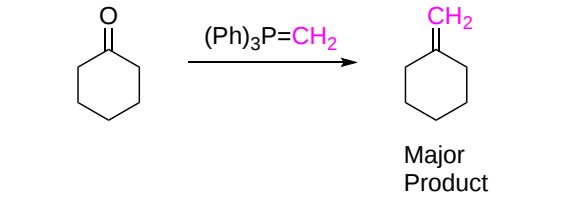


STEP 3: INTRAMOLECULAR ELIMINATION



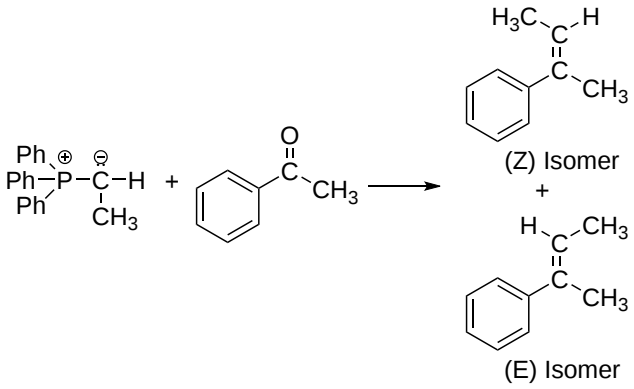
BENEFITS OF THE WITTIG REACTION

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 or other elimination reactions.



LIMITATIONS OF THE WITTIG REACTION

One limitation of the Wittig reaction is possibility of E and Z isomers of the alkene forming. With simple ylides, the product formed is usually primarily the Z-isomer, although a lesser amount of the E-isomer is often also formed. If the E-isomer is the desired product, variations of the Wittig reaction, such as the **Schlosser modification** which uses a stabilized ylide, may be used. It is common to avoid the possibility of forming E/Z isomer by either using symmetrical ketones or symmetrical ylides.

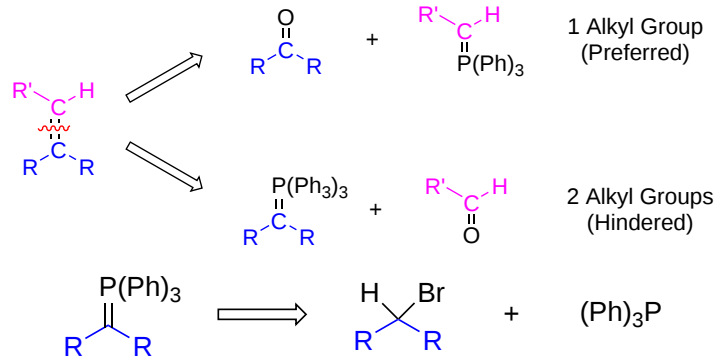


As mentioned above, the Wittig reagent itself is usually derived from an S_N2 reaction with an alkyl halide. Ylide formation with most secondary halides is inefficient. For this reason, Wittig reagents are rarely used to prepare tetrasubstituted alkenes. However, the Wittig reaction is robust and can tolerate the presence of many other functional groups including alkenes, aromatic rings, ethers, alcohols, and ester groups. Bis-ylides (containing two P=C bonds) have also been made and used successfully.

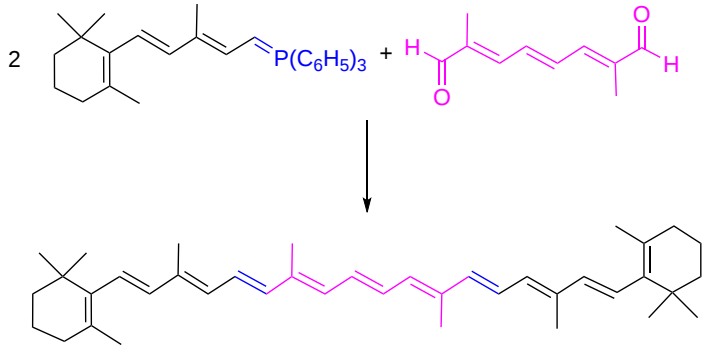
SYNTHESIS OF ALKENES USING THE WITTIG REACTION

When using retrosynthetic analysis to determine the preferred route to synthesize an alkene, it is important to remember that Wittig reagents are commonly prepared by using an S_N2 reaction. To find the possible reactants of a Wittig reaction, cleave the C=C bond in the target

molecule to create two pieces. Place an oxygen on one piece to create a carbonyl and place a $(Ph_3)P$ on the other piece to create the Wittig reagent. There are two possible combinations of this separation. The one whose Wittig reagent has the fewest number of alkyl groups will be easier to prepare by the required S_N2 reaction and will represent the preferred route.

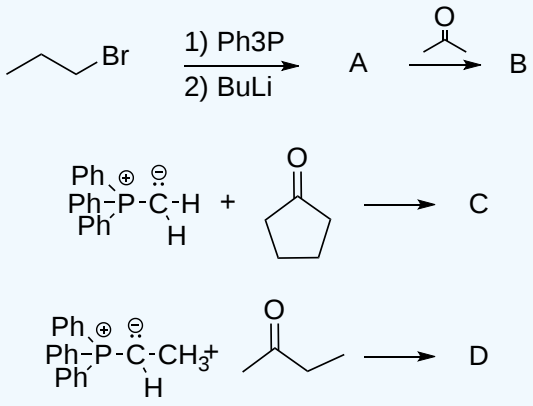


The Wittig reaction is commonly used in the preparations of pharmaceuticals and other commercial chemicals. The dietary source of **vitamin A (β-Carotene)** can be synthesized by a Wittig reaction using two equivalents of the ylide, **β-ionylideneacetaldehyde**.

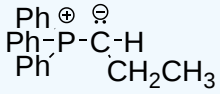


EXERCISE 19.11.1

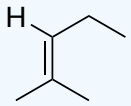
Draw the product of the following reactions.



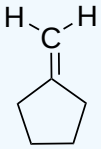
Answer



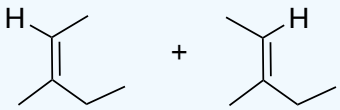
A



B



C

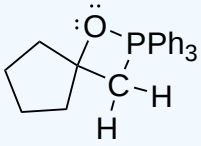


D

EXERCISE 19.11.2

Draw the structure of the oxaphosphetane which is made during the mechanism of the reaction given that produces product **C**.

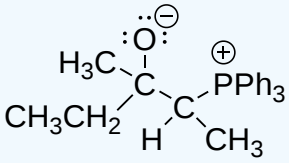
Answer



EXERCISE 19.11.3

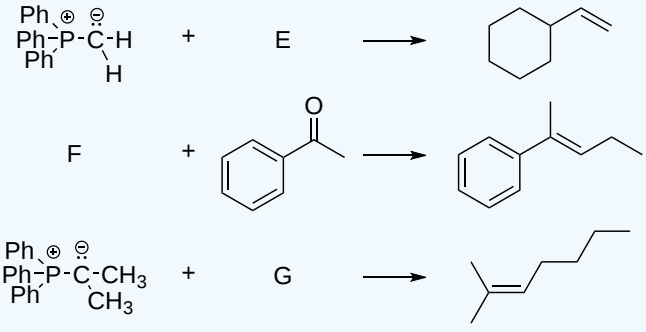
Draw the structure of the betaine which is made during the mechanism of the reaction given that produces product **D**.

Answer

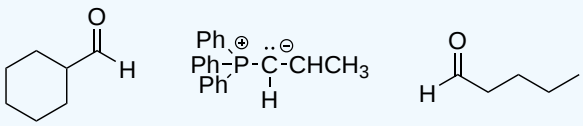


EXERCISE 19.11.4

Indicate the starting material required to produce the product in each reaction.



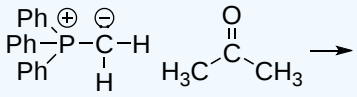
Answer



E F G

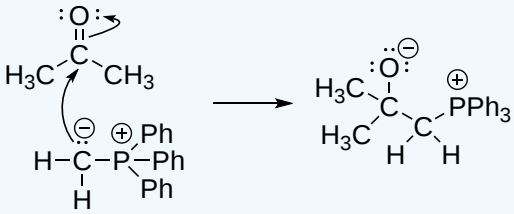
EXERCISE 19.11.6

Give a detailed mechanism and the final product of this reaction

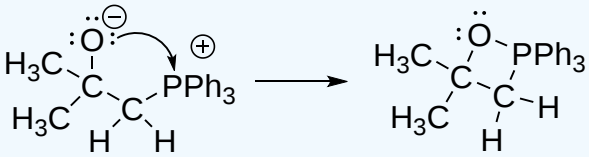


Answer

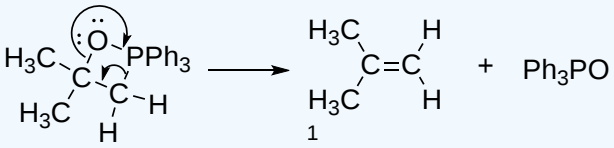
Step 1: Nucleophilic attack on the carbonyl



Step 2: Formation of a 4 membered ring



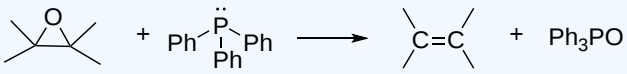
Step 3: Formation of the alkene



1

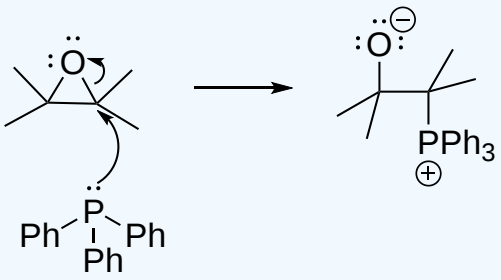
EXERCISE 19.11.7

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.

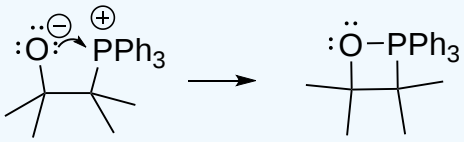


Answer

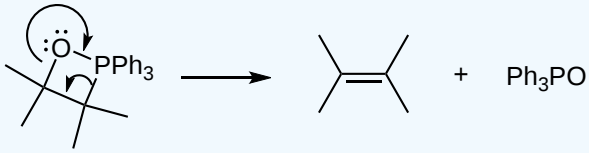
Nucleophillic attack on the epoxide



Formation of a 4 membered ring



Formation of the alkene



19.12: BIOLOGICAL REDUCTIONS

OBJECTIVES

After completing this section, you should be able to

- determine whether or not a given aldehyde will undergo the Cannizzaro reaction.
- write an equation to illustrate the Cannizzaro reaction.
- identify the products formed when a given aldehyde undergoes a Cannizzaro reaction.
- write the detailed mechanism of the Cannizzaro reaction.

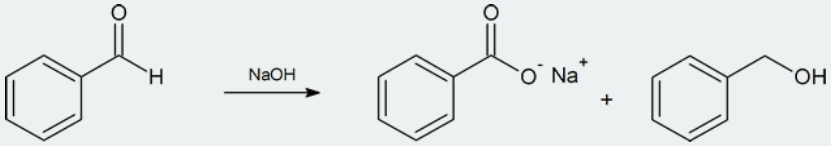
KEY TERMS

Make certain that you can define, and use in context, the key term below.

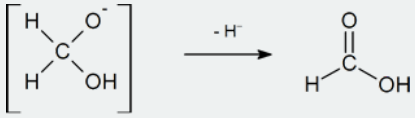
- Cannizzaro reaction

STUDY NOTES

In 1853 Stanislao Cannizzaro discovered that the base-induced disproportionation of an aldehyde resulted in a carboxylic acid (oxidation product) and an alcohol (reduction product).



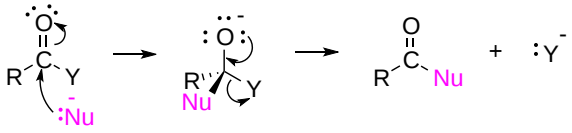
Note that in the mechanism shown in the reading has an intermediate generated from methanal (formaldehyde) that effectively becomes a hydride (H^-) donor, which reduces a second molecule of methanal to methanol.



hydride donor

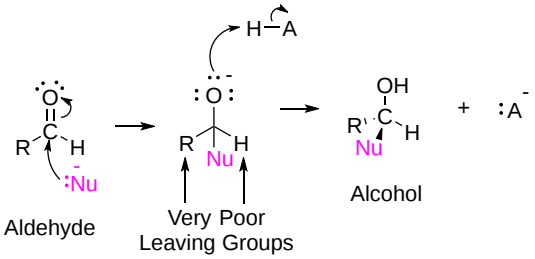
Carbonyl reductions are a part of important biological pathways in living organisms. Recall in Section 17.4 that NADH can donate H^- to reduce aldehydes and ketones. You may wish to review this section.

As seen in Section 18.11, nucleophilic addition reactions usually do not occur in many carboxylic acid derivatives due to the presence of a leaving group. Following nucleophilic addition, the tetrahedral alkoxide intermediate can reform the carbonyl by eliminating the leaving group as part of a reaction called **nucleophilic acyl substitution**. The nucleophilic acyl substitution reaction will be discussed in greater detail in Chapter 21.



Y = -Br, -Cl, -OR, -NR_2, -O_2R

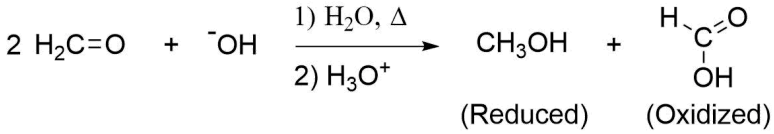
This reaction does not occur in aldehydes or ketones because alkyl or hydrogen substituents make very poor leaving groups. After nucleophilic addition, the negative charge on the tetrahedral alkoxide intermediate remains on the oxygen and is subsequently protonated to form a hydroxyl group (OH). This represents the 1,2 nucleophilc addition reaction discussed in most of this chapter.



THE CANNIZZARO REACTION

An important exception to the idea of hydrogen making a poor leaving group is seen in the **Cannizzaro reaction**, discovered in 1853 by Stanislao Cannizzaro. A characteristic reaction of aldehydes without α hydrogens is the self oxidation-reduction they undergo in the presence of strong base. If the aldehyde has α hydrogens, other reactions usually occur more rapidly. The Cannizzaro reaction, combines many features of other reactions studied in this chapter. During this reaction, nucleophilic addition of a hydroxide ($^{-}$OH) to an aldehyde gives a tetrahedral alkoxide intermediate. The alkoxide subsequently reforms the carbonyl, eliminating a hydride ion ($^{-}$:H) as a leaving group, and creating an oxidized carboxylic acid product. The eliminated hydride ion reduces a second aldehyde molecule, in a similar fashion as hydride containing reagents $LiAlH_4$ and $NaBH_4$, to create a reduced alcohol product. For example, methanal creates methanol (reduced) and methanoic acid (oxidized) when heated with aqueous NaOH.

EXAMPLE

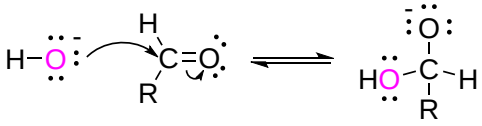


Methanal Undergoing a Cannizzaro Reaction to form Methanol and Methanoic Acid

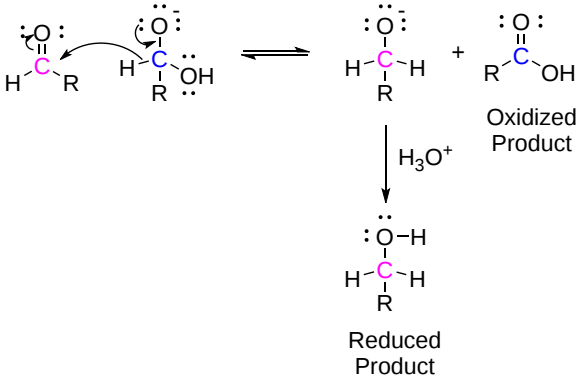
MECHANISM OF THE CANNIZZARO REACTION

The first step of the mechanism is the reversible nucleophilic addition of a hydroxide ion to the carbonyl group of an aldehyde. This is analogous to the first mechanistic step in the formation of a hydrate under basic conditions. The hydroxide nucleophile attacks the electrophilic carbonyl carbon forming a C-O single bond. The two electrons from the carbonyl pi bond are pushed onto the electronegative oxygen to form a tetrahedral alkoxide intermediate. In the second step of the mechanism, the alkoxide intermediate reforms the carbonyl, eliminating a hydride ion as the leaving group, and forms a carboxylic acid functional group as an oxidized product. The hydride ion acts as a nucleophile and attacks the carbonyl carbon of a second aldehyde forming a C-H bond. The two electrons from the second pi bond are pushed onto the electronegative oxygen to form a different alkoxide intermediate. This alkoxide intermediate is quickly protonated to form an alcohol functional group as a reduced product.

STEP 1: NUCLEOPHILIC ATTACK



STEP 2: HYDRIDE TRANSFER

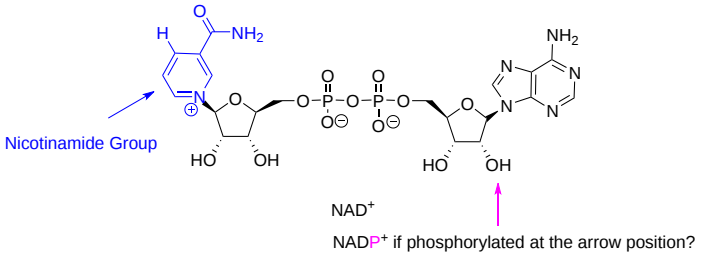


BIOLOGICAL REDUCTIONS USING HYDRIDE TRANSFER TO A CARBONYLS

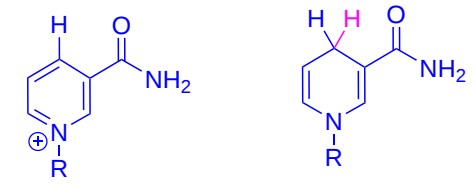
The Cannizzaro reaction is interesting because its mechanism is analogous to the hydride reductions of carbonyls which occur in the biological pathway of many living organisms. One of the most important biological reducing agents is NADH (the reduced form of nicotinamide adenine dinucleotide) which can act as a source of the hydride ion. NADH donates a hydride to carbonyls in an analogous fashion to the alkoxide ion intermediate of the Cannizzaro reaction. A set of lone pair electrons on a NADH nitrogen atom pushes the hydride off as a leaving group forming NAD+ (the oxidized form of nicotinamide adenine dinucleotide). The ejected hydride adds as a nucleophile to a wide variety of carbonyl containing biological molecules. Some examples of this addition are described below.

NICOTINAMIDE ADENINE DINUCLEOTIDE - A HYDRIDE TRANSFER COENZYME

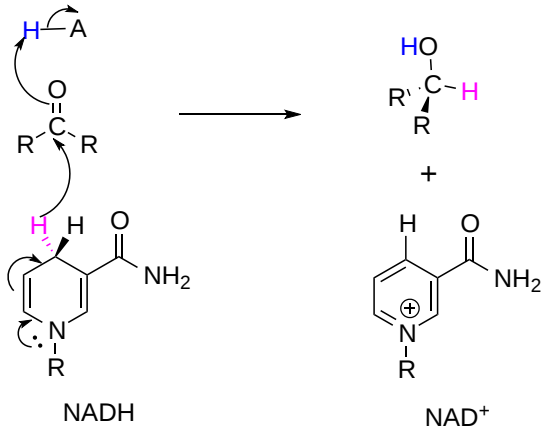
Although we are talking about hydrides acting as nucleophiles and leaving groups in this section, you already know that discreet hydride ions are far too unstable to exist as actual intermediates in the organic reactions of living cells. Biochemical redox reactions involving hydride transfer require the participation of a hydride transfer coenzyme. In reactions involving carbonyl compounds, a molecule called nicotinamide adenine dinucleotide generally plays this role. The full structure of the oxidized form of this coenzyme, abbreviated NAD+, is shown below, with the active nicotinamide group colored blue.



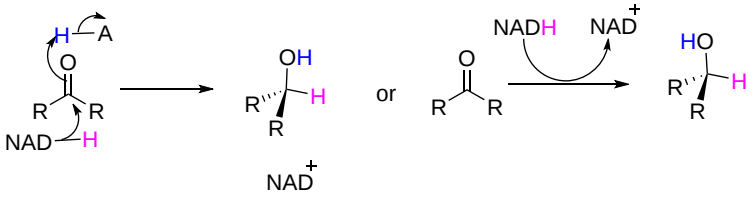
Because the redox chemistry occurs specifically at the nicotinamide part of the molecule, typically the rest of the molecule is simply designated as an 'R' group. NAD^+ and $NADP^+$ both function in biochemical redox reactions as hydride acceptors: that is, as oxidizing agents. The other forms of the coenzyme, NADH and NADPH, serve as hydride donors: that is, as reducing agents.



The phosphate on the nucleotide pentose group of NADP+ and NADPH is located far from the nicotinamide ring, and does not participate directly in the hydride transfer function of the cofactor.

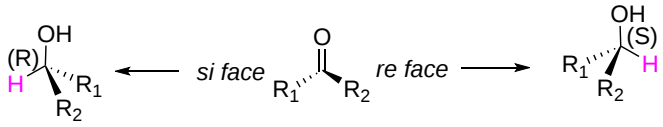


This reaction can be simplified in the following way:

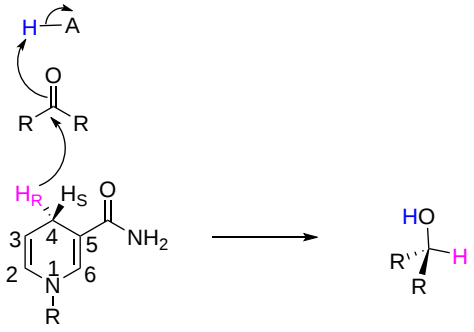


STEREOCHEMISTRY OF HYDRIDE TRANSFER REACTIONS

Ketone/aldehyde hydrogenase reactions are stereospecific in two distinct ways. In the hydrogenase direction, attack by the hydride can occur from either the *re* or the *si* face of an asymmetrical carbonyl, leading to the *S* or *R* alcohol depending on the priorities of R_1 and R_2 (in the example R_1 has higher priority than R_2).



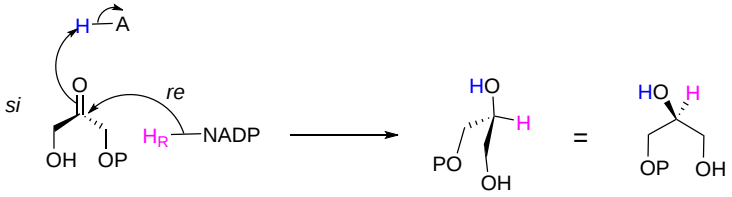
The specificity is determined by which side of the ketone or aldehyde substrate the NAD(P)H cofactor is bound to in the active site. In addition, hydrogenases specifically catalyze the transfer of either the *pro-R* or the *pro-S* hydrogen at C_4 of the nicotinamide ring. In the example below, the *pro-R* hydrogen of NADH is transferred to reduce the ketone.



NADH

EXAMPLES OF BIOLOGICAL HYDRIDE TRANSFER REACTIONS

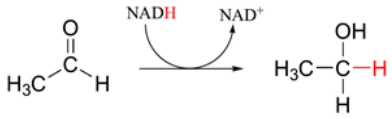
1. In 1997, an enzyme was discovered in a class of microbes known as 'archaea' that catalyzes the same reaction with the opposite substrate stereochemistry (J. Biochem 1997, 122, 572). The primary metabolic role of the enzyme is apparently to catalyze the reduction of dihydroxyacetone phosphate to (S)-glycerol phosphate, with transfer of the pro-R hydrogen atom from NADPH to the *re* face of dihydroxyacetone phosphate.



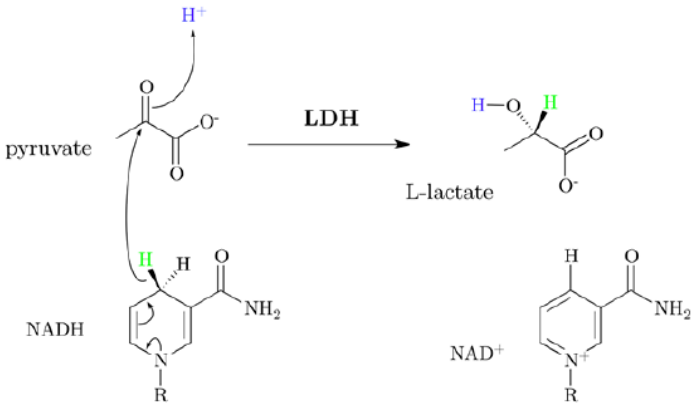
dihydroxyacetone phosphate

(S)-glycerol phosphate

2. In a reaction that is very important to people in the wine and beer-making industry, an NADH-dependent enzyme in yeast produces ethanol by reducing acetaldehyde. The acetaldehyde is derived from the thiamine diphosphate-dependent decarboxylation of pyruvate.

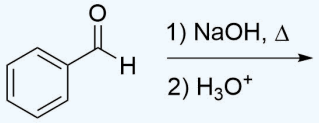


3. Lactic acid fermentation occurs by converting pyruvate into lactate through hydride addition using the enzyme lactate dehydrogenase and producing NAD+ in the process. This process takes place in oxygen depleted muscle and some bacteria. It is responsible for the sour taste of sauerkraut and yogurt.

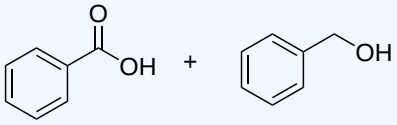


EXERCISE 19.12.1

Please draw the expected products of the following reaction:

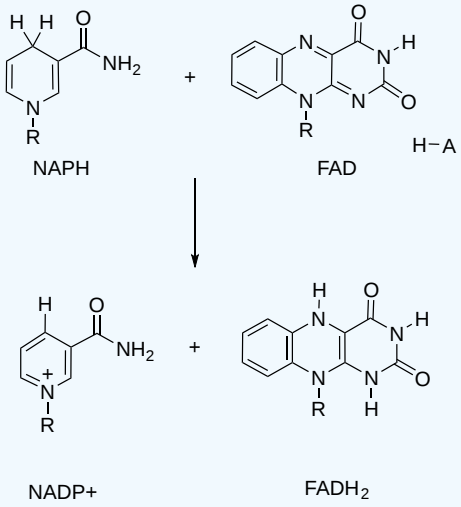


Answer

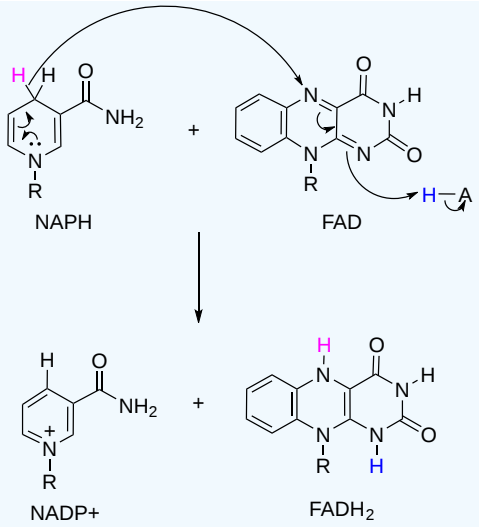


EXERCISE 19.12.2

Please draw the mechanism for the following hydride transfer reaction:



Answer



19.13: CONJUGATE NUCLEOPHILIC ADDITION TO A, B-UNSATURATED ALDEHYDES AND KETONES

OBJECTIVES

After completing this section, you should be able to

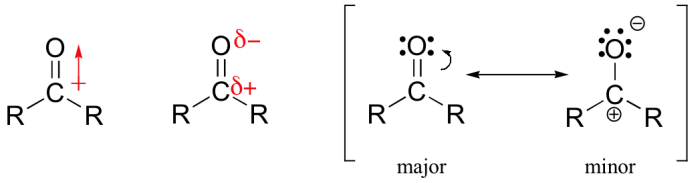
- explain how the carbonyl group which is present in α, β-unsaturated aldehydes and ketones activates the carbon-carbon double bond so that it is susceptible to attack by nucleophiles.
- write equations to illustrate the addition of amines, water and lithium diorganocopper reagents to α, β-unsaturated aldehydes and ketones.
- identify the product formed from the reaction of a given primary or secondary amine with a given α, β-unsaturated aldehyde or ketone.
- identify the aldehyde or ketone, the primary or secondary amine, or both, needed to prepare a given β-amino aldehyde or ketone.
- identify the product formed from the reaction of an α, β-unsaturated aldehyde or ketone with water.
- identify the product formed from the reaction of a given α, β-unsaturated aldehyde or ketone with a given lithium diorganocopper reagent.
- identify the α, β-unsaturated aldehyde or ketone, the lithium diorganocopper reagent, or both, needed to prepare a given product through a conjugate addition reaction.

STUDY NOTES

At first this section may appear to contain a considerable amount of information, but you should realize that much of the material presented is really repetition. Essentially we see how three different nucleophilic reagents, primary and secondary amines, water and lithium diorganocoppers can add across a carbon-carbon double bond when the latter is conjugated to the carbonyl group of an aldehyde or ketone. Note that the first reagent can also react directly with the carbonyl group of an aldehyde or ketone when there is no conjugated carbon-carbon double bond present, but that the third reagent, lithium dialkylcopper, cannot do so.

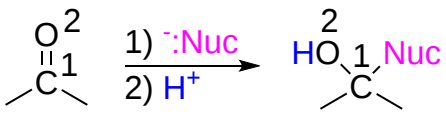
You may be confused about the designation of the product from the conjugate addition to an α, β-unsaturated aldehyde or ketone as a 1,4 adduct. You can more clearly understand this name if you recognize that the proton added in the second step of the reaction first adds to the oxygen of the enolate ion to produce an enol. The latter then tautomerizes to the more stable keto form.

One of the largest and most diverse classes of reactions involves nucleophilic additions to a carbonyl group. As discussed in Section 19.4, carbonyl carbons are electrophilic due to bond polarity created by resonance.

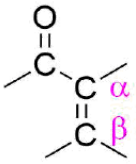


Previously in this chapter, we have discussed a nucleophilic addition to carbonyl carbons called a **1,2 addition**. During 1,2 addition the nucleophile adds to the carbonyl carbon which is defined as the one position. Subsequently, hydrogen adds to the carbonyl oxygen which considered the two position. Overall an atom is added in both the 1 and 2 position justifying the reaction name, 1,2 addition.

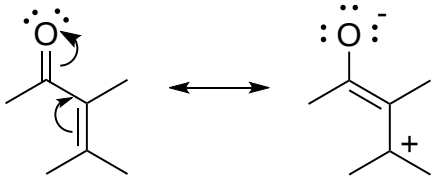
BASIC REACTION OF 1,2 ADDITION



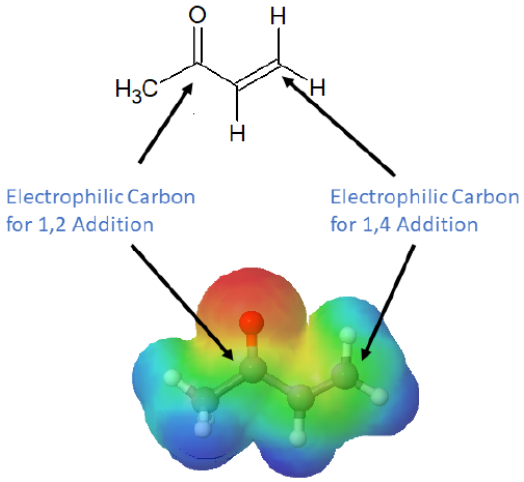
An important functional group is created when an alkene is placed in conjugation with a carbonyl. These conjugated carbonyl are called enones or **α, β-unsaturated carbonyls**. The term α commonly refers to the carbon adjacent to a carbonyl and β referrers to the next carbon in the chain.



Conjugation transmits the electrophilic character of the carbonyl carbon to the β-carbon of the **α, β-unsaturated carbonyl** double bond. The resonance structure shown below shows that the electronegative oxygen atom in α, β-unsaturated carbonyls pulls electrons away from the β carbon making it more electrophilic than a typical alkene carbon.

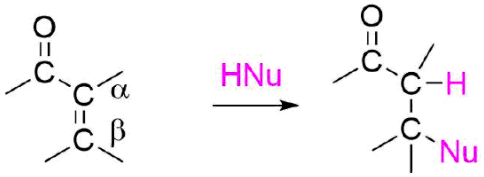


From this resonance form, it should be clear that nucleophiles may attack either at the carbonyl carbon or at the β-alkene carbon. These two modes of reaction are referred to as 1,2-addition and **1,4-addition** respectively. A 1,4-addition is also called a **conjugate addition**.



BASIC REACTION OF 1,4 CONJUGATE ADDITION

In 1,4 addition, a nucleophile is added to the carbon β to the carbonyl while a hydrogen is added to the carbon α to the carbonyl. Overall, the carbonyl is unaffected by the nucleophilic addition. It is important to note that this reaction only occurs because the alkene is conjugated with a carbonyl. The utility of 1,4 conjugate addition is shown by the wide variety of nucleophiles which can be added to a α, β unsaturated carbonyls.

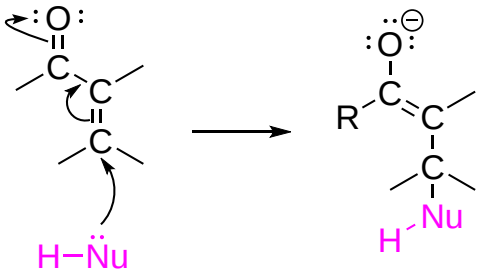


GENERAL MECHANISM FOR 1,4 CONJUGATE ADDITION

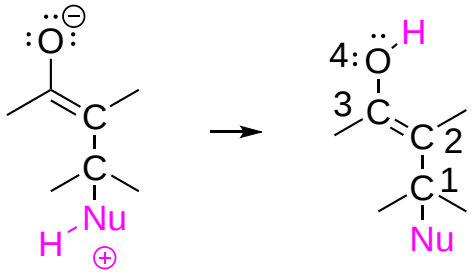
The mechanism starts with the nucleophile attacking the electrophilic β carbon forming a single bond. The two electrons from the alkene pi bond are pushed onto the electronegative carbonyl oxygen creating an enolate. In the next step the the enolate is protonated to form an enol. If the original nucleophile was neutral, this addition will cause it to become positively charge. A proton transfer will occur making the nucleophile neutral and turning the enolate into an enol. If the original nucleophile was negatively charged this protonation is accomplished by the subsequent addition of a proton source. The product of the second step of the mechanism shows why the reaction is called a 1,4 addition. The nucleophile bonds to the β alkene carbon which is considered the one position and the hydrogen adds to the carbonyl oxygen which is in the four position. Overall, addition occurs in the one and four position. In the final step of the mechanism, the enol undergoes a

rearranges to form a carbonyl during a process called tautomerization. Tautomerization causes the hydrogen to move from the oxygen to the β-carbon. The tautomerization process will be discussed in greater detail in Section 22.3.

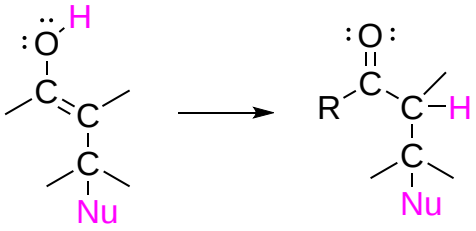
STEP 1: NUCLEOPHILIC ATTACK



STEP 2: PROTONATION

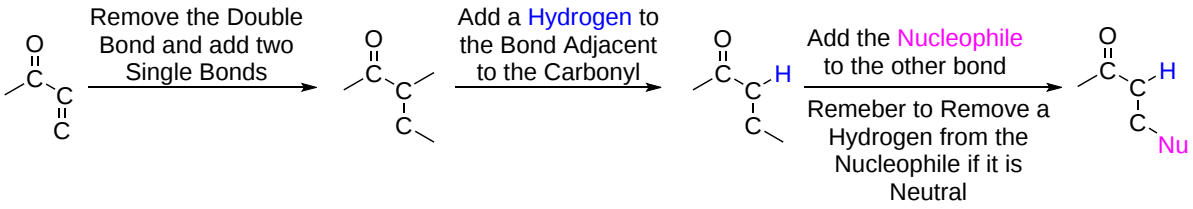


STEP 3: TAUTOMERIZATION



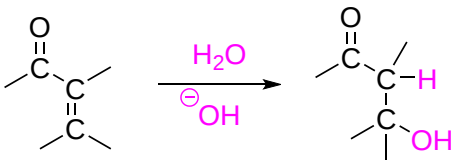
PREDICTING THE PRODUCTS OF A 1,4 CONJUGATE ADDITION

In total, 1,4 addition occurs across the alkene bond of the α, β unsaturated carbonyl. The alkene pi bonds is broken to form two single bonds, one on the α-carbon and one on the β-carbon. During 1,4 addition, the α-carbon of the α, β unsaturated carbonyl forms a bond with a hydrogen while the β-carbon forms a bond to the nucleophile. Remember that neutral nucleophiles typically lose a hydrogen during 1,4 addition.

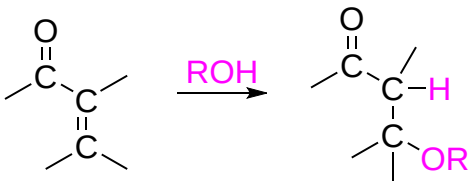


NUCLEOPHILES WHICH ADD 1,4 TO A, B UNSATURATED CARBONYLS

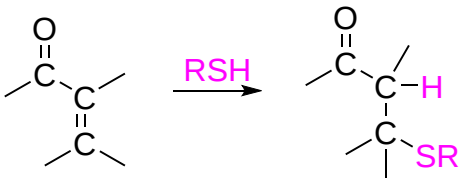
HYDROXIDE



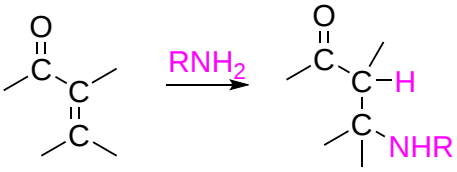
ALCOHOLS



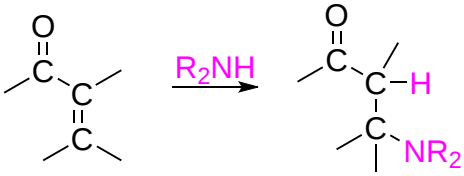
THIOLS



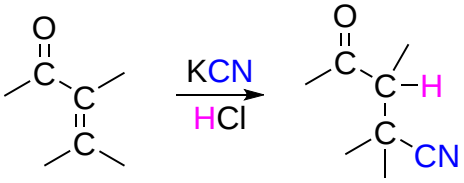
1^{O} AMINES



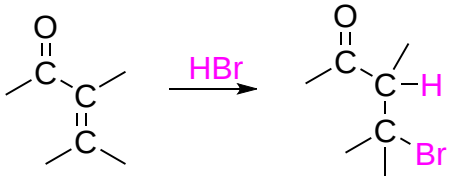
2^{O} AMINES



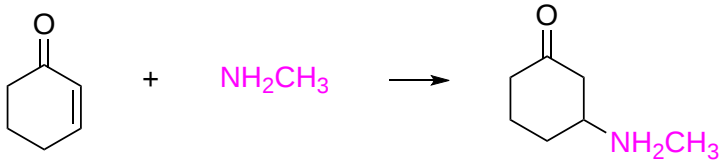
CYANIDES



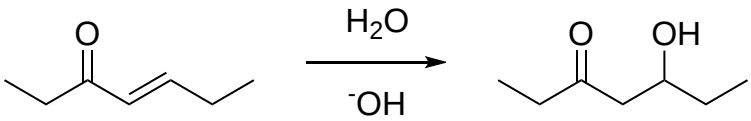
HBR



EXAMPLES



The synthesis of 3-(*N*-Methylamino)cyclohexanone



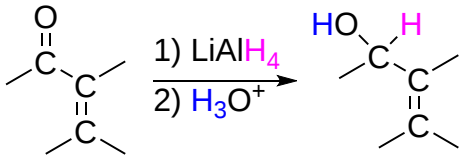
The Synthesis of 5-Hydroxy-3-heptenone

1,2 VS. 1,4 ADDITION

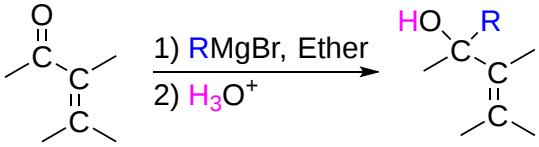
Whether 1,2 or 1,4-addition occurs to a α, β unsaturated carbonyl depends on multiple variables but is mostly determined by the nature of the nucleophile. During the addition of a nucleophile there is a competition between the formation 1,2 and 1,4 addition products. If the nucleophile is a strong base, such as Grignard reagents or metal hydrides, 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, water, alcohols or amines, then the possible 1,2 addition is usually reversible. This means the competition between 1,2 and 1,4 addition is under thermodynamic control. In this most cases, the 1,4-addition product dominates because the stable carbonyl group is retained.

NUCLEOPHILES WHICH ADD 1,2 TO A, B-UNSATURATED CARBONYLS

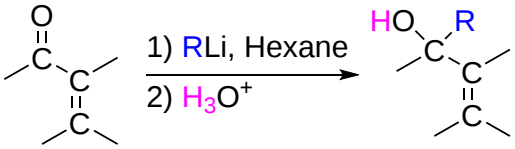
METAL HYDRIDES ($LiAlH_4$)



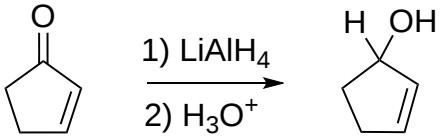
GRIGNARD REAGENTS



ORGANOLITHIUM REAGENTS

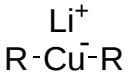


EXAMPLE



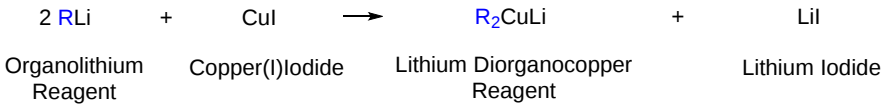
GILMAN REAGENTS

Another important reaction exhibited by organometallic reagents is metal exchange. Organolithium reagents react with cuprous iodide to give a **lithium diorganocopper reagent**, which often is referred to as a **Gilman reagent**. Remember that organolithium reagents are formed by a reaction of lithium metal with an organohalide. Lithium diorganocopper reagents are considered a source of carbanion like nucleophiles similar to Grignard and Organolithium reagents. However, the reactivity of lithium diorganocuprate reagents is slightly different and this difference will be exploited in different situations. Diorganocuprate reagents are made from the reaction of two equivalents of an organolithium reagent and copper (I) iodide (CuI). The created lithium diorganocuprate reagent acts as a source of $R:^-$

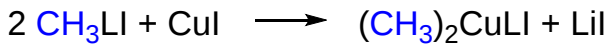


Lithium Diorganocopper (Gilman Reagent)

GENERAL REACTION



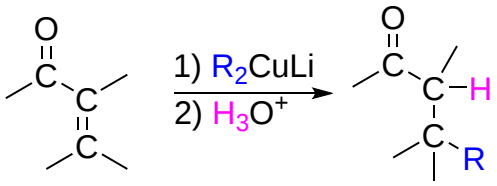
EXAMPLE



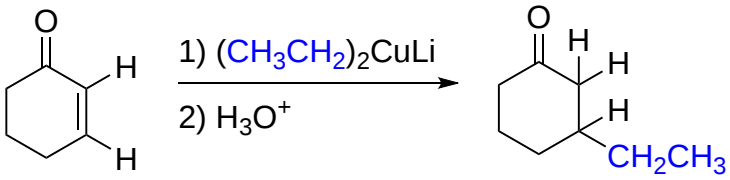
Formation of Lithium Dimethylcopper

REACTION OF 1,4 CONJUGATE ADDITION OF GILMAN REAGENTS TO A, B UNSATURATED KETONES

Lithium diorganocopper reagents, R_2CuLi, undergo 1,4 conjugate addition when reacted with α, β Unsaturated ketones. Using lithium diorganocopper reagents allows for a wide range of organic groups to undergo this 1,4 conjugate addition including alkyl, aryl, and alkenyl groups. Because a C-C single bond is formed this reaction is an excellent method for adding to the carbon framework of a ketone.

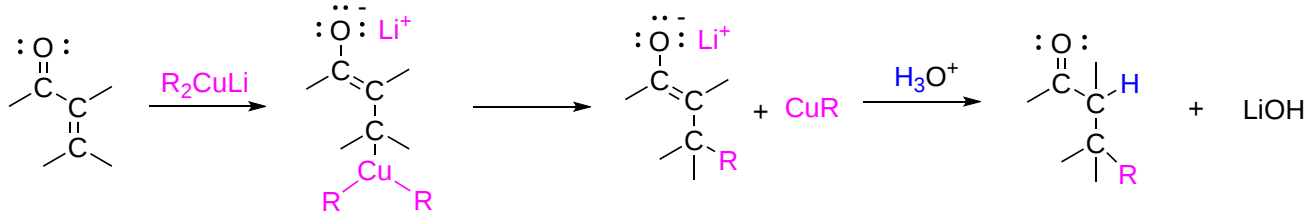


EXAMPLE



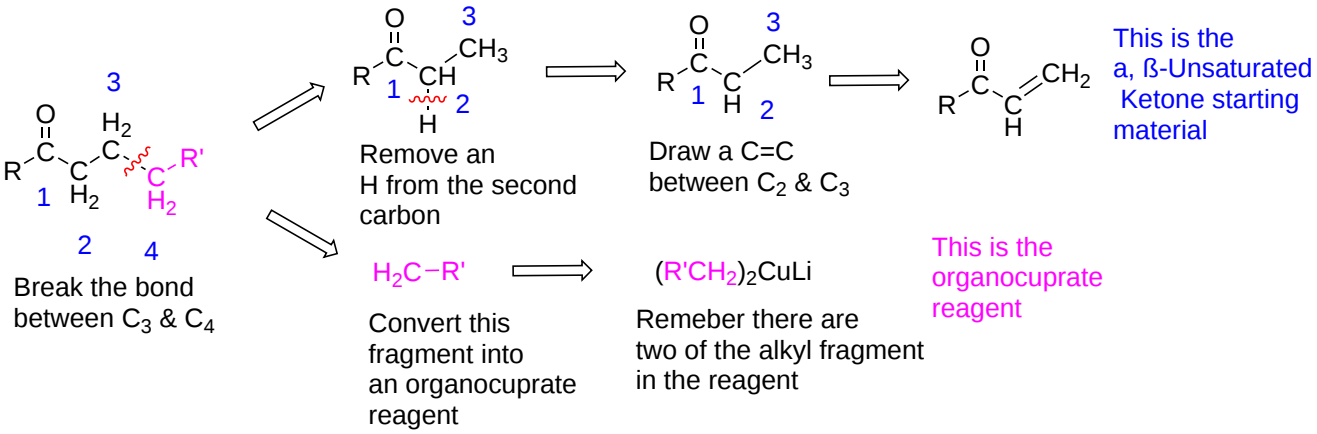
MECHANISM FOR THE 1,4 CONJUGATE ADDITION OF LITHIUM DIORGANOCOPPER REAGENTS TO A, B-UNSATURATED KETONE

This mechanism is only slightly different than the general mechanism for 1,4 conjugate addition described above. The mechanism starts with the nucleophilc diorganocopper anion (R_2Cu^-) adding to the electrophilc β alkene carbon forming a Cu-C bond. The R group from the diorganocopper is then transferred to the β alkene carbon with elimination of a neutral organocopper species (RCu). Protonation of the enolate ion followed by tautomerization creates the final 1,4 addition product.



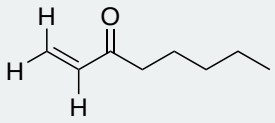
SYNTHESIS OF KETONES USING 1,4 CONJUGATE ADDITION OF LITHIUM DIORGANOCOPPER REAGENTS TO A, B UNSATURATED KETONES

When using retrosynthetic analysis to plan the synthesis of a ketone, remember this reaction allows for the formation of a C-C bond between third and fourth carbon away from a ketone. The carbonyl group in the target molecule will become a α, β unsaturated carbonyl in the probable reactant. To determine the structure of a possible reactant, start by cleaving the C-C between the third and fourth carbon away from the carbonyl to create two fragments. The take the fragment which retains the carbonyl and remove a hydrogen from the second carbon and connect the second and third carbon with a double bond. The creates the required α, β unsaturated carbonyl reactant. The other fragment will become the lithium diorganocopper reagent. Remember the lithium diorganocopper reagent contains two of the required R group. Note! If the fourth carbon away from the ketone in the target molecule is tertiary or quarternary there may be multiple bonds which could be retrosynthetically cleaved.



SOMETHING EXTRA: WHY DO METALS HAVE A SMELL WHEN THEY ARE NONVOLATILE?

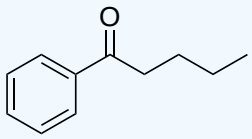
If you have ever encountered a metallic scent when counting coins or handling metals, especially copper, you were probably being fooled. The metallic smell could not have come from the metal because metals are non-volatile and do not evaporate. This means the odor molecules associated with metal scent must come from a different source. The volatile molecules that create the metallic smell are produced by a chemical reaction between skin oils and the metal itself. These volatile molecules, primarily aldehydes and ketones, create a sensory illusion that the metal is producing the smell, even though metals have no natural odor. The main molecule is the α, β Unsaturated Ketone, 1-Octen-3-one, which is described as smelling like mushrooms or metal. This is an illusion because the molecule doesn't smell like metals; metals smells like this molecule. Because we have smelled 1-Octen-3-one coming from metals for so long, we mistake its smell with the metal itself. This kind of chemical reaction also explain why blood produces a metallic smell when it comes into contact with skin. Blood contains iron in hemoglobin, and the same chemical reaction produces odor molecules when blood touches skin.



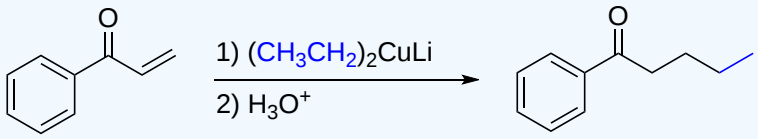
Structure of 1-Octen-3-one

EXERCISE 19.13.1

How would you make the following molecule using a 1,4 Conjugate Addition of a Gilman Reagent to a α, β Unsaturated Ketone?



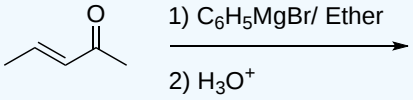
Answer



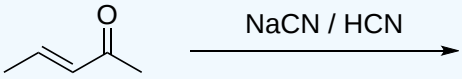
EXERCISE 19.13.2

Draw the bond-line structures for the products of the reactions below.

a)

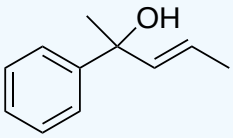


b)



Answer

A



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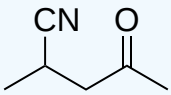
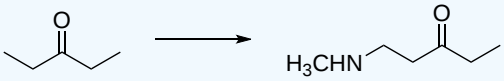


EXERCISE 19.13.3

Specify the reagents needed to perform the following chemical transformation.



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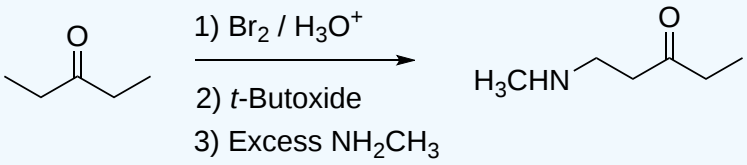


19.14: SPECTROSCOPY OF ALDEHYDES AND KETONES

OBJECTIVES

After completing this section, you should be able to

1. identify the region of the infrared spectrum in which the carbonyl absorption of aldehydes and ketones is found.
2. identify the region of the infrared spectrum in which the two characteristic C$\ce{-}$H absorptions of aldehydes are found.
3. use a table of characteristic absorption frequencies to assist in the determination of the structure of an unknown aldehyde or ketone, given its infrared spectrum and other spectral or experimental data.
4. identify the region of a proton NMR spectrum in which absorptions caused by the presence of aldehydic protons and protons attached to the *α*-carbon atoms of aldehydes and ketones occur.
5. identify two important fragmentations that occur when aliphatic aldehydes and ketones are subjected to analysis by mass spectrometry.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- McLafferty rearrangement

STUDY NOTES

The appearance of a strong absorption at 1660–1770 cm^{-1} in the infrared spectrum of a compound is a clear indication of the presence of a carbonyl group. Although you need not remember the detailed absorptions it is important that you realize that the precise wavenumber of the infrared absorption can often provide some quite specific information about the environment of the carbonyl group in a compound. Notice how conjugation between a carbonyl group and a double bond (*α*, *β*-unsaturated aldehyde or ketone or aromatic ring) lowers the absorption by about 25–30 cm^{-1}.

You may wish to review the McLafferty rearrangement and the alpha cleavage in Section 12.3.

IR SPECTRA

Ketones

The carbonyl (C=O) stretching vibration band of saturated aliphatic ketones appears at:

- Aliphatic ketones 1715 cm^{-1}
- *α*, *β*-unsaturated (enone) 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.

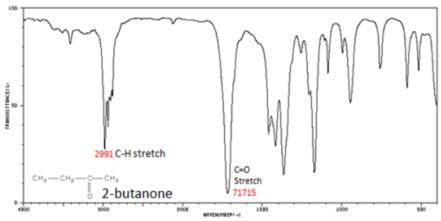


Figure 8. Infrared Spectrum of 2-Butanone

Aldehyde

In the IR spectra of an aldehyde, a peak usually appears around 2720 cm^{-1} and 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}
- *α*, *β*-unsaturated aldehydes (enones) 1710-1685 cm^{-1}

Figure 9. shows the spectrum of butyraldehyde.

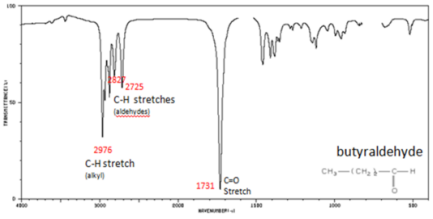
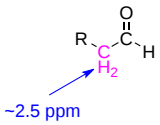


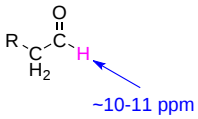
Figure 9. Infrared Spectrum of Butyraldehyde

^{1}H NMR SPECTRA

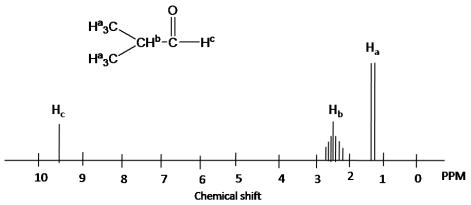
Hydrogens attached to a carbon adjacent to the sp^2 hybridized carbon in aldehydes and ketones are deshielded due the anisotropy created by the C=O bond and usually show up at 2.0-2.5 ppm.



Aldehyde hydrogens are highly deshielded, appearing far downfield at 9-10 ppm, due the anisotropy created by the pi electrons of the C=O bond, and induction caused by the highly electronegative oxygen atom.

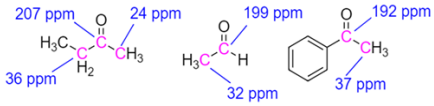


The ^{1}H NMR spectra of 2-methylpropanal is shown below. The methyl groups, (H_b), show up at 1.1 ppm. The -CH- group is moved downfield due to effect an adjacent aldehyde group (2.4 ppm). The chemical shift of aldehyde hydrogen is highly deshielded (9.6 ppm). Splitting pattern is determined by (N+1) rule: H_a 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.)



^{13}C NMR SPECTRA

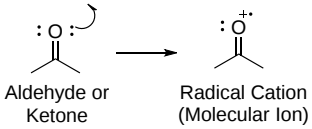
Aldehydes and ketones have distinctive ^{13}C NMR peaks which appear in the range 190 to 215 ppm range. Very few types of carbons absorb in this range so the presence of ^{13}C peak around 200 ppm is considered evidence for a carbonyl group.



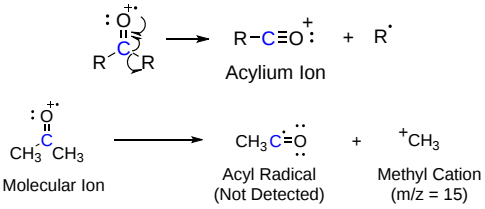
MASS SPECTRA

Aldehydes and ketones generally give moderately intense signals due to their molecular ions, M^+. Thus the determination of the molecular weight of a ketone by mass spectroscopy usually is not difficult. Furthermore, there are some characteristic fragmentation patterns that aid in structural identification. These are:

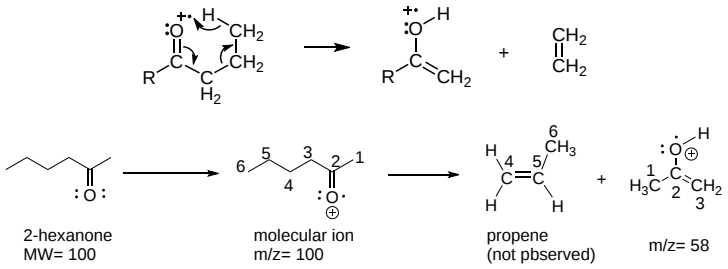
- Formation of the molecular ion:



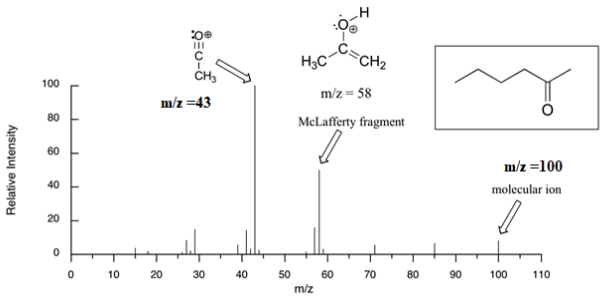
- *α cleavage to form an acylium ion. This is usually the base peak in the mass spectra.*



- *A common fragmentation pattern for larger carbonyl compounds is a transfer of γ hydrogen with β cleavage* called the **McLafferty rearrangement:**



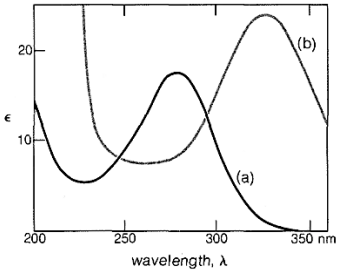
The mass spectrum of 2-hexanone shows a 'McLafferty fragment' at m/z = 58, while the propene fragment is not observed because it is a neutral species (remember, only cationic fragments are observed in MS). The base peak in this spectrum is an acylium ion formed after alpha cleavage is at m/z = 43. The molecular ion peak is at m/z =100.



ELECTRONIC ABSORPTION SPECTRA

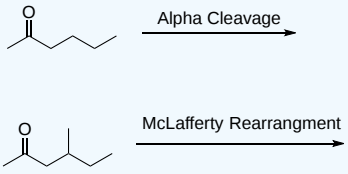
2-Butanone 3-Buten-2-one

The absorption at 277 nm for 2-butanone is an n → pi* transition, and with 3-buten-2-one, this absorption shifts to longer wavelengths (324 nm). There is also an intense absorption band for 3-buten-2-one at 219 nm, which is a pi →pi* transition. With 2-butanone a corresponding absorption occurs at 185 nm, which is out of the range of the spectrometer used to take the spectra.



EXERCISE 19.14.1

What are the masses of all the components in the following fragmentations?



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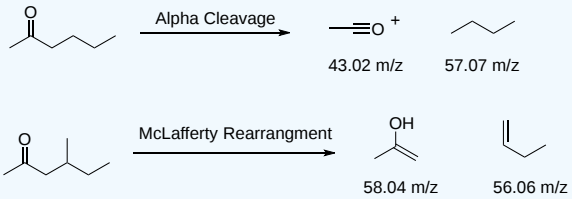
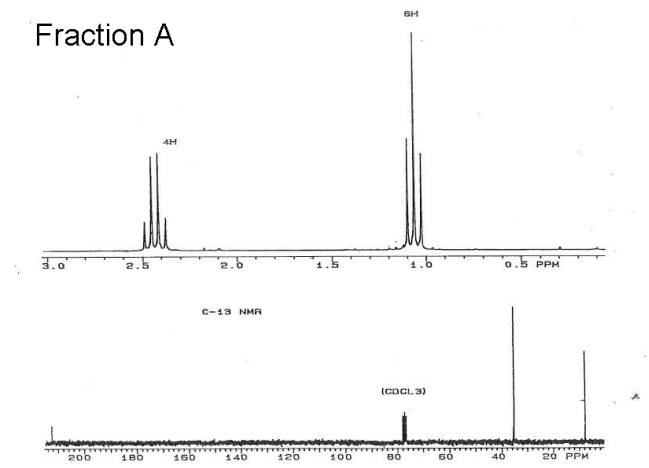
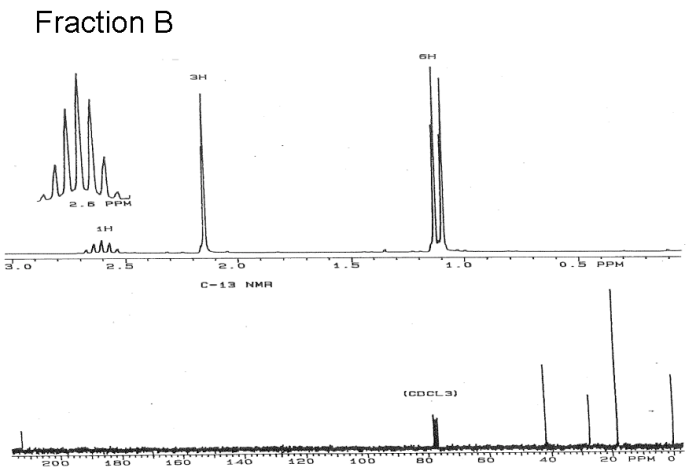
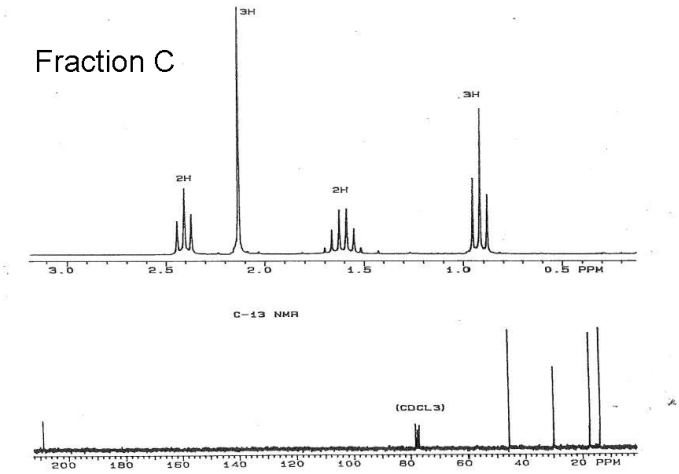


EXERCISE 19.14.2

A mixture was separated into three fractions: A, B, and C. Elemental analysis reveals that the fractions are structural isomers with the following composition: 69.72% C, 11.70% H, and 18.58% O. The IR spectra for all fractions show several moderate bands around 2950 cm^{-1}, and a strong band near 1700 cm^{-1}. The proton and ^{13}C NMR spectra for each fraction are shown below. Give the common name and draw the bond-line structure for each fraction and correlate the NMR signals with their respective atoms.







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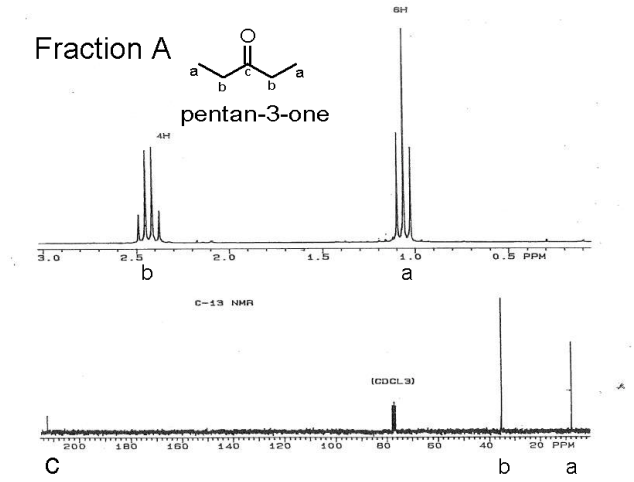
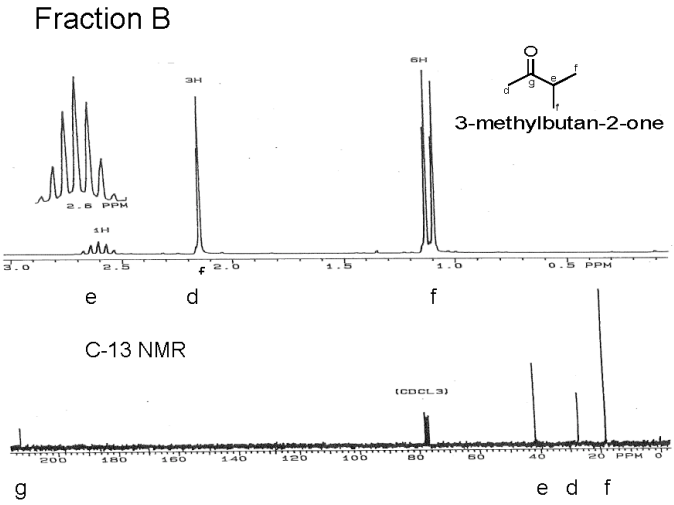
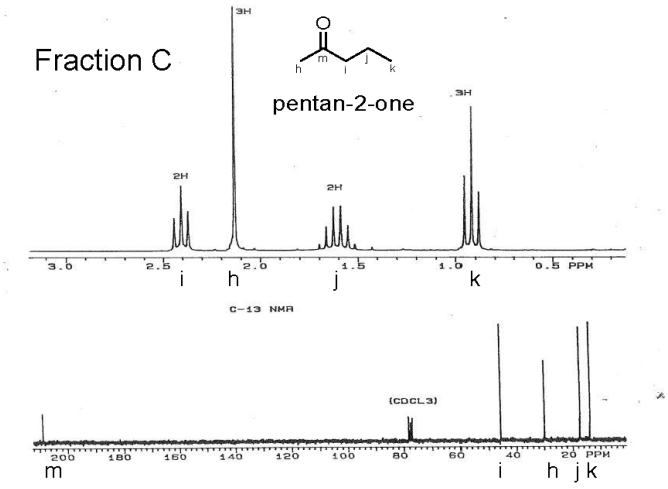






19.S: ALDEHYDES AND KETONES (SUMMARY)

CONCEPTS & VOCABULARY

19.0 Chapter Objectives and Preview of Carbonyl Chemistry

- Aldehydes are carbonyl compounds with an R group and a hydrogen attached to the carbonyl carbon.
- Ketones are carbonyl compounds with two R groups attached to the carbonyl carbon.

19.1 Naming Aldehydes and Ketones

- Aldehydes are named following IUPAC rules with the standard ending -al.
- Ketones are named following IUPAC rules with the standard ending -one.
- Aldehydes have priority over ketones when both appear in the same molecule.

19.2 Preparing Aldehydes and Ketones

- Primary alcohols can be oxidized to aldehydes with PCC (pyridinium chlorochromate) or DMP (Dess-Martin Periodinane).
- Terminal alkynes can be hydrated to form aldehydes through hydroboration-oxidation reactions.
- Esters can be reduced to aldehydes with DIBAL-H.
- Acid chlorides can be reduced to aldehydes with hydrides.
- Nitriles can be reduced to aldehydes with DIBAL-H.
- Secondary alcohols can be oxidized to ketones with chromic acid/Jones reagent.
- Alkynes can be hydrated to form ketones.
- Aryl ketones can be formed by Friedel-Crafts acylation of aromatic rings.
- Nitriles can be reacted with Grignard reagents to form ketones.
- Alkenes can be cleaved with ozone to form aldehydes or ketones.
- Acid halides can be converted to ketones by reacting with Gilman reagents.

19.3 Oxidation of Aldehydes and Ketones

- Aldehydes can be oxidized more easily than ketones due to the aldehyde hydrogen.
- Jones reagent is a mixture of CrO_3 and aqueous acid.
- Aldehydes can be oxidized to carboxylic acids with chromium trioxide/Jones reagent.
- Ketones can undergo oxidative cleavage with very strong oxidizing agents such as potassium permanganate.
- Ketones can be oxidized to esters by peroxycarboxylic acids in a reaction known as Baeyer-Villiger oxidation.

19.4 Nucleophilic Addition Reactions of Aldehydes and Ketones

- Carbonyl bonds are polarized with a partial positive charge on the carbon making it an electrophile and a target for attack by nucleophiles.
- Neither aldehydes nor ketones have a good leaving group causing both to undergo nucleophilic addition reactions.
- Aldehydes are more reactive than ketones to nucleophilic addition reactions.

19.5 Nucleophilic Addition Reactions of Water: Hydration

- Gem-diols are molecules that have two hydroxide groups attached to the same carbon.
- Aldehydes and ketones can react with water under either acidic or basic conditions to form gem-diols.

19.6 Nucleophilic Addition Reactions of HCN: Cyanohydrin Formation

- Cyanohydrins are molecules with a cyanide and a hydroxide attached to the same carbon.
- Cyanohydrins can be formed from aldehydes or ketones by reacting with cyanide ion and a weak acid.

19.7 Nucleophilic Addition Reactions of Hydride and Grignard Reagents: Alcohol Formation

- Metal hydrides can reduce aldehydes and ketones to alcohols.
- Organometallic reagents include carbon bonds to metals which react similarly to carbanions.
- Grignard reagents (R-Mg-X) and organolithium compounds add to aldehydes and ketones to form alcohols.

19.8 Nucleophilic Addition of Amines: Imine and Enamine

- Imines are characterized by a carbon-nitrogen double bond.
- Reaction of aldehydes and ketones with primary amines can form imines.
- Reaction of aldehydes and ketones with secondary amines can form enamines.

19.9 Nucleophilic Addition of Hydrazine - The Wolff-Kishner Reaction

- Hydrazine will react with aldehydes and ketones to form hydrazones (similar to imine formation). Heating of the hydrazone with base converts it to an alkane.
- The combination of hydrazone formation and reduction (of aldehydes and ketones) is called the Wolff-Kishner reaction.

19.10 Nucleophilic Addition of Alcohols: Acetal Formation

- Hemiacetals have one hydroxide and one ether attached to a carbon.
- Acetals have two ethers attached to a carbon.
- Reaction of an aldehyde or ketone with an alcohol under acidic conditions forms a hemi-acetal. Continuation of the same reaction results in an acetal.
- Acetals can reform the aldehyde or ketone by reacting with acid.
- Acetals are useful as protecting groups due to the reversible nature of acetal formation.

19.11 Nucleophilic Addition of Phosphorun Ylides: The Wittig Reaction

- A molecule with positive and negative charges on adjacent atoms is called an ylide.
- Wittig reagents are organophosphorus ylides which can be drawn as a double bonded structure called a phosphorane.
- The Wittig reaction is used to convert an aldehyde or ketone into an alkene by reacting with an organophosphrous ylide.
- Oxaphosphetane intermediates containing a 4 membered ring including one oxygen and one phosphorus atom occur during the Wittig reaction.

19.12 Biological Reductions

- The Cannizzaro reaction allows an aldehyde to react with another like molecule in strong base to form one oxidized molecule (carboxylic acid) and one reduced molecule (alcohol).
- NADH, one of the most important biological reducing agents, uses a similar mechanism to the Cannizzaro reaction while reducing ketones in biological systems to alcohols while being converted to NAD^+.

19.13 Conjugate Nucleophilic Addition of alpha, beta-Unsaturated Aldehydes and Ketones

- α, β-unsaturated carbonyls have an alkene attached to the carbonyl carbon.
- Due to resonance delocalization, the β-carbon of an α, β-unsaturated carbonyl is electrophilic and will react with nucleophiles.
- α, β-unsaturated carbonyls can undergo 1,2 or 1,4 addition.
- 1,4 addition is also called conjugate addition.
- Lithium diorganocopper reagents are called Gilman reagents.
- Gilman reagents typically react with α, β-unsaturated carbonyls via conjugate addition.

19.14 Spectroscopy of Aldehydes and Ketones

- IR of aldehydes and ketones is defined strongly by the carbonyl stretching vibration.
- ^{1}H NMR of aldehydes show the aldehyde proton between 10 and 11 ppm as well as the protons on carbon adjacent to the carbonyl at about 2.5 ppm.
- ^{1}H NMR of ketones show the protons on carbon adjacent to the carbonyl at about 2.5 ppm.
- ^{13}C NMR of aldehydes and ketones show the carbonyl carbon at about 200 ppm.
- Mass spectra of aldehydes and ketones typically yield moderately intense molecular ions, M^+. They also can undergo some rearrangements that yield common fragmentation patterns.

SKILLS TO MASTER

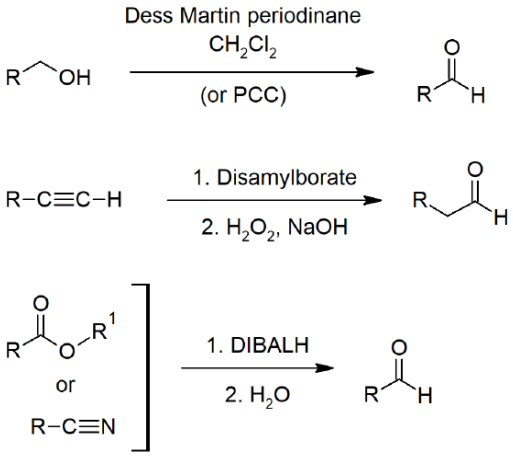
- Skill 19.1 Explain the relative reactivity of aldehydes vs. ketones to nucleophiles, based on carbonyl bond polarity.
- Skill 19.2 Name aldehydes and ketones using IUPAC rules.
- Skill 19.3 Draw the structure of an aldehyde or ketone from the IUPAC name.
- Skill 19.4 Interpret common names of aldehydes and ketones.
- Skill 19.5 Describe methods for preparing aldehydes and ketones.
- Skill 19.6 Draw mechanisms for oxidations of aldehydes and ketones.
- Skill 19.7 Explain general reactivity of aldehydes and ketones through the nucleophilic addition mechanism.
- Skill 19.8 Draw mechanisms for nucleophilic addition reactions to aldehydes and ketones including
  - Hydration
  - Cyanohydrin formation
  - Hydride Reduction
  - Organometallic reactions
  - Addition of amines
  - Wolff-Kishner reaction
  - Acetal formation

- Wittig reaction
- Cannizzaro reaction
- Conjugate addition

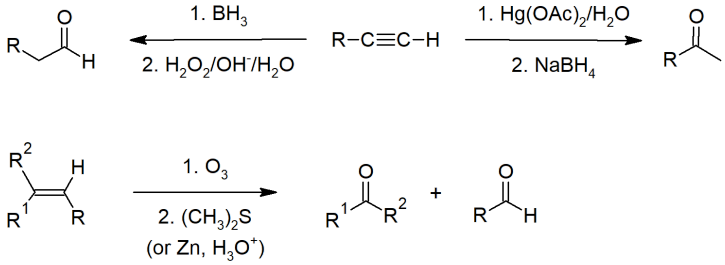
- Skill 19.9 Use IR, NMR and MS to identify aldehydes and ketones.

SUMMARY OF REACTIONS

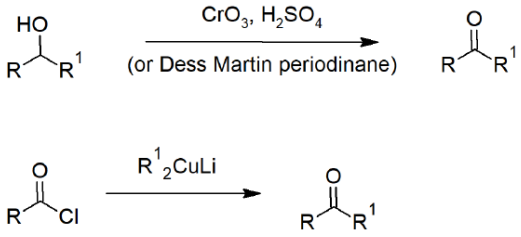
ALDEHYDE PREPARATION

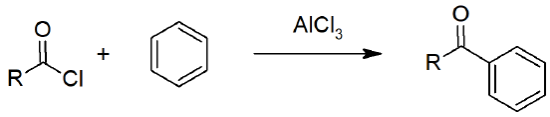


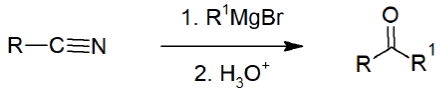
ALDEHYDE AND KETONE PREPARATION

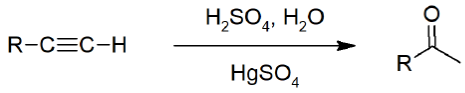


KETONE PREPARATION

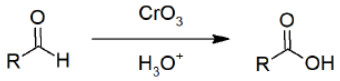


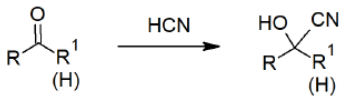


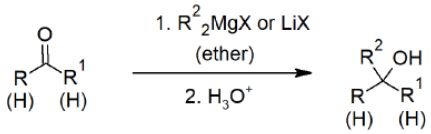


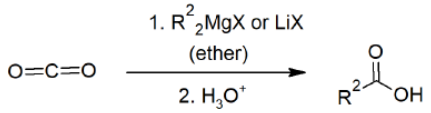


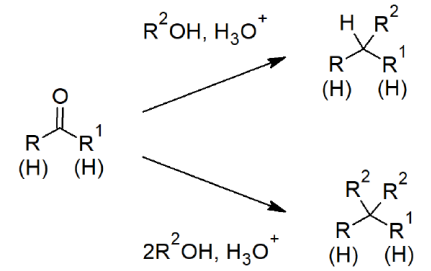
ALDEHYDE AND KETONE REACTIONS

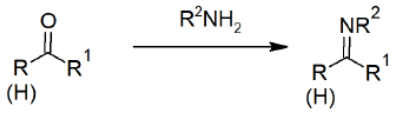


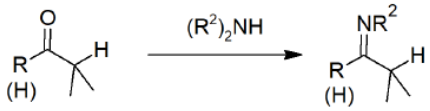


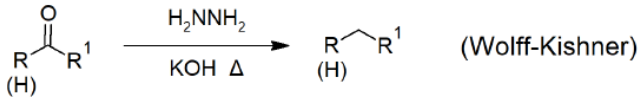


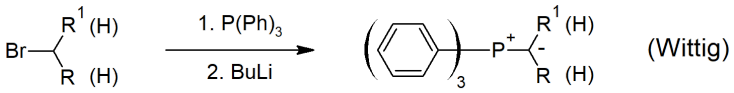


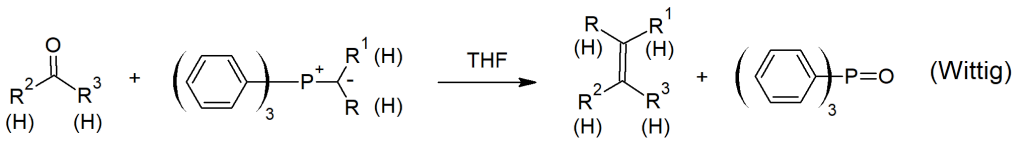


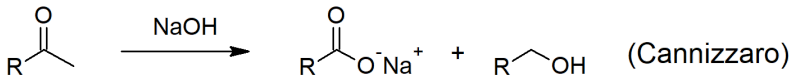




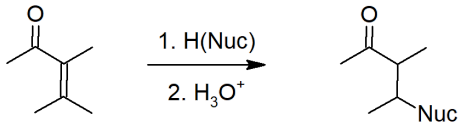




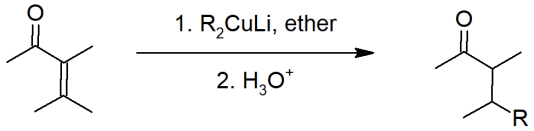




CONJUGATED ADDITION REACTIONS



where Nuc = OH, OR, SR, NH_2, NHR, Br, CN



CHAPTER OVERVIEW

20: CARBOXYLIC ACIDS AND NITRILES

This chapter presents a straightforward discussion of the chemistry of carboxylic acids (formerly called “fatty acids”) and nitriles. As usual, we begin with a description of how the compounds are named. We then consider the subtleties of their structure, and how these structural features influence physical properties, such as boiling point. We place considerable emphasis on the dissociation of carboxylic acids and the effect of substituents on acid strength.

We have already encountered a number of methods for preparing carboxylic acids. We shall review these methods, and learn about two additional procedures. The only reactions of carboxylic acids that we study in detail in this chapter are reduction and decarboxylation, although two other common reactions of carboxylic acids, alpha substitution and nucleophilic acyl substitution, will be described in later chapters.

We will then look at the formation of nitriles and their chemical reactivity; and our discussion of carboxylic acid and nitrile chemistry concludes with a look at the infrared and NMR spectra of these compounds, with emphasis on the characterization of carboxylic acids.

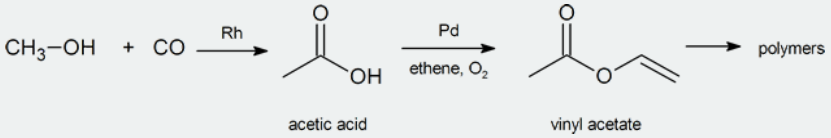
20.0: CHAPTER OBJECTIVES AND INTRODUCTION TO CARBOXYLIC ACIDS

OBJECTIVES

- fulfill all of the detailed objectives listed under each individual section.
- design multi-step syntheses in which the reactions introduced in this chapter are used in conjunction with any of the reactions described in previous chapters.
- solve road-map problems which require a knowledge of the chemistry of carboxylic acids.
- define, and use in context, the key terms introduced in this chapter.

STUDY NOTES

The global demand for acetic acid is about 6.5 million tonnes per year. A common industrial preparation of acetic acid is the catalytic oxidation of methanol with carbon monoxide. Much of the acetic acid produced is converted to vinyl acetate polymer and used in adhesives and paints.

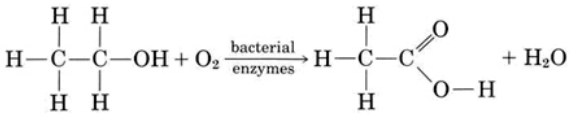


acetic acid vinyl acetate

Not only are carboxylic acids valuable, but they and their derivatives are useful starting materials for many synthetic products. Finally, carboxylic acids and their derivatives are also found in a variety of natural systems and important biological pathways.

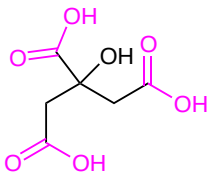
CARBOXYLIC ACIDS

Carboxylic acids have been known throughout human history. Prehistoric people likely made acetic acid when their fermentation reactions went awry and produced vinegar instead of wine. The Sumerians (2900–1800 BCE) used vinegar as a condiment, a preservative, an antibiotic, and a detergent. Vinegar contains 4 to 5 percent acetic acid. Acetic acid gives vinegar its sour taste and pungent odor and can do the same thing to wine. Acetic acid, CH_3COOH, is an example of the class of compounds called **carboxylic acids**, each of which contains one or more carboxyl groups, COOH. The general formula of a carboxylic acid is RCOOH.



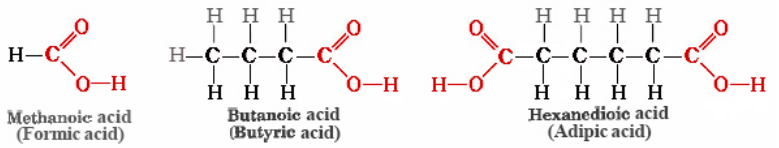
Ethanol **Ethanoic Acid (Acetic Acid)**

Citric acid was discovered by an Islamic alchemist, Jabir Ibn Hayyan (also known as Geber), in the 8th century, and crystalline citric acid was first isolated from lemon juice in 1784 by the Swedish chemist Carl Wilhelm Scheele. Medieval scholars in Europe were aware that the crisp, tart flavor of citrus fruits is caused by citric acid.



Citric acid

Naturalists of the 17th century knew that the sting of a red ant's bite was due to an organic acid that the ant injected into the wound. Formic acid (the name comes from Latin word *formica* meaning "ant") is present in ants and bees and is responsible for the burning pain of their bites and stings. Butyric acid, a component of rancid butter and Limburger cheese, has a vile odor. Adipic acid is an example of a dicarboxylic acid—it has two functional groups—and is used to make nylon



NATURALLY OCCURRING 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).

Table 17.4.1: Common Saturated Fatty Acids

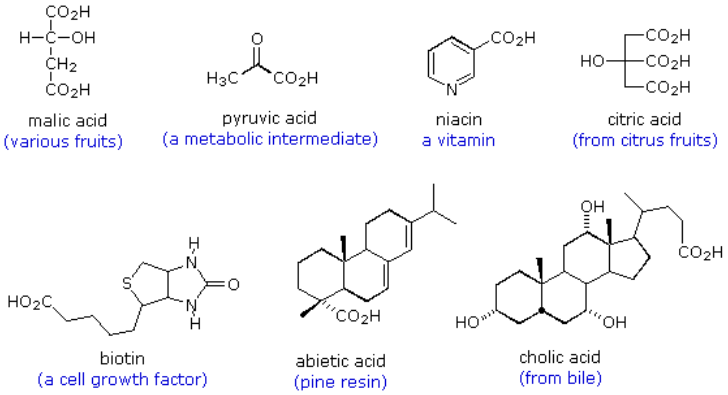
Formula	Common Name	Melting Point
$CH_3(CH_2)_{10}CO_2H$	lauric acid	45 ºC
$CH_3(CH_2)_{12}CO_2H$	myristic acid	55 ºC
$CH_3(CH_2)_{14}CO_2H$	palmitic acid	63 ºC
$CH_3(CH_2)_{16}CO_2H$	stearic acid	69 ºC
$CH_3(CH_2)_{18}CO_2H$	arachidic acid	76 ºC

Interestingly, the molecules of most natural fatty acids have an *even number of carbon atoms*. 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. Analogous compounds composed of odd numbers of carbon atoms are perfectly stable and have been made synthetically. All the double bonds in the unsaturated compounds listed on the table have *cis* (or Z) stereochemistry.

Table 17.4.2: Common Unsaturated Fatty Acids

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.

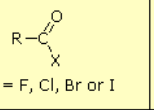
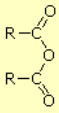
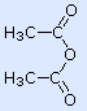
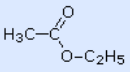
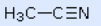


Naturally occurring carboxylic acids

CARBOXYLIC ACID DERIVATIVES

Other functional group combinations with the carbonyl group can be prepared from carboxylic acids, and are usually treated as related derivatives. The chemistry behind the conversion of carboxylic acids to carboxylic acid derivatives will be discussed in then next chapter. 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 shows the general formula for

each class, and the bottom row 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

20.1: NAMING CARBOXYLIC ACIDS AND NITRILES

OBJECTIVES

After completing this section, you should be able to

1. write the IUPAC name of a carboxylic acid, given its Kekulé, condensed or shorthand structure.
2. draw the condensed or shorthand structure of a carboxylic acid, given its IUPAC name.
3. draw the structure of the following carboxylic acids, given their trivial names: formic acid and acetic acid.
4. provide an acceptable name for a nitrile of given structure.
5. draw the condensed or shorthand structure of a nitrile, give either its trivial or IUPAC name.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- carboxylic acid
- nitrile

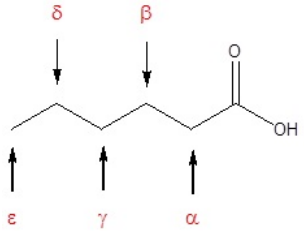
STUDY NOTES

You need not memorize all the trivial names listed in the table, just remember the two names identified in Objective 3, above.

CARBOXYLIC ACIDS, RCO_2H

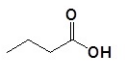
The IUPAC system of nomenclature assigns a characteristic suffix to these classes. The **–e** ending is removed from the name of the parent chain and is replaced **-oic acid**. Since a carboxylic acid group must always lie at the end of a carbon chain, it is always is given the #1 location position in 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 carboxylic acids, 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.

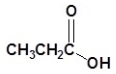


Formula	Common Name	Source	IUPAC Name	Melting Point	Boiling Point
HCO_2H	formic acid	ants (L. formica)	methanoic acid	8.4 ºC	101 ºC
CH_3CO_2H	acetic acid	vinegar (L. acetum)	ethanoic acid	16.6 ºC	118 ºC
$CH_3CH_2CO_2H$	propionic acid	milk (Gk. protus prion)	propanoic acid	-20.8 ºC	141 ºC
$CH_3(CH_2)_2CO_2H$	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

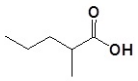
Example (Common Names Are in Red)



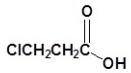
Butanoic acid
(Butyric Acid)



Propanoic acid
(Propionic Acid)



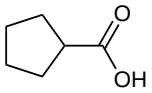
2-Methylpentanoic acid
(β-Methylvaleric acid)



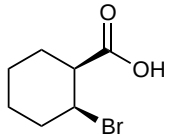
3-Chloropropanoic acid
(γ-Chloropropionic acid)

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.

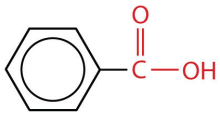


cyclopentanecarboxylic acid



(1S,2S)-2-bromocyclohexanecarboxylic acid

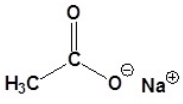
The acid with the carboxyl group attached directly to a benzene ring is called benzoic acid (C_6H_5COOH).



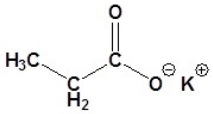
Benzoic acid

NAMING CARBOXYLATES

Salts of carboxylic acids are named by writing the name of the cation followed by the name of the carboxylic acid with the **–ic acid** ending replaced by an **–ate** ending. This is true for both the IUPAC and Common nomenclature systems.



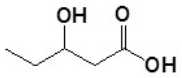
Sodium ethanoate
(Sodium Acetate)



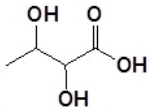
Potassium Propanoate
(Potassium propionate)

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.

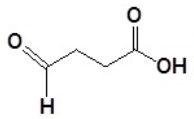


3-Hydroxypentanoic acid

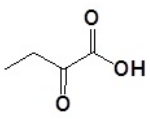


2,3-Dihydroxybutanoic acid

In the case of molecules containing a carboxylic acid and aldehydes and/or ketones functional groups, the carbonyl is named as an "Oxo" substituent.

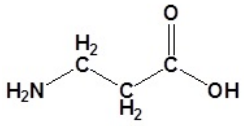


4-Oxobutanoic acid

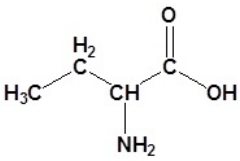


2-Oxobutanoic acid

In the case of molecules containing a carboxylic acid an amine functional group, the amine is named as an "amino" substituent.



3-Aminopropanoic acid

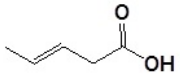


2-Aminobutanoic acid

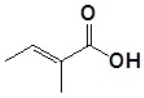
When carboxylic acids are included with an alkene the following order is followed:

(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.



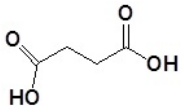
Trans-3-pentenoic acid



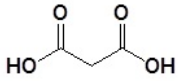
(E)-2-Methyl-2-butenoic acid

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 name.



Butanedioic acid



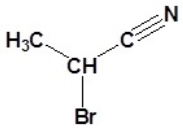
Propanedioic acid

NAMING NITRILES, R−C≡N

A **nitrile** is any organic compound with a −C≡N functional group. In literature the prefix **cyano-** is used interchangeably with the term nitrile to refer to the functional group. Nitriles used to be known as cyanides; the smallest organic nitrile is ethanenitrile, CH_3CN, (old name: methyl cyanide or acetonitrile).

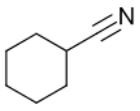
Open chain nitriles are named with the word **-nitrile** after the name of the parent alkane name. Remmber to include the carbon atom of the nitrile as part of the parent chain. For example, CH_3CN has two carbons including the nitrile carbon, therefore it is ethanenitrile. The carbon in the nitrile 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.

Butane nitrile

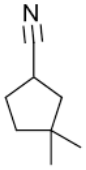


2-Bromopropane nitrile

When a nitrile is the highest priority functional group attached to a cycloalkane, the name of the parent cycloalkane is followed by the word **-carbonitrile**. The ring carbon attached to the nitrile is numbered C1 and the nitrile is not given a number in the name.

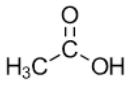


Cyclohexanecarbonitrile

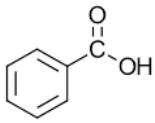


3,3-Dimethylcyclopentanecarbonitrile

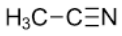
Nitriles are often named based off the common name of the corresponding carboxylic acid. This is done by replacing the -ic acid or -oic acid ending with **-onitrile**. In these cases the nitrile carbon is numbered C1 but the nitrile itself is not given a number in the name.



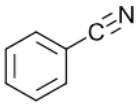
Acetic Acid



Benzoic Acid

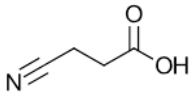


Acetonitrile



Benzonitrile

In the case of molecules containing a carboxylic acid and nitrile functional group, the nitrile is named as a "cyano" substituent. Note! The carbon in the nitrile is not counted as part of the parent chain when named as a cyano substituent.



3-Cyanopropanoic Acid

20.2: STRUCTURE AND PROPERTIES OF CARBOXYLIC ACIDS

OBJECTIVES

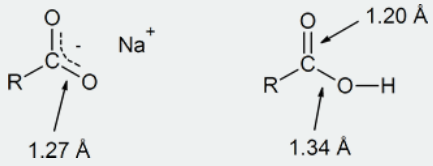
After completing this section, you should be able to

1. describe the geometry and electronic structure of a simple carboxylic acid; for example, acetic acid.
2. describe the hydrogen bonding that occurs between carboxylic acid molecules, and hence account for the relatively high boiling points of these compounds.
3. write an expression for the dissociation constant of a given carboxylic acid, and use it to calculate dissociation constants, percentage dissociation, etc.
4. identify carboxylic acids as being weaker acids than mineral acids, such as hydrochloric acid, but stronger acids than alcohols.
5. use the concept of resonance to explain why carboxylic acids are stronger acids than alcohols.
6. draw an orbital picture of a carboxylate anion to show the equivalence of the two oxygen atoms.
7. explain why the two carbon-oxygen bond lengths are identical in sodium carboxylate, but different in carboxylic acid.
8. write an equation for the reaction of a carboxylic acid with a base, such as sodium hydroxide.

STUDY NOTES

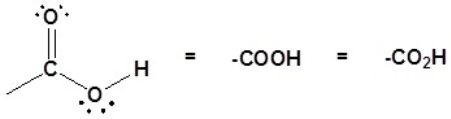
You might wish to review Sections 2.7, “Acids and Bases: The Brønsted-Lowry Definition” and 6.7, “Describing a Reaction: Equilibria, Rates, and Energy Changes” in conjunction with this section.

In the reading, the discussion of the role of resonance in the acidity of a carboxylic acid explains that the two carbon-oxygen bonds in the delocalized carboxylate anion are identical (both 1.27 Å). However, in the structure of a carboxylic acid the C−O bond (1.20 Å) is shorter than the C−OH bond (1.34 Å).



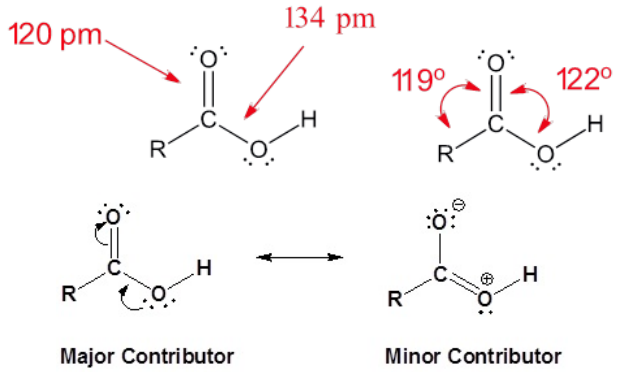
STRUCTURE OF THE CARBOXYL ACID GROUP

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.



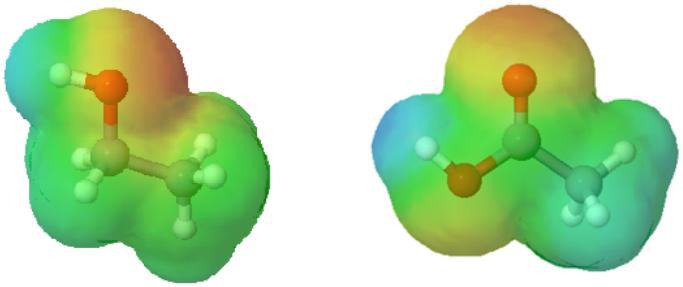
Carboxyl Group

The carbon and oxygen in the carbonyl are both sp^2 hybridized which gives a carboxylic acid a trigonal planar shape (around the carbonyl carbon) making the bond angles roughly 120º. A resonance structure exists where one of the lone pairs of the hydroxyl oxygen (OH) is conjugated with the pi bond system of the carbonyl group. The conjugation can be represented by the resonance structure shown below which holds all the atoms in the carboxylic acid in a co-planar arrangement.

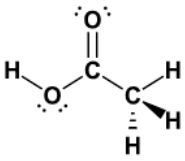


Major Contributor **Minor Contributor**

The effects of conjugation in a carboxylic acid can be seen when comparing the electrostatic potential maps of ethanol and acetic acid. Conjugation creates a greater polarization in the O-H bond in acetic acid, as shown by its darker blue color, which subsequently leads to a greater acidity in carboxylic acids.



Ethanol



Acetic Acid

ACIDITY OF CARBOXYLIC ACIDS

Carboxylic acids are named such because they tend to be more acidic than other functional groups in organic chemistry. In dilute aqueous solutions, they act as Brønsted–Lowry acids and partially dissociate to produce the corresponding carboxylate ion and hydronium (H_3O^+).

Carboxylic acid

Carboxylate ion

The extent of this dissociation is described by the K_a value of the carboxylic acid. In a 0.1 M solution of acetic acid ($K_a = 1.75 \times 10^{-5}$ @ 25 °C) only about 0.1% of the molecules are dissociated.

$$\begin{aligned} K_{eq} &= K_a \\ &= \frac{[\mathrm{RCOO^-}][\mathrm{H_3O^+}]}{[\mathrm{RCOOH}]} \\ &= 1.75 \times 10^{-5} \end{aligned}$$

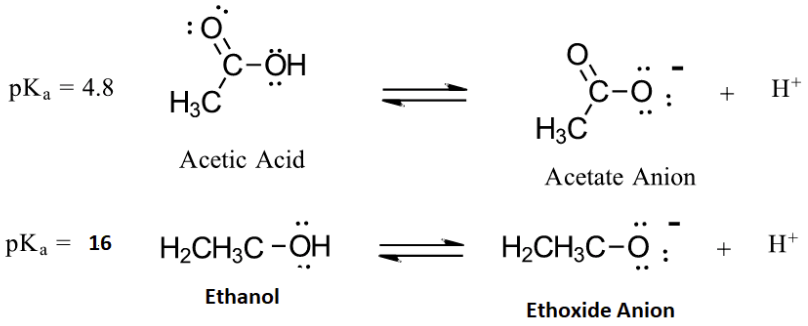
with $pK_a = -\log K_a$.

The pK_a's of some typical carboxylic acids are listed in Table 20.2.1. The factors which affect the acidity of different carboxylic acids will be discussed in the next section of this text.

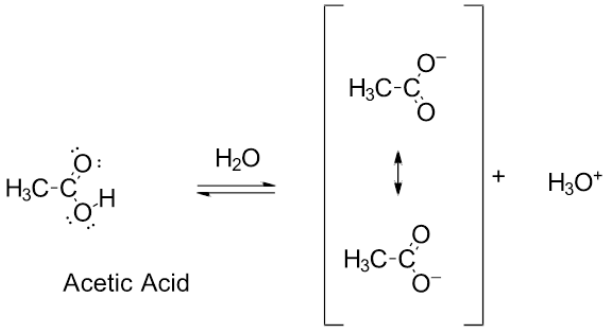
Table 20.2.1: Acidity of example carboxylic acids

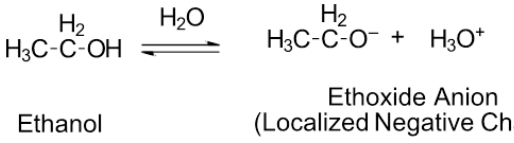
Compound	K_a	pK_a
F_3CCO_2H	0.59	0.23
Cl_3CCO_2H	0.22	0.66
p-$O_2NC_6H_4CO_2H$	3.39 X 10^{-4}	3.47
HCO_2H	1.78 X 10^{-4}	3.75
$C_6H_5CO_2H$	6.31 X 10^{-5}	4.20
p-$CH_3OC_6H_4CO_2H$	3.55 X 10^{-5}	4.45
CH_3CO_2H	1.75 X 10^{-5}	4.76
$CH_3CH_2CH_2CO_2H$	1.51 X 10^{-5}	4.82

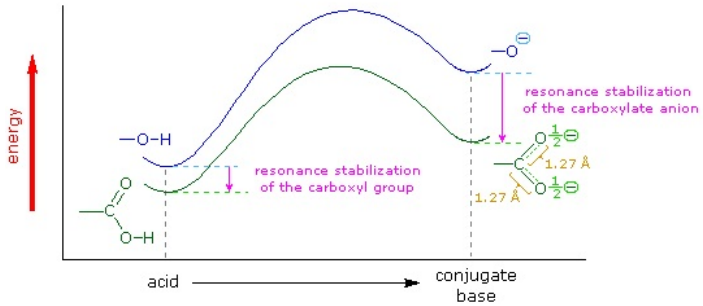
The acidity of carboxylic acids comes about, in part, due to resonance stabilization of the carboxylate conjugate base. A classic example compares the relative acidity of ethanol and acetic acid, but the conclusions we reach will be equally valid for all alcohol and carboxylic acid groups. Despite the fact that they are both oxygen acids, the pK_a values of ethanol and acetic acid are very different (acetic acid is more than 10^{11} times more acidic than ethanol). In both species, the negative charge on the conjugate base is held by an oxygen so electronegativity does not explain the difference in acidity.



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 allowing for the the negative charge on the acetate ion to be equally shared between two oxygens. In the ethoxide anion, by contrast, the negative charge is 'locked' on the single oxygen. This stabilization leads to a marked increase in stability of the acetate anion, as illustrated by the energy diagram shown below. The increased stabilization of the acetate anion conjugate base promotes the acidity of acetic acid.



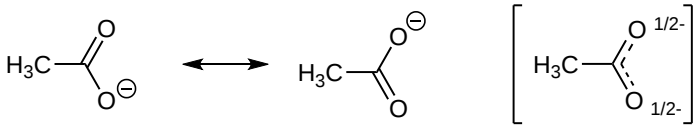




The delocalization of charge by resonance has a very powerful effect on the reactivity of organic molecules, enough to account for the difference of over 11 pK_a units between ethanol and acetic acid (and remember, pK_a is a log expression, so this represents a difference of

over 10^{11} between the acidity constants for the two molecules). The acetate anion is that much more stable than the ethoxide anion, all due to the effects of resonance delocalization.

X-ray crystallographic studies provide experimental evidence of the acetate anion resonance hybrid. Both C-O bonds in acetate are 126 pm which is roughly the average of C=O double bond (123 pm) and the C-O single bond (132 pm) of acetic acid. Both of the C-O bonds in the acetate anion are considered to have a bond order of 1 1/2. The negative charge is equally spread between the two oxygens giving them each a charge of -1/2.



Resonance structures and resonance hybrid of acetate ion.

PHYSICAL PROPERTIES OF SOME CARBOXYLIC ACIDS

Carboxylic acids tend to have higher boiling points when compared to ethers, alcohols, aldehydes, or ketones with a similar molecular weight. For example acetic acid and ethanol have boiling points of 117.9 ^{o}C and 78.3 ^{o}C respectively despite the fact that they both contain two carbons. Because carboxylic acids and alcohols both contain an O-H bond they are strongly associated by a hydrogen-bonding intermolecular force. The difference is that for carboxylic acids, two molecules of a carboxylic acid form two hydrogen bonds with each other to create a cyclic dimer (pair of molecules). Two alcohol molecules can only form one hydrogen bond between each other. Thus, carboxylic acids have stronger intermolecular forces and higher boiling points than their corresponding alcohols.

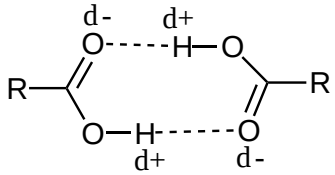
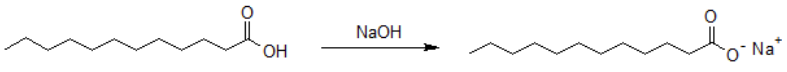


Table 20.2.2: Intermolecular hydrogen bonding in carboxylic acids.

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

WATER SOLUBILITY OF CARBOXYLIC ACIDS

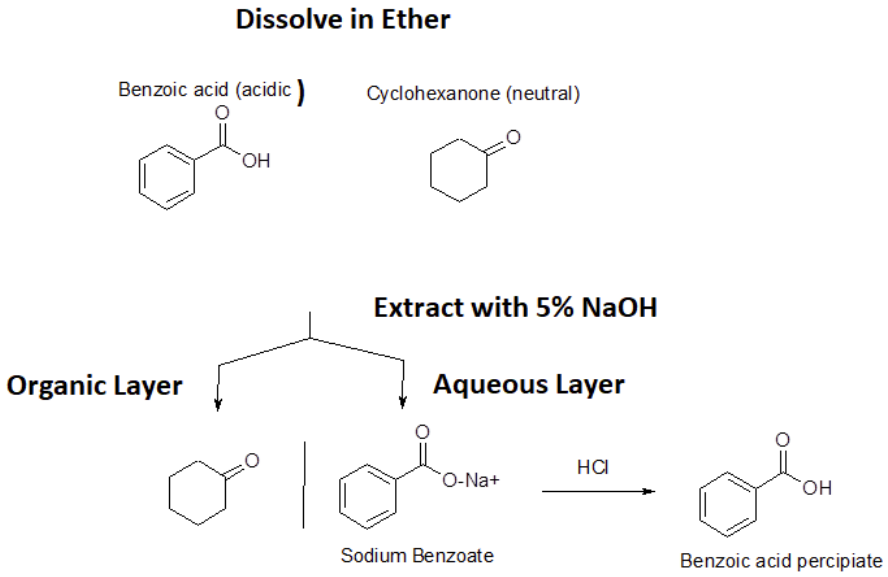
The ability to form hydrogen bonds gives carboxylic acids with low molecular weights some measure of solubility in water. Carboxylic acids with six or more carbons tend to only be slightly soluble in water. However, conversion to the corresponding carboxylate anion tends to immensely increase water solubility due to the creation of an ion-dipole intermolecular force. Typically a strong base is used to deprotonate a carboxylic acid and drive this reaction to completion as shown below.



NOT H_2O Soluble H_2O Soluble

This property of carboxylic acids allows many carboxylic acids to be purified by a technique called acid/base extraction. The figure below shows how a carboxylic acid (benzoic acid) can easily be separated from non-acidic water insoluble compounds (cyclohexanone) using an acid/base extraction. First, the two compounds are dissolved in an organic solvent immiscible with water (ether). Then a basic aqueous solution (5% NaOH) is added and two liquid layers are formed. As the layers are mixed, benzoic acid reacts with the basic solution to become sodium benzoate. Because sodium benzoate is soluble in water it is extracted into the aqueous layer while the non-acidic cyclohexanone remains in the organic layer. The two layers can be separated using a separatory funnel effectually removing the

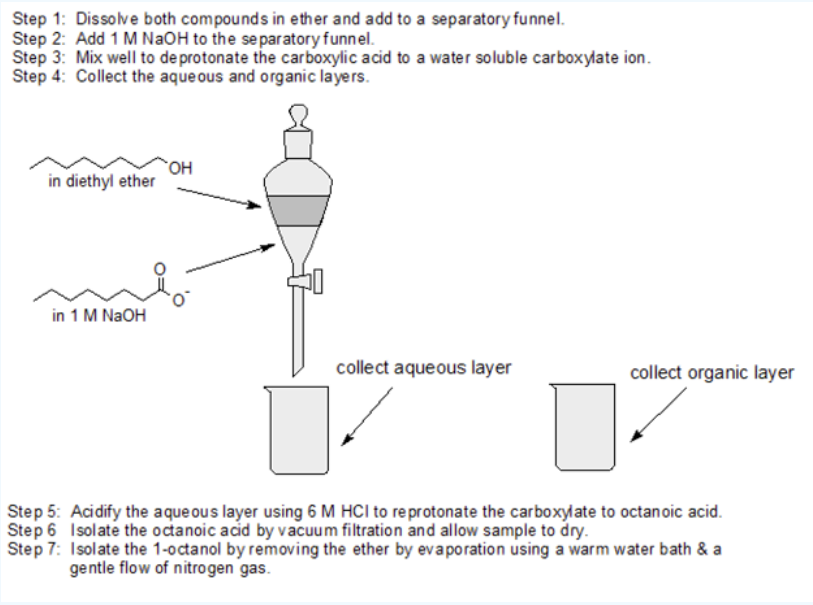
cyclohexanone. The aqueous layer can then be acidified with a strong acid causing sodium benzoate to become protonated, reforming benzoic acid. Because benzoic acid is insoluble in water it will form a precipitate which can easily be filtered off.



EXERCISE 20.2.1

Use acid-base chemistry and differences in water solubility to separate 1-octanol from octanoic acid using the following solutions: 1 M NaOH, ether, and 6 M HCl and any lab equipment.

Answer



EXERCISE 20.2.2

What percentage of propanoic acid (CH_3CH_2COOH) is dissociated into its conjugate base in a 0.20 M aqueous solution? $K_a = 1.32 \times 10^{-5}$

Answer

From the acid equilibrium expression we get that:

$[CH_3CH_2COO^-][H_3O^+]/[CH_3CH_2COOH] = K_a = 1.32 \times 10^{-5}$

$[X][X]/[0.20\ M - X] = 1.32 \times 10^{-5}$

Assume X is small compared to 0.20 M

$[X]^2/[0.20\ M] = 1.32 \times 10^{-5}$

$X = [CH_3CH_2COO^-] = 1.62 \times 10^{-3}$ M

$[CH_3CH_2COO^-] / [CH_3CH_2COOH]$ X 100 = %Disassociation

1.62×10^{-3} M / 0.20 M X 100 = **0.812%**

20.3: BIOLOGICAL ACIDS AND THE HENDERSON-HASSELBALCH EQUATION

OBJECTIVES

After completing this section, you should be able to

1. identify the form that carboxylic acids take within living cells.
2. use the Henderson-Hasselbalch equation to calculate the percentages of dissociated and undissociated acids [A^-] and [HA] in a solution, given the pK_a value of the acid and the pH of the solution.
3. explain why cellular carboxylic acids are always referred to by the name of their anion.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- Henderson-Hasselbalch equation
- physiological pH

CARBOXYLIC ACIDS IN BUFFERED SOLUTIONS

Due to the acidic nature of carboxylic acids, their level of dissociation is directly related to the pH of the solution. Under acidic conditions (low pH), carboxylic acids are almost completely undissociated and exist primarily in their protonated form ($RCOOH$). Under, basic conditions (high pH), carboxylic acids become nearly completely dissociated into their deprotonated carboxylate form ($RCOO^-$). Because the environment inside a living cell is an aqueous buffer with a nearly neutral pH = 7.3 (sometimes referred to as the **physiological pH**), then in what form do carboxylic acids exist? An important part of answering this question lies in the **Henderson-Hasselbalch equation**:

$$pH = pK_a + \log\left(\frac{[\text{ concentration of conjugate base }]}{[\text{ concentration of weak acid }]}\right) \tag{20.3.1}$$

This equation shows that the amount of dissociation in a carboxylic acid is related to the pH of the solution and the pK_a of the acid. In particular, the Henderson-Hasselbalch equation shows that when the concentration of a carboxylic acid is equal to the concentration of carboxylate then the pH of the solution equals the pK_a of the acid. Also, the Henderson-Hasselbalch allows for the pH of the solution to be calculated when the pK_a of the acid is known along with the concentrations of the carboxylic acid and carboxylate are known.

EXAMPLE 20.3.1

What is the pH of an aqueous buffer solution that is 30 mM in acetic acid and 40 mM in sodium acetate? The pK_a of acetic acid is 4.8.

Solution

This is a direct application of the Henderson-Hasselbalch equation (Equation 20.3.1).

$$pH = pK_a + \log\left(\frac{[\text{ concentration of conjugate base }]}{[\text{ concentration of weak acid }]}\right)$$

The ratio of base to acid is 40/30, or 1.33. Therefore, substituting these values and the pK_a results in

$$\begin{aligned} pH &= 4.8 + \log\left(\frac{40}{30}\right) \\ &= 4.8 + \log 1.33 \\ &= 4.8 + 0.125 \\ &= 4.9 \end{aligned}$$

The Henderson-Hasselbalch equation is particularly useful when determining the protonation state of different biomolecule functional groups under physiological pH conditions. This is done under the assumption that the concentration of the biomolecule is small compared to the concentration of the buffer components. (The actual composition of a physiological buffer is complex, but it is primarily based on phosphoric and carbonic acids.).

Aspartic acid is an amino acid with a carboxylic acid functional group as part of its side chain. When aspartic acid comprises an amino acid residue of a protein in a human cell, it's side chain is in full contact with the physiological buffer. In what state is the side chain functional group: the protonated state (a carboxylic acid) or the deprotonated state (a carboxylate ion)?

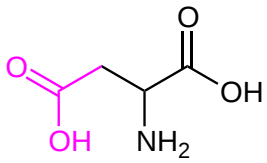


Figure 20.3.1: Aspartic acid with the carboxylic acid side-chain highlighted. (CC BY-SA 4.0; Layne Morsch via LibreTexts)

Using the buffer pH of 7.3 and a rough approximation of pK_a = 5 for the carboxylic acid side chain, we find that the ratio of carboxylate to carboxylic acid is about 200 to 1. The carboxylic acid is almost completely ionized to the carboxylate inside the cell. This result extends to all other carboxylic acid groups you might find on natural biomolecules or drug molecules. In the physiological environment, carboxylic acids are almost completely deprotonated. Indeed, cellular carboxylic acids are often referred to by the name of their anion. So rather than pyruvic acid, or acetic acid or lactic acid, they are discussed as pyruvate, acetate or lactate.

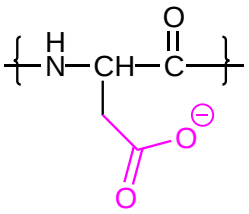


Figure 20.3.2: Aspartate (as part of a protein or polypeptide). (CC BY-SA 4.0; Layne Morsch via LibreTexts)

Using the same process, the Henderson-Hasselbalch equation (Equation 20.3.1) can also be used to determine the protonation state of carboxylic acids in solutions buffered to other pH levels.

$$pH = pK_a + \log\left(\frac{[\text{carboxylate}]}{[\text{carboxylic acid}]}\right)$$

$$7.3 = 5 + \log\left(\frac{[\text{carboxylate}]}{[\text{carboxylic acid}]}\right)$$

$$2.3 = \log\left(\frac{[\text{carboxylate}]}{[\text{carboxylic acid}]}\right)$$

$$199 = \frac{[\text{carboxylate}]}{[\text{carboxylic acid}]}$$

Therefore at physiological pH, the carboxylate anion is found with a 199-fold higher concentration than the protonated carboxylic acid. Naturally, changing the pH will alter this ratio.

? EXERCISE 20.3.1

What is the ratio of acetate ion to neutral acetic acid when a small amount of acetic acid (pK_a = 4.8) is dissolved in a buffer of pH 2.8? pH 3.8? pH 4.8? pH 5.8? pH 6.8?

Answer

We use the Henderson-Hasselbalch equation (Equation 20.3.1) and let the base to acid ratio be x.

For pH = 2.8:

$$2.8 = 4.8 + \log x$$

$x = 0.01 to 1$

- pH 3.8, the ratio is 0.10 to 1
- pH 4.8, the ratio is 1.0 to 1
- pH 5.8, the ratio is 10 to 1
- pH 6.8, the ratio is 100 to 1

20.4: SUBSTITUENT EFFECTS ON ACIDITY

OBJECTIVES

After completing this section, you should be able to

1. list a given series of carboxylic acids in order of increasing or decreasing acidity.
2. explain the difference in acidity between two or more given carboxylic acids.
3. arrange a series of substituted benzoic acids in order of increasing or decreasing acidity.
4. determine whether a given substituted benzoic acid will be more or less acidic than benzoic acid.
5. decide which of two or more substituted benzoic acids is the most acidic, and explain your decision on the basis of the electron-withdrawing or electron-releasing ability of the substituent.
6. use the K_a (or pK_a) of a substituted benzoic acid to predict the effect that the substituent has on the susceptibility of the benzene ring to electrophilic attack.

STUDY NOTES

You have already seen how the presence of an electron-withdrawing or electron-releasing group affects the stability of a positively charged carbocation. Now you see how these groups affect the stability of carboxylate anions, and in turn, determine the dissociation constant of a carboxylic acid.

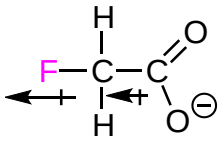
THE INDUCTIVE EFFECT

As seen in **Section 20.2**, there can be substantial range in the acidities of carboxylic acids. From the table in **Section 20.2**, we see that trifluoroacetic acid (K_a = 0.59) is almost than 60,000 times more acidic than butanoic acid (K_a = 1.51 X 10^{-5}). These vast differences in acidity can be almost exclusively explained by the inductive effect of substituents attached to the carboxylic acids.

The **inductive effect** is an experimentally observed effect of the transmission of charge through a chain of atoms in a molecule, resulting in a permanent dipole in a bond. In a carboxylic acid group the presence of halogens (such as fluorine) on adjacent carbons increases the acidity of the carboxylic acid group by stabilizing the carboxylate conjugate base.

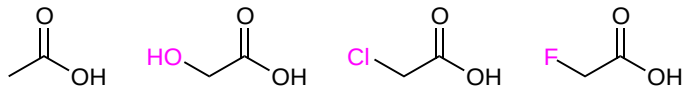
WITHDRAWING INDUCTIVE EFFECTS

A fluorine atom is more electronegative than a hydrogen atom, and thus it is able to ‘induce’, or ‘pull’ the electron density of covalent bonds towards itself. In the fluoroacetate anion, the electrons in the C-F covalent bond are pulled toward the fluorine giving the carbon a partial positive charge. The positively charged carbon, in turn, draws electron density away from the carboxylate anion, dispersing the charge, and creating a stabilizing effect. Stabilizing the carboxylate anion increases the acidity of the corresponding carboxylic acid. In this context, the fluorine substituent is acting as an **electron-withdrawing group**.



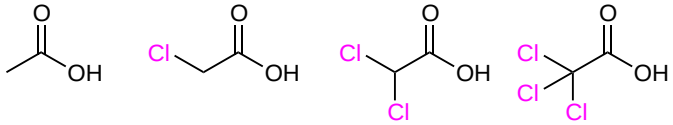
Fluoroacetate anion stabilized by electron withdrawing inductive effect of fluorine

A similar effect is seen when other electron-withdrawing groups are attached to -CH_2CO_2H. As the power of the electron-withdrawing group becomes stronger there is a corresponding drop in the pK_a of the carboxylic acid.



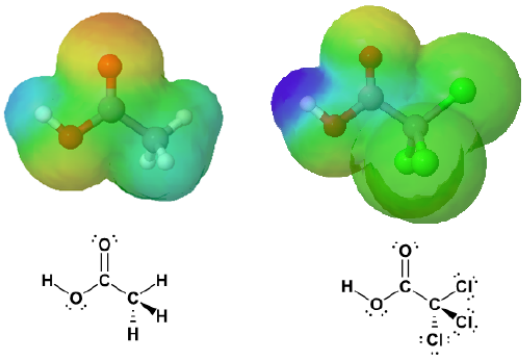
pK_a = 4.8 pK_a = 3.9 pK_a = 2.8 pK_a = 2.6

The presence of multiple electron-withdrawing groups compounds the inductive effect and continues to increase the acidity of the carboxylic acid. Dichloroacetic is a stronger acid than chloroacetic acid, and trichloroacetic acid is even stronger.



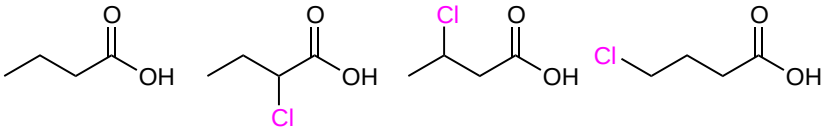
$pK_a = 4.8$ $pK_a = 2.8$ $pK_a = 1.3$ $pK_a = 0.64$

The inductive effects of chlorine be clearly seen when looking at the electrostatic potential maps of acetic acid (Left) and trichloroacetic acid (Right). The O-H bond in trichloroacetic acid is highly polarized, as shown by the dark blue color making it a much stronger acid than acetic acid.



Acetic Acid **Trichloroacetic Acid**

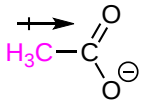
Because inductive effects are not transmitted effectively through covalent bonds, the acid-strengthening effect falls off rapidly as the number of sigma bonds between the carboxylic acid and the electron-withdrawing group increases. A distance of three sigma bonds almost completely eliminates chlorine's inductive effect in 4-chlorobutanoic acid, giving it a similar pK_a value to unsubstituted butanoic acid.



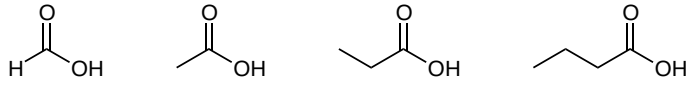
$pK_a = 4.8$ $pK_a = 2.8$ $pK_a = 4.0$ $pK_a = 4.5$

DONATING INDUCTIVE EFFECTS

Alkyl groups (hydrocarbons) are inductively electron-donating. In this case, the inductive effects pushes electron density onto the carboxylate anion, producing a destabilizing effect, decreasing the acidity of the carboxylic acid.



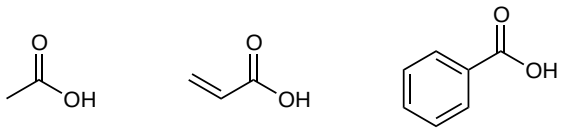
Lengthening the alkyl chain of a carboxylic acid can increase this inductive effect but it no longer decreases the acidity further after the chain is about three carbons long.



$pK_a = 3.75$ $pK_a = 4.76$ $pK_a = 4.87$ $pK_a = 4.82$

THE ACIDITY OF SUBSTITUTED BENZOIC ACIDS

Extensive research has been performed on the acidity of substituted benzoic acids. Benzoic acid itself is a somewhat stronger acid than acetic acid. The carboxyl group of benzoic acid is attached to an sp^2-hybridized carbon which is more electronegative and electron-withdrawing than the sp^3-hybridized carbon attached to the carboxyl group of acetic acid. In **Section 2.9** it was discussed that carbon becomes more electron-withdrawing as the s character of its hybrid orbitals increases. The same effect is seen in acrylic acid which is also more acidic than acetic acid.



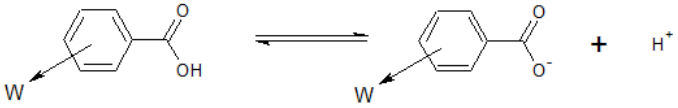
acetic acid
$pK_a = 4.8$

acrylic acid
$pK_a = 4.3$

benzoic acid
$pK_a = 4.2$

In **Section 16.4** it was discussed that substituents had a marked effect on the electron density of an aromatic ring and on the rate of electrophilic aromatic substitutions. Electron-donating substituents increase the electron density of the aromatic ring, activating it, and increasing the rate of electrophilic substitutions. Electron-withdrawing groups decreased electron density, deactivating the aromatic ring, and reduced the rate of electrophilic substitution.

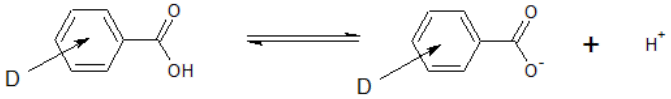
In a similar fashion, substituents have an effect on the acidity of benzoic acids. Benzoic acids with deactivating substituents, such a nitro group ($-NO_2$), in the *meta or para* position tend to be more acidic. The deactivating substituents remove electron density, stabilizes the negative charge of the carboxylate anion, and increasing the acidity of the carboxylic acid.



W = electron Withdrawing group

The carboxylate anion is stabilized by the electron withdrawing group increasing the acidity of the conjugate acid.

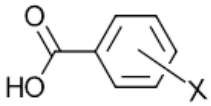
The opposite effect occurs with electron donating substituents. Electron-donating substituents in the meta or para position destabilize the carboxylate anion making the benzoic acid less acidic.



D = electron Donating group

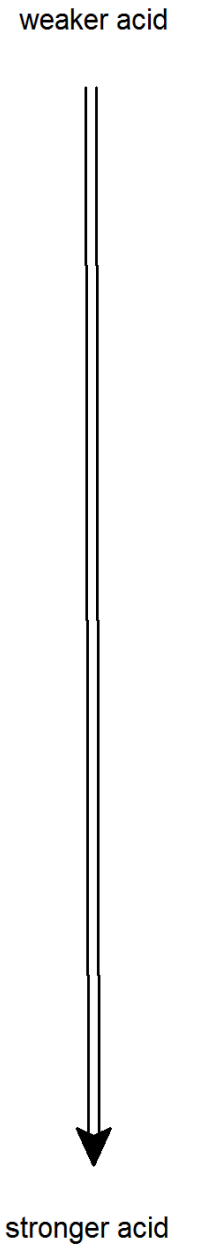
The carboxylate anion is destabilized by the electron withdrawing group decreasing the acidity of the conjugate acid.

A closer look at the effects of electron-withdrawing and electron-donating substituents in the meta or para position can be seen in the pK_a values of various benzoic acids as shown in the table below. Notice the trend in the following table where electron donating substituents (X) at the meta or para positions lead to weaker acids while those having more electron withdrawing substituents generate stronger acids.



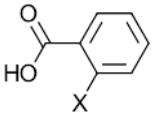
Dissociation Constants of *m* & *p*-Substituted Benzoic Acid

X	pK_a-*Para*	pK_a-*Meta*	Substituent Type
—NH_2	4.8	4.7	Donating
—OH	4.6	4.1	Donating
—OCH_3	4.50	4.1	Donating
—CH_3	4.4	4.3	Donating
—H	4.20	4.20	
—Cl	4.00	3.8	Withdrawing
—Br	4.0	3.8	Withdrawing
—NO_2	3.4	3.5	Withdrawing



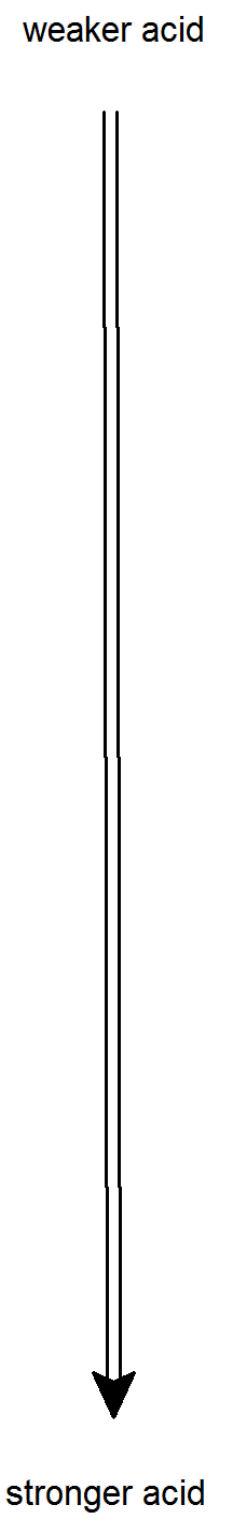
THE *ORTHO*-EFFECT

Almost all ortho-substituents increase the acid strength of a benzoic acid regardless of whether they are electron-donating or electron-withdrawing. This is called the *ortho*-effect and its cause is not completely understood. It is theorized to be a combination of both steric and electronic factors. There are exceptions of the ortho-effect, such as an amino substituent which still causes the benzoic acid to be less acidic.



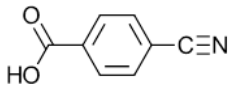
Dissociation Constants of *o*-Substituted Benzoic Acid

X	pK_a-*Ortho*	Substituent Type
—NH_2	4.7	Donating
—H	4.20	
—OCH_3	4.1	Donating
—CH_3	3.9	Donating
—OH	3.0	Donating
—Cl	2.9	Withdrawing
—Br	2.9	Withdrawing
—NO_2	2.2	Withdrawing



EXAMPLE

The following molecule, *p*-cyanobenzoic acid, has a pK_a of 3.55. Does the cyano substituent activate or deactivate the aromatic ring towards electrophilic aromatic substitution?



p-cyanobenzoic acid

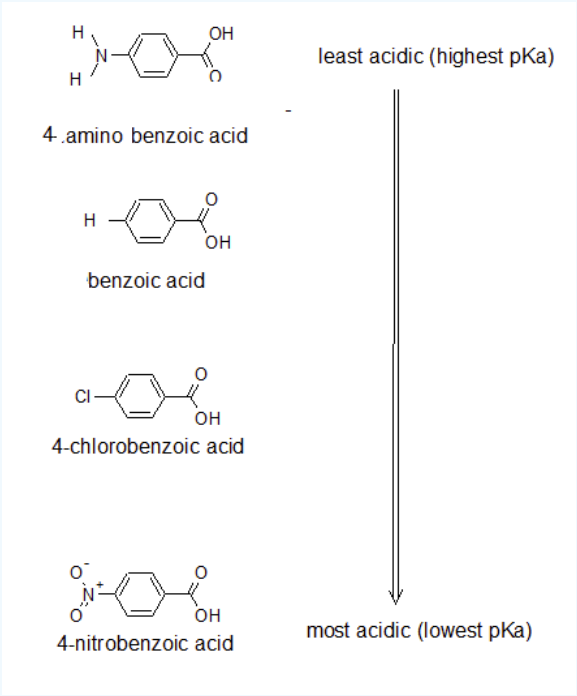
The pK_a of benzoic acid is 4.2 which means it is a weaker acid than *p*-cyanobenzoic acid. This this means that the cyano substituent is deactivating the ring.

? EXAMPLE

1. Draw the bond-line structures and arrange the following compounds in order of increasing acidity: 4-nitrobenzoic acid; 4-aminobenzoic acid; 4-chlorobenzoic acid; and benzoic acid. Try to use the expected inductive effects of the substituents to determine the acidity rather than looking at the pK_a table.

Answer

1.



EXERCISES

1) For the following pairs, which is expected to be the stronger acid? Explain your answer.

(a) $(CH_3)_3CCH_2CO_2H$ or $(CH_3)_3\overset{+}{N}CH_2CO_2H$

(b) $CH_3CH_2CO_2H$ or $CH_3\underset{\underset{OH}{|}}{C}HCO_2H$

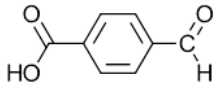
(c) $CH_3\overset{\overset{O}{\|}}{C}CO_2H$ or $CH_2{=}CHCO_2H$

d) acrylic aid vs. propiolic acid (image)

2) Oxalic acid is a dicarboxylic acid with two acidic protons. The first proton is much more acidic (pK_a = 1.20) than a typical carboxylic acid. However, Heptanedioic acid's first acidic proton has a pK_a much closer to that of a typical carboxylic acid. Explain these differences.

(image)

3) The carboxylic acid of 4-formylbenzoic acid has a pK_a of 3.75. Is this molecule likely to be more reactive or less reactive than benzene toward electrophilic aromatic substitution?



4-formylbenzoic

SOLUTIONS

1)

a) Consider the inductive effects of the substituents attached to the carboxylic acid. The *tert*-butyl group is electron-donating which should decrease the acidity of the carboxylic acid. The trimethylammonium substituent is positively charged and can be a powerful electron-withdrawing substituent. This should increase the acidity of the carboxylic acid. The compound $(CH_3)_3NCH_2CO_2H$ is expected to be a stronger acid than $(CH_3)_3CCH_2CO_2H$. The acidity constants for these two compounds match the predictions.

(image)

b) Having an electron-withdrawing hydroxyl group at the C-2 stabilizes the carboxylate ion of lactic acid through inductive effects.

(image)

This should make lactic acid more acidic than propanoic acid.

c) Due to the presence of a highly electronegative oxygen, the carbonyl group is expected to be more strongly electron-withdrawing than a carbon–carbon double bond. Thus, pyruvic acid should be a stronger acid than acrylic acid.

(image pyruvic and acrylic acid)

d) The main difference between the two compounds is the hybridization of the carbon attached to the carboxylic acid. The alkyne substituent has an sp hybridized carbon which should make it more electron-withdrawing than the alkene's sp^2 hybridized carbon.

2) With oxalic acid one carboxyl group acts as an inductive electron-withdrawing group which increases the acidity of the other carboxylic acid. This inductive effect is only relevant with the two carboxyl groups are separated by only a few bonds. In heptanedioic acid, the carboxyl groups are separated by five carbon which effectively negates the inductive effect.

3) Benzoic acid (pK_a = 4.2) has a higher pK_a and is more acidic than 4-formylbenzoic acid (pK_a = 3.75). This means that the formyl group is removing electrons from the aromatic ring making it deactivated toward electrophilic aromatic substitution.

20.5: PREPARING CARBOXYLIC ACIDS

OBJECTIVES

After completing this section, you should be able to

1. describe in detail the methods of preparing carboxylic acids discussed in previous chapters:
   a. the oxidation of alkylbenzenes.
   b. the oxidative cleavage of alkenes.
   c. the oxidation of primary alcohols and aldehydes.
2. discuss, in detail, the hydrolysis of nitriles:
   a. write an equation to illustrate the preparation of a carboxylic acid through nucleophilic attack by cyanide ion on an alkyl halide and hydrolysis of the nitrile which results.
   b. identify the carboxylic acid formed from the hydrolysis of a given nitrile, or from the reaction of a given alkyl halide with cyanide ion followed by hydrolysis of the resulting nitrile.
   c. identify the alkyl halide needed to prepare a given carboxylic acid by the formation and subsequent hydrolysis of a nitrile.
   d. identify the reagents needed to convert a given alkyl halide into a carboxylic acid containing one more carbon atom.
3. discuss, in detail, the carboxylation of Grignard reagents:
   a. write an equation describing the formation of a carboxylic acid from a Grignard reagent.
   b. identify the carboxylic acid obtained through the treatment of a given Grignard reagent with carbon dioxide followed by dilute acid.
   c. identify the Grignard reagent (or the alkyl halide required to form the Grignard reagent) that must be used to produce a given carboxylic acid by reaction with carbon dioxide.
   d. write the detailed mechanism for the formation of a carboxylic acid using a Grignard reagent.

STUDY NOTES

Review the methods of obtaining carboxylic acids presented in earlier sections:

1. oxidation of aromatic compounds—Section 16.9.
2. oxidative cleavage of alkenes—Section 8.8.
3. oxidation of primary alcohols and aldehydes—Sections 17.7 and 19.3.

Carboxylic acids can be prepared using a wide variety of reactions. Many carboxylic acid derivatives such as esters, amides, and anhydrides can undergo hydrolysis to form the parent carboxylic acids. The most common methods for synthesizing carboxylic acids can be separated into three major groups.

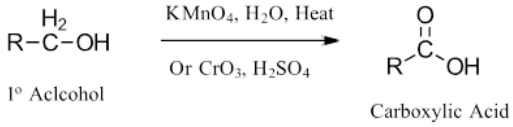
1. Oxidations
2. Carboxylation of Grignard Reagents
3. Hydrolysis of Nitriles

FORMING CARBOXYLIC ACIDS THROUGH OXIDATIONS

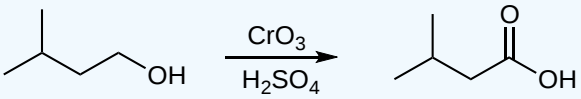
The carbon atom of a carboxyl group has a high oxidation state. It is not surprising, therefore, that many of the chemical reactions used for their preparation are oxidations. Such reactions have been discussed in previous sections of this text.

OXIDATION OF 1^{O} ALCOHOLS

The oxidation of 1^{o} alcohols to carboxylic acids can be performed with a wide variety of oxidizing agents including potassium permanganate ($KMnO_4$) and Jones reagent (CrO_3 & H_2SO_4). One of the main synthetic limitations of alcohol oxidations is that the necessary oxidizing agents often react with other oxidizable functional groups, such as aldehydes, alkyl arenes, and other alcohols. Because alcohols are often readily available this reaction is the most common oxidative reaction for creating simple carboxylic acids.



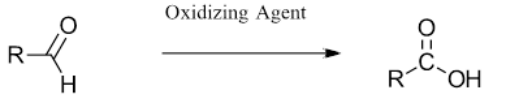
? EXERCISE 20.5.1



Oxidation of 3-methylbutan-1-ol to 3-methylbutanoic acid

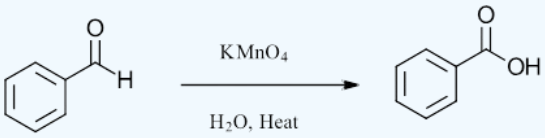
OXIDATION OF ALDEHYDES

In a similar fashion as 1^o alcohols, aldehydes are also converted to carboxylic acids using a wide variety of oxidizing agents including potassium permanganate and Jones reagent.



Aldehyde Carboxylic Acid

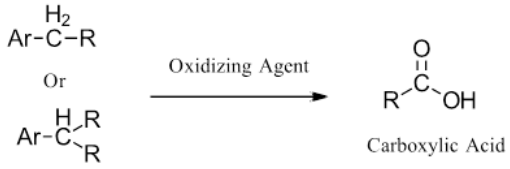
✓ EXAMPLE 20.5.1



Benzaldehyde Benzoic Acid

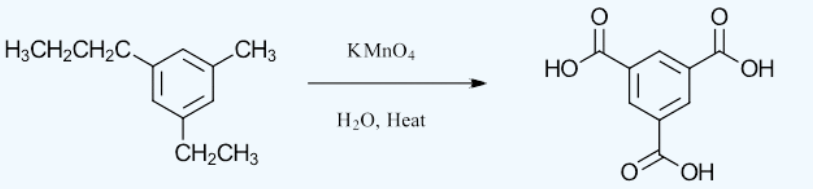
OXIDATION OF ALKYL ARENE SIDE-CHAINS

Primary and secondary carbons directly attached to an aromatic ring can be converted to carboxylic acids by reaction with strong oxidizing agents including potassium permanganate and Jones reagent. Tertiary carbons attached to an aromatic ring are not affected by these reactions. It should be noted that alkyl groups are ortho, para directors and after oxidation the carboxylic acid formed is a meta director.



Alkyl Substituted Arene Carboxylic Acid

✓ EXAMPLE



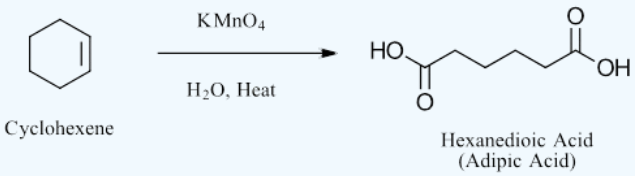
3-Ethyl-5-propyltoluene 1,3,5-Benzenetricarboxylic acid (Trimesic acid)

OXIDATIVE CLEAVAGE OF ALKENES

Alkenes can undergo oxidative cleavage to form carboxylic acids by reacting with hot alkaline $KMnO_4$.

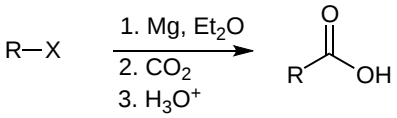
E or Z Alkene

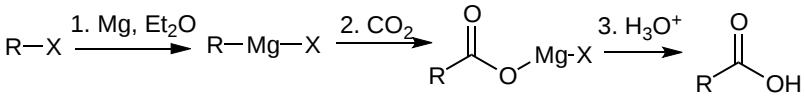
EXAMPLE



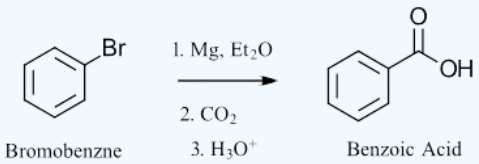
CARBOXYLATION OF GRIGNARD REAGENTS

In this method, an electrophilic halide is first transformed into a strongly nucleophilic Grignard reagent. The Grignard reagent adds to the C=O bond of carbon dioxide (an electrophile) to yield the salt of of a carboxylic acid called a halomagnesium carboxylate. This intermediate is then treated with a strong aqueous acid to form the carboxylic acid. Most alkyl or aryl halides can be used for this synthesis of carboxylic acids. The main limitation is that no functional groups incompatible with Grignard reagents can be present such has O-H, N-H, S-H, or C=O bonds.



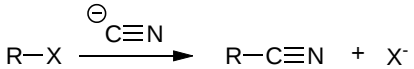


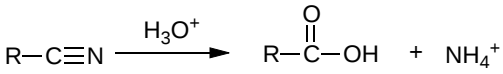
EXAMPLE



HYDROLYSIS OF NITRILES

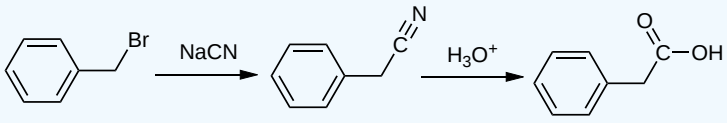
Hydrolysis of nitriles to carboxylic acids requires two steps. First, an alkyl halide is reacted with a nucleophilic cyanide anion to form a nitrile intermediate by an S_N2 reaction. Subsequent hydrolysis of the nitrile is typically performed by heating with an acidic or basic aqueous solution and uses a mechanism discussed later in this chapter. Due to the requirements of the S_N2 reaction, only primary and secondary alkyl halides may be used for this reaction. Tertiary alkyl halides typically produce an alkene through E2 elimination reaction and aryl halides usually do not react.



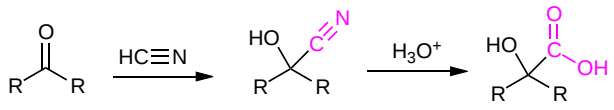


Two steps of nitrile formation and hydrolysis

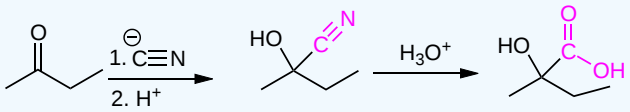
EXAMPLE



Aldehydes and ketones can be converted to cyanohydrins through nucleophilic addition of a cyanide anion to the carbonyl. The -CN group of the cyanohydrin can also be hydrolized to form an alpha hydroxy carboxylic acid.



EXAMPLE



conversion of butan-2-one to 2-hydroxy-2-methylbutanoic acid

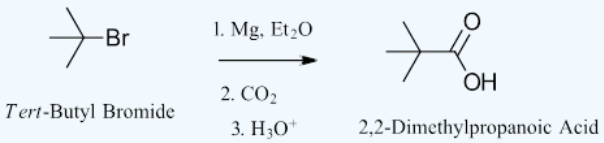
WORKED EXAMPLE 20.5.1: CHOOSING A SYNTHESIS PATHWAY TO A CARBOXYLIC ACID

Thus far this chapter has discussed three main methods for the creation of a carboxylic acid functional group: the oxidation of a 1° alcohol, the carboxylation of a Grignard reagent, and the hydrolysis of a nitrile. Select one of these three methods to perform the following transformation. Briefly explain why the other two methods would be unsuccessful.

a. Tert-Butyl Bromide → 2,2-Dimethylpropanoic acid.
b. Benzyl Bromide → Benzoic Acid
c. 3-Bromo-1-propanol → 4-Hydroxybutanoic acid

Solution A

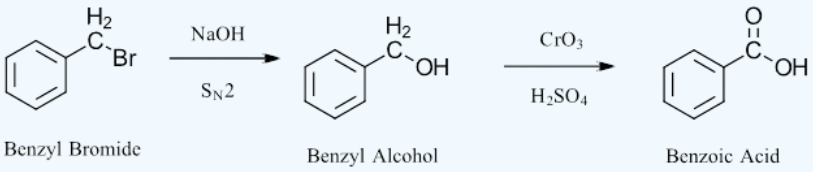
The product contains one more carbon than the reactant so the oxidation of a 1° alcohol would be an ineffective method. Also, the reactant contains a tertiary halide, so the S_N2 reaction required to form a nitrile would not be possible. The carboxylation of a Grignard reagent would be the most effective method because it allows for the addition of a carbon, it is not severely affected by the sterics of the tertiary halide, and there are no incompatible functional groups.



Tert-Butyl Bromide — 2,2-Dimethylpropanoic Acid

Solution B

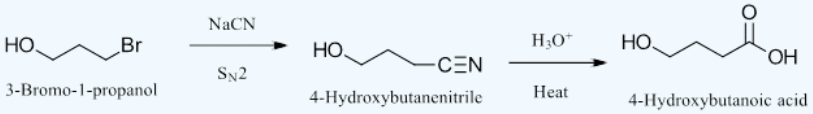
The product and reactant have the same number of carbons so both the carboxylation of a Grignard reagent and hydrolysis of a nitrile would be ineffective for this conversion. Benzyl bromide is a primary alkyl halide which can easily be converted to a primary alcohol by an S_N2 reaction with NaOH. Once formed, the primary alcohol can be converted to a carboxylic acid using an oxidation reaction.



Benzyl Bromide — Benzyl Alcohol — Benzoic Acid

Solution C

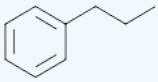
The product contains one more carbon than the reactant so the oxidation of a primary alcohol would not be an effective method. Also, the carboxylation of a Grignard reagent would not be an effect method because the presence of an incompatible alcohol functional group in the reactant. The reactant contains a primary halogen which can readily be converted to a nitrile by an S_N2 reaction with NaCN. The resulting nitrile can be converted to a carboxylic acid through hydrolysis.

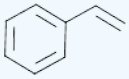


3-Bromo-1-propanol — 4-Hydroxybutanenitrile — 4-Hydroxybutanoic acid

EXERCISE 20.5.1

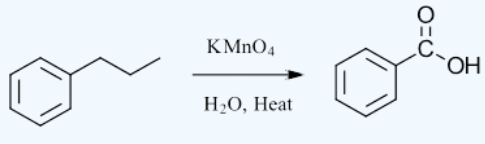
Show how the following molecules can be used to synthesize benzoic acid:

a. 

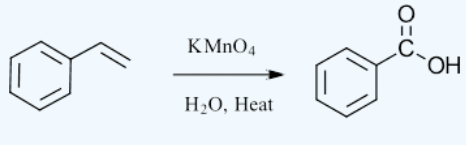
b. 

c. 

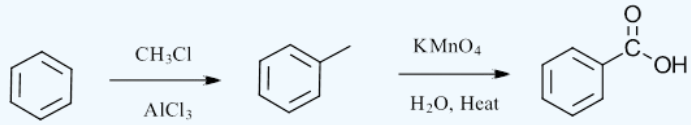
Answer

a. 

Benzoic Acid

b. 

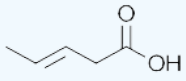
Benzoic Acid

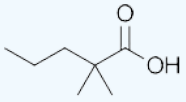
c. 

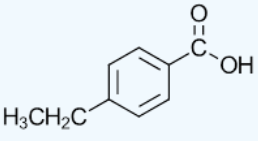
Benzoic Acid

EXERCISE 20.5.2

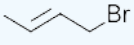
give the structure of the bromide required to make the following using the carboxylation of a Grignard reagent:

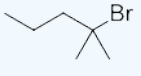
a. 

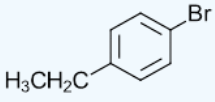
b. 

c. 

Answer

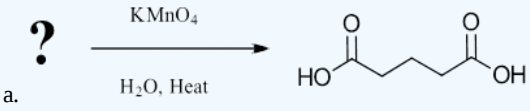
a. 

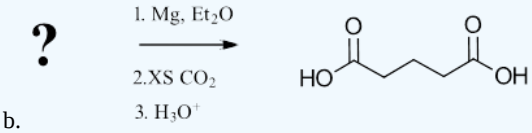
b. 

c. 

EXERCISE 20.5.3

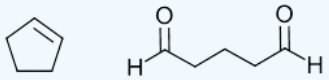
Give the possible reactants for the following reactions:

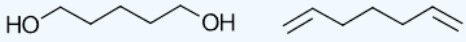
a. 

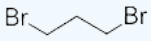
b. 

There are at least four possible answers for question a.

Answer



a. 

b. 

20.6: REACTIONS OF CARBOXYLIC ACIDS - AN OVERVIEW

OBJECTIVES

After completing this section, you should be able to identify the four types of reaction which a carboxylic acid can undergo.

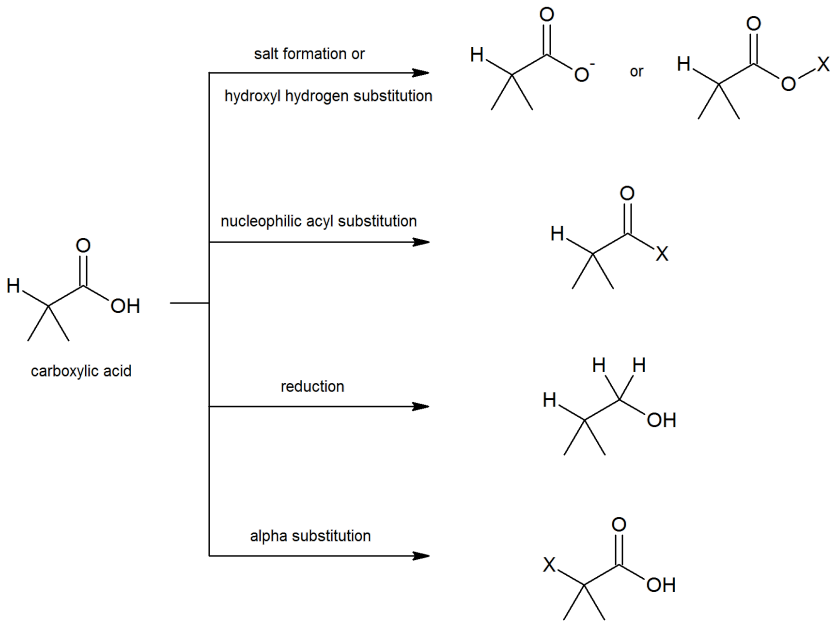
STUDY NOTES

You may wish to review Section 17.4 which discusses reduction of carbonyl compounds to form alcohols and Sections 20.2–20.4 which highlights the acidity of carboxylic acids, which is important to salt formation and substitution of the hydroxyl hydrogen. Nucleophilic acyl substitution (Chapter 21) and alpha substitutions (Chapter 22) are discussed later in more detail.

FOUR CATEGORIES OF CARBOXYLIC ACID REACTIONS

Carboxylic acid reactions are typically classified into four major categories:

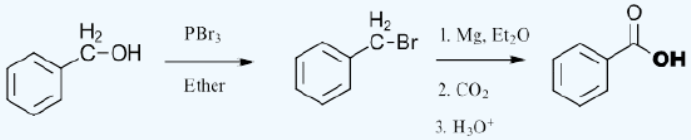
1. As carboxylic acids are easily deprotonated, they readily form a carboxylate salt which can then potentially be reacted with an electrophile to complete a substitution of the hydroxyl hydrogen.
2. Nucleophilic acyl substitution reactions allow substitution of the hydroxyl group which leads to several carboxylic acid derivatives (e.g. acid halides, esters, amides, thioesters, acid anhydrides etc.). We will see these reactions in more detail in Chapter 21.
3. Like other carbonyl compounds, carboxylic acids can be reduced by reagents such as $LiAlH_4$.
4. While the proton on the carbon alpha to the carbonyl group is not as acidic as the hydroxyl hydrogen, it can be removed leading to substitution at the alpha position. The scheme summarizes some of the general reactions that carboxylic acids undergo.



EXERCISE 20.6.1

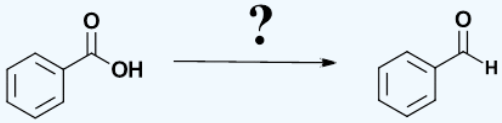
Show how the following transformation can be performed. Multiple steps may be required.

Answer

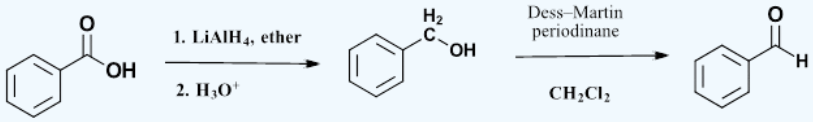


EXERCISE 20.6.2

Show how the following transformation can be performed. Multiple steps may be required.



Answer



20.7: CHEMISTRY OF NITRILES

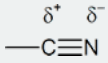
OBJECTIVES

After completing this section, you should be able to

1. discuss, in detail, the preparation of nitriles:
   a. write an equation to illustrate the formation of a nitrile by the nucleophilic attack of cyanide ion on an alkyl halide.
   b. write an equation to illustrate the formation of a nitrile by the dehydration of a primary amide.
   c. identify the product formed when a primary amide is treated with $SOCl_2$, P_2O_5, or $POCl_3$.
   d. identify the primary amide, the reagents, or both, needed to prepare a given nitrile by a dehydration reaction.
   e. write a detailed mechanism for the dehydration of a primary amide by thionyl chloride.
2. discuss, in detail, the reactions of nitriles:
   a. write an equation to describe the (acidic or basic) hydrolysis of a nitrile.
   b. write detailed mechanisms for the acidic and basic hydrolysis of nitriles.
   c. identify the products formed from the (acidic or basic) hydrolysis of a given nitrile.
   d. identify the nitrile, the reagents, or both, needed to obtain a given carboxylic acid from a hydrolysis reaction.
   e. write an equation to describe the reduction of a nitrile to give a primary amine.
   f. identify the product formed from the lithium aluminum hydride reduction of a given nitrile.
   g. identify the nitrile, the reagents, or both, needed to prepare a given amine by direct reduction.
   h. write a detailed mechanism for the reduction of a nitrile to a primary amine using lithium aluminum hydride.
   i. give an example of the reduction of a nitrile with diisobutylaluminum hydride.
   j. write an equation to illustrate the reaction of a nitrile with a Grignard reagent.
   k. identify the product formed from the reaction of a given nitrile with a given Grignard reagent.
   l. identify the nitrile, the Grignard reagent, or both, needed to prepare a given ketone.
   m. write a detailed mechanism for the reaction of a nitrile with a Grignard reagent.

STUDY NOTES

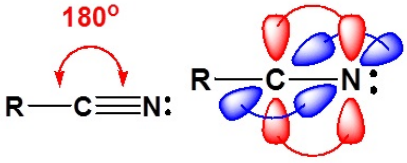
To be able to understand the driving force behind the reactions of nitriles, you must recognize the polarity of this group:



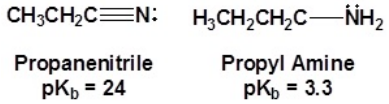
You can therefore expect to see similarities between the behaviour of the nitrile group and the similarly polarized carbonyl group:

PROPERTIES OF NITRILES

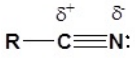
The electronic structure of nitriles is very similar to that of an alkyne with the main difference being the presence of a set of lone pair electrons on the nitrogen. Both the carbon and the nitrogen are *sp* hydridized which leaves them both with two p orbitals which overlap to form the two π bonds in the triple bond. The R-C-N bond angle in a nitrile is 180° which give a nitrile functional group a linear shape.



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 makes the lone pair electrons closer to the nucleus and therefore less basic when compared to lone pair electrons on sp^3 hybridized nitrogen (25% *s* character) containing compounds such as amines.



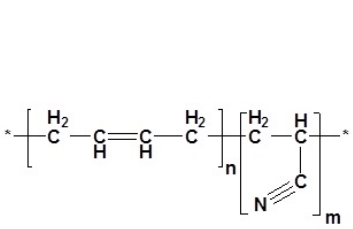
The presence of an electronegative nitrogen causes nitriles to be very polar molecules. Consequently, nitriles tend to have higher boiling points than molecules with a similar size. Also, the polar nature of nitriles promotes their solubility in water.



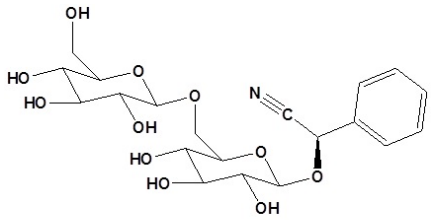
	Boiling Point
$CH_3CH_2C{\equiv}N$ Propanenitrile	96-98 °C
$CH_3CH_2C{\equiv}C{-}H$ Butyne	8.1 °C
$CH_3CH_2CH_2CH_3$ Butane	-1-1 °C

INTERESTING NITRILES

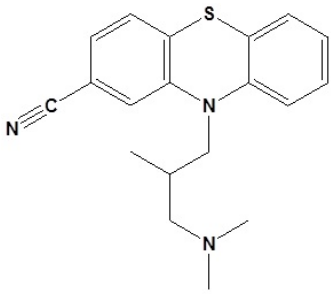
One of the most common occurrences of nitriles is in Nitrile rubber. Nitrile rubber is a synthetic copolymer of acrylonitrile and butadiene. This form of rubber is highly resistant to chemicals and is used to make protective gloves, hoses and seals. Amygdalin is a naturally occurring molecule contained by certain plants to protect themselves against herbivores and insects. Acting as a sort of natural pesticide, amygdalin degrades to release poisonous hydrogen cyanide (HCN) when any plant material is chewed by an insect or animal. There are also several nitrile containing molecules that have medicinal uses such as Cyamemazine, which is an antipsychotic drug primarily used to treat schizophrenia and certain types of anxiety. Also, Citalopram is an antidepressant primarily used to treat depression, panic disorder, and social phobia. It is currently among the most prescribed drugs in the United States (#21 in 2019 with over 26,000,000 prescriptions).



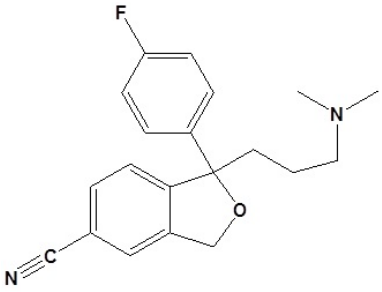
Nitrile Rubber



Amygdalin: Found in Bitter Almonds



Cyamemazine: an antipsychotic

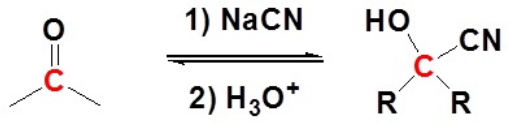


Citalopram: an antidepressant

PREPARATION OF NITRILES

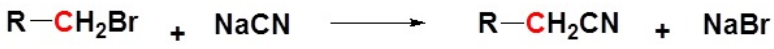
FORMATION OF A NITRILE FROM AN ALDEHYDE OR KETONE

Addition of cyanide ($^-$:C≡N) to an aldehyde or ketone forms a cyanohydrin



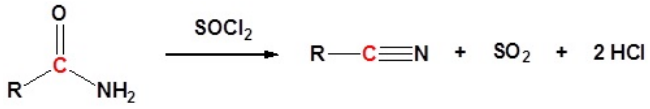
Aldehyde or Ketone — Cyanohydrin

Nitriles are formed by an S_N2 reaction between primary and secondary alkyl halides and sodium cyanide. Tertiary and aryl halides cannot be used for this reaction.



FORMATION OF A NITRILE FROM A 1° AMIDE

Primary amides can be converted to nitriles by dehydration with thionyl chloride ($SOCl_2$) or other dehydrating agents like such as P_2O_5, or $POCl_3$.

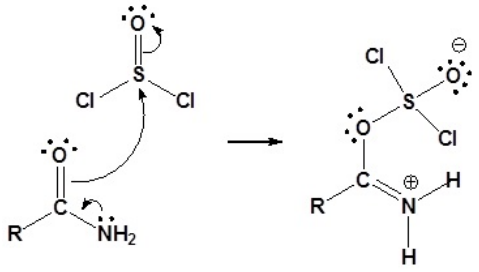


1° Amide — Nitrile

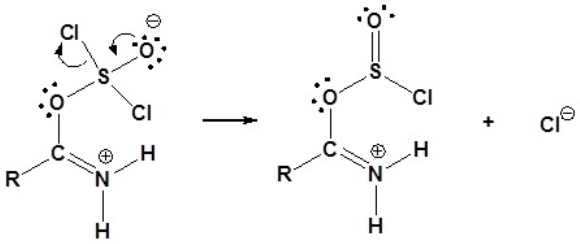
MECHANISM

For the reaction of primary amides with thionyl chloride, the mechanism begins with the lone pair of electrons from the nitrogen atom forming a protonated imine and pushing the pi electrons of the carbonyl to undergo nucleophilic attack on the sulfur of thionyl chloride. This forms a O-S sigma bond and causes the pi electrons of the thionyl bond (S=O) to be pushed onto the oxygen. The thionyl bond reforms in concert with the loss of a chloride leaving group (Cl^-). The protonated imine is neutralized by any base. The nitrile is then produced by an E2-like elimination reaction with a loss of sulfur dioxide (SO_2) and another chloride as the leaving groups.

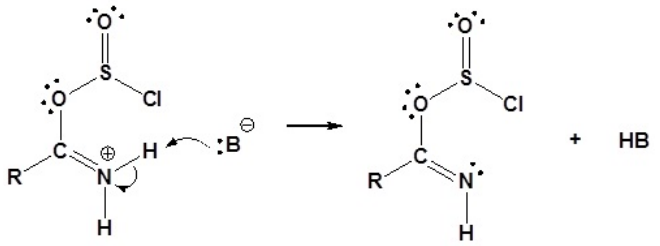
Step 1: Nucleophilic attack on thionyl chloride



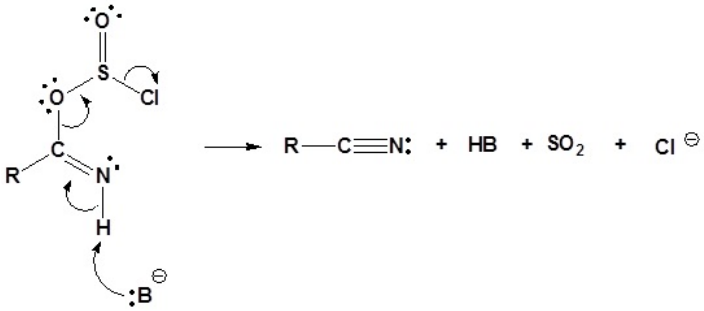
Step 2: Leaving group removal to reform the thionyl bond



Step 3: Deprotonation

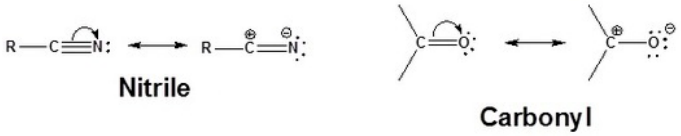


Step 4: E2-like reaction to form a nitrile

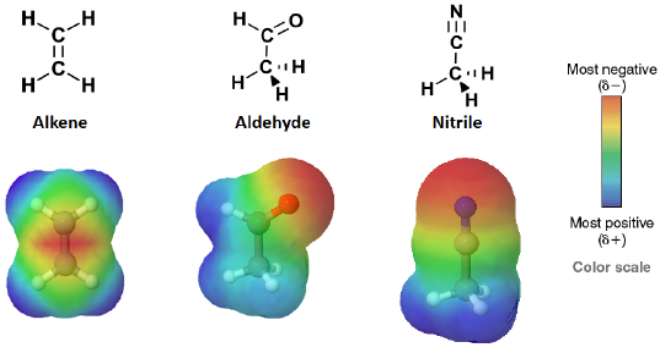


REACTIONS OF NITRILES

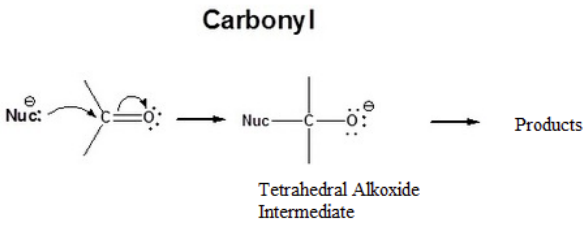
Nitriles are analogous to carbonyl groups in that they contain pi bonds, are strongly polarized, and contain electrophilic carbons.

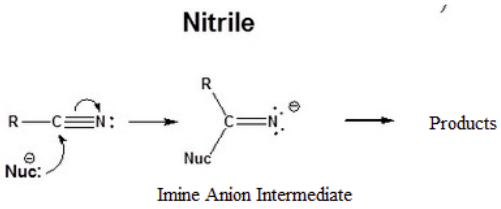


The bond polarization of a nitrile can clearly be seen when comparing the electrostatic potential maps of an alkene, an aldehyde, and a nitrile. In the maps of the aldehyde and nitrile, the electron density in the pi bonds is pulled away from the carbon toward the electronegative oxygen and nitrogen. This gives the functional group carbons a slight positive charge making them electrophilic. In the map of the alkene, the electron density is centered on the carbon making the pi bond non-polar and the carbons not electrophilic.



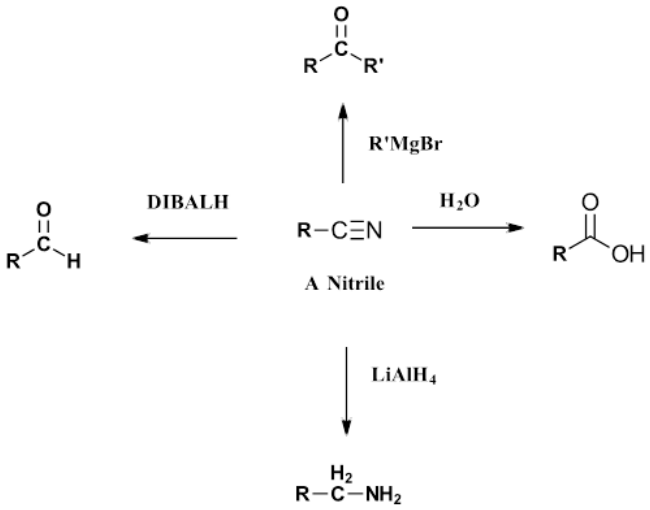
The triple bond of a nitrile reacts with negatively charged nucleophiles to form an imine anion intermediate in much the same fashion that carbonyls form a tetrahedral alkoxide intermediate. Because the imine anion intermediate still contains a pi bond and an electrophilic carbon, additional nucleophilic additions can occur to form a variety of functional groups including ketones, aldehydes, and amines.





GENERAL REACTIONS OF NITRILES

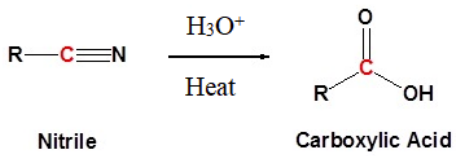
Nitriles undergo several types of reactions including hydrolysis to carboxylic acids, two different reductions with products that vary with the strength of the reducing agent and reaction with Grignard reagents that form ketones.



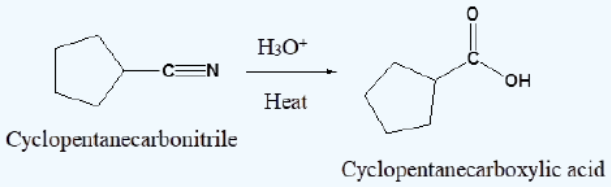
HYDROLYSIS OF NITRILES TO FORM CARBOXYLIC ACIDS

One of the more useful reaction involving nitriles is their hydrolysis to form carboxylic acids. This reaction occurs in either acidc or basic aqueous solutions with slight differences in each mechanism. In the case of acid catalysis, the nitrile becomes protonated. Protonation increases the electrophilicity of the nitrile so that it will accept water, a poor nucleophile. With base catalyzed hydrolysis, the strongly nucleophilic hydroxide anion is capable of directl addition to the carbon-nitrogen triple bond. During both mechanisms an amide intermediate is formed which usually is not isolated.

ACID CATALYZED HYDROLYSIS OF NITRILES



EXAMPLE

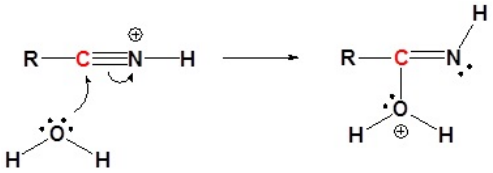


MECHANISM OF ACID CATALYZED HYDROLYSIS

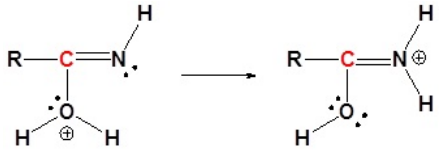
The mechanism begins with the protonation of the nitrile to promote the addition of the weakly nucleophilic water molecule to the C-N triple bond. Once water has reacted with the nitrile carbon, a proton transfer and resonance occur to produce a protonated amide. Water acts as a weak base, deprotonating the carbonyl to form an amide and regenerating the hydronium catalyst. Further hydrolysis converts the amide to the carboxylic acid. The nitrile nitrogen is eventually removed as a leaving group and eventually forms ammonium (NH_4^+)

Step 1: Protonation

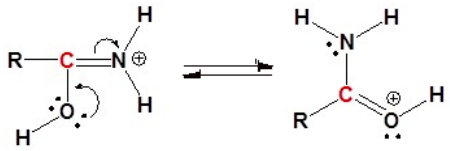
Step 2: Nucleophilic addition of water



Step 3: Proton Transfer

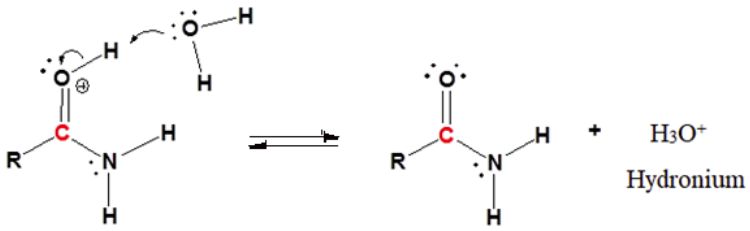


Step 4: Resonance to form a protonated amide



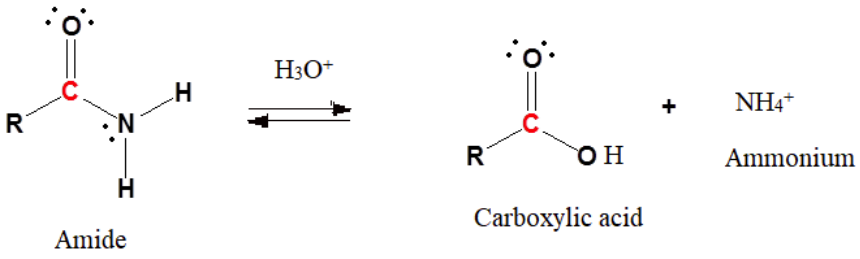
Protonated Amide

Step 5: Deprotonation to form an amide

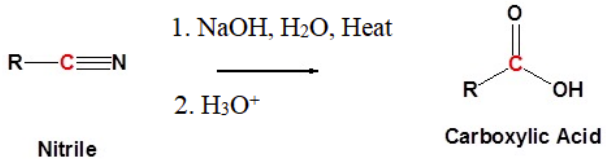


Amide

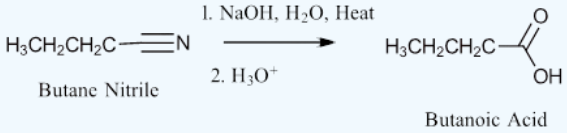
Step 6: Further hydrolysis of the amide forms a carboxylic acid. This mechanism can be found in Section 21.7



BASE CATALYZED HYDROLYSIS OF NITRILES



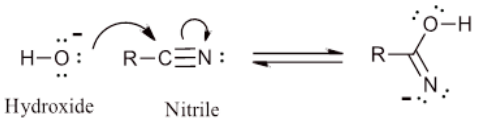
EXAMPLE



MECHANISM OF BASE CATALYZED HYDROLYSIS

Base catalyzed hydrolysis starts with the nucleophilic addition of a hydroxide ion to the C-N triple bond to form an imine anion. Subsequent protonation by water forms an amide tautomer, imidic acid, and regenerates the hydroxide catalyst. Tautomerization of imidic acid forms an amide which undergo further base catalyzed hydrolysis to form a carboxylic acid. During hydrolysis of the amide, nitrogen from the original nitrile is removed as a leaving group and eventually forms ammonium (NH_4^+)

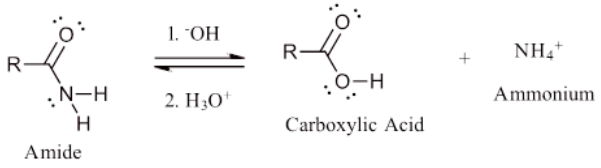
Step 1: Nucleophilic addition of hydroxide



Step 2: Protonation by water to form an imidic acid and hydroxide

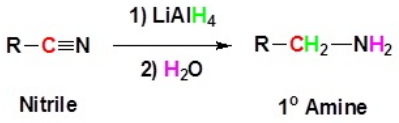
Step 3: Tautomerization of an imidic acid to form an amide

Step 4:) Further hydrolysis of the amide forms a carboxylic acid. This mechanism can be found in Section 21.7

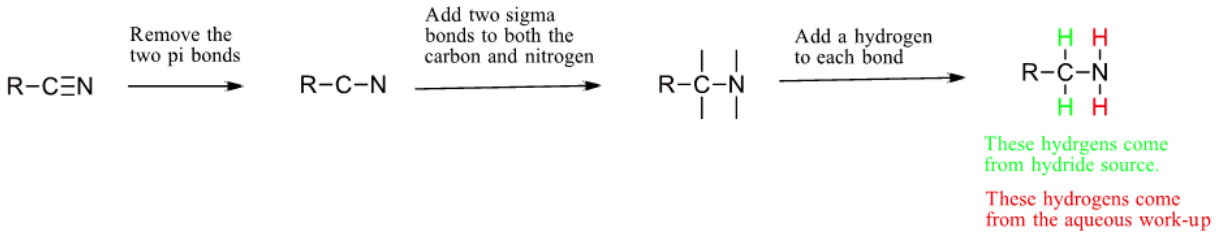


NITRILES CAN BE REDUCED TO 1° AMINES BY REACTION WITH $LiALH_4$

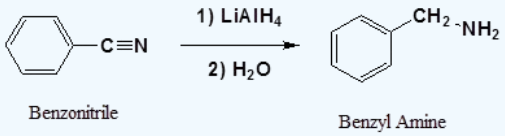
The reduction of nitriles with lithium aluminum hydride $LiAlH_4$ is an excellent method for the synthesis of primary amines. This reaction occurs via two nucleophilic additions of a hydride to the electrophilic carbon in the nitrile. Subsequent protonation with an aqueous work-up leads to the primary amine.



PREDICTING THE PRODUCT OF A HYDRIDE REDUCTION



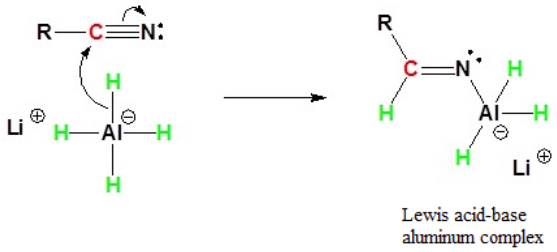
✔ EXAMPLE 20.7.1



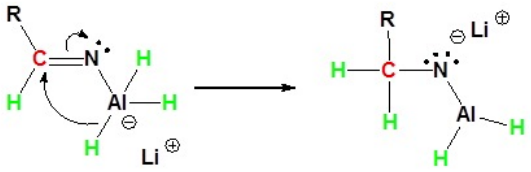
MECHANISM

During this reaction the hydride nucleophile reacts with the electrophilic carbon in the nitrile to form an imine anion. The imine ion is stabilized through formation of an anionic Lewis acid-base aluminum complex. The complex is vital for the continuation of the reaction because it shifts the negative charge from the nitrogen to the aluminum allowing for the imine carbon to remain electrophilic. Because the imine-aluminum complex still contains a pi bond and an electrophilic carbon, it can undergo a second nucleophilic addition of a hydride to form a dianion. The dianion is also stabilized through the formation of an anionic Lewis acid-base aluminum complex. During the aqueous work-up, the dianion is protonated by water to form a primary amine.

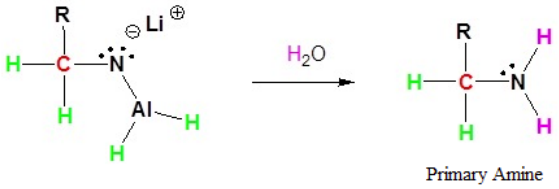
Step 1: Nucleophilic Attack by the Hydride



Step 2: Second nucleophilic attack by the hydride.

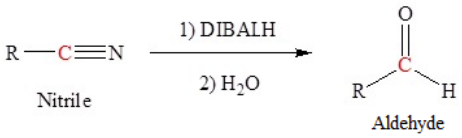


Step 3: Protonation by addition of water to give a primary amine

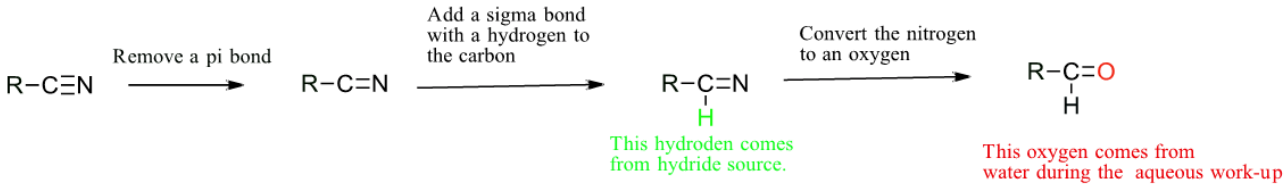


THE CONVERSION OF NITRILES TO ALDEHYDES BY REACTION WITH DIBALH

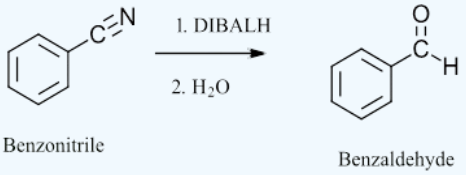
The use of DIBALH as a hydride source offers an efficient method for the synthesis of aldehydes. DIBALH only contains on hydride so the addition of one equivalent to a nitrile at low temperature (-78^{0}C) allows for the conversion to an aldehyde.



PREDICTING THE PRODUCT OF A REACTION WITH DIBALH

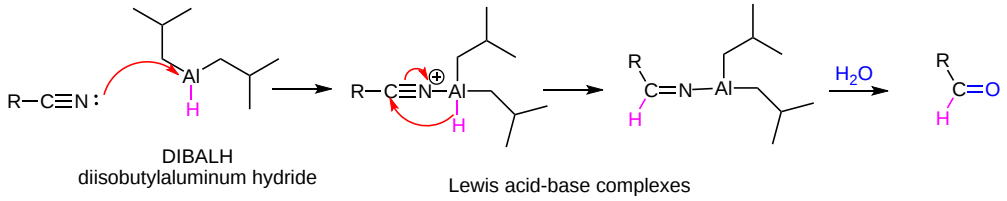


EXAMPLE 20.7.1



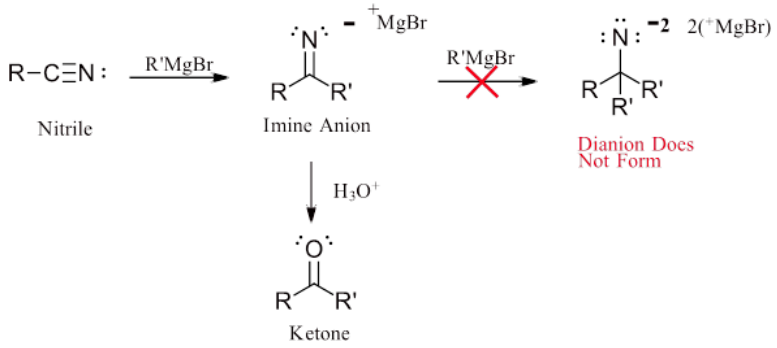
MECHANISM OF DIBALH REDUCTION OF NITRILES

The mechanism starts with the formation of a Lewis acid-base complex which increases the electrophilic character of the nitrile's carbon. The nucleophilic addition of a hydride forms an imine anion which is also stabilized through formation of a Lewis acid-base aluminum complex. Unlike the reduction with $LiAlH_4$, DIBALH only has a single hydride so a second nucleophlic addition to the imine anion does not occur. Subsequently, the imine anion undergoes hydrolysis during acidic aqueous work-up to from an aldehyde. The mechanism of imine anion hydrolysis is the reverse of an imine formation previously discussed.



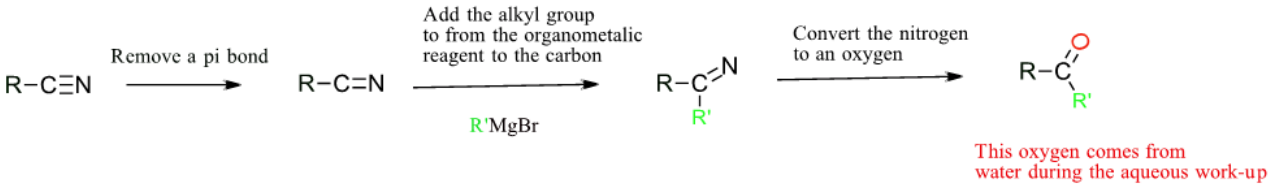
CONVERSION OF NITRILES TO KETONES WITH ORGANOMETALIC REAGENTS

Some organometalic species, such as Grignard reagents or organolithium reagents, undergo nucleophilic addition to the electophillic carbon of a nitrile to form an intermediate imine anion. Despite the presence of a pi bond, the negative charge of the imine anion prevents any further nucleophilic additions. During an aqueous work-up, the imine anion is hydrolyzed by water to form a ketone.

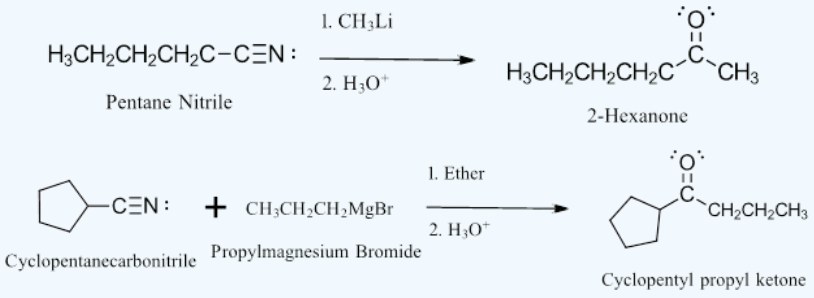


GENERAL REACTION

PREDICTING THE PRODUCT OF A REACTION WITH AN ORGANOMETALIC



EXAMPLES

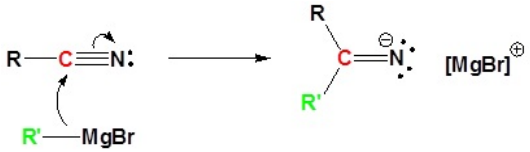


MECHANISM OF ORGANOMETALLIC ADDITION

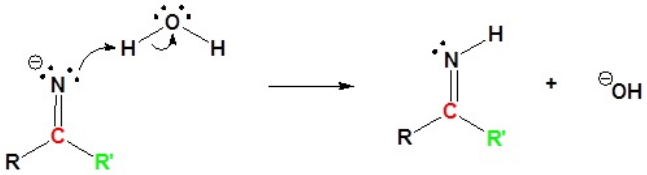
The mechanism begins with the nucleophilic Grignard reagent reacting with the electrophilic carbon of the nitrile to form a salt of the imine anion. The imine salt is protonated to form an imine which is subsequently protonated to form a positively charged iminium ion. After

nucleophilic attack by water and a proton transfer, the nitrogen from the nitrile is removed as a leaving group in the from of ammonia (NH_3). This step forms a protonated ketone called a ketonium ion which is subsequently deprotonated by ammonia to the neutral ketone and ammonium (NH_4^+).

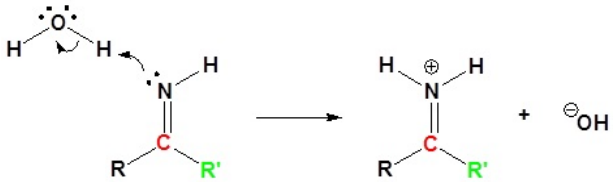
Step 1: Nucleophilic Attack by the Grignard Reagent to form an imine anion



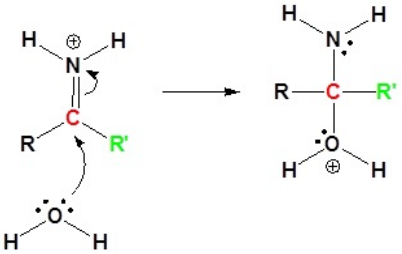
Step 2: Protonation to form an imine



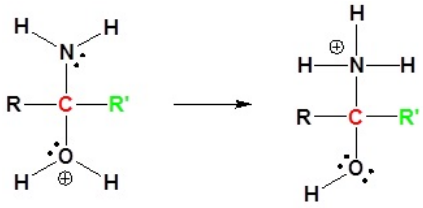
Step 3: Protonation to form an iminium ion



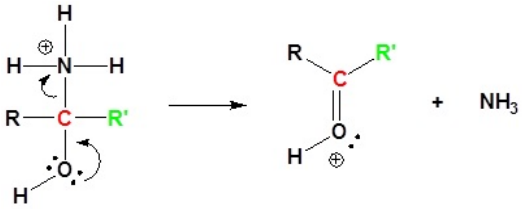
Step 4: Nucleophilic attack by water



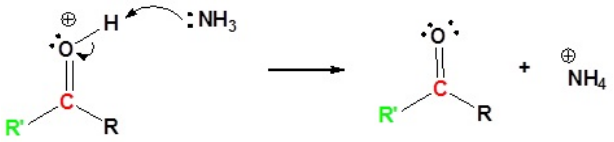
Step 5: Proton Transfer



Step 6: Removal of NH_3 as a leaving group to form a ketonium ion

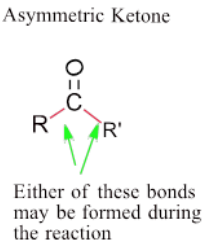


7) Deprotonation to form a ketone

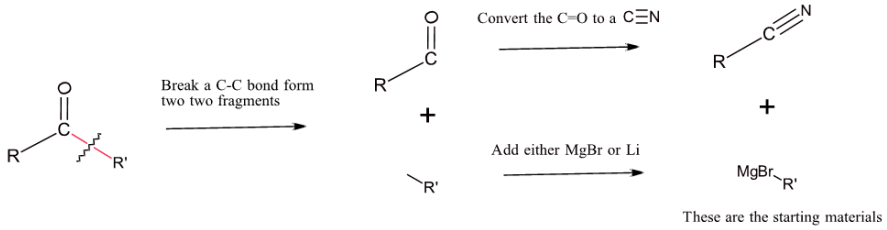


PLANNING THE SYNTHESIS OF A KETONE FROM A NITRILE

These reactions can be employed to plan synthetic routes to desired molecules from nitriles. Because a C-C bond is formed, the reaction of an organometallic reagent with nitrile is an effective method for the synthesis of ketones. Also, asymmetrical ketones offer the possibility of two separate synthesis routes.

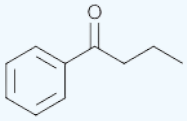


To plan a synthesis, we often think in reverse. Begin with the intended product (in this case the ketone). Break a C-C bond between the carbon in the carbonyl and an adjacent carbon. The fragment with the C=O becomes the nitrile starting material. The other fragment becomes either a Grignard or an organolithium reagent.



EXAMPLE 20.7.1

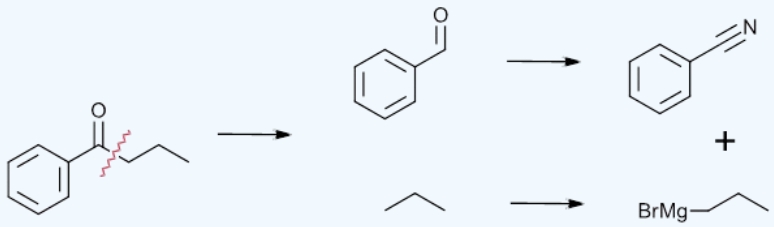
Plan a synthesis of the following molecule using the reaction of a organometallic reagent and a nitrile.



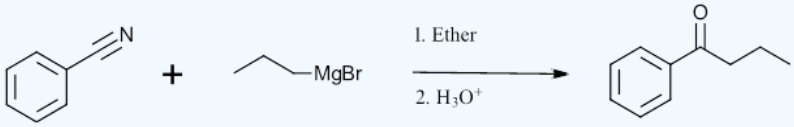
Solution

There are two possible pathways to synthesize this molecule.

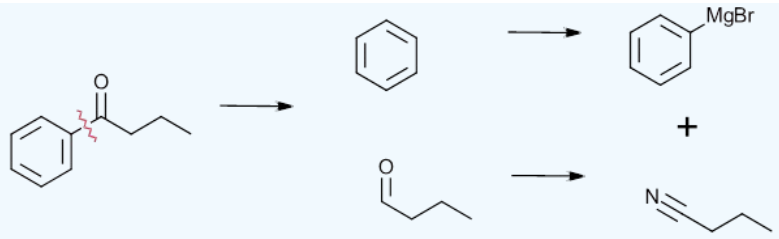
Solution 1



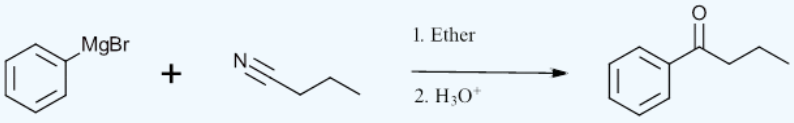
Pathway 1)



Solution 2



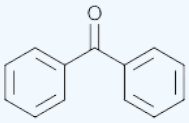
Pathway 2)



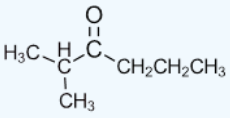
EXERCISE 20.7.1

Show how the following compounds could be prepared from a nitrile:

a.

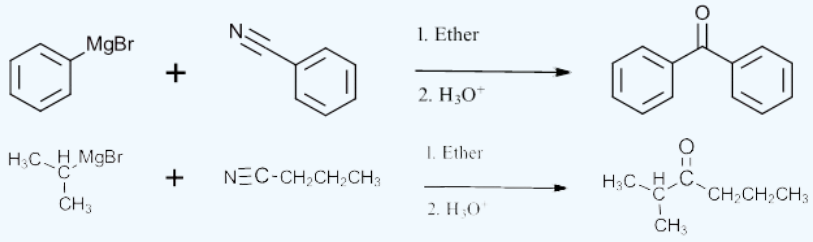


b.



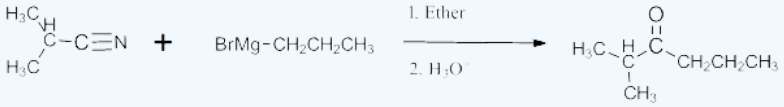
Answer

a.



Or

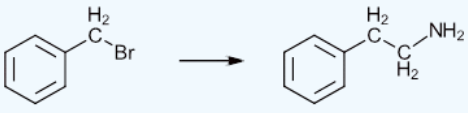
b.



EXERCISE 20.7.2

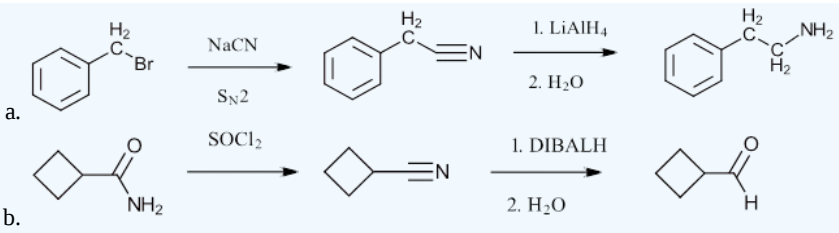
Show how the following transformations could be preformed:

a.



b.

Answer



20.8: SPECTROSCOPY OF CARBOXYLIC ACIDS AND NITRILES

OBJECTIVES

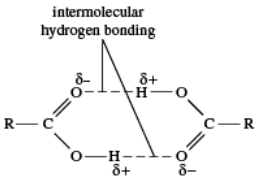
After completing this section, you should be able to

1. identify the two characteristic infrared absorptions displayed by all carboxylic acids.
2. state the approximate ^{1}H NMR absorption of a carboxylic acid proton.
3. use infrared and NMR spectroscopy data to assist in the identification of an unknown carboxylic acid, with or without the assistance of a table of characteristic absorptions.

SPECTROSCOPY OF CARBOXYLIC ACIDS

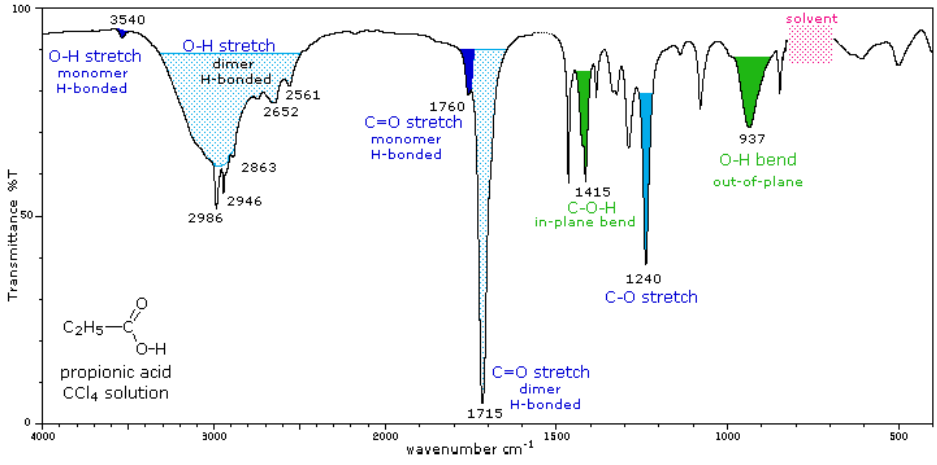
INFRARED SPECTROSCOPY

The carboxyl group is associated with two characteristic infrared stretching absorptions which change markedly with hydrogen bonding. The spectrum of propionic acid (propanoic acid) dissolved in CCl_4, shown below, is illustrative. Carboxylic acids exist predominantly as hydrogen bonded dimers in condensed phases.



The Hydrogen Bonding Dimer of Carboxylic Acids

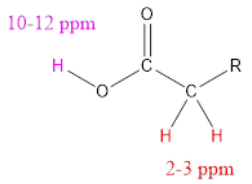
The O-H stretching absorption for such dimers is very strong and broad, extending from 2500 to 3300 cm^{-1}. This absorption overlaps the sharper C-H stretching peaks, which may be seen extending beyond the O-H envelope at 2990, 2950 and 2870 cm^{-1}. The smaller peaks protruding near 2655 and 2560 cm^{-1} 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.



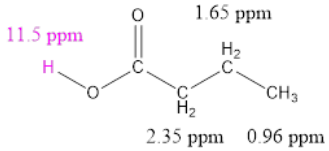
The Infrared Spectrum of Propanoic Acid

^{1}H NUCLEAR MAGNETIC SPECTROSCOPY

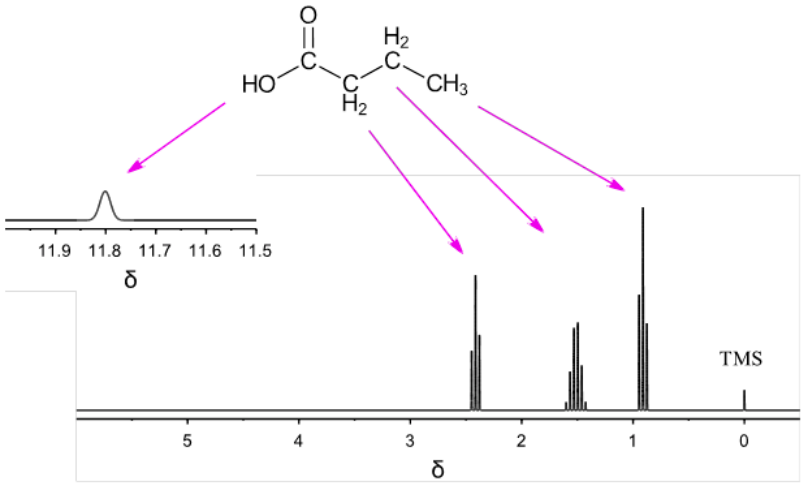
The acidic O-H protons of carboxylic acids are highly deshielded due to the electronegativity of oxygen and anisotropy from the C=O carbonyl bond. They tend to be among the least shielded protons appearing far downfield in the 10–12 ppm region which is considered distinctive for carboxylic acids. Due to hydrogen bonding the proton of a carboxylic acid often appears as a broad singlet and adding D_2O causes the signal to disappear due to hydrogen-deuterium exchange. Protons on carbons adjacent to a carboxylic acid absorb in the 2-3 ppm region. Some deshielding occurs due to the fact that the carbonyl oxygen is pulling electron density away from the carbonyl carbon which inductively pulls electron density away from the adjacent carbon.



The Typical ^{1}H Peaks for a Carboxylic Acid



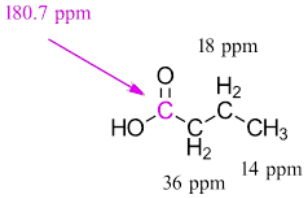
The ^{1}H Peaks for Butanoic Acid



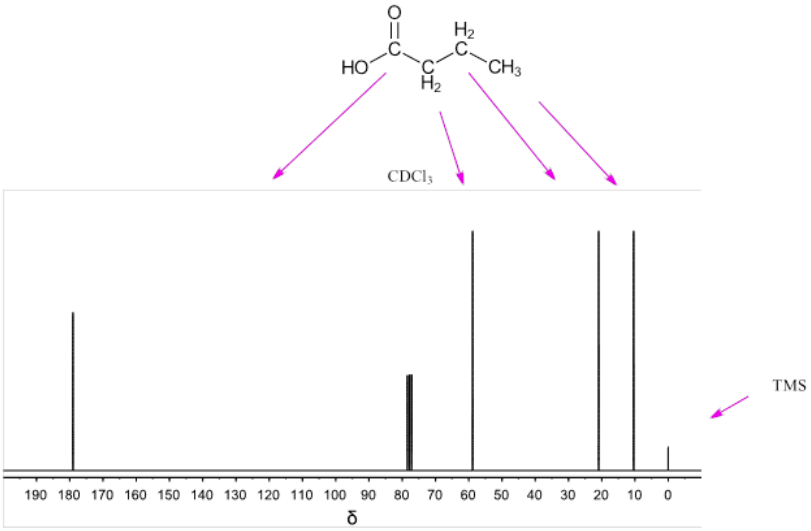
A ^{1}H NMR Spectra for Butanoic Acid

^{13}C NUCLEAR MAGNETIC SPECTROSCOPY

The carbonyl carbon of a carboxylic acid is strongly deshielded (160-180 ppm) due to the presence of the highly electronegative oxygen. However, they are not as deshielded as the carbonyl carbon of an aldehyde or ketone (180-220 ppm).



The ^{13}C Peaks for Butanoic Acid



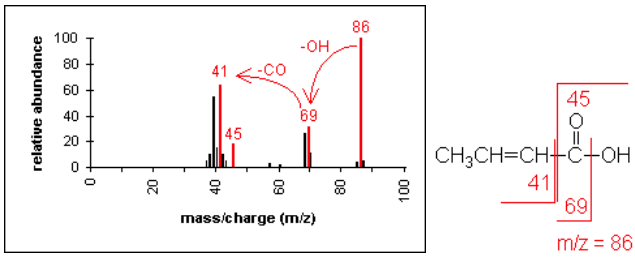
A ^{13}C NMR Spectra for Butanoic Acid

UV/VIS SPECTROSCOPY

Without additional conjugation, carboxylic acids absorb at about 210 nm, which is too low to be useful.

MASS SPECTROMETRY

In short chain acids, peaks due to the loss of OH (molecular ion less 17) and COOH (molecular ion less 45) are prominent due to cleavage of bonds next to C=O.

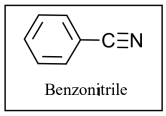


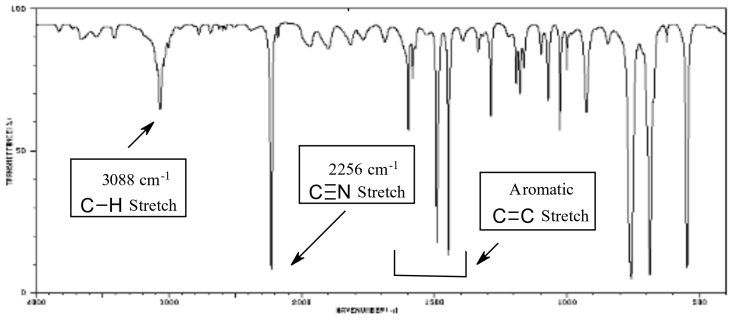
The Fragmentation of 2-Butenoic acid ($C_4H_6O_2$): MW = 86.09

SPECTROSCOPY OF NITRILES

INFRARED SPECTROSCOPY

The CN triple bond stretch of nitriles appears in a distinctive region of an IR spectra, near 2250 cm^{-1}. One of the only other absorptions to appear in this region is the CC triple bond stretch of an alkyne (2100-2250 cm^{-1}).

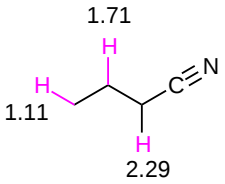




Infrared Spectrum of Benzonitrile

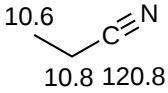
^{1}H NUCLEAR MAGNETIC SPECTROSCOPY

Protons on carbons adjacent to a nitrile absorb in the 2-3 ppm region. Some deshielding occurs due to the fact that the sp hybridized nitrile carbon is more electronegative than the adjacent sp^3 hybridized carbon.



^{13}C NUCLEAR MAGNETIC SPECTROSCOPY

The nitrile carbon absorbs in the 115–120 ppm region which not as far downfield as a typical carbonyl carbon (180-220 ppm).

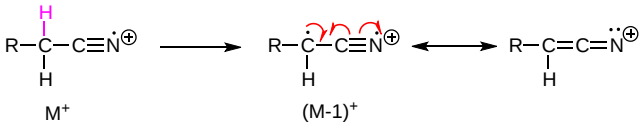


UV/VIS SPECTROSCOPY

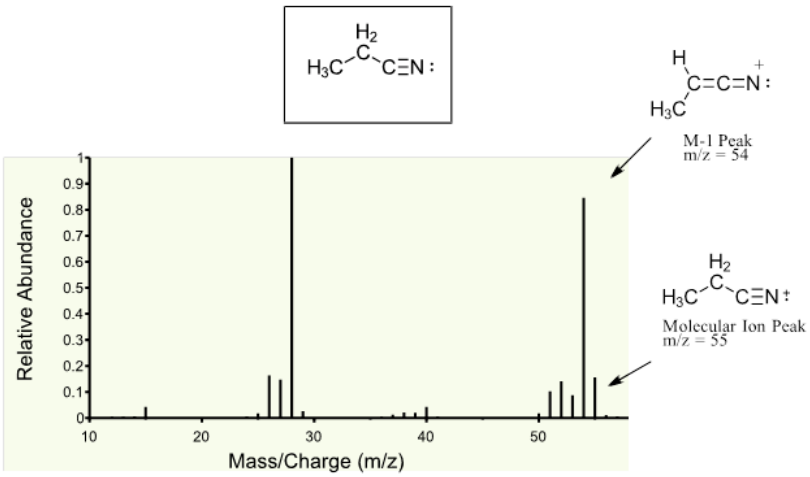
Most nitriles do not show absorption above 200 nm which does not make UV/Vis spectroscopy a useful tool to characterize them.

MASS SPECTROMETRY

The molecular ion (M^+) peaks of simple nitriles are often weak or not present in a mass spectra. There is often a M-1 peak due to the loss of a -H.



Mechanism for the Formation of a M-1 Peak in Mass Spectra

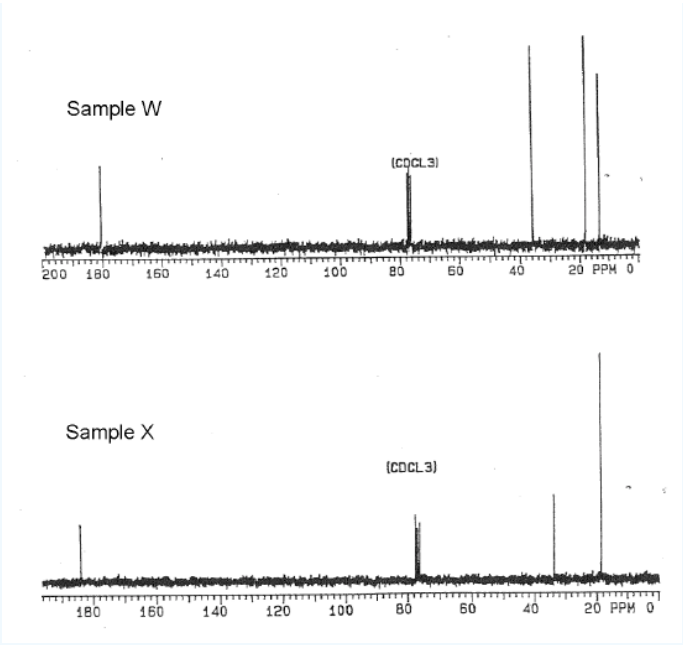


Mass Spectra of Propanenitrile

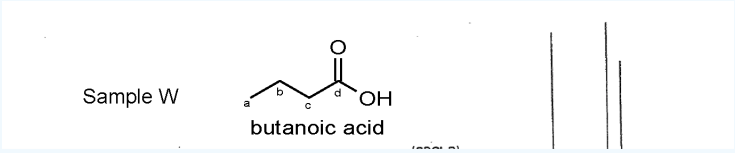
? EXERCISE

Sample W is a reactant for a wide range of biochemical processes. Sample X was isolated from vanilla beans. Elemental analysis indicated the compounds are structural isomers with the composition: 54.52% C, 9.16% H and 36.32% O. The IR spectrum for each compound showed a broad absorption from 3500 - 2500 cm^{-1} and a strong band near 1710 cm^{-1}. The ^{1}H NMR is being serviced, so only the ^{13}C NMR spectra shown below were available.

Name and draw the bond-line structures for Samples W and X and correlate the ^{13}C NMR spectral signals to their respective compounds.



Answer



IR spectrum of benzonitrile. Source: SDBSWeb : http://riodb01.ibase.aist.go.jp/sdbs/ (National Institute of Advanced Industrial Science and Technology of Japan, 14 July 2008)

20.S: CARBOXYLIC ACIDS AND NITRILES (SUMMARY)

CONCEPTS & VOCABULARY

20.0 Chapter Objectives and Introduction to Carboxylic Acids

- Carboxylic acids are defined as molecules that have a hydroxyl group bonded to a carbonyl group (RCOOH).
- Fatty acids are naturally occurring carboxylic acids that are important components of lipids.
- Fatty acids can either be saturated (all carbon-carbon bonds are single bonds) and unsaturated (one or more carbon-carbon double bonds).
- Several other functional groups can be prepared from carboxylic acids and are considered derivatives (acyl halides, anhydrides, esters, amides and nitriles).

20.1 Naming Carboxylic Acids and Nitriles

- Carboxylic acids are named following IUPAC rules with ending -oic acid.
- When carboxylic acids are named as an attachment to a ring, add -carboxylic acid to the name of the cyclic compound.
- Nitriles are named following IUPAC rules with the ending -nitrile or -carbonitrile.

20.2 Structure and Properties of Carboxylic Acids

- Carboxylic acids have trigonal planar shape around the carbonyl carbon and due to resonance structures, all the atoms of the functional group are co-planar.
- Conjugation in carboxylic acids increases acidity of the hydroxyl hydrogen compared to alcohols. The conjugate base (carboxylate) is stabilized by resonance.
- Carboxylic acids form hydrogen bonded dimers yielding higher boiling points than for other molecules of similar size.
- Small carboxylic acids are often soluble in water due to hydrogen bonding. Larger carboxylic acids are often slightly soluble in water, though when converted to a carboxylate salt by treating with base, become water soluble.

20.3 Biological Acids and the Henderson-Hasselbalch Equation

- Carboxylic acids are fully protonated in acidic solutions.
- Carboxylic acids are fully dissociated in basic solutions.
- The Henderson-Hasselbalch equation can be used to relate pH, pKa and ratio of concentrations of acid and conjugate base.

20.4 Substituent Effects on Acidity

- Withdrawing groups (through inductive or resonance effects) can stabilize carboxylates, increasing acidity of carboxylic acids.
- Donating groups (through inductive or resonance effects) destabilize carboxylates, decreasing acidity of carboxylic acids.
- Nearly all substituents in ortho positions increase acid strength whether donating or withdrawing, this is called the *ortho*-effect.

20.5 Preparing Carboxylic Acids

- Carboxylic acids can be prepared through oxidation of several functional groups including: 1^{o} alcohols, aldehydes, alkyl arene side chains, and alkenes.
- Carboxylic acids can also be prepared by carboxylation of Grignard reagents and hydrolysis of nitriles.

20.6 Reactions of Carboxylic Acids: An Overview

- There are four main categories of carboxylic acid reactions:
  - Acid/base reaction (salt formation)
  - Nucleophilic acyl substitution
  - Reduction
  - Substitution alpha to the carbonyl

20.7 Chemistry of Nitriles

- Nitriles have linear geometry due to the *sp* hybrid orbitals on carbon and nitrogen.
- Nitriles are less basic than amines.
- Nitriles can be prepared from aldehydes, ketones, or amides.
- Nitriles react similarly to carbonyl compounds where nucleophiles will attack the carbon end of the nitrile.
- Nitriles can be hydrolyzed to carboxylic acids under basic or acidic conditions.
- Nitriles can be reduced to amines by hydride reduction.
- Nitriles can be converted to aldehyde by reaction with DIBALH.
- Nitriles can be converted to ketones by reaction with organometallic compounds.

20.8 Spectroscopy of Carboxylic Acids and Nitriles

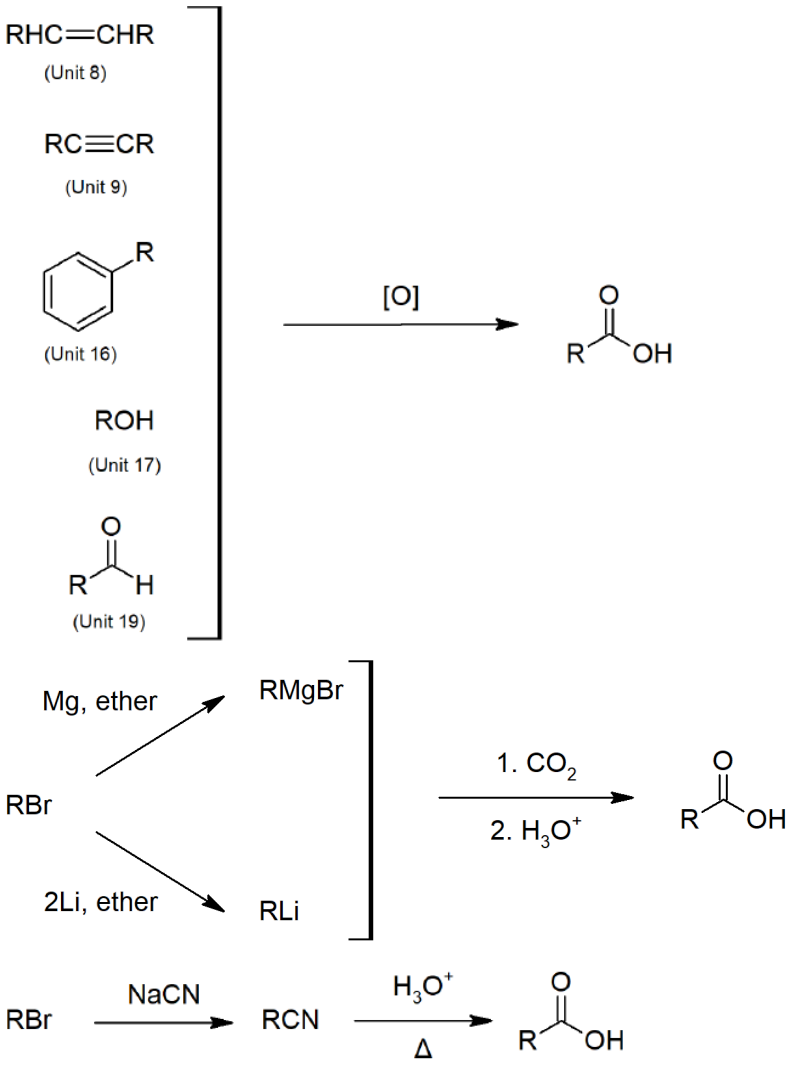
- IR of carboxylic acids typically show a very strong and broad OH stretch from about 2500 to 3300 cm^{-1} as well as a strong carbonyl stretch around 1710 cm^{-1}.
- ^{1}H NMR of carboxylic acids show the OH proton between 10-12 ppm as well as hydrogens on carbon adjacent to the carbonyl around 2-3 ppm.
- ^{13}C NMR of carboxylic acids show the carbonyl carbon at 160-180 ppm.
- Mass spectra of carboxylic acids often have fragments for OH (loss of 17) and COOH (loss of 45).
- The most identifying characteristic of IR of nitriles is the CN triple bond stretch which appears near 2250 cm^{-1}.
- ^{1}H NMR of nitriles show protons on the carbon next to the nitrile at around 2-3 ppm.
- ^{13}C NMR of nitriles show the nitrile carbon in the 115-120 ppm range.
- Mass spectra of nitriles will often not have a visible molecular ion, but instead exhibit a strong M-1 peak.

SKILLS TO MASTER

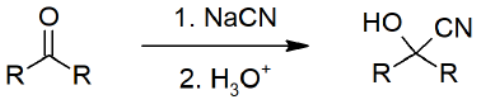
- Skill 20.1 Name carboxylic acids and nitriles using IUPAC rules.
- Skill 20.2 Draw the structure of carboxylic acids and nitriles from the IUPAC name.
- Skill 20.3 Describe the geometries and approximate bond angles of carboxylic acids and nitriles.
- Skill 20.4 Explain the acidity of carboxylic acids based on conjugate base stabilization.
- Skill 20.5 Explain physical properties of carboxylic acids.
- Skill 20.6 Describe the structure of carboxylic acids in buffered solutions.
- Skill 20.7 Use the Henderson-Hasselbach equation to relate pH, pK_a, and acid/conjugate base concentrations.
- Skill 20.8 Explain inductive effects on acidity.
- Skill 20.9 Explain relative acidity of aromatic acids.
- Skill 20.10 Draw mechanisms for preparing carboxylic acids including:
  - Oxidations
  - Carboxylation of Grignard reagents
  - Hydrolysis of Nitriles
- Skill 20.11 List the four categories of carboxylic acid reactions.
- Skill 20.12 Draw reactions for preparing nitriles including formation from:
  - aldehyde or ketone
  - 1^{o} amide
- Skill 20.13 List general reactions of nitriles.
- Skill 20.14 Draw mechanisms for reactions of nitriles including:
  - Hydrolysis to acids (acidic and basic mechanisms)
  - Reduction to 1^{o} amines
  - Conversion to aldehyde by reaction with DIBALH.
  - Conversion to ketones by reaction with organometallic compounds.
- Skill 20.15 Plan a synthesis of a ketone from a nitrile.
- Skill 20.16 Use IR, NMR and MS to identify carboxylic acids and nitriles.

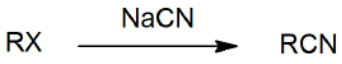
SUMMARY OF REACTIONS

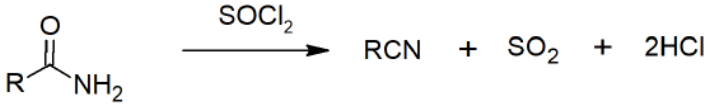
Carboxylic Acid Preparation



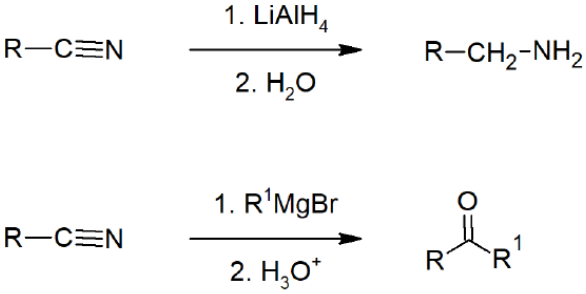
Nitrile Preparation







Reaction of Nitriles



CHAPTER OVERVIEW

21: CARBOXYLIC ACID DERIVATIVES- NUCLEOPHILIC ACYL SUBSTITUTION REACTIONS

The compounds discussed in this chapter are all considered to be derived from carboxylic acids, and include acid halides, acid anhydrides, esters and amides (thioesters and acyl phosphates are also briefly mentioned). As you proceed through the chapter, you should be looking for similarities in behaviour among the various classes of compounds. These similarities can be readily understood once you appreciate the fact that, in most of their reactions, carboxylic acid derivatives react via the nucleophilic acyl substitution mechanism.

In this chapter, we describe the nomenclature of the various types of carboxylic acid derivatives, and explain the relative reactivity of these compounds in terms of resonance contributions to the ground state of each type of compound.

We describe the reactions of carboxylic acids, acid halides, acid anhydrides, esters, amides, polyamides and polyesters in detail, and discuss the biological importance of thiol esters briefly. The chapter concludes with a look at how infrared spectroscopy and NMR spectroscopy can be used in the identification of unknown carboxylic acid derivatives.

21.0: CHAPTER OBJECTIVES AND INTRODUCTION TO CARBOXYLIC ACID DERIVATIVES

OBJECTIVES

1. fulfill all of the detailed objectives listed under each individual section.
2. design multi-step syntheses in which the reactions introduced in this chapter are used in conjunction with any of the reactions described in previous chapters.
3. solve road-map problems that require a knowledge of the chemistry of carboxylic acid derivatives.
4. define, and use in context, any of the key terms introduced in this chapter.

After completing this section, you should be able to

1. identify, and give an example of
   a. an acid halide.
   b. an acid anhydride.
   c. an ester.
   d. an amide.
2. write the general form of a nucleophilic acyl substitution reaction.

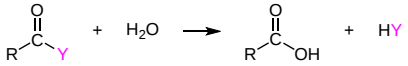
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

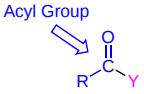
- acyl derivative
- nucleophilic acyl substitution reaction

CARBOXYLIC ACID DERIVATIVES

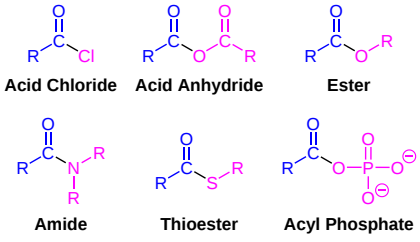
Carboxylic acid derivatives are formed when the hydroxyl group of a carboxylic acid is replaced by some other group, Y, such that it can be hydrolyzed back to the acid.



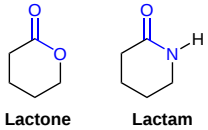
These compounds are also called the **acyl derivatives** of a carboxylic acid because they usually contain an acyl group bonded to a substituent which can act as a leaving group in a nucleophilic acyl substitution reaction.



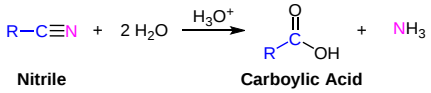
Although there are many types of carboxylic acid derivatives known, this chapter focuses on six: acid halides (acyl halides), anhydrides, esters, amides, thioesters, and acylphosphates.



Cyclic esters and amides are referred to as **lactones** and **lactams**, respectively.

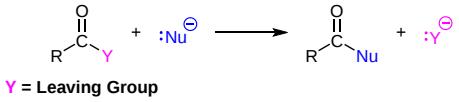


Nitriles, $RC \equiv N$, discussed in the last chapter, are often are considered to be carboxylic acid derivatives, even though the acyl group is not present, because hydrolysis of nitriles leads to carboxylic acids.



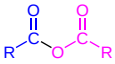
NUCLEOPHILIC ACYL SUBSTITUTION REACTION

The main type of reaction for carboxylic acid derivatives is called nucleophilic acyl substitution. This reaction involves the replacement of the Y group by attack of a nucleophile $Nu^{\ominus}$ at the carbonyl carbon with subsequent cleavage of the $C-Y$ bond.



PHYSICAL PROPERTIES OF CARBOXYLIC ACID DERIVATIVES

The intermolecular forces of the respective acyl group combine with the size and structure of the Y-group to determine the physical properties of the the carboxylic acid derivatives as shown in the summary below.

Name	Structure	Intermolecular Forces	Relative Boiling Point (^{o}C)	Soluble in H_2O	General Comments
Acid Chloride		Polar, No H-Bonding	51	No	Acrid Piercing Odors
Acid Anhydride		Polar, No H-Bonding	140	No	Acrid Piercing Odors
Ester		Polar, No H-Bonding	57	No	Volatile Fragrant Liquids
Carboxylic Acid		H-Bonding Dimer	118	Yes, if C < 5	Acrid Piercing Odors
Amide		Complex H-Bonding	221	Yes if C < 4	Biological Important (Proteins)
Nitrile		Among the most polar compounds with out H-Bonding	82	Yes if C < 4	CH_3CN is a useful polar aprotic solvent

21.1: NAMING CARBOXYLIC ACID DERIVATIVES

OBJECTIVES

After completing this section, you should be able to

1. provide a satisfactory name for an acid halide of given structure.
2. draw the condensed or shorthand structure of an acid halide, given either its commonly used or systematic name.
3. provide a satisfactory name for an acid anhydride of given structure.
4. draw the condensed or shorthand structure of an acid anhydride, given either its trivial or IUPAC name.
5. provide an acceptable name for an amide of given structure.
6. draw the condensed or shorthand structure of an amide, given its trivial or IUPAC name.
7. provide an acceptable name for an ester of given structure.
8. draw the condensed or shorthand structure of an ester, given either its trivial or IUPAC name.
9. provide an acceptable name for a thioester of given structure.
10. draw the condensed or shorthand structure of a thioester, given its trivial or IUPAC name.
11. provide an acceptable name for an acyl phosphate.
12. draw the condensed or shorthand structure of an acyl phosphate, given either its trivial or IUPAC name.

NOMENCLATURE OF ACID HALIDES, RCOX

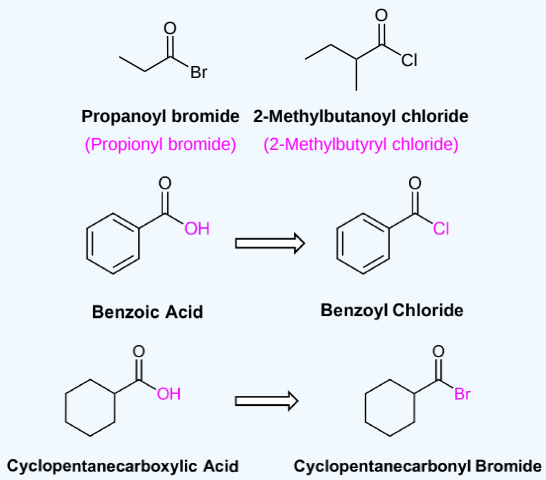
The nomenclature of acid halides starts with the name of the corresponding carboxylic acid. If the corresponding carboxylic acid has an **–oic acid** or **–ic acid** ending it is removed and replaced with the ending **-oyl** followed by the first syllable of the name of the halogen along with an **–ide** ending.

However there are a number of specific exceptions where IUPAC allows the ending **-yl** to be used instead. Examples are formic ⇒ formyl, acetic ⇒acetyl, propionic ⇒propionyl, butyric ⇒butyryl, oxalic ⇒ oxalyl, and succinic ⇒ succinyl.

When the corresponding acid includes a **-carboxylic acid** ending, it is removed and replaced with the ending **-carbonyl.** This is followed by the first syllable of the name of the halogen along with an **–ide** ending

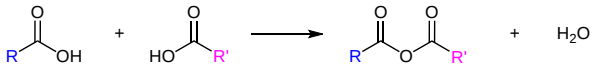
The carbonyl carbon is given the #1 location number. The acid halide functional group is assumed to be on the end of the parent chain, so it is not necessary to include the functional group location number in the name.

EXAMPLE 21.1.1



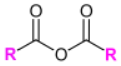
NOMENCLATURE OF ANHYDRIDES, RCO_2COR'

An anhydride functional group results when two carboxylic acids combine and lose water (anhydride = without water). The names of anhydrides come from the names of the two combined carboxylic acids. The carbonyl carbon is given the #1 location number on both chains. The anhydride functional group is assumed to be on the end of the each parent chain, so it is not necessary to include the functional group location number in the name.



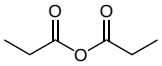
Carboxylic Acids **Anhydride** **Water**

Symmetrical anhydrides made from unsubstituted carboxylic acids and cyclic anhydrides made from dicarboxylic acids are named based on their corresponding carboxylic acid. The ending **-acid** is replaced with **-anhydride**. This is true for both the IUPAC and common nomenclature. An anhydride is symmetrical when it is acyclic and the acyl R groups are the same.

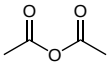


Symmetrical Anhydride

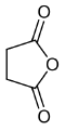
EXAMPLE



Propanoic anhydride
(Propionic anhydride)

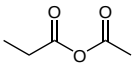


Ethanoic anhydride
(Acetic anhydride)

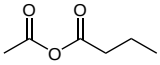


Succinic Anhydride

An unsymmetrical anhydride is created from two different carboxylic acids. For unsymmetrical anhydrides, name both acids *alphabetically* with a space between them. Then add the end word **anhydride**.



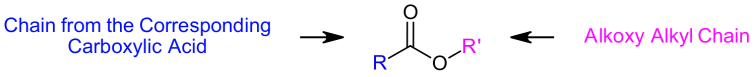
Ethanoic propanoic anhydride
(Acetic propionic anhydride)



Butanoic ethanoic anhydride
(Acetic butyic anhydride)

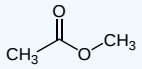
NOMENCLATURE OF ESTERS, RCO_2R'

Esters consist of two distinctly different carbon chains which need to be named separately. One carbon chain is from the corresponding carboxylic acid and the other chain, attached to the singly bonded oxygen, is called the alkoxy alkyl chain.

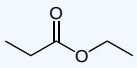


Esters are named as if the alkoxy alkyl chain is a substituent **(Prefix + yl)**. This is followed by the name of the corresponding carboxylic acid part of the ester with **-ic acid** or **-oic acid** replaced with the ending **–ate**. The carbonyl carbon is given the #1 location number. The carbonyl functional group is assumed to be on the end of the parent chain, so it is not necessary to include the functional group location number in the name.

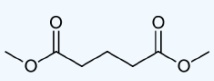
✔ EXAMPLE 21.1.2



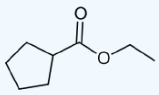
Methyl ethanoate



Ethyl propanoate



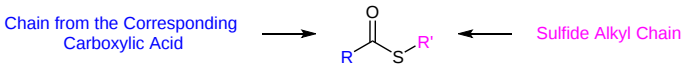
Dimethyl glutarate



Ethyl cyclopentanecarboxylate

NOMENCLATURE OF THIOESTERS, RCOSR'

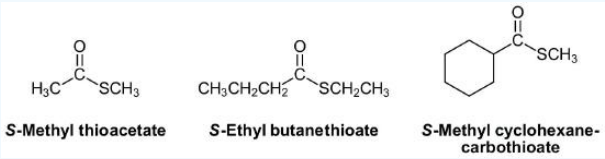
Thioesters have two distinctly different carbon chains. One carbon chain is from the corresponding carboxylic acid and the other chain, attached to the sulfur, is called the sulfide alkyl chain.



Thioesters are named as if the sulfide alkyl chain is a substituent with the letter *S* preceding **(*S*-Prefix + yl)**. This is followed by the parent chain of the corresponding carboxylic acid, named as an alkane with the ending **–thioate** added. For thioesters attached to a carbon ring the ending **-carboxylic acid** is replaced with **-carbothioate**. When using the common names of the carboxylic acid the **-ic acid** ending is replaced **-ate** and the prefix **thio-** is added.

The carbonyl carbon is given the #1 location number. The carbonyl functional group is assumed to be on the end of the parent chain, so it is not necessary to include the functional group location number in the name.

EXAMPLE 21.1.3

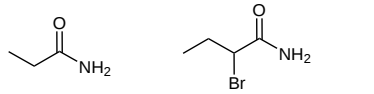


***S*-Methyl thioacetate** | ***S*-Ethyl butanethioate** | ***S*-Methyl cyclohexane-carbothioate**

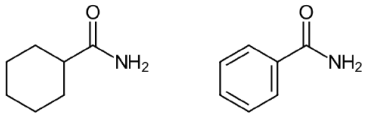
NOMENCLATURE OF AMIDES, $RCONH_2$, RCONHR', RCONR'R"

Primary amides ($RCONH_2$) are named by changing the name of the corresponding acid by removing the **-oic acid** or **-ic acid** endings and adding **-amide**. Amides derived from a cyclic carboxylic acid have the **-carboxylic acid** ending replaced with **-carboxamide**. 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

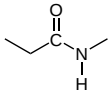


Propanamide | **2-Bromobutanamide**

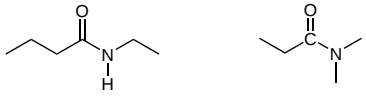


Cyclohexanecarboxamide | **Benzamide**

Secondary (RCONHR') and tertiary (RCONR'R") amides are named by using an upper case N to designate that the alkyl groups are attached to the nitrogen atom. These alkyl groups are named as substituents **(Prefix + yl)**.

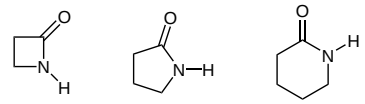


N-Methylpropanamide



N-Ethylbutanamide | **N,N-Dimethylpropanamide**

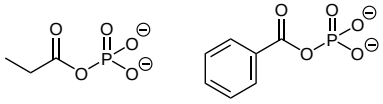
Cyclic amides are called lactams. A Greek letter identifies the location of the nitrogen on the alkyl chain relative to the carboxyl carbonyl group.



b-Lactam | **g-Lactam** | **d-Lactam**

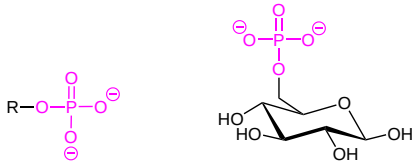
NOMENLCATURE OF ACYL PHOSPHATES, $RCOOPO_3^{2-}$

Acyl phosphates are named following the rules as acid halides except name of the halogen is replaced with the word **phosphate**. If there is an alkyl group attached to one of the phosphate oxygens, it is named as a substituent **(parent + yl)** and listed before the end word phosphate.



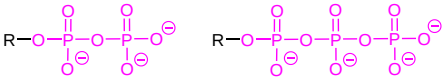
Propanoyl Phospate **Benzoyl Phosphate**

When a phosphate ion is attached to a carbon atom on an organic molecule, the chemical linkage is referred to as a phosphate ester, and the whole species is called an organic monophosphate. Glucose-6-phosphate is an example.



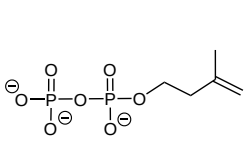
Organic monophosphate **Glucose-6-phosphate**

If an organic molecule is linked to two or three phosphate groups, the resulting species are called organic diphosphates and organic triphosphates.

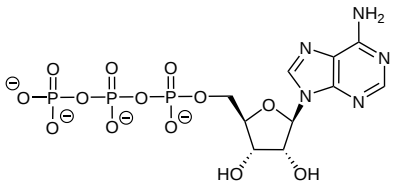


Organic diphosphate (ROPP) **Organic triphosphate (ROPPP)**

Isopententyl diphosphate and adenosine triphosphate (ATP) are good examples:

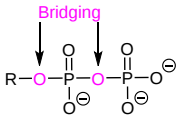


Isopentenyl diphosphate

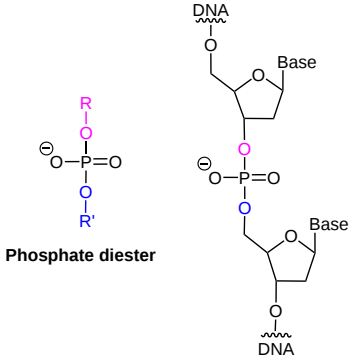


ATP

Oxygen atoms in phosphate groups are referred to either 'bridging' and 'non-bridging', depending on their position. An organic diphosphate has two bridging and five non-bridging oxygens.



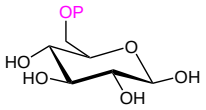
When a single phosphate is linked to two organic groups, the term 'phosphate diester' is used. The backbone of DNA is composed of phosphate diesters.



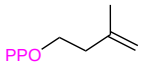
Phosphate diester

The term 'phosphoryl group' is a general way to refer to all of the phosphate-based groups mentioned above.

Phosphate groups on organic structures are sometimes abbreviated simply as 'P', a convention that we will use throughout this text. For example, glucose-6-phosphate and isopentenyl diphosphate are often depicted as shown below. Notice that the 'P' abbreviation includes the oxygen atoms and negative charges associated with the phosphate groups.

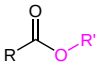
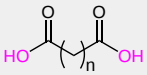
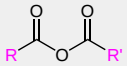
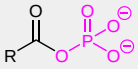


Glucose-6-phosphate



Isopentenyl diphosphate

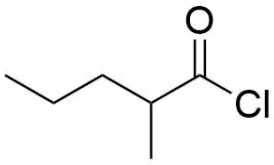
Nomenclature of Carboxylic Acids and Carboxylic Acid Derivatives

Functional Group	Structure	Suffix Name
Carboxylic acid		-oic acid
Carboxylate		-oate
Ester		-oate
Dicarboxylic acid		-dioic acid
Acyl halide		-oyl halide
Anhydride		-ic anhydride
Amide		-an amide
Acyl Phosphate		-oyl phosphate
Nitrile		-ane nitrile

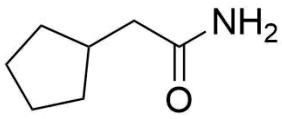
EXERCISES

1) Name the following compounds using IUPAC conventions

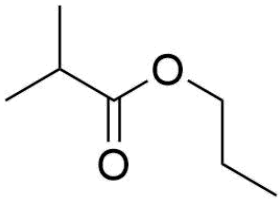
(a)



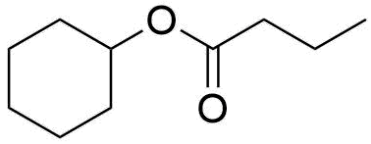
(b)



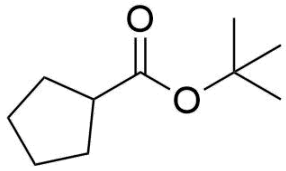
(c)



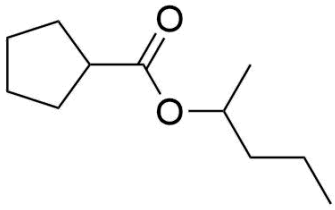
(d)



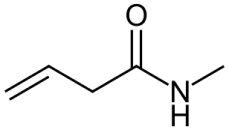
(e)



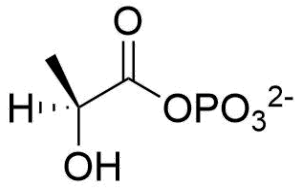
(f)



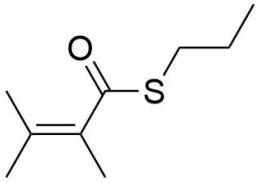
(g)



(h)



(i)



2) Draw structures corresponding to the following names:

a. benzoic anhydride
b. phenyl hexanoate
c. methyl benzoate
d. 3-chloro-N-ethylbenzamide
e. pentanamide
f. N-phenylethanamide
g. Methyl 1-methylcyclohexanecarboxylate
h. Ethyl 3-oxopentanoate
i. *S*-Methyl *p*-bromothiobenzoate
j. Formic propanoic anhydride
k. cis-2-Methylcyclopentanecarbonyl bromide

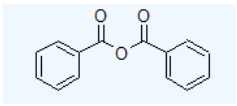
SOLUTIONS

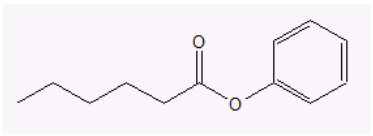
1)

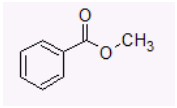
a. 2-methylpentanoyl chloride
b. 2-cyclopentylacetamide
c. propyl 2-methylpropanoate
d. cyclohexylbutanoate

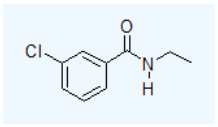
e. sec-butyl cyclopentanecarboxylate
f. 1-methylbutylcyclopentane carboxylate
g. N-methyl-3-butenamide
h. (S)-2-hydroxypropanoyl phosphate
i. *S*-propyl 2,3-dimethyl-2-butenethioate

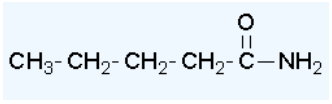
2)

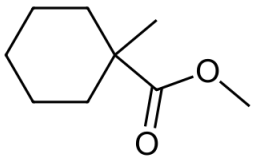
a. 

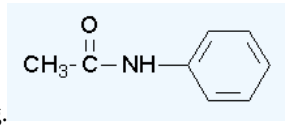
b. 

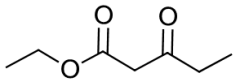
c. 

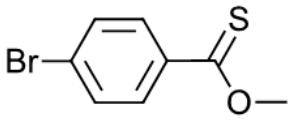
d. 

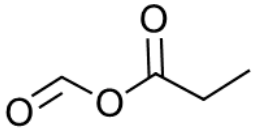
e. 

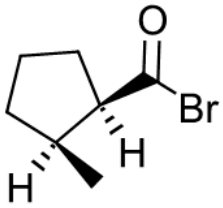
f. 

g. 

h. 

i. 

j. 

k. 

21.2: NUCLEOPHILIC ACYL SUBSTITUTION REACTIONS

OBJECTIVES

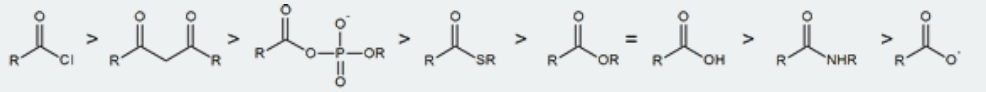
After completing this section, you should be able to

1. compare the reactions of carboxylic acid derivatives with nucleophiles to the reactions of aldehydes and ketones with nucleophiles.
2. arrange a given list of carboxylic acid derivatives in order of increasing or decreasing reactivity towards nucleophiles.
3. explain the difference in reactivity towards nucleophiles of two or more given carboxylic acid derivatives.
4. explain why esters and amides are commonly found in nature, but acid halides and acid anhydrides are not.

STUDY NOTES

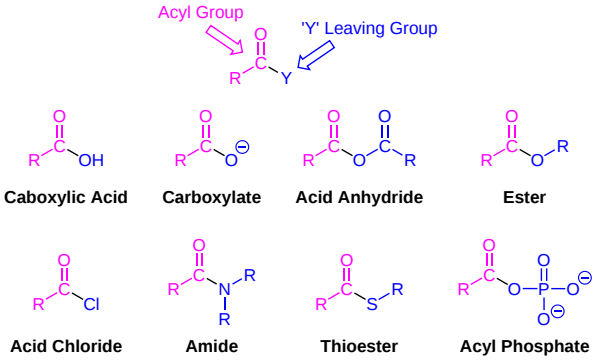
The general nucleophilic acyl substitution reaction, and its mechanism, were discussed earlier in "III. General Reactions of Carbonyl Compounds." Review if necessary.

The reading describes the relative reactivities of "biologically relevant acyl groups." Both acid anhydrides and acid halides readily react with water and cannot exist for any length of time in living organisms. The following scheme illustrates the relative reactivities of most carboxylic acid derivatives that you will encounter.



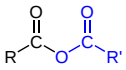
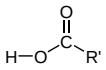
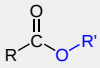
CARBOXYLIC ACID DERIVATIVES AND ACYL GROUPS

Carboxylic acid derivatives can be distinguished from aldehydes and ketones by the presence of a group containing an electronegative heteroatom - usually oxygen, nitrogen, sulfur or phosphorus – bonded directly to the carbonyl carbon and represented by the symbol **Y**. The rest of the carboxylic acid derivative is called the **acyl group** which is made up of the carbonyl group and the attached alkyl group (R). Being electronegative, the Y group has the potential of receiving electrons from the alkoxide intermediate created during a nucleophilic acyl substitution and acting as a leaving group. Elimination of a leaving group allows for carbonyl bond reformation and C-Y bond cleavage to complete a substitution reaction.



The stability of a negative charge on a Y group can be gauged by the pK_a of its corresponding conjugate acid (HY). A low conjugate acid pK_a implies that the Y leaving group is a weak base with a stable negative charge and thus would make an efficient leaving group. Likewise, a high conjugate acid pK_a means the Y group would likely make a poor leaving group. As shown in the table below, the conjugate acids of the possible carbide ($R:^-$) and hydride ($H:^-$) leaving groups of aldehydes and ketones have a relatively high pK_a, while those of the Y leaving groups of carboxylic acid derivatives are much lower. In fact, the stability of the leaving groups is an important factor in determining the reactivity of different carboxylic acid derivatives toward nucleophilic acyl substitutions. Based on the pK_a data we can deduce that amides will most likely be the least reactive of the carboxylic acid derivatives.

Carbonyl Compounds and their Leaving Groups

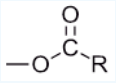
Name	Carbonyl Compound	Leaving Group	Conjugate Acid of the Leaving Group	pK_a
Acid Chloride		Cl^-	H-Cl	-7
Acid Anhydride				3-5
Ester		$^-OR'$	H-OR'	15-16
Carboxylic Acid		^-OH	H-OH	15.7
Amide		$^-NH_2$	$H-NH_2$	36
Ketone		$^-R'$	H-R'	50
Aldehyde		^-H	H-H	Very Large

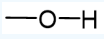
EXAMPLE 21.2.1

What is the 'Y' group in:

a. an acid anhydride?
b. a carboxylic acid?

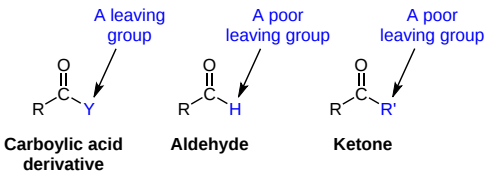
Answers

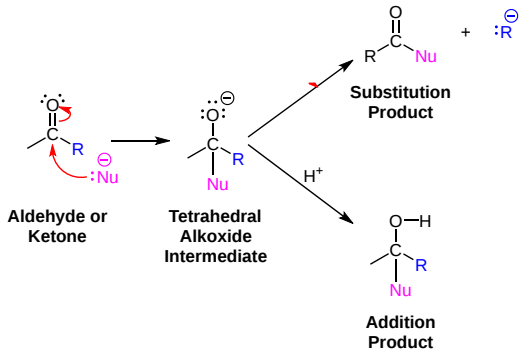
a. 

b. 

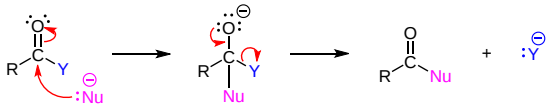
THE MECHANISM OF NUCLEOPHILIC ACYL SUBSTITUTION

Aldehydes and ketones, along with carboxylic acid derivatives all have the C=O carbonyl bond in common. Thus, the electrophilic character of the carbonyl carbon plays an important part in the reactivity of all of these compounds. Because the carbonyl carbon of aldehydes and ketones do not contain suitable leaving groups, their primary reaction is fundamentally different than carboxylic acid derivatives. Remember that aldehydes and ketones tend to undergo nucleophilic addition to form a tetrahedral alkoxide intermediate. Once formed, the negative charge of the alkoxide intermediate cannot be transferred to other substituents because the potential carbide ($R:^-$) and hydride ($H:^-$) leaving groups are too unstable. Instead the negative charge is held by the alkoxide until protonation converts it into an alcohol.

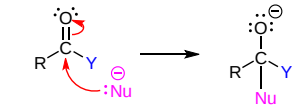




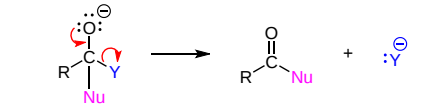
Carboxylic acid derivatives tend to undergo a reaction called nucleophilic acyl substitution. In the same fashion as nucleophilic addition, this mechanism starts with a nucleophilic attack on an electrophilic carbonyl carbon, forming a tetrahedral alkoxide intermediate. The alkoxide negative charge can gain stability by being transferred to the Y leaving group. Elimination of the Y leaving group in the second mechanistic step, allows the C=O carbonyl bond to reform thus creating a new acyl compound. The reaction is considered a substitution due to the Y group of the carboxylic acid derivative being exchanged with an incoming nucleophile.



1) NUCLEOPHILIC ADDITION



2) LEAVING GROUP REMOVAL

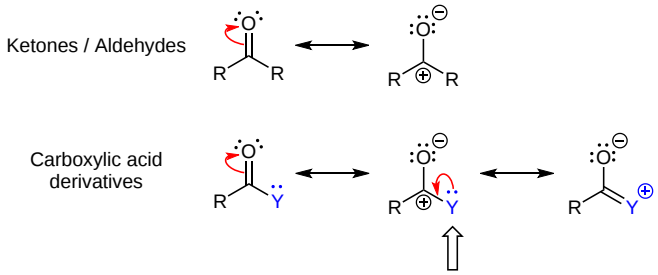


THE RELATIVE REACTIVITY OF CARBOXYLIC ACID DERIVATIVES

The relative reactivity of carboxylic acid derivatives is an important concept for entering into a detailed examination of nucleophilic acyl substitutions. There are two main concepts directly relating to the mechanism which when combined lead to an overall explanation of the differences in reactivity: the stability of the carbonyl and the effectiveness of the Y leaving group.

CARBONYL STABILITY

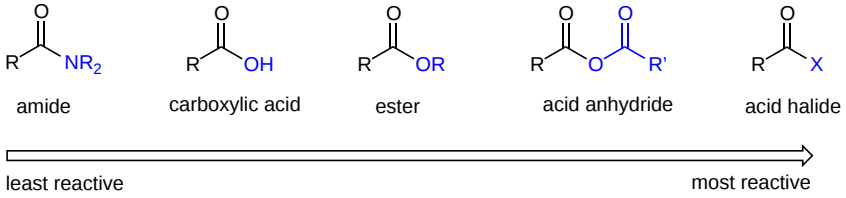
The rate of the first mechanistic step is mainly affected by the stability of the carbonyl moiety. Stabilization reduces the electrophilic character of the carbonyl carbon by reducing its partial positive charge which in turn reduces the rate of this step of the mechanism. The ability of substituents attached to the carbonyl carbon to donate or withdraw electron density is the primary factor determining carbonyl stabilization. As previously discussed, the presence of two electron donating alkyl substituents reduces the partial positive charge on the carbonyl carbon of ketones making them less reactive to nucleophilic attack than aldehydes. The Y group heteroatom's ability to stabilize a carbonyl by donating electrons through resonance makes most carboxylic acid derivatives even less reactive. Overall, delocalization of the carbonyl carbon's partial positive charge onto the adjacent Y group heteroatom reduces the electrophilic character of the carbonyl. The electronegativity of the Y group heteroatom generally determines extent of this stabilization. The less electronegative the Y group heteroatom the better it is able to stabilize the resonance structure with the delocalized positive charge reducing the carbonyl's electrophilicity.



LEAVING GROUP ABILITY

The leaving group ability of the Y group is the most important factor in determining the rate of the second mechanistic step of nucleophilic acyl substitution. As discussed above, the effectiveness of a leaving group is related to its ability to stabilize a negative charge particularly through having a relatively high electronegativity or having the ability to delocalize the negative charge through resonance. The Y group structural features which allow for the stabilization of a negative charge also allow for the stabilization of the transition state of the second step of the mechanism. Overall, the better the leaving group ability of the Y group, the higher the rate of second step of the mechanism.

These two effects, carbonyl stability and leaving group ability, when combined predict the relative reactivity of carboxylic acid derivatives. Fortunately, the effects tend to work synergistically. Y groups that are effective leaving groups also tend to poorly stabilize carbonyls through resonance making reaction rates of nucleophilic acyl substitution higher. Likewise, poor leaving groups tend to effectively stabilize carbonyls through resonance and reduce reaction rates. In fact, depending on the carbonyl structure, either step one or step two of the mechanism can be the rate determining step. For Y groups with a poor leaving group ability, the second step of the mechanism is rate determining because of the weakly stabilized transition state. The first step of the mechanism is rate determining for Y groups with good leaving group ability because they tend to stabilize the starting material's carbonyl increasing the energy distance to the first transition state.

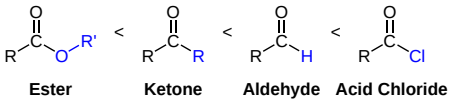


How the two effects actually combine to produce the overall reactivity for each carboxylic acid derivative is slightly different. As comparison of one of the more reactive carboxylic acid derivatives, acid chlorides, and one of the least reactive, amides, will be used as a discussion.

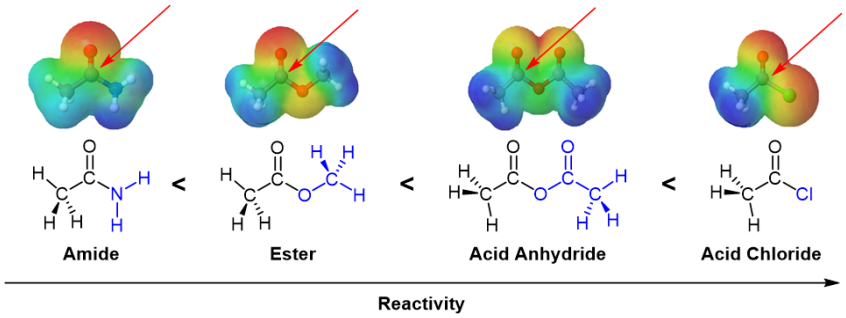
In amides, the nitrogen atom is a powerful electron donating group by resonance. Nitrogen is less electronegative than oxygen and can therefore better stabilize the resonance structure of the delocalized positive charge than most other acid derivatives. This lowers the energy of the starting material which increases the overall energy barrier. Likewise, $-NH_2$ is a relatively poor leaving group (since it is the conjugate base of a very weak acid RNH_2) which increases the transition state energy of the second step of the mechanism also increasing the overall energy barrier. The two effects combine to increase the overall energy barrier which must be overcome during the reaction, causing reaction rates to decrease and making amides very unreactive toward nucleophilic acyl substitution.

In acid chlorides the -Cl is a very effective leaving group making the energy barrier of the second step relatively small. However, this does not have a significant effect since the first step of the mechanism is rate determining. The resonance stabilization offered by the chlorine atom is ineffective due to the poor overlap between the chlorine 3p orbital and the carbon 2p orbital. The poor overlap means that acid chlorides are much less stabilized by resonance than amides. In addition, since chlorine is more electronegative than nitrogen was in the amide example, the inductive electron-withdrawing effects of chlorine become important. This destabilizes the carbonyl and increases the electrophilic character of the carbonyl carbon. The energy barrier of the first step of the mechanism is small due to the lack of stabilization in the acid chloride starting material. Therefore the overall rate of reaction for acid chlorides is high making them very reactive towards nucleophilic acyl substitutions.

As a general rule, stabilizing effects from the Y heteroatom tends to make carboxylic acid derivatives less reactive toward the initial nucleophilic attack than aldehydes and ketone. One notable exception is acid chlorides, where the destabilizing inductive electron-withdrawing properties of the chlorine outweigh the resonance stabilizing effects making them more reactive towards nucleophilic attack. This point will become important later in the chapter where it will be used to explain the outcome of certain reactions.

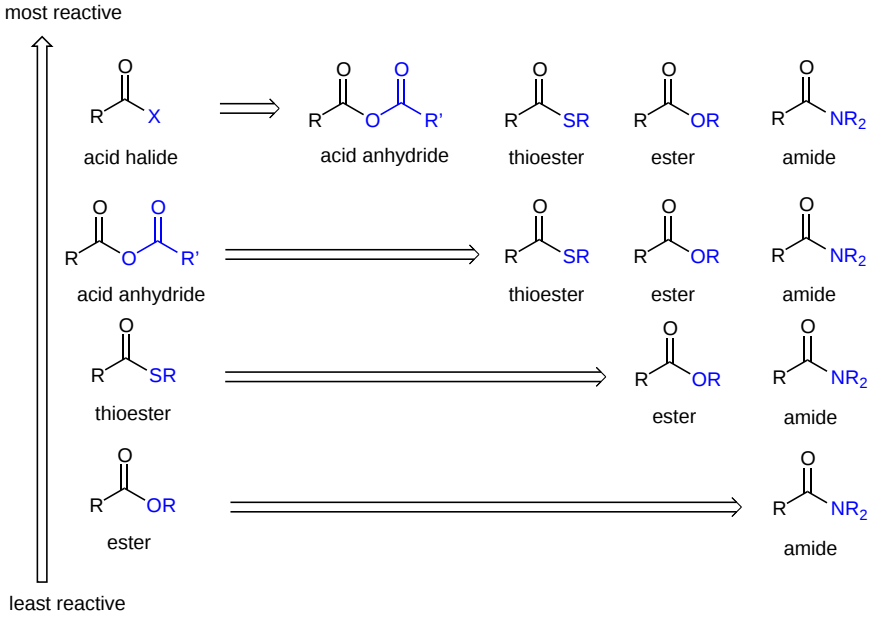


The reactivity of a carboxylic acid derivative can be visualized by using an electrostatic potential map to look at the electron density around the carbonyl carbon. A blue/green color represents the amount of positive charge present. The carbonyl carbons of the amide and ester have a relatively small amount of positive charge making them among the least reactive toward nucleophilic attack. The acid chloride's and anhydride's carbonyl carbon has more of a blue/color color indicating a higher positive charge and making them more reactive than the amide and ester.



ACID DERIVATIVE INTERCONVERSION

From this understanding of reactivity, multiple step synthesis strategies can be developed. Typically more reactive carboxylic acid derivatives can be used to synthesize less reactive derivatives as illustrated in the diagram below. As will be shown later in this chapter, highly reactive acid chlorides, when combined with the appropriate nucleophile, can be directly converting into acid anhydrides, thioester, esters, and amides. However, the less reactive amides cannot be directly converted into ester, thioester, anhydrides, or acid chlorides. It is possible to make these conversions with an amide but multiple reaction steps are required.



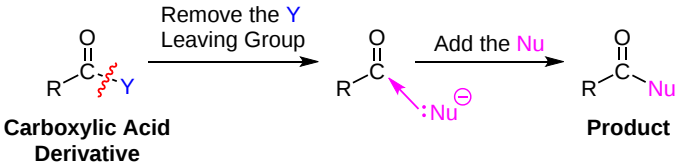
The nucleophiles required to make the conversion from one carboxylic acid derivative to another are common and have been discussed multiple times in this text. Because the same nucleophile is typically used to convert to a specific carboxylic acid derivative conversion, the reactions are given generic names.

- **Hydrolysis:** A reaction with water as a nucleophile to create a carboxylic acid.
- **Alcoholysis:** A reaction with an alcohol nucleophile to create an ester.
- **Aminolysis:** A reaction with ammonia or an amine nucleophile to create an amide.
- **Reduction:** A reaction with a hydride nucleophile to create an aldehyde or 1° alcohol.
- **Organometallic:** A reaction with a carbanion nucleophile from an organometallic reagent to create a ketone or a 3° alcohol.

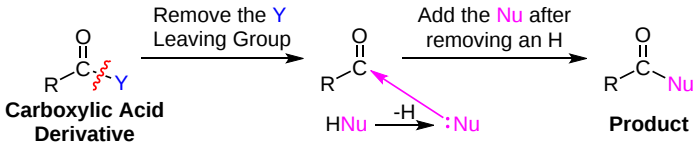
PREDICTING THE PRODUCT OF A NUCLEOPHILIC ACYL SUBSTITUTION REACTION

There are two major pieces of a nucleophilic acyl substitution reaction which need to be identified in order to predict the product: the leaving group of the carboxylic acid derivative (Y) and the nucleophile. It is important to identify if the nucleophile is neutral (i.e. water, alcohols, ammonia, amines) or negatively charged (i.e. hydroxide, alkoxides, hydrides, carbanions). Also, it is important to note that certain hydride and organometallic reagents are capable of a double addition to carboxylic acid derivatives where the first step is a nucleophilic acyl substitution and the second is a nucleophilic addition.

Negatively Charged Nucleophiles



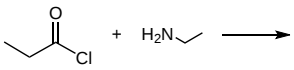
Neutral Nucleophiles



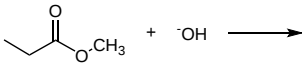
WORKED EXAMPLE

Draw the expected products of the following reactions:

a)

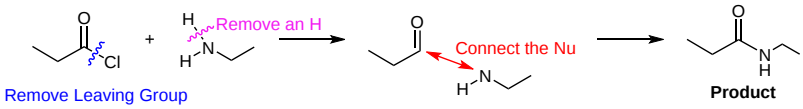


b)

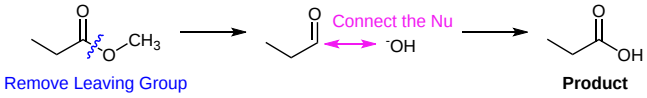


SOLUTIONS

a) The nucleophile is neutral.



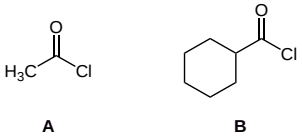
b) The nucleophile is negatively charged.



EXAMPLES

1) Which of the following compounds would be expected to be the most reactive towards nucleophilic acyl substitution? Briefly explain your answer.

a)

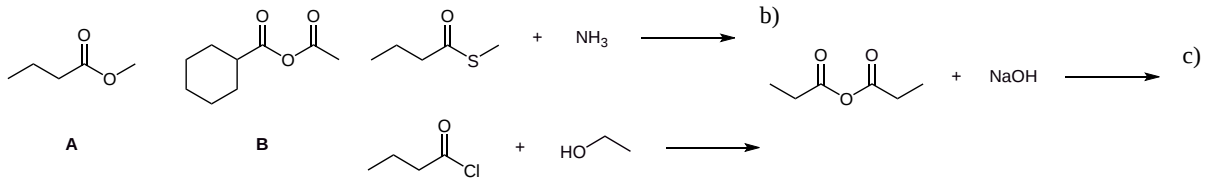


A **B**

b)

2) Draw the expected products of the following reactions:

a)



SOLUTIONS

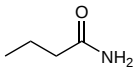
1)

a) Compound A would expected to be the more reactive. For two compounds with the same carboxylic acid derivative group the one with the least steric crowding on the acyl side is typically the most reactive.

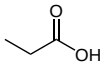
b) Compound B would be expected to be the more reactive. In general acid anhydrides are more reactive than ester.

2)

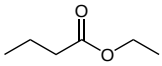
a)



b)



c)



21.3: NUCLEOPHILIC ACYL SUBSTITUTION REACTIONS OF CARBOXYLIC ACIDS

OBJECTIVES

After completing this section, you should be able to

1. write an equation to describe the formation of
   a. an acid chloride from a carboxylic acid.
   b. an ester from a carboxylic acid.
   c. an amide from a carboxylic acid.
   d. an alcohol from carboxylic acid.
2. write an equation to represent the formation of a cyclic anhydride from a dicarboxylic acid.
3. write the detailed mechanism for the reaction of a carboxylic acid with thionyl chloride.
4. identify the reagents necessary to convert a given carboxylic acid to a given acid chloride, ester, amide or alcohol.
5. identify the carboxylic acid required for a direct synthesis of a given acid chloride, amide, ester or alcohol.
6. write an equation to describe the formation of an ester through the nucleophilic attack of a carboxylate anion on an alkyl halide.
7. write a detailed mechanism for the Fischer esterification reaction.
8. describe the evidence from isotopic labelling experiments that is commonly cited to support the generally accepted mechanism of the Fischer esterification reaction.
9. explain why the direct conversion of a carboxylic acid to an amide can only be achieved with difficulty and at a high temperature.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- Fischer esterfication reaction

STUDY NOTES

If necessary, review the S_N2 reaction between a carboxylate anion and a primary alkyl halide (Sections 11.2 and 11.3).

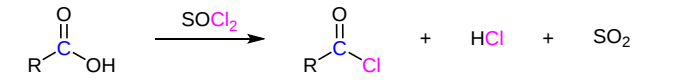
You should recall that the oxygen-18 isotope, ^{18}O, has a nucleus containing eight protons and ten neutrons. Because it is non-radioactive, ^{18}O can be safely employed in the investigation of reaction mechanisms.

The poor leaving group ability of -OH makes carboxylic acids relatively unreactive towards nucleophilic acyl substitutions. The addition of a strong acid protonates the carbonyl oxygen making the carbonyl carbon more electrophilic and circumventing this problem. Also, the substitution reaction can be promoted by converting -OH into a better leaving group. Despite the lack of reactivity, under the right conditions carboxylic acids can be successfully converted into acid chlorides, acid anhydrides, esters, and amides through nucleophilic acyl substitution.

CONVERSION OF CARBOXYLIC ACIDS TO ACID CHLORIDES

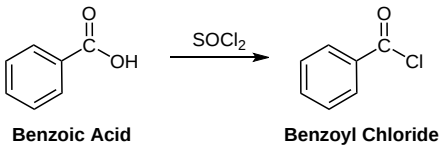
Carboxylic acids can be converted to acid chlorides by reaction with thionyl chloride ($SOCl_2$). During the reaction with thionyl chloride, the hydroxyl group of the carboxylic acid is converted to an acyl chlorosulfite moiety which is a better leaving group. During the reaction a nucleophilic chloride anion is produced which reacts with the acyl chlorosulfite intermediate through nucleophilic acyl substitution to produce an acid halide.

GENERAL REACTION



Carboylic Acid **Acid Chloride** **Sulfurdioxide**

EXAMPLE

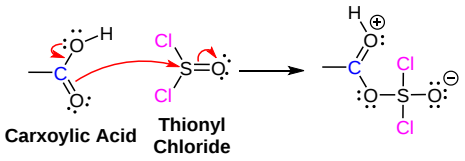


Benzoic Acid **Benzoyl Chloride**

MECHANISM

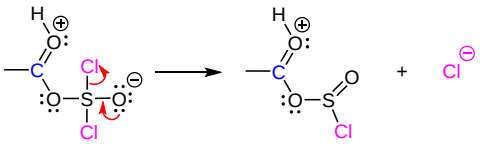
The O=S-Cl bonds of thionyl chloride are analogous to the O=C-Cl bonds of an acid halide in that they can undergo a type of nuleophilicy acyl substitution. During the first step of the mechanism, the carboxylic acid reactant acts as a nucleophile and attacks the electrophilic sulfur of thionyl chloride, pushing the pi electrons of the S=O bond onto oxygen. Reforming the S=O bond and eliminating a cloride anion (Cl^-) as a leaving group creates a protonated acyl chlorosulfite. The chlorosulfite group represents an excellent leaving group due to its ability to stabilize a negative charge. The carbonyl of the protonated acyl chlorosulfite intermediate is activated to nucleophilic attack, and promptly reacts with the nucleophilic chloride anion created during the second step of the mechanism to produce a tetrahedral alkoide intermediate. Subsequent reforming of the protonated carbonyl bond eliminates the chlorosulfite group as sulfurdioxide (SO_2) and a chloride anion. Lastly, the chloride anion deprotonates the carbonyl to form the acid chloride product.

1) Nucleophilic attack on S=O bond



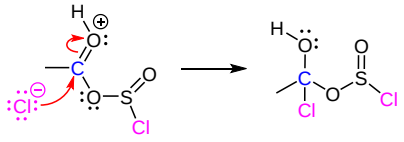
Carxoylic Acid **Thionyl Chloride**

2) Removal of Cl leaving group

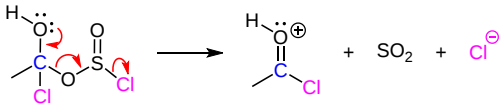


Protonated Acyl Chlorosulfite

3) Nucleophilic attack on the carbonyl

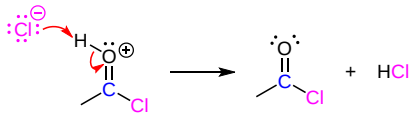


4) Leaving group removal



Protonated Acid Chloride

5) Deprotonation

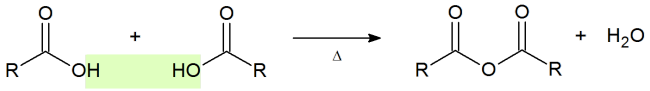


Acid Chloride

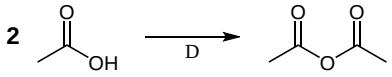
ACID ANHYDRIDE FORMATION

An acid anhydride (or just anhydride) is the product of condensation of two carboxylic acid molecules with the release of a water molecule. The most common anhydride in organic chemistry is acetic anhydride, due to the high temperatures needed to remove water.

GENERAL REACTION



EXAMPLE

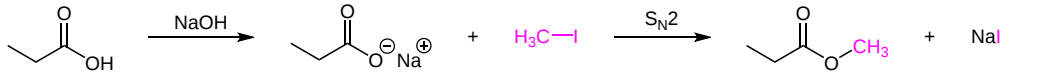


Acetic Acid **Acetic Anhydride**

CONVERSION OF CARBOXYLIC ACIDS INTO ESTERS BY ALKYLATION

Carboxylic acids can be easily converted into their conjugate bases through deprotonation with a base, such as sodium hydroxide. The resulting carboxylate can be alkylated using by an S_N2 reaction with either a methyl or primary halide. If a methyl ester is required, methyl iodide (CH_3I) is a commonly used reagent.

EXAMPLE



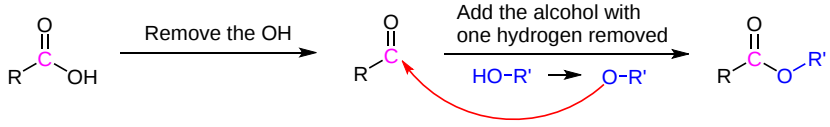
Propanoic Acid **Sodium Propanoate** **Methyl Iodide** **Methyl Propanoate** **Sodium Iodide**

CONVERSION OF CARBOXYLIC ACIDS TO ESTERS: THE FISCHER ESTERIFICATION

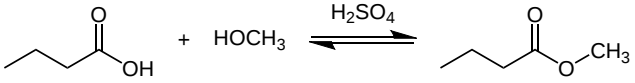
Alcohols can be used as nucleophiles to convert carboxylic acids to esters. Due to the poor leaving group ability of -OH in carboxylic acids, an acid catalyst is required to speed up the reaction. Usually the alcohol starting material is used as the reaction solvent so that it can be present in a large excess. This helps to increase the reaction's yield by pushing reaction equilibrium to the right which can be understood via Le Chatelier's principle.

GENERAL REACTION

PREDICTING THE PRODUCTS OF A FISCHER ESTERIFICATION



EXAMPLE

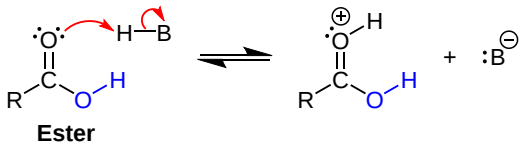


Butanoic Acid **Methyl Butanoate**

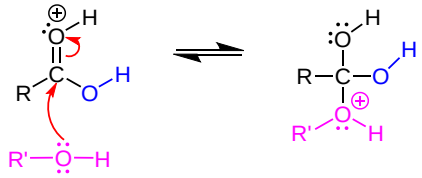
MECHANISM

The mechanism begins with protonation of the carbonyl to increase its electrophilic character. A tetrahedral alkoxide intermediate is formed when the alcohol nucleophile adds to the protonated carbonyl, pushing the carbonyl pi electrons onto the oxygen. A different tetrahedral alkoxide intermediate is created when a proton is then transferred to one of the hydroxides (OH), turning it into a good leaving group. Reforming the protonated carbonyl bond then eliminates water as a leaving group. Finally, deprotonation of the carbonyl by water creates the ester product and regenerates the acid catalyst. All the steps of the mechanism are reversible

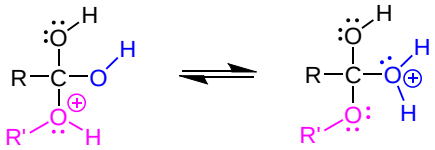
1) Protonation of the carbonyl



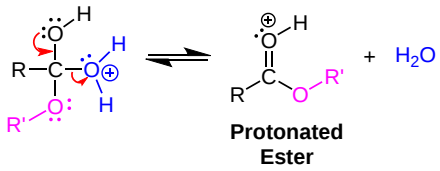
2) Nucleophilic attack on the carbonyl



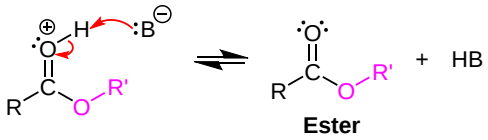
3) Proton transfer



4) Removal of water as a leaving group

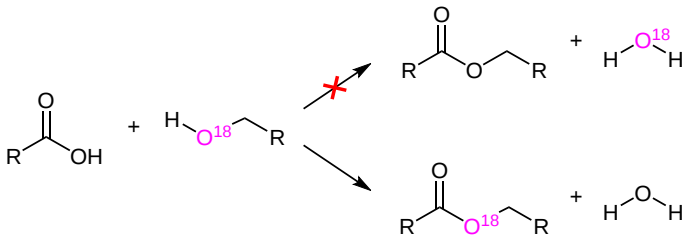


5) Deprotonation



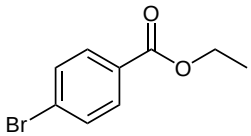
ISOTOPIC LABELING

Evidence to support the Fischer esterification mechanism comes from isotopic labeling experiments with oxygen-18. If the reaction is carried out with an oxygen-18 labeled alcohol, the isotope is found exclusively in the ester and not the water generated. This shows that the C-OH bond of the carboxylic acid and the H-OR bond of the alcohol that is broken during the reaction.

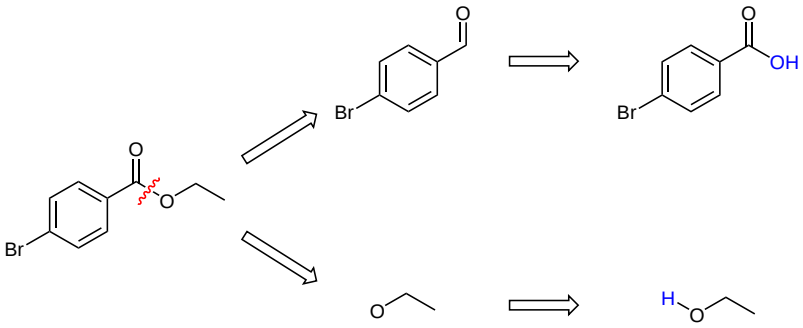


WORKED EXAMPLE: PLANNING A SYNTHESIS USING A FISCHER ESTERIFICATION

HOW COULD THE FOLLOWING MOLECULE BE MADE USING A FISCHER ESTERIFICATION?

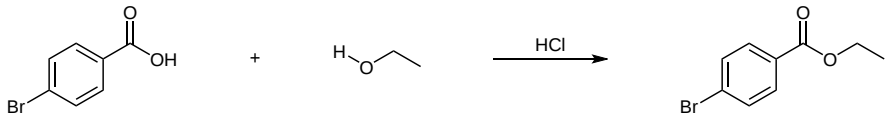


ANALYSIS



The key bond formed during a Fischer Esterification is the C-O sigma bond. The target molecule can be separated into the two required starting materials by breaking this bond. The carbonyl carbon fragment gains an –OH to become a carboxylic acid and the oxygen fragment gains an H to become an alcohol. The carboxylic acid and the alcohol are reacted using a strong acid catalyst.

SOLUTION



***p*-Bromo Benzoic Acid** **Ethanol** **Ethyl *p*-Bromo Benzoate**

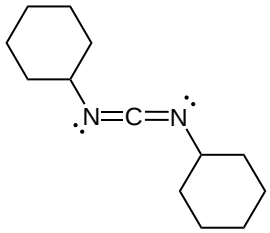
DIRECT CONVERSION OF CARBOXYLIC ACIDS TO AMIDES

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 stable carboxylate salt. However when the ammonium carboxylate salt is heated to a temperature above 100 ^{o}C, water is driven off and an amide is formed. Due to the extreme conditions, this reaction is rarely used. When converting to an amide it is preferred to convert the carboxylic acid to a more reactive form such as an acid chloride first and then convert this molecule to an amide.

GENERAL REACTION

CONVERSION OF CARBOXYLIC ACIDS TO AMIDES USING DCC

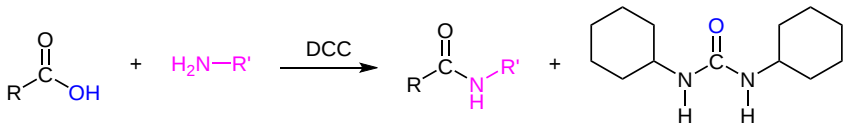
The formation of amides from carboxylic acids and amines is a reaction of great importance in biochemistry. Proteins are formed through the creating of amide bonds between amino acid residues, so a great deal of research has been performed to find efficient methods. The direct conversion of a carboxylic acids to amides is difficult because amines are basic and tend to convert carboxylic acids to their highly unreactive carboxylates. One solution to this problem is through the use of dialkylcarbodiimides (R-N=C=N-R) coupling reagents, such as dicyclohexylcarbodiimide (DCC).



Dicyclohexylcarbodiimide (DCC)

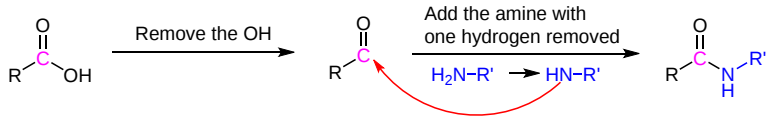
During a DCC amide coupling, the OH of a carboxylic acid is made into a good leaving group which can then be replaced by an amine during nucleophilic acyl substitution. Using DCC as a coupling reagent, 1^{o} and 2^{o} amines can be used to create 2^{o} and 3^{o} amides respectfully.

BASIC REACTION

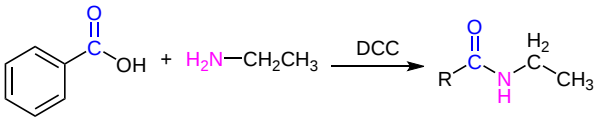


Carboxylic Acid **Amine** **Amide** **N,N'-Dicyclohexylurea**

PREDICTING THE PRODUCTS OF DCC COUPLING



EXAMPLE

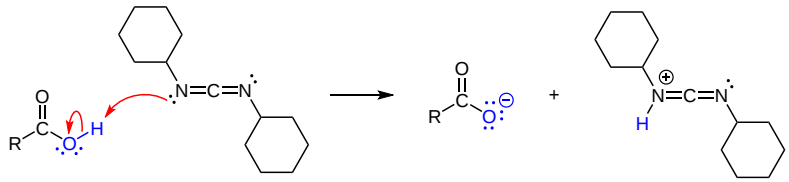


Benzoic Acid **Ethyl Amine** **N-Ethylbenzamide**

MECHANISM

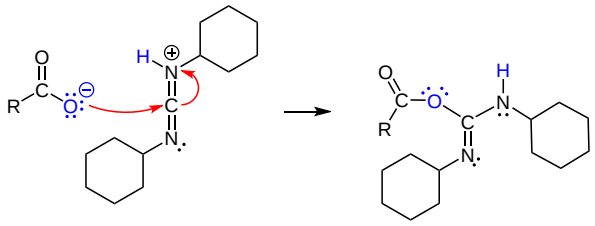
DCC deprotonates the carboxylic acid to form a carboxylate, which is a better nucleophile. The corresponding protonation of DCC increases the electrophilic character of its C=N imide bond. The caboxylate nucleophile then adds to the imide bond and pushes the C=N pi electrons onto the nitrogen. The amine nucleophile can now add itself to the carbonyl bond as part of a nuleophilic acyl substitution. The DCC coupled oxygen is eliminated as dicyclohexylurea, a good leaving group, to create the amide product.

1) Deprotonation

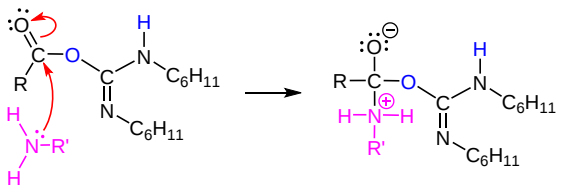


Carboxylic Acid **DCC** **Carboxylate** **Protonated DCC**

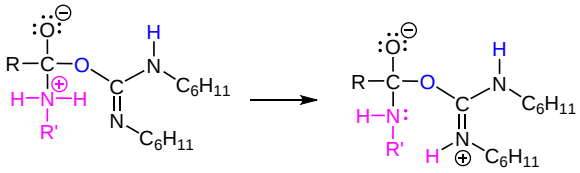
2) Nucleophilic attack by the carboxylate



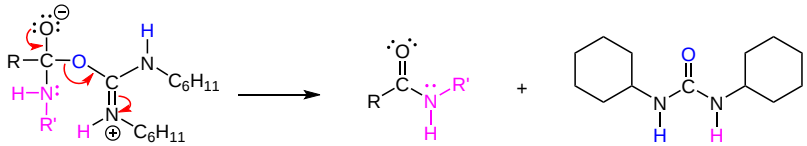
3) Nucleophilic attack by the amine



4) Proton transfer



5) Leaving group removal

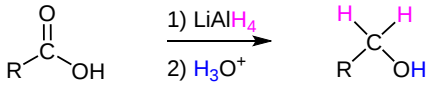


CONVERSION OF CARBOXYLIC ACIDS TO 1^{O} ALCOHOLS

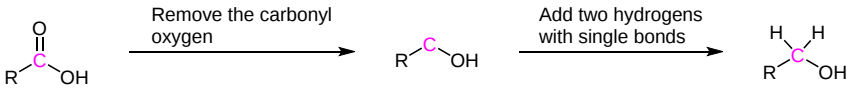
LITHIUM ALUMINUM HYDRIDE ($LiALH_4$)

Hydride nucleophiles from lithium aluminum hydride ($LiAlH_4$) can reduce carboxylic acids to 1^{o} alcohols. Note that $NaBH_4$ is not a strong enough reducing agent to convert carboxylic acids or esters to alcohols. Because the incoming nucleophile is an "H" the reaction first produces an aldehyde intermediate which available for further hydride additions. The aldehyde intermediate is difficult to isolate because it is more reactive than the original carboxylic acid. This reaction represents the first example in this chapter where a carboxylic acid derivative can undergo a double nucleophilic addition. In the mechanism of this reaction, a nucleophilic acyl substitution is followed by a nucleophilic addition allowing for two hydride nucleophiles being added to the electrophilic carbonyl carbon of a carboxylic acid.

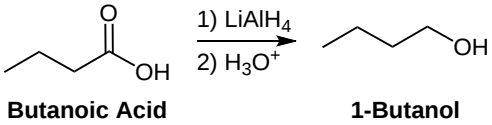
GENERAL REACTION



PREDICTING THE PRODUCT OF A HYDRIDE REDUCTION



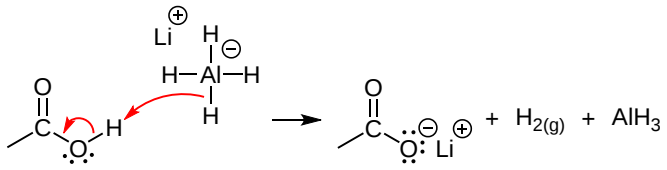
EXAMPLE



POSSIBLE MECHANISM

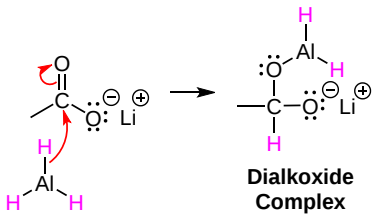
Although the mechanism of this reaction is not precisely known, much of it is understood. Initially, a hydride deprotonates the carboxylic acid to form a lithium carboxylate, hydrogen gas (H_2), and aluminum hydride. Then a hydride nucleophile, from aluminum hydride, adds to the carbonyl carbon as part of a nucleophile acyl substitution. The resulting high-energy dianion intermediate forms a Lewis Acid/Base complex with aluminum, making one of the oxygens a good leaving group (the negative charge on the oxygen complexed to aluminum is not shown in step 2 below). The carbonyl bond is reformed along with the elimination of $OAlH_2$ as a leaving group to form an aldehyde. A hydride nucleophile from another molecule of $LiAlH_4$ adds to the re-formed carbonyl carbon as part of a nucleophilic addition. The resulting alkoxide intermediate is protonated during an acidic work-up to form the 1^{o} alcohol product. Due to the formation of a dianion intermediate the reaction requires relatively high temperature and long reaction times.

1) Deprotonation



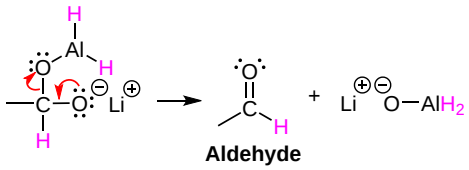
Carboxylic Acid

2) Nucleopilic attack by a hydride anion



Dialkoxide Complex

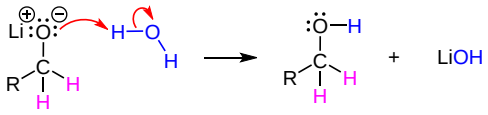
3) Leaving group removal



Aldehyde

4) Nucleopilic attack by a hydride anion

5) Alkoxide protonation

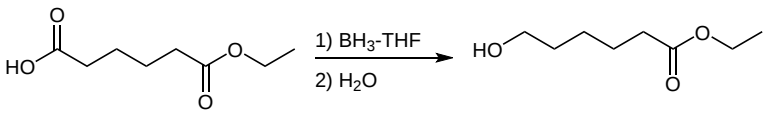


1^o Alcohol

BORANE TETRAHYDROFURAN COMPLEX

Solutions of a borane tetrahydrofuran complex (BH_3-THF) rapidly reduce carboxylic acids at room temperature with often high yields. The borane tetrahydrofuran complex offers a safer and easier alternative to $LiAlH_4$ reductions.

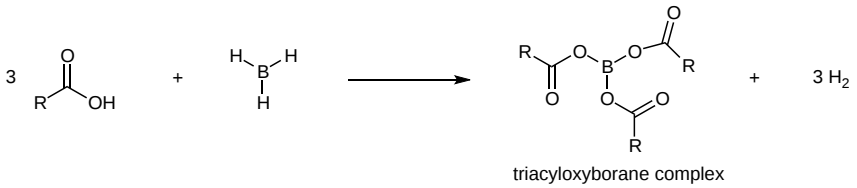
EXAMPLE



Adipic acid monoethyl ester **Ethyl 6-hydroxyhexanoate, (88% Yield)**

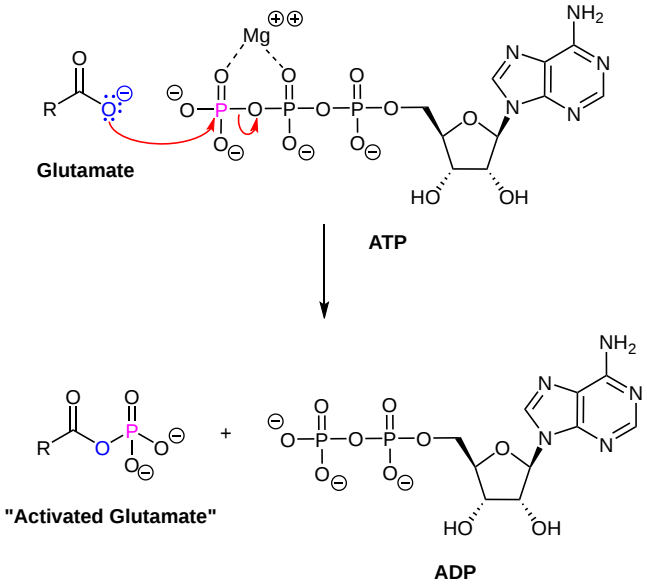
The acidic hydrogen of carboxylic acids allows them react faster with the borane tetrahydrofuran complex faster than any other functional group, allowing them to be selectively reduced in the presence of other carbonyls. In the first step of the reduction mechanism, which is rate

determining, the acidic hydrogens of three carboxylic acids along with the three hydrogens from BH_3 are rapidly removed to form hydrogen gas (H_2) and a triacyloxyborane complex. A subsequent aqueous work-up converts the complex into a primary alcohol as shown in the general reaction above.



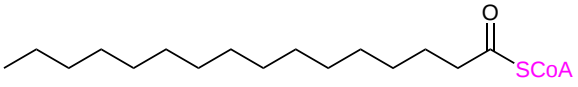
BIOLOGIC CONVERSION OF CARBOXYLIC ACIDS

In biological chemistry direct conversion of a carboxylic acid to an acyl derivative by nucleophilic acyl substitution does not occur. 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: phosphorylation of a carboxylate oxygen with ATP as the phosphate donor.



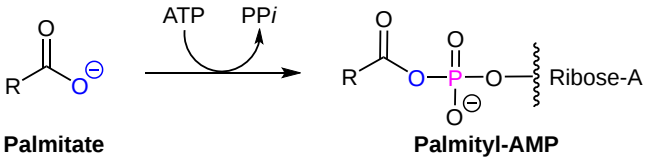
Note that this is just one of the many ways that ATP is used as a energy storage unit: in order to make a high energy acyl phosphate molecule from a low energy carboxylate, the cell must 'spend' the energy of one ATP molecule.

An excellent example of biological activated carboxylic acids is seed in the biosynthesis of fatty acids. In the biologically active form of fatty acids, the carboxylate groups have been converted to thioesters using coenzyme A. For example, the activated form of the C_{16} fatty acid palmitate is:

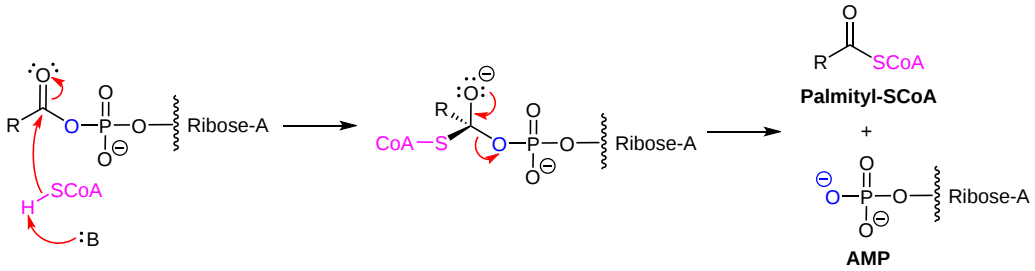


Palmityl-SCoA

Let's take a look at how this activation takes place, in a reaction catalyzed by an enzyme called acyl CoA synthetase. You already know that carboxylates are not themselves good substrates for acyl substitution reactions, and must be activated. Thus, you might predict that the first step of this reaction requires ATP to make a high-energy acyl phosphate intermediate. In fact, the activated carboxylate in this case is an acyl-AMP, formed in the same way as the acyl-AMP intermediate in the asparagine synthetase reaction (section 12.2B).



The activated acyl-AMP intermediate is then attacked by the thiol sulfur of coenzyme A, and the AMP group is expelled to form the fatty acyl CoA.



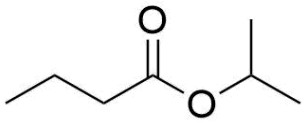
EXERCISES

Q21.3.1

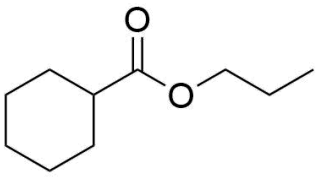
How would you create the following esters from the corresponding acids?

(a)

(b)

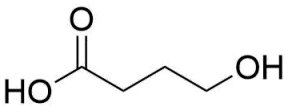


(c)



Q21.3.2

The following molecule is treated with acid and undergoes an intramolecular Fischer Esterification. Draw the product.

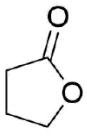


SOLUTIONS

S21.3.1

a. Acetic acid + ethanol
b. Butanoic acid + isopropanol
c. Cyclohexanecarboxylic acid + propanol

S21.3.2



21.4: CHEMISTRY OF ACID HALIDES

OBJECTIVES

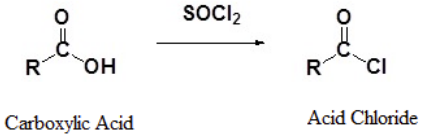
After completing this section, you should be able to

1. identify the reagent normally used to convert a carboxylic acid to an acid bromide.
2. write equations to show how an acid halide may be converted into each of the following: a carboxylic acid, an ester, an amide.
3. write a detailed mechanisms for the reaction of an acid halide with each of the following: water, an alcohol, ammonia, a primary or secondary amine.
4. identify the product formed when a given acid halide reacts with any of the following reagents: water, an alcohol, a primary or secondary amine.
5. identify the acid halide, the reagents, or both, needed to prepare a given carboxylic acid, ester or amide.
6. identify the product formed when a given acid halide reacts with water, a given alcohol, ammonia, or a given primary or secondary amine.
7. identify lithium aluminum hydride as a reagent for reducing acid halides to primary alcohols, and explain the limited practical value of this reaction.
8. identify the partial reduction of an acid halide using lithium tri-*tert*-butoxyaluminum to form an aldehyde.
9. write an equation to describe the formation of a tertiary alcohol by the reaction of an acid halide with a Grignard reagent.
10. write a detailed mechanism for the reaction of an acid halide with a Grignard reagent.
11. identify the product formed from the reaction of a given acid halide with a given Grignard reagent.
12. identify the acid halide, the Grignard reagent, or both, needed to prepare a given tertiary alcohol.
13. write an equation to illustrate the reaction of an acid halide with a lithium diorganocopper reagent.
14. identify the product formed from the reaction of a given acid halide with a given lithium diorganocopper reagent.
15. identify the acid halide, the lithium diorganocopper reagent, or both, that must be used to prepare a given ketone.

Acid halides are highly reactive carboxylic acid derivatives. As such they are able to be used to synthesize many other carboxylic acid derivatives.

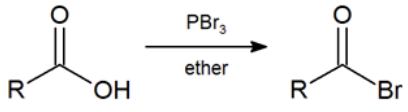
FORMATION OF ACID HALIDES

Carboxylic acids react with thionyl chloride ($SOCl_2$) to form acid chlorides. A nucleophilic acyl substitution allows for the replacement of the carboxylic acid –OH with a chloride atom.



Carboxylic Acid Acid Chloride

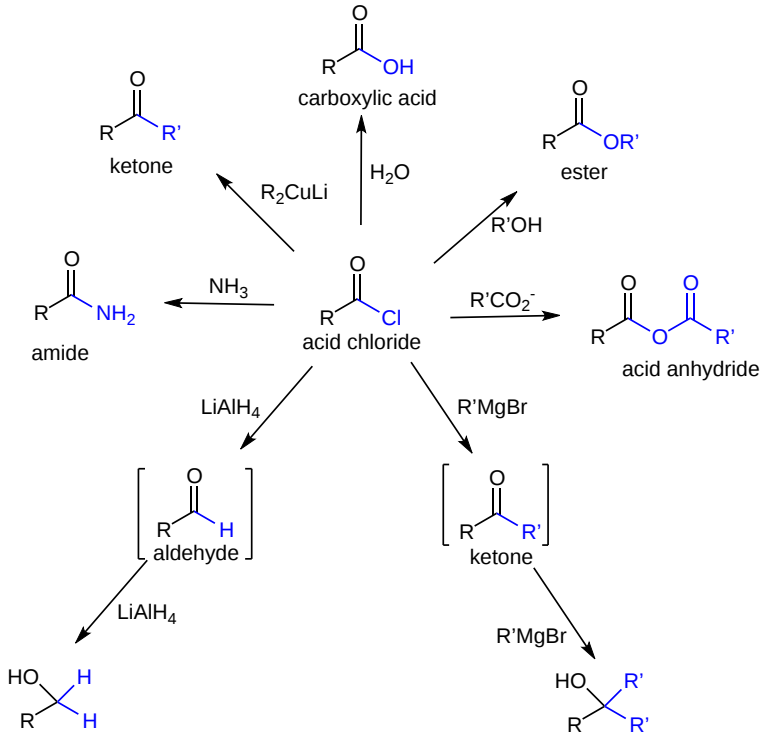
Earlier (Section 10.5), we saw that primary and secondary alcohols react with phosphorous tribromide (PBr_3) to afford the corresponding alkyl bromide. In a similar fashion, acid bromides can be formed from the corresponding carboxylic acid by reaction with PBr_3.



Carboxylic Acid Acid Bromide

REACTIONS OF ACID HALIDES

The high reactivity of acid halides allows them to be easily converted into other acyl compound through nucleophilic acyl substitution. Depending on the nucleophilic reagent applied, acid halides can be used to create carboxylic acids, anhydrides, esters, amides, or ketones. Also, acid halides undergo a double nucleophilic addition with LiAlH4 to produce primary alcohols and Grignard reagents to produce tertiary alcohols. Although this section will only represent reactions with acid chlorides, other acid halides undergo similar reactions.

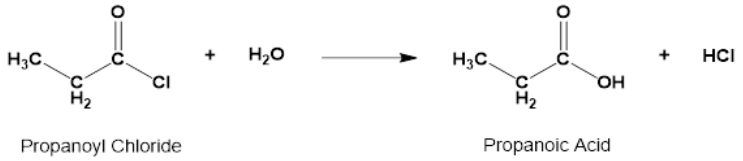


CONVERSION OF ACID CHLORIDES TO CARBOXYLIC ACIDS: HYDROLYSIS

Acid chlorides are converted into carboxylic acids through a nucleophic acyl substitution with water. This reaction follows the typical mechanism where a water nucleophile attacks the electrophilic carbonyl carbon to form a tetrahedral alkoxide intermediate. The carbonyl bond is reformed and Cl- is eliminated as a leaving group. Because water is a neutral nucleophile, an oxonium intermediate in produced. The oxonium intermediate is deprotonated by the chloride anion to produce a neutral carboxylic acid and HCl. The HCl is commonly removed from the reaction mixture by a basic work-up.

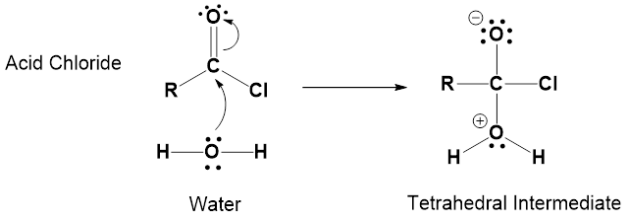
GENERAL REACTION

EXAMPLE

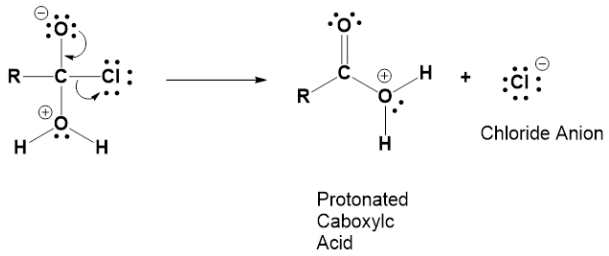


MECHANISM

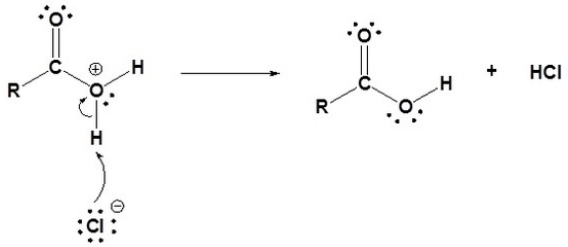
1) Nucleophilic attack by water



2) Leaving group is removed



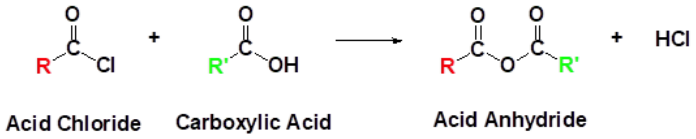
3) Deprotonation



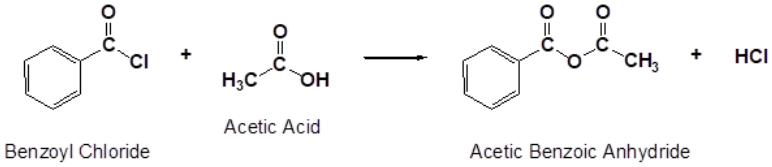
CONVERSION OF ACID CHLORIDES TO ANHYDRIDES

Acid chlorides react with carboxylic acids to form anhydrides through a nucleophilic acyl substitution. Because the carboxylic acid nucleophile is neutral, HCl is produced as a side-product during the reaction and is typically removed as part of a basic work-up. Both symmetrical and asymmetrical anhydrides can be created using this reaction. Carboxylates can also be used to form anhydrides in a similar reaction under basic conditions.

GENERAL REACTION

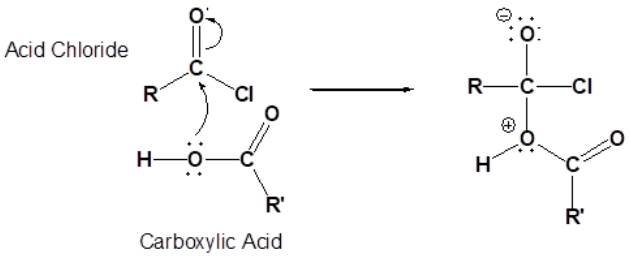


EXAMPLE

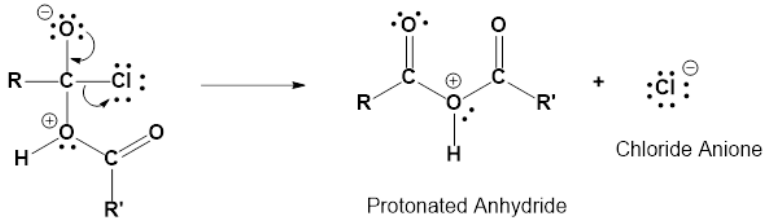


MECHANISM

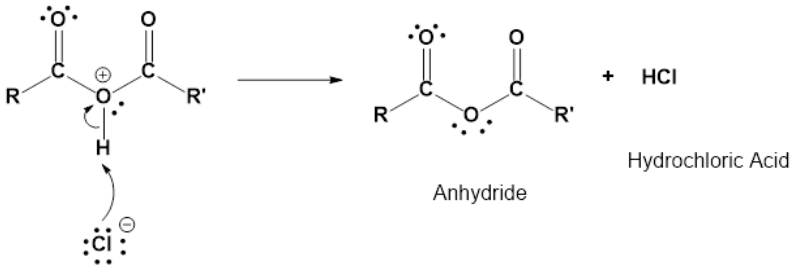
1) Nucleophilic attack by a carboxylic acid



2) Leaving group removal



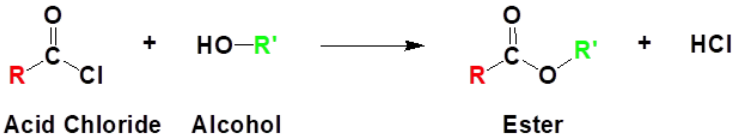
3) Deprotonation



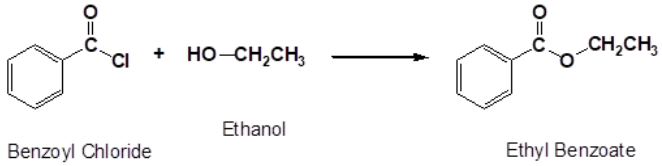
CONVERSION OF ACID CHLORIDES TO ESTERS: ALCOHOLYSIS

Acid chlorides react with alcohol nucleophiles to produce esters. This reaction is the preferred method for preparing esters. Pryidine is often added to the reaction mixture to remove the HCl produced.

GENERAL REACTION

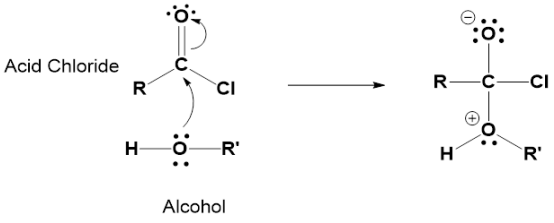


EXAMPLE

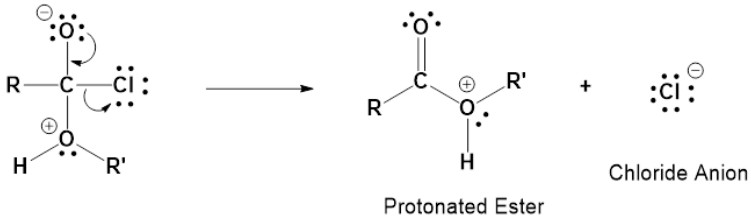


MECHANISM

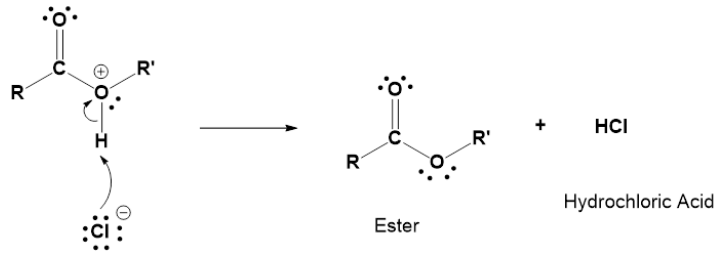
1) Nucleophilic attack by an alcohol



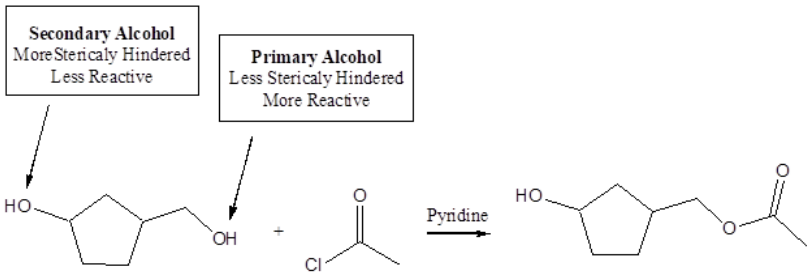
2) Leaving group removal



3) Deprotonation

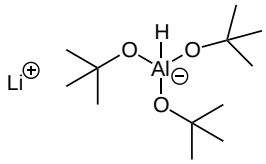


This reaction is particularly affected by steric hindrance so bulky alkyl groups on either the acid chloride or the alcohol significantly decrease the rate. For a given acid chloride there is a reactivity order among alcohols of primary > secondary > tertiary. If a compound has multiple alcohols the less hindered one will be selectively esterified.

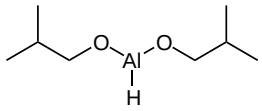


CONVERSION OF ACID CHLORIDES TO ALDEHYDES: REDUCTION

Acid chlorides can be converted to aldehydes using a hindered reducing agent such as lithium tri-tert-butoxyaluminum hydride LiAlH(Ot-Bu)$_3$ or diisobutylaluminum hydride (DIBALH). These hydride sources are weaker reducing agents than lithium aluminum hydride in part because they are sterically hindered. Also, they have only one equivalent of hydride which makes stoichiometric control of hydride addition much easier.



lithium tri-tert-butoxyaluminum hydride

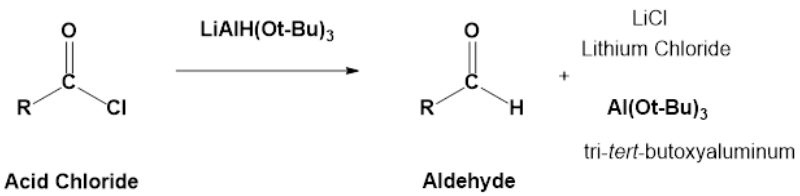


diisobutylaluminum hydride

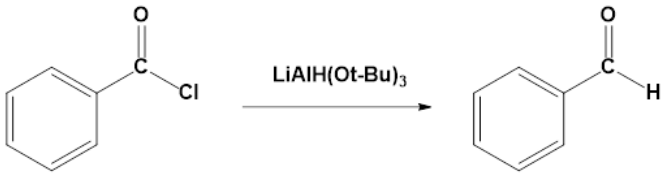
The mechanism of this reaction is analogous to the hydride reduction of carboxylic acids. We have previously seen that $LiAlH_4$ will reduce carboxylic acids to 1^o alcohols thorough an aldehyde intermediate. In that case, the aldehyde intermediate was actually more reactive to hydride reduction than the carboxylic starting material. This prevented the isolation of the aldehyde intermediate because of it quick conversion to the 1^o alcohol. $LiAlH_4$ would also convert acid chlorides to 1^o alcohols but this reaction would be inefficient because it would be easier to perform the reaction on the corresponding carboxylic acid.

Because acid chlorides are highly activated, they will still react with the weaker hydride sources, to form an aldehyde. Once formed, the aldehyde competes with the remaining acid chloride for the remaining hydride reagent. However, acid chlorides are more reactive towards nucleophilic attack than aldehydes. The acid chloride starting material is quickly consumed by hydride reduction before the aldehyde has a chance to react allowing for isolation of the resulting aldehyde. Using a reaction temperature of -78 ^{o}C also helps to isolate the aldehyde as the product by further slowing the aldehyde reduction reaction.

GENERAL REACTION



EXAMPLE



Benzoyl Chloride

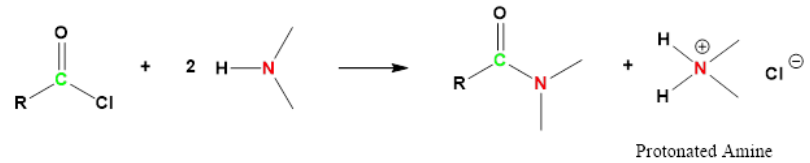
Benzaldehyde

CONVERSION OF ACID CHLORIDES TO AMIDES: AMINOLYSIS

Ammonia, 1º amines, and 2º amines react with acid chlorides to form 1º, 2º, and 3º amides respectively. These reactions typically take place rapidly at room temperature and provides high reaction yields.

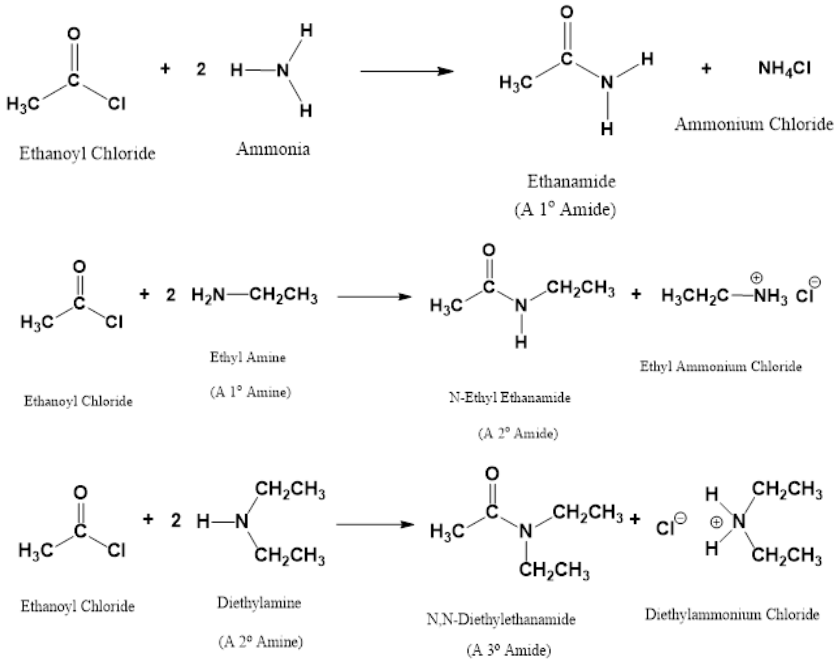
The reaction is commonly run with an excess of the amine starting material. Without the excess the amine reactant would eventually become protonated by the HCl produced by the reaction to form a non-nucleophilic ammonium compound. If the amine is not readily available, the reaction is usually run with a base, such as NaOH or pyridine, to neutralize the HCl produced.

GENERAL REACTION



Acid Chloride **Amine** **Amide** Protonated Amine

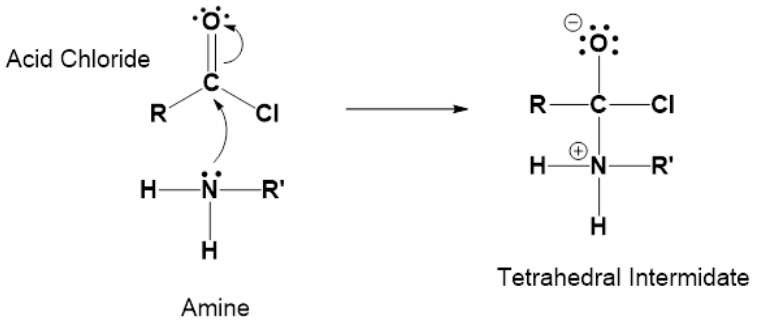
EXAMPLES



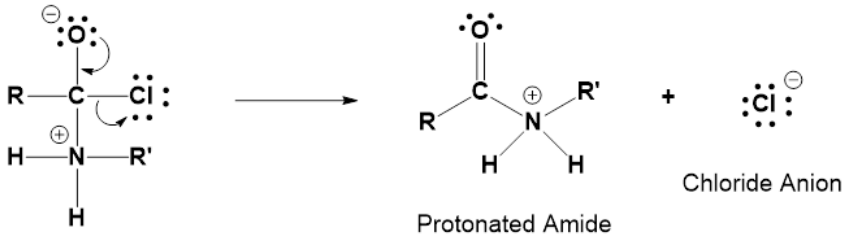
MECHANISM

The mechanism of aminolysis follows a typical nucleophilic acyl substitution. The amine nucleophile attacks the carbonyl carbon of the acid chloride forming an alkoxide tetrahedral intermediate. The -Cl leaving group is eliminated, allowing the carbonyl bond to be reformed. Because amines are neutral nuleophiles a protonated amide is produced after this step. In the last step of the mechanism, a second amine acts as a base, removing a proton, and allowing for the amide product to be formed.

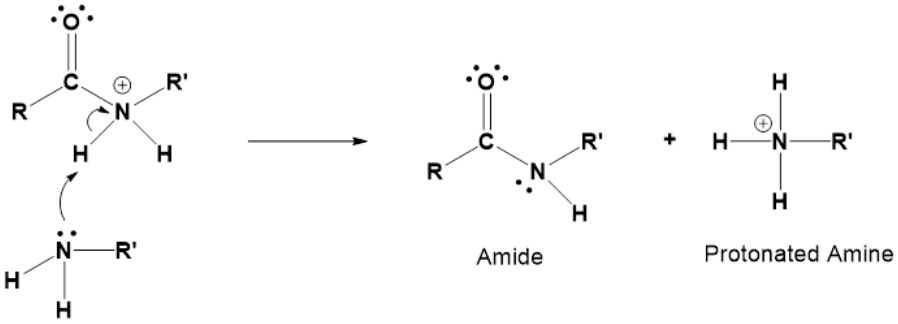
1) Nucleophilic attack by an amine



2) Leaving group removal

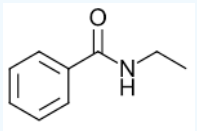


3) Deprotonation



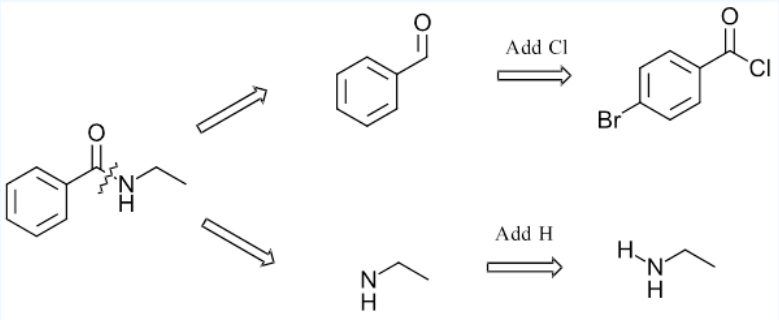
EXAMPLE 21.4.1

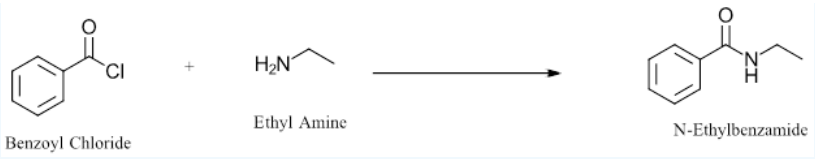
How could the following molecule be synthsized using an aminolysis of an acid chloride?



Solution

The key bond formed during this reaction is the C-N sigma bond between the carbonyl carbon and the nitrogen. Breaking this bond separated the target molecule into the two required starting materials. The carbonyl carbon gains an –Cl to become an acid chloride and the nitrogen fragment gains an H to become a 1^{o} amine. The acid chloride and the 1^{o} amine can then be joined to form the product.

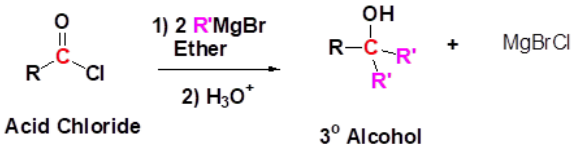




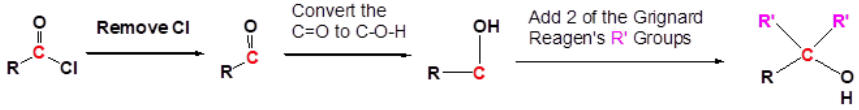
CONVERSION OF ACID CHLORIDES TO 3^{O} ALCOHOLS: GRIGNARD REAGENTS

Addition of Grignard reagents converts acid halides to 3º alcohols while forming two C-C bonds. The Grignard reagent adds to the carbonyl carbon twice during this reaction. First, as part of a nucleophilic acyl substitution to form a ketone intermediate. Then as part of a nucleophilic addition to the ketone to form a 3º alcohol.

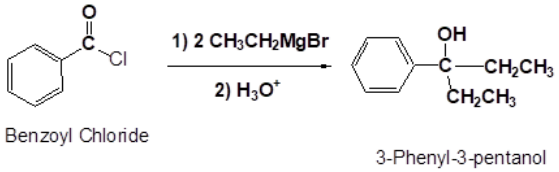
GENERAL REACTION



PREDICTING THE PRODUCT OF A GRIGNARD REAGENT

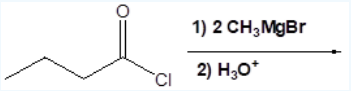


EXAMPLE



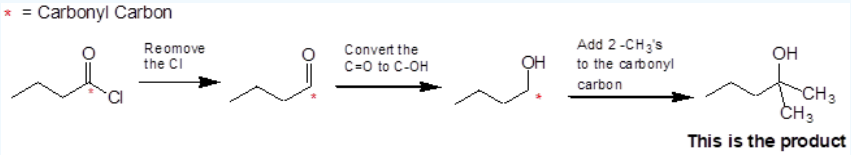
✔ EXAMPLE 21.4.2

Draw the products of the following reaction.



Solution

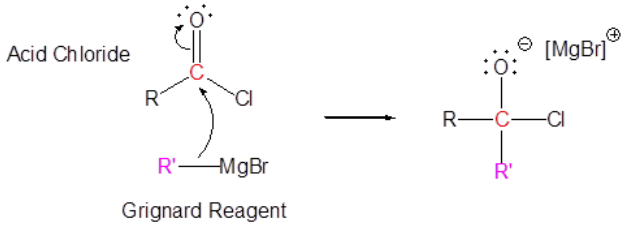
The carbanion nucleophile from the Grignard reagent is added to the carbonyl carbon twice. Once as part of a nucleophilic acyl substitution which eliminates the Cl leaving group. Then again as part of a nucleophilic addition which converts the carbonyl C=O into an alcohol OH. These steps are combined to form a 3º alcohol.



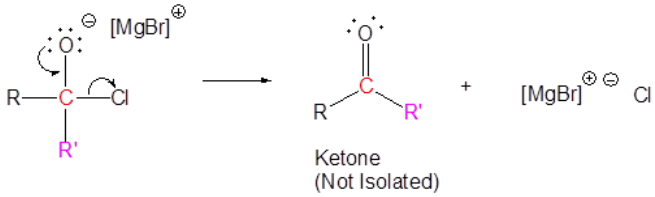
MECHANISM

The mechanism starts with the Grignard reagent's carbanion nucleophile adding to the acid halide carbonyl to form a tetrahedral alkoxide intermediate. The chloride leaving group is then eliminated, reforming the carbonyl to create a ketone intermediate. Once formed, the ketone is in competition with the acid chloride for the Grignard reagent remaining. Although acid chlorides are more reactive toward nucleophilic addition than ketones, the high reactivity of Grignard reagents makes isolating the ketone intermediate difficult. The reaction mechanism continues with the addition of a second carbanion nucleophile to the ketone to form another tetrahedral alkoxide intermediate. Protonation of the alkoxide as part of an acidic work-up creates the 3º alcohol product.

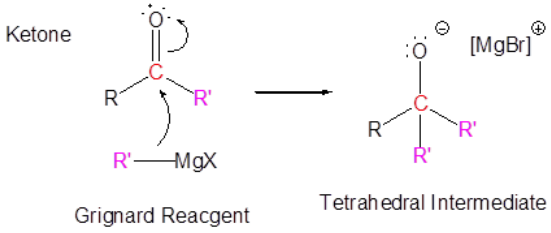
1) Nucleophilic attack



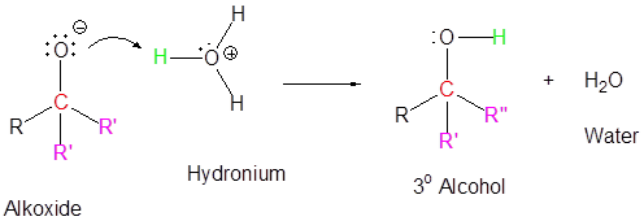
2) Leaving group removal



3) Nucleophilic attack



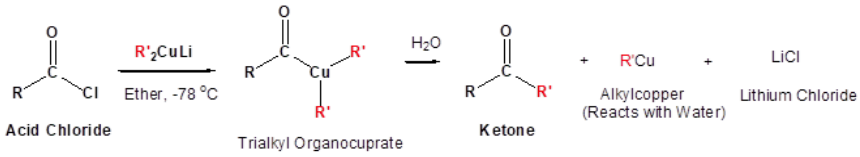
4) Protonation



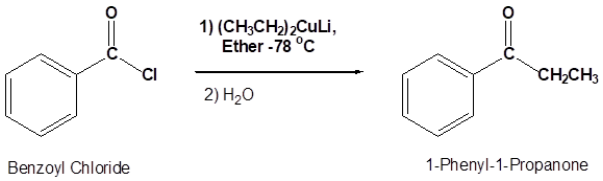
CONVERSION OF ACID CHLORIDES TO KETONES: GILMAN REAGENTS

When acid chlorides are reacted with Grignard reagents the ketone intermediate is difficult to isolate because the addition of a second equivalent of the highly reactive Grignard reagent rapidly occurs. Organocuprates however are significantly less reactive than organolithium and organomagnesium reagents and when an acid chloride is reacted with a diorganocuprate (Gillman) reagent (R_2CuLi), a ketone product is produced in excellent yields.

GENERAL REACTION



EXAMPLE



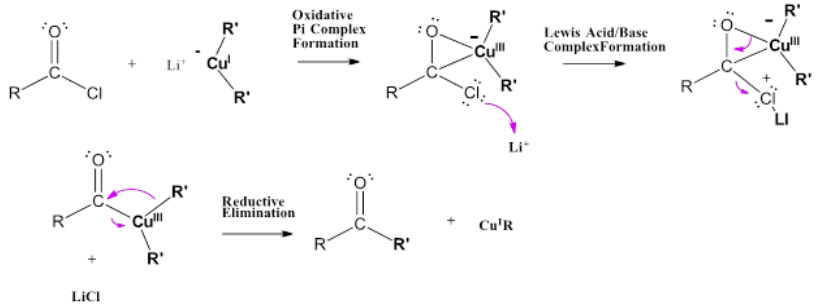
MECHANISM

The copper atom in organocuprate reagents radically changes the reaction mechanism for their nucleophilic addition to acid chlorides. Computational studies suggest that the reaction mechanism is more complicated than the typical “addition-elimination” sequence seen in

nucleophilic acyl substitutions but rather involves multiple mechanistic steps involving complexation with copper and lithium.

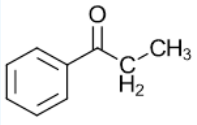
The mechanism starts with an oxidative pi-complex formation between the Cu atom in Gilman reagents and the C=O carbonyl bond in acid chlorides. Next, the chloride atom is activated toward elimination through formation of a Lewis Acid/Base complex with a lithium cation. The subsequent elimination of the –Cl leaving cleaves the C-Cl bond and forms a Cu-C bond creating a triorganocopper(III) intermediate. A ketone product is formed when reductive elimination breaks the Cu^{III}-C bond of the intermediate and forms a C-C bond between the carbonyl carbon and an alkyl group from the organocuprate reagent. During the reduction step, copper gains two electrons forming an alkylcopper (CuR) compound as a side product.

This mechanism, in part, explains the selectivity of organocuprates for acid chlorides. Acid chlorides are promoted for this reaction due to the strong electrostatic interaction between chlorine and the lithium cation present. Most other carbonyls compounds, such as ketones, carboxylic acids, esters, acid anhydrides, or amides lack this Cl-Li interaction and react with organocuprate reagents either very slowly or not at all. Because ketones do not react with organocuprate reagents, they are not subject to further nucleophilic additions and are easily isolated as the product of this reaction.



EXAMPLE 21.4.3

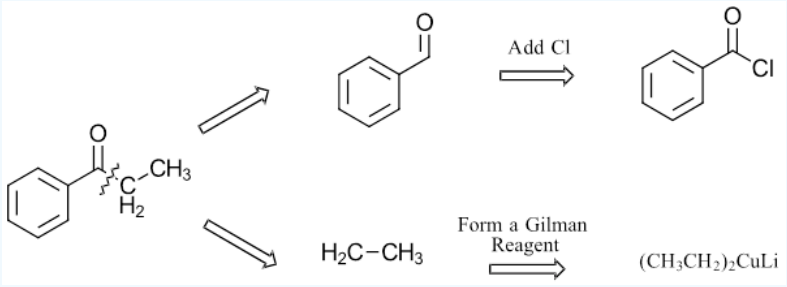
How could the following molecule be synthesized using a Gilman reagent and an acid chloride?



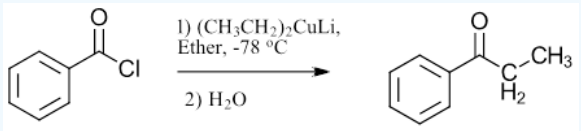
Solution

The key bond formed during this reaction is the C-C sigma bond between the carbonyl carbon and an alpha carbon. Breaking this bond separated the target molecule into two possible two starting materials. The carbonyl carbon gains an –Cl to become an acid chloride and the alkyl fragment becomes part of a Gilman Reagent R_2CuLi. The required alkyl fragment becomes the R group in the Gilman reagent. Remember that the Gilman reagent has contains two of the alkyl fragment. Because ketones have two alpha carbons there should be two possible acid chloride/Gilman reagent combinations to make this molecule.

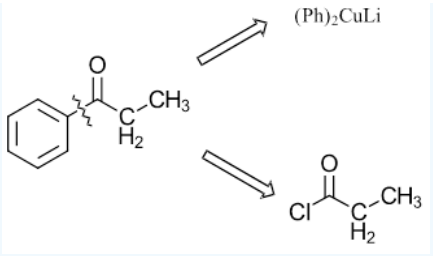
Pathway 1



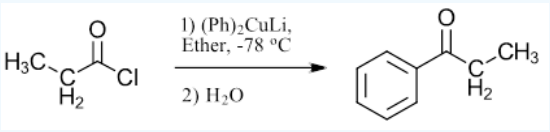
Solution 1



Pathway 2



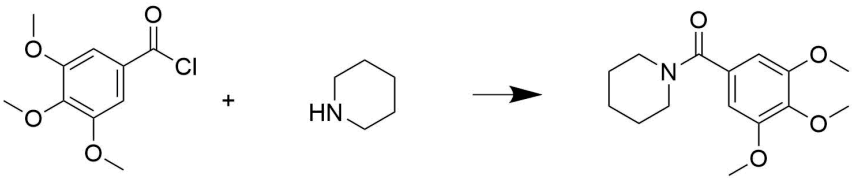
Solution 2



EXERCISES

Q21.4.1

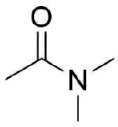
Draw the mechanism for the following reaction



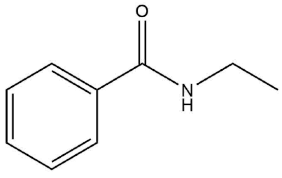
Q21.4.2

Propose a synthesis of the following molecules from an acid chloride and an amide.

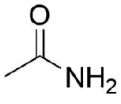
(a)



(b)

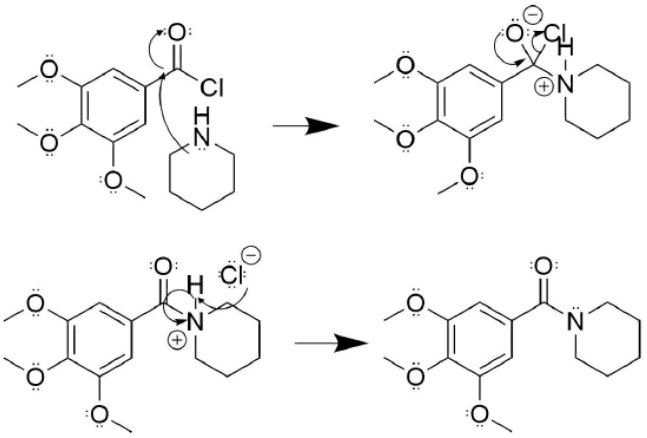


(c)



SOLUTIONS

S21.4.1



S21.4.2

a. Acetyl chloride and dimethylamine
b. Benzoyl chloride and ethylamine
c. Acetyl chloride and ammonia

21.5: CHEMISTRY OF ACID ANHYDRIDES

OBJECTIVES

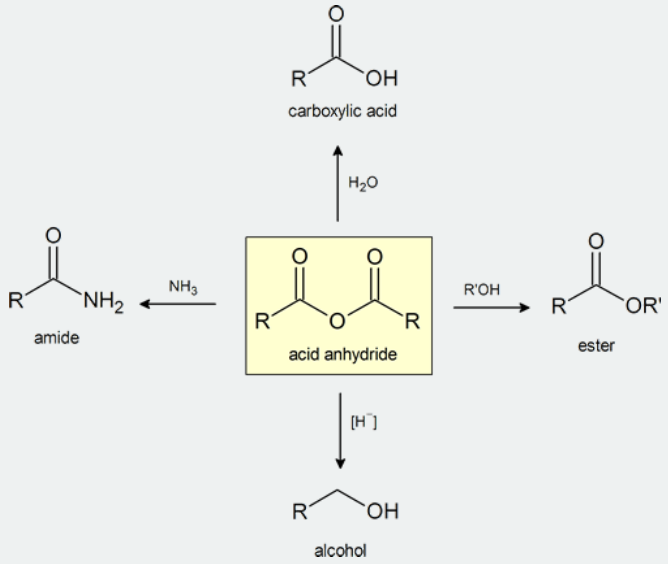
After completing this section, you should be able to

1. write an equation to illustrate the preparation of an acid anhydride from an acid halide and the sodium salt of a carboxylic acid.
2. identify the product formed from the reaction of a given acid halide with the sodium salt of a given carboxylic acid.
3. identify the acid halide, carboxylate salt, or both, required to prepare a given acid anhydride.
4. write an equation to describe the reaction of an acid anhydride with each of the following: water, alcohol, ammonia, a primary or secondary amine, lithium aluminum hydride.
5. identify the product formed when a given acid anhydride is reacted with any of the reagents listed in Objective 4, above.
6. write a detailed mechanism for the reaction of an acid anhydride with any of the reagents listed in Objective 4, above.
7. identify the acid anhydride, the nucleophilic reagent, or both, needed to prepare a specified carboxylic acid, ester, amide, or primary alcohol.

STUDY NOTES

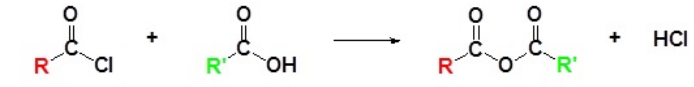
The reactions described in this section are, in principle, identical to those discussed in Section 21.4. Once you have understood the mechanism of nucleophilic acyl substitution, these reactions should not present you with any great difficulty, and memorization can be kept to a minimum.

This figure provides a convenient general summary of a few of the reactions described in Section 21.5. Note that from a synthetic perspective the ester- and amide-forming reactions are the most common, so they are the focus of this section.



PREPARATION OF ACID ANHYDRIDES

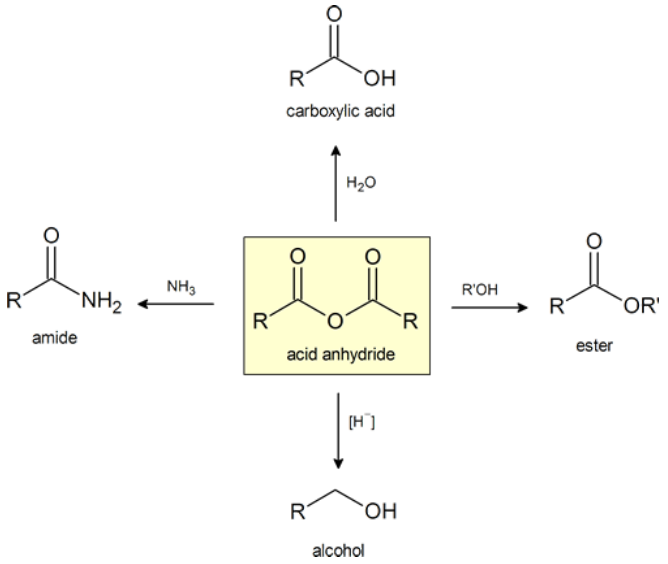
As show in Section 21.4, acid anhydrides are generally made using a nucleophilic acyl substitution reaction of an acid chloride with a carboxylic acid or a carboxylate anion.



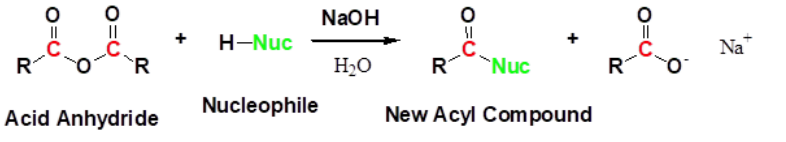
CHEMISTRY OF ANHYDRIDES

Anhydrides are highly reactive to nucleophilic attack and undergo many of the same reactions as acid chlorides that were explored in section 21.4. Although slower reacting than acid chlorides, anhydrides react with water to form carboxylic acids, with alcohols to form esters, and with amines to form amides. Anhydrides can also be reduced to 1^o alcohols by hydride reduction. Because many anhydrides are made from the coupling of two carboxylic acids, reactions using anyhydrides waste one equivalent of the carboxylic acid as a leaving group.

As a consequence, reactions are only commonly performed with inexpensive, readily available anhydrides, such as acetic anhydride or benzoic anhydride. Anydrides have the advantage of being easier to work with than acid chlorides.



GENERIC REACTION WITH AN ANHYDRIDE

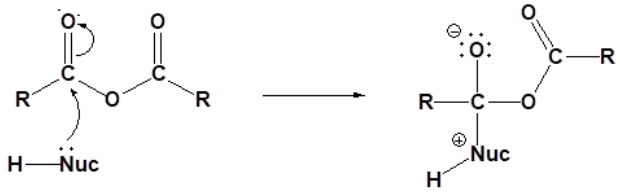


H—NUC = H_2O, NH_3, H_2NR, HNR_2 HOR

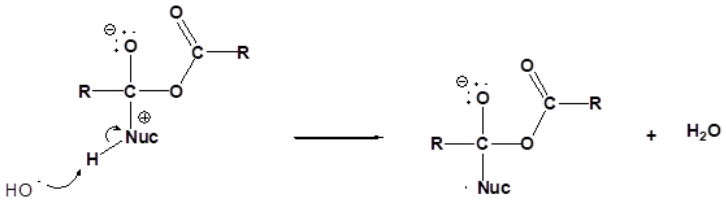
GENERIC MECHANISM OF NUCLEOPHILIC ACYL SUBSTITUTION USING AN ANHYDRIDE

The following nucleophilic acyl substitution reactions are all similar and can be represented by one generic mechanism. The nuceophile (water, ammonia, amine, or alcohol) adds to one of the carbonyl carbons in the anhydride forming a tetrahedral alkoxide intermediate. The reforming of the carbonyl C=O bond eliminates a carboxylate leaving group. Because the nucleophile is neutral, a protonated intermediate is formed. A base deprotonates the intermediate to form the neutral carboxylic acid derivative product (carboxylic acid, ester, amide).

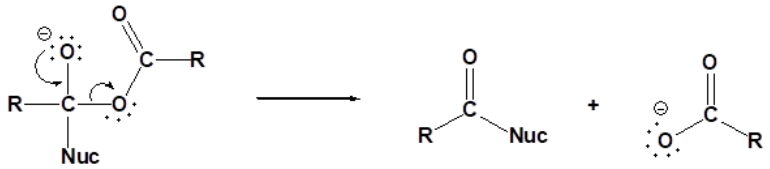
1) Nucleophilic attack



2) Deprotonation

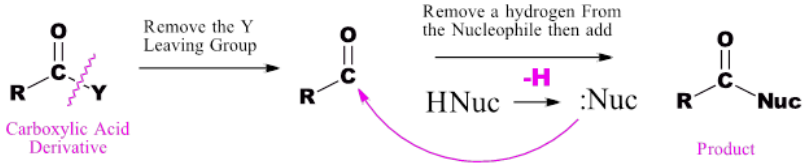


3) Leaving group removal



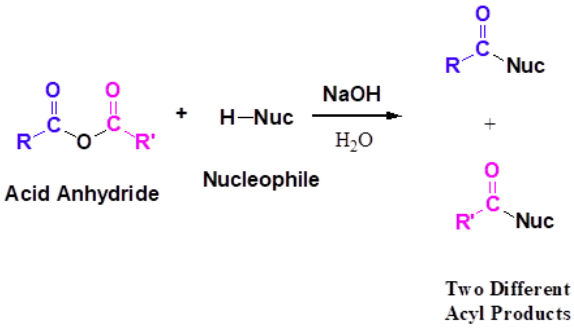
PREDICTING THE PRODUCTS OF AN ANHYDRIDE REACTION

An anhydride and a neutral nucleophile react to form a new acyl compound through nucleophilic acyl substitution. During this reaction there are three changes in bonding. The leaving group is removed from the anhydride. The neutral nucleophile loses a hydrogen. A C-Nuc bond is formed between the nucleophile and the anhydride's electrophilic carbonyl carbon.



REACTIONS WITH ASYMMETRICAL ANHYDRIDES

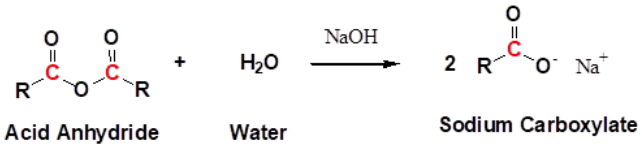
Asymmetrical anhydrides are typically not used in the formation of esters and amides because they have the possibility of forming two different products. This is not the case when symmetrical anhydrides are used.



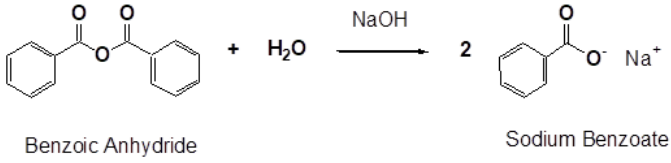
CONVERSION OF ACID ANHYDRIDES TO CARBOXYLIC ACIDS: HYDROLYISIS

Anhydrides react rapidly with water to form two carboxylic acids compounds. Because anhydrides are often prepared from carboxylic acids this reaction serves little synthetic value. However, this reaction serves as a reminder to prevent the exposure of anhydrides to moisture because they will become contaminated with the corresponding carboxylic acids.

GENERAL REACTION



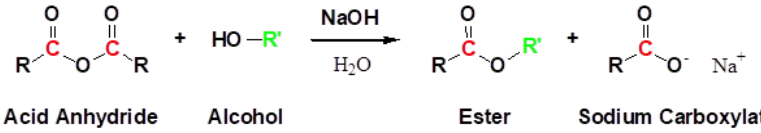
EXAMPLE



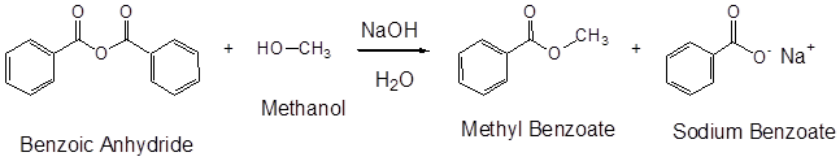
CONVERSION OF ACID ANHYDRIDES TO ESTERS: ALCOHOLYISIS

Anhydrides react with alcohols to form esters as the main product and a carboxylate as a side product. The reaction is typically run with a base, such as NaOH or pyridine, to remove any acid produced. Notice that one acyl group from the anhydride is incorporated into the ester and the other acyl group forms a carboxylate.

GENERAL REACTION

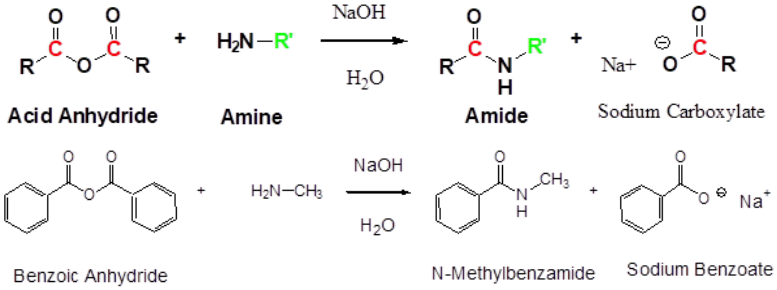


EXAMPLE



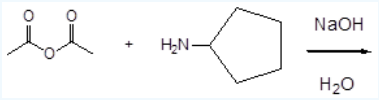
CONVERSION OF ACID ANHYDRIDES TO AMIDES: AMINOLYSIS

Acid anhydrides react with ammonia, 1^o, or 2^o amines to form the corresponding amides. Two molar equivalents of amine are required. It is important to run this reaction with a base to neutralize the acid produced otherwise the amine reactant would be become protonated to form a non-nucleophilic ammonium compound. During the reaction, one acyl group from the anhydride becomes part of the amide while the other acyl group becomes a carboxylate.



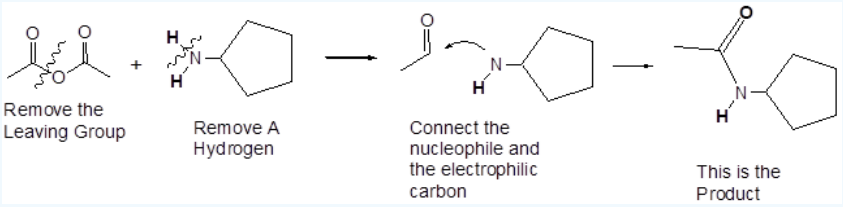
EXAMPLE 21.5.1

Draw the products of the following reaction:



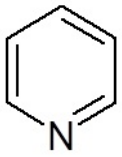
Solution

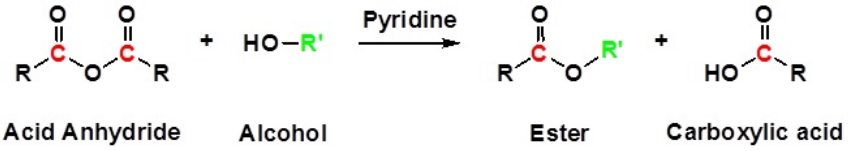
The reaction of an anhydride and an amine form an amide through nucleophilic acyl substitution. During this reaction three changes in bonding occur. The leaving group is removed from the anhydride. The amine loses a hydrogen. A C-N bond is formed between the amine and the electrophilic carbonyl carbon.



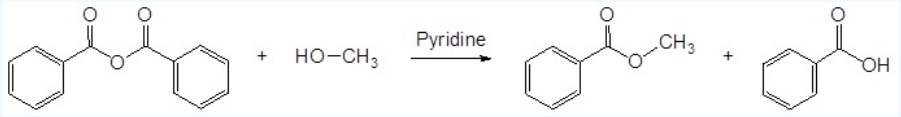
ACID ANHYDRIDES REACT WITH ALCOHOLS TO FORM ESTERS

Reactions of anhydrides use Pyridine as a solvent



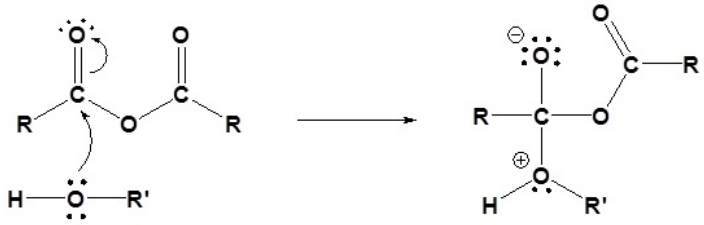


EXAMPLE 21.5.1

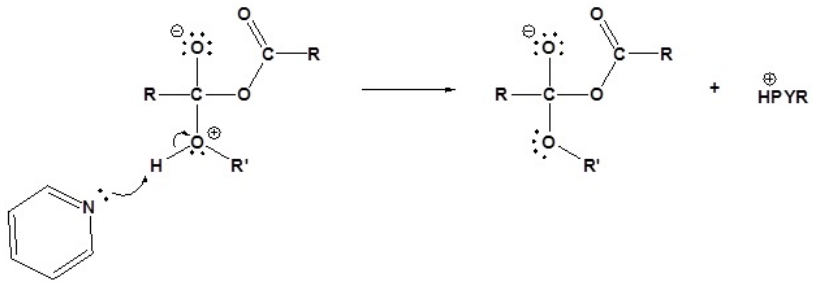


MECHANISM

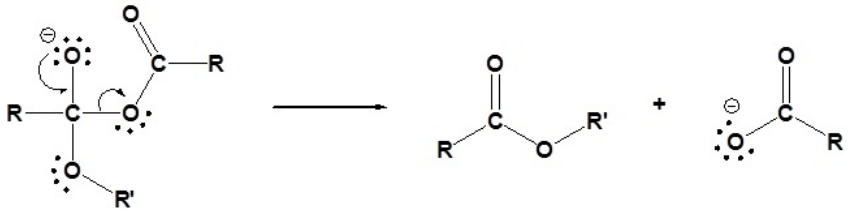
1) Nucleophilic Attack by the Alcohol



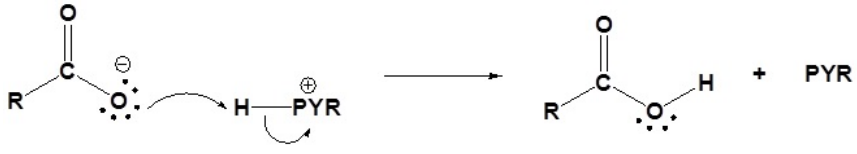
2) Deprotonation by pyridine



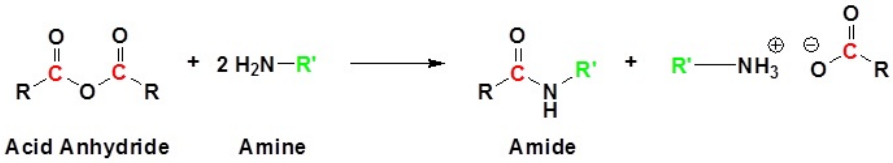
3) Leaving group removal



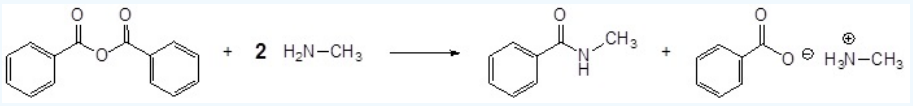
4) Protonation of the carboxylate



ACID ANHYDRIDES REACT WITH AMINES TO FORM AMIDES

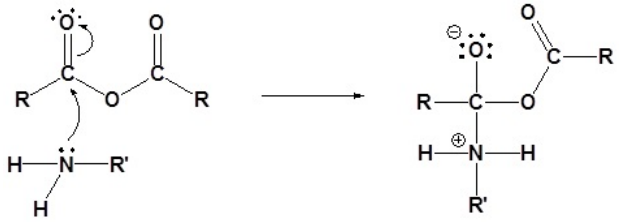


EXAMPLE 21.5.2

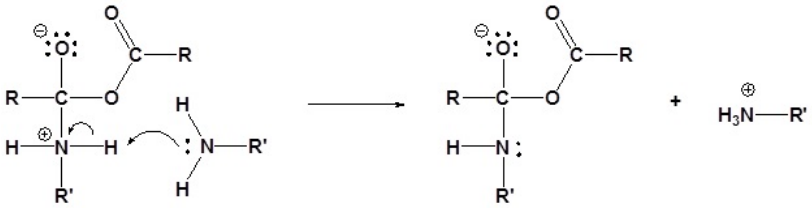


MECHANISM

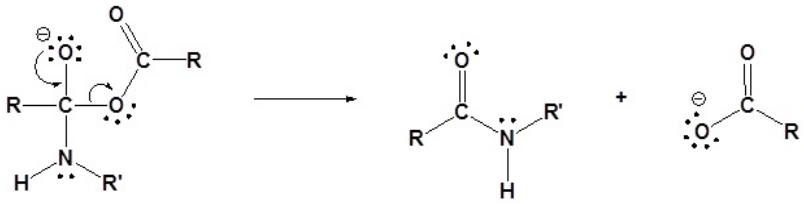
1) Nucleophilic Attack by the Amine



2) Deprotonation by the amine



3) Leaving group removal

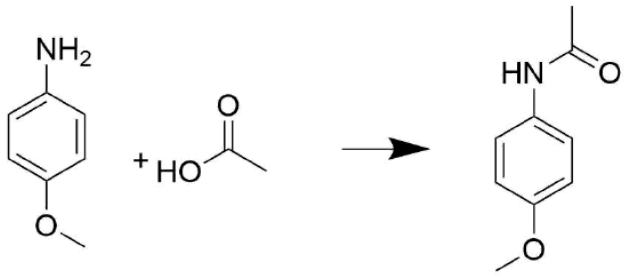


EXERCISES

QUESTIONS

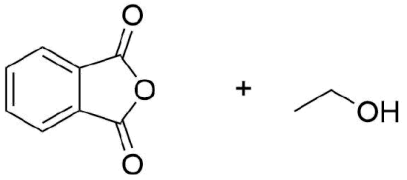
Q21.5.1

Draw out the mechanism for the following reaction.



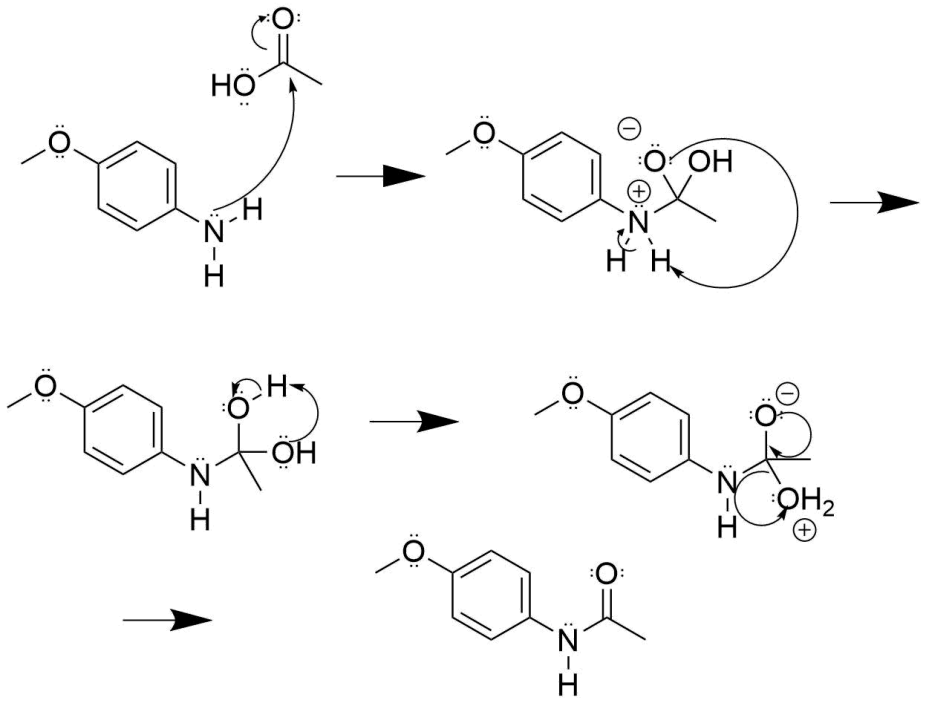
Q21.5.2

Draw the product of the reaction between these two molecules.

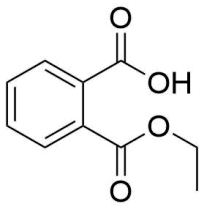


SOLUTIONS

S21.5.1



S21.5.1



21.6: CHEMISTRY OF ESTERS

OBJECTIVES

After completing this section, you should be able to

1. discuss the wide occurrence of esters in nature, and their important commercial uses, giving one example of an ester linkage in nature, and one example of a commercially important ester.
2. write an equation to describe the hydrolysis of an ester under acidic or basic conditions.
3. identify the products formed from the hydrolysis of an given ester.
4. identify the reagents that can be used to bring about ester hydrolysis.
5. identify the structure of an unknown ester, given the products of its hydrolysis.
6. write the mechanism of alkaline ester hydrolysis.
7. write the mechanism of acidic ester hydrolysis.
8. write an equation to describe the reduction of an ester with lithium aluminum hydride.
9. identify the product formed from the reduction of a given ester (or lactone) with lithium aluminum hydride.
10. identify the ester, the reagents, or both, that should be used to prepare a given primary alcohol.
11. write a detailed mechanism for the reduction of an ester by lithium aluminum hydride.
12. identify diisobutylaluminum hydride as a reagent for reducing an ester to an aldehyde, and write an equation for such a reaction.
13. write an equation to describe the reaction of an ester with a Grignard reagent.
14. identify the product formed from the reaction of a given ester with a given Grignard reagent.
15. identify the ester, the Grignard reagent, or both, needed to prepare a given tertiary alcohol.
16. write a detailed mechanism for the reaction of an ester with a Grignard reagent.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- lactone
- saponification

STUDY NOTES

Many esters have characteristic aromas and flavours. Some examples are listed below.

Basic structure:

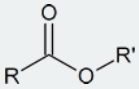
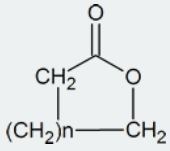


Table 21.1 Structures and characteristic odours of selected esters

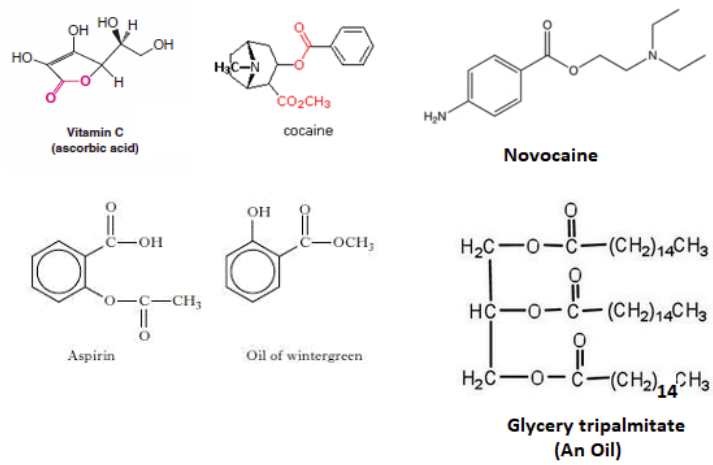
IUPAC name	R	R′	Aroma
octyl ethanoate	CH_3	$CH_3(CH_2)_6CH_2$	orange
propyl ethanoate	CH_3	$CH_3CH_2\ CH_2$	pear
2-methylpropyl propanoate	CH_3CH_2	$(CH_3)_2CHCH_2$	rum
methyl butanoate	$CH_3CH_2CH_2$	CH_3	apple
ethyl butanoate	$CH_3CH_2CH_2$	CH_3CH_2	pineapple

A “lactone” is a cyclic ester and has the general structure

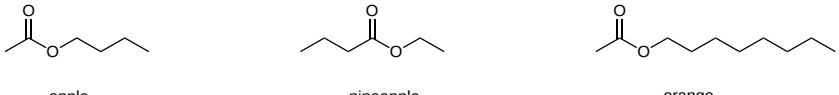


By recognizing that the steps in the acidic hydrolysis of an ester are exactly the same as those in a Fischer esterification (but in the reverse order!), you can again minimize the amount of memorization that you must undertake. The details of both mechanisms can be deduced from the knowledge that both reactions are acid-catalyzed nucleophilic acyl substitutions.

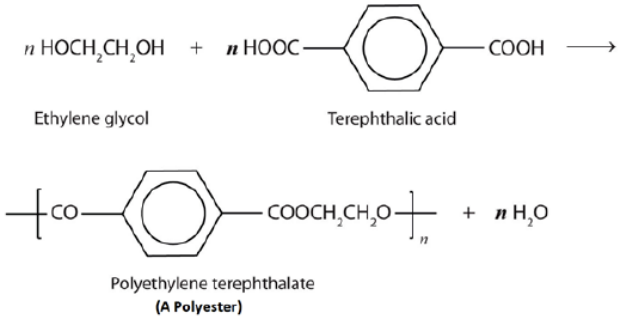
Esters are present in a many biologically important molecules, which have a wide range of effects including fats, waxes, Vitamin C, Cocaine, Novacaine, oil of wintergreen, and aspirin.



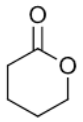
Esters compounds are often the source of the pleasant aromas of many fruits.



Esters are also present in a number of important commercial and synthetic application. For example, 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. The most important polyester, polyethylene terephthalate (PET), is made from terephthalic acid and ethylene glycol monomers. PET is used to make bottles for water and other beverages. It is also formed into films called Mylar which is used in balloons. Synthetic arteries can be made from PET, polytetrafluoroethylene (PTFE), and other polymers.

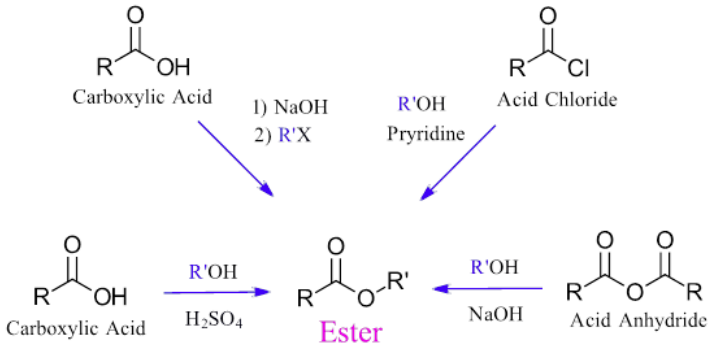


Lactones, cyclic esters, have similar reactivity as acyclic esters.



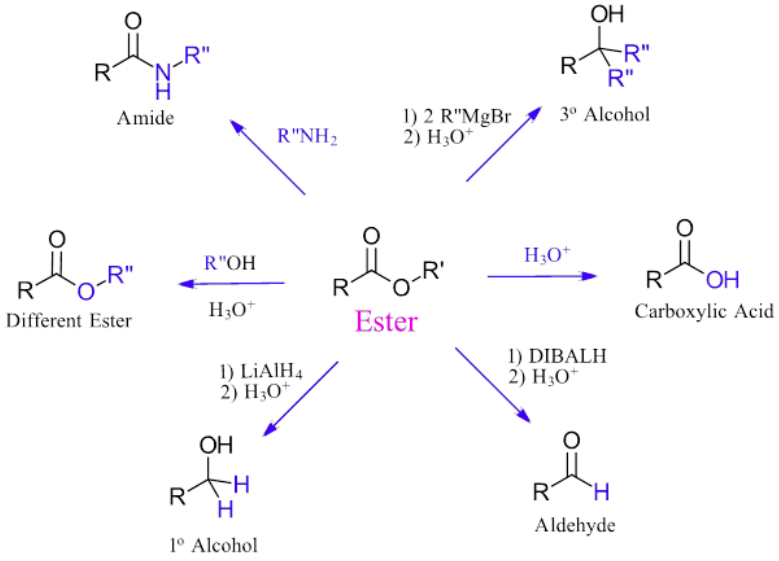
PREPARATION OF ESTERS

The most versatile method for the preparations of esters is the nucleophilic acyl substitution of of an acid chloride with an alcohol. Acid ahydrides and carboxylic acids can also react with alcohols to form esters but both reactions are limited to formation of simple esters. Esters can also be formed by deprotonating a carboxylic acid to form a carboxylate and then reacting it with a primary alkyl halide using an S_N2 reaction.



REACTIONS OF ESTERS

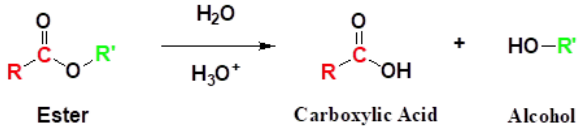
Esters are one of the more useful functional groups. Their low reactivity makes the easy to work with and they are stable enough to be used as a solvent in organic reactions (ex. ethyl acetate). Esters are still reactive enough to undergo hydrolysis to form carboxylic acids, alcoholysis, to form different esters, and aminolysis to form amides. Also, they can react with Grignard reagents to form 3^{o} alcohols and hydride reagents to form 1^{o} alcohols or aldehydes.



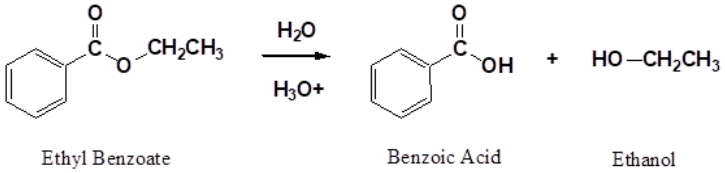
CONVERSION OF ESTERS TO CARBOXYLIC ACIDS: HYDROLYSIS

Esters can be cleaved back into a carboxylic acid and an alcohol through reaction with water and a catalytic amount of strong acid. This reaction represents the reverse of the acid catalyzed esterification of a carboxylic acid and an alcohol discussed in Section 21.3. Both the ester formation and cleavage reactions are part of an equilibrium which can be manipulated using Le Chatelier's principle. For ester hydrolysis, the equilibrium is shifted toward carboxylic acid formation by using a large excess of water in the reaction.

GENERAL REACTION



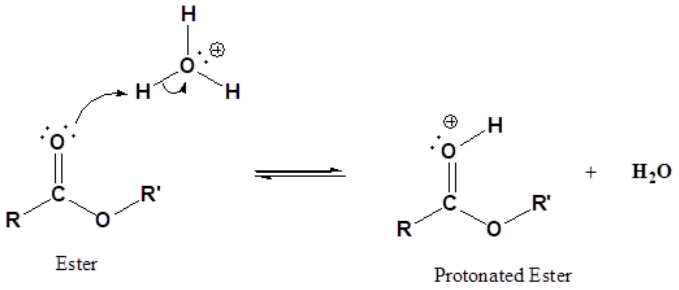
EXAMPLE



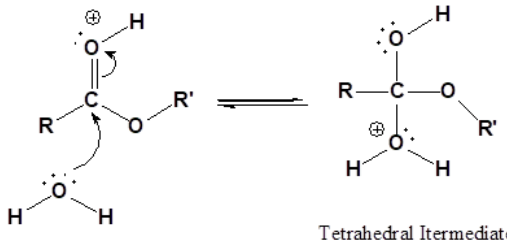
MECHANISM

Acid catalysis is required during ester hydrolysis due to water being a weak nucleophile. Protonation of the ester carbonyl increases the partial positive charge on the carbonyl carbon increasing its electrophilicity. After protonation, water adds to the carbonyl carbon causing the formation of a tetrahedral alkoxide intermediate. Then a proton transfers to the –OR group, increasing its ability to act as a leaving group. Reforming the carbonyl double bond causes the elimination of an alcohol (HOR) as a leaving group, creating a protonated carboxylic acid. In the last step of the mechanism, water acts as a base, removing a hydrogen, to form a carboxylic acid and regenerating the acid catalyst.

1) Protonation of the carbonyl

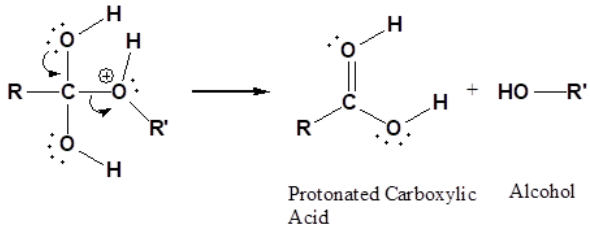


2) Nucleophilic attack by water

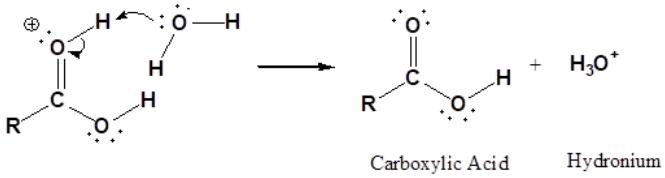


3) Proton transfer

4) Leaving group removal

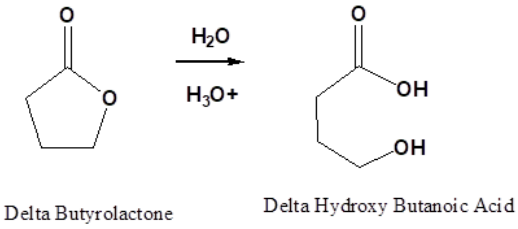


5) Deprotonation



HYDROLYSIS OF LACTONES

Lactones (Cyclic esters) undergo typical reactions of esters including hydrolysis. Hydrolysis of the lactone under acidic conditions creates a hydroxyacid.



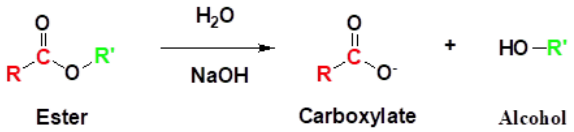
Delta Butyrolactone Delta Hydroxy Butanoic Acid

CONVERSION OF ESTERS TO CARBOXYLIC ACIDS: SAPONIFICATION

Esters can also be cleaved into a carboxylate and an alcohol through reaction with water and a base. The reaction is commonly called a saponification from the Latin sapo which means soap. This name comes from the fact that soap used to me made by the ester hydrolysis of fats.

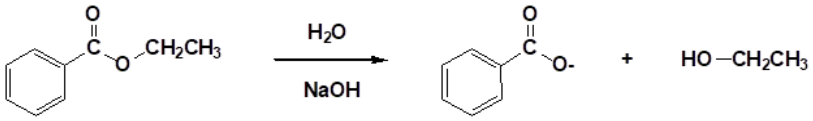
Saponification reaction utilize a better nucleophile (hydroxide) and are typically faster than an acid catalyzed hydrolysis. The carboxylation ions produced by saponification are negatively charged and very unreactive toward further nucleophilic substitution which makes the reaction irreversible.

GENERAL REACTION



Ester Carboxylate Alcohol

EXAMPLE



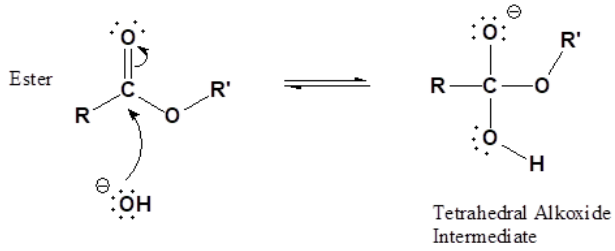
Ethyl Benzoate Benzoate Ethanol

MECHANISM

The base-promoted hydrolysis of an ester follows the typical nucleophilic acyl substitution mechanism. A full equivalent of hydroxide anion is used, so the reaction is called base-promoted and not base catalyzed. The mechanism of ester saponification begins with the nucleophilic addition of a hydroxide ion at the carbonyl carbon to give a tetrahedral alkoxide intermediate. The carbonyl bond is reformed along with the elimination of an alkoxide (-OR) leaving group yielding a carboxylic acid. The alkoxide base deprotonates the carboxylic acid to for a carboxylate salt and an alcohol as products.

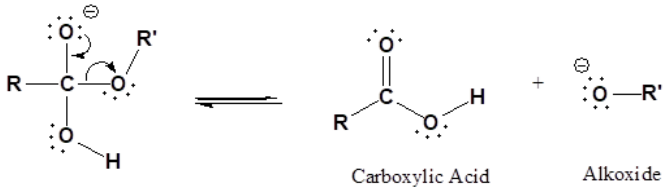
The last deprotonation step essentially removes the carboxylic acid from the equilibrium which drives the saponification towards completion. Because the carboxylic acid is no longer part of the equilibrium the reaction is effectively irreversible.

1) Nucleophilic attack by hydroxide



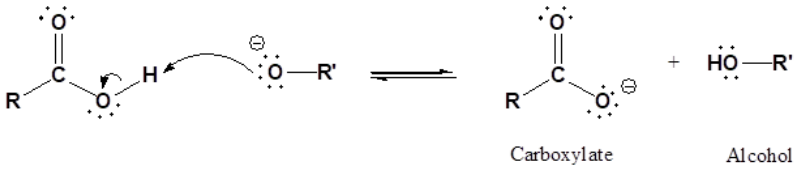
Tetrahedral Alkoxide Intermediate

2) Leaving group removal

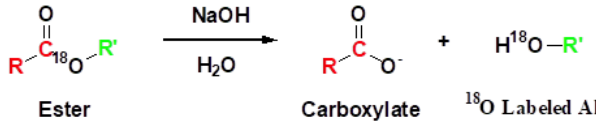


Carboxylic Acid Alkoxide

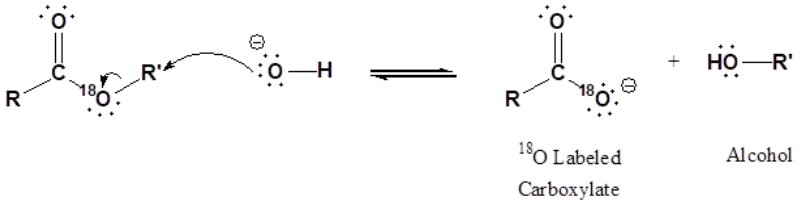
3) Deprotonation



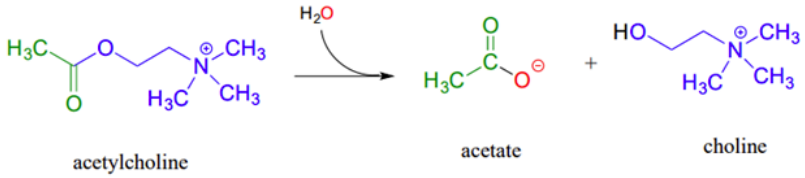
This mechanism is supported by experiments performed using isotopically labeled esters. When the ether-type oxygen of the ester was labeled with ^{18}O, the labeled oxygen showed up in the alcohol product after hydrolysis.



An alternative mechanism would be if the hydroxide participated in an S_N2 reaction to create the carboxylate product. If this were to happen the alcohol reaction product would not contain the labeled oxygen.



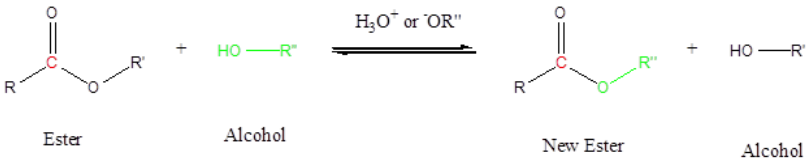
Ester saponification in biological systems, called hydrolytic acyl substitution reactions, are common. In particular, acetylcholinesterase, an enzyme present in the synapse, catalyzes hydrolysis of the ester group in acetylcholine which is a neurotransmitter that triggers muscle contraction. Like many other hydrolytic enzymes, the acetylcholinesterase reaction proceeds in two phases: first, a covalent enzyme-substrate intermediate is formed when the acyl group of acetylcholine is transferred to an active-site serine on the enzyme (a transesterification reaction). A water nucleophile then attacks this ester, driving off acetate and completing the hydrolysis



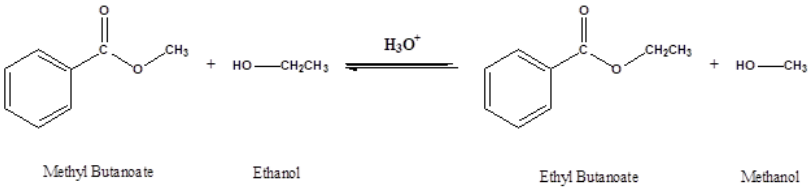
CONVERSION OF ESTERS TO DIFFERENT ESTERS: TRANSESTERIFICATION

Transesterification is a reaction where an ester is converted to a different ester through reaction with an alcohol. Because there is typically very little difference in stability between both esters, the equilibrium constant of this reaction is usually near one. Using a large excess of the reactant alcohol or removing the alcohol side-product can push the reaction equilibrium towards the products by Le Chatelier's principal. Transesterifications also shows that great care should be taken when an ester containing compound is used in a reaction involving an alcohol.

GENERAL REACTION



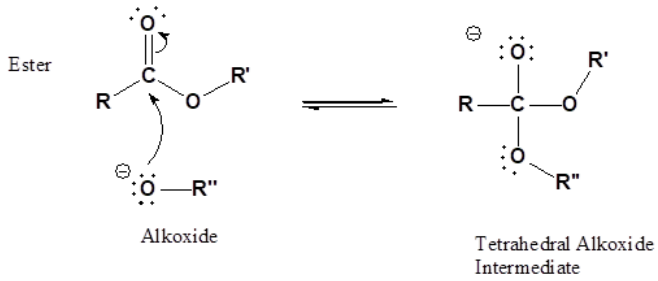
EXAMPLE



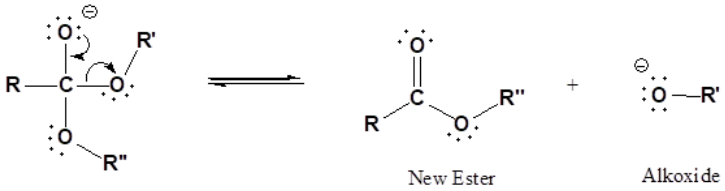
MECHANISM IN BASIC CONDITIONS

The reaction follows the basic mechanism of a nucleophilic acyl substitution. The alkoxide leaving group of the ester is replace by an incoming alkoxide nucleophile creating a different ester.

1) Nucleophilic attack by an alkoxide



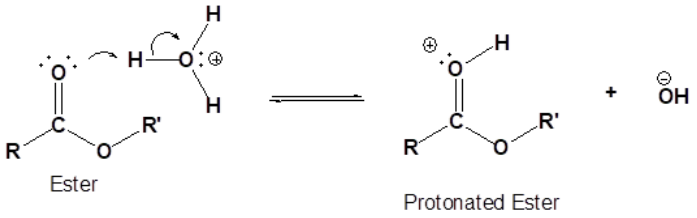
2) Leaving group removal



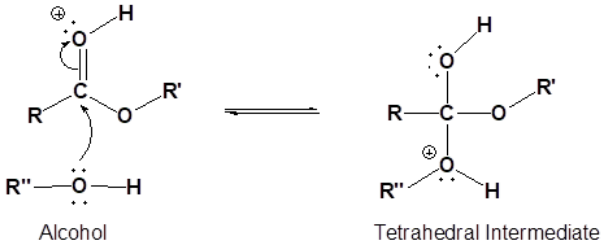
MECHANISM IN ACIDIC CONDITIONS

Protonation allows the alcohol reactant to add to the ester carbonyl. Proton transfer to the ester's alkoxy group increases it ability to act as a leaving group. Reforming the C=O carbonyl bond removes the leaving group and subsequent deprotonation by water forms the ester product.

1) Protonation of the carbonyl

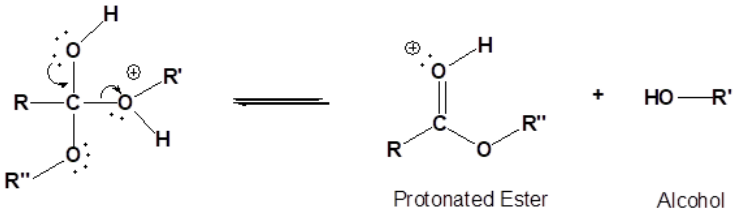


2) Nucleophilic attack on the carbonyl

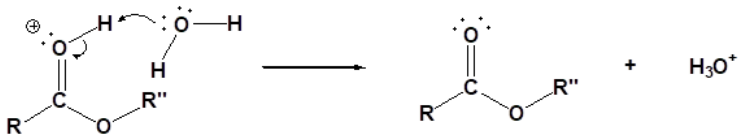


3) Proton transfer

4) Removal of the leaving group

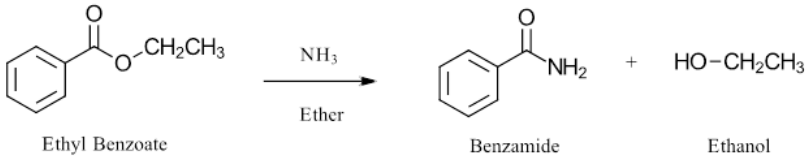


5) Deprotonation



CONVERSION OF ESTER TO AMIDES: AMINOLYSIS

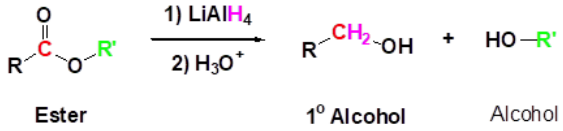
It is possible to convert esters to amides through direct reaction with ammonia or amines. However, these reactions are not commonly used because the formation of an amide using an acid chloride is a much simpler reaction.



CONVERSION OF ESTERS TO 1^{O} ALCOHOLS: HYDRIDE REDUCTION

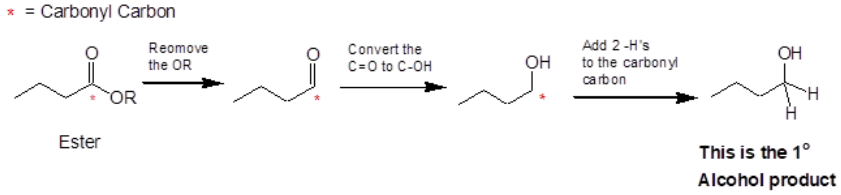
Esters can undergo hydride reduction with $LiAlH_4$ to form two alcohols. The alcohol derived from the acyl group of the ester will be 1^{o} and is typically considered the main product of the reaction. The other alcohol is derived from the ester's alkoxy group and is typically considered a side-product of the reaction. Note! Sodium borohydride ($NaBH_4$) is not a reactive enough hydride agent to reduce esters or carboxylic acids. In fact, $NaBH_4$ can selectively reduce aldehydes and ketones in the presence of ester functional groups.

GENERAL REACTION

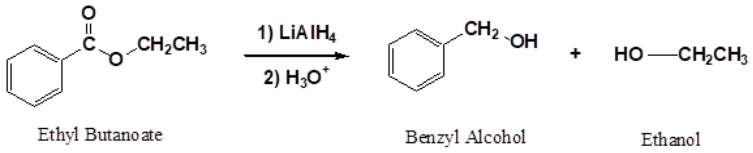


PREDICTING THE PRODUCTS OF A HYDRIDE REDUCTION

There are three major changes in bonding during this reaction: 1) The –OR leaving group is removed from the ester. 2) The C=O carbonyl bond is converted to a C-O-H, an alcohol. 3) Two C-H bonds are formed as two of the hydride nucleophiles are added to the original carbonyl carbon of the ester.



EXAMPLE

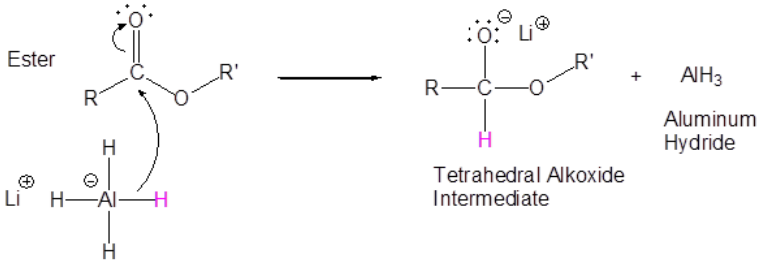


MECHANISM

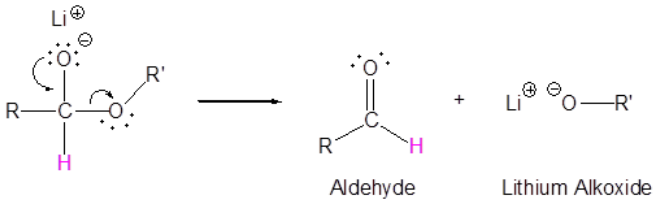
The mechanisms for the hydride reduction of esters is analogous to the hydride reduction of carboxylic acids. Nucleophilic acyl substitution replaces the –OR leaving group in ester with a hydride nucleophile to form an aldehyde intermediate. Because aldehydes are more reactive

than esters, they rapidly undergo a second nucleophilic hydride addition to form a tetrahedral alkoxide intermediate. An acid work-up protonates the alkoxide to create a 1° alcohol.

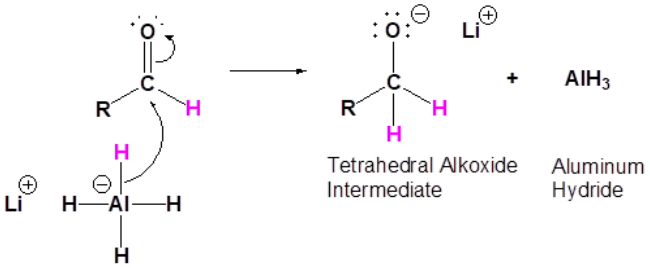
1) Nucleophilic attack by the hydride



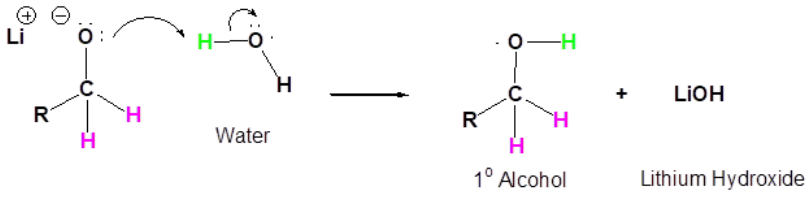
2) Leaving Group Removal



3) Nucleopilic attack by the hydride anion



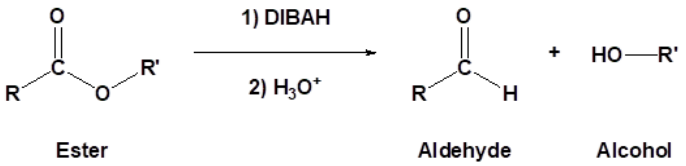
4) The alkoxide is protonated



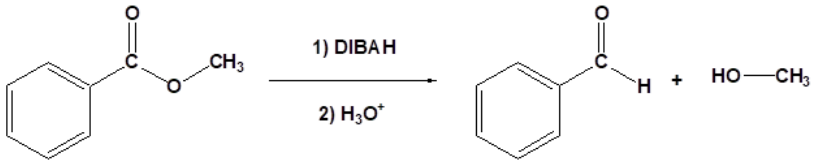
CONVERSION OF ESTERS TO ALDEHYDES: HYDRIDE REDUCTION

Much like acid chlorides, esters can be converted to aldehydes using the weaker reducing reagent diisobutylaluminum hydride (DIBALH). As shown above, an aldehyde intermediate is produced after an ester undergoes nucleophilic acyl substitution with a hydride. When DIBALH is used as the hydride source, the aldehyde does not react further and is isolated as the product of the reaction. The reaction is usually carried out at -78 ºC to help isolate the aldehyde product.

GENERAL REACTION



EXAMPLE

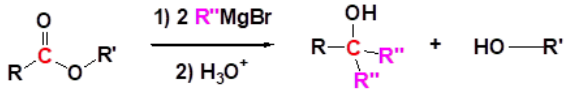


Methyl Butanoate | Benzaldehyde | Methanol

CONVERSION OF ESTERS TO 3^O ALCOHOLS: GRIGNARD REAGENTS

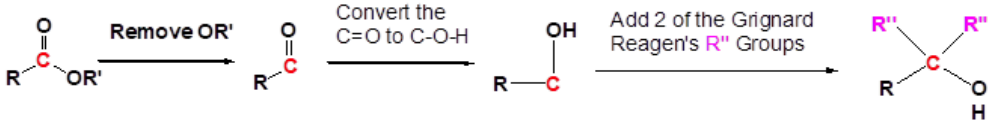
Addition of Grignard reagents converts esters to two alcohols, one 3^o alcohols (main product) and one 1^o alcohol (considered a side product). The Grignard reagent adds to the ester twice, once during a nucleophilic acyl substitution to form a ketone intermediate then again during a nucleophilic addition to form the 3^o alcohol product. Overall, during this reaction two C-C bonds are formed on the ester's original carbonyl carbon.

GENERAL REACTION

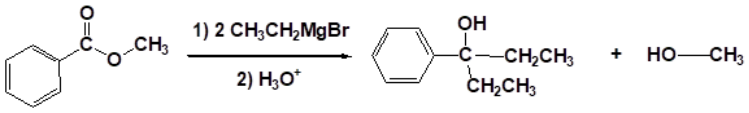


Ester | 3^o Alcohol | Alcohol

PREDICTING THE PRODUCTS OF A GRIGNARD REACTION



EXAMPLE

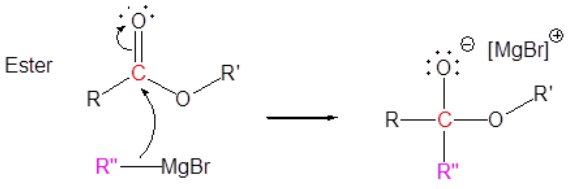


Methyl Benzoate | 3-Phenyl-3-Pentanol | Methanol

MECHANISM

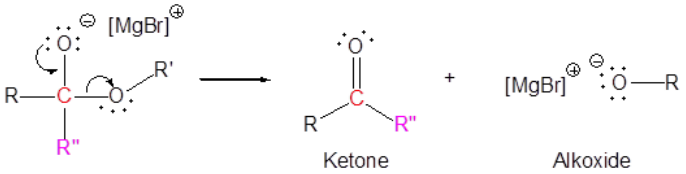
In the first two steps of the mechanism, the OR leaving group from the ester is replaced by the R group from the Grignard reagent through a nucleophilic acyl substitution. This forms a ketone intermediate which is not isolated because ketones, which are more reactive than esters, rapidly undergo nucleophilic addition with a second equivalent of the Grignard reagent to form an alkoxide intermediate. An acid work-up protonates the alkoxide to form the 3^o alcohol product.

1) Nucleophilic Attack



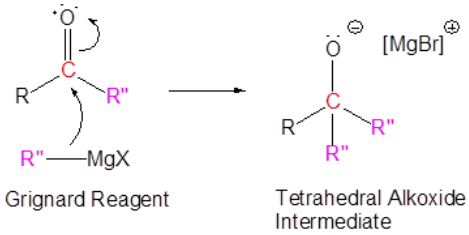
Grignard Reagent | Tetrahedral Alkoxide Intermediate

2) Leaving group removal

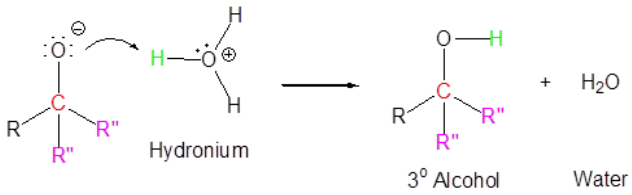


Ketone | Alkoxide

3) Nucleophilic attack

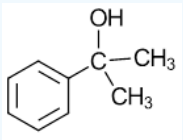


4) Protonation



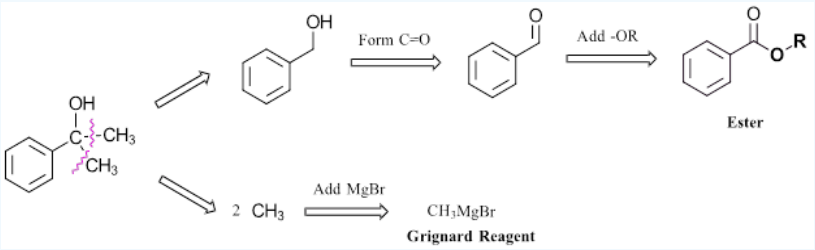
EXAMPLE 21.6.1

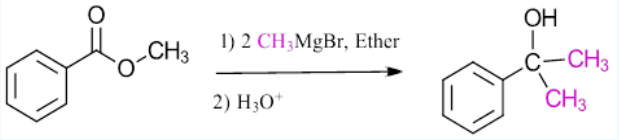
How could the following molecule be made using a Grignard reagent and an ester?



Solution

The key bond breaks for this example are two C-C sigma bonds between the carbonyl carbon and two alpha carbons. Reactions with esters involve a double addition of the Grignard reagent so the fragments removed must be the same. In this example, the C-C bonds involving the two methyl groups are broken. Breaking these bonds separate the target molecule into the required starting materials. The fragment which contains the alcohol carbon forms a C=O carbonyl bond and gains an –OR to become an ester. The R group of the ester is largely unimportant to the overall reaction and is typically a methyl or ethyl group. The alkyl fragments gain MgBr to form a Grignard reagent. Remember that the Grignard reagent only contains one alkyl fragment.

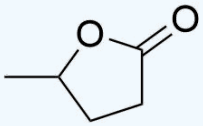




EXERCISES 21.6.1

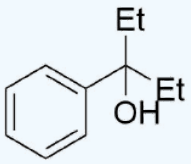
1) Why is the alkaline hydrolysis of an ester not a reversible process? Why doesn't the reaction with a hydroxide ion and a carboxylic acid produce an ester?

2) Draw the product of the reaction between the following molecule and $LiAlH_4$, and the product of the reaction between the following molecule and DIBAL.

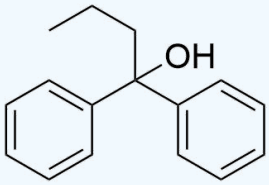


3) How might you Prepare the following molecules from esters and Grignard reagents?

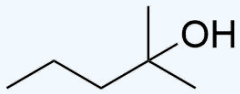
(a)



(b)



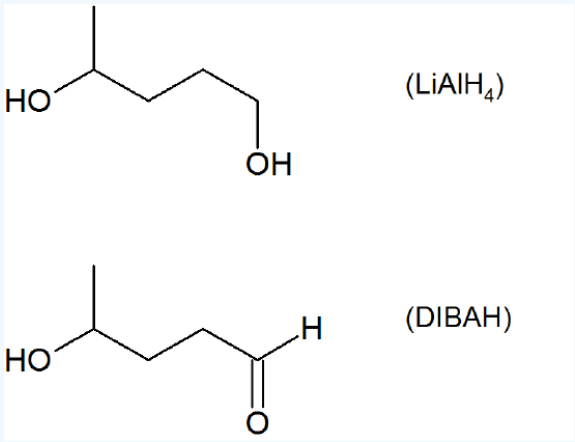
(c)



Answers

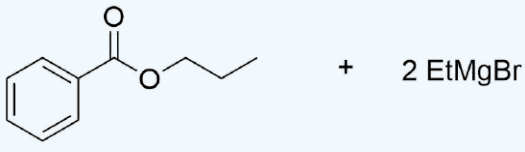
1) The reaction between a carboxylic acid and a hydroxide ion is an acid base reaction, which produces water and a carboxylate anion.

2)

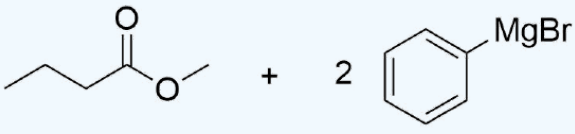


3)

(a)



(b)



(c)

21.7: CHEMISTRY OF AMIDES

OBJECTIVES

After completing this section, you should be able to

1. write an equation to describe the preparation of an amide from an acid chloride.
2. identify the amide linkage as the basic unit from which all proteins are made, and hence recognize the importance of the amide linkage to biologists and biochemists.
3. write detailed mechanisms for the acidic and basic hydrolysis of amides.
4. write an equation to describe the reduction of an amide to an amine.
5. write a detailed mechanism for the reduction of an amide to an amine.
6. identify the product formed when a given amide is reduced with lithium aluminum hydride.
7. identify the amide, the reagents, or both, necessary to prepare a given amine by direct reduction.
8. identify lactams as being cyclic amides which undergo hydrolysis and reduction in a manner analogous to that of their acyclic counterparts.

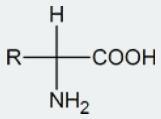
KEY TERMS

Make certain that you can define, and use in context, the key term below.

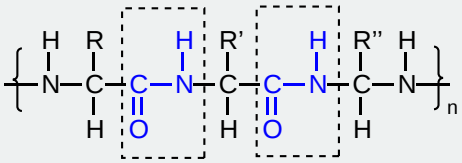
- lactam

STUDY NOTES

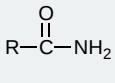
When we talk about amino acids, we are generally referring to α-amino acids; that is, compounds in which an amino (NH_2) group and a carboxyl group are attached to the same carbon atom:



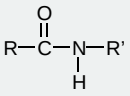
Notice that such compounds contain a chiral carbon atom (unless R = H, which is glycine). Proteins can be considered to consist of amino acid residues joined by amide (or peptide) links. These peptide links consist of exactly the same structural units that we find in *N*-substituted primary amides.



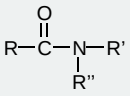
peptide (amide) links



primary amide

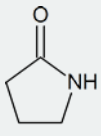


N—substituted primary amide

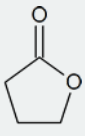


N, *N*—disubstituted primary amide

A lactam is a cyclic amide, in the same way that a lactone is a cyclic ester:

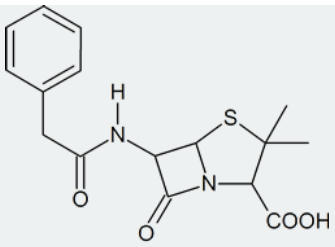


a lactam



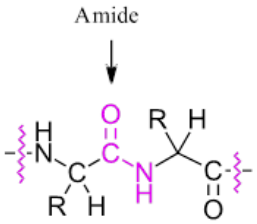
a lactone

Among the most important molecules that contain lactam rings are the penicillins:



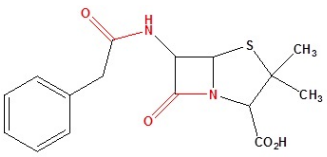
penicillin G (benzylpenicillin)

The amide functional group is extremely important for biological molecules because amides make up the backbone of proteins. Proteins are actually polymers of amino acids, linked by amide groups known as peptide bonds. Proteins (polymers of ~40 amino acids or more) and peptides (shorter polymers) are formed when the amino group of one amino acid monomer reacts with the carboxylate carbon of another amino acid to form an amide linkage, which in protein terminology is a **peptide bond**. The individual amino acids within a peptide or protein are called **amino acid residues**.

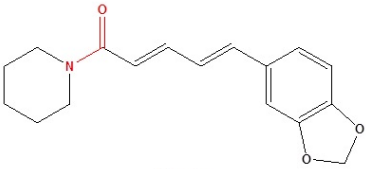


Protein Backbone

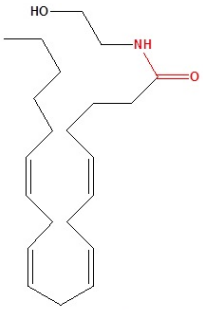
Compounds containing amides have a wide range of biological activity and include penicillin G an antibiotic, piperine which is responsible for the pungent flavor of black pepper, and anandamide which provides some of the pleasurable sensations gained from eating chocolate.



Penicillin G
(An Antibiotic)



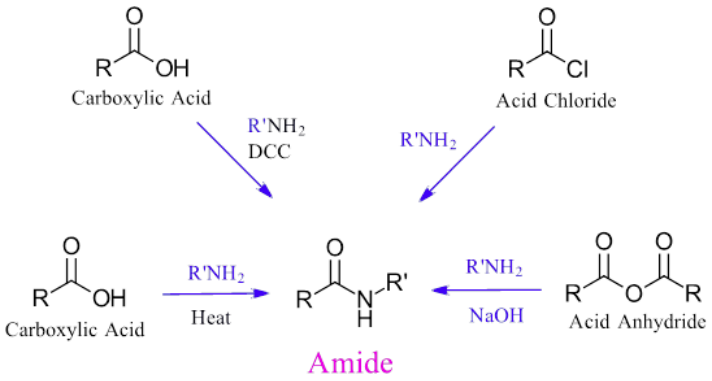
Piperine
(From Black Pepper)



Anandamide
(From Chocolate)

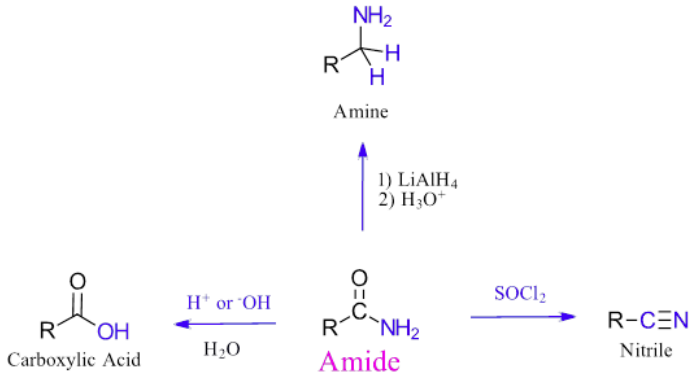
PREPARATION OF AMIDES

Amides are most commonly prepared though the reaction of an acid chloride with ammonia, a 1º amine, or 2º amine. In an analogous reaction, an amide can be prepared through the reaction of a carboxylic acid and an amine using a coupling agent such as DCC. Simple amides can be prepared by reacting an acid anhydride with an amine. Lastly, amides can be formed through the direct reaction of a carboxylic acid and an amine. However, this reaction is rarely used because the conditions are relatively severe.

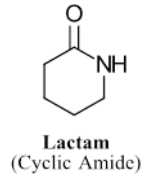


REACTIONS OF AMIDES

Amides are relatively unreactive towards nucleophilic acyl substitutions due to the poor leaving group ability of its nitrogen containing Y group. Despite this, amides can react with water under acidic or basic conditions to create a carboxylic acid through nucleophilic acyl substitution. Reaction of primary amides with thionyl chloride ($SOCl_2$) creates nitriles. Hydride reduction using $LiAlH_4$ causes the carbonyl oxygen of the amide to eliminate as a leaving group creating the corresponding amine.



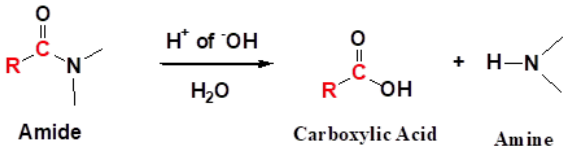
Lactams, cyclic amides, are affected by these reactions in the same fashion as acyclic amides.



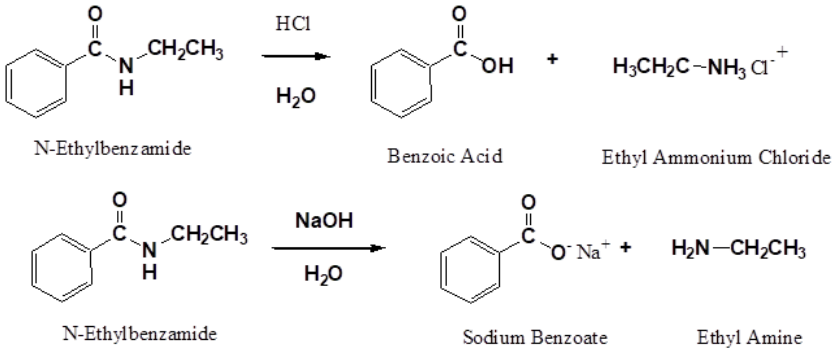
CONVERSION OF AMIDES TO CARBOXYLIC ACIDS: HYDROLYSIS

Amides can be hydrolyzed into a carboxylic acid and ammonia or an amine by heating in an acidic or basic aqueous solution. In both cases, acid-base reactions occurring with the products make the overall reaction irreversible. Under acidic conditions the amine produced by the reaction is protonated to form a non-nucleophilic ammonium compound. Under basic conditions the carboxylic acid produced by the reaction is deprotonated to a non-electrophilic carboxylate.

GENERAL REACTION



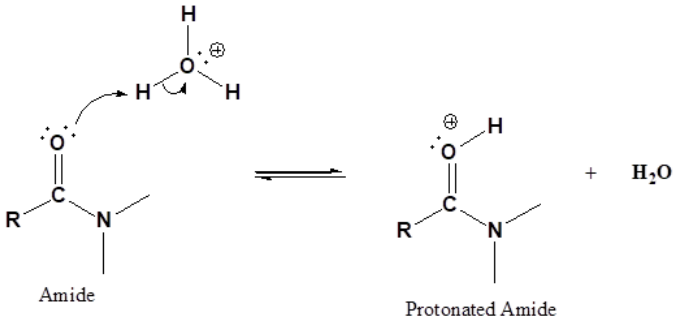
EXAMPLES



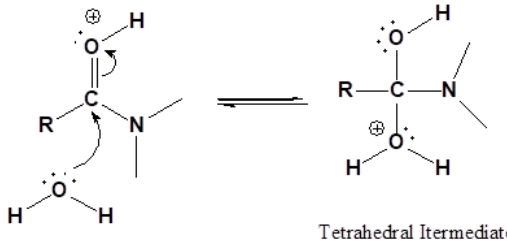
MECHANISM UNDER ACIDIC CONDITIONS

Protonation of the amide increases the electrophilicity of the carbonyl carbon allowing water to add causing formation of a tetrahedral oxonium intermediate. Next a proton is transferred to the amide nitrogen giving it a positive charge and increasing its ability to act as a leaving group. Reforming the carbonyl double bond causes the elimination of an amine as a leaving group, creating a protonated carboxylic acid. In the last step of the mechanism, the produced amine acts as a base, removing a hydrogen, to form a carboxylic acid and an ammonium compound. This final deprotonation step essentially removes the amine from the equilibrium which drives the reaction towards completion. Since the amine is no longer part of the equilibrium, the reaction is effectively irreversible.

1) Protonation of the carbonyl

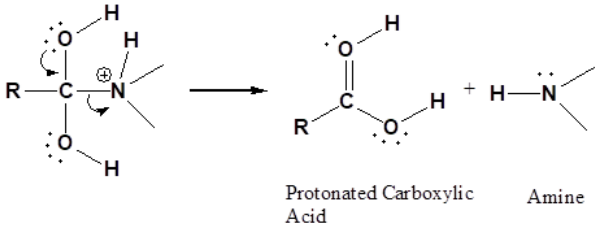


2) Nucleophilic attack by water

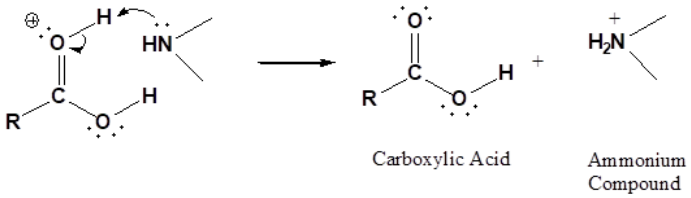


3) Proton transfer

4) Leaving group removal



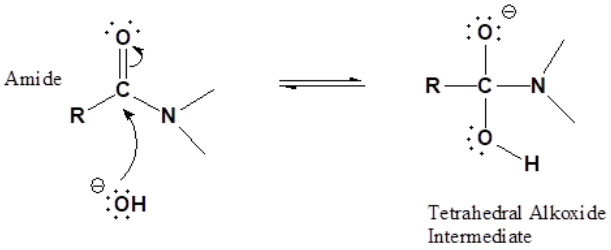
5) Deprotonation



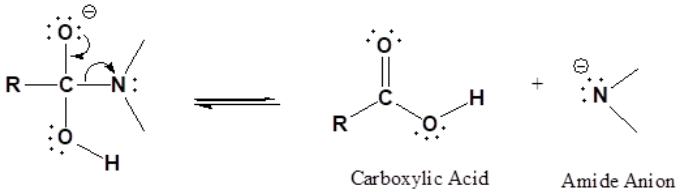
MECHANISM UNDER BASIC CONDITIONS

The base-promoted hydrolysis of an amide follows the typical nucleophilic acyl substitution mechanism. A full equivalent of hydroxide anion is used, so the reaction is called base-promoted and not base catalyzed. The mechanism of basic amide hydrolysis begins with the nucleophilic addition of a hydroxide ion at the carbonyl carbon creating a tetrahedral alkoxide intermediate. The carbonyl bond is reformed along with the elimination of an amide ion (-NHR) leaving group (note this is a different use of the word amide meaning an amine anion), forming a carboxylic acid. In the last step, the amide ion deprotonates the carboxylic acid to form a carboxylate salt and an amine as products. This final deprotonation step essentially removes the carboxylic acid from the equilibrium which drives the reaction towards completion. Since the carboxylic acid is no longer part of the equilibrium, the reaction is effectively irreversible.

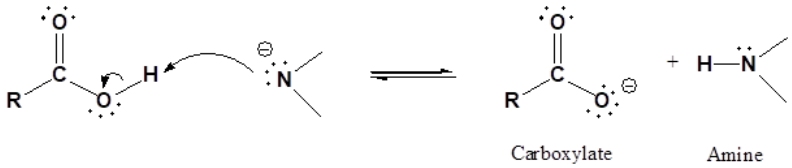
1) Nucleophilic attack by hydroxide



2) Leaving group removal

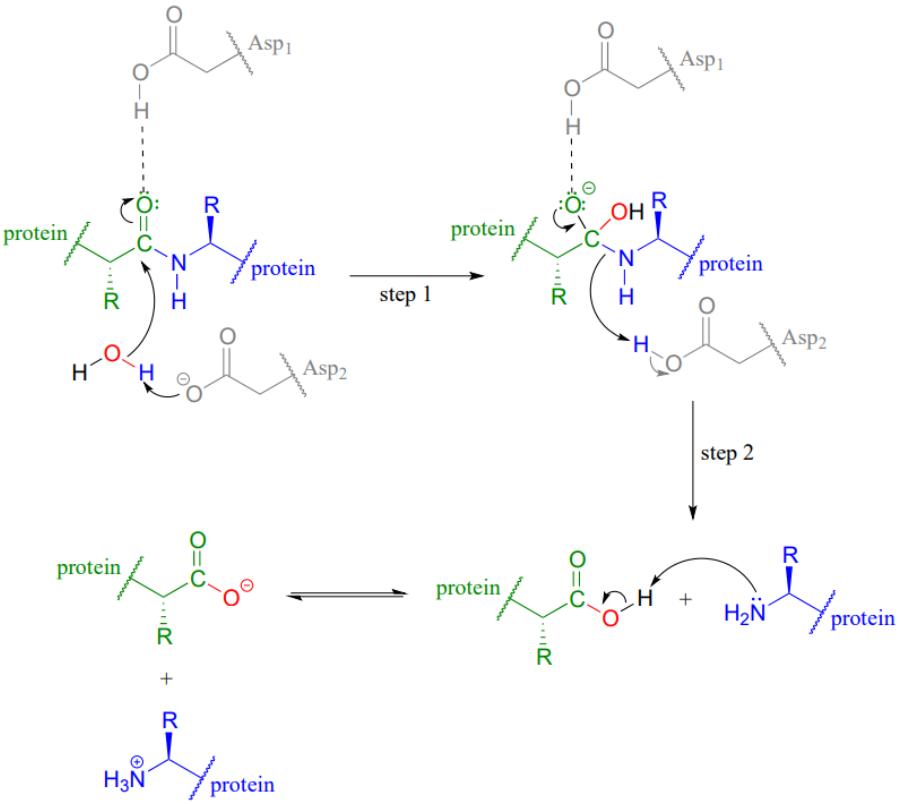


3) Deprotonation



HYDROLYSIS OF PROTEINS

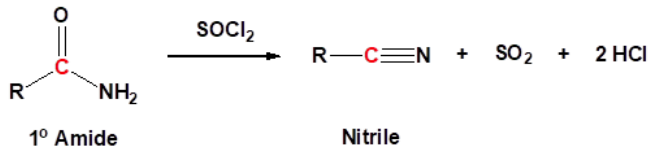
Hydrolysis of amide bonds is the first step in the metabolism of dietary proteins. Protein hydrolysis is catalyzed by protease enzymes (abbreviated Asp_1 and Asp_2 in the figure below). The mechanisms starts with the nucleophilic acyl substitution by water while breaking the amide C-N bond. This produces a protein fragment with an amine and another with a carboxylic acid. The amine fragment will deprotonate the carboxylic acid forming the carboxylate and ammonium fragments.

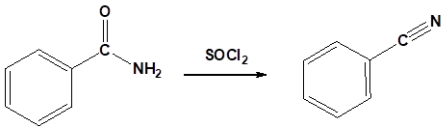


CONVERSION OF 1^{O} AMIDES TO NITRILES: DEHYDRATION

1^{o} Amides can be converted into a nitrile through reaction with thionyl chloride ($SOCl_2$). Sulfurdioxide (SO_2) and hydrochloric acid are produced as byproducts.

GENERAL REACTION

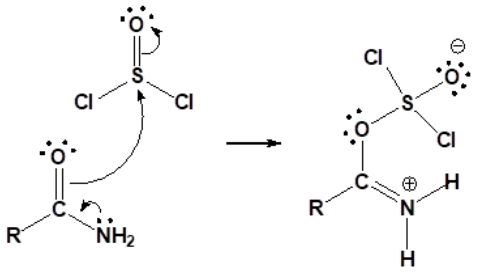




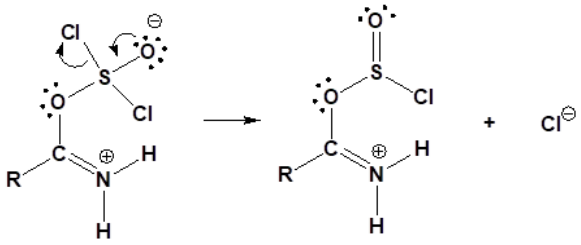
MECHANISM FOR THE CONVERSION OF A 1^{O} AMIDE TO A NITRILE

During the first step of the mechanism, the amide acts as a nucleophile and attacks the electrophilic sulfur of thionyl chloride, pushing the pi electrons of the S=O bond onto oxygen. Removal of a chloride anion as a leaving group allows the sulfoxide S=O bond to reform creating a protonated imine chlorosulfite. Deprotonation forms an imine chlorosulfite intermediate. A second deprotonation eliminates the chlorosulfite leaving group as sulfur dioxide and a chloride anion and forms the C-N triple bond of the nitrile product.

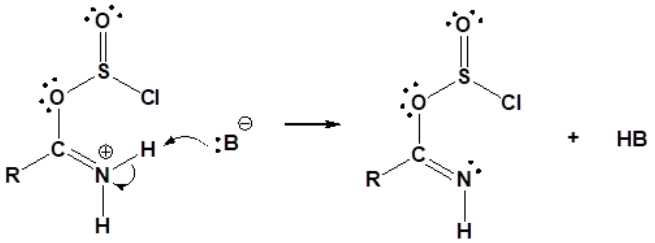
1) Nucleophilic attach on thionyl chloride



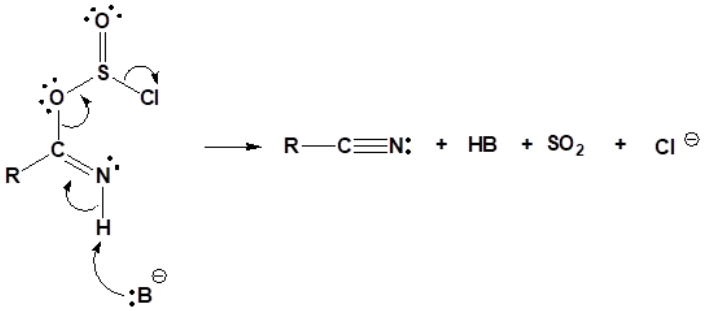
2) Leaving group removal



3) Deprotonation



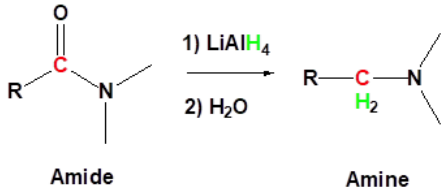
4) Leaving group removal



CONVERSION OF AMIDES TO 1^{O}, 2^{O} OR 3^{O} AMINES: HYDRIDE REDUCTION

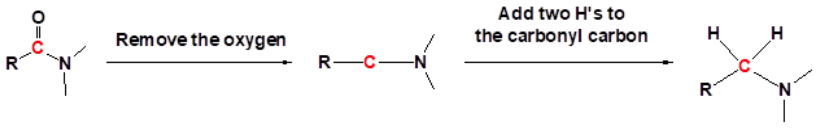
Amides are reduced to amines by treatment with $LiAlH_4$, and this has proven to be one of the most general methods for preparing all classes of amines (1º, 2º & 3º). Due to the nitrogen in the Y group of amides, the outcome of $LiAlH_4$ reductions is distinctly different than for esters since amide anions are poorer leaving groups than alkoxide anions. Furthermore, oxygen forms especially strong bonds to aluminum. During this reaction the carbonyl oxygen of the amide is removed as a leaving group and not the nitrogen containing Y group. Removal of the leaving group allows for a formation of a C=N iminium bond which can accept a second addition of a hydride nucleophile to form the amine.

GENERAL REACTION

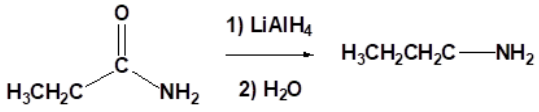


PREDICTING THE PRODUCTS OF A HYDRIDE REDUCTION

There are two major changes in bonding during this reaction: 1) The C=O carbonyl is removed from the starting material 2) Two hydride nucleophiles are added to what was the carbonyl carbon of the amide.

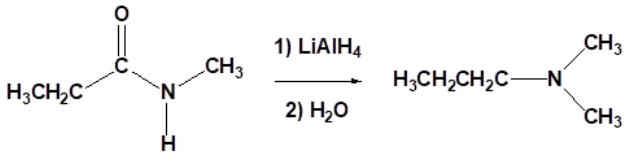


EXAMPLE

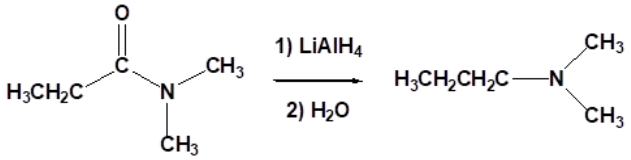


Propanamide — Propyl Amine

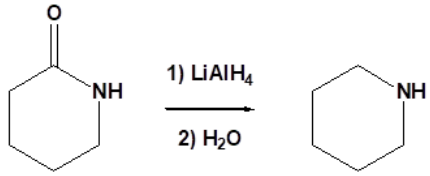
Alkyl groups attached to the nitrogen do not affect the reaction.



N-Methylpropanamide — N-Methylpropylamine



N,N-Dimethylpropanamide — N,N-Dimethylpropylamine

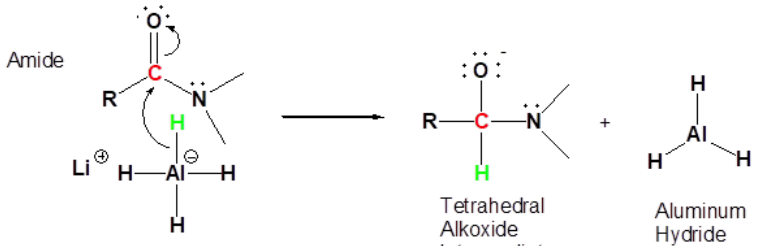


δ-Valerolactam — Piperidine

MECHANISM FOR THE HYDRIDE REDUCTION OF AN AMIDE TO FORM AN AMINE

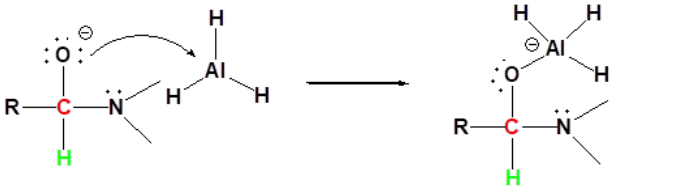
Addition of a hydride nucleophile to the carbonyl carbon of the amide produces a tetrahedral alkoxide intermediate. A Lewis acid-base interaction occurs between the alkoxide (Lewis Base) and AlH_3 (Lewis acid) forming a complex with an O-Al bond. The nitrogen lone pair forms a double bond with the previous carbonyl carbon ejecting a metal oxide species (e.g. $[H3Al–O]^{2–}$) as a leaving group, and while forming an iminium double bond. Addition of a second equivalent of hydride nucleophile to the iminium carbon produces an amine.

1) Nucleophilic attack by the hydride

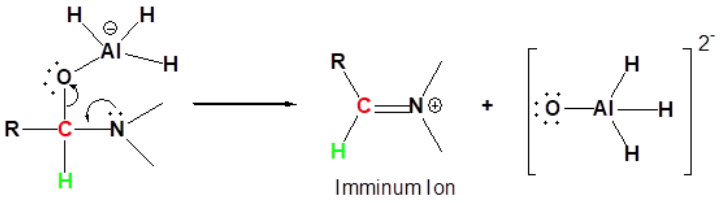


Lithium Aluminum Hydride

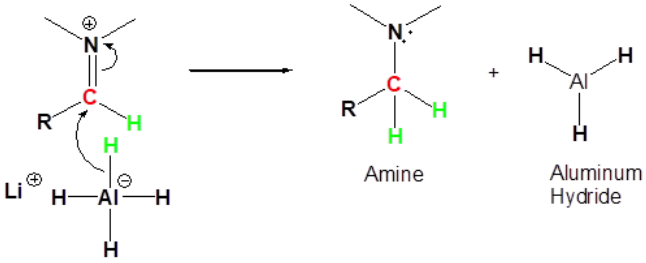
2) Complex formation



3) Leaving group removal

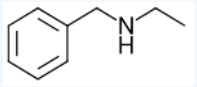


4) Nucleophilic attach by the hydride



EXAMPLE 21.7.1

How could the following molecule be synthesized using an aminolysis of an acid chloride?



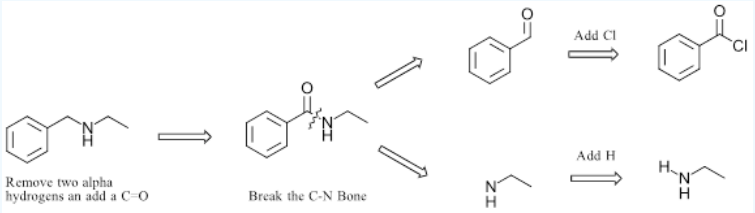
Answer

One of the preferred methods for making amines is through a nucleophilic acyl substitution using an acid chloride and amine to form an amide. The amide is then reduced to the amine during a hydride reduction with $LiAlH_4$.

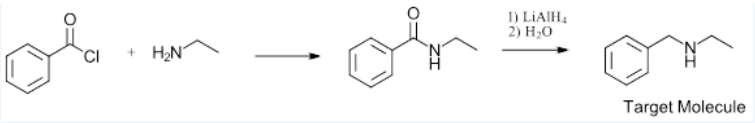
In the first step of retrosynthetic analysis, one of the carbons alpha to the amine nitrogen is converted to a carbonyl thus creating an amide intermediate. The key bond formed during this pathway is the C-N sigma bond between the carbonyl carbon and the nitrogen created during amide formation. Breaking this bond separated the target molecule into the two starting materials for the pathway. The carbonyl carbon gains a –Cl to become an acid chloride and the nitrogen fragment gains an H to become a 1^o amine. In the forward reaction pathway, the acid chloride and the 1^o amine are linked to from an amide in the first step of the reaction. Subsequent hydride reduction of the amide using $LiAlH_4$ produces the amine target molecule.

The target molecule has two alpha carbons which could possibly be converted to a carbonyl. This allows there to be two possible synthetic pathways.

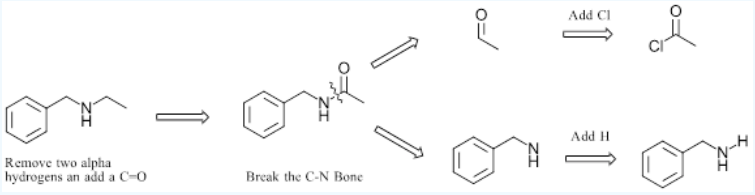
Pathway 1



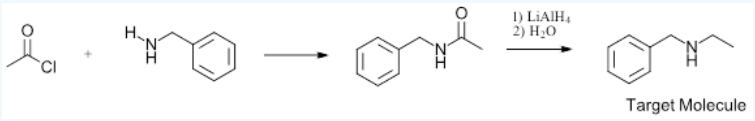
Solution 1



Pathway 2



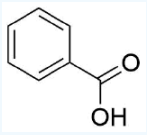
Solution 2



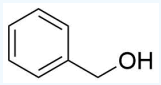
EXERCISE 21.7.1

1) How would you prepare the following compounds from N-Propypl benzamide?

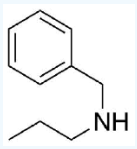
(a)



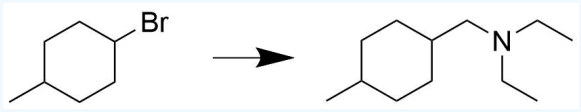
(b)



(c)



2) Propose a synthesis pathway for the following conversion:



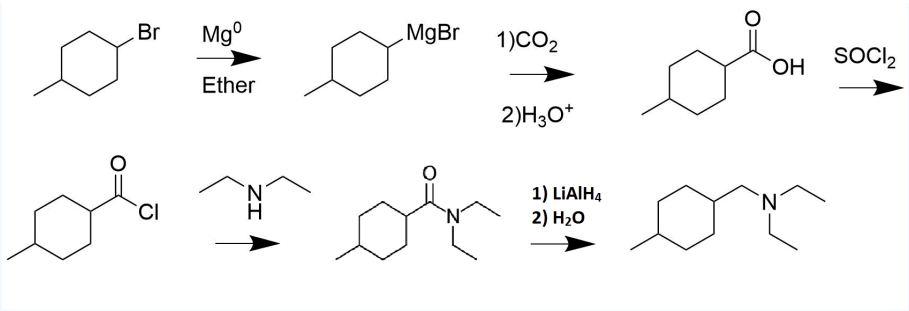
Answer

1) (a) NaOH, H_2O

(b) NaOH, H_2O, then $LiAlH_4$

(c) $LiAlH_4$

2)



21.8: CHEMISTRY OF THIOESTERS AND ACYL PHOSPHATES - BIOLOGICAL CARBOXYLIC ACID DERIVATIVES

OBJECTIVES

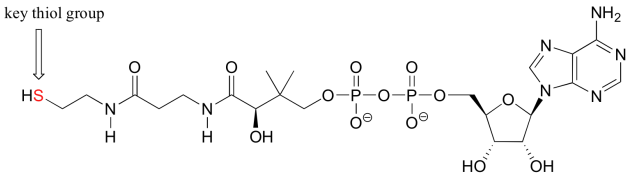
After completing this section, you should be able to

1. discuss, briefly, the role played in nature by acetylating agents, such as acetyl coenzyme A, and explain what is happening in reactions such as the acetylation in biological systems, without necessarily being able to write a detailed equation.
2. rank the reactivity of thioesters and acyl phosphates towards nucleophiles compared with other carboxylic acid derivatives.

INTRODUCTION TO THIOESTERS AND COENZYME A

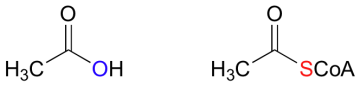
Acyl phosphates and acyl adenosine phosphates are not the only activated forms of carboxylate groups in biochemical reactions. Slightly lower on the reactivity scale are thioesters. In the metabolism of lipids (fats and oils), thioesters are the principal form of activated carboxylate groups. They are employed as acyl carriers, assisting with the transfer of acyl groups such as fatty acids from one acyl X substrate to another.

The 'acyl X group' in a thioester is a thiol. The most important thiol compound used to make thioesters is called coenzyme A, which has the following structure:



Coenzyme A
(HSCoA)

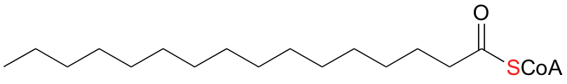
Coenzyme A is often abbreviated HSCoA, in order to emphasize that it is the thiol sulfur that provides the critical thioester linkage to acyl groups. When fuel (carbohydrate and fat) is broken down in your body, it is eventually converted to a simple two-carbon unit called acetyl CoA, which is essentially a thioester derivative of acetic acid:



acetic acid acetyl-SCoA

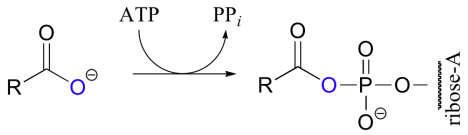
ACTIVATION OF FATTY ACIDS BY COENZYME A: A THIOESTERIFICATION REACTION

In the biologically active form of fatty acids, the carboxylate groups have been converted to thioesters using coenzyme A. For example, the activated form of the C_{16} fatty acid palmitate is:



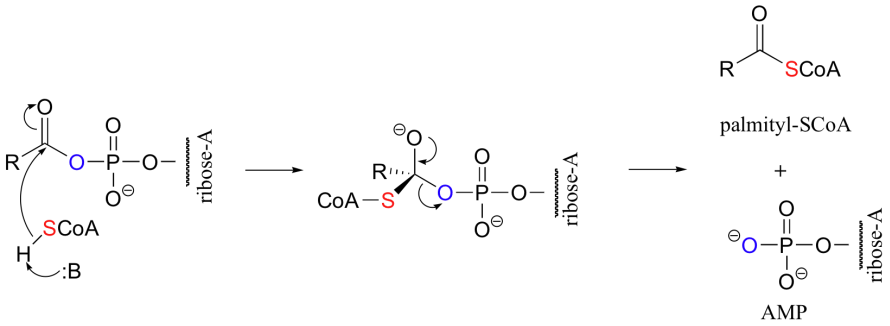
palmityl-SCoA

Let's take a look at how this activation takes place, in a reaction catalyzed by an enzyme called acyl CoA synthetase. You already know that carboxylates are not themselves good substrates for acyl substitution reactions, and must be activated. Thus, you might predict that the first step of this reaction requires ATP to make a high-energy acyl phosphate intermediate. In fact, the activated carboxylate in this case is an acyl-AMP, formed in the same way as the acyl-AMP intermediate in the asparagine synthetase reaction (section 12.2B).



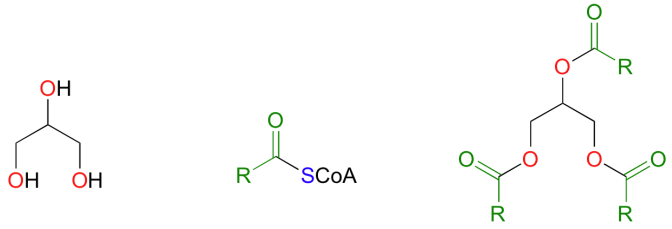
palmitate palmityl-AMP

The activated acyl-AMP intermediate is then attacked by the thiol sulfur of coenzyme A, and the AMP group is expelled to form the fatty acyl CoA.

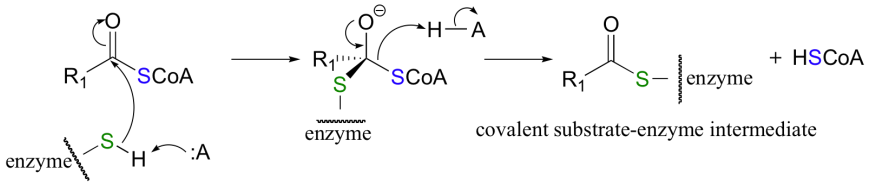


TRANSFER OF FATTY ACYL GROUPS TO GLYCEROL: A THIOESTER TO ESTER SUBSTITUTION

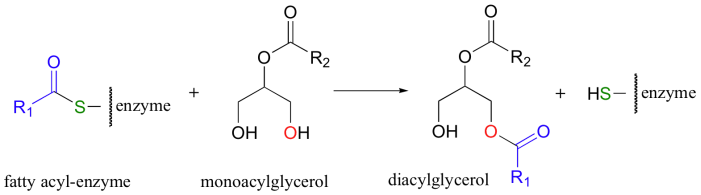
The -SCoA thioester form of the fatty acid is a good substrate for a number of metabolic transformations. This is the form of fatty acid, for example, that is oxidized and broken down for energy in the mitochondria of your cells. Fatty acyl CoA also serves as substrate for the construction of triacylglycerol, which is the fat molecule that your body uses to store energy in fat cells. Recall (section 12.1B) that triacylglycerol is composed of a glycerol 'backbone' connected to three fatty acid groups through ester linkages.



The reaction in which a fatty acid acyl group is linked to glycerol represents the conversion of a thioester (fatty acyl CoA) to an ester. First, however, a **transthioesterification** reaction occurs. A transthioesterification is merely the conversion of one thioester to another. In the case of monoacylglycerolacyltransferase, the fatty acyl group first trades its thioester link to coenzyme A for another thioester link to a cysteine residue in the active site of the enzyme. It is a common strategy for enzymes to first form a covalent link to one substrate before catalyzing the principle chemical reaction.



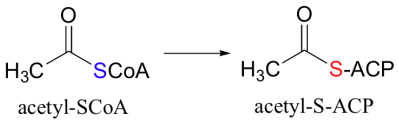
The fatty acyl group is now ready to be transferred to glycerol, trading its thioester linkage to the cysteine for a new ester linkage to one of the alcohol groups on glycerol. The attacking nucelophile in this reaction is of course the alcohol oxygen of monoacylglycerol.



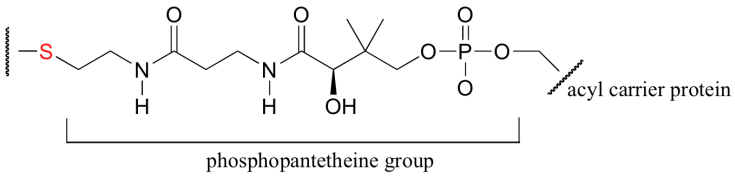
Because esters are more stable than thioesters, this is an energetically downhill reaction.

TRANSTHIOESTERIFICATION REACTIONS

In the previous section we saw one example of a transthioesterification. Another important transthioesterification reaction involves acetyl CoA, the activated form of acetic acid and the basic two-carbon building block for fats and oils. Before it can be incorporated into a growing fatty acid molecule, acetyl CoA must first be linked to a so-called 'acyl carrier protein' (ACP). The acetyl group is linked to the acyl carrier protein *via* a thiol group on a carrier molecule that is covalently attached to the protein.

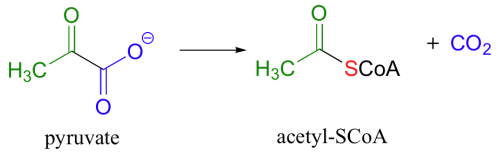


-S-ACP =

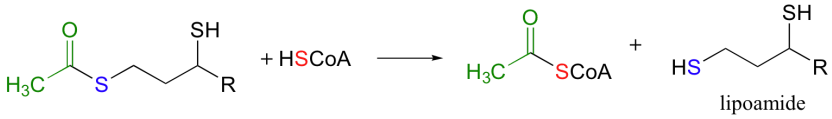


Notice that the structure of this carrier group (called phosphopantetheine) is identical to the region of coenzyme A (structure shown earlier in this section) near the thiol group. Once attached to the ACP, the two-carbon acetyl group condenses with another acyl group (which is also attached to its own ACP), and the fatty acid chain begins to grow. We will study these important carbon-carbon bond forming reactions in section 13.4.

Finally, a transthioesterification is the final step in one of the most important and well-studied reactions in animal metabolism: the conversion of pyruvate to acetyl CoA by a cluster of enzymes called the pyruvate dehydrogenase complex.



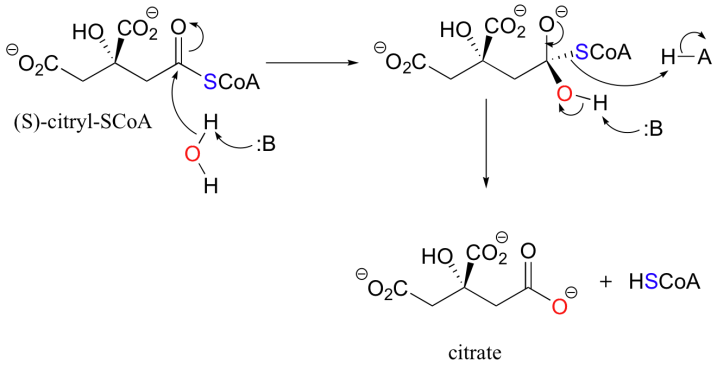
The overall reaction looks simple, but is actually quite complex and involves several intermediate species. The final step in the process is a transthioesterification, involving a dithiol molecule called lipoamide:



We will look more closely at the complete biochemical transformation catalyzed by the pyruvate dehydrogenase complex in section 16.12B.

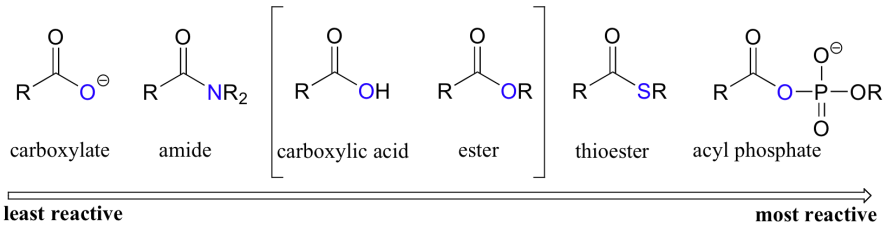
HYDROLYSIS OF THIOESTERS

The acyl group of a thioester can be transferred to a water molecule in a hydrolysis reaction, resulting in a carboxylate. An example of thioester hydrolysis is the conversion of (S)-citryl CoA to citrate in the citric acid cycle (also known as the Krebs cycle).



REACTIVITY OF THIOESTERS AND ACYL PHOSPHATES

Recall from Section 21.2 that thioesters and acyl phosphates are the most reactive among the biologically relevant acyl groups. However, neither is as reactive as an acid chloride or acid anhydride.



Relative reactivity of biologically relevant acyl groups

21.9: POLYAMIDES AND POLYESTERS - STEP-GROWTH POLYMERS

OBJECTIVES

After completing this section, you should be able to

1. write an equation to represent the formation of nylon 66 from adipic acid and hexamethylenediamine.
2. write an equation to represent the formation of nylon 6 from caprolactam.
3. predict the structure of the step-growth polymer formed from the reaction of two given monomers.
4. identify the monomers needed to prepare a step-growth polymer of a given structure.
5. write an equation to describe the formation of a polyester, such as poly(ethylene terephthalate), from a given diol and diester.
6. write an equation to describe the formation of a polycarbonate from a carbonate and a bisphenol.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- chain-growth polymer
- polyamide
- polyester
- step-growth polymer

STUDY NOTES

You may wish to review chain-growth polymerization in Section 8.10 and Section 14.6. In this section we discuss another important class of polymerization kknow as step-growth polymerization.

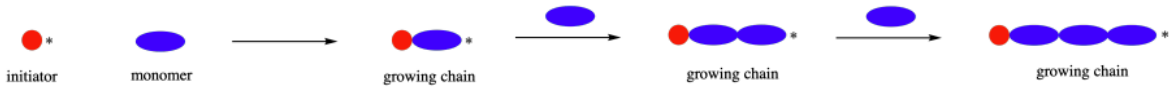
As you can see from the equation given in the discussion on forming condensation polymers, Dacron is formed from two monomers, one of which possesses two carboxylate groups and the other two hydroxyl groups.

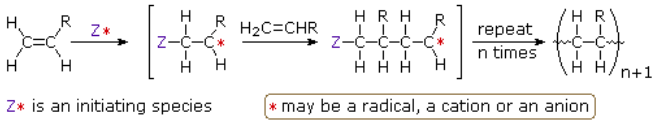
It is also possible to form a polyester using two monomers that each possesse one carboxyl group and one hydroxyl group. An example is the polymer formed between lactic acid and glycolic acid. This polymer has been used to produce absorbable staples that provide surgeons with a convenient method of closing incisions made during operations on the bladder or intestines, or during hysterectomies. Two advantages of this polyester in such applications are, first, that it begins to hydrolyze in the body after six to eight weeks, and then, that the products of the hydrolysis are both compounds normally present in the body.

lactic acid (2-hydroxypropanoic acid) | glycolic acid (2-hydroxyethanoic acid)

STEP-GROWTH POLYMERIZATIONS

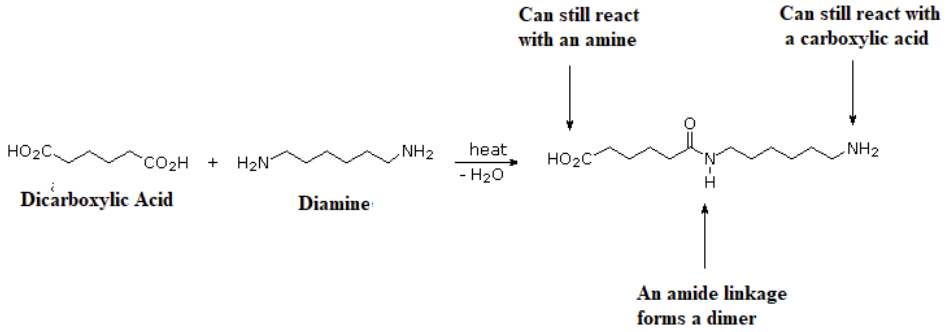
Step-growth and chain-growth are two broad classes of polymerization methods. Sections 8.11 and 14.7 discussed how chain-growth polymers usually start with a single alkene containing monomer, which is unreactive until an initiator is added. The initiator converts one monomer molecule into a reactive intermediate (radical, cation, anion) which is capable of reacting with another monomer forming a C-C bond and creating a new reactive intermediate. This reactive intermediate reacts with another monomer and the process is repeated as a chain reaction to form a polymer.



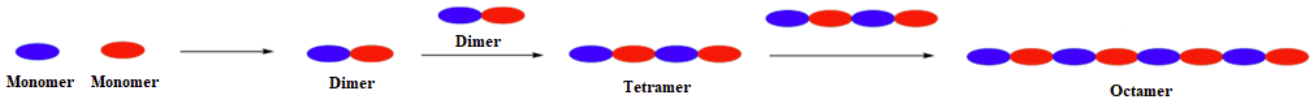


A Chain-Growth Polymerization

The process of step-growth polymerizations are fundamentally different than in chain-growth. In step-growth polymerizations, monomers are generally linked by a carbon-heteroatom bond (C-O & C-N) formed in non-sequential steps. Often, the reactions used to link these monomers include multiple nucleophilic acyl substitutions. Step-growth polymerizations usually use two different monomers, neither of which would undergo polymerization on its own. The two monomers are multifuntional and complementary to each other, such that each provides the other with a reactive partner. In this section, we will be focusing on monomers which are **difunctional**, meaning they contain two of the same reactive functional group. A step-growth polymerization starts with two complementary functional groups on different monomers reacting to form a dimer. Because both monomers were difunctional, each retains a reactive group and can react with additional complementary monomers.

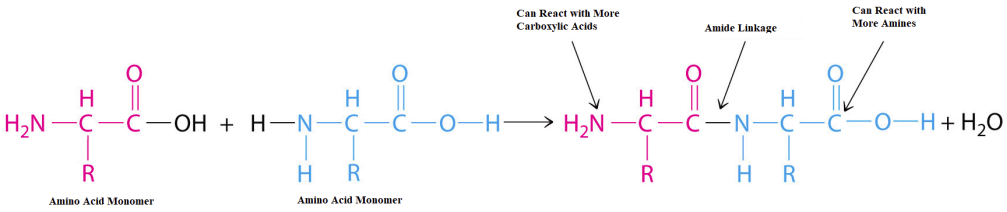


In fact the difuctionality of the monomers, allows step-growth polymers to grow in two directions at once. First, two complementary monomers react with each other to form a dimer. Assuming that monomers react at roughly similar rates, when one end of the dimer reacts again it will likely find another dimer and form a tetramer. Then when the tetramer goes to react again it will most likely find another tetramer and form an octamer. This process is repeated allowing the polymer to grow in two directions at the same time.



The Step-Growth Polymerization Process

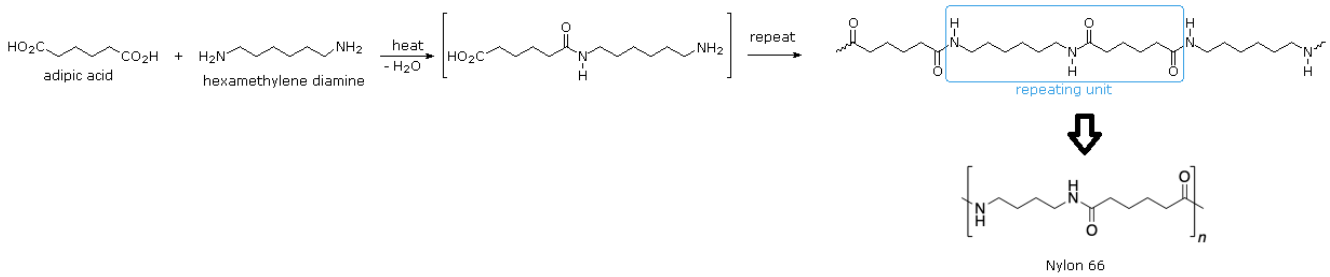
Virtually all fibers are made from some form of polymer. In particular, silk and wool are composed of a naturally occurring protein polymer. The monomers of proteins are called **amino acid residues**. These residues are connected by amide linkages which are also called **peptide bonds**. Many of the early efforts of polymer chemistry were to artificially create fibers which mimicked the properties of silk and wool.



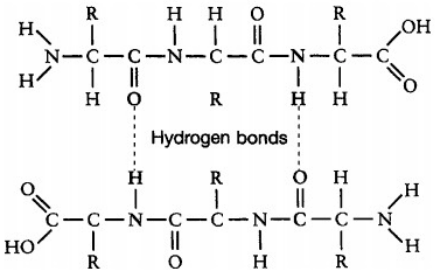
POLYAMIDES

The first fully synthetic polymer fiber, nylon-6,6, was produced in 1938 by the company DuPont. The lead chemist of DuPont's work was Wallace H. Carothers, who reasoned that the properties of silk could be mimicked by constructing a polymer chain created with repeating amide bonds, just like the proteins in silk. Nylon-6,6 was created by first reacting 1,6-hexanedioic acid (adipic acid) and 1,6-hexanediamine to give a salt which was then heated creating multiple amide bonds through nucleophilic acyl substitution. The product of this particular

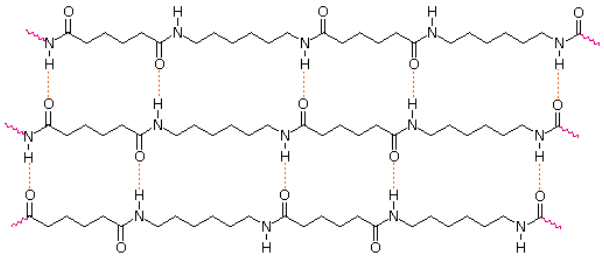
reaction is a polyamide called nylon-6,6. The numbers of the name indicate how many carbons are contained in each monomer. The first "6" stands for the number of carbons in the diamine monomer while the second number indicated the number of carbons in the dicarboxylic acid. Simply by varying the number of carbons in each monomer, a wide variety of nylon polymers can be made.



Nylons are among the most widely used synthetic fibers—for example, they are used in ropes, sails, carpets, clothing, tires, brushes, and parachutes. Known for their high strength and abrasion resistance, nylons can be molded into blocks for use in electrical equipment, gears, bearings, and valves. The strength of nylon fibers comes, in part, from their ability to form strong hydrogen bonding intermolecular forces with each other in much the same fashion as proteins.



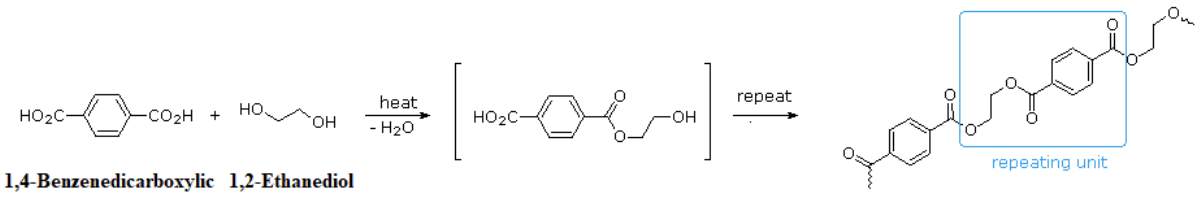
The Hydrogen Bonding between Proteins



The Hydrogen Bonding between Nylon Polyamides

POLYESTERS

Esterfication, via nucleophilic acyl substitutions, can also be used to form the primary linkages in step-growth polymers. A polyester is typically produced when a dicarboxylic acid and a diol are reacted together. After the initial reaction, the ester product contains a free (unreacted) carboxyl group at one end and a free alcohol group at the other. Further esterification using a step-growth polymerization, produces a polyester. The most important polyester, polyethylene terephthalate (PET), is made from the reaction of 1,4-benzenedicarboxylic (terephthalic acid) and 1,2-ethanediol (ethylene glycol) monomers.



1,4-Benzenedicarboxylic 1,2-Ethanediol

poly(ethyleneterephthalate) (PET)

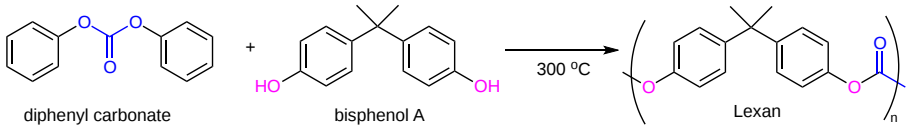
A Polyester

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 and other beverages. It is also formed into films called Mylar. When magnetically coated, Mylar tape is used in audio- and videocassettes.

POLYCARBONATES

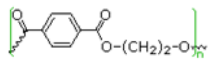
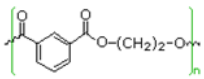
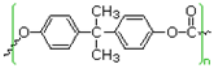
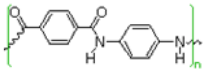
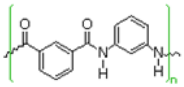
Beyond carboxylic acid derivatives, virtually any reaction which involves reactive species on two different molecules can be used to perform a step-growth polymerization. A variation involves using a monomer containing a carbonate functional group. A carbonate acts like a double ester and can undergo a type of double transesterification reaction with two alcohols to form a new carbonate containing compound.

In effect, a carbonate is difunctional and can be reacted with a diol to form polymers containing repeated carbonate groups in their structure called polycarbonates. An example of a polycarbonate is the polymer, Lexan, which is created when diphenyl carbonate and bisphenol A (a diol) are reacted together.



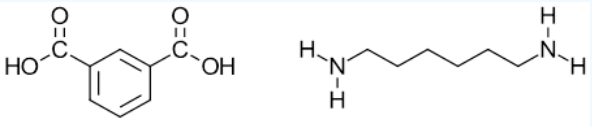
Polycarbonates used in engineering are strong, tough materials, and some grades are optically transparent. They are easily worked, molded, and thermoformed. Because of these properties, polycarbonates find many applications. One major application of polycarbonates is the production of compact discs, DVDs, and Blu-ray discs.

Bisphenol (BPA), primarily used to make polycarbonate, is one of the highest-volume chemicals produced in the world, with over six billion pounds made each year. Because polycarbonate is used to make plastic bottles, the lining for food cans, and the lining for beverage cans there has been much concern about trace amounts of BPA leaching from the containers and being ingested. A study conducted in 2003 and 2004 by the Center for Disease Control and Prevention found trace amounts BPA in the tissues of 93% of people in the United States. Consequently, this has led to many beverage companies switching to non-polycarbonate 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

EXAMPLE 21.9.1

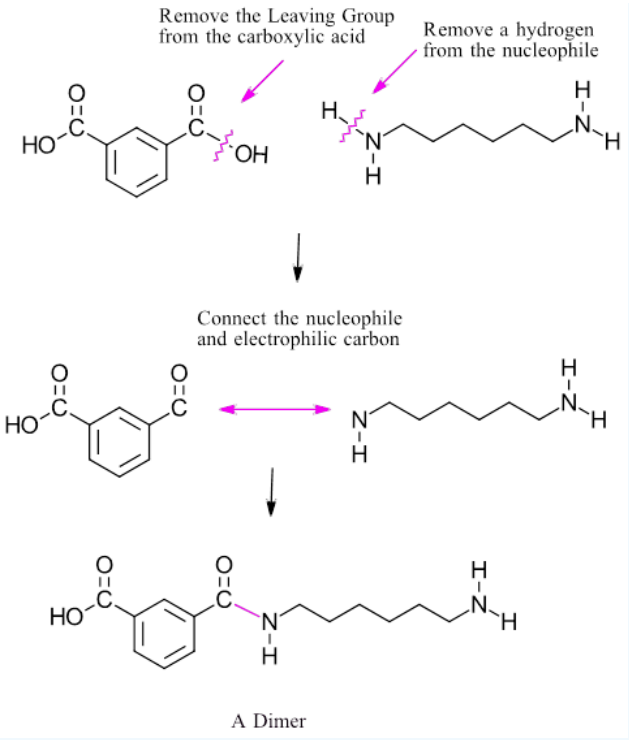
Provide the structure of the polyamide made from the monomers as indicated. Please use bracketed notation.



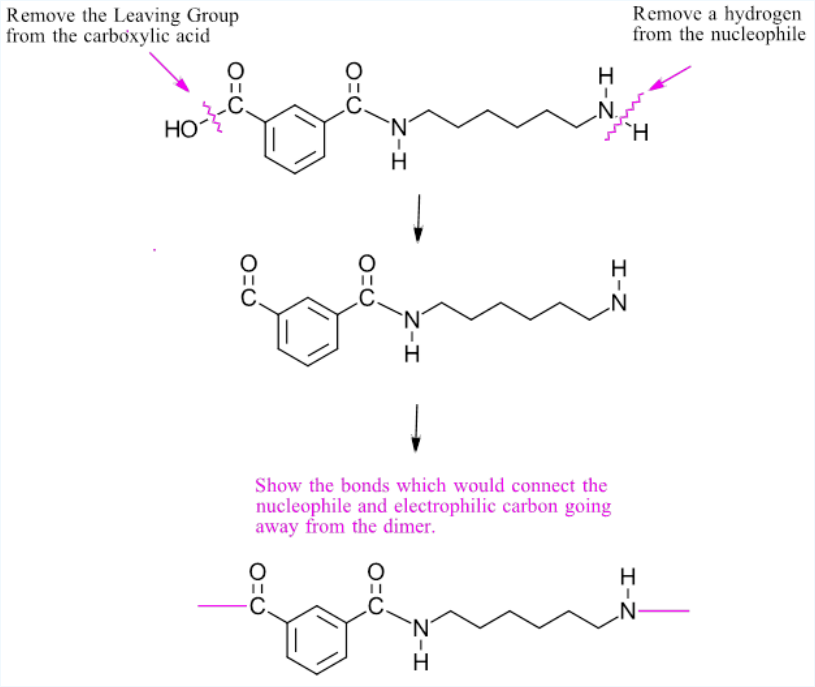
Solution

When drawing the polymer product of a step-growth polymerization, it is important to first identify the reaction which forms the repetitive linkage between monomers. In this case, the reaction is anucleophilic acyl substitution btween a carboxylic acid and an amine to form an amide. In total, the bracket structure of a polymer shows two versions of the linkage formation. The first is clearly shows connecting the monomers to form the dimer making up the repeating unit in the polymer. The second version involves bonds going out of the bracket and represents how the linkage repeats throughout the polymer.

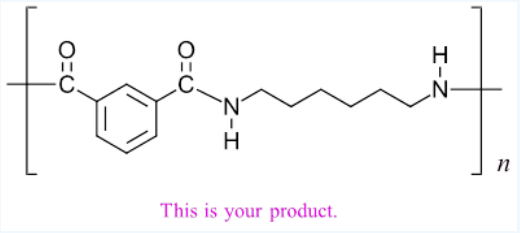
1) The connect two monomers to make a dimer using the indicated reaction.



2) Beak the same bonds as before ecepptt the bonds for the final connection will be shown going away from the dimer.

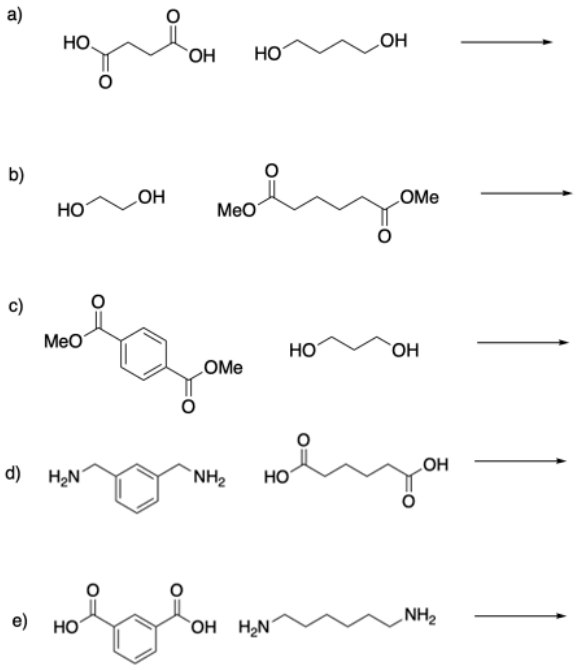


3) Place brackets around the dimer and put an italicized lower case "n" in the lower right.

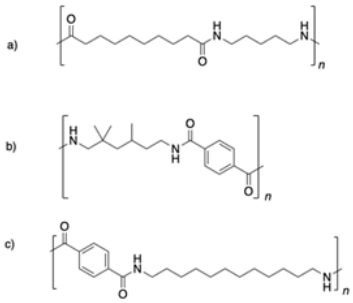


EXERCISES

1) Provide structures of the polyesters made from the monomers as indicated.

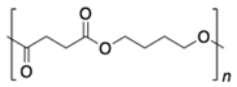


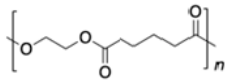
2) Identify the monomers that would be used to produce these polymers.

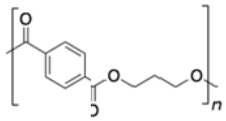


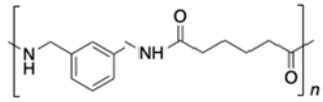
SOLUTIONS

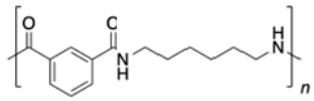
1)

a) 

b) 

c) 

d) 

e) 

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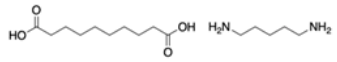
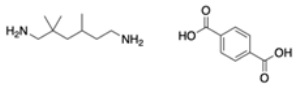
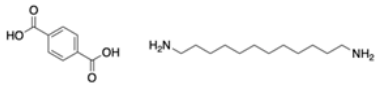
a) 

b) 

c) 

21.10: SPECTROSCOPY OF CARBOXYLIC ACID DERIVATIVES

OBJECTIVES

After completing this section, you should be able to

1. identify the region of the infrared spectrum in which absorptions resulting from the carbonyl group of carboxylic acid derivatives occur.
2. identify the characteristic features of the infrared spectra of acid anhydrides and nitriles that allow us to use infrared spectroscopy to distinguish between these compounds and the others discussed in this unit.
3. use a table of characteristic infrared absorptions to interpret the infrared spectra of carbonyl-containing compounds.
4. use infrared spectroscopy and ^{1}H NMR spectroscopy in the deduction of the structure of an unknown compound.

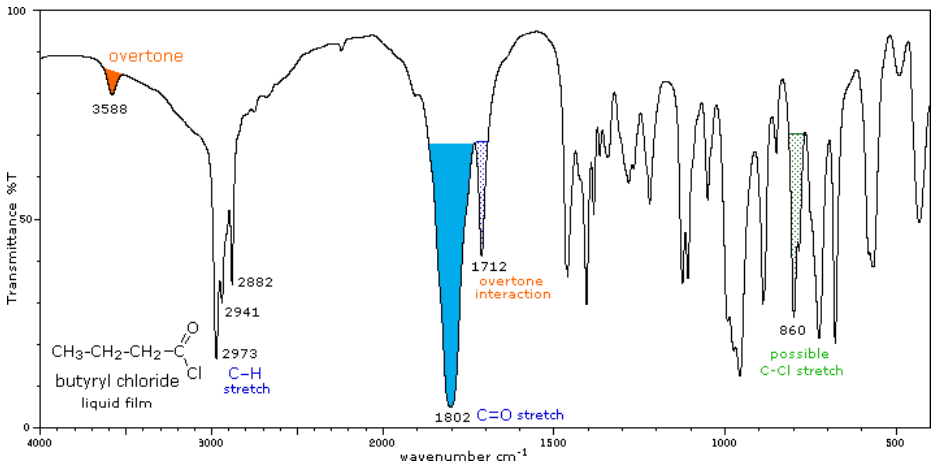
STUDY NOTES

Note: You should recognize that protons on carbon atoms next to carbonyl groups are slightly deshielded, and absorb near 2 δ in the ^{1}H NMR spectrum.

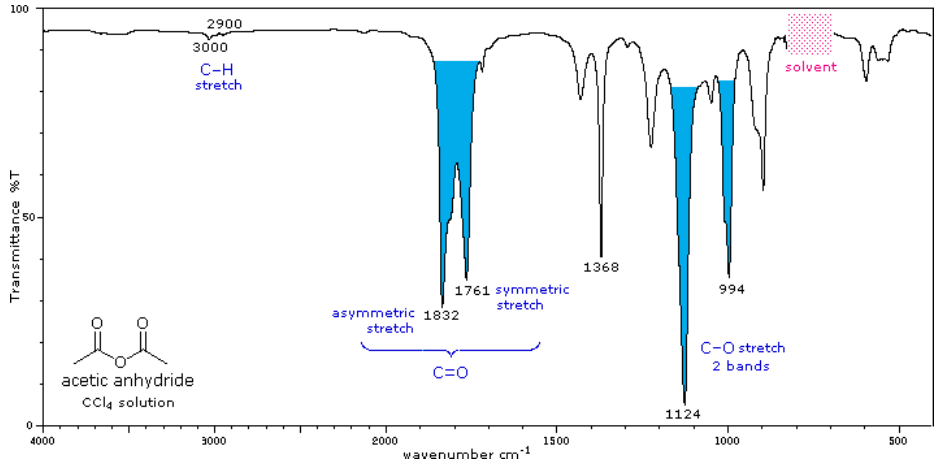
The influence of heteroatom substituents on the reactivity of carbonyl functions toward nucleophiles was discussed earlier with respect to carboxylic acid derivatives. A useful relationship exists between the reactivity of these derivatives and their carbonyl stretching frequencies. Thus, the very reactive 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.

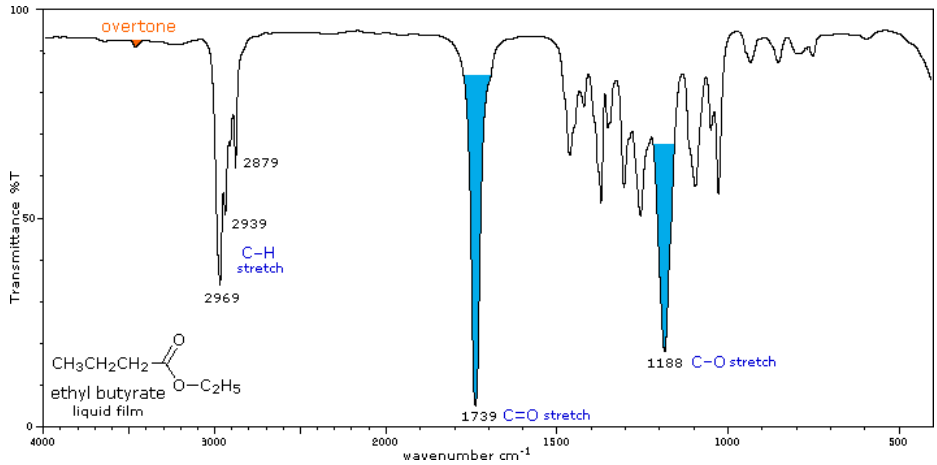
Carbonyl Derivative	Carbonyl Absorption	Comments
Acyl Halides (RCOX)	**C=O stretch**	Conjugation lowers the C=O frequencies reported here, as with aldehydes & ketones. In acyl chlorides a lower intensity shoulder or peak near 1740 cm^{-1} is due to an overtone interaction.
X = F	1860 ± 20 cm^{-1}	
X = Cl	1800 ± 15	
X = Br	1800 ± 15	
Acid Anhydride, $(RCO)_2O$	**C=O stretch** (2 bands)	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.
acyclic	1750 & 1820 cm^{-1}	
6-membered ring	1750 &1820	
5-membered ring	1785 & 1865	
Esters & Lactones (RCOOR')	**C=O stretch**	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}
esters	1740 cm ± 10 cm^{-1}	
6-membered lactone	1740 cm ± 10	
5-membered lactone	1765 cm± 5	
4-membered lactone	1840 cm ± 5	
Amides & Lactams ($RCONR_2$)	**C=O bands**	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.
1° & 2°-amides	1510 to 1700 cm^{-1} (2 bands)	
3°-amides	1650± 15 (one band)	
6-membered lactams	1670 ± 10 (one band)	
5-membered lactams	1700 ± 15	
4-membered lactams	1745 ± 15	



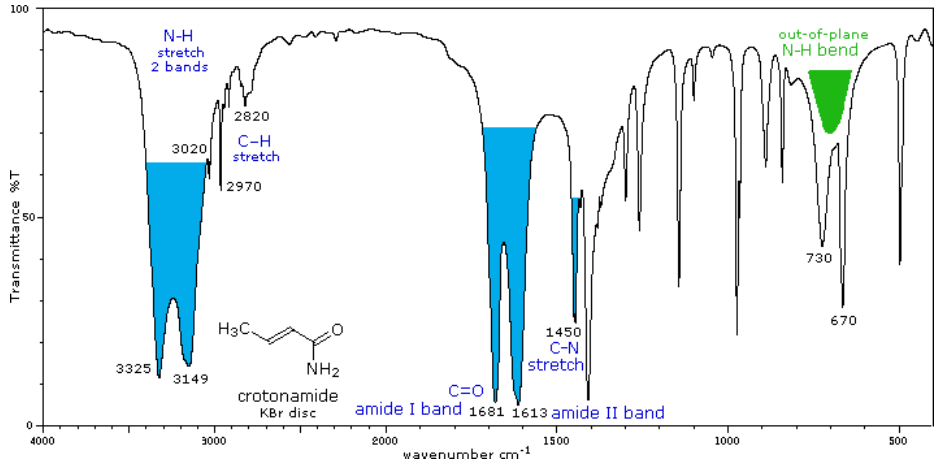
IR - Carbonyl peak of an acid halide



IR - Carbonyl and carbon-oxygen single bond peaks of an acid anhydride



IR - Carbonyl and carbon-oxygen single bond peaks of an ester



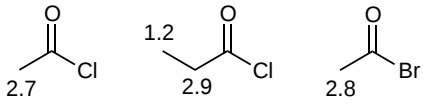
IR - Carbonyl, carbon-nitrogen and nitrogen-hydrogen bond peaks of an amide

^{1}H NUCLEAR MAGNETIC SPECTROSCOPY

Alpha protons of carboxylic acid derivatives, due to the presence of a carbonyl, resonate in the 2.0-3.0 ppm region of a ^{1}H NMR spectra. The downfield shift occurs from deshielding due to higher electronegativity of the sp^2 hybridized carbonyl carbon relative to the sp^3 hybridized alpha carbons. This effect is reduced for protons which are further from the carbonyl group as seen in the figure below.

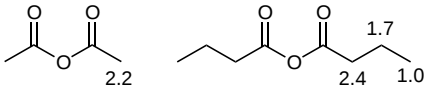
ACID HALIDES

The X groups of acid halides do not contain additional protons and thus do not provide any distinctive ^{1}H NMR peaks. The protons on carbon adjacent to the carbonyl appear at similar chemical shift to other carbonyl containing compounds (2-3 ppm).



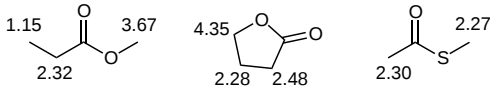
ACID ANHYDRIDES

Many anhydrides used in organic chemistry are symmetrical, therefore the alkyl chains on either side of the carbonyls produce equivalent protons.



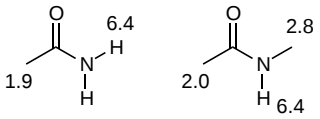
ESTERS AND THIOESTERS

The Y groups of esters, and thioesters have alkyl groups attached to their heteroatom which provide additional ^{1}H NMR peaks. Protons on carbons attached to the alkoxide oxygen in esters show up in the 3.5-4.5 ppm region while those attached to the sulfur in thioesters show up in the 2.0-3.0 ppm region. The downfield shift in these protons is attributable to the deshielding caused by the electronegativity of oxygen and sulfur.

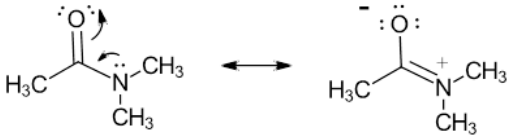


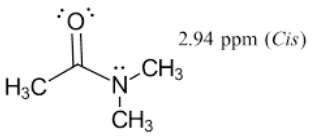
AMIDES

Amides have the possibility of alkyl groups or hydrogens attached to their Y group both of which provide distinctive ^{1}H NMR peaks. Resonances from protons directly attached to the carbon bonded to nitrogen in an amide tend to resonate in the 2.0-3.0 ppm region of an NMR spectra. The NH protons of primary and secondary amides resonate in the 7.5-8.5 ppm regions. Like other hydrogen bonding protons, these NH proton peaks appear broad and can be washed out by the hydrogen-deuterium exchange created by D_2O addition.



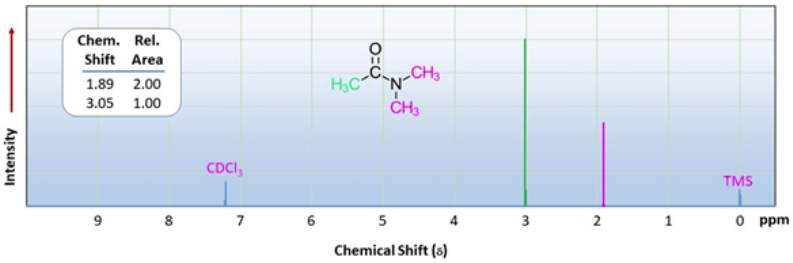
An interesting facet of amide structure is shown when looking at the ^{1}H NMR spectra of N,N-dimethylacetamide. The two N-methyl groups are in fact non-equivalent and appear as two singlets with difference chemical shifts. Resonance in the amide bond provides a significant amount of double bond character reducing the rate of rotation about the OC-N bond. The rotation is slow enough that on the time scale of an NMR experiment the two methyl appears to be frozen as if it is part of a double bond. This causes the N-methyl groups to have different chemical shifts because one appears to be cis to the carbonyl oxygen and the other trans during an NMR experiment.





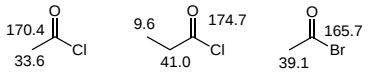
2.94 ppm (*Cis*)

3.02 ppm (Trans)

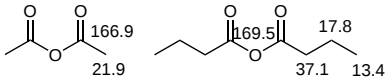


^{13}C NUCLEAR MAGNETIC SPECTROSCOPY

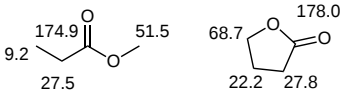
The carbonyl carbons of carboxylic acid derivatives are strongly deshielded (160-180 ppm) due to the close presence (due to the double bond) of a highly electronegative oxygen. However, they are not as deshielded as the carbonyl carbon of an aldehyde or ketone (180-220 ppm) due to the electron donating effects of the Y group. Carbons attached to the alkoxide oxygen of esters appear in the range of 50-90 ppm. Carbons attached to the nitrogen of an amide appear in the 20-65 ppm range and those attached to the sulfur of thioesters appear at 20-45 ppm.



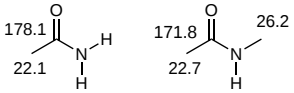
Acid halide ^{13}C NMR chemical shifts (ppm)



Anhydride ^{13}C NMR chemical shifts (ppm)



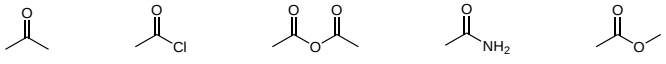
Ester ^{13}C NMR chemical shifts (ppm)



Amide ^{13}C NMR chemical shifts (ppm)

UV/VIS SPECTROSCOPY

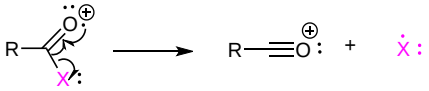
Carboxylic acid derivatives show the n→π* absorption typical for carbonyl containing compounds. The Y group of acid derivatives give a hypsochromic shift (wavelength lowering) to the absorption due to the inductive effect of the electronegative oxygen, nitrogen, and halogens present. Electrons are inductively removed from the carbonyl carbon which causes the lone pair electrons on the carbonyl oxygen to be held more firmly. This causes them to require higher energy photons to transition which corresponds to a lower wavelength λ_{max} when compared to other carbonyls such as a ketone.



UV-Visible absorption of carbonyl compounds (showing λ_{max} in nm)

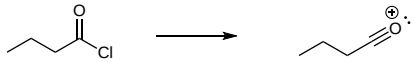
MASS SPECTROMETRY

In the mass spectra of most carboxylic acid derivatives, the base peak is due to the cleavage of C-Y bond to form an acylium ion (R-CO$^+$). Other than the molecular ion peak, the acylium ion is one of the only major peaks present in the mass spectra of acid halides and thioesters. Amide and ester often show additional fragmentations.



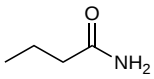
Acid halides

The molecular ion peak of acid chlorides is often not seen. When they do occur, acid chlorides and acid bromides would have an important M + 2 peak due to the two isotopic forms of the halogens. The base peak fragmentation involves the alpha cleavage of C-X bond to from an acylium ion. In butanoyl chloride this peak shows up at m/z = 72.

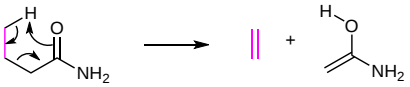


Amide

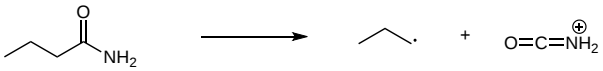
Amides, like other compounds containing nitrogen, follow the Nitrogen Rule. This means that a compound with an odd number of nitrogen atoms will also have an odd-numbered molecular weight. This is shown in butanamide (C_4H_9NO) which has the odd-numbered molecular weight of 87.12 g/mol.



Primary amides show a base peak due to the McLafferty rearrangement which appears at m/z = 59. Secondary and tertiary amides give analogous peaks at higher m/z values.

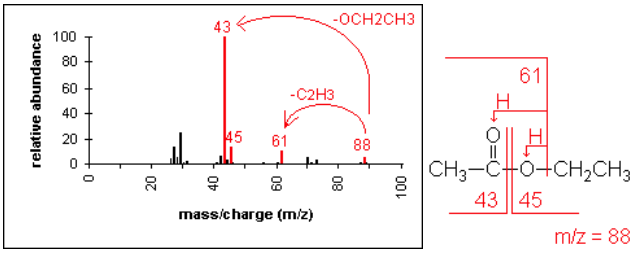


Amides can also cleave the alkyl group attached to the carbonyl forming an amide stabilized acelium ion. For butanamide, like other primary amines, this peak shows up at m/z = 44.



Ester

Esters have multiple fragmentation pathways which are often dependent on the overall size of the ester. The most important fragmentation appears due to alpha-cleavage bond of the C-O to produce the corresponding acylium ion RCO^+. In the mass spectra of ethyl acetate the acylium ion peak appears at 43 m/z and the alkoxy ion peak (RO^+) shows up a 45 m/z. Other important fragments include the loss or the alkyl group (R^+) from the acyl side and the alkoxy side of the ester. Loss of the alkyl group on the alkyoxy side of ethyl acetate ($^+CH_2CH_3$) produces a peak at m/z 61.



SDBSWeb : https://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, date of access

NIST Chemistry WebBook: https://webbook.nist.gov/chemistry/ (National Insitute of Standards and Technology)

21.S: CARBOXYLIC ACID DERIVATIVES (SUMMARY)

CONCEPTS & VOCABULARY

21.0 Chapter Objectives and Introduction to Carboxylic Acid Derivatives

- Carboxylic acid derivatives formed when the hydroxyl group of the carboxylic acid is replaced by a different group.
- Carboxylic acid derivatives are also known as acyl derivatives.
- Many types of carboxylic acid derivatives, the chapter focused on acid halides (acyl halides), anhydrides, esters, amides, thioesters, and acylphosphates.
- Cyclic esters are referred to as lactones and cyclic amides are referred to as lactams.
- Nucleophilic acyl substitution reactions convert the carboxylic acid to one of the derivatives.

21.1 Naming Carboxylic Acid Derivatives

- Acid halide are named following the IUPAC rules with the carboxylic acid ending with -oyl or -yl and the halide ending in an -ide.
- Anhydrides are named following the IUPAC rules with the carboxylic acid ending -acid being replaced by -anhydride.
- Esters are named following the IUPAC rules with the carboxylic acid ending with -oic acid being replaced by -ate and the alkoxy alkyl chain as a substituent.
- Thioesters are named following the IUPAC rules with the carboxylic acid ending with -oic acid being replaced by -thioate and the sulfide alkyl chain as a substituent.
- Primary amides are named following the IUPAC rules with the carboxylic acid ending with -oic acid being replaced by -amide.
- Secondary or tertiary amides are named as primary amides are, but in additon an upper case N is used to designate the alkyl groups attached to the nitrogen atom, which are names as substituents.
- Cyclic amides (lactams) use a Greek letter to identify the location of the nitrogen in relation the carbonyl group.
- Acyl phosphates are named following the IUPAC rules with the carboxylic acid ending with -oyl or -yl and -phosphate.

21.2 Nucleophilic Acyl Substitution Reactions

- Carboxylic acid derivatives contain an electronegative heteroatom (typically oxygen, nitrogen, sulfur, or phosphorus) bonded directly to the carbonyl carbon represented by the symbol Y.
- The acyl group is the remainder of the molecule, which includes the carbonyl and the attached alkyl group.
- The Y group acts as a leaving group during the nucleophilic acyl substitution reaction.
- Stability of the negative charge on the Y group can be guaged by the pK_a of its corresponding acid (HY).
- Carboxylic acid derivatives undergo a reaction called nucleophilic acyl substitution.
- The electrophile is the carbon of the carbonyl, which undergoes an attack by a nucelophile followed by the elimination of the Y group in the carboxylic acid derivative.
- The Y group is substituted for the nucleophile.
- The reactivity of the carboxylic acid derivatives depends on the stability of the carbonyl and the effectiveness of the leaving group.
- Stabilization of the carbonyl reduces the electrophilic character of the carbonyl group.
- The ability of the leaving group to stabilize negative charge creates a more effective leaving group.
- More reactive carboxylic acid derivatives can be used to make less reactive carboxylic acid derivatives.

21.3 Nucleophilic Acyl Substitution Reactions of Carboxylic Acids

- The hydroxyl of a carboxylic acid is a poor leaving group, but activating the carbonyl and converting the hydroxyl to a better leaving group allow for reactions to occur.
- Carboxylic acids can be converted to acid chlorides using thionyl chloride ($SOCl_2$).
- Carboxylic acids can be converted into anhydrides by condensing two carboxylic acids together and the loss of water.
- Carboxylic acids can be converted into esters in two ways.
  - Using the carboxylate in an SN_2 mechanism.
  - The Fischer Esterification
    - Acid catalyzed
    - Pushing equilibrium in the forward direction using Le Chatelier's principle
- Carboxylic acids can be converted into amides in two ways.
  - Direct conversion by heating ammonium carboxylate salts
  - Using a coupling agent like dicyclohexylcarbodiimide (DCC)
- Carboxylic acids can be reduced to primary alcohols using lithium aluminum hydride or borane tetrahydrofurane (THF).
- In biological chemistry, carboxylate anions are converted to an acyl phosphate, which requires phosphrylation using TAP as the phosphate donor or thioesters using coenzyme A.

21.4 Chemistry of Acid Halides

- Carboxylic acids react with thionyl chloride to form acid chlorides.
- Carboxylic acids react with phosphorus tribromide to form acid bromides.
- Acid chlorides are the most reactive carboxylic acid derivative, which allows them to easily convert to other acyl compounds.
- Acid chlorides undergo hydrolysis to form carboxylic acids.
- Acid chlorides react with carboxylic acid to from anhydrides through a nucleophilic acyl substitution.
- Acid chlorides react with alcohol nucleophiles to produce esters with pyridine being used to neutralize the HCl produced.
- Acid chlorides can be reduced to aldehydes using hindered reducing agents that have only one equivalent of hydride.
- Acid chlorides react with amines to form amides, usually an excess of amine is used to neutralize the HCl produced.
- Acid chlorides react with Grignard reagents to from tertiary alcohols.
- Acid chlorides react with Gillman reagents to produce ketones.

21.5 Chemistry of Acid Anhydrides

- Anhydrides generally made by nucleophlic acyl substitution reactions using an acid chloride and a carboxylic acid or carboxylate anion.
- Anhydrides are not as reactive as acid chlorides, but still undergo many of the same reactions.
- Asymmetrical anhydrides not used to make amides or esters since multiple products can be formed.
- Anhydrides undergo hydrolysis to form carboxylic acids.
- Anhydrides react with alcohol nucleophiles to produce esters.
- Anhydrides can react with amines to form the corresponding amides.

21.6 Chemistry of Esters

- Esters are present in many biologically important molecules.
- Esters are often the sources of pleasant aromas of many fruits and perfumes.
- Esters are also present in commercial and synthetic applications.
- Esters are prepared
  - most often using nucleophilic acyl substitution using an acid chloride and an alcohol
  - using nucleophilic acyl substitution using an anhydride and an alcohol
  - using nucleophilic acyl substitution using a carboxylic acid and an alcohol
  - deprotonating a carboxlylic acid for an SN_2 reaction
- Esters can be converted to a carboxylic acid through a reaction witt water and a catalytic amount of strong acid.
- Saponification is the reaction between an ester and water under basic conditions to produce a carboxylate anion.
- Esters can be inter-converted using a transesterfication reaction.
- Esters can be converted into amides using an ester and a large excess of amine.
- Esters can be reduced to primary alcohols using lithium aluminum hydride.
- Like acid chlorides, esters can be reduced to aldehydes using weak, bulky reducing agents.
- Esters can react with Grignard reagents to form tertiary alcohols.

21.7 Chemistry of Amides

- Amides make up the backbone of proteins when the amino group of one amino acid reacts with the carboxylate carbon of another amino acid and from an amide linkage (peptide bond).
- Amides are most commonly prepared through the reaction of an acid chloride and amine.
- Amides are relatively unreactive towards nucleophilic acyl substitutions due to the poor leaving group ability of its nitrogen containing Y group.
- Amides can be hydrolzyed to a carboxylic acid and ammonia or amine by heating the reaction under acidic or basic aqueous solutions.
- Hydrolysis of amines is the first step in metabolism of dietary proteins.
- Primary amines can be converted into a nitrile through a reaction with thionyl chloride.
- Amides are reduced to amines by treatment with lithium aluminum hydride.

21.8 Chemistry of Thioesters and Acyl Phosphates - Biological Carboxylic Acid Derivatives

- Acyl phosphates, acyl adenosine phosphophates, and thioesters are all activated forms of carboxylate groups in biochemical reactions.
- Carboxylate groups of fatty acids are converted to thioesters using coenzyme A
- Thioesters are a good substrate for a number of metabolic transformations.
- Thioesters can be hydrolyzed, resulting back to a carboxylate anion.
- Thioesters and acyl phosphates are the most reactive biologically relevant acyl groups, but not as reactive as an acid chloride or anhydride.

21.9 Polyamides and Polyesters - Step-Growth Polymers

- Step-growth is one of two broad classes of polymerization methods.
- Step-growth polymerizations are linked by a carbon-heteroatom bond formed in non-sequential steps.
- A step-growth polymerization starts with two complementary functional groups on different monomers reacting to form a dimer.
- Using a difunctional monomer, allows step-growth polymers to grow in two directions at once.
- Fibers are made from some form of polymer.
- Nylon
  - First successful fully synthetic polymer was nylon-6,6 in 1938 by the company DuPont, which is a polyamide.
  - Nylons are widely used synthetic fibers, which are found in commercial products such as rope, sails, clothing, and more.
- Esterfication
  - Can also be used to form primary linkages in step-growth polymers.
  - Polyester is typically produced when a dicarboxylic acid and a diol react together.
  - The most important polyester is polyethylene terephthalate (PET), which is used to make bottles for soda.
  - Polyesters are fibers often used in many fabrics.
- Polycarbonates
  - Monomer is a carbonate, which acts like a double ester and can undergo a type of double transesterification reaction with two alcohols.
  - A carbonate is difunctional and can react with a diol to form polymers called polycarbonates.
  - Used in engineering because they are strong materials, but easily molded.
  - Polycarbonates are found in DVDs, compact discs, and Blu-ray discs.

21.10 Spectroscopy of Carboxylic Acid Derivatives

- IR of acid chlorides shows a strong carbonyl stretch around 1800 cm^{-1}.
- IR of anhydrides show two strong carbonyl stretch around 1750 and 1820 cm^{-1}.
- IR of esters shows a strong carbonyl stretch around 1740 cm^{-1} and a strong CO-O stretch around 1150 to 1250 cm^{-1}.
- IR of amides shows a strong carbonyl stretch around 1700 cm^{-1}, primary and secondary amides have two bands and tertiary amides have one band and a strong N-H stretch around 3170 to 3500 cm^{-1} in primary and secondary amides.
- ^{1}H NMR of acid halides do not have any distinctive peaks.
- ^{1}H NMR of anhydrides do not have any distinctive peaks, but symmetrical anhydrides will produce equivalent protons on either side.
- ^{1}H NMR of esters and thioesters have an alkyl group attached to the heteroatom. For esters, the alkoxide protons will show up in the 3.5-4.5 ppm region, while those attached to the sulfur in thioesters will show up in the 2.0-3.0 ppm region.
- ^{1}H NMR of amides have the possibility of alkyl groups or hydrogens attached. Resonances for protons attached to the carbon bonded to the nitrogen of the amide resonate between 2.0-3.0 ppm region. The NH protons of primary and secondary amides resonate in the 7.5-8.5 ppm regions, which will be broad.
- ^{13}C NMR of carboxylic acid derivatives show the carbonyl carbon at 160-180 ppm.
- ^{13}C NMR of esters also have the carbon attached to the alkoxide of the ester, which appears at 50-90 ppm.
- ^{13}C NMR of amides also have the carbon attached to the nitrogen of the amide, which appears at 20-65 ppm.
- ^{13}C NMR of thioesters also have the carbon attached to the sulfur, which appears at 20-45 ppm.
- Mass spectra of carboxylic acid derivatives show a base peak due to the acylium ion.

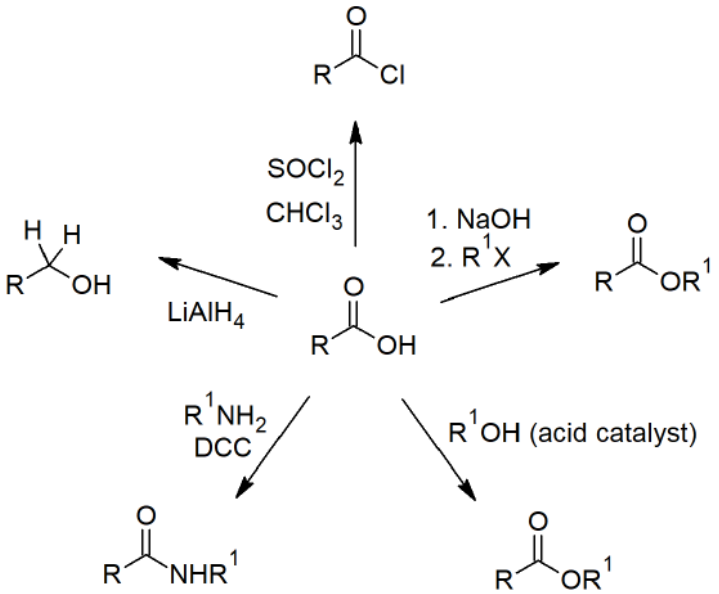
Skills to Master

- Skill 21.1 Name carboxyilic acid derivatives using IUPAC rules.
- Skill 21.2 Draw the structure of carboxylic acid derivatives from the IUPAC name.
- Skill 21.3 Compare the stability of different carboxylic acid derivatives to determine reactivity.
- Skill 21.4 Determine the products for nucleophilic acyl substitution reactions.
- Skill 21.5 Provide step-by-step mechanism for the Fischer esterification.
- Skill 21.6 Show how to synthesize an ester from a carboxylic acid and alcohol.
- Skill 21.7 Show mechanisms for the different carboxylic acid derivatives starting from an acid chloride.
- Skill 21.8 Show how to synthesize the different carboxylic acid derivatives starting from an acid chloride.
- Skill 21.9 Provide step-by-step mechanisms for the different carboxylic acid derivatives starting from an anhydride.
- Skill 21.10 Show how to synthesize the different carboxylic acid derivatives starting from an anhydride.
- Skill 21.11 Understand why the hydrolysis of an ester is not reversible under basic conditions and why the reverse does not produce an ester.
- Skill 21.12 Be able to synthesize tertiary alcohols from esters.
- Skill 21.13 Provide a step-by-step mechanism for the hydrolysis of an amide under acidic and basic conditions.

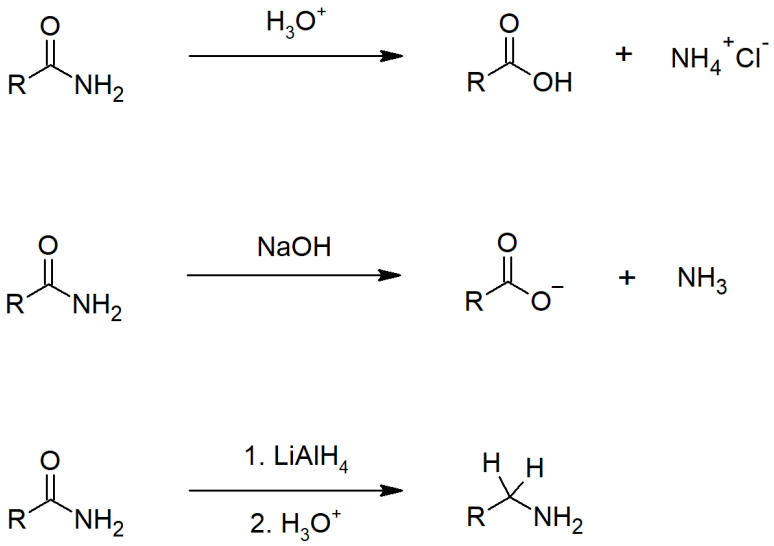
- Skill 21.14 Provide the structure of different polymers using the bracketed notation and the monomers from the polymer.
- Skill 21.15 Use IR, NMR, and MS to identify different carboxylic acid derivatives.

SUMMARY OF REACTIONS

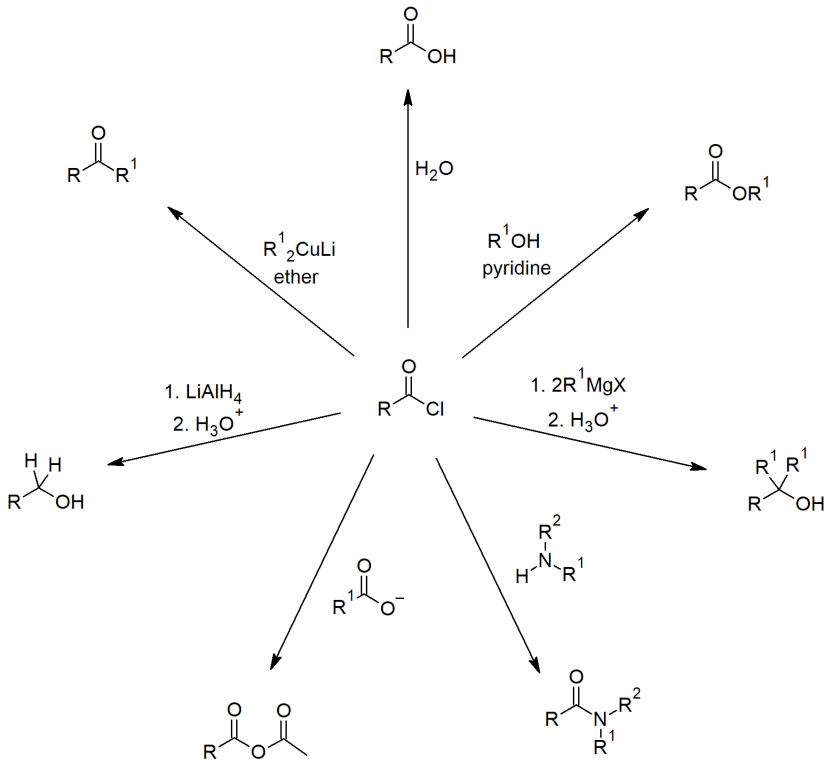
Carboxylic Acid Reactions



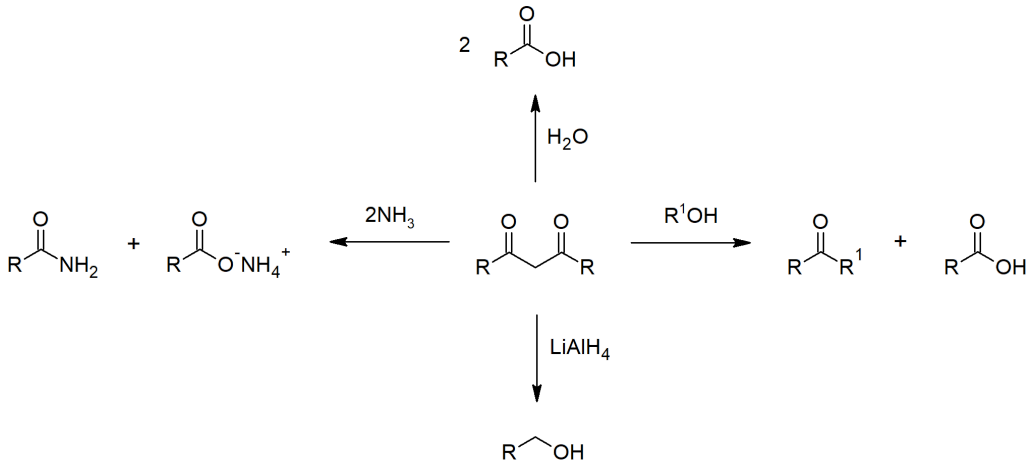
Amide Reactions



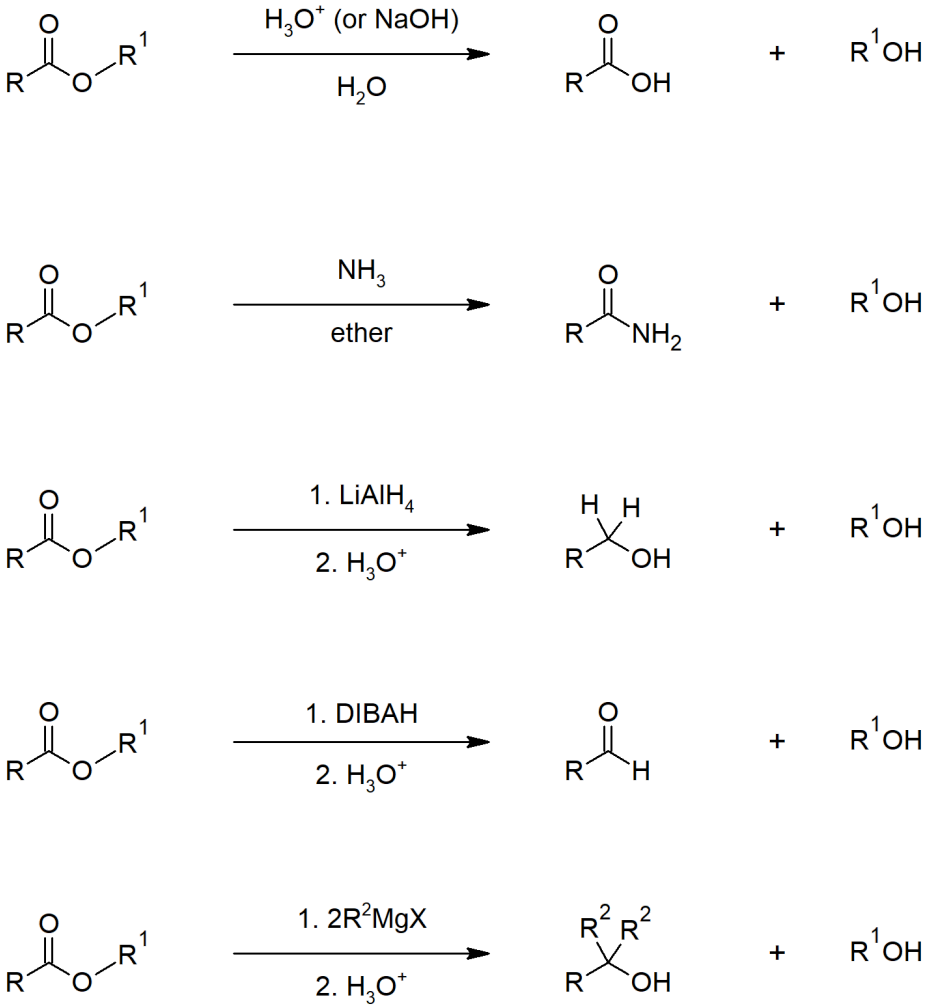
Acid Chloride Reactions



Acid Anhydride Reactions



Ester Reactions



CHAPTER OVERVIEW

22: CARBONYL ALPHA-SUBSTITUTION REACTIONS

LEARNING OBJECTIVES

When you have completed Chapter 22, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. design multi-step syntheses in which the reactions introduced in this unit are used in conjunction with any of the reactions described in previous units.
3. solve road-map problems that require a knowledge of carbonyl alpha-substitution reactions.
4. define, and use in context, the key terms introduced.

Alpha-substitution reactions are the third major type of reaction that you will study in your investigation of the chemistry of carbonyl compounds. As you will see, these reactions proceed through the formation of the enol form of the carbonyl compound.

After a brief review of keto-enol tautomerism, we begin our discussion of alpha-substitution reactions by looking at the methods in which the enol form of the carbonyl compound is directly involved. After discussing the factors that influence the formation and stability of enolate anions, we will examine some halogenation reactions in which an enolate ion is formed as an intermediate.

The chapter concludes with a study of the alkylation of enolate anions. These reactions are of tremendous use in organic syntheses, as they provide a method of forming new carbon-carbon bonds, and hence facilitate the laboratory preparation of increasingly complex compounds.

22.0: CHAPTER OBJECTIVES AND INTRODUCTION TO CARBONYL ALPHA-SUBSTITUTION REACTIONS

OBJECTIVES

After completing this section, you should be able to write a general mechanism for an alpha-substitution reaction of a carbonyl compound.

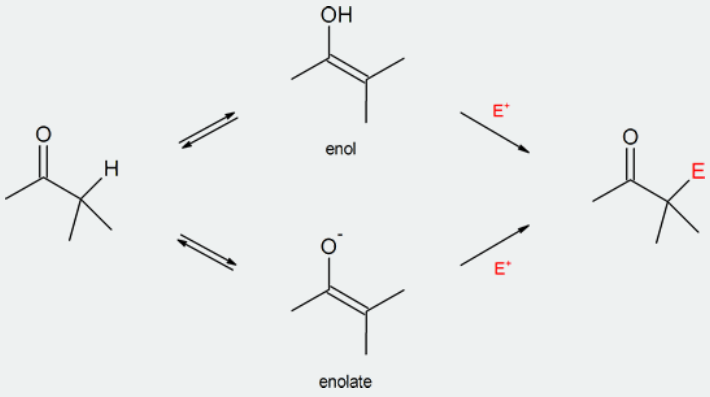
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- alpha (α) position
- alpha-substitution reaction

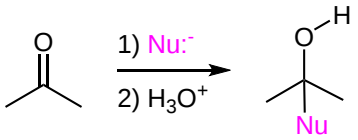
STUDY NOTES

An "alpha-substitution reaction" of a carbonyl compound is a reaction in which one of the hydrogen atoms on the carbon adjacent to the carbonyl group is substituted by some other atom or group. Attack by the electrophile (E^+) can occur on the enol or enolate intermediate.



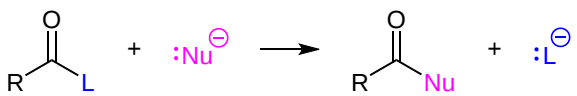
There are four common types of reactions involving compounds containing a carbonyl bond. The first two, nucleophilic addition and nucleophilic acyl substitution, have been discussed in previous chapters.

Nucleophilic addition occurs due to the electrophilic nature of the carbonyl carbon. After addition of a nucleophile, the carbonyl becomes a tetrahedral alkoxide intermediate which is usually protonated to become an -OH group.



Nucleophilic Addition to a Carbonyl

Nucleophilic acyl substitution is similar in that a tetrahedral alkoxide intermediate is formed after nucleophilic addition to the carbonyl. However, subsequent removal of the leaving group allows for the C=O (carbonyl) bond to reform. Overall, there is a substitution of the leaving group with the incoming nucleophile.

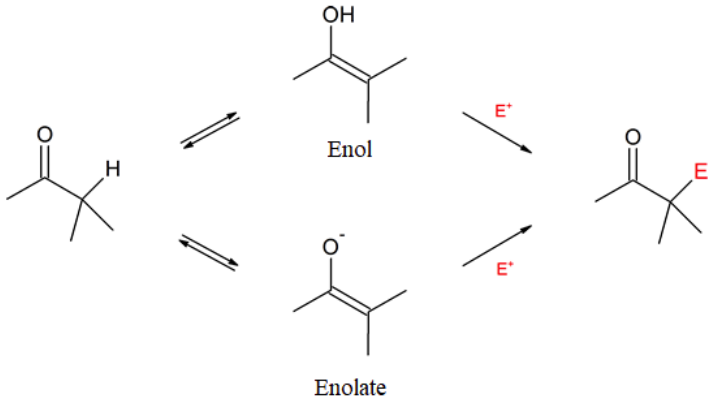


L = Leaving Group

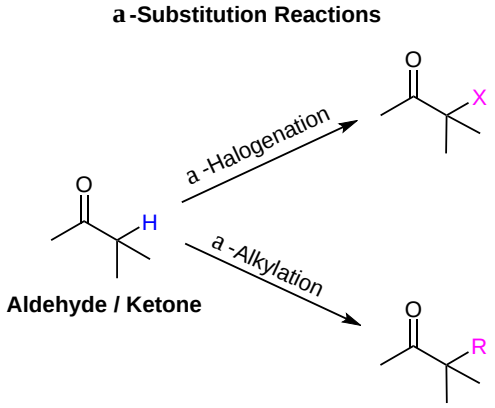
Nucleophilic Acyl Substitution Involving a Carbonyl

REACTIONS AT THE ALPHA CARBON

The remaining common carbonyl reaction types are α-substitutions and carbonyl condensations. Both utilize the special properties of carbons directly adjacent to carbonyls which are called **α-carbons**. These reactions, which can be regarded as the backbone of much synthetic organic chemistry, usually result in the replacement of a hydrogen attached to an α-carbon with some type of electrophile. These reactions involve two new nucleophilic species called the enol and the enolate.



This chapter will focus on α-substitutions reactions. Although there are many carbonyl containing functional groups, the initial investigation in this chapter will focus on α-substitutions reactions using aldehydes and ketones. Important examples considered in this chapter include α-halogenation and α-alkylation.



22.1: KETO-ENOL TAUTOMERISM

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate keto-enol tautomerism.
2. write a detailed mechanism for acid-catalyzed keto-enol tautomerism.
3. write a detailed mechanism for base-catalyzed keto-enol tautomerism.
4. draw the structure of the enol form of a given carbonyl compound.

KEY TERMS

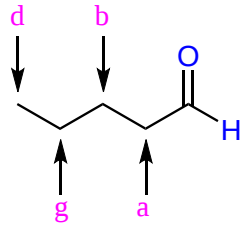
Make certain that you can define, and use in context, the key terms below.

- enol
- keto
- tautomerism
- tautomers
- enolate ion

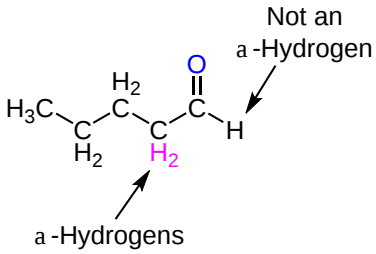
STUDY NOTES

Keto-enol tautomerism was first introduced in Section 9.4, in the discussion of the hydration of alkynes. The subject was raised again in the chapter entitled A Preview of Carbonyl Compounds, during the brief overview of the alpha-substitution reactions of carbonyl compounds. You may wish to review these sections before proceeding.

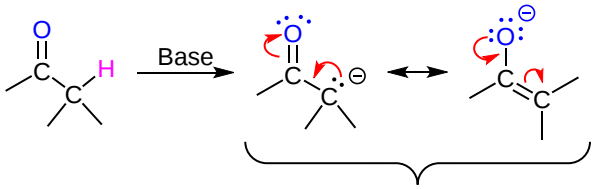
Often, the position of a carbon atom near a carbonyl group is designated using Greek letters. The atom adjacent to the carbonyl is alpha, the next removed is beta and so on. The carbon in the carbonyl group is used as reference point and is not assigned a Greek letter. Likewise, hydrogens bare the same Greek letter as the carbon atoms to which they are attached. α-Hydrogens are bonded to α-carbons and β-hydrogens are bonded to β-carbons etc.



The presence of α-hydrogens in a molecule provides the possibility of certain chemical reactions, which will be discussed in this chapter and in **Chapter 23**. Because of this, the ability to identify α-hydrogens is an important skill. As shown below, pentanal has two α-hydrogens. Note that aldehyde hydrogens are not given a Greek letter, they are simply referred to as an aldehyde hydrogen.

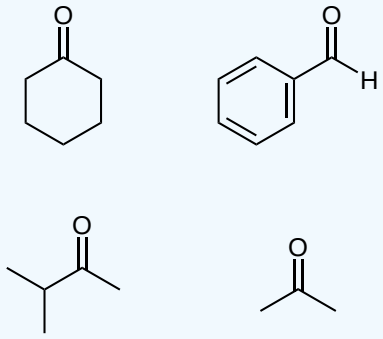


α-hydrogens, which are attached to a carbon directly adjacent to a carbonyl group, display unusual acidity. This is almost exclusively due to the resonance stabilization of the carbanion conjugate base, called an enolate, as illustrated in the diagram below. The effect of the the stabilizing C=O is seen when comparing the pK_a for the α-hydrogens of aldehydes (~16-18), ketones (~19-21), and esters (~23-25) to that of a typical alkyl C-H bond (~40-50).

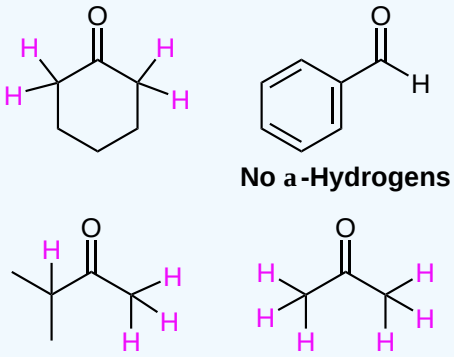


EXAMPLE 22.1.1

Indicate any α-hydrogens contained in the following molecules:



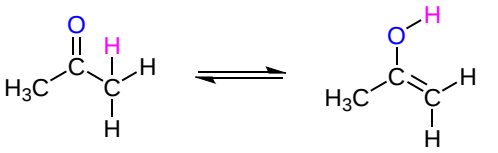
Solution



KETO-ENOL TAUTOMERIZATION

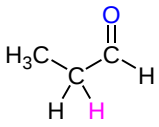
Because of the acidity of α-hydrogens, many carbonyl containing compounds undergo a proton-transfer equilibrium called tautomerism. Tautomers are readily interconverted constitutional isomers, usually distinguished by a different location for an atom or a group. Because tautomers involve the rearrangement of atoms, they are distinctly different than resonance forms, which only differ in the position of bonds and lone pair electrons. This discussion focuses on carbonyl groups with α-hydrogens, which undergo keto-enol tautomerism. Keto implies that the tautomer contains a carbonyl bond while enol implies the presence of a double bond and a hydroxyl group.

The keto-enol tautomerization equilibrium is dependent on stabilization factors of both the keto tautomer and the enol tautomer. For simple carbonyl compounds under normal conditions, the equilibrium usually strongly favors the keto tautomer (acetone, for example, is >99.999% keto tautomer). The keto tautomer is preferred because it is usually more stable than the enol tautomer by about 45–60 kJ/mol, which is mainly due to the C=O double bond (-749 kJ/mol) being stronger than the C=C double bond (-611 kJ/mol). Because ketones have two alky groups donating electron density into the carbonyl carbon, they tend to be more stable and therefore less apt to form the enol tautomer than aldehydes. For example, propanal is 1000 times more likely to be in its enol tautomer than acetone. With carboxylic acid derivatives, the leaving group tends to stabilize the carbonyl through electron donation which makes the formation of the enol tautomer much less likely. In general, ketones are over 100,000,000 times more likely to be in an enol tautomer form than esters.

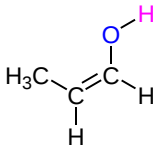


Acetone
Keto Tautomer
(>99.999%)

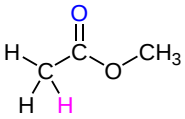
Propen-2-ol
Enol Tautomer
(~1.7 x 10^{-7}%)



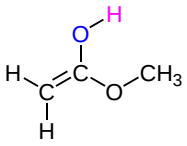
Propanal



Propen-1-ol
(~1 x 10^{-4}%)

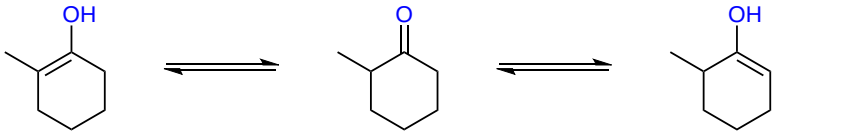


Ethyl Ethanoate



1-Methoxyethen-1-ol
(<1 x 10^{-15}%)

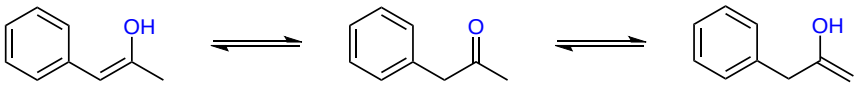
Aldehydes and symmetrical ketones typically only have one possible enol tautomer while asymmetrical ketones can have two or more. The preferred enol tautomer formed can be often be predicted by considering effects which can stabilize alkenes, such as conjugation and alkyl group substitution. The asymmetrical ketone, 2-methylcyclohexanone has two possible enol tautomers. Of the two tautomers, 2-methyl-1-cyclohexen-1-ol, is the more stable and therefore preferred due to the presence of an additional alkyl substituent. Likewise, 1-phenyl-1-propen-2-ol is the more stable enol tautomer of 1-phenyl-2-propanone due to conjugation with the phenyl ring.



Double Bond has more alkyl substituents
(More Stable Enol Tautomer)

2-Methylcyclohexanone

Double Bond has fewer alkyl substituents



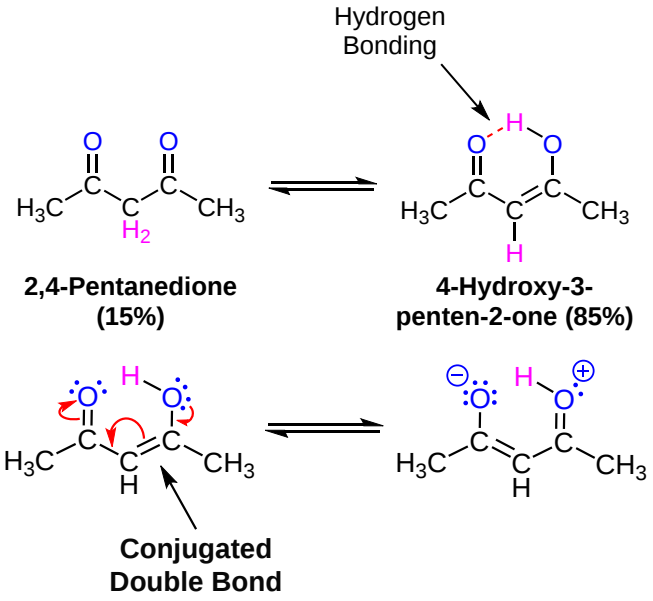
Double Bond is conjugated with the phenyl ring
(More Stable Enol Tautomer)

1-Phenyl-2-propanone

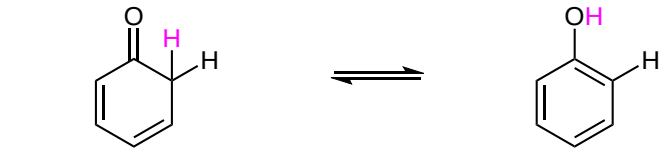
Double Bond is not conjugated with the phenyl ring

1,3-DICARBONYLS

In certain cases additional stabilizing effects allow the enol tautomer to be preferred in the tautomerization equilibrium. In particular, the 1,3 arrangement of two carbonyl groups can work synergistically to stabilize the enol tautomer, increasing the amount present at equilibrium. The diketone, 2,4-pentanedione, is in its enol form 85% of the time under normal conditions. The positioning of the carbonyl groups allows for the formation of a stabilizing intramolecular hydrogen bond between the hydroxyl group of the enol and the carbonyl oxygen. The alkene group of the enol tautomer is also conjugated with the carbonyl double bond which provides additional stabilization. Both of these stabilizing effects are not possible in the keto tautomer.



Another effect which can stabile an enol tautomer is aromaticity. When considering the molecule 2,4-cyclohexadienone, the enol tautomer is the aromatic molecule phenol. The stabilization gained by forming an aromatic ring is sufficient to make phenol the exclusive tautomer present in the equilibrium.



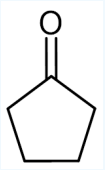
2,4-Cyclohexandienone
(Keto form, Non-aromatic)

Phenol
(Enol form,aromatic)

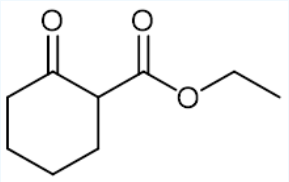
EXAMPLE 22.1.1

Please all of the possible enol tautomers for the following compounds. If more than one is possible then indicate which is the most stable and why.

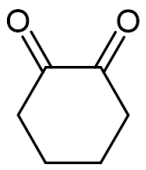
a)



b)

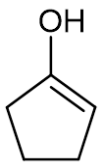


c)

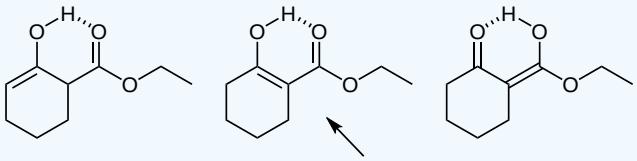


Solution

a)

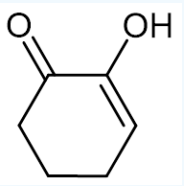


b)



This enol tautomer is the most stable due to hydrogen bonding, conjugation, and the ketone being in the enol form rather than the ester.

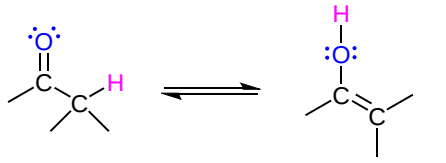
c)



MECHANISM FOR CATALYZED KETO-ENOL TAUTOMERIZATION

The enol tautomer has valuable nucleophilic characteristics. In neutral media, tautomerization is slow but it can be speed up by catalysis with acids or bases. Both pathways involve two separate proton transfer steps. Because enols are a key reactive intermediate, these mechanistic steps will be used repeatedly in later reactions. The following mechanistic steps represent the continuous interconversion between the keto and enol tautomers.

Overall Process



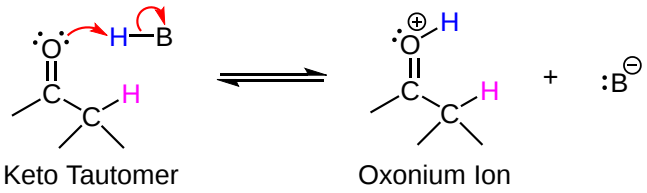
Keto Tautomer **Enol Tautomer**

ACIDIC CONDITIONS

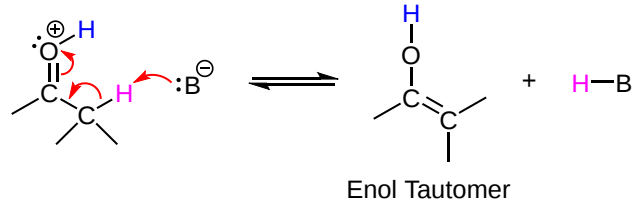
Keto Tautomer → Enol Tautomer

In the first step, the carbonyl oxygen is protonated by an acid to form an intermediate oxonium ion. A base removes an α-hydrogen during the second step forming a double bond by an E2 type reaction. This causes the pi electrons of the protonated carbonyl to move to the oxygen to form the hydroxyl group of the enol product and regenerating the acid catalyst.

1) Protonation of the carbonyl to form an oxonium ion



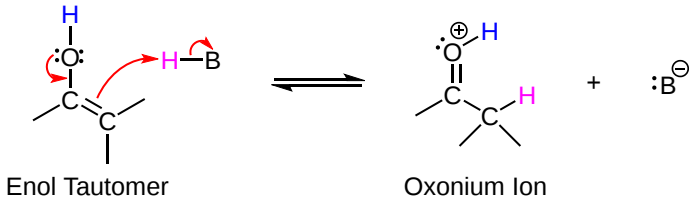
2) Deprotonation of an α-hydrogen to form an enol



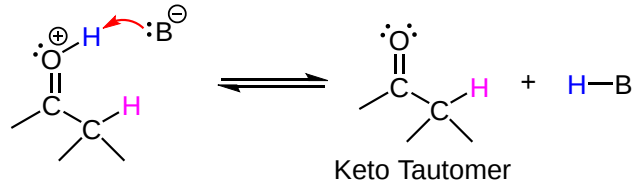
Enol Tautomer → Keto Tautomer

First, one of the lone pairs of electrons on the enol oxygen moves to form a pi bond with the adjacent carbon to create a oxonium ion. This also causes the pi bond electrons from the enol double bond to attack the electrophilic H^+ provided by acid catalyst forming a C-H bond in the α-position. This produced oxonium ion intermediate is subsequently deprotonated to form the neutral ketone and regenerate the acid catalyst.

1) Protonation at the α-carbon



2) Deprotonation

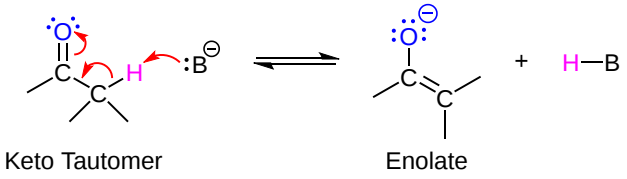


UNDER BASIC CONDITIONS

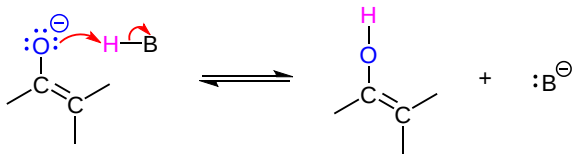
Keto Tautomer → Enol Tautomer

In the first step, a base removes an α-hydrogen from a carbonyl containing compound to form an alkene by an E2 like process. The causes the pi electrons of the carbonyl bond to move onto the carbonyl oxygen to form an enolate anion. The oxygen of the enolate anion is protonated in the second step to create a neutral enol and regenerate the base catalyst.

1) Deprotonation of a α-hydrogen to form an enolate ion



2) Protonation the enolate ion to form an enol

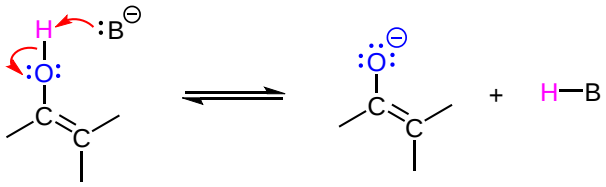


l

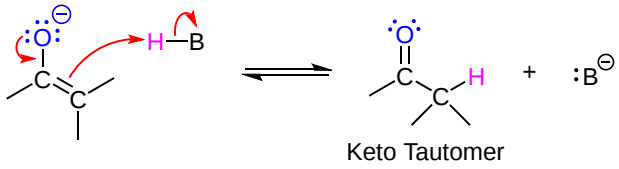
Enol Tautomer → Keto Tautomer

The mechanistic return to the keto tautomer begins with deprotonation of the hydroxyl hydrogen to produce an enolate ion. Then lone pair electrons from the enolate anion attack an electrophilic H^+ through conjugation with the double bond. This simultaneously forms the carbonyl double bond, adds an alpha hydrogen, and regenerates the base catalyst.

1) Deprotonation of the enol hydrogen

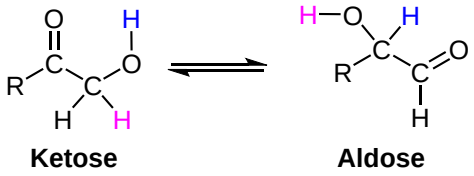


2) Protonation of the α-carbon



BIOLOGICAL ENOL FORMING REACTIONS

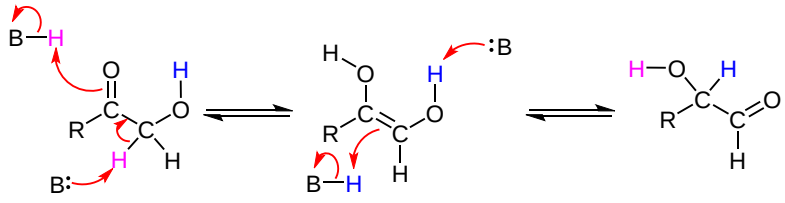
One very important family of isomerase enzymes catalyzes the shifting of a carbonyl group in sugar molecules using a process called an carbonyl isomerization. Carbonyl isomerization often involves converting between a ketose and an aldose. (recall that the terms ketose and aldose refer to sugar molecules containing ketone and aldehyde groups, respectively).



Carbonyl Isomerization

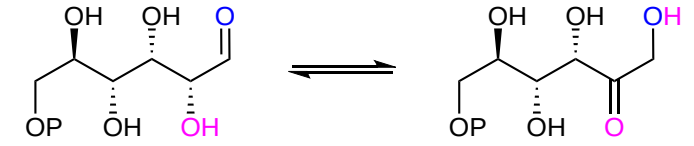
Mechanism

Carbonyl isomerization can only occur if there is an OH group adjacent to the carbonyl. Isomerization forms an ene-diol intermediate which has both OH hydrogens available to be removed to form a carbonyl. If the hydrogen from the original OH group is removed a new carbonyl bond is formed.



Carbonyl isomerization is involved in the metabolism of carbohydrates (starches and sugars) to their eventual conversion to CO_2 and H_2O. First, starches are broken down into glucose in the digestive tract. In the cells, the first step of the glycolysis pathway involves an enzyme converting glucose to glucose-6-phosphate. This is followed by the enzyme-catalyzed tautomerization of glucose-6-phosphate (an aldose) to

fructose-6-phosphate (a ketose) through an enediol intermediate. Notice how the carbonyl has moved from the 1-carbon (terminal) to the 2-carbon.



Glucose-6-phosphate Fructose-6-phosphate

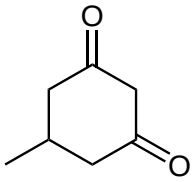
EXERCISES

1) Draw the enol forms of the following molecules

a. 4-methylcyclohexanone
b. Ethyl thioactetate
c. Methyl acetate
d. Butanal
e. 1-phenyl-2-butanone

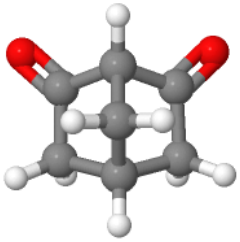
2) How many α-hydrogens do each of the molecules from the previous question have? Label them.

3) Draw all of the mono-enol forms for the following molecule. Which ones are most stable? Why?

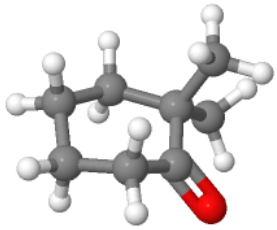


4) Under normal conditions cyclohexanone exists in the enol tautomer in a much higher percentage than acetone. Explain.

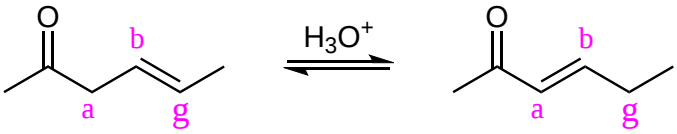
5) The 1,3-dicarbonyl shown below is only as acidic as acetone and does not form a detectable amount of the enol tautomer. Please explain.



6) For the following compound please identify the most acidic hydrogen atom. Remember that for an enolate conjugate base to be stabilized through conjugation, the lone pair electrons need to be contained in a p orbital which is parallel to the p orbitals which form the C=O pi bond.



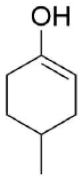
7) Nonconjugated ß, gamma-unsaturated ketones, such as 2-hexen-4-one, can be converted to their *α*, ß-unsaturated isomers by treatment with an acid catalyst. Please propose a mechanism for this isomerization.



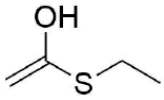
SOLUTIONS

1)

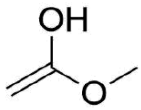
(a)



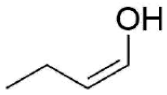
(b)



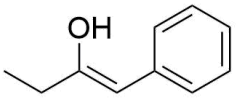
(c)



(d)

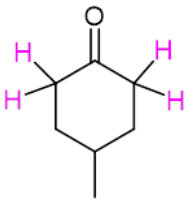


(e)

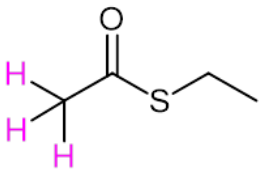


2)

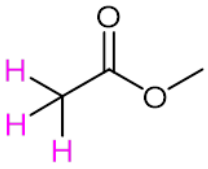
(a)



(b)



(c)



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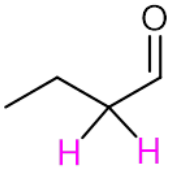
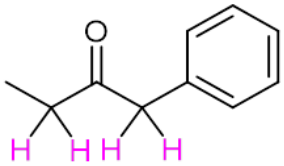


(e)



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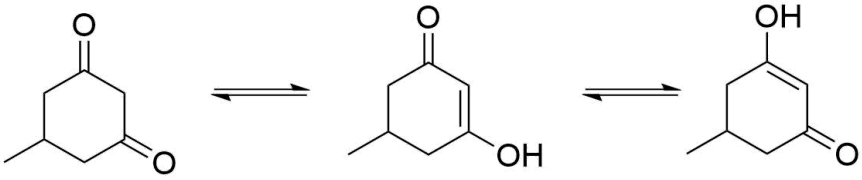
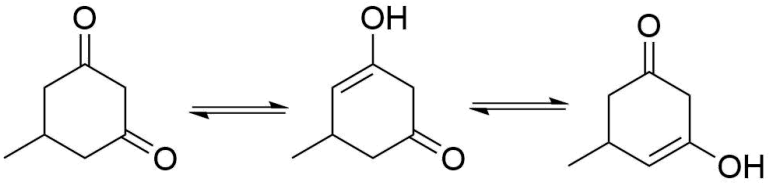


Additional resonance forms stabilizes this enol.

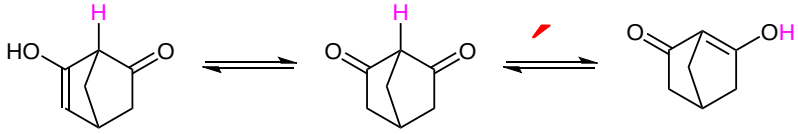


This enol has fewer resonance forms and is therefore less stable.

4) The enol tautomer of cyclohexanone has more alky substituents than the enol tautomer of acetone. This makes the double bond of the enol double bond of cyclohexanone more stable and easier to form.

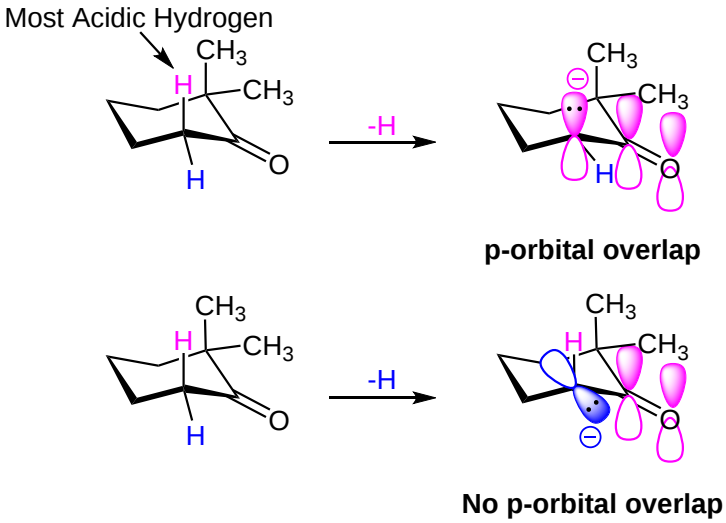
Enol of Cyclohexane **Enol of Acetone**

5) In many situations, the enol tautomer fo the a 1,3-dicarbonyl is preferred in the tautomerization equilibrium due to stabilizing effects created by the second carbonyl. However, in this case the alpha hydrogen used to create the enol tautomer is attached to a brigehead carbon of a bicyclic ring system. The positioning of the enol and the carbonyl prevents the formation of a stabilizing intramolecular hydrogen bond between the hydroxyl group of the enol and the carbonyl oxygen. Also, the inherent steric restrictions of a bicyclic ring system prevents the formation of a double bond using a bridgehead carbon. Instead, an enol tautomer of the molecule would be expected to form outside the 1,3-dicarbonyl. This enol lacks the stabilizing effects typical of a 1,3-dicarbonyl, so it is not preferred in the tautomerization equilibrium.

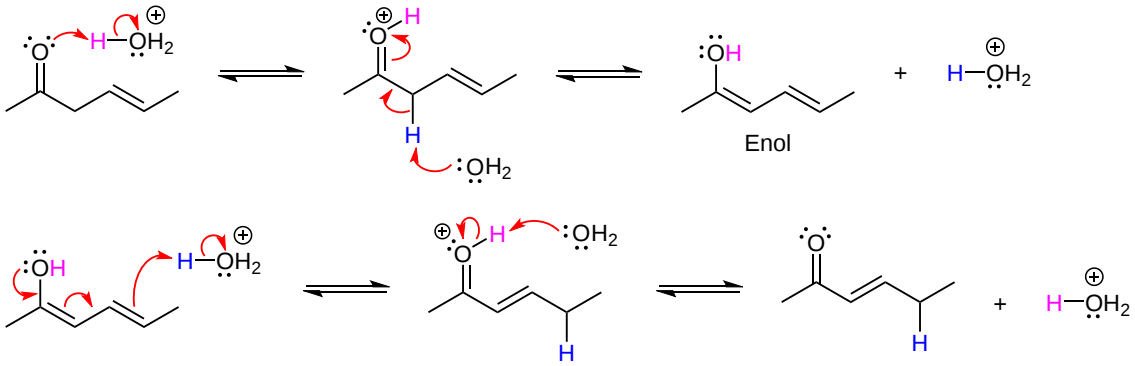


Not Formed

6) The presence of two methyl groups on one of the α-carbons of the carbonyl means that the two hydrogens on the other α-carbon may be deprotonated to form an enolate. When the indicated axial hydrogen is deprotonated the p-orbital formed is parallel with the carbonyl p-orbitals and can participate in overlap. If the equatorial hydrogen were to be deprotonated, the p-orbital formed would be perpendicular with the carbonyl p-orbitals and prevented from participating in overlap.



7)



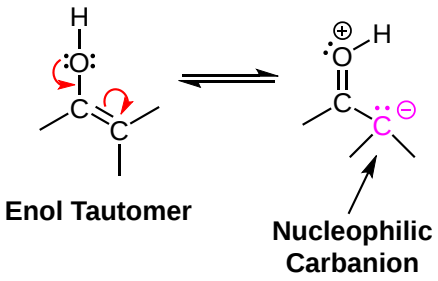
22.2: REACTIVITY OF ENOLS- THE MECHANISM OF ALPHA-SUBSTITUTION REACTIONS

OBJECTIVES

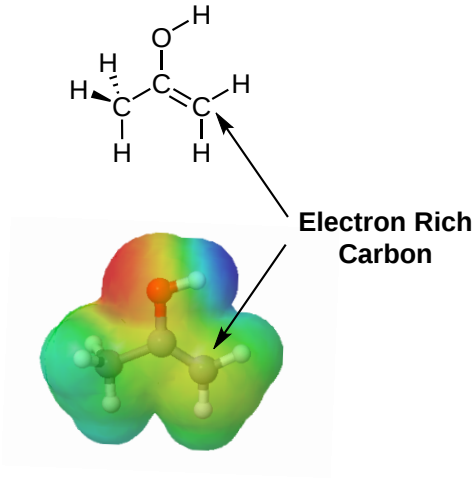
After completing this section, you should be able to write a detailed mechanism for an acid-catalyzed, alpha-substitution reaction of a carbonyl compound.

HOW ENOLS REACT

The oxygen of an enol can donate electron density into its double bond making it electron-rich and more reactive than typical alkenes.



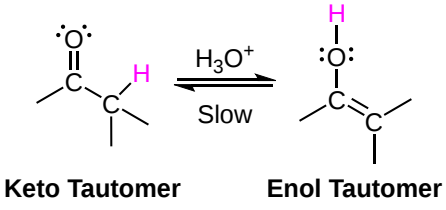
As seen in the electrostatic potential map for propen-2-ol ($CH_3COH=CH_2$), the enol tautomer of acetone, shows an increased electron density on the α-carbon (yellow) especially when compared to the -CH_3 carbon (blue/green). One of the resonance forms of an enol places a lone pair of electrons and a negative charge on the α-carbon forming a carbanion nucleophile. Enols react with electrophiles in a similar fashion as other carbanion nucleophiles, such as Grignard reagents.



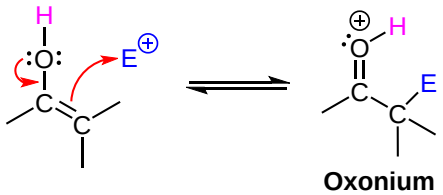
MECHANISM OF ALPHA SUBSTITUTION REACTIONS USING AN ENOL

The mechanism begins with the acid-catalyzed tautomerization to form an enol via the mechanism discussed in **Section 22.1**. Lone pair electrons on the enol oxygen move to become a C=O pi bond thus creating a positively charged oxonium ion. This also causes electrons from the C=C enol pi bond to attack an electrophile forming a C-E sigma bond. These two electron movements in concert represent the enol acting as a nucleophile. In the last step, an H^+ is removed from the carbonyl oxygen, regenerating the acid catalyst, and forming an α-substituted carbonyl .

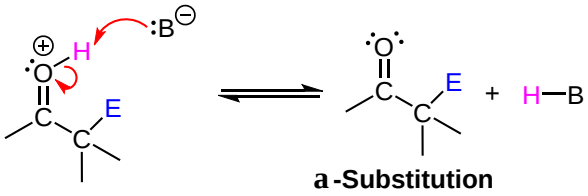
1) Acid catalyzed tautomerization to form an enol



2) The nucleophilic enol attacks the electrophile



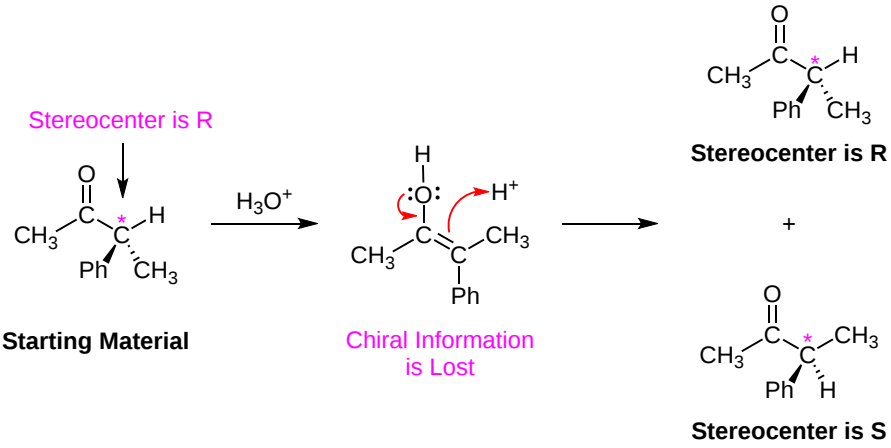
3) Deprotonation of the carbonyl to produce an α-substituted product



STEREOCHEMICAL IMPLICATION OF ENOL FORMATION

During an acid-catalyzed enol formation, an α-hydrogen is removed to form a sp^2-hybridized, trigonal planar C=C bond which removes any chiral information from the original alpha carbon. Because the enol alkene is planar the incoming electrophile can attack from either the top or the bottom of the molecule. If the α-carbon of the starting material has a defined stereochemistry or if a new stereocenter if formed during the reaction, the product will typically be a racemic mixture of enantiomers at the site of substitution.

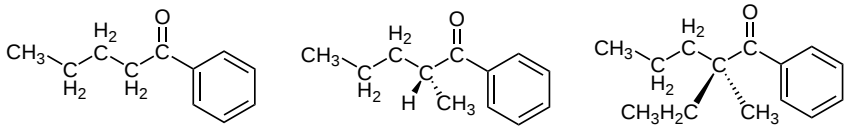
One of the easiest ways of displaying this process is through acid-catalyzed racemization. If a carbonyl compound has an α-carbon with a defined stereochemisty and an α-hydrogen, a racemic mixture can be formed simply through tautomerization. The addition of acid promotes the formation of the enol tautomer which removes the chiral information of the α-carbon. The enol then attacks an H^+ electrophile to reform the keto tautomer which then contains a racemic mixture of enantiomers.



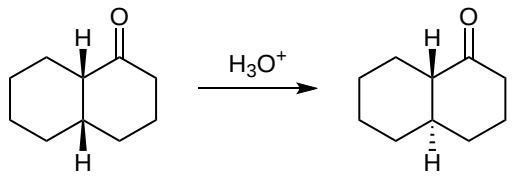
Example of Acid-Catalyzed Racemization

EXERCISES

1) Which of the following optically active ketones would undergo acid-catalyzed racemization? Explain.



2) When *cis*-Decalone is treated with an acid it becomes *trans*-Decalone almost exclusively becomes *trans*-Decalone. Explain.



***Cis*-Decalone** ***Trans*-Decalone**

SOLUTIONS

1) Molecule A would not because the alpha carbon is not a stereocenter. Molecule B would because the alpha carbon is a stereocenter and contains a hydrogen. Molecule C would not because it does not contain an alpha hydrogen.

2) This change involves a process call epimerization. Epimers as diastereomers which differ at only one chiral carbon. Epimerization is a process where only one of multiple chiral carbons is changed. In this example, the stereocenter in questions is a chiral carbon. The addition of an acid promotes this carbon becoming part of an enol thereby losing its chiral information. When the enol tautomer converts back the ketone tautomer the a mixture of both *cis* and *trans* epimers should form. However, as discussed in a previous section, we know that the *trans* isomer of the decalin ring system is more stable than the *cis*. Because there is a defined difference in stability, the trans isomer of decalone is preferred.

22.3: ALPHA HALOGENATION OF ALDEHYDES AND KETONES

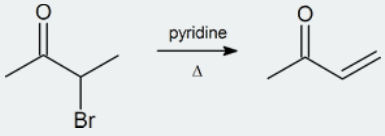
OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate the alpha halogenation of aldehydes and ketones.
2. identify the product formed from the alpha halogenation of a given aldehyde or ketone.
3. identify the carbonyl compound, the reagents, or both, needed to prepare a given α-halogenated aldehyde or ketone.
4. illustrate the importance of the alpha halogenation of carbonyl compounds as an intermediate step in the synthesis of α,β-unsaturated aldehydes and ketones.
5. write a detailed mechanism for the acid-catalyzed halogenation of a ketone.
6. describe the evidence provided by kinetic experiments supporting the suggestion that the acid-catalyzed, alpha halogenation of ketones proceeds via the rate-determining formation of an enol.

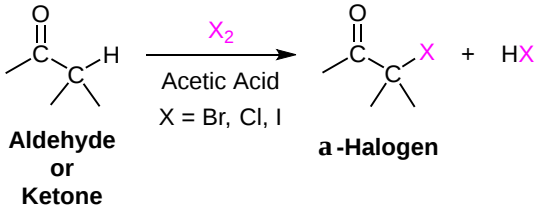
STUDY NOTES

Note: α-bromo ketones are a good starting material to generate α,β-unsaturated ketones by dehydrobromination.

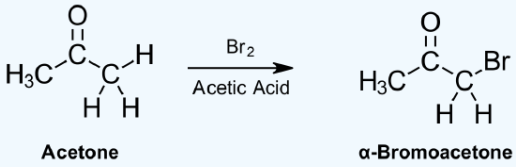


Aldehydes and ketones can substitute an α-hydrogen for a halogen atom in the presence of an acid. This reaction takes place using acid catalyzed tautomerization to form a nucleophilic enol, which then reacts with an electrophilic halogen (Cl_2, Br_2 or I_2). Because an enol intermediate is used, a racemic mixture of products can be produced. A particularly useful variation of this reaction uses bromine in an acetic acid solvent. The α-bromo substituted product can then be readily transformed into an α, β-unsaturated carbonyl through reaction with pyridine and heat.

GENERAL REACTION (*A* SUBSTITUTION)



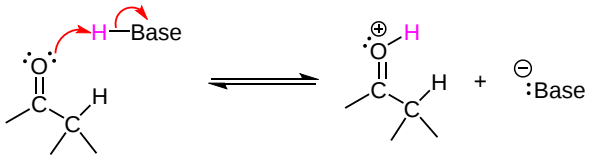
EXAMPLE 22.3.1



ACID CATALYZED MECHANISM

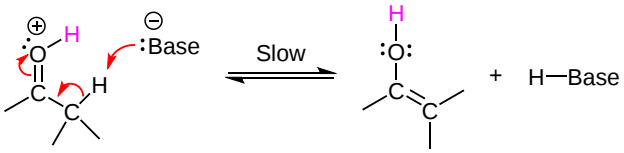
The mechanism begins with protonation of the carbonyl oxygen followed by removal of an α-hydrogen to form the enol. Lone pair electrons from the enol oxygen move to form a carbonyl while the pi electrons from the double bond attack the halogen forming an oxonium ion intermediate with a C-X sigma bond in the α-position. Deprotonation of the oxonium ion intermediate provides the α-halogen substituted product and regenerates the acid catalyst.

1) Protonation by the acid catalyst



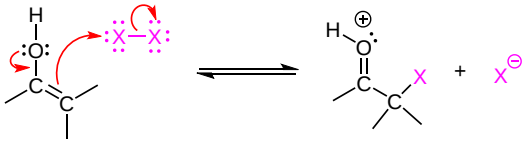
Aldehyde or Ketone **Oxonium**

2) Removal of an α-hydrogen to form the enol. This step is slow and represent the rate determine step.

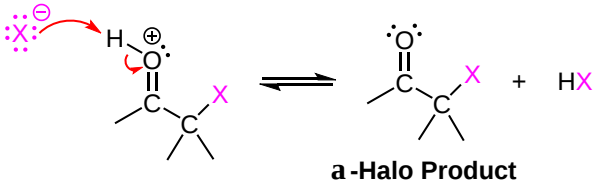


Enol

3) Nucleophilic attack on the halogen



4) Deprotonation



a-Halo Product

EXPERIMENTAL EVIDENCE OF THE ENOL INTERMEDIATE

This reaction was the focus of one of the first mechanistic investigations in organic chemistry. In the early 1900's chemist Arthur Lapworth showed that the rates of chlorination, bromination, and iodination of acetone were all the same. Also, it was shown that the rates for all three halogenation reactions were first-order with respect to acetone and the acid catalyst but independent of the halogen concentration (overall second-order for the mechanism). The rate law expression for the α-halogenation of a ketone can be given by:

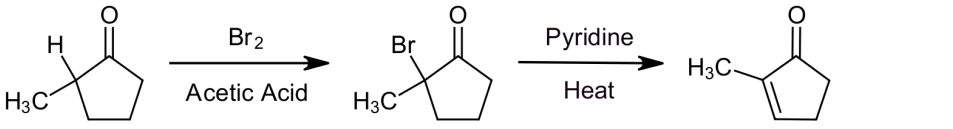
$$\text{rate} = k\,[\text{ketone}]\,[H^+]$$

This implies that the halogen participates in the mechanism through a fast step which occurs after the rate-determining step. These observations led Lapworth to theorize that the rate-determining step of the mechanism involves converting acetone to a more reactive form. The fact that the substitution occurs on the α-carbon led Lapworth to propose that the more reactive form was an enol tautomer of acetone.

Synthetic Uses for α-Halogenated Carbonyls

The product of an α-bromination can be converted to an α, β-unsaturated carbonyl by reaction with pyridine and heat which causes the elimination of H and Br. This reaction takes place by an E2 elimination mechanism and creates a C=C double bond which is conjugated with the carbonyl. In order to promote an E2 reaction, a sterically hindered base, pyridine, is often used.

An example of this reaction involves the α-bromination of 2-methylcyclopentanone to form 2-bromo-2-methylcyclopentanone. Because enol tautomers prefer to form on the more substituted α-carbon, α-bromination also occurs on the more substituted α-carbon. Although the enol intermediate causes a racemic mixture of the α-brominated compound to form, it is irrelevant because the chiral carbon is subsequently converted to an achiral alkene. Subsequent reaction with pyridine and heat forms the α,β-unsaturated ketone, 2-methyl-2-cyclopentenone.

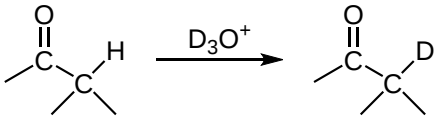


2-Methylcyclopentanone **(Racemic Mixture)** **2-Methyl-2-cyclopentenone**

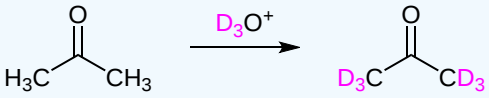
DEUTERIUM EXCHANGE

More evidence for the formation of an enol intermediate was provided using a reaction called deuterium exchange. Deuterium is an isotope of hydrogen which contains one proton and one neutron. Due to the acidic nature of α-hydrogens, they can be exchanged with deuterium by reaction with the isotopic form of water, D_2O (deuterium oxide-heavy water). The process is accelerated by addition of the deuterium equivalent of a strong acid, such as deuterium chloride (DCl), which quickly reacts with D_2O to form D_3O^+, the deuterium equivalent of hydronium (H_3O^+). If an excess of D_2O is used, the exchange process continues to the end result of all α-hydrogens present in a given compound being replaced with deuterium. Deuterium exchange is an effective method for introducing an isotopic label into a molecule. Also, deuterium does not appear in ^1H NMR, so deuterium exchange can help determine peak assignments.

GENERAL REACTION (DEUTERIUM EXCHANGE)



EXAMPLE 22.3.2



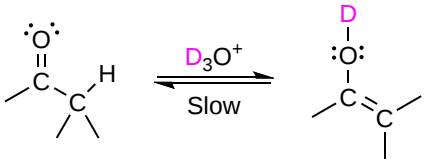
Acetone

Hexadeuteroacetone
Acetone-d6
Deuterated Acetone

MECHANISM IN ACIDIC CONDITIONS

The mechanism for deuterium exchange is virtually the same as keto-enol tautomerism under acidic conditions, as shown in **Section 22.2**. The only difference is that when the keto tautomer is reformed a deuterium is placed in the *α*-position.

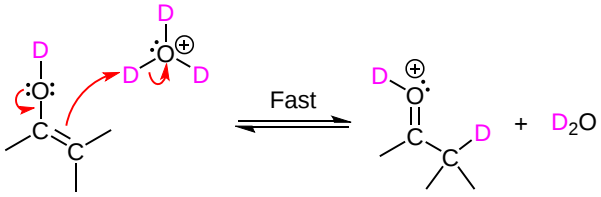
1) Formation of an enol



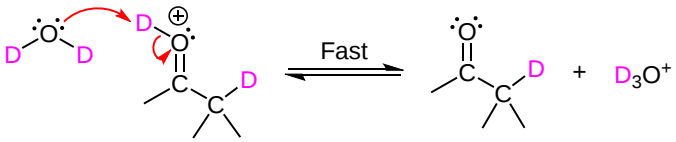
Aldehyde or Ketone

Enol

2) α-Deuteration



3) De-deuteration to form the keto tautomer



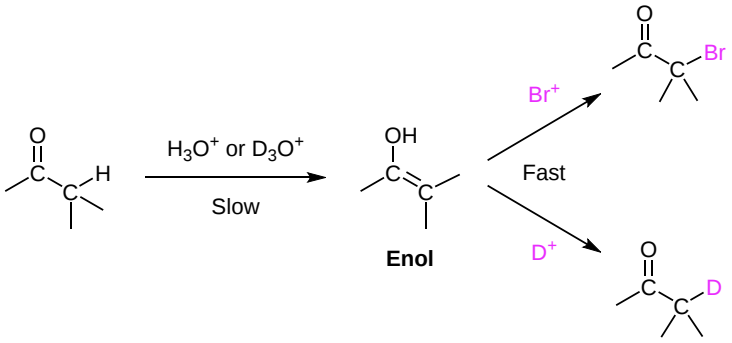
EXAMPLE 22.3.1

A simple method for determining the number of α-hydrogen in a compound is through reaction of D_3O^+. The reaction product is then isolated and its molecular weight is determined by mass spectrometry. For example, if cyclopentanone is reacted with D_3O^+, the isolated product has a molecular weight of 88 g/mol. Please explain how this method works and how many α-hydrogens cyclopentanone is predicted to have.

Solution

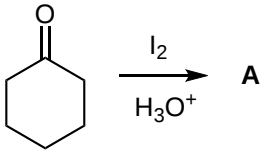
During acid catalyzed deuterium exchange each α-hydrogen in the compound is replaced with a deuterium. For each proton (AW = 1) replaced with a deuterium (AW = 2) the molecular weight of the compound is increased by one. Since cyclopentanone has a molecular weight of 84 g/mol and the isolated product has a molecular weight of 88 g/mol it can be predicted that cyclopentanone has four α-hydrogens.

Kinetic investigations into the mechanism of this reaction provided further evidence for the formation of a reactive enol intermediate. It was shown that the rate of deuterium exchange was the same as the rate of halogenation for ketones. This implies that both reactions have a common intermediate involved in the rate determining step of their mechanism, an enol.

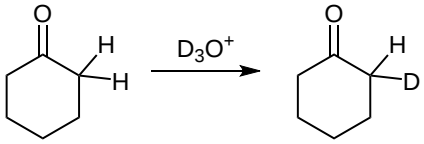


EXERCISES

1) Please draw the products of the following reactions

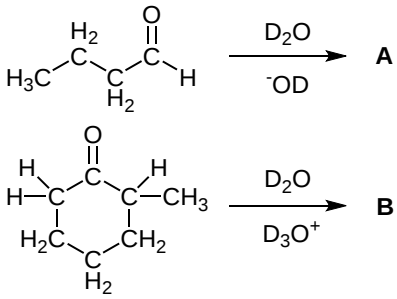


2)Draw out the mechanism for the following reaction.

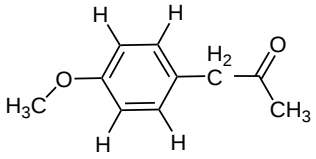


3) How might you form 2-hepten-4-one from 4-heptanone?

4) Show the products of the following reactions:

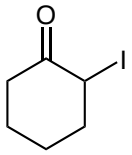


5) The following compound was reacted with D_3O^+. The only signals that could be found in the 1H NMR spectrum of the product were at 3.9 ppm (3H) and 6.6-6.9 ppm (4H). Please explain the results of the NMR.



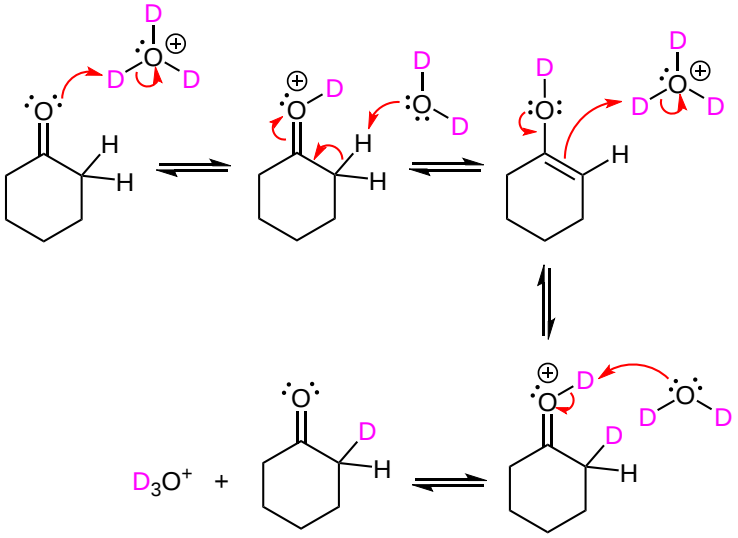
SOLUTIONS

1)



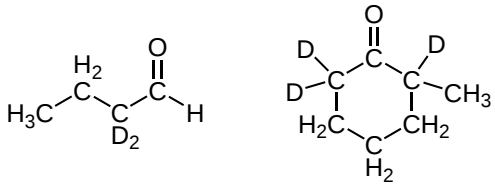
A

2)



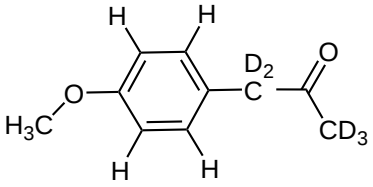
3) [1) Br_2, H_3O^+; 2) Pyridine, Heat]

4)



A **B**

5) A deuterium exchange reaction occurred. All of the alpha-hydrogens in the molecule have been exchanged with deuterium. Because detueriums do not appear in a typical ^1H NMR, only the remaining hydrogens appear.



22.4: ALPHA BROMINATION OF CARBOXYLIC ACIDS

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate the Hell-Volhard-Zelinskii reaction.
2. identify the product formed from the reaction of a given carboxylic acid with bromine and phosphorus tribromide.
3. identify the carboxylic acid, the reagents, or both, needed to synthesize a given α-bromo carboxylic acid.
4. outline the stereochemical implications of the fact that the Hell-Volhard-Zelinskii reaction proceeds through the formation of an acid bromide enol.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- Hell-Volhard-Zelinskii reaction

STUDY NOTES

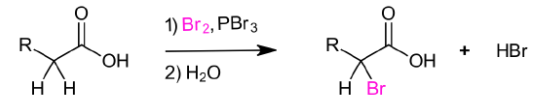
The reagents for the Hell-Volhard-Zelinskii reaction are given as bromine and phosphorus tribromide. In some questions, you may observe that only bromine and phosphorus are listed as reagents. Really there is no difference, as phosphorus tribromide would be formed *in situ* by the combination of bromine and red phosphorus:

$$3\,BR_2 + 2\,P \rightarrow 2\,PBr_3$$

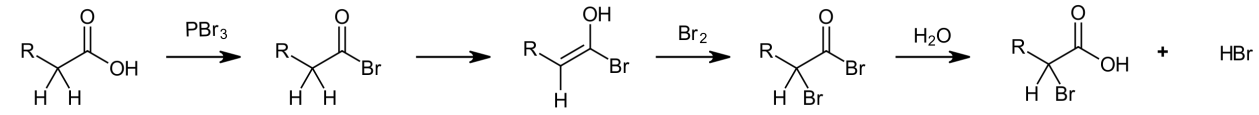
Excess bromine is required to ensure that enough reagent is available for the reaction with the enol.

HELL-VOLHARD-ZELINSKII REACTION

Although the α-bromination of some carbonyl compounds, such as aldehydes and ketones, can be accomplished with Br_2 under acidic conditions, the reaction will generally not occur with carboxylic acids, esters, and amides. Carboxylic acids do not enolize to a sufficient extent since the carboxylic acid proton is preferably removed before an α-hydrogen. However, carboxylic acids, can be brominated in the α-position with a mixture of Br_2 and phosphorus tribromide (PBr_3) in what is called the Hell-Volhard-Zelinskii reaction.

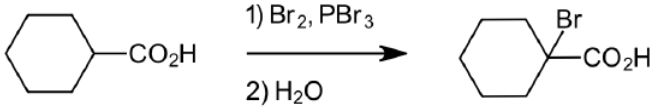


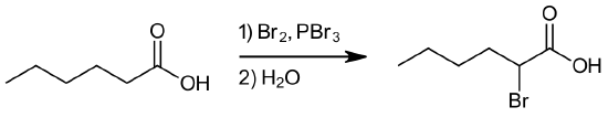
MECHANISM



This reaction is the combination of three separate reaction mechanisms all of which have been previously discussed. The mechanism starts with the reaction of the carboxylic acid with PBr_3 to form an acid bromide and HBr. Formation of an acid bromide is vital to this reaction because they lack the acidic carboxylic acid proton and can enolize much more readily making α-bromination possible. Next, HBr catalyzes the tautomerization of the acid bromide into its enol tautomer, acid bromide enol, which subsequently reacts with Br_2 to give α-bromination. Lastly, the product undergoes nucleophilic acyl substitution which cause the hydrolysis of the acid bromide to reform the carboxylic acid and the HBr catalyst. Because an enol intermediate is formed, this reaction will form a racemic mixture at the α-carbon.

EXAMPLES

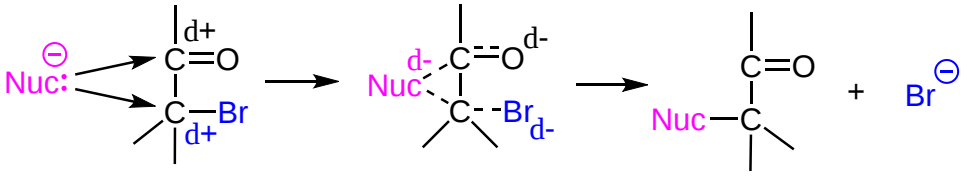




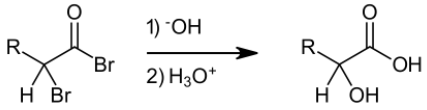
(Racemic)

FURTHER REACTIONS OF *A*-BROMO CARBOXYLIC ACIDS

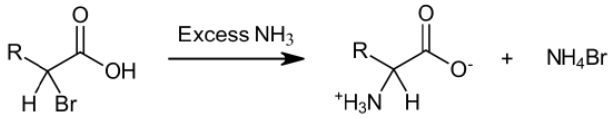
α-Bromo carboxylic acids are extremely useful synthetic intermediates because the halogen is highly reactive towards S_N2 reactions. Having the electrophilic carbon of the carbonyl adjacent to the electrophilic *α*-carbon attached to the bromine allows an incoming nucleophile to share its charge between the two. This stabilizes the transition state of the S_N2 reaction, lowering the energy of activation, and increasing reaction rates. Primary *α*-Halogenated carbonyls have S_N2 reaction rates which are much greater than the corresponding primary aliphatic halogens.



Because bromides are capable of reacting with a wide variety of nucleophiles, *α*-bromo carboxylic acids serve as important intermediates. Reaction of *α*-bromo carboxylic acids with an aqueous basic solution followed by an acidic work-up produces *α*-hydroxy carboxylic acids. Reaction of *α*-bromo carboxylic acids with an excess of ammonia provides *α*-amination, which provides a possible route to amino acids.

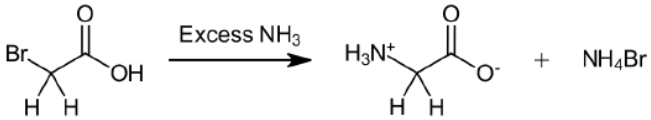


α-Bromo Carboxylic Acid **α-Hydroxy Carboxylic Acid**



α-Amino Carboxylic Acid

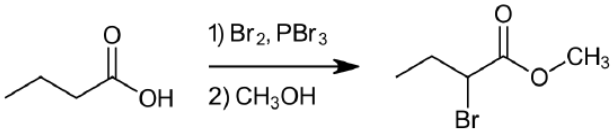
EXAMPLE



Bromoacetic acid **Glycine**

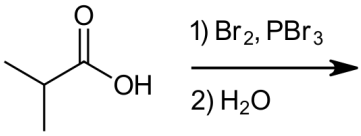
EXERCISES

1) Explain why the following reaction occurs.

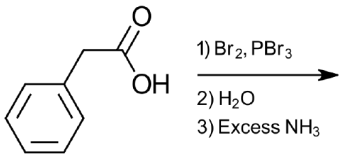


2) Draw the products of the following reactions:

a)

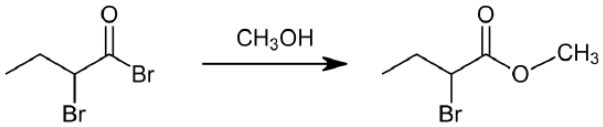


b)



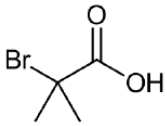
SOLUTIONS

1) The first step represents the beginning of the Hell-Volhard-Zelinskii reaction which provides a-bromination and creates and acid bromide intermediate. The second step adds methanol which reacts with the acid bromide to produce an ester.



2)

a)



b)

22.5: ACIDITY OF ALPHA HYDROGEN ATOMS- ENOLATE ION FORMATION

OBJECTIVES

After completing this section, you should be able to

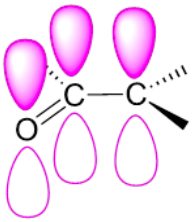
1. explain why the alpha hydrogens of carbonyl compounds are more acidic than the hydrogens in a typical hydrocarbon.
2. list the properties that make lithium diisopropylamide a suitable reagent for converting a wide range of carbonyl compounds into their enolate anions.
3. arrange a given list of carbonyl compounds in order of increasing or decreasing acidity.
4. determine whether a given carbonyl-containing compound is more or less acidic than selected other compounds, such as water, ammonia, alcohols, alkanes, alkenes, alkynes and amines.
5. explain why dicarbonyl compounds, such as *β*-diketones, are more acidic than compounds that contain only a single carbonyl group.

KEY TERMS

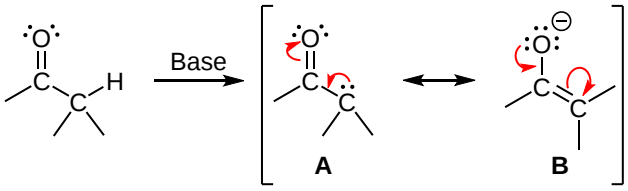
Make certain that you can define, and use in context, the key terms below.

- *β*-diketone
- *β*-keto ester

α-hydrogens are weakly acidic because their conjugate base, called an enolate, is stabilized though conjugation with the π orbitals of the adjacent carbonyl. Removal of an α-hydrogen creates an sp^2 hybridized carbon anion. The negative charge and lone pair electrons of the carbon anion are contained in an unhybridized p orbital. Orbital overlap with p orbitals from the adjacent carbonyl pi bond allows for the lone pair electrons and negative charge to be shared with the electronegative Carbonyl oxygen, stabilizing the negative charge of the enolate ion.

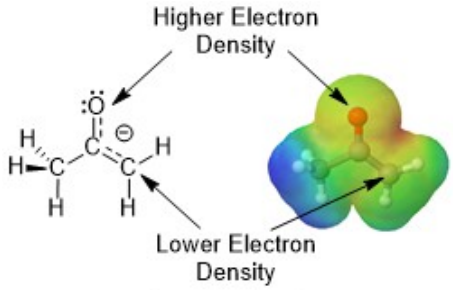


Enolate conjugation can be represent by two major resonance forms represented by structures A and B which share the negative charge (Shown Below). In resonance form A, the negative charge is on a carbon while in resonance form B the negative change is on an oxygen.



Enolate Ion

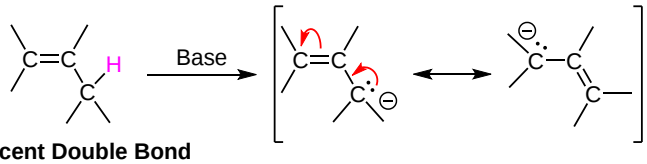
Resonance form B is preferred because oxygen is highly electronegative and better able to stabilize the negative charge. Both resonance form contribute to an overall resonance hybrid but not equally. Due to its stability, resonance form A makes a greater contribution to the resonance hybrid structure. Form A's increased contribution to the hybrid is seen when considering the electrostatic potential map of an acetone enolate. The red/yellow color shows there is a high electron density around the oxygen. The yellow/green color around the enolate carbon shows that there is a lower but still significant electron density present. Notice that the electron density on the enolate carbon is much larger than the non-enolate carbon (blue color).



Acetone Enolate Resonance Hybrid

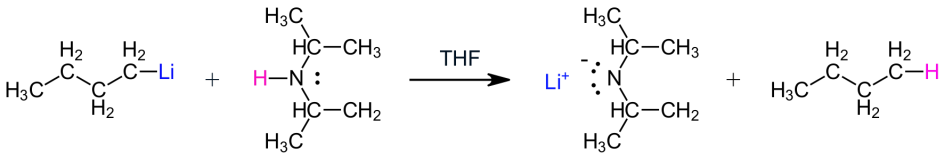
The effect of an adjacent carbonyl on the acidity of α-hydrogens is seen when comparing the pK_a of aldehydes (~16-18) and ketones (~19-21) to the pK_a of an alkane (~50). The ability of the electronegative oxygen to stabilize a negative charge can be seen by considering the pK_a of an allyl C-H bond (~42). Having a C-H bond adjacent to a C=C double bond allows the conjugate base created by deprotonating an allyl C-H bond to be stabilized by conjugation. However, the stability gained only provides a 10^8 increase in acidity when compared to an alkane. In comparison, the presence of an electronegative oxygen allows the acidity of an α-hydrogen to be 10^{20} times greater than that of an alkane.

Aldehydes and Ketones (pK_a ~ 20) **Alkanes (pK_a ~ 50)**



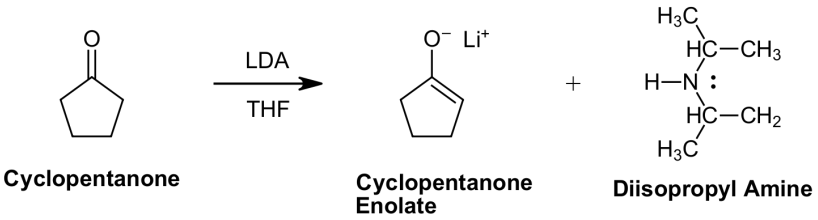
Adjacent Double Bond (pK_a ~ 42)

Although α-hydrogens are weakly acidic, typical strong bases such as a hydroxide or alkoxides are only capable of forming the enolate ion in very low concentrations. This can leave a significant concentration of the electrophilic carbonyl carbon remaining, which can react with the bases or the enolate. To achieve the complete deprotonation of aldehyde or ketone reactants to their enolate conjugate bases, a very strong base such as LDA (lithium diisopropylamide) must be used. Complete deprotonation removes the carbonyl groups of the starting material from the reaction mixture and prevents their ability to form unwanted products. Also, the large alkyl substituents sterically hinder the ability of LDA and its corresponding amine (diisopropyl amine) to undergo nucleophilic addition to the carbonyl. In addition to aldehydes and ketones, LDA readily deprotonates a wide variety of carbonyl containing functional groups including esters, amides and nitriles. Ether solvents like tetrahydrofuran (THF) are commonly used for enolate formation reactions using LDA. 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 the carbonyl groups. Nevertheless, these very strong bases are useful in the preparation of LDA. By reacting *n*-butyllithium with diisopropylamine (pK_a 36), LDA can be easily formed.

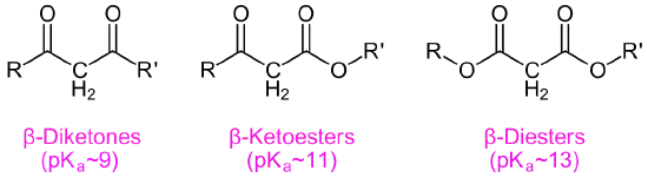


n-Butyllithium **Diisopropyl Amine** **Lithium Diisopropyl Amide (LDA)** **Butane**

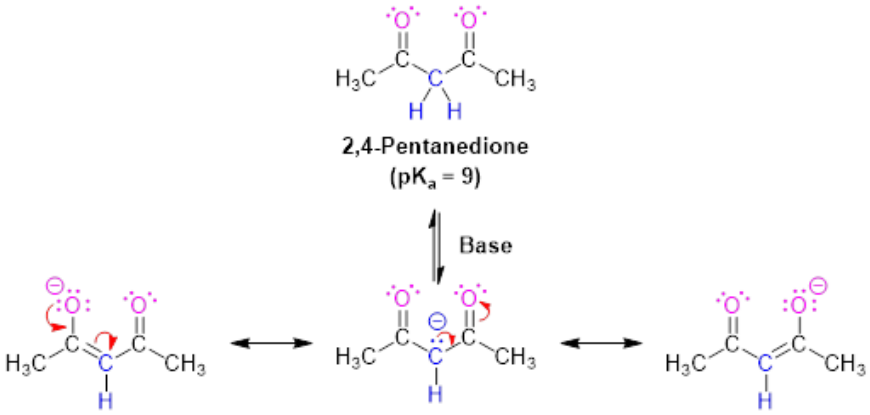
EXAMPLE



Hydrogen atoms with two or more adjacent carbonyl groups are more acidic than typical α-hydrogens.



The enolate ions of compound such as *β*-diketones, *β*-keto-esters, and *β*-diesters are stabilized through additional resonance forms which share the negative charge with multiple carbonyl oxygens. The acidity of these compounds is increased to the point where weaker bases, such as sodium ethoxide ($NaOCH_2CH_3$) can be used to form the enolate.



The pK_a and acidic hydrogens of multiple functional groups are shown in the table below.

* = a functional group with two ketones.

Functional Group	Structure	pK_a
carboxylic acid	HO–(C=O)R	5
nitro	RCH_2–NO_2	9
β-diketone *	R(O=C)–CH_2–(C=O)R	9
β-ketoester *	R(O=C)–CH_2–(C=O)OR	11
β-diester *	RO(O=C)–CH_2–(C=O)OR	13
amide	RNH–(C=O)R	15
alcohol	RCH_2–OH	16
aldehyde	RCH_2–(C=O)H	17
ketone	RCH_2–(C=O)R	20
thioester	RCH_2–(C=O)SR	21
ester	RCH_2–(C=O)OR	25
nitrile	RCH_2–C≡N	25
sulfone	RCH_2–SO_2R	25
amide	RCH_2–(C=O)$N(CH_3)_2$	30
alkane	CH_3–R	50

22.6: REACTIVITY OF ENOLATE IONS

OBJECTIVES

After completing this section, you should be able to

1. identify the two possible ways in which a given enolate anion could conceivably react with an electrophile.
2. write an equation to illustrate the haloform reaction.
3. identify the products formed from the reaction of a given methyl ketone with a halogen and excess base.
4. identify the methyl ketone, the reagents, or both, needed to obtain a specified carboxylic acid through a haloform reaction.

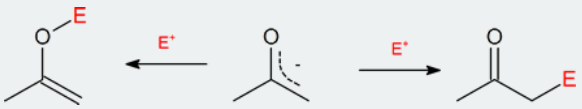
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- haloform
- haloform reaction

STUDY NOTES

Because the negative charge on an enolate ion is delocalized, there are two reactive sites and therefore two potential products. The α-substituted product is much more common.



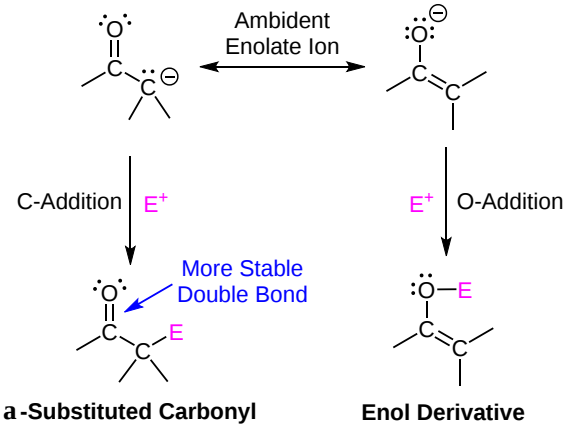
A "haloform" is any compound of the type CHX_3, where X = Cl, Br or I. Of these three compounds, chloroform is the most common.

The haloform reaction describedin the reading is usually carried out with iodine. This reaction is called the "iodoform test," and is one of the reactions carried out in the laboratory as a simple qualitative test for methyl ketones.

HOW ENOLATES REACT

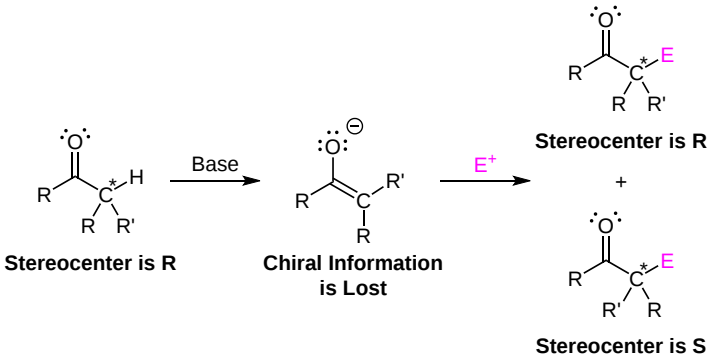
Due to their negative charges, enolates are better and more versatile nucleophiles than enols. The increased reactivity of enolates makes them capable of a wider range of reactions than enols. Also, α-hydrogen containing compounds can be completely converted to an enolate by reaction with a strong base. Whereas enols can only be created in small amounts through manipulating their equilibrium.

Since the negative charge of an enolate anion is delocalized between the α-carbon and an oxygen, electrophiles may bond to either atom. Reactants having two or more reactive sites are called ambident, so this term applies to enolate anions. Either the C of the O reactive site in an enolate may act as a nucleophile depending on the reaction conditions. Reactions with the oxygen would create a new O-E bond and produce an enol derivative. Reactions with the α-carbon creates a new C-E bond and creates an α-substituted carbonyl compound. Although reactions with the nucleophilic oxygen are possible, reactions involving the nucleophilic α-carbon are much more common, partially due to the thermodynamic stability of the C=O bonds in the final products. Also, the enolate counter ion, such as Li^+ or Na^+, is more tightly associated with the negatively charged enolate oxygen which can then block incoming electrophiles, reducing their chance of reaction at the oxygen.



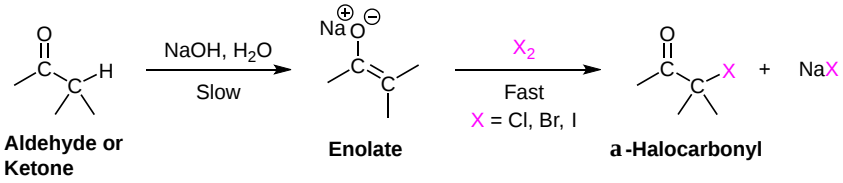
STEREOCHEMICAL IMPLICATION OF ENOLATE FORMATION

During enolate formation, an α-hydrogen is removed to form a sp^2-hybridized, trigonal planar C=C bond which removes any chiral information from the original α-carbon. Because the enol alkene is planar, the incoming electrophile can attack from either the top or the bottom. If the α-carbon of the starting material has a defined stereochemistry or if a new stereocenter is formed during the reaction, the product will be a racemic mixture of enantiomers.



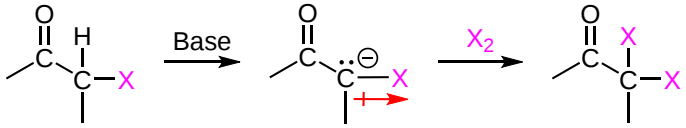
BASE PROMOTED A-HALOGENATION

An enolate reacts rapidly with a halogen to produce α-halogenated carbonyl products. This reaction has the tendency to overreact and create polyhalogenated products. If a monohalogenated product is sought, the acid catalyzed halogenation reaction discussed in section 22.3 is preferred. Because complete formation to the enolate is not necessary, weak bases, such as the hydroxide anion, are sufficient to produce this reaction. Once a small amount of enolate is formed, it quickly reacts with the halogen. This removes the enolate and shifts the equilibrium toward forming more enolate by Le Chatelier's principle.



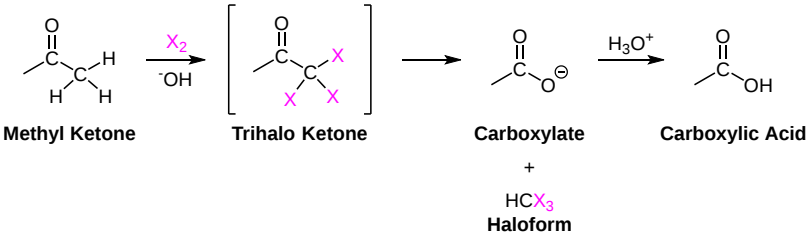
OVERREACTION DURING BASE PROMOTED A-HALOGENATION

The α-hydrogens of halogenated carbonyl products are usually more acidic than the corresponding non-halogenated compounds. The inductive electron withdrawing effect of the electronegative halogen stabilizes the negative charge of the enolate ion. This promotes further enolate formation and also further halogenation of the α-carbon. Monohalogenated carbonyls form an enolate over 100 times faster than their non-halogenated counterparts making multiple halogenations of the α-carbon frequent. This effect is exploited to cause the haloform reaction.

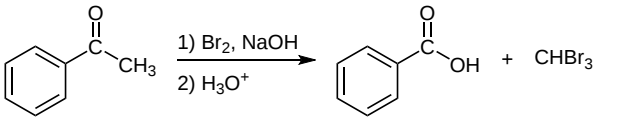


THE HALOFORM REACTION

Overall, the haloform reaction represents a method for the conversion of methyl ketones to carboxylic acids. Due to the increased reactivity of α-halogenated products, methyl ketones typically undergo base promoted halogenation three times to give a trihalo-ketone. A halomethyl ion leaving group is then substituted with a hydroxide ion during nucleophilic acyl substitution. The resulting carboxylate can then be protonated to form a carboxylic acid.



EXAMPLE



Acetophenone **Benzoic Acid** **Bromoform**

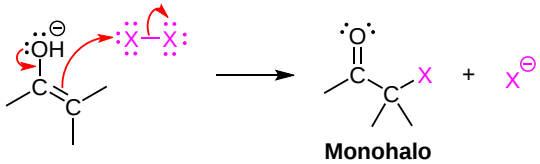
MECHANISM

Note! This reaction is considered to be base promoted and not base catalyzed because an entire equivalent of base is required for each α-halogenation. Deprotonation of an α-hydrogen with hydroxide produces the nucleophilic enolate ion which subsequently reacts with the halogen. The increasing acidity of α-halogenated ketone causes this reaction to occur two more times. Once formed, the -CX_3 group attached to the carbonyl can act as a leaving group. Nucleophilic acyl substitution with a hydroxide anion causes C-C bond cleavage and eventually produces a haloform ($CHCl_3$, $CHBr_3$, CHI_3) and a carboxylate anion. The carboxylate ion is easily protonated with acid to form a carboxylic acid functional group. Often, this reaction is performed using iodine (I_2) because the subsequent iodoform (CHI_3) side-product is a bright yellow solid which is easily filtered off.

This reaction represents one of the few examples of a carbanion leaving group. The trihalomethyl ion ($^{-}:CX_3$) is particularly stabilized due to the inductive electron-withdrawing effects of the three halogens. The stability of the carbanion can be seen when considering the pK_a corresponding conjugate acid. In particular, bromoform ($CHBr_3$) has a pK_a of 13.7 which is more than 10^{20} times more acidic than a typical alkane C-H bond.

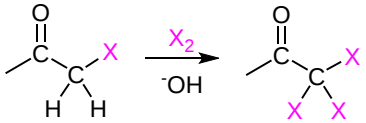
1) Enolate formation

2) Nucleophilic attack on the halogen



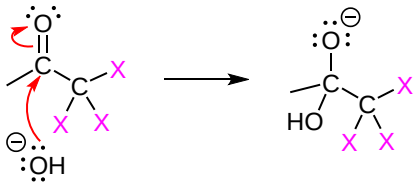
Monohalo Carbonyl

3) Repeat the halogenation two more times

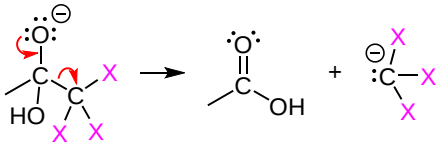


Trihalo Ketone

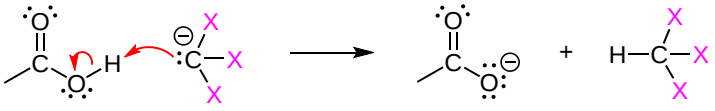
4) Nucleophilic attack on the electrophilic carbonyl carbon



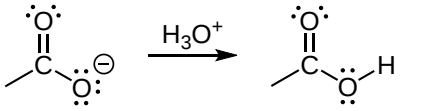
5) Nucleophilic acyl substitution



6) Deprotonation



7) Protonation of the carboxylate



BIOLOGICAL HALOFORM REACTION

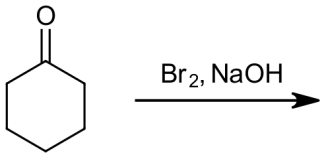
Interest in the haloform reaction has increased since the discovery that certain plants and marine algae can biosynthize chloroform, bromoform, and other small halocarbons through an analogous process. Previously it was assumed that these toxic compounds were present in the environment as a man-made pollutants.

The likely starting material of the biosynthesis are biogenic methyl ketones, a halogen anion, and oxygen. The enzyme, chloroperoxidase, catalyzes the polyhalogenation of the methyl groups. As in the haloform reaction, the final biosynthesis step involves a nucleophilic acyl substitution with a hydroxide anion to create a haloform and a carboxylate anion.

EXERCISES

1) Please predict the expected products of the following reactions:

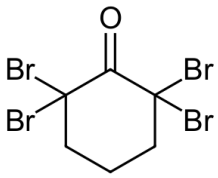
a)



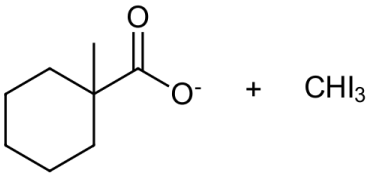
b)

SOLUTIONS

a)



b)



- **22.6: Reactivity of Enolate Ions** by Dietmar Kennepohl, Layne Morsch, Steven Farmer is licensed CC BY-SA 4.0.

22.7: ALKYLATION OF ENOLATE IONS

OBJECTIVES

After completing this section, you should be able to

1. write a general mechanism for the attack of an enolate anion on an alkyl halide.
2. write a reaction sequence to illustrate the preparation of carboxylic acids via the malonic ester synthesis.
3. identify the product formed, and all the intermediates, in a given malonic ester synthesis.
4. identify all of the compounds needed to prepare a given carboxylic acid by a malonic ester synthesis.
5. write a detailed mechanism for each of the steps involved in a malonic ester synthesis.
6. write a reaction sequence to illustrate the preparation of ketones through the acetoacetic ester synthesis.
7. identify the product formed, and all the intermediates, in a given acetoacetic ester synthesis.
8. identify all of the compounds needed to prepare a given ketone by an acetoacetic ester synthesis.
9. write a detailed mechanism for each of the steps involved in an acetoacetic ester synthesis.
10. identify the product or products formed when a given lactone, ester, nitrile or ketone is treated with lithium diisopropylamide followed by an alkyl halide.
11. identify the compounds needed to prepare a given α-substituted ketone, ester, lactone or nitrile by a method involving the alkylation of an enolate anion.

KEY TERMS

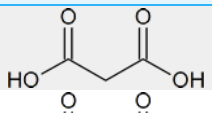
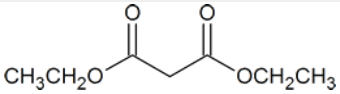
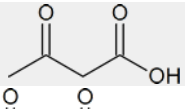
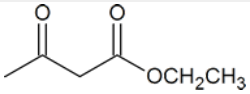
Make certain that you can define, and use in context, the key terms below.

- alkylation
- malonic ester synthesis

STUDY NOTES

The two syntheses discussed in this section provide routes to a wide variety of carboxylic acids and methyl ketones. You may wish to review the factors influencing S_N2 reactions (Section 11.3) in conjunction with this section.

You should try to memorize the structures of malonic ester and ethyl acetoacetate. The IUPAC names of these compounds are shown in the table below.

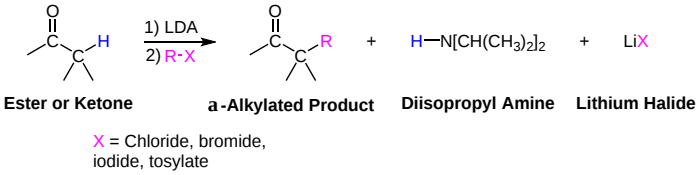
Structure	Common name	IUPAC name
	malonic acid	propanedioic acid
	malonic ester or diethyl malonate	diethyl propanedioate
	acetoacetic acid	3-oxobutanoic acid
	ethyl acetoacetate or acetoacetic ester	ethyl 3-oxobutanoate

ALKYLATION OF ENOLATES

Enolates can be alkylated in the alpha position through an S_N2 reaction with alkyl halides. During this reaction an α-hydrogen is replaced with an alkyl group and a new C-C bond is formed. The limitations of S_N2 reactions still apply. This includes preferring a good primary or secondary leaving group, X = chloride, bromide, iodide, tosylate. Tertiary leaving groups cannot be used in this reaction and typically give undesired E2 elimination products. A very strong base, such as LDA, is often used because of its ability to form the enolate completely. Removal of the carbonyl starting material from the reaction mixture makes it unavailable for nucleophilic addition by the enolate. Aldehydes are usually not directly alkylated because their enolates prefer to undergo the carbonyl condensation reactions discussed later in **Section 23.1**. In addition, the acidic hydrogen on carboxylic acids inhibits the formation of an enolate, and makes their direct alkylation

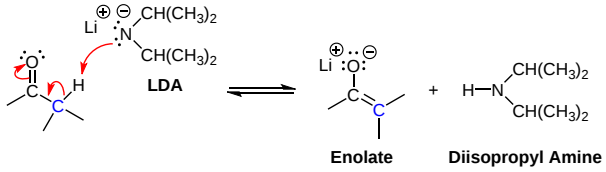
difficult. Esters, including lactones, and symmetrical ketones readily undergo direct alkylation. However, direct alkylations, like all enolate-based reactions, can form a racemic mixture if the alkylated α-carbon produced is chiral.

GENERAL REACTION

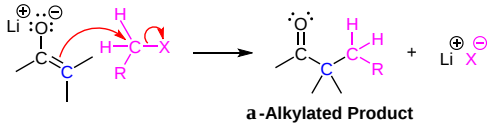


MECHANISM

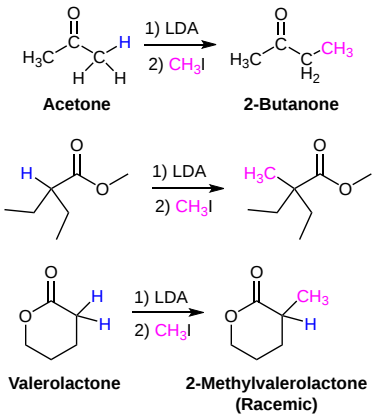
1) Enolate formation



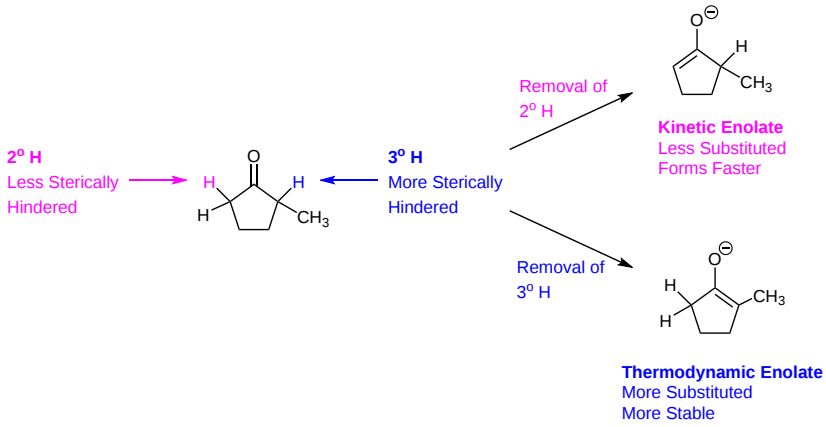
2) S_N2 attack



EXAMPLES



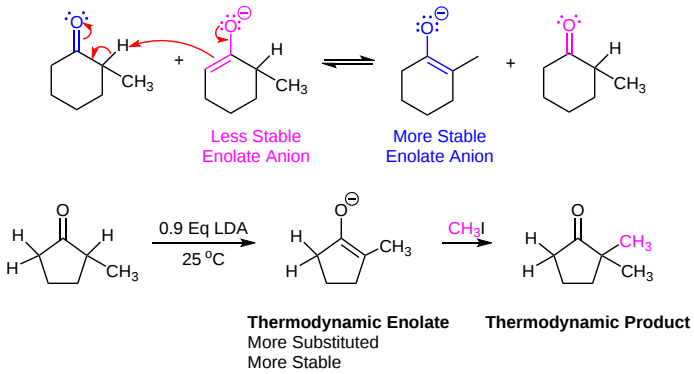
When an unsymmetrical ketone with two sets of non-equivalent α-hydrogens is treated with a base, two possible enolates can form. Regioselective enolate formation is possible under the proper conditions. The main determinant is whether the reaction is under kinetic control (rate) or thermodynamic control (equilibrium). Although a predominant product can be produced, a mixture of products is usually formed causing a reduction in product yield.



THERMODYNAMIC ENOLATES

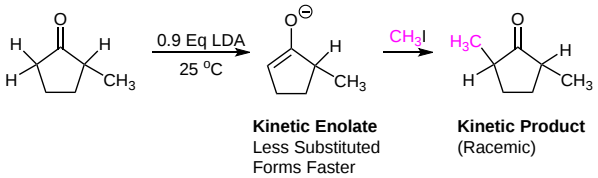
The thermodynamic enolate is formed when the more substituted α-hydrogen is removed. This leads to the more alkyl substituted, therefore the more stable, enolate to be formed. The presence of additional alkyl groups causes the formation of the thermodynamic enolate to be sterically hindered and kinetically slow, especially when a bulky base like LDA is used. Thermodynamic enolates are favored by conditions which allow for equilibration between the possible enolates. When the ketone starting material is not completely deprotonated, equilibrium between the possible enolates and the α-hydrogens of the ketone can occur. During equilibrium, interconversion between the enolates allows the lower energy of the thermodynamic enolate to dominate. Other conditions can also promote the formation of the thermodynamic enolate, such as higher reaction temperatures, or the use of a smaller less sterically hindered base such as sodium hydride (NaH). Weaker bases, such as sodium ethoxide, do not completely deprotonate the ketone starting material which also allows for enolate equilibrium to occur.

Example of enolate equilibration



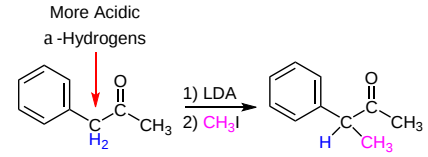
KINETIC ENOLATES

Kinetic enolates are favored under conditions which do not allow for equilibration between the enolates, such as the use of a strong bulky base, like LDA, in a molar equivalent to the ketone starting material. Kinetic enolates are formed when the less substituted α-hydrogen is deprotonated. Being less sterically hindered allows this α-hydrogen to be deprotonated faster even though it forms a less thermodynamically stable enolate. Using a molar equivalent of LDA completely converts the ketone starting material to an enolate, removing it from the reaction mixture and preventing equilibration between the possible enolates. Low reaction temperatures (-78 °C) prevent enolate equilibration and promote the formation of the kinetic enolate.



When and enolate of an asymmetric ketone is stabilized through additional resonance forms there is no competition between possible enolates despite kinetic or thermodynamics conditions. The resonance stabilized enolate will be preferentially alkylated to the point that formation of the alkylated products of other possible enolates will be minimal.

EXAMPLE

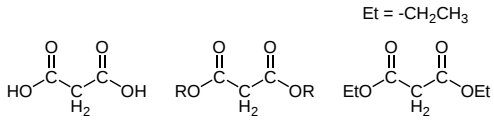


1-Phenyl-2-propanone **1-Methyl-1-phenyl-2-propanone (Racemic)**

MALONIC ESTER SYNTHESIS

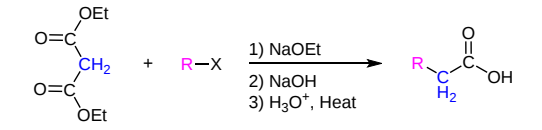
The malonic ester synthesis is a series of reactions which converts an alkyl halide to a carboxylic acid with two additional carbons. One important use of this synthesis pathway is that it allows for the creation of α-alkylated carboxylic acids which cannot be created by direct alkylation.

The starting material of this reaction is a malonic ester: a diester derivative of malonic acid. Diethyl propanedioate, also known as diethyl malonate, is the malonic ester most commonly used in pathway. Since it is a 1,3-dicarbonyl compound, diethyl malonate has relatively acidic α-hydrogens (pK_a = 12.6) and can be transformed to its enolate using sodium ethoxide as a base. Other alkoxide bases are not typically used given the possibility of a transesterification reaction.



Malonic Acid **Malonic Ester** **Diethyl Malonate**

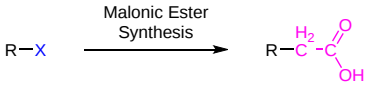
GENERAL REACTION



Diethyl malonate **Alkyl Halide** **a-Alkyl Carboxylic Acid**

PREDICTING THE PRODUCT OF A MALONIC ESTER SYNTHESIS

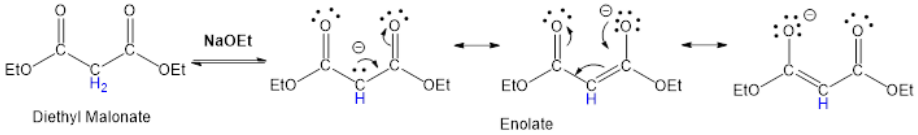
The product of a Malonic Ester Synthesis can be created by simply replacing the halogen on the alkyl halide with a $-CH_2CO_2H$ group.



MALONIC ESTER SYNTHESIS TAKES PLACE IN FOUR STEPS:

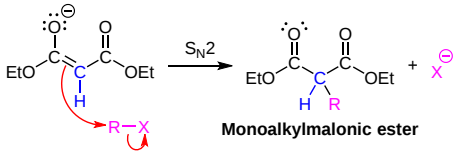
1) Enolate Formation

Reacting diethyl malonate with sodium ethoxide (NaOEt) forms a resonance-stabilized enolate.



2) Alkylation

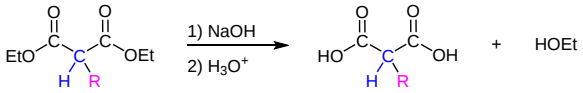
The enolate is alkylated via an S_N2 reaction to form an monoalkylmalonic ester.



Monoalkylmalonic ester

3) Ester hydrolysis and protonation

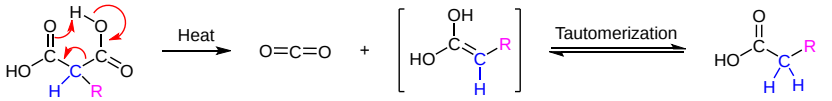
After alkylation, the diester undergoes hydrolysis with sodium hydroxide to form a dicarboxylate. Subsequent protonation with acid forms a monoalkyl malonic acid.



Monoalkyl Malonic Acid

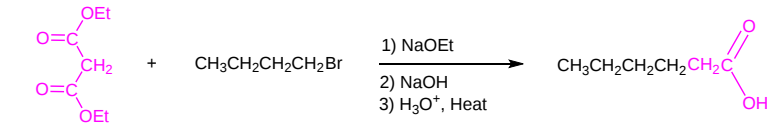
4) Decarboxylation & Tautomerization

Monoalkyl malonic acids decarboxylate when heated, forming an α-alkyl carboxylic acid and carbon dioxide (CO_2). Decarboxylation can only occur in compounds with a second carbonyl group two atoms away from carboxylic acid such as in malonic acids and β-keto acids. The mechanism occurs via a concerted mechanism involving a proton transfer between the carboxyl acid hydrogen and the nearby carbonyl group to form the enol of a carboxylic acid and CO_2. The enol undergoes tautomerization to form the carboxylic acid.



Carbon Dioxide **Carboxylic Acid Enol** **a-Alkylated Carboxylic acid**

EXAMPLE

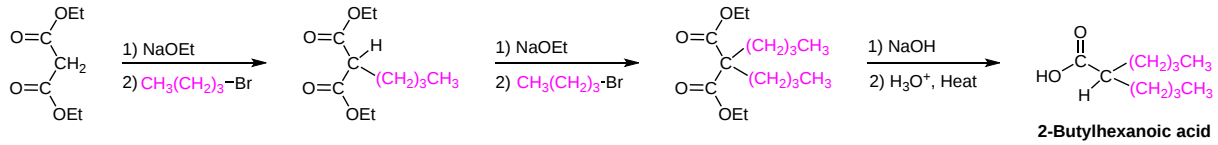


Diethyl malonate **1-Bromobutane** **Hexanoic Acid**

DIALKYLATION

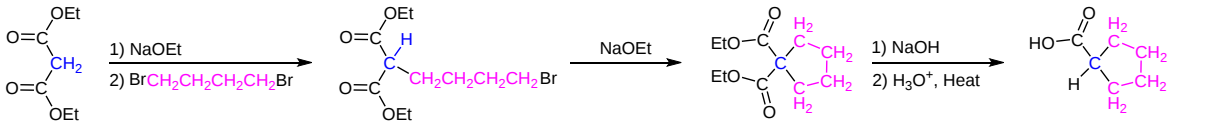
The presence of two α-hydrogens in malonic esters allows for a second alkylation to be performed prior to decarboxylation. This leads to dialkylated carboxylic acids. Due to the lack of stereochemical control inherent in enolate based reactions, if the two added alkyl groups are different, a racemic mixture of products will result.

EXAMPLES



2-Butylhexanoic acid

In a variation of the dialkylation reaction - if one molar equivalent of malonic ester is reacted with one molar equivalent of a dihaloalkane and two molar equivalents of sodium ethoxide, a cyclization reaction occurs. By changing the dihaloalkane, three, four, five, and six-membered rings can be created.

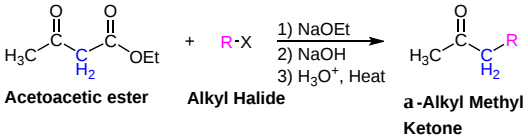


Cyclopentanecarboxylic acid

THE ACETOACETIC ESTER SYNTHESIS

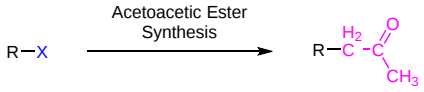
The acetoacetic ester synthesis is a series of reactions which converts alkyl halides into a methyl ketone with three additional carbons. This reaction creates an α-substituted methyl ketone without side-products. The starting reagent for this pathway is ethyl 3-oxobutanoate, also called ethyl acetoacetate, or acetoacetic ester. Like other 1,3-dicarbonyl compounds, ethyl acetoacetate is more acidic than ordinary esters being almost completely converted to an enolate by sodium ethoxide.

GENERAL REACTION



PREDICTING THE PRODUCT OF AN ACETOACETIC ESTER SYNTHESIS

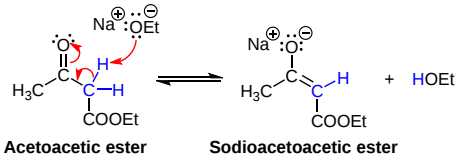
The product of a acetoacetic ester synthesis can be created by replacing halogen on the alkyl halide with a $-CH_2COCH_3$ group.



REACTION STEPS

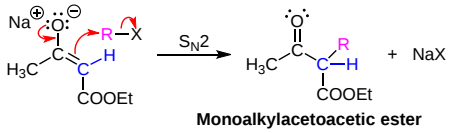
1) Formation of the enolate

As previously described, the α-hydrogens of acetoacetic ester are rather acidic (pK_a = 10.7) allowing the enolate to be easily formed when sodium ethoxide is used as a base.



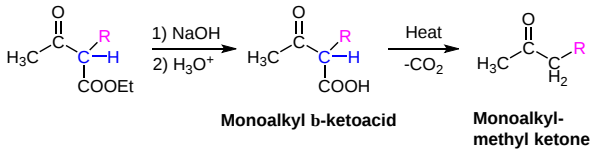
2) Alkylation via an S_N2 Reaction

Subsequent reaction with an alkyl halide produces a monoalkylacetoacetic ester.

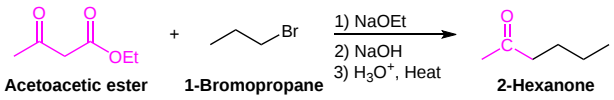


3) Ester hydrolysis and decarboxylation

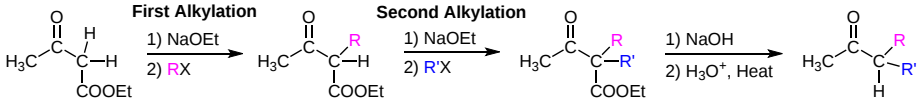
Hydrolysis with NaOH followed by protonation produces an alkylated beta-ketoacid. β-ketoacids are easily decoboxylated to form an α-alkyl substituted methyl ketone and carbon dioxide (CO_2) using a similar mechanism as the malonic ester synthesis.



EXAMPLES

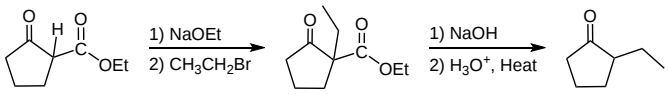


Much like the malonic ester synthesis, a second alkyl group can added before the decarboxylation step.



The reaction steps of the acetoacetic ester synthesis can also be applied to other β-keto esters with acidic α-hydrogens. Because the α-hydrogens between the two carbonyls are the most acidic, they are preferentially deprotonated allowing for a single enolate to be formed. Even cyclic beta-keto esters can be alkylated and subsequently decarboxylated to give an α-alkylated cyclic ketone.

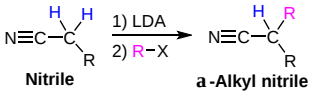
EXAMPLES



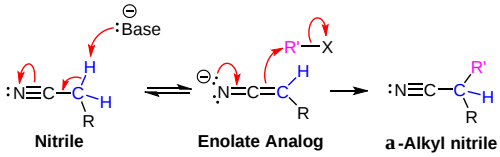
DIRECT ALKYLATION OF NITRILES

The presence of acidic α-hydrogens in nitriles gives them the ability to form an enolate equivalent which can be also be directly alkylated.

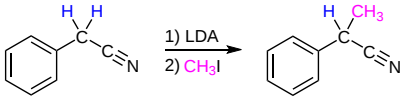
GENERAL REACTION



MECHANISM



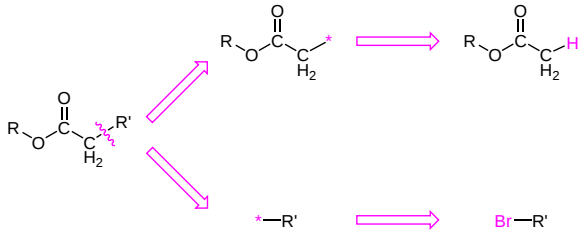
EXAMPLE



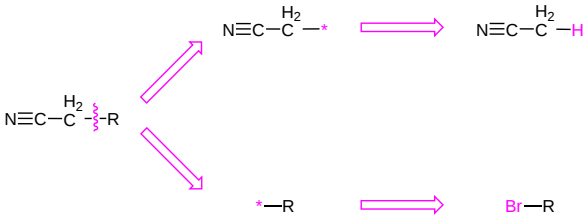
PLANNING A SYNTHESIS USING ENOLATE ALKYLATIONS

When planning a synthesis that could involve enolates, the key is to recognize the functionality which can form an enolate. During retrosynthetic analysis a C-C bond is broken between the α-carbon and the β-carbon away from this functionality. It is also important to be able to identify specific groups of atoms which indicate if a malonic ester or an acetoacetic ester synthesis can be used. Having multiple C-C bonds which can be broken allows for multiple synthetic pathways.

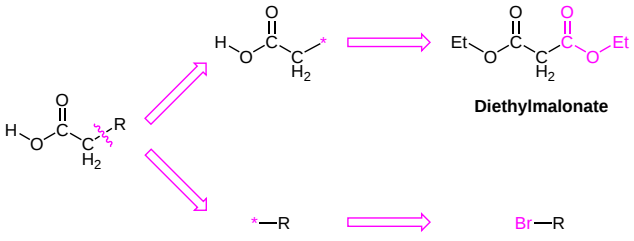
After retrosynthetically breaking the C-C bond, the fragment with the functionality will gain a hydrogen and the other fragment will gain a halogen. Sometimes the fragment with the functionality will become diethyl malonate or acetoacetic ester.

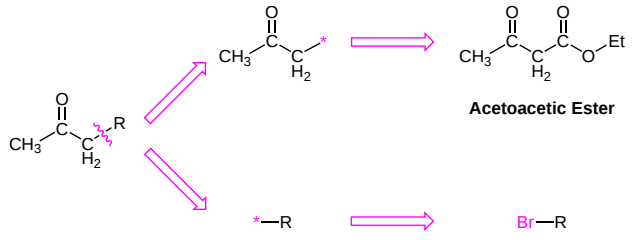


Direct Alkylation of an Ester



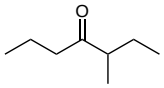
Direct Alkylation of a Nitrile



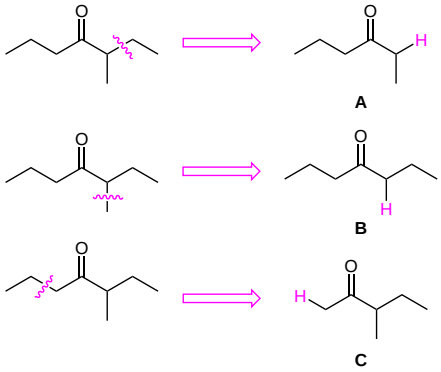


WORKED OUT EXAMPLE:

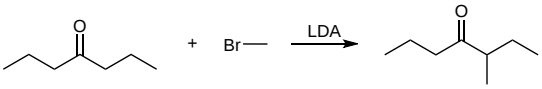
Plan a synthesis of the following molecule using an alkylation of an enolate. Consider multiple pathways and explain which is preferable.



The target molecule does not contain the appropriate fragments to utilize either the malonic ester or acetoacetic acid synthesis so direct alkylation of a ketone will likely be used. When analyzing this molecule, there are three α-β C-C bonds which could be cleaved to create a possible starting material. When looking at the possible starting materials, A and C are asymmetrical ketones and therefore can create multiple products during alkylation. B is a symmetrical ketone and should be the most likely to create the target molecule in high yield.



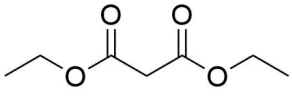
Possible Synthesis

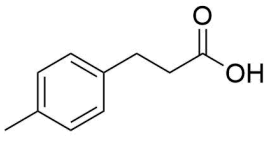


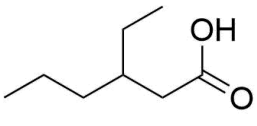
EXERCISES

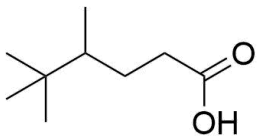
QUESTIONS

1) Propose a synthesis for each of the following molecules from this malonic ester.



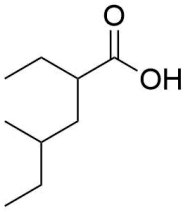
(a) 

(b) 

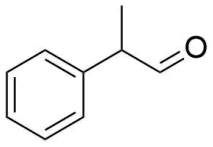
(c) 

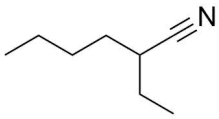
2) Why can't you prepare tri substituted acetic acids from a malonic ester?

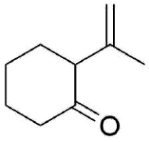
3) Propose a synthesis for the following molecule via a malonic ester.

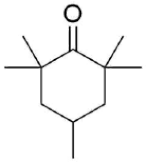


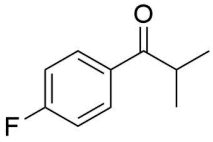
4) How might you prepare the following compounds from an alkylation reaction?

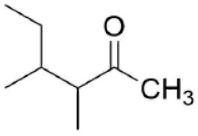
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

SOLUTIONS

1

(a) 1) Malonic Ester, NaOEt, 2) 4-Methylbenzyl Bromide, 3) Base, 4) Acid, Heat

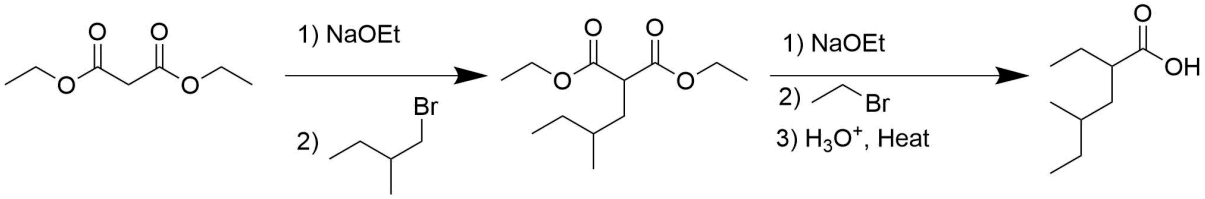
(b) 1) Malonic Ester, NaOEt, 2) 3-bromohexane, 3) Base, 4) Acid, Eat

(c) 1) Malonic Ester, NaOEt, 2) 1-Bromo-2,3,3-trimethylbutane, 3) Base, 4) Acid, Heat

2

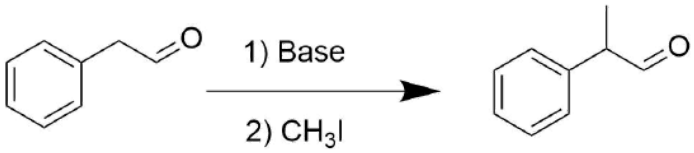
Malonic esters only contain two acid protons.

3



4

(a)



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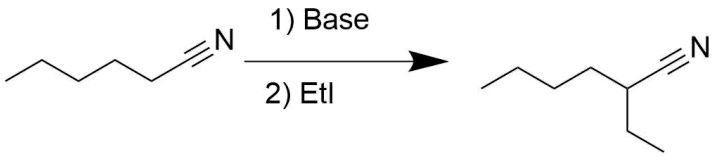

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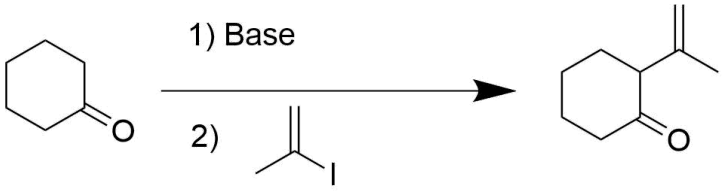

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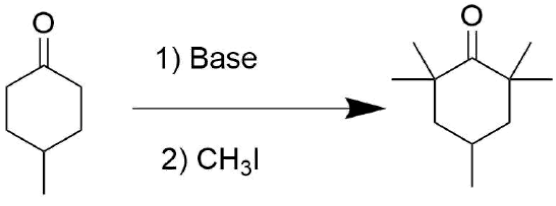

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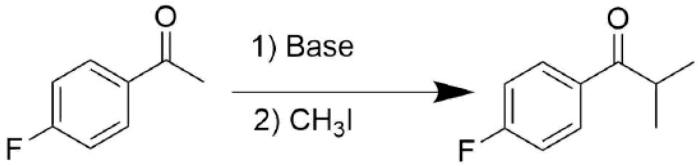

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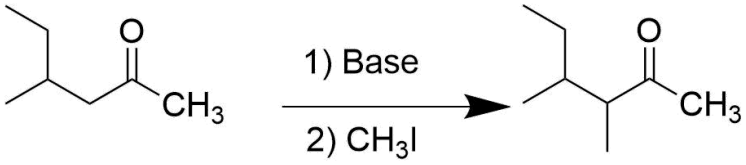


22.S: CARBONYL ALPHA-SUBSTITUTION REACTIONS (SUMMARY)

CONCEPTS & VOCABULARY

- Four common types of reactions involving carbonyl reactions: 1) nucleophilic addition; 2) nucleophilic acyl substitution; 3) alpha substitution; 4) carbonyl condensations. The first two were previously discussed and the second two involve the properties of the carbon directly adjacent to the carbonyls, **α carbons**.
- Alpha-substitution reactions results in the replacement of an H attached to the alpha carbon with an electrophile.
- The nucleophile in these reactions are new and called enols and enolates.
- In this chapter, the focus is on α substitutions reactions with aldehydes and ketones.

22.1 Keto-Enol Tautomerization

- Greek letters are used to denote the carbon atoms near carbonyls.
- The carbon in the carbonyl is the reference point and the alpha carbon is adjacent to the carbonyl carbon.
- Hydrogen atoms attached the these carbons denoted with Greek letters will have the same designation, so an alpha hydrogen is attached to an alpha carbon.
- Aldehyde hydrogens not given Greek leters.
- α hydrogens display unusual acidity, due to the resonance stabilization of the carbanion conjugate base, called an enolate.
- Tautomers are readily interconverted constitutional isomers, usually distinguished by a different location for an atom or a group, which is different than resonance.
- The tautomerization in this chapter focuses on the carbonyl group with alpha hydrogen, which undergo keto-enol tautomerism.
- Keto refers to the tautomer containing the carbonyl while enol implies a double bond and a hydroxyl group present in the tautomer.
- The keto-enol tautomerization equilibrium is dependent on stabilization factors of both the keto tautomer and the enol tautomer, though the keto form is typically favored for simple carbonyl compounds.
- The 1,3 arrangement of two carbonyl groups can work synergistically to stabilize the enol tautomer, increasing the amount present at equilibrium.
- The positioning of the carbonyl groups in the 1,3 arrangement allows for the formation of a stabilizing intramolecular hydrogen bond between the hydroxyl group of the enol and the carbonyl oxygen as well as the alkene group of the enol tautomer is also conjugated with the carbonyl double bond which provides additional stabilization.
- Aromaticity can also stabilize the enol tautomer over the keto tautomer.
- Under neutral conditions, the tautomerization is slow, but both acid and base catalysts can be utilized to speed the reaction up.
- Biological enol forming reactions use isomerase enzymes to catalyze the shifting of a carbonyl group in sugar molecules, often converting between a ketose and an aldose in a process called carbonyl isomerization.

22.2 Reactivity of Enols: The Mechanism of Alpha-Substitution Reactions

- The oxygen of the enol donates electron density to the double bond making it more electron rich and thus more reactive than a typical alkene.
- The mechanism starts with an acid-catalyzed tautomerization to form an enol.
- The double bond is then able to act as a nucleophile and attack an electrophile.
- The final product is an alpha-substituted carbonyl after the deprotonation of the carbonyl to also regenerate the acid-catalyst.
- The enol formed has planar geometry, which means the electrophile can attach on the top or bottom of the alpha-carbon.
- A racemic mixture can result if a sterocenter is created at the site of substitution.

22.3 Alpha Halogenation of Aldehydes and Ketones

- Aldehydes and ketons can undergo a substitution of an alpha hydrogen to a halogen.
- An acid-catalyzed tautomerization starts the mechanism followed by the enol attacking molecular halogens.
- The nucleophile in this reaction is the enol and the electrophile is the halogen.
- Mechanistic studies showed that the reaction was a first-order in the ketone.
- The halogen is part of a fast step after the rate-determing step.
- The formation of an enol intermediate was provided using a reaction called deuterium exchange.
- Due to the acidic nature of α hydrogens they can be exchanged with deuterium by reaction with the isotopic form of water, D_2O.
- The mechanism for deuterium exchange is virtually the same as that of keto-enol tautomerism under acidic conditions, the difference being a deuterium is placed in the *α*-position.
- Both alpha halogenation and deuterium exhange reactions were found to have a common intermediate involved in the rate determining step of their mechanism, an enol.

22.4 Alpha Bromination of Carboxylic Acids

- The α-bromination of some carbonyl compounds, such as aldehydes and ketones, can be accomplished with Br_2 under acidic conditions, but the reaction will generally not occur with more stable carboxylic acid derivatives.
- Carboxylic acids do not enolize to a sufficient extent since the carboxylic acid proton is preferably removed before an α-hydrogen.
- Carboxylic acids, can be brominated in the α position with a mixture of Br_2 and phosphorus tribromide (PBr_3) in what is called the Hell-Volhard-Zelinskii reaction.
- α-Bromo carboxylic acids are extremely useful synthetic intermediates because the halogen is highly reactive towards S_N2 reaction.
- Reaction of a α-bromo carboxylic acids with an excess of ammonia provides α-amination, which is a possible route to amino acids.

22.5 Acidity of Alpha Hydrogen Atoms: Enolate Ion Formation

- α hydrogens are weakly acidic because the conjugate base, called an enolate, is stabilized though conjugation with the π orbitals of the adjacent carbonyl.
- The enolate has two resonance structures to contribute to the resonance hybrid.
- While α-hydrogens are weakly acidic, typical strong bases such as hydroxide or alkoxide are only capable of forming the enolate ion in very low concentrations.
- To achieve complete deprotonation of aldehyde or ketone reactants to their enolate conjugate bases, a very strong base such as LDA (lithium diisopropylamide) must be used.
- Hydrogen atoms with two or more adjacent carbonyl groups are more acidic than typical α hydrogens, such as β-diketones, β-keto-esters, and β-diesters, which create enolates that are stabilized through additional resonance forms which share the negative charge with multiple carbonyl carbons.
- The acidity of these compounds is increased to the point where typical strong bases such as hydroxide and alkoxide can be used to form the enolate.

22.6 Reactivity of Enolate Ions

- Enolates are better nucleophlies than enols.
- α-hydrogen containing compounds can be completely converted to an enolate by reaction with a strong base whereas enols can only be created in small amounts through manipulating their equilibrium.
- Either the C of the O reactive site in an enolate may act as a nucleophile depending on the reaction conditions, but reactions involving the nucleophilic α-carbon are more common, partially due to the thermodynamic stability of the C=O bonds in the final products.
- An enolate reacts rapidly with a halogen to produce α-halogenated carbonyl products.
- The α-hydrogens of halogenated carbonyl products are usually more acidic than the corresponding non-halogenated compounds, which promotes polyhalogenated products.
- The Haloform reaction represents a method for the conversion of methyl ketones to carboxylic acids.
- This reaction is considered a base promoted and not base catalyzed because an entire equivalent of base is required for each α-halogenation.
- Deprotonation of an α-hydrogen with hydroxide produces the nucleophilic enolate ion which subsequently reacts with the halogen.
- The increasing acidity of α-halogenated ketone causes this reaction to occur two more times.
- Once formed, the CX_3 group attached to the carbonyl can act as a leaving group, eventually produces a haloform ($CHCl_3$, $CHBr_3$, CHI_3) and a carboxylate anion.

22.7 Alkylation of Enolate Ions

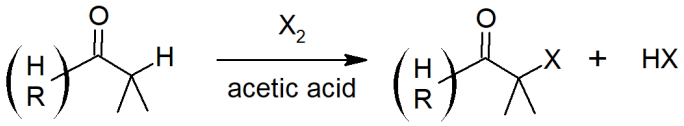
- Enolates can be alkylated in the alpha position through an S_N2 reaction with alkyl halides.
- An α hydrogen is replaced with an alkyl group and a new C-C bond is formed.
- Very strong bases like LDA are often used to fully deprotonate the carbonyl and completely form the enolate.
- Direct alkylations, like all enolate-based reactions, will form a racemic mixture if the alkylated alpha carbon is chiral.
- When an unsymmetrical ketone with two sets of nonequivalent alpha hydrogens is treated with a base, two possible enolates can form.
- The main determinant for which enolate is formed is whether the reaction is under kinetic control (rate) or thermodynamic (equilibrium) control.
- The thermodynamic enolate is formed when the more substituted alpha hydrogen is removed, yielding the more alkyl substituted, therefore the most stable, enolate.
- Formation of the thermodynamic enolate is sterically hindered and is kinetically slow, especially with a bulky base like LDA.
- Kinetic enolates are formed when the less substituted alpha hydrogen is deprotonated, being less sterically hindered allows this alpha hydrogen to be deprotonated faster even though it forms a less thermodynamically stable enolate.
- The malonic ester synthesis is a series of reactions which converts an alkyl halide to a carboxylic acid with two additional carbons.
- The importance of this synthesis pathways is that it allows for the creation of alpha alkylated carboxylic acids which cannot be created by direct alkylation.
- The acetoacetic ester synthesis is a series of reaction which converts alkyl halides into a methyl ketone with three additional carbons.
- This reaction creates an alpha substituted methyl ketone without side-products.

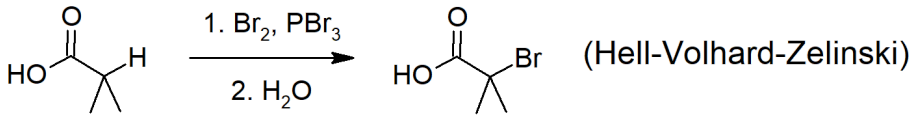
- In retrosynthetic analysis, a C-C bond is broken between the alpha carbon and the beta carbon away from this functionality.

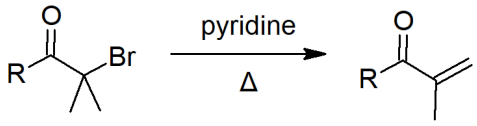
SKILLS TO MASTER

- Skill 22.1 Determine alpha carbons and alpha hydrogens.
- Skill 22.2 Draw the enols formed from carbonyl derivatives.
- Skill 22.3 Provide the mechanism for the keto-enol tautomerization under neutral, acidic and basic conditions.
- Skill 22.4 Provide the mechanism for the enol-keto tautomerization under neutral, acidic and basic conditions.
- Skill 22.5 Draw the products of halogenation reactions.
- Skill 22.6 Provide the mechanism for halogenation reactions.
- Skill 22.7 Write an equation to illustrate the Hell-Volhard-Zelinskii reaction.
- Skill 22.8 Identify the product formed from the reaction of a given carboxylic acid with bromine and phosphorus tribromide.
- Skill 22.9 Explain why the alpha hydrogen of carbonyl compounds are more acidic than a typical hydrogen.
- Skill 22.10 Explain why dicarbonyl protons are more acidic than compounds that contain a single carbonyl.
- Skill 22.11 Provide a mechanism for the haloform reaction.
- Skill 22.12 Provide a mechanism for an alkylation reaction with an enolate.
- Skill 22.13 Provide a mechanism for malonic ester synthesis.
- Skill 22.14 Propose synthesis for alkylated carboxylic acids.
- Skill 22.15 Provide a mechanism for acetoacetic acid synthesis.
- Skill 22.16 Propose a synthesis for alkylated methyl ketones.

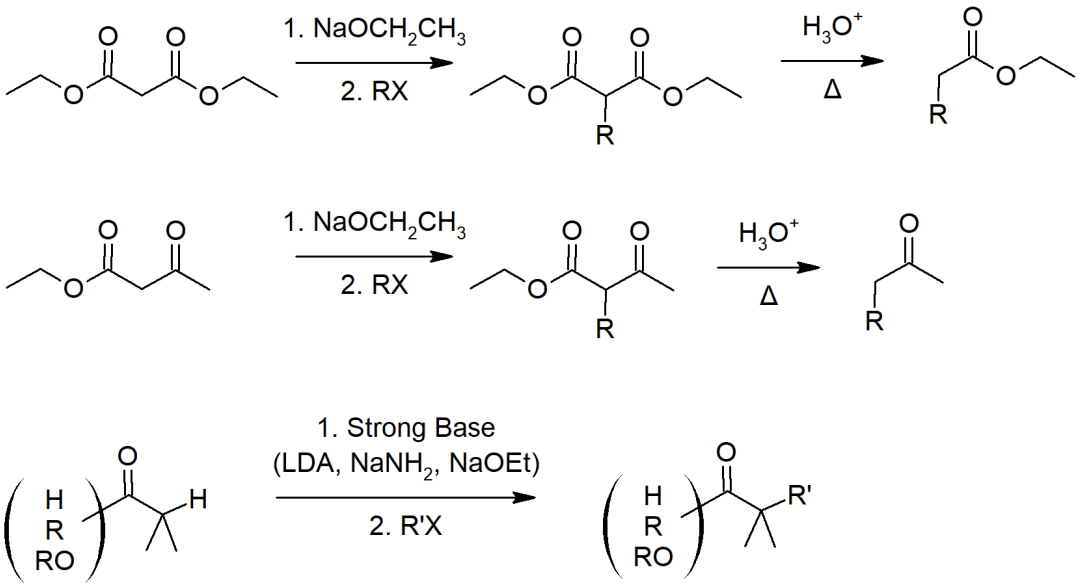
SUMMARY OF REACTIONS







Alkylation



CHAPTER OVERVIEW

23: CARBONYL CONDENSATION REACTIONS

LEARNING OBJECTIVES

When you have completed Chapter 23, you should be able to

- fulfill all of the detailed objectives listed under each individual section.
- design multi-step syntheses in which the reactions introduced in this unit are used in conjunction with any of the reactions described in previous units.
- solve road-map problems that require a knowledge of carbonyl condensation reactions.
- define, and use in context, any of the key terms introduced.

In this chapter, we consider the fourth and final general type of reaction that carbonyl compounds undergo—the carbonyl condensation reaction. Carbonyl condensation reactions take place between two carbonyl-containing reactants, one of which must possess an alpha-hydrogen atom. The first step of the reaction involves the removal of an alpha-hydrogen atom by a base. In the second step, the enolate anion that results from this removal attacks the carbonyl-carbon of the second reacting molecule. In the final step of the reaction, a proton is transferred to the tetrahedral intermediate formed in the second step, although in some cases the product that results may subsequently be dehydrated.

23.0: CHAPTER OBJECTIVES

The importance of carbonyl condensation reactions to synthetic organic chemistry arises from the large number of combinations of carbonyl compounds that can be used in such reactions. Aldehydes or ketones can be used in a simple aldol condensation to produce β-hydroxy aldehydes, β-hydroxy ketones, or their dehydration products. Mixtures of aldehydes, ketones, or both, can be used in a mixed aldol condensation. Internal aldol condensations can occur in compounds containing two suitable carbonyl groups. Aldol-like condensations can be brought about between aldehydes and a variety of compounds containing acidic alpha-hydrogen atoms, including diethyl malonate, acetic anhydride, nitriles and nitro compounds. Esters can be used in Claisen condensations and 1,6- and 1,7-diesters can give rise to internal condensations, called Dieckmann cyclizations. Related reactions include the Michael reaction, in which an α,β-unsaturated carbonyl compound is reacted with an enolate anion; and the Stork enamine reaction, where an enamine adds to an α,β-unsaturated ketone.

The chapter concludes with a look at how condensation reactions can be used in the synthesis of complex ring-containing organic compounds, and at the role played by carbonyl condensation reactions in biological systems.

23.1: CARBONYL CONDENSATIONS - THE ALDOL REACTION

OBJECTIVES

After completing this section, you should be able to

1. write a general mechanism for carbonyl condensation reactions.
2. write an equation to illustrate the aldol condensation reaction.
3. identify the product formed when an aldehyde or ketone having an alpha-hydrogen atom is treated with base in a protic medium.
4. identify the aldehyde or ketone, and other reagents required to produce a given β-hydroxy carbonyl compound by an aldol reaction.
5. determine whether a given aldehyde or ketone will undergo an aldol reaction.
6. write the detailed mechanism of the aldol reaction.

KEY TERMS

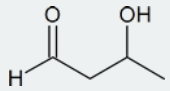
- aldol
- aldol reaction
- carbonyl condensation reaction (see Chapter 18 Affix)

STUDY NOTES

It is important that you understand the general mechanism of carbonyl condensation described in this section: once you grasp this mechanism, you will see that all the reactions that follow are very similar.

The aldol reaction is sometimes referred to as the aldol condensation. However, a condensation reaction is often regarded as a reaction in which two molecules join together with the elimination of a molecule of water (or some other compound of low molar mass). Thus, the aldol reaction described here is not a true condensation; the true aldol condensation is described later, in Section 23.3. It is perhaps unfortunate that the reactions discussed in this unit are all described as condensation reactions whether or not water is eliminated.

The term “aldol” (from "aldehyde alcohol") is used both to describe the specific compound 3-hydroxybutanal:

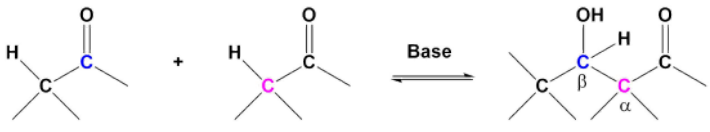


and to describe β-hydroxy aldehydes in general.

A useful carbon-carbon bond-forming reaction known as the Aldol Reaction is another example of electrophilic substitution at the alpha carbon in enolate anions. This reaction requires the formation of an enolate so at least one of the reactants must have an α-hydrogen. Due to the carbanion like nature of enolates, they can add to carbonyls through nucleophilic addition much like Grignard reagents.

The aldol reaction takes advantage of a carbonyl compound’s ability to undergo both alpha substitution and nucleophilic addition reactions. The fundamental transformation in the aldol reaction is a dimerization of an aldehyde (or ketone) to form a beta-hydroxy aldehyde (or ketone). A C-C bond is formed between the alpha carbon of one reactant molecule and the carbonyl carbon of a second reactant molecule. In the reaction’s product, the formed C-C bond links a carbon in the alpha position and a carbon in the beta position away from the carbonyl.

GENERAL ALDOL REACTION



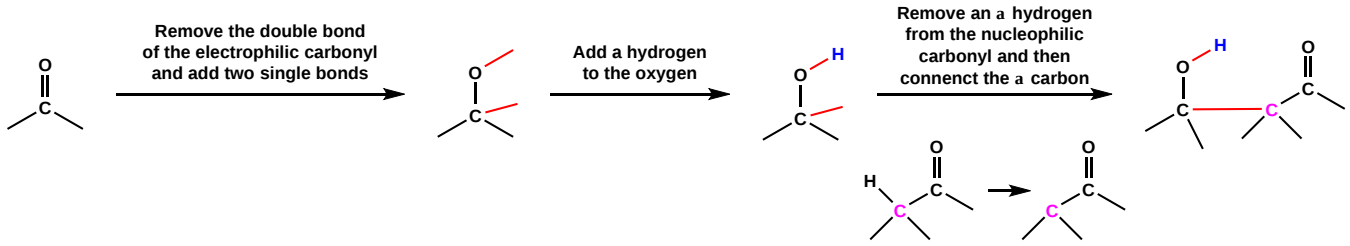
β–Hydroxycarbonyl

A typical example involves two molecules of acetaldehyde (ethanal) reacting to form beta-hydroxybuteraldehyde (3-hydroxybutanal). This product and other beta-hydroxy aldehydes are generically called “aldols” because they contain both an aldehyde and an alcohol functional group.

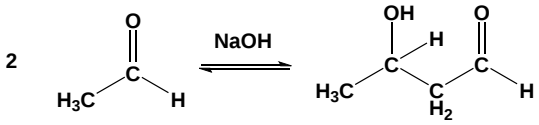
An aldol reaction, like many carbonyl addition reactions, is an equilibrium reaction and is reversible. The presence of an equilibrium means weaker bases, such a hydroxides or alkoxides, can be used to perform this reaction. The reaction equilibrium favors the products when aldehydes with little steric hindrance around the carbonyl are used. However, the reaction equilibrium for ketones and sterically hindered

aldehydes favors the reactants. To provide good reaction yields when using these reactants, the equilibrium must be pushed towards the products. Typically, this is done by utilizing a method to remove the product as it is formed during the reaction.

PREDICTING THE PRODUCT OF AN ALDOL REACTION



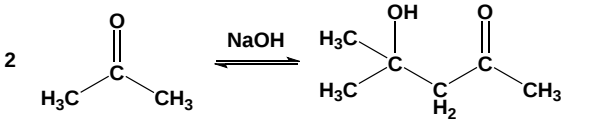
EXAMPLES



Ethanal

3-Hydroxybutanal

Aldol



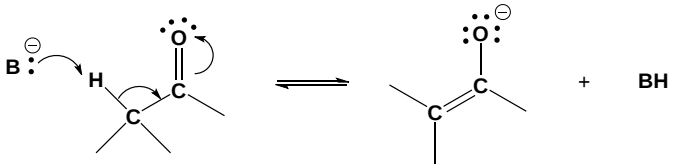
Acetone

4-Hydroxy-4-methyl-2-pentanone

MECHANISM OF ALDOL REACTION

1) ENOLATE FORMATION

The reaction starts with a base removing an alpha hydrogen to form a nucleophilic enolate.

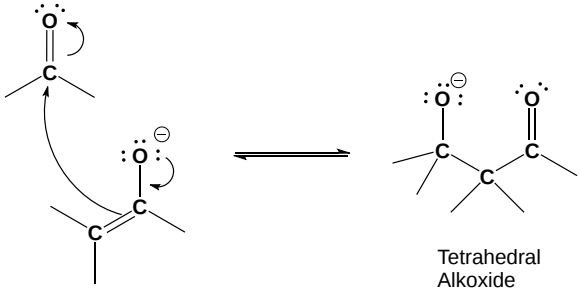


Aldehyde or Ketone

Enolate

2) NUCLEOPHILIC ATTACK BY THE ENOLATE

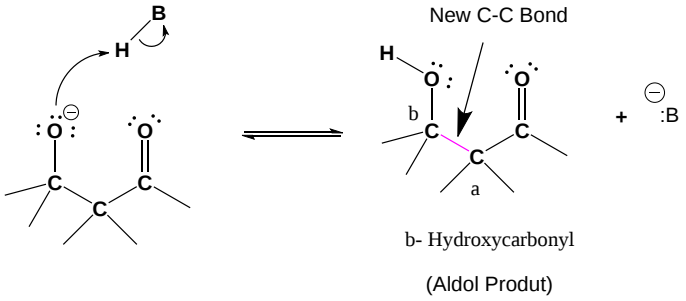
Through nucleophilic addition, the enolate adds to the electrophilic carbonyl group on a second molecule. As with other nucleophilic addition reaction a tetrahedral alkoxide intermediate is formed.



Tetrahedral Alkoxide Intermediate

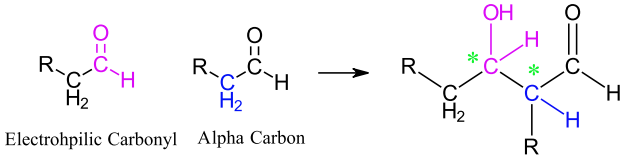
3) PROTONATION

Protonation of the alkoxide forms the neutral aldol product and regenerates the base.



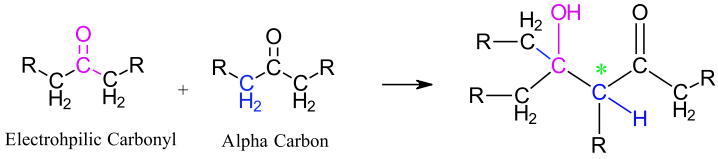
STEREOCHEMICAL RAMIFICATIONS OF THE ALDOL REACTION

As previously discussed, both nucleophilic addition and alpha-substitution reactions have the possibility of creating chiral carbons. The alpha carbon and the electrophilic carbon of the reactants should be identified in the aldol product to assess their possible chirality. Most aldehydes produce chirality in both of these carbons. Most symmetrical ketones create a chiral carbon from the alpha-carbon of the reactant.



Aldehyde Reactants

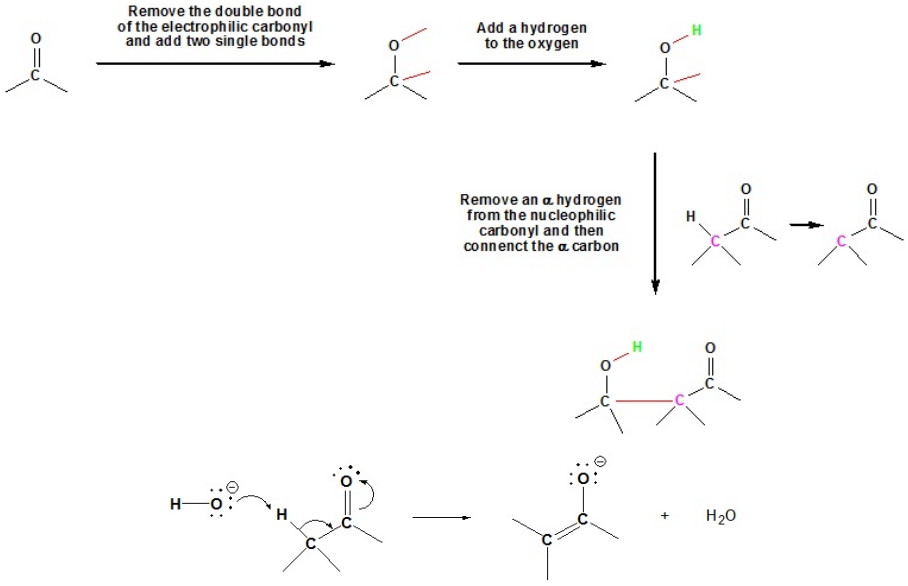
Aldol Product with two Chiral Carbons



Symmetrical Ketone Reactants

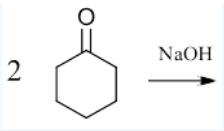
Aldol Product with one Chiral Carbon

GOING FROM REACTANTS TO PRODUCTS SIMPLY



? WORKED EXAMPLE

What would be the expect product of the following aldol reaction?

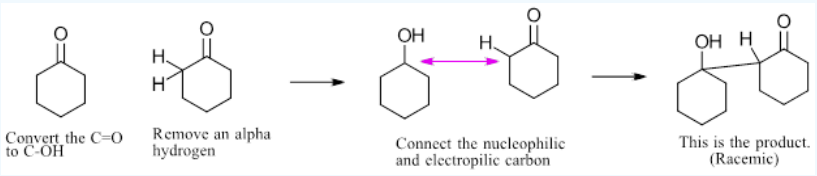


Answer

Analysis:

When considering the product of an aldol reaction it is vital to consider each reactant molecule separately. Also,

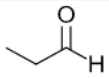
Identify electrophilic carbonyl carbon and any alpha hydrogens present.



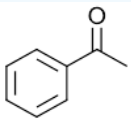
EXERCISES 23.1.1

1) Predict the product of an aldol reaction with the following molecules:

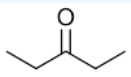
a)



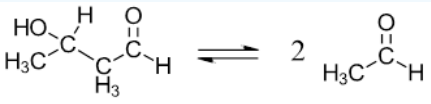
b)



c)



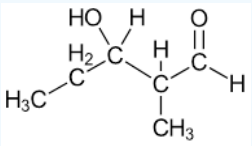
2) Because the aldol reaction is reversible it is possible for a beta-hydroxy carbonyl compound to undergo a retro-aldol reaction. Please draw the mechanism or the based catalyzed retro-aldol reaction shown below.



Answers

1)

a)



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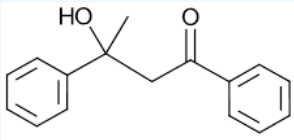

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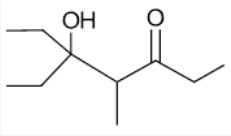
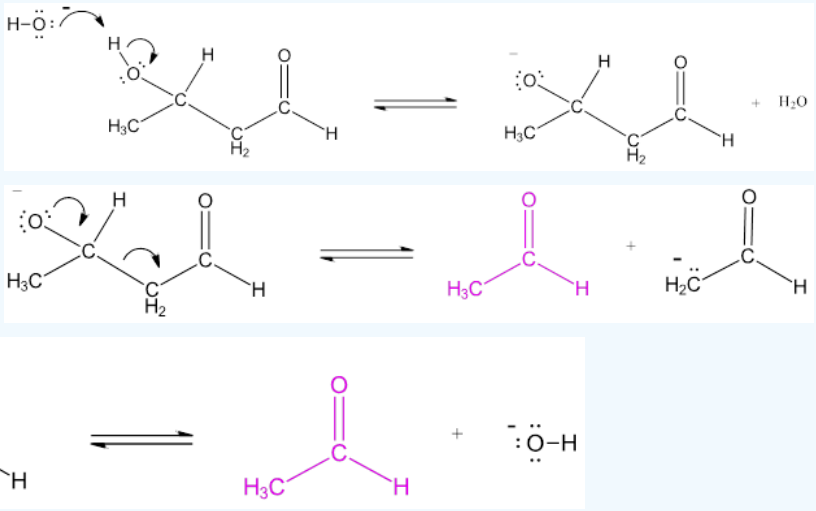


2)



23.2: CARBONYL CONDENSATIONS VERSUS ALPHA SUBSTITUTIONS

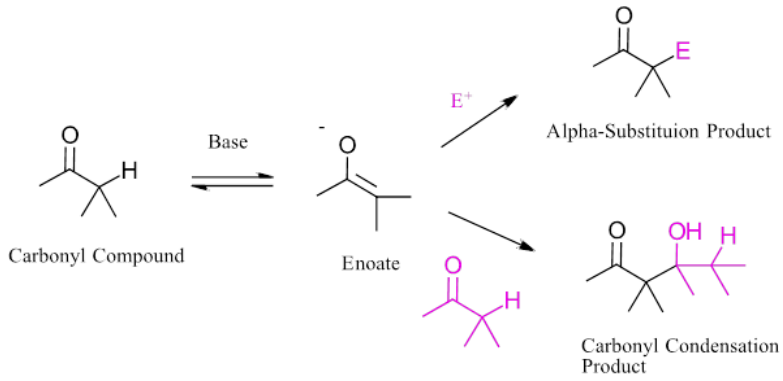
OBJECTIVES

After completing this section, you should be able to describe the difference between a carbonyl condensation reaction and an alpha-substitution reaction, and determine which of these two types of reaction is most likely to occur, given the appropriate experimental data.

STUDY NOTES

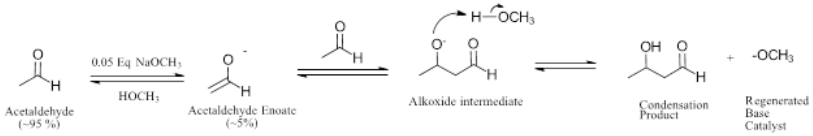
So far we have discussed three of the four general reactions of carbonyl compounds: nucleophilic additions of aldehydes and ketones (Chapter 19), nucleophilic acyl substitution reactions of carboxylic acid derivatives (Chapter 21) and alpha-substitution reactions (Chapter 22). The fourth general reaction, carbonyl condensation, is similar to the alpha-substitution reaction, so you need to appreciate how it differs from the other three and the conditions under which it occurs.

Carbonyl condensation and alpha-substitution reactions both involve the formation of a reactive enolate ion intermediate. How is it possible to generate an enolate ion for a alpha substitution reaction without a carbonyl condensation also occurring? What reaction conditions are required to cause one reaction and not the other?



In a carbonyl condensation a catalytic amount of base is used to generate only a small amount of the the enolate ion. Most of the carbonyl compound is unreacted and can react with the enolate. During the reaction the base catalyst is regenerated which can then produce more enolate ion and continue the cycle.

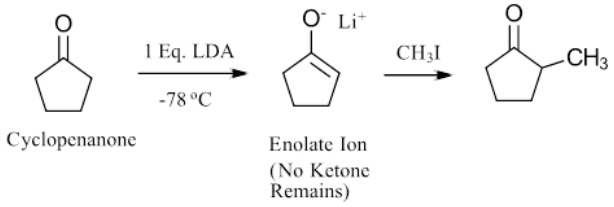
If acetaldehyde was reacted with 0.05 equivalents of sodium methoxide in a methanol solvent only a small amount (~5%) of the enolate would form. The majority of the acetaldehyde would be unchanged and capable of undergoing a condensation reaction with the enolate present. The alkoxide intermediate produced is protonated by methanol to the neutral condensation product and regenerates the methoxide base catalyst. Methoxide can then deprotonate a new acetaldehyde molecule to create another enolate allowing the reaction cycle to continue.



These steps are all reversible and it should be noted that reactants and products that are close in energy level can potentially undergo the reverse reaction if conditions change enough. While from a synthetic point of view in the laboratory this may mean increasing yields by driving the reaction to completion (e.g. adding heat, removing product), in biological systems it can have more drastic consequences. Indeed, depending on metabolic conditions, retro-aldol reactions (the reverse of aldol condensations, in which carbon-carbon bonds are broken) can occur.

In contrast, the alpha-substitution reaction is often more directional by design. To reduce unwanted competition from carbonyl condensation, the enolate ion intermediate is generated all at once with a full equivalent of strong base at low temperature. This effectively removes the carbonyl from the reactive mixture making it difficult for a carbonyl condensation to occur. The reactive enolate intermediate then is quickly quenched by rapid addition of the electrophile to complete the substitution reaction. As discussed in Section 22.7, for direct alkylation, strong bases like $NaNH_2$ and LDA were used to generate the enolate intermediate followed by addition of an alkylhalide.

An example is shown with the alpha-alkylation reaction of cyclopentanone. During this reaction, one equivalent of lithium diisopropyamide (LDA) is added to the reactant at -78 ºC which completely converts cyclopenanone to the corresponding enolate ion. This leaves none of the ketone carbonyl remaining to undergo a condensation reaction. Methyliodide is quickly added to react with enolate ion forming the alpha-alkylated product.



23.3: DEHYDRATION OF ALDOL PRODUCTS - SYNTHESIS OF ENONES

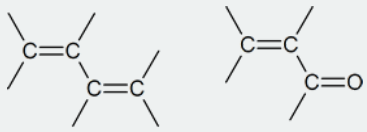
OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate the formation of a conjugated enone from a β-hydroxy aldehyde or ketone.
2. write a detailed mechanism for the basic or acidic elimination of water from a β-hydroxy aldehyde or ketone.
3. explain why β-hydroxy aldehydes and ketones undergo elimination reactions much more readily than most other alcohols.
4. identify the enone products from the aldol condensation of a given aldehyde or ketone.

STUDY NOTES

Conjugated enones, like conjugated dienes, have more inherent stability compared with their non-conjugated counterparts. You may wish to review Section 14.1 on dienes, which gives a molecular orbital description showing π electron distribution over four atomic centres.

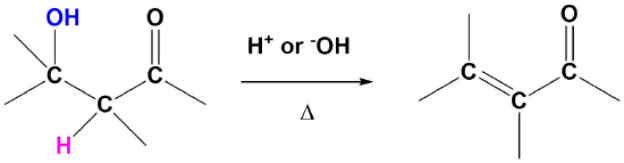


diene enone

Note that both of the elimination mechanisms described here (acidic and basic) involve either the enol form or the enolate anion of the β-hydroxy carbonyl compound.

ALDOL CONDENSATION

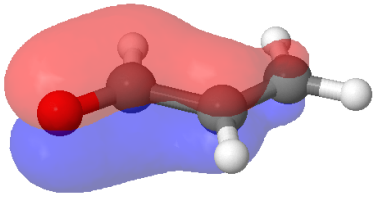
Reactions in which a larger molecule is formed from smaller components, with the elimination of a very small by-product such as water are termed Condensations. Hence the following examples are properly referred to as aldol condensations.

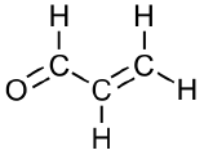


DEHYDRATION OF ALDOL PRODUCTS TO SYNTHESIZE A, B UNSATURATED CARBONYL (ENONES)

The products of aldol reactions, with heating, often undergo a subsequent elimination of water, made up from an alpha-hydrogen and the beta-hydroxyl group. The product of this acid or base-catalyzed E1cB elimination reaction (Section 11-10) reaction is an α,β-unsaturated aldehyde or ketone (Enones). Although there may be multiple position where the alkene may form, it will always prefer to be in conjugation with the carbonyl.

Conjugated enone products are more stable than non-conjugated due to extended P orbital overlap. Conjugation of the p electrons of the alkene and carbonyl bonds provide a molecular-orbital description showing the interaction of p electrons of all four atoms. The additional stability provided by the conjugated carbonyl system of the product makes many aldol reactions thermodynamically factorable.



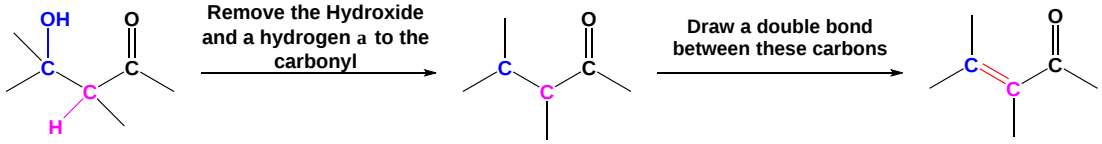


Propenal

A representation of pi bonding molecular orbitals of the conjugated enone, propenal, are delocalized through p-orbital overlap

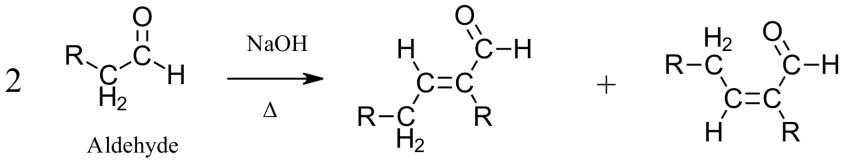
The elimination of water from the reaction mixture can be used to drive the equilibrium towards the products by Le Chatelier's principal. This coupled with the thermodynamic stability of the conjugated product allow for good reaction yields when the formation of the initial aldol intermediate is unfavorable (ketones & sterically hindered aldehydes).

PREDICTING THE PRODUCT OF AN ENONE FORMATION

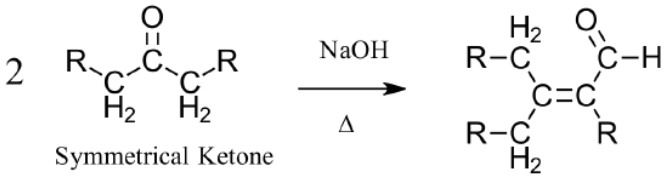


STEREOCHEMICAL CONSIDERATIONS

When aldehyde starting materials are used for an aldol condensation, there is the possibility of forming both E and Z alkene isomers. When symmetrical ketones are used, the alkene formed lacks the ability to form isomers so a single product is made.

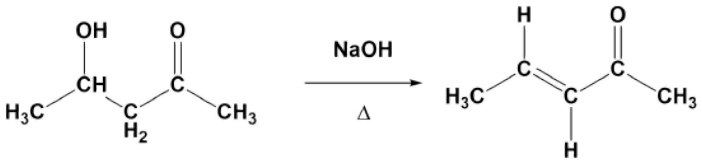


Aldehyde E Isomer Z Isomer

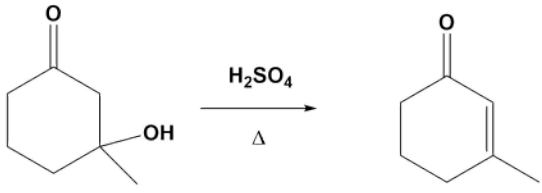


Symmetrical Ketone No Isomers Possible

Examples



4-Hydroxy-2-Pentanone 3-Penten-2-one



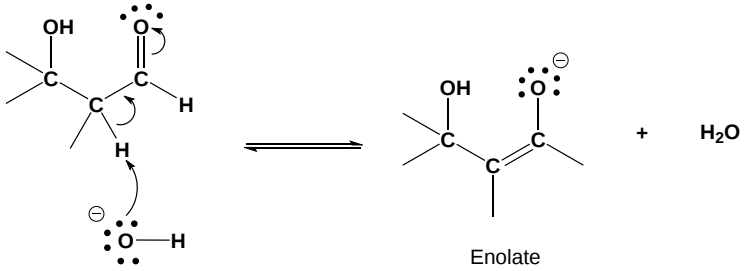
3-Hydroxy-3-methylcyclohexanone 3-Methyl-2-Cyclohexenone

MECHANISM

BASE CATALYZED MECHANISM

1) FORM AN ENOLATE

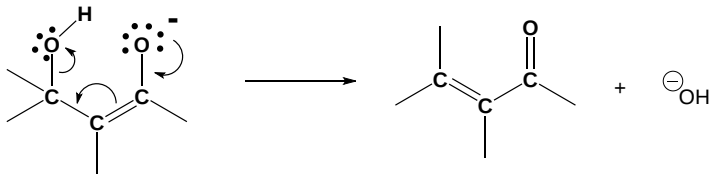
The mechanism starts with the base removing an alpha-hydrogen to form an enolate ion.



Enolate

2) FORM THE ENONE

The alkoxide reforming the carbonyl C=O bond promotes the elimination of alcohol OH as a leaving group which reforms the base catalyst. Although the base catalyzed elimination of alcohols is rare, it happens in this case in part due to the stability of the conjugated enone product.

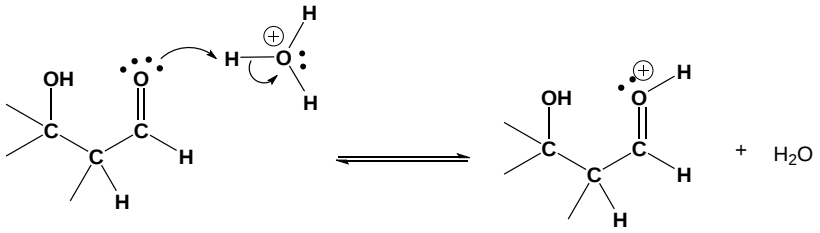


Enone

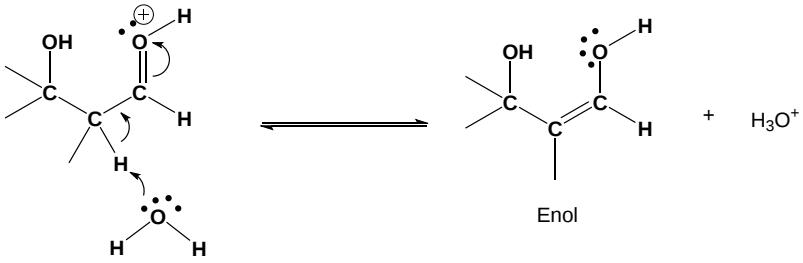
ACIDIC CONDITIONS MECHANISM

1) PROTONATION

The mechanism starts with the two step tautomerization process to form an enol.



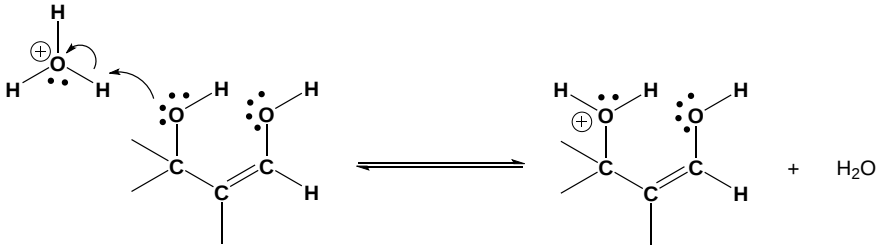
2) FORM AN ENOL



Enol

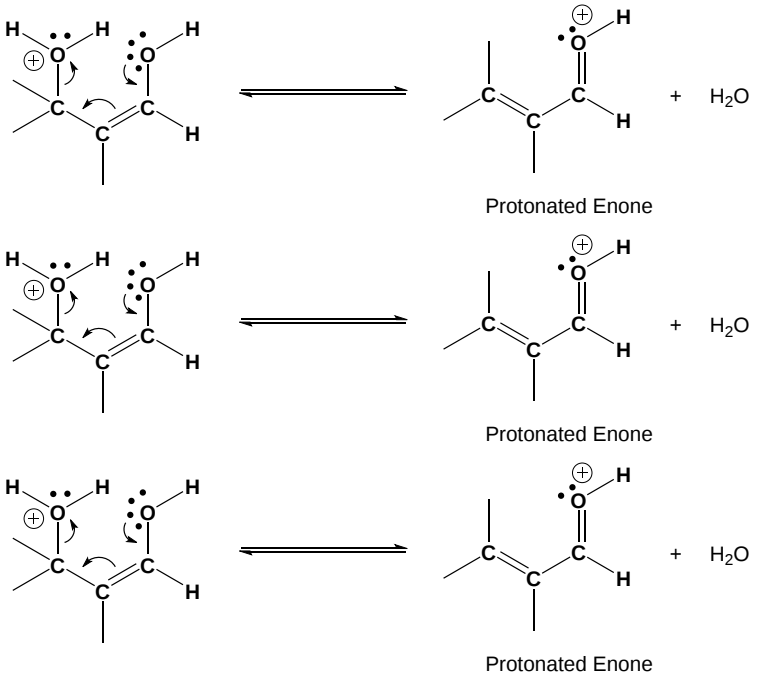
3) PROTONATION

Protonation of the alcohol OH increases its ability to act as a leaving group.



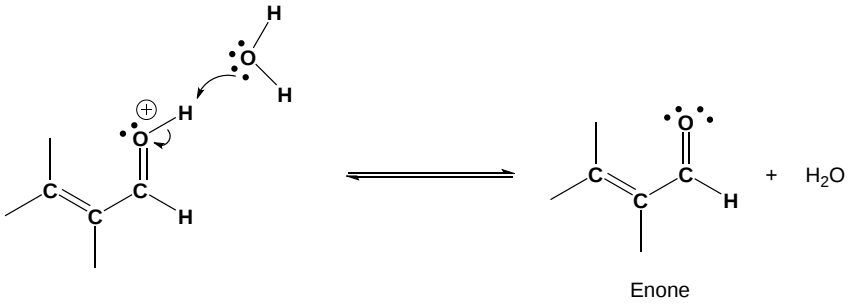
4) ELIMINATION

Lone pair electrons from the enol reform the carbonyl C=O bond and promoted the elimination of water as a leaving group.



5) DEPROTONATION

Deprotonation by water in the final step create the neutral enone product and regenerates the acid catalyst.

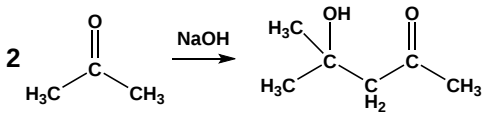


ALDOL CONDENSATION

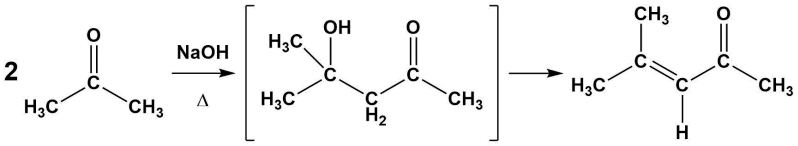
Whether an aldol reaction or an aldol condensation product is formed during a reaction largely depends on the reaction conditions. Typically, a reaction with a base at room temperature provides the aldol reaction product. However, if the reaction mixture is heated the aldol product is quickly converted into the aldol condensation product. If the condensation product is desired the aldol intermediate is usually not isolated.

Examples

Aldol Reaction

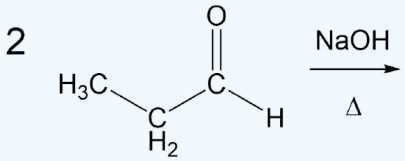


Aldol Condensation



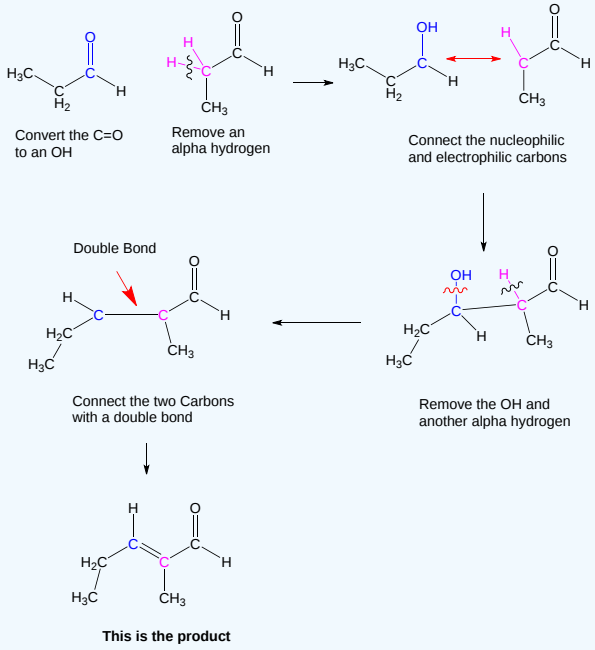
? WORKED EXAMPLE

Draw the product of an aldol condensation with the following molecule:



Answer

The overall reaction is a combination of two major steps, an aldol reaction followed by a dehydration to form the enone. In this situation it is best to consider the aldol product first (as discussed in Section 23.3, then convert it to the enone. Note! The double bond always forms in conjugation with the carbonyl.



23.4: USING ALDOL REACTIONS IN SYNTHESIS

OBJECTIVES

After completing this section, you should be able to identify the aldehyde or ketone and other necessary reagents that should be used to prepare a given enone by an aldol condensation.

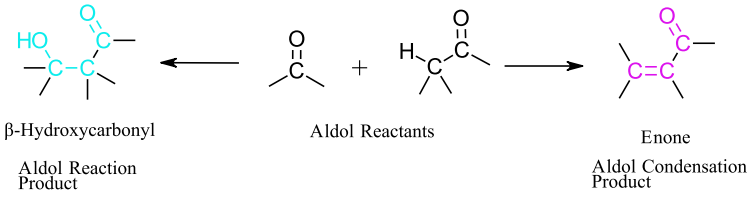
STUDY NOTES

This section stresses the importance of being able to think logically.

The experience that you have already gained through designing multi-step syntheses and solving road-map problems should help you to recognize when an aldol reaction may have been one of the steps in the synthesis of a given compound.

It is important that you recognize that the aldol condensation is an important part of a synthetic chemist's repertoire, both because it involves the formation of a new carbon-carbon bond, and also because it yields a product containing two functional groups.

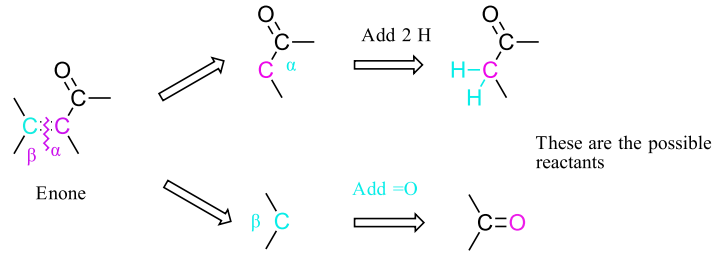
Aldol reactions are excellent methods for the synthesis of many enones or beta-hydroxy carbonyls. Because of this, being able to predict when an aldol reaction might be used in a synthesis in an important skill. This can be accomplished by identifying these combinations of atoms and bonds and then, working backwards, theoretically breaking the target molecule apart into possible reactants.



Fragments which are easily formed by an aldol reaction

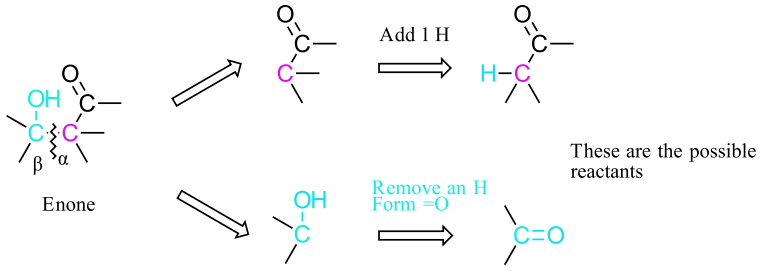
DETERMINING THE REACTANTS FOR AN ALDOL CONDENSATION

During an aldol condensation a C-C sigma and a C-C pi bond are formed. This makes the key bond cleavage in the target molecule the C=C bond between the carbons alpha and beta away from the carbonyl. After the cleavage, the carbon that was in the alpha position (on the fragment with the carbonyl) gains two hydrogens. The carbon that was in the beta gains a =O to form a carbonyl.



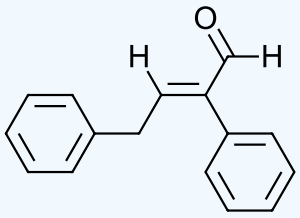
DETERMINING THE REACTANTS FOR AN ALDOL REACTION

During an aldol condensation a C-C sigma bond is formed. This makes the key bond cleavage in the target molecule the C-C bond between the carbons alpha and beta away from the carbonyl. After the cleavage, the carbon that was in the alpha position (the fragment with the carbonyl) gains one hydrogen. The fragment loses a hydrogen from the OH and then forms a C=O carbonyl bond.



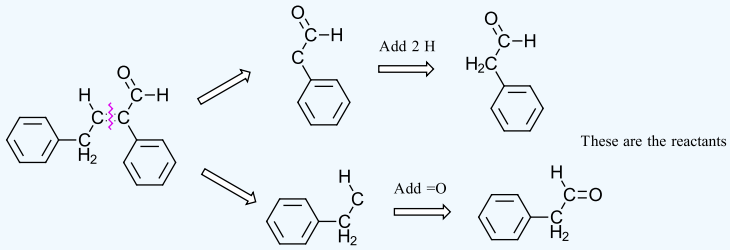
Worked Example

Show how the following molecule could be made using an aldol condensation?

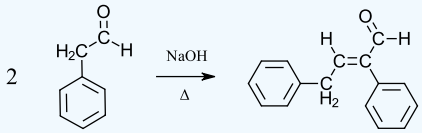


Answer

Analysis: The C=C bond in the target molecule is cleaved to form two fragments. The fragment with the carbonyl gains two alpha hydrogens. The other fragment gains a =O to form a carbonyl. Both fragments end up producing the same reactant which is typical for an aldol condensation.

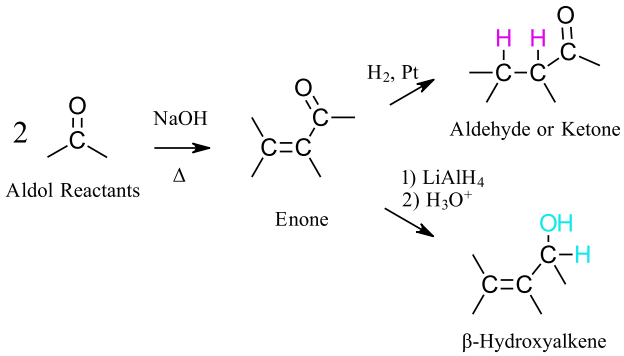


Solution



ADDITIONAL SYNTHETIC CONSIDERATIONS

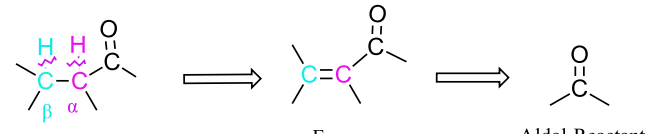
The enone product of an aldol condensation is versatile because it contains two functional groups (alkene & carbonyl) which can be subject to further reactions. Among many possible reactions, an enone can undergo hydrogenation to produce an aldehyde or ketone. Also, the carbonyl group can undergo hydride reduction to produce a beta-hydroxyalkene.



These additional reactions can be applied with the consideration of using an aldol reaction in the synthesis of a target molecule. A similar analysis can be extrapolated to the other reactions possible with the alkene and carbonyl present in an enone.

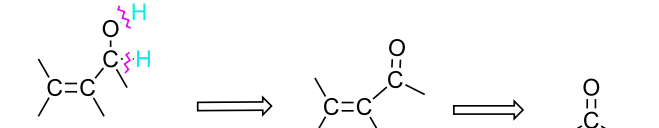
Analysis for Hydrogenation

To consider a hydrogenation, remove a hydrogen from a carbon in both the alpha and beta positions relative to the carbonyl. Then connect these two carbons with a C=C double bond. This create a possible enone which can be broken apart further using the analysis described above. Target molecules can have often have multiple alkyl chains which can be used to form a double bond.



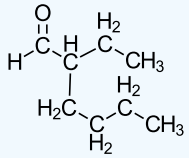
Analysis for Hydride Reduction

To consider a hydride reduction remove a hydrogen from the alcohol oxygen then a hydrogen from the adjacent carbon. Connect the oxygen and carbon with a double bond to form a C=O carbonyl. This provides an enone which can undergo further analysis.



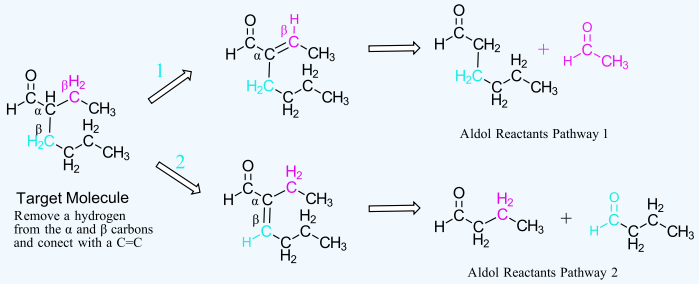
EXERCISE 23.4.1

Please devise a synthesis pathway for the following molecule using an aldol reaction:

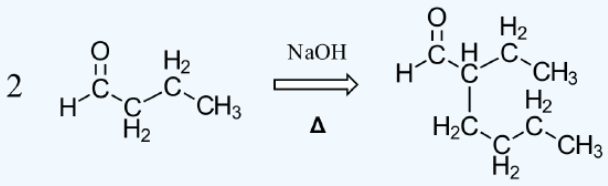


Answer

Analysis: Because the target molecule has two beta-carbons with hydrogens there are two possible synthesis pathways. Both should be considered for their effectiveness. Because a carbonyl is already present fragmentations will first be performed to create two possible enone intermediates. These enones will both be broken into their aldol reactants. When looking a possible aldol reactants produced by each pathway it is clear that pathway 2 is preferred. Because both fragments are the same they will react to form on major product.

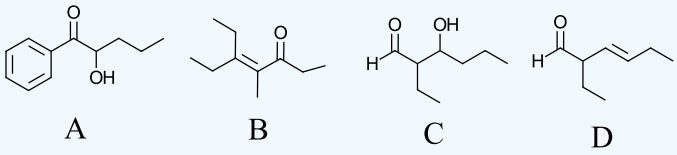


Solution



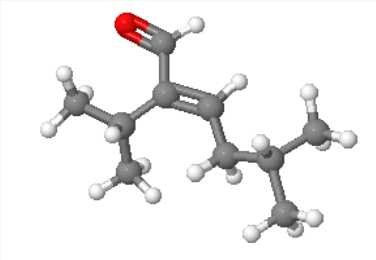
EXERCISES 23.4.1

1) Which of the following molecules could be made using an aldol reaction or condensation. Please show the starting material for the reactions that are possible.



2) Please show the reaction steps required to make 4-methyl-2-pentanol from an aldol condensation.

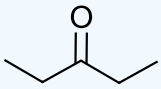
3) Please design a synthesis for the following molecule: Red = Oxygen, Grey = Carbon, White = Hydrogen



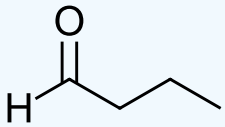
Answers

1) Molecules A and C are possible.

Solution for molecule A

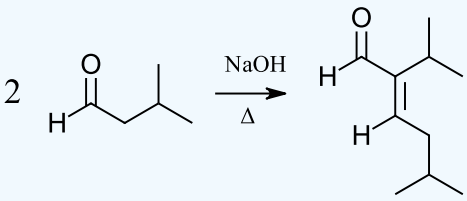


Solution for molecule C



2)

3)



23.5: MIXED ALDOL REACTIONS

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate a mixed aldol reaction.
2. identify the structural features necessary to ensure that two carbonyl compounds will react together in a mixed aldol reaction to give a single product rather than a mixture of products.
3. determine whether a given mixed aldol reaction is likely to produce a single product or a mixture of products.
4. identify the product or products formed in a given mixed aldol reaction.
5. identify the carbonyl compounds needed to produce a given enone or β-hydroxy aldehyde or ketone by a mixed aldol reaction.

STUDY NOTES

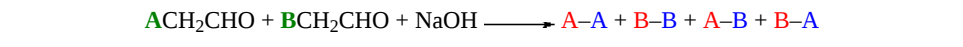
You should satisfy yourself that you understand how the four products shown in Example 23.5.2 arise from the condensation of 2-propanone and 2-phenylacetaldehyde.

MIXED ALDOL REACTION AND CONDENSATIONS

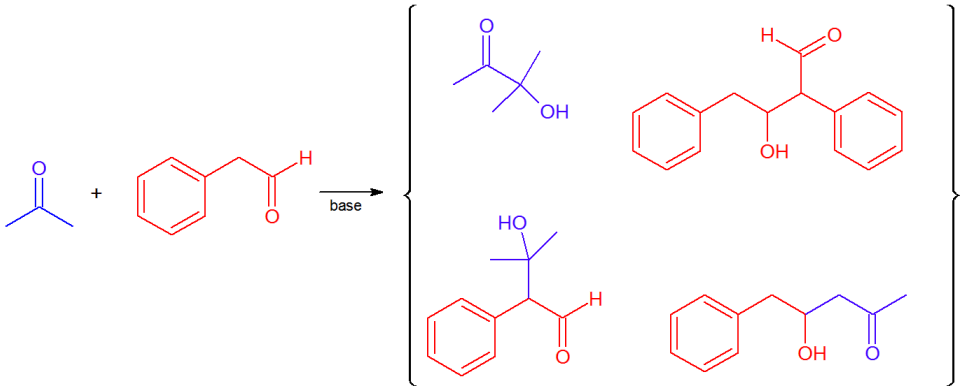
The previous examples of aldol reactions and condensations used a common reactant as both the enolate donor and the electrophilic acceptor. The product in such cases is always a dimer of the reactant carbonyl compound. Aldol condensations between different carbonyl reactants are called crossed or mixed reactions, and under certain conditions such crossed aldol condensations can be effective.

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 a H's

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.



Products of a Uncontrolled Mixed Aldol Reaction

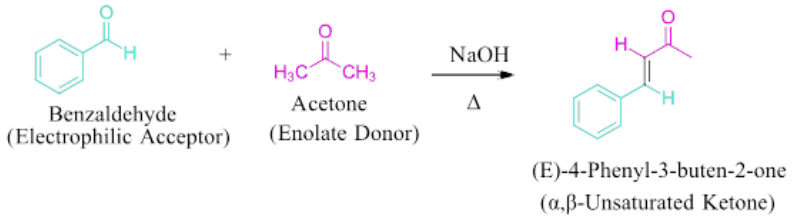


To avoid complex reaction mixtures the reactants should be chosen to favor one particular donor/acceptor reaction. Successful mixed aldol reactions usually use one of two combination of factors.

1) A reaction of an aldehyde with no alpha-hydrogens with a ketone that has alpha hydrogens: Aldehydes lacking alpha-hydrogens cannot form an enolate so they can only function as electrophilic acceptor reactants. This reduces the number of possible products by half. Although it would be possible for the ketone to react with itself it is unlikely. Aldehydes are more reactive acceptor electrophiles than ketones. This makes the preferred reaction one with the ketone as an enoloate donor and the aldehyde as an electrophilic acceptor.

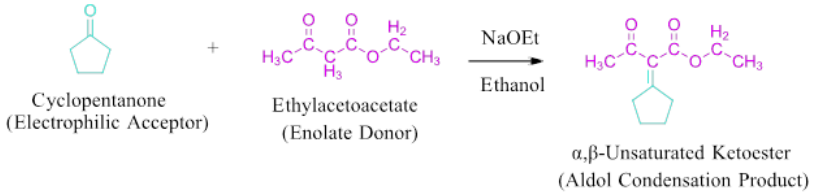
The aldol condensation between an aromatic aldehyde with no α-hydrogens and an aliphatic aldehyde or ketone with α-hydrogen is called a **Claisen–Schmidt condensation**. The reaction product is a highly conjugated α,β-unsaturated aldehyde or ketone which forms in the more stable (E)-alkene isomer.

Example: Claisen–Schmidt Condensation



2) One of the reactants has alpha-hydrogens which are highly acidic: The acidic compound will be preferably converted into an enolate donor which removes the possibility of its carbonyl acting as an electrophilic acceptor. An example is the aldol condensation of ethylacetoacetate and cyclopentanone. Ethylacetoacetate has α-hydrogens which are particularly acidic due to their conjugate base being stabilized by two carbonyl bonds (**Section 22.5**). Upon reaction with base, ethylacetoacetate is converted to the enolate donor leaving cyclopentanone to be the electrophilic acceptor. This provides one predominant aldol condensation product. In this reaction sodium ethoxide is used as a base to prevent hydrolysis side-reactions with the ester of ethylacetoacetate.

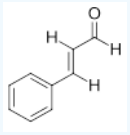
Example



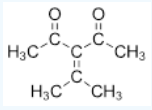
EXERCISES 23.5.1

1) Show the reactants required to make the following using a mixed aldol condensation. Indicate those which would be likely to produce a mixture of products.

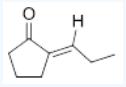
a)



b)

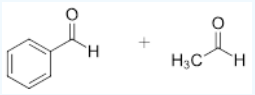


c)

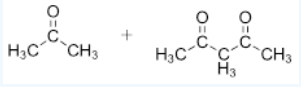


Answers

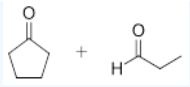
a)



b)



c) Because both reactants have α-hydrogens and neither are particularly acidic, the reaction probably will produce a mixture of condensation products.



23.6: INTRAMOLECULAR ALDOL REACTIONS

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate an intramolecular aldol reaction.
2. identify the product formed when a given dicarbonyl compound undergoes an intramolecular aldol condensation.
3. identify the dicarbonyl compound which, when treated with a suitable base, could be used to prepare a given cyclic enone by an intramolecular aldol condensation.

STUDY NOTES

"Intramolecular " means "within the same molecule." You have already seen some examples of intramolecular reactions in previous chapters. Another term for intramolecular aldol reaction is "internal aldol reaction."

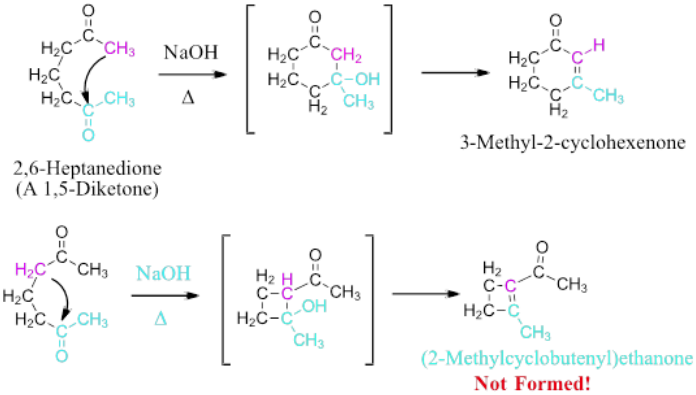
INTRAMOLECULAR ALDOL REACTION

Molecules which contain two carbonyl functionalities have the possibility of forming a ring through an intramolecular aldol reaction. The term "Intramolecular" means "within the same molecule." In this case, it means that the enolate donor and the electrophilic acceptor of an aldol reaction are contained in the same molecule such as dialdehydes, keto aldehydes, or diketones. In these cases, the small distance between the donor and acceptor leads to faster reaction rates for intramolecular condensations making intermolecular condensations (which require two molecules to collide in solution) less favorable.

In most cases multiple sets of α-hydrogens need to be considered when determining the donor/acceptor roles for the reaction, which might lead to a mixture of products. The intramolecular aldol reaction of a 1,5-diketone, 2,6-heptanedione, could possibly yield either the six-membered ring product, 3-methyl-2-cyclohexenone, or the four-membered ring product, (2-methylcyclobutenyl)ethanone. However, the cyclohexanone product is exclusively formed.

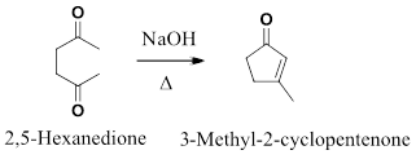
This product selectivity is possible due to all of the steps of the mechanism being reversibly, which tends to produce the most stable product. As with most ring forming reactions, five and six membered rings are preferred due to their relative lack of ring strain compared to other sized rings (See Sections 4.4 & 4.5). Once equilibrium is reached, the relatively strain free and therefore more thermodynamically stable, cyclohexanone product will be preferably formed.

Example



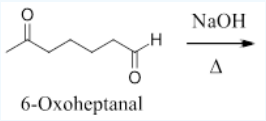
Similar analysis can be used to predict the products of other intramolecular aldol reactions. In a similar reaction, 1,4-diketones, such as 2,5-hexanedione, only form the five-membered ring product, ex. 3-methyl-2-cyclopentenone, without any of the possible cyclopropane product forming.

Example



WORKED EXAMPLE

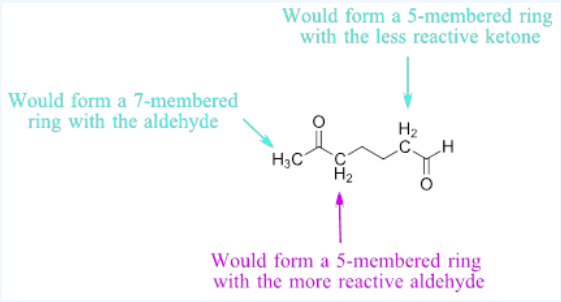
Please draw the expected product of an intramolecular aldol condensation with the following molecule:



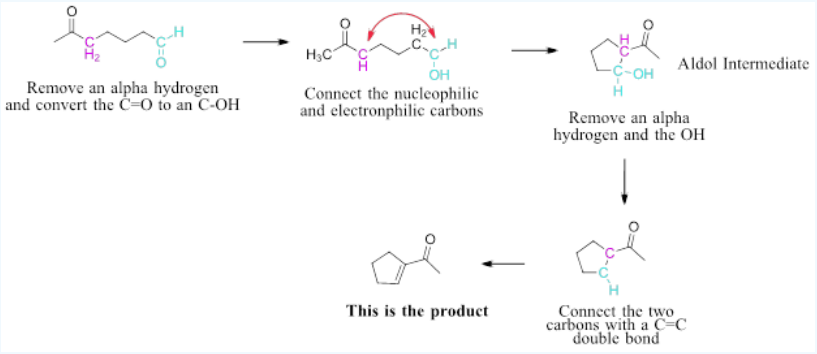
6-Oxoheptanal

Answer

Analysis: 6-Oxoheptanal has three unique sets of alpha-hydrogens which could be deprotonated to form an enolate. Selecting the correct set involves analyzing the carbonyl reactivity's along with the possible ring sizes of the products.



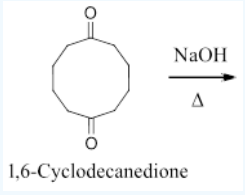
Solution: Once the preferred alpha-hydrogens are determined go through the steps discussed in the previous sections to determine the aldol condensation product. Remember to form the aldol intermediate first.



EXERCISES 23.6.1

1) Briefly explain why the molecule, 2,4-pentanedione, when reacted with a base would mostly likely not produce an intramolecular aldol condensation product.

2) Draw the product of the following aldol condensation:

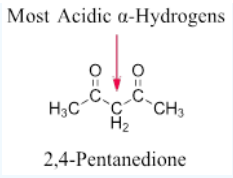


1,6-Cyclodecanedione

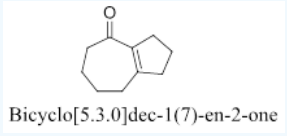
Answers

1) 2,4-Pentanedione like other 1,3-Diketones have particularly acidic alpha-hydrogens between the two carbonyl. When base is applied these will be the first to deprotonate and form an enolate. For an intramolecular aldol condensation to occur an alpha-hydrogen one of the methyl groups would have to be removed which would be difficult.

2)



2,4-Pentanedione



Bicyclo[5.3.0]dec-1(7)-en-2-one

23.7: THE CLAISEN CONDENSATION REACTION

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate a Claisen condensation reaction.
2. write a detailed mechanism for a Claisen condensation reaction or its reverse.
3. identify the product formed in a given Claisen condensation reaction.
4. identify the ester and other reagents needed to form a given β-keto ester by a Claisen condensation reaction.

KEY TERMS

- Claisen condensation reaction

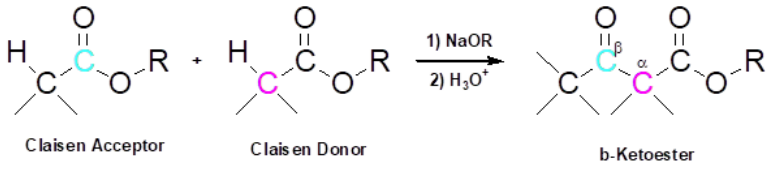
STUDY NOTES

You have already seen that ethyl acetoacetate-type compounds are very useful in organic syntheses. Any reaction which results in the formation of these compounds will also be of importance. In the next section, you will see how the range of β-keto esters that can be prepared by this method is extended through the use of two different esters as starting materials.

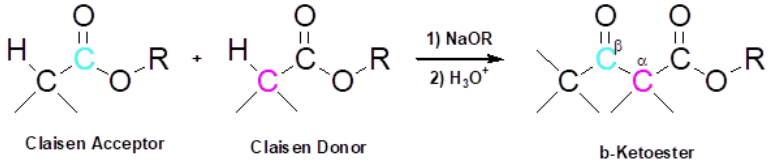
CLAISEN CONDENSATION

Because esters commonly contain both α-hydrogens and a carbonyl bond, they can undergo a reversible condensation similar to the aldol reaction called a Claisen Condensation. In a fashion similar to the aldol reaction, one ester acts as a Claisen enolate donor (nucleophile) while a second ester acts as the Claisen acceptor (electrophile). During the reaction a new carbon-carbon is formed to produce a β-keto ester product. This reaction is considered a condensation because it eliminates a small alcohol as an unwanted side-product.

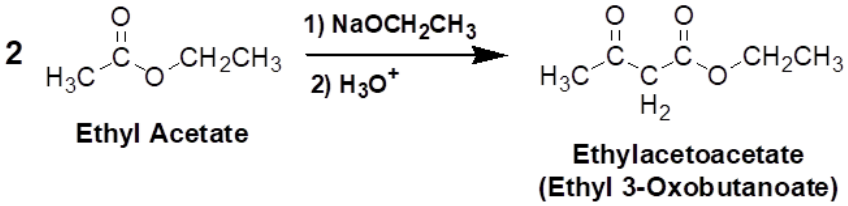
GENERAL REACTION



PREDICTING THE PRODUCT OF A CLAISEN CONDENSATION



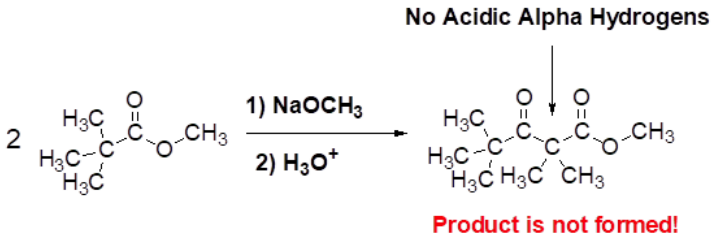
EXAMPLE



Although they may appear similar, there are a number of fundamental differences between an aldol and Claisen condensation. During the mechanism of the reaction, the formed tetrahedral alkoxide intermediate is not protonated to from an “aldol” type product. Rather, the alkoxide intermediate will reform the C=O carbonyl bond and eliminate a (-OR) leaving group to produce a nucleophilic acyl substitution product.

Claisen condensations cannot use a hydroxide for the reaction base due to the possibility of ester hydrolysis. Also, to prevent transesterification side products, the alkoxide base typically has the same alkyl group as alkoxy group present in the ester starting material.

Lastly, the β-keto ester products of Claisen condensation can be acidic enough to be deprotonated by the reaction's base during the final steps of the mechanism. This means the base is not catalytically regenerated during the reaction and a full equivalent of base is required. The β-keto ester condensation products are removed from the equilibrium by this deprotonation, which causes the reaction to be driven forward by Le Chatelier's principle. This concept is so important that a Claisen product will not form unless it contains an alpha hydrogen acidic enough to react completely with the reaction base. This requires that the ester starting materials have at least two alpha-hydrogens for a Claisen condensation product to form. One is removed to form an ester enolate and the second is removed to drive the reaction forward.

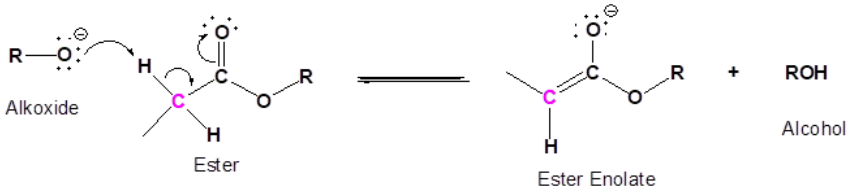


MECHANISM

The Claisen condensation mechanism is analogous to the ester saponification reaction seen in *Section 21.6*.

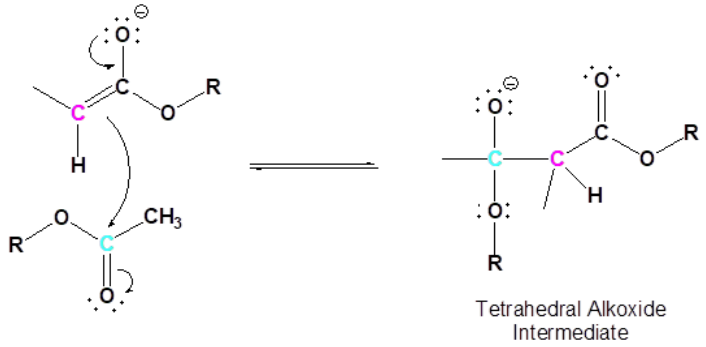
1) ENOLATE FORMATION

The mechanism starts with the alkoxide base removing an alpha-hydrogen from the ester to form a nucleophilic ester enolate ion.



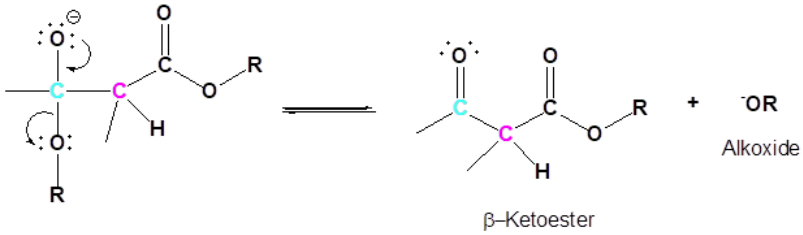
2) NUCLEOPHILIC ATTACK

The enolate nucleophile adds to carbonyl carbon of a different ester, forming a tetrahedral alkoxide intermediate.



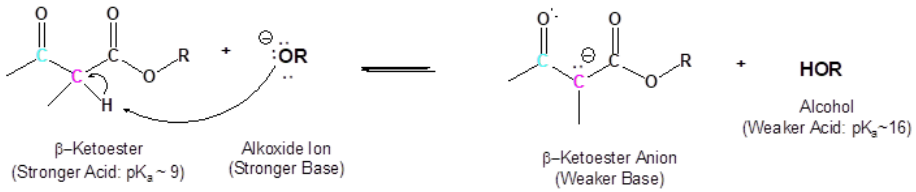
3) REMOVAL OF LEAVING GROUP

The alkoxide then reforms the carbonyl, eliminating the –OR leaving group to form a beta-ketoester.



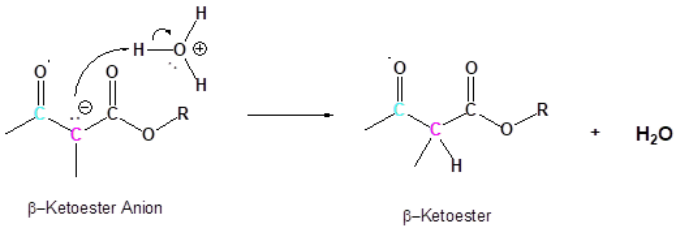
4) DEPROTONATION

The acidity of beta-ketoesters (pK_a ~9) is high enough to allow them to be completely deprotonated by alkoxide bases (pK_a of an alcohol ~16) to form a second enolate. This make the equilibrium of this step very favorable, which is enough to drive the whole reaction towards the product.



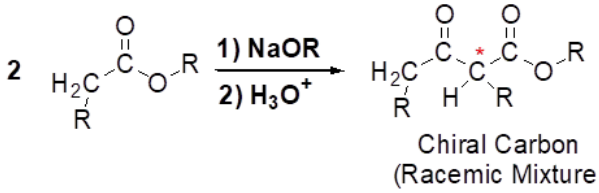
5) PROTONATION

The enolate is protonated in an acid work-up to form the neutral beta-ketoester product.



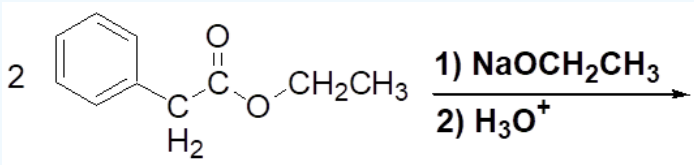
Stereochemical Considerations

The alpha-carbon gains a substituent during the reaction which means it will most likely form a chiral carbon. The fact that the alpha-carbon is temporarily converted to an enolate in the last step of the mechanism means that a racemic mixture of enantiomers will form.



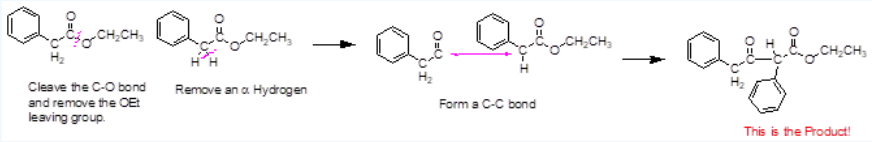
? WORKED EXAMPLE

Draw the products of the following reaction:



Answer

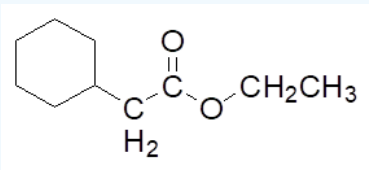
Analysis: Remember to consider each start ester separately.



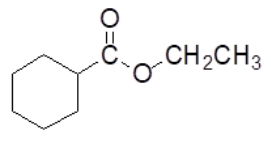
? EXERCISE 23.7.1

Please draw the products if the following molecules were to undergo a Claisen condensation.

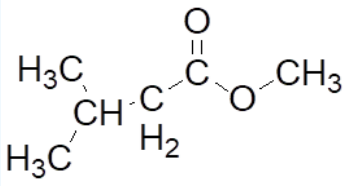
a)



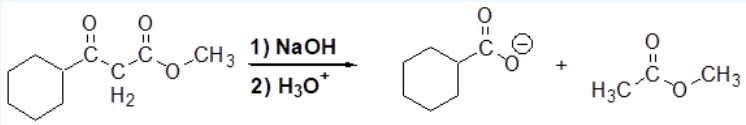
b)



c)

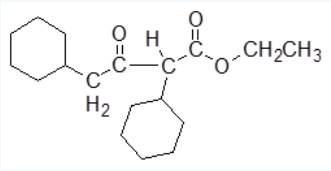


2) The beta-keto ester product of a claisen condensation can under hydrolysis with Sodium Hydroxide as shown in the reaction below. Please draw a curved arrow mechanism to explain how the products are formed. Also, explain why the ketone functional group preferably reacts with hydroxide instead of the ester.

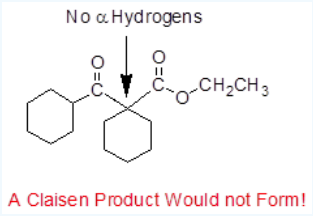


Answers

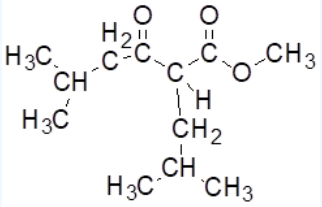
a)



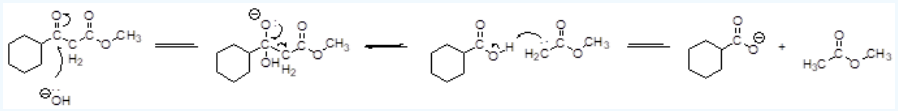
b)



c)



2) The carbonyl of the ketone is more likely to be attacked by the hydroxide nucleophile because is more reactive than the ester's



23.8: MIXED CLAISEN CONDENSATIONS

OBJECTIVES

After completing this section, you should be able to

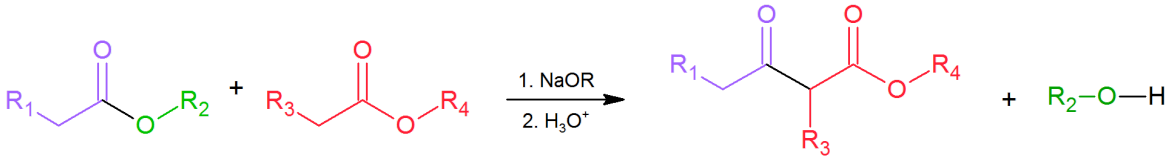
1. write an equation to illustrate a mixed Claisen condensation.
2. identify the structural features that should be present in the two esters if a mixed Claisen condensation is to be successful.
3. determine whether a given pair of esters is likely to produce a good yield of a single product when subjected to a mixed Claisen condensation.
4. identify the product formed when a given pair of esters is used in a mixed Claisen condensation.
5. identify the esters that should be used to produce a given β-keto ester by a mixed Claisen condensation.
6. write an equation to illustrate the formation of a β-diketone through a mixed Claisen-type condensation between an ester and a ketone.
7. identify the β-diketone formed as the result of a mixed Claisen-type condensation between a given ester and a given ketone.
8. identify the reagents necessary to synthesize a given β-diketone by a mixed Claisen-type condensation between an ester and a ketone.
9. write detailed mechanisms for mixed Claisen reactions and reactions that are related to the mixed Claisen reaction, including those in which both reacting moieties are present in the same compound.

STUDY NOTES

Just as we can react together two different aldehydes or ketones in a mixed aldol condensation, so can we react together two different esters in a mixed (or "crossed") Claisen condensation. Again, by carefully selecting our substrates we can obtain a good yield of the desired product and minimize the number of possible by-products. Note that even if we replace one of the esters with a ketone, the reaction is still referred to as Claisen condensation. The important thing to realize as you study these reactions is that they all take place by essentially the same mechanism—attack by an enolate anion on a carbonyl group.

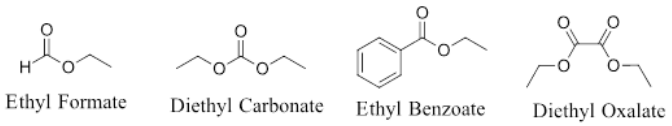
CROSSED CLAISEN CONDENSATION

Claisen condensations between different ester reactants are called **Crossed Claisen** reactions. Crossed Claisen reactions in which both reactants can serve as Claisen donors and Claisen acceptors generally give complex mixtures which are difficult to separate.



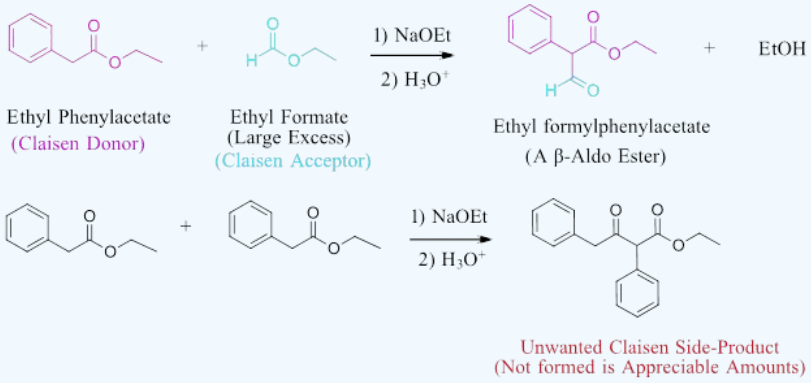
General Reaction for a Crossed Claisen

To avoid complex mixtures most Crossed Claisen reactions are usually not successful unless one of the two esters has no alpha-hydrogens as in the following examples.



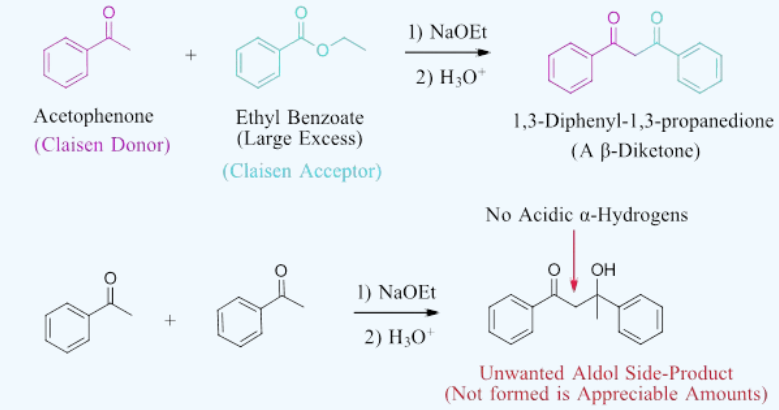
This forces the ester with alpha-hydrogens to be the Claisen donor (enolate) and the ester without alpha-hydrogens to be the Claisen acceptor (electrophile). Even with this differentiation, it is possible for the ester with alpha-hydrogens to undergo a Claisen Condensation with itself to produce an unwanted side-product. This is typically partially prevented by using the ester without alpha-hydrogens in a large excess.

EXAMPLE: NO ALPHA HYDROGENS



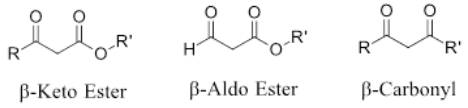
Another type of crossed Claisen condensation occurs when a ketone is reacted with an ester. The use of an ester without alpha-hydrogens is not necessary due to the greater reactivity of the ketone. The alpha-hydrogens of the ketone are much more acidic (pKa~20) than those of the ester (pKa~25). The alpha hydrogens of ketone will be preferably deprotonated to make it the enolate Claisen donor. The ester will therefore be the electrophilic Claisen acceptor and is likewise commonly used in a large excess. There is still a possibility of the ketone reacting with itself to form the product of an aldol reaction however the equilibrium is unfavorable. Also, the formation of the aldol product is reversible due to its lack of an acidic alpha hydrogen. The beta-diketone Claisen product can be irreversibly deprotonated due to its more acidic alpha-hydrogens, making it the reaction's main product.

✔ EXAMPLE: ESTER WITH KETONE

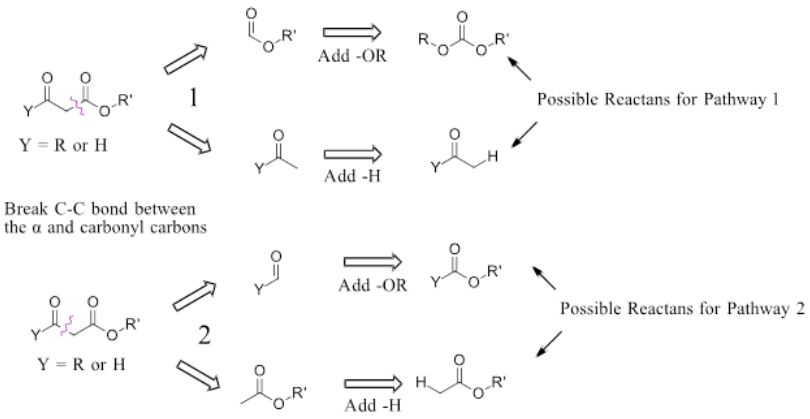


PLANING A SYNTHESIS USING A CLAISEN OR CROSSED CLAISEN-LIKE REACTION

A Claisen reaction should be considered for a synthesis pathway if the target molecule contains a beta-keto esters, a beta-aldo ester or a beta-dicarbonyl.



A beta-keto ester or a beta-aldo ester could possibly be made by a Claisen condensation of two esters. A beta-dicarbonyl could possibly be made by a Claisen-like condensation between a ketone and an ester. Here, the key bond cleavage is a C-C bond between one of the carbonyls and the alpha-carbon which lies between the carbonyl. In each of these situations there are two such C-C bonds so there will be two possible pathways to consider. After the C-C bond cleavage the fragment with the alpha-carbon will gain a hydrogen. The fragment with the bare carbonyl will gain an –OR group to become an ester. The –OR group added will be the same as any ester present in the target molecule. If none are present $–OCH_2CH_3$ is typically used.

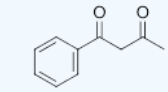


Analysis for Beta-Keto and Aldo Esters

A similar analysis can be performed on a 1,3-diketone and will be presented in the worked example below.

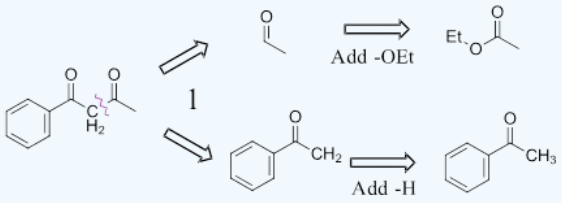
EXAMPLE 23.8.1

Show how the following molecule can be made using a Claisen-like condensation.

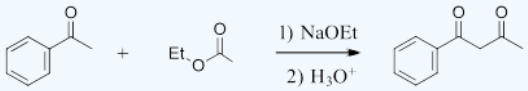


1-Phenyl-1,3-butanedione

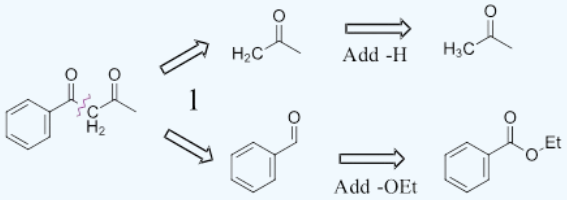
Pathway 1



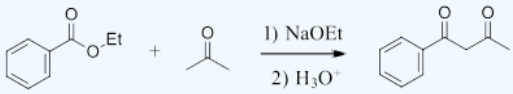
Answer Pathway 1



Pathway 2



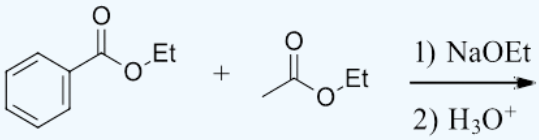
Answer Pathway 2



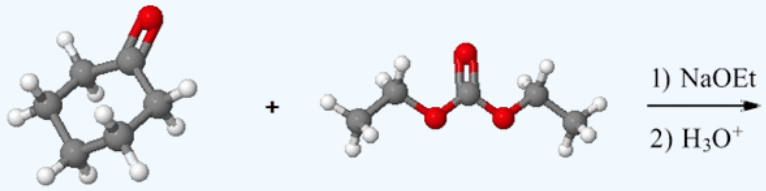
EXERCISE 23.8.1

Draw the product of the following reactions:

a.

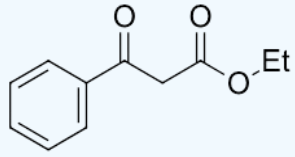


b.

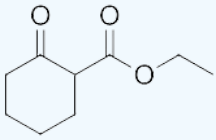


Answers

a.



b.



23.9: INTRAMOLECULAR CLAISEN CONDENSATIONS - THE DIECKMANN CYCLIZATION

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate an internal Claisen condensation, that is, a Dieckmann cyclization.
2. identify the product formed when a 1,6- or 1,7-diester undergoes an internal Claisen condensation.
3. identify the diester needed to prepare a given cyclic β-keto ester by an internal Claisen condensation.
4. identify the structural features present in a diester that lead to the formation of more than one product in an internal Claisen condensation.

KEY TERMS

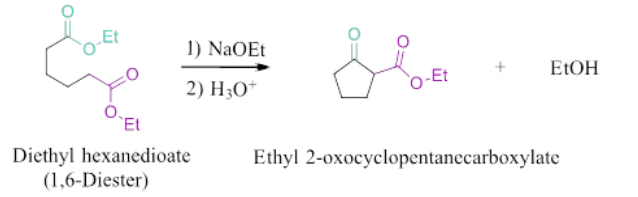
- Dieckmann cyclization

STUDY NOTES

Essentially no new material is introduced in this section; Dieckmann cyclizations are intramolecular Claisen condensations. These reactions occur for 1,6- and 1,7-diesters, as these substances result in the formation of compounds containing five- and six-membered rings, respectively. You may recall that the formation of such ring systems is favoured because they are relatively free of strain.

THE DIECKMANN CYCLIZATION

Diesters can undergo an intramolecular reaction, called the Dieckmann condensation, to produce cyclic beta-keto esters. This reaction works best with 1,6-diesters, which produce five-membered rings, and 1,7-diesters which produce six membered rings.

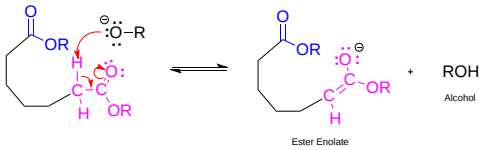


Examples of the Dieckmann Cyclization reaction.

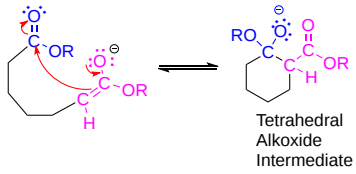
MECHANISM

The mechanism of the Dieckmann condensation is the same as a Claisen condensation. An alkoxide base removes an alpha-hydrogen from one of the esters to form an ester enolate. The enolate then adds to the carbonyl carbon of the other ester to form a tetrahedral alkoxide intermediate. The alkoxide reforms the carbonyl bond which causes the elimination of the –OR leaving group and forms a cyclic beta-keto ester. The high acidity of the beta-keto ester allows it to be deprotonated by the reactions base to form a second enolate. Like the Claisen condensation, this deprotonation step drives the equilibrium towards the products and is required for the reaction to occur. A full equivalent of base is necessary during this reaction.

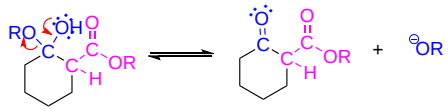
STEP 1: ENOLATE FORMATION



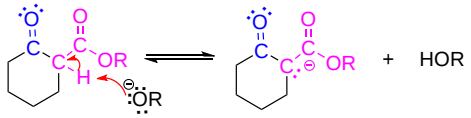
STEP 2: NUCLEOPHILIC ATTACK



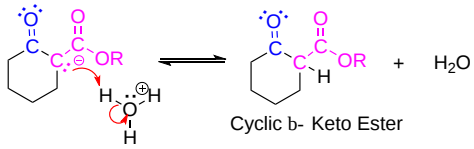
STEP 3: REMOVAL OF LEAVING GROUP



STEP 4: DEPROTONATION

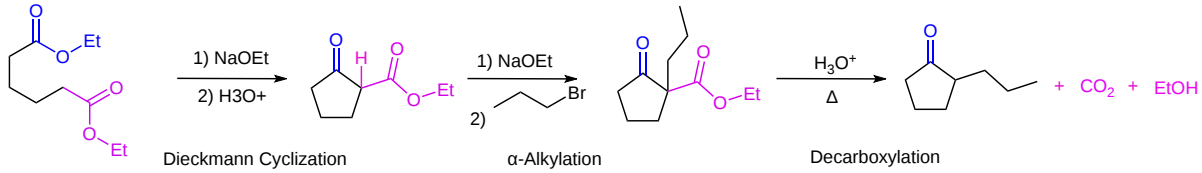


STEP 5: PROTONATION



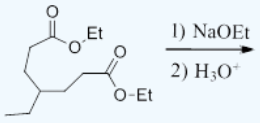
FURTHER REACTIONS OF THE DIECKMANN CYCLIZATION PRODUCT

The cyclic beta-keto ester product of a Dieckmann cyclization can be modified by reaction similar to those used in the acetoacetic ester synthesis (**Section 22-7**). The acidic alpha-hydrogens of the beta-keto ester allow it to easily be deprotonated and alkylated in an alpha-substitution reaction. Having a carbonyl group in the beta position allows the ester to be removed through decarboxylation. The combination of these three reactions (1) Dieckmann cyclization, (2) alpha alkylation, and (3) decarboxylation provides an efficient method for preparing 2-substituted cyclopentanones and cyclohexanones.

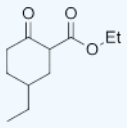


? EXERCISE 23.9.1

Draw the expected product for the following reaction:

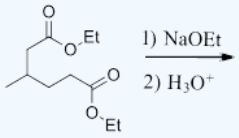


Answer

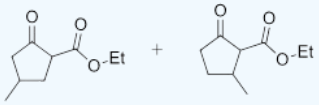


EXERCISE 23.9.2

The Dieckmann cyclization of the following molecule is expected to give a mixture of two cyclized products. Draw the structure of the two products and briefly explain why a mixture is formed.



Answers



Each has the ability to act as a Claisen donor and a Claisen acceptor. The reaction should produce a roughly 50/50 mixture where each ester acts as a Claisen acceptor.

23.10: CONJUGATE CARBONYL ADDITIONS - THE MICHAEL REACTION

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate the Michael reaction.
2. write a detailed mechanism for a given typical Michael reaction.
3. identify the product formed in a given Michael reaction.
4. identify the reagents necessary to synthesize a given compound by a Michael reaction.

KEY TERMS

- Michael reaction

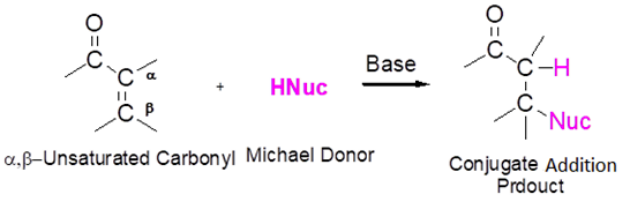
STUDY NOTES

Before studying this section in detail, you should review conjugate addition to *α,β*-unsaturated carbonyl compounds (Section 19.13).

Notice the wide variety of compounds that can take part in a Michael reaction. As usual, you should not feel overwhelmed by the number of different compounds that can be used, just keep in mind that in all cases the mechanism is essentially the same.

MICHAEL REACTION

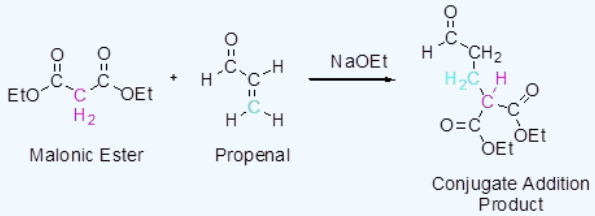
Certain nucleophiles undergo conjugate addition with the alkene of an α, β-unsaturated carbonyl compounds rather than undergo direct nucleophilic addition with the carbonyl. During conjugate addition, a nucleophile adds to the electrophilic β-alkene carbon to from a C-Nuc bond. If the starting materials contains an ester the corresponding alkoxide is used as the base in the reaction. Otherwise a hydroxide base, such as sodium or potassium hydroxide, is commonly used.



General Reaction of the Michael Reaction

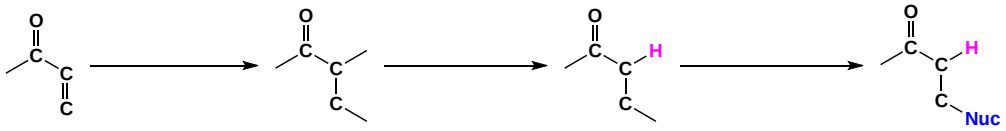
When enolate nucleophiles undergo conjugate addition with an α, β-unsaturated carbonyl the process is called a Michael Reaction. The Michael reaction works best with particularly acidic enolate donors such as malonic esters, β-keto esters, etc. Enolates which are weaker acids tend to undergo nucleophilic addition to the carbonyl rather than conjugate addition. For example, malonic ester's acidic alpha-hydrogens can be easily deprotonated by sodium ethoxide to form an enolate. The enolate adds to propenal to form the conjugate addition product.

EXAMPLE 23.10.1



PREDICTING THE PRODUCT OF A MICHAEL REACTION

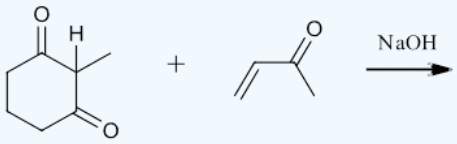
During the is reaction the C=C pi bond of the α, β-unsaturated carbonyl is broken. An C-H bond is formed on the carbon in the α-position from the carbonyl. An acidic hydrogen is removed from the nucleophile and then it is used to form a C-C bond with the carbon in the beta position from the carbonyl.



a. In the first step, remove the double bond and add two single bonds
b. Add a hydrogen to the bond adjacent to the carbonyl
c. Add the nucleophile to the other end of the double bond (remember to remove a hydrogen from the nucleophile)

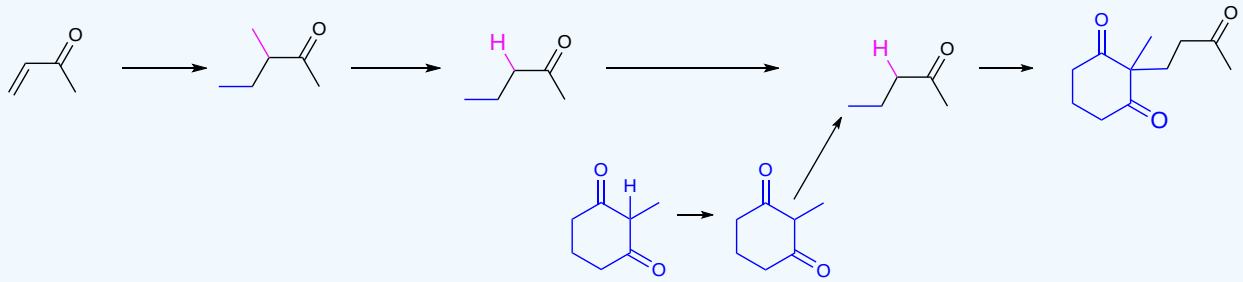
? WORKED EXAMPLE 23.10.1

What would be the product of the following conjugate addition?



Solution

1. Break the double bond and add two single bonds
2. Add a hydrogen to the bond adjacent to the carbonyl
3. Remove a hydrogen from the nucleophile.
4. Add the nucleophile to the other end of the double bond.



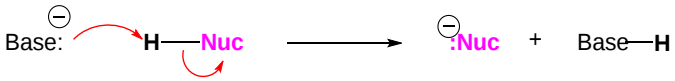
MECHANISM OF MICHAEL REACTION

During a Michael reaction the enolate acts as a nucleophilic donor and the α, β-unsaturated carbonyl acts as the electrophilic acceptor. The mechanism is a mixture of an alpha-substitution for the enolate and a conjugate addition for the α, β-unsaturated carbonyl.

Notice that the Michael Reaction does not require the deprotonation of the product to push the reaction towards completion. The reaction is thermodynamically favorable because the C-C bond formed in the product is stronger than the C=C bond in the starting material. This means that, unlike the Claisen condensation, this reaction only requires a catalytic amount of reaction base.

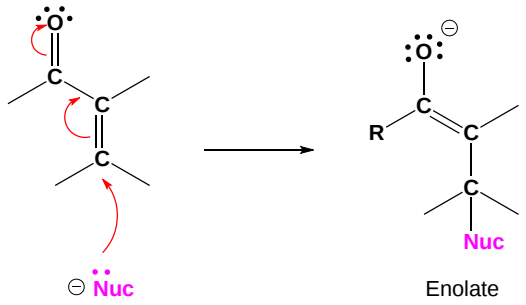
STEP 1: DEPROTONATION

The alkoxide base removes an alpha-hydrogen to from an enolate nucleophile.



STEP 2: NUCLEOPHILIC ATTACK ON THE CARBON B TO THE CARBONYL

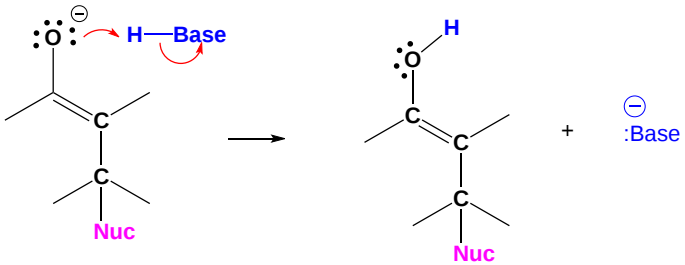
The enolate nucleophile then adds to the electrophilic β-carbon of the α, β-unsaturated carbonyl. Conjugation pushes the C=C pi bond electrons onto the carbonyl oxygen, forming a new enolate enolate.



Enolate

STEP 3: PROTONATION

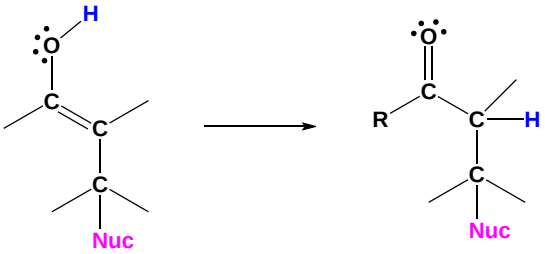
The alkoxide is protonated, forming an enol.



Enol

STEP 4: TAUTOMERIZATION

Tautomerization converts the enol back into a carbonyl forming the neutral conjugate addition product.



The Michael reaction can be performed with a wide variety of α, β-unsaturated carbonyl electrophilic acceptors and enolate donors. Michael acceptors such as α, β-unsaturated ketones, aldehydes, esters, amides, and nitro compounds can all participate in this reaction. Michael donors with particularly acidic α-hydrogens, such as β-diketones, β-keto esters, β-keto nitriles, α-nitro ketones, malonic esters, and nitro compounds can be used.

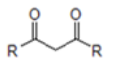
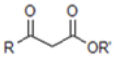
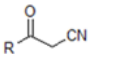
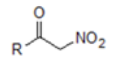
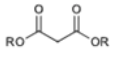
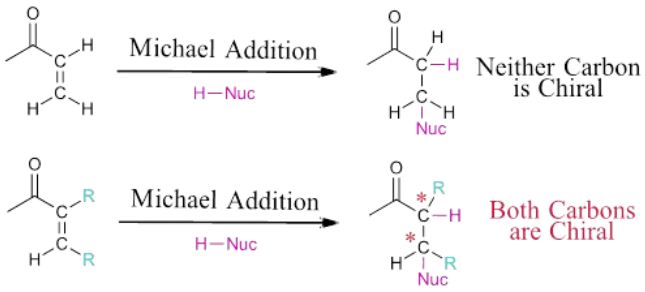
Michael Donors (aka nucleophile)	Michael Acceptors (aka electrophile)
 β-diketone	 α,β-unsaturated aldehyde
 β-ketoester	 α,β-unsaturated ketone
 β-keto nitrile	 α,β-unsaturated ester
 α-nitro ketone	 α,β-unsaturated amide
 malonic esters	 α,β-unsaturated nitrile
 nitro compound	 nitroethylene

Table 23.10.1 : Possible Donors and Acceptors Which can be used in a Michael Reaction

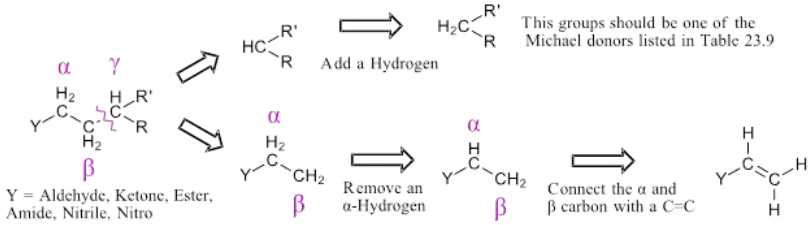
STEREOCHEMICAL CONSIDERATION OF MICHEAL REACTIONS

During a Michael reaction two sp^2 hybridized carbons are both converted to sp^3 hybridization. Both of them have the possibility of creating a chiral carbon. Michael reactions are often performed using an α, β-unsaturated carbonyl with only hydrogen substituents on the alkene to prevent the formation of chiral carbons. If either carbon in the alkene has an alkyl substituent it will likely form a chiral carbon in the Michael reaction product. The α-carbon of the enolate donor also has the possibility of forming a chiral carbon as discussed in **Section 22-6.**



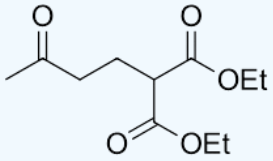
PLANNING A SYNTHESIS USING A MICHAEL REACTION

The true utility of the Michael reaction is seen when considering it use in a synthesis. The reaction can be used to prepare aldehydes, ketones, esters, amides, nitriles, and nitro compounds. A target molecule can possibly be made using a Michael reaction if it contains one of these functional groups and an alkyl chain at least three carbons long. The key bond cleavage is a C-C bond between β and gamma carbons from a carbonyl-like group. The fragment with the Y group loses an α-hydrogen and then forms a C=C bond between the α and beta carbon. The carbon of the other fragment gains a hydrogen. This fragment should possess an acidic α-hydrogen and should be made up of Michael donor fragments such as those listed in **Table 23.10.1** . In some cases, there may be more than one fragmentation variation. Each variation should be investigated and the possible starting materials compared for viability.



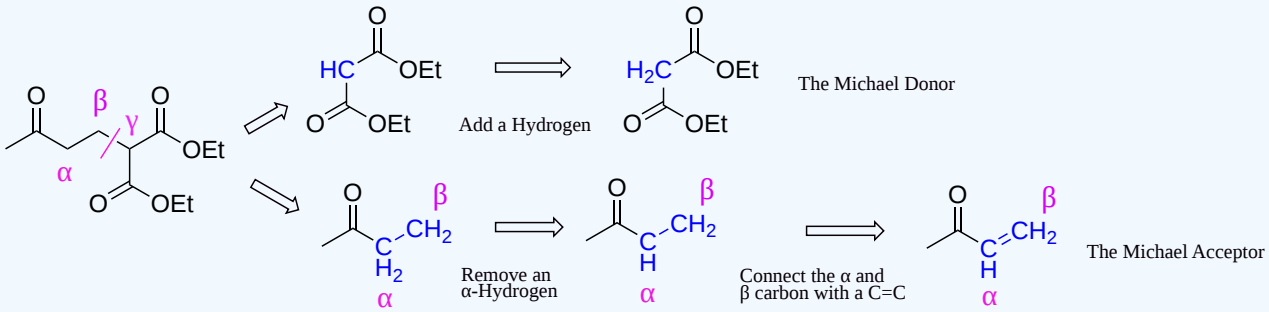
EXAMPLE

How could the following molecule be synthesized using a Michael Reaction?

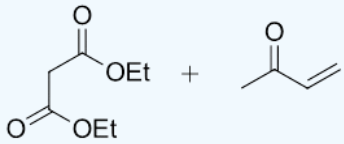


Answer

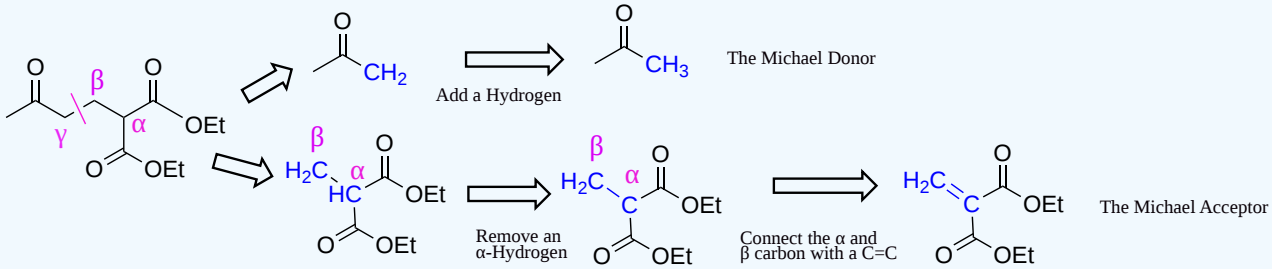
Pathway 1



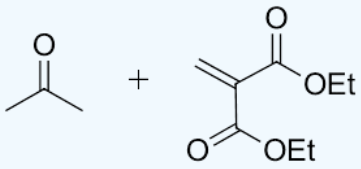
Starting Materials 1



Pathway 2

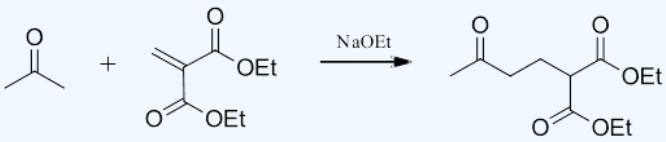


Starting Material 2



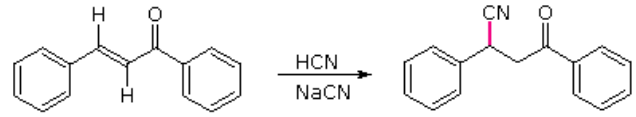
Solution

When comparing the two sets of possible starting materials of pathway 1 are preferred. The Michael enolate donor is particularly acidic because its conjugate base is stabilized by two carbonyls. The Michael enolate donor for pathway 2 does not have the same acidity. Consequently, the enolate would preferably undergo nucleophilic addition rather than conjugate addition. The makes the starting materials of pathway 1 preferred for the synthesis of the starting material.

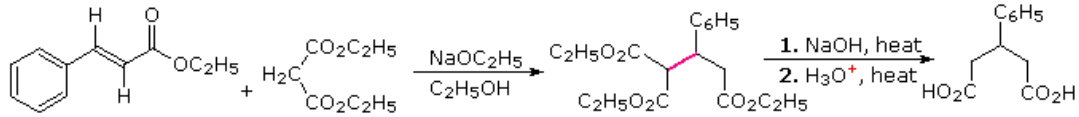


In combination with alkylations and condensations, the Michael reaction may be used to construct a wide variety of complex molecules from relatively simple starting materials. The carbon nucleophiles used in the following examples include cyanide ion, sodium diethylmalonate and the conjugate base of cyclohexane-1,3-dione. These anions are sufficiently stable that their addition reactions may be presumed reversible. If this is so, the thermodynamic argument used for hetero-nucleophile additions would apply here as well, and would indicate preferential formation of 1,4-addition products. Cyanide addition does not always follow this rule, and aldehydes often give 1,2-products (cyanohydrins). In each case the initial reaction is a Michael addition, and the new carbon-carbon bond is colored magenta. Any subsequent bonds that are formed by other reactions are colored orange.

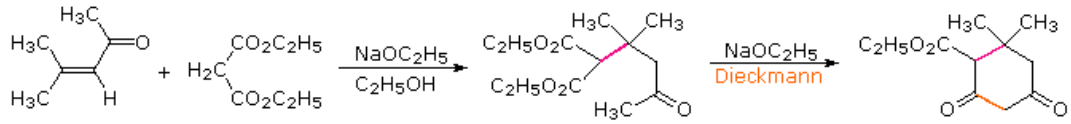
1.



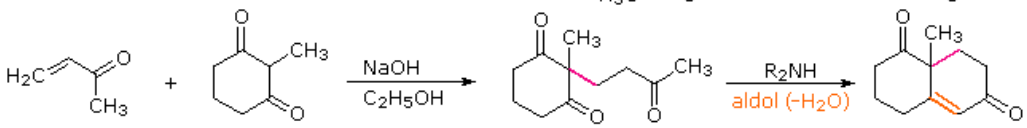
2.



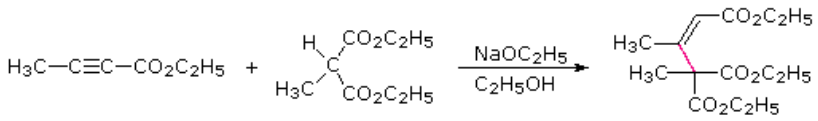
3.



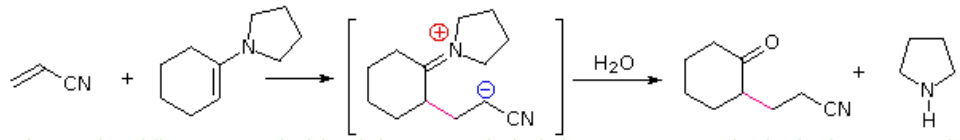
4.



5.

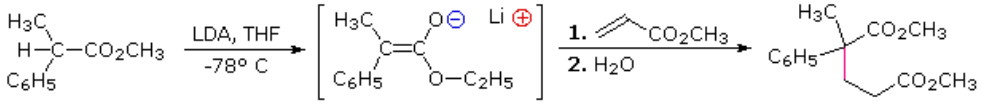


6.



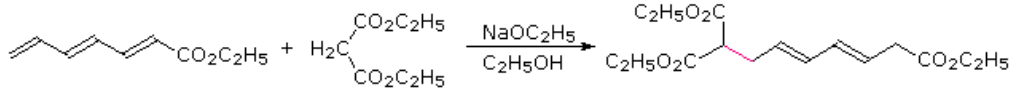
Enamine nucleophiles are good Michael donors. Hydrolysis is necessary to obtain the ketone product.

7.



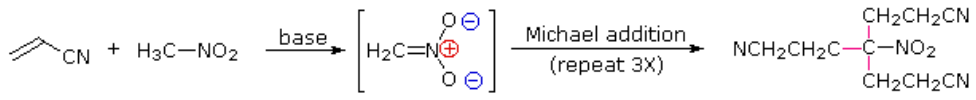
Weak carbon acids may be converted to their enolate anions prior to addition of the Michael acceptor.

8.



Extended vinylagous Michael acceptors have been used. This is a 1,6-addition (1,8 if the enol is counted).

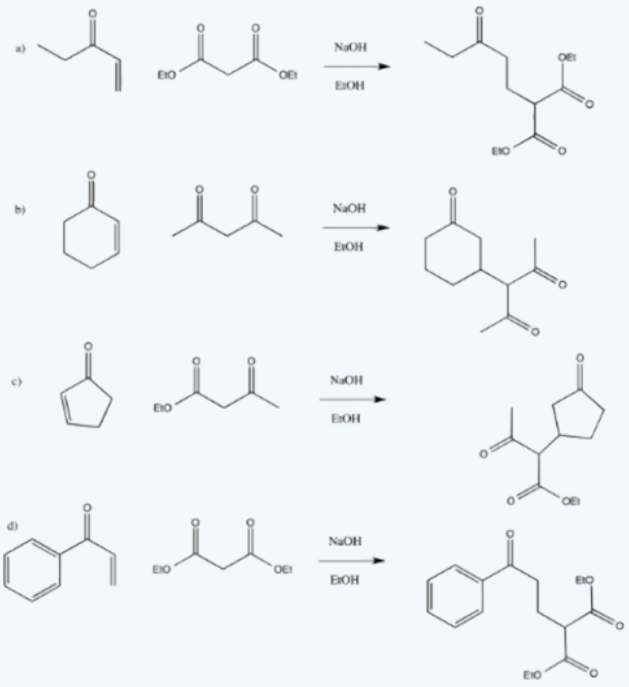
9.



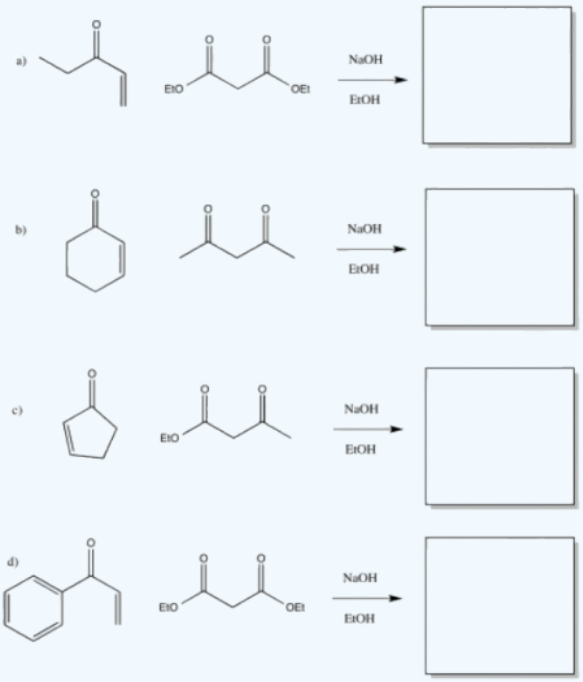
Nitroalkanes have acidic α-hydrogens and make excellent Michael donors.

EXERCISE 23.10.1

Provide the products of the following Michael additions:

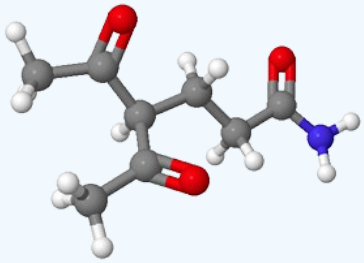


Answer

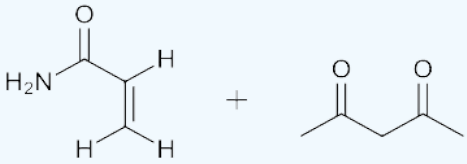


EXERCISE 23.10.2

What would be the starting materials required to make the following molecule using a Michael reaction? Red = Oxygen, Grey = Carbon, White = Hydrogen, Blue = Nitrogen.



Answers



23.11: CARBONYL CONDENSATIONS WITH ENAMINES - THE STORK REACTION

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate the three-step Stork enamine reaction.
2. write a detailed mechanism for each of the three steps of the Stork enamine reaction.
3. identify the product formed, and the various intermediates (i.e., the enamine, the Michael-type adduct), in a given Stork enamine reaction.
4. identify the reagents needed to synthesize a given compound by a Stork enamine reaction.

KEY TERMS

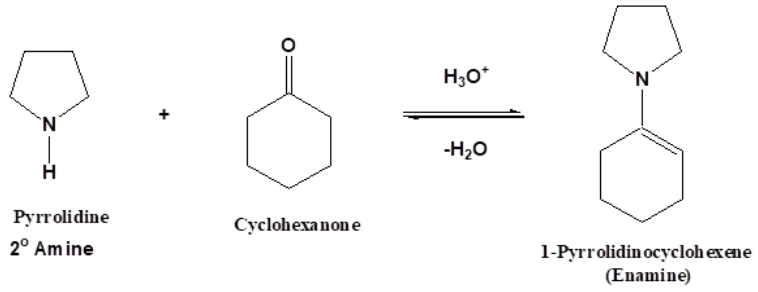
- Stork enamine reaction

STUDY NOTES

If we try to use a monoketone as a donor molecule in a Michael reaction, we will obtain a poor yield. An alternative route to the product that would be expected from such a synthesis is via the Stork enamine reaction. You may wish to review the formation of enamines (from ketones and secondary amines) before you proceed with this section; if so, review Section 19.8.

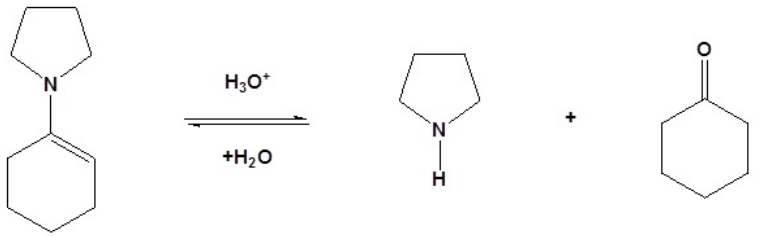
SYNTHESIS OF ENAMINES

As previously seen in **Section 19.8**, aldehydes and ketones react with 2° amines to reversibly form enamines. Enamines can add to acid halides to form 1,3-diketones and α, β-unsaturated Michael acceptors to from 1,5-dicarbonyls.

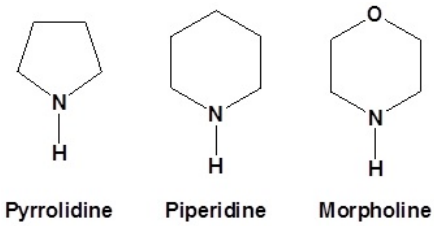


General Reaction

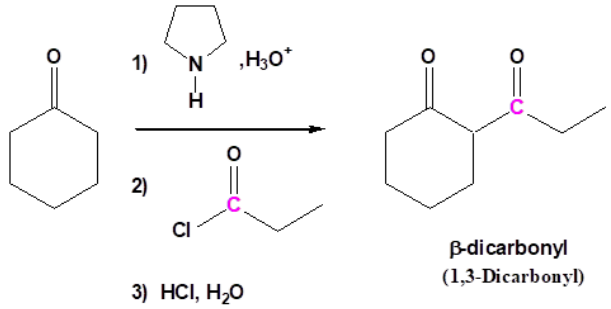
REVERSIBILITY



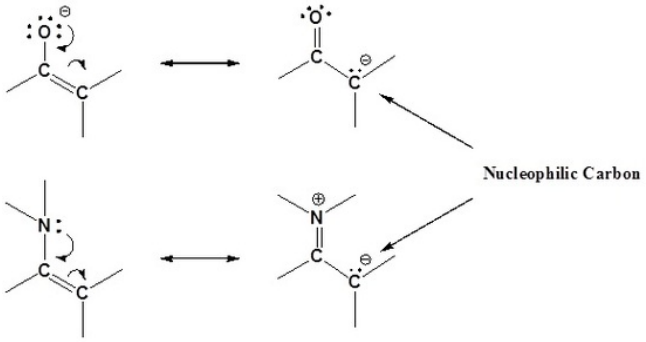
Typically the following 2° amines are used for enamine reactions



Enamines have resonance structures similar to enolates. The lone pair electrons on the nitrogen are conjugated with the double bond and can donate electron density to the α-carbon. This allows the α-carbon of enamines to be nucleophilic in much the same fashion as enolates. The increased electron density of the α-carbon enamine, N,N-Dimethylaminoethylene, is shown as a yellow/green color in its electrostatic map. This is analogous to the increased electron density of the α-carbon of an enolate.

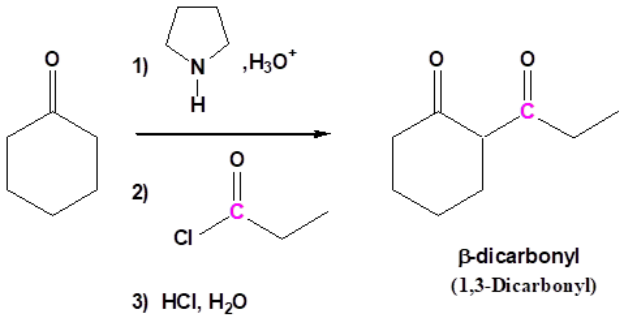


Enamines act as nucleophiles in a fashion similar to enolates. Because of this enamines can be used as synthetic equivalents as enolates in many reactions. This process requires a three steps: 1) Formation of the enamine, 2) Reaction with an electrophile to form an iminium salt, 3) Hydrolysis of the iminium salt to reform the aldehyde or ketone. Some of the advantages of using an enamine over an enolate are enamines are neutral, easier to prepare, and usually prevent the overreaction problems plagued by enolates. Also, enamine are more effective at the Michael reaction compared to a mono-carbonyl enolate.



ACYLATION OF ENAMINES

Acylation of Enamines involves the addition of an acyl group (RCO^-) to an enamines, resulting in the formation of an α-acylated product.

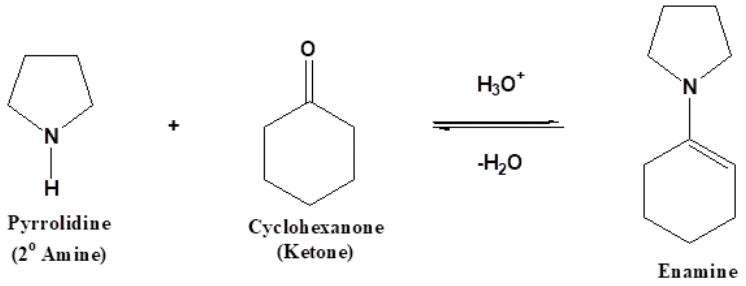


Example of an acylation of of an enamine.

MECHANISM ON ENAMINE ACYLATION

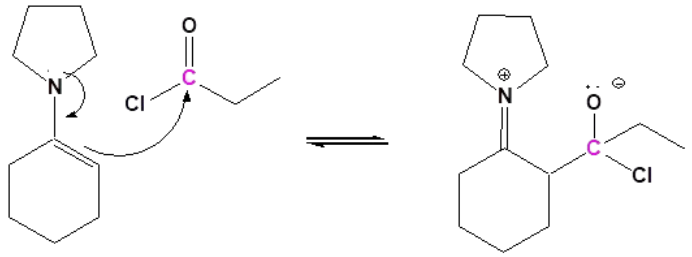
STEP 1 FORMATION OF THE ENAMINE

The mechanism starts with the formation of an enamine.



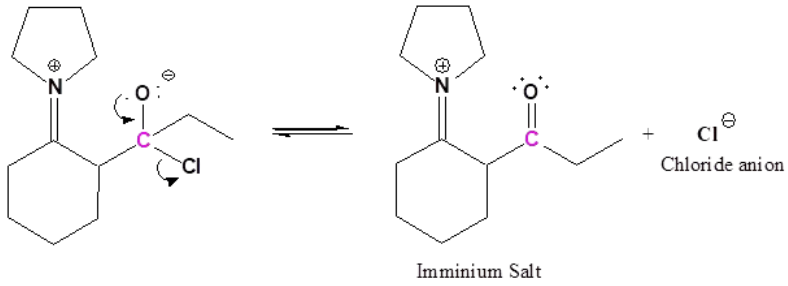
STEP 2: NUCLEOPHILIC ATTACK

The enamine adds to the electrophilic carbonyl carbon of the acid halide to form an iminium bond with tetrahedral alkoxide as an intermediate.



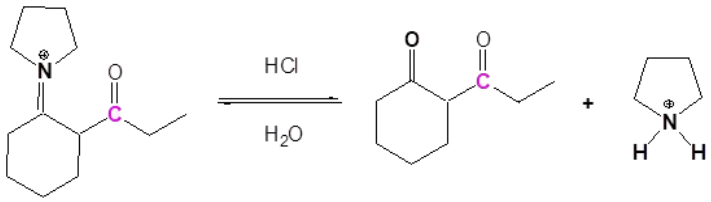
STEP 3: LEAVING GROUP REMOVAL

The alkoxide reforms the carbonyl bond and eliminate a halide anion as a leaving group.



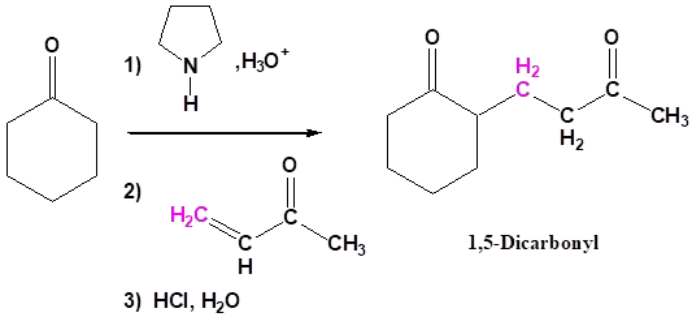
STEP 4: REFORM THE CARBONYL BY HYDROLYSIS

The iminium bond is then hydrolyzed to reform the carbonyl to create a 1,3-dicarbonyl compound as the product of a nucleophilic acyl substitution.



MICHAEL REACTION USING ENAMINES: THE STORK REACTION

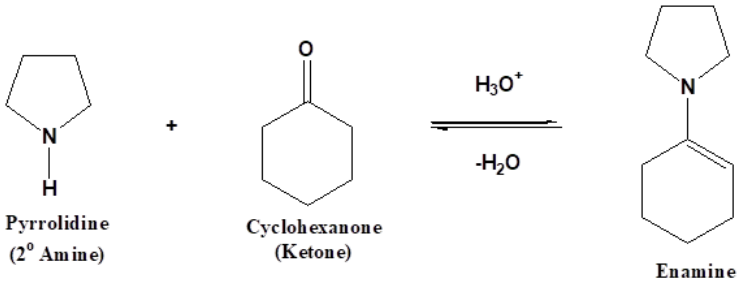
Enamines add to α, β-unsaturated carbonyls in a Michael-like reaction. The net reaction is the addition of a ketone to a α, β-unsaturated carbonyl to product a 1,5 dicarbonyl compound as the end product. This reaction is commonly known as the Stork enamine reaction after Gilbert Stork of Columbia University who originated the work.



Example of a The Stork Reaction

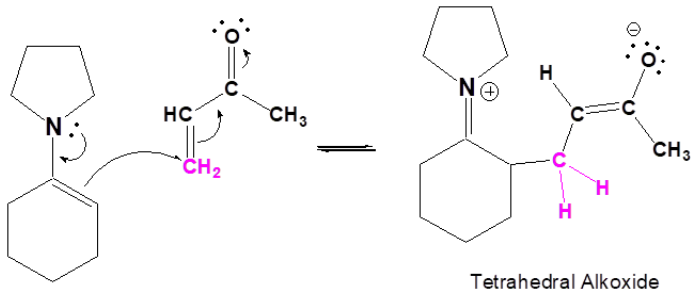
MECHANISM OF THE STORK REACTION

STEP 1: FORMATION OF THE ENAMINE



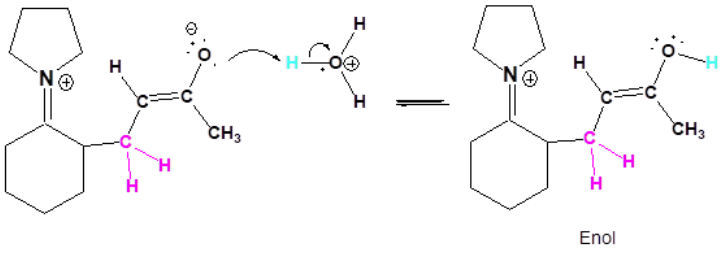
STEP 2: NUCLEOPHILIC ATTACK ON THE CARBON B TO THE CARBONYL

After formation, the enamine adds to the electrophilic alkene carbon of the a α, β-unsaturated carbonyl form an iminium bond. The pi electrons of the alkene are pushed onto the oxygen through conjugation to form an alkoxide as an intermediate.



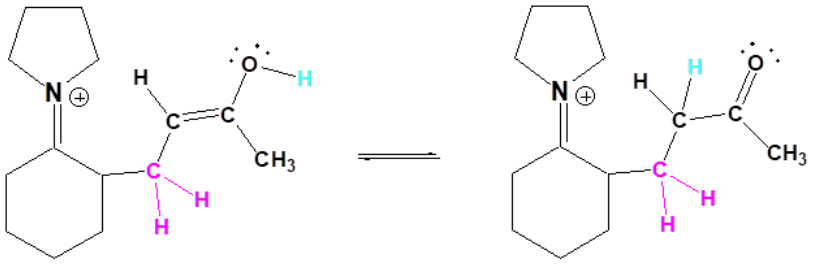
STEP 3: PROTONATION

Protonation of the alkoxide forms an enol.



STEP 4: TAUTOMERIZATION

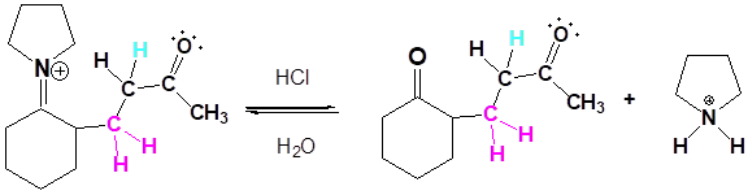
The enol undergoes tautomerization to reform the ketone.



Conjugate Additon Product

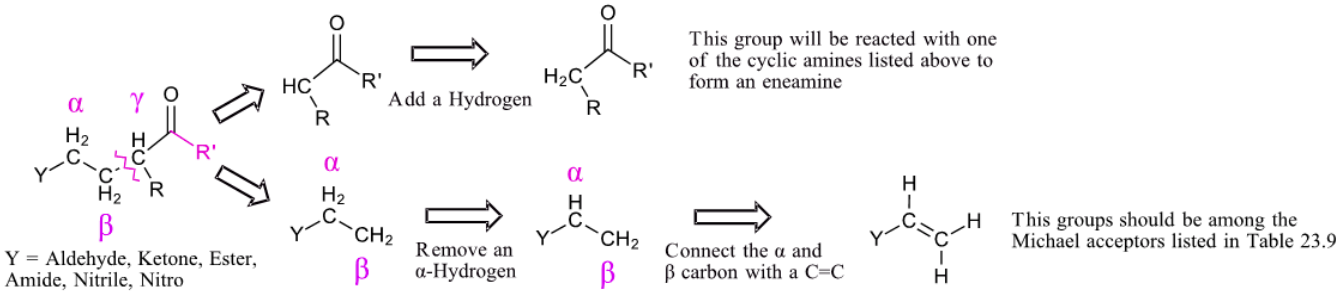
STEP 4: REFORM THE CARBONYL BY HYDROLYSIS

In the last step of the mechanism, the iminium bond is hydrolyzed to reform the carbonyl to create a 1,5-dicarbonyl compound as the product of a Michael-like reaction.



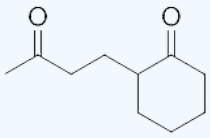
PLANNING A SYNTHESIS USING THE STORK ENAMINE SYNTHESIS

Planning a synthesis using a Stork enamine reaction is very similar to that of a Michael reaction (Section 23-10). A target molecule can possibly be made using a Stork enamine reaction if it contains a 1,5-dicarbonyl. Like the Michael reaction, the key bond cleavage is a C-C bond between beta and gamma carbons from a carbonyl-like group. The fragment with the Y group loses an alpha-hydrogen and then forms a C=C bond between the alpha and beta carbon. The carbon of the other fragment gains a hydrogen. This fragment should possess an acidic alpha-hydrogen and should be made up of Michael donor fragments.



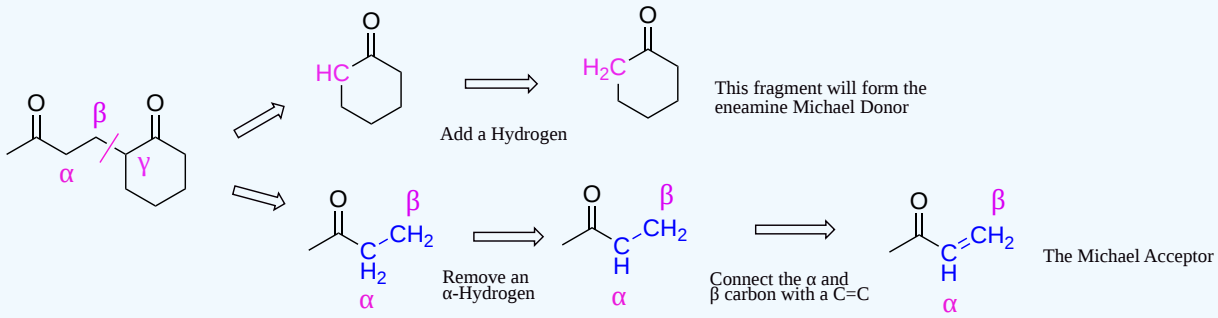
? WORKED EXAMPLE

How could the following molecule be made using a Michael Reaction?

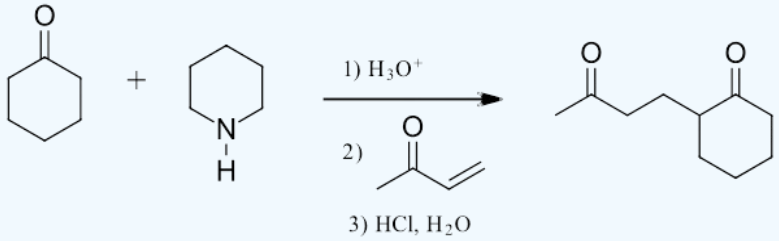


Answer

Pathway 1



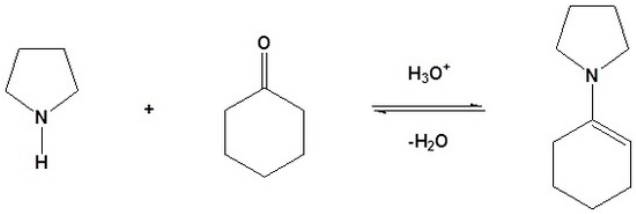
Solution



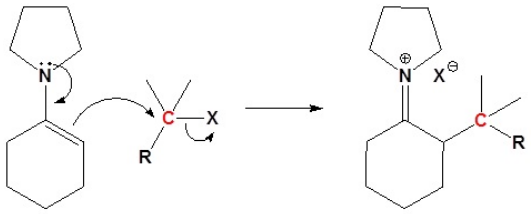
ALKYLATION OF AN ENAMINE

Enamines undergo an S_N2 reaction with reactive alkyl halides to give the iminium salt. The iminium salt can be hydrolyzed back into the carbonyl. The individual steps are below.

STEP 1: FORMATION OF AN ENAMINE

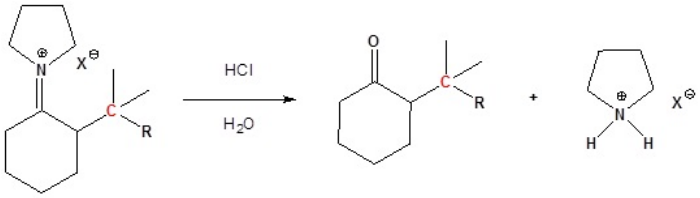


STEP 2: S_N2 ALKYLATION

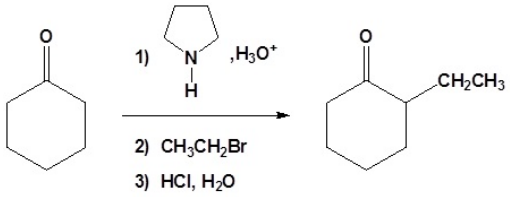


Iminium Salt

STEP 3: REFORM THE CARBONYL BY HYDROLYSIS

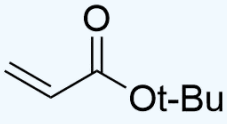


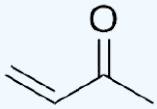
All three steps together:

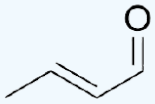


EXERCISE 23.11.1

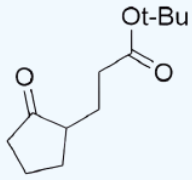
Draw the product of the reaction with the enamine prepared from cyclopentanone and pyrrolidine, and the following molecules.

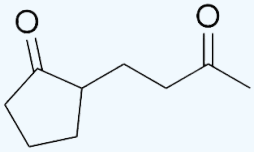
a. 

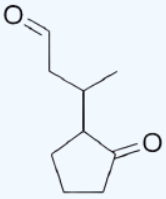
b. 

c. 

Answer

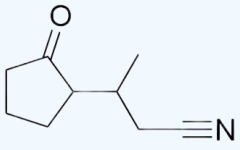
a. 

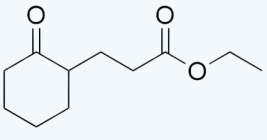
b. 

c. 

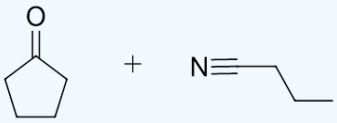
EXERCISE 23.11.2

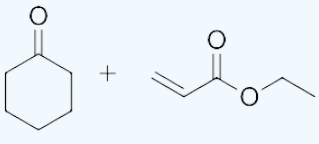
What would be the starting materials necessary to make the following molecules during a Stork enamine reaction.

1. 

2. 

Answers

a. 

b. 

23.12: THE ROBINSON ANNULATION REACTION

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate the Robinson annulation reaction.
2. identify the cyclic product formed when a 1,5-diketone is treated with base.
3. identify the carbonyl compounds and any other reagents needed to synthesize a given cyclic compound by a series of reactions, one of which is a Robinson annulation.

KEY TERMS

- Robinson annulation reaction

STUDY NOTES

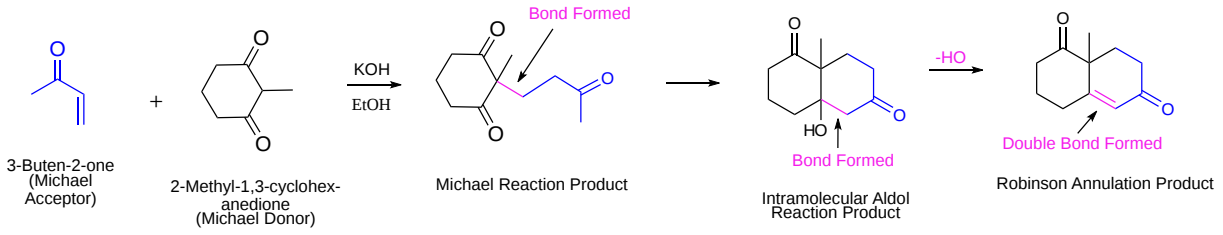
The building of an alicyclic compound from acyclic starting materials can present an interesting challenge to the synthetic organic chemist. One route by which such a synthesis can be achieved is through the use of the Robinson annulation reaction. This reaction, which may at first look very complex, can be readily understood once you realize that it simply involves a Michael reaction followed by an intramolecular aldol condensation. Both of these steps involve attack by enolate anions.

As in some of the other syntheses that you have studied, when you are simply given the structure of a compound and asked how it could have been prepared, it can be difficult to recognize which reactions might have been used. In this instance, keep in mind that you have studied relatively few reactions which have resulted in the formation of an alicyclic compound. Thus, when asked how such a compound might be prepared, you should keep the possibility of using a Robinson annulation reaction in mind.

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.

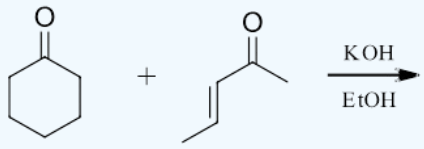
The nucleophilic enolate donor is typically an enolate ion or enamine of a cyclic ketone, β-keto ester or β-diketone. The electrophilic acceptor is usually an α, β-unsaturated ketone. In the example below, 2-methyl-1,3-cyclohexanedione is deprotonated to form an enolate which affects a Michael reaction addition on 3-buten-2-one forming a C-C bond. The product contains a 1,5-diketone fragment which can undergo an intramolecular aldol condensation. This occurs through creation of a new enolate at the methyl ketone which undergoes an intramolecular aldol reaction. A new C-C bond is formed to one of the ring carbonyls, creating a new six-membered ring. In the last step, the resulting alcohol is eliminated to form a α, β-unsaturated ketone as the final Robinson annulation product. Because the Robinson Annulation involves an aldol reaction, a full equivalent of base is required.



Example

EXAMPLE

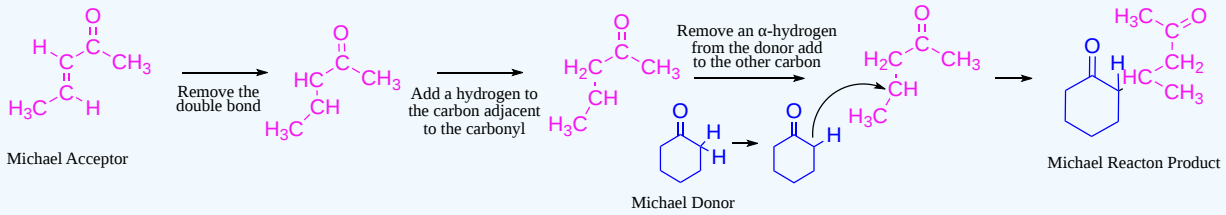
Draw the product of the following Robinson Annulation.



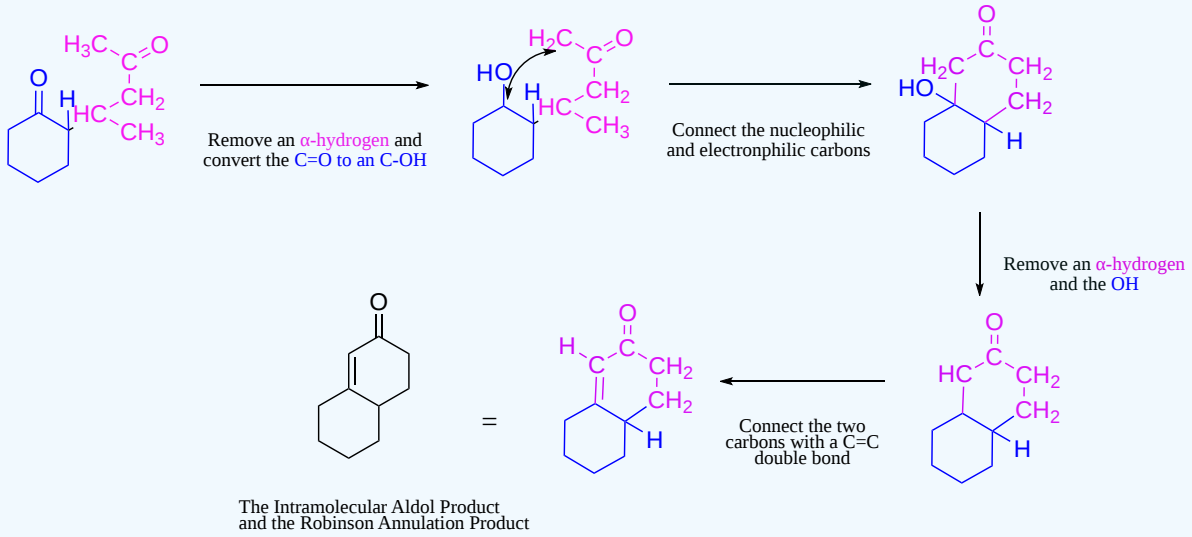
ANALYSIS

When considering the product of a Robinson annulation it is usually best to consider each reaction individually. Use the steps discussed in Section 23.10 to convert the starting materials into the product of a Michael reaction, then into the product of an intramolecular aldol condensation. If the starting materials are drawn in a skeletal structure it may be helpful to convert to a condensed formula to better keep track of carbons and hydrogens.

Formation of the Michael reaction product

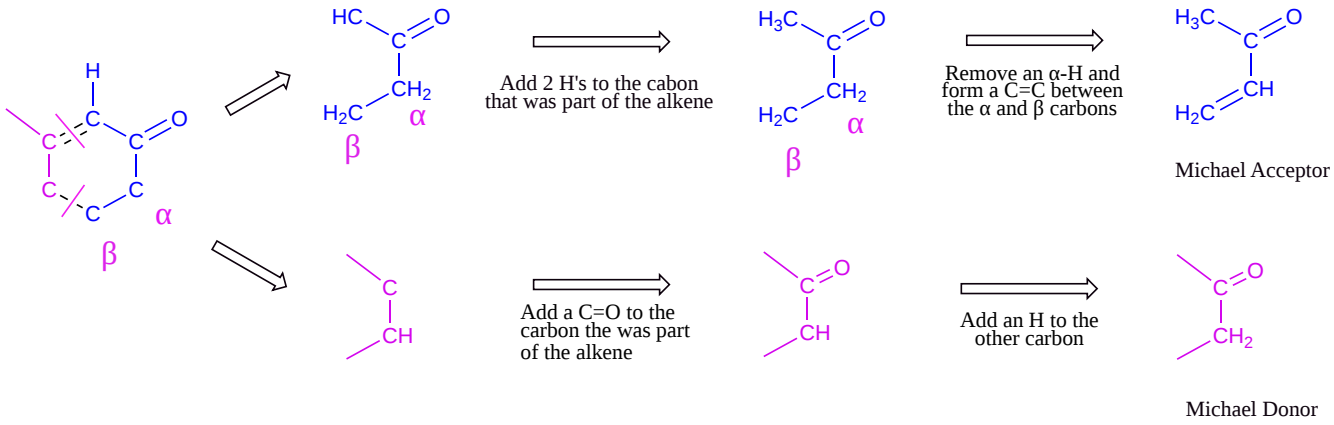


Formation of the intramolecular Aldol condensation product



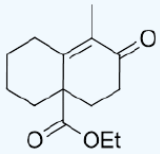
PLANNING A SYNTHESIS USING A ROBINSON ANNULATION

The presence of a cyclic, six-membered α, β-unsaturated ketone in a target molecule suggest that a Robinson Annulation may be utilized in its synthesis. The key bond cleavages are the C=C bond of the α, β-unsaturated ketone and the C-C bond between carbons in the a and g on the opposite alkyl chain of the ketone.

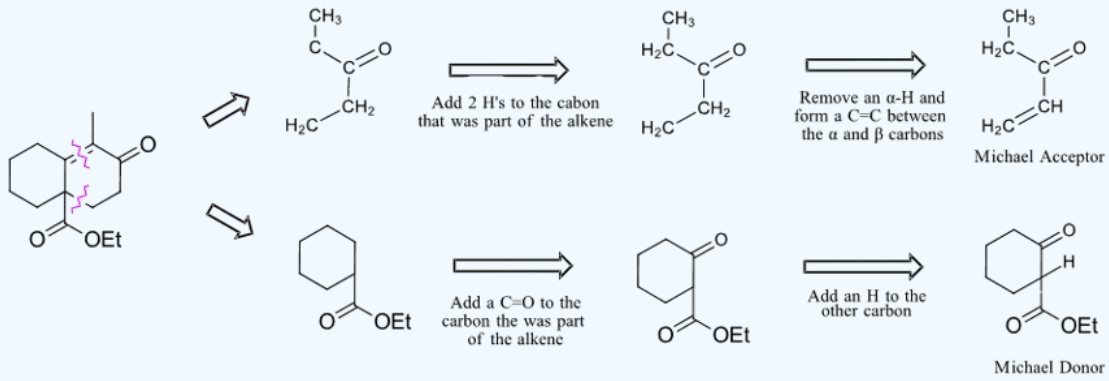


EXAMPLE

What would be the starting materials used if the following molecule was made using a Robinson annulation?

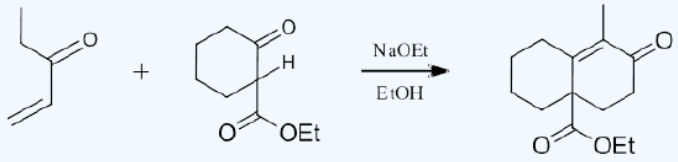


ANALYSIS



SOLUTION

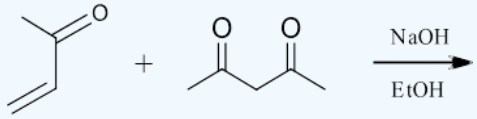
It is necessary to use sodium ethoxide as the reaction base due to the presence of an ester.



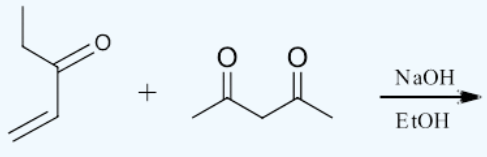
EXERCISE 23.12.1

Provide products of the following Robinson annulations.

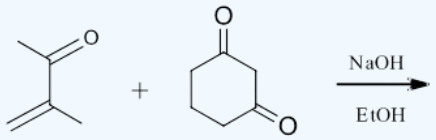
a.



b.

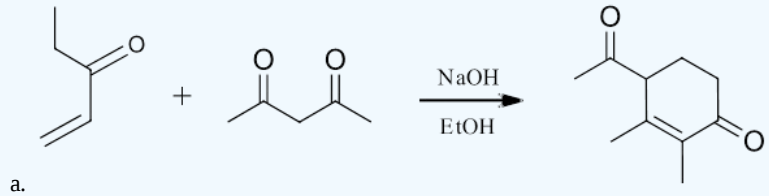


c.

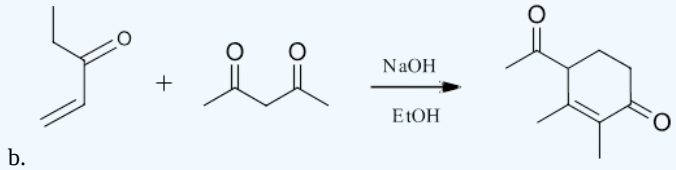


Answer

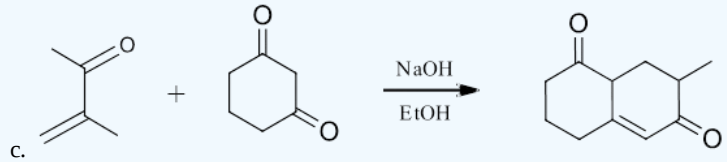
a.



b.

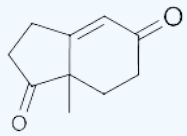


c.

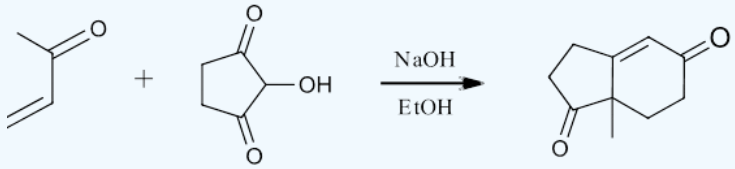


? EXERCISE 23.12.2

What would be the starting materials required to make the following molecule using a Robinson annulation?



Answer



23.13: SOME BIOLOGICAL CARBONYL CONDENSATION REACTIONS

OBJECTIVES

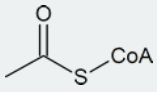
After completing this section, you should be able to

1. identify acetyl coenzyme A as an important biomolecule which undergoes carbonyl condensation reactions.
2. identify aldoases as enzymes that catalyze aldol reactions in biological systems.
3. identify the steps in which a carbonyl condensation reaction has occurred, given a general outline of a specific biosynthesis.

STUDY NOTES

Carbonyl condensation reactions occur in biological systems; for example, in the biosynthesis of citric acid.

You first met acetyl coenzyme A in Section 21.8. Again, we stress that it is not essential that you know the detailed structure of this compound (or other large biochemical stuctures discussed), but you should know that it may be represented as



and that it has the ability to behave just as any other acetyl-containing compound.

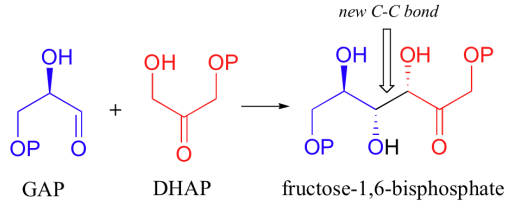
ALDOL REACTIONS IN NATURE

So far, we have examined the non-enzymatic reaction of an aldehyde or ketone with itself (a so-called 'self-condensation' reaction, where 'condensation' means the formation of one larger molecule from two smaller ones). However, aldol reactions occur in several biological pathways, most commonly in the metabolism of carbohydrates (sugars). The enzymes that catalyze aldol reactions are called, not surprisingly, '**aldolases**'. They occur in all organisms, but note that **Class I aldoases** are usually found in animals and higher plants, while **Class II aldoases** normally appear in bacteria and fungi.

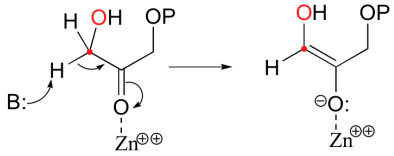
TYPICAL ALDOLASE REACTIONS - THREE VARIATIONS ON A THEME

The first step in an aldolase reaction is the deprotonation of an alpha-carbon to generate a nucleophilic carbanion. Nature has evolved several distinct strategies to stabilize the intermediate that results. Some aldolases use a metal ion to stabilize the negative charge on an enolate intermediate, while others catalyze reactions that proceed through neutral Schiff base or enol intermediates.

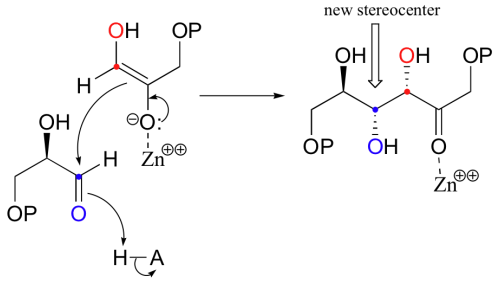
Let's examine first a reaction catalyzed by a so-called **'Class II' aldolase**, in which a metal cation - generally Zn^{2+} - bound in the active site serves to stabilize the negative charge on an enolate intermediate. Fructose 1,6-bisphosphate aldolase is an enzyme that participates in both the glycolytic (sugar burning) and gluconeogenesis (sugar building) biochemical pathways. For now, we will concentrate on its role in the gluconeogenesis pathway, but we will see it again later in its glycolytic role. The reaction catalyzed by fructose 1,6-bisphosphate aldolase is a condensation between two 3-carbon sugars, glyceraldehyde-3-phosphate (GAP) and dihydroxyacetone phosphate (DHAP), forming a six-carbon product (which leads, after three more enzymatic steps, to glucose).



In the first step of the condensation, an alpha-carbon on DHAP is deprotonated, leading to an enolate intermediate. The strategy used to stabilize this key intermediate is to coordinate the negatively-charged enolate oxygen to an enzyme-bound zinc cation.

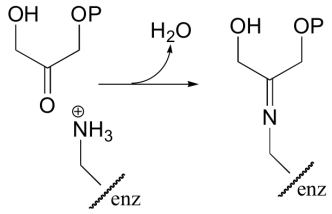


Next, the deprotonated a-carbon attacks the carbonyl carbon of GAP in a nucleophilic addition reaction, and protonation of the resulting alcohol leads directly to the fructose 1,6-bisphosphate product.

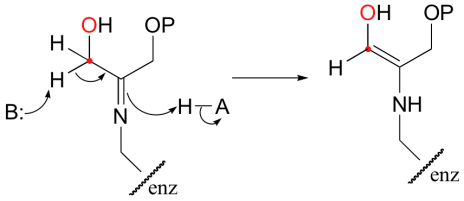


As with many other nucleophilic carbonyl addition reactions, a new stereocenter is created in this reaction, as a planar, achiral carbonyl group is converted to a tetrahedral, chiral alcohol. The enzyme-catalyzed reaction, not surprisingly, is completely stereospecific: the DHAP substrate is positioned in the active site so as to attack the *re* (front)face of the GAP carbonyl group, leading to the *R* configuration at the new stereocenter.

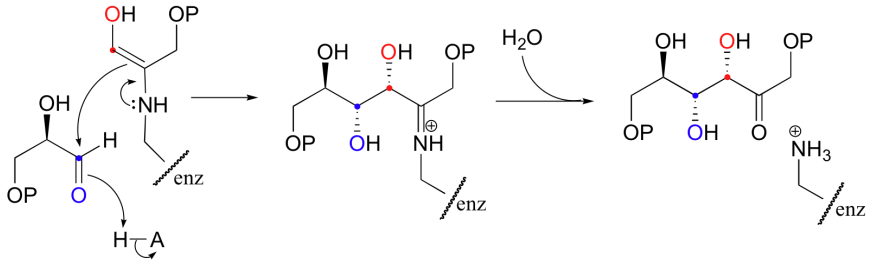
Interestingly, it appears that in bacteria, the fructose bisphosphate aldolase enzyme evolved separately from the corresponding enzyme in plants and animals. In plants and animals, the same aldol condensation reaction is carried out by a significantly different mechanism, in which the key intermediate is not a zinc-stabilized enolate but an enamine. The nucleophilic substrate (DHAP) is first linked to the enzyme through the formation of an imine (also known as a Schiff base) with a lysine residue in the active site.



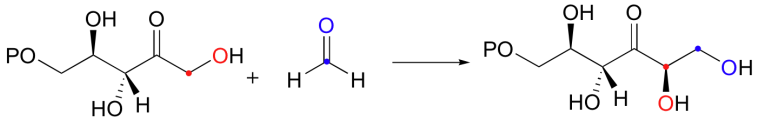
The alpha-proton is then abstracted by an active site base to form an enamine.



In the next step, the alpha-carbon attacks the carbonyl carbon of GAP, and the new carbon-carbon bond is formed. In order to release the product from the enzyme active site and free the enzyme to catalyze another reaction, the imine is hydrolyzed back to a ketone group.



There are many more examples of **'Class I' aldolase** reactions in which the key intermediate is a lysine-linked imine. Many bacteria are able to incorporate formaldehyde, a toxic compound, into carbohydrate metabolism by condensing it with ribulose monophosphate. The reaction proceeds through imine and enamine intermediates.



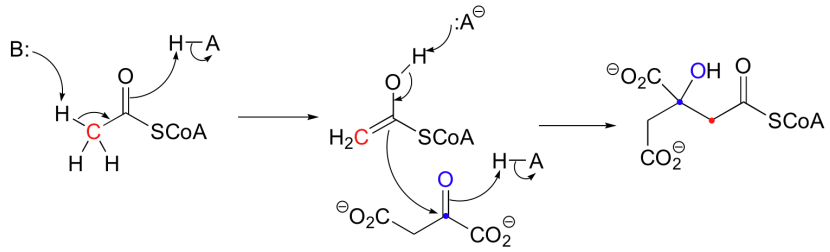
ribulose-5-phosphate formaldehyde hexulose-6-phosphate

EXAMPLE 23.13.1

a. Propose a complete mechanism for the condensation reaction shown above.
b. Propose a complete mechanism for the conversion of hexulose-6-phosphate (formed from the condensation of ribulose-5-phosphate and formaldehyde) into fructose-6-phosphate.

Solution

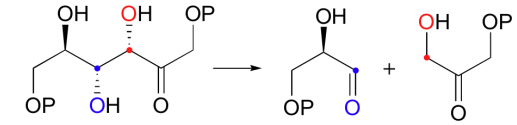
Along with aldehydes and ketones, esters and thioesters can act as the nucleophilic partner in aldol condensations. In the first step of the citric acid (Krebs) cycle, acetyl CoA condenses with oxaloacetate to form (S)-citryl CoA.



Notice that in this aldol reaction, the nucleophilic intermediate is stabilized by protonation, rather than by formation of an imine (as in the Class I aldolases) or by a metal ion (as in the Class II aldolases).

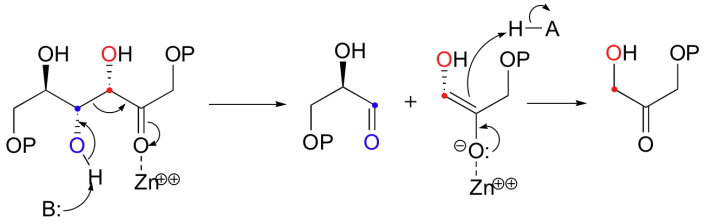
GOING BACKWARDS: THE RETROALDOL REACTION

Although aldol reactions play a very important role in the formation of new carbon-carbon bonds in metabolic pathways, it is important to emphasize that they are also highly reversible: in most cases, the energy level of starting compounds and products are very close. This means that, depending on metabolic conditions, aldolases can also catalyze **retro-aldol** reactions (the reverse of aldol condensations, in which carbon-carbon bonds are *broken*). Recall that fructose 1,6-bisphosphate aldolase (section 13.3B) is active in the direction of sugar breakdown (glycolysis) as well as sugar synthesis (gluconeogenesis). In the glycolytic direction, the enzyme catalyzes - either by zinc cation or by imine/enamine mechanisms, depending on the organism - the retro-aldol cleavage of fructose bisphosphate into DHAP and GAP.

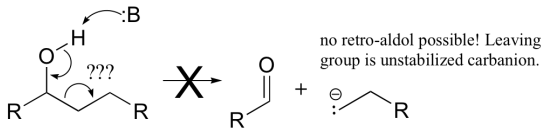


fructose-1,6-bisphosphate GAP DHAP

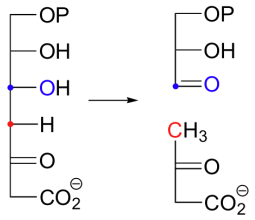
The mechanism is the exact reverse of the condensation reaction. Shown below is the mechanism for a Zn^{2+} - dependent (Type II) retroaldol cleavage. Notice that in the retroaldol reaction, the enolate intermediate is the *leaving group*, rather than the nucleophile.



The key thing to keep in mind when looking for a possible retro-aldol mechanism is that, when the carbon-carbon bond breaks, the electrons must have some place to go, where they will be stabilized by resonance. Generally, this means that there *must* be a carbonyl or imine group on the next carbon. If there is no adjacent carbonyl or imine group, the carbon-carbon bond is not free to break.



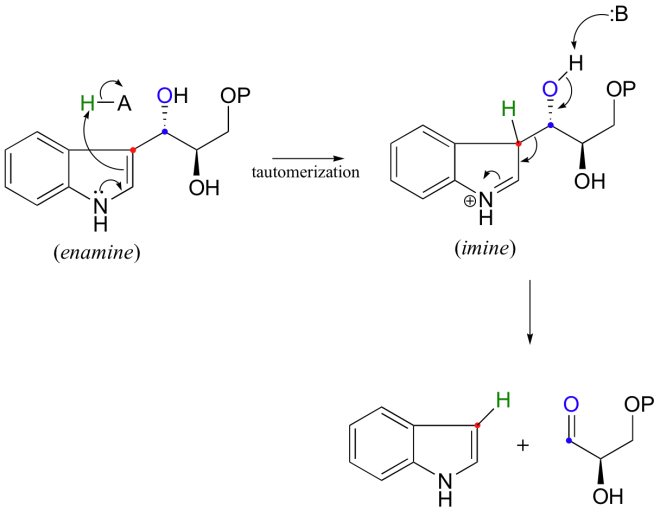
Here are two more examples of retro-aldol reactions. Bacterial carbohydrate metabolism involves this reversible, class I retro-aldol cleavage: (*Proc. Natl. Acad. Sci* **2001**, *98*, 3679).



EXAMPLE 23.13.2

Draw the structure of the enamine intermediate in the retroaldol reaction shown above.

Another interesting example is the retro-aldol cleavage of indole-3-glycerol phosphate, a step in the biosynthesis of tryptophan.



Look carefully at this reaction - how is the leaving group stabilized? There is an imine group involved, but no participation by an enzymatic lysine. The imine is 'built into' the starting compound, available from the initial tautomerization of the cyclic enamine group in indole-3-glycerol phosphate.

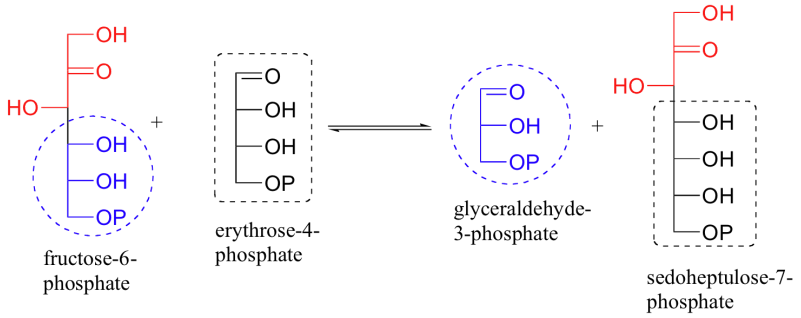
EXAMPLE 23.13.3

Draw the reverse (aldol condensation) direction of the reaction above.

Solution

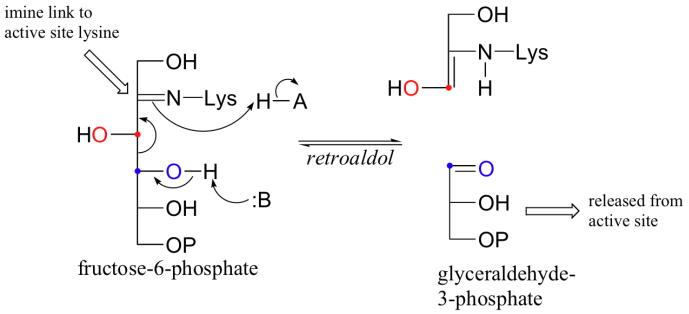
GOING BOTH WAYS: TRANSALDOLASE

An enzyme called transaldolase, which is part of the 'pentose phosphate pathway' of carbohydrate metabolism, catalyzes an interesting combination of class I aldol and retro-aldol reactions. The overall reaction, which can proceed in either direction depending on metabolic requirements, converts 3- and 7-carbon sugars into 6- and 4-carbon sugars. Essentially, a 3-carbon unit breaks off from a ketone sugar (ketose) and then is condensed directly with an aldehyde sugar (aldose).

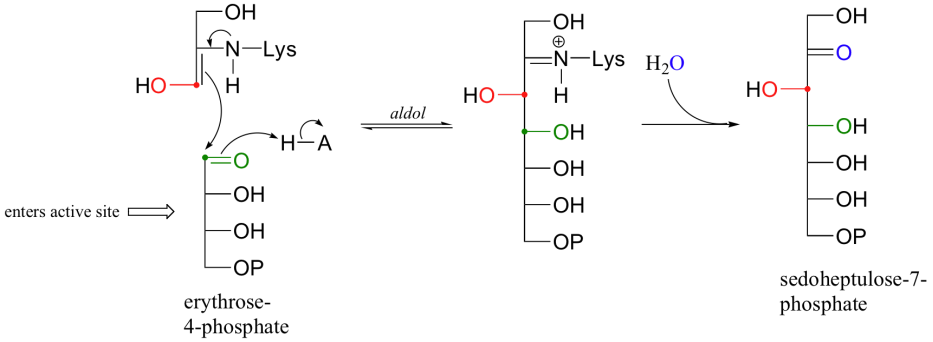


Let's follow the progress of the reaction in the left-to-right direction as depicted above. Because this is a class I aldolase, the first step is the formation of an imine linkage between the ketone carbon of fructose-6-phosphate (F6P) and a lysine group from the enzyme. The enzyme-

substrate adduct then undergoes a retro-aldol step to free glyceralde-3-phosphate (GAP), which leaves the active site.



The second substrate, erythrose 4-phosphate (E4P), enters the active site, and an aldol condensation occurs between E4P and the 3-carbon fragment remaining from the cleavage of fructose-6-phosphate.



The final step is hydrolysis of the imine and subsequent dissociation of sedoheptulose 7-phosphate from the active site.

23.S: CARBONYL CONDENSATION REACTIONS (SUMMARY)

CONCEPTS & VOCABULARY

- Design multi-step syntheses in which the reactions introduced in this unit are used in conjunction with any of the reactions described in previous units.
- Solve road-map problems that require a knowledge of carbonyl condensation reactions.
- Define, and use in context, any of the key terms introduced.

23.1 Carbonyl Condensations - The Aldol Reaction

- A carbon-carbon bond forming reaction at the alpha carbon through an enolate nucleophile.
- The Aldol Reaction proceeds by first making an enolate nucelophile on an aldehyde (or ketone).
- The enolate nucleophile then dimerizes by attacking the carbonyl of the same aldehyde (or ketone).
- The final product is a beta-hydroxy aldehyde (or ketone).

23.2 Carbonyl Condensations versus Alpha Substitutions

- Carbonyl condensation reactions are a type of alpha substitution reaction.
- Both involve an enolate nucleophile and end with an alpha substitution product.
- In carbonyl condensations, the electrophile is another carbonyl compound.
- Carbonyl condensations are reversible and use a catalytic amount of base.
- The electrophile is already present in the reaction as the enolate is formed in carbonyl condensations.
- Alpha substitution reactions are more directional by design, since a full equivalent of base is used to generate the enolate.
- The electrophile is introduced after the enolate is generated.

23.3 Dehydration of Aldol Products - Synthesis of Enones

- The aldol reaction can undergo a dehydration (loss of water) to yield an α,β-unsaturated aldehyde or ketone.
- The additional stability provided by the conjugated carbonyl system makes some of the products thermodynamically driven.
- The of small products, such as water in this case, are termed condensations, so this reaction is aldol condesation.
- Heat promotes the condensation reactions.
- Under basic conditions, the β-elimination occurs through an E1cb mechanism.
- Under acidic conditions, the β-elimination occurs through an E1 or E2 mechanism.

23.4 Using Aldol Reactions in Synthesis

- If the target contains a β-hydroxy carbonyl compound or an α,β-unsaturated carbonyl compound, then synthetically think aldol reaction or condensation.
- To reverse the aldol condensation, break the enone at the double bond.
- To reverse the aldol reaction, break the C-C bond between the alpha carbon and the carbon attached to the hydroxy group.

23.5 Mixed Aldol Reactions

- Aldol condensations between different reactants are called mixed or crossed Claisen reactions.
- Multiple products are possible, so the success of the mixed aldol reactions depends on two things:
  - The electrophile (or acceptor) is an aldehyde.
  - The aldehyde acceptor has no alpha protons.
- Mixed aldols in which both reactants can serve as donors and acceptors generally give complex mixtures of both dimeric (homo) aldols and crossed aldols.
- The aldol condensation of ketones with aryl aldehydes to form α,β-unsaturated derivatives is called the Claisen-Schmidt reaction.

23.6 Intramolecular Aldol Reactions

- Molecules which contain two carbonyl functionalities have the possibility of forming a ring through an intramolecular aldol reaction.
- In these intramolecular reactions, two sets of α-hydrogens need to be considered and most ring forming reaction five and six membered rings are preferred.

23.7 The Claisen Condensation Reaction

- Esters can contain α hydrogens, so can undergo a condensation reaction similar to the aldol reaction called a Claisen Condensation.
- One ester reacts as a nucleophile while the other reacts as an electrophile.
- A new C-C bond is formed in the reaction to form a β-keto ester product.
- An alkoxide that matches the ester group is used to help prevent side reactions in the Claisen Condensation.
- There is a thermodynamic driving step forming an enolate, which is followed by a protonation to obtain the neutral product.

23.8 Mixed Claisen Condensation Reactions

- 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.

23.9 Intramolecular Claisen Condensation Reactions - The Dieckmann Cyclization

- A diester can undergo an intramolecular reaction called a Dieckmann condensation.

23.10 Conjugate Carbonyl Additions - The Michael Reaction

- In 1,4 additions the nucleophile is added to the carbon β to the carbonyl while the hydrogen is added to the carbon α to the carbonyl.
- Enolates undergo 1,4 addition to α, β-unsaturated carbonyl compounds (product of the Aldol condensation) is a process called a Michael addition.
- A new C-C bond is formed between an enolate and the 4-C of the α, β-unsaturated carbonyl compound.
- The product is a 1,5-dicarbonyl species.

23.11 Carbonyl Condensations with Enamines - The Stork Reaction

- Aldehydes and ketones react with 2^o amines to reversibly form enamines.
- Enamines act as nucleophiles similar to enolates.
- This process requires a three steps:
  - Formation of the enamine
  - Reaction with an eletrophile to form an iminium salt
  - Hydrolysis of the iminium salt to reform the aldehyde or ketone
- Advantages of using an enamine over an enolate
  - Neutral
  - Easier to prepare
  - Prevent overreaction issue that occurs when using enolates.
- Enamines undergo an S_N2 reaction with alkyl halides to yield the iminium salt.
- Enamines can react with acid halides to form β-dicarbonyls.
- Enamines can also be used as a nucleophile in a Michael reaction.

23.12 The Robinson Annulation Reaction

- Forms a cyclic product from acyclic starting materials by first creating a new C-C bond followed by ring formation.
- The Robinson Annulation reaction starts with a Michael reaction followed by an intramolecular Aldol condensation.
- The formation of 5 or 6 membered rings is preferred.

23.13 Some Biological Carbonyl Condensation Reactions

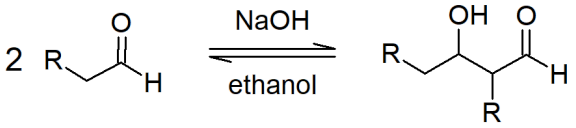
- Aldol reactions occur in several biological pathways.
- Enzymes that catalyze aldol reactions are called, not surprisingly, 'aldolases'.
- The first step in an aldolase reaction is the deprotonation of an alpha-carbon to generate a nucleophilic carbanion.
- Nature has evolved several distinct strategies to stabilize the intermediate that results.
  - Some aldolases use a metal ion to stabilize the negative charge on an enolate intermediate.
  - Others catalyze reactions that proceed through neutral Schiff base or enol intermediates.

SKILLS TO MASTER

- Skill 23.1 Identify the product of an aldol reaction.
- Skill 23.2 Write the detailed mechanism for the aldol reaction.
- Skill 23.3 Describe the difference between a carbonyl condensation reaction and an alpha-substitution reaction.
- Skill 23.4 Know what an enone is.
- Skill 23.5 Write a detailed mechanism for the aldol condensation under basic conditions.
- Skill 23.6 Write a detailed mechanism for the aldol condensation under acidic conditions.
- Skill 23.7 Determine the products of an aldol condensation reaction.
- Skill 23.8 Provide the reactants for a target aldol condensation product.
- Skill 23.9 Write an equation to illustrate a mixed aldol reaction.
- Skill 23.10 Identify the structural features necessary to ensure that two carbonyl compounds will react together in a mixed aldol reaction to give a single product rather than a mixture of products.
- Skill 23.11 Determine whether a given mixed aldol reaction is likely to produce a single product or a mixture of products.

- Skill 23.12 Identify the carbonyl compounds needed to produce a given enone or β-hydroxy aldehyde or ketone by a mixed aldol reaction.
- Skill 23.13 Write a detailed mechanism for the intramolecular aldol condensation.
- Skill 23.14 Write an equation to illustrate a Claisen condensation reaction.
- Skill 23.15 Write a detailed mechanism for a Claisen condensation reaction or its reverse.
- Skill 23.16 Identify the ester and other reagents needed to form a given β-keto ester by a Claisen condensation reaction.
- Skill 23.17 Write an equation to illustrate a mixed Claisen condensation.
- Skill 23.18 Identify the structural features that should be present in the two esters if a mixed Claisen condensation is to be successful.
- Skill 23.19 Identify the product formed when a given pair of esters is used in a mixed Claisen condensation.
- Skill 23.20 Identify the esters that should be used to produce a given β-keto ester by a mixed Claisen condensation.
- Skill 23.21 Write detailed mechanisms for mixed Claisen condensation.
- Skill 23.22 Write a detailed mechanism for an intramolecular Claisen condensation.
- Skill 23.23 Write a detailed mechanism for a given typical Michael reaction.
- Skill 23.24 Identify the product formed in a given Michael reaction.
- Skill 23.25 Identify the reagents necessary to synthesize a given compound by a Michael reaction.
- Skill 23.26 Write a detailed mechanism for each of the three steps of the Stork enamine reaction.
- Skill 23.27 Identify the reagents needed to synthesize a given compound by a Stork enamine reaction.
- Skill 23.28 Write a detailed mechanism for the Robinson Annulation reaction.
- Skill 23.29 Identify the product from an enone and an dicarbonyl under basic conditions.
- Skill 23.30 Identify the steps in which a carbonyl condensation reaction has occurred, given a general outline of a specific biosynthesis.

SUMMARY OF REACTIONS



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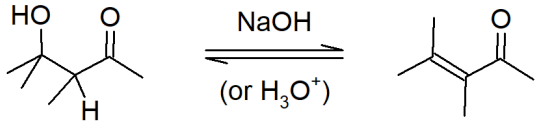

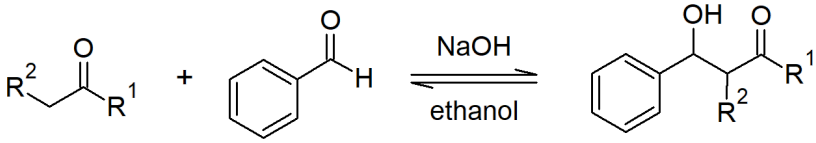

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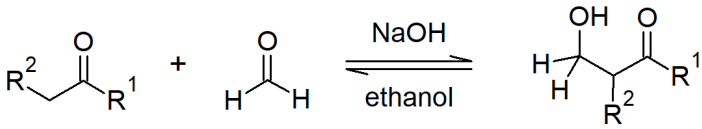

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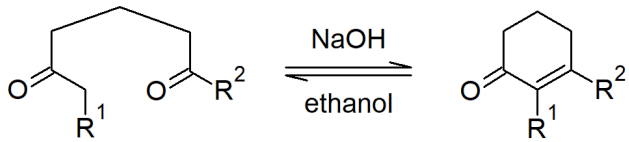
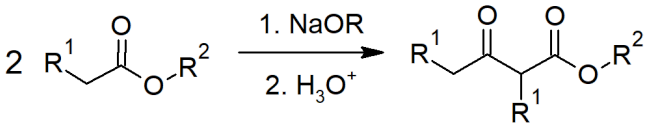
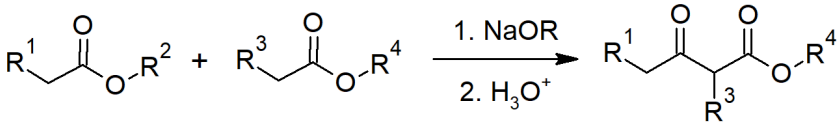


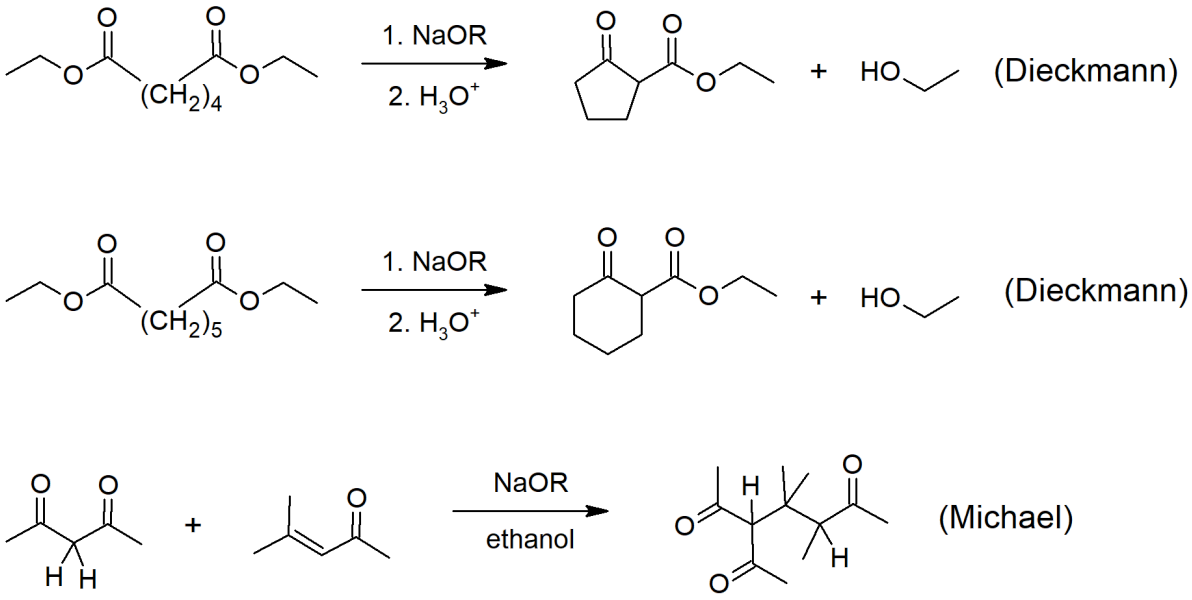
(intramolecular Aldol)



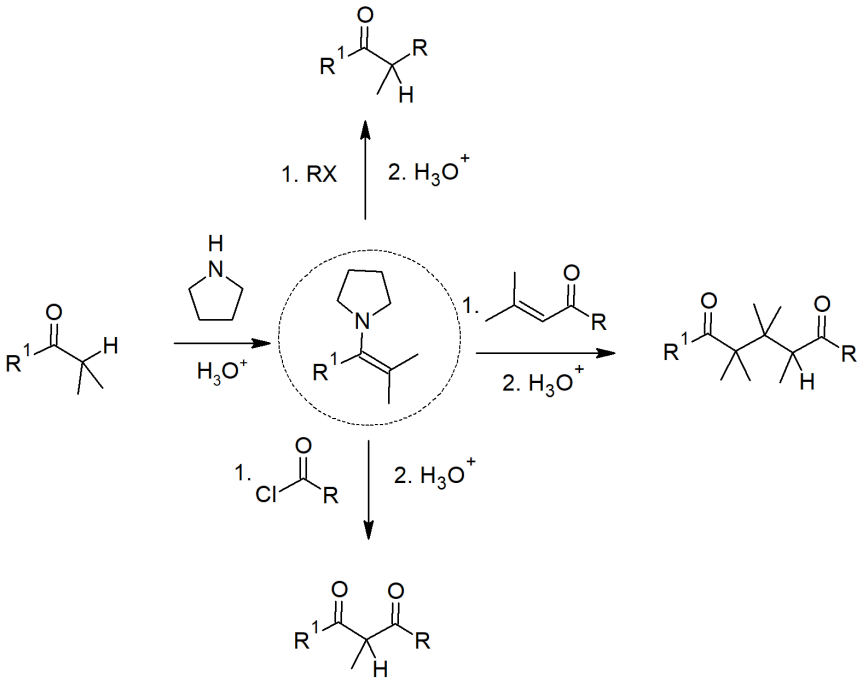
(Claisen)



(mixed Claisen)



Stork Enamine Reactions



Index

Glossary

3′ End | The end of a nucleic acid chain with a free hydroxyl group at C3′.

5′ End | The end of a nucleic acid chain with a free hydroxyl group at C5′.

Absolute configuration | The exact three-dimensional structure of a chiral molecule. Absolute configurations are specified verbally by the Cahn–Ingold–Prelog *R*,*S* convention.

Absorbance (*A*) | In optical spectroscopy, the logarithm of the intensity of the incident light divided by the intensity of the light transmitted through a sample; $A = \log I_0/I$.

Absorption spectrum | A plot of wavelength of incident light versus amount of light absorbed. Organic molecules show absorption spectra in both the infrared and the ultraviolet regions of the electromagnetic spectrum.

Acetals | A type of functional group consisting of two −OR groups bonded to the same carbon, $R_2C(OR')_2$. Acetals are often used as protecting groups for ketones and aldehydes.

Acetoacetic ester synthesis | The synthesis of a methyl ketone by alkylation of an alkyl halide with ethyl acetoacetate, followed by hydrolysis and decarboxylation.

Acetyl group | The CH_3CO^- group.

Acetylide anion | The anion formed by removal of a proton from a terminal alkyne, \ce{R–C≡C:^{−}}.

Achiral | Having a lack of handedness. A molecule is achiral if it has a plane of symmetry and is thus superimposable on its mirror image.

Acid anhydrides | A type of functional group with two acyl groups bonded to a common oxygen atom, RCO_2COR'.

Acid halides | A type of functional group with an acyl group bonded to a halogen atom, RCOX.

Acidity constant | A measure of acid strength. For any acid HA, the acidity constant is given by the expression K_a=[\ce{H3O^{+}}][\ce{A^{−}}][\ce{HA}].

Activating groups | Electron-donating groups such as hydroxyl (−OH) or amino ($-NH_2$) that increase the reactivity of an aromatic ring toward electrophilic aromatic substitution.

Activation energy | The difference in energy between ground state and transition state in a reaction. The amount of activation energy determines the rate at which the reaction proceeds. Most organic reactions have activation energies of 40–100 kJ/mol.

Active site | The pocket in an enzyme where a substrate is bound and undergoes reaction.

Acyclic diene metathesis (ADMET) | A method of polymer synthesis that uses the olefin metathesis reaction of an open-chain diene.

Acyl group | A −COR group.

Acyl phosphates | A type of functional group with an acyl group bonded to a phosphate, $RCO_2PO_3^{2-}$.

Acylation | The introduction of an acyl group, −COR, onto a molecule. For example, acylation of an alcohol yields an ester, acylation of an amine yields an amide, and acylation of an aromatic ring yields an alkyl aryl ketone.

Acylium ion | A resonance-stabilized carbocation in which the positive charge is located at a carbonyl-group carbon, R–C+═O ↔ R–C≡O+. Acylium ions are intermediates in Friedel–Crafts acylation reactions.

Adams' catalyst | The PtO_2 catalyst used for alkene hydrogenations.

Addition reactions | Occur when two reactants add together to form a single product with no atoms left over.

Adrenocortical hormones | Steroid hormones secreted by the adrenal glands. There are two types of these hormones: mineralocorticoids and glucocorticoids.

Alcohols | A class of compounds with an −OH group bonded to a saturated, sp^3-hybridized carbon, ROH.

Aldaric acid | The dicarboxylic acid resulting from oxidation of an aldose.

Aldehydes (RCHO) | A class of compounds containing the −CHO functional group.

Alditol | The polyalcohol resulting from reduction of the carbonyl group of a sugar.

Aldol reaction | The carbonyl condensation reaction of an aldehyde or ketone to give a *β*-hydroxy carbonyl compound.

Aldonic acids | Monocarboxylic acids resulting from oxidation of the −CHO group of an aldose.

Aldoses | A type of carbohydrate with an aldehyde functional group.

Alicyclic | A nonaromatic cyclic hydrocarbon such as a cycloalkane or cycloalkene.

Aliphatic | A nonaromatic hydrocarbon such as a simple alkane, alkene, or alkyne.

Alkaloids | Naturally occurring organic bases, such as morphine.

Alkanes | A class of compounds of carbon and hydrogen that contains only single bonds.

Alkene | A hydrocarbon that contains a carbon–carbon double bond, R2C═CR2R2C═CR2.

Alkoxide ion | The anion formed by deprotonation of an alcohol.

Alkoxymercuration | A method for synthesizing ethers by mercuric-ion catalyzed addition of an alcohol to an alkene followed by demercuration on treatment with $NaBH_4$.

Alkyl group | The partial structure that remains when a hydrogen atom is removed from an alkane.

Alkyl halide | A compound with a halogen atom bonded to a saturated, sp^3-hybridized carbon atom.

Alkylamines | Amino-substituted alkanes RNH_2, R_2NH, or R_3N.

Alkylation | Introduction of an alkyl group onto a molecule. For example, aromatic rings can be alkylated to yield arenes, and enolate anions can be alkylated to yield *α*-substituted carbonyl compounds.

Alkyne | A hydrocarbon that contains a carbon–carbon triple bond, CRRC≡CR.

Allyl group | A H2C═CHCH2−H2C═CHCH2− substituent.

Allylic | The position next to a double bond. For example, H2C═CHCH2BrH2C═CHCH2Br is an allylic bromide.

Amides | A class of compounds containing the $-CONR_2$ functional group.

Amidomalonate synthesis | A method for preparing *α*-amino acids by alkylation of diethyl amidomalonate with an alkyl halide followed by deprotection and decarboxylation.

Amines | A class of compounds containing one or more organic substituents bonded to a nitrogen atom, RNH_2, R_2NH, or R_3N.

Amino acid | *See* *α*-Amino acid.

Amino sugar | A sugar with one of its −OH groups replaced by $-NH_2$.

Amphiprotic | Capable of acting either as an acid or as a base. Amino acids are amphiprotic.

Amplitude | The height of a wave measured from the midpoint to the maximum. The intensity of radiant energy is proportional to the square of the wave's amplitude.

Anabolic steroids | Synthetic androgens that mimic the tissue-building effects of natural testosterone.

Anabolism | The group of metabolic pathways that build up larger molecules from smaller ones.

Androgen | A male steroid sex hormone.

Angle strain | The strain introduced into a molecule when a bond angle is deformed from its ideal value. Angle strain is particularly important in small-ring cycloalkanes, where it results from compression of bond angles to less than their ideal tetrahedral values.

Annulation | The building of a new ring onto an existing molecule.

Anomeric center | The hemiacetal carbon atom in the cyclic pyranose or furanose form of a sugar.

Anomers | Cyclic stereoisomers of sugars that differ only in their configuration at the hemiacetal (anomeric) carbon.

Antarafacial | A pericyclic reaction that takes place on opposite faces of the two ends of a \pi electron system.

Anti conformation | The geometric arrangement around a carbon–carbon single bond in which the two largest substituents are 180° apart as viewed in a Newman projection.

Anti periplanar | Describing the stereochemical relationship in which two bonds on adjacent carbons lie in the same plane at an angle of 180°.

Anti stereochemistry | The opposite of syn. An anti addition reaction is one in which the two ends of the double bond are attacked from different sides. An anti elimination reaction is one in which the two groups leave from opposite sides of the molecule.

Antiaromatic | Referring to a planar, conjugated molecule with $4n$ π electrons. Delocalization of the \pi electrons leads to an increase in energy.

Antibonding MO | A molecular orbital that is higher in energy than the atomic orbitals from which it is formed.

Anticodon | A sequence of three bases on tRNA that reads the codons on mRNA and brings the correct amino acids into position for protein synthesis.

Antisense strand | The template, noncoding strand of double-helical DNA that does not contain the gene.

Arene | An alkyl-substituted benzene.

Arenediazonium salt | An aromatic compound Ar–N+≡N X−; used in the Sandmeyer reaction.

Aromaticity | The special characteristics of cyclic conjugated molecules, including unusual stability and a tendency to undergo substitution reactions rather than addition reactions on treatment with electrophiles. Aromatic molecules are planar, cyclic, conjugated species with $4n + 2$ \pi electrons.

Arylamines | Amino-substituted aromatic compounds, $ArNH_2$.

Atactic | A chain-growth polymer in which the stereochemistry of the substituents is oriented randomly along the backbone.

Atomic mass | The weighted average mass of an element's naturally occurring isotopes.

Atomic number | The number of protons in the nucleus of an atom.

ATZ Derivative | An anilinothiazolinone, formed from an amino acid during Edman degradation of a peptide.

Aufbau principle | The rules for determining the electron configuration of an atom.

Axial bonds | Bonds or positions in chair cyclohexane that lie along the ring axis, perpendicular to the rough plane of the ring.

Azide synthesis | A method for preparing amines by S_N2 reaction of an alkyl halide with azide ion, followed by reduction.

Azo compounds | A class of compounds with the general structure \ce{R–N=N–R'}.

Backbone | The continuous chain of atoms running the length of a protein or other polymer.

Base peak | The most intense peak in a mass spectrum.

Basicity constant | A measure of base strength in water. For any base B, the basicity constant is given by the expression H2O ⇄ BH+ + OH–Kb = [BH+] [OH–] [B]B + H2O ⇄ BH+ + OH–Kb = [BH+] [OH–][B]

Bent bonds | The bonds in small rings such as cyclopropane that bend away from the internuclear line and overlap at a slight angle, rather than head-on. Bent bonds are highly strained and highly reactive.

Benzoyl | The \ce{C6H5CO−} group.

Benzyl | The \ce{C6H5CH2−} group.

Benzylic | The position next to an aromatic ring.

Benzyne | An unstable compound having a triple bond in a benzene ring.

Betaine | A neutral dipolar molecule with nonadjacent positive and negative charges. For example, the adduct of a Wittig reagent with a carbonyl compound is a betaine.

Bicycloalkane | A cycloalkane that contains two rings.

Bimolecular reaction | A reaction whose rate-limiting step occurs between two reactants.

Block copolymers | Polymers in which different blocks of identical monomer units alternate with one another.

Boat cyclohexane | A conformation of cyclohexane that bears a slight resemblance to a boat. Boat cyclohexane has no angle strain but has a large number of eclipsing interactions that make it less stable than chair cyclohexane.

Boc derivative | A butyloxycarbonyl N-protected amino acid.

Bond angle | The angle formed between two adjacent bonds.

Bond dissociation energy | The amount of energy needed to break a bond and produce two radical fragments.

Bond length | The equilibrium distance between the nuclei of two atoms that are bonded to each other.

Bond strength | An alternative name for bond dissociation energy.

Bonding MO | A molecular orbital that is lower in energy than the atomic orbitals from which it is formed.

Branched-chain alkanes | Alkanes that contain a branching connection of carbons as opposed to straight-chain alkanes.

Bridgehead | An atom that is shared by more than one ring in a polycyclic molecule.

Bromohydrin | A 1,2-bromoalcohol; obtained by addition of HOBr to an alkene.

Bromonium ion | A species with a divalent, positively charged bromine, R_2Br^+.

Brønsted–Lowry acid | A substance that donates a hydrogen ion (proton; H^+) to a base.

Brønsted–Lowry base | A substance that accepts H^+ from an acid.

C-terminal amino acid | The amino acid with a free $-CO_2H$ group at the end of a protein chain.

Cahn–Ingold–Prelog sequence rules | A series of rules for assigning relative rankings to substituent groups on a chirality center or a double-bond carbon atom.

Cannizzaro reaction | The disproportionation reaction of an aldehyde on treatment with base to yield an alcohol and a carboxylic acid.

Carbanion | A carbon anion, or substance that contains a trivalent, negatively charged carbon atom ($R_3C:^-$). Alkyl carbanions are sp^3-hybridized and have eight electrons in the outer shell of the negatively charged carbon.

Carbene | A neutral substance that contains a divalent carbon atom having only six electrons in its outer shell ($R_2C:$).

Carbinolamine | A molecule that contains the $R_2C(OH)NH_2$ functional group. Carbinolamines are produced as intermediates during the nucleophilic addition of amines to carbonyl compounds.

Carbocation | A carbon cation, or substance that contains a trivalent, positively charged carbon atom having six electrons in its outer shell (R_3C^+).

Carbohydrates | Polyhydroxy aldehydes or ketones. Carbohydrates can be either simple sugars, such as glucose, or complex sugars, such as cellulose.

Carbonyl condensation reactions | A type of reaction that joins two carbonyl compounds together by a combination of α-substitution and nucleophilic addition reactions.

Carbonyl group | The \ce{C=O} functional group.

Carboxyl group | The $-CO_2H$ functional group.

Carboxylation | The addition of CO_2 to a molecule.

Carboxylic acid derivative | A compound in which an acyl group is bonded to an electronegative atom or substituent that can act as a leaving group in a substitution reaction. Esters, amides, and acid halides are examples.

Carboxylic acids | Compounds containing the $-CO_2H$ functional group.

Catabolism | The group of metabolic pathways that break down larger molecules into smaller ones.

Catalyst | A substance that increases the rate of a chemical transformation by providing an alternative mechanism but is not itself changed in the reaction.

Cation radical | A reactive species, typically formed in a mass spectrometer by loss of an electron from a neutral molecule and having both a positive charge and an odd number of electrons.

Chain reaction | A reaction that, once initiated, sustains itself in an endlessly repeating cycle of propagation steps. The radical chlorination of alkanes is an example of a chain reaction that is initiated by irradiation with light and then continues in a series of propagation steps.

Chain-growth polymers | Polymers whose bonds are produced by chain reaction mechanisms. Polyethylene and other alkene polymers are examples.

Chair conformation | A three-dimensional conformation of cyclohexane that resembles the rough shape of a chair. The chair form of cyclohexane is the lowest-energy conformation of the molecule.

Chemical shift | The position on the NMR chart where a nucleus absorbs. By convention, the chemical shift of tetramethylsilane (TMS) is set at zero, and all other absorptions usually occur downfield (to the left on the chart). Chemical shifts are expressed in delta units (δ), where 1 δ equals 1 ppm of the spectrometer operating frequency.

Chiral | Having handedness. Chiral molecules are those that do not have a plane of symmetry and are therefore not superimposable on their mirror image. A chiral molecule thus exists in two forms, one right-handed and one left-handed. The most common cause of chirality in a molecule is the presence of a carbon atom that is bonded to four different substituents.

Chiral environment | The chiral surroundings or conditions in which a molecule resides.

Chirality center | An atom (usually carbon) that is bonded to four different groups.

Chlorohydrin | A 1,2-chloroalcohol; obtained by addition of HOCl to an alkene.

Chromatography | A technique for separating a mixture of compounds into pure components. Different compounds adsorb to a stationary support phase and are then carried along it at different rates by a mobile phase.

Cis–trans isomers | Stereoisomers that differ in their stereochemistry about a ring or double bond.

Citric acid cycle | The metabolic pathway by which acetyl CoA is degraded to CO_2.

Claisen condensation reaction | The carbonyl condensation reaction of two ester molecules to give a β-keto ester product.

Claisen rearrangement | The pericyclic conversion of an allyl phenyl ether to an *o*-allylphenol or an allyl vinyl ether to a γ,δ-unsaturated ketone by heating.

Coding strand | The sense strand of double-helical DNA that contains the gene.

Codon | A three-base sequence on a messenger RNA chain that encodes the genetic information necessary to cause a specific amino acid to be incorporated into a protein. Codons on mRNA are read by complementary anticodons on tRNA.

Coenzyme | A small organic molecule that acts as a cofactor in a biological reaction.

Cofactor | A small nonprotein part of an enzyme that is necessary for biological activity.

Combinatorial chemistry | A procedure in which anywhere from a few dozen to several hundred thousand substances are prepared simultaneously.

Complex carbohydrates | Carbohydrates that are made of two or more simple sugars linked together by glycoside bonds.

Concerted reaction | A reaction that takes place in a single step without intermediates. For example, the Diels–Alder cycloaddition reaction is a concerted process.

Condensed structures | A shorthand way of writing structures in which carbon–hydrogen and carbon–carbon bonds are understood rather than shown explicitly. Propane, for example, has the condensed structure $CH_3CH_2CH_3$.

Configuration | The three-dimensional arrangement of atoms bonded to a chirality center.

Conformational analysis | A means of assessing the energy of a substituted cycloalkane by totaling the steric interactions present in the molecule.

Conformations | The three-dimensional shape of a molecule at any given instant, assuming that rotation around single bonds is frozen.

Conformers | Conformational isomers.

Conjugate acid | The product that results from protonation of a Brønsted–Lowry base.

Conjugate addition | Addition of a nucleophile to the β carbon atom of an α,β-unsaturated carbonyl compound.

Conjugate base | The product that results from deprotonation of a Brønsted–Lowry acid.

Conjugation | A series of overlapping *p* orbitals, usually in alternating single and multiple bonds. For example, 1,3-butadiene is a conjugated diene, 3-buten-2-one is a conjugated enone, and benzene is a cyclic conjugated triene.

Conrotatory | A term used to indicate that *p* orbitals must rotate in the same direction during electrocyclic ring-opening or ring-closure.

Constitutional isomers | Isomers that have their atoms connected in a different order. For example, butane and 2-methylpropane are constitutional isomers.

Cope rearrangement | The sigmatropic rearrangement of a 1,5-hexadiene.

Copolymers | Polymers obtained when two or more different monomers are allowed to polymerize together.

Coupled reactions | Two reactions that share a common intermediate so that the energy released in the favorable step allows the unfavorable step to occur.

Coupling constant | The magnitude (expressed in hertz) of the interaction between nuclei whose spins are coupled.

Covalent bond | A bond formed by sharing electrons between atoms.

Cracking | A process used in petroleum refining in which large alkanes are thermally cracked into smaller fragments.

Crown ethers | Large-ring polyethers; used as phase-transfer catalysts.

Crystallites | Highly ordered crystal-like regions within a long polymer chain.

Curtius rearrangement | The conversion of an acid chloride into an amine by reaction with azide ion, followed by heating with water.

Cyanohydrins | A class of compounds with an −OH group and a −CN group bonded to the same carbon atom; formed by addition of HCN to an aldehyde or ketone.

Cycloaddition reaction | A pericyclic reaction in which two reactants add together in a single step to yield a cyclic product. The Diels–Alder reaction between a diene and a dienophile to give a cyclohexene is an example.

Cycloalkane | An alkane that contains a ring of carbons.

d | The racemic mixture of a chiral compound.

D Sugars | Sugars whose hydroxyl group at the chirality center farthest from the carbonyl group has the same configuration as D-glyceraldehyde and points to the right when drawn in Fischer projection.

Deactivating groups | Electron-withdrawing substituents that decrease the reactivity of an aromatic ring toward electrophilic aromatic substitution.

Deamination | The removal of an amino group from a molecule, as occurs with amino acids during metabolic degradation.

Debyes (D) | Units for measuring dipole moments; 1 D = 3.336×10^{-30} coulomb meter (C · m).

Decarboxylation | The loss of carbon dioxide from a molecule. β-Keto acids decarboxylate readily on heating.

Degenerate orbitals | Two or more orbitals that have the same energy level.

Degree of unsaturation | The number of rings and/or multiple bonds in a molecule.

Dehydration | The loss of water from an alcohol to yield an alkene.

Dehydrohalogenation | The loss of HX from an alkyl halide. Alkyl halides undergo dehydrohalogenation to yield alkenes on treatment with strong base.

Delocalization | A spreading out of electron density over a conjugated \pi electron system. For example, allylic cations and allylic anions are delocalized because their charges are spread out over the entire \pi electron system. Aromatic compounds have $4n + 2$ \pi electrons delocalized over their ring.

Delta (δ) scale | An arbitrary scale used to calibrate NMR charts. One delta unit (δ) is equal to 1 part per million (ppm) of the spectrometer operating frequency.

Denatured | The physical changes that occur in a protein when secondary and tertiary structures are disrupted.

Deoxy sugar | A sugar with one of its −OH groups replaced by an −H.

Deoxyribonucleic acid (DNA) | The biopolymer consisting of deoxyribonucleotide units linked together through phosphate–sugar bonds. Found in the nucleus of cells, DNA contains an organism's genetic information.

Deoxyribonucleic acid (DNA) | Chemical carriers of a cell's genetic information.

DEPT-NMR | An NMR method for distinguishing among signals due to CH_3, CH_2, CH, and quaternary carbons. That is, the number of hydrogens attached to each carbon can be determined.

Deshielding | An effect observed in NMR that causes a nucleus to absorb toward the left (downfield) side of the chart. Deshielding is caused by a withdrawal of electron density from the nucleus.

Dess–Martin periodinane | An iodine-based reagent commonly used for the laboratory oxidation of a primary alcohol to an aldehyde or a secondary alcohol to a ketone.

Deuterium isotope effect | A tool used in mechanistic investigations to establish whether a C−H bond is broken in the rate-limiting step of a reaction.

Dextrorotatory | A word used to describe an optically active substance that rotates the plane of polarization of plane-polarized light in a right-handed (clockwise) direction.

Diastereomers | Non–mirror-image stereoisomers; diastereomers have the same configuration at one or more chirality centers but differ at other chirality centers.

Diastereotopic | Hydrogens in a molecule whose replacement by some other group leads to different diastereomers.

Diazonium salts | A type of compound with the general structure \ce{RN2^{+} X^{−}}.

Diazotization | The conversion of a primary amine, RNH_2, into a diazonium ion, RN_2^+, by treatment with nitrous acid.

Dieckmann cyclization reaction | An intramolecular Claisen condensation reaction of a diester to give a cyclic β-keto ester.

Diels–Alder reaction | The cycloaddition reaction of a diene with a dienophile to yield a cyclohexene.

Dienophile | A compound containing a double bond that can take part in the Diels–Alder cycloaddition reaction. The most reactive dienophiles are those that have electron-withdrawing groups on the double bond.

Digestion | The first stage of catabolism, in which food is broken down by hydrolysis of ester, glycoside (acetal), and peptide (amide) bonds to yield fatty acids, simple sugars, and amino acids.

Dihedral angle | The angle between two bonds on adjacent carbons as viewed along the C−C bond.

Dipole moment | A measure of the net polarity of a molecule. A dipole moment arises when the centers of mass of positive and negative charges within a molecule do not coincide.

Dipole–dipole forces | Noncovalent electrostatic interactions between dipolar molecules.

Disaccharide | A carbohydrate formed by linking two simple sugars through an acetal bond.

Dispersion forces | Noncovalent interactions between molecules that arise because of constantly changing electron distributions within the molecules.

Disrotatory | A term used to indicate that *p* orbitals rotate in opposite directions during electrocyclic ring-opening or ring-closing reactions.

Disulfides (RSSR′) | A class of compounds of the general structure RSSR′.

Double bond | A covalent bond formed by sharing two electron pairs between atoms.

Double helix | The structure of DNA in which two polynucleotide strands coil around each other.

Doublet | A two-line NMR absorption caused by spin–spin splitting when the spin of the nucleus under observation couples with the spin of a neighboring magnetic nucleus.

Downfield | Referring to the left-hand portion of the NMR chart.

***E* geometry** | A term used to describe the stereochemistry of a carbon–carbon double bond. The two groups on each carbon are ranked according to the Cahn–Ingold–Prelog sequence rules, and the two carbons are compared. If the higher-ranked groups on each carbon are on opposite sides of the double bond, the bond has *E* geometry.

E1 reaction | A unimolecular elimination reaction in which the substrate spontaneously dissociates to give a carbocation intermediate, which loses a proton in a separate step.

E1cB reaction | A unimolecular elimination reaction in which a proton is first removed to give a carbanion intermediate, which then expels the leaving group in a separate step.

E2 reaction | A bimolecular elimination reaction in which C−H and C−X bond cleavages are simultaneous.

Eclipsed conformation | The geometric arrangement around a carbon–carbon single bond in which the bonds to substituents on one carbon are parallel to the bonds to substituents on the neighboring carbon as viewed in a Newman projection.

Eclipsing strain | The strain energy in a molecule caused by electron repulsions between eclipsed bonds. Eclipsing strain is also called torsional strain.

Edman degradation | A method for N-terminal sequencing of peptide chains by treatment with *N*-phenylisothiocyanate.

Eicosanoid | A lipid derived biologically from 5,8,11,14-eicosatetraenoic acid, or arachidonic acid. Prostaglandins, thromboxanes, and leukotrienes are examples.

Elastomer | An amorphous polymer that has the ability to stretch out and spring back to its original shape.

Electrocyclic reaction | A unimolecular pericyclic reaction in which a ring is formed or broken by a concerted reorganization of electrons through a cyclic transition state. For example, the cyclization of 1,3,5-hexatriene to yield 1,3-cyclohexadiene is an electrocyclic reaction.

Electromagnetic spectrum | The range of electromagnetic energy, including infrared, ultraviolet, and visible radiation.

Electron configuration | A list of the orbitals occupied by electrons in an atom.

Electron shells | A group of an atom's electrons with the same principal quantum number.

Electron-dot structure | A representation of a molecule showing valence electrons as dots.

Electron-transport chain | The final stage of catabolism in which ATP is produced.

Electronegativity (EN) | The ability of an atom to attract electrons in a covalent bond. Electronegativity increases across the periodic table from left to right and from bottom to top.

Electrophile | An "electron-lover," or substance that accepts an electron pair from a nucleophile in a polar bond-forming reaction.

Electrophilic addition reactions | Addition of an electrophile to a carbon–carbon double bond to yield a saturated product.

Electrophilic aromatic substitution reaction | A reaction in which an electrophile (E^+) reacts with an aromatic ring and substitutes for one of the ring hydrogens.

Electrophoresis | A technique used for separating charged organic molecules, particularly proteins and DNA fragments. The mixture to be separated is placed on a buffered gel or paper, and an electric potential is applied across the ends of the apparatus. Negatively charged molecules migrate toward the positive electrode, and positively charged molecules migrate toward the negative electrode.

Electrostatic potential maps | Molecular representations that use color to indicate the charge distribution in molecules as derived from quantum-mechanical calculations.

Elimination reactions | What occurs when a single reactant splits into two products.

Elution | The passage of a substance from a chromatography column.

Embden–Meyerhof pathway | An alternative name for glycolysis.

Enamines | Compounds with the $\ce{R2N–CR=CR2}$ functional group.

Enantiomers | Stereoisomers of a chiral substance that have a mirror-image relationship. Enantiomers have opposite configurations at all chirality centers.

Enantioselective synthesis | A reaction method that yields only a single enantiomer of a chiral product starting from an achiral reactant.

Enantiotopic | Hydrogens in a molecule whose replacement by some other group leads to different enantiomers.

Endergonic | A reaction that has a positive free-energy change and is therefore nonspontaneous. In an energy diagram, the product of an endergonic reaction has a higher energy level than the reactants.

Endo | A term indicating the stereochemistry of a substituent in a bridged bicycloalkane. An endo substituent is syn to the larger of the two bridges.

Endothermic | A reaction that absorbs heat and therefore has a positive enthalpy change.

Energy diagram | A representation of the course of a reaction, in which free energy is plotted as a function of reaction progress. Reactants, transition states, intermediates, and products are represented, and their appropriate energy levels are indicated.

Enol | A vinylic alcohol that is in equilibrium with a carbonyl compound, $\ce{C=C–}$.

Enolate ion | The anion of an enol, $\ce{C=C–O^{-}}$.

Enthalpy change (ΔH) | The heat of reaction. The enthalpy change that occurs during a reaction is a measure of the difference in total bond energy between reactants and products.

Entropy change (ΔS) | The change in amount of molecular randomness. The entropy change that occurs during a reaction is a measure of the difference in randomness between reactants and products.

Enzyme | A biological catalyst. Enzymes are large proteins that catalyze specific biochemical reactions.

Epimers | Diastereomers that differ in configuration at only one chirality center but are the same at all others.

Epoxide | A three-membered-ring ether functional group.

Equatorial bonds | Bonds or positions in chair cyclohexane that lie along the rough equator of the ring.

ESI | Electrospray ionization; a "soft" ionization method used for mass spectrometry of biological samples of very high molecular weight.

Essential amino acid | One of nine amino acids that are biosynthesized only in plants and microorganisms and must be obtained by humans in the diet.

Essential monosaccharide | One of eight simple sugars that is best obtained in the diet rather than by biosynthesis.

Essential oil | The volatile oil obtained by steam distillation of a plant extract.

Esters | A class of compounds containing the $-CO_2R$ functional group.

Estrogens | Female steroid sex hormones.

Ethers | A class of compounds that has two organic substituents bonded to the same oxygen atom, ROR′.

Exergonic | A reaction that has a negative free-energy change and is therefore spontaneous. On an energy diagram, the product of an exergonic reaction has a lower energy level than that of the reactants.

Exo | A term indicating the stereochemistry of a substituent in a bridged bicycloalkane. An exo substituent is anti to the larger of the two bridges.

Exon | A section of DNA that contains genetic information.

Exothermic | A reaction that releases heat and therefore has a negative enthalpy change.

Fats | Solid triacylglycerols derived from an animal source.

Fatty acids | A long, straight-chain carboxylic acid found in fats and oils.

Fiber | A thin thread produced by extruding a molten polymer through small holes in a die.

Fibrous proteins | A type of protein that consists of polypeptide chains arranged side by side in long threads. Such proteins are tough, insoluble in water, and used in nature for structural materials such as hair, hooves, and fingernails.

Fingerprint region | The complex region of the infrared spectrum from 1500–400 cm^{-1}.

First-order reaction | Designates a reaction whose rate-limiting step is unimolecular and whose kinetics therefore depend on the concentration of only one reactant.

Fischer esterification reaction | The acid-catalyzed nucleophilic acyl substitution reaction of a carboxylic acid with an alcohol to yield an ester.

Fischer projections | A means of depicting the absolute configuration of a chiral molecule on a flat page. A Fischer projection uses a cross to represent the chirality center. The horizontal arms of the cross represent bonds coming out of the plane of the page, and the vertical arms of the cross represent bonds going back into the plane of the page.

Fmoc derivative | A fluorenylmethyloxycarbonyl N-protected amino acid.

Formal charges | The difference in the number of electrons owned by an atom in a molecule and by the same atom in its elemental state.

Formyl | A −CHO group.

Frequency | The number of electromagnetic wave cycles that travel past a fixed point in a given unit of time. Frequencies are expressed in units of cycles per second, or hertz.

Friedel–Crafts reaction | An electrophilic aromatic substitution reaction to alkylate or acylate an aromatic ring.

Frontier orbitals | The highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbitals.

FT-NMR | Fourier-transform NMR; a rapid technique for recording NMR spectra in which all magnetic nuclei absorb at the same time.

Functional | An atom or group of atoms that is part of a larger molecule and has a characteristic chemical reactivity.

Functional RNAs | An alternative name for small RNAs.

Furanose | The five-membered-ring form of a simple sugar.

Gabriel amine synthesis | A method for preparing an amine by S_N2 reaction of an alkyl halide with potassium phthalimide, followed by hydrolysis.

Gauche conformation | The conformation of butane in which the two methyl groups lie 60° apart as viewed in a Newman projection. This conformation has 3.8 kJ/mol steric strain.

Geminal | Referring to two groups attached to the same carbon atom. For example, the hydrate formed by nucleophilic addition of water to an aldehyde or ketone is a geminal diol.

Gibbs free-energy change (ΔG) | The free-energy change that occurs during a reaction, given by the equation $\Delta G=\Delta H-T\Delta S$. A reaction with a negative free-energy change is spontaneous, and a reaction with a positive free-energy change is nonspontaneous.

Gilman reagent (LiR_2Cu) | A diorganocopper reagent.

Glass transition temperature | The temperature at which a hard, amorphous polymer becomes soft and flexible.

Globular proteins | A type of protein that is coiled into a compact, nearly spherical shape. Globular proteins, which are generally water-soluble and mobile within the cell, are the structural class to which enzymes belong.

Gluconeogenesis | The anabolic pathway by which organisms make glucose from simple three-carbon precursors.

Glycal | An unsaturated sugar with a C1–C2 double bond.

Glycal assembly method | A method for linking monosaccharides together to synthesize polysaccharides.

Glycerophospholipids | Lipids that contain a glycerol backbone linked to two fatty acids and a phosphoric acid.

Glycoconjugate | A molecule in which a carbohydrate is linked through its anomeric center to another biological molecule such as a lipid or protein.

Glycol | A diol, such as ethylene glycol, $HOCH_2CH_2OH$.

Glycolipid | A biological molecule in which a carbohydrate is linked through a glycoside bond to a lipid.

Glycolysis | A series of ten enzyme-catalyzed reactions that break down glucose into 2 equivalents of pyruvate, $CH_3COCO_2^-$.

Glycoprotein | A biological molecule in which a carbohydrate is linked through a glycoside bond to a protein.

Glycoside | A cyclic acetal formed by reaction of a sugar with another alcohol.

Graft copolymers | Copolymers in which homopolymer branches of one monomer unit are "grafted" onto a homopolymer chain of another monomer unit.

Green chemistry | The design and implementation of chemical products and processes that reduce waste and minimize or eliminate the generation of hazardous substances.

Grignard reagent (RMgX) | An organomagnesium halide.

Ground-state electron configuration | The most stable, lowest-energy electron configuration of a molecule or atom.

Haloform reaction | The reaction of a methyl ketone with halogen and base to yield a haloform (CHX_3) and a carboxylic acid.

Halogenation | The reaction of halogen with an alkene to yield a 1,2-dihalide addition product or with an aromatic compound to yield a substitution product.

Halohydrin | A 1,2-haloalcohol, such as that obtained on addition of HOBr to an alkene.

Halonium ion | A species containing a positively charged, divalent halogen. Three-membered-ring bromonium ions are intermediates in the electrophilic addition of Br_2 to alkenes.

Hammond postulate | A postulate stating that we can get a picture of what a given transition state looks like by looking at the structure of the nearest stable species. Exergonic reactions have transition states that resemble reactant; endergonic reactions have transition states that resemble product.

Heat of combustion | The amount of heat released when a compound burns completely in oxygen.

Heat of hydrogenation | The amount of heat released when a carbon–carbon double bond is hydrogenated.

Heat of reaction | An alternative name for the enthalpy change in a reaction, ΔH.

Hell–Volhard–Zelinskii (HVZ) reaction | The reaction of a carboxylic acid with Br_2 and phosphorus to give an α-bromo carboxylic acid.

Hemiacetal | A functional group having one −OR and one −OH group bonded to the same carbon.

Henderson–Hasselbalch equation | An equation for determining the extent of dissociation of a weak acid at various pH values.

Hertz | A unit of measure of electromagnetic frequency, the number of waves that pass by a fixed point per second.

Heterocycle | A cyclic molecule whose ring contains more than one kind of atom. For example, pyridine is a heterocycle that contains five carbon atoms and one nitrogen atom in its ring.

Heterolytic bond breakage | The kind of bond-breaking that occurs in polar reactions when one fragment leaves with both of the bonding electrons: $A:B \rightarrow A^+ + B:^-$.

Highest occupied molecular orbital (HOMO) | The symmetries of the HOMO and LUMO are important in pericyclic reactions.

Hofmann elimination reaction | The elimination reaction of an amine to yield an alkene by reaction with iodomethane followed by heating with Ag_2O.

Hofmann rearrangement | The conversion of an amide into an amine by reaction with Br_2 and base.

Homolytic bond breakage | The kind of bond-breaking that occurs in radical reactions when each fragment leaves with one bonding electron: $A:B \rightarrow A^+ + B:^-$.

Homopolymers | A polymer made up of identical repeating units.

Homotopic | Hydrogens in a molecule that give the identical structure on replacement by X and thus show identical NMR absorptions.

Hormones | Chemical messengers that are secreted by an endocrine gland and carried through the bloodstream to a target tissue.

HPLC | High-pressure liquid chromatography; a variant of column chromatography using high pressure to force solvent through very small absorbent particles.

Hund's rule | If two or more empty orbitals of equal energy are available, one electron occupies each, with their spins parallel, until all are half-full.

Hybrid orbital | An orbital derived from a combination of atomic orbitals. Hybrid orbitals, such as the sp^3, sp^2, and sp hybrids of carbon, are strongly directed and form stronger bonds than atomic orbitals do.

Hydration | Addition of water to a molecule, such as occurs when alkenes are treated with aqueous sulfuric acid to give alcohols.

Hydride shift | The shift of a hydrogen atom and its electron pair to a nearby cationic center.

Hydroboration | Addition of borane (BH_3) or an alkylborane to an alkene. The resultant trialkylborane products can be oxidized to yield alcohols.

Hydrocarbons | A class of compounds that contain only carbon and hydrogen.

Hydrogen bond | A weak attraction between a hydrogen atom bonded to an electronegative atom and an electron lone pair on another electronegative atom.

Hydrogenated | Addition of hydrogen to a double or triple bond to yield a saturated product.

Hydrogenolysis | Cleavage of a bond by reaction with hydrogen. Benzylic ethers and esters, for instance, are cleaved by hydrogenolysis.

Hydrophilic | Water-loving; attracted to water.

Hydrophobic | Water-fearing; repelled by water.

Hydroquinones | 1,4-dihydroxybenzene.

Hydroxylation | Addition of two −OH groups to a double bond.

Hyperconjugation | An electronic interaction that results from overlap of a vacant p orbital on one atom with a neighboring C−H σ bond. Hyperconjugation is important in stabilizing carbocations and substituted alkenes.

Hückel $4n + 2$ rule | A rule stating that monocyclic conjugated molecules having $4n + 2$ \pi electrons (n = an integer) are aromatic.

Imide | A compound with the −CONHCO− functional group.

Imines | A class of compounds with the R2C═NR functional group.

Inductive effect | The electron-attracting or electron-withdrawing effect transmitted through σ bonds. Electronegative elements have an electron-withdrawing inductive effect.

Infrared (IR) spectroscopy | A kind of optical spectroscopy that uses infrared energy. IR spectroscopy is particularly useful in organic chemistry for determining the kinds of functional groups present in molecules.

Initiator | A substance that is used to initiate a radical chain reaction or polymerization. For example, radical chlorination of alkanes is initiated when light energy breaks the weak Cl−Cl bond to form Cl · radicals.

Integrating | A technique for measuring the area under an NMR peak to determine the relative number of each kind of proton in a molecule.

Intermediate | A species that is formed during the course of a multistep reaction but is not the final product. Intermediates are more stable than transition states but may or may not be stable enough to isolate.

Intramolecular | A reaction that occurs within the same molecule is intramolecular; a reaction that occurs between two molecules is intermolecular.

Intron | A section of DNA that does not contain genetic information.

Ion pairs | A loose association between two ions in solution. Ion pairs are implicated as intermediates in S_N1 reactions to account for the partial retention of stereochemistry that is often observed.

Ionic bond | The electrostatic attraction between ions of unlike charge.

Isoelectric point (p*I*) | The pH at which the number of positive charges and the number of negative charges on a protein or an amino acid are equal.

Isomers | Compounds that have the same molecular formula but different structures.

Isoprene rule | An observation to the effect that terpenoids appear to be made up of isoprene (2-methyl-1,3-butadiene) units connected head-to-tail.

Isotactic | A chain-growth polymer in which the stereochemistry of the substituents is oriented regularly along the backbone.

Isotopes | Atoms of the same element that have different mass numbers.

IUPAC system of nomenclature | Rules for naming compounds, devised by the International Union of Pure and Applied Chemistry.

Kekulé structure | An alternative name for a line-bond structure, which represents a molecule by showing covalent bonds as lines between atoms.

Ketals | An alternative name for acetals derived from a ketone rather than an aldehyde and consisting of two −OR groups bonded to the same carbon, $R_2C(OR')_2$. Ketals are often used as protecting groups for ketones.

Ketones (R_2CO) | A class of compounds with two organic substituents bonded to a carbonyl group, R2C ═O.

Ketoses | Carbohydrates with a ketone functional group.

Keto–enol tautomerism | The equilibration between a carbonyl form and vinylic alcohol form of a molecule.

Kiliani–Fischer synthesis | A method for lengthening the chain of an aldose sugar.

Kinetic control | A reaction that follows the lowest activation energy pathway is said to be kinetically controlled. The product is the most rapidly formed but is not necessarily the most stable.

Kinetics | Referring to reaction rates. Kinetic measurements are useful for helping to determine reaction mechanisms.

Koenigs–Knorr reaction | A method for the synthesis of glycosides by reaction of an alcohol with a pyranosyl bromide.

Krebs cycle | An alternative name for the citric acid cycle, by which acetyl CoA is degraded to CO_2.

L Sugar | A sugar whose hydroxyl group at the chirality center farthest from the carbonyl group points to the left when drawn in Fischer projection.

Lactams | Cyclic amides.

Lactones | Cyclic esters.

Lagging strand | The complement of the original 3′ → 5′ DNA strand that is synthesized discontinuously in small pieces that are subsequently linked by DNA ligases.

LD50 | The amount of a substance per kilogram body weight that is lethal to 50% of test animals.

LDA | Lithium diisopropylamide, $LiN(i\text{-}C_3H_7)_2$, a strong base commonly used to convert carbonyl compounds into their enolate ions.

Leading strand | The complement of the original 5′ → 3′ DNA strand that is synthesized continuously in a single piece.

Leaving group | The group that is replaced in a substitution reaction.

Levorotatory | An optically active substance that rotates the plane of polarization of plane-polarized light in a left-handed (counterclockwise) direction.

Lewis acid | A substance with a vacant low-energy orbital that can accept an electron pair from a base. All electrophiles are Lewis acids.

Lewis base | A substance that donates an electron lone pair to an acid. All nucleophiles are Lewis bases.

Lewis structures | Representations of molecules showing valence electrons as dots.

Lindlar catalyst | A hydrogenation catalyst used to convert alkynes to cis alkenes.

Line-bond structure | An alternative name for a Kekulé structure, which represents a molecule by showing covalent bonds as lines between atoms.

Lipid bilayer | The ordered lipid structure that forms a cell membrane.

Lipids | Naturally occurring substances isolated from cells and tissues by extraction with a nonpolar solvent. Lipids belong to many different structural classes, including fats, terpenoids, prostaglandins, and steroids.

Lipoprotein | A complex molecule with both lipid and protein parts that transports lipids through the body.

Locant | A number in a chemical name that locates the positions of the functional groups and substituents in the molecule.

Lone-pair electrons | Nonbonding valence-shell electron pairs. Lone-pair electrons are used by nucleophiles in their reactions with electrophiles.

Lowest unoccupied molecular orbital (LUMO) | The symmetries of the LUMO and the HOMO are important in determining the stereochemistry of pericyclic reactions.

Magnetic resonance imaging | A medical diagnostic technique based on nuclear magnetic resonance.

Magnetogyric ratio | A ratio of the isotope's magnetic moment to its angular momentum.

MALDI | Matrix-assisted laser desorption ionization; a soft ionization method used for mass spectrometry of biological samples of very high molecular weight.

Malonic ester synthesis | The synthesis of a carboxylic acid by alkylation of an alkyl halide with diethyl malonate, followed by hydrolysis and decarboxylation.

Markovnikov's rule | A guide for determining the regiochemistry (orientation) of electrophilic addition reactions. In the addition of HX to an alkene, the hydrogen atom bonds to the alkene carbon that has fewer alkyl substituents.

Mass number (*A*) | The total of protons plus neutrons in an atom.

Mass spectrometry (MS) | A technique for measuring the mass, and therefore the molecular weight (MW), of ions.

McLafferty rearrangement | A mass-spectral fragmentation pathway for carbonyl compounds.

Mechanism | A complete description of how a reaction occurs. A mechanism accounts for all starting materials and all products and describes the details of each individual step in the overall reaction process.

Meisenheimer complex | An intermediate formed by addition of a nucleophile to a halo-substituted aromatic ring.

Melt transition temperature | The temperature at which crystalline regions of a polymer melt to give an amorphous material.

Mercapto group | An alternative name for the thiol group, −SH.

Meso compounds | Compounds that contain chirality centers but are nevertheless achiral because they contain a symmetry plane.

Messenger RNA (mRNA) | A kind of RNA formed by transcription of DNA and used to carry genetic messages from DNA to ribosomes.

Meta (*m*) | A naming prefix used for 1,3-disubstituted benzenes.

Metabolism | A collective name for the many reactions that go on in the cells of living organisms.

Metallacycle | A cyclic compound that contains a metal atom in its ring.

Methylene group | A $-CH_2-$ or $=CH2$ group.

Micelles | Spherical clusters of soaplike molecules that aggregate in aqueous solution. The ionic heads of the molecules lie on the outside, where they are solvated by water, and the organic tails bunch together on the inside of the micelle.

Michael reaction | The conjugate addition reaction of an enolate ion to an unsaturated carbonyl compound.

Molar absorptivity (ε) | A quantitative measure of the amount of UV light absorbed by a sample.

Molecular ion | The cation produced in a mass spectrometer by loss of an electron from the parent molecule. The mass of the molecular ion corresponds to the molecular weight of the sample.

Molecular mechanics | A computer-based method for calculating the minimum-energy conformation of a molecule.

Molecular orbital (MO) theory | A description of covalent bond formation as resulting from a mathematical combination of atomic orbitals (wave functions) to form molecular orbitals.

Molecule | A neutral collection of atoms held together by covalent bonds.

Molozonide | The initial addition product of ozone with an alkene.

Monomers | The simple starting units from which polymers are made.

Monosaccharides | Simple sugars.

Monoterpenoids | Ten-carbon lipids.

Multiplet | A pattern of peaks in an NMR spectrum that arises by spin–spin splitting of a single absorption because of coupling between neighboring magnetic nuclei.

Mutarotation | The change in optical rotation observed when a pure anomer of a sugar is dissolved in water. Mutarotation is caused by the reversible opening and closing of the acetal linkage, which yields an equilibrium mixture of anomers.

***n* + 1 rule** | A hydrogen with *n* other hydrogens on neighboring carbons shows *n* + 1 peaks in its ^1H NMR spectrum.

N-terminal amino acid | The amino acid with a free $-NH_2$ group at the end of a protein chain.

Natural gas | A naturally occurring hydrocarbon mixture consisting chiefly of methane, along with smaller amounts of ethane, propane, and butane.

Natural product | A catchall term generally taken to mean a secondary metabolite found in bacteria, plants, and other living organisms.

New molecular entity | A new biologically active chemical substance approved for sale as a drug by the U.S. Food and Drug Administration.

Newman projection | A means of indicating stereochemical relationships between substituent groups on neighboring carbons. The carbon–carbon bond is viewed end-on, and the carbons are indicated by a circle. Bonds radiating from the center of the circle are attached to the front carbon, and bonds radiating from the edge of the circle are attached to the rear carbon.

Nitration | The substitution of a nitro group onto an aromatic ring.

Nitriles | A class of compounds containing the C≡N functional group.

Nitrogen rule | A compound with an odd number of nitrogen atoms has an odd-numbered molecular weight.

Node | A surface of zero electron density within an orbital. For example, a *p* orbital has a nodal plane passing through the center of the nucleus, perpendicular to the axis of the orbital.

Nonbonding electrons | Valence electrons that are not used in forming covalent bonds.

Noncoding strand | An alternative name for the antisense strand of DNA.

Noncovalent interactions | One of a variety of nonbonding interactions between molecules, such as dipole–dipole forces, dispersion forces, and hydrogen bonds.

Nonessential amino acid | One of the eleven amino acids that are biosynthesized by humans.

Normal alkanes | Straight-chain alkanes, as opposed to branched alkanes. Normal alkanes are denoted by the suffix *n*, as in $n\text{-}C_4H_{10}$ (*n*-butane).

NSAID | A nonsteroidal anti-inflammatory drug, such as aspirin or ibuprofen.

Nuclear magnetic resonance (NMR) spectroscopy | A spectroscopic technique that provides information about the carbon–hydrogen framework of a molecule. NMR works by detecting the energy absorptions accompanying the transitions between nuclear spin states that occur when a molecule is placed in a strong magnetic field and irradiated with radiofrequency waves.

Nucleic acid | Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA); biological polymers made of nucleotides joined together to form long chains.

Nucleophile | An electron-rich species that donates an electron pair to an electrophile in a polar bond-forming reaction. Nucleophiles are also Lewis bases.

Nucleophilic acyl substitution reaction | A reaction in which a nucleophile attacks a carbonyl compound and substitutes for a leaving group bonded to the carbonyl carbon.

Nucleophilic addition reaction | A reaction in which a nucleophile adds to the electrophilic carbonyl group of a ketone or aldehyde to give an alcohol.

Nucleophilic aromatic substitution reactions | The substitution reactions of an aryl halide by a nucleophile.

Nucleophilic substitution reactions | Reactions in which one nucleophile replaces another attached to a saturated carbon atom.

Nucleophilicity | The ability of a substance to act as a nucleophile in an S_N2 reaction.

Nucleoside | A nucleic acid constituent consisting of a sugar residue bonded to a heterocyclic purine or pyrimidine base.

Nucleotides | Nucleic acid constituents consisting of a sugar residue bonded both to a heterocyclic purine or pyrimidine base and to a phosphoric acid. Nucleotides are the monomer units from which DNA and RNA are constructed.

Nylons | Synthetic polyamide step-growth polymers.

Okazaki fragments | Short segments of a DNA lagging strand that is biosynthesized discontinuously and then linked by DNA ligases.

Olefin | An alternative name for an alkene.

Olefin metathesis polymerization | A method of polymer synthesis based on using an olefin metathesis reaction.

Olefin metathesis reaction | A reaction in which two olefins (alkenes) exchange substituents on their double bonds.

Oligonucleotides | Short segments of DNA.

Optical isomers | An alternative name for enantiomers. Optical isomers are isomers that have a mirror-image relationship.

Optically active | A property of some organic molecules wherein the plane of polarization is rotated through an angle when a beam of plane-polarized light is passed through a solution of the molecules.

Orbital | A wave function, which describes the volume of space around a nucleus in which an electron is most likely to be found.

Organic chemistry | The study of carbon compounds.

Organohalides | Compounds that contain one or more halogen atoms bonded to carbon.

Organometallic compound | A compound that contains a carbon–metal bond. Grignard reagents, RMgX, are examples.

Organophosphate | A compound that contains a phosphorus atom bonded to four oxygens, with one of the oxygens also bonded to carbon.

Ortho (*o*) | A naming prefix used for 1,2-disubstituted benzenes.

Oxidation | A reaction that causes a decrease in electron ownership by carbon, either by bond formation between carbon and a more electronegative atom (usually oxygen, nitrogen, or a halogen) or by bond-breaking between carbon and a less electronegative atom (usually hydrogen).

Oximes | Compounds with the R2C═NOH functional group.

Oxirane | An alternative name for an epoxide.

Oxymercuration | A method for double-bond hydration by reaction of an alkene with aqueous mercuric acetate followed by treatment with $NaBH_4$.

Ozonide | The product initially formed by addition of ozone to a carbon–carbon double bond. Ozonides are usually treated with a reducing agent, such as zinc in acetic acid, to produce carbonyl compounds.

Para (*p*) | A naming prefix used for 1,4-disubstituted benzenes.

Paraffins | A common name for alkanes.

Parent peak | The peak in a mass spectrum corresponding to the molecular ion. The mass of the parent peak therefore represents the molecular weight of the compound.

Pauli exclusion principle | No more than two electrons can occupy the same orbital, and those two must have spins of opposite sign.

Peptide bond | An amide bond in a peptide chain.

Peptides | A type of short amino acid polymer in which the individual amino acid residues are linked by amide bonds.

Pericyclic reaction | A reaction that occurs in a single step by a reorganization of bonding electrons in a cyclic transition state.

Periplanar | A conformation in which bonds to neighboring atoms have a parallel arrangement. In an eclipsed conformation, the neighboring bonds are syn periplanar; in a staggered conformation, the bonds are anti periplanar.

Peroxides | Molecules containing an oxygen–oxygen bond functional group, ROOR′ or ROOH.

Peroxyacid | A compound with the $-CO_3H$ functional group. Peroxyacids react with alkenes to give epoxides.

Phenols | A class of compounds with an −OH group directly bonded to an aromatic ring, ArOH.

Phenoxide ion | The anion of a phenol.

Phenyl | The name for the $-C_6H_5$ unit when the benzene ring is considered as a substituent. A phenyl group is abbreviated as −Ph.

Phosphine | A trivalent phosphorus compound, R_3P.

Phosphite | A compound with the structure $P(OR)_3$.

Phospholipids | Lipids that contain a phosphate residue. For example, glycerophospholipids contain a glycerol backbone linked to two fatty acids and a phosphoric acid.

Phosphoramidite | A compound with the structure $R_2NP(OR)_2$.

Phosphoric acid anhydride | A substance that contains PO_2PO link, analogous to the CO_2CO link in carboxylic acid anhydrides.

Photochemical reactions | A reaction carried out by irradiating the reactants with light.

Physiological pH | The pH of 7.3 that exists inside cells.

Pi (*π*) bond | The covalent bond formed by sideways overlap of atomic orbitals. For example, carbon–carbon double bonds contain a \pi bond formed by sideways overlap of two *p* orbitals.

PITC | Phenylisothiocyanate; used in the Edman degradation.

pK_a | The negative common logarithm of the K_a; used to express acid strength.

Plane of symmetry | A plane that bisects a molecule such that one half of the molecule is the mirror image of the other half. Molecules containing a plane of symmetry are achiral.

Plane-polarized light | Light that has its electromagnetic waves oscillating in a single plane rather than in random planes. The plane of polarization is rotated when the light is passed through a solution of a chiral substance.

Plasticizers | Small organic molecules added to polymers to act as a lubricant between polymer chains.

Polar aprotic solvents | Polar solvents that can't function as hydrogen ion donors. Polar aprotic solvents such as dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) are particularly useful in S_N2 reactions because of their ability to solvate cations.

Polar covalent bond | A covalent bond in which the electron distribution between atoms is unsymmetrical.

Polar reactions | Reactions in which bonds are made when a nucleophile donates two electrons to an electrophile and in which bonds are broken when one fragment leaves with both electrons from the bond.

Polarity | The unsymmetrical distribution of electrons in a molecule that results when one atom attracts electrons more strongly than another.

Polarizability | The measure of the change in a molecule's electron distribution in response to changing electrostatic interactions with solvents or ionic reagents.

Polycarbonates | Polyesters in which the carbonyl groups are linked to two −OR groups, [O═C(OR)2].

Polycyclic | Containing more than one ring.

Polycyclic aromatic compound | A compound with two or more benzene-like aromatic rings fused together.

Polymer | A large molecule made up of repeating smaller units. For example, polyethylene is a synthetic polymer made from repeating ethylene units, and DNA is a biopolymer made of repeating deoxyribonucleotide units.

Polymerase chain reaction (PCR) | A method for amplifying small amounts of DNA to produce larger amounts.

Polysaccharides | A type of carbohydrate that is made of many simple sugars linked together by glycoside (acetal) bonds.

Polyunsaturated fatty acids | Fatty acids that contain more than one double bond.

Polyurethane | A step-growth polymer prepared by reaction between a diol and a diisocyanate.

Posttranslational modification | A chemical modification of a protein that occurs after translation from DNA.

Primary structure | The amino acid sequence in a protein.

pro-*R* | One of two identical atoms or groups of atoms in a compound whose replacement leads to an *R* chirality center.

pro-*S* | One of two identical atoms or groups of atoms in a compound whose replacement leads to an *S* chirality center.

Prochiral | A molecule that can be converted from achiral to chiral in a single chemical step.

Prochirality center | An atom in a compound that can be converted into a chirality center by changing one of its attached substituents.

Promoter sequence | A short sequence on DNA located upstream of the transcription start site and recognized by RNA polymerase.

Propagation step | A step in a radical chain reaction that carries on the chain. The propagation steps must yield both product and a reactive intermediate.

Prostaglandins | Lipids derived from arachidonic acid. Prostaglandins are present in nearly all body tissues and fluids, where they serve many important hormonal functions.

Protecting group | A group that is introduced to protect a sensitive functional group toward reaction elsewhere in the molecule. After serving its protective function, the group is removed.

Protein Data Bank | A worldwide online repository of X-ray and NMR structural data for biological macromolecules. To access the Protein Data Bank, go to https://www.rcsb.org.

Proteins | Large peptides containing 50 or more amino acid residues. Proteins serve both as structural materials and as enzymes that control an organism's chemistry.

Protic solvents | Solvents such as water or alcohol that can act as a proton donor.

Pyramidal inversion | The rapid stereochemical inversion of a trivalent nitrogen compound.

Pyranose | The six-membered, cyclic hemiacetal form of a simple sugar.

Quadrupole mass analyzer | A type of mass spectrometer that uses four cylindrical rods to create an oscillating electrostatic field. Ion trajectories are determined by their *m*/*z* ratios. At a given field, only one *m*/*z* value will make it through the quadrupole region—the others will crash into the quadrupole rods or the walls of the instrument and never reach the detector.

Quartet | A set of four peaks in an NMR spectrum, caused by spin–spin splitting of a signal by three adjacent nuclear spins.

Quaternary ammonium salt | An ionic compound containing a positively charged nitrogen atom with four attached groups, $R_4N^+ X^-$.

Quaternary structure | The highest level of protein structure, involving an ordered aggregation of individual proteins into a larger cluster.

Quinone | A 2,5-cyclohexadiene-1,4-dione.

R | A generalized abbreviation for an organic partial structure.

***R* configuration** | The configuration at a chirality center as specified using the Cahn–Ingold–Prelog sequence rules.

Racemate | A mixture consisting of equal parts (+) and (−) enantiomers of a chiral substance; also called a racemic mixture.

Radical | A species that has an odd number of electrons, such as the chlorine radical, Cl ·.

Radical reactions | Reactions in which bonds are made by donation of one electron from each of two reactants and in which bonds are broken when each fragment leaves with one electron.

Rate constant | The constant *k* in a rate equation.

Rate equation | An equation that expresses the dependence of a reaction's rate on the concentration of reactants.

Rate-limiting step | The slowest step in a multistep reaction sequence; also called the rate-determining step. The rate-limiting step acts as a kind of bottleneck in multistep reactions.

Re face | One of two faces of a planar, sp^2-hybridized atom.

Rearrangement reactions | What occurs when a single reactant undergoes a reorganization of bonds and atoms to yield an isomeric product.

Reducing sugars | Sugars that reduce silver ion in the Tollens test or cupric ion in the Fehling or Benedict tests.

Reduction | A reaction that causes an increase of electron ownership by carbon, either by bond-breaking between carbon and a more electronegative atom or by bond formation between carbon and a less electronegative atom.

Reductive amination | A method for preparing an amine by reaction of an aldehyde or ketone with ammonia and a reducing agent.

Refining | The process by which petroleum is converted into gasoline and other useful products.

Regiochemistry | A term describing the orientation of a reaction that occurs on an unsymmetrical substrate.

Regiospecific | A term describing a reaction that occurs with a specific regiochemistry to give a single product rather than a mixture of products.

Replication | The process by which double-stranded DNA uncoils and is replicated to produce two new copies.

Replication forks | The point of unraveling in a DNA chain where replication occurs.

Residues | Amino acids in a protein chain.

Resolution | The process by which a racemate is separated into its two pure enantiomers.

Resonance effect | The donation or withdrawal of electrons through orbital overlap with neighboring \pi bonds. For example, an oxygen or nitrogen substituent donates electrons to an aromatic ring by overlap of the O or N orbital with the aromatic ring *p* orbitals.

Resonance forms | Individual structural forms of a resonance hybrid.

Resonance hybrid | A molecule, such as benzene, that can't be represented adequately by a single Kekulé structure but must instead be considered as an average of two or more resonance forms. The resonance forms themselves differ only in the positions of their electrons, not their nuclei.

Restriction endonucleases | Enzymes that are able to cleave a DNA molecule at points in the chain where a specific base sequence occurs.

Retrosynthetic | Planning an organic synthesis by working backward from the final product to the starting material.

Ribonucleic acid (RNA) | The biopolymer found in cells that serves to transcribe the genetic information found in DNA and uses that information to direct the synthesis of proteins.

Ribosomal RNA (rRNA) | A kind of RNA used in the physical makeup of ribosomes.

Ring-current | The circulation of \pi electrons induced in aromatic rings by an external magnetic field. This effect accounts for the downfield shift of aromatic ring protons in the ^{1}H NMR spectrum.

Ring-flip | A molecular motion that interconverts two chair conformations of cyclohexane. The effect of a ring-flip is to convert an axial substituent into an equatorial substituent.

Ring-opening metathesis polymerization (ROMP) | A method of polymer synthesis that uses an olefin metathesis reaction of a cycloalkene.

RNA | Ribonucleic acid.

Robinson annulation reaction | A method for synthesis of cyclohexenones by sequential Michael reaction and intramolecular aldol reaction.

***S* configuration** | The configuration at a chirality center as specified using the Cahn–Ingold–Prelog sequence rules.

***s*-Cis conformation** | The conformation of a conjugated diene that is cis-like around the single bond.

Saccharide | A sugar.

Salt bridge | An ionic attraction between two oppositely charged groups in a protein chain.

Sandmeyer reaction | The nucleophilic substitution reaction of an arenediazonium salt with a cuprous halide to yield an aryl halide.

Sanger dideoxy method | A commonly used method of DNA sequencing.

Saponification | An old term for the base-induced hydrolysis of an ester to yield a carboxylic acid salt.

Saturated | A molecule that has only single bonds and thus can't undergo addition reactions. Alkanes are saturated, but alkenes are unsaturated.

Sawhorse representations | A manner of representing stereochemistry that uses a stick drawing and gives a perspective view of the conformation around a single bond.

Schiff bases | An alternative name for an imine, R2C═NR′, used primarily in biochemistry.

Second-order reaction | A reaction whose rate-limiting step is bimolecular and whose kinetics are therefore dependent on the concentration of two reactants.

Secondary metabolite | A small naturally occurring molecule that is not essential to the growth and development of the producing organism and is not classified by structure.

Secondary structure | The level of protein substructure that involves organization of chain sections into ordered arrangements such as *β*-pleated sheets or *α* helices.

Semiconservative replication | The process by which DNA molecules are made containing one strand of old DNA and one strand of new DNA.

Sense strand | The coding strand of double-helical DNA that contains the gene.

Sequence rules | A series of rules for assigning relative rankings to substituent groups on a double-bond carbon atom or on a chirality center.

Sesquiterpenoids | 15-carbon lipids.

Sharpless epoxidation | A method for enantioselective synthesis of a chiral epoxide by treatment of an allylic alcohol with *tert*-butyl hydroperoxide, $(CH_3)_3C–OOH$, in the presence of titanium tetraisopropoxide and diethyl tartrate.

Shielding | An effect observed in NMR that causes a nucleus to absorb toward the right (upfield) side of the chart. Shielding is caused by donation of electron density to the nucleus.

Si face | One of two faces of a planar, sp^2-hybridized atom.

Sialic acid | One of a group of more than 300 carbohydrates based on acetylneuramic acid.

Side chain | The substituent attached to the *α* carbon of an amino acid.

Sigma (*σ*) bond | A covalent bond formed by head-on overlap of atomic orbitals.

Sigmatropic reaction | A pericyclic reaction that involves the migration of a group from one end of a \pi electron system to the other.

Silyl ether | A substance with the structure $R_3Si–O–R$. The silyl ether acts as a protecting group for alcohols.

Simmons–Smith reaction | The reaction of an alkene with CH_2I_2 and Zn−Cu to yield a cyclopropane.

Simple sugars | Carbohydrates that cannot be broken down into smaller sugars by hydrolysis.

Single bond | A covalent bond formed by sharing one electron pair between atoms.

Skeletal structures | A shorthand way of writing structures in which carbon atoms are assumed to be at each intersection of two lines (bonds) and at the end of each line.

Small RNAs | A type of RNA that has a variety of functions within the cell, including silencing transcription and catalyzing chemical modifications of other RNA molecules.

S_N1 reaction | A unimolecular nucleophilic substitution reaction.

S_N2 reaction | A bimolecular nucleophilic substitution reaction.

Solid-phase synthesis | A technique of synthesis whereby the starting material is covalently bound to a solid polymer bead and reactions are carried out on the bound substrate. After the desired transformations have been effected, the product is cleaved from the polymer.

Solvation | The clustering of solvent molecules around a solute particle to stabilize it.

***sp* hybrid orbitals** | Hybrid orbitals derived from the combination of an *s* and a *p* atomic orbital. The two *sp* orbitals that result from hybridization are oriented at an angle of 180° to each other.

***sp*^{2} hybrid orbitals** | Hybrid orbitals derived by combination of an *s* atomic orbital with two *p* atomic orbitals. The three *sp*^{2} hybrid orbitals that result lie in a plane at angles of 120° to each other.

***sp*^{3} hybrid orbitals** | Hybrid orbitals derived by combination of an *s* atomic orbital with three *p* atomic orbitals. The four *sp*^{3} hybrid orbitals that result are directed toward the corners of a regular tetrahedron at angles of 109° to each other.

Specific rotation | The optical rotation of a chiral compound under standard conditions.

Sphingomyelins | Phospholipids that have sphingosine as the backbone rather than glycerol.

Spin–spin splitting | The splitting of an NMR signal into a multiplet because of an interaction between nearby magnetic nuclei whose spins are coupled. The magnitude of spin–spin splitting is given by the coupling constant, *J*.

Staggered conformation | The three-dimensional arrangement of atoms around a carbon–carbon single bond in which the bonds on one carbon bisect the bond angles on the second carbon as viewed end-on.

Statin | A drug that controls cholesterol biosynthesis in the body by blocking the HMG-CoA reductase enzyme.

Step-growth polymers | Polymers in which each bond is formed independently of the others. Polyesters and polyamides (nylons) are examples.

Stereocenter | An alternative name for a chirality center.

Stereochemistry | The branch of chemistry concerned with the three-dimensional arrangement of atoms in molecules.

Stereogenic center | An alternative name for a chirality center.

Stereoisomers | Isomers that have their atoms connected in the same order but have different three-dimensional arrangements. The term *stereoisomer* includes both enantiomers and diastereomers.

Stereospecific | A term indicating that only a single stereoisomer is produced in a given reaction rather than a mixture.

Steric strain | The strain imposed on a molecule when two groups are too close together and try to occupy the same space. Steric strain is responsible both for the greater stability of trans versus cis alkenes and for the greater stability of equatorially substituted versus axially substituted cyclohexanes.

Steroids | Lipids whose structure is based on a tetracyclic carbon skeleton with three 6-membered and one 5-membered ring. Steroids occur in both plants and animals and have a variety of important hormonal functions.

Stork enamine reaction | The conjugate addition of an enamine to an *α*,*β*-unsaturated carbonyl compound, followed by hydrolysis to yield a 1,5-dicarbonyl product.

STR loci | Short tandem repeat sequences of noncoding DNA that are unique to every individual and allow DNA fingerprinting.

Straight-chain alkanes | Alkanes whose carbon atoms are connected without branching.

Substitution reactions | What occurs when two reactants exchange parts to give two new products. S_N1 and S_N2 reactions are examples.

Sulfides | A class of compounds that has two organic substituents bonded to the same sulfur atom, RSR′.

Sulfonation | The substitution of a sulfonic acid group ($-SO_3H$) onto an aromatic ring.

Sulfone | A compound of the general structure RSO_2R'.

Sulfonium ions | A species containing a positively charged, trivalent sulfur atom, R_3S^+.

Sulfoxide | A compound of the general structure RSOR′.

Suprafacial | A word used to describe the geometry of pericyclic reactions. Suprafacial reactions take place on the same side of the two ends of a \pi electron system.

Suzuki–Miyaura reaction | The palladium-catalyzed coupling reaction of an aromatic or vinylic halide with an aromatic or vinylic boronic acid.

Symmetry plane | A plane that bisects a molecule such that one half of the molecule is the mirror image of the other half. Molecules containing a plane of symmetry are achiral.

Symmetry-allowed | A symmetry-allowed reaction is a pericyclic process that has a favorable orbital symmetry for reaction through a concerted pathway. A symmetry-disallowed reaction is one that does not have favorable orbital symmetry for reaction through a concerted pathway.

Syn periplanar | Describing a stereochemical relationship in which two bonds on adjacent carbons lie in the same plane and are eclipsed.

Syn stereochemistry | The opposite of anti. A syn addition reaction is one in which the two ends of the double bond react from the same side. A syn elimination is one in which the two groups leave from the same side of the molecule.

Syndiotactic | A chain-growth polymer in which the stereochemistry of the substituents alternates regularly on opposite sides of the backbone.

Tautomers | Isomers that interconvert spontaneously, usually with the change in position of a hydrogen.

Terpenoids | Lipids that are formally derived by head-to-tail polymerization of isoprene units.

Tertiary structure | The level of protein structure that involves the manner in which the entire protein chain is folded into a specific three-dimensional arrangement.

Thermodynamic control | An equilibrium reaction that yields the lowest-energy, most stable product is said to be thermodynamically controlled.

Thermoplastics | Polymers that have a high T_g and are hard at room temperature but become soft and viscous when heated.

Thermosetting resins | Polymers that become highly cross-linked and solidify into a hard, insoluble mass when heated.

Thioesters | A class of compounds with the RCOSR′ functional group.

Thiolate ion | The anion of a thiol, RS^-.

Thiols | A class of compounds containing the −SH functional group.

TMS | Tetramethylsilane; used as an NMR calibration standard.

TOF | Time-of-flight mass spectrometry; a sensitive method of mass detection accurate to about 3 ppm.

Tollens' reagent | A solution of Ag_2O in aqueous ammonia; used to oxidize aldehydes to carboxylic acids.

Torsional strain | The strain in a molecule caused by electron repulsion between eclipsed bonds. Torsional strain is also called eclipsing strain.

Tosylate | A *p*-toluenesulfonate ester; useful as a leaving group in nucleophilic substitution reactions.

Transamination | The exchange of an amino group and a keto group between reactants.

Transcription | The process by which the genetic information encoded in DNA is read and used to synthesize RNA in the nucleus of the cell. A small portion of double-stranded DNA uncoils, and complementary ribonucleotides line up in the correct sequence for RNA synthesis.

Transfer RNA (tRNA) | A kind of RNA that transports amino acids to the ribosomes, where they are joined together to make proteins.

Transimination | The exchange of an amino group and an imine group between reactants.

Transition state | An activated complex between reactants, representing the highest energy point on a reaction curve. Transition states are unstable complexes that can't be isolated.

Translation | The process by which the genetic information transcribed from DNA onto mRNA is read by tRNA and used to direct protein synthesis.

Tree diagram | A diagram used in NMR to sort out the complicated splitting patterns that can arise from multiple couplings.

Triacylglycerols | Lipids, such as those found in animal fat and vegetable oil, that are a triester of glycerol with long-chain fatty acids.

Tricarboxylic acid cycle | An alternative name for the citric acid cycle by which acetyl CoA is degraded to CO_2.

Triple bonds | A type of covalent bond formed by sharing three electron pairs between atoms.

Triplet | A symmetrical three-line splitting pattern observed in the ^{1}H NMR spectrum when a proton has two equivalent neighbor protons.

Turnover number | The number of substrate molecules acted on by an enzyme molecule per unit time.

Twist-boat conformation | A conformation of cyclohexane that is somewhat more stable than a pure boat conformation.

Ultraviolet (UV) spectroscopy | An optical spectroscopy employing ultraviolet irradiation. UV spectroscopy provides structural information about the extent of \pi electron conjugation in organic molecules.

Unimolecular reaction | A reaction that occurs by spontaneous transformation of the starting material without the intervention of other reactants. For example, the dissociation of a tertiary alkyl halide in the S_N1 reaction is a unimolecular process.

Unsaturated | A molecule that has one or more multiple bonds.

Upfield | The right-hand portion of the NMR chart.

Urethane | A functional group in which a carbonyl group is bonded to both an −OR and an $-NR_2$.

Uronic acid | A monocarboxylic acid formed by oxidizing the $-CH_2OH$ end of an aldose without affecting the −CHO end.

Valence bond theory | A bonding theory that describes a covalent bond as resulting from the overlap of two atomic orbitals.

Valence shell | The outermost electron shell of an atom.

van der Waals forces | Intermolecular forces that are responsible for holding molecules together in the liquid and solid states.

Vegetable oils | Liquid triacylglycerols derived from a plant source.

Vicinal | A term used to refer to a 1,2-disubstitution pattern. For example, 1,2-dibromoethane is a vicinal dibromide.

Vinyl group | A \ce{=CH–} substituent.

Vinyl monomer | A substituted alkene monomer used to make a chain-growth polymer.

Vinylic | A term that refers to a substituent at a double-bond carbon atom. For example, chloroethylene is a vinylic chloride, and enols are vinylic alcohols.

Vitamin | A small organic molecule that must be obtained in the diet and is required in trace amounts for proper growth and function.

Vulcanization | A technique for cross-linking and hardening a diene polymer by heating with a few percent by weight of sulfur.

Walden inversion | The inversion of configuration at a chirality center that accompanies an S_N2 reaction.

Wave equation | A mathematical expression that defines the behavior of an electron in an atom.

Wave function | A solution to the wave equation for defining the behavior of an electron in an atom. The square of the wave function defines the shape of an orbital.

Wavelength | The length of a wave from peak to peak. The wavelength of electromagnetic radiation is inversely proportional to frequency and inversely proportional to energy.

Waxes | A mixture of esters of long-chain carboxylic acids with long-chain alcohols.

Williamson ether synthesis | A method for synthesizing ethers by S_N2 reaction of an alkyl halide with an alkoxide ion.

Wittig reaction | The reaction of a phosphorus ylide with a ketone or aldehyde to yield an alkene.

Wohl degradation | A method for shortening the chain of an aldose sugar by one carbon.

Wolff–Kishner reaction | The conversion of an aldehyde or ketone into an alkane by reaction with hydrazine and base.

X-ray crystallography | A technique that uses X rays to determine the structure of molecules.

Ylide | A neutral species with adjacent + and − charges, such as the phosphoranes used in Wittig reactions.

***Z* geometry** | A term used to describe the stereochemistry of a carbon–carbon double bond. The two groups on each carbon are ranked according to the Cahn–Ingold–Prelog sequence rules, and the two carbons are compared. If the higher ranked groups on each carbon are on the same side of the double bond, the bond has *Z* geometry.

Zaitsev's rule | A rule stating that E2 elimination reactions normally yield the more highly substituted alkene as major product.

Ziegler–Natta catalysts | Catalysts of an alkylaluminum and a titanium compound used for preparing alkene polymers.

Zwitterion | A neutral dipolar molecule in which the positive and negative charges are not adjacent. For example, amino acids exist as zwitterions, H3CN+–CHR–CO2−

***α* Anomer** | The cyclic hemiacetal form of a sugar that has the hemiacetal −OH group cis to the −OH at the lowest chirality center in a Fischer projection.

***α* Helix** | The coiled secondary structure of a protein.

***α* Position** | The position next to a carbonyl group.

***α*-Amino acids** | A type of difunctional compound with an amino group on the carbon atom next to a carboxyl group, $RCH(NH_2)CO_2H$.

***α*-Substitution reaction** | The substitution of the *α* hydrogen atom of a carbonyl compound by reaction with an electrophile.

***β* Anomer** | The cyclic hemiacetal form of a sugar that has the hemiacetal −OH group trans to the −OH at the lowest chirality center in a Fischer projection.

***β* Diketone** | A 1,3-diketone.

***β* Lactam** | A four-membered lactam, or cyclic amide. Penicillin and cephalosporin antibiotics contain *β*-lactam rings.

***β*-Keto ester** | A 3-oxoester.

***β*-Oxidation pathway** | The metabolic pathway for degrading fatty acids.

***β*-Pleated sheet** | A type of secondary structure of a protein.

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