ORGANIC CHEMISTRY III

Layne Morsch et al.
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Organic Chemistry Vol III

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ABOUT THE AUTHORS

This text has many contributors. Some of the key authors and content creators include:

Dr. Layne Morsch is a Professor of Organic Chemistry and leads the Center for Faculty Excellence at the University of Illinois Springfield. He received his PhD in Organic Chemistry from the University of Illinois Chicago in 2002. Layne has received several distinguished teaching awards including Apple Distinguished Educator (class of 2015), UIS College of Liberal Arts and Sciences Faculty Excellence Award in Teaching (2017), the Burks Oakley II Distinguished Online Teaching Award (2018) and the UIS Pearson Faculty Award for Outstanding Teaching (2019). He has been a faculty fellow and senior faculty fellow with the Center for Online Learning Research and Service at UIS and is currently a mentor to Faculty Fellows in Teaching. His research interests in chemistry education focus on international collaborative learning between student partners and disciplinary language development through organic chemistry courses.

Dr. Steven Farmer is a Professor of Organic Chemistry at Sonoma State University (SSU). He received his Ph.D. in Organic Chemistry from the University of California, Davis in 2002. Dr. Farmer has received multiple teaching awards including the SSU Sarlo Excellence in Teaching Award (2011), the Santa Rosa Chamber of Commerce Excellence in Education Award (2012), the SSU Educational Experience Enhancement Award, and the inaugural SSU Affordable Learning Hero Award (2019). His research and scholarship interests focus on Chemical Education, Affordable Learning, and Public Outreach. He is the author of the book, *Strange Chemistry: The Stories Your Chemistry Teacher Wouldn't Tell You*, which discusses the many fascinating ways chemistry shows up in everyday life.

Dr. Krista Cunningham

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Dietmar Kennepohl, BSc(Hons) PhD FCIC is Professor of Chemistry and former Associate Vice President Academic at Athabasca University. Most of his teaching experience has been in a distributed and online setting. He holds university, national, and international teaching awards and is a Society for Teaching and Learning in Higher Education 3M National Teaching Fellow. He is a well-published and sought-after presenter on topics including learning design, learning outcomes, assessment, PLAR, transfer credit, distance and online education, and emerging educational technologies. His research in chemistry education concentrates on the use of online course access

including innovative distance delivery methods for undergraduate laboratory work. He has edited several books including *Teaching Science Online: Practical Guidance for Effective Instruction and Lab Work* (2016) and *Accessible Elements: Teaching Science Online and at a Distance* (2010). The latter was winner of the 2010 Charles A. Wedemeyer Award and is a freely available publication.

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CHAPTER OVERVIEW

24: AMINES AND HETEROCYCLES

LEARNING OBJECTIVES

When you have completed Chapter 24, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. design a multi-step synthesis that involves the use of any of the reactions described in this unit, and any of the reactions described in any previous unit.
3. solve road-map problems that require a knowledge of amine chemistry in addition to any of the chemistry discussed in previous units.
4. define, and use in context, the key terms introduced.

Amines are the first nitrogen-containing compounds that we study in detail in this course. We begin the chapter with an explanation of the differences in structure among primary, secondary and tertiary amines. We explain the nomenclature of aliphatic and arylamines, and examine the structure and bonding of these compounds, relating these features to their physical properties and basicity. We describe the use of amines to resolve racemic mixtures of chiral carboxylic acids.

Amines may be prepared by a number of different synthetic methods. We describe each of these methods and assess the relative merits of each. After a description of the reactions of aliphatic amines, we devote sections to a discussion of the use of tetraalkylammonium salts as phase-transfer agents. The chapter concludes with a summary of the spectroscopic properties of amines.

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24.0: CHAPTER OBJECTIVES

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24.1: NAMING AMINES

OBJECTIVES

After completing this section, you should be able to

1. classify a given amine as being primary, secondary or tertiary.
2. explain, briefly, the difference in meaning of the terms primary, secondary and tertiary when they are applied to the structures of amines and alcohols.
3. determine whether a given structure represents a quaternary ammonium cation.
4. provide an acceptable IUPAC name for an amine, given its Kekulé, condensed or shorthand structure.
5. draw the structure of an amine, given its IUPAC name.
6. give the name and structure of one typical heterocyclic amine (e.g., pyridine).

KEY TERMS

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

- amine
- primary amine
- secondary amine
- quaternary ammonium cation
- tertiary amine

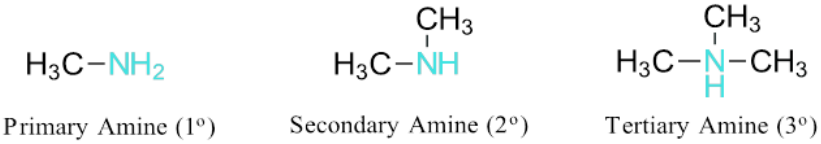
STUDY NOTES

You should recognize that heterocyclic amines—compounds in which the nitrogen atom occurs as part of a ring—are very common in organic chemistry. Be prepared to meet such compounds throughout this, and subsequent chapters, but do not try to memorize all of the names and structures givenin the reading. You should, however, commit the structures of pyridine and pyrrole to memory.

CLASSIFICATION OF AMINES

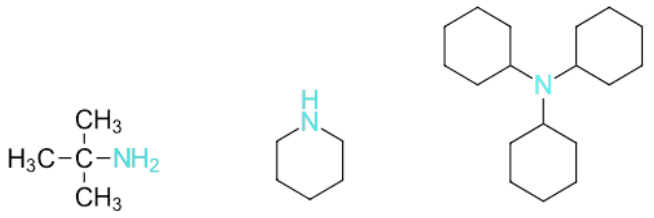
Amines are made up of an sp^3 hybridized nitrogen and are either alkyl substituted (alkylamines) or aryl substituted (arylamines).

Amines are classified as primary, secondary, or tertiary based on the number or organic substituents directly attached to the nitrogen. An amine attached to one substituent is primary (1°), two substituents is secondary (2°), and three substituents is tertiary (3°).



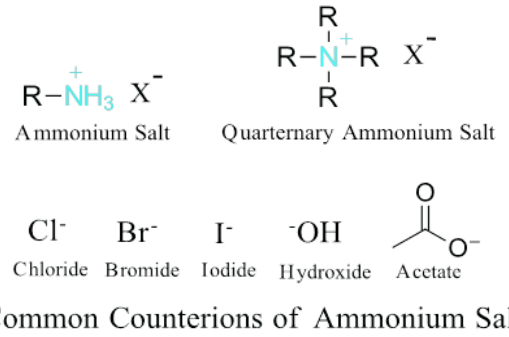
Primary Amine (1°) Secondary Amine (2°) Tertiary Amine (3°)

EXAMPLE



Primary Amine (1°) Secondary Amine (2°) Tertiary Amine (3°)

Amines attached to 4 substituents and at least one substituent is a hydrogen are called ammonium salts. Amines attached to 4 alkyl substituents are called quaternary ammonium salts. The nitrogen in ammonium salts lacks lone pair electrons and carries a formal positive charge. Ammonium salts are also require a negatively charged counter-ion which can vary in composition.

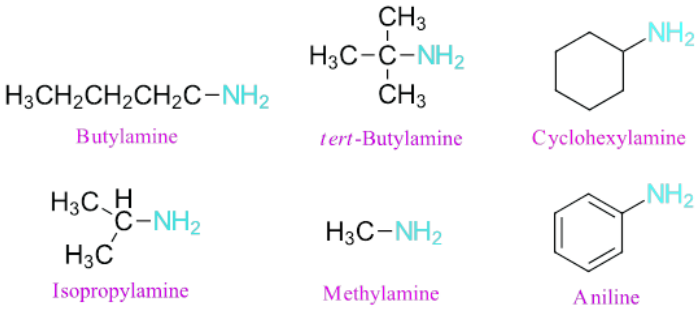


Common Counterions of Ammonium Salts

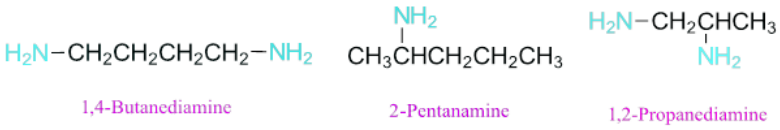
NOMENCLATURE OF AMINES

NOMENCLATURE OF PRIMARY AMINES

Primary amines are named in two main ways using the IUPAC system. They can either be named as alkylamines or as alkanamines. Most 1° amines which are attached to linear alkanes, cycloalkanes, and alkyl groups with common names (Section 3.3), tend to be named as alkylamines. The alkyl groups is named as a substituent (**prefix + yl**) then the suffix -amine is added. Many amines have common names that are used by IUPAC, for example the primary arylamine ($C_6H_5NH_2$) is called aniline.

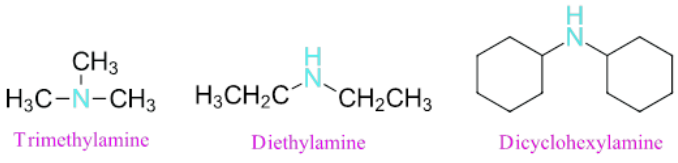


Other primary amines tend to be named as alkanamines. The alkyl group is named as an alkane (**prefix+ane**) and –e ending is replaced with the suffix **-amine**. The –e ending is not removed for diamines.



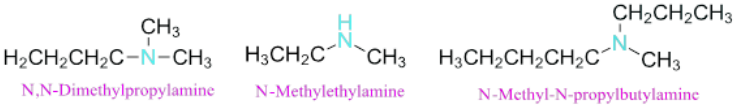
NOMENCLATURE OF SYMMETRICAL SECONDARY AND TERTIARY AMINES

Symmetrical 2° and 3° amines (where all substituents are identical) are named as alkylamines and the prefix di- or tri -added to indicate the number of substituents.



NOMENCLATURE OF UNSYMMETRICAL SECONDARY AND TERTIARY AMINES

Unsymmetrical 2° and 3° amines are named with the largest chain being the base chain (**prefix+yl+amine**). The other alkyl groups are named as N-substituents. This notation is used to indicate that the substituent is attached to the amine nitrogen and not an alkyl carbon.



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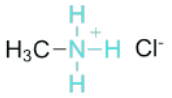
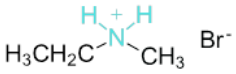
NOMENCLATURE OF AMMONIUM SALTS

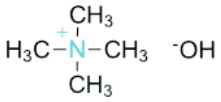
Ammonium salts and quaternary ammonium salts are named using the same rules as 2° and 3° amines except the –amine suffix is replaces with -ammonium + the name of the counter ion. The counter ion name is separated with a space.



Methylammonium Chloride

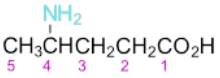


N-Methylethylammonium Bromide

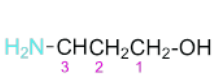


Tetramethylammonium Hydroxide

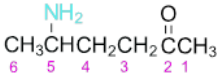
Amines have one of the lower functional group priorities in the IUPAC nomenclature system. When present in a compound with a functional group of higher priority, the amine group is named as a substituent called **"amino."**



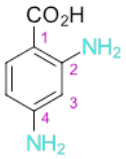
4-Aminopentanoic Acid



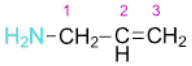
3-Amino-1-propanol



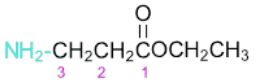
4-Amino-2-Butanone



2,4-Diaminobenzoic Acid

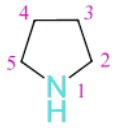


2-Propen-1-amine
(NH_2 Has Priority)

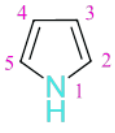


Ethyl 3-aminopropionate

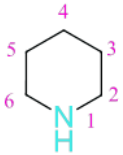
Heterocyclic amine have one or more nitrogens as part of the ring and can be aliphatic or aromatic. Most heterocyclic amine ring systems have a common name and are numbered such that a nitrogen always gets position 1. An amine attached to a heterocyclic ring is named as an amino substituent.



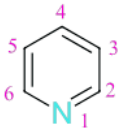
Pyrrolidine



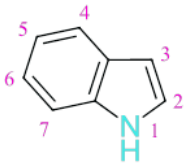
Pyrrole



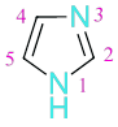
Piperidine



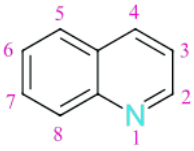
Pyridine



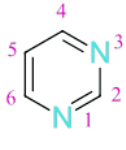
Indole



Imidazole

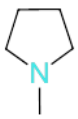


Quinoline

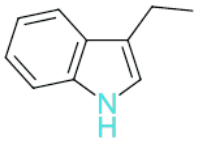


Pyrimidine

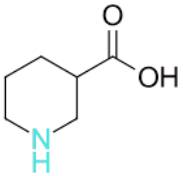
EXAMPLE



1-Methylpyrrolidine



3-Ethylindole



3-Piperidinecarboxylic acid

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EXERCISES 24.1.1

Name the following compounds:

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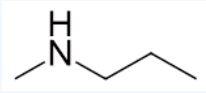

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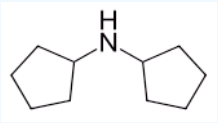

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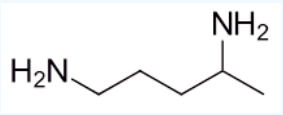

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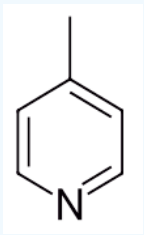
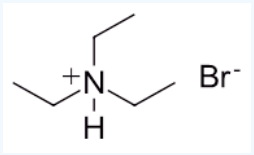


e)



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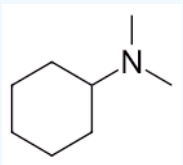


Answers

a. N-Methylpropylamine
b. Dicyclopentylamine
c. 1,4-Pentanediamine
d. 4-Methylpyridine
e. Triethylammonium Bromide
f. N,N-Dimethylcyclohexylamine

EXERCISE 24.1.1

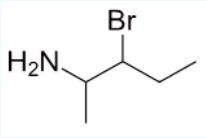
Draw the structures corresponding to the following names:

a. 3-Bromo-pentan-2-amine
b. Cyclopentanamine

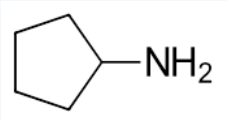
c. *Trans*-3-ethylcyclohexanamine
d. *Sec*-butyl-*tert*-butyl amine
e. N,N-Dimethyl-3-pentanamine
f. 4-Methyl-2-hexanamine
g. 6-Bromo-4-amino-2-heptanol3)

Answer

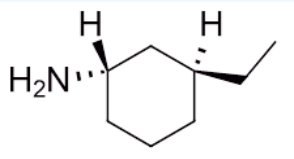
a)



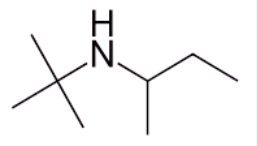
b)



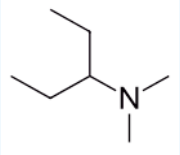
c)



d)



e)



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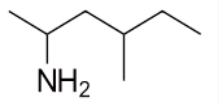
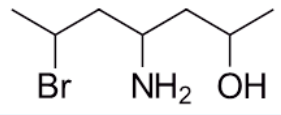


g)



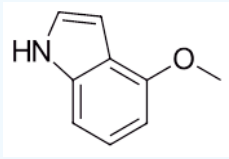
EXERCISE 24.1.3

Draw the structures of the following heterocyclic compounds:

a. 4-Methoxyindole
b. 1,4-Dimethylpyrrole
c. 3-(N,N-Dimethylamino)pyridine
d. 2-Aminopyrimidine

Answer

a)



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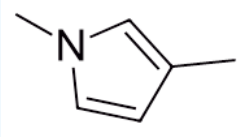

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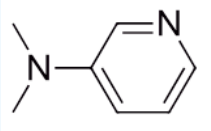
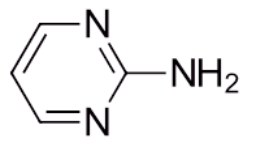


d)



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24.2: STRUCTURE AND PROPERTIES OF AMINES

OBJECTIVES

After completing this section, you should be able to

1. describe the geometry and bonding of simple amines.
2. explain why most chiral amines cannot be resolved into their two enantiomers.

KEY TERMS

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

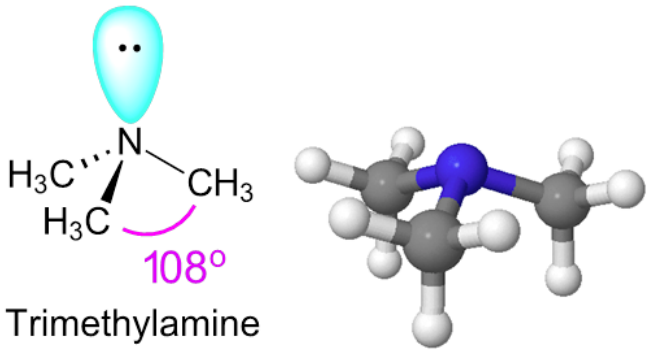
- pyramidal inversion

STUDY NOTES

Molecular models may help you to understand pyramidal inversion.

BONDING, SHAPE, AND HYBRIDIZATION OF AMINES

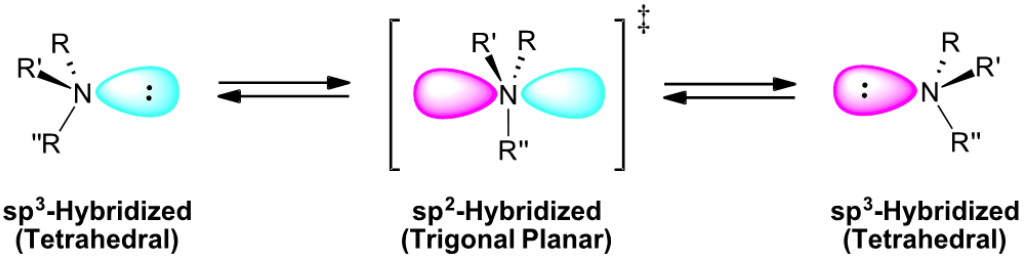
The nitrogen atom in most amines is sp^3 hybridized. Three of the sp^3 hybrid orbitals form sigma bonds with the fourth orbital carrying the lone pair electrons. Single-bonded nitrogen is trigonal pyramidal in shape, with the non-bonding lone electron pair pointing to the unoccupied corner of a tetrahedron. Due to crowding by the lone pair electrons, the C-N-C bond angle between alkyl substituents on an amine is roughly 108° which is slightly less than the 109.5° bond angle for a perfect tetrahedral geometry.



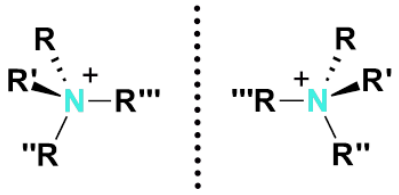
The C-N bonds (147 pm) of non-conjugated amines is shorter than C-C bond (154 pm) in alkanes, and longer than the C-O bond (143 pm) present in alcohols. This difference in bond length is expected given that the relative atom sizes are C > O > N.

CHIRALITY OF AMINES

Due to their tetrahedral configuration, amines with three different substituents are chiral. The R and S enantiomeric forms of a chiral amine cannot be resolved due to their rapid interconversion by a process called pyramidal or nitrogen inversion. During the inversion, the sp^3 hybridized amine momentarily rehybridizes to a sp^2 hybridized, trigonal planar, transition state where the lone pair electrons occupy a p orbital. The nitrogen then returns to a tetrahedral sp^3 hybridization causing the lone pair electrons to return to a sp^3 orbital on the opposite side of the nitrogen. During this process substituents invert to form the enantiomer. The thermodynamic barrier for this inversion (~25 kJ/mol) is low enough to allow rapid inversion at room temperature, leading to a mixture of interconverting R and S configurations. At room temperature a nitrogen atom exists as a racemic mixture of R and S configurations at equilibrium.



Quarternary amines lack lone pair electrons and therefore do not undergo pyramidal inversions. Quarternary amines with four different substituents are chiral and are readily resolved into separate enantiomers.

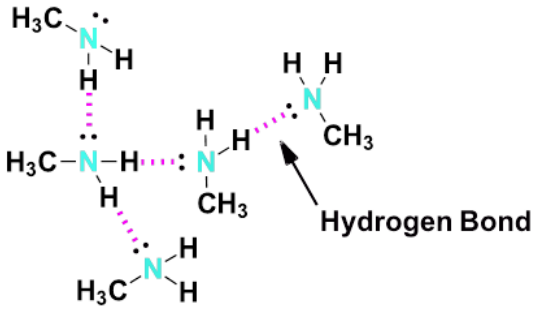


Enantiomers of a Chiral Quarternary Amine

BOILING POINT AND WATER SOLUBILITY

Methyl, dimethyl, trimethyl, and ethyl amines are gases under standard conditions. Most common alkyl amines are liquids, and high molecular weight amines are, quite naturally, solids at standard temperatures.

It is instructive to compare the boiling points and water solubility of amines with those of corresponding alcohols and ethers. The dominant factor here is hydrogen bonding, and the first table below documents the powerful intermolecular attraction that results from -O-H---O- hydrogen bonding in alcohols (light blue columns). Corresponding -N-H---N- hydrogen bonding is weaker, as the lower boiling points of similarly sized amines demonstrate. Alkanes provide reference compounds in which hydrogen bonding is not possible, and the increase in boiling point for equivalent 1º-amines is roughly half the increase observed for equivalent alcohols.



A Representation of the Hydrogen Bonding in Methyamine

Compound	CH_3CH_3	CH_3OH	CH_3NH_2	$CH_3CH_2CH_3$	CH_3CH_2OH	$CH_3CH_2NH_2$
Mol.Wt.	30	32	31	44	46	45
Boiling Point ºC	-88.6º	65º	-6.0º	-42º	78.5º	16.6º

The second table illustrates differences associated with isomeric 1º, 2º & 3º-amines, as well as the influence of chain branching. Since 1º-amines have two hydrogens available for hydrogen bonding, we expect them to have higher boiling points than isomeric 2º-amines, which in turn should boil higher than isomeric 3º-amines (no hydrogen bonding). Indeed, 3º-amines have boiling points similar to equivalent sized ethers; and in all but the smallest compounds, corresponding ethers, 3º-amines and alkanes have similar boiling points. In the examples shown here, it is further demonstrated that chain branching reduces boiling points by 10 to 15 ºC.

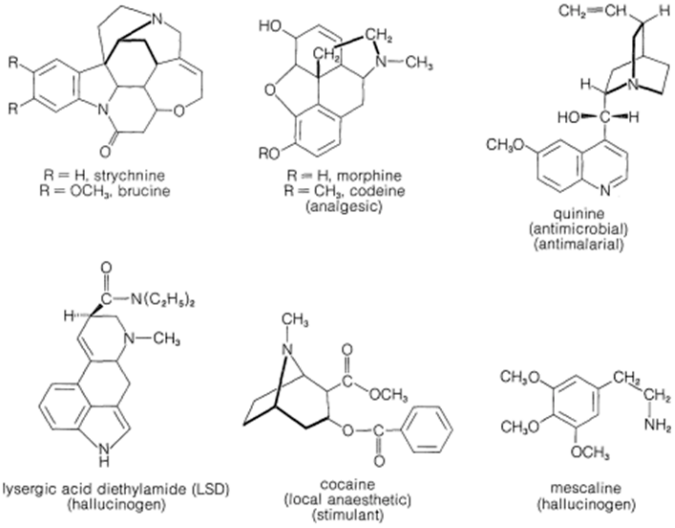
Compound	$CH_3(CH_2)_2CH_3$	$CH_3(CH_2)_2OH$	$CH_3(CH_2)_2NH_2$	$CH_3CH_2NHCH_3$	$(CH_3)_3CH$	$(CH_3)_2CHOH$	$(CH_3)_2CHNH_2$	$(CH_3)_3N$
Mol.Wt.	58	60	59	59	58	60	59	59
Boiling Point ºC	-0.5º	97º	48º	37º	-12º	82º	34º	3º

Most aliphatic amines display some solubility in water, reflecting their ability to form hydrogen bonds. Solubility decreases proportionally with the increase in the number of carbon atoms in the molecule – especially when the carbon atom number is greater than six. Aliphatic amines also display significant solubility in organic solvents, especially in polar organic solvents.

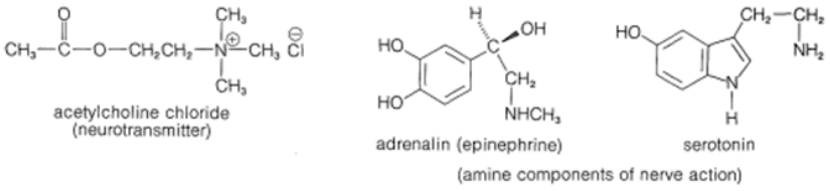
The water solubility of 1º and 2º-amines is similar to that of comparable alcohols. As expected, the water solubility of 3º-amines and ethers is also similar. The basicity of amines allows them to be dissolved in dilute mineral acid solutions, and this property facilitates their separation from neutral compounds such as alcohols and hydrocarbons by partitioning between the phases of non-miscible solvents.

NATURALLY OCCURRING AMINES

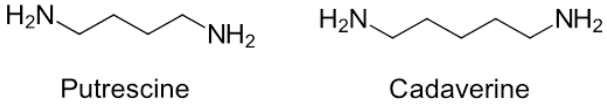
A large and widespread class of naturally occurring amines is known as alkaloids. The structures of the plant alkaloids are extraordinarily complex, yet they are related to the simple amines in being weak nitrogen bases. In fact, the first investigator to isolate an alkaloid in pure form was F. W. A. Sertürner who, in 1816, described morphine as basic, salt-forming, and ammonia-like. He used the term "organic alkali" from which is derived the name alkaloid. Alkaloids include compounds that may be classified as antimicrobial (quinine), as analgesics (morphine, codeine), as hallucinogens (mescaline, LSD), and as topical anesthetics (cocaine).



Certain amines and ammonium compounds play key roles in the function of the central nervous system as neurotransmitters and the balance of amines in the brain is critical for normal brain functioning. The amines acetylcholine chloride, adrenalin, and serotonin play important roles in nerve function in the human body.



Most amines have “interesting” odors. The simple ones smell very much like ammonia. Higher aliphatic amines smell like decaying meat. The stench of rotting meat is due in part to two diamines: putrescine and cadaverine. They are made during the decarboxylation of the amino acids, ornithine and lysine, by bacteria.



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24.3: BASICITY OF AMINES

OBJECTIVES

After completing this section, you should be able to

1. account for the basicity and nucleophilicity of amines.
2. explain why amines are more basic than amides, and better nucleophiles.
3. describe how an amine can be extracted from a mixture that also contains neutral compounds illustrating the reactions which take place with appropriate equations.
4. explain why primary and secondary (but not tertiary) amines may be regarded as very weak acids, and illustrate the synthetic usefulness of the strong bases that can be formed from these weak acids.

KEY TERMS

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

- amide

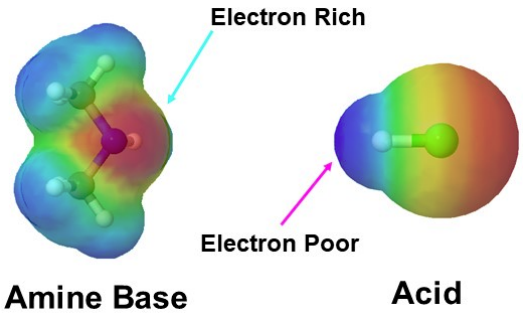
STUDY NOTES

The lone pair of electrons on the nitrogen atom of amines makes these compounds not only basic, but also good nucleophiles. Indeed, we have seen in past chapters that amines react with electrophiles in several polar reactions (see for example the nucleophilic addition of amines in the formation of imines and enamines in Section 19.8).

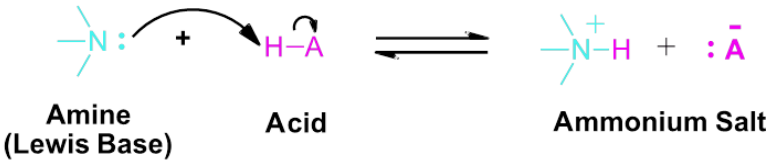
The ammonium ions of most simple aliphatic amines have a pK_a of about 10 or 11. However, these simple amines are all more basic (i.e., have a higher pK_a) than ammonia. Why? Remember that, relative to hydrogen, alkyl groups are electron releasing, and that the presence of an electron-releasing group stabilizes ions carrying a positive charge. Thus, the free energy difference between an alkylamine and an alkylammonium ion is less than the free energy difference between ammonia and an ammonium ion; consequently, an alkylamine is more easily protonated than ammonia, and therefore the former has a higher pK_a than the latter.

BASICITY OF NITROGEN GROUPS

In this section we consider the relative basicity of amines. When evaluating the basicity of a nitrogen-containing organic functional group, the central question we need to ask ourselves is: how reactive (and thus how basic and nucleophilic) is the lone pair on the nitrogen? In other words, how much does that lone pair want to break away from the nitrogen nucleus and form a new bond with a hydrogen. The lone pair electrons makes the nitrogen in amines electron dense, which is represents by a red color in the electrostatic potential map present below left. Amine are basic and easily react with the hydrogen of acids which are electron poor as seen below.



Amines are one of the only neutral functional groups which are considered basis which is a consequence of the presence of the lone pair electrons on the nitrogen. During an acid/base reaction the lone pair electrons attack an acidic hydrogen to form a N-H bond. This gives the nitrogen in the resulting ammonium salt four single bonds and a positive charge.



https://chem.libretexts.org/@go/page/474249

Amines react with water to establish an equilibrium where a proton is transferred to the amine to produce an ammonium salt and the hydroxide ion, as shown in the following general equation:

$$RNH2_{(aq)} + H_2O_{(l)} \rightleftharpoons RNH3^+_{(aq)} + OH^-_{(aq)} \tag{24.3.1}$$

The equilibrium constant for this reaction is the base ionization constant (K_b), also called the base dissociation constant:

$$K_b = \frac{[RNH3^+][OH^-]}{[NH2]} \tag{24.3.2}$$

$$pK_b = -\log K_b$$

Just as the acid strength of a carboxylic acid can be measured by defining an acidity constant K_a (Section 2-8), the base strength of an amine can be measured by defining an analogous basicity constant K_b. The larger the value of K_b and the smaller the value of pK_b, the more favorable the proton-transfer equilibrium and the stronger the base.

However, Kb values are often not used to discuss relative basicity of amines. It is common to compare basicity's of amines by using the K_a's of their conjugate acids, which is the corresponding ammonium ion. Fortunately, the K_a and K_b values for amines are directly related.

Consider the reactions for a conjugate acid-base pair, $RNH_3^+ - RNH_2$:

$$\mathrm{RNH_3^+}(aq) + \mathrm{H_2O}(l) \rightleftharpoons \mathrm{RNH_2}(aq) + \mathrm{H_3O^+}(aq) \quad K_\mathrm{a} = \frac{[\mathrm{RNH_2}][\mathrm{H_3O}]}{[\mathrm{RNH_3^+}]}$$

$$\mathrm{RNH_2}(aq) + \mathrm{H_2O}(l) \rightleftharpoons \mathrm{RNH_3^+}(aq) + \mathrm{OH^-}(aq) \quad K_\mathrm{b} = \frac{[\mathrm{RNH_3^+}][\mathrm{OH-}]}{[\mathrm{RNH_2}]}$$

Adding these two chemical equations together yields the equation for the autoionization for water:

$$\cancel{\mathrm{RNH_3^+}(aq)} + \mathrm{H_2O}(l) + \cancel{\mathrm{RNH_2}(aq)} + \mathrm{H_2O}(l) \rightleftharpoons \mathrm{H_3O^+}(aq) + \cancel{\mathrm{RNH_2}(aq)} + \mathrm{OH^-}(aq) + \cancel{\mathrm{RNH_3^+}(aq)}$$

$$2\,\mathrm{H_2O}(l) \rightleftharpoons \mathrm{H_3O^+}(aq) + \mathrm{OH^-}(aq)$$

Given that the *K* expression for a chemical equation formed from adding two or more other equations is the mathematical product of the input equations' *K* constants.

$$K_a \text{ X } K_b = \{2\ H_2O\} / (H_3O^+)\{OH^-\} = Kw$$

$$K_\mathrm{a} = \frac{K_\mathrm{w}}{K_\mathrm{b}}$$

$$pK_a + pK_b = 14$$

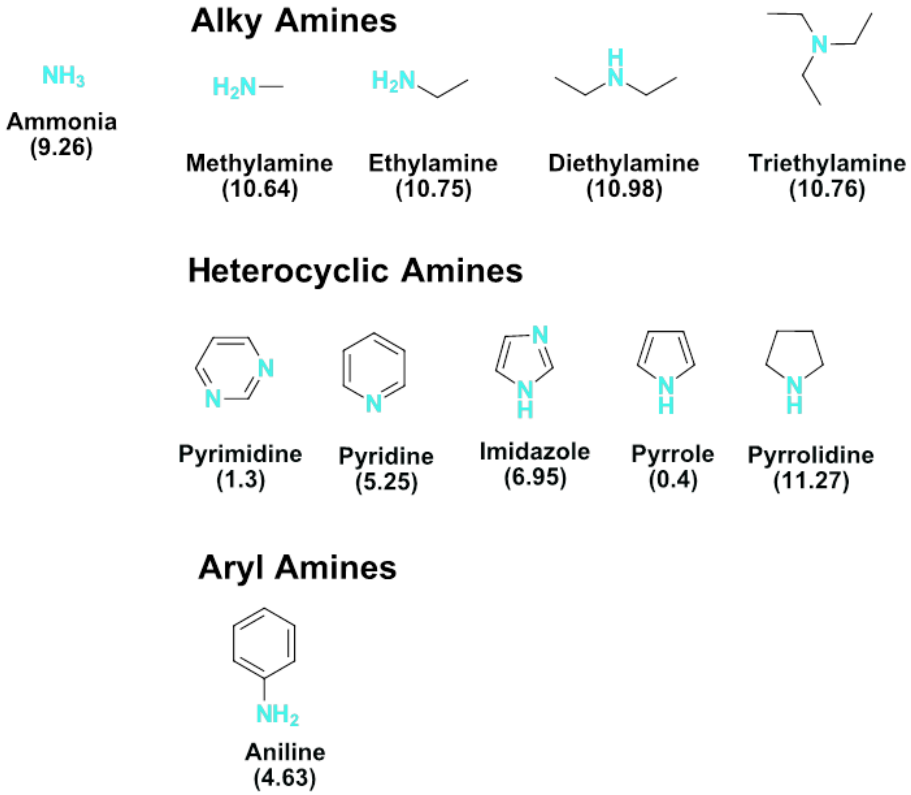
Thus if the K_a for an ammonium ion is know the K_b for the corresponding amine can be calculated using the equation $K_b = K_w / K_a$. This relationship shows that as an ammonium ion becomes more acidic (K_a increases / pK_a decreases) the correspond base becomes weaker (K_b decreases / pK_b increases)

Weaker Base = Larger K_a and Smaller pK_a of the Ammonium ion

Stronger Base = Smaller K_a and Larger pK_a of the Ammonium ion

Like ammonia, most amines are Brønsted-Lowry and Lewis bases, but their base strength can be changed enormously by substituents. Most simple alkyl amines have pK_a's in the range 9.5 to 11.0, and their aqueous solutions are basic (have a pH of 11 to 12, depending on concentration).

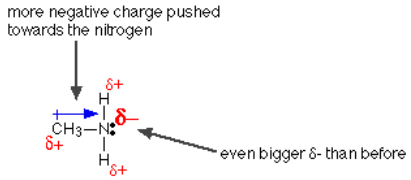
Aromatic herterocyclic amines (such as pyrimidine, pyridine, imidazole, pyrrole) are significantly weaker bases as a consequence of three factors. The first of these is the hybridization of the nitrogen. In each case the heterocyclic nitrogen is sp^2 hybridized. The increasing s-character brings it closer to the nitrogen nucleus, reducing its tendency to bond to a proton compared to sp^3 hybridized nitrogens. The very low basicity of pyrrole reflects the exceptional delocalization of the nitrogen electron pair associated with its incorporation in an aromatic ring. Imidazole (pK_a = 6.95) is over a million times more basic than pyrrole because the sp^2 nitrogen that is part of one double bond is structurally similar to pyridine, and has a comparable basicity.



Basicity of common amines (pK_a of the conjugate ammonium ions)

INDUCTIVE EFFECTS IN NITROGEN BASICITY

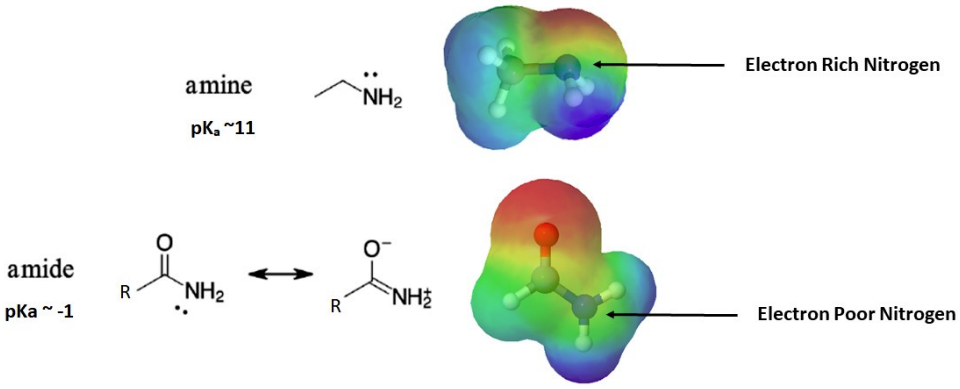
Alkyl groups donate electrons to the more electronegative nitrogen. The inductive effect makes the electron density on the alkylamine's nitrogen greater than the nitrogen of ammonia. The small amount of extra negative charge built up on the nitrogen atom makes the lone pair even more attractive towards hydrogen ions. Correspondingly, primary, secondary, and tertiary alkyl amines are more basic than ammonia.



Compound	pK_a
NH_3	9.3
CH_3NH_2	10.66
$(CH_3)_2NH$	10.74
$(CH_3)_3N$	9.81

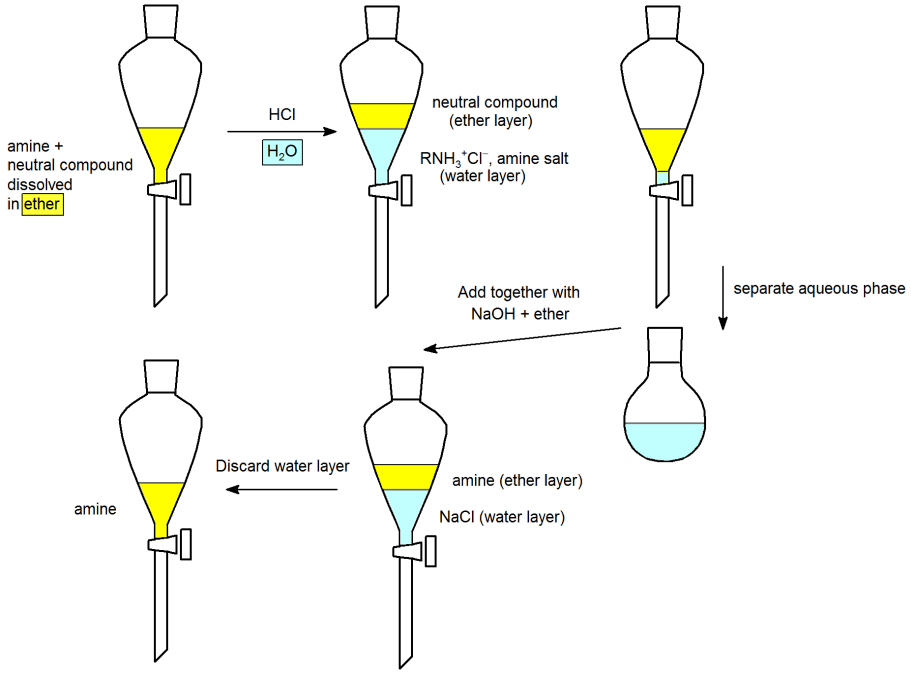
COMPARING THE BASICITY OF ALKYLAMINES TO AMIDES

The nitrogen atom is strongly basic when it is in an amine, but *not* significantly basic when it is part of an amide group. While the electron lone pair of an amine nitrogen is localized in one place, the lone pair on an amide nitrogen is delocalized by resonance. The electron density – in the form of a lone pair – is stabilized by resonance delocalization, even though there is not a negative charge involved. Here's another way to think about it: the lone pair on an amide nitrogen is not as available for bonding with a proton – these two electrons are too stable being part of the delocalized pi-bonding system. The electrostatic potential map shows the effect of resonance on the basicity of an amide. The map shows that the electron density, shown in red, is almost completely shifted towards the oxygen. This greatly decreases the basicity of the lone pair electrons on the nitrogen in an amide.



AMINE EXTRACTION IN THE LABORATORY

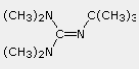
Extraction is often employed in organic chemistry to purify compounds. Liquid-liquid extractions take advantage of the difference in solubility of a substance in two immiscible liquids (e.g. ether and water). The two immiscible liquids used in an extraction process are (1) the solvent in which the solids are dissolved, and (2) the extracting solvent. The two immiscible liquids are then easily separated using a separatory funnel. For amines one can take advantage of their basicity by forming the protonated salt ($RNH_2^+Cl^-$), which is soluble in water. The salt will extract into the aqueous phase leaving behind neutral compounds in the non-aqueous phase. The aqueous layer is then treated with a base (NaOH) to regenerate the amine and NaCl. A second extraction-separation is then done to isolate the amine in the non-aqueous layer and leave behind NaCl in the aqueous layer.



IMPORTANT REAGENT BASES

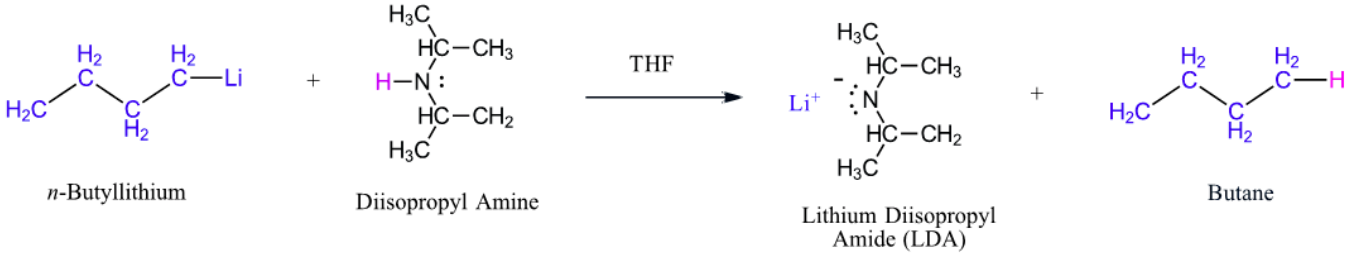
The significance of all these acid-base relationships to practical organic chemistry lies in the need for organic bases of varying strength, as reagents tailored to the requirements of specific reactions. The common base sodium hydroxide is not soluble in many organic solvents, and is therefore not widely used as a reagent in organic reactions. Most base reagents are alkoxide salts, amines or amide salts. Since alcohols are much stronger acids than amines, their conjugate bases are weaker than amine bases, and fill the gap in base strength between amines and amide salts.

Basicity of common amines (pK_a of the conjugate ammonium ions)

Base Name	Pyridine	Triethyl Amine	Hünig's Base	Barton's Base	Potassium t-Butoxide	Sodium HMDS	LDA
Formula		$(C_2H_5)_3N$			$(CH_3)_3CO^{(-)}\ K^{(+)}$	$[(CH_3)_3Si]_2N^{(-)}\ Na^{(+)}$	$[(CH_3)_2CH]_2N^{(-)}\ Li^{(+)}$
pK_a of conjugate acid	5.3	10.7	11.4	14	19	26	35.7

Pyridine is commonly used as an acid scavenger in reactions that produce mineral acid co-products. Its basicity and nucleophilicity may be modified by steric hindrance, as in the case of 2,6-dimethylpyridine (pK_a=6.7), or resonance stabilization, as in the case of 4-dimethylaminopyridine (pK_a=9.7). Hünig's base is relatively non-nucleophilic (due to steric hindrance), and is often used as the base in E2 elimination reactions conducted in non-polar solvents. Barton's base is a strong, poorly-nucleophilic, neutral base that serves in cases where electrophilic substitution of other amine bases is a problem. The alkoxides are stronger bases that are often used in the corresponding alcohol as solvent, or for greater reactivity in DMSO. Finally, the two amide bases see widespread use in generating enolate bases from carbonyl compounds and other weak carbon acids.

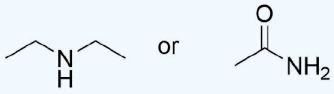
In addition to acting as a base, 1° and 2° amines can act as very weak acids. Their N-H proton can be removed if they are reacted with a strong enough base. An example is the formation of lithium diisopropylamide (LDA, $LiN[CH(CH_3)_2]_2$) by reacting *n*-butyllithium with diisopropylamine (pK_a 36) **(**Section 22-5**)**. LDA is a very strong base and is commonly used to create enolate ions by deprotonating an alpha-hydrogen from carbonyl compounds **(**Section 22-7**)**.



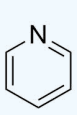
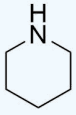
n-Butyllithium + Diisopropyl Amine → Lithium Diisopropyl Amide (LDA) + Butane

EXERCISE 24.3.1

Select the more basic amine from each of the following pairs of compounds.

(a)  or

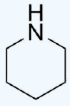
(b)  or NaOH

(c)  or 

Answer

(a)

(b) NaOH

(c) 

EXERCISE 24.3.1

The 4-methylbenzylammonium ion has a pKa of 9.51, and the butylammonium ion has a pKa of 10.59. Which is more basic? What's the pKb for each compound?

Answer

The butylammonium is more basic. The pKb for butylammonium is 3.41, the pKb for 4-methylbenzylammonium is 4.49.

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24.4: BASICITY OF ARYLAMINES

OBJECTIVES

After completing this section, you should be able to

1. use the concept of resonance to explain why arylamines are less basic than their aliphatic counterparts.
2. arrange a given series of arylamines in order of increasing or decreasing basicity.
3. discuss, in terms of inductive and resonance effects, why a given arylamine is more or less basic than aniline.

STUDY NOTES

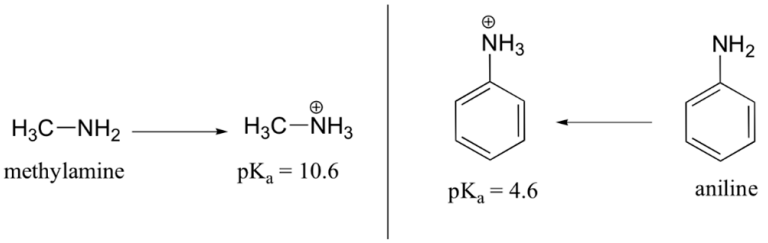
With reference to the discussion of base strength, the traditional explanation for the base-strengthening effect of electron-releasing (I) substituents is that such substituents help to stabilize the positive charge on an arylammonium ion more than they stabilize the unprotonated compound, thereby lowering $\Delta G°$.

The electron-withdrawing (i.e., deactivating) substituents decrease the stability of a positively charged arylammonium ion.

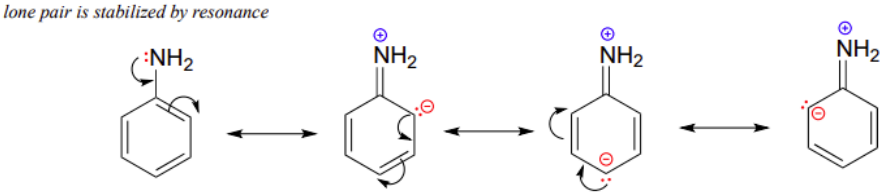
Note that the arylammonium ion derived from aniline, $PhNH_3^+$, is commonly referred to as the anilinium ion.

BASICITY OF ANILINE

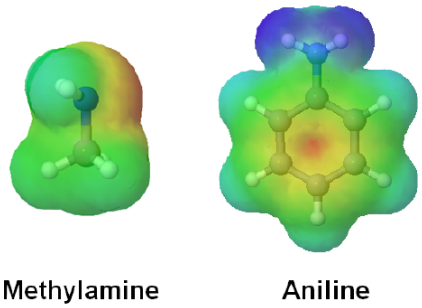
Aniline is substantially less basic than methylamine, as is evident by looking at the pK_a values for their respective ammonium conjugate acids (remember that the lower the pKa of the conjugate acid, the weaker the base).



This difference is basicity can be explained by the observation that, in aniline, the lone pair of electrons on the nitrogen are delocalized by the aromatic p system, making it less available for bonding to H^+ and thus less basic. The lone pair electrons of aniline are involved in four resonance forms making them more stable and therefore less reactive relative to alkylamines.



The effect of delocalization can be seen when viewing the electrostatic potential maps of aniline an methyl amine. The nitrogen of methyl amine has a significant amount of electron density on its nitrogen, shown as a red color, which accounts for it basicity compared to aniline. While the electron density of aniline's nitrogen is delocalized in the aromatic ring making it less basic.



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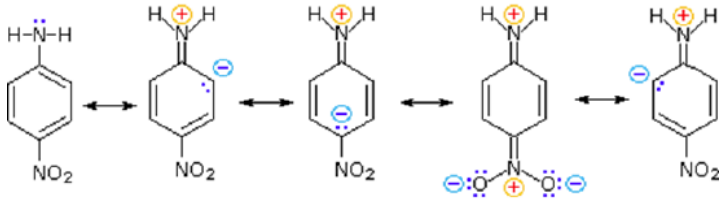
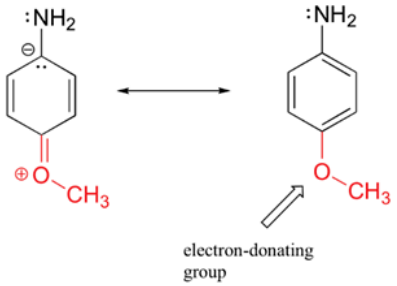
BASICITY OF SUBSTITUTED ARYLAMINES

The addition of substituents onto the aromatic ring can can make arylamines more or less basic. Substituents which are electron-withdrawing (-Cl, -CF_3, -CN, -NO_2) decrease the electron density in the aromatic ring and on the amine making the arylamine less basic. In particular, the nitro group of *para*-nitroaniline allows for an additional resonance form to be drawn, which further stabilizes the lone pair electrons from the nitrogen, making the substituted arylamine less basic than aniline. This effect is analogous to the one discussed for the acidity of substituted phenols in **Section 17.2**.



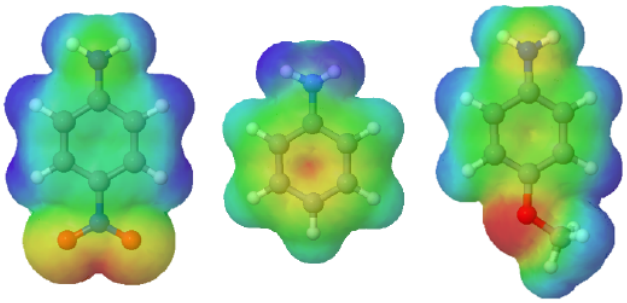
Reduced Basicity of *para*-Nitroaniline due to Electron Pair Delocalization

Substituents which are electron-donating (-CH_3, -OCH_3, -NH_2) increase the electron density in the aromatic ring and on the amine making the arylamine more basic. In the case of *para*-methoxyaniline, the lone pair on the methoxy group donates electron density to the aromatic system, and a resonance contributor can be drawn in which a negative charge is placed on the carbon adjacent to the nitrogen, which makes the substituted arylamine more basic than aniline.



Increased Basicity of para-Methoxyaniline due to Electron-Donation

The shifting electron density of aniline, *p*-nitroaniline, and *p*-methoxyaniline are seen in their relative electrostatic potential maps. For *p*-Nitroaniline virtually all of the electron density, shown as a red/yellow color. is pulled toward the electron-withdrawing nitro group. In *p*-methoxyaninline the electron donating methoxy group donates electron density into the ring. The amine in p-methoxyaniline is shown to have more electron density, shown as a yellow color, when compared to the amine in aniline.



***p*-Nitroaniline** **Aniline** ***p*-Methoxyaniline**

? EXERCISE S24.4.1

Using the knowledge of the electron donating or withdrawing effects of subsituents gained in Section 16.6, rank the following compound in order of decreasing basicity.

a. *p*-Nitroaniline, methyl p-aminobenzoate, *p*-chloroaniline
b. *p*-Bromoaniline, *p*-Aminobenzonitrile, *p*-ethylaniline
c. p-(Trifluoromethyl)aniline, *p*-methoxyaniline, *p*-methylaniline

Answers

a. *p*-Chloroaniline, methyl p-aminobenzoate, *p*-nitroaniline
b. *p*-Ethylaniline, *p*-Bromoaniline, *p*-aminobenzonitrile
c. *p*-Methoxyaniline, *p*-methylaniline, *p*-(trifluoromethyl)aniline

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24.5: BIOLOGICAL AMINES AND THE HENDERSON-HASSELBALCH EQUATION

OBJECTIVES

1. identify the form that amine bases take within living cells.
2. use the Henderson-Hasselbalch equation to calculate the percentage of a base that is protonated in a solution, given the pK_a value of the associated ion and the pH of the solution.
3. explain why organic chemists write cellular amines in their protonated form and amino acids in their ammonium carboxylate form.

The Henderson-Hasselbalch equation is very useful relating the pKa of a buffered solution to the relative amounts of an acid and its conjugate base. In **Section 20-3**, we used the Henderson-Hasselbalch equation to show that under physiological pH, carboxylic acids are almost completely dissociated into their carboxylate ions.

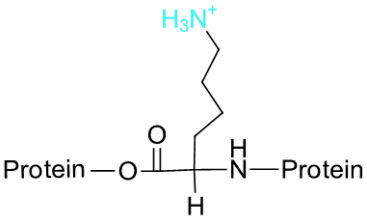
$$\mathrm{pH} = \mathrm{pK_a} + \log\left(\frac{\text{concentration of conjugate base}}{\text{concentration of weak acid}}\right) \quad \text{(Henderson-Hasselbalch equation)}$$

So, what does the side chain of a lysine amino acid residue look like if it is on the surface of a protein in an aqueous solution buffered pH 7.0? Is it protonated or deprotonated? The values in the Henderson-Hasselbalch can be used for an amine with the ammonium salt written as, HA = RNH_3^+, and the amine as being, A^- = RNH_2. With an approximate pK_a of 10.8 for the protonated amine HA, it should be >99% protonated, in the positively-charged, ammonium form:

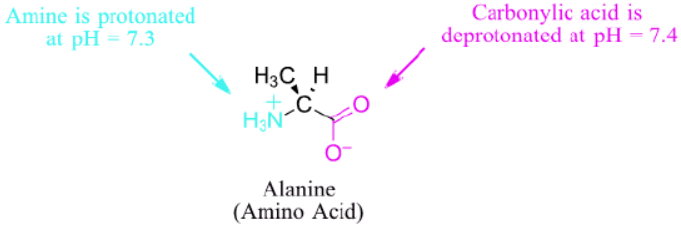
$$7.0 = 10.8 + \log\left(\frac{[\mathrm{RNH_2}]}{[\mathrm{RNH_3^+}]}\right)$$

$$\frac{[\mathrm{RNH_2}]}{[\mathrm{RNH_3^+}]} = 1.6 \times 10^{-4}$$

So, $[\mathrm{RNH_3^+}] \gg [\mathrm{RNH_2}]$ at this pH. Consequently, in an aqueous solution buffered at pH 7, carboxylic acid groups can be expected to be essentially 100% deprotonated and negatively charged (ie. in the carboxylate form), and amine groups essentially 100% protonated and positively charged (i.e., in the ammonium form).



Alcohols are fully protonated and neutral at pH 7, as are thiols. The imidazole group on the histidine side chain has a pK_a near 7, and thus exists in physiological solutions as mixture of both protonated and deprotonated forms.



EXERCISE 24.5.1

Would you expect an aromatic hetererocycle, pyrrole, to be protonated at pH = 7.3? Use the Henderson-Hasselbalch equation to determine your answer. pKa of protonated pyrrole is 0.4.

Answer

$$7.3 = 0.4 + \log\left(\frac{[\mathrm{RNH_2}]}{[\mathrm{RNH_3^+}]}\right)$$

$$\frac{[\mathrm{RNH_2}]}{[\mathrm{RNH_3^+}]} = 7.9 \times 10^6$$

So, $[\mathrm{RNH_2}] \gg [\mathrm{RNH_3^+}]$. Thus pyrrole would be almost completely unprotonated at pH = 7.

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24.6: SYNTHESIS OF AMINES

OBJECTIVES

After completing this section, you should be able to

1. write equations to illustrate the synthesis of amines by
   a. reduction of nitriles or amides and nitro compounds.
   b. reactions involving alkyl groups:
      i. S_N2 reactions of alkyl halides, ammonia and other amines.
      ii. nucleophilic attack by an azide ion on an alkyl halide, followed by reduction of the azide so formed.
      iii. alkylation of potassium phthalimide, followed by hydrolysis of the *N*-alkyl phthalimide so formed (i.e., the Gabriel synthesis).
   c. reductive amination of aldehydes or ketones.
   d. Hofmann or Curtius rearrangements.
2. write detailed mechanisms for each of the steps involved in the synthetic routes outlined in Objective 1.
3. identify the product or products formed when
   a. a given nitrile or amide is reduced using lithium aluminum hydride.
   b. a given alkyl halide is reacted with ammonia or an alkylamine.
   c. a given alkyl halide is reacted with azide ion and the resulting product is reduced.
   d. a given alkyl halide is reacted with potassium phthalimide and the resulting product is hydrolyzed.
   e. a given aldehyde or ketone is reacted with ammonia or an amine in the presence of nickel catalyst.
   f. a given amide is treated with halogen and base.
   g. a given acyl azide is heated and then hydrolyzed.
4. identify the starting material, the other reagents, or both, needed to synthesize a given amine by any of the routes listed in Objective 1.
5. write a general equation to illustrate the preparation of an arylamine by the reduction of a nitro compound, and balance such an equation.
6. identify the product formed from the reduction of a given aromatic nitro compound.
7. identify the organic compound, the inorganic reagents, or both, needed to prepare a given arylamine.

KEY TERMS

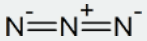
Make certain that you can define, and use in context, the key terms below.

- azide synthesis
- Curtius rearrangement
- Hofmann rearrangement
- Gabriel synthesis
- imide
- reductive amination

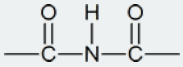
STUDY NOTES

You may wish to review the mechanism of S_N2 reactions which is discussed in some detail in Sections 11.2 and 11.3.

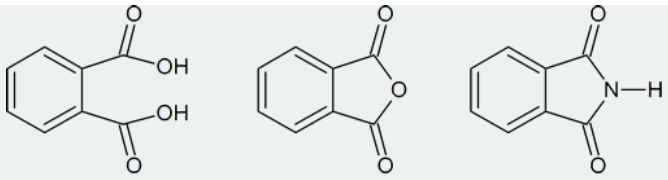
Azide synthesis is the first method on the table of synthesis of primary amines. The Lewis structure of the azide ion, N_3^-, is as shown below.



An “imide” is a compound in which an N$\ce{-}$H group is attached to two carbonyl groups; that is,



You should note the commonly used trivial names of the following compounds.



phthalic acid phthalic anhydride phthalimide

The phthalimide alkylation mentioned in the reading is also known as the Gabriel synthesis.

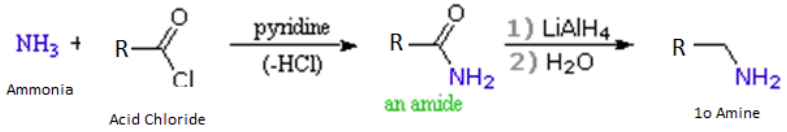
If necessary, review the reduction of nitriles (Section 20.7) and the reduction of amides (Section 21.7).

Before you read the section on reductive amination you may wish to remind yourself of the structure of an imine (see Section 19.8).

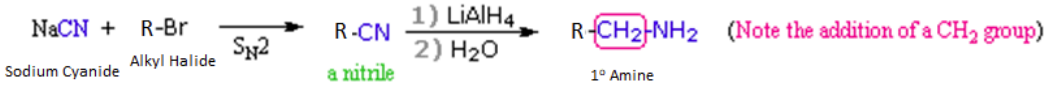
The Hofmann rearrangement is usually called the Hofmann degradation. In a true rearrangement reaction, no atoms are lost or gained; however, in this particular reaction one atom of carbon and one atom of oxygen are lost from the amide starting material, thus the term "rearrangement" is not really appropriate. There is a rearrangement step in the overall degradation process, however: this is the step in which the alkyl group of the acyl nitrene migrates from carbon to nitrogen to produce an isocyanate.

REDUCTION OF NITRILES, AMIDES, AND NITRO COMPOUNDS

Acid chlorides react with ammonia to give amides, by an addition-elimination path, and these are reduced to amines by $LiAlH_4$ (**Section 21-7**).

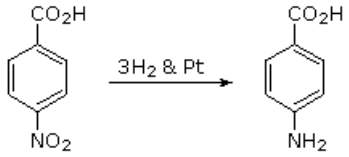


Alkyl halides can be converted to primary amines through a two-step process. First an S_N2 reaction with a cyanide anion converts the alkyl halide into a nitrile. Then the nitrile is reduced to a primary amine by $LiAlH_4$ (**Section 20-7**). During this reaction sequence an additional carbon atom is added.

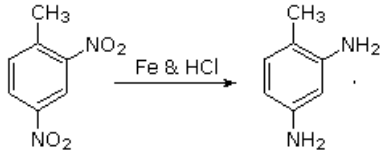


Arylamines are typically prepared by the reduction of a nitro group on an aromatic ring. Several methods for reducing nitro groups to amines are known. These include catalytic hydrogenation (H_2 + platinum catalyst), and zinc, iron, or tin(II) chloride in dilute mineral acid. The procedures described above are sufficient for most cases. Catalytic hydrogenation can be problematic because it is known to reduce other functional groups such as alkenes, alkynes, and some carbonyl groups.

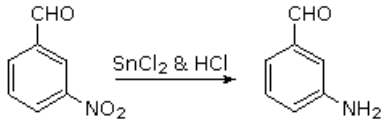
Nitro Group Reduction



p-Nitrobenzoic acid p-Aminobenzoic acid



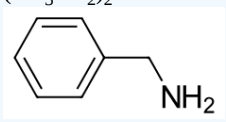
2,4-Dinitrotoluene 2,4-Toluenediamine



p-Nitrobenzaldehyde p-Aminobenzaldehyde

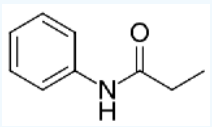
? EXERCISE 24.6.1

Propose structures of the starting materials needed to make the the following amines using the reduction of a nitrile or an amide:

a. $CH_3CH_2CH_2CH_2NH_2$
b. $(CH_3CH_2)_2NH$
c. 

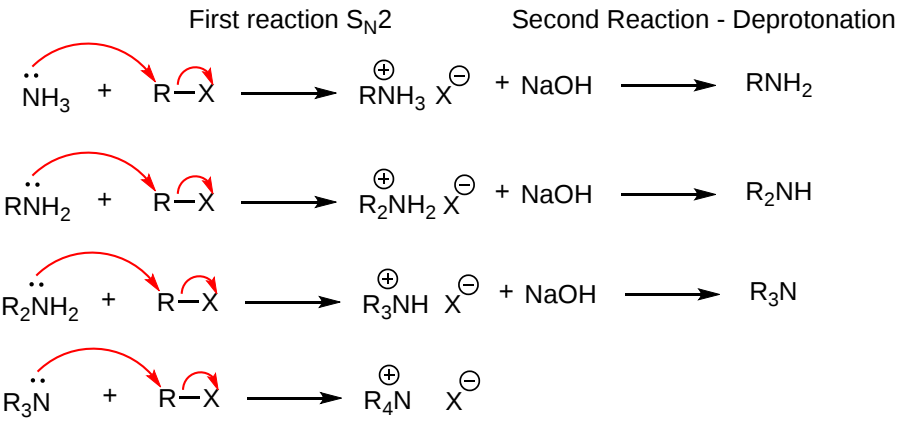
d. N-Propylaniline

Answer

a. $CH_3CH_2CH_2CONH_2$
b. $CH_3CONHCH_2CH_3$
c.
d. 

S_N2 REACTIONS OF ALKYL HALIDES

Because they posses lone pair electrons, ammonia and amines are considered good nucleophiles. Ammonia and amines can by alkylated by an S_N2 reaction with alkyl halides. The product of the reaction is an ammonium salt where the negative counter-ion is the halogen of the alkyl halide. When the alkylated products are 1º, 2º, and 3º amines, they can be deprotonated with NaOH to produce the neutral amine. When a 3º amine is alkylated, a quaternary ammonium salt is produced.



Alkylation is an efficient method for the synthesis of 3° and 4° amines. However, when 1° and 2° amines are alkylated a mixture of products is typically produced. When ammonia is reacted with an alkylhalide an monoalkylammonium salt is formed.

$$RX + NH_3 \rightarrow RNH_3^+ + X^-$$

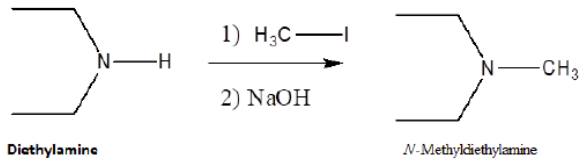
It is possible for any remaining ammonia present in the reaction to deprotonate the ammonium salt to produce the neutral monoalkyl amine.

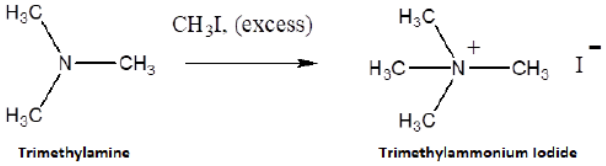
$$RNH_3^+ + NH_3 \rightarrow RNH_2 + NH_4^+$$

The monoalkyl amine is then free to react with a second alkyl halide creating a dialkylammonium salt. This process can be repeated to to eventually to create a tetralkylammonium salt. Typically when a alkyl halide is reacted with ammonia, a mixture of mostly 1° and 2° amines, with trace amounts of 3° amines and 4° ammonium salts, is produced.

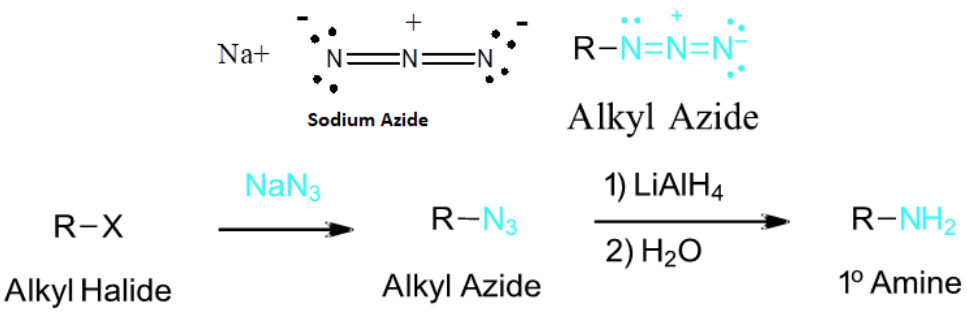
$$RNH_2 + RX \rightarrow R_2NH_2^+ + X^-$$

Example

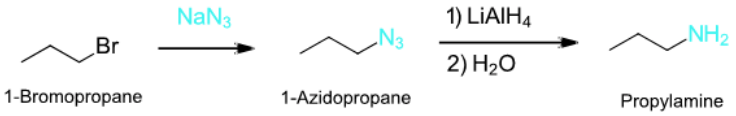




To synthesize a 1° or 2° amine, specific reactions are usually employed. A more efficient method starts with an S_N2 reaction between a 1° or 2° alkyl halide and the nucleophilic azide anion (N_3^-) to produce an alkyl azide. The alkyl azide is not nucleophilic so it cannot react with additional alkyl halide to produce overalkylation. Alkyl azide is then reduced with $LiAlH_4$ to produce a 1° amine.

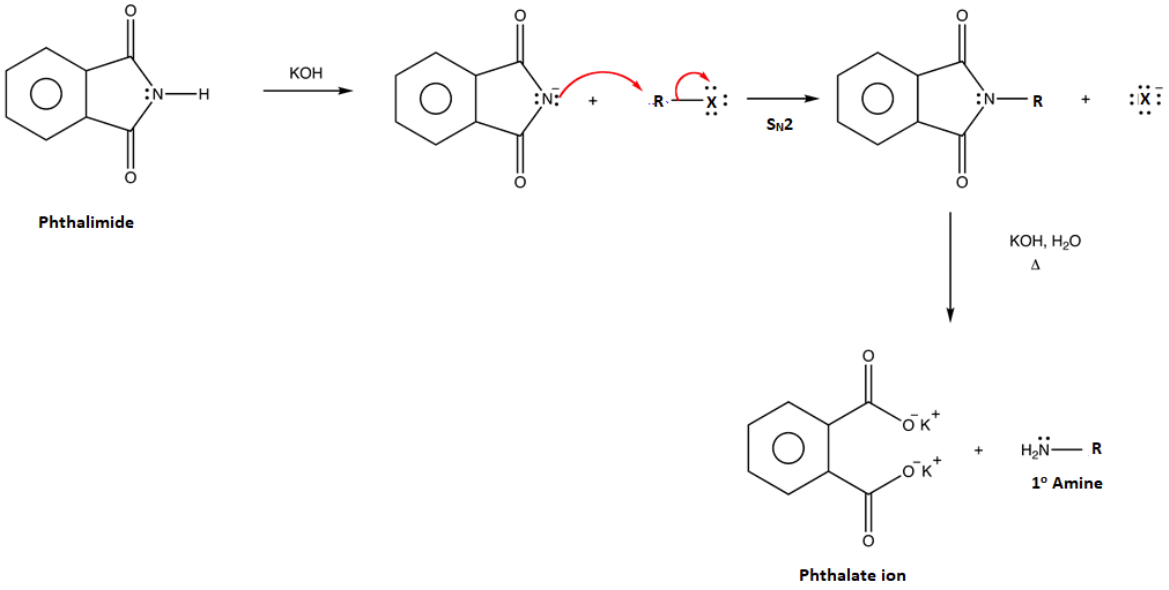


Example

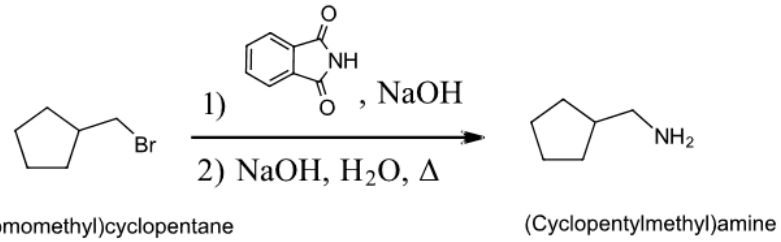


GABRIEL AMINE SYNTHESIS

Another common method for the synthesis of 1° amines is called the **Gabriel amine synthesis**. This reaction starts with the deprotonation of phthalimide by a hydroxide base such as potassium hydroxide (KOH). The N-H hydrogen of an imide functional group is acidic because its conjugate base is resonance stabilized by two carbonyl groups. The phthalimide anion is nucleophilic and easily alkylated through an S_N2 reaction with an alkyl halide. The resulting N-alkylated phthalimide then undergoes base hydrolysis to produce a 1° amine product. The mechanism for the base promoted hydrolysis of the N-alkylated phthalimide is analogous to the hydrolysis of an amide (Section 21-7).



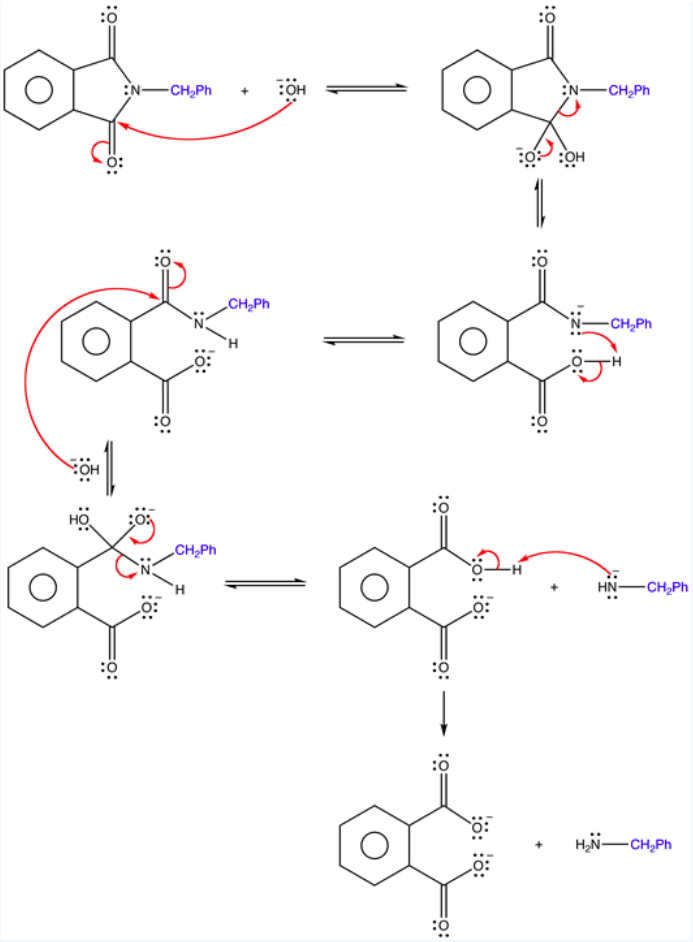
Example



? EXERCISES 24.6.1

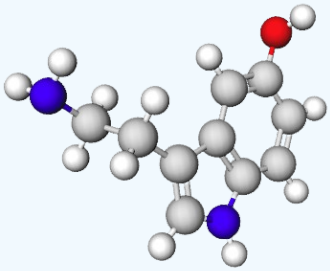
Write the mechanism for the base promoted hydrolysis of an N-alkyl phthalimide to create a 1° amine and the phthalate ion.2)

Answers

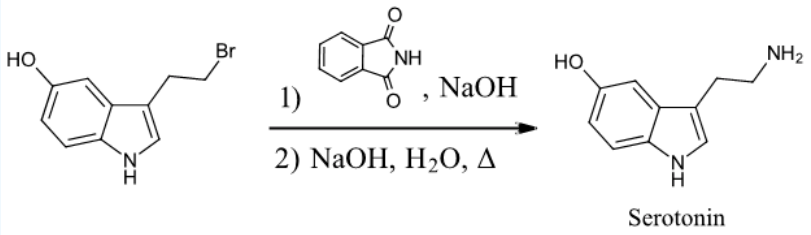


EXERCISE 24.6.2: SEROTONIN

Starting with any alkyl halide, show two methods to synthesize the neurotransmitter serotonin.



Answer



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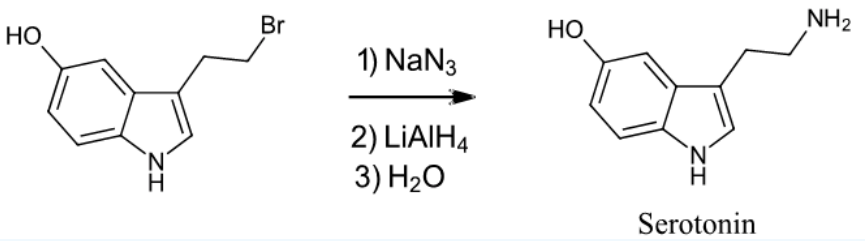
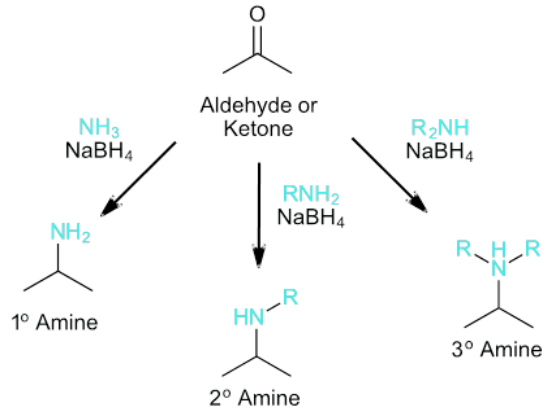


REDUCTIVE AMINATION

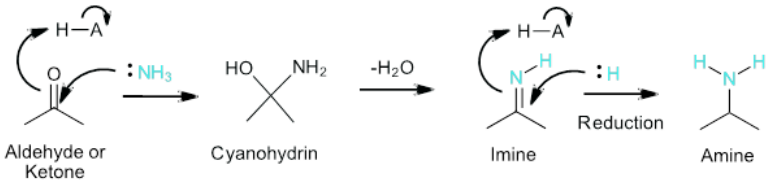
Aldehydes and ketones can be converted into 1°, 2° and 3° amines using **reductive amination**. The reaction takes place in two parts. The first step is the nucleophiic addition of ammonia, a 1° amine, or a 2° amine to a carbonyl group to form an imine **(Section 19-8)**. The second step is the reduction of the imine to an amine using a hydride reducing agent. Some common reducing agents used for this reaction are: sodium borohydride ($NaBH_4$), sodium cyanoborohydride ($NaBH_3CN$), $NaBH(OAc)_3$, or hydrogen gas (H_2) over a nickel catalyst.

General Reaction

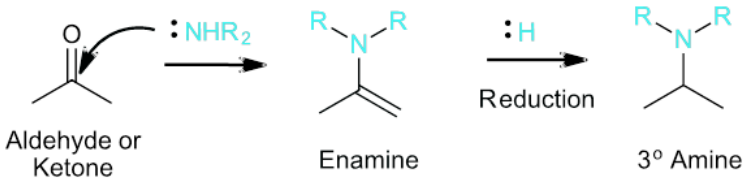


MECHANISM

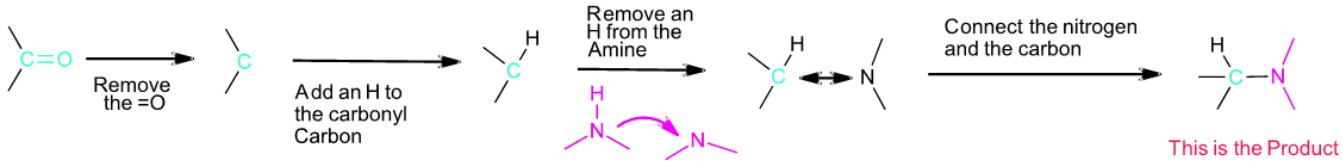
Reductive amination starts with the nucleophilic addition of ammonia or a 1° amine to an aldehyde or ketone forms a cyanohydrin intermediate. Subsequent dehydration forms an imine intermediate (Section 19-8). The imine undergoes hydride reduction in a similar fashion as C=O carbonyl bonds are reduced to an alcohol.



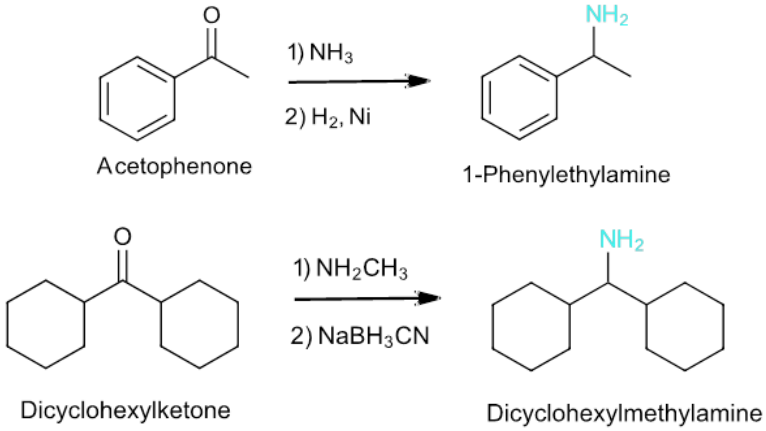
When a 2° amine is used for reductive amination, an enamine intermediate is formed which then undergoes hydride reduction to form a 3° amine.



PREDICTING THE PRODUCTS OF A REDUCTIVE AMINATION

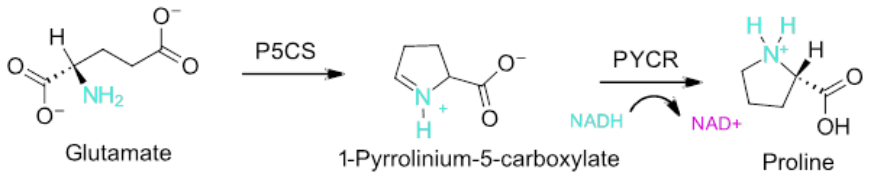


Examples



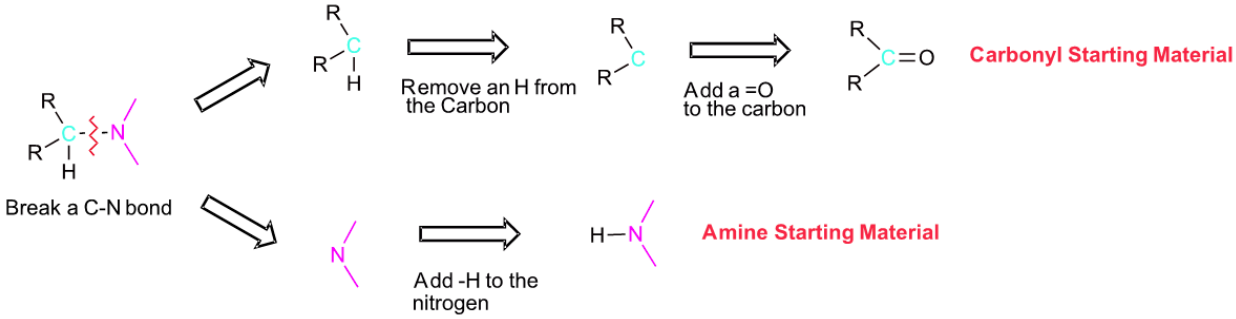
BIOLOGICAL REDUCTIVE AMINATIONS

Reductive amination is used in the biosynthesis of the amino acid proline. The enzyme pyrroline-5-carboxylate synthase (**P5CS)** catalyzes glutamate undergoing an intramolecular imine formation to produce 1-pyrrolinium 5-carboxylate. Then the enzyme pyrroline-5-carboxylate reductase **(PYCR)** catalyzed the nucleophilic hydride reduction of the C=N bond to produce proline. The biological hydride reducing agent for this sequence is reduced nicotinamide adenine dinucleotide **(NADH).**



PLANNING A SYNTHESIS USING A REDUCTIVE AMINATION

If you are trying to develop a synthesis of an amine molecule, the key bond break is a C-N bond in the target molecule. There may be multiple C-N bonds present, so each should be broken separately to produce a possible set of starting materials. Because the amine is commonly used in excess during a reductive animation, the pathway which provides the simplest amine starting material is preferred. The carbon from the broken C-N bond goes on to become a carbonyl starting material. The nitrogen gains a hydrogen to become the amine starting material.



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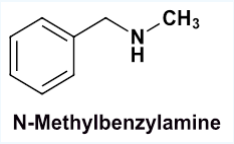
WORKED EXERCISE 24.6.1

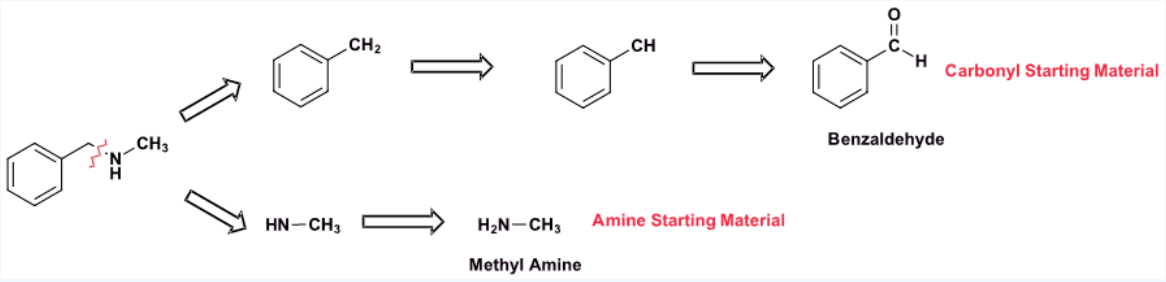
Show how N-methylbenzylamine can be synthesized using a reductive amination. If more than one pathway is possible, draw them both and determine which one would be preferred.



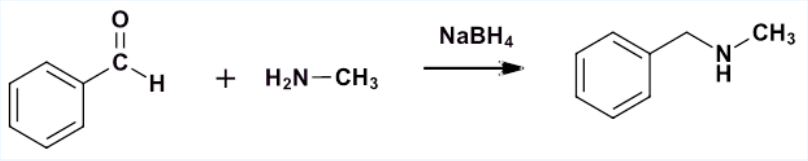
N-Methylbenzylamine

Answer

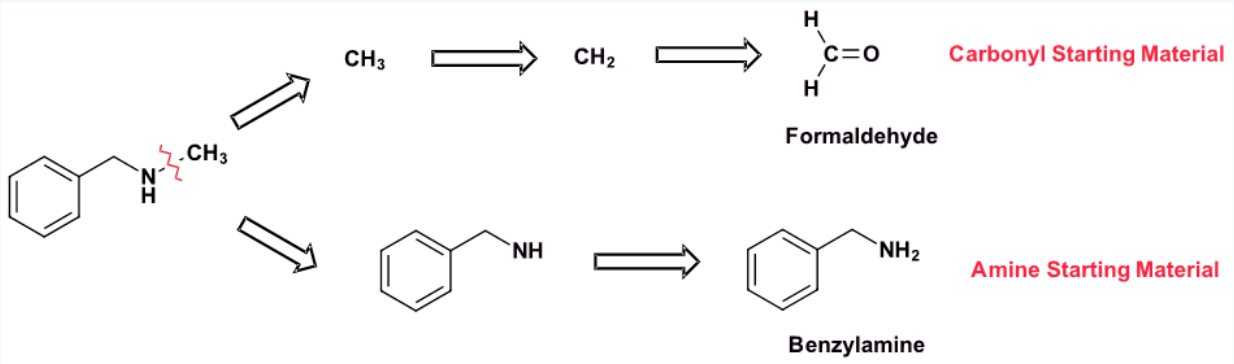
Pathway 1



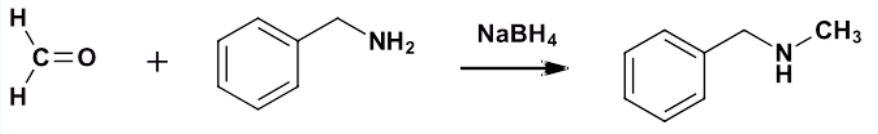
Solution 1



Pathway 2



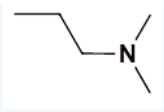
Solution 2

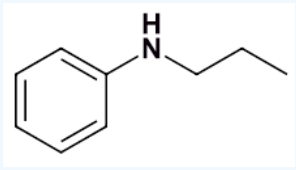


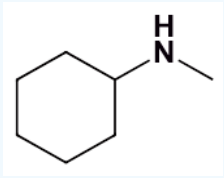
Because N-methylbenzylamine has two C-N bonds there are two possible synthesis pathways. Pathway 1 is most likely preferred because it uses the simplest amine starting material, methyl amine.

EXERCISE 24.6.1

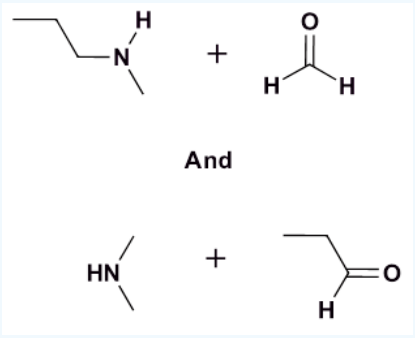
Provide starting materials which could be used to prepare the following compounds using a reductive amination. Show all possible pathways.

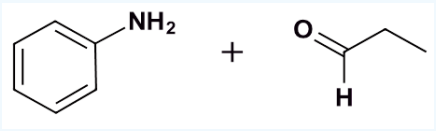
a. 

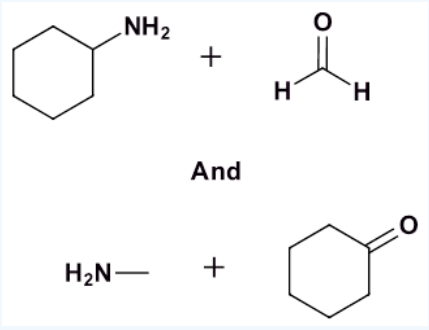
b. 

c. 

Answers

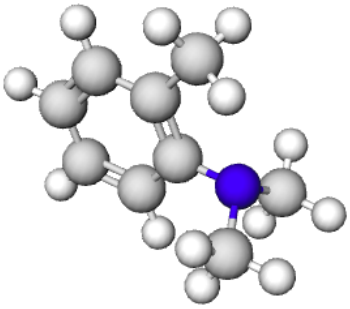
a. 

b. 

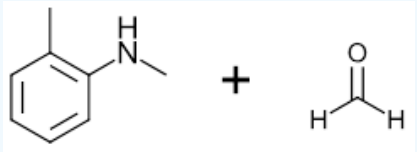
c. 

EXERCISE 24.6.4

Identify the starting materials which could provide the following molecule using a reductive amination.



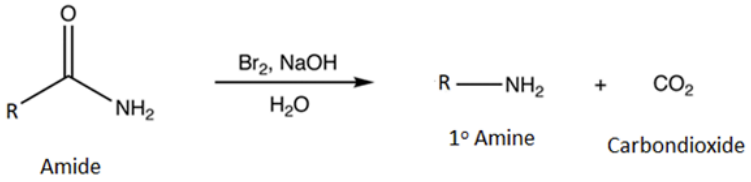
Answer



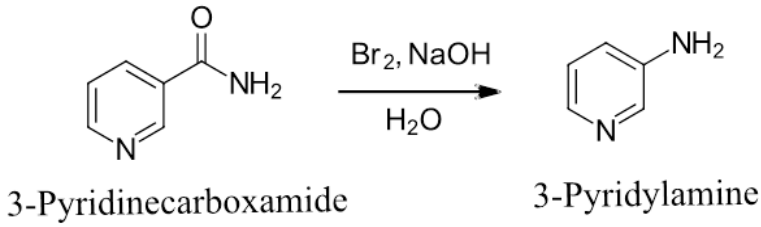
HOFMANN REARRANGEMENT

The Hofmann rearrangement occurs when a 1° amide is reacted with bromine (Br_2) and a base. The products are a 1° amine with one less carbon and carbon dioxide (CO_2).

General Reaction

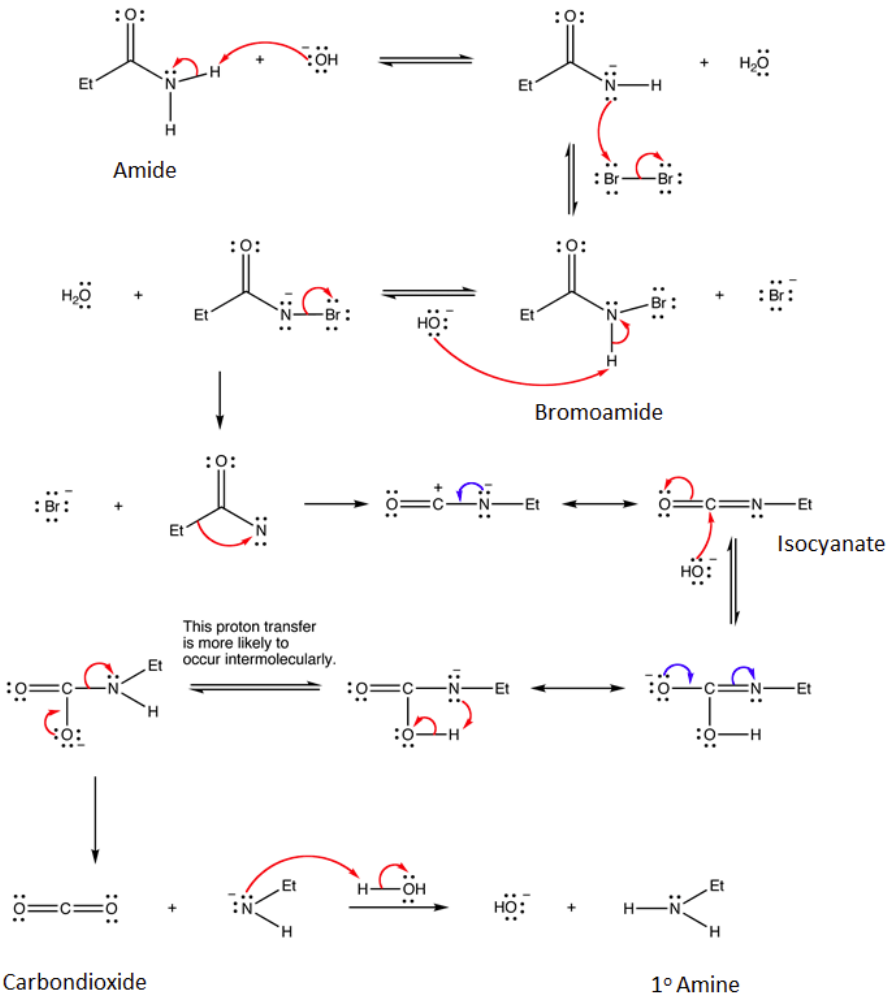


Example



Mechanism

The mechanism for the Hofmann rearrangement is quite complex. The mechanism starts with the deprontation of the primary amide by a base. The nitrogen is brominated during an S_N2 reaction with Br_2 to produce an N-bromoamide. Bromide is eliminated as a leaving group to produce a electron deficient nitrene-like nitrogen. Electrons from the adjacent C-C bond migrate to the nitrogen as part of a rearrangment to finally produce an isocyanate. The carbon in the isocyante is electrophilic and reacts with a nucleophilic hydroxide to create a C-O bond. After movement of electrons through resonance and a proton transfer a carbamate intermediate is formed. The carbamate decomposes to create an amide anion and a stable CO_2 molecule. Finally, water protonates the amide anion to produce a 1^o amine.

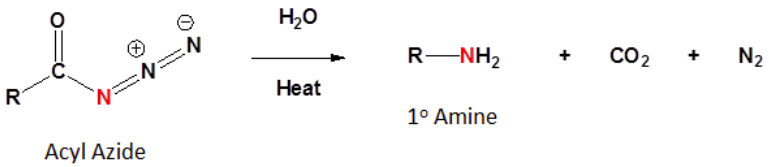


CURTIUS REARRANGEMENT

The Curtius Rearrangement is another method used to synthesize a 1° amine.

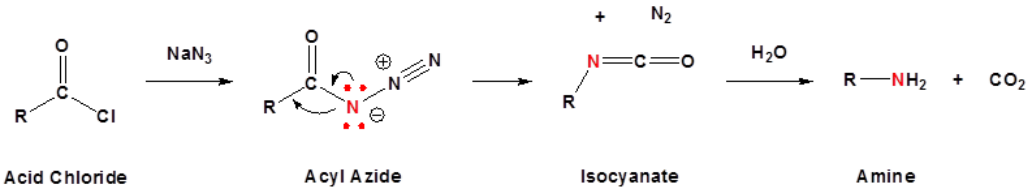
General Reaction

The Curtius rearrangement involves an acyl azide reacting with water and heat to produce a 1° amine along with CO_2 and N_2. The acyl azide is usually made by a nucleophilic substitution of an acid chloride with sodium azide (NaN_3)

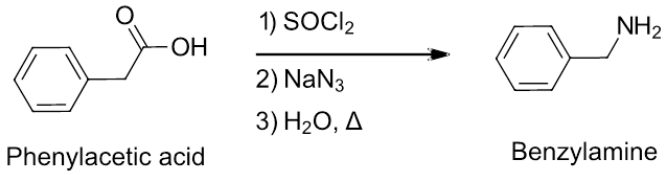


Mechanism

The mechanism of the Curtius rearrangement is quite similar to the Hoffman rearrangement. The loss of N_2 as a leaving group creates an electron deficient nitrogen. The adjacent -R group migrates to form an isocyanate. Reaction of the isocyanate forms a carbamate which decomposes to form a 1° amine and CO_2.

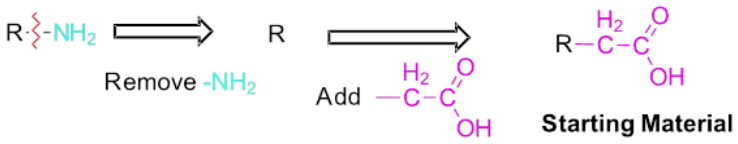


Example



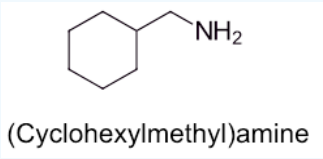
Planning a Synthesis using a Hoffman or Curtius Rearrangement

Because the amide and the acyl azide required for these rearrangements both are best made from an acid chloride, synthesis of amines using these reaction are best started from the corresponding carboxylic acid. For retrosynthetic analysis starting from the desired amine product - the key break is the C-NH_2 bond. The amine is removed and replaced with a -CH_2CO_2H fragment to provide the required carboxylic acid starting material.



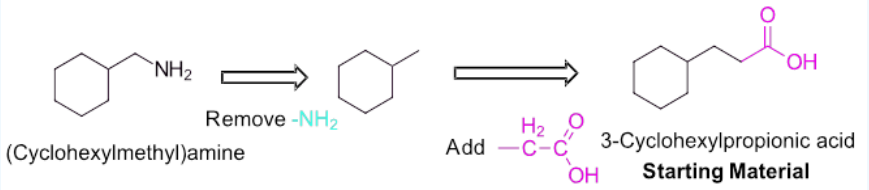
WORKED EXAMPLE 24.6.1

Show how the following molecule could be prepared from a carboxylic acid starting material using both the Hoffman and Curtius rearrangements.



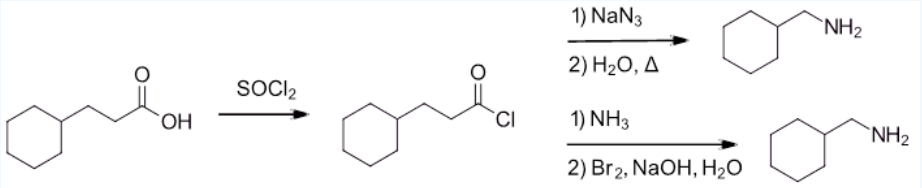
Answer

First determine the structure of the carboxylic acid starting material. This will be the starting material for both rearrangements. In the first step, convert the carboxylic acid into an acid halide using thionyl chloride ($SOCl_2$). Then use the required conditions for each rearrangement.



Solution

The top solution shows the Curtius Rearrangement, while the bottom is an example using the Hofmann Rearrangement.



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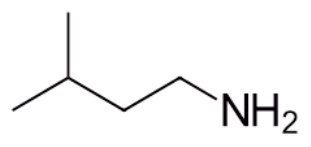
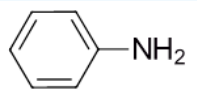
EXERCISES 24.6.1

1) Using a carboxylic acid starting material explain how to prepare the following molecules using both the Hoffman and Curtius rearrangements.

a)



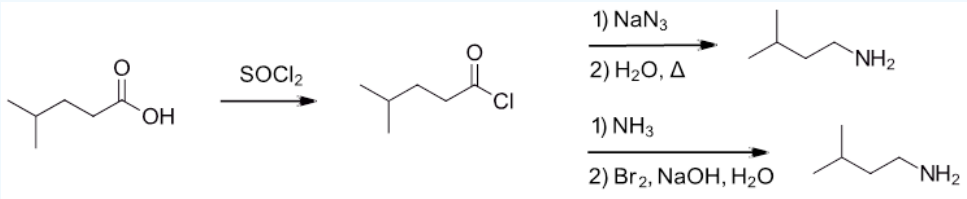
b)



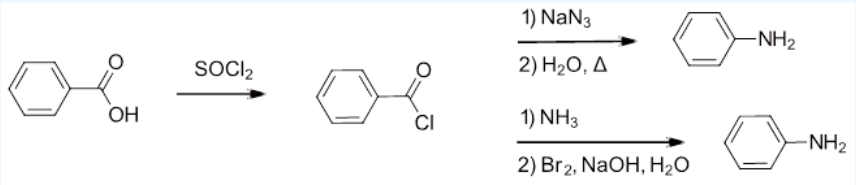
Answers

1)

a) The top solution shows the Curtius Rearrangement, while the bottom is an example using the Hofmann Rearrangement.



b) The top solution shows the Curtius Rearrangement, while the bottom is an example using the Hofmann Rearrangement.



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24.7: REACTIONS OF AMINES

OBJECTIVES

After completing this section, you should be able to

1. write an equation to represent the reaction that takes place between ammonia, a primary or secondary amine, and an acid chloride.
2. identify the product formed when a given amine reacts with a given acid chloride.
3. identify the amine, the acid chloride, or both, needed to synthesize a given amide.
4. write a reaction sequence to illustrate the overall conversion of an amine to an alkene via a Hofmann elimination.
5. identify the alkene most likely to be formed when a given quaternary ammonium salt is heated with moist silver oxide (or silver hydroxide).
6. deduce the structure of an unknown quaternary ammonium salt, given the identity of the alkene or alkenes produced when the salt is heated with moist silver oxide.

KEY TERMS

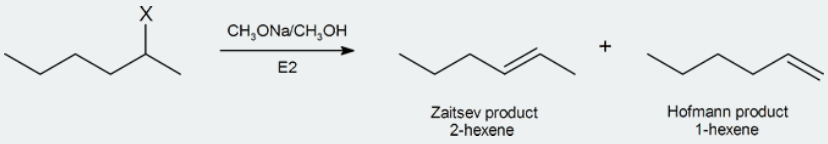
Make certain that you can define, and use in context, the key term below.

- Hofmann elimination

STUDY NOTES

The alkylation and acylation of amines have been dealt with in previous sections: alkylation in Section 24.6 and acylation in Sections 21.4 and 21.5. Review these sections if necessary.

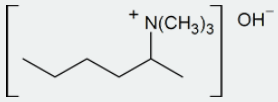
One explanation is given for Hofmann elimination further on in this reading. Another argument, based on the consideration of the structures of the possible transition states, has been suggested by Joseph Bunnett and is widely accepted. We can begin to understand Bunnett's reasoning by considering the elimination products formed from by the dehydrohalogenation of a number of substituted hexanes in the reaction



The table below describes the proportion of each product you would expect when X in the above reaction represents a given halogen.

X	% 2-hexene	% hexene
I	81	19
Br	72	28
Cl	67	33
F	30	70

As we descend this table, the electron-withdrawing ability of X increases, and the percentage of Hofmann product also increases. Given that the $(CH_3)_3N^+$ group is strongly electron-withdrawing, it is quite consistent for a compound of the type



to give 96% Hofmann product and 4% Zaitsev product in an E2 elimination reaction. But why does the proportion of Hofmann product increase as the electron-withdrawing ability of X increases? Bunnett suggests that the transition state in an E2 process can vary from being "carbocation-like" on one hand to "carbanion-like" on the other.

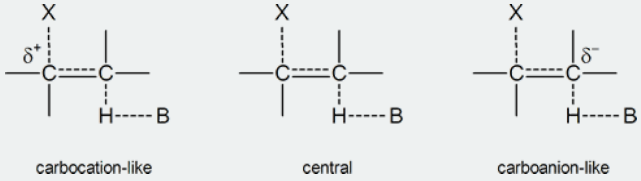


Figure 24.1 Various transition states for an E2 elimination reaction

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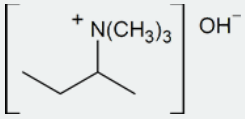
In a carbocation-like transition state, the C-X bond is broken to a greater extent than the C-H bond; in the central transition state both, the C-X bond and the C-H bond are broken to an equal extent; and in the carbanion-like transition state, the C-H bond is broken to a greater extent than the C-X bond. In the latter case, a partial negative charge will develop on the carbon atom to which the hydrogen is attached, hence the term “carbanion-like.” As we already know, any species or transition state bearing a full or partial negative charge is stabilized by the presence of electron-withdrawing groups and destabilized by the presence of electron-releasing groups.

Let us now consider the two possible transition states for an E2 elimination of $(CH_3)_3NH^+$ from a quaternary ammonium hydroxide,



One transition state leads to Zaitsev elimination, the other to Hofmann elimination.

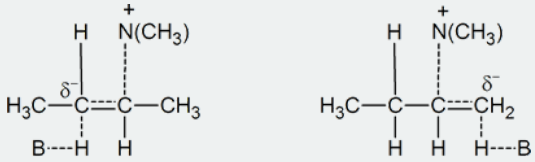
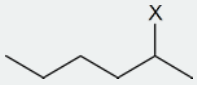


Figure 24.2 Possible carbanion-like transition states

In the transition state leading to the Zaitsev product, the carbon atom carrying the partial negative charge is bonded to an electron-releasing methyl group. This is clearly a less favourable situation than the one that exists in the transition state leading to Hofmann elimination, where there are no electron-releasing groups attached to the carbon atom bearing the partial negative charge. Bunnett’s argument is that carbanion-like transition states are much more likely when the atom or group X in a compound such as



is strongly electron withdrawing, because the \(\ce{C-X}\) bond becomes stronger as the electron-withdrawing ability of X increases.

Thus, as we go along the series X = I, Br, Cl, F, $(CH_3)_3N^+$, the electron-withdrawing ability of X increases, the C-X bond becomes more difficult to break, the transition state becomes more carbanion-like in character, and Hofmann elimination becomes more pronounced.

ALKYLATION OF AMINES

It is instructive to examine these nitrogen substitution reactions using the common alkyl halide class of electrophiles. Thus, reaction of a primary alkyl bromide with a large excess of ammonia yields the corresponding 1°-amine, presumably by an S_N2 mechanism. The hydrogen bromide produced in the reaction combines with some of the excess ammonia, giving ammonium bromide as a by-product. Water does not normally react with 1°-alkyl halides to give alcohols, so the enhanced nucleophilicity of nitrogen relative to oxygen is clearly demonstrated.

$$2\,RCH_2Br + NH_3\,(\text{large excess}) \longrightarrow RCH_2NH_2 + NH_4^{(+)}Br^{(-)}$$

It follows that simple amines should also be more nucleophilic than their alcohol or ether equivalents. If, for example, we wish to carry out an S_N2 reaction of an alcohol with an alkyl halide to produce an ether (the Williamson synthesis), it is necessary to convert the weakly nucleophilic alcohol to its more nucleophilic conjugate base for the reaction to occur. In contrast, amines react with alkyl halides directly to give N-alkylated products. Since this reaction produces HBr as a byproduct, hydrobromide salts of the alkylated amine or unreacted starting amine (in equilibrium) will also be formed.

$$2\,RNH_2 + C_2H_5Br \longrightarrow RNHC_2H_5 + RNH_3^{(+)}Br^{(-)} \rightleftharpoons RNH_2C_2H_5^{(+)}Br^{(-)} + RNH_2$$

Unfortunately, the direct alkylation of 1° or 2°-amines to give a more substituted product does not proceed cleanly. If a 1:1 ratio of amine to alkyl halide is used, only 50% of the amine will react because the remaining amine will be tied up as an ammonium halide salt (remember that one equivalent of the strong acid HX is produced). If a 2:1 ratio of amine to alkylating agent is used, as in the above equation, the HX issue is solved, but another problem arises. Both the starting amine and the product amine are nucleophiles. Consequently, once the reaction has started, the product amine competes with the starting material in the later stages of alkylation, and some higher alkylated products are also formed. Even 3°-amines may be alkylated to form quaternary (4°) ammonium salts. When tetraalkyl ammonium salts are desired, as shown in the following example, Hünig's base (N,N-diisopropylethylamine) may be used to scavenge the HI produced in the three S_N2 reactions. Steric hindrance prevents this 3°-amine (Hünig's base) from being methylated.

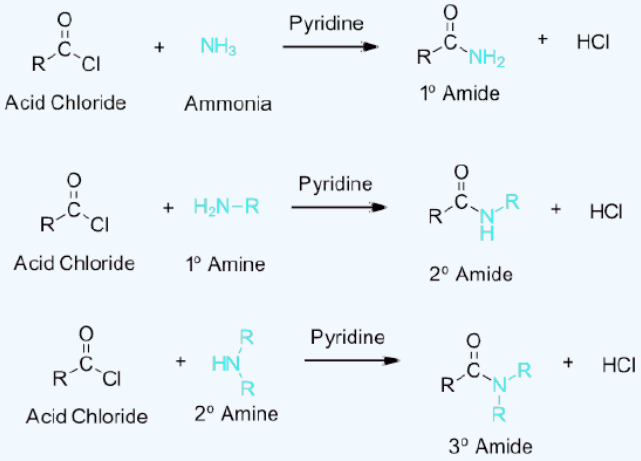
$$C_6H_5NH_2 + 3\,CH_3I + \text{Hünig's base} \longrightarrow C_6H_5N(CH_3)_3^{(+)}I^{(-)} + \text{HI salt of Hünig's base}$$

ACYLATION OF AMINES

Ammonia, 1° amines, and 2° amines react rapidly with acid chlorides or acid anhydrides to form 1°, 2°, and 3° amides respectively **(Sections 21-4 and 21.5)**. These reactions typically take place rapidly at room temperature and provide high reaction yields.

The reaction is commonly run with a base, such as NaOH or pyridine, to neutralize the HCl produced. Over-acylation does not occur because the lone pair electrons on the amide nitrogen are conjugated with the carbonyl making it less nucleophilic than an amine starting material.

EXAMPLE 24.7.1

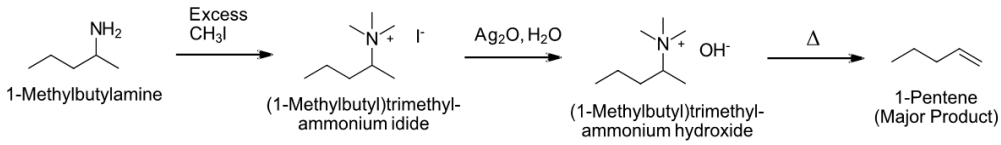


HOFMANN ELIMINATION

Amine functions seldom serve as leaving groups in nucleophilic substitution or base-catalyzed elimination reactions. Indeed, they are even less effective in this role than are hydroxyl and alkoxyl groups. As noted earlier, 1° and 2°-amines are much weaker acids than alcohols, so it is not surprising that it is difficult to force the nitrogen function to assume the role of a leaving group. In this context we note that the acidity of the potential ammonium leaving group is at least ten powers of ten less than that of an analogous oxonium species. However, amines can be turned into a good leaving group by alkylation with an alkyl halide to form a quarternary ammonium salt. Upon elimination the quarternary ammonium salt produces a stable 3° amine as a leaving group.

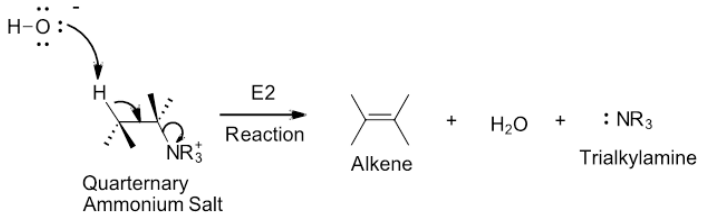
Elimination reactions of 4°-ammonium salts are termed **Hofmann eliminations**. Since the counter anion in most 4°-ammonium salts is halide, this is often replaced by the more basic hydroxide ion through reaction with silver hydroxide (or silver oxide). The resulting hydroxide salt must then be heated (100 - 200 °C) to affect the E2-like elimination of a 3°-amine. For an elimination to occur one of the alkyl substituents on nitrogen must have one or more beta-hydrogens, which is similar to elimination reactions of alkyl halides. Simple amines are easily converted to the necessary 4°-ammonium salts by exhaustive alkylation, usually with methyl iodide (methyl has no beta-hydrogens and cannot compete in the elimination reaction).

General Reaction



MECHANISM

During the Hofmann elimination, the hydroxide counter ion acts as a base to remove a beta-hydrogen and cause an E2 elimination to form an alkene. A trialkyl amine is eliminated as a leaving group during this reaction.



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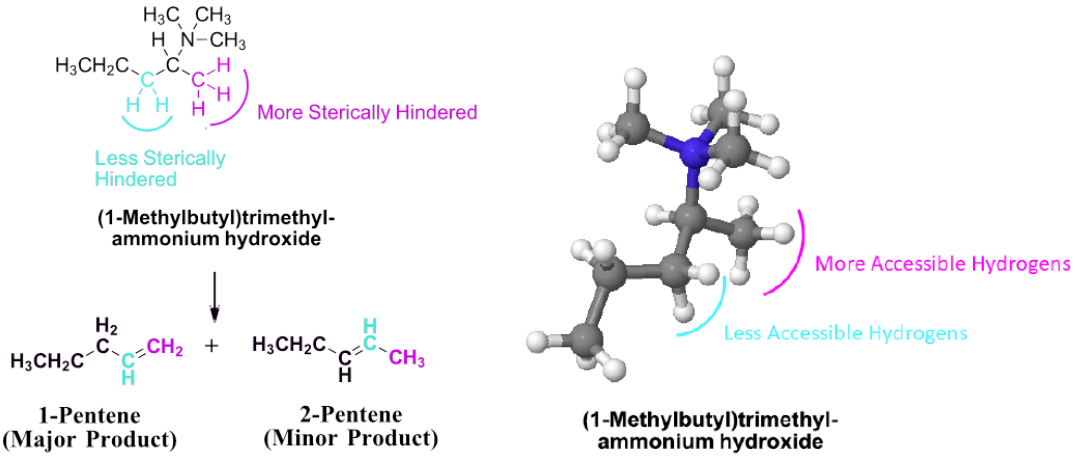
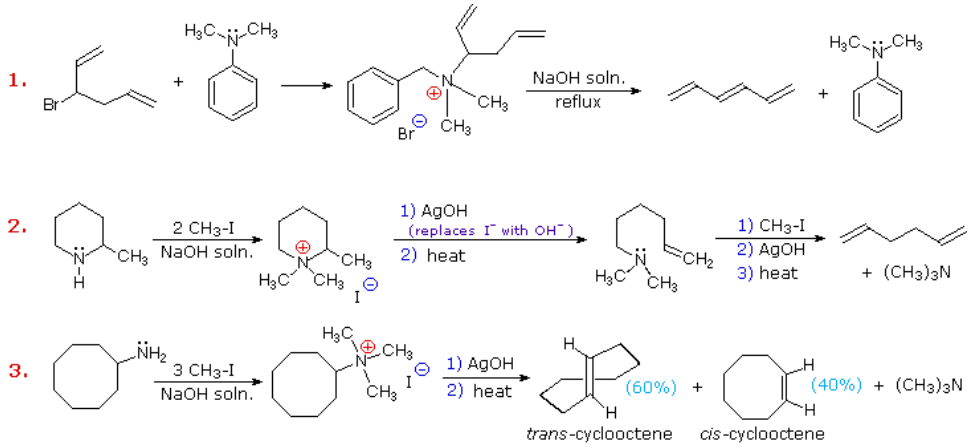
When predicting the products of an E2 elimination, the more substituted alkene is expected to be the preferred product based on Zaitsev's rule. The tendency of Hofmann eliminations to give the less-substituted double bond isomer is commonly referred to as the **Hofmann Rule**. To understand why the base-induced elimination of 4º-ammonium salts behaves differently from that of alkyl halides it is necessary to reexamine the nature of the E2 transition state.

The reason for the difference in products in a Hofmann elimination is most likely due to steric hindrance of the base. The large size of of the quaternary ammonium group forces the base to remove a hydrogen from the least sterically hindered position. This correspondingly leads to the alkene with the least number of substituents to be preferred.



Examples



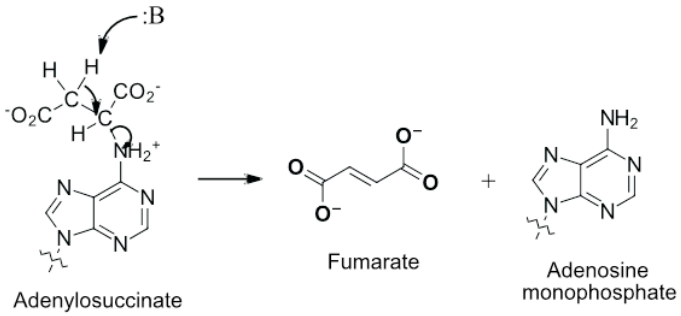
Example #1 is interesting in two respects. First, it generates a 4º-ammonium halide salt in a manner different from exhaustive methylation. Second, this salt is not converted to its hydroxide analog prior to elimination. A concentrated aqueous solution of the halide salt is simply dropped into a refluxing sodium hydroxide solution, and the volatile hydrocarbon product is isolated by distillation.

Example #2 illustrates an important aspect of the Hofmann elimination. If the nitrogen atom is part of a ring, then a single application of this elimination procedure does not remove the nitrogen as a separate 3º-amine product. In order to sever the nitrogen function from the molecule, a second Hofmann elimination must be carried out. Indeed, if the nitrogen atom was a member of two rings (fused or spiro), then three repetitions of the Hofmann elimination would be required to remove the nitrogen from the remaining molecular framework.

Example #3 is noteworthy because the less stable trans-cyclooctene is the chief product, accompanied by the cis-isomer. An anti-E2-transition state would necessarily give the cis-cycloalkene, so the trans-isomer must be generated by a syn-elimination. The cis-cyclooctene produced in this reaction could also be formed by a syn-elimination. Cyclooctane is a conformationally complex structure. Several puckered conformations that avoid angle strain are possible, and one of the most stable of these is shown on the right. Some eclipsed bonds occur in all these conformers, and transannular hydrogen crowding is unavoidable. Since the trimethylammonium substituent is large (about the size of tert-butyl) it will probably assume an equatorial-like orientation to avoid steric crowding. An anti-E2 transition state is likely to require an axial-like orientation of this bulky group, making this an unfavorable path.

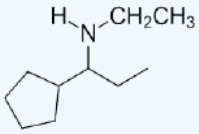
Eliminations analogous to the Hofmann elimination are often seen in biological systems. In these cases, ammonium ions (protonated amines) are used instead of quaternary ammonium salts. An example is seen in the biosynthesis of nucleic acids where a biological base

causes a Hofmann-like elimination of protonated adenylosuccinate to produce the alkene containing fumarate and adenosine monophosphate.



WORKED EXERCISE 24.7.1

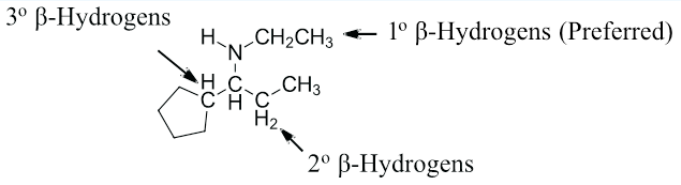
Predict the preferred product of a Hofmann elimination with the following molecule.



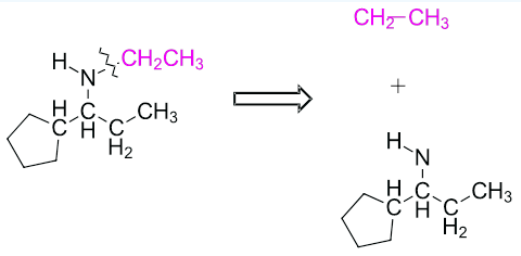
Answer

Predicting the product of a Hofmann elimination can be difficult so it is best done stepwise.

Step 1: Find the least sterically hindered beta hydrogens. Beta hydrogens are on the second carbon away from the nitrogen. The order of preferred hydrogens are 1º > 2º > 3º. If the molecule is presented as a line structure it is usually beneficial to convert to a condensed structure first.



Step 2: Break the C-N bond of the alkyl group which contains the preferred hydrogens. This will form two fragments.



Step 3: Remove one of the original beta hydrogens in the alkyl fragment then draw a C=C between the alpha and beta carbon. This produces the alkene product of the Hofmann elimination. Sometimes the amine fragment of a Hofmann elimination is of interest. Remember that prior to elimination the amine is exhaustively alkylated with CH_3I. This means any hydrogens attached to amine will starting material will be removed and the amine product will have enough methyl ($-CH_3$) groups added to become a tertiary amine. In this case two methyl groups are added to the nitrogen. The end result are the two products of a Hofmann elimination.

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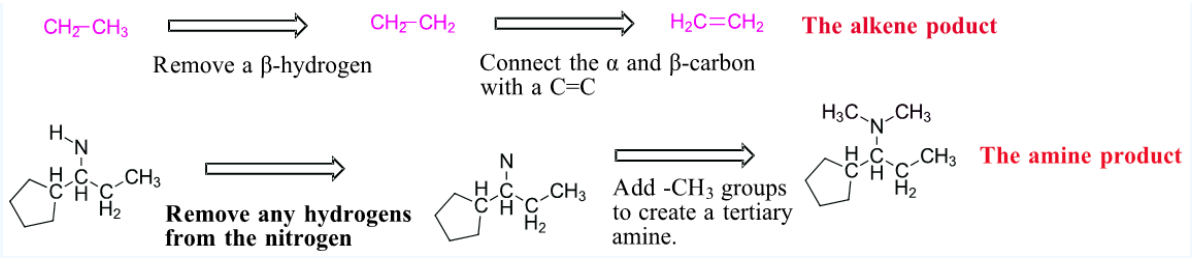
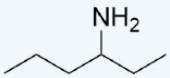
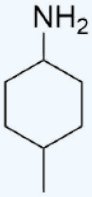
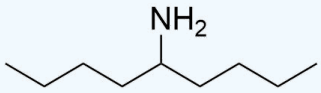


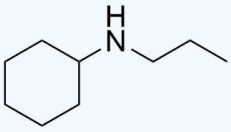
EXERCISE 24.7.1

Draw the product for a Hofmann elimination for each of the following molecules.

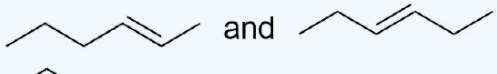
a. 

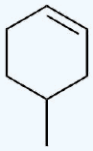
b. 

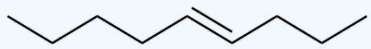
c. 

d. 

Answer

a. 

b. 

c. 

d. 

EXERCISE 24.7.2

Draw the product of a Hofmann elimination for the following molecule.

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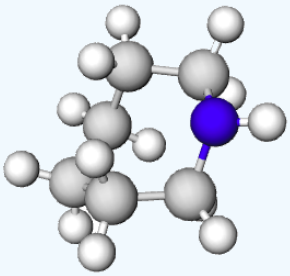
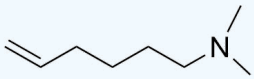


Azepane

Answer



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24.8: REACTIONS OF ARYLAMINES

OBJECTIVES

After completing this section, you should be able to

1. a. identify the product formed when a given arylamine is reacted with aqueous bromine.
   b. give an appropriate example to illustrate the high reactivity of arylamines in electrophilic aromatic substitution reactions.
   c. explain why arylamines cannot be used in Friedel-Crafts reactions.
2. a. show how the problems associated with carrying out electrophilic aromatic substitution reactions on arylamines can be circumvented by first converting the amine to an amide, and illustrate this process with an appropriate example.
   b. outline a possible synthetic route for the preparation of a given sulfa drug.
   c. identify the starting material, the necessary organic reagents, inorganic reagents, or both, and the intermediate compounds formed during the synthesis of a given sulfa drug.
   d. design a multi-step synthesis for a given compound in which it is necessary to protect the amino group by acetylation.
3. a. write a general equation to describe the formation of an arenediazonium salt.
   b. identify the product formed when a given arenediazonium salt is reacted with any of the following compounds: copper(I) chloride, copper(I) bromide, sodium iodide, copper(I) cyanide, hot aqueous acid, hypophosphorous acid.
   c. identify the arenediazonium salt, the inorganic reagents, or both, needed to produce a given compound by a diazonium replacement reaction.
4. a. illustrate, with appropriate examples, the importance to the synthetic chemist of the overall reaction sequence A nitration, B reduction, C diazotization, and D replacement.
   b. show how the removal of an amino (or nitro) group from an aromatic ring through the reaction of an arenediazonium salt with hypophosphorous acid (H_3PO_2) can sometimes be of use in organic synthesis.
5. a. write a general equation to represent a diazonium coupling reaction.
   b. write the detailed mechanism for the coupling reaction which takes place between arenediazonium salts and the electon-rich aromatic rings of phenols and arylamines.
   c. identify the product formed from the reaction of a given arenediazonium salt with a given arylamine or phenol.
   d. identify the arenediazonium salt and the arylamine or phenol needed to prepare a given azo compound.

KEY TERMS

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

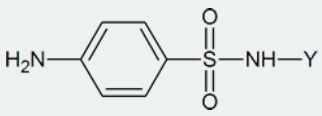
- arenediazonium salt
- azo compound
- Sandmeyer reaction
- sulfa drug

STUDY NOTES

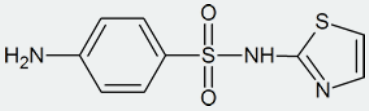
This section contains a considerable amount of new information. To absorb all of it, you should use the three subsections indicated in the reading: electrophilic aromatic substitution and overreaction of aniline (Objectives 1 and 2), the preparation of diazonium salts and the Sandmeyer reaction (Objectives 3 and 4), and diazonium coupling reactions (Objective 5).

The general process in which an aromatic amine is reacted with acetic anhydride, substituted, and then hydrolyzed is known as “protecting the amino group.”

Sulfa drugs have the general formula



Typical examples are sulfathiazole



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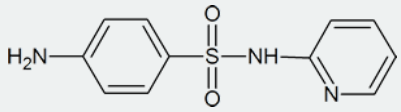
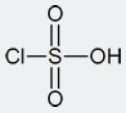
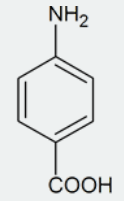
and sulfapyridine



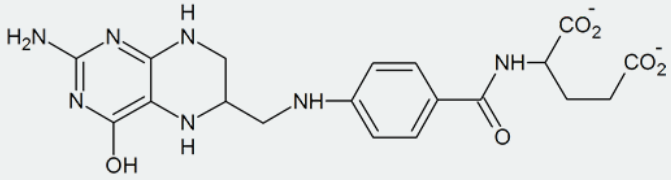
The reagent used to bring about the chlorosulfonation of acetanilide is chlorosulfuric acid



Sulfanilamide itself is toxic to humans, but derivatives of this compound, such as sulfathiazole, are less harmful to humans and are effective in killing many types of bacteria. The drugs work by "deceiving" the bacteria in the following way. To survive, many micro-organisms use *p*-aminobenzoic acid to synthesize folic acid, a coenzyme in a number of biochemical processes. These micro-organisms cannot distinguish between sulfa drugs and *p*-aminobenzoic acid; so, when the drug is administered, the bacteria use it to produce a compound which has a structure similar to that of folic acid, but which is unable to act as a coenzyme in essential biochemical processes. The result is that many of the bacteria's amino acids and nucleotides cannot be made, and the bacteria die. Amino acids are discussed in Chapter 26; nucleotides are discussed in Section 28.1.

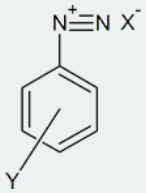


p-aminobenzoic acid



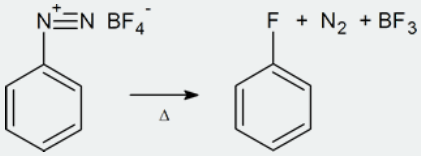
folic acid

An "arenediazonium salt" is formed by the reaction of an aromatic amine with nitrous acid at 0–5°C, and has the structure shown below.



Alkanediazonium salts are very unstable; therefore, arenediazonium salts are often simply referred to as **diazonium salts**.

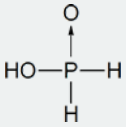
As is mentioned in the textbook, arenediazonium salts are very useful intermediates from which a wide variety of aromatic compounds can be prepared. You should be thoroughly familiar with the use of diazonium salts to prepare each of the classes of compounds. In addition, you should be aware that fluoroarenes can also be prepared from diazonium salts, as follows:



In this case the diazonium salt is prepared using fluoroboric acid, HBF_4, and sodium nitrite. The thermal decomposition of the salt, called the Schiemann reaction, can be quite hazardous.

Note that the IUPAC-preferred name for cuprous chloride is copper(I) chloride; similarly, cuprous cyanide is called copper(I) cyanide.

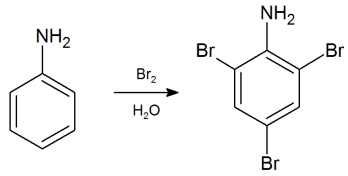
Hypophosphorous acid has the structure shown below:



The presence of the letters "azo" in a compound's name usually implies that a nitrogen-nitrogen double bond is present in its structure. Azo compounds t in which two aryl groups are joined by a $-N{=}N^-$ linkage are usually very colorful.

OVERREACTION OF ANILINE

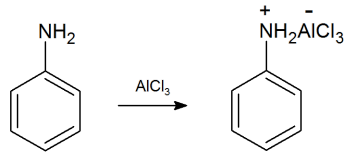
Arylamines are very reactive towards electrophilic aromomatic substitution. The strongest activating and ortho/para-directing substituents are the amino (-NH_2) and hydroxyl (-OH) groups. Direct nitration of phenol (hydroxybenzene) by dilute nitric acid gives modest yields of nitrated phenols and considerable oxidative decomposition to tarry materials; aniline (aminobenzene) is largely destroyed. Monobromination of both phenol and aniline is difficult to control, with di- and tri-bromo products forming readily.



Because of their high nucleophilic reactivity, aniline and phenol undergo substitution reactions with iodine, a halogen that is normally unreactive with benzene derivatives. The mixed halogen iodine chloride (ICl) provides a more electrophilic iodine moiety, and is effective in iodinating aromatic rings having less powerful activating substituents.

$$C_6H_5–NH_2 + I_2 + NaHCO_3 \longrightarrow p–I–C_6H_4–NH_2 + NaI + CO_2 + H_2O$$

In addition to overreactivity, we have previously seen (Section 16.3) that Friedel-Crafts reactions employing $AlCl_3$ catalyst does not work with aniline. A salt complex forms and prevents electrophilic aromatic substitution.



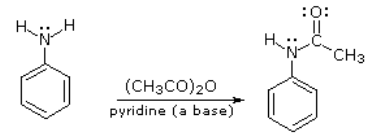
Both this problem and the aniline overreactivity can be circumvented by first going through the corresponding amide.

MODIFYING THE INFLUENCE OF STRONG ACTIVATING GROUPS

By acetylating the heteroatom substituent on aniline, its activating influence can be substantially attenuated. For example, acetylation of aniline gives acetanilide (first step in the following equation), which undergoes nitration at low temperature, yielding the para-nitro product in high yield. The modifying acetyl group can then be removed by acid-catalyzed hydrolysis (last step), to yield para-nitroaniline. Although the activating influence of the amino group has been reduced by this procedure, the acetyl derivative remains an ortho/para-directing and activating substituent.

	pyridine (a base)		HNO_3 , 5 ºC		$H_3O^{(+)}$ & heat	
$C_6H_5–NH_2 + (CH_3CO)_2O$	⟶	$C_6H_5–NHCOCH_3$	⟶	$p\text{-}O_2N–C_6H_4–NHCOCH_3$	⟶	$p\text{-}O_2N–C_6H_4–NH$

The following diagram illustrates how the acetyl group acts to attenuate the overall electron donating character of oxygen and nitrogen. The non-bonding valence electron pairs that are responsible for the high reactivity of these compounds (blue arrows) are diverted to the adjacent carbonyl group (green arrows). However, the overall influence of the modified substituent is still activating and ortho/para-directing.



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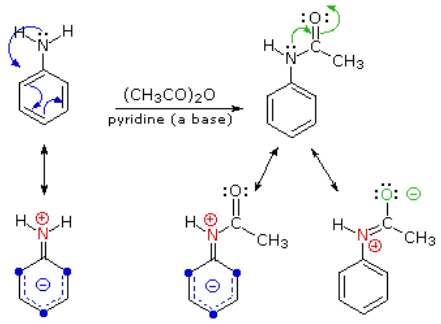
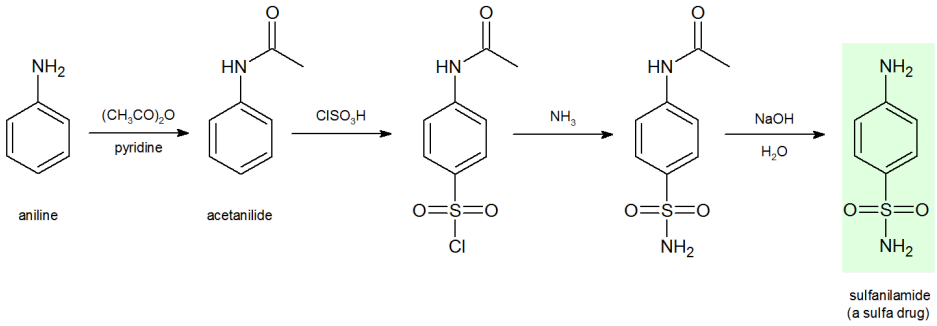


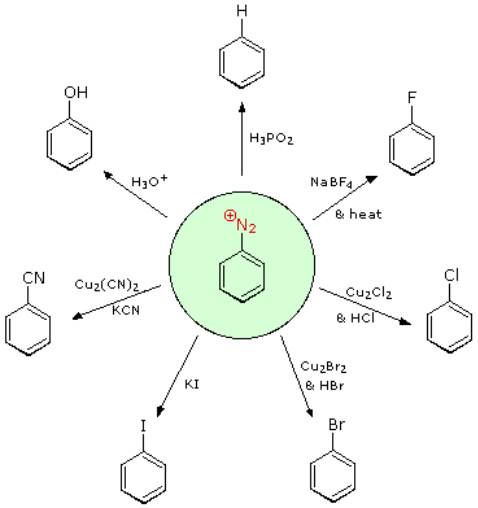
SULFA DRUG SYNTHESIS

Sulfa drugs are an important group of synthetic antimicrobial agents (pharmaceuticals) that contain the sulfonamide group. The synthesis of sulfanilamide (a sulfa drug) illustrates how the reactivity of aniline can be modified to make possible an electrophilic aromatic substitution. The corresponding acetanilide undergoes chlorosulfonation. The resulting 4-acetamidobenzenesulfanyl chloride is treated with ammonia to replace the chlorine with an amino group and affords 4-acetamidobenzenesulfonamide. The subsequent hydrolysis of the sulfonamide produces the sulfanilamide.



DIAZONIUM SALTS: THE SANDMEYER REACTION

Aryl diazonium salts are important intermediates. They are prepared in cold (0 ° to 10 ºC) aqueous solution, and generally react with nucleophiles with loss of nitrogen. Some of the more commonly used substitution reactions are shown in the following diagram. Since the leaving group (N_2) is thermodynamically very stable, these reactions are energetically favored. Those substitution reactions that are catalyzed by cuprous salts are known as **Sandmeyer reactions**. Fluoride substitution occurs on treatment with $BF_4^{(-)}$, a reaction known as the **Schiemann reaction**. Stable diazonium tetrafluoroborate salts may be isolated, and on heating these lose nitrogen to give an arylfluoride product. The top reaction with hypophosphorus acid, H_3PO_2, is noteworthy because it achieves the reductive removal of an amino (or nitro) group. Unlike the nucleophilic substitution reactions, this reduction probably proceeds by a radical mechanism.



These aryl diazonium substitution reactions significantly expand the tactics available for the synthesis of polysubstituted benzene derivatives. Consider the following options:

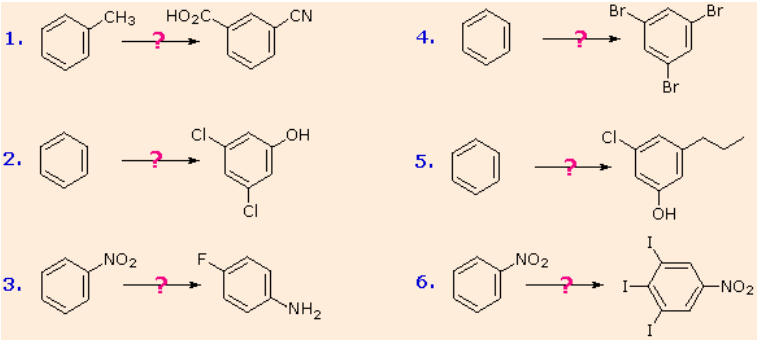
I. The usual precursor to an aryl amine is the corresponding nitro compound. A nitro substituent deactivates an aromatic ring and directs electrophilic substitution to meta locations.

II. Reduction of a nitro group to an amine may be achieved in several ways. The resulting amine substituent strongly activates an aromatic ring and directs electrophilic substitution to ortho & para locations.

III. The activating character of an amine substituent may be attenuated by formation of an amide derivative (reversible), or even changed to deactivating and meta-directing by formation of a quaternary-ammonium salt (irreversible).

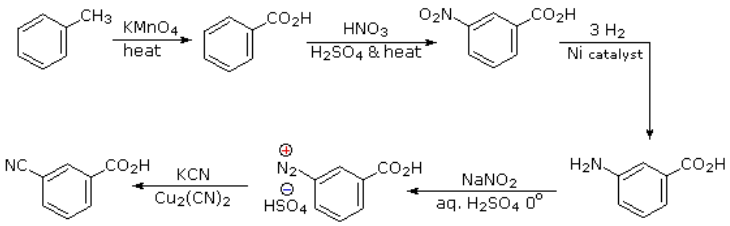
IV. Conversion of an aryl amine to a diazonium ion intermediate allows it to be replaced by a variety of different groups (including hydrogen), which may in turn be used in subsequent reactions.

The following examples illustrate some combined applications of these options to specific cases. You should try to conceive a plausible reaction sequence for each. Once you have done so, you may check suggested answers below.



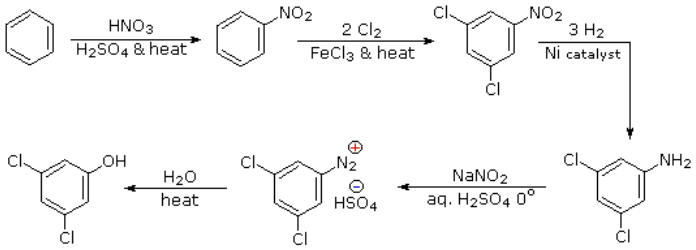
Answer 1:

It should be clear that the methyl substituent will eventually be oxidized to a carboxylic acid function. The timing is important, since a methyl substituent is ortho/para-directing and the carboxyl substituent is meta-directing. The cyano group will be introduced by a diazonium intermediate, so a nitration followed by reduction to an amine must precede this step.



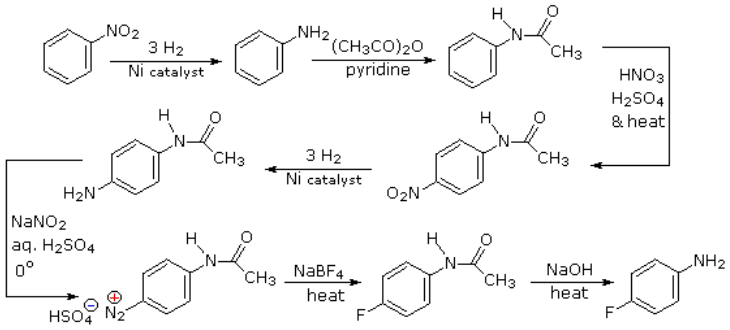
Answer 2:

The hydroxyl group is a strong activating substituent and would direct aromatic ring chlorination to locations ortho & para to itself, leading to the wrong product. As an alternative, the nitro group is not only meta-directing, it can be converted to a hydroxyl group by way of a diazonium intermediate. The resulting strategy is self evident.



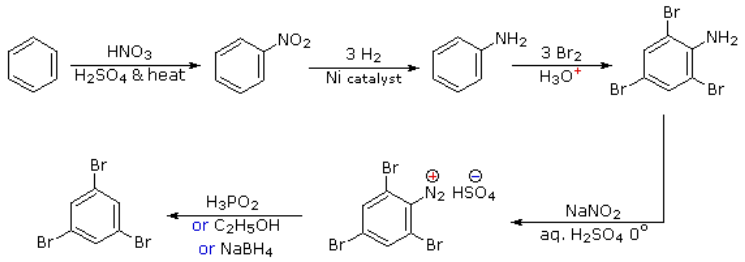
Answer 3:

Selective introduction of a fluorine is best achieved by treating a diazonium intermediate with boron tetrafluoride anion. To get the necessary intermediate we need to make p-nitroaniline. Since the nitro substituent on the starting material would direct a new substituent to a meta-location, we must first reduce it to an ortho/para-directing amino group. Amino groups are powerful activating substituents, so we deactivate it by acetylation before nitration. The acetyl substituent also protects the initial amine function from reaction with nitrous acid later on. It is removed in the last step.



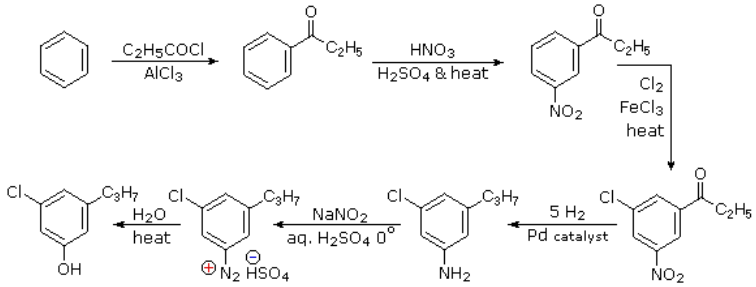
Answer 4:

Polybromination of benzene would lead to ortho/para substitution. In order to achieve the mutual meta-relationship of three bromines, it is necessary to introduce a powerful ortho/para-directing prior to bromination, and then remove it following the tribromination. An amino group is ideal for this purpose. Reductive removal of the diazonium group may be accomplished in several ways (three are shown).



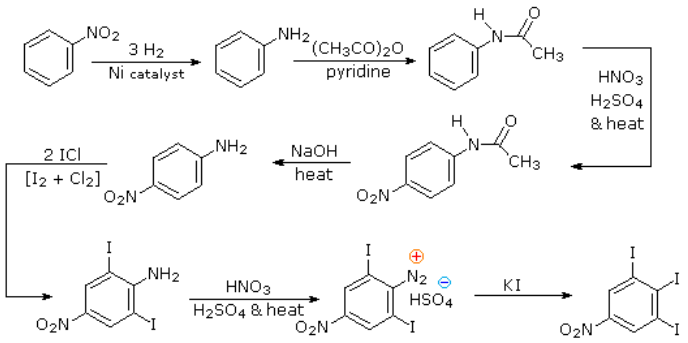
Answer 5:

The propyl substituent is best introduced by Friedel-Crafts acylation followed by reduction, and this cannot be carried out in the presence of a nitro substituent. Since an acyl substituent is a meta-director, it is logical to use this property to locate the nitro and chloro groups before reducing the carbonyl moiety. The same reduction method can be used to reduce both the nitro group (to an amine) and the carbonyl group to propyl. We have already seen the use of diazonium intermediates as precursors to phenols.



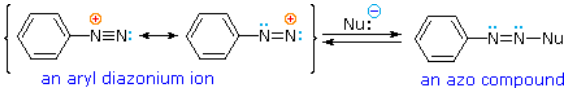
Answer 6:

Aromatic iodination can only be accomplished directly on highly activated benzene compounds, such as aniline, or indirectly by way of a diazonium intermediate. Once again, a deactivated amino group is the precursor of p-nitroaniline (prb.#3). This aniline derivative requires the more electrophilic iodine chloride (ICl) for ortho-iodination because of the presence of a deactivating nitro substituent. Finally, the third iodine is introduced by the diazonium ion procedure.



DIAZONIUM COUPLING REACTIONS

A resonance description of diazonium ions shows that the positive charge is delocalized over the two nitrogen atoms. It is not possible for nucleophiles to bond to the inner nitrogen, but bonding (or coupling) of negative nucleophiles to the terminal nitrogen gives neutral azo compounds. As shown in the following equation, this coupling to the terminal nitrogen should be relatively fast and reversible. The azo products may exist as E / Z stereoisomers. In practice it is found that the E-isomer predominates at equilibrium.



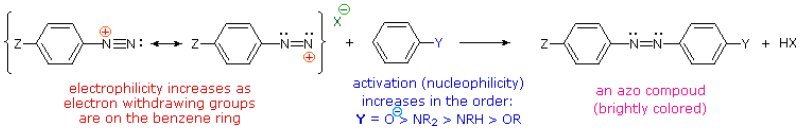
Unless these azo products are trapped or stabilized in some manner, reversal to the diazonium ion and slow nucleophilic substitution at carbon (with irreversible nitrogen loss) will be the ultimate course of reaction, as described in the previous section. For example, if phenyldiazonium bisufate is added rapidly to a cold solution of sodium hydroxide a relatively stable solution of sodium phenyldiazoate (the conjugate base of the initially formed diazoic acid) is obtained. Lowering the pH of this solution regenerates phenyldiazoic acid (pK_a ca. 7), which disassociates back to the diazonium ion and eventually undergoes substitution, generating phenol.

$$\underbrace{C_6H_5N_2^{(+)}HSO_4^{(-)}}_{\text{phenyldiazonium bisulfate}} + NaOH(\text{cold solution}) \rightleftharpoons \underbrace{C_6H_5N_2-OH}_{\text{phenyldiazoic acid}} + NaOH(\text{cold}) \rightleftharpoons \underbrace{C_6H_5N_2-O^{(-)}Na^{(+)}}_{\text{sodium phenyldiazoate}}$$

Aryl diazonium salts may be reduced to the corresponding hydrazines by mild reducing agents such as sodium bisulfite, stannous chloride or zinc dust. The bisulfite reduction may proceed by an initial sulfur-nitrogen coupling, as shown in the following equation.

$$Ar-N_2^{(+)}X^{(-)} \xrightarrow{NaHSO_3} Ar-N=N-SO_3H \xrightarrow{NaHSO_3} Ar-NH-NH-SO_3H \xrightarrow{H_2O} Ar-NH-NH_2 + H_2SO_4$$

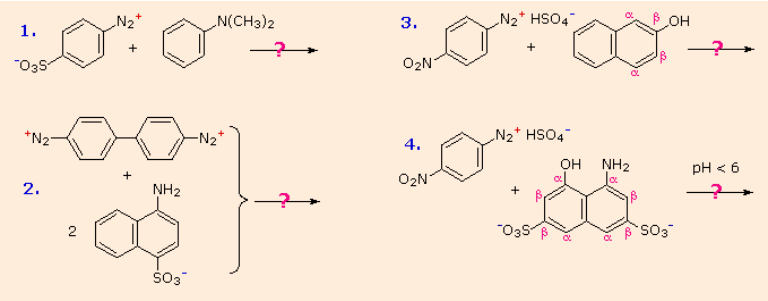
The most important application of diazo coupling reactions is electrophilic aromatic substitution of activated benzene derivatives by diazonium electrophiles. The products of such reactions are highly colored aromatic azo compounds that find use as synthetic dyestuffs, commonly referred to as azo dyes. Azobenzene (Y=Z=H) is light orange; however, the color of other azo compounds may range from red to deep blue depending on the nature of the aromatic rings and the substituents they carry. Azo compounds may exist as cis/trans isomer pairs, but most of the well-characterized and stable compounds are trans.



Some examples of azo coupling reactions are shown below. A few simple rules are helpful in predicting the course of such reactions:

I. At acid pH (< 6) an amino group is a stronger activating substituent than a hydroxyl group (i.e. a phenol). At alkaline pH (> 7.5) phenolic functions are stronger activators, due to increased phenoxide base concentration.
II. Coupling to an activated benzene ring occurs preferentially para to the activating group if that location is free. Otherwise ortho-coupling will occur.
III. Naphthalene normally undergoes electrophilic substitution at an alpha-location more rapidly than at beta-sites; however, ortho-coupling is preferred. See the diagram for examples of α / β notation in naphthalenes.

You should try to conceive a plausible product structure for each of the following couplings.

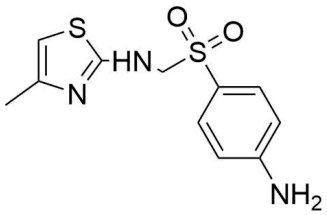


EXERCISES

QUESTIONS

Q24.8.1

Propose a synthesis for the following compound via benzene and any amine you may require.



Q24.8.2

Proposes synthesis for each of the following compounds via benzene.

(a) *N*,*N*-Diethylaniline

(b) *p*-Bromoaniline

(c) *m*-Bromoaniline

(d) 2,4-Diethylaniline

Q24.8.3

Propose a synthesis for each of the following molecules from benzene via the diazonium ion.

(a) *p*-Chlorobenzoic acid

(b) *m*-Chlorobenzoic acid

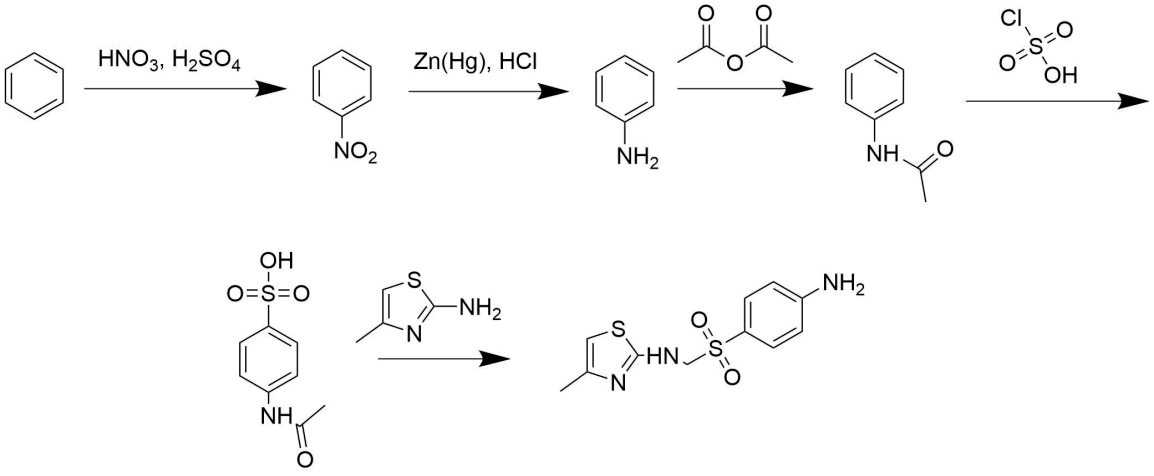
(c) *m*-Dichlorobenzene

(d) *p*-Ethylbenzoic acid

(e) 1,2,4-Trichlorobenzene

SOLUTIONS

S24.8.1



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S24.8.2

(a) 1. HNO_3, H_2SO_4; 2. Zn(Hg), HCl; 3. EtBr

(b) 1. HNO_3, H_2SO_4; 2. Zn(Hg), HCl; 3. $(CH_3CO)O_2$; 4. Br_2, $FeBr_3$; 5. H_2O, NaOH

(c) 1. HNO_3, H_2SO_4; 2. Br_2, $FeBr_3$; 3. Zn(Hg), HCl

(d) 1. HNO_3, H_2SO_4; 2. Zn(Hg), HCl; 3. $(CH_3CO)O_2$; 4. EtCl, $AlCl_3$; 5. H_2O, NaOH

S24.8.3

(a) 1. CH_3CH_2Cl, $AlCl_3$; 2. HNO_3, H_2SO_4; 3. $SnCl_2$; 4. $NaNO_2$, H_2SO_4; 5. CuBr; 6. $KMnO_4$, H_2O

(b) 1. HNO_3, H_2SO_4; 2. Cl_2, $FeCl_3$; 3. $SnCl_2$, H_3O^+; 4. $NaNO_2$, H_2SO_4; 5. CuCN; 6. H_3O^+

(c) 1. HNO_3, H_2SO_4; 2. Cl_2, $FeCl_3$; 3. $SnCl_2$; 4. $NaNO_2$, H_2SO_4; 5. CuCl

(d) 1. CH_3CH_2Cl, $AlCl_3$. 2. HNO_3, H_2SO_4; 3. $SnCl_2$; 4. $NaNO_2$, H_2SO_4; 5. CuCN; 6. H_3O^+

(e) 1. HNO_3, H_2SO_4; 2. H_2/PtO_2; 3. $(CH_3CO)_2O$; 4. 2 Cl_2; 5. H_2O, NaOH; 6. $NaNO_2$, H_2SO_4; 7. CuCl

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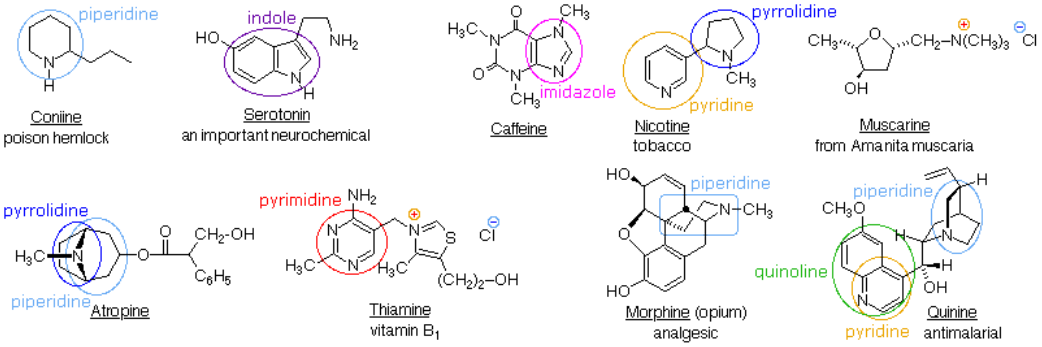
24.9: HETEROCYCLIC AMINES

OBJECTIVES

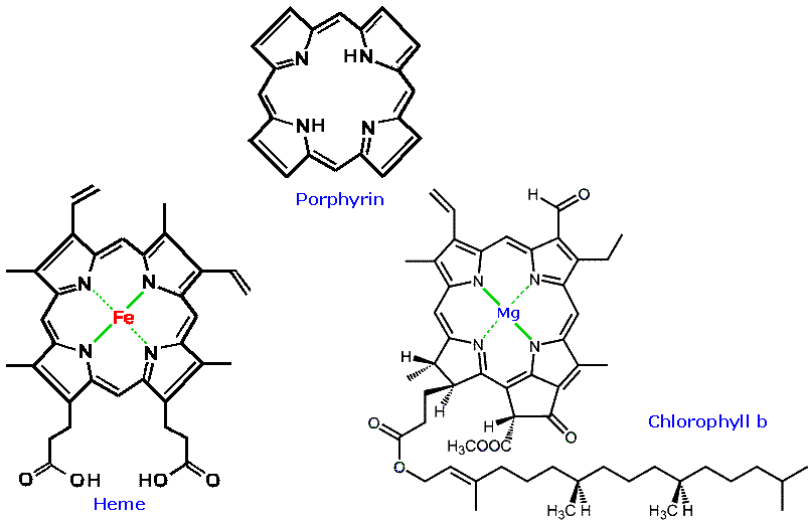
After completing this section, you should be able to

1. draw the structure of furan, pyrrole and imidazole.
2. use the Hückel $2n + 4$ rule to explain the aromaticity of pyrrole.
3. predict the product formed when pyrrole is subjected to an aromatic electrophilic substitution, such as nitration, etc.
4. write the detailed mechanism for the electrophilic aromatic substitution of pyrrole to account for the fact that substitution takes place at C2 rather than C3.
5. describe the geometry of the pyridine molecule.
6. account for the difference in basicity between pyridine, pyrrole and other amines.
7. explain why pyridine undergoes electrophilic substitution much less readily than does benzene.
8. identify the presence of a fused-ring heterocycle in a given structure.
9. make predictions about the chemical behaviour of the fused-ring heterocycle based on what you have learned about pyrrole, imidazole, pyridine and pyrimidine.

Heterocyclic structures containing nitrogen are found in many natural products. Examples of some nitrogen compounds, known as alkaloids because of their basic properties, were given in the amine chapter.



The porphyrin aromatic heterocycle contains multiple pyrrole ring strictures. The porphyrines, heme and chlorophyll b play vital parts in the metabolism of plants and animals.



PYRROLE

Pyrrole is obtained commercially by the reaction of furan with ammonia .

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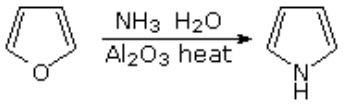
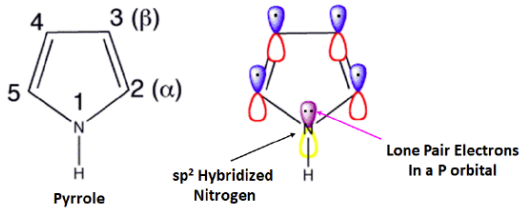
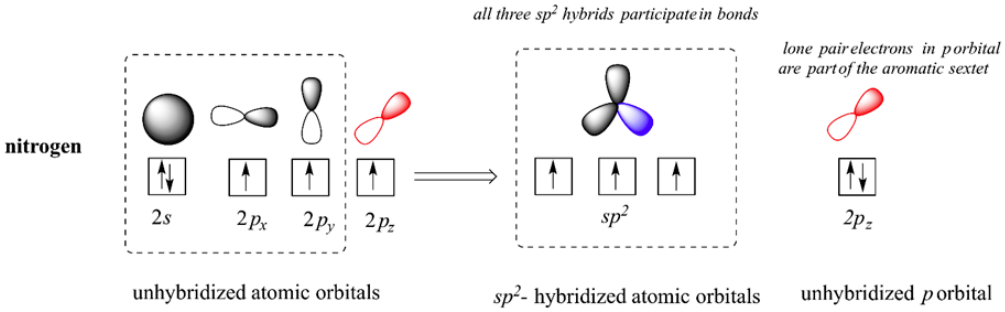
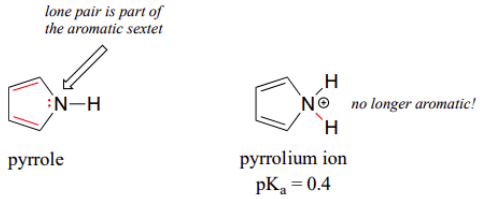


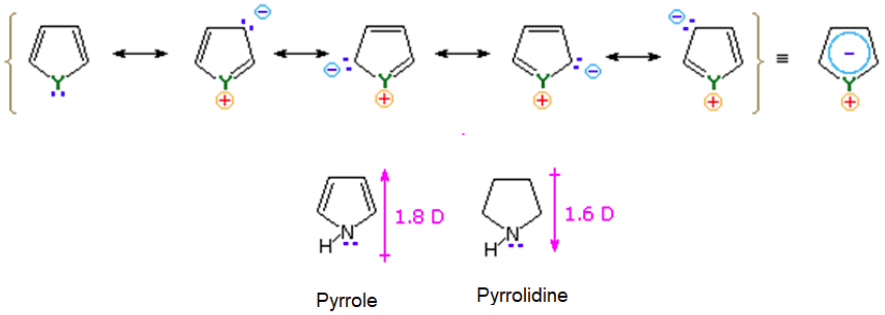
As discussed in Section 15-5, pyrrole has six pi electrons contributing to its aromaticity. Each carbon in pyrrole contributes one pi electron. The nitrogen in pyrrole contributes two pi electron by becoming sp^2 hybridized and placing its lone pair electrons into a p orbital. Because the nitrogen lone 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 aromatic system is destroyed). For these reasons, pyrrole nitrogens are not strongly basic. Pyrrole is a very weak base: the conjugate acid is a strong acid with a pK_a of 0.4.







The involvement of the nitrogen lone pair electrons in pyrrole's aromatic conjugation creates charge separated structures not normally found for benzene. The combination of these resonance forms creates an overall separation of charge which increases the electron density around the ring carbons and decreases the electron density on the nitrogen. This effect has a number of ramifications. First is that pyrrole has a large dipole moment (1.8 D) pointing away from the ring nitrogen. This is in sharp contrast to the non-aromatic heterocycle pyrrolidine where the dipole moment (1.5 D) points towards the ring nitrogen.



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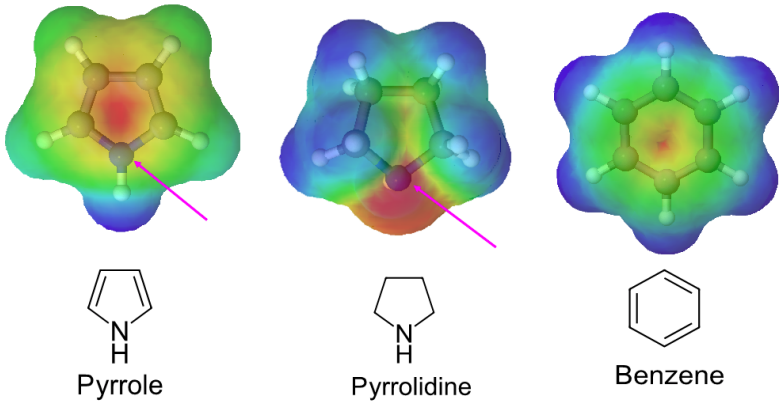
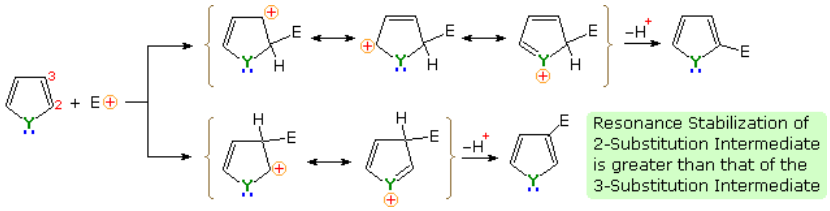
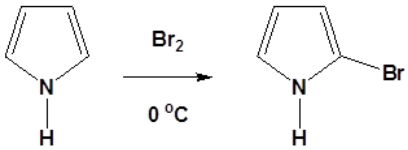
Due to the resonance forms, pyrrole has less electron density around it than the nitrogen in a typical alkyl amine. This agrees with fact that that pyrrole is a much weaker base than pyrrolidine. The electrostatic potential map of pyrrole (Shown Below) shows less electron density (shown as a red color) on the ring nitrogen when compared to its aliphatic equivalent, pyrrolidine. The map of pyrrole also shows that the resonance forms increase the electron density of pyrrole's ring carbons when compared to the ring carbons of benzene. The involvement of nitrogen's lone pair electrons in the aromaticity of pyrrole makes the ring activated towards electrophilic aromatic substitution.



Pyrrole can undergo many of the same electrophilic aromatic substitution reactions as benzene. Because of the activation of pyrrole's aromatic ring, many of these reactions are performed under a reduced temperature compared to a similar reaction with benzene. There is a clear preference for substitution at the 2-position (α) of the pyrrole ring. An explanation for the general α-selectivity of these substitution reactions is apparent from the mechanism outlined below. The intermediate formed by electrophile attack at C-2 is stabilized by charge delocalization to a greater degree than the intermediate from C-3 attack. From the Hammond postulate we may then infer that the activation energy for substitution at the former position is less than the latter substitution.

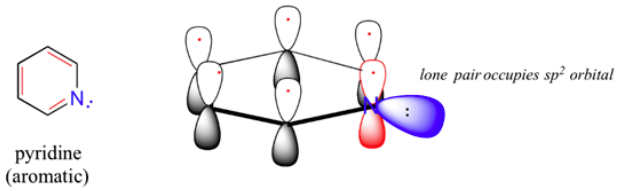


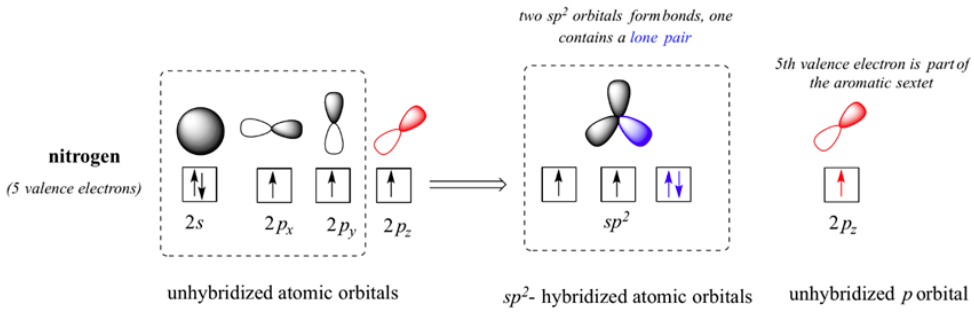
EXAMPLE



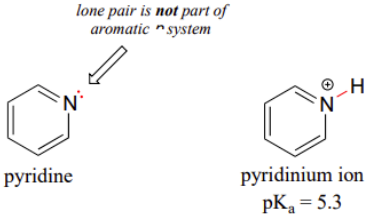
PYRIDINE

Pyridine is an example of a six-membered aromatic heterocycle. 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. The unhybridized *p* orbital contains a single electron, which is part of the 6 pi-electron aromatic system delocalized around the ring.

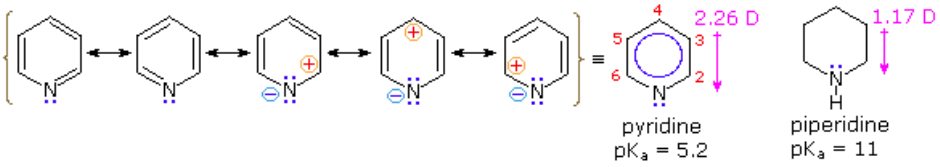




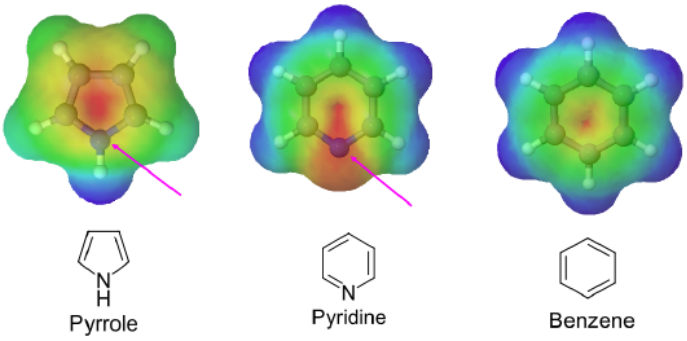
Pyridine's nitrogen lone pair occupies an sp^2-hybrid orbital, and *is not* part of the aromatic sextet. Thus, its electron pair is available for forming a bond to a proton, making pyridine's nitrogen atom (conjugate acid $pK_a = 5.25$) more basic than pyrrole's ($pK_a = 0.4$). However, pyridine is is less basic than a typical alkylamine ($pK_a \sim 10$-11). The difference is due to nitrogen hybridization. The lone pair electrons on a pyridine nitrogen occupy an sp^2 hybrid orbital, while the lone pair electrons on an amine nitrogen occupy an sp^3 hybrid orbital. sp^2 orbitals are composed of one part *s* and two parts *p* atomic orbitals, meaning that they have about 33% *s* character. sp^3 orbitals, conversely, are only 25% *s* character (one part *s*, three parts *p)* . An *s* atomic orbital holds electrons closer to the nucleus than a *p* orbital, thus *s* orbitals are more electronegative than *p* orbitals. Therefore, sp^2 hybrid orbitals, with their higher s-character, are more electronegative than sp^3 hybrid orbitals. Lone pair electrons in the more electronegative sp^2 hybrid orbitals of pyridine are held more tightly to the nitrogen nucleus, and are therefore less 'free' to break away and form a bond to a proton - in other words, they are less basic.



The lack of involvement of pyrrole's nitrogen lone pair electrons in the aromatic conjugation creates charge separated structures not normally found for benzene. The combination of the resonance forms creates an overall charge separation which increases the electron density around the ring's nitrogen and decreases the electron density on the ring carbons. This causes pyridine to have a larger dipole moment (2.26 D) than its non-aromatic equivalent piperidine where the dipole moment (1.17 D). In both cases the dipole moment points towards the ring nitrogen.

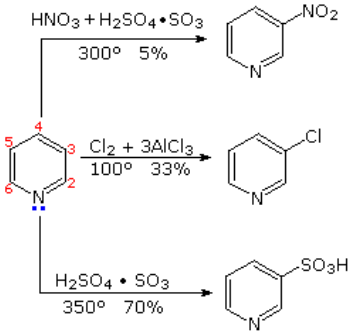


Due to the resonance forms, pyridine has more electron density around its nitrogen than in a typical alkyl amine. The electrostatic potential map of pyridine (Shown Below) shows more electron density (shown as a red color) on the ring nitrogen of pyridine when compared to pyrrole. The map of pyridine also shows that the resonance forms decrease the electron density of pyridine's ring carbons (Show as a blue/green color) when compared to those of benzene. The involvement of the nitrogen's lone pair electrons in the aromaticity of pyridine makes the ring deactivated towards electrophilic aromatic substitution.



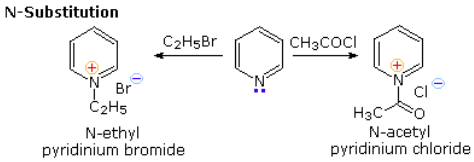
From the previous resonance description of pyridine, we expect this aromatic amine to undergo electrophilic substitution reactions far less easily than does benzene. Furthermore, the electrophilic reagents and catalysts employed in these reactions coordinate with the nitrogen electron pair, exacerbating the positive charge at positions 2,4 & 6 of the pyridine ring. When these reactions do occur then tend to produce the 3-substituted product. Three examples of the extreme conditions required for electrophilic substitution are shown below.

Example

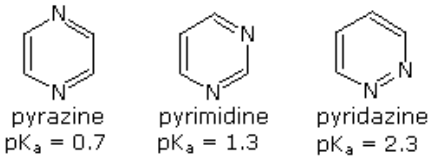


Friedel-Crafts reactions are not feasible because alkyl halides and acid halides prefer to react with pyridine nucleophilic ring nitrogen to provide a N-substituted product. As shown below, N-alkylation and N-acylation products may be prepared as stable crystalline solids in the absence of water or other reactive nucleophiles. Pyridine is a modest base (pK_a=5.2). Since the lone pair electrons on pyridine's nitrogen are not part of the aromatic sextet, the pyridinium species produced by N-substitution retains the aromaticity of pyridine.

Example

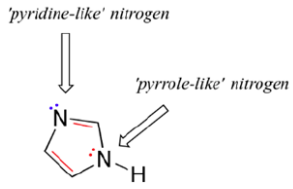


Other six-membered nitrogen contain aromatic heterocycles include pyrazine, pyrimidine, and pyridazine. The inductive effect of a second nitrogen makes all three of these heterocycles less basic than pyridine.

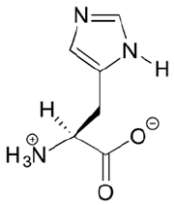


IMIDAZOLE

Imidazole is another important example of an aromatic heterocycle found in biomolecules - the side chain of the amino acid histidine contains an imidazole ring. The two nitrogens in imidazole are quite different. One nitrogen is pyrrole-like and donates its lone pair electrons, like pyrrole, to make imidazole aromatic. The other nitrogen is pyridine like and its lone pair electrons are contained is a sp^2 hybridized orbital. These lone pair electrons are readily available for bonding which imidazole (pK_a = 6.95) much more basic than pyrrole (pK_a = 0.4).



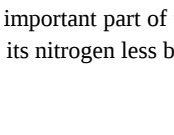
imidazole



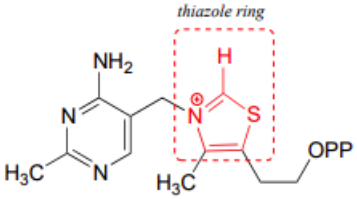
histidine

THIAZOLE

Thiazole is a five-membered sulfur containing aromatic ring system which is found in biological systems, such as thiamine diphosphate. Thiamine diphosphate (ThDP, sometimes also abbreviated TPP or ThPP) is a coenzyme which, like PLP, acts as an electron sink to stabilize key carbanion intermediates. The most important part of the ThDP molecule from a catalytic standpoint is its thiazole ring. The presence of sulfur in thiazole's aromatic ring makes its nitrogen less basic (pK_a = 2.44) than imidazole.



Thiazole

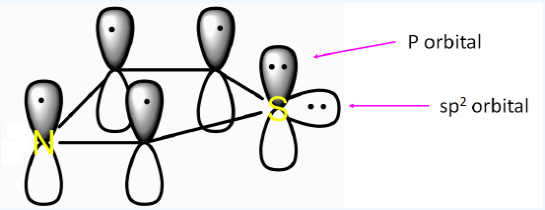


thiamine diphosphate (ThDP)

? EXERCISE 24.9.1

Describe how thiazole is aromatic. Use an orbital picture and include the lone pair electrons on sulfur. Assume the sulfur is sp^2 hybridized.

Answer



? EXERCISE 24.9.2

Would you expect a thiazole ring to be protonated at the physiological pH of 7.3 **(Section 24-5)**?

Answer

7.3 = 2.44 + log ($[RNH_2]$ / $[RNH_3^+]$)

($[RNH_2]$ / $[RNH_3^+]$) = 7.2 x 10^4

. . . so, $[RNH_2]$ >> $[RNH_3^+]$ so thiazole would be almost completely unprotonated at pH = 7.3.

POLYCYCLIC HETEROCYCLES

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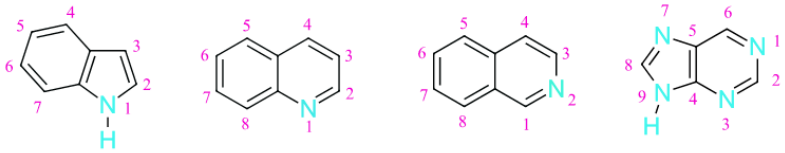
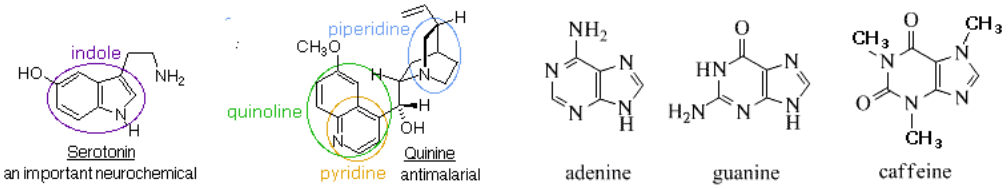


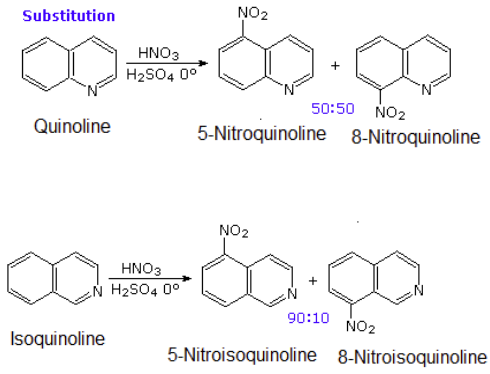
Indole (pK_a = -2) Quinoline (pK_a = 4.9) Isoquinoline (pK_a = 5.4) Purine

Indole, quinoline, isoquinoline, and purine are all polycyclic aromatic heterocycles commonly found in nature. 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.



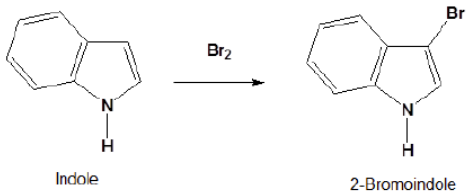
The pyridine-like nitrogen atom in quinoline and isoquinoline withdraws electrons making them both less reactive to electrophilic substitution than benzene. Likewise, quinoline (pK_a = 4.9) and isoquinoline (pK_a = 5.4) are less basic that a typical amine (pK_a ~10-11). Quinoline and isoquinoline can both undergo electrophilic aromatic substitution but substitution on the pyridine-like ring is avoided. Quinoline usually makes a roughly equal mixture of 5 and 8 substituted products. Isoquinoline favors making the 5 substituted product with a small amount of an 8 substituted side product.

Example

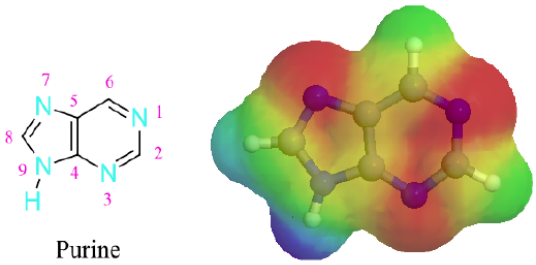


Indole has a ring nitrogen similar to to pyrrole. The lone pair electrons for this nitrogen are contained in a p orbital and are part of indole's 10 pi aromaticity. This makes indole relatively non-basic (pK_a = -2) and activated toward electrophilic substitution. Indole undergo electrophilic substitution more easily than benzene and substitution typically occurs at the 3 position on the pyrrole ring.

Example

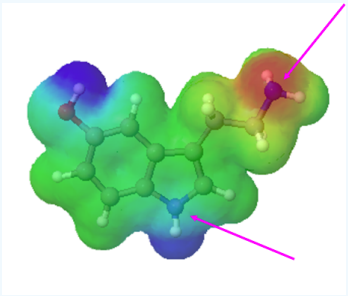


The purine ring system contain three pyridine-like nitrogens. This lone pair electrons of theses nitrogen are contained in sp^2 hybrid orbitals, making them not not part of purine's 10 pi aromaticity, allowing them to retain base-like characteristics. The lone pair electrons for the remaining, pyrrole-like, nitrogen are contained in a p orbital and are part of purine's 10 pi aromaticity. This makes the remaining nitrogen relatively non-basic.

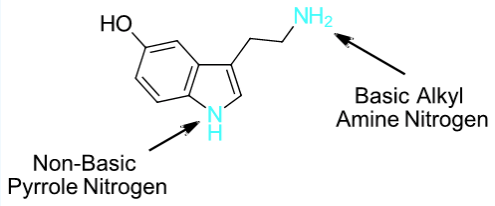


EXERCISE 24.9.1

Which nitrogen atom in the neurotransmitter serotonin is expected to be the most basic. Please explain your answer.



Answer

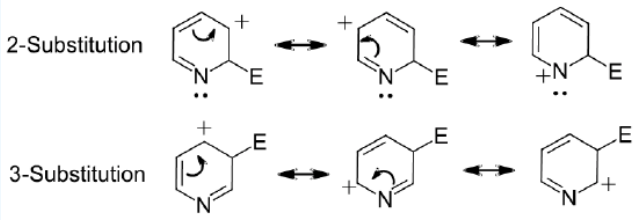


EXERCISE 24.9.2

Pyridine reacts with electrophiles to product a 3-substituted product rather than a 2-substituted product. Write a series of resonance forms for the cation intermediate formed during the reaction. Use these structures to explain the experimental result.

Answer

The resonance forms of 2-substitution places a positive charge on the ring nitrogen. The resonance forms of 3-substitution do not place a positive charge on the ring nitrogen. Having a positive charge on a nitrogen is less stable than on a carbon. Nitrogen is more electronegative than carbon making it less able to stabilize the positive charge. The 3-substituted product is preferred because it causes resonance forms which are more stable.



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24.10: SPECTROSCOPY OF AMINES

OBJECTIVES

After completing this section, you should be able to

1. identify the region of the infrared spectrum that shows absorptions resulting from the N−H bonds of primary and secondary amines.
2. describe a characteristic change that occurs in the infrared spectrum of an amine when a small amount of mineral acid is added to the sample.
3. use ^{1}H NMR spectra in determining the structure of an unknown amine.
4. use the “nitrogen rule” of mass spectrometry to determine whether a compound has an odd or even number of nitrogen atoms in its structure.
5. predict the prominent peaks in the mass spectrum of a given amine.
6. use the mass spectrum of an unknown amine in determining its structure.

KEY TERMS

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

- nitrogen rule

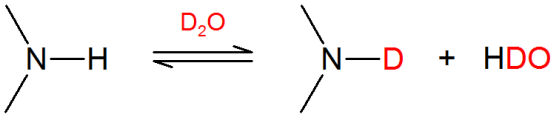
STUDY NOTES

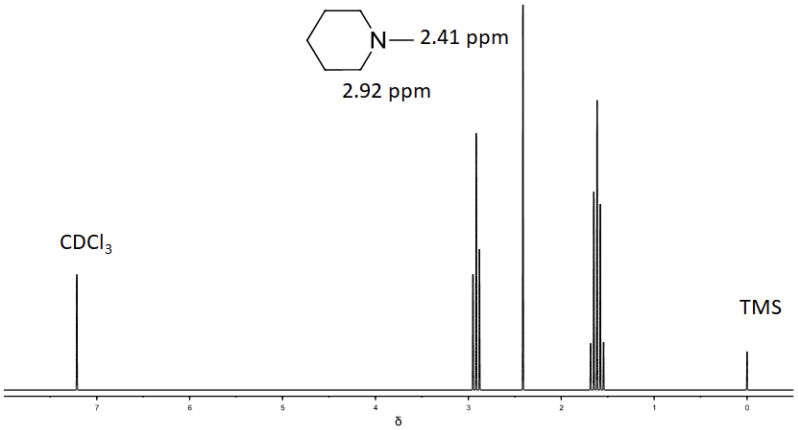
You should note the spectroscopic similarities between amines and alcohols: both have infrared absorptions in the 3300–3360 cm^{-1} region, and in both cases, the proton that is attached to the heteroatom gives rise to an often indistinct signal in the ^{1}H NMR spectrum.

^{1}H NMR OF AMINES

The hydrogens attached to an amine show up ~ 0.5-5.0 ppm. The location is dependent on the amount of hydrogen bonding and the sample's concentration. The hydrogens on carbons directly bonded to an amine typically appear ~2.3-3.0 ppm. These hydrogens are deshielded by the electron-withdrawing effects of nitrogen and appear downfield in an NMR spectra compared to alkane hydrogens.

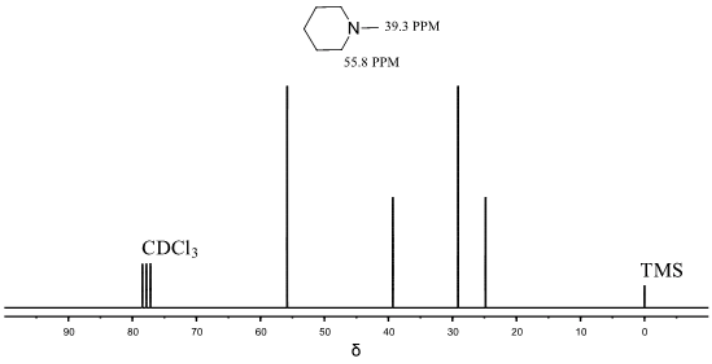
Addition of D_2O will normally cause all hydrogens on non-carbon atoms to exchange with deuterium, thus making these resonances "disappear." Addition of a few drops of D_2O causing a signal to vanish can help confirm the presence of -NH.





^{13}C NMR OF AMINES

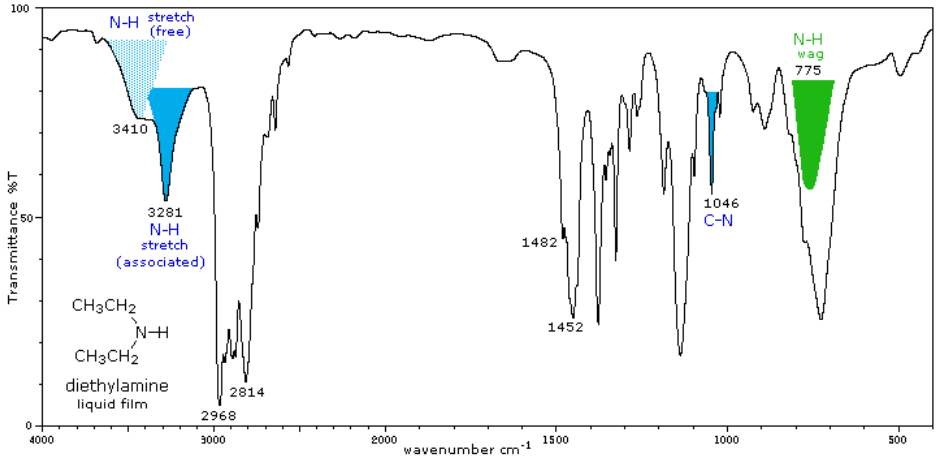
Carbons directly attached to the nitrogen appear in 10-65 ppm region of a ^{13}C NMR spectra. They are shifted slightly downfield compared to alkane carbons due to the electron-withdrawing effect of nitrogen again causing deshielding.

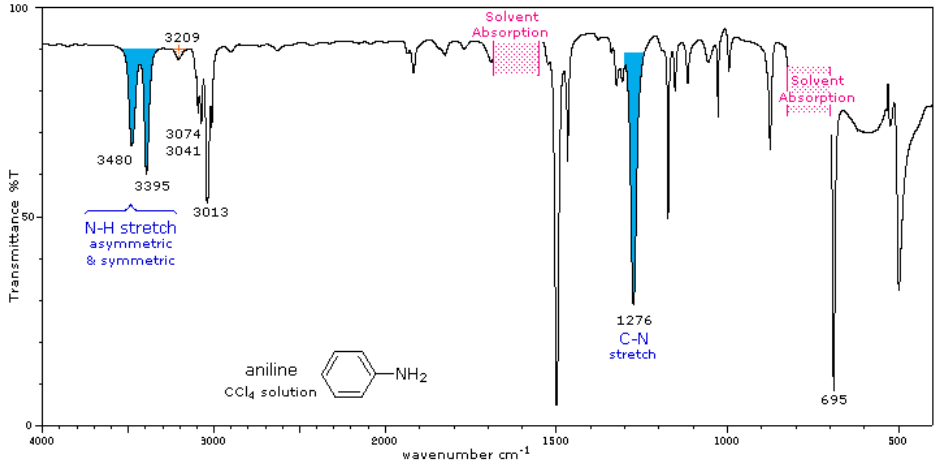


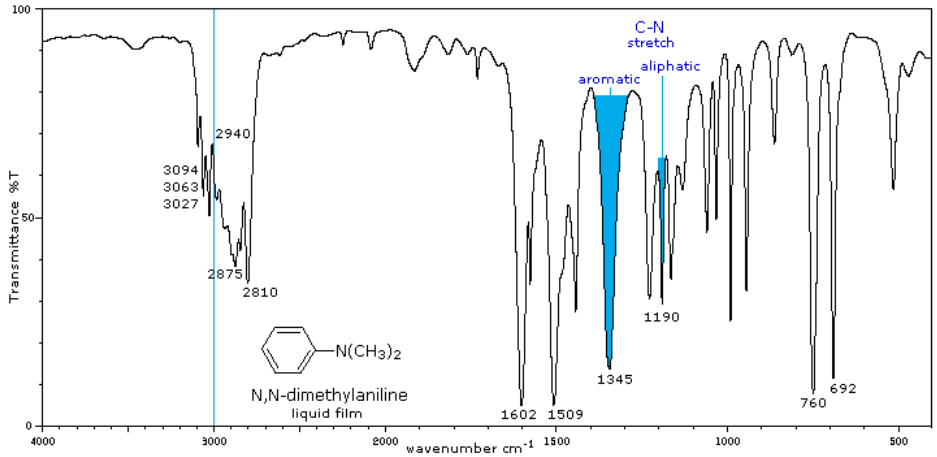
IR OF AMINES

The infrared spectra of several amines are shown beneath the following table. Some of the characteristic absorptions for C-H stretching and aromatic ring substitution are also marked, but not colored.

Amine Class	Stretching Vibrations	Bending Vibrations
Primary (1°)	The N-H stretching absorption is less sensitive to hydrogen bonding than are O-H absorptions. In the gas phase and in dilute CCl_4 solution free N-H absorption is observed in the 3400 to 3500 cm^{-1} region. Primary aliphatic amines display two well-defined peaks due to asymmetric (higher frequency) and symmetric N-H stretching, separated by 80 to 100 cm^{-1}. In aromatic amines these absorptions are usually 40 to 70 cm^{-1} higher in frequency. A smaller absorption near 3200 cm^{-1} (shaded orange in the spectra) is considered to be the result of interaction between an overtone of the 1600 cm^{-1} band with the symmetric N-H stretching band. C-N stretching absorptions are found at 1200 to 1350 cm^{-1} for aromatic amines, and at 1000 to 1250 cm^{-1} for aliphatic amines.	Strong in-plane NH_2 scissoring absorptions at 1550 to 1650 cm^{-1}, and out-of-plane wagging at 650 to 900 cm^{-1} (usually broad) are characteristic of 1°-amines.
Secondary (2°)	Secondary amines exhibit only one absorption near 3420 cm^{-1}. Hydrogen bonding in concentrated liquids shifts these absorptions to lower frequencies by about 100 cm^{-1}. Again, this absorption appears at slightly higher frequency when the nitrogen atom is bonded to an aromatic ring. The C-N absorptions are found in the same range, 1200 to 1350 cm^{-1}(aromatic) and 1000 to 1250 cm^{-1} (aliphatic) as for 1°-amines.	A weak N-H bending absorption is sometimes visible at 1500 to 1600 cm^{-1}. A broad wagging absorption at 650 to 900 cm^{-1} may be discerned in liquid film samples.
Tertiary (3°)	No N-H absorptions. The C-N absorptions are found in the same range, 1200 to 1350 cm^{-1} (aromatic) and 1000 to 1250 cm^{-1} (aliphatic) as for 1°-amines.	Aside from the C-N stretch noted on the left, these compounds have spectra characteristic of their alkyl and aryl substituents.







UV/VIS SPECTRA OF AMINES

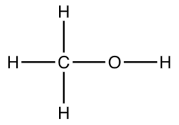
Alky Amines absorb in the region around 200 nm which make them of little value. In arylamines, the lone pair electron on the nitrogen interacts with pi electron system of the aromatic ring shifting the ring 's absorption to longer wavelengths. An example is benzene's lambda max of 256 nm while aniline's lambda max of 280 nm.

MASS SPECTRA OF AMINES

Nitrogen Rule

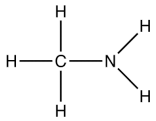
The nitrogen rule states that a molecule that has no or even number of nitrogen atoms has an even nominal mass, whereas a molecule that has an odd number of nitrogen atoms has an odd nominal mass.

Example



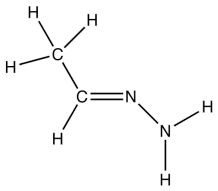
molecular formula = CH_4O
nominal mass = (1x12) + (4x1) + (1x16)
= 32

N atoms = 0
nominal mass = 32 (even #)



molecular formula = CH_5N
nominal mass = (1x12) + (5x1) + (1x14)
= 31

N atoms = 1 (odd #)
nominal mass = 31 (odd #)

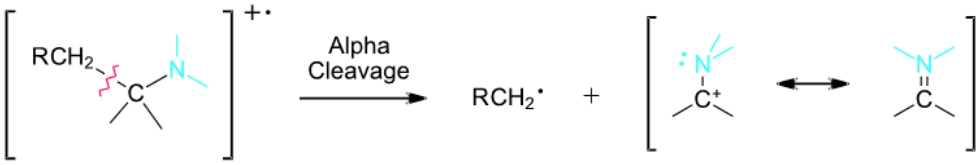


molecular formula = $C_2H_6N_2$
nominal mass = (2x12) + (6x1) + (2x14)
= 58

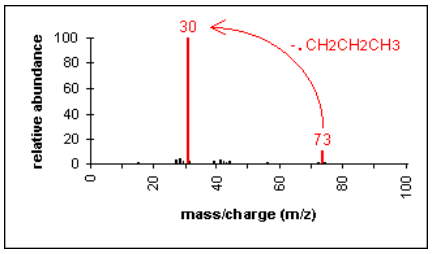
N atoms = 2 (even #)
nominal mass = 58 (even #)

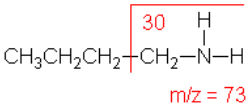
Fragmentation Patterns

The molecular ion peak is an odd number any time there is an odd number of nitrogen atoms in a molecule.. The mass spectra of amines is dominated by alpha-cleavage which produces an alkyl radical on a resonance stabilized nitrogen containing cation. Secondary and tertiary amines have the possibility of multiple alpha-cleavages.



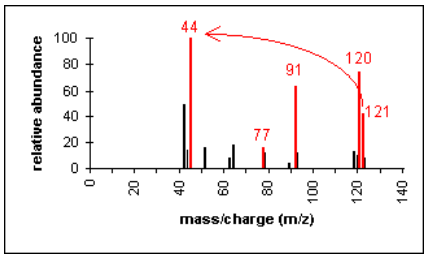
N-Butylamine ($C_4H_{11}N$) with MW = 73.13

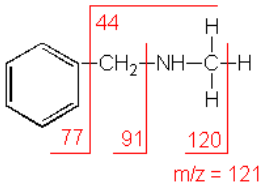




Another example is a secondary amine shown below. Again, the molecular ion peak is an odd number. The base peak (m/z = 44) is from the C-C cleavage adjacent to the C-N bond. Other important peaks come from the cleavage of the N-H bond (m/z = 120) and cleavage at the benzylic position (m/z = 91).

N-Methylbenzylamine ($C_8H_{11}N$) with MW = 121.18





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24.S: AMINES AND HETEROCYCLES (SUMMARY)

CONCEPTS & VOCABULARY

- Design a multi-step synthesis that involves the use of any of the reactions described in this unit.
- Solve road-map problems that require a knowledge of amine chemistry.
- Define, and use in context, the key terms introduced.

24.1 Naming Amines

- Amines are derivatives of ammonia in which one or more of the hydrogens has been replaced by an alkyl or aryl group.
- Several different nomenclature systems exist for naming amines, which is complicates this topic since there is no preferred option.
- The terms primary (1º), secondary (2º) & tertiary (3º) are used to classify amines by referring to the number of alkyl (or aryl) substituents bonded to the nitrogen atom.
- A nitrogen bonded to four alkyl groups will necessarily be positively charged, and is called a quaternary (4º)-ammonium cation.
- Amines are named following the IUPAC rules with -amino being added as a substitutent.
- Amines are named following the Chemical Abstract Service which the suffix -amine is attached to the root alkyl name.
- Amines are named with a common system where each alkyl substituent on nitrogen in alphabetical order, followed by the suffix -amine.

24.2 Structure and Properties of Amines

- Neutral amines have three bonds and one lone pair.
- The central nitrogen has sp^3 hybridization, which leads to trigonal pyramidal geometry with bond angles of 109.5º.
- Nitrogen does not lend to isolable stereisomers since it rapidly inverts its configuration (equilibrium arrows) by passing through a planar, sp^2-hybridized transition state, leading to a mixture of interconverting *R* and *S* configurations.
- Hydrogen bonding is the dominant factor for amines.
- Branching of amines (less bonds to Hydrogen) lowers the boiling point of amines.

24.3 Basicity of Amines

- When evaluating the basicity of a nitrogen-containing organic functional group, the central question we need to ask ourselves is: how reactive (and thus how basic) is the lone pair on the nitrogen?
- For amines, the more alkyl groups attached, the more basic the amine is due to the electron-donating effect of the alkyl group.
- The lone pair on the nitrogen atom in an amide is in resonance with the double bond making it a more stabilized lone pair and less basic.
- When a nitrogen atom is incorporated into a ring, the bascicity depends on where the lone pair resides.
- In a ring where the lone pair on the nitrogen atom resides in a hybrid orbital, then that lone pair is basic with the more basic equating with more s character in the hybrid orbital.
- In a ring where the lone pair on the nitrogen atom resides in a p orbital, then that lone pair is delocalized and less basic.
- In extraction, one can take advantage of amines and their basicity by forming the protonated salt ($RNH_2^+Cl^-$), which is soluble in water, in order to separate them.
- Amines are also acidic and the same factors that decreased the basicity of amines increase their acidity.
- Amines are often utilized as bases in reactions.

24.4 Basicity of Arylamines

- Nitrogen atoms as part of aromatic rings are less basic than methylamine.
- The basic lone pair on the nitrogen is to some extent tied up in – and stabilized by – the aromatic p system.
- This effect is accentuated by the addition of an electron-withdrawing groups.
- Imines are somewhat basic, which can be explained using orbital theory and the inductive effect: the sp^2 orbitals of an imine nitrogen are one part *s* and two parts *p*, meaning that they have about 67% *s* character.

24.5 Biological Amines and the Henderson-Hasselbalch Equation

- The chemistry of life occurs in a buffer that consists of a mixture of various phosphate and ammonium compounds.
- In an aqueous solution buffered at pH 7, carboxylic acid groups can be expected to be essentially 100% deprotonated and negatively charged (ie. in the carboxylate form), and amine groups essentially 100% protonated and positively charged (i.e., in the ammonium form).
- The imidizole group on the histidine side chain has a pK_a near 7, and thus exists in physiological solutions as mixture of both protonated and deprotonated forms.

24.6 Synthesis of Amines

- Secondary amines and their salts can be synthesized from primary amines and an alkyl halide.
- Tertiary amines and their salts can be synthesized from primary amines and an alkyl halide.

- Quaternary ammonium salts can be synthesized from primary amines and an alkyl halide.
- While a primary amine can by synthesized from ammonia and an alkyl halide, there are other better options.
- The reactions that provide a more pure primary amine in high yield occur in two steps.
  - First form a carbon-nitrogen bond by reacting a nitrogen nucleophile with a carbon electrophile.
  - Second, any extraneous nitrogen substituents that may have facilitated this bonding are removed to give the amine product.
- Another option to synthesize amines is to reduce nitro groups, which include catalytic hydrogenation, zinc or tin in dilute mineral acid, and sodium sulfide in ammonium hydroxide solution.
- Reacting a nitrile with lithium aluminum hydride will yield a primary amine.
- Amides can be reduced to primary, secondary or tertiary amines using lithium aluminum hydride.
- Aldehydes and ketones can be converted to primary, secondary, or tertiary amines using reductive amination.
- Hofmann rearrangement is the reaction of a primary amide with a halogen in strongly basic conditions to give a primary amine as a product.
- The Curtius rearrangement converts an acid chloride to an amine by the migration of an -R group form the carbonyl carbon to the the neighboring nitrogen in the acyl azide intermediate.

24.7 Reactions of Amines

- The direct alkylation of 1º or 2º-amines gives a more substituted product does not proceed cleanly.
- Acid chlorides can react with amines to form amides.
- Elimination reactions of 4º-ammonium salts are termed Hofmann eliminations, where the products are a tertiary amine and a alkene.
- The double bond Hofmann eliminations tends to give the less-substituted double bond isomer due to the Hofmann Rule.

24.8 Reactions of Arylamines

- Arylamines are very reactive towards electrophilic aromatic substitution substitutions.
- Aniline is a strong activating group and can overreact in electrophilic aromatic substitutions.
- Changing the functional group from an amine to an amide on an aromatic ring alters the reactivity in electrophilic aromatic substitutions for more control in the reaction.
- Sulfa drugs are an important group of synthetic antimicrobial agents (pharmaceuticals) that contain the sulfonamide group.
- The synthesis of sulfanilamide (a sulfa drug) illustrates how the reactivity of aniline can be modified to make possible an electrophilic aromatic substitution.
- Aryl diazonium salts are important intermediates, since the leaving group (N_2) is thermodynamically very stable, these reactions are energetically favored.
- Diazonium ions show that the positive charge is delocalized over the two nitrogen atoms while it is not possible for nucleophiles to bond to the inner nitrogen, negative nucleophiles can bond to the terminal nitrogen gives neutral azo compounds.
- The most important application of diazo coupling reactions is electrophilic aromatic substitution of activated benzene derivatives by diazonium electrophiles.
- The products of such reactions are highly colored aromatic azo compounds that find use as synthetic dyestuffs, commonly referred to as azo dyes.

24.9 Heterocyclic Amines

- Heterocyclic structures are found in many natural products an example of some nitrogen compounds, known as alkaloids because of their basic properties.
- Pyrrole is obtained commercially by the reaction of furan with ammonia.
- In a pyrrole ring, the nitrogen lone pair is part of the aromatic sextet, thus not very basic.
- Substitution preference is on the 2-position of pyrrole.
- Imidazole is another five-membered heterocyclic amine, which is part of the amino acid histidine.
- Thiazole is a five-membered ring system which is found in biological systems.
- When a nitrogen atom is incorporated directly into an aromatic ring, its basicity depends on the bonding context.
- In pyridine, the nitrogen lone pair occupies an sp^2-hybrid orbital, and is not part of the aromatic sextet, therefore, its electron pair is available for forming a bond to a proton, and thus the pyridine nitrogen atom is somewhat basic.
- The aromatic stabilization energy of pyridine is 21 kcal/mole based on heat of combustion measurements.
- Polycyclic heterocyclic structures are found in many natural products like caffeine.
- Derivatives of the simple fused ring heterocycle purine constitute an especially important and abundant family of natural products.
- The amino compounds adenine and guanine are two of the complementary bases that are essential components of DNA.

24.10 Spectroscopy of Amines

- The hydrogens attached to an amine show up ~ 0.5-5.0 ppm in ^1H NMR.
- The broad range is due to the fact that the location is dependent on the amount of hydrogen bonding and the sample's concentration.

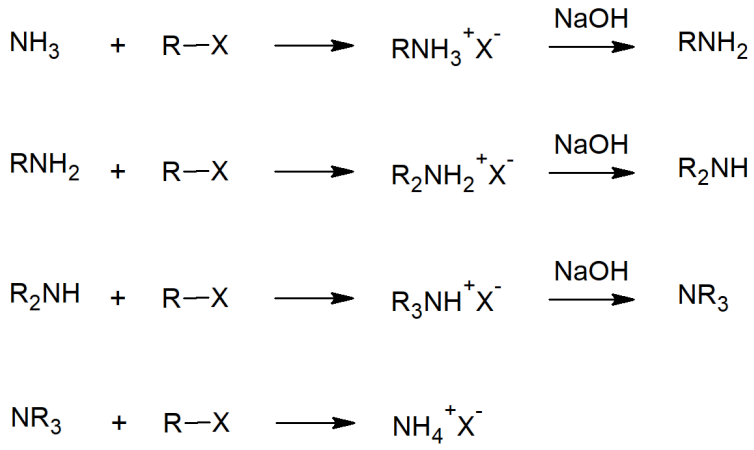
- The hydrogens on carbons directly bonded to an amine typically appear ~2.3-3.0 ppm in ^{1}H NMR.
- IR for primary amines a free N-H absorption is observed in the 3400 to 3500 cm^{-1} region as two well-defined peaks.
- IR for amines the C-N stretching absorptions are found at 1200 to 1350 cm^{-1} for aromatic amines, and at 1000 to 1250 cm^{-1} for aliphatic amines.
- Secondary amines exhibit only one absorption near 3420 cm^{-1} in IR.
- For tertiary amines, there is not N-H stretch.

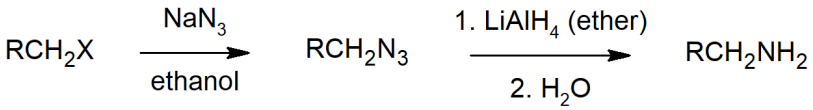
SKILLS TO MASTER

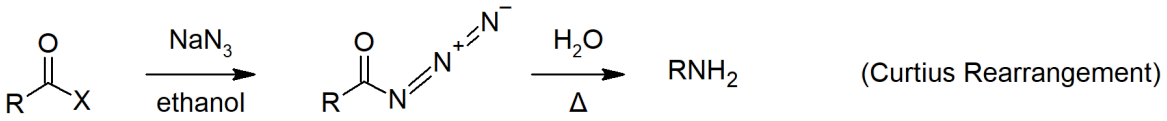
- Skill 24.1 Name amines using IUPAC rules.
- Skill 24.2 Draw the structure of amines from the IUPAC name.
- Skill 24.3 Describe the geometries and approximate bond angles of amines.
- Skill 24.4 Explain physical properties of amines.
- Skill 24.5 Explain why one amine is more basic than another.
- Skill 24.6 Explain how the basicity of an amine when the Nitrogen atom is incorporated in a ring depends on the bonding context.
- Skill 24.7 Describe how an amine can be extracted from a mixture that also contains neutral compounds illustrating the reactions which take place with appropriate equations.
- Skill 24.8 Explain why primary and secondary (but not tertiary) amines may be regarded as very weak acids.
- Skill 24.9 Use the concept of resonance to explain why arylamines are less basic than their aliphatic counterparts.
- Skill 24.10 Arrange a given series of arylamines in order of increasing or decreasing basicity.
- Skill 24.11 Explain using inductive and resonance effects arguments as to why a given arylamine is more or less basic than aniline.
- Skill 24.12 Identify the form that amine bases take within living cells.
- Skill 24.13 Use the Henderson-Hasselbalch equation to calculate the percentage of a base that is protonated in a solution, given the pK_a value of the associated ion and the pH of the solution.
- Skill 24.14 List general ways to synthesize amines.
- Skill 24.15 Draw mechanisms for preparing amines including:
  - reduction of nitriles, amides and nitro compounds.
  - reactions involving alkyl groups:
    1. S_N2 reactions of alkyl halides, ammonia and other amines.
    2. nucleophilic attack by an azide ion on an alkyl halide, followed by reduction of the azide so formed.
    3. alkylation of potassium phthalimide, followed by hydrolysis of the *N*-alkyl phthalimide so formed (i.e., the Gabriel synthesis).
  - reductive amination of aldehydes or ketones.
  - Hofmann or Curtius rearrangements.
- Skill 24.16 Write an equation to represent the reaction that takes place between ammonia, a primary or secondary amine, and an acid chloride.
- Skill 24.17 Identify the product formed when a given amine reacts with a given acid chloride.
- Skill 24.18 Draw the product for a Hoffman elimination.
- Skill 24.19 Propose a synthesis of arylamines using diazonium coupling reactions.
- Skill 24.20 Be able to draw the structure of furan, pyrrole and imidazole.
- Skill 24.21 Use the Hückel $2n + 4$ rule to explain the aromaticity of pyrrole.
- Skill 24.22 Be able to predict the product formed when pyrrole is subjected to an aromatic electrophilic substitution.
- Skill 24.23 Write the detailed mechanism for the electrophilic aromatic substitution of pyrrole to account for the fact that substitution takes place at C2 rather than C3.
- Skill 24.24 Explain the difference in basicity between pyridine, pyrrole and other amines.
- Skill 24.25 Explain why pyridine undergoes electrophilic substitution much less readily than does benzene.
- Skill 24.17 Use IR, NMR and MS in combination with the nitrogen rule to identify amines.

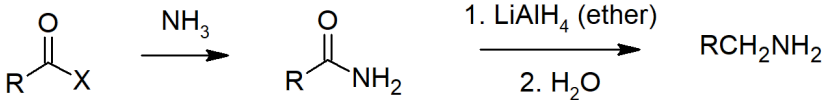
SUMMARY OF REACTIONS

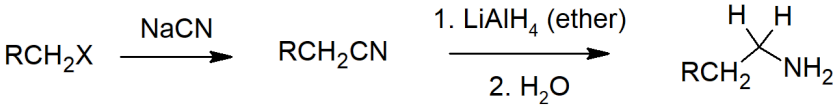
Amine Preparation

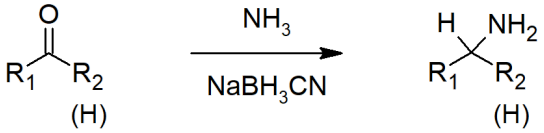












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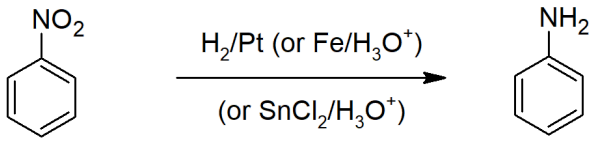
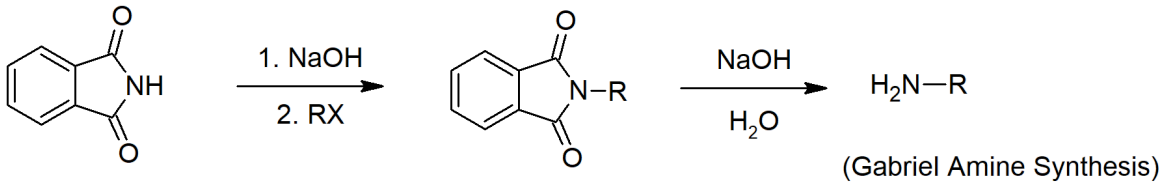
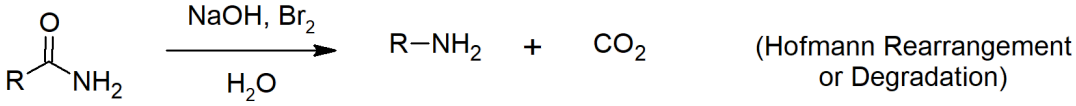


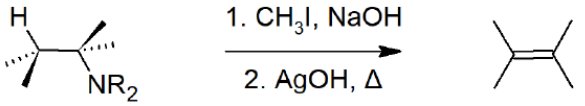


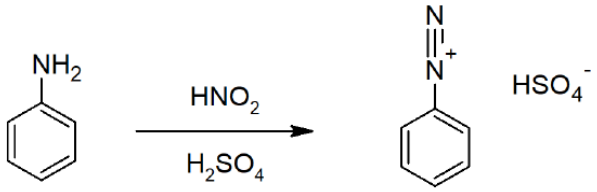
(Gabriel Amine Synthesis)

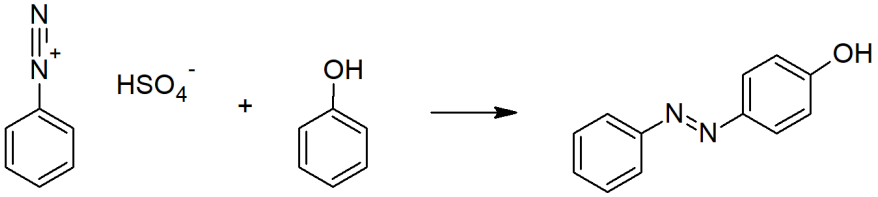


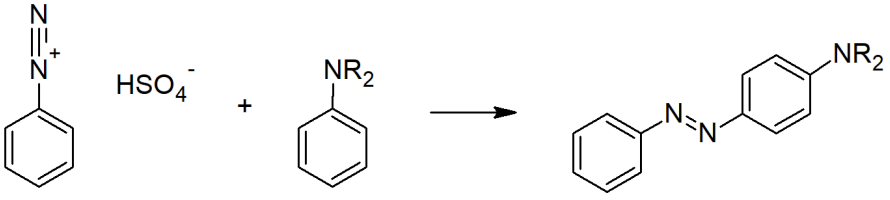
(Hofmann Rearrangement or Degradation)

Amine Reactions









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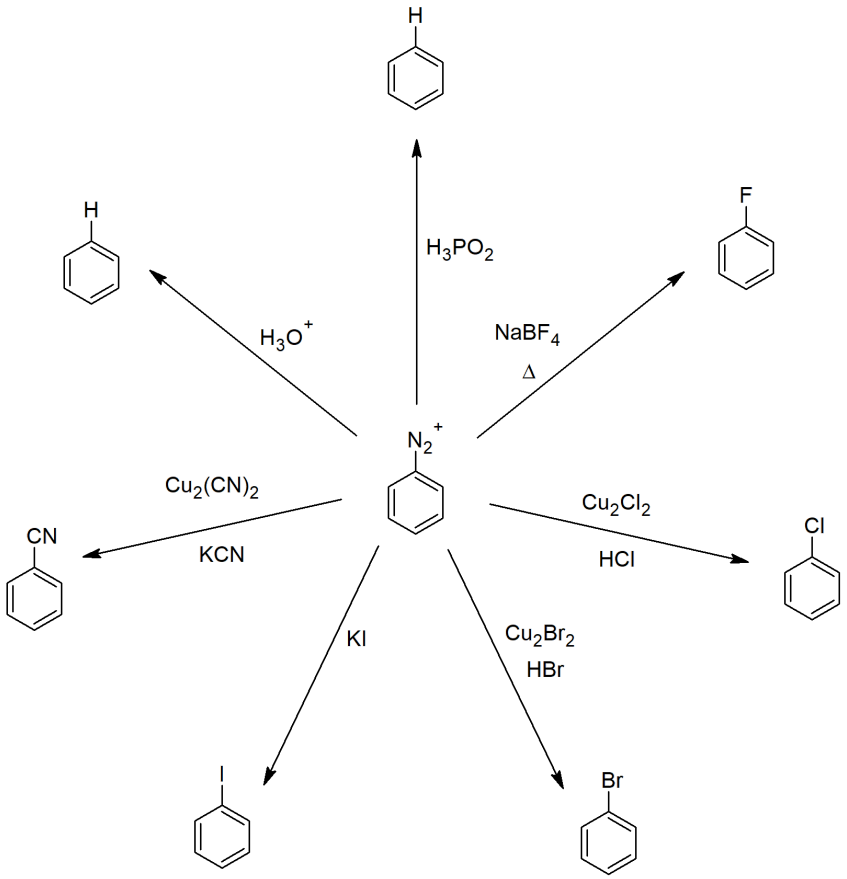

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CHAPTER OVERVIEW

25: CARBOHYDRATES

This chapter is designed to provide you with an overview of the biologically important group of compounds known as carbohydrates. Many of the compounds you will encounter while studying this chapter may appear to have very complex structures, but much of their chemistry can be readily understood in terms of the concepts and reactions discussed in earlier chapters of the course.

The chapter begins with an explanation of the classification schemes used to simplify the study of carbohydrates. We make extensive use of Fischer projection formulas throughout the chapter. We place considerable emphasis on gaining an appreciation of the configurations of carbohydrates, particularly of the aldoses. We describe the disadvantages of representing monosaccharides by open-chain structures, and at this point, introduce you to cyclic representations—called Haworth projections—of these substances. We describe the mutarotation of glucose, explaining it in terms of the existence of anomers. We then examine some reactions of monosaccharides, including the formation of ethers and esters, the formation of glycosides, and reduction and oxidation. We discuss the structures of some common disaccharides and polysaccharides, and conclude the chapter with a brief explanation of the role played by carbohydrates in cell recognition.

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25.0: INTRODUCTION

OBJECTIVES

After completing this section, you should be able to

1. identify carbohydrates (sugars) as being polyhydroxylated aldehydes and ketones.
2. describe, briefly, the process of photosynthesis, and identify the role played by carbohydrates as an energy source for living organisms.

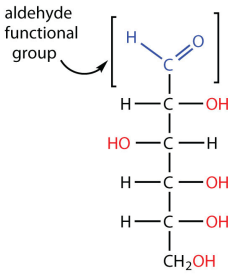
KEY TERMS

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

- carbohydrate

INTRODUCTION

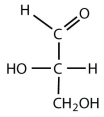
All carbohydrates consist of carbon, hydrogen, and oxygen atoms and are polyhydroxy aldehydes or ketones or are compounds that can be broken down to form such compounds. Examples of carbohydrates include starch, fiber, the sweet-tasting compounds called sugars, and structural materials such as cellulose. The term *carbohydrate* had its origin in a misinterpretation of the molecular formulas of many of these substances. For example, because its formula is $C_6H_{12}O_6$, glucose was once thought to be a "carbon hydrate" with the structure $C_6 \cdot 6H_2O$.



Because glucose has an aldehyde functional group and several –OH (hydroxyl) groups, it is described as a polyhydroxy aldehyde.

EXAMPLE 1

Which compounds would be classified as carbohydrates?

a. 

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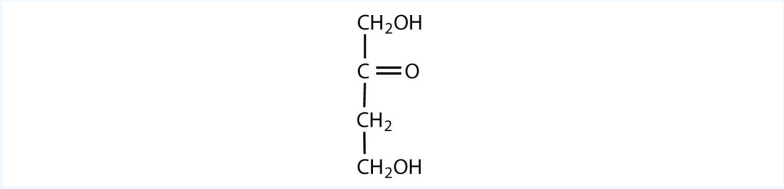
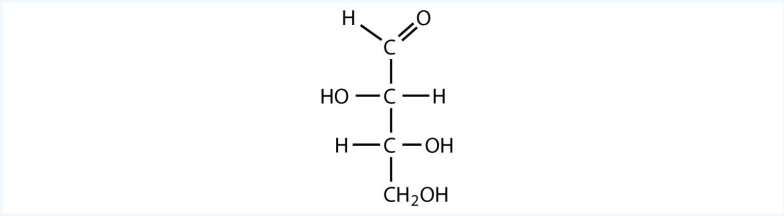
Solution

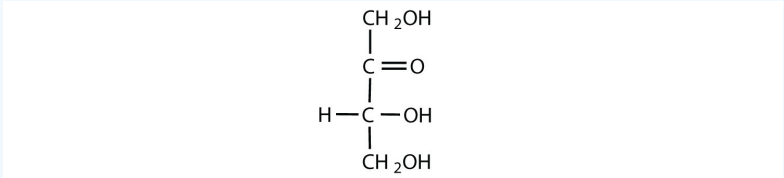
a. This is a carbohydrate because the molecule contains an aldehyde functional group with OH groups on the other two carbon atoms.
b. This is not a carbohydrate because the molecule does not contain an aldehyde or a ketone functional group.
c. This is a carbohydrate because the molecule contains a ketone functional group with OH groups on the other two carbon atoms.
d. This is not a carbohydrate; although it has a ketone functional group, one of the other carbons atoms does not have an OH group attached.

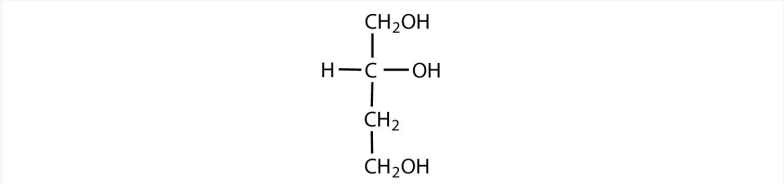
EXERCISE 1

Which compounds would be classified as carbohydrates?

1. 

- 

- 

- 

Green plants are capable of synthesizing glucose ($C_6H_{12}O_6$) from carbon dioxide (CO_2) and water (H_2O) by using solar energy in the process known as photosynthesis:

$$6\,CO_2 + 6\,H_2O + 2870\,kJ \longrightarrow C_6H_{12}O_6 + 6\,O_2$$

(The 2870 kJ comes from solar energy.) Plants can use the glucose for energy or convert it to larger carbohydrates, such as starch or cellulose. Starch provides energy for later use, perhaps as nourishment for a plant's seeds, while cellulose is the structural material of plants. We can gather and eat the parts of a plant that store energy—seeds, roots, tubers, and fruits—and use some of that energy ourselves. Carbohydrates are also needed for the synthesis of nucleic acids and many proteins and lipids.

Animals, including humans, cannot synthesize carbohydrates from carbon dioxide and water and are therefore dependent on the plant kingdom to provide these vital compounds. We use carbohydrates not only for food (about 60%–65% by mass of the average diet) but also for clothing (cotton, linen, rayon), shelter (wood), fuel (wood), and paper (wood).

CONTRIBUTORS AND ATTRIBUTIONS

- *The Basics of General, Organic, and Biological Chemistry* by David W. Ball, John W. Hill, and Rhonda J. Scott.

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25.1: CLASSIFICATION OF CARBOHYDRATES

OBJECTIVES

After completing this section, you should be able to

1. classify a specific carbohydrate as being a monosaccharide, disaccharide, trisaccharide, etc., given the structure of the carbohydrate or sufficient information about its structure.
2. classify a monosaccharide according to the number of carbon atoms present and whether it contains an aldehyde or ketone group.

KEY TERMS

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

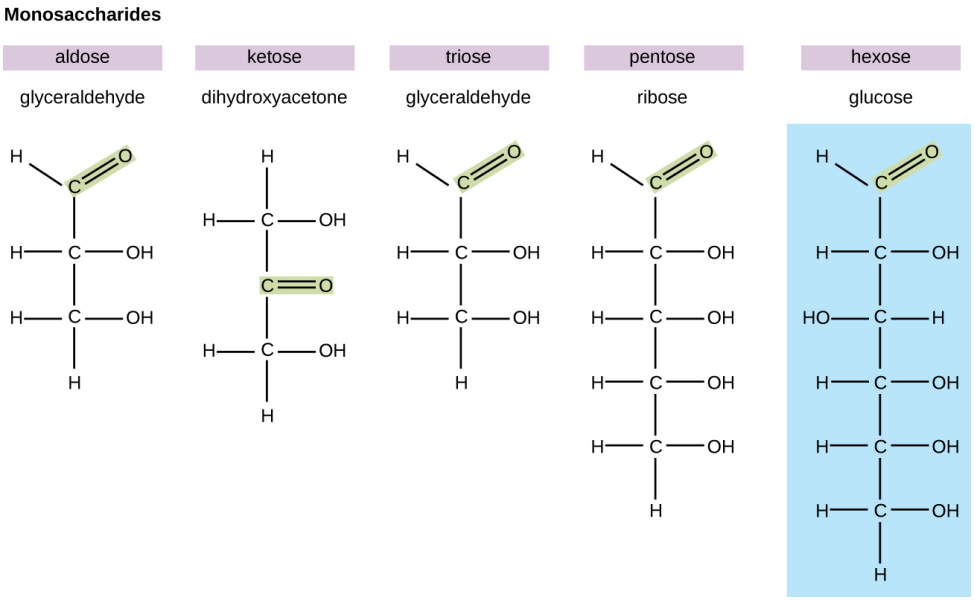
- aldose
- disaccharide
- ketose
- monosaccharide (simple sugar)
- polysaccharide

WHAT ARE CARBOHYDRATES?

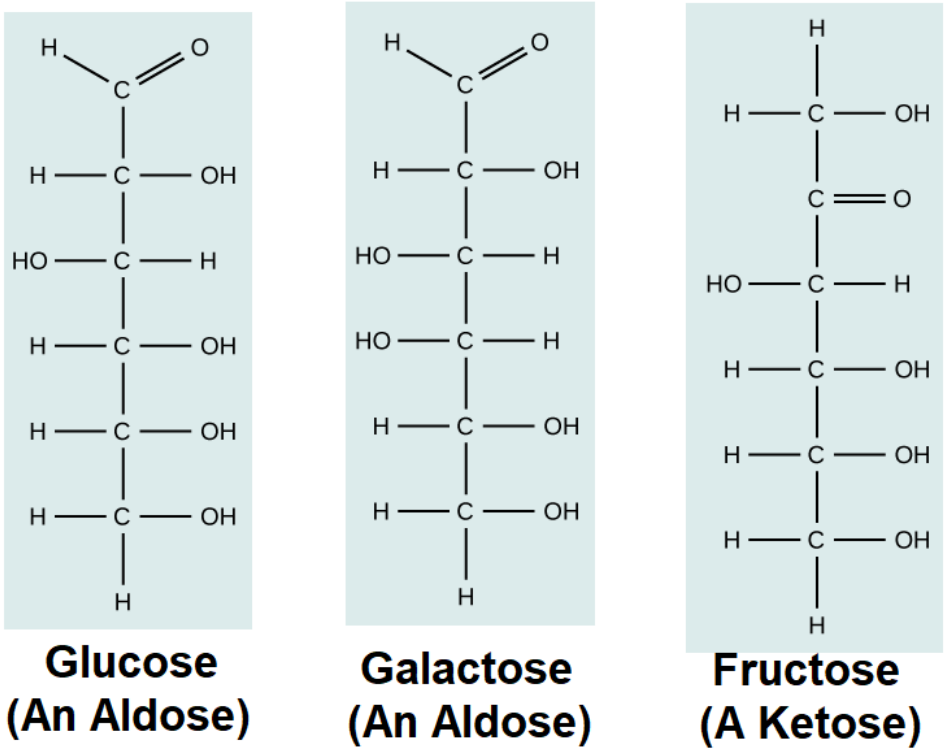
The most abundant biomolecules on earth are carbohydrates. From a chemical viewpoint, carbohydrates are primarily a combination of carbon and water, and many of them have the empirical formula $(CH_2O)_n$, where *n* is the number of repeated units. This view represents these molecules simply as "hydrated" carbon atom chains in which water molecules attach to each carbon atom, leading to the term "carbohydrates." Although all carbohydrates contain carbon, hydrogen, and oxygen, there are some that also contain nitrogen, phosphorus, and/or sulfur. Carbohydrates have myriad different functions. They are abundant in terrestrial ecosystems, many forms of which we use as food sources. These molecules are also vital parts of macromolecular structures that store and transmit genetic information (i.e., DNA and RNA). They are the basis of biological polymers that impart strength to various structural components of organisms (e.g., cellulose and chitin), and they are the primary source of energy storage in the form of starch and glycogen.

MONOSACCHARIDES

In biochemistry, carbohydrates are often called saccharides, from the Greek *sakcharon*, meaning sugar, although not all the saccharides are sweet. The simplest carbohydrates are called monosaccharides, or simple sugars. They are the building blocks (monomers) for the synthesis of polymers or complex carbohydrates, as will be discussed further in this section. Monosaccharides are classified based on the number of carbons in the molecule. General categories are identified using a prefix that indicates the number of carbons and the suffix *–ose*, which indicates a saccharide; for example, triose (three carbons), tetrose (four carbons), pentose (five carbons), and hexose (six carbons). The hexose D-glucose is the most abundant monosaccharide in nature. Other very common and abundant hexose monosaccharides are galactose, used to make the disaccharide milk sugar lactose, and the fruit sugar fructose.



A second comparison can be made when looking at glucose, galactose, and **fructose**. All three are hexoses; however, there is a major structural difference between glucose and galactose versus fructose: the carbon that contains the **carbonyl** (C=O). In glucose and galactose, the carbonyl group is on the C_1 carbon, forming an **aldehyde** group. In fructose, the carbonyl group is on the C_2 carbon, forming a **ketone** group. The former sugars are called **aldoses** based on the aldehyde group that is formed; the latter is designated as a **ketose** based on the ketone group. Again, this difference gives fructose different chemical and structural properties from those of the related aldoses, glucose, and galactose, even though fructose, glucose, and galactose all have the same chemical composition: $C_6H_{12}O_6$.

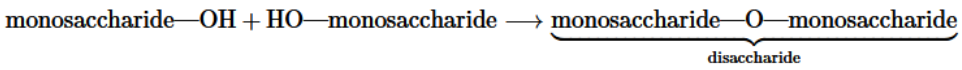


COMPLEX CARBOHYDRATES

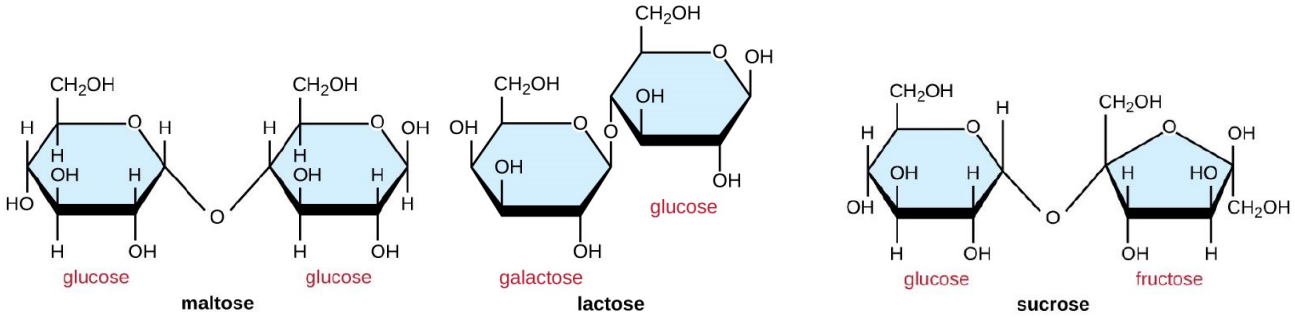
The simple sugars form the foundation of more complex carbohydrates. The cyclic forms of two sugars can be linked together by means of a condensation reaction to form a disaccharide. Multiple sugars can be linked to form polysaccharides.

DISACCHARIDES

Two monosaccharide molecules may chemically bond to form a disaccharide. The name given to the covalent bond between the two monosaccharides is a glycosidic bond. **Glycosidic bonds** form between hydroxyl groups of the two saccharide molecules, an example of the dehydration synthesis described later in this chapter.



Common disaccharides are the grain sugar maltose, made of two glucose molecules; the milk sugar lactose, made of one galactose and one glucose molecule; and the table sugar sucrose, made of one glucose and one fructose molecule.

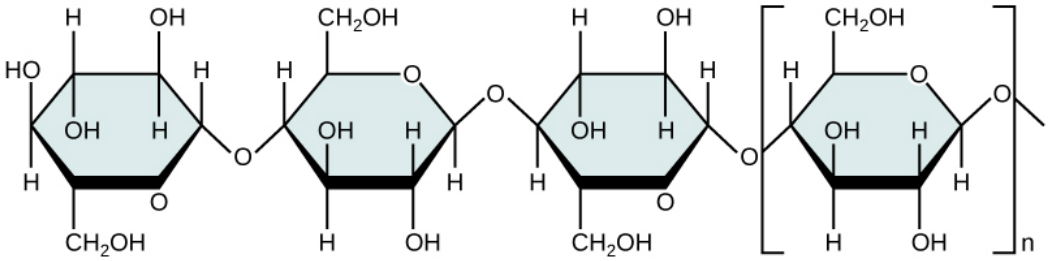


POLYSACCHARIDES

Polysaccharides, also called glycans, are large polymers composed of hundreds of monosaccharide monomers. Unlike mono- and disaccharides, polysaccharides are not sweet and, in general, they are not soluble in water. Like disaccharides, the monomeric units of polysaccharides are linked together by glycosidic bonds.

Polysaccharides are very diverse in their structure. Three of the most biologically important polysaccharides—starch, glycogen, and cellulose—are all composed of repetitive glucose units, although they differ in their structure. **Cellulose** consists of a linear chain of glucose molecules and is a common structural component of cell walls in plants and other organisms. **Glycogen** and **starch** are branched polymers; glycogen is the primary energy-storage molecule in animals and bacteria, whereas plants primarily store energy in starch. The orientation of the glycosidic linkages in these three polymers is different as well and, as a consequence, linear and branched macromolecules have different properties.

Cellulose structure



SUMMARY

Complexity	**Simple Carbohydrates** monosaccharides	**Complex Carbohydrates** disaccharides, oligosaccharides & polysaccharides

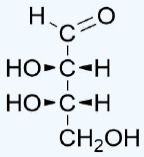
Size	**Tetrose** C_4 sugars	**Pentose** C_5 sugars	**Hexose** C_6 sugars	**Heptose** C_7 sugars	etc.

C=O Function	**Aldose** sugars having an aldehyde function or an acetal equivalent. **Ketose** sugars having a ketone function or an acetal equivalent.

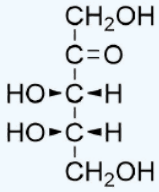
EXERCISE 25.1.1

1) Classify each of the following sugars.

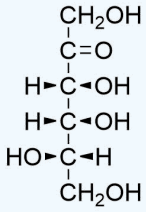
a)



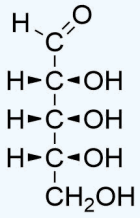
b)



c)



d)



Answer

a. Aldoterose
b. Ketopentose
c. Ketohexose
d. Aldopentose

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25.2: DEPICTING CARBOHYDRATE STEREOCHEMISTRY - FISCHER PROJECTIONS

OBJECTIVES

After completing this section, you should be able to

1. draw the Fischer projection of a monosaccharide, given its wedge and dash structure or a molecular model.
2. draw the wedge and dash structure of a monosaccharide, given its Fischer projection or a molecular model.
3. construct a molecular model of a monosaccharide, given its Fischer projection or wedge and dash structure.

KEY TERMS

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

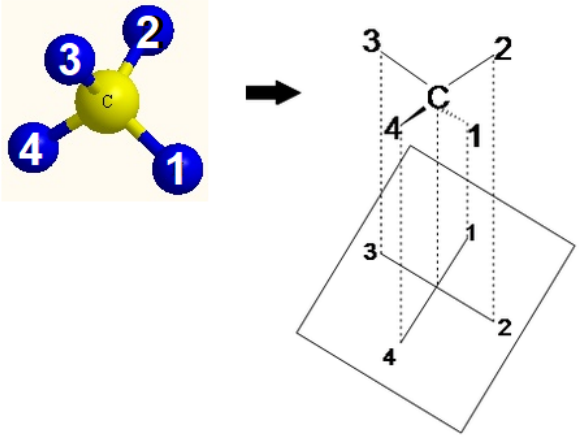
- Fischer projection

STUDY NOTES

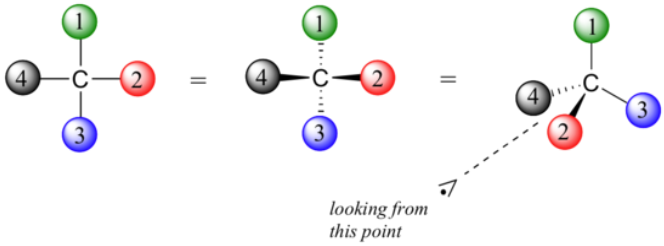
When studying this section, use your molecular model set to assist you in visualizing the structures of the compounds that are discussed. It is important that you be able to determine whether two apparently different Fischer projections represent two different structures or one single structure. Often the simplest way to check is to construct a molecular model corresponding to each projection formula, and then compare the two models.

DRAWING REPRESENTATIONS OF 3D STRUCTURES

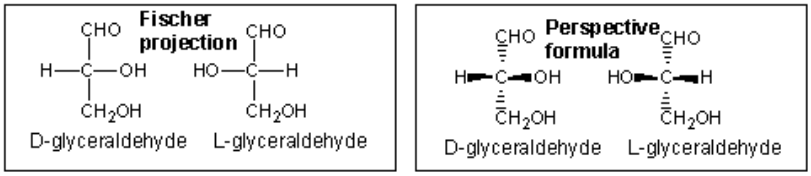
The problem of drawing three-dimensional configurations on a two-dimensional surface, such as a piece of paper, has been a long-standing concern of chemists. The wedge and dash notations we have been using are effective, but can be troublesome when applied to compounds having many chiral centers. As part of his Nobel Prize-winning research on carbohydrates, the great German chemist Emil Fischer, devised a simple notation that is still widely used. Fischer Projections allow us to represent 3D molecular structures in a 2D environment without changing their properties and/or structural integrity.



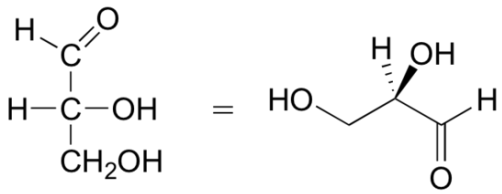
Fisher projections show sugars in their open chain form. In a Fischer projection, the carbon atoms of a sugar molecule are connected vertically by solid lines, while carbon-oxygen and carbon-hydrogen bonds are shown horizontally. Stereochemical information is conveyed by a simple rule: vertical bonds point into the plane of the page, while horizontal bonds point out of the page.



Sugars can be drawn in the straight chain form as either Fisher projections or perspective structural formulas. When drawing Fischer projections, the aldehyde group is written at the top, and the H and OH groups that are attached to each chiral carbon are written to the right or left. The arrangement of the atoms distinguishes one stereoisomer from the other.

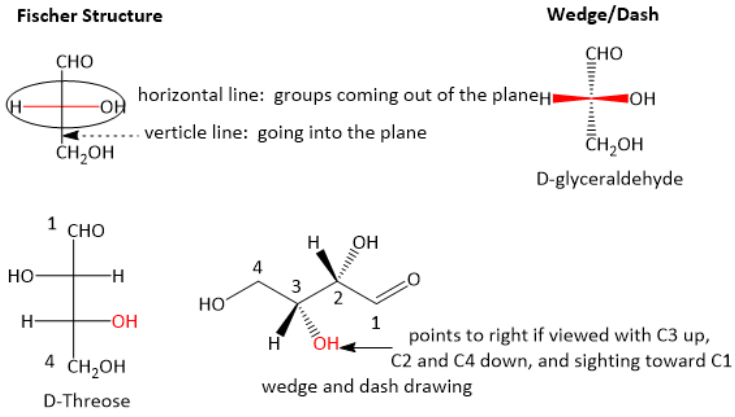


Below are two different representations of (R)-glyceraldehyde, the smallest sugar molecule (also called D-glyceraldehyde in the stereochemical nomenclature used for sugars):



(R)-glyceraldehyde
(D-glyceraldehyde)

In the Fisher projection, the vertical bonds point down into the plane of the paper. That's easy to visualize for 3C molecules. but more complicated for bigger molecules. For those draw a wedge and dash line drawing of the molecule. When determining the orientation of the hydroxides on each C, orient the wedge and dash drawing in your mind so that the C atoms adjacent to the one of interest are pointing down. Sighting towards the carbonyl C, if the OH is pointing to the right in the Fisher project, it should be pointing to the right in the wedge and dash drawing, as shown below for D-erthyrose and D-glucose.



Below are three representations of the open chain form of D-glucose: in the conventional Fischer projection, a wedge/dash version of a Fischer projection, and finally in the 'zigzag' style that is preferred by many organic chemists.

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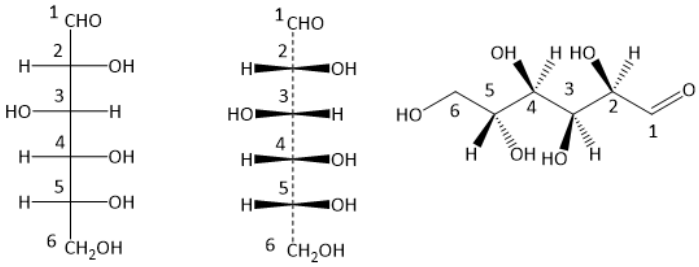
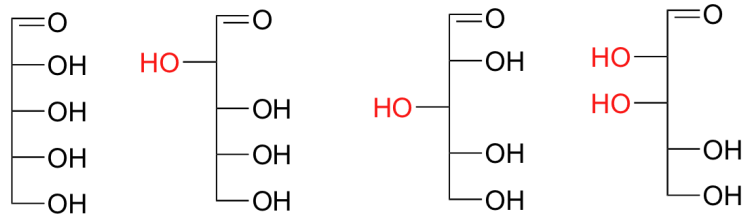


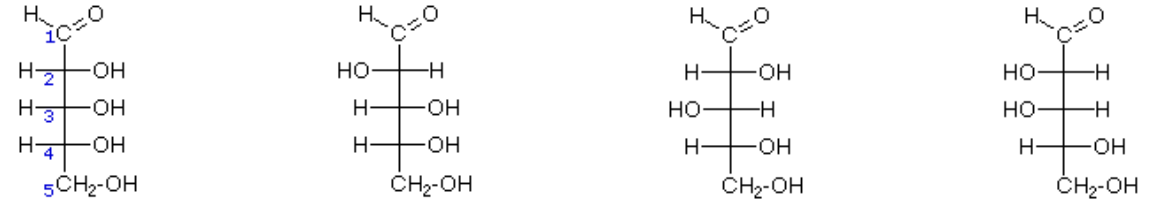
D-Glucose

Fischer projections are useful when looking at many different diastereomeric sugar structures, because the eye can quickly pick out stereochemical differences according to whether a hydroxyl group is on the left or right side of the structure.



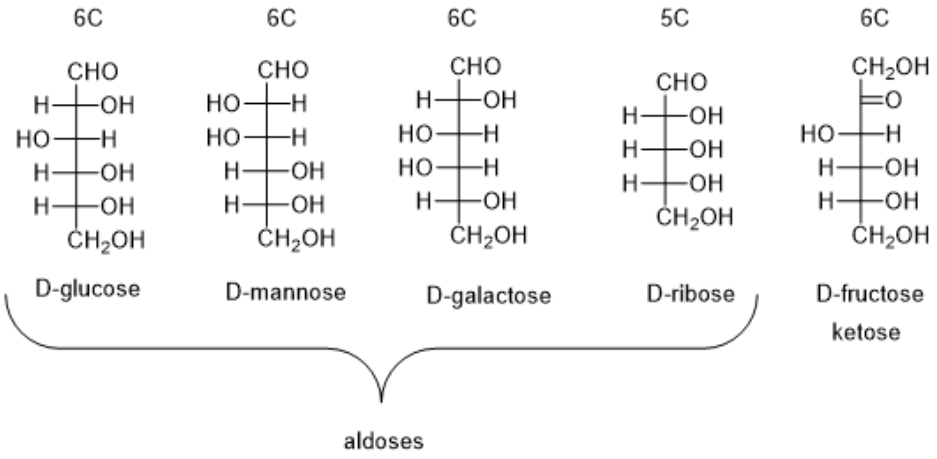
The usefulness of this notation to Fischer, in his carbohydrate studies, is evident in the following diagram. There are eight stereoisomers of 2,3,4,5-tetrahydroxypentanal, a group of compounds referred to as the aldopentoses (aldo- since the oxidized carbon is an aldehyde and -pentose since the molecules contain 5 carbons). Since there are three chiral centers in this constitution, we should expect a maximum of 2^3 stereoisomers. These eight stereoisomers consist of four sets of enantiomers. If the configuration at C-4 is kept constant (*R* in the examples shown here), the four stereoisomers that result will be **diastereomers**.

Four Diastereomeric $C_5H_{10}O_5$ Aldopentoses



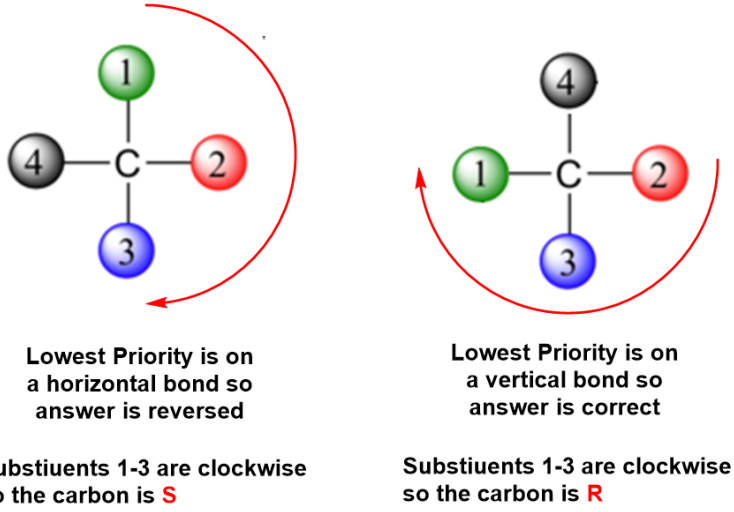
The aldopentose structures drawn above are all diastereomers. A more selective term, **epimer**, is used to designate diastereomers that differ in configuration at only one chiral center. Thus, ribose and arabinose are epimers at C-2, and arabinose and lyxose are epimers at C-3. However, arabinose and xylose are not epimers, since their configurations differ at both C-2 and C-3.

The Fisher structures of the most common monosaccharides (other than glyceraldehyde and dihydroxyacetone), which you will encounter most frequently are shown below.



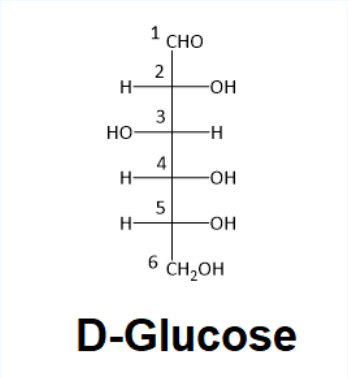
DETERMINING R AND S IN FISCHER PROJECTIONS

Determining whether a chiral carbon is R or S may seem difficult when using Fischer projections, but it is actually quite simple. If the lowest priority group (often a hydrogen) is on a vertical bond, the configuration is given directly from the relative positions of the three higher-ranked substituents. If the lowest priority group is on a horizontal bond, the positions of the remaining groups give the wrong answer (you are in looking at the configuration from the wrong side), so you simply reverse it.



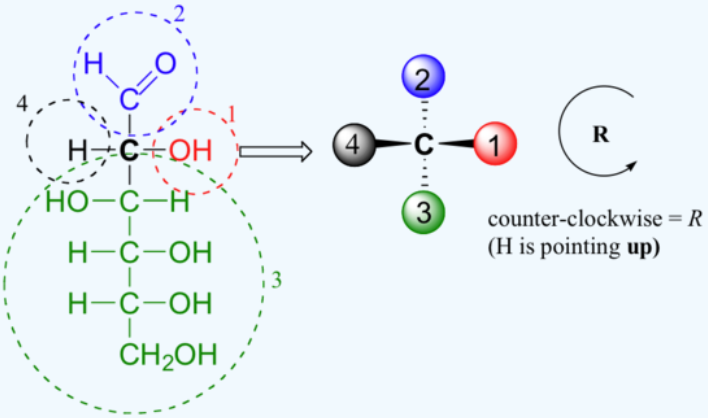
Worked Example 25.2.1

Determine if carbon #2 in D-glucose is R or S.



Answer

When deciding whether a stereocenter in a Fischer projection is *R* or *S*, realize that the hydrogen, in a horizontal bond. Therefore, the orientation of the three remaining substituents is reversed to create the correct answer or a counterclockwise circle means *R*, and a clockwise circle means *S*. For carbon #2 in D-Glucose substituent 1, 2, and 3 form a counterclockwise circle so the carbon is R.



HOW TO MAKE FISCHER PROJECTIONS

To make a Fischer Projection, it is easier to show through examples than through words. Lets start with the first example, turning a 3D structure of ethane into a 2D Fischer Projection.

EXERCISE 25.2.1

Start by mentally converting a 3D structure into a Dashed-Wedged Line Structure. Remember, the atoms that are pointed toward the viewer would be designated with a wedged lines and the ones pointed away from the viewer are designated with dashed lines.

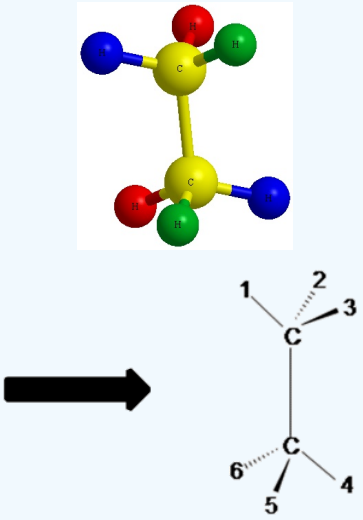


Figure B

Notice the red balls (atoms) in Figure A above are pointed away from the screen. These atoms will be designated with dashed lines like those in Figure B by number 2 and 6. The green balls (atoms) are pointed toward the screen. These atoms will be designated with wedged lines like those in Figure B by number 3 and 5. The blue atoms are in the plane of the screen so they are designated with straight lines.

Now that we have our Dashed- Wedged Line Structure, we can convert it to a Fischer Projection. However, before we can convert this Dashed-Wedged Line Structure into a Fischer Projection, we must first convert it to a "flat" Dashed-Wedged Line Structure. Then from there we can draw our Fischer Projection. Lets start with a more simpler example. Instead of using the ethane shown in Figure A and B, we will start with a methane. The reason being is that it allows us to only focus on one central carbon, which make things a little bit easier.

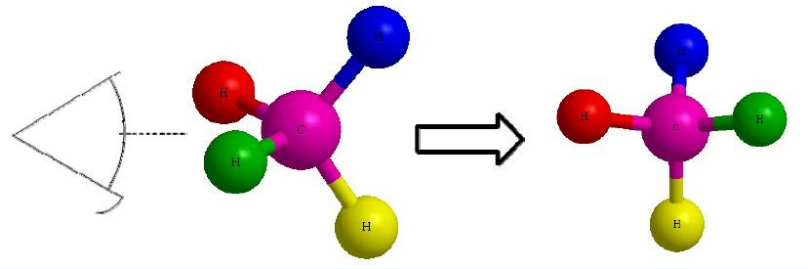
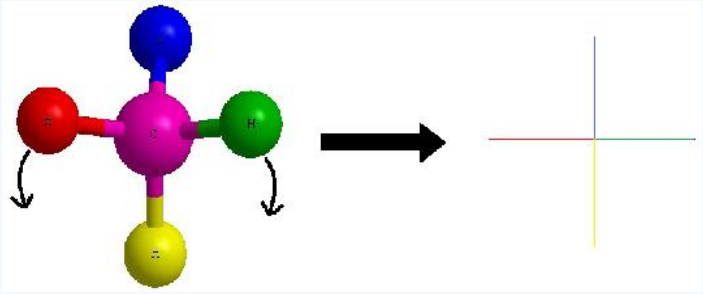


Figure D

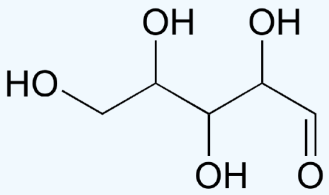
Lets start with this 3D image and work our way to a dashed-wedged image. Start by imagining yourself looking directly at the central carbon from the left side as shown in Figure C. It should look something like Figure D. Now take this Figure D and flatten it out on the surface of the paper and you should get an image of a cross.



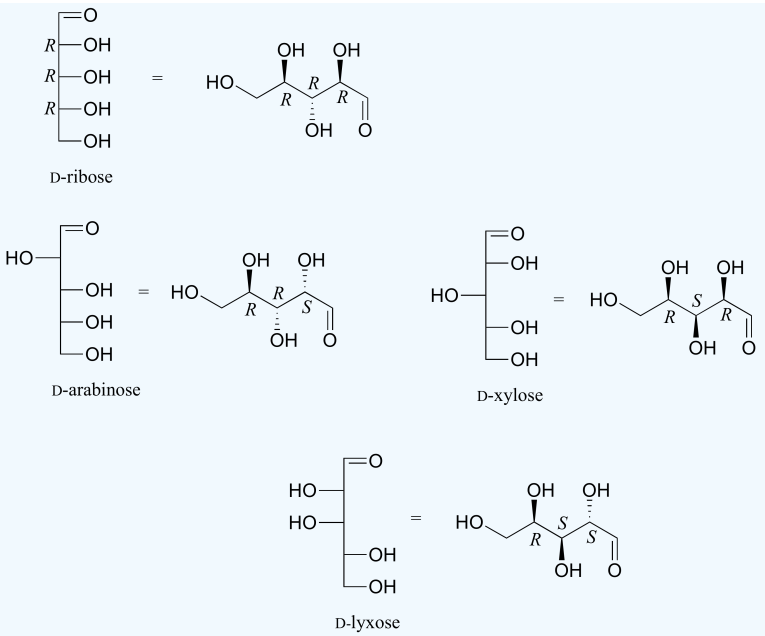
As a reminder, the horizontal line represents atoms that are coming out of the paper and the vertical line represents atoms that are going into the paper. The cross image to the right of the arrow is a Fischer projection.

? EXERCISE 25.2.1

Draw 'zigzag' structures (using the solid/dash wedge convention to show stereochemistry) for the four sugars in the figure below. Label all stereocenters *R* or *S*.



Answer



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25.3: D, L SUGARS

OBJECTIVES

After completing this section, you should be able to

1. identify a specific enantiomer of a monosaccharide as being D or L, given its Fischer projection.
2. identify the limitations of the D, L system of nomenclature for carbohydrates.
3. assign an *R* or *S* configuration to each of the chiral carbon atoms present in a monosaccharide, given its Fischer projection.
4. draw the Fischer projection formula for a monosaccharide, given its systematic name, complete with the configuration of each chiral carbon atom.
5. construct a molecular model of a monosaccharide, given its systematic name, complete with the configuration of each chiral carbon atom.

KEY TERMS

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

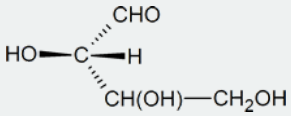
- D sugar
- L sugar

STUDY NOTES

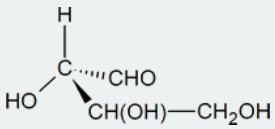
If you find that you have forgotten the meanings of terms such as dextrorotatory and polarimeter, refer back to Section 5.3 in which the fundamentals of optical activity were introduced.

How would you set about the task of deciding whether each chiral carbon has an *R* or an *S* configuration? True, you could use molecular models, but suppose that a model set had not been available—what would you have done then?

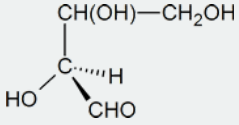
One approach is to focus on the carbon atom of interest and sketch a three-dimensional representation of the configuration around that atom, remembering the convention used in Fischer projections: vertical lines represent bonds going into the page, and horizontal lines represent bonds coming out of the page. Thus, the configuration around carbon atom 2 in structure a can be represented as follows:



In your mind, you should be able to imagine how this molecule would look if it was rotated so that the bonds that are shown as coming out of the page are now in the plane of the page. [One possible way of doing this is to try and imagine how the molecule would look if it was viewed from a point at the bottom of the page.] What you should see in your mind is a representation similar to the one drawn below.



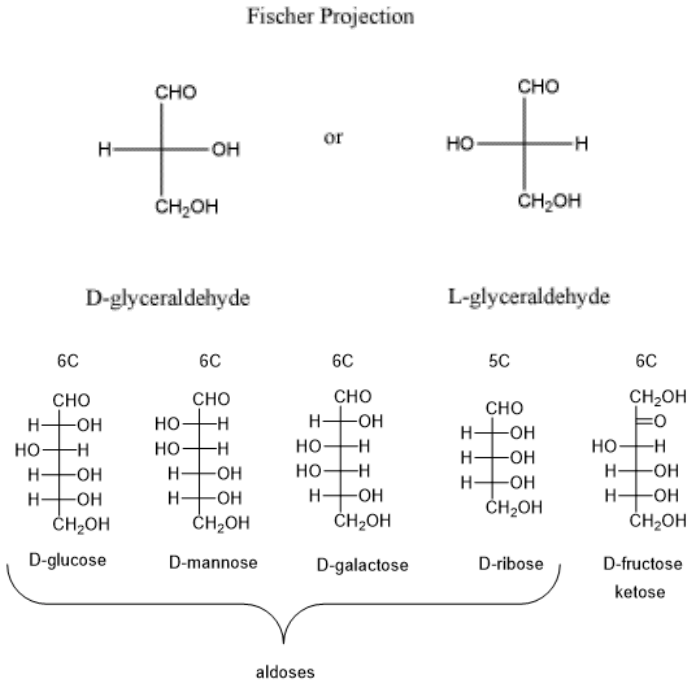
To determine whether the configuration about the central carbon atom is *R* or *S*, we must rotate the molecule so that the group with the lowest priority (H), is directed away from the viewer. This effect can be achieved by keeping the hydroxyl group in its present position and moving each of the other three groups one position clockwise.



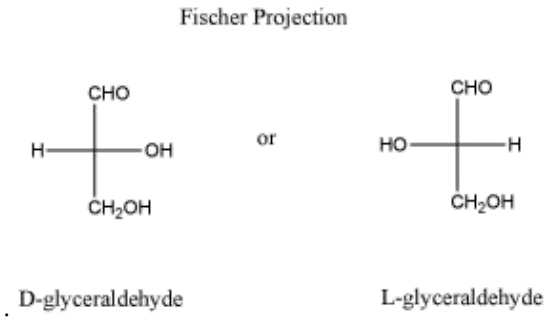
The Cahn-Ingold-Prelog order of priority for the three remaining groups is OH > CHO > $CH(OH)CH_2OH$; thus, we see that we could trace out a counterclockwise path going from the highest-priority group to the second- and third-highest, and we conclude that the central carbon atom has an *S* configuration.

D AND L LABELING OF MONOSACCHARIDE STEREOCHEMISTRY

Glyceraldehyde, the simplest possible aldose, is made up of three carbons and only one these is chiral. Glyceraldehyde has two stereoisomers, an R/S pair of enantiomers. Before the R,S system for designating chiral configuration was adopted by organic chemists (R)-glyceraldehyde was called D-glyceraldehyde (Latin for right: dexter) and (S)-glyceraldehdye was called L-glyceraldehyde (Latin for left:laevus). D- and L-glyceraldehyde were then used to provide reference points for designating and drawing all other monosaccharides. Sugars whose Fischer projections have the same configuration at the chiral carbon furthest from the carbonyl group as D-glyceraldehyde are designated as **D sugars**; those with the same configuration as L-glyceraldehyde are designated as **L sugars**. D and L designations of sugars are based on the position of the hydroxyl on the chiral carbon farthest from the carbonyl group in the Fischer projection of the molecule. All D-sugars have the –OH on the right side and L-sugars have the –OH on the left side.



D-sugars predominate in nature, though L-forms of some sugars, such as fucose, do exist. The D and L designation is a bit more complicated than it would appear on the surface. The confusion about D and L arises because the L sugars of a given name (glucose, for example) are mirror images of the D sugars of the same name. This concept is most easily seen with glyceraldehyde. In the same way D- and L- glyceraldehyde represent two enantiomers, the D- and L- forms larger monosaccharides are enantiomers of one another. The figure below shows the structure of D- and L- glucose. Notice that D-glucose is not converted into L-glucose simply by flipping the configuration of the fifth carbon in the molecule. Rather all of the arrangement around all of the chiral centers (horizontal lines) in the Fischer project of D-glucose need to be opposite to make L-glucose.



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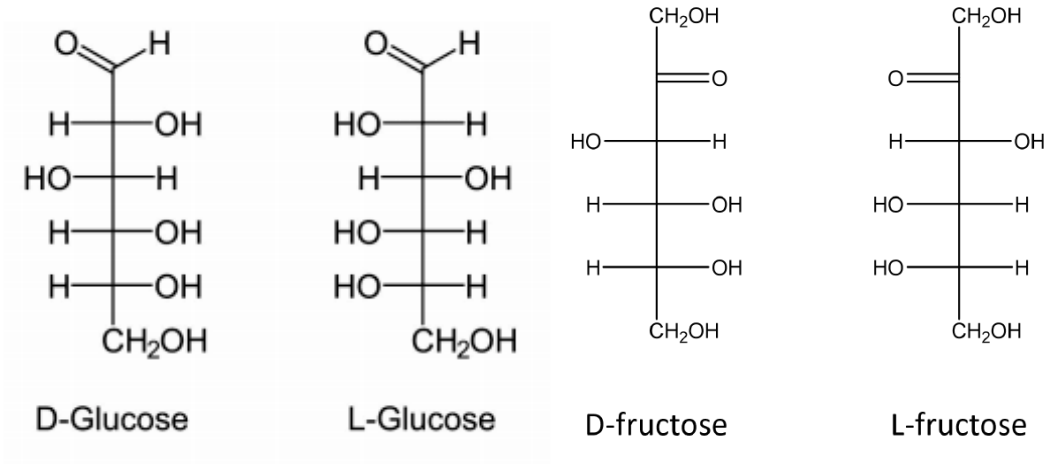


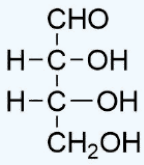
Figure 6. Fischer projections of enantiomers of glucose (left) and fructose (right).

It is important to recognize that the sign of a compound's specific rotation of plane polarized light (+)/(−) does not correlate with its configuration (D or L). The D/L labeling does not indicate which enantiomer is (+)/(−). Rather, it says that the compound's stereochemistry is related to that of the D or L enantiomer of glyceraldehyde. It is a simple matter to measure an optical rotation with a polarimeter. Determining an absolute configuration usually requires chemical interconversion with known compounds by stereospecific reaction paths.

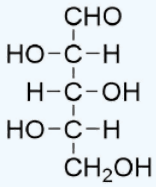
EXERCISE 25.3.1

In the following Fischer projections, assign R and S for each chiral center and determine whether each sugar is a D or L sugar.

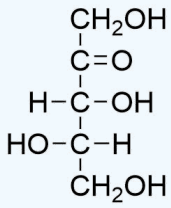
a)



b)



c)



Answer

a) From top to bottom, 2R, 3R, and it is a D sugar.

b) From top to bottom, 2S, 3R, 4S, and it is an L sugar.

c) From to to bottom, 3R, 4S, and it is an L sugar.

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25.4: CONFIGURATIONS OF ALDOSES

OBJECTIVES

After completing this section, you should be able to

1. draw the structures of all possible aldotetroses, aldopentoses, and aldohexoses, without necessarily being able to assign names to the individual compounds.
2. draw the Fischer projection of D-glyceraldehyde, D-ribose and D-glucose from memory.

The four chiral centers in glucose indicate there may be as many as sixteen (2^4) stereoisomers having this constitution. These would exist as eight diastereomeric pairs of enantiomers, and the initial challenge was to determine which of the eight corresponded to glucose. This challenge was accepted and met in 1891 by the German chemist Emil Fischer. His successful negotiation of the stereochemical maze presented by the aldohexoses was a logical tour de force, and it is fitting that he received the 1902 Nobel Prize for chemistry for this accomplishment. At the time Fischer undertook the glucose project it was not possible to establish the **absolute configuration** of an enantiomer. Consequently, Fischer made an arbitrary choice for (D)-glucose and established a network of related aldose configurations that he called the **D**-family. The mirror images of these configurations were then designated the **L**-family of aldoses. To illustrate using present day knowledge, Fischer projection formulas and names for the D-aldose family (three to six-carbon atoms) are shown below, with the asymmetric carbon atoms (chiral centers) colored red.

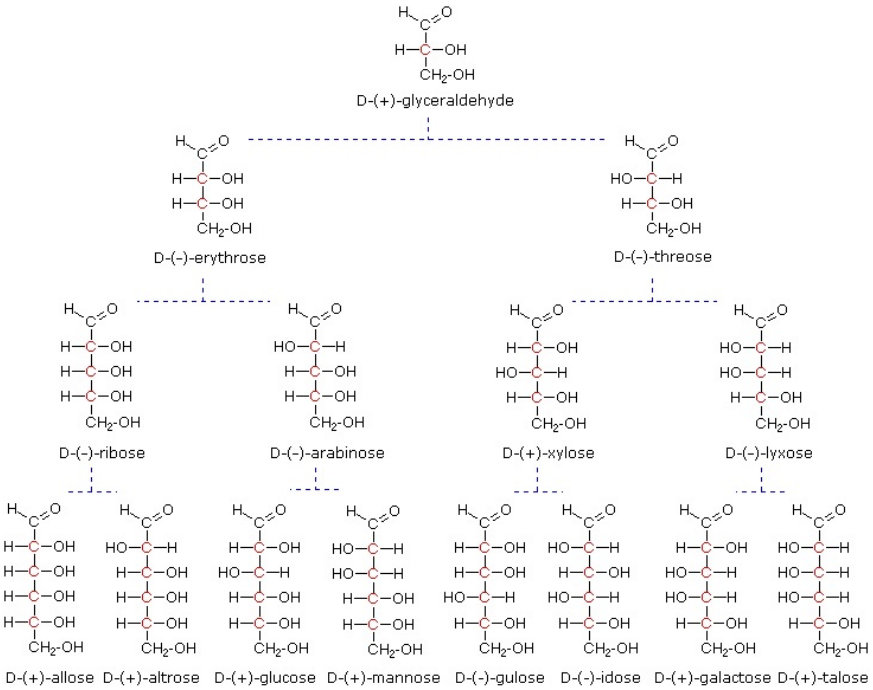
Aldotrioses: 3 carbon sugars with one chiral center. Aldotrioses have two (2^1) possible stereoisomers. A pair of enantiomers called D-gylceraldehyde and L-glyceraldehyde.

Aldotetroses: 4 carbon sugars with two chiral centers. Aldotetroses have four (2^2) possible stereoisomers. Two pairs of D/L enantiomers called erythrose and threose.

Aldopentoses: 5 carbon sugars with three chiral centers. Aldopentoses have eight (2^3) possible stereoisomers. Four pairs of D/L enantiomers called ribose, arabinose, xylose, and lyxose.

Aldohexoses: 6 carbon sugars with four chiral centers. Aldohexoses have sixteen (2^4) possible stereoisomers. five pairs of D/L enantiomers called allose, altrose, glucose, mannose, gulose, idose, galactose, and talose.

Below are the Fischer projects 3-6 carbon aldoses. Starting with the three carbon aldose D-glyceraldehyde, each additional carbon adds a new chiral center and doubles the number of possible stereoisomers of the D-aldoses. Remember that only D-aldoses are represented below. Each D-aldose has an L-aldose enantiomer which is not shown. The L-aldose versions can be draw by inverting all of the chiral centers in the D-aldose's Fischer projection as discussed in the previous section.



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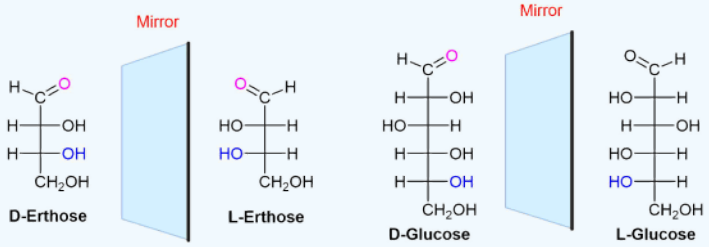
WORKED EXAMPLE 25.4.1

Draw the Fisher projection of L-erythrose and L-Glucose

Solution

Use the Fischer projection provided above and reverse all of the chiral centers to provide the L-sugar. Note that in both cases the D sugars have the OH going to the right on the chiral center furthest away from the carbonyl. The L-sugars have the OH going to the left.



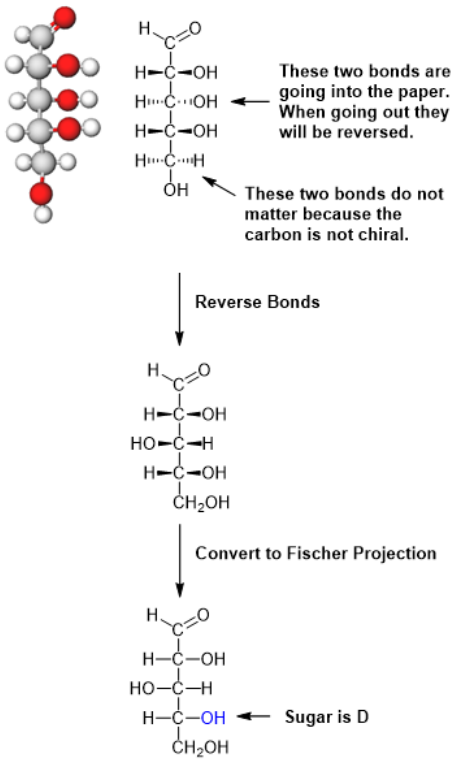
WORKED EXAMPLE 25.4.2

Please draw the Fischer projection fo the following aldopentose and determine if the sugars is D or L.

GLmol

Solution

First, rotate the model so that the carbonyl is at the top. This is requirement of a Fischer projection. Next rotate the model so that the H and OH of the chiral carbon just below the carbonyl are facing towards you. In this orientation, a dash/wedge model will have every other set of bonds going into the plane of the page. This is not the correct orientation of a Fischer project so they must be modified. The H and OH bonds need to be coming out of the plane of the page in a Fisher projects. When converting bonds from going into the page to going out of the page the orientation of the H and OH are reversed. Remember that the last -CH_2OH of a sugar is achiral so the orientation does not need to be shown. Once the bonds are oriented correctly the wedge bonds can be converted to those of a Fischer projection.



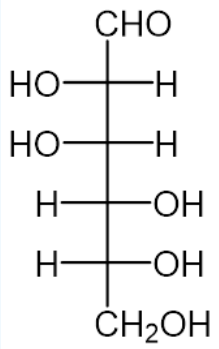
EXERCISE 25.4.1

For the following model of a sugar, please draw its Fischer projection and name it.

GLmol

Answer

D-Mannose



EXERCISE 25.4.2

How many heptose stereoisomers would there expected to be? How many would be D-Sugars?

Answer

There would be $2^5 = 32$ heptose stereoisomers. Half of these would be D-sugars or 16.

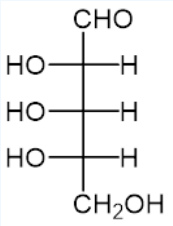
EXERCISE 25.4.3

Draw the Fischer projection of the following sugars.

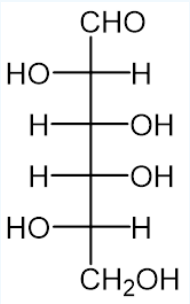
a. L-Ribose
b. L-Galactose
c. L-Talose

Answer

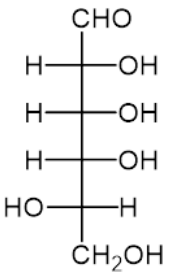
a)



b)



c)



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25.5: CYCLIC STRUCTURES OF MONOSACCHARIDES - ANOMERS

OBJECTIVES

After completing this section, you should be able to

1. determine whether a given monosaccharide will exist as a pyranose or furanose.
2. draw the cyclic pyranose form of a monosaccharide, given its Fischer projection.
3. draw the Fischer projection of a monosaccharide, given its cyclic pyranose form.
4. draw, from memory, the cyclic pyranose form of D-glucose.
5. determine whether a given cyclic pyranose form represents the D or L form of the monosaccharide concerned.
6. describe the phenomenon known as mutarotation.
7. explain, through the use of chemical equations, exactly what happens at the molecular level during the mutarotation process.

KEY TERMS

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

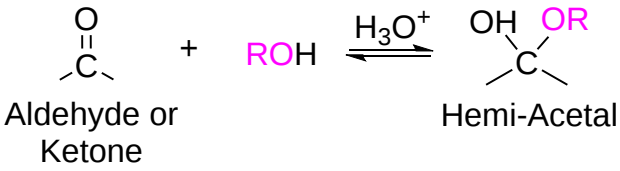
- alpha anomer
- anomer
- anomeric centre
- beta anomer
- furanose
- mutarotation
- pyranose

STUDY NOTES

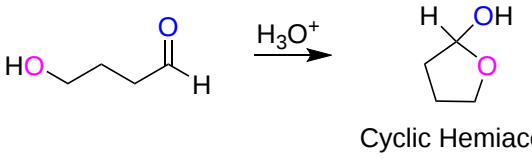
If necessary, before you attempt to study this section, review the formation of hemiacetals discussed in Section 19.10.

CYCLIC MONOSACCHARIDES

In Section 19-10 it was discussed that the reaction of 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') (*hemi*, Greek, half).



Molecules which have both an alcohol and a carbonyl can undergo an intramolecular version of the same reaction forming a cyclic hemiacetal.



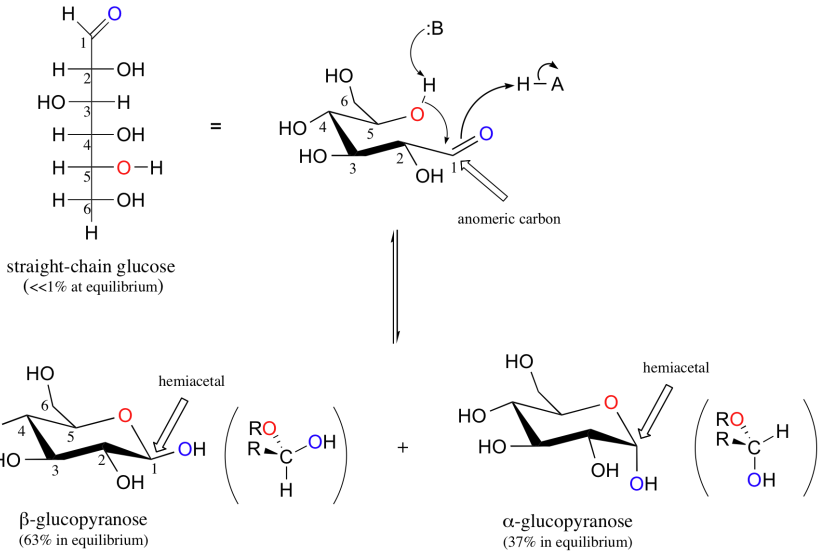
Because sugars often contain alcohol and carbonyl functional groups, intramolecular hemiacetal formation is common in carbohydrate chemistry. Five and six-membered rings are favored over other ring sizes because of their low angle and eclipsing strain. Cyclic structures of this kind are termed furanose (five-membered) or pyranose (six-membered), reflecting the ring size relationship to the common heterocyclic compounds furan and pyran shown below.

Furan (5-membered ring) and pyran (6-membered ring) structures

Unlike most of the biochemical reactions you will see in this text, sugar cyclization reactions are not catalyzed by enzymes: they occur spontaneously and reversibly in aqueous solution. Sugars are often shown in their open-chain form, however, in aqueous solution, glucose, fructose, and other sugars of five or six carbons rapidly interconvert between straight-chain and cyclic forms. For most five- and six-carbon sugars, the cyclic forms predominate in equilibrium since they are more stable. The size of the cyclic hemiacetal ring adopted by a given sugar is not constant, but may vary with substituents and other structural features.

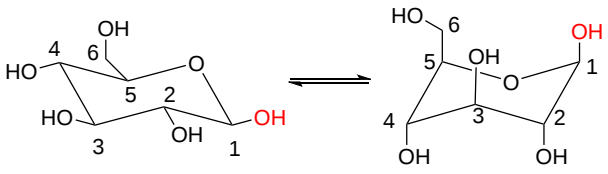
Aldohexoses usually form pyranose rings and their pentose homologs tend to prefer the furanose form, but there are many counter examples. At equilibrium less than 1% of glucose is in an open chain form with the rest being almost exclusively in its cyclic pyranose form. The pyranose ring is formed by attack of the hydroxyl on carbon 5 of glucose to the aldehyde carbon (carbon #1, also called the anomeric carbon in carbohydrate terminology). The cyclic form of glucose is called glucopyranose. Notice that for glucose and other aldohexoses the hydroxyl that forms the cyclic hemiacetal is also the one that determines the D/L designation of a sugar.

Pyranose rings are often drawn in a chair conformation like cyclohexane rings (**Section 4-6)** with substituents being either an axial or equatorial position. Pyranose rings are even capable of undergoing a ring flip to change between chair conformations. By convention the ring oxygen is placed to the right and to the rear of the structure (top right of the drawing). Groups which go to the right in a Fischer projection will be orientend 'down' of the pyranose ring while groups to the left are oriented 'up' in the chair structure. Also, the terminal -CH_2OH group is oriented up on the pyranose ring for D-sugars and down for L-Sugars.



When D-glucose cyclizes it forms a 37/63 mixture of the alpha and beta anomer respectively. The beta anomer is preferred because β-D-glucopyranose is the only aldohexose which can be drawn with all its bulky substituents (-OH and -CH_2OH) in equatorial positions, making it the most stable of the eight D-aldohexoses, which probably accounts for its widespread prevalence in nature.

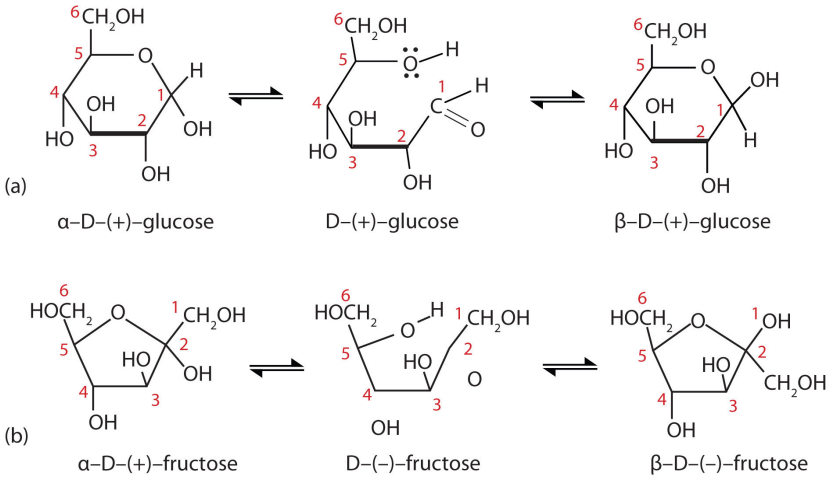
Conformational Isomers



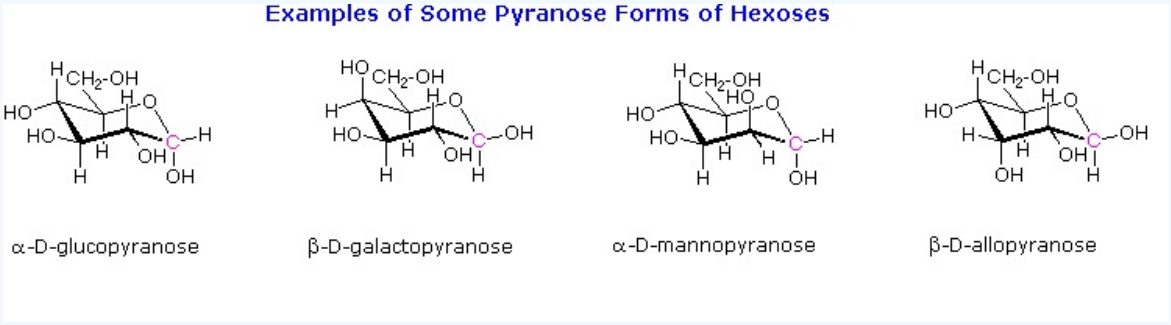
b-D-glucopyranose

https://chem.libretexts.org/@go/page/473965

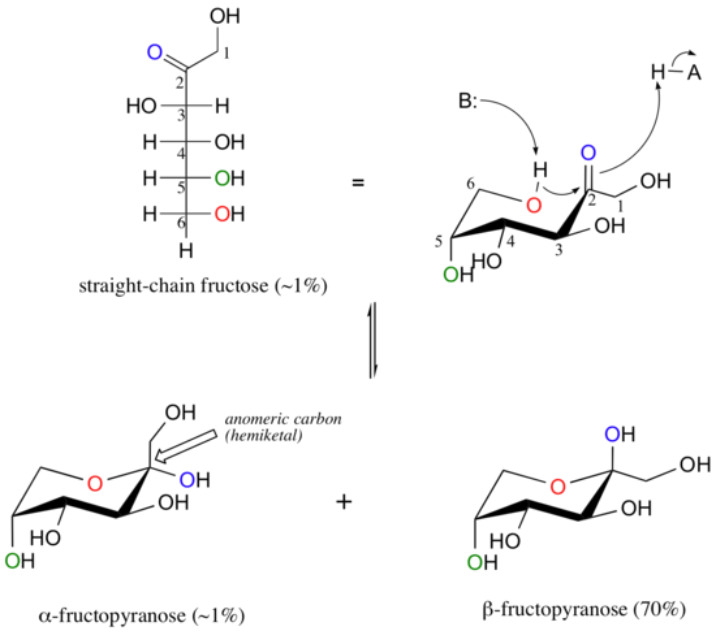
It is possible to obtain a sample of crystalline glucose in which all the molecules have the α structure or all have the β structure. The α form melts at 146°C and has a specific rotation of +112°, while the β form melts at 150°C and has a specific rotation of +18.7°. When the sample is dissolved in water, however, a mixture is soon produced containing both anomers as well as the straight-chain form, in dynamic equilibrium. You can start with a pure crystalline sample of glucose consisting entirely of either anomer, but as soon as the molecules dissolve in water, they open to form the carbonyl group and then re-close to form either the α or the β anomer. The opening and closing repeats continuously in an ongoing interconversion between anomeric forms and is referred to as mutarotation (Latin *mutare*, meaning "to change"). At equilibrium, the mixture consists of about 36% α-D-glucose, 64% β-D-glucose, and less than 0.02% of the open-chain aldehyde form. The observed rotation of this solution is +52.7°.



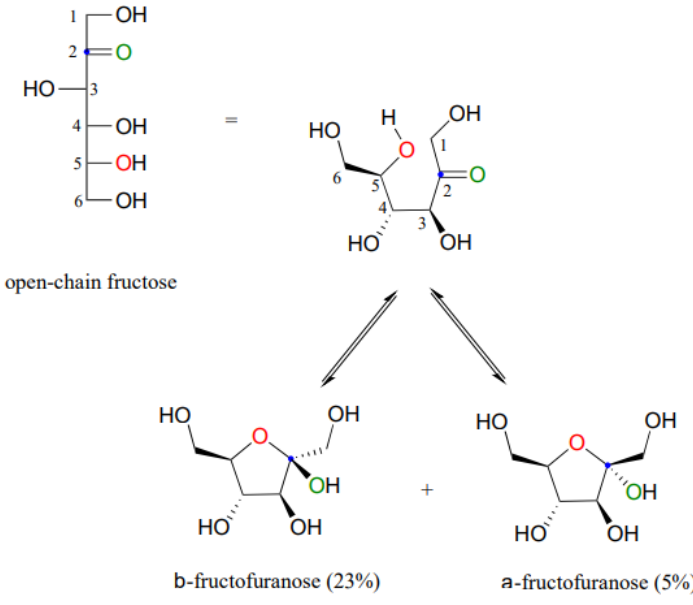
EXAMPLE 25.5.1



Fructose in aqueous solution forms a six-membered cyclic hemiketal called fructopyranose when the hydroxyl oxygen on carbon #6 attacks the ketone carbon (carbon #2, the anomeric carbon in fructose).



In this case, the β anomer is heavily favored in equilibrium by a ratio of 70:1, because in the minor α anomer the bulkier -CH_2OH group occupies an axial position. Notice in the above figure that the percentages of α and β anomers present at equilibrium do not add up to 100%. Fructose also exists in solution as a five-membered cyclic hemiketal, referred to in carbohydrate nomenclature as fructofuranose. In the formation of fructofuranose from open-chain fructose, the hydroxyl group on the fifth carbon attacks the ketone.



In aqueous solution, then, fructose exists as an equilibrium mixture of 70% β-fructopyranose, 23% β-fructofuranose, and smaller percentages of the open chain and cyclic α-anomers. The β-pyranose form of fructose is one of the sweetest compounds known, and is the main component of high-fructose corn syrup. The β-furanose form is much less sweet.

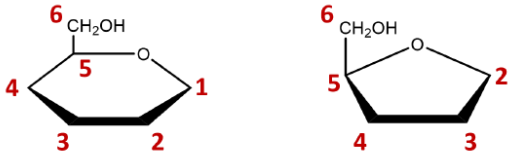
Although we have been looking at specific examples for glucose and fructose, other five- and six-carbon monosaccharides also exist in solution as equilibrium mixtures of open chains and cyclic hemiacetals and hemiketals. Shorter monosaccharides are unlikely to undergo analogous ring-forming reactions, however, due to the inherent instability of three and four-membered rings.

DRAWING CYCLIC STRUCTURES OF MONOSACCHARIDES

The cyclic forms of sugars are commonly depicted as **Haworth projections**. This convention, first suggested by the English chemist Walter N. Haworth, shows molecules drawn as planar rings with darkened edges representing the side facing toward the viewer. The structure is simplified to show only the functional groups attached to the carbon atoms. Any group written to the *right* in a Fischer projection appears *below (bottom face)* the plane of the ring in a Haworth projection, and any group written to the *left* in a Fischer projection appears *above* (top face) the plane in a Haworth projection.

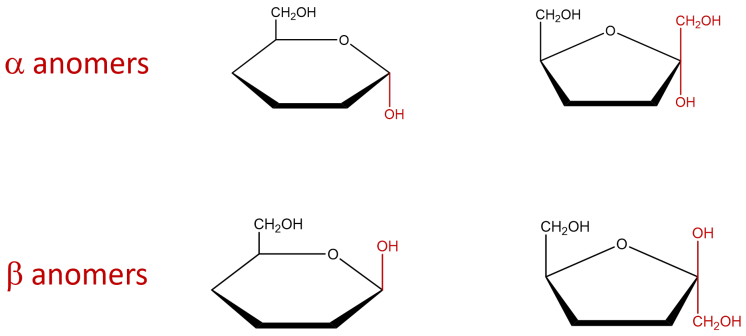
Figure: Conversion of the Fischer projection of D-glucose to the Haworth projection of ß-D-glucose.

1. When converting a Fischer projection (line) to a Haworth projection, you must first identify the type of monosaccharide involved. If the carbohydrate represents an aldohexose, the **pyranose** ring is typically used. A pyranose is a cyclic structure that contains five carbon atoms and an oxygen. If the carbohydrate represents a ketohexose, the **furanose** ring is typically used. The furanose ring contains four carbon atoms and an oxygen.

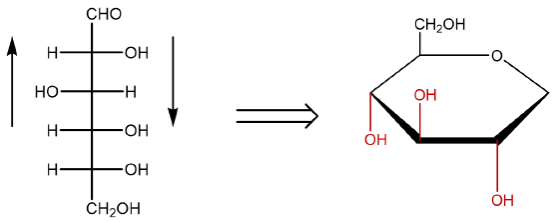


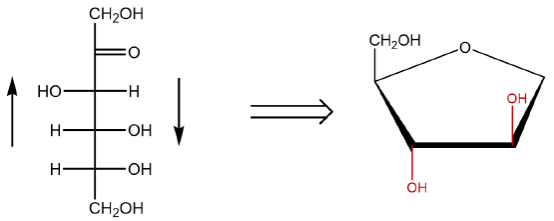
pyranose furanose

2. Indicate the arrangement of the hydroxyl group attached to the anomeric carbon to identify the sugar as an alpha or beta anomer. The α and β anomers are determined with respect to carbon 6. If the molecule represents a D-sugar, carbon 6 will be above the plane of the ring (top face) and form an L-sugar, carbon 6 will be below the plane of the ring (ring). The α anomer occurs when the OH on the anomeric carbon is trans to carbon 6 and the β anomer occurs when the OH on the anomeric carbon is cis to carbon 6. If the cyclic structure contains a furanose, since carbon 1 is not included within the ring, that carbon group would be arranged in the opposite direction of the OH group.

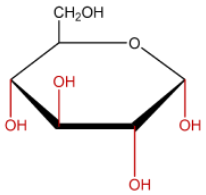


3. The remaining chiral centers (carbons 2, 3 and 4 of the pyranose or carbons 3 and 4 of the furanose) are arranged based on the directions of the hydroxyl from the Fischer projection structures. Groups to the left of the Fischer projection would point up (top face), while groups to the right would point down (bottom face).

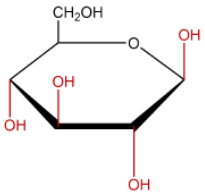




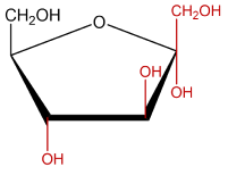
Since the Fischer Projection of any given carbohydrate is always the same, the Haworth Projection is essentially always the same. The only differences between the Haworth Projection of the alpha or beta form of a single carbohydrate, is how the OH (and carbon 1 if furanose ring) is arranged around the anomeric carbon to determine whether the molecule is alpha or beta.



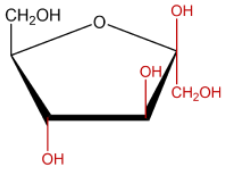
α-D-glucose
(or α-D-glucopyranose)



β-D-glucose
(or β-D-glucopyranose)



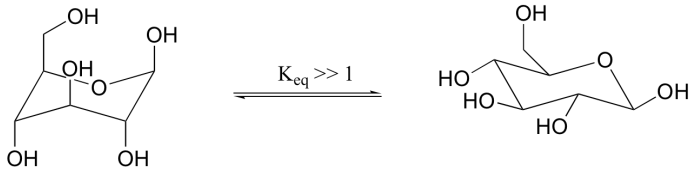
α-D-fructose
(or α-D-fructofuranose)



β-D-fructose
(or β-D-fructofuranose)

STABILITY OF CHAIR CONFORMATION IN PYRANOSE SUGARS

Previously, we have seen the six ring atoms of cyclic glucose drawn in two dimensions. A more accurate depiction shows that the molecule adopts, as expected, a chair conformation.



all axial

all equitorial

The conformation in which all substituents are equatorial is lower in energy. The two isomeric forms are referred to by the Greek letters alpha (α) and beta (β).

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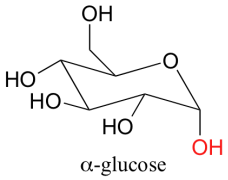
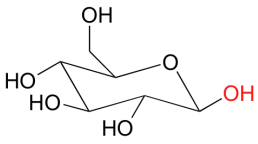


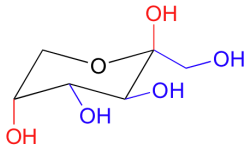
α-glucose



β-glucose

We have not learned about stereoisomerism quite yet, but you can still recognize that the bonding configuration on one carbon is different. On the alpha isomer, one of the hydroxyl groups is axial – this isomer is not able to adopt a chair conformation in which all non-hydrogen substituents are equatorial. The lower energy conformation is the one in which four of the five substituents are equatorial, but the presence of the one axial hydroxyl group means that the alpha isomer is, overall, less stable than the beta isomer.

The most abundant form of fructose in aqueous solution is also a six-membered ring.



fructose
(major form)

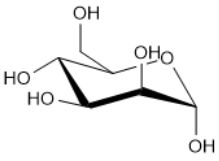
The lower energy chair conformation is the one with three of the five substituents (including the bulky $–CH_2OH$ group) in the equatorial position.

EXERCISE 25.5.1

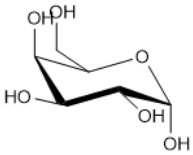
Draw the following in their most stable chair conformation: α-D-galactopyranose and α-D-mannopyranose. Which is expected to be the more stable?

Answer

Because the both have two axial OH's their chair conformations should be roughly the same stability.



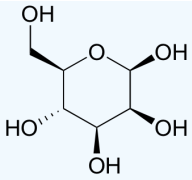
a-D-Mannose



a-D-Galactose

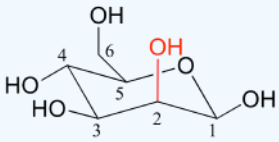
EXERCISE 25.5.2

Draw the two chair conformations of the sugar called mannose, being sure to clearly show each non-hydrogen substituent as axial or equatorial. Predict which conformation is likely to be more stable, and explain why.

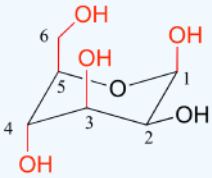


mannose

Answer



major chair form of mannose
(only one substituent axial)

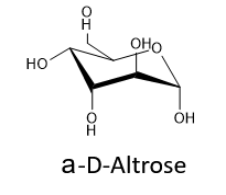


minor chair form of mannose
(four substituents axial)

EXERCISE 25.5.3

Draw the cyclic structure of α-D-altrose.

Answer

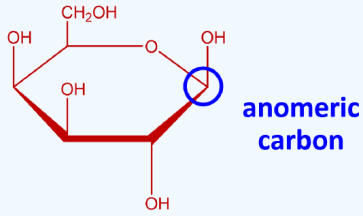


a-D-Altrose

EXERCISE 25.5.4

Draw the cyclic structure for β-D-galactose. Identify the anomeric carbon.

Answer

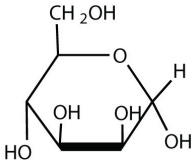


To identify the structure, we should first start with the Fischer projection of D-galactose. Since it is an aldohexose, we will start with the pyranose ring. The beta anomer was requested, so the OH on the anomeric carbon (C1) is cis to C6. Since C6 is top face (pointing up), the OH will be top face. Carbons 2, 3, and 4 are then arranged based on the Fischer projection arrangement at those carbons (C2 right, C3 left, and C4 left).

EXERCISE 25.5.5

Given that the aldohexose D-mannose differs from D-glucose only in the configuration at the second carbon atom, draw the cyclic structure for α-D-mannose.

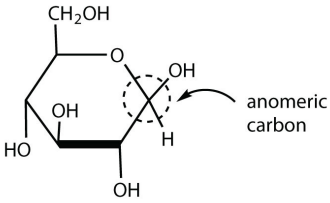
Answer



EXERCISE 25.5.6

Draw the cyclic structure for β-D-glucose. Identify the anomeric carbon.

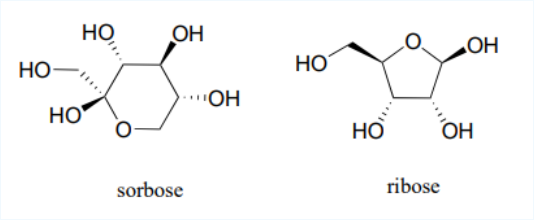
Answer



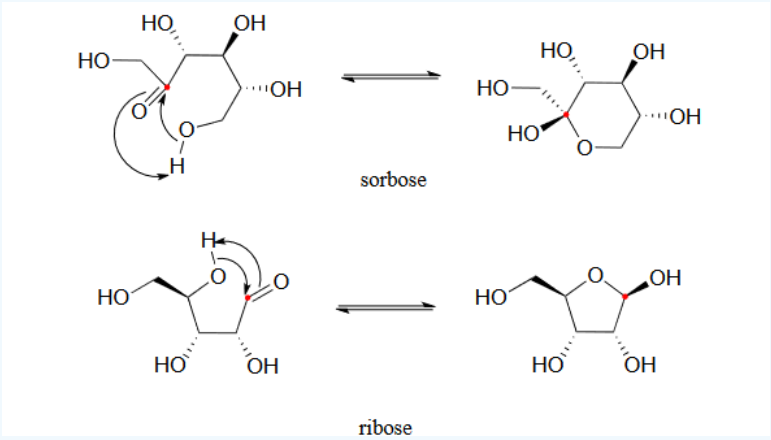
EXERCISE 25.5.7

a) Identify the anomeric carbon of each of the sugars shown below, and specify whether the structure shown is a hemiacetal or hemiketal.

b) Draw mechanisms for cyclization of the open-chain forms to the cyclic forms shown.



Answer



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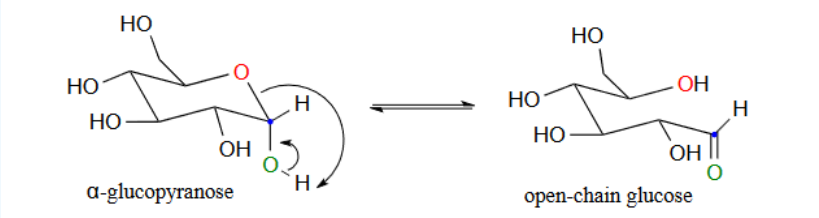
EXERCISE 25.5.8

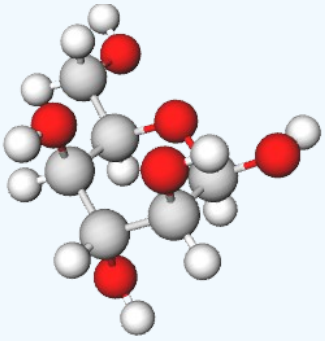
Draw a mechanism for the conversion of α-glucopyranose to open-chain glucose.

Answer



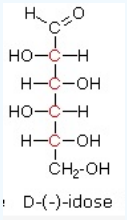
EXERCISE 25.5.9

Identify the following monosaccharide, write its full name, and draw its open-chain form as a Fischer projection.



Answer

β-D-idopyranose.



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25.6: REACTIONS OF MONOSACCHARIDES

OBJECTIVES

After completing this section, you should be able to

1. a. write equations to illustrate that the hydroxyl groups of carbohydrates can react to form esters and ethers.
   b. identify the product formed when a given monosaccharide is reacted with acetic anhydride or with silver oxide and an alkyl halide.
   c. identify the reagents required to convert a given monosaccharide to its ester or ether.
2. a. write an equation to show how a monosaccharide can be converted to a glycoside using an alcohol and an acid catalyst.
   b. identify the product formed when a given monosaccharide is treated with an alcohol and an acid catalyst.
   c. write a detailed mechanism for the formation of a glycoside by the reaction of the cyclic form of a monosaccharide with an alcohol and an acid catalyst.
3. identify the ester formed by phosphorylation in biologically important compounds.
4. a. identify the product formed when a given monosaccharide is reduced with sodium borohydride.
   b. identify the monosaccharide which should be reduced in order to form a given polyalcohol (alditol).
5. a. explain that a sugar with an aldehyde or hemiacetal can be oxidized to the corresponding carboxylic acid (also known as aldonic acid). **Note:** The sugar is able to reduce an oxidizing agent, and is thus called a reducing sugar. Tests for reducing sugars include the use of Tollens' reagent, Fehling's reagent and Benedict's reagent.
   b. explain why certain ketoses, such as fructose, behave as reducing sugars even though they do not contain an aldehyde group.
   c. identify warm HNO_3 as the reagent needed to form dicarboxylic acid (an aldaric acid).
6. a. describe the chain-lengthening effect of the Kiliani-Fischer synthesis.
   b. predict the product that would be produced by the Kiliani-Fischer synthesis of a given aldose.
   c. identify the aldose that would yield a given product following Kiliani-Fischer synthesis.
7. a. describe the chain-shortening effect of the Wohl degradation.
   b. predict the product that would be produced by the Wohl degradation of a given aldose.
   c. identify the aldose or aldoses that would yield a given product following Wohl degradation.

KEY TERMS

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

- aldaric acid
- aldonic acid
- alditol
- aldonic acid
- glycoside
- Kiliani-Fischer synthesis
- neighbouring group effect
- reducing sugar
- Wohl degradation

STUDY NOTES

While several reactions are covered in this section, keep in mind that you have encountered them in previous sections. The active functional groups on monosaccharides are essentially carbonyls and hydroxyls. Although they now are a part of much larger molecules, their chemistry should be familiar.

The formation of esters and ethers is quite straightforward and should not require further clarification.

Note that glycosides are in fact acetals, and that glycoside formation is therefore analogous to acetal formation. To refresh your memory about the chemistry of acetals, quickly review Section 19.10

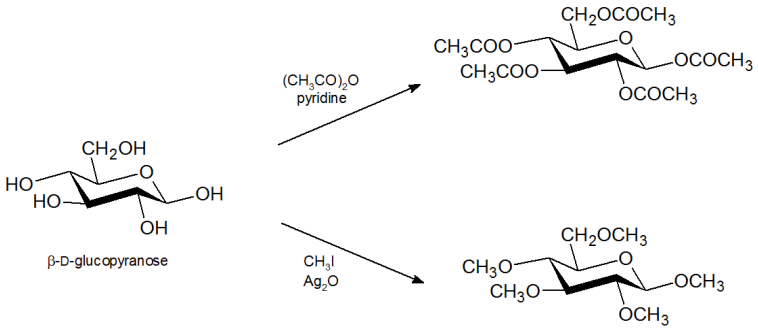
Monosaccharides contain both alcohol and carbonyl functional groups. This allows monosaccharides to undergo many of the reactions typical for these functional groups. In particular, alcohols can be converted to esters, converted to ethers, converted to acetals, or oxidized. Carbonyls can be reacted with nucleophiles, be reduced to form alcohols, or be oxidized to form carboxylic acids.

ESTER AND ETHER FORMATION

The hydroxyl groups of monosaccharides are often converted to ether or ester groups to increase solubility in organic solvents. Also, the conversion allows the sugar to be easily purified and crystallized.

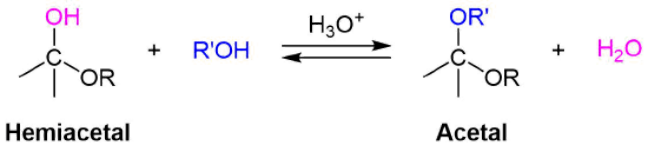
The -OH groups on a monosaccharide can be readily converted to esters and ethers. Esterfication can be done with an acid chloride (Section 21.4) or acid anhydride (Section 21.5) in the presence of a base. During these reactions all of the -OH groups are converted to esters. The monosaccharide, D-glucopyranose can be coverted to the pentacetate through reaction with acetic anhydride.

Treatment of carbohydrates with an alkyl halide by a Williamson ether synthesis (Section 18.2) leads to the formation of ethers. The strongly basic conditions typically used for the Williamson ether synthesis can degrade some sugar molecules. Instead, milder bases or silver oxide (Ag_2O) are used to provide ethers in high yields. The monosaccharide, D-glucopyranose can be converted to the pentamethyl ether through reaction with iodomethane and silver oxide.

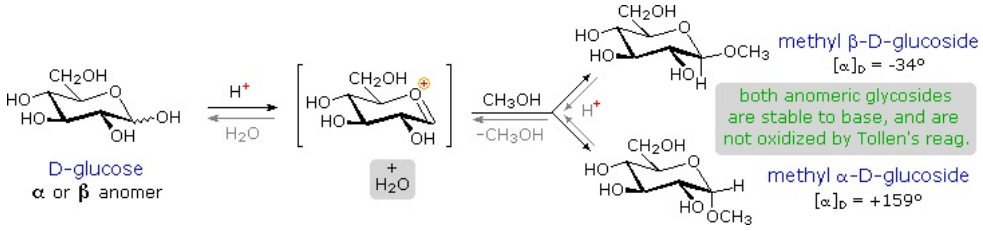


GLYCOSIDE FORMATION

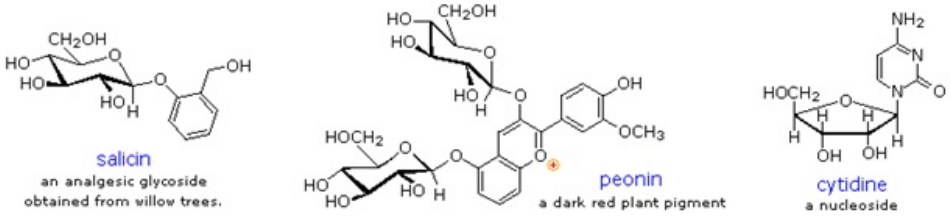
Reacting a hemiacetal with an alcohol and an acid catalyst produces an acetal in which the anomeric hydroxide has been replaced by an ether group.



Monosaccharide acetal derivatives, called glycosides, are formed when a hemiacetal reacts with an alcohol in the presence of an acid catalyst. During the reaction the -OH group from the anomeric carbon is replaced by a -OR group from the alcohol. A mixture of alpha and beta products are formed regardless of the conformation of the reactant. In naming of glycosides, the "ose" suffix of the sugar name is replaced by "oside", and the alcohol group name is placed first. This reaction is illustrated below for D-glucopyranose and methanol which forms a mixture of alpha and beta methyl-glucopyranosides. As is generally true for most acetals, glycoside formation involves the loss of an equivalent of water. The acetal product is stable to base and alkaline oxidants such as Tollen's reagent. They are not in equilibrium with the open-chain form and thus do not undergo mutarotation. Since this acid-catalyzed reaction is reversible, glycosides may be hydrolyzed back to their alcohol and sugar components by aqueous acid.



Two examples of naturally occurring glycosides and one example of an amino derivative are displayed below.



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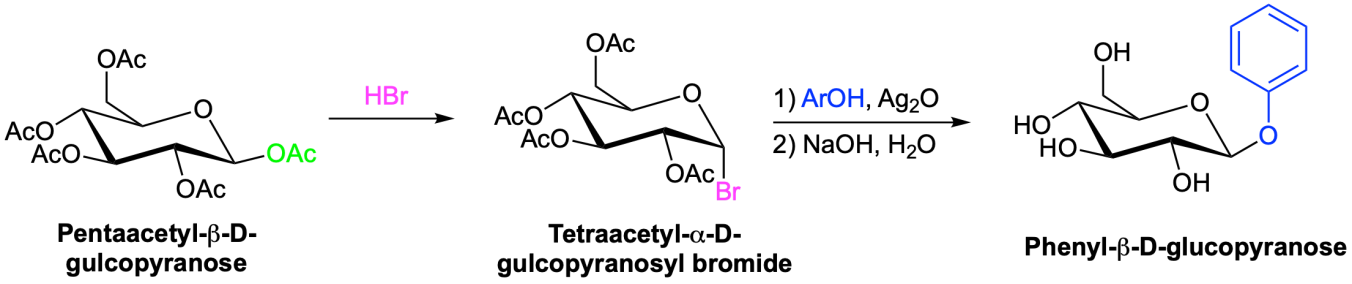
- Salicin, one of the oldest herbal remedies known, was the model for the synthetic analgesic aspirin.
- A large class of hydroxylated, aromatic oxonium cations called anthocyanins provide the red, purple and blue colors of many flowers, fruits and some vegetables. Peonin is one example of this class of natural pigments, which exhibit a pronounced pH color dependence. The oxonium moiety is only stable in acidic environments, and the color changes or disappears when base is added. The complex changes that occur when wine is fermented and stored are in part associated with glycosides of anthocyanins.
- Amino derivatives of ribose, such as cytidine play important roles in biological phosphorylating agents, coenzymes and information transport and storage materials.

KOENIGS–KNORR REACTION

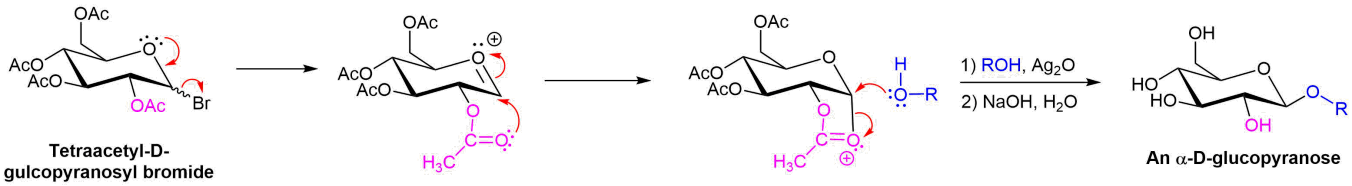
The presence of multiple -OH groups on a sugar molecular makes the synthesis of glycosides particularly difficult. One of the oldest glycosylation reactions, called the **Koenigs–Knorr reaction**, is effective for preparing the beta-glycosides of glucose. The pathway starts with the reaction of glucose pentaacetate with HBr to form a pyranosyl bromide. Addition of silver oxide allows for the nucleophilic addition of the chosen alcohol. Hydrolysis of the remaning acetal groups forms the beta-glucopyranoside.



Although the final step of the reaction appears to show the inversion characteristic of an S_N2 reaction, the same product forms if either the alpha or beta anomers of the glucopyranosyl bromide is used. This provides evidence that stereochemical control is lost at some point during the mechanism of the reaction.

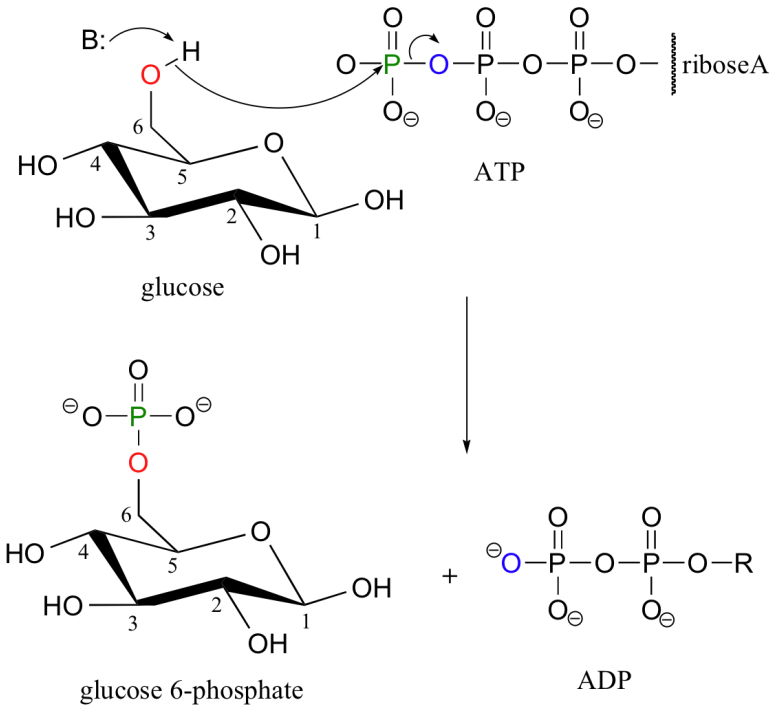
KOENIGS–KNORR REACTION MECHANISM

The mechanism starts with the S_N1 like removal of the bromine leaving group which is promoted by the formation of an oxonium ion intermediate. Either anomer of the glucopyranosyl bromide will produce the same oxonium intermediate. Lone pair electrons from the carbonyl oxygen of an adjacent acetate group adds to the oxonium ion in an internal ring-forming reaction. Because the adjacent acetate was on the bottom of the glucose ring the newly form C-O bond is also on the bottom. During this step a new oxonium ion is formed. The alcohol then displaces the oxonium ion as a leaving groups during an S_N2 reaction. The inversion of configuration of the S_N2 reaction produces a beta-glycoside. Participation of an adjacent acetate group in the mechanism of the Koenigs–Knorr reaction is called a **neighboring-group effect**.



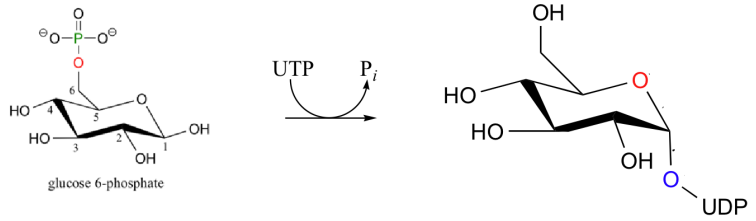
BIOLOGICAL ESTER FORMATION: PHOSPHORYLATION

Recall that almost all biomolecules are charged species, which 1) keeps them water soluble, and 2) prevents them from diffusing across lipid bilayer membranes. Although many biomolecules are ionized by virtue of negatively charged carboxylate and positively charged amino groups, the most common ionic group in biologically important organic compounds is phosphate - thus the phosphorylation of alcohol groups is a critical metabolic step. In alcohol phosphorylations, ATP is almost always the phosphate donor, and the mechanism is very consistent: the alcohol oxygen acts as a nucleophile, attacking the gamma-phosphorus of ATP and expelling ADP.

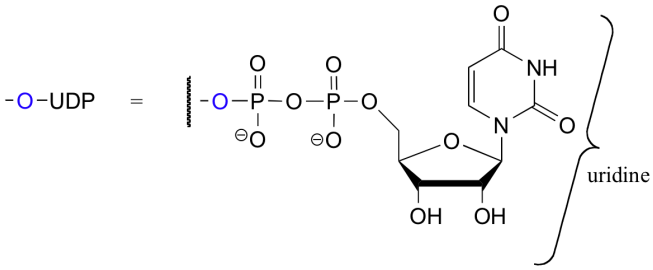


Carbohydrates are covalently attached to many different biomolecules, including lipids, to form glycolipids, and proteins, to form glycoproteins. Called glycoconjugates these sugar bonded molecules are often found in biological membranes, to which they are anchored through covalent bonds. These compounds are crucial to determine to how different cell types recognized one another which will be discussed further in **Section 25.11**.

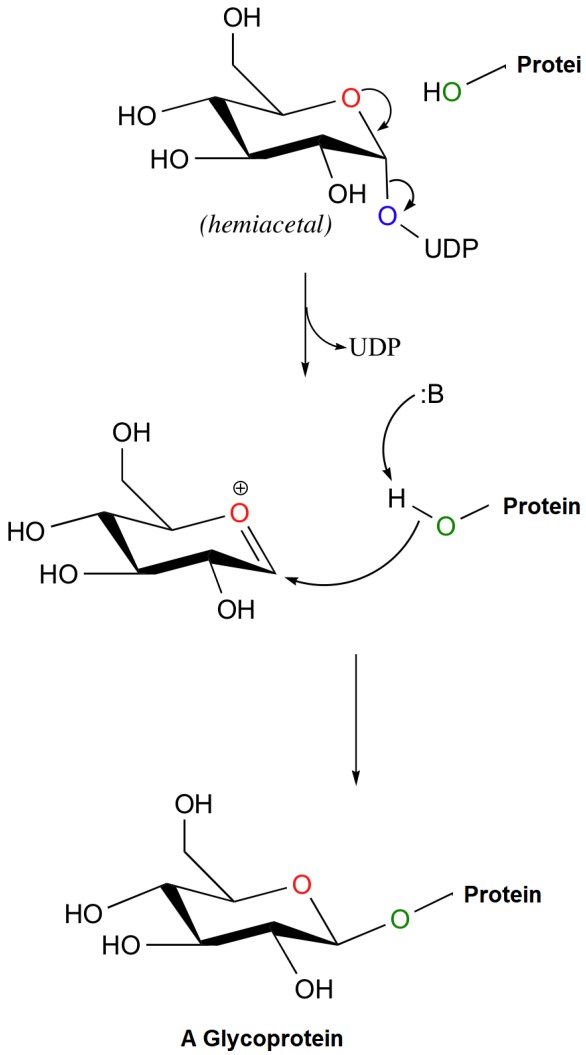
Glycoconjugate formation begins with the formation of a phosphorylated sugar such as glucose-6-phosphate which is then reacted with uridine triphosphate (UTP), to give a glycosyl uridine diphosphate. The phosphorylation makes the anomeric -OH of the sugar a better leaving group. During nucleophilic substitutions reaction with a protein or a lipid to form a glycoconjugate the anomeric -OH does not leave as a water molecule, but rather as part of a uridine nucleotide diphosphate group.



Glycouridine 5'-diphosphate



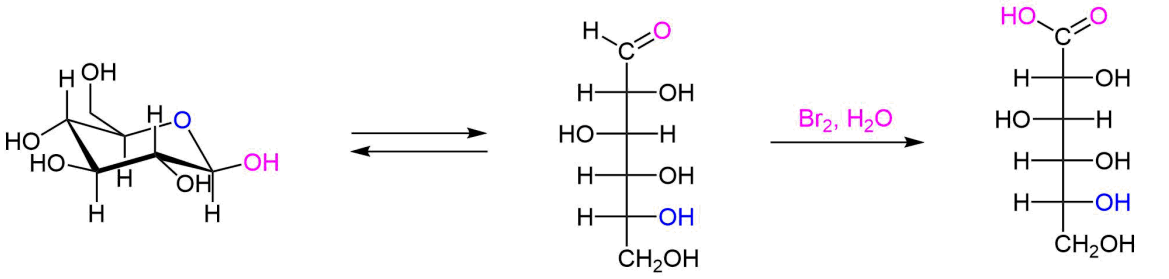
To form a glycoprotein the anomeric carbon of a glucopyranose-UDP derivative is attacked from above by an -OH of -NH_2 group from a protein. The UDP leaving group is displaced, and inversion of stereochemistry results at the anomeric carbon.



A Glycoprotein

OXIDATION OF MONOSACCHARIDES

When the aldehyde function of an aldose is oxidized to a carboxylic acid the product is called an **aldonic acid**. Because of the 2º hydroxyl functions that are also present in these compounds, a mild oxidizing agent such as aqueous Br_2 can be used for this conversion. The oxidation occurs by reaction of the open-chain form of the sugar. Because of the equilibrium between the open and ring form of the sugar, eventually the entire sample will undergo the reaction.

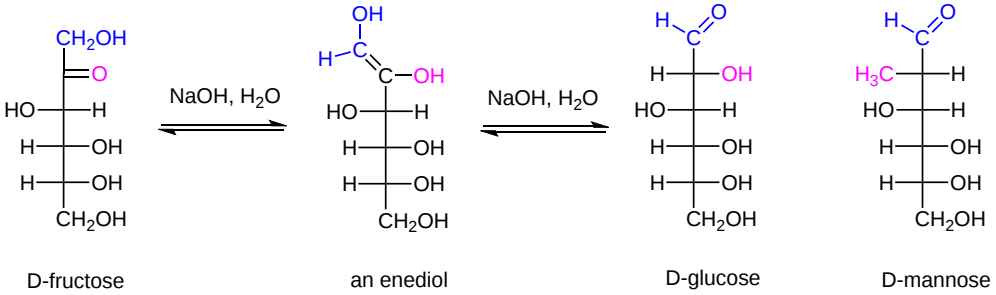


β-D-Glucopyranose **D-Glucose** **D-Gluconic acid (An Aldonic acid)**

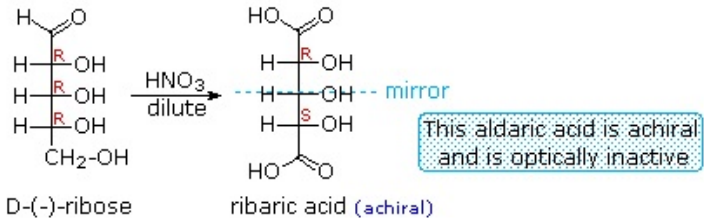
Historically sugars have been classified as **reducing** or **non-reducing** based on their reactivity with **Tollens'** (Ag^+ in NH_3) or **Benedict's** (Cu^{2+} and sodium citrate) reagents. If a sugar is oxidized by these reagents it is called a reducing sugar, since the oxidant ($Ag^{(+)}$ or $Cu^{(+2)}$) is

reduced in the reaction, as evidenced by formation of a silver mirror or precipitation of cuprous oxide. The Tollens' test is commonly used to detect aldehyde functions; and because of the facile interconversion of ketoses and aldoses under the basic conditions of this test, ketoses such as fructose also react and are classified as reducing sugars.

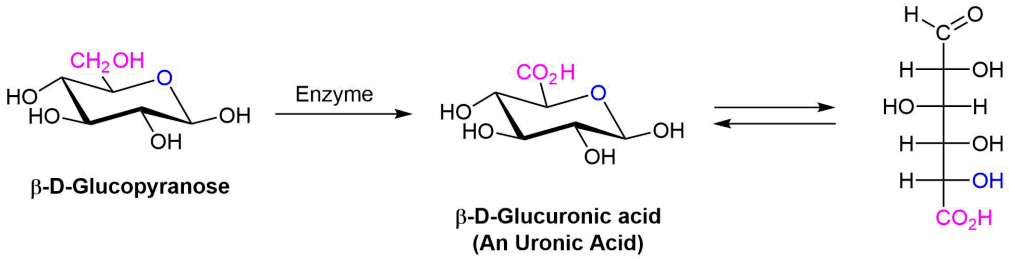
Becuase aldoses contain an aldehyde group they are reducing sugars and will be oxidized by Tollen's and Benedict's reagent. Some ketoses are also reducing sugars. Despite not having an aldehyde groups, fructose is capable of isomerizing to glucose and mannose by keto-enol tautomerism under basic conditions. Once formed, these aldoses are capable of being oxidized by Tollens reagent.



Aldoses can be oxidized to a dicarboxylic acid by dilute nitric acid. Nitric acid is a strong enough oxidizing agent to cause both the aldehyde carbonyl and the -CH_2OH group to be oxidized to carboxylic acids. If both ends of an aldose chain are oxidized to carboxylic acids, the product is called an aldaric acid. By converting an aldose to its corresponding aldaric acid derivative, the ends of the chain become identical. Such an operation will disclose any latent symmetry in the remaining molecule and possibly form an achiral meso compound. Thus, ribose, xylose, allose and galactose yield achiral aldaric acids which are, of course, not optically active. The ribose oxidation is shown below.



If the -CH_2OH group of an aldose is oxidized to a carboxylic acid while the aldehyde carbonyl is not affected, the monocarboxylic acid product is called a uronic acid. This selective oxidation is difficult to accomplish and can only be done enzymatically.

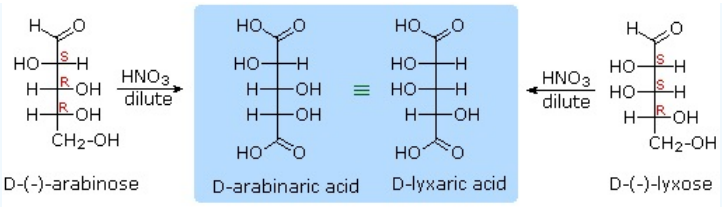


? EXERCISE 25.6.1

D-arabinose and D-lyxose produce the same chiral aldaric acid product when oxidized with dilute HNO_3. Please explain.

Answer

1) Remember, a Fischer projection formula may be rotated by 180º in the plane of projection without changing its configuration.



EXERCISE 25.6.2

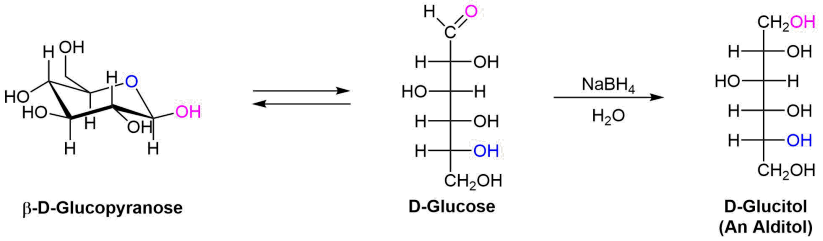
Which two D-aldohexoses are oxidized to produce an optically inactive (meso) aldaric acid?

Answer

D-Allose and D-galactose.

REDUCTION OF MONOSACCARIDES

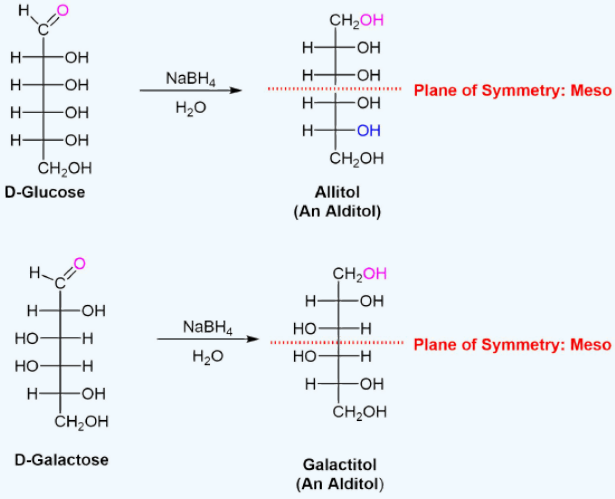
Treatment of an aldose or ketose with sodium borohydride reduces it to a polyalcohol called an alditol. The reduction occurs by reaction of the open-chain form. Although only a small amount of the open-chain form is present at any given time, that small amount is reduced, more is produced by opening of the pyranose form, that additional amount is reduced, and so on, until the entire sample has undergone reaction. The reaction products can be formally named by removing the **-ose** ending from the open-chain sugar and replacing it with **-itol**. Note! The alditol products have identical end groups, $HOCH_2(CHOH)_nCH_2OH$ which means that forming an achiral meso compound is possible.



EXERCISE 25.6.3

Allitol and galactitol from the reduction of allose and galactose are achiral. Explain why this occurs.

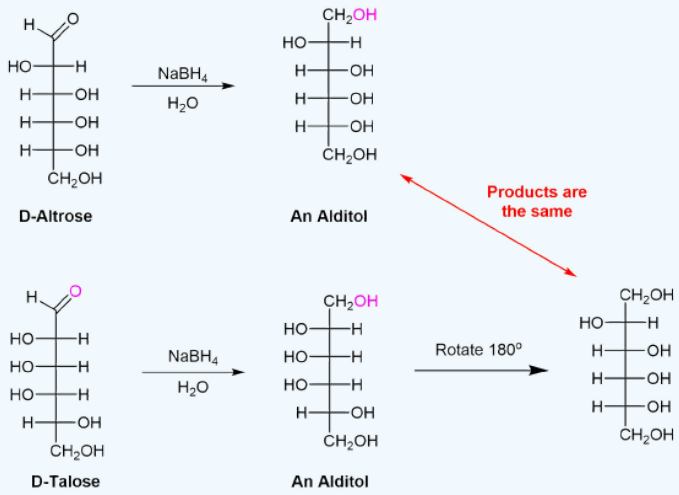
Answer



EXERCISE 25.6.4

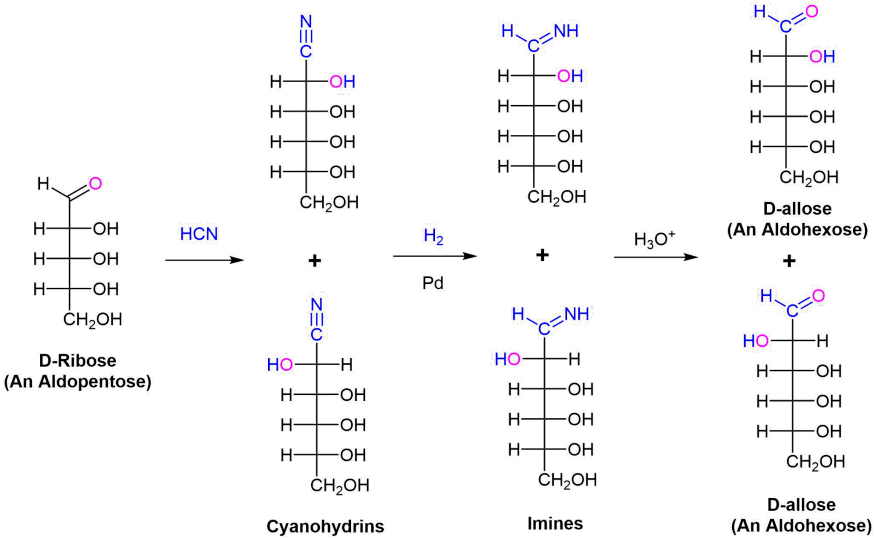
Altrose and talose are reduced to the same chiral alditol. Explain why this occurs.

Answer



CHAIN LENGTHENING: THE KILIANI–FISCHER SYNTHESIS

The Kiliani–Fischer synthesis lengthens the carbon chain of an aldose by one carbon atom. In doing this two new sugar epimers are created. The synthesis starts by reacting an aldose with HCN. Nucleophilic addition adds the cyanide nucleophile to the electrophilic carbon of the aldose aldehyde forming a cyanohydrin intermediate. The cyanide nucleophile adds a carbon. Stereochemical control is lost, so a racemic mixture of two cyanohydrins differing in the stereochemistry at C2 is formed. The nitrile group of the cyanohydrin is reduced to an imine intermediate by hydrogenation over a palladium catalyst. Finally, the imine is hydrolyzed to an aldehyde to create two new aldoses with an additional carbon. For example performing the Kiliani–Fischer synthesis on D-ribose produces a mixture of D-allose and D-altrose.



EXERCISE 25.6.5

What products would you expect from Kiliani–Fischer reaction of D-xylose?

Answer

D-Gluose and D-idose

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EXERCISE 25.6.6

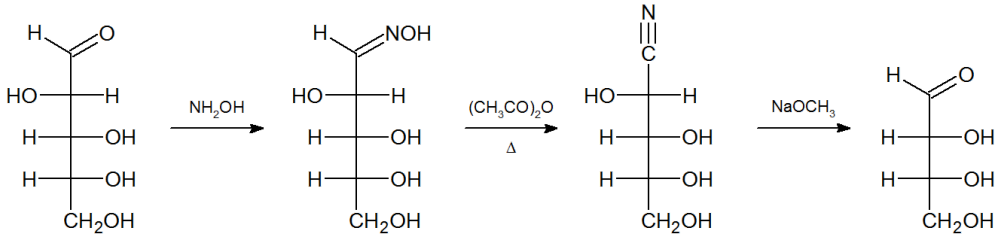
What aldopentose would be expected to produce a mixture of D-xylose and D-lyxose from an Kiliani–Fischer synthesis?

Answer

D-Threose

CHAIN SHORTENING: THE WOHL DEGRADATION

The ability to shorten (degrade) an aldose chain by one carbon was an important tool in the structure elucidation of carbohydrates. This is commonly accomplished the **Wohl degradation**, which is virtually the reverse of the Kiliani–Fischer synthesis. The aldose aldehyde is converted to an oxime (Section 19-8) by treatment with hydroylamine (NH_2OH). Dehydration of the oxime with acetic anhydride forms a cyanohydrin. Under basic conditions, the cyanohydrine loses HCN to reform an aldehyde carbonyl. The following equation illustrates the application of this procedure to the aldopentose, D-arabinose to form the aldotetrose, D-erythrose.



EXERCISE 25.6.7

Two of the four D- aldopentoses yield D-erythrose on Wohl degradation. What are their structures?

Answer

D-Ribose and D-arabinose

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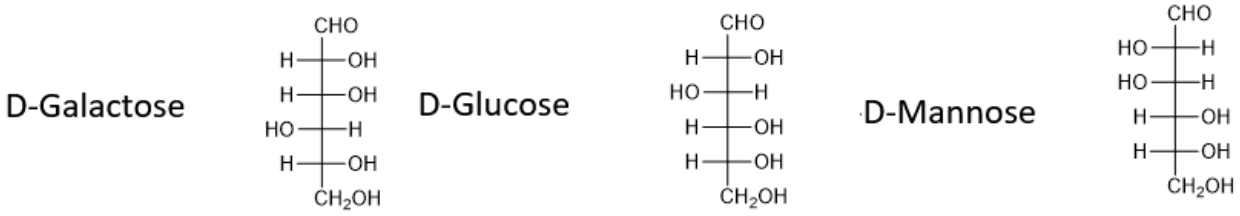
25.7: THE EIGHT ESSENTIAL MONOSACCHARIDES

OBJECTIVES

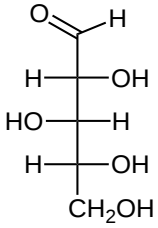
1. identify and draw the eight essential monosaccharides

Eight monosaccharides are required for the proper functioning of human beings. Although they are typically supplied through a healthy diet, they can be biosynthesized if required. The eight monosaccharides are L-fucose, D-galactose, N-acetyl-D-glucosamine, N-acetyl-D-galactosamine, D-glucose, D-mannose, N-acetyl-D-neuraminic acid, and D-xylose.

D-Galactose, D-Glucose, and D-Mannose are commonly found aldohexoses:

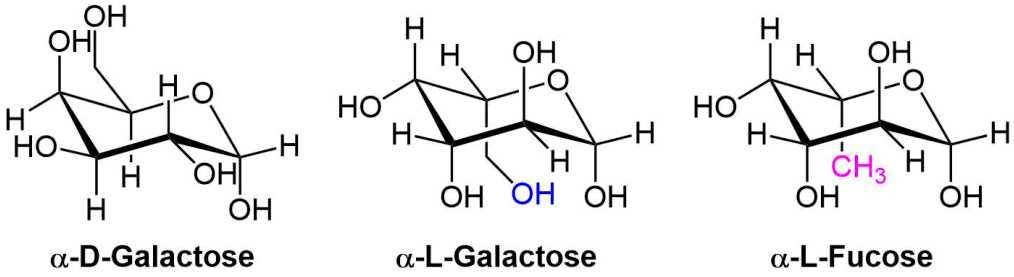


D-Xylose is a common aldopentose.

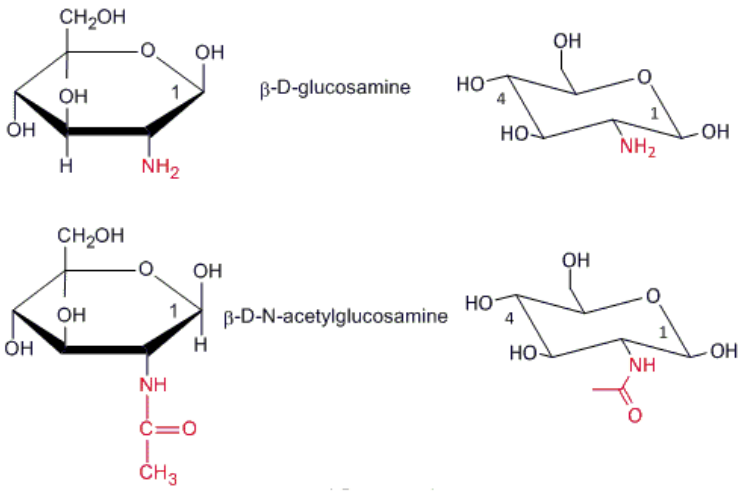


D-Xylose

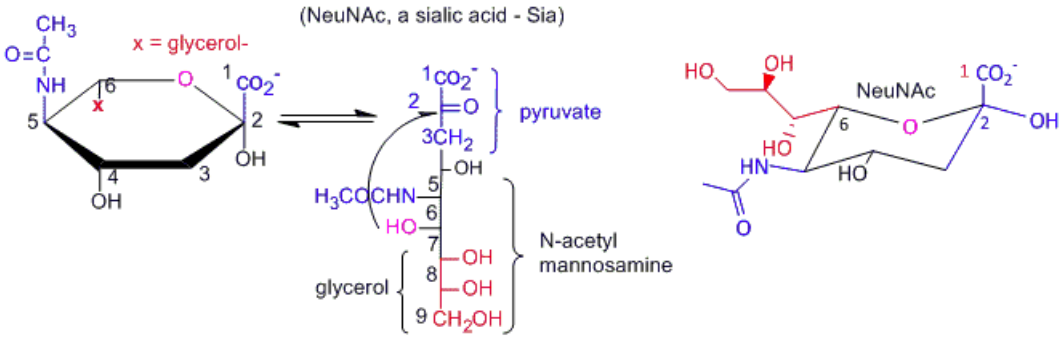
L-Fucose is a deoxy sugar. Fucose is is the monosaccaride L-galactose with the -OH group on C6 replaced with an -H.



N-acetylgalactosamine and N-acetylglucosamine are derivatives where the corresponding amino sugars have been converted to amides by N-acylation. Amino sugars have had their -OH groups at C2 replaced by an $-NH_2$.

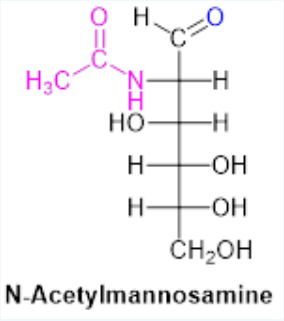


N-Acetylneuraminic acid is nine carbon sugar created by an aldol reaction between N-acetymannosamine and pyruvate. N-acetylneuaminic acid forms a pyranose ring by a intramolecular hemiacetal formation between the -OH on C6 and the ketone functional group in the pyruvate moiety.



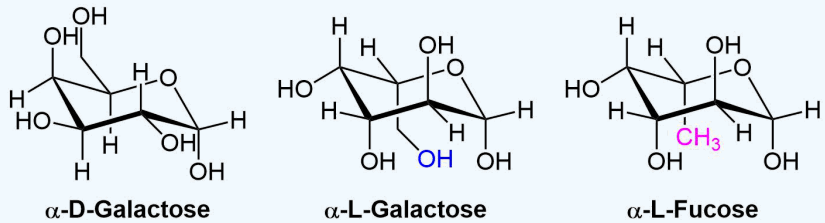
EXERCISE 25.7.1

1) Please show the mechanism of the aldol reaction between *N*-acetylmannosamine and pyruvate to form neuraminic acid.



Answer

1)



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25.8: DISACCHARIDES

OBJECTIVES

After completing this section, you should be able to

1. identify disaccharides as compounds consisting of two monosaccharide units joined by a glycoside link between the C1 of one sugar and one of the hydroxyl groups of a second sugar.
2. identify the two monosaccharide units in a given disaccharide.
3. identify the type of glycoside link (e.g., 1,4′-*β*) present in a given disaccharide structure.
4. draw the structure of a specific disaccharide, given the structure of the monosaccharide units and the type of glycoside link involved.

   Note: If *α*- or *β*-D-glucose were one of the monosaccharide units, its structure would not be provided.
5. identify the structural feature that determines whether or not a given disaccharide behaves as a reducing sugar and undergoes mutarotation, and write equations to illustrate these phenomena.
6. identify the products formed from the hydrolysis of a given disaccharide.

KEY TERMS

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

- 1,4′ link
- disaccharide (see Section 25.1)
- invert sugar

STUDY NOTES

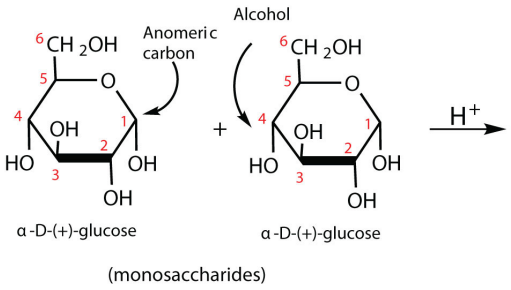
Notice that most of the disaccharides discussed in this section contain one unit of D-glucose. You are not expected to remember the detailed structures of maltose, lactose and sucrose. Similarly, we do not expect you to remember the systematic names of these substances.

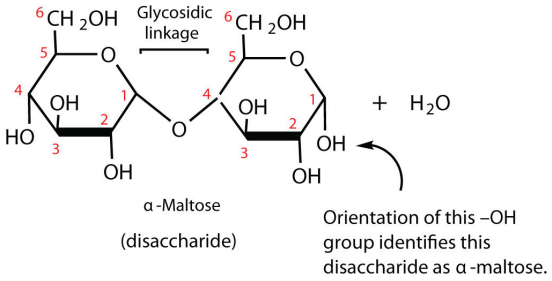
Previously, you learned that monosaccharides can form cyclic structures by the reaction of the carbonyl group with an OH group. These cyclic molecules can in turn react with another alcohol to form a glycoside. When the alcohol component of a glycoside is provided by a hydroxyl function on another monosaccharide, the compound is called a disaccharide. Disaccharides ($C_{12}H_{22}O_{11}$) are sugars composed of two monosaccharide units that are joined by a carbon–oxygen-carbon linkage known as a glycosidic linkage. This linkage is formed from the reaction of the anomeric carbon of one cyclic monosaccharide with the OH group of a second monosaccharide. The disaccharides differ from one another in their monosaccharide constituents and in the specific type of glycosidic linkage connecting them. There are three common disaccharides: maltose, lactose, and sucrose. All three are white crystalline solids at room temperature and are soluble in water.

MALTOSE

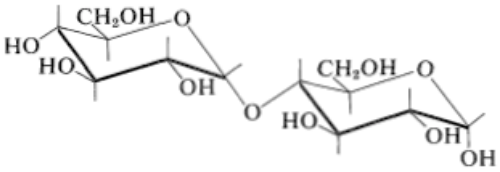
Maltose occurs to a limited extent in sprouting grain. It is formed most often by the partial hydrolysis of starch and glycogen. In the manufacture of beer, maltose is liberated by the action of malt (germinating barley) on starch; for this reason, it is often referred to as *malt sugar*. Maltose is about 30% as sweet as sucrose. The human body is unable to metabolize maltose or any other disaccharide directly from the diet because the molecules are too large to pass through the cell membranes of the intestinal wall. Therefore, an ingested disaccharide must first be broken down by hydrolysis into its two constituent monosaccharide units. In the body, such hydrolysis reactions are catalyzed by enzymes such as *maltase*. The same reactions can be carried out in the laboratory with dilute acid as a catalyst, although in that case the rate is much slower, and high temperatures are required. Whether it occurs in the body or a glass beaker, the hydrolysis of maltose produces two molecules of D-glucose

The glucopyranose units in maltose are joined in a *head-to-tail* fashion through an α-linkage from the first carbon atom of one glucopyranose molecule to the fourth carbon atom of the second glucopyranose molecule (an α-1,4-glycosidic linkage). The bond from the anomeric carbon of the first monosaccharide unit is directed downward, which is why this is known as an α-glycosidic linkage. The OH group on the anomeric carbon of the second glucopyranose can be in either the α or the β position.



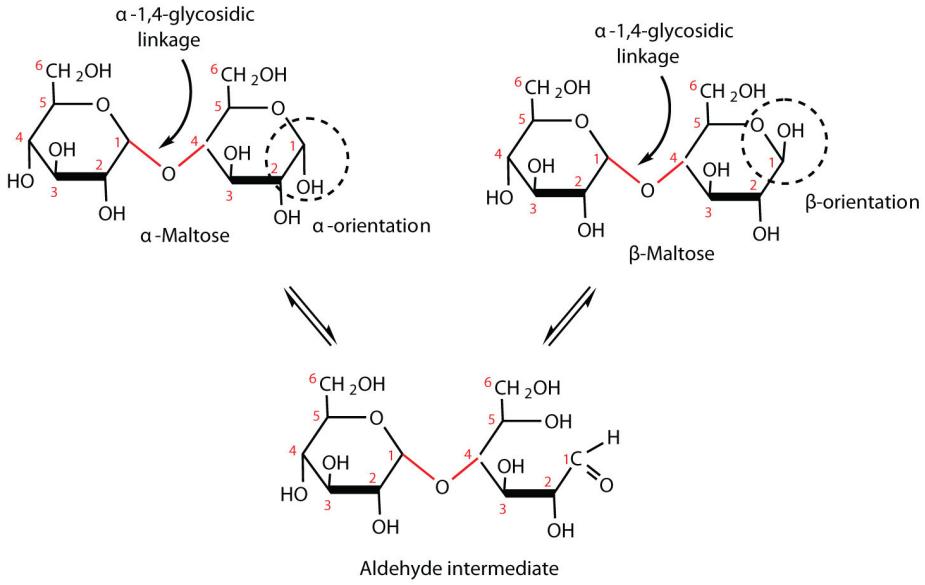


Cellobiose is a disaccharide made up of two D-glucopyranose molecules linked with a β-1,4-glycosidic linkage. Like maltose, the OH group on the anomeric carbon of the second glucopyranose of cellobiose can be in either the α or the β position. Although the difference between maltose and cellobiose seems small they have vastly different biological properties. Maltose can be digested by humans whereas cellobiose cannot.



maltose, **25**

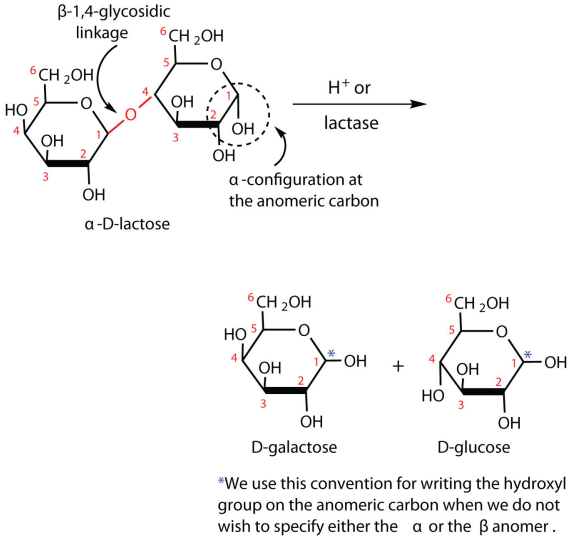
Maltose is a reducing sugar. Thus, its two D-glucopyranose molecules must be linked in such a way as to leave one anomeric carbon that can open to form an aldehyde group. Although one anomeric carbon in maltose and cellobiose is used to form the 1,4-glycosidic linkage, the anomeric carbons on the second glucopyranose remain a hemiacetal. Like an individual monosaccharide, the second glucopyranose subunit undergoes mutarotation and thus is in equilibrium with its aldehyde and both anomer forms. For this reason, maltose and cellobiose contain a mixture of α and β anomers of the second glucopyranose.



LACTOSE

Lactose is known as *milk sugar* because it occurs in the milk of humans, cows, and other mammals. In fact, the natural synthesis of lactose occurs only in mammary tissue, whereas most other carbohydrates are plant products. Human milk contains about 7.5% lactose, and cow's milk contains about 4.5%. This sugar is one of the lowest ranking in terms of sweetness, being about one-sixth as sweet as sucrose. Lactose is produced commercially from whey, a by-product in the manufacture of cheese. It is important as an infant food and in the production of penicillin.

Lactose is a disaccharide composed of one molecule of D-galactopyranose and one molecule of D-glucopyranose joined by a β-1,4-glycosidic bond between the 1 of D-galactopyranose and the C4 of glucose. Lactose is a reducing sugar and undergoes mutarotation to exhibit both anomers of the D-glucopyranose subunit. The two monosaccharides are obtained from lactose by acid hydrolysis or the catalytic action of the enzyme *lactase*.

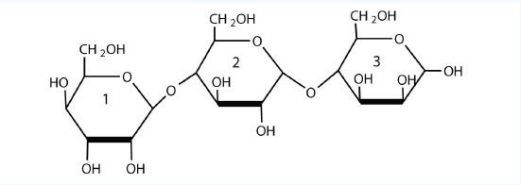


*We use this convention for writing the hydroxyl group on the anomeric carbon when we do not wish to specify either the α or the β anomer.

Many adults and some children suffer from a deficiency of lactase. These individuals are said to be lactose intolerant because they cannot digest the lactose found in milk. A more serious problem is the genetic disease galactosemia, which results from the absence of an enzyme needed to convert galactose to glucose. Certain bacteria can metabolize lactose, forming lactic acid as one of the products. This reaction is responsible for the "souring" of milk.

EXAMPLE 1

For this trisaccharide, indicate whether each glycosidic linkage is α or β.



Solution

The glycosidic linkage between sugars 1 and 2 is β because the bond is directed up from the anomeric carbon. The glycosidic linkage between sugars 2 and 3 is α because the bond is directed down from the anomeric carbon.

TO YOUR HEALTH: LACTOSE INTOLERANCE AND GALACTOSEMIA

Lactose makes up about 40% of an infant's diet during the first year of life. Infants and small children have one form of the enzyme lactase in their small intestines and can digest the sugar easily; however, adults usually have a less active form of the enzyme, and about 70% of the world's adult population has some deficiency in its production. As a result, many adults experience a reduction in the ability to hydrolyze lactose to galactose and glucose in their small intestine. For some people the inability to synthesize sufficient enzyme increases with age. Up to 20% of the US population suffers some degree of lactose intolerance.

In people with lactose intolerance, some of the unhydrolyzed lactose passes into the colon, where it tends to draw water from the interstitial fluid into the intestinal lumen by osmosis. At the same time, intestinal bacteria may act on the lactose to produce organic acids and gases. The buildup of water and bacterial decay products leads to abdominal distention, cramps, and diarrhea, which are symptoms of the condition.

The symptoms disappear if milk or other sources of lactose are excluded from the diet or consumed only sparingly. Alternatively, many food stores now carry special brands of milk that have been pretreated with lactase to hydrolyze the lactose. Cooking or fermenting milk causes at least partial hydrolysis of the lactose, so some people with lactose intolerance are still able to enjoy cheese, yogurt, or cooked foods containing milk. The most common treatment for lactose intolerance, however, is the use of lactase preparations (e.g., Lactaid), which are available in liquid and tablet form at drugstores and grocery stores. These are taken orally with dairy foods—or may be added to them directly—to assist in their digestion.

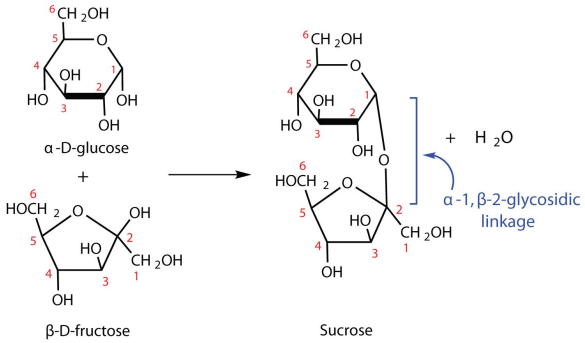
Galactosemia is a condition in which one of the enzymes needed to convert galactose to glucose is missing. Consequently, the blood galactose level is markedly elevated, and galactose is found in the urine. An infant with galactosemia experiences a lack of appetite,

weight loss, diarrhea, and jaundice. The disease may result in impaired liver function, cataracts, mental retardation, and even death. If galactosemia is recognized in early infancy, its effects can be prevented by the exclusion of milk and all other sources of galactose from the diet. As a child with galactosemia grows older, he or she usually develops an alternate pathway for metabolizing galactose, so the need to restrict milk is not permanent. The incidence of galactosemia in the United States is 1 in every 65,000 newborn babies.

SUCROSE

Sucrose, probably the largest-selling pure organic compound in the world, is known as *beet sugar*, *cane sugar*, *table sugar*, or simply *sugar*. Most of the sucrose sold commercially is obtained from sugar cane and sugar beets (whose juices are 14%–20% sucrose) by evaporation of the water and recrystallization. The dark brown liquid that remains after the recrystallization of sugar is sold as molasses.

The sucrose molecule is unique among the common disaccharides in having an α-1,β-2-glycosidic (head-to-head) linkage. Because this glycosidic linkage is formed by the OH group on the anomeric carbon of α-D-glucose and the OH group on the anomeric carbon of β-D-fructose, it ties up the anomeric carbons of both glucose and fructose.



This linkage gives sucrose certain properties that are quite different from those of maltose and lactose. As long as the sucrose molecule remains intact, neither monosaccharide is in equilibrium with its open-chain form. Thus, sucrose is incapable of mutarotation and exists in only one form both in the solid state and in solution. In addition, sucrose does not undergo reactions that are typical of aldehydes and ketones. Therefore, sucrose is a nonreducing sugar.

The hydrolysis of sucrose in dilute acid or through the action of the enzyme *sucrase* (also known as invertase) gives an equimolar mixture of glucose and fructose. This 1:1 mixture is referred to as *invert sugar* because it rotates plane-polarized light in the opposite direction than

sucrose. The hydrolysis reaction has several practical applications. Sucrose readily recrystallizes from a solution, but invert sugar has a much greater tendency to remain in solution. In the manufacture of jelly and candy and in the canning of fruit, the recrystallization of sugar is undesirable. Therefore, conditions leading to the hydrolysis of sucrose are employed in these processes. Moreover, because fructose is sweeter than sucrose, the hydrolysis adds to the sweetening effect. Bees carry out this reaction when they make honey.

The average American consumes more than 100 lb of sucrose every year. About two-thirds of this amount is ingested in soft drinks, presweetened cereals, and other highly processed foods. The widespread use of sucrose is a contributing factor to obesity and tooth decay. Carbohydrates such as sucrose, are converted to fat when the caloric intake exceeds the body's requirements, and sucrose causes tooth decay by promoting the formation of plaque that sticks to teeth.

SUMMARY

Maltose is composed of two molecules of glucose joined by an α-1,4-glycosidic linkage. It is a reducing sugar that is found in sprouting grain. Lactose is composed of a molecule of galactose joined to a molecule of glucose by a β-1,4-glycosidic linkage. It is a reducing sugar that is found in milk. Sucrose is composed of a molecule of glucose joined to a molecule of fructose by an α-1,β-2-glycosidic linkage. It is a nonreducing sugar that is found in sugar cane and sugar beets.

? EXERCISE 25.8.1

What monosaccharides are obtained by the hydrolysis of each disaccharide?

a. sucrose
b. maltose
c. lactose

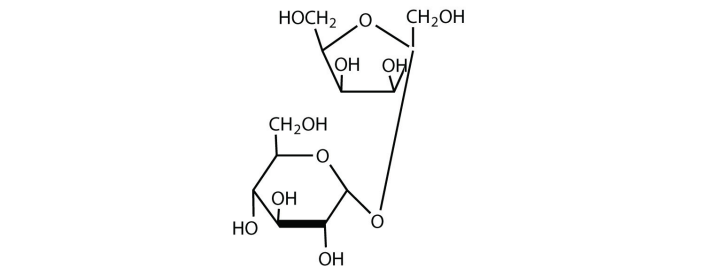
Answer

a. D-glucose and D-fructose
b. two molecules of D-glucose
c. D-glucose and D-galactose

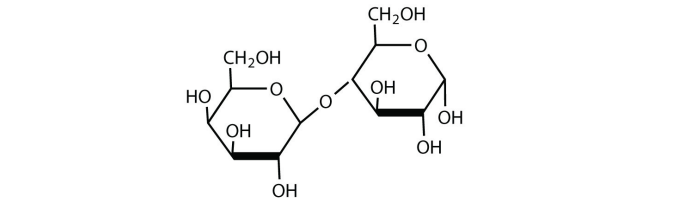
? EXERCISE 25.8.2

For each disaccharide, indicate whether the glycosidic linkage is α or β.

a)



b)



Answer

a)

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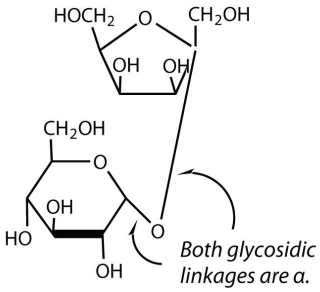
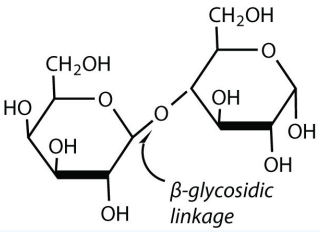


b)



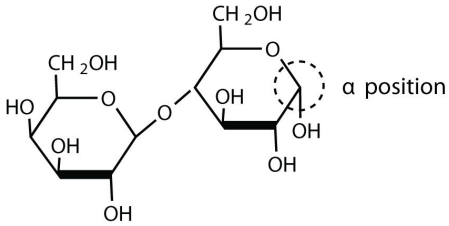
EXERCISE 25.8.3

Identify each disaccharide in Exercise 2 as a reducing or nonreducing sugar. If it is a reducing sugar, draw its structure and circle the anomeric carbon. State if the OH group at the anomeric carbon is in the α or the β position.

Answer

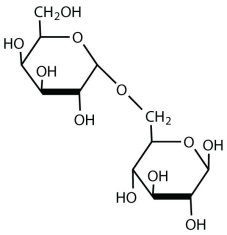
a) nonreducing

b) reducing



EXERCISE 25.8.4

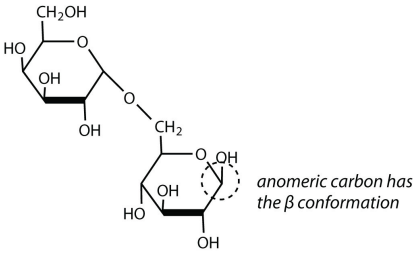
Melibiose is a disaccharide that occurs in some plant juices. Its structure is as follows:



a. What monosaccharide units are incorporated into melibiose?
b. What type of linkage (α or β) joins the two monosaccharide units of melibiose?
c. Melibiose has a free anomeric carbon and is thus a reducing sugar. Circle the anomeric carbon and indicate whether the OH group is α or β

Answer

a) galactose and glucose



.

b) α-glycosidic linkage

c) β.

CONTRIBUTORS AND ATTRIBUTIONS

- *The Basics of General, Organic, and Biological Chemistry* by David W. Ball, John W. Hill, and Rhonda J. Scott.

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25.9: POLYSACCHARIDES AND THEIR SYNTHESIS

OBJECTIVES

After completing this section, you should be able to

1. identify the structural difference between cellulose and the cold-water-insoluble fraction of starch (amylose), and identify both of these substances as containing many glucose molecules joined by 1,4′-glycoside links.
2. identify the cold-water-soluble fraction of starch (amylopectin) as having a more complex structure than amylose because of the existence of 1,6′-glycoside links in addition to the 1,4′-links.
3. compare and contrast the structures and uses of starch, glycogen and cellulose.

KEY TERMS

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

- amylopectin
- amylose
- polysaccharide

The polysaccharides are the most abundant carbohydrates in nature and serve a variety of functions, such as energy storage or as components of plant cell walls. Polysaccharides are very large polymers composed of tens to thousands of monosaccharides joined together by glycosidic linkages. The three most abundant polysaccharides are starch, glycogen, and cellulose. These three are referred to as *homopolymers* because each yields only one type of monosaccharide (glucose) after complete hydrolysis. *Heteropolymers* may contain sugar acids, amino sugars, or noncarbohydrate substances in addition to monosaccharides. Heteropolymers are common in nature (gums, pectins, and other substances) but will not be discussed further in this textbook. The polysaccharides are nonreducing carbohydrates, are not sweet tasting, and do not undergo mutarotation.

STARCH

Starch is the most important source of carbohydrates in the human diet and accounts for more than 50% of our carbohydrate intake. It occurs in plants in the form of granules, and these are particularly abundant in seeds (especially the cereal grains) and tubers, where they serve as a storage form of carbohydrates. The breakdown of starch to glucose nourishes the plant during periods of reduced photosynthetic activity. We often think of potatoes as a “starchy” food, yet other plants contain a much greater percentage of starch (potatoes 15%, wheat 55%, corn 65%, and rice 75%). Commercial starch is a white powder.

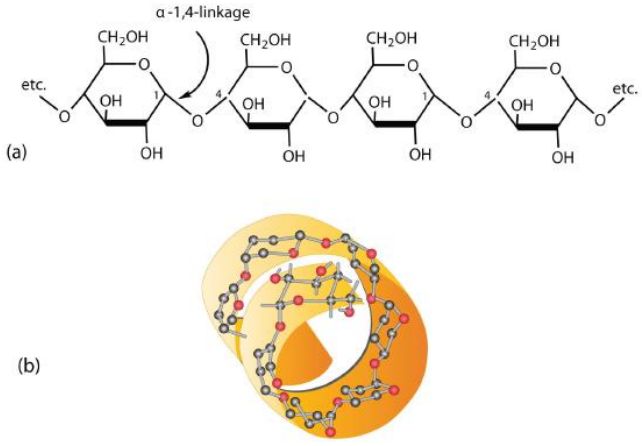


Figure 25.9.1: Amylose. (a) Amylose is a linear chain of α-D-glucose units joined together by α-1,4-glycosidic bonds. (b) Because of hydrogen bonding, amylose acquires a spiral structure that contains six glucose units per turn. (CC BY-SA-NC 3.0; Anonymous via LibreTexts)

Starch is a mixture of two polymers: amylose and amylopectin. Natural starches consist of about 10%–30% amylose and 70%–90% amylopectin. Amylose is a linear polysaccharide composed entirely of D-glucose units joined by the α-1,4-glycosidic linkages we saw in maltose (part (a) of Figure 25.9.1). Experimental evidence indicates that amylose is not a straight chain of glucose units but instead is coiled like a spring, with six glucose monomers per turn (part (b) of Figure 25.9.1). When coiled in this fashion, amylose has just enough room in

its core to accommodate an iodine molecule. The characteristic blue-violet color that appears when starch is treated with iodine is due to the formation of the amylose-iodine complex. This color test is sensitive enough to detect even minute amounts of starch in solution.

Amylopectin is a branched-chain polysaccharide composed of glucose units linked primarily by α-1,4-glycosidic bonds but with occasional α-1,6-glycosidic bonds, which are responsible for the branching. A molecule of amylopectin may contain many thousands of glucose units with branch points occurring about every 25–30 units (Figure 25.9.2). The helical structure of amylopectin is disrupted by the branching of the chain, so instead of the deep blue-violet color amylose gives with iodine, amylopectin produces a less intense reddish brown.

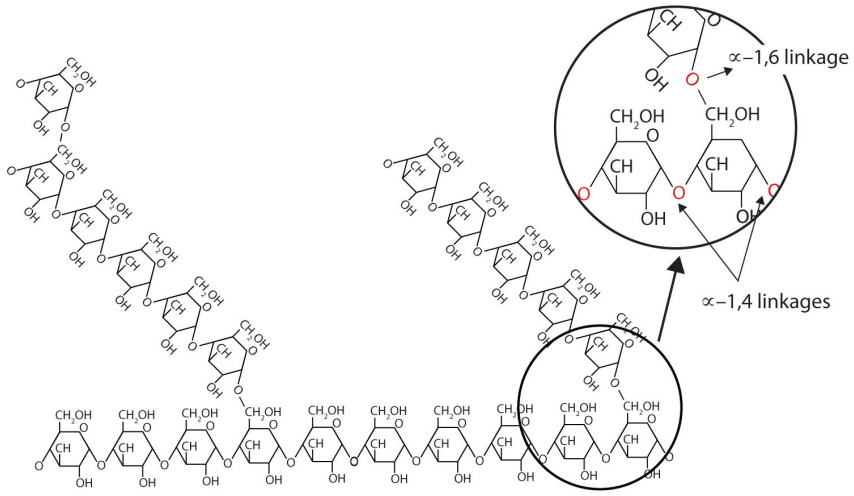


Figure 25.9.2: Representation of the Branching in Amylopectin and Glycogen. Both amylopectin and glycogen contain branch points that are linked through α-1,6-linkages. These branch points occur more often in glycogen.

Dextrins are glucose polysaccharides of intermediate size. The shine and stiffness imparted to clothing by starch are due to the presence of dextrins formed when clothing is ironed. Because of their characteristic stickiness with wetting, dextrins are used as adhesives on stamps, envelopes, and labels; as binders to hold pills and tablets together; and as pastes. Dextrins are more easily digested than starch and are therefore used extensively in the commercial preparation of infant foods.

The complete hydrolysis of starch yields, in successive stages, glucose:

$$\text{starch} \rightarrow \text{dextrins} \rightarrow \text{maltose} \rightarrow \text{glucose}$$

In the human body, several enzymes known collectively as amylases degrade starch sequentially into usable glucose units.

GLYCOGEN

Glycogen is the energy reserve carbohydrate of animals. Practically all mammalian cells contain some stored carbohydrates in the form of glycogen, but it is especially abundant in the liver (4%–8% by weight of tissue) and in skeletal muscle cells (0.5%–1.0%). Like starch in plants, glycogen is found as granules in liver and muscle cells. When fasting, animals draw on these glycogen reserves during the first day without food to obtain the glucose needed to maintain metabolic balance.

Glycogen is structurally quite similar to amylopectin, although glycogen is more highly branched (8–12 glucose units between branches) and the branches are shorter. When treated with iodine, glycogen gives a reddish brown color. Glycogen can be broken down into its D-glucose subunits by acid hydrolysis or by the same enzymes that catalyze the breakdown of starch. In animals, the enzyme phosphorylase catalyzes the breakdown of glycogen to phosphate esters of glucose.

> About 70% of the total glycogen in the body is stored in muscle cells. Although the percentage of glycogen (by weight) is higher in the liver, the much greater mass of skeletal muscle stores a greater total amount of glycogen.

CELLULOSE

Cellulose, a fibrous carbohydrate found in all plants, is the structural component of plant cell walls. Because the earth is covered with vegetation, cellulose is the most abundant of all carbohydrates, accounting for over 50% of all the carbon found in the vegetable kingdom. Cotton fibrils and filter paper are almost entirely cellulose (about 95%), wood is about 50% cellulose, and the dry weight of leaves is about 10%–20% cellulose. The largest use of cellulose is in the manufacture of paper and paper products. Although the use of non-cellulose synthetic fibers is increasing, rayon (made from cellulose) and cotton still account for over 70% of textile production.

Like amylose, cellulose is a linear polymer of glucose. It differs, however, in that the glucose units are joined by β-1,4-glycosidic linkages, producing a more extended structure than amylose (part (a) of Figure 25.9.3). This extreme linearity allows a great deal of hydrogen

bonding between OH groups on adjacent chains, causing them to pack closely into fibers (part (b) of Figure 25.9.3). As a result, cellulose exhibits little interaction with water or any other solvent. Cotton and wood, for example, are completely insoluble in water and have considerable mechanical strength. Because cellulose does not have a helical structure, it does not bind to iodine to form a colored product.

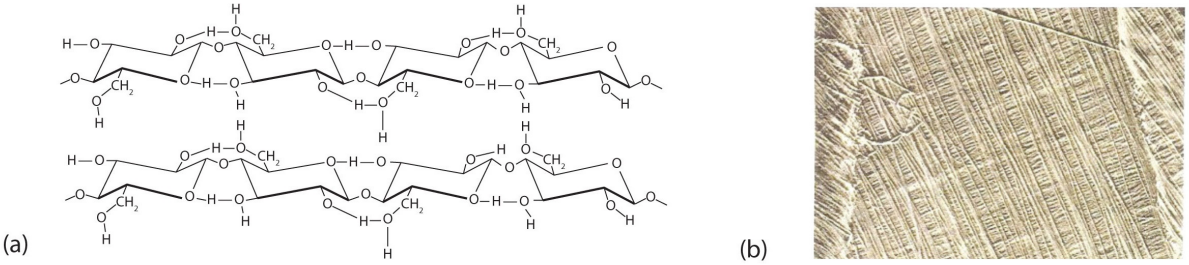
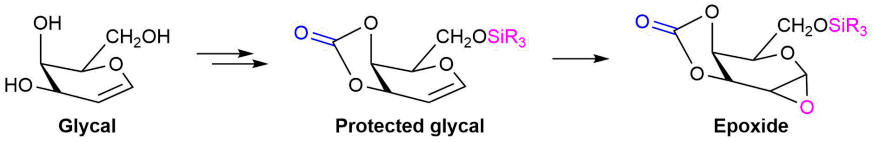


Figure 25.9.3: Cellulose. (a) There is extensive hydrogen bonding in the structure of cellulose. (b) In this electron micrograph of the cell wall of an alga, the wall consists of successive layers of cellulose fibers in parallel arrangement.

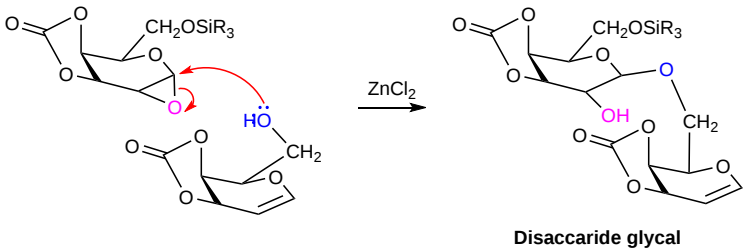
Cellulose yields D-glucose after complete acid hydrolysis, yet humans are unable to metabolize cellulose as a source of glucose. Our digestive juices lack enzymes that can hydrolyze the β-glycosidic linkages found in cellulose, so although we can eat potatoes, we cannot eat grass. However, certain microorganisms can digest cellulose because they make the enzyme cellulase, which catalyzes the hydrolysis of cellulose. The presence of these microorganisms in the digestive tracts of herbivorous animals (such as cows, horses, and sheep) allows these animals to degrade the cellulose from plant material into glucose for energy. Termites also contain cellulase-secreting microorganisms and thus can subsist on a wood diet. This example once again demonstrates the extreme stereospecificity of biochemical processes.

POLYSACCARIDE SYNTHESIS

The presence of multiple -OH groups in monosaccarides makes the laboratory synthesis of polysaccharides difficult. One modern method for the synthesis of polysaccharides is called the **glycal assembly method**. A glycal is a sugar which has been dehydrated to form a double bond. Glycals are typically prepared from the corresponding monosaccharide. As part of the synthesis pathway, the primary alcohol of the glycal is protected by forming a silyl ether (Section 17-8). Also, two adjacent secondary alcohols are protected by forming a cyclic carbonate ester. Now there are no -OH groups remanding in the protected glycal. The double bond of the protected glycal is then converted into a epoxide functional groups.



Epoxides ring can be opened by the acid-catalyzed S_N2 backside attack by an alcohol (section 18-6). This reaction is exploited by reacting a protected glycal epoxide with a second glycal with an unprotected primary alcohol in the presence $ZnCl_2$ as a Lewis acid. The disaccharide formed in this reaction is a glycal so it can be epoxidized and coupled with another glycal to form a trisaccharide etc. Once the monosaccharides are combined to form a chain of the desired length, the remaining silyl ether and cyclic carbonate protecting groups are removed by hydrolysis and the polysaccharide is formed.



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25.10: OTHER IMPORTANT CARBOHYDRATES

OBJECTIVES

After completing this section, you should be able to identify deoxy and amino sugars, given their structures.

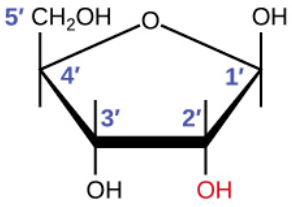
KEY TERMS

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

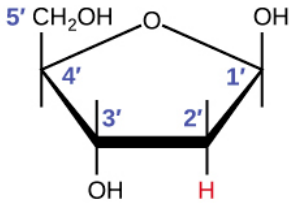
- amino sugar
- deoxy sugar

DEOXY SUGARS

As shown in **Section 25-7**, deoxy sugars are missing an oxygen atom. The most common deoxy sugar is 2-deoxyribose, a modified form of another sugar called ribose. When compared to ribose, 2-deoxyribose has an -OH group replaced with an -H at the 2 position. 2-deoxyribose is best known for being the sugar found in the structure of deoxyribonucleic acid (DNA).

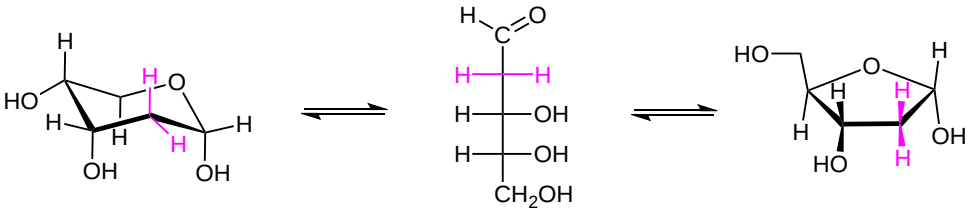


Ribose



Deoxyribose

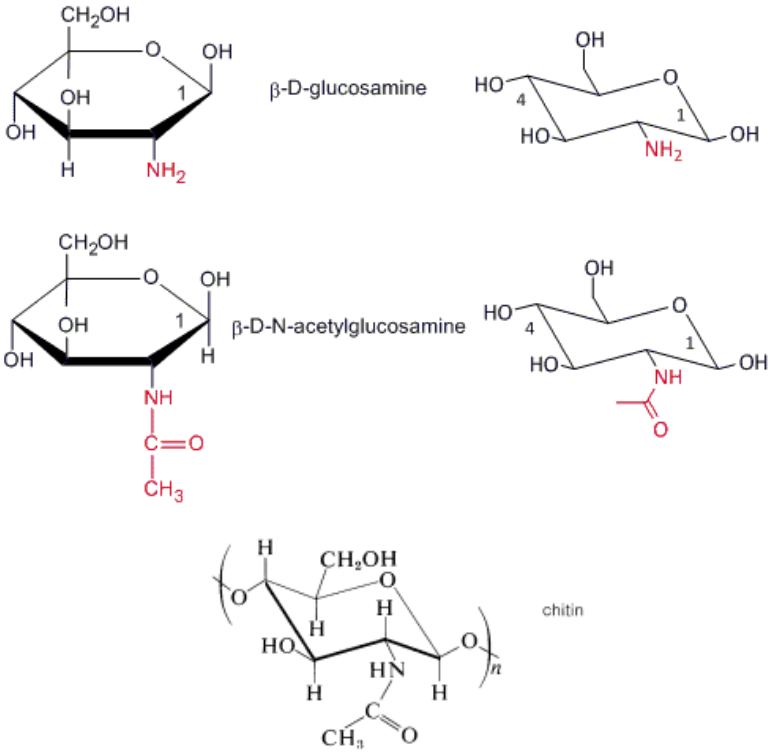
In water, 2-deoxyribose is an equilibrium mixture of both the furanose and pyranose ring forms. The pyranose form the most stable (40% alpha anomer and 35% beta anomer), followed by the furanose structures (13% alpha anomer and 12% beta), with the uncyclized form making up the remaining 0.7%.



Pyranose, uncyclized and furanose forms of 2-deoxyribose. The more stable alpha isomer is shown for both the pyranose and furanose forms. Note the missing hydroxide at the 2 position (highlighted magenta)

AMINO SUGARS

An amino sugar (or more technically a 2-amino-2-deoxysugar) is a sugar molecule in which a hydroxyl group has been replaced with an amine group. More than 60 amino sugars are known, with one of the most abundant being *N*-acetylglucosamine, which is the main component of chitin.



Chitin is a polymer of 2-deoxy-2- N -ethanamidoglucose (N-acetyl-β-D-glucosamine) and is found in many places throughout the natural world. It is a characteristic component of the cell walls of fungi, the exoskeletons of arthropods such as crustaceans (e.g., crabs, lobsters and shrimps) and insects, the radulae of molluscs, and the beaks and internal shells of cephalopods, including squid and octopuses and on the scales and other soft tissues of fish and lissamphibians. Amino sugars are also found in antibiotics such as amikacin and tobramicin.

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25.11: CELL-SURFACE CARBOHYDRATES AND INFLUENZA VIRUSES

OBJECTIVES

After completing this section, you should be able to:

1. Explain how carbohydrates are related to blood type.
2. Explain how influenza works and how it is influenced by carbohydrates.

OLIGOSACCHARIDES

An **oligosaccharide** is a saccharide polymer containing a small number (typically two to ten) of monosaccharides. Oligosaccharides can have many functions; for example, they are commonly found on the plasma membrane of animal cells where they can play a role in cell-cell recognition. In general, they are found attached to compatible amino acid side-chains in proteins or to lipids. Oligosaccharides are often found as a component of **glycoproteins** or **glycolipids**. They can be used as chemical markers on the outside of cells, often for cell recognition. Oligosaccharides are also responsible for determining blood type.

GLYCOPROTEINS

Carbohydrates are covalently attached to many different biomolecules, including lipids, to form glycolipids, and proteins, to form glycoproteins. Glycoproteins and glycolipids are often found in biological membranes, to which they are anchored by through nonpolar interactions. What is the function of these carbohydrates? Two are apparent. First, glycosylation of proteins helps protect the protein from degradation by enzyme catalysts within the body. However, their main functions arises from the fact that covalently attached carbohydrates that "decorate" the surface of glycoproteins or glycolipids provide new binding site interactions that allow interactions with other biomolecules. Hence glycosylation allows for cell:cell, cell:protein, or protein:protein interactions. Unfortunately, bacteria and viruses often recognize glycosylated molecules on cell membranes as well, allowing for their import into the cell.

BLOOD TYPE

Cell markers are carbohydrate chains on the surface of cells where they act as “road signs” allowing molecules to distinguish one cell from another. Blood markers are exclusively made from four monosaccharides: D-galactose, L-fucose, N-acetylgalactosamine, and N-acetylglucosamine.

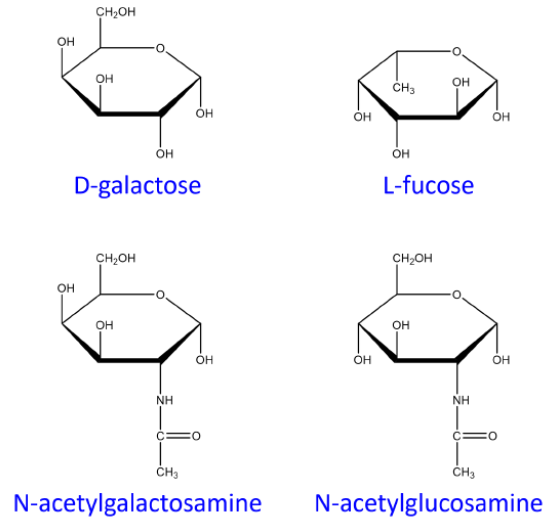


Figure 25.11.1: Structures of monosaccharide units present in ABO blood markers

ABO blood markers found on red blood cells are made up of oligosaccharides that contain either three or four sugar units as shown below. Oligosaccharides attached to red blood cells determine the ABO blood type.

Of the four blood types, type O has the fewest types of saccharides attached to it while type AB has the most. As a result, type O blood is considered the universal donor because it doesn't have any saccharides present that will appear as foreign when transfused into blood of another type. The reverse is not true. For example:

- If type A blood is given to a patient with type O blood, it will be rejected by the body because there is an unknown species being introduced to the body. Type A blood cells contain N-acetylgalactosamine which is not present in type O blood.
- Since type AB blood has all possible saccharides, type AB blood is considered the **universal acceptor**.

The Rhesus factor (Rh) in blood also affects donor and acceptor properties but it does not depend on carbohydrates. The Rh factor is determined by the presence (Rh+) or absence (Rh-) of a specific protein on the surface of red blood cells.

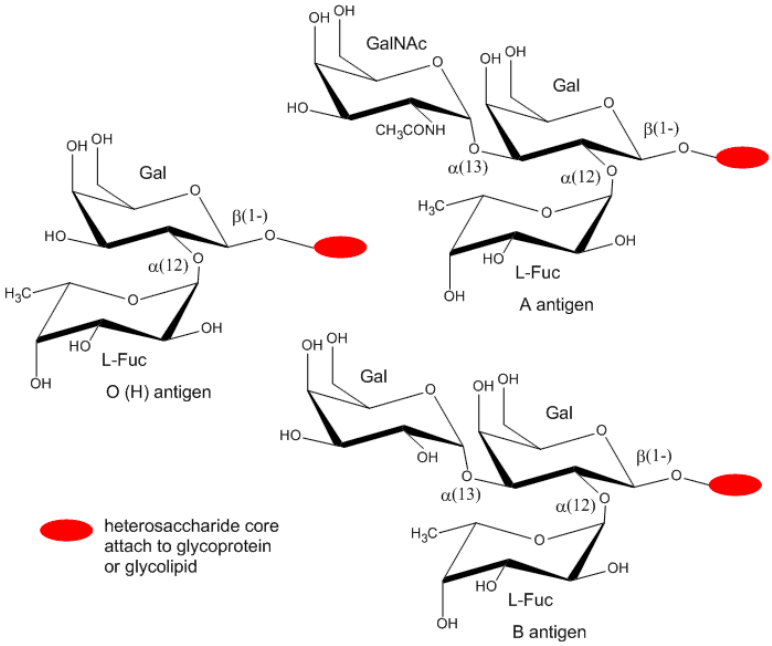


Figure 25.11.2 ABO blood types.

INFLUENZA AND THE AVIAN FLU

Three pandemics of influenza have swept the world since the "Spanish" flu of 1918.

- The "Asian" flu pandemic of 1957;
- the "Hong Kong" flu pandemic of 1968;
- the "Swine" flu pandemic that began in April of 2009.

The influenza virus is a simple yet deadly virus. It interacts with human cells through a surface protein, hemagglutinin (HA). The virus binds to host cells through interaction of HA with cell surface carbohydrates. Once bound the virus internalizes, ultimately leading to release of the RNA genome of the virus into the host cell. The HA protein is the most abundant protein on the viral surface (as surmised by antibody formation).

The influenza virus is typically classified by two kinds of glycoproteins on the surface of the virus: in addition to HA is the enzyme neuraminidase. Two viral strains which have been often discussed are H5N1 and H1N1 which stands for hemagglutinin (H: type 5 or type 1) and neuraminidase (N: type 1). 15 avian and mammalian variants have been identified (based on antibody studies). Only 3 adapted to humans in the last 100 yr, giving pandemic strains H1 (1918), H2 (957) and H3 (1968). Three recent avian variants (H5, H7, and H9) have jumped directly to humans recently but have low human to human transmissibility.

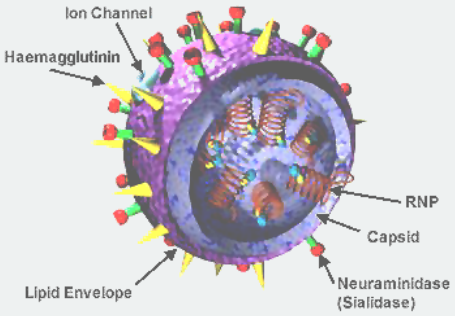
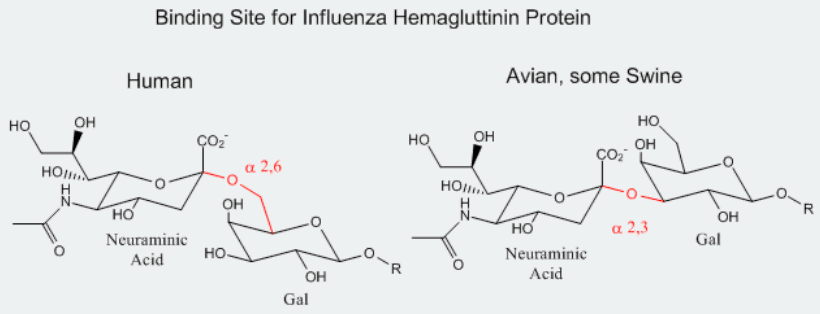


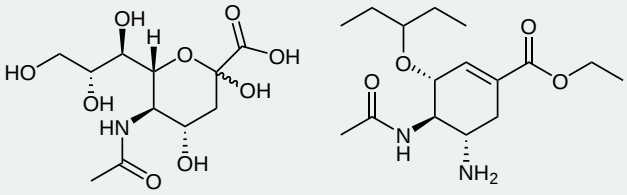
Figure 25.11.3 Structure (3D) of the Influenza Virus: The image depicts the major components of the virus structure, including the neuraminidase. (Public Domain; National Institutes of Health via Wikipedia)

Influenza Virus binds to Cell Surface Glycoproteins with Neu5Ac - A protein on the surface of influenza virus. Hemagluttinin binds to sialic acid (Sia), which is covalently attached to many cell membrane glycoproteins. The sialic acid is usually connected through an alpha (2,3) or alpha (2,6) link to galactose on N-linked glycoproteins. The subtypes found in avian (and equine) influenza isolates bind

preferentially to Sia (alpha 2,3) Gal which predominates in avian GI tract where viruses replicate. Human virus of H1, H2, and H3 subtype (cause of the 1918, 1957, and 1968 pandemics) recognize Sia (alpha 2,6) Gal, as the major form in the human respiratory tract. The swine influenza HA bind to Sia (alpha 2,6) Gal and some Sia (alpha 2,3) both of which are commonly found in swine.



The virus, before it leaves the cell, forms a bud on the intracellular side of the cell with the HA and NA in the cell membrane of the host cell. The virus in this state would not leave the cell since its HA molecules would interact with sialic acid residues in the host cell membrane, holding the virus in the membrane. Neuraminidase hydrolyzes sialic acid from cell surface glycoproteins, allowing the virus to complete the budding process and be released from the cell as new viruses. By mimicking the structure of sialic acid, the drugs Oseltamivir (Tamiflu) and zanamivir (Relenza) bind to and inhibit neuraminidase whose activity is necessary for viral release from infected cells. Tamiflu appears to work against N1 of the present H5N1 avian influenza viruses. Governments across the world are stockpiling this drug in case of a pandemic caused by the avian virus jumping directly to humans and becoming transmissible from human to human.



Sialic Acid **Tamiflu**

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25.S: BIOMOLECULES- CARBOHYDRATES (SUMMARY)

CONCEPTS & VOCABULARY

- fulfill all of the detailed objectives listed under each individual section.
- define, and use in context, any of the key terms introduced in this chapter.

25.1 Introduction

- Carbohydrates are composed of carbon, hydrogen, and oxygen atoms and are polyhydroxy aldehydes and ketones.
- Examples of carbohydrates are starch, fibers, sugar, and cellulose.
- Green plants use glucose for energy or making larger carbohydrates.
- Carbohydrates are needed for the synthesis of nucleic acids, proteins, and lipids.
- Animals rely on plants to provide them with carbohydrates, which are used for food and clothing.

25.2 Classification of Carbohydrates

- Carbohydrates originate as products from photosynthesis.
- The generic formula is $C_n(H_2O)_n$.
- Carbohydrates play a vital role in a major food source, but are also used as structural material, recognition sites on cells, and other tasks.
- Carbohydrates are called saccharides and can be classified as simple or complex.

25.3 Fischer Projections

- The Fischer projection is a type of notation often used when multiple chiral centers are present in a molecule.
- In a Fischer projection:
  - the four bonds to a chiral carbon make a cross with the carbon atom at the intersection of the horizontal and vertical lines.
  - the two horizontal bonds are directed toward the viewer (forward of the stereogenic carbon).
  - the two vertical bonds are directed behind the central carbon (away from the viewer).
- Determining whether a chiral carbon is R or S
  - If the lowest priority group is on a vertical bond, the configuration is given directly from the relative positions of the three higher-ranked substituents.
  - If the lowest priority group is on a horizontal bond, the positions of the remaining groups give the wrong answer, so you reverse it.
- Epimer is used to designate diastereomers that differ in configuration at only one chiral center.

25.4 D,L Sugars

- To determine absolute configuration for carbohydrates, Emil Fischer started with an arbitrary choice that (+)-glucose would be the D-family and related aldoses.
- The last chiral center in an aldose chain (farthest from the aldehyde group) was chosen by Emil Fischer as the D / L designator site.
- The L-family is the mirror image of the D-family.
- If the hydroxyl group in the projection formula pointed to the right, it was defined as a member of the D-family.
- A left directed hydroxyl group then represented the L-family.
- It is important to recognize that the sign of a compound's specific rotation (an experimental number) does not correlate with its configuration (D or L).
- Determining an absolute configuration usually requires chemical interconversion with known compounds by stereospecific reaction paths.

25.5 Configurations of Aldoses

- The aldose family is composed of three to six carbon atoms.
- Emil Fischer determined a way to determine absolute configuration of aldoses.
- In 1951 x-ray fluorescence studies of (+)-tartaric acid, carried out in the Netherlands by Johannes Martin Bijvoet, proved that Fischer's choice was correct.

25.6 Anomers

- The preferred structural form of monosaccharides is a cyclic hemiacetal, especially for five and six-membered rings due to low angle strain and eclipsing strain.
- Five-membered cyclic sugars are termed furanose and six-membered cyclic sugars are pyranose.
- By convention for the D-family, the five-membered furanose ring is drawn in an edgewise projection with the ring oxygen positioned away from the viewer.
- The cyclic pyranose forms of various monosaccharides are often drawn in a flat projection known as a Haworth formula.

- In the D-family, the alpha and beta bonds have the same orientation defined for the furanose ring.
- The size of the cyclic hemiacetal ring adopted by a given sugar is not constant, but may vary with substituents and other structural features.
- Derivatizations of this kind permit selective reactions to be conducted at different locations in these highly functionalized molecules.
- When a straight-chain monosaccharide forms a cyclic structure, the carbonyl oxygen atom may be pushed either up or down, giving rise to two stereoisomers.
  - When the OH group on the first carbon atom projected downward, this is called the *alpha (α) form*.
  - When the OH group on the first carbon atom pointed upward, is the *beta (β) form*.
- These two stereoisomers of a cyclic monosaccharide are known as anomers.
- You can start with a pure crystalline sample of glucose consisting entirely of one anomer, but as soon as the molecules dissolve in water, they open to form the carbonyl group and then reclose to form either the α or the β anomer.
- The opening and closing repeats continuously in an ongoing interconversion between anomeric forms and is referred to as mutarotation.

25.7 Reactions of Monosaccharides

- The -OH groups on a monosaccharide can be readily converted to esters and ethers.
- Acetal derivatives formed when a monosaccharide reacts with an alcohol in the presence of an acid catalyst are called glycosides.
- Phosphorylation of the -OH group using ATP.
- Oxidation can occur with the monosaccharides, which is why some sugars are classified as reducing.
- When the aldehyde function of an aldose is oxidized to a carboxylic acid the product is called an aldonic acid.
- If both ends of an aldose chain are oxidized to carboxylic acids the product is called an aldaric acid.
- Sodium borohydride reduction of an aldose makes the ends of the resulting alditol chain identical like aldaric acid.
- Monosaccharides can react to have the chain length increased or decreased, which can be important in elucidation of the carbohydrate's structure.

25.8 The Eight Essential Monosaccharides

- The eight essential monosaccharides are: L-fructose, D-galactose, D-glucose, D-mannose, N-acetyl-D-glucosamine, N-acetyl-D-galacosamine, D-xylose, N-acetyl-D-neuraminic acid.
- These eight monosaccaharides are obtained through diet.

25.9 Disaccharides

- Disaccharides are sugars composed of two monosaccharide units that are joined by a carbon–oxygen-carbon linkage known as a glycosidic linkage.
- The glycosidic linkage is formed from the reaction of the anomeric carbon of one cyclic monosaccharide with the OH group of a second monosaccharide.
- The disaccharides differ from one another in their monosaccharide constituents and in the specific type of glycosidic linkage connecting them.
- There are three common disaccharides: maltose, lactose, and sucrose.
- Maltose is two glucose molecules linked in a *head-to-tail* fashion through an α-linkage from the first carbon atom of one glucose molecule to the fourth carbon atom of the second glucose molecule.
- Lactose is composed of one molecule of D-galactose and one molecule of D-glucose joined by a β-1,4-glycosidic bond.
- Sucrose is has an α-1,β-2-glycosidic (head-to-head) linkage, which is formed by the OH group on the anomeric carbon of α-D-glucose and the OH group on the anomeric carbon of β-D-fructose, it ties up the anomeric carbons of both glucose and fructose.

25.10 Polysaccharides and Their Synthesis

- Polysaccharides are very large polymers composed of tens to thousands of monosaccharides joined together by glycosidic linkages.
- The three most abundant polysaccharides are starch, glycogen, and cellulose.

25.11 Other Important Carbohydrates

- The backbone of DNA is based on a repeated pattern of a sugar group and a phosphate group, the sugar present - deoxyribose.
- An amino sugar is a sugar molecule in which a hydroxyl group has been replaced with an amine group.

25.12 Cell-Surface Carbohydrates and Influenza Viruses

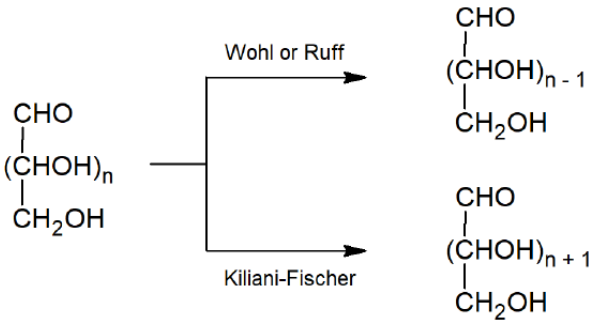
- Carbohydrates are covalently attached to many different biomolecules, including lipids, to form glycolipids, and proteins, to form glycoproteins.
- Glycoproteins and glycolipids are often found in biological membranes that allow other biomolecules to interact and bind to the protein.
- Bacteria and viruses often recognize glycosylated molecules on cell membranes, allowing for their import into the cell.
- This is how the influenza virus enters the body.

SKILLS TO MASTER

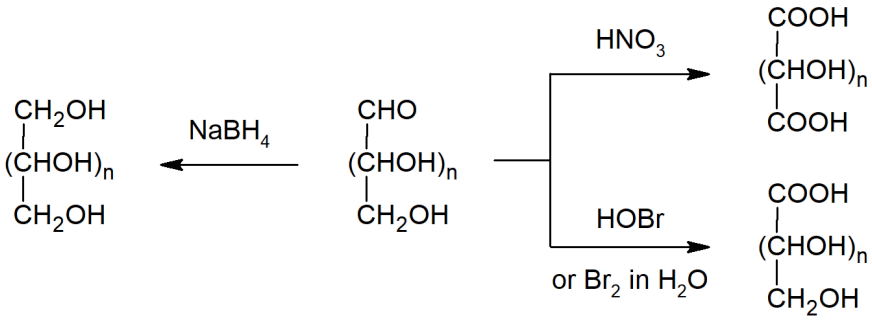
- Skill 25.1 Determine which molecules can be classified as carbohydrates.
- Skill 25.2 Distinguish between monosaccharide, disaccharide, and trisaccharides given the structure.
- Skill 25.3 Classify a monosaccharide according to the number of carbon atoms present and whether it contains an aldehyde or ketone group.
- Skill 25.4 Draw the Fischer projection of a monosaccharide, given its wedge-and-broken-line structure or a molecular model.
- Skill 25.5 Draw the wedge-and-broken-line structure of a monosaccharide, given its Fischer projection or a molecular model.
- Skill 25.6 Construct a molecular model of a monosaccharide, given its Fischer projection or wedge-and-broken-line structure.
- Skill 25.7 Identify a specific enantiomer of a monosaccharide as being D or L, given its Fischer projection.
- Skill 25.8 Assign an *R* or *S* configuration to each of the chiral carbon atoms present in a monosaccharide, given its Fischer projection.
- Skill 25.9 Draw the Fischer projection formula for a monosaccharide, given its systematic name, complete with the configuration of each chiral carbon atom.
- Skill 25.10 Draw configurations of aldoses.
- Skill 25.11 Determine whether a given monosaccharide will exist as a pyranose or furanose.
- Skill 25.12 Draw the cyclic pyranose form of a monosaccharide, given its Fischer projection.
- Skill 25.13 Determine whether a given cyclic pyranose form represents the D or L form of the monosaccharide concerned.
- Skill 25.14 Describe the phenomenon known as mutarotation.
- Skill 25.15 Explain why certain ketoses, such as fructose, behave as reducing sugars even though they do not contain an aldehyde group.
- Skill 25.16 Predict the product that would be produced by the Kiliani-Fischer synthesis of a given aldose.
- Skill 25.17 Identify the aldose that would yield a given product following Kiliani-Fischer synthesis.
- Skill 25.18 Predict the product that would be produced by the Wohl degradation of a given aldose.
- Skill 25.19 Identify the aldose that would yield a given product following Wohl degradation synthesis.
- Skill 25.20 Identify disaccharides as compounds consisting of two monosaccharide units joined by a glycoside link between the C1 of one sugar and one of the hydroxyl groups of a second sugar.
- Skill 25.21 Identify the two monosaccharide units in a given disaccharide.
- Skill 25.22 Identify the type of glycoside link (e.g., 1,4′-β) present in a given disaccharide structure.
- Skill 25.23 Draw the structure of a specific disaccharide, given the structure of the monosaccharide units and the type of glycoside link involved.
- Skill 25.24 Identify the products formed from the hydrolysis of a given disaccharide.

SUMMARY OF REACTIONS

Chain Length

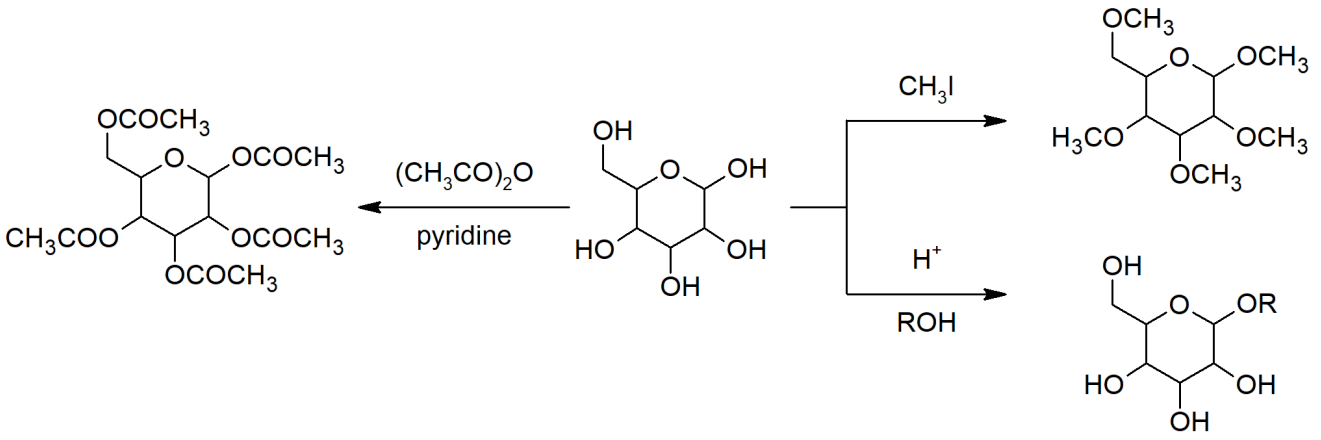


Oxidation - Reduction



Ester and Ether Formation

https://chem.libretexts.org/@go/page/473979



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CHAPTER OVERVIEW

26: AMINO ACIDS, PEPTIDES, AND PROTEINS

LEARNING OBJECTIVES

When you have completed Chapter 26, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. use the information provided by an amino acid analysis, an Edman degradation and a carboxypeptidase hydrolysis to determine the structure of an unknown polypeptide.
3. outline the approach that you would use to synthesize a given peptide, providing appropriate mechanistic details if requested to do so.
4. define, and use in context, the key terms introduced in this chapter.

Amino acids are important biochemicals, as they are the building blocks from which proteins and polypeptides are assembled. We begin this chapter with an examination of some of the fundamental chemistry of amino acids: their structures, stereochemistry and synthesis. We then discuss the nature of peptides and of the peptide bond, and present the complex issue of determining the order in which the various amino-acid residues occur in a given peptide. Once a chemist knows the exact order the of the residues in a given peptide, the next challenge is to determine a method by which the same peptide can be prepared in the laboratory. Thus, two sections are devoted to the problem of protein synthesis. The final sections in the chapter deal with the classification, overall structure and denaturation of proteins.

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26.0: CHAPTER OBJECTIVES

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26.1: INTRODUCTION

OBJECTIVES

After completing this section, you should be able to

1. give examples of the various biological roles played by proteins.
2. identify amino acids as being the building blocks from which all proteins are made.
3. show, in a general way, how the joining together of a number of amino acids through the formation of peptide bonds results in the formation of proteins.

KEY TERMS

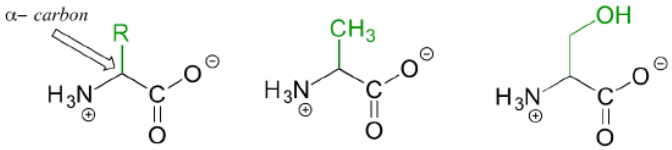
Make certain that you can define, and use in context, the key terms below.

- amino acid
- enzyme
- peptide bond
- protein

STUDY NOTES

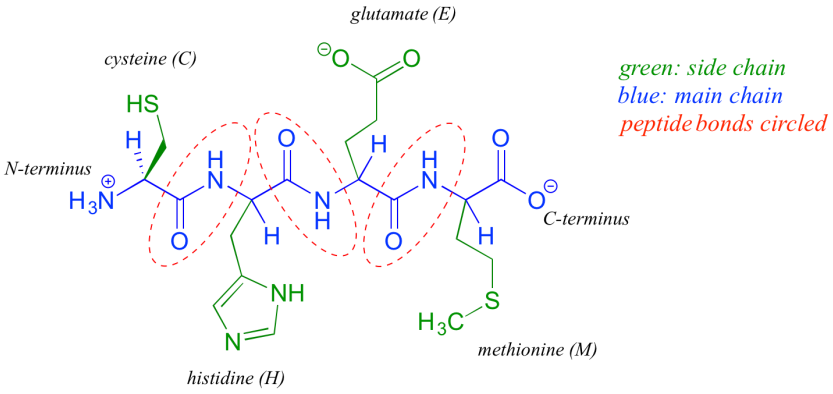
The “peptide bond” or “peptide linkage” that is formed between the amino group of one amino acid and the carboxyl group of a second amino acid is identical to the C$\ce{-}$N bond present in amides (see Section 21.7). We shall review the nature of such bonds in Section 26.4.

Proteins are polymers of **amino acids**, linked by amide groups known as **peptide bond**s. An amino acid can be thought of as having two components: a 'backbone', or 'main chain', composed of an ammonium group, an 'alpha-carbon', and a carboxylate, and a variable 'side chain' (in green below) bonded to the alpha-carbon.



There are twenty different side chains in naturally occurring amino acids, and it is the identity of the side chain that determines the identity of the amino acid: for example, if the side chain is a -CH_3 group, the amino acid is alanine, and if the side chain is a -CH_2OH group, the amino acid is serine. Many amino acid side chains contain a functional group (the side chain of serine, for example, contains a primary alcohol), while others, like alanine, lack a functional group, and contain only a simple alkane.

The two 'hooks' on an amino acid monomer are the amine and carboxylate groups. Proteins (polymers of ~50 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**. Which amino acids are linked, and in what order - the protein **sequence** - is what distinguishes one protein from another, and is coded for by an organism's DNA. Protein sequences are written in the amino terminal (N-terminal) to carboxylate terminal (C-terminal) direction, with either three-letter or single-letter abbreviations for the amino acids (see amino acid table). Below is a four amino acid peptide with the sequence "cysteine - histidine - glutamate - methionine". Using the single-letter code, the sequence is abbreviated CHEM.



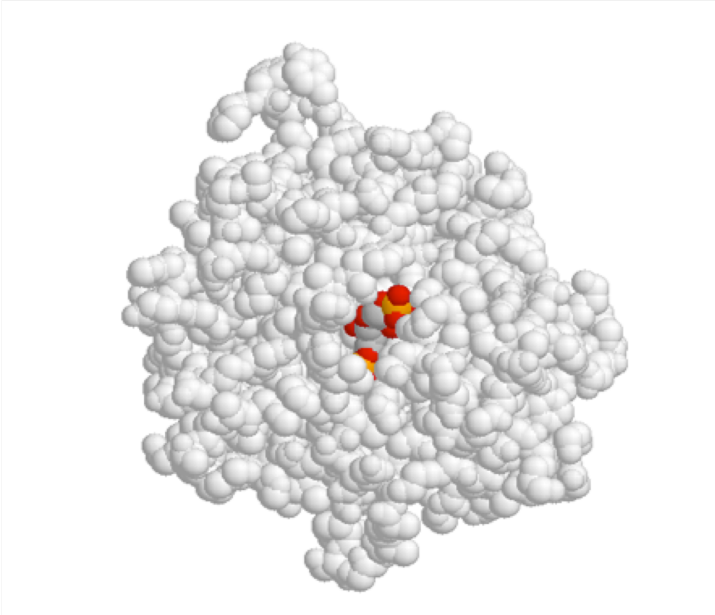
CHEM peptide

When an amino acid is incorporated into a protein it loses a molecule of water and what remains is called a **residue** of the original amino acid. Thus we might refer to the 'glutamate residue' at position 3 of the CHEM peptide above.

Once a protein polymer is constructed, it in many cases folds up very specifically into a three-dimensional structure, which often includes one or more 'binding pockets' in which other molecules can be bound. It is this shape of this folded structure, and the precise arrangement of the functional groups within the structure (especially in the area of the binding pocket) that determines the function of the protein.

Enzymes are proteins which catalyze biochemical reactions. One or more reacting molecules - often called **substrates** - become bound in the **active site** pocket of an enzyme, where the actual reaction takes place. **Receptors** are proteins that bind specifically to one or more molecules - referred to as **ligands** - to initiate a biochemical process. For example, we saw in the introduction to this chapter that the TrpVI receptor in mammalian tissues binds capsaicin (from hot chili peppers) in its binding pocket and initiates a heat/pain signal which is sent to the brain.

Shown below is an image of the glycolytic enzyme fructose-1,6-bisphosphate aldolase (in grey), with the substrate molecule bound inside the active site pocket.



(x-ray crystallographic data are from *Protein Science* **1999**, 8, *291*; pdb code 4ALD. Image produced with JMol First Glance)

Intro to nucleic acids ⇒

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26.2: STRUCTURES OF AMINO ACIDS

OBJECTIVES

After completing this section, you should be able to

1. identify the structural features present in the 20 amino acids commonly found in proteins.

   Note: You are not expected to remember the detailed structures of all these amino acids, but you should be prepared to draw the structures of the two simplest members, glycine and alanine.

2. draw the Fischer projection formula of a specified enantiomer of a given amino acid.

   Note: To do so, you must remember that in the *S* enantiomer, the carboxyl group appears at the top of the projection formula and the amino group is on the left.

3. classify an amino acid as being acidic, basic or neutral, given its Kekulé, condensed or shorthand structure.
4. draw the zwitterion form of a given amino acid.
5. account for some of the typical properties of amino acids (e.g., high melting points, solubility in water) in terms of zwitterion formation.
6. write appropriate equations to illustrate the amphoteric nature of amino acids.

KEY TERMS

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

- *α*-amino acids
- amphoteric
- essential amino acids
- zwitterion

STUDY NOTES

This is a good point at which to review some of the principles of stereochemistry presented in Chapter 5. Be sure to make full use of molecular models when any stereochemical issues arise.

You should recognize that a three-letter shorthand code is often used to represent individual amino acids. You need not memorize this code.

The distinction between essential and nonessential amino acids is not as clear-cut as one might suppose. For example, arginine is often regarded as being nonessential.

INTRODUCTION TO AMINO ACIDS

Amino acids form polymers through a nucleophilic attack by the amino group of an amino acid at the electrophilic carbonyl carbon of the carboxyl group of another amino acid. The carboxyl group of the amino acid must first be activated to provide a better leaving group than OH^-. (We will discuss this activation by ATP later in the course.) The resulting link between the amino acids is an amide link which biochemists call a peptide bond. In this reaction, water is released. In a reverse reaction, the peptide bond can be cleaved by water (hydrolysis).

- Structure and Property of the Naturally-Occurring Amino Acids (Too large to include in text: print separately)

When two amino acids link together to form an amide link, the resulting structure is called a dipeptide. Likewise, we can have tripeptides, tetrapeptides, and other polypeptides. At some point, when the structure is long enough, it is called a protein. There are many different ways to represent the structure of a polypeptide or protein, each showing differing amounts of information.

Figure: Different Representations of a Polypeptide (Heptapeptide)

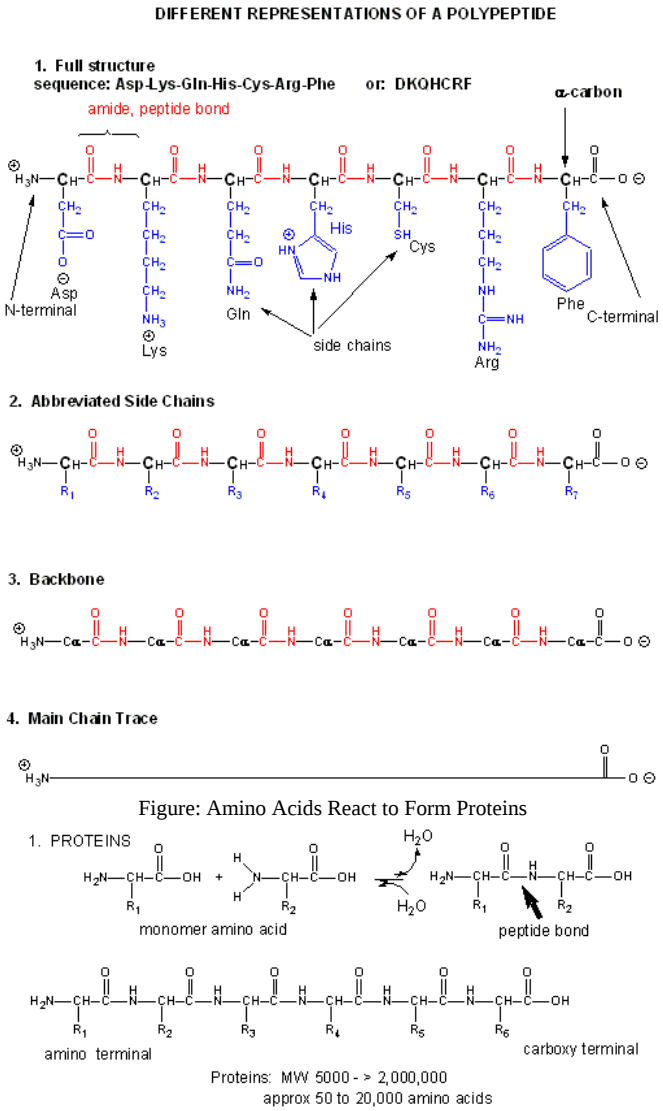


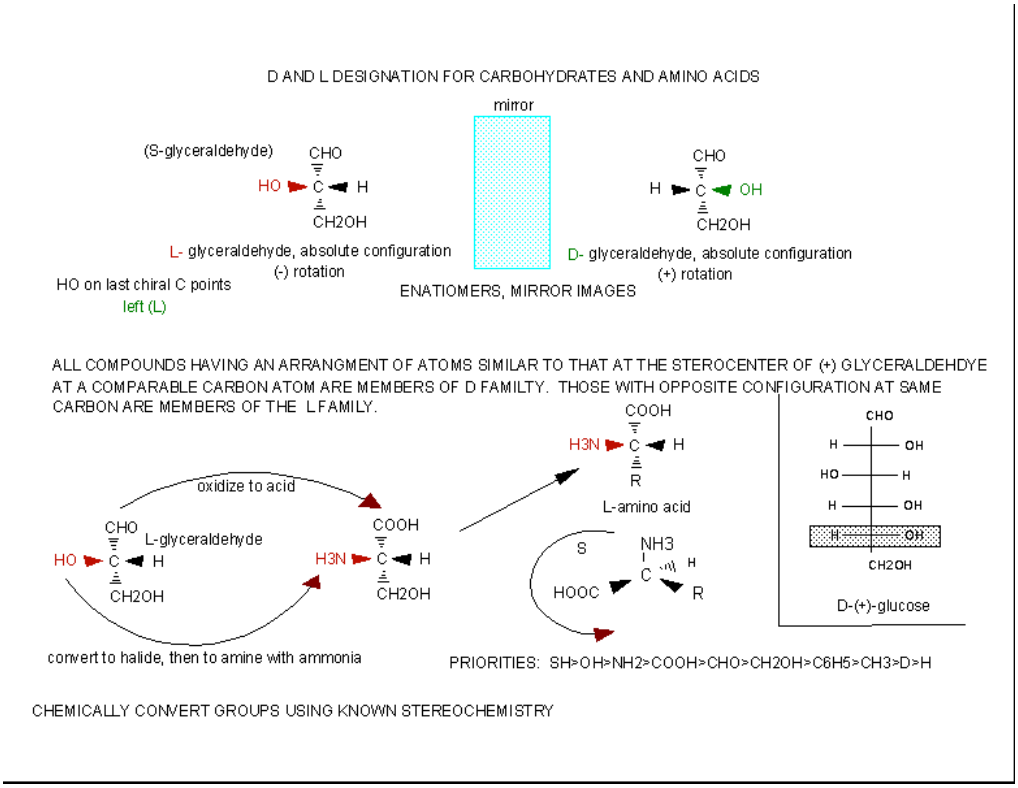
Figure: Amino Acids React to Form Proteins

(Note: above picture represents the amino acid in an unlikely protonation state with the weak acid protonated and the weak base deprotonated for simplicity in showing removal of water on peptide bond formation and the hydrolysis reaction.) Proteins are polymers of twenty naturally occurring amino acids. In contrast, nucleic acids are polymers of just 4 different monomeric nucleotides. Both the sequence of a protein and its total length differentiate one protein from another. Just for an octapeptide, there are over 25 billion different possible arrangements of amino acids. Compare this to just 65536 different oligonucleotides of 8 monomeric units (8mer). Hence the diversity of possible proteins is enormous.

STEREOCHEMISTRY

The amino acids are all chiral, with the exception of glycine, whose side chain is H. As with lipids, biochemists use the L and D nomenclature. All naturally occuring proteins from all living organisms consist of L amino acids. The absolute stereochemistry is related to L-glyceraldehyde, as was the case for triacylglycerides and phospholipids. Most naturally occurring chiral amino acids are S, with the exception of cysteine. As the diagram below shows, the absolute configuration of the amino acids can be shown with the H pointed to the rear, the COOH groups pointing out to the left, the R group to the right, and the NH_3 group upwards. You can remember this with the anagram CORN.

Figure: *Stereochemistry of Amino Acids.*



Why do biochemists still use D and L for sugars and amino acids? This explanation (taken from the link below) seems reasonable.

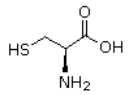
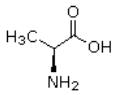
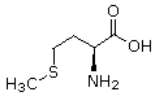
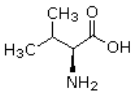
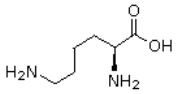
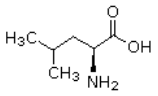
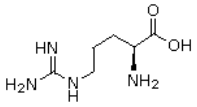
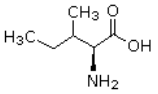
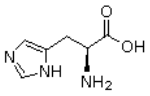
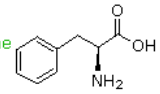
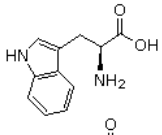
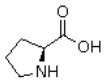
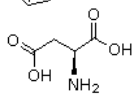
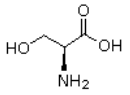
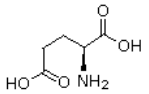
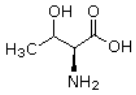
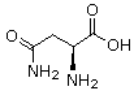
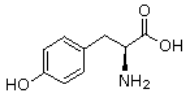
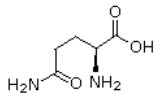
"In addition, however, chemists often need to define a configuration unambiguously in the absence of any reference compound, and for this purpose the alternative (R,S) system is ideal, as it uses priority rules to specify configurations. These rules sometimes lead to absurd results when they are applied to biochemical molecules. For example, as we have seen, all of the common amino acids are L, because they all have exactly the same structure, including the position of the R group if we just write the R group as R. However, they do not all have the same configuration in the (R,S) system: L-cysteine is also (R)-cysteine, but all the other L-amino acids are (S), but this just reflects the human decision to give a sulphur atom higher priority than a carbon atom, and does not reflect a real difference in configuration. Worse problems can sometimes arise in substitution reactions: sometimes inversion of configuration can result in no change in the (R) or (S) prefix; and sometimes retention of configuration can result in a change of prefix.

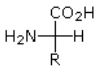
It follows that it is not just conservatism or failure to understand the (R,S) system that causes biochemists to continue with D and L: it is just that the DL system fulfils their needs much better. As mentioned, chemists also use D and L when they are appropriate to their needs. The explanation given above of why the (R,S) system is little used in biochemistry is thus almost the exact opposite of reality. This system is actually the only practical way of unambiguously representing the stereochemistry of complicated molecules with several asymmetric centres, but it is inconvenient with regular series of molecules like amino acids and simple sugars. "

NATURAL A-AMINO ACIDS

Hydrolysis of proteins by boiling aqueous acid or base yields an assortment of small molecules identified as α-aminocarboxylic acids. More than twenty such components have been isolated, and the most common of these are listed in the following table. Those amino acids having green colored names are **essential** diet components, since they are not synthesized by human metabolic processes. The best food source of these nutrients is protein, but it is important to recognize that not all proteins have equal nutritional value. For example, peanuts have a higher weight content of protein than fish or eggs, but the proportion of essential amino acids in peanut protein is only a third of that from the two other sources. For reasons that will become evident when discussing the structures of proteins and peptides, each amino acid is assigned a one or three letter abbreviation.

NATURAL A-AMINO ACIDS

Name	Formula	Abbreviations		Name	Formula	Abbreviations	
Glycine		Gly	G	Cysteine		Cys	C
Alanine		Ala	A	Methionine		Met	M
Valine		Val	V	Lysine		Lys	K
Leucine		Leu	L	Arginine		Arg	R
Isoleucine		Ile	I	Histidine		His	H
Phenylalanine		Phe	F	Tryptophan		Trp	W
Proline		Pro	P	Aspartic Acid		Asp	D
Serine		Ser	S	Glutamic Acid		Glu	E
Threonine		Thr	T	Asparagine		Asn	N
Tyrosine		Tyr	Y	Glutamine		Gln	Q


L-Amino Acid

Some common features of these amino acids should be noted. With the exception of proline, they are all 1°-amines; and with the exception of glycine, they are all chiral. The configurations of the chiral amino acids are the same when written as a Fischer projection formula, as in the drawing on the right, and this was defined as the **L-configuration** by Fischer. The R-substituent in this structure is the remaining structural component that varies from one amino acid to another, and in proline R is a three-carbon chain that joins the nitrogen to the alpha-carbon in a five-membered ring. Applying the Cahn-Ingold-Prelog notation, all these natural chiral amino acids, with the exception of cysteine, have an **S**-configuration. For the first seven compounds in the left column the R-substituent is a hydrocarbon. The last three entries in the left column have hydroxyl functional groups, and the first two amino acids in the right column incorporate thiol and sulfide groups respectively. Lysine and arginine have basic amine functions in their side-chains; histidine and tryptophan have less basic nitrogen heterocyclic rings as substituents. Finally, carboxylic acid side-chains are substituents on aspartic and glutamic acid, and the last two compounds in the right column are their corresponding amides.

The formulas for the amino acids written above are simple covalent bond representations based upon previous understanding of mono-functional analogs. **The formulas are in fact incorrect**. This is evident from a comparison of the physical properties listed in the following table. All four compounds in the table are roughly the same size, and all have moderate to excellent water solubility. The first two are simple carboxylic acids, and the third is an amino alcohol. All three compounds are soluble in organic solvents (e.g. ether) and have relatively low melting points. The carboxylic acids have pK_a's near 4.5, and the conjugate acid of the amine has a pK_a of 10. The simple amino acid alanine is the last entry. By contrast, it is very high melting (with decomposition), insoluble in organic solvents, and a million times weaker as an acid than ordinary carboxylic acids.

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Physical Properties of Selected Acids and Amines

Compound	Formula	Mol.Wt.	Solubility in Water	Solubility in Ether	Melting Point	pK_a
isobutyric acid	$(CH_3)_2CHCO_2H$	88	20g/100mL	complete	-47 ºC	5.0
lactic acid	$CH_3CH(OH)CO_2H$	90	complete	complete	53 ºC	3.9
3-amino-2-butanol	$CH_3CH(NH_2)CH(OH)CH_3$	89	complete	complete	9 ºC	10.0
alanine	$CH_3CH(NH_2)CO_2H$	89	18g/100mL	insoluble	ca. 300 ºC	9.8

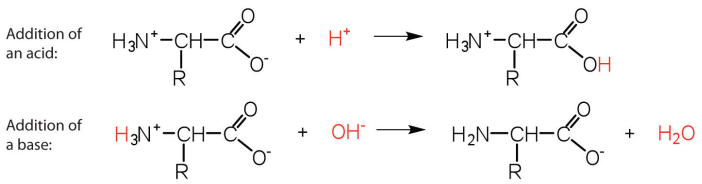
ZWITTERION

These differences above all point to internal salt formation by a proton transfer from the acidic carboxyl function to the basic amino group. The resulting ammonium carboxylate structure, commonly referred to as a **zwitterion**, is also supported by the spectroscopic characteristics of alanine.

$$CH_3CH(NH_2)CO_2H \rightleftharpoons CH_3CH(NH_3)^{(+)}CO_2^{(-)}$$

As expected from its ionic character, the alanine zwitterion is high melting, insoluble in nonpolar solvents and has the acid strength of a 1º-ammonium ion. Examples of a few specific amino acids may also be viewed in their favored neutral zwitterionic form. Note that in lysine the amine function farthest from the carboxyl group is more basic than the alpha-amine. Consequently, the positively charged ammonium moiety formed at the chain terminus is attracted to the negative carboxylate, resulting in a coiled conformation.

The structure of an amino acid allows it to act as both an acid and a base. An amino acid has this ability because at a certain pH value (different for each amino acid) nearly all the amino acid molecules exist as zwitterions. If acid is added to a solution containing the zwitterion, the carboxylate group captures a hydrogen (H^+) ion, and the amino acid becomes positively charged. If base is added, ion removal of the H^+ ion from the amino group of the zwitterion produces a negatively charged amino acid. In both circumstances, the amino acid acts to maintain the pH of the system—that is, to remove the added acid (H^+) or base (OH^-) from solution.

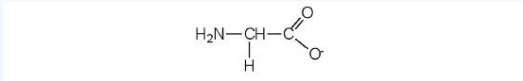


EXAMPLE 26.1

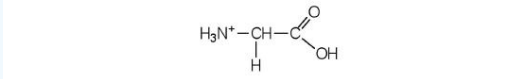
a. Draw the structure for the anion formed when glycine (at neutral pH) reacts with a base.
b. Draw the structure for the cation formed when glycine (at neutral pH) reacts with an acid.

Solution

a. The base removes H^+ from the protonated amine group.

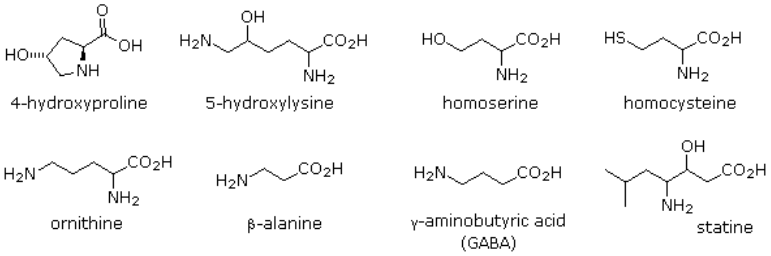


The acid adds H^+ to the carboxylate group.



OTHER NATURAL AMINO ACIDS

The twenty alpha-amino acids listed above are the primary components of proteins, their incorporation being governed by the genetic code. Many other naturally occurring amino acids exist, and the structures of a few of these are displayed below. Some, such as hydroxylysine and hydroxyproline, are simply functionalized derivatives of a previously described compound. These two amino acids are found only in collagen, a common structural protein. Homoserine and homocysteine are higher homologs of their namesakes. The amino group in beta-alanine has moved to the end of the three-carbon chain. It is a component of pantothenic acid, $HOCH_2C(CH_3)_2CH(OH)CONHCH_2CH_2CO_2H$, a member of the vitamin B complex and an essential nutrient. Acetyl coenzyme A is a pyrophosphorylated derivative of a pantothenic acid amide. The gamma-amino homolog GABA is a neurotransmitter inhibitor and antihypertensive agent.



Many unusual amino acids, including D-enantiomers of some common acids, are produced by microorganisms. These include ornithine, which is a component of the antibiotic bacitracin A, and statin, found as part of a pentapeptide that inhibits the action of the digestive enzyme **pepsin**.

EXERCISES

QUESTIONS

Q26.1.1

Why is cysteine the only L amino acid with an R configuration at the alpha carbon?

Q26.1.2

Isoleucine has two stereogenic centers.

(a) Draw a Fischer projection of isoleucine.

(b) Draw a Fischer projection of an isoleucine diastereomer, and label each stereocenter as R or S.

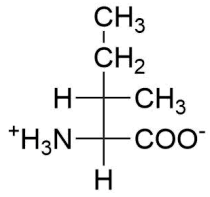
SOLUTIONS

S26.1.1

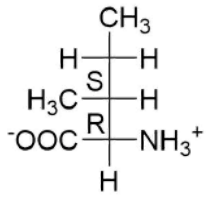
The sulfur atom in the side chain causes the side chain to have higher priority than the other substituents.

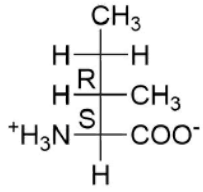
S26.1.2

(a)



(b)





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26.3: AMINO ACIDS, THE HENDERSON-HASSELBALCH EQUATION, AND ISOELECTRIC POINTS

OBJECTIVES

After completing this section, you should be able to

1. draw the predominant form of a given amino acid in a solution of known pH, given the isoelectric point of the amino acid.
2. describe, briefly, how a mixture of amino acids may be separated by paper electrophoresis.

KEY TERMS

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

- electrophoresis
- isoelectric point

Since amino acids, as well as peptides and proteins, incorporate both acidic and basic functional groups, the predominant molecular species present in an aqueous solution will depend on the pH of the solution. In order to determine the nature of the molecular and ionic species that are present in aqueous solutions at different pH's, we make use of the **Henderson-Hasselbalch Equation**, written below. Here, the pK_a represents the acidity of a specific conjugate acid function (HA). When the pH of the solution equals pK_a, the concentrations of HA and $A^{(-)}$ must be equal (log 1 = 0).

$$pK_a = pH + \log_{10} \frac{[HA]}{A^-]}$$

The titration curve for alanine in Figure 26.3.2 demonstrates this relationship. At a pH lower than 2, both the carboxylate and amine functions are protonated, so the alanine molecule has a net positive charge. At a pH greater than 10, the amine exists as a neutral base and the carboxyl as its conjugate base, so the alanine molecule has a net negative charge. At intermediate pH's the zwitterion concentration increases, and at a characteristic pH, called the **isoelectric point** (**pI**), the negatively and positively charged molecular species are present in equal concentration. This behavior is general for simple (difunctional) amino acids. Starting from a fully protonated state, the pK_a's of the acidic functions range from 1.8 to 2.4 for $-CO_2H$, and 8.8 to 9.7 for $-NH_3^{(+)}$. The isoelectric points range from 5.5 to 6.2. Titration curves show the neutralization of these acids by added base, and the change in pH during the titration.

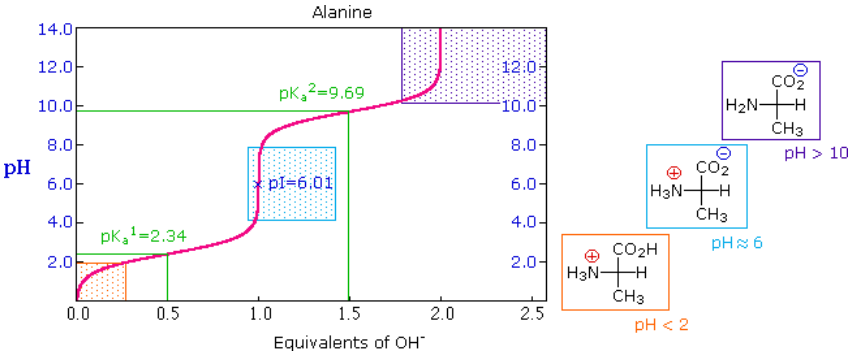


Figure 26.3.1: Titration curves for many other amino acids may be examined at a useful site provided by The University of Virginia in Charlottesville.

The distribution of charged species in a sample can be shown experimentally by observing the movement of solute molecules in an electric field, using the technique of **electrophoresis** (Figure 26.3.2). For such experiments an ionic buffer solution is incorporated in a solid matrix layer, composed of paper or a crosslinked gelatin-like substance. A small amount of the amino acid, peptide or protein sample is placed near the center of the matrix strip and an electric potential is applied at the ends of the strip, as shown in the following diagram. The solid structure of the matrix retards the diffusion of the solute molecules, which will remain where they are inserted, unless acted upon by the electrostatic potential.

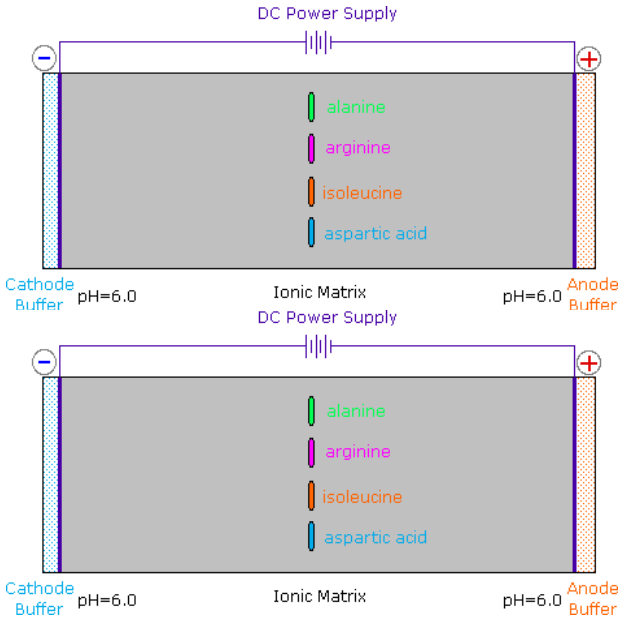
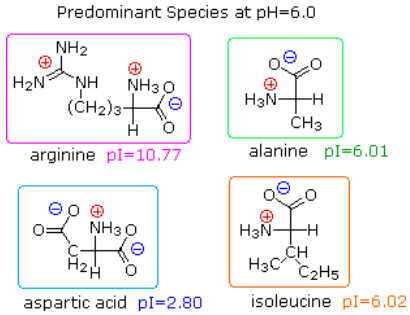


Figure 26.3.2: In the example shown here, four different amino acids are examined simultaneously in a pH 6.00 buffered medium. To see the result of this experiment, click on the illustration. Note that the colors in the display are only a convenient reference, since these amino acids are colorless.

At pH 6.00 alanine and isoleucine exist on average as neutral zwitterionic molecules, and are not influenced by the electric field. Arginine is a basic amino acid. Both base functions exist as "onium" conjugate acids in the pH 6.00 matrix. The solute molecules of arginine therefore carry an excess positive charge, and they move toward the cathode. The two carboxyl functions in aspartic acid are both ionized at pH 6.00, and the negatively charged solute molecules move toward the anode in the electric field. Structures for all these species are shown to the right of the display.



It should be clear that the result of this experiment is critically dependent on the pH of the matrix buffer. If we were to repeat the electrophoresis of these compounds at a pH of 3.80, the aspartic acid would remain at its point of origin, and the other amino acids would move toward the cathode. Ignoring differences in molecular size and shape, the arginine would move twice as fast as the alanine and isoleucine because its solute molecules on average would carry a double positive charge.

As noted earlier, the titration curves of simple amino acids display two inflection points, one due to the strongly acidic carboxyl group (pK_a^1 = 1.8 to 2.4), and the other for the less acidic ammonium function (pK_a^2 = 8.8 to 9.7). For the 2º-amino acid proline, pK_a^2 is 10.6, reflecting the greater basicity of 2º-amines.

Table 26.3.1: pKa Values of Polyfunctional Amino Acids

Amino Acid	α-CO_2H pK_a^1	α-NH_3 pK_a^2	Side Chain pK_a^3	pI
Arginine	2.1	9.0	12.5	10.8
Aspartic Acid	2.1	9.8	3.9	3.0
Cysteine	1.7	10.4	8.3	5.0
Glutamic Acid	2.2	9.7	4.3	3.2
Histidine	1.8	9.2	6.0	7.6
Lysine	2.2	9.0	10.5	9.8
Tyrosine	2.2	9.1	10.1	5.7

Some amino acids have additional acidic or basic functions in their side chains. These compounds are listed in Table 26.3.1. A third pK_a, representing the acidity or basicity of the extra function, is listed in the fourth column of the table. The pI's of these amino acids (last

column) are often very different from those noted above for the simpler members. As expected, such compounds display three inflection points in their titration curves, illustrated by the titrations of arginine and aspartic acid (Figure\ (\PageIndex{3}\)). For each of these compounds four possible charged species are possible, one of which has no overall charge. Formulas for these species are written to the right of the titration curves, together with the pH at which each is expected to predominate. The very high pH required to remove the last acidic proton from arginine reflects the exceptionally high basicity of the guanidine moiety at the end of the side chain.

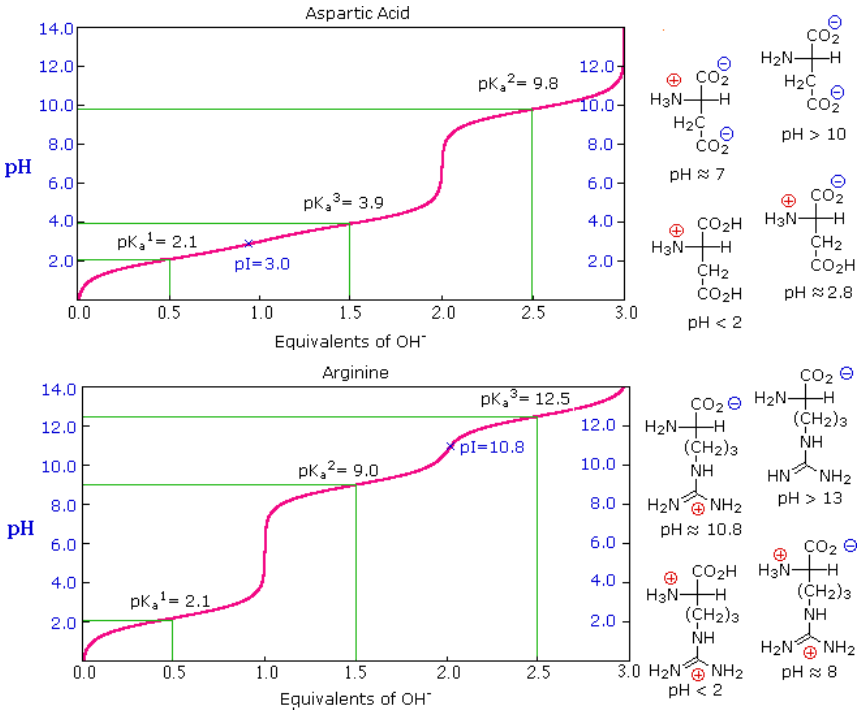


Figure 26.3.3

THE ISOELECTRIC POINT

The isoelectric point, **pI**, is the pH of an aqueous solution of an amino acid (or peptide) at which the molecules on average have no net charge. In other words, the positively charged groups are exactly balanced by the negatively charged groups. For simple amino acids such as alanine, the pI is an average of the pK_a's of the carboxyl (2.34) and ammonium (9.69) groups. Thus, the pI for alanine is calculated to be: (2.34 + 9.69)/2 = 6.02, the experimentally determined value. If additional acidic or basic groups are present as side-chain functions, the pI is the average of the pK_a's of the two most similar acids. To assist in determining similarity we define two classes of acids. The first consists of acids that are neutral in their protonated form (e.g. CO_2H & SH). The second includes acids that are positively charged in their protonated state (e.g. $-NH_3^+$). In the case of aspartic acid, the similar acids are the alpha-carboxyl function (pK_a = 2.1) and the side-chain carboxyl function (pK_a = 3.9), so pI = (2.1 + 3.9)/2 = 3.0. For arginine, the similar acids are the guanidinium species on the side-chain (pK_a = 12.5) and the alpha-ammonium function (pK_a = 9.0), so the calculated pI = (12.5 + 9.0)/2 = 10.75

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26.4: SYNTHESIS OF AMINO ACIDS

OBJECTIVES

After completing this section, you should be able to

1. outline, by means of equations, how a racemic mixture of given amino acid can be prepared from a carboxylic acid using reactions you studied earlier in the course.
2. a. outline, by means of equations, the preparation of a given amino acid by the amidomalonate synthesis.
   b. identify the amino acid formed from using a given alkyl halide in an amidomalonate synthesis.
   c. identify the alkyl halide needed to produce a given amino acid by the amidomalonate synthesis.
3. describe, by means of equations, how an α-keto acid can be transformed to an amino acid by reductive amination.
4. a. describe a general method for resolving a racemic mixture of a given amino acid.
   b. provide a brief example of how a biological method may be employed to resolve a racemic mixture of a given amino acid.
   c. show the enantioselective preparation of an amino acid from the corresponding *Z* enamido acid.

KEY TERMS

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

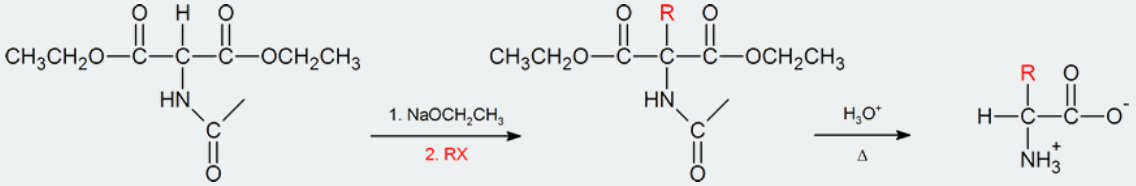
- amidomalonate synthesis
- enantioselective synthesis
- racemic mixture

STUDY NOTES

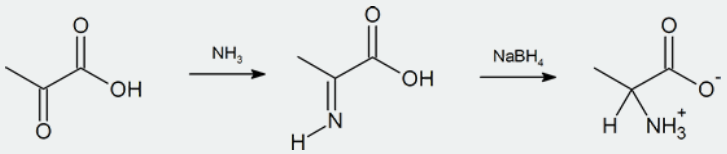
Do not be alarmed by the number of methods to synthesize amino acids described in this section.You have seen many of these reactions in previous sections and should already be familiar with the approaches discussed here.

To fulfill the requirements of Objective 1, review the Hell-Volhard-Zelinskii reaction (Section 22.4) and the Gabriel phthalimide synthesis (Section 24.6).

The **amidomalonate synthesis** is a simple variation of the malonic ester synthesis (Section 22.7). A base abstracts a proton from the alpha carbon, which is then alkylated with an alkyl halide. Then both the hydrolysis of the esters and the amide protecting group under aqueous acidic conditions generates the α-amino acid.

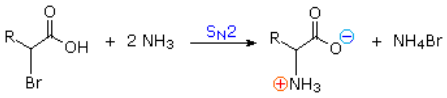


Another method of getting to the α-amino acid is by **reductive amination** of the α-keto acid which you have also previously encountered (Section 24.6).

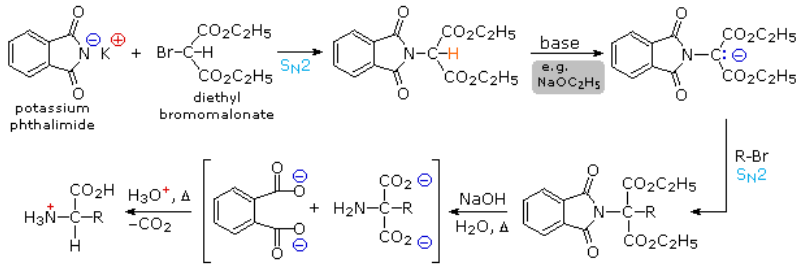


SYNTHESIS OF A-AMINO ACIDS

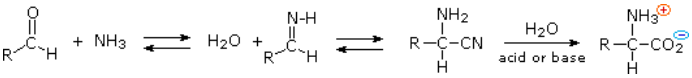
1) Amination of alpha-bromocarboxylic acids, illustrated by the following equation, provides a straightforward method for preparing alpha-aminocarboxylic acids. The bromoacids, in turn, are conveniently prepared from carboxylic acids by reaction with Br_2 + PCl_3. Although this direct approach gave mediocre results when used to prepare simple amines from alkyl halides, it is more effective for making amino acids, thanks to the reduced nucleophilicity of the nitrogen atom in the product. Nevertheless, more complex procedures that give good yields of pure compounds are often chosen for amino acid synthesis.



2) By modifying the nitrogen as a phthalimide salt, the propensity of amines to undergo multiple substitutions is removed, and a single clean substitution reaction of 1º- and many 2º-alkylhalides takes place. This procedure, known as the Gabriel synthesis, can be used to advantage in aminating bromomalonic esters, as shown in the upper equation of the following scheme. Since the phthalimide substituted malonic ester has an acidic hydrogen (colored orange), activated by the two ester groups, this intermediate may be converted to an ambident anion and alkylated. Finally, base catalyzed hydrolysis of the phthalimide moiety and the esters, followed by acidification and thermal decarboxylation, produces an amino acid and phthalic acid (not shown).

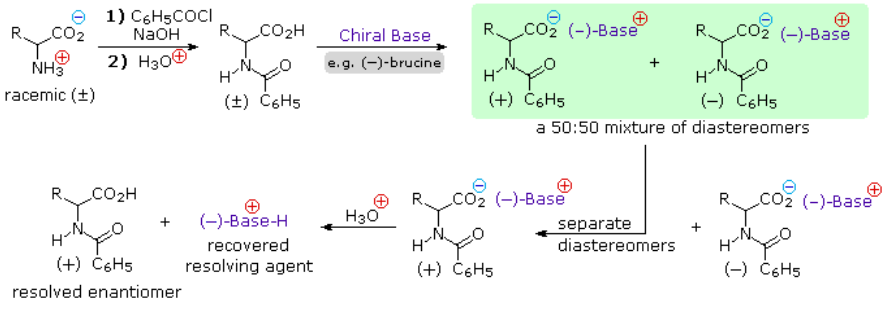


3) An elegant procedure, known as the **Strecker synthesis**, assembles an alpha-amino acid from ammonia (the amine precursor), cyanide (the carboxyl precursor), and an aldehyde. This reaction (shown below) is essentially an imino analog of cyanohydrin formation. The alpha-amino nitrile formed in this way can then be hydrolyzed to an amino acid by either acid or base catalysis.



4) Resolution The three synthetic procedures described above, and many others that can be conceived, give racemic amino acid products. If pure **L** or **D** enantiomers are desired, it is necessary to resolve these racemic mixtures. A common method of resolving racemates is by diastereomeric salt formation with a pure chiral acid or base. This is illustrated for a generic amino acid in the following diagram. Be careful to distinguish charge symbols, shown in colored circles, from optical rotation signs, shown in parenthesis.

In the initial display, the carboxylic acid function contributes to diastereomeric salt formation. The racemic amino acid is first converted to a benzamide derivative to remove the basic character of the amino group. Next, an ammonium salt is formed by combining the carboxylic acid with an optically pure amine, such as brucine (a relative of strychnine). The structure of this amine is not shown, because it is not a critical factor in the logical progression of steps. Since the amino acid moiety is racemic and the base is a single enantiomer (levorotatory in this example), an equimolar mixture of diastereomeric salts is formed (drawn in the green shaded box). Diastereomers may be separated by crystallization, chromatography or other physical manipulation, and in this way one of the isomers may be isolated for further treatment, in this illustration it is the (+):(-) diastereomer. Finally the salt is broken by acid treatment, giving the resolved (+)-amino acid derivative together with the recovered resolving agent (the optically active amine). Of course, the same procedure could be used to obtain the (-)-enantiomer of the amino acid.



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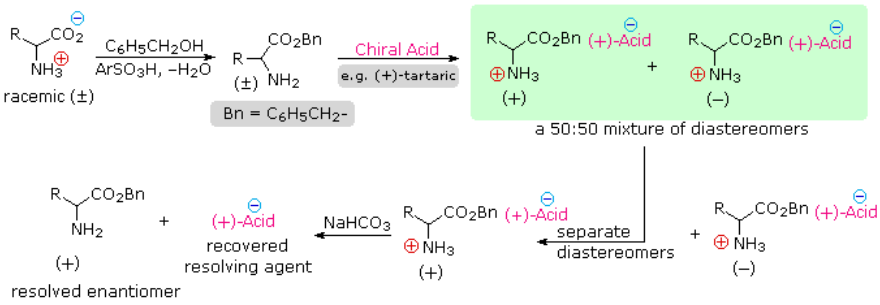

Since amino acids are amphoteric, resolution could also be achieved by using the basic character of the amine function. For this approach we would need an enantiomerically pure chiral acid such as tartaric acid to use as the resolving agent. This alternative resolution strategy will be illustrated. Note that the carboxylic acid function is first esterified, so that it will not compete with the resolving acid.

Resolution of aminoacid derivatives may also be achieved by enzymatic discrimination in the hydrolysis of amides. For example, an aminoacylase enzyme from pig kidneys cleaves an amide derivative of a natural L-amino acid much faster than it does the D-enantiomer. If the racemic mixture of amides shown in the green shaded box above is treated with this enzyme, the L-enantiomer (whatever its rotation) will be rapidly converted to its free zwitterionic form, whereas the D-enantiomer will remain largely unchanged. Here, the diastereomeric species are transition states rather than isolable intermediates. This separation of enantiomers, based on very different rates of reaction, is called **kinetic resolution**.

ENANTIOSELECTIVE SYNTHESIS

Till now all of the synthetic routes to α-amino acids we have discussed yield a racemic mixture. Once produced one could resolve the mixture to obtain pure **L** or **D** enantiomers. However, enantioselective synthetic methods to produce pure compounds directly are being developed. For instance, several catalysts are now available for reduction of C=C to expose enantiopure amino acids. A good example is the industrial synthesis of L-DOPA, a drug used in the treatment of Parkinson's disease. W.S. Knowles shared the 2001 Nobel Price with R. Noyori and K.B. Sharpless for their contributions in the area of asymmetric catalytic reductions**.** Knowles developed several chiral phosphine–metal catalysts for asymmetric reductions. The rhodium(I) catalyst shown, which is complexed by large organic ligands, facilitates production of almost pure L-DOPA.

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26.5: PEPTIDES AND PROTEINS

OBJECTIVES

After completing this section, you should be able to

1. a. show, by means of a diagram, how two different amino acid residues can be combined to give two different dipeptides.
   b. draw the structure of a relatively simple peptide, given its full or abbreviated name and the structures of the appropriate amino acids.
   c. draw, or name, the six possible isomeric tripeptides that can be formed by combining three different amino acid residues (amino acid units) of given structure.
2. account for the fact that there is restricted rotation about the C$\ce{-}$N bonds in peptides.
3. illustrate the formation of a disulfide linkage between two cysteine residues, and show how such bonds can link together two separate peptide chains or can provide a bridge between two cysteine residues present in a single peptide molecule.

KEY TERMS

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

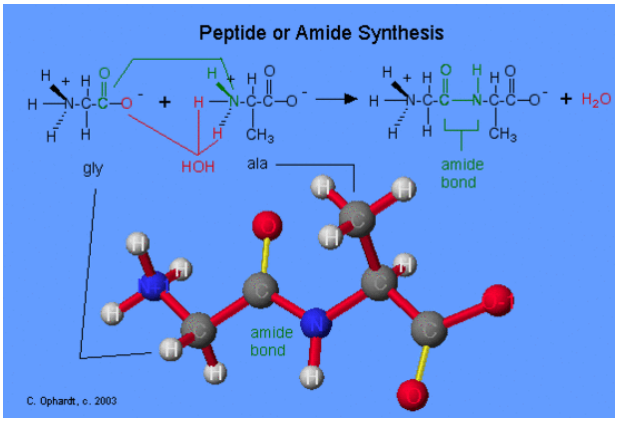
- C-terminal amino acid
- N-terminal amino acid
- peptides
- residues

STUDY NOTES

If necessary, review the discussion of the delocalization of the nitrogen lone-pair electrons in amides that was presented in Section 24.3. Similarly, you may wish to refer back to Section 18.8 to review the interconversion of thiols and disulfides.

PEPTIDE BOND FORMATION OR AMIDE SYNTHESIS

The formation of peptides is nothing more than the application of the **amide synthesis reaction**. By convention, the amide bond in the peptides should be made in the order that the amino acids are written. The amine end (N terminal) of an amino acid is always on the left, while the acid end (C terminal) is on the right. The reaction of glycine with alanine to form the dipeptide glyclalanine is written as shown in the graphic on the left. Oxygen (red) from the acid and hydrogens (red) on the amine form a water molecule. The carboxyl oxygen (green) and the amine nitrogen (green) join to form the amide bond.



If the order of listing the amino acids is reversed, a different dipeptide is formed such as alaninylglycine.

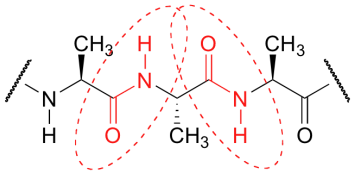
EXERCISE 26.5.1

Write the reactions for:

a. ala + gly ---> Answer graphic
b. phe + ser ----> Answer graphic

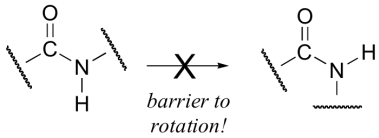
RESONANCE CONTRIBUTORS FOR THE PEPTIDE BONDS

A consideration of resonance contributors is crucial to any discussion of the amide functional group. One of the most important examples of amide groups in nature is the ‘peptide bond’ that links amino acids to form polypeptides and proteins.

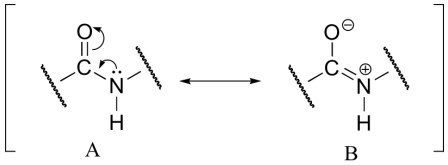


peptide bonds in a polypeptide

Critical to the structure of proteins is the fact that, although it is conventionally drawn as a single bond, the C-N bond in a peptide linkage has a significant barrier to rotation, almost as if it were a double bond.



This, along with the observation that the bonding around the peptide nitrogen has trigonal planar geometry, strongly suggests that the nitrogen is sp^2-hybridized. An important resonance contributor has a C=N double bond and a C-O single bond, with a separation of charge between the oxygen and the nitrogen.



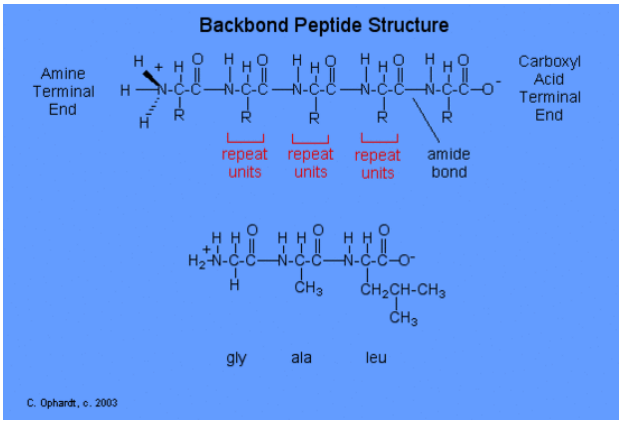
Although B is a minor contributor due to the separation of charges, it is still very relevant in terms of peptide and protein structure – our proteins would simply not fold up properly if there was free rotation about the peptide C-N bond.

BACKBONE PEPTIDE OR PROTEIN STRUCTURE

The structure of a peptide can be written fairly easily without showing the complete amide synthesis reaction by learning the structure of the "backbone" for peptides and proteins.

The peptide backbone consists of repeating units of "N-H 2, CH, C double bond O; N-H 2, CH, C double bond O; etc. See the graphic on the left .

After the backbone is written, go back and write the specific structure for the side chains as represented by the "R" as gly-ala-leu for this example. The amine end (N terminal) of an amino acid is always on the left (gly), while the acid end (C terminal) is on the right (leu).



? EXERCISE 26.5.2

Write the tripeptide structure for val-ser-cys. First write the "backbone" and then add the specific side chains.

Solution

https://chem.libretexts.org/@go/page/473993

 Answer graphic

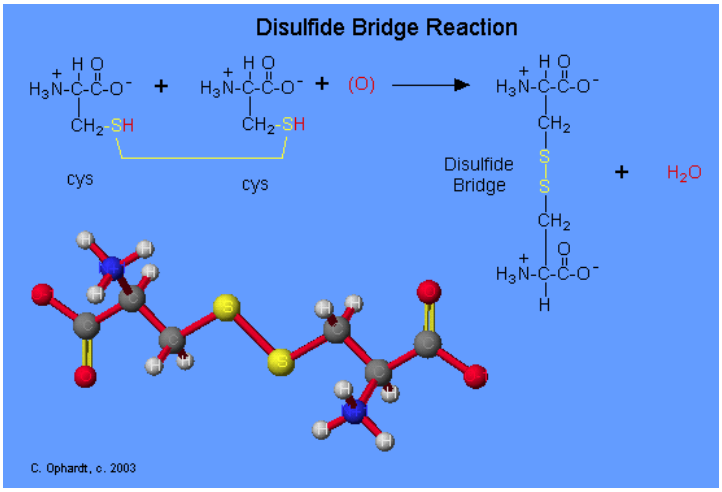
QUES. Write the structure for the tripeptide:

2 a) glu-cys-gly ---> Answer graphic

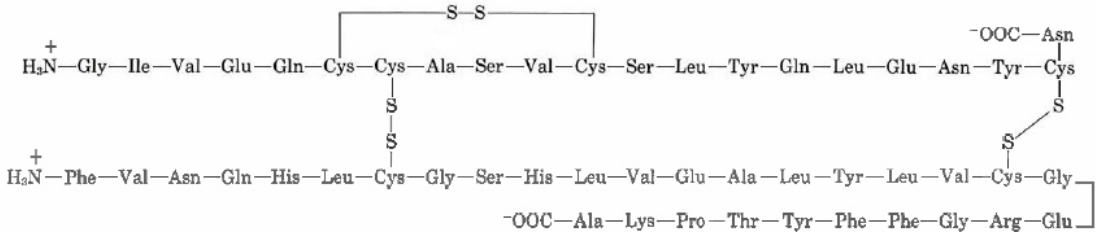
2 b) phe-tyr-asn ---> Answer graphic

DISULFIDE BRIDGES AND OXIDATION-REDUCTION

The amino acid cysteine undergoes oxidation and reduction reactions involving the -SH (sulfhydryl group). The oxidation of two sulfhydryl groups results in the formation of a **disulfide bond** by the removal of two hydrogens. The **oxidation** of two cysteine amino acids is shown in the graphic. An unspecified oxidizing agent (O) provides an oxygen which reacts with the hydrogen (red) on the -SH group to form water. The sulfurs (yellow) join to make the **disulfide bridge**. This is an important bond to recognize in protein tertiary structure. The reduction of a disulfide bond is the opposite reaction which again leads to two separate cysteine molecules. Remember that reduction is the addition of hydrogen.



Cysteine residues in the the peptide chain can form a loop buy forming the disulfide bond (—S—S—), while cysteine residues in different peptide chains can actually link what were otherwise separate chains. Insulin was the first protein whose amino acid sequence was determined. This pioneering work, completed in 1953 after some 10 years of effort, earned a Nobel Prize for British biochemist Frederick Sanger (born 1918). He found the primary structure to comprise of two chains linked by two cysteine disulfide bridges. Also note the first peptide chain possesses an internal loop.



Insulin

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26.6: AMINO ACID ANALYSIS OF PEPTIDES

OBJECTIVES

After completing this section, you should be able to describe, briefly, how the identity and amounts of each amino acid residue present in a peptide of unknown structure may be determined.

KEY TERMS

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

- amino acid analyzer

STUDY NOTES

You need not memorize the reaction between ninhydrin and an α-amino acid.

ION-EXCHANGE CHROMATOGRAPHY

When a protein is to be analysed, it is first heated with acid to hydrolyse all the peptide bonds. When such a mixture of amino acids is to be purified and estimated quantitatively, ion-exchange chromatography is the technique of choice. Fully automated amino acid analyzers are now available, which are equipped with a solvent pump to deliver the required buffer(s) in a programmed manner. There is a column, filled with Dowex 50 resin (Fig 26.5.1). This solid support is made up of polymeric beads. Chemically speaking they are polymers bearing arylsulfonic acid groups. The cation exchange resin helps in the separation of amino acids. In a typical run (Fig 26.5.2), the eluent is a buffer. The pH value of the buffer could be varied as step elution or as gradient elution. The chromatogram shown in Fig 26.5.2 is a chromatogram run with gradient elution technique, using **ninhydrin** as the post column treatment. The detector is a UV detector scanning the wavelengths 570 nm and 440 nm.

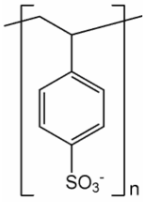


Fig 26.5.1: A Cation Rasin like Dowex 50 is a polymeric bead bearing aryl sulfonic acid groups

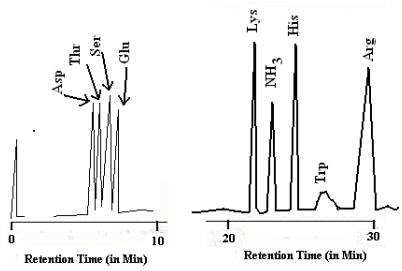
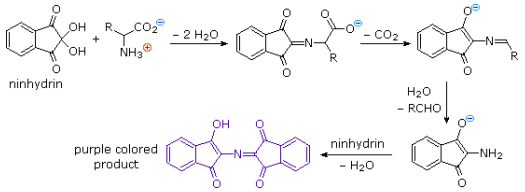


Fig 26.5.2: Some typical chromatograms from an amino acid analyzer

THE NINHYDRIN REACTION

Alpha-amino acids show reactivity at their the carboxylic acid and amine sites typical of those functional groups. In addition to these common reactions of amines and carboxylic acids, common alpha-amino acids, except proline, undergo a unique reaction with the triketohydrindene hydrate known as ninhydrin. Among the products of this unusual reaction (shown on the left below) is a purple colored imino derivative, which provides as a useful color test for these amino acids, most of which are colorless. A common application of the ninhydrin test is the visualization of amino acids in paper chromatography. As shown in the graphic on the right, samples of amino acids or mixtures thereof are applied along a line near the bottom of a rectangular sheet of paper (the baseline). The bottom edge of the paper is immersed in an aqueous buffer, and this liquid climbs slowly toward the top edge. As the solvent front passes the sample spots, the compounds in each sample are carried along at a rate which is characteristic of their functionality, size and interaction with the cellulose matrix of the paper. Some compounds move rapidly up the paper, while others may scarcely move at all. The ratio of the distance a compound moves from the baseline to the distance of the solvent front from the baseline is defined as the retardation (or retention) factor R_f. Different amino acids usually have different R_f's under suitable conditions. In the example on the right, the three sample compounds (1, 2 & 3) have respective R_f values of 0.54, 0.36 & 0.78.



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26.7: THE EDMAN DEGRADATION

OBJECTIVES

After completing this section, you should be able to

1. describe how an Edman degradation is used to determine the sequence of the amino acid residues in peptides containing up to 20 such residues.
2. describe, briefly, how the procedure is modified to deal with peptides and proteins containing more than 20 amino acid residues.
3. write a detailed mechanism for the Edman degradation.
4. determine the structure of a peptide, given a list of the fragments that are produced by a partial acid hydrolysis.
5. determine the structure of a peptide, given a list of the fragments that are produced when the peptide is cleaved by a specific enzyme and the details of the types of bonds cleaved by that enzyme.
6. predict the fragments that would be produced when a peptide of known structure is cleaved by a specific enzyme, given sufficient information about the types of bonds that are cleaved by the enzyme in question.

KEY TERMS

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

- Edman degradation

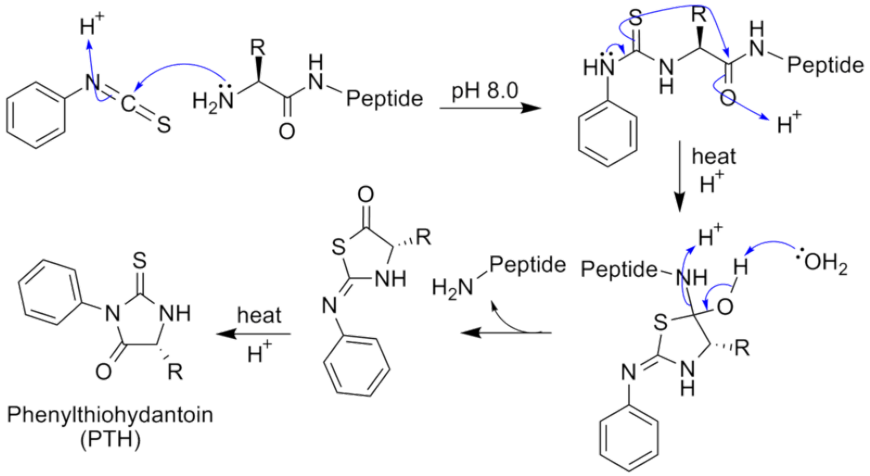
STUDY NOTES

The reagent used in the Edman degradation is phenyl isothiocyanate. You may find it helpful to review the relationship between cyanates, isocyanates, thiocyanates and isothiocyanates.

R–O–C≡N	cyanate (such compounds do not exist)
R–N=C=O	isocyanate
R–S–C≡N	thiocyanate
R–N=C=S	isothiocyanate

You need not memorize the specific peptide bonds that are broken by the enzymes trypsin and chymotrypsin.

Edman degradation is the process of purifying protein by sequentially removing one residue at a time from the amino end of a peptide. To solve the problem of damaging the protein by hydrolyzing conditions, Pehr Edman created a new way of labeling and cleaving the peptide. Edman thought of a way of removing only one residue at a time, which did not damage the overall sequencing. This was done by adding Phenyl isothiocyanate, which creates a phenylthiocarbamoyl derivative with the N-terminal. The N-terminal is then cleaved under less harsh acidic conditions, creating a cyclic compound of phenylthiohydantoin PTH-amino acid. This does not damage the protein and leaves two constituents of the peptide. This method can be repeated for the rest of the residues, separating one residue at a time.



Edman degradation is very useful because it does not damage the protein. This allows sequencing of the protein to be done in less time. Edman sequencing is done best if the composition of the amino acid is known. As we saw in Section 26.5, to determine the composition of the amino acid, the peptide must be hydrolyzed. This can be done by denaturing the protein and heating it and adding HCl for a long time. This causes the individual amino acids to be separated, and they can be separated by ion exchange chromatography. They are then dyed with ninhydrin and the amount of amino acid can be determined by the amount of optical absorbance. This way, the composition but not the sequence can be determined

SEQUENCING LARGER PROTEINS

Larger proteins cannot be sequenced by the Edman sequencing because of the less than perfect efficiency of the method. A strategy called divide and conquer successfully cleaves the larger protein into smaller, practical amino acids. This is done by using a certain chemical or enzyme which can cleave the protein at specific amino acid residues. The separated peptides can be isolated by chromatography. Then they can be sequenced using the Edman method, because of their smaller size.

In order to put together all the sequences of the different peptides, a method of overlapping peptides is used. The strategy of divide and conquer followed by Edman sequencing is used again a second time, but using a different enzyme or chemical to cleave it into different residues. This allows two different sets of amino acid sequences of the same protein, but at different points. By comparing these two sequences and examining for any overlap between the two, the sequence can be known for the original protein.

For example, trypsin can be used on the initial peptide to cleave it at the carboxyl side of arginine and lysine residues. Using trypsin to cleave the protein and sequencing them individually with Edman degradation will yield many different individual results. Although the sequence of each individual cleaved amino acid segment is known, the order is scrambled. Chymotrypsin, which cleaves on the carboxyl side of aromatic and other bulky nonpolar residues, can be used. The sequence of these segments overlap with those of the trypsin. They can be overlapped to find the original sequence of the initial protein. However, this method is limited in analyzing larger sized proteins (more than 100 amino acids) because of secondary hydrogen bond interference. Other weak intermolecular bonding such as hydrophobic interactions cannot be properly predicted. Only the linear sequence of a protein can be properly predicted assuming the sequence is small enough.

CONTRIBUTORS AND ATTRIBUTIONS

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26.8: PEPTIDE SYNTHESIS

OBJECTIVES

After completing this section, you should be able to

1. describe why it is necessary to protect certain amino and carboxyl groups during the synthesis of a peptide.
2. describe, using appropriate equations, how carboxyl groups are protected by ester formation and amino groups are protected by the formation of their *tert*-butoxycarbonyl amide derivatives.
3. write a detailed mechanism for the formation of a peptide link between an amino acid with a protected amino group and an amino acid with a protected carboxyl group using dicyclohexylcarbodiimide.
4. outline the five steps required in order to form a dipeptide from two given amino acids.

In order to synthesize a peptide from its component amino acids, two obstacles must be overcome. The first of these is statistical in nature, and is illustrated by considering the dipeptide Ala-Gly as a proposed target. If we ignore the chemistry involved, a mixture of equal molar amounts of alanine and glycine would generate four different dipeptides. These are: **Ala-Ala, Gly-Gly, Ala-Gly & Gly-Ala**. In the case of tripeptides, the number of possible products from these two amino acids rises to eight. Clearly, some kind of selectivity must be exercised if complex mixtures are to be avoided.

The second difficulty arises from the fact that carboxylic acids and 1º or 2º-amines do not form amide bonds on mixing, but will generally react by proton transfer to give salts (the intermolecular equivalent of zwitterion formation).

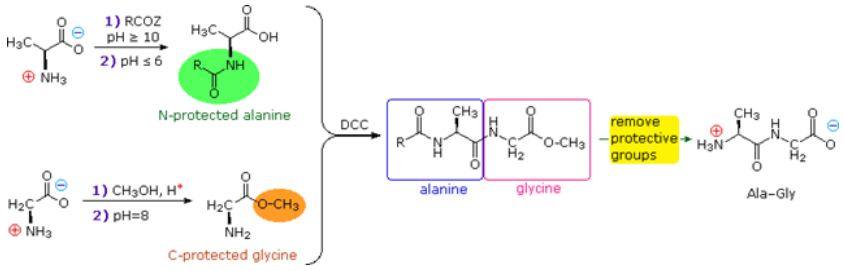
From the perspective of an organic chemist, peptide synthesis requires selective acylation of a free amine. To accomplish the desired amide bond formation, we must first deactivate all extraneous amine functions so they do not compete for the acylation reagent. Then we must selectively activate the designated carboxyl function so that it will acylate the one remaining free amine. Fortunately, chemical reactions that permit us to accomplish these selections are well known.

First, the basicity and nucleophilicity of amines are substantially reduced by amide formation. Consequently, the acylation of amino acids by treatment with acyl chlorides or anhydrides at pH > 10, as described earlier, serves to protect their amino groups from further reaction.

Second, acyl halide or anhydride-like activation of a specific carboxyl reactant must occur as a prelude to peptide (amide) bond formation. This is possible, provided competing reactions involving other carboxyl functions that might be present are precluded by preliminary ester formation. Remember, esters are weaker acylating reagents than either anhydrides or acyl halides, as noted earlier.

Finally, dicyclohexylcarbodiimide (DCC) effects the dehydration of a carboxylic acid and amine mixture to the corresponding amide under relatively mild conditions. The structure of this reagent and the mechanism of its action have been described. Its application to peptide synthesis will become apparent in the following discussion.

The strategy for peptide synthesis, as outlined here, should now be apparent. The following example shows a selective synthesis of the dipeptide Ala-Gly.



An important issue remains to be addressed. Since the N-protective group is an amide, removal of this function might require conditions that would also cleave the just formed peptide bond. Furthermore, the harsh conditions often required for amide hydrolysis might cause extensive racemization of the amino acids in the resulting peptide. This problem strikes at the heart of our strategy, so it is important to give careful thought to the design of specific N-protective groups. In particular, three qualities are desired:

1. The protective amide should be easy to attach to amino acids.
2. The protected amino group should not react under peptide forming conditions.
3. The protective amide group should be easy to remove under mild conditions.

A number of protective groups that satisfy these conditions have been devised; and two of the most widely used, **carbobenzoxy** (Cbz) and **t-butoxycarbonyl** (BOC or t-BOC), are described here.

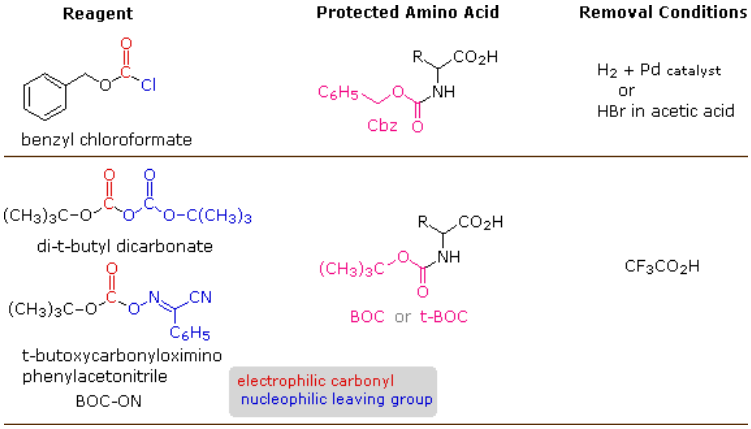


Figure_3.png" />

The reagents for introducing these N-protective groups are the acyl chlorides or anhydrides shown in the left portion of the above diagram. Reaction with a free amine function of an amino acid occurs rapidly to give the "protected" amino acid derivative shown in the center. This can then be used to form a peptide (amide) bond to a second amino acid. Once the desired peptide bond is created the protective group can be removed under relatively mild non-hydrolytic conditions. Equations showing the protective group removal will be displayed above by are shown above. Cleavage of the reactive benzyl or tert-butyl groups generates a common carbamic acid intermediate (HOCO-NHR) which spontaneously loses carbon dioxide, giving the corresponding amine. If the methyl ester at the C-terminus is left in place, this sequence of reactions may be repeated, using a different N-protected amino acid as the acylating reagent. Removal of the protective groups would then yield a specific tripeptide, determined by the nature of the reactants and order of the reactions.

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26.9: THE MERRIFIELD SOLID-PHASE TECHNIQUE

OBJECTIVES

After completing this section, you should be able to describe, briefly, the Merrifield solid-phase technique for the synthesis of polypeptides.

KEY TERMS

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

- solid-phase method (solid-phase synthesis)

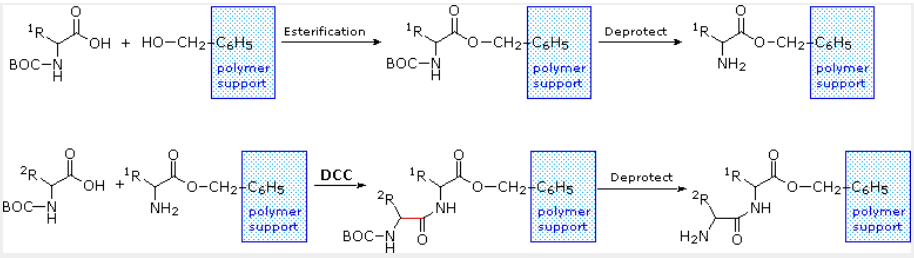
STUDY NOTES

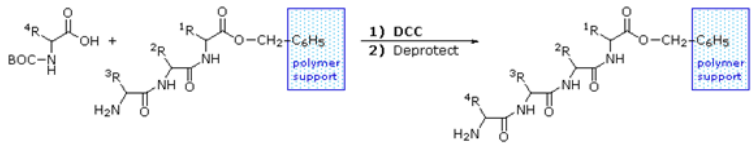
The solid-phase used in this method is a polymer support. You will not be examined on the details of the Merrifield solid-phase method; however, you should be prepared to write a couple of paragraphs describing this important process.

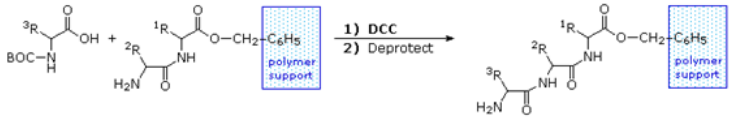
For his work on the synthesis of peptides, Bruce Merrifield was awarded the 1984 Nobel Prize in chemistry.

The synthesis of a peptide of significant length (e.g. ten residues) by this approach requires many steps, and the product must be carefully purified after each step to prevent unwanted cross-reactions. To facilitate the tedious and time consuming purifications, and reduce the material losses that occur in handling, a clever modification of this strategy has been developed. This procedure, known as the **Merrifield Synthesis** after its inventor R. Bruce Merrifield, involves attaching the C-terminus of the peptide chain to a polymeric solid, usually having the form of very small beads. Separation and purification is simply accomplished by filtering and washing the beads with appropriate solvents. The reagents for the next peptide bond addition are then added, and the purification steps repeated. The entire process can be automated, and peptide synthesis machines based on the Merrifield approach are commercially available. A series of equations illustrating the Merrifield synthesis may be viewed below. The final step, in which the completed peptide is released from the polymer support, is a simple benzyl ester cleavage. This is not shown in the display.

The Merrifield Peptide Synthesis







Two or more moderately sized peptides can be joined together by selective peptide bond formation, provided side-chain functions are protected and do not interfere. In this manner good sized peptides and small proteins may be synthesized in the laboratory. However, even if chemists assemble the primary structure of a natural protein in this or any other fashion, it may not immediately adopt its native secondary,

tertiary and quaternary structure. Many factors, such as pH, temperature and inorganic ion concentration influence the conformational coiling of peptide chains. Indeed, scientists are still trying to understand how and why these higher structures are established in living organisms.

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26.10: PROTEIN STRUCTURE

OBJECTIVES

After completing this section, you should be able to

1. discuss, with reference to a suitable example (either given or of your own choice), the structure of proteins, paying particular attention to distinguishing between the primary, secondary, tertiary and quaternary structure.
2. describe the α-helical secondary structure displayed by many proteins.
3. describe the β-pleated-sheet structure displayed by many proteins.

KEY TERMS

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

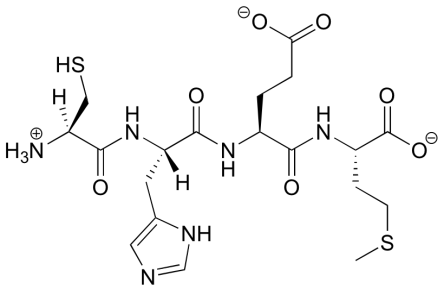
- α helix
- β pleated sheet
- primary structure
- quaternary structure
- secondary structure
- tertiary structure

STUDY NOTES

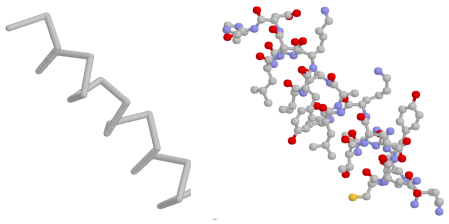
Note that in a diagram of the α-helical structure of a protein, the C-terminal of the protein is at the bottom of the diagram and the N-terminal is at the top. In an α helix, such as the one shown in Figure 26.9.1, the bulky R groups are all found on the outside of the helix, where they have the most room.

THE FOUR LEVELS OF PROTEIN STRUCTURE

Protein structure can be discussed at four distinct levels. A protein's **primary structure** is two-dimensional - simply the sequence of amino acids in the peptide chain. Below is a Lewis structure of a short segment of a protein with the sequence CHEM (cysteine - histidine - glutamate - methionine)

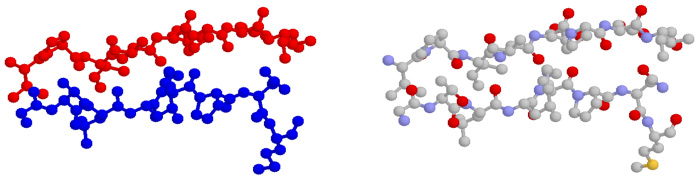


Secondary structure is three-dimensional, but is a local phenomenon, confined to a relatively short stretch of amino acids. For the most part, there are three important elements of secondary structure: helices, beta-sheets, and loops. In a helix, the main chain of the protein adopts the shape of a clockwise spiral staircase, and the side chains point out laterally.



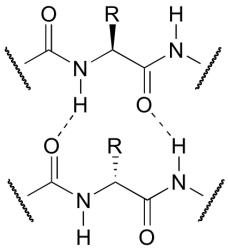
main chain view main chain + side chain

In a beta-sheet (or beta-strand) structure, two sections of protein chain are aligned side-by-side in an extended conformation. The figure below shows two different views of the same beta-sheet: in the left-side view, the two regions of protein chain are differentiated by color.



Loops are relatively disordered segments of protein chain, but often assume a very ordered structure when in contact with a second protein or a smaller organic compound.

Both helix and the beta-sheet structures are held together by very specific hydrogen-bonding interactions between the amide nitrogen on one amino acid and the carbonyl oxygen on another. The hydrogen bonding pattern in a section of a beta-strand is shown below.



hydrogen bonding in a β-strand

Secondary structure refers to the shape of a folding protein due exclusively to hydrogen bonding between its backbone amide and carbonyl groups. Secondary structure does not include bonding between the R-groups of amino acids, hydrophobic interactions, or other interactions associated with tertiary structure. The two most commonly encountered secondary structures of a polypeptide chain are α-helices and beta-pleated sheets. These structures are the first major steps in the folding of a polypeptide chain, and they establish important topological motifs that dictate subsequent tertiary structure and the ultimate function of the protein.

A-HELICES

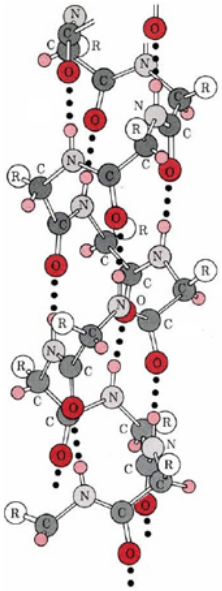


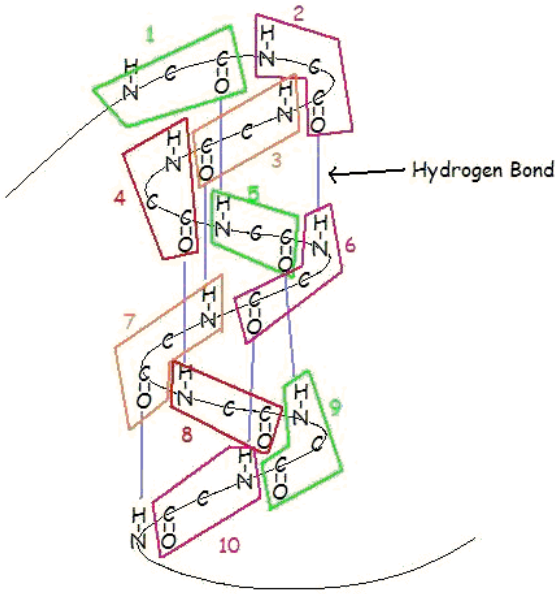
Figure 26.9.1 *Ball-and-stick model of the α helix. Hydrogen bonds are shown as dotted bonds. Note that R groups extend almost perpendicular from the axis.*

An α-helix is a right-handed coil of amino-acid residues on a polypeptide chain, typically ranging between 4 and 40 residues. This coil is held together by hydrogen bonds between the oxygen of C=O on top coil and the hydrogen of N-H on the bottom coil. Such a hydrogen bond is formed exactly every 4 amino acid residues, and every complete turn of the helix is only 3.6 amino acid residues. This regular pattern gives the α-helix very definite features with regards to the thickness of the coil and the length of each complete turn along the helix axis.

The structural integrity of an α-helix is in part dependent on correct steric configuration. Amino acids whose R-groups are too large (tryptophan, tyrosine) or too small (glycine) destabilize α-helices. Proline also destabilizes α-helices because of its irregular geometry; its R-

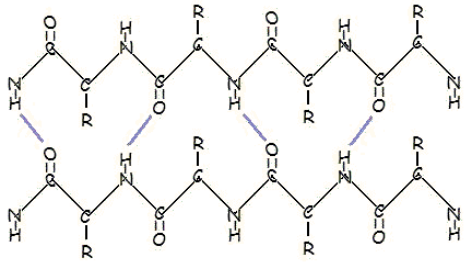
group bonds back to the nitrogen of the amide group, which causes steric hindrance. In addition, the lack of a hydrogen on Proline's nitrogen prevents it from participating in hydrogen bonding.

Another factor affecting α-helix stability is the total dipole moment of the entire helix due to individual dipoles of the C=O groups involved in hydrogen bonding. Stable α-helices typically end with a charged amino acid to neutralize the dipole moment.



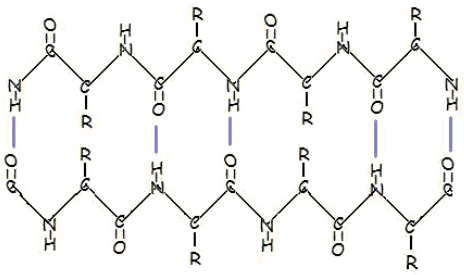
BETA-PLEATED SHEETS

This structure occurs when two (or more, e.g. ψ-loop) segments of a polypeptide chain overlap one another and form a row of hydrogen bonds with each other. This can happen in a parallel arrangement:



Parallel

Or in anti-parallel arrangement:



Anti-Parallel

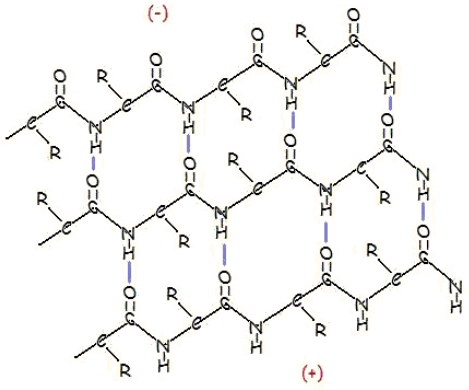
Parallel and anti-parallel arrangement is the direct consequence of the directionality of the polypeptide chain. In anti-parallel arrangement, the C-terminus end of one segment is on the same side as the N-terminus end of the other segment. In parallel arrangement, the C-terminus end and the N-terminus end are on the same sides for both segments. The "pleat" occurs because of the alternating planes of the peptide bonds between amino acids; the aligned amino and carbonyl group of each opposite segment alternate their orientation from facing towards each other to facing opposite directions.

The parallel arrangement is less stable because the geometry of the individual amino acid molecules forces the hydrogen bonds to occur at an angle, making them longer and thus weaker. Contrarily, in the anti-parallel arrangement the hydrogen bonds are aligned directly opposite each other, making for stronger and more stable bonds.

Commonly, an anti-parallel beta-pleated sheet forms when a polypeptide chain sharply reverses direction. This can occur in the presence of two consecutive proline residues, which create an angled kink in the polypeptide chain and bend it back upon itself. This is not necessary for distant segments of a polypeptide chain to form beta-pleated sheets, but for proximal segments it is a definite requirement. For short distances, the two segments of a beta-pleated sheet are separated by 4+2n amino acid residues, with 4 being the minimum number of residues.

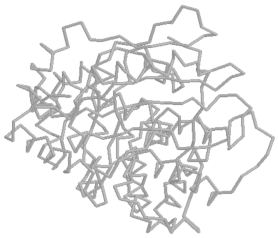
A-PLEATED SHEETS

A similar structure to the beta-pleated sheet is the α-pleated sheet. This structure is energetically less favorable than the beta-pleated sheet, and is fairly uncommon in proteins. An α-pleated sheet is characterized by the alignment of its carbonyl and amino groups; the carbonyl groups are all aligned in one direction, while all the N-H groups are aligned in the opposite direction. The polarization of the amino and carbonyl groups results in a net dipole moment on the α-pleated sheet. The carbonyl side acquires a net negative charge, and the amino side acquires a net positive charge.

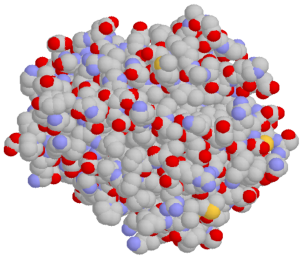


Alpha-Pleated Sheet

A protein's **tertiary structure** is the shape in which the entire protein chain folds together in three-dimensional space, and it is this level of structure that provides protein scientists with the most information about a protein's specific function.

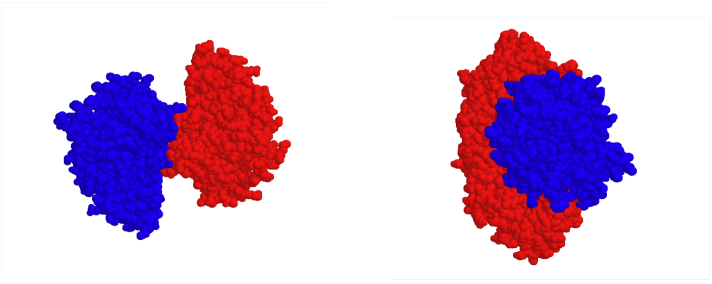


folded protein chain
(main chain view)



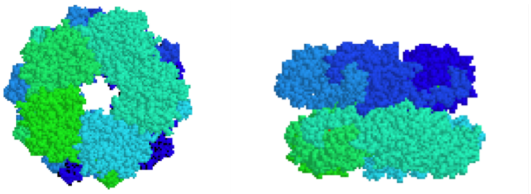
folded protein chain
('space-filling' view)

While a protein's secondary and tertiary structure is defined by how the protein chain folds together, **quaternary structure** is defined by how two or more folded protein chains come together to form a 'superstructure'. Many proteins consist of only one protein chain, or **subunit**, and thus have no quaternary structure. Many other proteins consist of two identical subunits (these are called homodimers) or two non-identical subunits (these are called heterodimers).



a homodimer a heterodimer

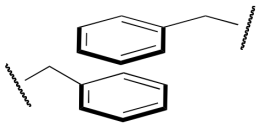
Quaternary structures can be quite elaborate: below we see a protein whose quaternary structure is defined by ten identical subunits arranged in two five-membered rings, forming what can be visualized as a 'double donut' shape (this is fructose 1,6-bisphosphate aldolase):



top view side view

THE MOLECULAR FORCES THAT HOLD PROTEINS TOGETHER

The question of exactly how a protein 'finds' its specific folded structure out of the vast number of possible folding patterns is still an active area of research. What *is* known, however, is that the forces that cause a protein to fold properly and to remain folded are the same basic noncovalent forces that we talked about in chapter 2: ion-ion, ion-dipole, dipole-dipole, hydrogen bonding, and hydrophobic (van der Waals) interactions. One interesting type of hydrophobic interaction is called 'aromatic stacking', and occurs when two or more planar aromatic rings on the side chains of phenylalanine, tryptophan, or tyrosine stack together like plates, thus maximizing surface area contact.



Hydrogen bonding networks are extensive within proteins, with both side chain and main chain atoms participating. Ionic interactions often play a role in protein structure, especially on the protein surface, as negatively charged residues such as aspartate interact with positively-charged groups on lysine or arginine.

One of the most important ideas to understand regarding tertiary structure is that *a protein, when properly folded, is polar on the surface and nonpolar in the interior*. It is the protein's surface that is in contact with water, and therefore the surface must be hydrophilic in order for the whole structure to be soluble. If you examine a three dimensional protein structure you will see many charged side chains (e.g. lysine, arginine, aspartate, glutamate) and hydrogen-bonding side chains (e.g. serine, threonine, glutamine, asparagine) exposed on the surface, in direct contact with water. Inside the protein, out of contact with the surrounding water, there tend to be many more hydrophobic residues such as alanine, valine, phenylalanine, etc. If a protein chain is caused to come unfolded (through exposure to heat, for example, or extremes of pH), it will usually lose its solubility and form solid precipitates, as the hydrophobic residues from the interior come into contact with water. You can see this phenomenon for yourself if you pour a little bit of vinegar (acetic acid) into milk. The solid clumps that form in the milk are proteins that have come unfolded due to the sudden acidification, and precipitated out of solution.

In recent years, scientists have become increasing interested in the proteins of so-called 'thermophilic' (heat-loving) microorganisms that thrive in hot water environments such as geothermal hot springs. While the proteins in most organisms (including humans) will rapidly unfold and precipitate out of solution when put in hot water, the proteins of thermophilic microbes remain completely stable, sometimes even in water that is just below the boiling point. In fact, these proteins typically only gain full biological activity when in appropriately hot water - at room-temperature they act is if they are 'frozen'. Is the chemical structure of these thermostable proteins somehow unique and exotic? As it turns out, the answer to this question is 'no': the overall three-dimensional structures of thermostable proteins look very much like those of 'normal' proteins. The critical difference seems to be simply that thermostable proteins have more extensive networks of noncovalent interactions, particularly ion-ion interactions on their surface, that provides them with a greater stability to heat. Interestingly, the proteins of 'psychrophilic' (cold-loving) microbes isolated from pockets of water in arctic ice show the opposite characteristic: they have far fewer ion-ion interactions, which gives them greater flexibility in cold temperatures but leads to their rapid unfolding in room temperature water.

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26.11: ENZYMES AND COENZYMES

OBJECTIVES

After completing this section, you should be able to

1. describe the catalytic role of an enzyme in a biochemical reaction.
2. give an example of one fat-soluble and one water-soluble vitamin.

KEY TERMS

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

- coenzyme
- cofactor
- enzyme
- substrate
- vitamin

STUDY NOTES

You should have a general knowledge of the function of enzymes, but you need not memorize specific names or the classification system.

A **catalyst** is any substance that increases the *rate* or speed of a chemical reaction without being changed or consumed in the reaction. **Enzymes** are biological catalysts, and nearly all of them are proteins. In addition, enzymes are highly specific in their action; that is, each enzyme catalyzes only one type of reaction in only one compound or a group of structurally related compounds. The compound or compounds on which an enzyme acts are known as its **substrates**. Enzymes are classified by reaction type into six categories show in Table 26.11.1.

Table 26.11.1: ***Classes of Enzymes***

Class	Type of Reaction Catalyzed	Examples
oxidoreductases	oxidation-reduction reactions	Dehydrogenases catalyze oxidation-reduction reactions involving hydrogen and reductases catalyze reactions in which a substrate is reduced.
transferases	transfer reactions of groups, such as methyl, amino, and acetyl	Transaminases catalyze the transfer of amino group, and kinases catalyze the transfer of a phosphate group.
hydrolases	hydrolysis reactions	Lipases catalyze the hydrolysis of lipids, and proteases catalyze the hydrolysis of proteins
lyases	reactions in which groups are removed without hydrolysis or addition of groups to a double bond	Decarboxylases catalyze the removal of carboxyl groups.
isomerases	reactions in which a compound is converted to its isomer	Isomerases may catalyze the conversion of an aldose to a ketose, and mutases catalyze reactions in which a functional group is transferred from one atom in a substrate to another.
ligases	reactions in which new bonds are formed between carbon and another atom; energy is required	Synthetases catalyze reactions in which two smaller molecules are linked to form a larger one.

Enzyme-catalyzed reactions occur in at least two steps. In the first step, an enzyme molecule (E) and the substrate molecule or molecules (S) collide and react to form an intermediate compound called the *enzyme-substrate* (E–S) *complex* (Equation 26.11.1). This step is reversible because the complex can break apart into the original substrate or substrates and the free enzyme. Once the E–S complex forms, the enzyme is able to catalyze the formation of product (P), which is then released from the enzyme surface (Equation 26.11.2):

$$S + E \rightleftharpoons E\text{–}S \tag{26.11.1}$$

$$E\text{–}S \rightarrow P + E \tag{26.11.2}$$

Hydrogen bonding and other electrostatic interactions hold the enzyme and substrate together in the complex. The structural features or functional groups on the enzyme that participate in these interactions are located in a cleft or pocket on the enzyme surface. This pocket, where the enzyme combines with the substrate and transforms the substrate to product is called the active site of the enzyme (Figure 26.11.1).

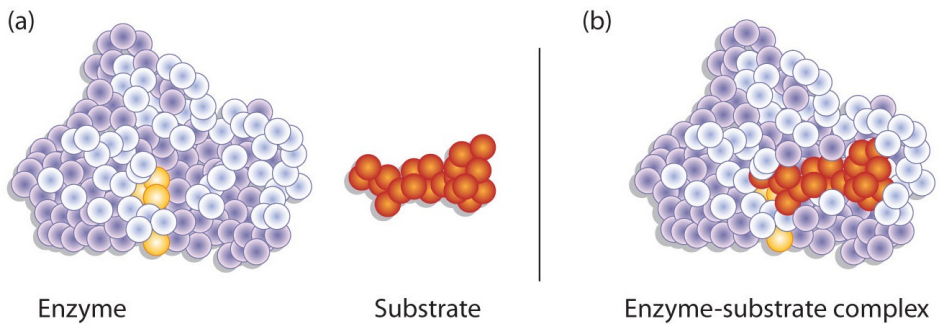


***Figure* 26.11.1 :** *Substrate Binding to the Active Site of an Enzyme. The enzyme dihydrofolate reductase is shown with one of its substrates: $NADP^+$ (a) unbound and (b) bound. The $NADP^+$ (shown in red) binds to a pocket that is complementary to it in shape and ionic properties.*

The active site possesses a unique conformation (including correctly positioned bonding groups) that is complementary to the structure of the substrate, so that the enzyme and substrate molecules fit together in much the same manner as a key fits into a tumbler lock. In fact, an early model describing the formation of the enzyme-substrate complex was called the lock-and-key model (Figure 26.11.2). This model portrayed the enzyme as conformationally rigid and able to bond only to substrates that exactly fit the active site.

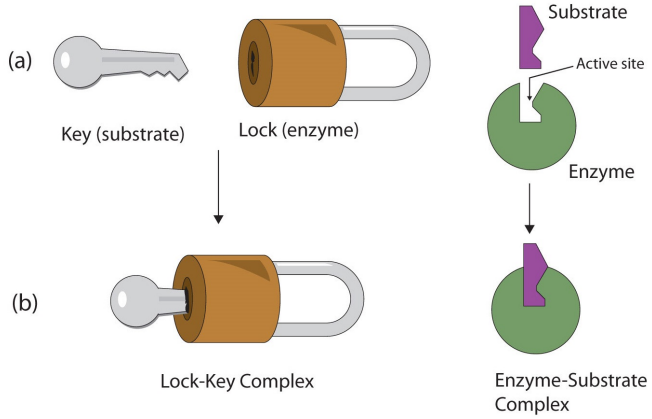


Figure 26.11.2 The Lock-and-Key Model of Enzyme Action. (a) Because the substrate and the active site of the enzyme have complementary structures and bonding groups, they fit together as a key fits a lock. (b) The catalytic reaction occurs while the two are bonded together in the enzyme-substrate complex.

Working out the precise three-dimensional structures of numerous enzymes has enabled chemists to refine the original lock-and-key model of enzyme actions. They discovered that the binding of a substrate often leads to a large conformational change in the enzyme, as well as to changes in the structure of the substrate or substrates. The current theory, known as theinduced-fit model, says that enzymes can undergo a change in conformation when they bind substrate molecules, and the active site has a shape complementary to that of the substrate only after the substrate is bound, as shown for hexokinase in Figure 26.11.3. After catalysis, the enzyme resumes its original structure.

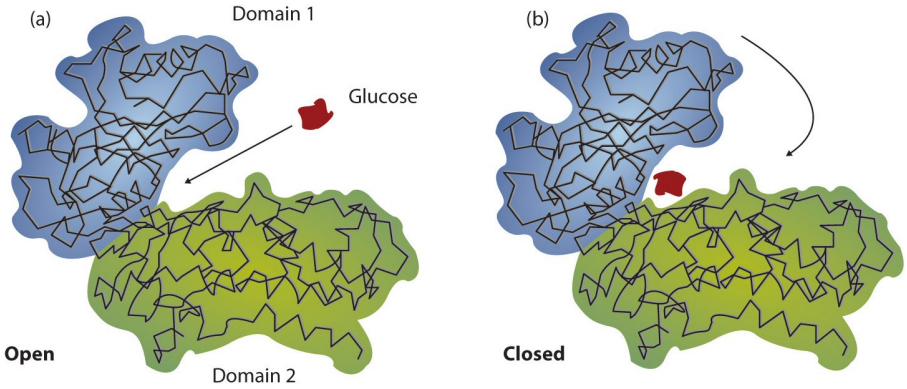


Figure 26.11.3 The Induced-Fit Model of Enzyme Action. (a) The enzyme hexokinase without its substrate (glucose, shown in red) is bound to the active site. (b) The enzyme conformation changes dramatically when the substrate binds to it, resulting in additional interactions between hexokinase and glucose.

The structural changes that occur when an enzyme and a substrate join together bring specific parts of a substrate into alignment with specific parts of the enzyme's active site. Amino acid side chains in or near the binding site can then act as acid or base catalysts, provide binding sites for the transfer of functional groups from one substrate to another or aid in the rearrangement of a substrate. The participating amino acids, which are usually widely separated in the primary sequence of the protein, are brought close together in the active site as a result of the folding and bending of the polypeptide chain or chains when the protein acquires its tertiary and quaternary structure. Binding to enzymes brings reactants close to each other and aligns them properly, which has the same effect as increasing the concentration of the reacting compounds.

✔ EXAMPLE 26.11.1

a. What type of interaction would occur between an OH group present on a substrate molecule and a functional group in the active site of an enzyme?
b. Suggest an amino acid whose side chain might be in the active site of an enzyme and form the type of interaction you just identified.

Solution

a. An OH group would most likely engage in hydrogen bonding with an appropriate functional group present in the active site of an enzyme.
b. Several amino acid side chains would be able to engage in hydrogen bonding with an OH group. One example would be asparagine, which has an amide functional group.

? EXERCISE 26.11.1

a. What type of interaction would occur between an COO^- group present on a substrate molecule and a functional group in the active site of an enzyme?
b. Suggest an amino acid whose side chain might be in the active site of an enzyme and form the type of interaction you just identified.

ENZYME COFACTORS AND VITAMINS

Many enzymes are simple proteins consisting entirely of one or more amino acid chains. Other enzymes contain a nonprotein component called a **cofactor** that is necessary for the enzyme's proper functioning. There are two types of cofactors: inorganic ions [e.g., zinc or Cu(I) ions] and organic molecules known as coenzymes. Most **coenzymes** are vitamins or are derived from vitamins.

Vitamins are organic compounds that are essential in very small (trace) amounts for the maintenance of normal metabolism. They generally cannot be synthesized at adequate levels by the body and must be obtained from the diet. The absence or shortage of a vitamin may result in a vitamin-deficiency disease. In the first half of the 20th century, a major focus of biochemistry was the identification, isolation, and characterization of vitamins. Despite accumulating evidence that people needed more than just carbohydrates, fats, and proteins in their diets for normal growth and health, it was not until the early 1900s that research established the need for trace nutrients in the diet.

Table 26.11.2 Fat-Soluble Vitamins and Physiological Functions

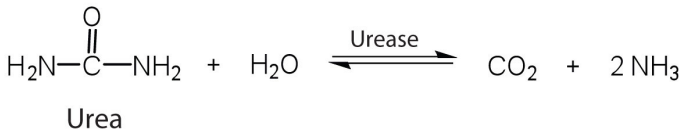
Vitamin	Physiological Function	Effect of Deficiency
vitamin A (retinol)	formation of vision pigments; differentiation of epithelial cells	night blindness; continued deficiency leads to total blindness
vitamin D (cholecalciferol)	increases the body's ability to absorb calcium and phosphorus	osteomalacia (softening of the bones); known as rickets in children
vitamin E (tocopherol)	fat-soluble antioxidant	damage to cell membranes
vitamin K (phylloquinone)	formation of prothrombin, a key enzyme in the blood-clotting process	increases the time required for blood to clot

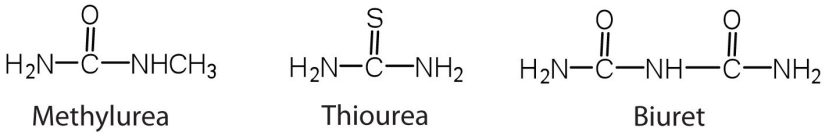
Because organisms differ in their synthetic abilities, a substance that is a vitamin for one species may not be so for another. Over the past 100 years, scientists have identified and isolated 13 vitamins required in the human diet and have divided them into two broad categories: the *fat-soluble vitamins* (Table 26.11.2), which include vitamins A, D, E, and K, and the *water-soluble vitamins*, which are the B complex vitamins and vitamin C (Table 26.11.3). All fat-soluble vitamins contain a high proportion of hydrocarbon structural components. There are one or two oxygen atoms present, but the compounds as a whole are nonpolar. In contrast, water-soluble vitamins contain large numbers of electronegative oxygen and nitrogen atoms, which can engage in hydrogen bonding with water. Most water-soluble vitamins act as coenzymes or are required for the synthesis of coenzymes. The fat-soluble vitamins are important for a variety of physiological functions.

Table 26.11.3 ***Water-Soluble Vitamins and Physiological Functions***

Vitamin	Coenzyme	Coenzyme Function	Deficiency Disease
vitamin B_1 (thiamine)	thiamine pyrophosphate	decarboxylation reactions	beri-beri
vitamin B_2 (riboflavin)	flavin mononucleotide or flavin adenine dinucleotide	oxidation-reduction reactions involving two hydrogen atoms	—
vitamin B_3 (niacin)	nicotinamide adenine dinucleotide or nicotinamide adenine dinucleotide phosphate	oxidation-reduction reactions involving the hydride ion (H^-)	pellagra
vitamin B_6 (pyridoxine)	pyridoxal phosphate	variety of reactions including the transfer of amino groups	—
vitamin B_{12} (cyanocobalamin)	methylcobalamin or deoxyadenoxylcobalamin	intramolecular rearrangement reactions	pernicious anemia
biotin	biotin	carboxylation reactions	—
folic acid	tetrahydrofolate	carrier of one-carbon units such as the formyl group	anemia
pantothenic Acid	coenzyme A	carrier of acyl groups	—
vitamin C (ascorbic acid)	none	antioxidant; formation of collagen, a protein found in tendons, ligaments, and bone	scurvy

One characteristic that distinguishes an enzyme from all other types of catalysts is its *substrate specificity*. An inorganic acid such as sulfuric acid can be used to increase the reaction rates of many different reactions, such as the hydrolysis of disaccharides, polysaccharides, lipids, and proteins, with complete impartiality. In contrast, enzymes are much more specific. Some enzymes act on a single substrate, while other enzymes act on any of a group of related molecules containing a similar functional group or chemical bond. Some enzymes even distinguish between D- and L-stereoisomers, binding one stereoisomer but not the other. Urease, for example, is an enzyme that catalyzes the hydrolysis of a single substrate—urea—but not the closely related compounds methyl urea, thiourea, or biuret. The enzyme carboxypeptidase, on the other hand, is far less specific. It catalyzes the removal of nearly any amino acid from the carboxyl end of any peptide or protein.





Enzyme specificity results from the uniqueness of the active site in each different enzyme because of the identity, charge, and spatial orientation of the functional groups located there. It regulates cell chemistry so that the proper reactions occur in the proper place at the proper time. Clearly, it is crucial to the proper functioning of the living cell.

CONCEPT REVIEW EXERCISES

1. Distinguish between the lock-and-key model and induced-fit model of enzyme action.
2. Which enzyme has greater specificity—urease or carboxypeptidase? Explain.

ANSWERS

1. The lock-and-key model portrays an enzyme as conformationally rigid and able to bond only to substrates that exactly fit the active site. The induced fit model portrays the enzyme structure as more flexible and is complementary to the substrate only after the substrate is bound.
2. Urease has the greater specificity because it can bind only to a single substrate. Carboxypeptidase, on the other hand, can catalyze the removal of nearly any amino acid from the carboxyl end of a peptide or protein.

TAKEAWAYS

- A substrate binds to a specific region on an enzyme known as the active site, where the substrate can be converted to product.
- The substrate binds to the enzyme primarily through hydrogen bonding and other electrostatic interactions.
- The induced-fit model says that an enzyme can undergo a conformational change when binding a substrate.
- Enzymes exhibit varying degrees of substrate specificity.

EXERCISES

1. What type of interaction would occur between each group present on a substrate molecule and a functional group of the active site in an enzyme?
   a. COOH
   b. NH_3^+
   c. OH
   d. $CH(CH_3)_2$
2. What type of interaction would occur between each group present on a substrate molecule and a functional group of the active site in an enzyme?
   a. SH
   b. NH_2
   c. C_6H_5
   d. COO^-
3. For each functional group in Exercise 1, suggest an amino acid whose side chain might be in the active site of an enzyme and form the type of interaction you identified.
4. For each functional group in Exercise 2, suggest an amino acid whose side chain might be in the active site of an enzyme and form the type of interaction you identified.

ANSWERS

1. a. hydrogen bonding
   b. ionic bonding
   c. hydrogen bonding
   d. dispersion forces
3. a. The amino acid has a polar side chain capable of engaging in hydrogen bonding; serine (answers will vary).
   b. The amino acid has a negatively charged side chain; aspartic acid (answers will vary).
   c. The amino acid has a polar side chain capable of engaging in hydrogen bonding; asparagine (answers will vary).
   d. The amino acid has a nonpolar side chain; isoleucine (answers will vary).

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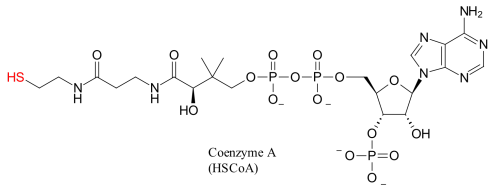
26.12: HOW DO ENZYMES WORK? CITRATE SYNTHASE

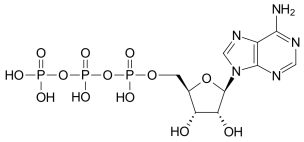
OBJECTIVES

After completing this section, you should be able to

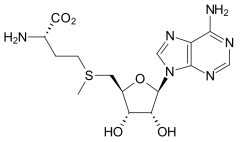
1. describe and explain the general function of an enzyme like citrate synthase in a reaction.
2. identify the structures of ten common coenzymes.



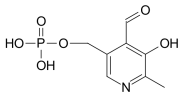
Coenzyme A
(HSCoA)



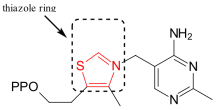
adenosine triphosphate
(ATP)



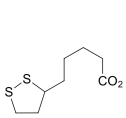
S-adenosyl methionine
(SAM)



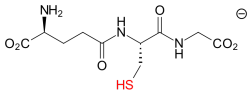
pyridoxal phosphate
(PLP)



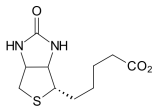
thiamine diphosphate
TPP)



lipoate



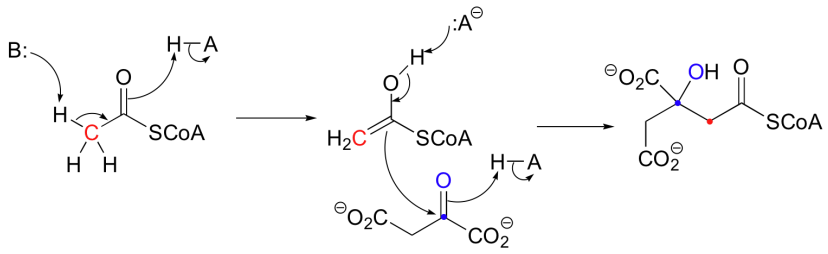
Glutathione
(GSH)



biotin

OXALOACETATE TO CITRATE CATALYZED BY CITRATE SYNTHASE

Citrate synthase is a protein with 433 amino acids with various functional groups that can react with substrates. This enzyme catalyzes oxaloacetate to eventually produce citrate as part of the citric acid (Krebs) cycle. In the first step of the citric acid (Krebs) cycle, acetyl CoA condenses with oxaloacetate to form (S)-citryl CoA. The carboxylate group of an aspartic acid (B:) on citrate synthase removes the acidic alpha proton on acetyl CoA, while a histidine site (H-A) donates a proton to form the enol. Then a second histidine site (H-A) protonates the carbonyl oxygen of oxaloacetate, while the carbon of the carbonyl is attacked by the enol. Simultaeously, that first histidine ($:A^-$) deprotonates the acetyl CoA enol. (S)-citryl CoA is generated.



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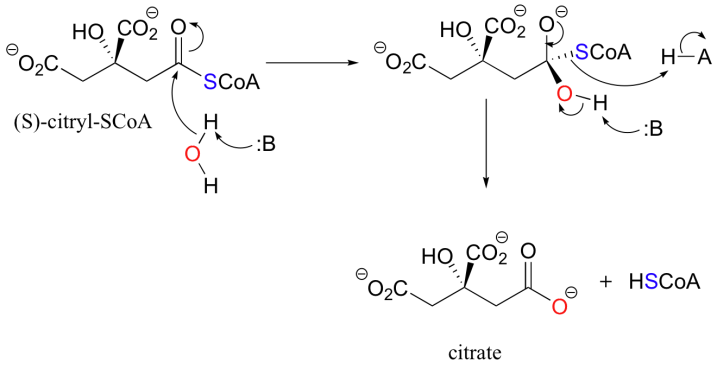
The acyl group of a thioester of (S)-citryl CoA can be transferred to a water molecule in a hydrolysis reaction to converting (S)-citryl CoA to citrate. Again histidine sites on citrate synthase are an integral part of the mechanism and assist with removal and addition of protons.



citrate

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CHAPTER OVERVIEW

27: LIPIDS

LEARNING OBJECTIVES

- When you have completed Chapter 27, you should be able to
- fulfill all of the detailed objectives listed under each individual section.
- distinguish among fats and oils, phospholipids, prostaglandins, terpenes and steroids, and be familiar with the sources and biological roles of these substances.
- define, and use in context, the key terms introduced in this chapter.

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27.0: INTRODUCTION TO LIPIDS

OBJECTIVES

After completing this section, you should be able to identify fats and steroids as being examples of lipids.

KEY TERMS

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

- lipid

Lipids are naturally occurring organic compounds that can be extracted from cells and tissues using nonpolar solvents. Although many lipids have complex structures, their chemistry can often be understood quite readily by applying the basic concepts you have studied in previous chapters. We begin the chapter with a study of fats and oils, and explain the different origins of these structurally similar substances. A discussion of soaps follows, as soap is obtained by the reaction of a fat with sodium hydroxide. Phospholipids are substances whose structures are somewhat similar to those of fats, except that the former contain a phosphate group. Prostaglandins are lipids that play important roles in biological systems and are of great interest to those involved in the medical and pharmaceutical professions. Terpenoids form a series of compounds whose structural similarity can be seen through the application of the isoprene rule. The chapter concludes with a discussion of steroids, with particular attention being paid to the stereochemistry of these substances.

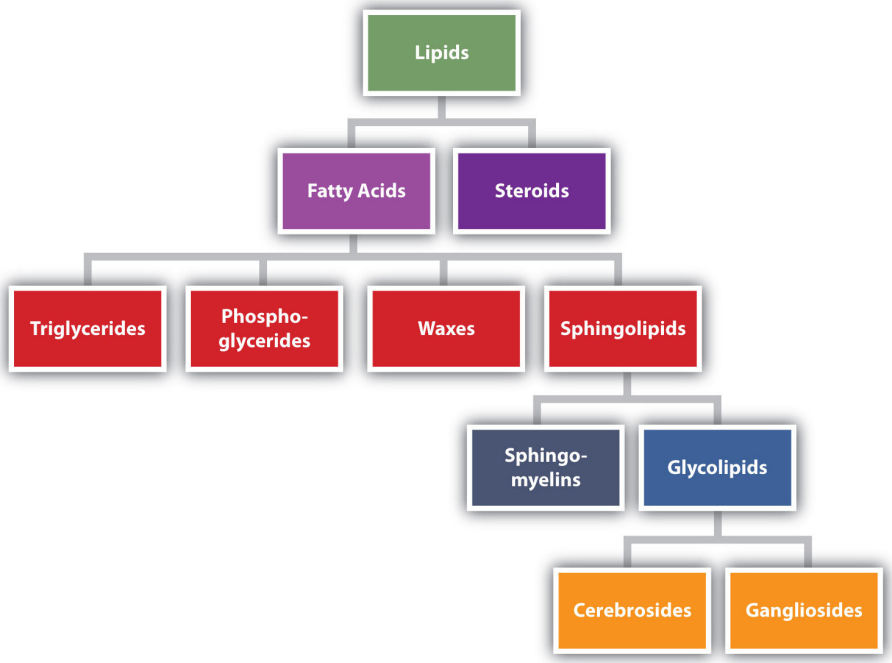

Figure 27.0.1: Lipid Organization Based on Structural Relationships

Lipids are not defined by the presence of specific functional groups, as carbohydrates are, but by a physical property—solubility. Compounds isolated from body tissues are classified as lipids if they are more soluble in organic solvents, such as dichloromethane, than in water. By this criterion, the lipid category includes not only **fats and oils**, which are esters of the trihydroxy alcohol glycerol and fatty acids, but also compounds that incorporate functional groups derived from phosphoric acid, carbohydrates, or amino alcohols, as well as **steroid compounds** such as cholesterol. Figure 27.0.1 presents one scheme for classifying the various kinds of lipids.

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27.1: WAXES, FATS, AND OILS

OBJECTIVES

After completing this section, you should be able to

1. identify waxes as being mixtures of long-chain esters, and write the general structure for such compounds.
2. identify fats and oils as being triacylglycerols, and write a general structure for such compounds.
3. relate the physical properties of animal fats and vegetable oils to their structures.
4. predict the behaviour of a given fat or oil when it is subjected to some of the more common reactions discussed in previous units; examples would include hydrolysis, reduction and ozonolysis.

KEY TERMS

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

- fat
- fatty acids
- triacylglycerols

STUDY NOTES

You are not expected to memorize the trivial names or formulas of the fatty acids listed in Table 27.1.1. The systematic names for these compounds are shown in the tables below.

Saturated Fatty Acids

Table 27.1.1: Systematic names of some common saturated fatty acids

Trivial Name	Systematic Name
lauric acid	dodecanoic acid
myristic acid	tetradecanoic acid
palmitic acid	hexadecanoic acid
stearic acid	octadecanoic acid
arachidic acid	eicosanoic acid

Unsaturated Fatty Acids

Table 27.1.2: Systematic names of some common unsaturated fatty acids

Trivial Name	Systematic Name
palmitoleic acid	(*Z*)-9-hexadecenoic acid
oleic acid	(*Z*)-9-octadecenoic acid
ricinoleic acid	(*Z*)-12-hydroxy-9-octadecenoic acid
linoleic acid	(*Z*,*Z*)-9,12-octadecadienoic acid
linolenic acid	(*Z*,*Z*,*Z*)-9,12,15-octadecatrienoic acid
arachidonic acid	(*Z*,*Z*,*Z*,*Z*)-5,8,11,14-eicosatetraenoic acid

The systematic names in these tables may be somewhat unfamiliar, but they are derived in exactly the same way as the names of the simpler carboxylic acids that we discussed in Chapter 20. You may wish to review the alkane names (Section 3.2) and the *E*,*Z* system (Section 7.5) to satisfy yourself that you understand how these names originate.

In many older textbooks, the term “fatty acid” is used to describe all carboxylic acids, not only those that are obtained from the hydrolysis of triacylglycerols.

Fats play an important role in human nutrition, and most people are aware of the desirability of limiting their dietary intake of saturated fats, as these compounds have been associated with heart disease. Unsaturated fats are generally considered to be much more desirable from the point of view of good health. Notice that all the fatty acids derived from naturally occurring fats have a *Z* (i.e., cis) configuration.

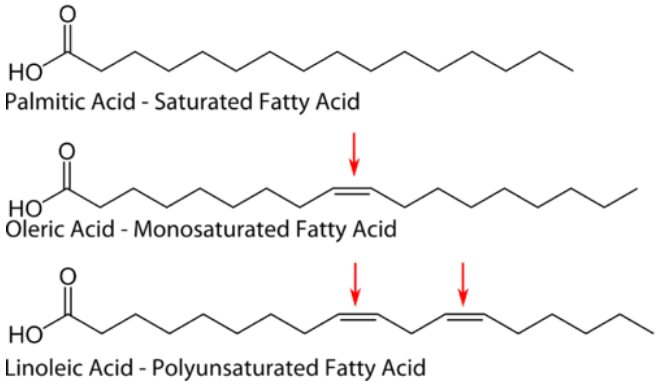
Linoleic acid is an “essential” nutrient; that is, it cannot be made by the body in sufficient quantity to meet our physiological needs, and must be obtained from food. A deficiency in linoleic acid results in skin problems and liver abnormalities. Historically, linolenic and

> arachidonic acids were also thought to be essential nutrients, but recent research suggests that they can be synthesized in the body if sufficient linoleic acid is present.

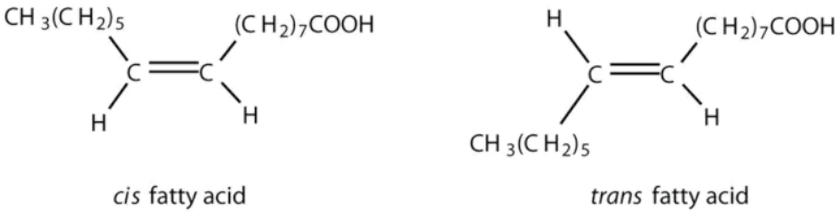
FATTY ACIDS

Fatty acids are structural components of fats, oils, and all other categories of lipids, except steroids. **Fatty acids** are long-chain carboxylic acids that have the general formula $CH_3(CH_2)_nCOOH$, where n usually ranges from 2 to 28 and is always an even number. More than 70 have been identified in nature. They are generally unbranched, and can be classified by the presence and number of carbon-to-carbon double bonds.

A **saturated fat** is a fat that consists of triglycerides whose carbon chains consist entirely of carbon-carbon single bonds. Therefore, the carbon chains are saturated with the maximum number of hydrogen atoms possible. An **unsaturated fat** is a fat that consists of triglycerides whose carbon chains contain one or more carbon-carbon double bonds. A fat with one double bond is called monounsaturated, while a fat with multiple double bonds is called polyunsaturated (see figure below).



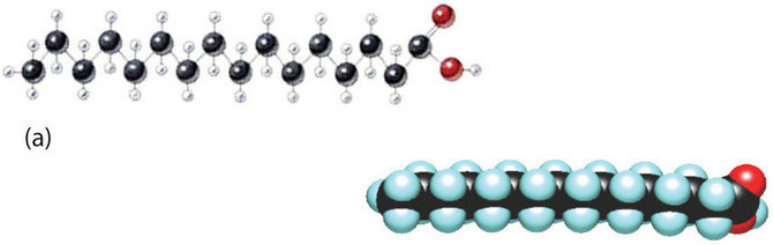
Each of the double bonds in unsaturated fatty acids can have either cis or trans stereochemistry and the type of fatty acid is further defined as a **cis fatty acid** or **trans fatty acid**. These are what are commonly referred to in food as cis or trans fats.



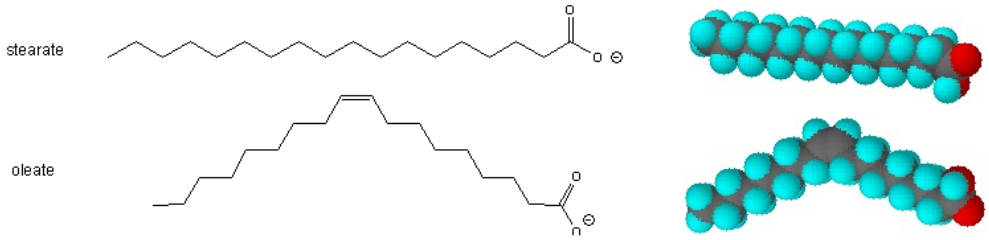
Saturated Fatty Acids		
Formula	**Common Name**	**Melting Point**
$CH_3(CH_2)_{10}CO_2H$	lauric acid	45 °C
$CH_3(CH_2)_{12}CO_2H$	myristic acid	55 °C
$CH_3(CH_2)_{14}CO_2H$	palmitic acid	63 °C
$CH_3(CH_2)_{16}CO_2H$	stearic acid	69 °C
$CH_3(CH_2)_{18}CO_2H$	arachidic acid	76 °C

Unsaturated Fatty Acids		
Formula	**Common Name**	**Melting Point**
$CH_3(CH_2)_5CH{=}CH(CH_2)_7CO_2H$	palmitoleic acid	0 °C
$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$	oleic acid	13 °C
$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$	linoleic acid	-5 °C
$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$	linolenic acid	-11 °C
$CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2CO_2H$	arachidonic acid	-49 °C

The higher melting points of the saturated fatty acids reflect the uniform rod-like shape of their molecules. Viewed as a whole, however, the saturated fatty acid molecule is relatively straight (Figure 17.1.2b). Such molecules pack closely together into a crystal lattice, maximizing the strength of dispersion forces and causing fatty acids and the fats derived from them to have relatively high melting points.

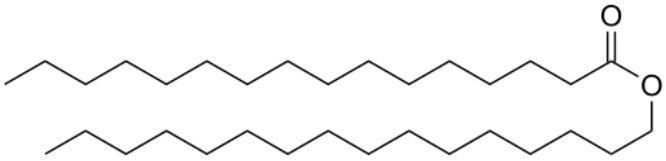


The cis-double bond(s) in the unsaturated fatty acids introduce a kink in their shape, which makes it more difficult to pack their molecules together in a stable repeating array or crystalline lattice. As a result, the intermolecular attractions of unsaturated fatty acids (and unsaturated fats) are weaker, causing these substances to have lower melting points. Most are liquids at room temperature.



WAXES

Waxes are esters of long-chain fatty acids with long-chain monohydric alcohols (one hydroxyl group). The carboxylic acid and the alcohol typically each have an even number of carbons. Cetyl palmitate is a typical wax, it is the ester of cetyl alcohol ($CH_3(CH_2)_{15}OH$) and palmitic acid ($CH_3(CH_2)_{14}COOH$). Most waxes have a similar structure.



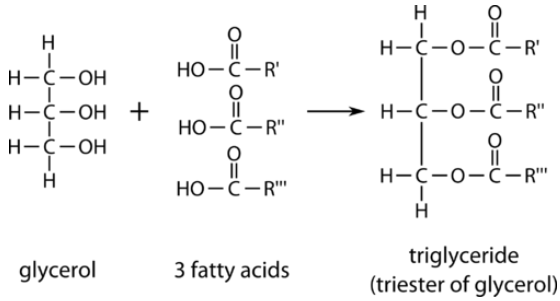
Cetyl palmitate, a typical wax ester.

Waxes are widely distributed in nature. The leaves and fruits of many plants have waxy coatings, which may protect them from dehydration and small predators. The feathers of birds and the fur of some animals have similar coatings which serve as a water repellent. Carnauba wax is valued for its toughness and water resistance. The formulas for three well known waxes are given below, with the carboxylic acid moiety colored red and the alcohol colored blue.

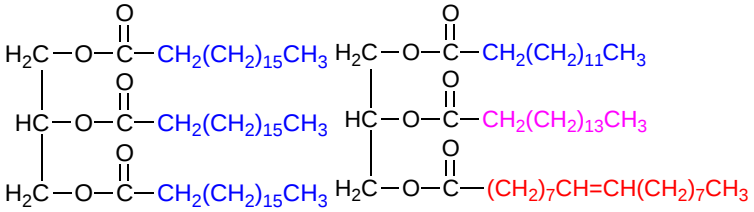
	Spermaceti	Beeswax	Carnauba wax
Alcohol	$CH_3(CH_2)_{14}CH_2$-OH	$CH_3(CH_2)_{28}CH_2$-OH	$CH_3(CH_2)_{28}CH_2$-OH
Fatty Acid	$CH_3(CH_2)_{14}COOH$	$CH_3(CH_2)_{14}COOH$	$CH_3(CH_2)_{24}COOH$
Wax	$CH_3(CH_2)_{14}CO_2$-$(CH_2)_{15}CH_3$	$CH_3(CH_2)_{24}CO_2$-$(CH_2)_{29}CH_3$	$CH_3(CH_2)_{30}CO_2$-$(CH_2)_{33}CH_3$

TRIGLYCERIDES

Fats and oils often exist as **triglycerides** (or ***triacylcylgerols*** because they are esters composed of three fatty acid units joined to *glycerol*, a trihydroxy alcohol (IUPAC name is 1,2,3-propanetriol)):



If all three OH groups on the glycerol molecule are esterified with the same fatty acid, the resulting ester is called a ***simple triglyceride***. Although simple triglycerides have been synthesized in the laboratory, they rarely occur in nature. Instead, a typical triglyceride obtained from naturally occurring fats and oils contains two or three different fatty acid components and is thus termed a ***mixed triglyceride***.



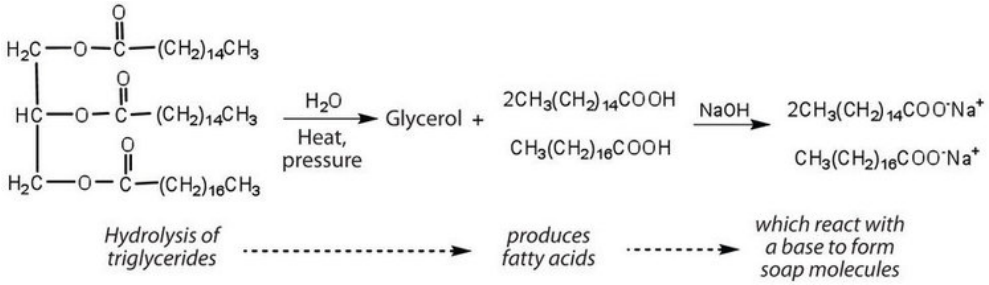
Tristearin: a simple triglyceride (left) and a mixed triglyceride (right)

A triglyceride is called a **fat** if it is a solid at 25°C; it is called an **oil** if it is a liquid at that temperature. These differences in melting points reflect differences in the degree of unsaturation (as discussed above) and number of carbon atoms in the constituent fatty acids. Triglycerides obtained from animal sources are usually solids, while those of plant origin are generally oils. Therefore, we commonly speak of animal fats and vegetable oils. No single formula can be written to represent the naturally occurring fats and oils because they are highly complex mixtures of triglycerides in which many different fatty acids are represented. The table below shows the fatty acid compositions of some common fats and oils. The composition of any given fat or oil can vary depending on the plant or animal species it comes from as well as on dietetic and climatic factors.

Table 27.1.3: Some common fats and oils including fatty acid content are listed below.

glycerides					
Fat or Oil	Saturated		Unsaturated		
	Palmitic	Stearic	Oleic	Linoleic	Other
Animal Origin					
Butter	29	9	27	4	31
Lard	30	18	41	6	5
Beef	32	25	38	3	2
Vegetable Origin					
Corn oil	10	4	34	48	4
Soybean	7	3	25	56	9
Peanut	7	5	60	21	7
Olive	6	4	83	7	-

Fats and oils can participate in a variety of chemical reactions—for example, because triglycerides are esters, they can be hydrolyzed in the presence of an acid, a base, or specific enzymes known as lipases. The hydrolysis of fats and oils in the presence of a base is used to make soap and is called saponification. Today most soaps are prepared through the hydrolysis of triglycerides (often from tallow, coconut oil, or both) using water under high pressure and temperature [(~50 atm or 5,000 kPa) and 200°C]. Sodium carbonate or sodium hydroxide is then used to convert the fatty acids to their sodium salts (soap molecules):



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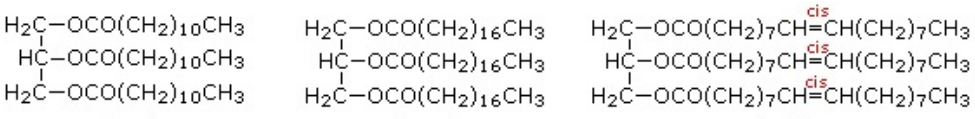
Chemical reaction of the saponification (base hydrolysis) of a triglyceride.

As might be expected from the properties of the fatty acids, fats have a predominance of saturated fatty acids, and oils are composed largely of unsaturated acids. Thus, the melting points of triglycerides reflect their composition, as shown by the following examples. Natural mixed triglycerides have somewhat lower melting points, the melting point of lard being near 30 ° C, whereas olive oil melts near -6 ° C. Since fats are valued over oils by some Northern European and North American populations, vegetable oils are extensively converted to solid triglycerides (e.g. Crisco) by partial hydrogenation of their unsaturated components. Some of the remaining double bonds are isomerized (to trans) in this operation. These saturated and trans-fatty acid glycerides in the diet have been linked to long-term health issues such as atherosclerosis.

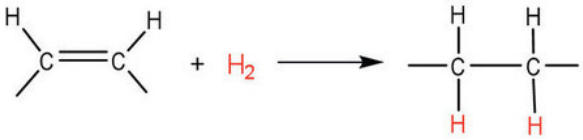


trilaurin
mp 45° C

tristearin
mp 71° C

triolein
mp -4° C

The double bonds in fats and oils can undergo hydrogenation and also oxidation. The hydrogenation of vegetable oils to produce semisolid fats is an important process in the food industry. Chemically, it is essentially identical to the catalytic hydrogenation reaction described for alkenes.



In commercial processes, the number of double bonds that are hydrogenated is carefully controlled to produce fats with the desired consistency (soft and pliable). Inexpensive and abundant vegetable oils (canola, corn, soybean) are thus transformed into margarine and cooking fats.

Many people have switched from butter to margarine or vegetable shortening because of concerns that saturated animal fats can raise blood cholesterol levels and result in clogged arteries. However, during the hydrogenation of vegetable oils, an isomerization reaction occurs that produces the trans fatty acids mentioned in the opening essay. However, studies have shown that trans fatty acids also raise cholesterol levels and increase the incidence of heart disease. Trans fatty acids do not have the bend in their structures, which occurs in cis fatty acids and thus pack closely together in the same way that the saturated fatty acids do. Consumers are now being advised to use polyunsaturated oils and soft or liquid margarine and reduce their total fat consumption to less than 30% of their total calorie intake each day.

? EXERCISE 27.1.1

Why do unsaturated fatty acids have lower melting points than saturated fatty acids?

Answer

Unsaturated fatty acids cannot pack as tightly together as saturated fatty acids due to the presence of the cis double bond that puts a “kink” or bend in the hydrocarbon chain.

? EXERCISE 27.1.2

Classify each fatty acid as saturated or unsaturated and indicate the number of carbon atoms in each molecule.

a. palmitoleic acid
b. myristic acid
c. linoleic acid

Answer

a. unsaturated; 16 carbon atoms
b. saturated; 14 carbon atoms
c. unsaturated; 18 carbon atoms

EXERCISE 27.1.3

Write the condensed structural formula for each fatty acid.

a. lauric acid
b. palmitoleic acid
c. linoleic acid

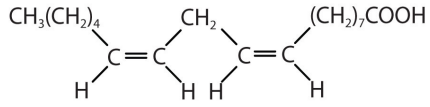
Answer

a. $CH_3(CH_2)_{10}COOH$
b. $CH_3(CH_2)_5CH{=}CH(CH_2)_7COOH$
c. $CH_3(CH_2)_3(CH_2CH{=}CH)_2(CH_2)_7COOH$

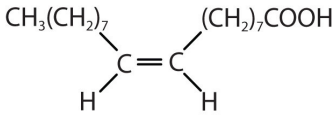
EXERCISE 27.1.4

Arrange these fatty acids (all contain 18 carbon atoms) in order of increasing melting point. Justify your arrangement.

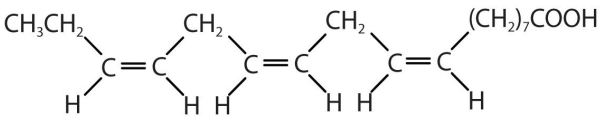
a)



b)



c)

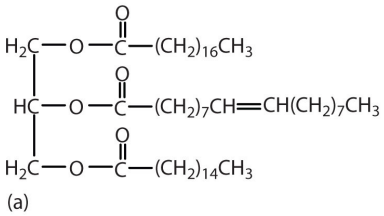


Answer

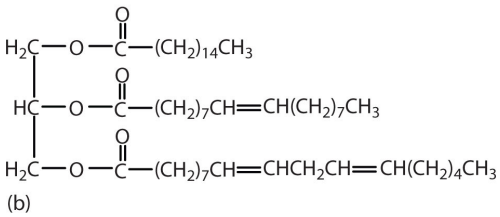
c < a < b; an increase in the number of double bonds will lower the melting point because it is more difficult to closely pack the fatty acids together.

EXERCISE 27.1.5

Which of these triglycerides would you expect to find in higher amounts in oils? In fats? Justify your choice.



(a)



(b)

Answer

The triglyceride labeled as (a) is expected to be present in higher amounts in fats because it is composed of a greater number of saturated fatty acids. The triglyceride labeled as (b) is expected to be present in higher amounts in oils because it is composed of a greater number of unsaturated fatty acids.

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27.2: SOAP

LEARNING OBJECTIVES

After completing this section, you should be able to

- write an equation to represent the formation of a soap.
  - identify the structure of the fat required to produce a given soap.
  - identify the structure of a soap, given the structure of the fat from which it is produced.
- describe the mechanism by which soaps exert their cleansing action.
- give a chemical explanation of the problems encountered when carboxylate soaps are used in hard-water areas, and explain how they may be overcome by the use of sulphonate detergents.

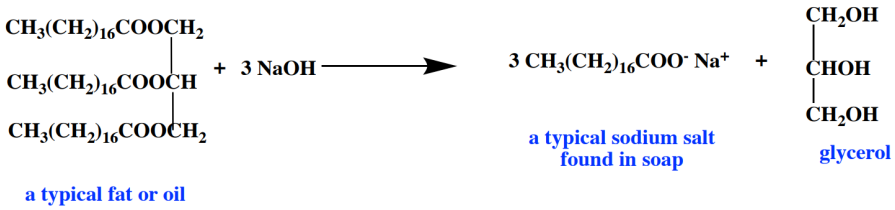
KEY TERMS

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

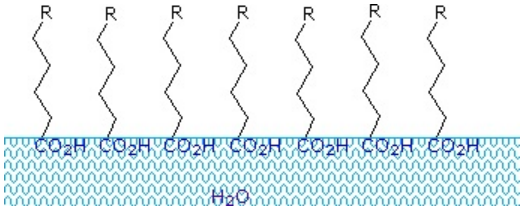
- hydrophilic
- lipophilic (hydrophobic)
- amphiphilic
- micelles

Soap making has remained unchanged over the centuries. The ancient Roman tradition called for mixing rain water, potash and animal tallow (rendered form of beef or mutton fat). Making soap was a long and arduous process. First, the fat had to be rendered (melted and filtered). Then, potash solution was added. Since water and oil do not mix, this mixture had to be continuously stirred and heated sufficiently to keep the fat melted. Slowly, a chemical reaction called saponification would take place between the fat and the hydroxide which resulted in a liquid soap. When the fat and water no longer separated, the mixture was allowed to cool. At this point salt, such as sodium chloride, was added to separate the soap from the excess water. The soap came to the top, was skimmed off, and placed in wooden molds to cure. It was aged many months to allow the reaction to run to completion.

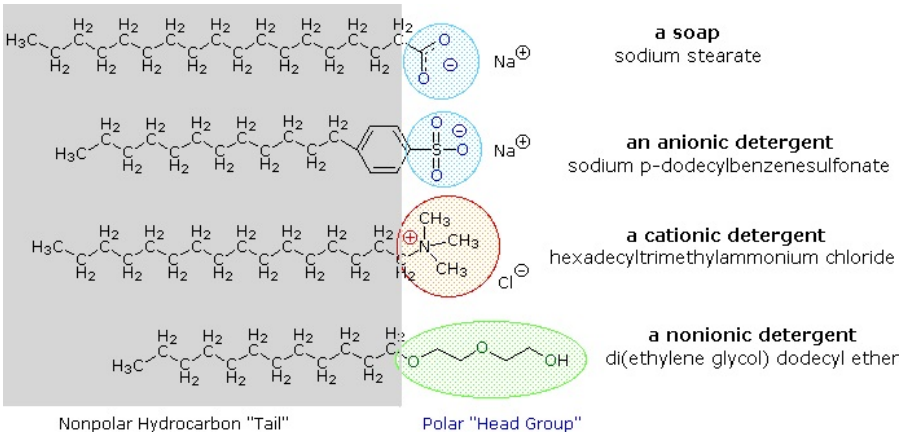
All soap is made from fats and oils, mixed with alkaline (basic) solutions. There are many kinds of fats and oils, both animal and vegetable. As previously discussed, fats are usually solid at room temperature, but many oils are liquid at room temperature. Liquid cooking oils originate from corn, peanuts, olives, soybeans, and many other plants. For making soap, all different types of fats and oils can be used – anything from lard to exotic tropical plant oils.



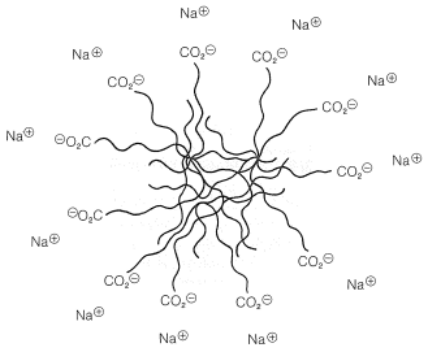
Carboxylic acids and salts having alkyl chains longer than eight carbons exhibit unusual behavior in water due to the presence of both hydrophilic (CO_2) and hydrophobic (alkyl) regions in the same molecule. Such molecules are termed **amphiphilic** (Gk. amphi = both) or **amphipathic**. Fatty acids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



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

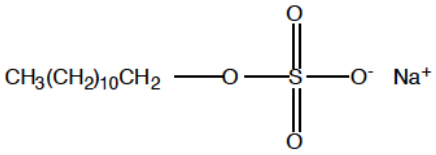


When minute amounts of soaps are put into water, instead of forming simple solutions, the molecules become concentrated at the surface of the water, with the saltlike ends sticking down into the water and the hydrocarbon chains forming a layer on the surface. This arrangement greatly reduces the surface tension of the water and contributes to the startling properties of soap films and bubbles. At higher concentrations, the solutions become turbid as the result of **micelle** formation. Micelles are spherical aggregates of soap molecules, wherein the hydrocarbon chains form a region of low polarity that is stabilized by having the polar salt ends of the molecules in contact with the water. By gathering the hydrophobic chains together in the center of the micelle, disruption of the hydrogen bonded structure of liquid water is minimized, and the polar head groups extend into the surrounding water where they participate in hydrogen bonding.



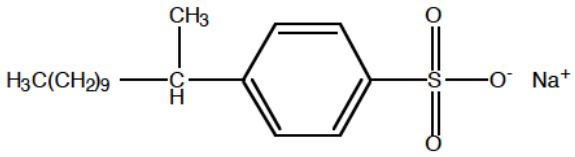
The importance of soap to human civilization is documented by history, but some problems associated with its use have been recognized. One of these is caused by the weak acidity (pKa ca. 4.9) of the fatty acids. Solutions of alkali metal soaps are slightly alkaline (pH 8 to 9) due to hydrolysis. If the pH of a soap solution is lowered by acidic contaminants, insoluble fatty acids precipitate and form a scum. A second problem soaps are less effective in hard water, which is water that contains a significant concentration of magnesium, calcium and iron ions. These ions form precipitates with soap molecules, and this precipitate is often seen as a gray line on a bathtub or sink and is often called “soap scum”. Since soap forms a precipitate with these ions, it means that many of the soap molecules are no longer present in the solution. Therefore, soap will form fewer suds in hard water. “Soft water” is water that contains very few or no ions that precipitate with soap. Soap will therefore be much more effective in soft water than in hard water.

These problems have been alleviated by the development of synthetic soaps called detergents. Detergents are similar to soaps in that they have a charged head group and a long nonpolar tail group, but they are not prepared from natural fats or oils. Detergents are useful because they do not form precipitates with magnesium, iron or calcium ions, which means that they work in both soft and hard water. By using a much stronger acid for the polar head group, water solutions of detergents are less sensitive to pH changes. Also the sulfonate functions used for virtually all anionic detergents confer greater solubility on micelles incorporating the alkaline earth cations found in hard water. Variations on the detergent theme have led to the development of other classes, such as the cationic and nonionic detergents shown above. Cationic detergents often exhibit germicidal properties, and their ability to change surface pH has made them useful as fabric softeners and hair conditioners. These versatile chemical "tools" have dramatically transformed the household and personal care cleaning product markets over the past fifty years



Sodium Lauryl Sulfate (a non-biodegradable detergent)

After detergents started being widely used, it was discovered that they were not broken down in sewage treatment plants. Many streams and lakes became contaminated with detergents and large amounts of foam appeared in natural waters. Biodegradable detergents were then developed. Shown below is an example of a biodegradable detergent, sodium laurylbenzenesulfonate.



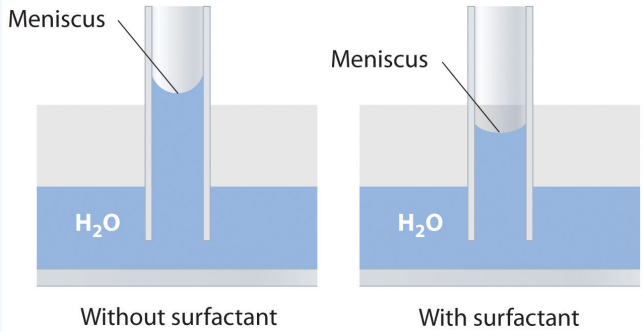
Sodium Laurylbenzenesulfonate (a biodegradable detergent)

EXERCISE 27.2.1

Explain how soaps or surfactants decrease the surface tension of a liquid. How does the meniscus of an aqueous solution in a capillary change if a surfactant is added? Illustrate your answer with a diagram.

Answer

Adding a soap or a surfactant to water disrupts the attractive intermolecular interactions between water molecules, thereby decreasing the surface tension. Because water is a polar molecule, one would expect that a soap or a surfactant would also disrupt the attractive interactions responsible for adhesion of water to the surface of a glass capillary. As shown in the sketch, this would decrease the height of the water column inside the capillary, as well as making the meniscus less concave.



EXERCISE 27.2.2

Draw the structure of calcium stearate, a component of soap scum.

Answer

$(C_{17}H_{35}COO)_2Ca^{2+}$

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27.3: PHOSPHOLIPIDS

LEARNING OBJECTIVES

After completing this section, you should be able to

- draw the general structure of a phosphoglyceride.
- describe the occurrence and importance of phosphoglycerides in plant and animal tissues.

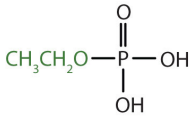
KEY TERMS

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

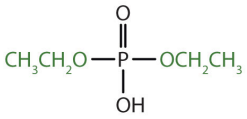
- phosphoglyceride
- phospholipid

PHOSPHATE ESTERS

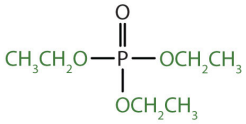
Similarly to carboxylic acids, inorganic acids such as nitric acid (HNO_3), sulfuric acid (H_2SO_4), and phosphoric acid (H_3PO_4) also can form esters. The esters of phosphoric acid are especially important in biochemistry. A phosphoric acid molecule can form a monoalkyl, a dialkyl, or a trialkyl ester by reaction with one, two, or three molecules of an alcohol.



Ethyl dihydrogen phosphate

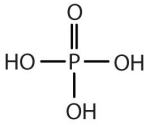


Diethyl hydrogen phosphate

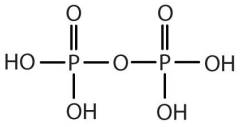


Triethyl phosphate

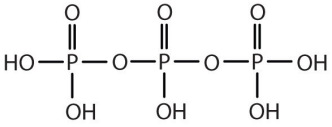
Esters of pyrophosphoric acid and triphosphoric acid are also important in biochemistry.



Phosphoric acid



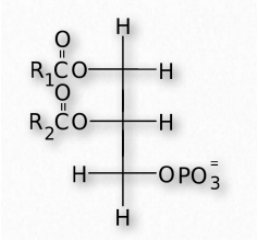
Pyrophosphoric acid



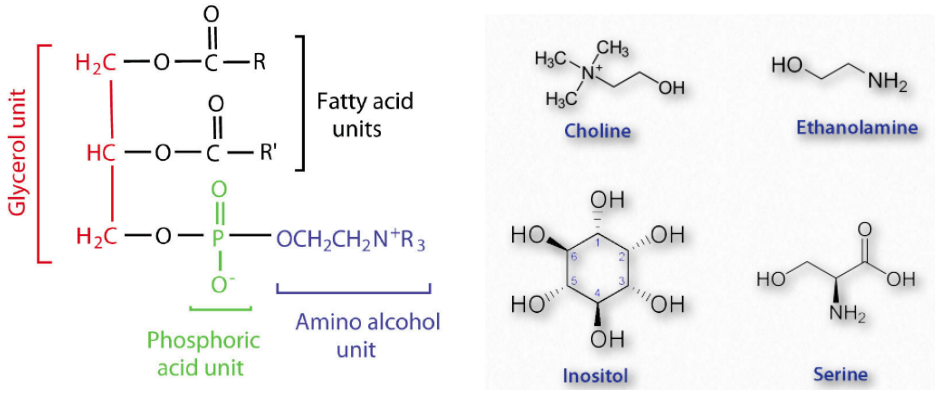
Triphosphoric acid

PHOSPHOLIPIDS

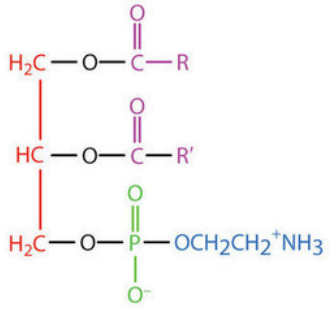
The two main types of phospholipids are **glycerophospholipids** and **sphingomyelins**. Glycerophospholipids are important components of the lipid bilayer of cellular membranes. Glycerophospholipids are structurally related to fats, as both are derived from phosphatidic acid, which has the basic structure of glycerol with two ester bonds with fatty acids and one ester bond with phosphoric acid.



Phosphatidic acid is converted into a glycerophospholipid by esterifying various groups, such as ethanolamine, serine, choline, inositol, and others to the phosphate of phosphatidic acid. These compounds have a chiral center at C2 and have an R configuration when found in nature.

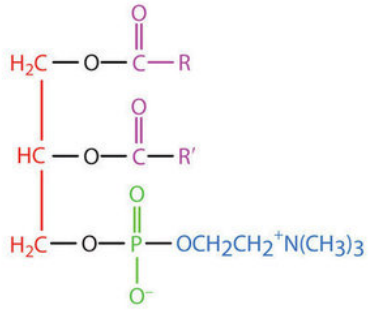


The **phosphatidylethanolamines** are found in all living cells and are one of the most common phosphatides. They are common constituents of brain tissue and in the spinal cord, making up as much as 45% of the total phospholipids. Phosphatidylethanolamines are asymmetrically distributed across membranes, being preferentially located on the inner leaflet (closest to the cytoplasm) of the plasma membrane.



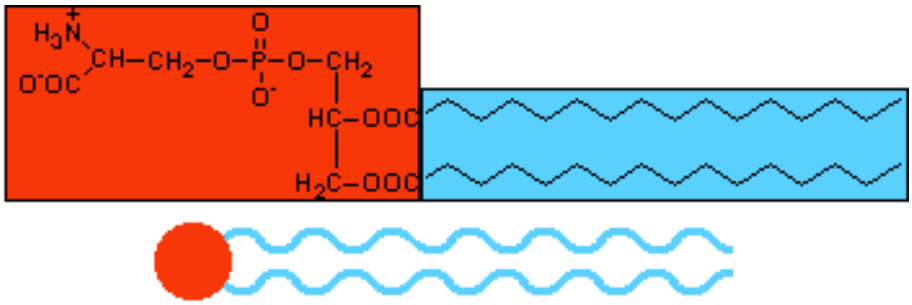
Phosphatidylethanolamine
(cephalin)

Metabolically, phosphatidylethanloamines are precursors of **phosphatidylcholines**. Phosphatidylcholines are another group of important membrane components. They tend to be found more commonly on the outer leaflet of the plasma membrane. Nutritionally, the compounds are readily obtained from eggs and soybeans. Phosphatidylcholines are moved across membranes by Phosphatidylcholine transfer protein (PCTP).



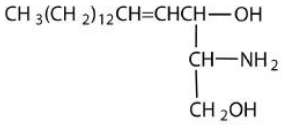
Phosphatidycholine
(lecithin)

Like the phosphatidylethanolamines, **phosphatidylserines** are preferentially located on the inner leaflet of the plasma membrane. When apoptosis (cell suicide) occurs, the preferential distribution is lost and the phosphatidylserines appear on the outer leaflet where they serve as a signal to macrophages to bind and destroy the cell.

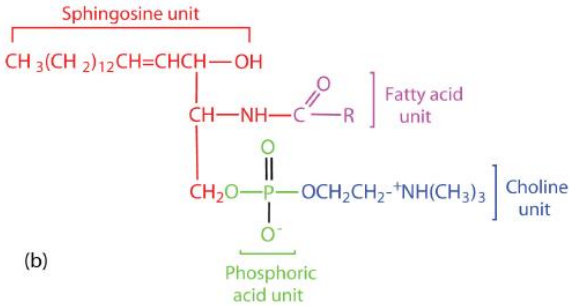


Phosphatidylserine, a polar phospholipid. A serine head group has been added on to a phosphate group on a glycerol functional group, all shown in orange. The fatty acid chains are in blue.

Sphingomyelins, the simplest sphingolipids, each contain a fatty acid, a phosphoric acid, sphingosine, and choline. Because they contain phosphoric acid, they are also classified as phospholipids. Sphingomyelins are important constituents of the myelin sheath surrounding the axon of a nerve cell. Multiple sclerosis is one of several diseases resulting from damage to the myelin sheath.



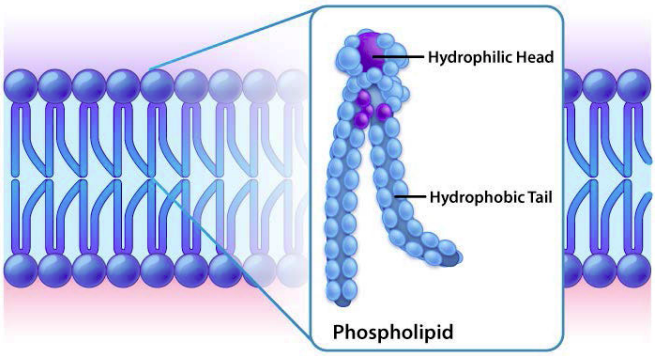
(a) Sphingosine



(b)

LIPID BILAYER

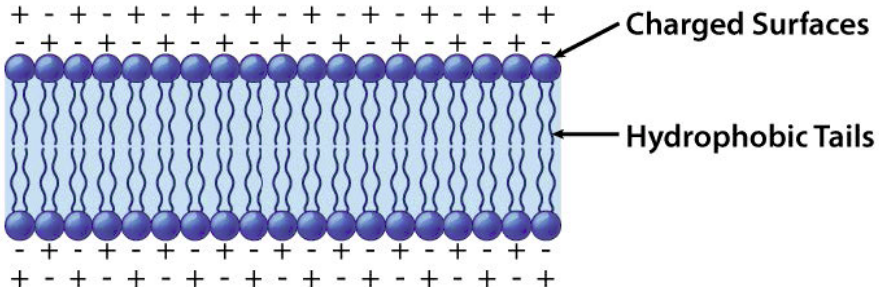
In one sense the polar lipids are like the anions of fatty acids, only more so. They contain two hydrophobic hydrocarbon tails and a head which may have several electrically charged sites. As in the case of soap and detergent molecules, the tails of polar lipids tend to avoid water and other polar substances, but the heads are quite compatible with such environments.



Lipid bilayer closeup Image by Aleia Kim

As ionic amphiphiles, phospholipids aggregate or self-assemble when mixed with water, but in a different manner than the soaps and detergents. Because of the two pendant alkyl chains present in phospholipids and the unusual mixed charges in their head groups, micelle

formation is unfavorable relative to a bilayer structure. If a phospholipid is smeared over a small hole in a thin piece of plastic immersed in water, a stable planar bilayer of phospholipid molecules is created at the hole. As shown in the following diagram, the polar head groups on the faces of the bilayer contact water, and the hydrophobic alkyl chains form a nonpolar interior.



Organization of the lipid bilayer Image by Aleia Ki

The polar lipids are most commonly found as components of cell walls and other membranes. Nearly all hypotheses regarding membrane structure take as a fundamental component a lipid bilayer. Bilayers made in the laboratory have many properties in common with membranes. Ions such as Na^+, K^+, and Cl^- cannot pass through them, but water molecules can. Certain carrier molecules can transport K^+ and other ions across a bilayer, apparently by wrapping a hydrophobic cloak around them to disguise their charges. Membrane proteins in a bilayer also allow for transport of ions and other molecules across the bilayer which could not cross otherwise.

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27.4: PROSTAGLANDINS AND OTHER EICOSANOIDS

LEARNING OBJECTIVES

After completing this section, you should be able to

- describe the general structure of the prostaglandins, and identify a prostaglandin from a given list of organic structures.
- identify at least two important biological functions of prostaglandins.

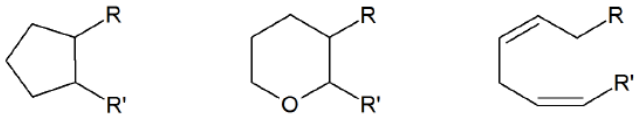
KEY TERMS

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

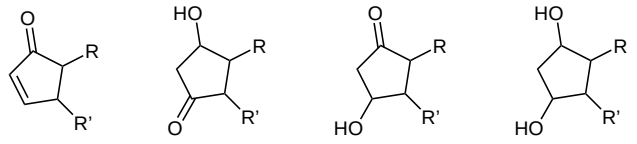
- eicosanoid
- prostaglandin

EICOSANOIDS

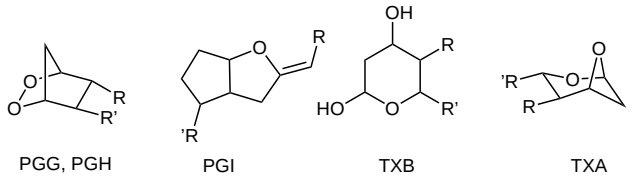
The members of this group of structurally related natural hormones have an extraordinary range of biological effects. They can lower gastric secretions, stimulate uterine contractions, lower blood pressure, influence blood clotting and induce asthma-like allergic responses. Because their genesis in body tissues is tied to the metabolism of the essential fatty acid arachadonic acid (5,8,11,14-eicosatetraenoic acid) they are classified as **eicosanoids**. Many properties of the common drug aspirin result from its effect on the cascade of reactions associated with these hormones. Eicosanoids include prostaglandins, leukotrienes, and thromboxanes.



Eicosanoids are primarily named off the ring system present in the molecule prostaglandin (PG), thromboxane (TX), leukotriene (LT). Common substitution patterns on the ring system are indicated with a letter in the name. Also, the number of double bonds in the molecule is indicated with a subscript number.

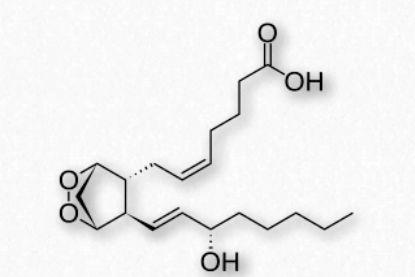


Prostaglandin structures for PGA, PGD, PGE and PGF



Structures for prostaglandins PGG, PGH and PGI and thromboxanes TXA and TXB

Thus the molecule PGH_2 means that it has the prostaglandin ring system with a type H Substitution pattern. The subscript 2 indicated that the molecule contains two double bonds.



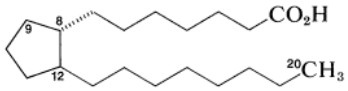
Prostaglandin PGH_2

PROSTAGLANDINS

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

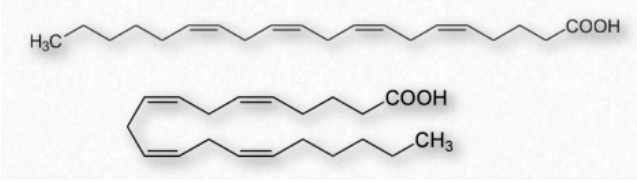
Prostaglandins are found in low concentrations distributed in a large number of organs, tissues, and body fluids of mammals. They exhibit a broad spectrum of physiological activity and are remarkably potent. Their precise biological role is not entirely clear, but they are known to induce strong contractions of smooth muscle tissue (lungs, uterus) and to lower blood pressure and sodium levels. Prostaglandins also have been implicated in the control of pituitary hormones released from the hypothalamus, and in the incidence of "pain" as a response to fever and inflammation. In fact, the analgesic property of aspirin possibly may result from the inhibition of prostaglandin biosynthesis

Prostaglandins are unsaturated carboxylic acids, consisting of of a 20 carbon skeleton that also contains a five member ring and are based upon prostanoic acid, which is a C20 fatty acid in which there is a cyclopentane ring formed by connecting the C8 and C12 positions.



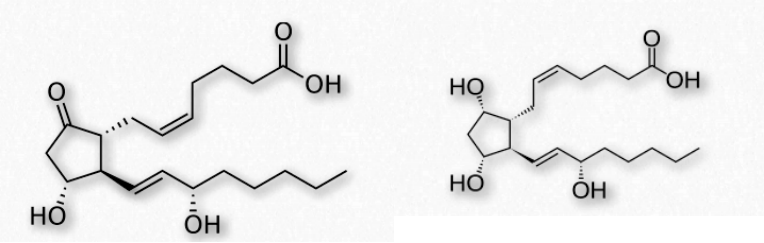
prostanoic acid

They are biochemically synthesized from the fatty acid, arachidonic acid. The unique shape of the arachidonic acid caused by a series of cis double bonds helps to put it into position to make the five member ring of the prostaglandin.



Arachidonic acid

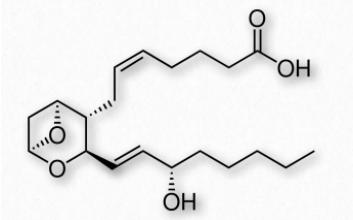
There are a variety of functional groups present in prostaglandin structures. The can have one, two, or three double bonds. On the five member ring there may also be double bonds, a ketone, or alcohol groups. Some typical structures are shown below.



Prostaglandin E2 (left) and Prostaglandin $F_{2\alpha}$ (Right)

THROMBOXANES

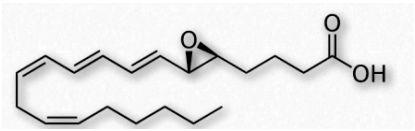
Thromboxanes play roles in clot formation and named for their role in thrombosis. They are potent vasoconstrictors and facilitate platelet aggregation. They are synthesized in platelets, as well. The anti-clotting effects of aspirin have their roots in the inhibition of synthesis of PGH2, which is the precursor of the thromboxanes. The most common thromboxanes are A2 (Figure 2.217) and B2.



Thromboxane $A2_2$

LEUKOTRIENES

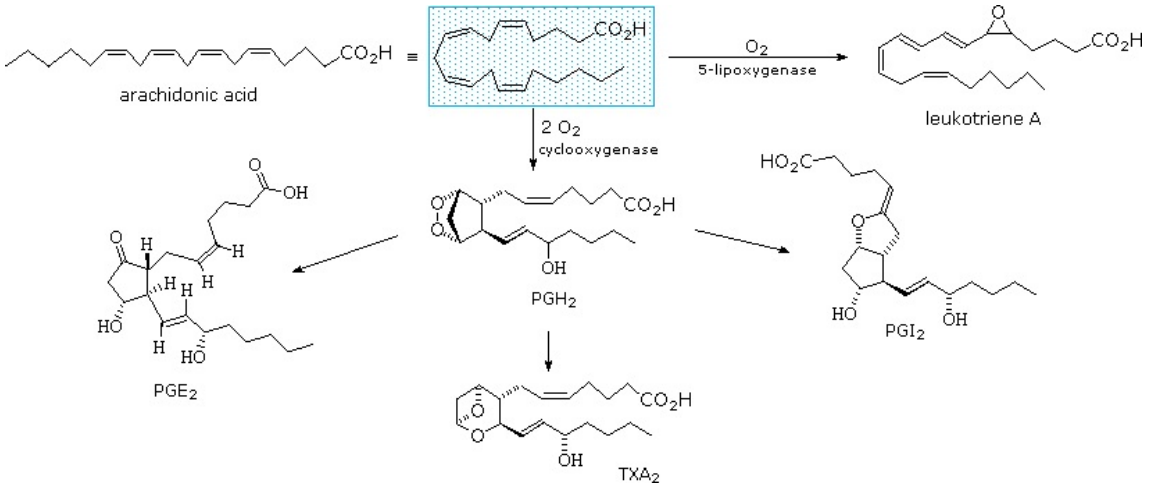
Another group of eicosanoid compounds are the leukotrienes (Figure 2.219). Like prostaglandins, leukotrienes are made from arachidonic acid. The enzyme catalyzing their formation is a dioxygenase known as arachidonate 5-lipoxygenase. Leukotrienes are involved in regulating immune responses. They are found in leukocytes and other immunocompetent cells, such as neutrophils, monocytes, mast cells, eosinophils, and basophils. Leukotrienes are associated with production of histamines and prostaglandins, which act as mediators of inflammation. Leukotrienes also trigger contractions in the smooth muscles of the bronchioles. When overproduced, they may pay a role in asthma and allergic reactions. Some treatments for asthma aim at inhibiting production or action of leukotrienes.



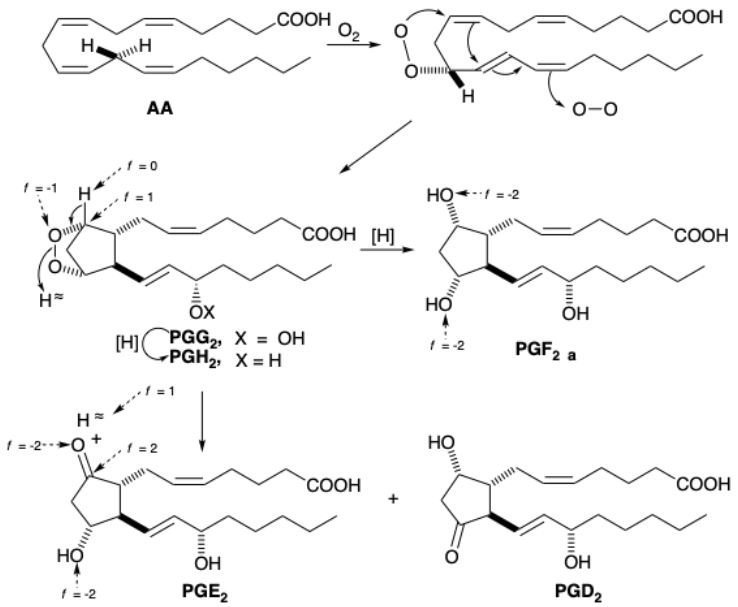
Leukotriene A_4 (LTA_4)

EICOSANOID BIOSYNTHESIS

The biosynthesis of eicosanoids begins with the reaction of arachidonic acid with O_2 which can be catalyzed by two different cyclooxygenase enzymes (COX-1 & COX-2).



In nature, prostaglandins arise by an oxidative cyclization of poly-unsaturated twenty-carbon fatty acids, which begins with enantiospecific removal of the L-hydrogen atom of the prochiral methylene group at C-13 coupled with enantiospecific introduction of oxygen at the allylic C-15 position. Subsequent cyclization and termination by addition of a second molecule of oxygen leads to a 15-hydroperoxy bicyclic peroxide (PGG), that is reduced to a 15-hydroxy bicyclic peroxide (PGH). These intermediates, known as prostaglandin endoperoxides, have been isolated and shown to yield prostaglandins. Reduction of the peroxy bridge gives PGF, while disproportionation gives β-hydroxy ketones PGE and PGD. The carbons in prostaglandins are numbered one to twenty starting at the carboxyl carbon and following the numbering system of the biosynthetic precursor fatty acids.



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27.5: TERPENOIDS

OBJECTIVES

After completing this section, you should be able to

1. identify a terpene from a given list of organic structures.
2. analyze the structure of a given terpene in terms of the isoprene rule.
3. classify a given terpene structure according to the number of isoprene units present; that is, determine whether a given terpene is a monoterpene, sesquiterpene, diterpene, etc.
4. identify and draw the structure of the precursors of isopentenyl diphosphate: (*R*) mevalonate or 1-deoxy-D-xylulose 5-phosphate.

KEY TERMS

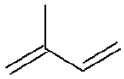
Make certain that you can define, and use in context, the key terms below.

- isoprene rule
- terpenoid
- terpene

STUDY NOTES

You are not expected to memorize all the details of the synthetic mechanisms for terpenoids. However, you should know the overall general synthetic pathway illustrated under "Terpenoid Biosynthesis." As you read through the details of these mechanisms, realize that they may be complex, but they are based on experimental evidence. You should also note the important role of enzymes in many natural systems transformations. Finally, you will recognize that essentially, individual steps are often reactions you have already encountered in previous sections.

The terpenoids (aka isoprenoids) are a large (estimated 60% of known natural products) and diverse group of lipids derived from five-carbon isoprene units assembled in thousands of combinations. Technically a terpenoid contains oxygen, while a terpene is a hydrocarbon. Often the two terms are used to refer collectively to both groups.



isoprene

ISOPRENE RULE

Compounds classified as terpenes constitute what is arguably the largest and most diverse class of natural products. A majority of these compounds are found only in plants, but some of the larger and more complex terpenes (e.g. squalene & lanosterol) occur in animals. Terpenes incorporating most of the common functional groups are known, so this does not provide a useful means of classification. Instead, the number and structural organization of carbons is a definitive characteristic. Terpenes may be considered to be made up of isoprene (more accurately isopentane) units, an empirical feature known as the isoprene rule. Because of this, terpenes usually have $5n$ carbon atoms (n is an integer), and are subdivided as follows:

Classification	Isoprene Units	Carbon Atoms
monoterpenes	2	C_{10}
sesquiterpenes	3	C_{15}
diterpenes	4	C_{20}
sesterterpenes	5	C_{25}
triterpenes	6	C_{30}

Isoprene itself, a C_5H_8 gaseous hydrocarbon, is emitted by the leaves of various plants as a natural byproduct of plant metabolism. Next to methane it is the most common volatile organic compound found in the atmosphere. Examples of C10 and higher terpenes, representing the four most common classes are shown in the following diagrams. Most terpenes may be structurally dissected into isopentane segments. How this is done can be seen in the diagram directly below.

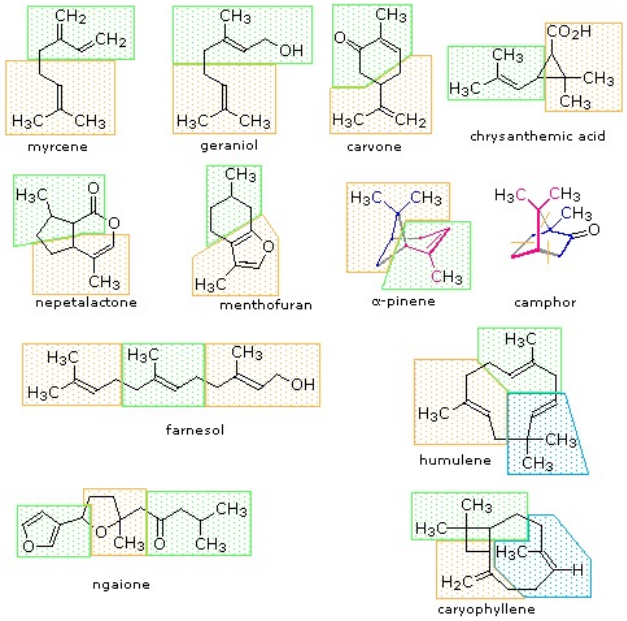


Figure 27.5.1: Monoterpenes and sesquiterpenes

The isopentane units in most of these terpenes are easy to discern, and are defined by the shaded areas. In the case of the monoterpene camphor, the units overlap to such a degree it is easier to distinguish them by coloring the carbon chains. This is also done for alpha-pinene. In the case of the triterpene lanosterol we see an interesting deviation from the isoprene rule. This thirty carbon compound is clearly a terpene, and four of the six isopentane units can be identified. However, the ten carbons in center of the molecule cannot be dissected in this manner. Evidence exists that the two methyl groups circled in magenta and light blue have moved from their original isoprenoid locations (marked by small circles of the same color) to their present location. This rearrangement is described in the biosynthesis section. Similar alkyl group rearrangements account for other terpenes that do not strictly follow the isoprene rule.

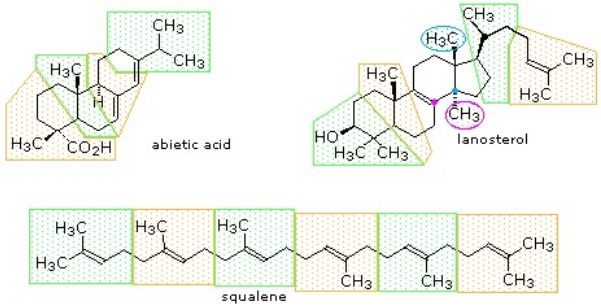
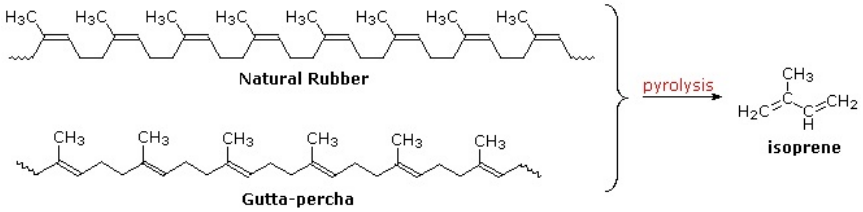


Figure 27.5.2: Triterpenes

Polymeric isoprenoid hydrocarbons have also been identified. Rubber is undoubtedly the best known and most widely used compound of this kind. It occurs as a colloidal suspension called latex in a number of plants, ranging from the dandelion to the rubber tree (*Hevea brasiliensis*). Rubber is a polyene, and exhibits all the expected reactions of the C=C function. Bromine, hydrogen chloride and hydrogen all add with a stoichiometry of one molar equivalent per isoprene unit. Ozonolysis of rubber generates a mixture of levulinic acid ($CH_3COCH_2CH_2CO_2H$) and the corresponding aldehyde. Pyrolysis of rubber produces the diene isoprene along with other products.

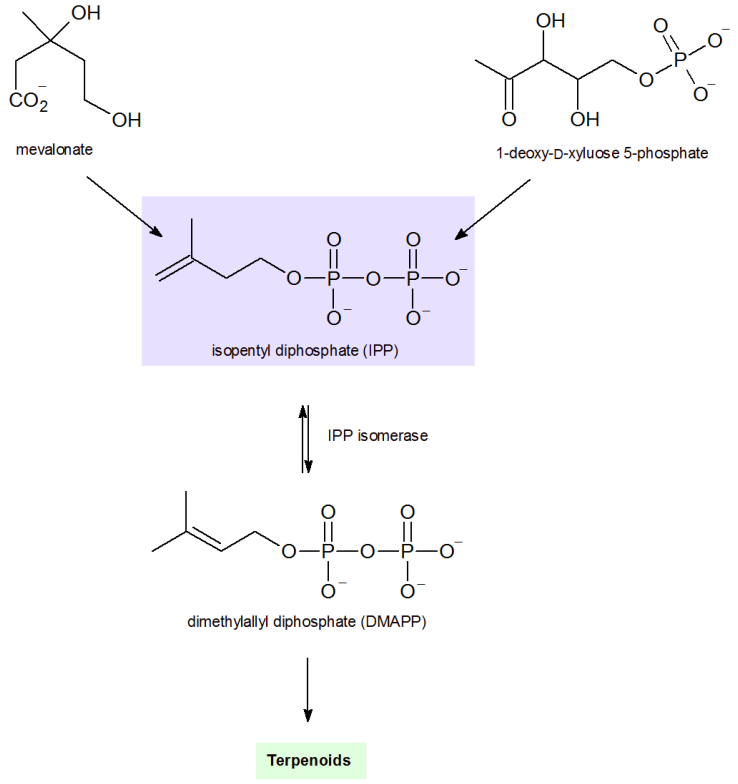


The double bonds in rubber all have a Z-configuration, which causes this macromolecule to adopt a kinked or coiled conformation. This is reflected in the physical properties of rubber. Despite its high molecular weight (about one million), crude latex rubber is a soft, sticky, elastic substance. Chemical modification of this material is normal for commercial applications. Gutta-percha (structure above) 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.

TERPENOID BIOSYNTHESIS

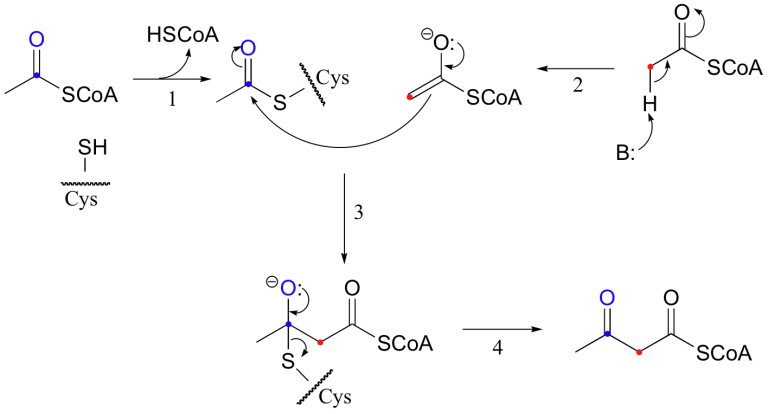
While we can identify isoprene units within a terpenoid structure and use that in its classification, the building block for terpenoid synthesis in nature is isopentenyl diphosphate (formerly called isopentenyl pyrophosphate and abbreviated IPP). There are two major routes to the synthesis of IPP; namely (1) the mevalonate pathway and (2) the 1-deoxyxylulose pathway.



MEVALONATE PATHWAY

Step 1 - Claisen Condensation

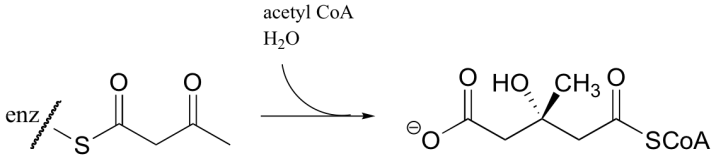
An early step in the biosynthesis of cholesterol and other 'isoprenoid' compounds is a Claisen condensation between two acetyl CoA molecules. An initial trans-thioesterase process transfers the acetyl group of the first acetyl CoA to an enzymatic cysteine (Reaction 1). In the Claisen condensation phase of the reaction, the alpha-carbon of a second acetyl CoA is deprotonated, forming an enolate (Reaction 2).



The enolate carbon attacks the electrophilic thioester carbon, forming a tetrahedral intermediate (Reaction 3) which quickly collapses to expel the cysteine thiol (Reaction 4) and produce acetoacetyl CoA.

Step 2 - Aldol Condensation

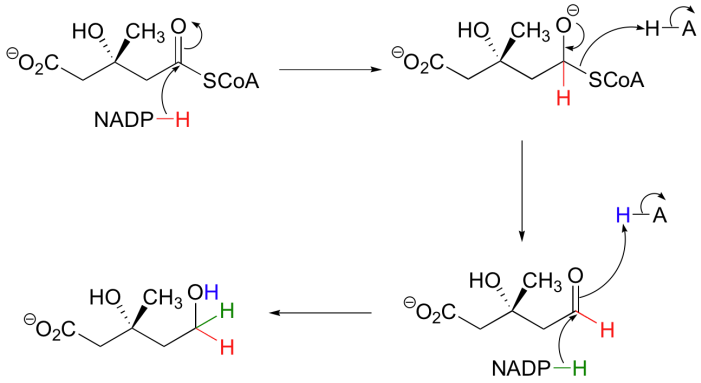
Acetyl CoA then reacts with the acetoacetyl CoA in an aldol-like addition. Subsequent hydrolysis produces (3*S*)-3-hydroxy-3-methylglutaryl CoA (HMG-CoA).



Generating HMG-CoA

Step 3 - Reduction of the Thioester

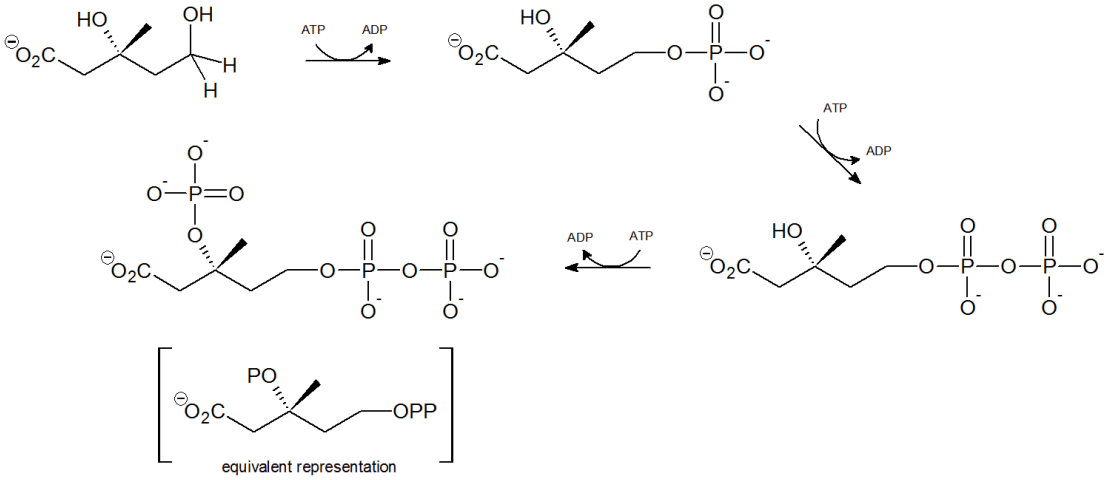
The thioester is reduced first to an aldehyde, then to a primary alcohol by two equivalents of NADPH producing (*R*)-mevalonate. The enzyme catalyzing this reaction is the target of the statin family of cholesterol-lowering drugs.



Generating (*R*)-Mevalonate

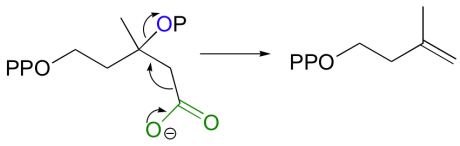
Step 4 - Mevalonate Phosphorylation

Two phsophorylations by adenosine triphosphate (ATP) occur at the terminal hydroxyl/phosphorus group through nucleophilic substitution, followed by a third ATP phosphorylation of the tertiary hydroxyl group.



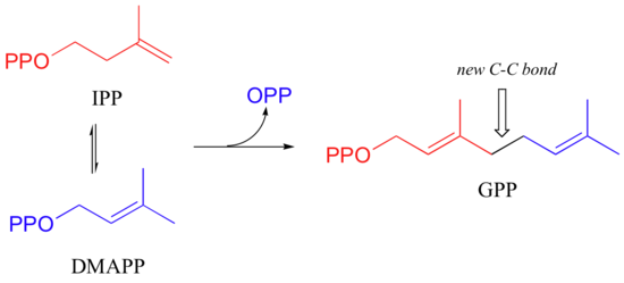
Step 5 - Decarboxylation

Finally isopentenyl diphosphate (IPP), the 'building block' for all isoprenoid compounds, is formed from a decarboxylation-elimination reaction.

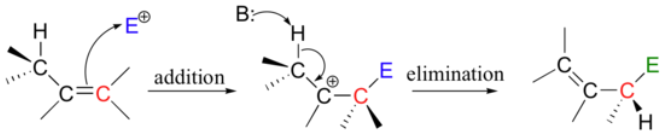


CONVERSION OF IPP TO TERPENOIDS

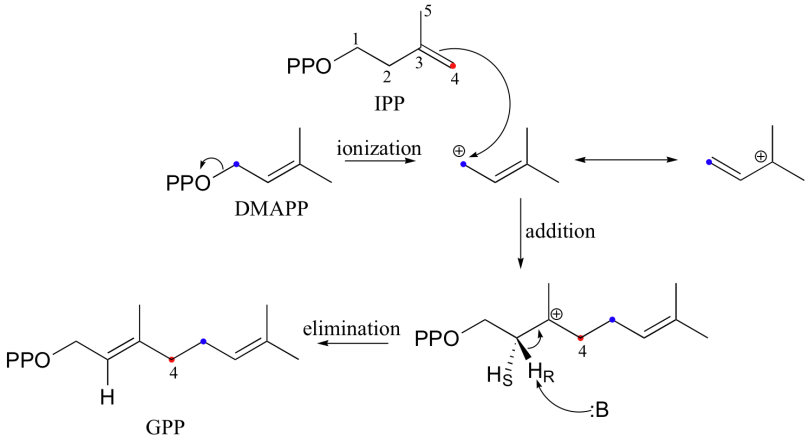
The electrophilic double bond isomerization catalyzed by IPP isomerase is a highly reversible reaction, with an equilibrium IPP:DMAPP ratio of about 6:1. In the next step of isoprenoid biosynthesis, the two five-carbon isomers condense to form a 10-carbon isoprenoid product called geranyl diphosphate (GPP).



This is a nice example of an electrophilic addition/elimination mechanism:

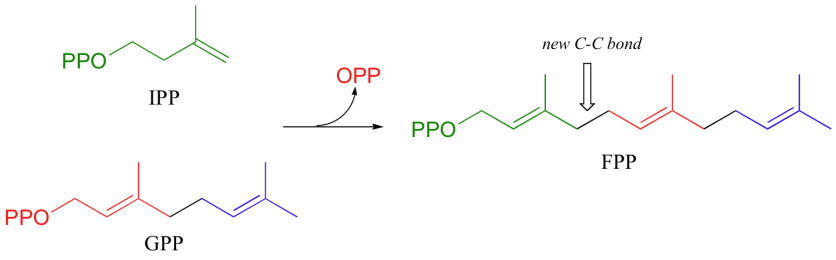


The first step is ionization of the electrophile - in other words, the leaving group departs and a carbocation intermediate is formed. In this case, the pyrophosphate group on DMAPP is the leaving group, and the electrophilic species is the resulting allylic carbocation.

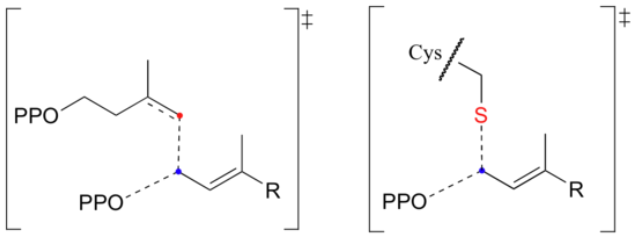


In the condensation (addition) step, the C_3-C_4 double bond in IPP attacks the positively-charged C_1 of DMAPP, resulting in a new carbon-carbon bond and a second carbocation intermediate, this time at a tertiary carbon. In the elimination phase, proton abstraction leads to re-establishment of a double bond in the GPP product. Notice that the enzyme specifically takes the *pro-R* proton in this step.

To continue the chain elongation process, another IPP molecule can then condense, in a very similar reaction, with C_1 of geranyl diphosphate to form a 15-carbon product called farnesyl diphosphate (FPP).



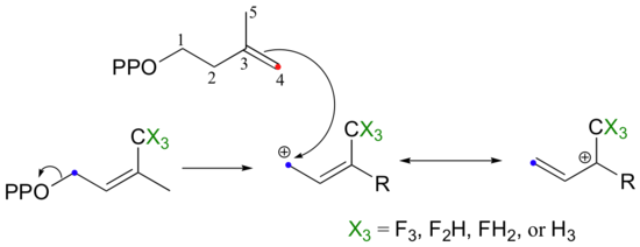
How do we know that these are indeed S_N1-like mechanisms with carbocation intermediates, rather than concerted S_N2-like mechanisms? First of all, recall that the question of whether a substitution is dissociative (S_N1-like) or associative (S_N2-like) is not always clear-cut - it could be somewhere in between, like the protein prenyltransferase reaction. The protein prenyltransferase reaction and the isoprenoid chain elongation reactions are very similar: the electrophile is the same, but in the former the nucleophile is a thiolate, while in the latter the nucleophile is a pi bond.



chain elongation TS protein prenylation TS

This difference in the identity of the nucleophilic species would lead one to predict that the chain elongation reaction has more S_N1-like character than the protein prenylation reaction. A thiolate is a very powerful nucleophile, and thus is able to *push* the pyrophosphate leaving group off, implying some degree of S_N2 character. The electrons in a pi bond, in contrast, are only weakly nucleophilic, and thus need to be *pulled* in by a powerful electrophile - *ie*. a carbocation.

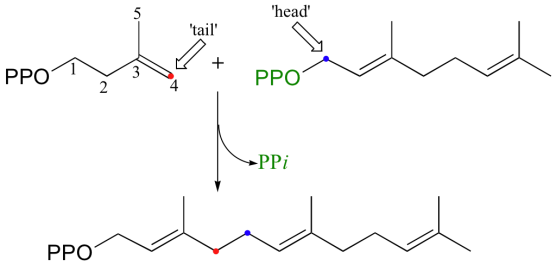
So it makes perfect sense that the chain elongation reaction should more S_N1-like than S_N2-like. Is this in fact the case? We know how to answer this question experimentally - just run the reaction with fluorinated DMAPP or GPP substrates and observe how much the fluorines slow things down.



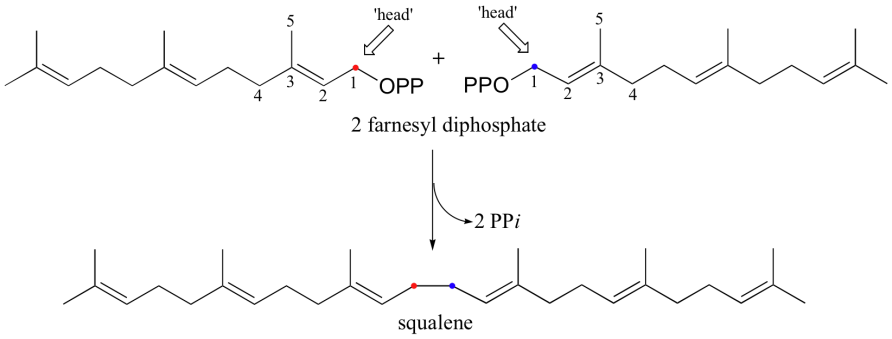
If the reaction is S_N1-like, the electron-withdrawing fluorines should destabilize the allylic carbocation intermediate and thus slow the reaction down considerably. If the mechanism is S_N2-like, the fluorine substitutions should not have a noticeable effect, because a carbocation intermediate would not be formed. When this experiment was performed with FPP synthase, the results were dramatic: the presence of a single fluorine slowed down the rate of the reaction by a factor of about 60, while two and three fluorines resulted in a reaction that was 500,000 and 3 million times slower, respectively (*J. Am. Chem. Soc*. **1981**, *103*, 3926.) These results strongly suggest indicate the formation of a carbocation intermediate in an S_N1-like displacement.

In this section, we will briefly examine the reaction catalyzed by an enzyme called squalene synthase, an important enzymatic transformation that involves some very interesting and unusual electrophilic additions, rearrangements, and reactive intermediates. This particular enzyme is also of interest because it represents a potential new target for cholesterol-lowering drugs.

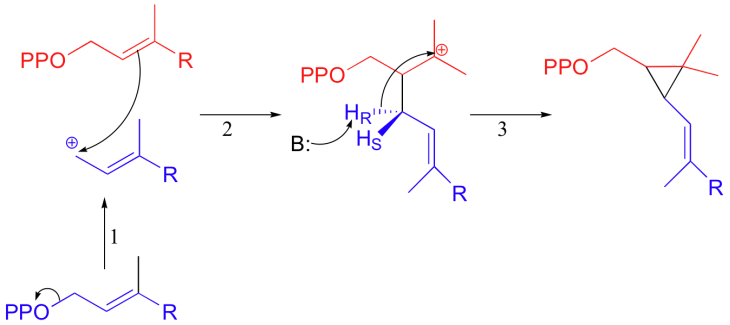
Cholesterol, as we discussed earlier in this chapter, is derived from a 30-carbon isoprenoid molecule called squalene. Squalene, in turn, is derived from the condensation of two molecules of farnesyl diphosphate (FPP), a 15-carbon isoprenoid. You may recall that FPP is the product of the C_4 to C_1, or 'head to tail' electrophilic condensation of isoprenoid chains:



The condensation of two molecules of FPP to form squalene, however, is something different: this is a 'head to head' condensation, where C_1 of the first molecule forms a bond to C_1 of the second. The chemistry involved is quite a bit more complicated.

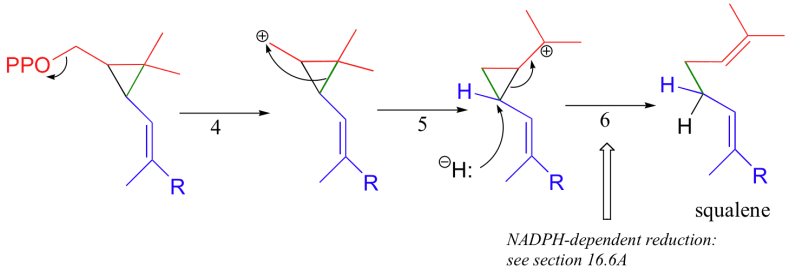


The first two steps are familiar: first, the pyrophosphate on one FPP molecule leaves (step 1), resulting in an allylic carbocation that is attacked by the C_2-C_3 π bond of the second molecule (step 2).

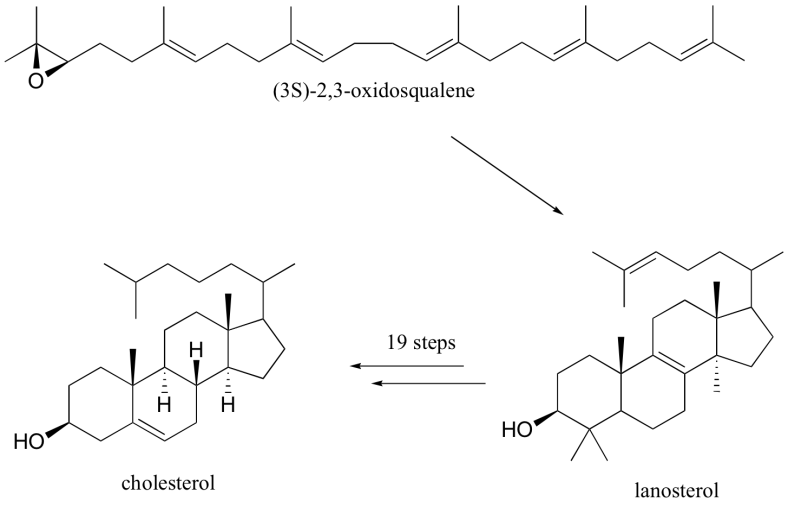


This results in a new carbon-carbon bond between the two FPP molecules, but with incorrect C_1 to C_2 connectivity (remember, the overall reaction is a C_1 to C_1 condensation). In step 3, a proton is abstracted and the electrons from the broken C-H bond bridge across a 2-carbon gap to form a cyclopropyl intermediate.

In the second stage of squalene synthesis, the second pyrophosphate group leaves, generating a cyclopropylcarbinyl cation (step 4). Because this is a primary carbocation, you probably are wondering about how stable it could be (and thus how likely an intermediate). As it turns out, such carbocations are remarkably stable, due to favorable interactions between the empty orbital and orbitals on the three-membered ring (the level of bonding theory needed to really understand this idea is beyond the scope of this text, but you may learn about it if you take a class in advanced organic chemistry). What occurs next is an alkyl shift leading to a tertiary carbocation (step 5).

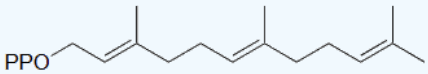


Discussion of the final step (step 6) will need to be put off - this is a reduction with a hydride nucleophile derived from a coenzyme called NADPH. Although this may seem like an extremely convoluted (and perhaps unlikely!) mechanism, there is much experimental evidence to back it up.



EXERCISE 27.5.1

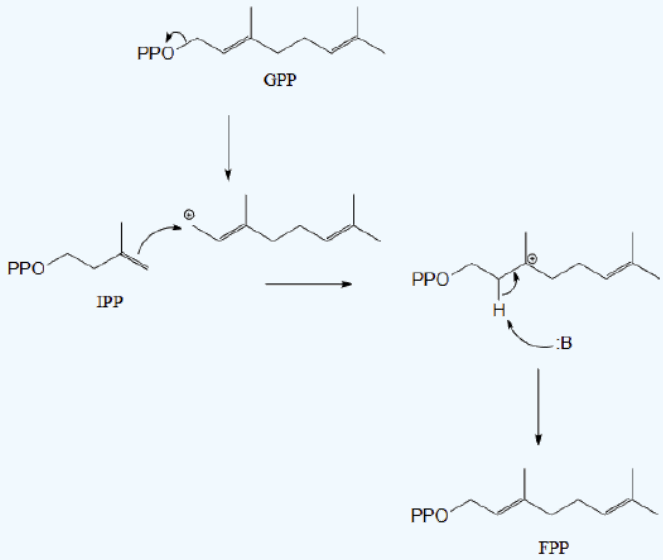
Farnesyl diphosphate (FPP) is synthesized by adding another five-carbon building block to geranyl diphosphate. What is this building block - IPP or DMAPP? Draw a mechanism for the formation of FPP.



farnesyl diphosphate

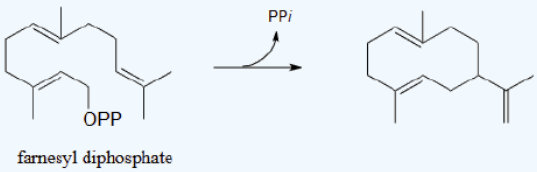
Answer

IPP is the five-carbon species added to geranyl diphosphate to make the 15-carbon farnesyl diphosphate.



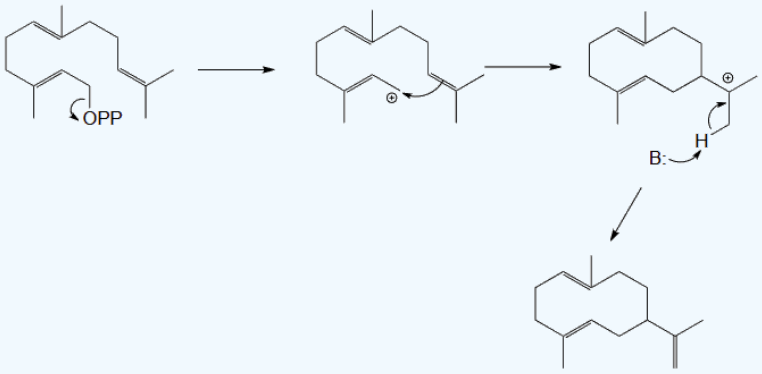
EXERCISE 27.5.2

Propose a likely mechanism for the following transformation, which is the first stage in a somewhat complex reaction in the synthesis of an isoprenoid compound in plants. (Science 1997, 277, 1815)



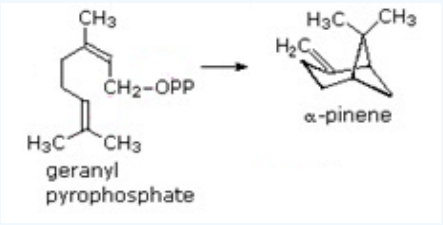
farnesyl diphosphate

Answer

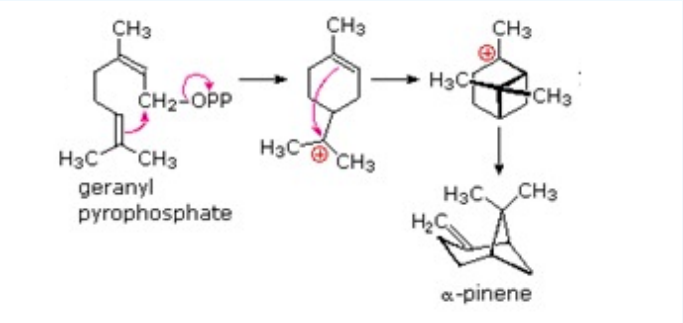


EXERCISE 27.5.3

Propose a likely mechanism for the following transformation.



Answers



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27.6: STEROIDS

OBJECTIVES

After completing this section, you should be able to

1. draw the tetracyclic ring system on which the structure of all steroids is based.
2. identify the occurrence and biological roles of at least two common steroids.
3. sketch the stereochemical conformation of a steroid, given an adequate wedge and dash structure, and determine whether the ring substituents in such a compound occupy axial or equatorial positions.
4. construct a molecular model of a steroid, given a suitable written description or a wedge and dash structure from which to work.

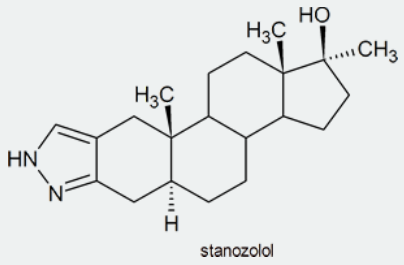
KEY TERMS

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

- steroid

STUDY NOTES

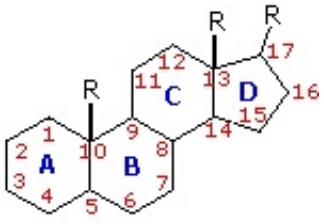
Since the 1988 Olympic Games in Seoul, even individuals who have no interest in chemistry or sport have heard the word “steroid” and are aware that some athletes use these substances to enhance their athletic abilities. Stanozolol, the substance which Canadian sprinter, Ben Johnson, was found to have used, has the structure shown below:



stanozolol

GENERAL STEROID STRUCTURE

The important class of lipids called **steroids** are actually metabolic derivatives of terpenes, but they are customarily treated as a separate group. Steroids may be recognized by their tetracyclic skeleton, consisting of three fused six-membered and one five-membered ring, as shown in the diagram below. The four rings are designated A, B, C & D as noted, and the peculiar numbering of the ring carbon atoms (shown in red) is the result of an earlier misassignment of the structure. The substituents designated by R are often alkyl groups, but may also have functionality. The R group at the A:B ring fusion is most commonly methyl or hydrogen, that at the C:D fusion is usually methyl. The substituent at C-17 varies considerably, and is usually larger than methyl. The most common locations of functional groups are C-3, C-4, C-7, C-11, C-12 & C-17. Ring A is sometimes aromatic. Since a number of tetracyclic triterpenes also have this tetracyclic structure, it cannot be considered a unique identifier.

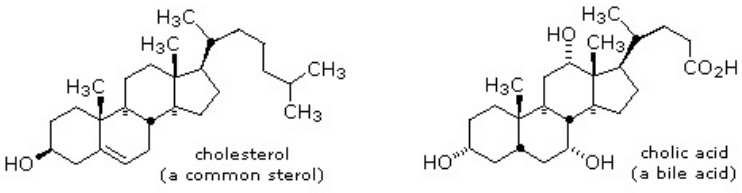


The Steroid Carbon Skeleton

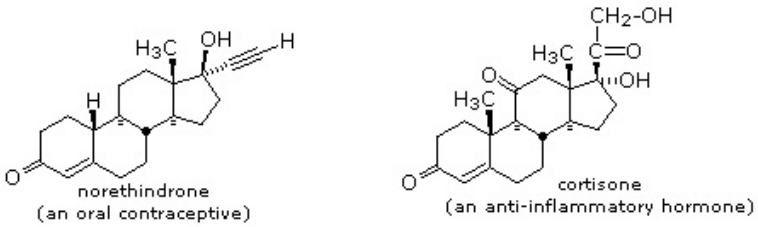
COMMON STEROIDS

Steroids are widely distributed in animals, where they are associated with a number of physiological processes. Examples of some important steroids are shown in the following diagram. Norethindrone is a synthetic steroid, all the other examples occur naturally.

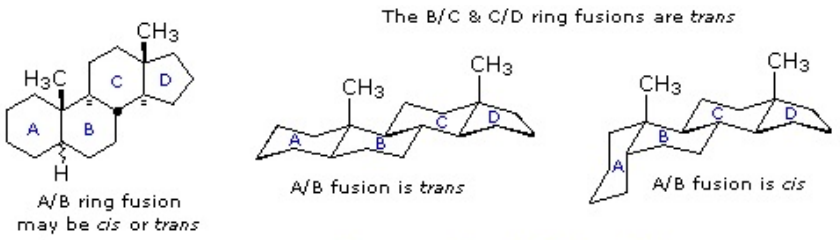
The generic steroid structure drawn above has seven chiral stereocenters (carbons 5, 8, 9, 10, 13, 14 & 17), which means that it may have as many as 128 stereoisomers. With the exception of C-5, natural steroids generally have a single common configuration.



Typical Animal Steroids



Medicinally Useful Steroids

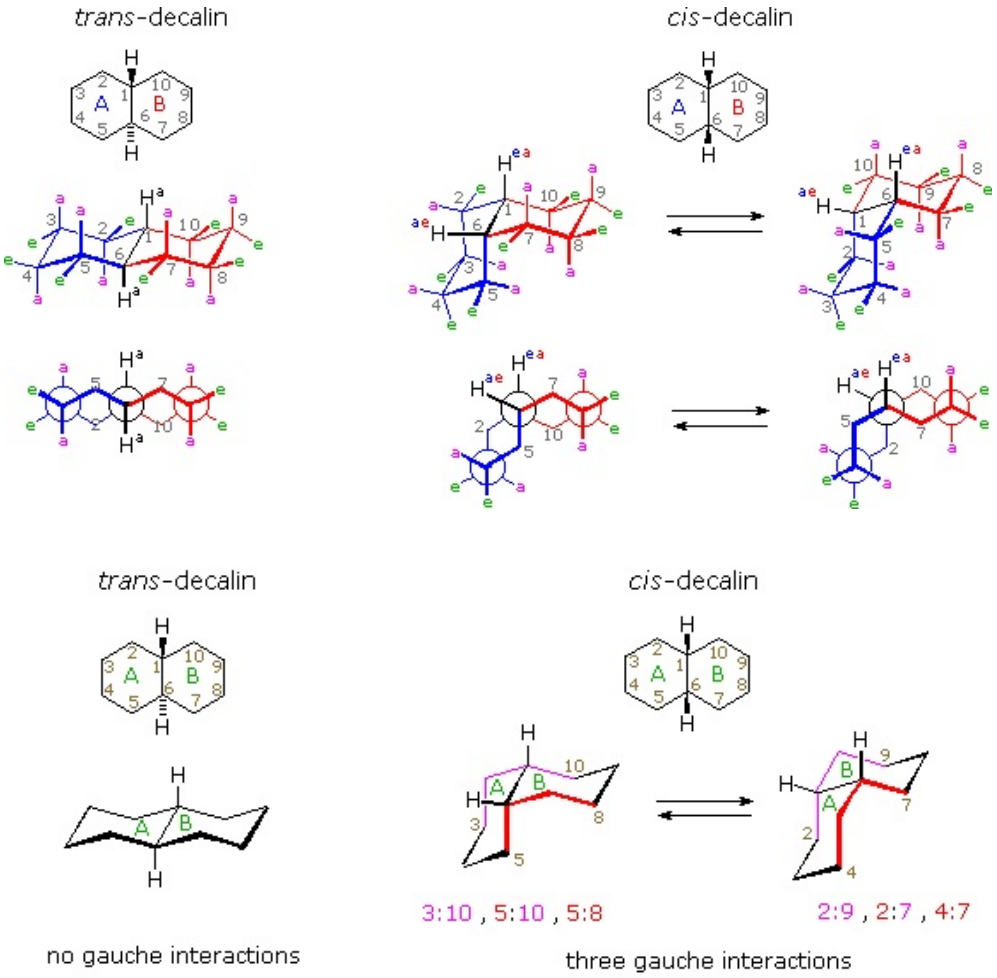


Common Steroid Conformations

Chemical studies of the steroids were very important to our present understanding of the configurations and conformations of six-membered rings. Substituent groups at different sites on the tetracyclic skeleton will have axial or equatorial orientations that are fixed because of the rigid structure of the trans-fused rings. This fixed orientation influences chemical reactivity, largely due to the greater steric hindrance of axial groups versus their equatorial isomers. Thus an equatorial hydroxyl group is esterified more rapidly than its axial isomer.

DECALIN AS A MODEL SYSTEM

It is instructive to examine a simple bicyclic system as a model for the fused rings of the steroid molecule. Decalin, short for decahydronaphthalene, exists as cis and trans isomers at the ring fusion carbon atoms. Planar representations of these isomers are drawn at the top of the following diagram, with corresponding conformational formulas displayed underneath. The numbering shown for the ring carbons follows IUPAC rules, and is different from the unusual numbering used for steroids. For purposes of discussion, the left ring is labeled A (colored blue) and the right ring B (colored red). In the conformational drawings the ring fusion and the angular hydrogens are black.



The trans-isomer is the easiest to describe because the fusion of the A & B rings creates a rigid, roughly planar, structure made up of two chair conformations. Each chair is fused to the other by equatorial bonds, leaving the angular hydrogens (Ha) axial to both rings. Note that the bonds directed above the plane of the two rings alternate from axial to equatorial and back if we proceed around the rings from C-1 to C-10 in numerical order. The bonds directed below the rings also alternate in a complementary fashion.

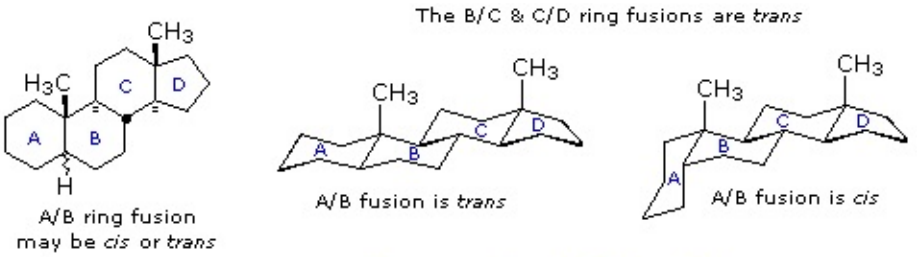
Conformational descriptions of cis- decalin are complicated by the fact that two energetically equivalent fusions of chair cyclohexanes are possible, and are in rapid equilibrium as the rings flip from one chair conformation to the other. In each of these all chair conformations the rings are fused by one axial and one equatorial bond, and the overall structure is bent at the ring fusion. In the conformer on the left, the red ring (B) is attached to the blue ring (A) by an axial bond to C-1 and an equatorial bond to C-6 (these terms refer to ring A substituents). In the conformer on the right, the carbon bond to C-1 is equatorial and the bond to C-6 is axial. Each of the angular hydrogens (Hae or Hea) is oriented axial to one of the rings and equatorial to the other. This relationship reverses when double ring flipping converts one cis-conformer into the other.

Cis-decalin is less stable than trans-decalin by about 2.7 kcal/mol (from heats of combustion and heats of isomerization data). This is due to steric crowding (hindrance) of the axial hydrogens in the concave region of both cis-conformers, as may be seen in the model display activated by the following button. This difference is roughly three times the energy of a gauche butane conformer relative to its anti conformer. Indeed three gauche butane interactions may be identified in each of the cis-decalin conformations, as will be displayed by clicking on the above conformational diagram. These gauche interactions are also shown in the model.

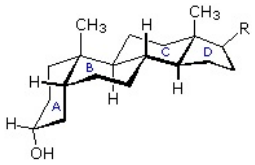
STEROID CONFORMATIONS

Steroids in which rings A and B are fused cis, such as the example on the right, do not have the same conformational mobility exhibited by cis-decalin. The fusion of ring C to ring B in a trans configuration prevents ring B from undergoing a conformational flip to another chair form. If this were to occur, ring C would have to be attached to ring B by two adjacent axial bonds directed 180º apart. This is too great a distance to be bridged by the four carbon atoms making up ring C. Consequently, the steroid molecule is locked in the all chair conformation shown here. Of course, all these steroids and decalins may have one or more six-membered rings in a boat conformation.

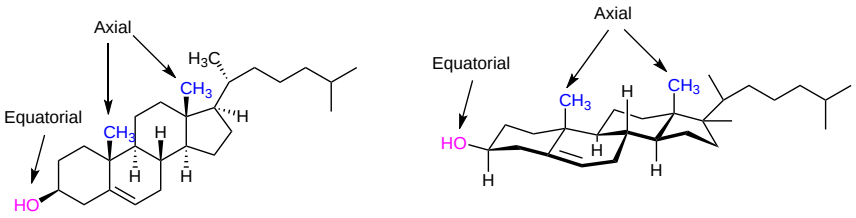
However the high energy of boat conformers relative to chairs would make such structures minor components in the overall ensemble of conformations available to these molecules.



Common Steroid Conformations



Much like cyclohexanes substituents (**Section 4-7**) on a steroid ring system can be either an axial or equatorial position. Fused rings makes steroids ridge and unable to undergo cyclohexane ring-flips Because of sterics, substituents in the equatorial posltion tend to be more energetically favorable. The -OH group present in cholesterol is in the more stable equatorial position while the two -CH_3 groups on the steroid ring are both in an axial position.

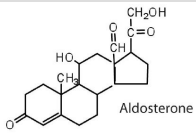
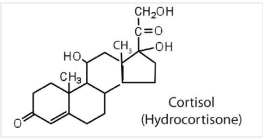
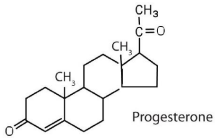
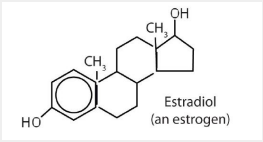
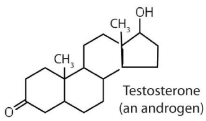


STEROID HORMONES

Hormones are chemical messengers that are released in one tissue and transported through the circulatory system to one or more other tissues. One group of hormones is known as steroid hormones because these hormones are synthesized from cholesterol, which is also a steroid. There are two main groups of steroid hormones: adrenocortical hormones and sex hormones.

The adrenocortical hormones, such as aldosterone and cortisol (Table 27.6.1), are produced by the adrenal gland, which is located adjacent to each kidney. Aldosterone acts on most cells in the body, but it is particularly effective at enhancing the rate of reabsorption of sodium ions in the kidney tubules and increasing the secretion of potassium ions and/or hydrogen ions by the tubules. Because the concentration of sodium ions is the major factor influencing water retention in tissues, aldosterone promotes water retention and reduces urine output. Cortisol regulates several key metabolic reactions (for example, increasing glucose production and mobilizing fatty acids and amino acids). It also inhibits the inflammatory response of tissue to injury or stress. Cortisol and its analogs are therefore used pharmacologically as immunosuppressants after transplant operations and in the treatment of severe skin allergies and autoimmune diseases, such as rheumatoid arthritis.

Table 27.6.1 Representative Steroid Hormones and Their Physiological Effects

Hormone	Effect
 Aldosterone	regulates salt metabolism; stimulates kidneys to retain sodium and excrete potassium
 Cortisol (Hydrocortisone)	stimulates the conversion of proteins to carbohydrates
 Progesterone	regulates the menstrual cycle; maintains pregnancy
 Estradiol (an estrogen)	stimulates female sex characteristics; regulates changes during the menstrual cycle
 Testosterone (an androgen)	stimulates and maintains male sex characteristics

The sex hormones are a class of steroid hormones secreted by the gonads (ovaries or testes), the placenta, and the adrenal glands. Testosterone and androstenedione are the primary male sex hormones, or *androgens*, controlling the primary sexual characteristics of males, or the development of the male genital organs and the continuous production of sperm. Androgens are also responsible for the development of secondary male characteristics, such as facial hair, deep voice, and muscle strength. Two kinds of sex hormones are of particular importance in females: progesterone, which prepares the uterus for pregnancy and prevents the further release of eggs from the ovaries during pregnancy, and the estrogens, which are mainly responsible for the development of female secondary sexual characteristics, such as breast development and increased deposition of fat tissue in the breasts, the buttocks, and the thighs. Both males and females produce androgens and estrogens, differing in the amounts of secreted hormones rather than in the presence or absence of one or the other.

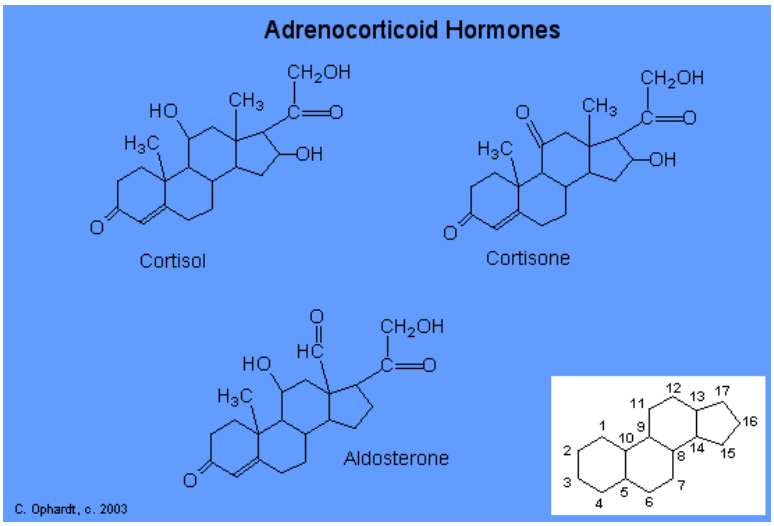
Sex hormones, both natural and synthetic, are sometimes used therapeutically. For example, a woman who has had her ovaries removed may be given female hormones to compensate. Some of the earliest chemical compounds employed in cancer chemotherapy were sex hormones. For example, estrogens are one treatment option for prostate cancer because they block the release and activity of testosterone. Testosterone enhances prostate cancer growth. Sex hormones are also administered in preparation for sex-change operations, to promote the development of the proper secondary sexual characteristics. Oral contraceptives are synthetic derivatives of the female sex hormones; they work by preventing ovulation.

ADRENOCORTICOID HORMONES

The adrenocorticoid hormones are products of the adrenal glands ("adrenal" means adjacent to the renal (kidney). The most important adrenocorticoid is **aldosterone**, which regulates the reabsorption of sodium and chloride ions in the kidney tubules and increases the loss of potassium ions. Aldosterone is secreted when blood sodium ion levels are too low to cause the kidney to retain sodium ions. If sodium levels are elevated, aldosterone is not secreted, so that some sodium will be lost in the urine. Aldosterone also controls swelling in the tissues.

Cortisol, the most important glucocortinoid, has the function of increasing glucose and glycogen concentrations in the body. These reactions are completed in the liver by taking fatty acids from lipid storage cells and amino acids from body proteins to make glucose and glycogen.

In addition, cortisol and its ketone derivative, **cortisone**, have the ability to inflammatory effects. Cortisone or similar synthetic derivatives such as prednisolone are used to treat inflammatory diseases, rheumatoid arthritis, and bronchial asthma. There are many side effects with the use of cortisone drugs, so there use must be monitored carefully.

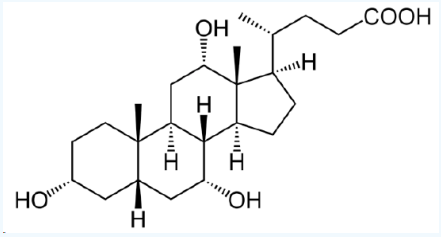


SYNTHETIC STEROIDS

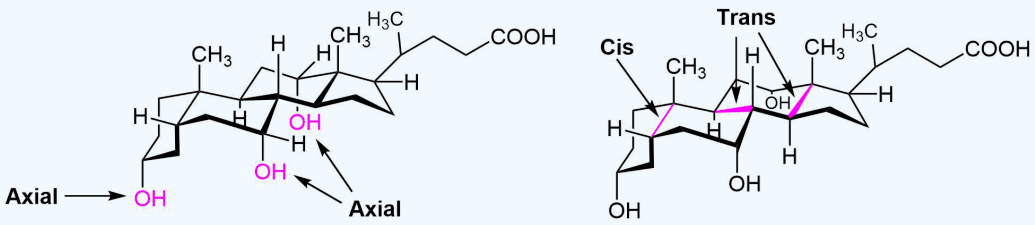
In the hope of producing new drugs, thousands of steroid derivatives have been synthesized and test by pharmaceutical companies. The two classes of synthetic steroids most commonly know by the public are oral contraceptives and anabolic steroids. Oral contraceptives contain synthetic versions of the hormones estrogen (ethynylestradiol) and progestin (norethindrone). They prevent pregnancy by interfering with ovulation, fertilization, and/or implantation of the fertilized egg. Anabolic steroids (methandrostenolone) mimic the effects of natural testosterone.

EXERCISE 27.6.1

The following molecule is cholic acid. Draw it showing the chair conformations. Determine if the three fused bonds have a *cis* or *trans* configuration. Determine if the OH groups are axial or equatorial.



Answer



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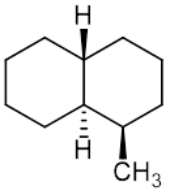
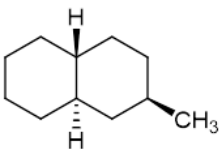
EXERCISE 27.6.2

Draw the following decalin molecules in chair conformations. Determine if the -CH_3 groups are axial or equatorial.

a)

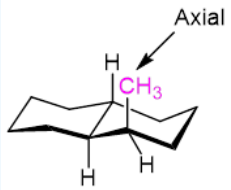


b)

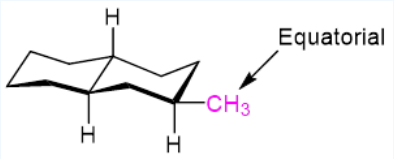


Answer

a)



b)



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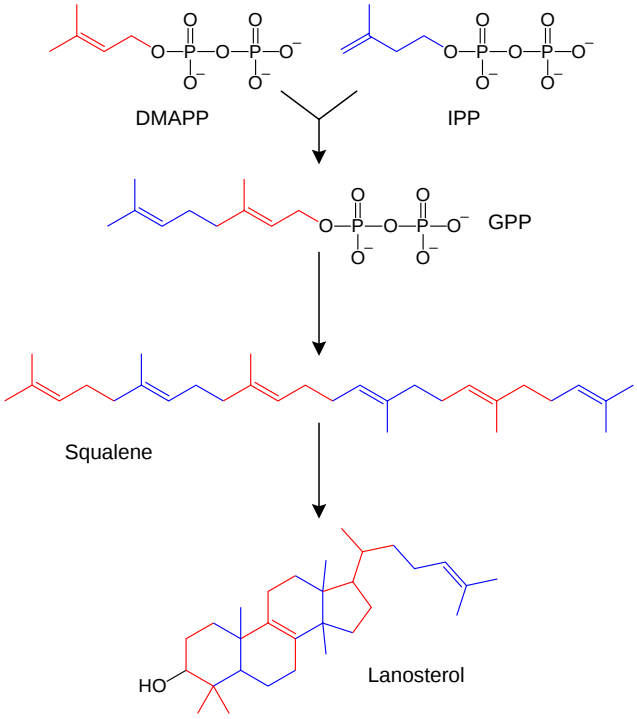
27.7: BIOSYNTHESIS OF STEROIDS

OBJECTIVES

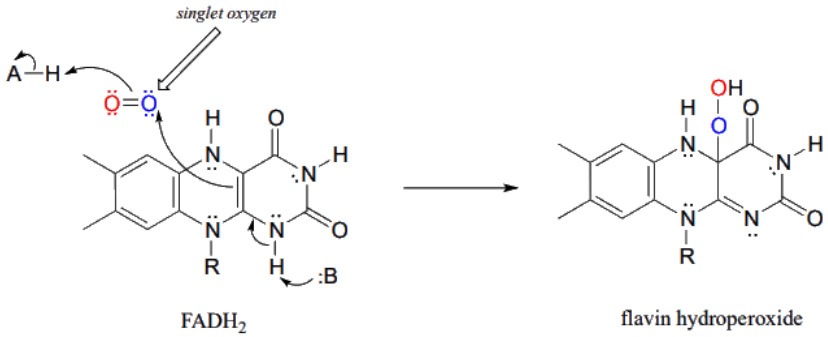
After completing this section, you should be able to

- give an overview of how steroids are synthsized.
- describe changes to molecules through the biosynthesis of steroids.

Steroid biosynthesis is an anabolic metabolic pathway that produces steroids from simple precursors. A unique biosynthetic pathway is followed in animals compared to many other organisms, making the pathway a common target for antibiotics and other anti-infective drugs. In humans and other animals, the biosynthesis of steroids follows the **mevalonate pathway** that uses acetyl-CoA as building blocks to form dimethylallyl pyrophosphate (DMAPP) and isopentenyl pyrophosphate (IPP). These two compounds are coupled to form geranyl pyrophosphate (GPP) which is then converted to the hydrocarbon polyene squalene. After an oxidation and multiple rearrangements, lanosterol the first steroid in the pathway is formed. Further conversions can yield different steroids.



The key step in the biosynthesis of lanosterol is the regioselective epoxidation of squalene to give (3*S*)-2,3-oxidosqualene. This reaction is catalyzed by the monooxygenase enzyme squalene epoxidase. In this step, flavin hydroperoxide serves as the direct oxidizing agent. In flavin hydroperoxide, the peroxide group is linked to one of the carbons of the reactive triple-ring system of the coenzyme. A possible mechanism for the formation of flavin peroxide from $FADH_2$ and molecular oxygen is shown below.



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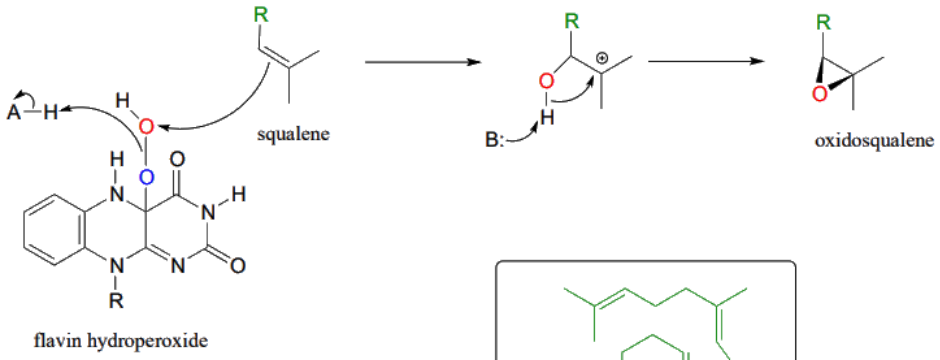
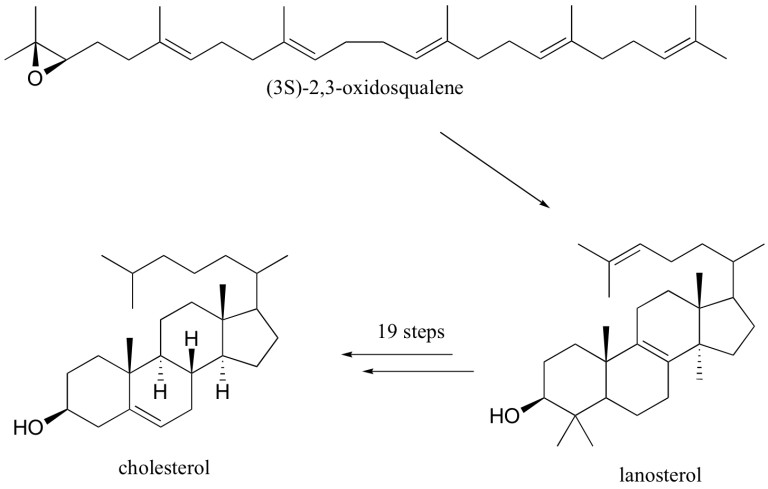
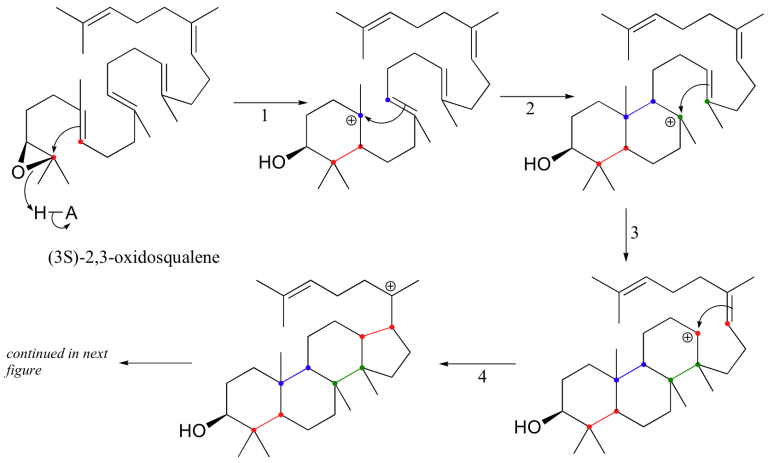
The mechanism for the flavin-hydroperoxide-dependent epoxidation of squalene is initiated by the nucleophilic attack of the pi electrons of a squalene double bond on the electrophilic terminal hydroperoxide oxygen.



Oxidosqualene goes on to cyclize to lanosterol in a complex and fascinating electrophilic reaction which catalyzed by oxidosqualene-lanosterol cyclase. This reaction has two phases. The first phase, in which the actual cyclization takes place, is a series of electrophilic addition steps. The second phase is a series of hydride and methyl shifts. There is some argument about whether these processes occur in a stepwise fashion (with discreet carbocation intermediates) or in a concerted manner. For the sake of clarity, we will show the reaction proceeding stepwise. After lanosterol is formed the pathway continued to form cholesterol which is the precursor that all other steroids are derived.

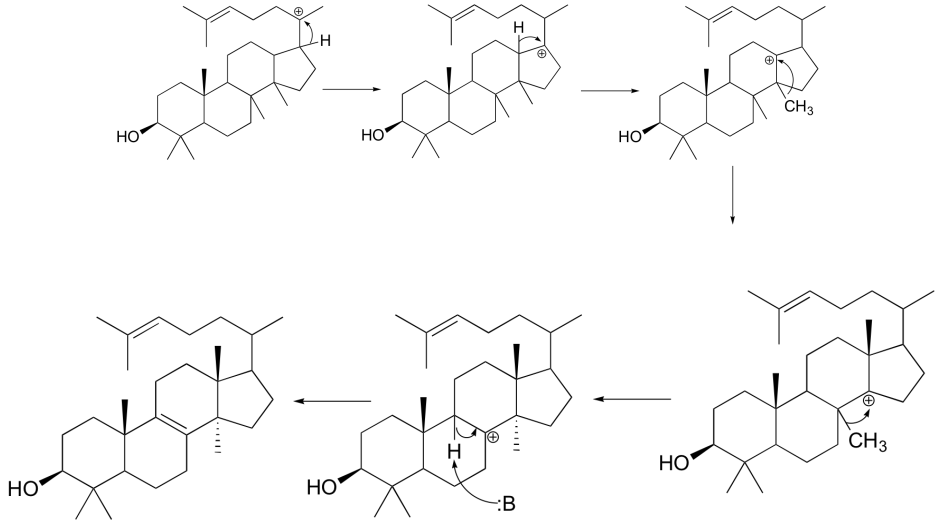


The cyclization phase begins with attack by pi electrons on an epoxide electrophile. The epoxide ring opens to form an alcohol after protonation. A relatively stable tertiary carbocation is also formed. Steps 2, 3, and 4 are simply successive attacks by pi electrons on the carbocation generated by the previous attack. The overall result of this electrophilic cascade is the opening of the epoxide ring, and closure of three six-membered and one five-membered ring.



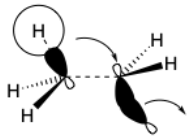
(3S)-2,3-oxidosqualene

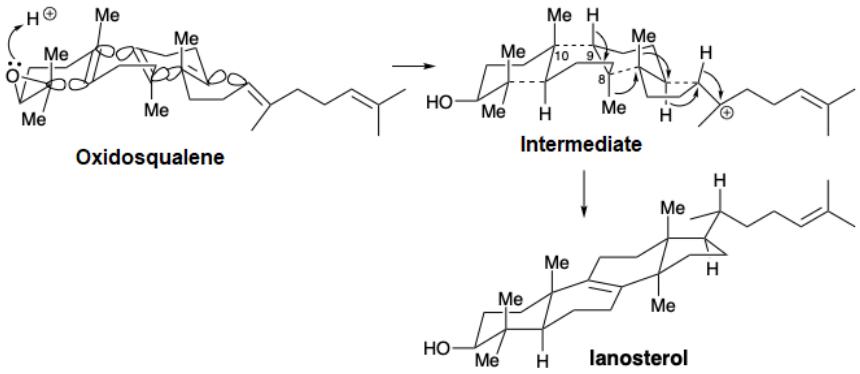
Next comes the rearrangement phase of the reaction in which a series of two 1,2-hydride and two 1,2-methyl shifts to give lanosterol after proton loss from the 9 position.



lanosterol

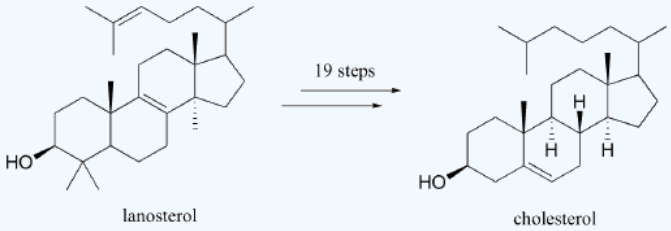
Especially interesting are the stereochemical details of the polyene cyclization and subsequent rearrangement. The polyene cyclization involves stereospecific **anti-periplanar** addition across three C=C bonds in oxidosqualene (see below). The folded conformation of oxidosqualene, required for cyclization is probably imposed by the enzyme involved since appreciable steric congestion is present in both oxidosqualene and the intermediate. Relief of steric strain provides a large driving force for the rearrangements to lanosterol that involves stereospecific inversion of configuration at each stereocenter during 1,2-hydrogen or methyl shifts. Thus, each 1,2-hydride or 1,2-methyl shift occurs to the backside of the orbital connected to the leaving group in what can be viewed as a series of nucleophilic substitution reactions – where σ-bonding electron pairs serve as the nucleophiles.





EXERCISE 27.7.1

What changes must be made to the structure of lanosterol to convert it to cholesterol?



Answer

Three methyl groups and a double bond are removed. Another double bond is moved to the other side of a six-membered ring.

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27.S: BIOMOLECULES - LIPIDS (SUMMARY)

CONCEPTS & VOCABULARY

- fulfill all of the detailed objectives listed under each individual section.
- define, and use in context, any of the key terms introduced in this chapter.

25.1 Introduction

- Carbohydrates are composed of carbon, hydrog

25.2 Classification of Carbohydrates

- Carbohydrates originate as products from photosynt

25.3 Fischer Projections

- The Fischer projection is a type of notation often used when multip

25.4 D,L Sugars

- To determine absolute configuration for carbohydrates, Emil Fischer started with an arb

25.5 Configurations of Aldoses

- The aldos

25.6 Anomers

- The preferred structural form of mon

25.7 Reactions of Monosaccharides

- The -OH groups on a monosacc

25.8 The Eight Essential Monosaccharides

- The eight essential monos

25.9 Disaccharides

- Disaccharides are sugars com

25.10 Polysaccharides and Their Synthesis

- Polysaccharides are very large polymers co

25.11 Other Important Carbohydrates

- The backbone of DNA is based on a repeated

25.12 Cell-Surface Carbohydrates and Influenza Viruses

- Carbohydrates a

SKILLS TO MASTER

- Skill 25.1 Determine which molecules can be classified as carbohydr
-

SUMMARY OF REACTIONS

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CHAPTER OVERVIEW

28: NUCLEIC ACIDS

LEARNING OBJECTIVES

When you have completed Chapter 28, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. draw the structure of a given nucleotide.
3. discuss the structure of DNA and RNA.
4. describe the processes involved in DNA replication, transcription, translation, and protein synthesis.
5. define, and use in context, the key terms introduced in this chapter.

Two types of nucleic acids are found in cells—deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). These highly complex substances are built up from a number of simpler units, called nucleotides. Each nucleotide consists of three parts: a phosphoric acid residue, a sugar and a nitrogen-containing heterocyclic base. Thus, in order to understand the biochemistry of the nucleic acids, you must first study the chemistry of the sugars (see Chapter 25) and simple heterocyclic systems. We have already discussed certain aspects of the structure of heterocyclic ring systems during our study of aromaticity (Sections 15.5–15.6). You may find it helpful to review this chapter.

Chapter 28 examines the structure and replication of DNA and then describes the structure and synthesis of RNA. The chapter closes with a brief study of the role played by RNA in the biosynthesis of proteins.

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28.0: Chapter Objectives

Learning Objectives

- Understand the components and chemical structure of nucleotides, and their role in forming DNA and RNA molecules.
- Analyze the principles of base pairing and hydrogen bonding in nucleic acids, and how they contribute to the stability and specificity of DNA and RNA structures.
- Examine the chemical mechanisms involved in nucleic acid synthesis (polymerization) and degradation (hydrolysis), and the enzymatic processes of DNA replication, RNA transcription, and repair.
- Explore the different conformations of nucleic acids, including their impact on function and interactions with other molecules.
- Learn about analytical techniques used to study nucleic acids, and how they provide insights into structure, function, and interactions.

Nucleic acids are biopolymers found in all living organisms, serving as the essential molecules for the storage, transmission, and expression of genetic information. These complex macromolecules are composed of repeating units called nucleotides, which consist of three main components: a nitrogenous base, a five-carbon sugar (ribose or deoxyribose), and a phosphate group.

There are two primary types of nucleic acids: deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). DNA is the genetic blueprint of an organism, encoding the instructions for the synthesis of proteins and the regulation of cellular activities. It exists in the form of a double helix, with two complementary strands held together by hydrogen bonds between the nitrogenous bases adenine (A) and thymine (T), and guanine (G) and cytosine (C).

RNA, on the other hand, plays diverse roles in gene expression, including messenger RNA (mRNA) which carries genetic information from DNA to the ribosomes for protein synthesis, transfer RNA (tRNA) which brings amino acids to the ribosomes during protein synthesis, and ribosomal RNA (rRNA) which forms the structural and catalytic core of ribosomes.

The structure and function of nucleic acids are intricately linked. The sequence of nitrogenous bases along the nucleic acid chain determines the genetic code, with each triplet of bases (codon) encoding a specific amino acid or serving as a signal for regulatory functions. The ability of nucleic acids to undergo replication, transcription, and translation enables the faithful transmission and expression of genetic information from one generation to the next.

Beyond their role in genetics, nucleic acids also participate in various cellular processes, including DNA repair, RNA processing, and gene regulation. Moreover, advances in biotechnology have led to the manipulation and engineering of nucleic acids for applications such as genetic engineering, molecular diagnostics, and gene therapy.

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28.1: NUCLEOTIDES AND NUCLEIC ACIDS

OBJECTIVES

After completing this section, you should be able to

- outline the relationship between nucleic acids, nucleotides and nucleosides.
- identify, in general terms, the enzymatic hydrolysis products of nucleosides.
- explain the structural difference between the sugar components of DNA and RNA.
- identify by name the four heterocyclic amine bases found in deoxyribonucleotides.
- identify by name the four heterocyclic amine bases found in ribonucleotides.
- draw the general structure of a nucleotide and a nucleoside.
- indicate the nitrogen atom by which a given purine or pyrimidine base attaches to the sugar component in nucleotides and nucleosides.
- sketch a section of nucleic acid to show how the nucleotide units are joined together.

KEY TERMS

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

- deoxyribonucleic acid (DNA)
- nucleosides nucleotides
- ribonucleic acid (RNA)

STUDY NOTES

The five bases that are found in nucleotides are often represented by their initial letter: adenine, A; guanine, G; cytosine, C; thymine, T; and uracil, U. Note that A, G, C and T occur in DNA; A, G, C and U occur in RNA. You are not required to memorize the structures of these bases, but you must know how each one bonds to the sugar unit in a nucleotide.

To fulfill Objective 6, you should be able to reproduce the figure below.

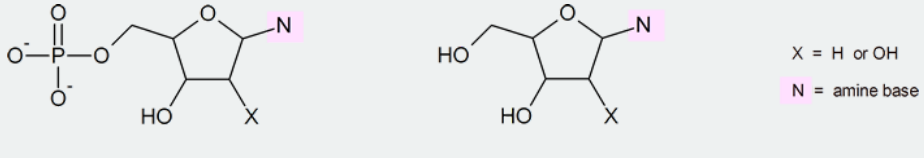


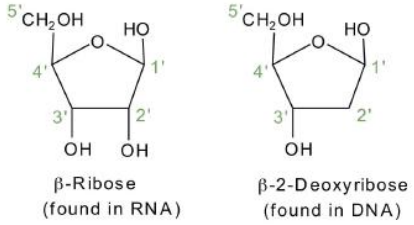
Figure 28.1.0 The Pyrimidine and Purine Nucleotides below.

The Learning Objective of this Module is to identify the different molecules that combine to form nucleotides.

The repeating, or monomer, units that are linked together to form **nucleic acids** are known as **nucleotides**. The deoxyribonucleic acid (DNA) of a typical mammalian cell contains about 3×10^9 nucleotides. Nucleotides can be further broken down to a phosphate group (PO_4^{-3}) and a nucleoside which is composed of a aldopentose sugar (a sugar with five carbon atoms), and a heterocyclic purine or pyrimidine base (a base containing nitrogen atoms).

$$\text{nucleic acids} \xrightarrow[\text{down into}]{\text{can be broken}} \text{nucleotides} \xrightarrow[\text{down into}]{\text{can be broken}} H_3PO_4 + \text{nitrogen base} + \text{pentose sugar}$$

If the pentose sugar is ribose, the nucleotide is more specifically referred to as a *ribonucleotide*, and the resulting nucleosides are used in ribonucleic acid (RNA). If the sugar is 2-deoxyribose, the nucleotide is a *deoxyribonucleotide*, and the nucleoside are used in deoxyribonucleic acid (DNA). The prefix -deoxy implies that there is an oxygen missing from the 2' position of ribose.



The nitrogenous bases found in nucleotides are classified as pyrimidines or purines. Pyrimidines are heterocyclic amines with two nitrogen atoms in a six-member ring and include uracil, thymine, and cytosine. Purines are heterocyclic amines consisting of a pyrimidine ring fused to a five-member ring with two nitrogen atoms. Adenine and guanine are the major purines found in nucleic acids (Figure 28.1.1). The numbering convention is that primed numbers designate the atoms of the pentose ring, and unprimed numbers designate the atoms of the purine or pyrimidine ring.

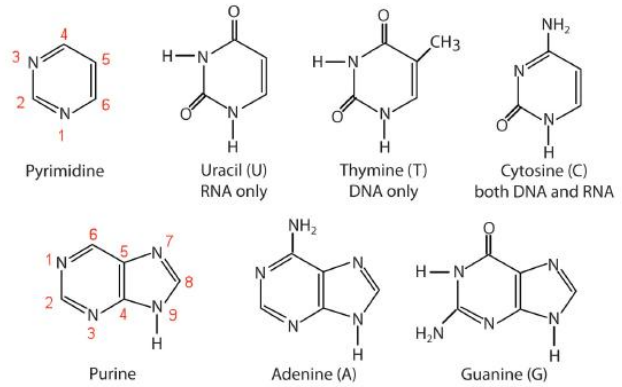
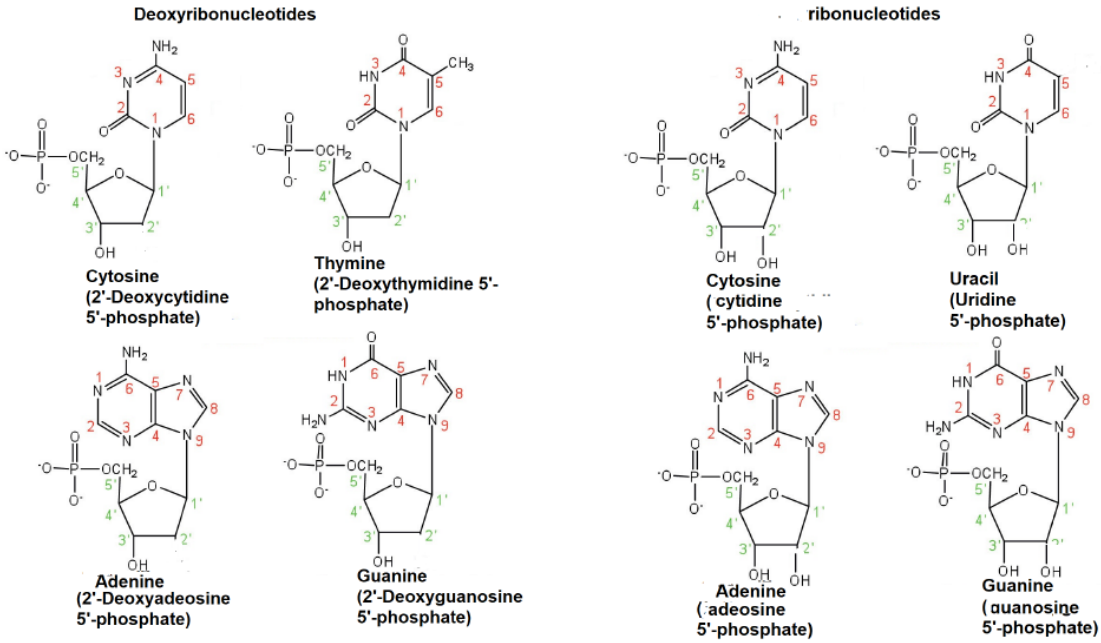


Figure 28.1.1: The Nitrogenous Bases Found in DNA and RNA

Nucleosides are formed by a bond between the anomeric C1′ of the pentose sugar and N1 position of the pyrimidine base or the N9 position of the purine base. The addition of a phospate groups at the 5' position of a nucleoside creates a corresponding nucleotide. DNA is made from four deoxyribonucleotides (Cytosine, Thymine, Adenine, Guanine) and RNA is made from four ribonucleotides Cytosine, Uracil, Adenine, Guanine. The names and structures of the major ribonucleotides and deoxyribonucleotides are given in Figure 28.1.2.



Apart from being the monomer units of DNA and RNA, the nucleotides and some of their derivatives have other functions as well. Adenosine diphosphate (ADP) and adenosine triphosphate (ATP), shown in Figure 28.1.3, have a role in cell metabolism. Moreover, a number of coenzymes, including flavin adenine dinucleotide (FAD), nicotinamide adenine dinucleotide (NAD^+), and coenzyme A, contain adenine nucleotides as structural components.

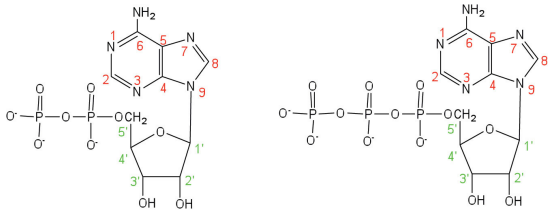


Figure 28.1.3: Structures of Two Important Adenine-Containing Nucleotides

PRIMARY STRUCTURE OF NUCLEIC ACIDS

Nucleotides are joined together through the phosphate group of one nucleotide connecting in an ester linkage to the OH group on the 3' carbon atom of the sugar unit of a second nucleotide. This unit joins to a third nucleotide, and the process is repeated to produce a long nucleic acid chain (Figure 28.1.4). The backbone of the chain consists of alternating phosphate and sugar units (2-deoxyribose in DNA and ribose in RNA). The purine and pyrimidine bases branch off this backbone.

Like proteins, nucleic acids have a primary structure that is defined as the sequence of their nucleotides. Unlike proteins, which have 20 different kinds of amino acids, there are only 4 different kinds of nucleotides in nucleic acids. For amino acid sequences in proteins, the convention is to write the amino acids in order starting with the N-terminal amino acid. In writing nucleotide sequences for nucleic acids, the convention is to write the nucleotides (usually using the one-letter abbreviations for the bases, shown in Figure 28.1.4) starting with the nucleotide having a free phosphate group, which is known as the 5′ end, and indicate the nucleotides in order. For DNA, a lowercase *d* is often written in front of the sequence to indicate that the monomers are deoxyribonucleotides. The final nucleotide has a free OH group on the 3′ carbon atom and is called the *3′ end*. The sequence of nucleotides in the DNA segment shown in Figure 28.1.4 would be written 5′-dG-dT-dA-dC-3′, which is often further abbreviated to dGTAC or just GTAC.

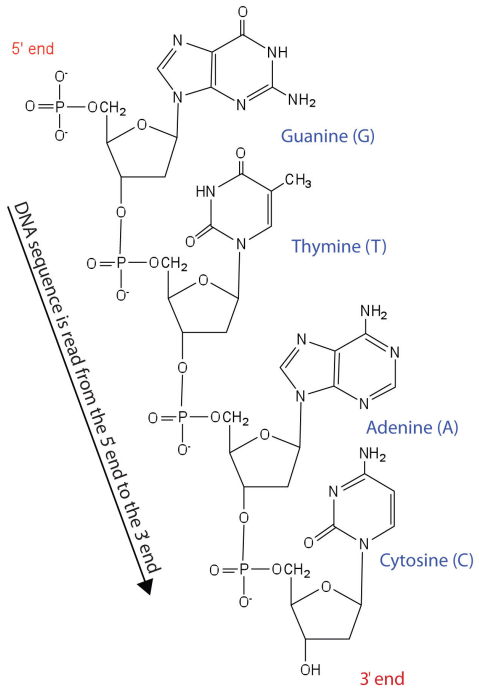


Figure 28.1.4: Structure of a Segment of DNA. A similar segment of RNA would have OH groups on each C2′, and uracil would replace thymine.

NOTE

Each phosphate group has one acidic hydrogen atom that is ionized at physiological pH. This is why these compounds are known as nucleic acids.

EXERCISE 28.1.1

Classify each compound as a pentose sugar, a purine, or a pyrimidine.

a. adenine
b. guanine
c. deoxyribose
d. thymine
e. ribose
f. cytosine

Answer

a. purine
b. purine
c. pentose sugar
d. pyrimidine
e. pentose sugar
f. pyrimidine

EXERCISE 28.1.2

Identify the three molecules needed to form the nucleotides in each nucleic acid.

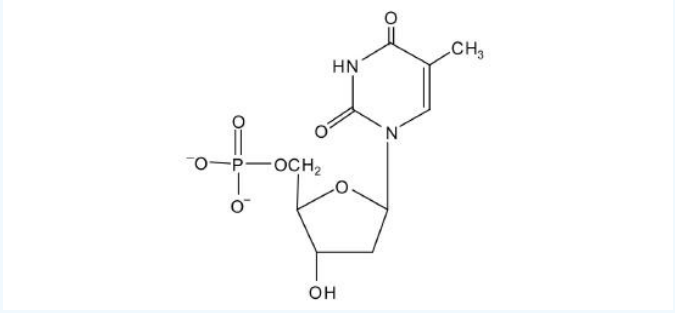
a. DNA
b. RNA

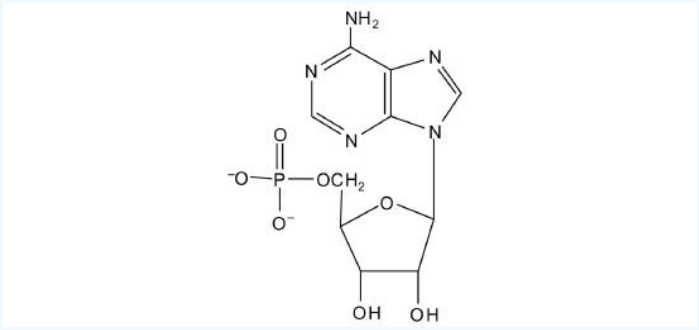
Answer

a. nitrogenous base (adenine, guanine, cytosine, and thymine), 2-deoxyribose, and H_3PO_4
b. nitrogenous base (adenine, guanine, cytosine, and uracil), ribose, and H_3PO_4

EXERCISE 28.1.3

For each structure, circle the sugar unit and identify the nucleotide as a ribonucleotide or a deoxyribonucleotide.

a. 

• 

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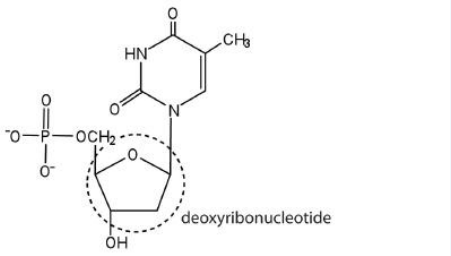
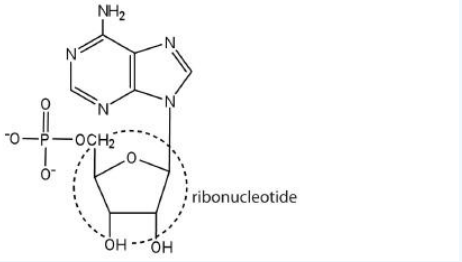
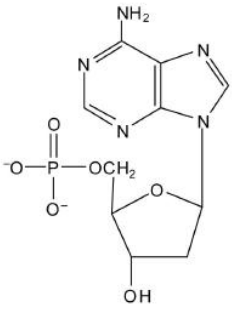
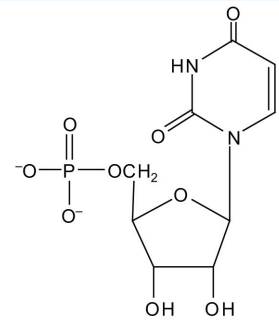
a. 

b. 

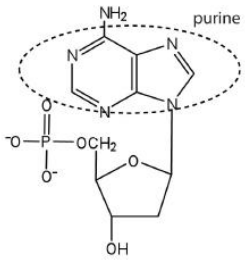
EXERCISE 28.1.4

For each structure, circle the nitrogenous base and identify it as a purine or pyrimidine.

a. 

- 

Answer

a. 

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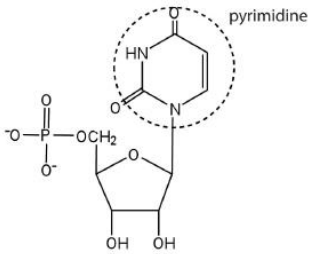
b. 

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28.2: BASE PAIRING IN DNA - THE WATSON-CRICK MODEL

OBJECTIVES

After completing this section, you should be able, given the necessary Kekulé structures, to show how hydrogen bonding can occur between thymine and adenine, and between guanine and cytosine; and to explain the significance of such interactions to the primary and secondary structures of DNA.

STUDY NOTES

Watson and Crick received the Nobel Prize in 1962 for elucidating the structure of DNA and proposing the mechanism for gene reproduction. Their work rested heavily on X-ray crystallographic work done on RNA and DNA by Franklin and Wilkins. Wilkins shared the Nobel Prize with Watson and Crick, but Franklin had been dead four years at the time of the award (you cannot be awarded the Nobel Prize posthumously).

The history of Watson and Crick's proposed DNA model is controversial and a travesty of scientific ethics. Rosalind Franklin was deeply involved in the determination of the structure of DNA, and had collected numerous diffraction patterns. Watson attended a departmental colloquium at King's College given by Franklin, and came into possession of an internal progress report she had written. Both departmental colloquia and progress reports are merely methods of discussion between colleagues; works presented in these fora are not considered by scientists to be "published" works, and therefore are not in the public domain. Watson and Crick not only were aware of Franklin's work, but used her unpublished data, presented in confidence within her own college.

The final blow came about a year after the colloquium. Watson visited Wilkins at King's College, and Wilkins inexplicably handed over Franklin's diffraction photographs without her consent. Had Franklin's work not been secretly taken from her, she might quite possibly have solved the DNA structure before Watson and Crick, who at the time did not yet have their own photographs. This is truly one of the sadder episodes of questionable scientific ethics and discovery that I have ever encountered.

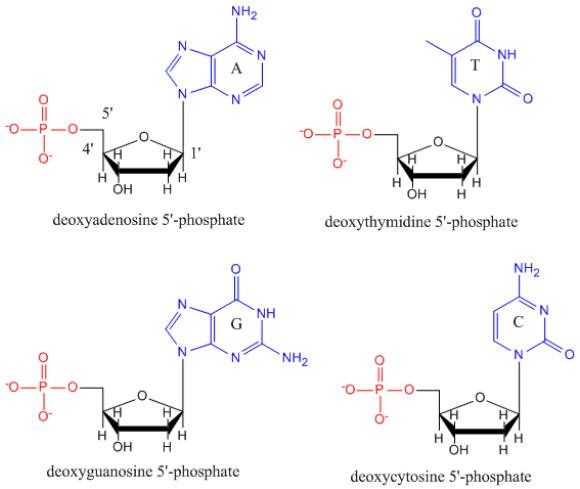
References

Kass-Simon, G., and P. Farnes. Women of Science: Righting the Record. Bloomington, IN: Indiana University Press, 1990.

Maddox, B. Rosalind Franklin: The Dark Lady of DNA. New York: HarperCollins, 2002.

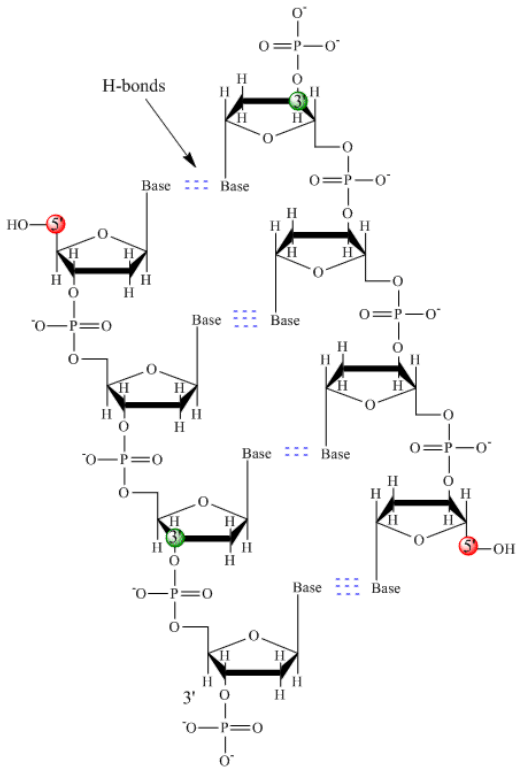
INTERMOLECULAR FORCES IN NUCLEIC ACIDS

The nucleic acids RNA and DNA are involved in the storage and expression of genetic information in a cell. Both are polymers of monomeric nucleotides. DNA exists in the cell as double-stranded helices while RNA typically is a single-stranded molecule which can fold in 3D space to form complex secondary (double-stranded helices) and tertiary structures in a fashion similar to proteins. The complex 3D structures formed by RNA allow it to perform functions other than simple genetic information storage, such as catalysis. Hence most scientists believe that RNA preceded both DNA and proteins in evolution as it can both store genetic information and catalyze chemical reactions.

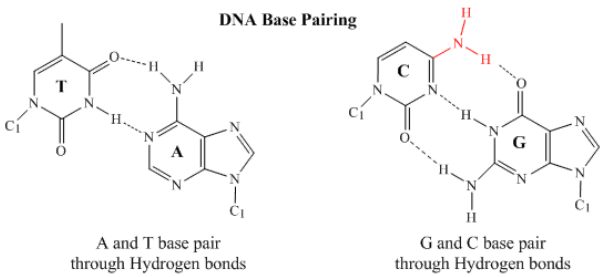


DNA

DNA is a polymer, consisting of monomers call deoxynucleotides. The monomer contains a simple sugar (deoxyribose, shown in black above), a phosphate group (in red), and a cyclic organic R group (in blue) that is analogous to the side chain of an amino acid. Only four bases are used in DNA (in contrast to the 20 different side chains in proteins) which we will abbreviate, for simplicity, as A, G, C and T. They are bases since they contain amine groups that can accept protons. The polymer consists of a sugar - phosphate - sugar - phosphate backbone, with one base attached to each sugar molecule. As with proteins, the DNA backbone is polar but also charged. It is a polyanion. The bases, analogous to the side chains of amino acids, are predominately polar. Given the charged nature of the backbone, you might expect that DNA does not fold to a compact globular (spherical) shape, even if positively charged cations like Mg bind to and stabilize the charge on the polymer. Instead, DNA exists usually as a double-stranded (ds) structure with the sugar-phosphate backbones of the two different strands running in opposite directions (5'-3' and the other 3'-5'). The strands are held together by hydrogen bonds between bases on complementary strands. Hence like proteins, DNA has secondary structure but in this case, the hydrogen bonds are not within the backbone but between the "side chain" bases on opposing strands. It is actually a misnomer to call dsDNA a molecule, since it really consists of two different, complementary strands held together by hydrogen bonds. A structure of ds-DNA showing the opposite polarity of the strands is shown below.

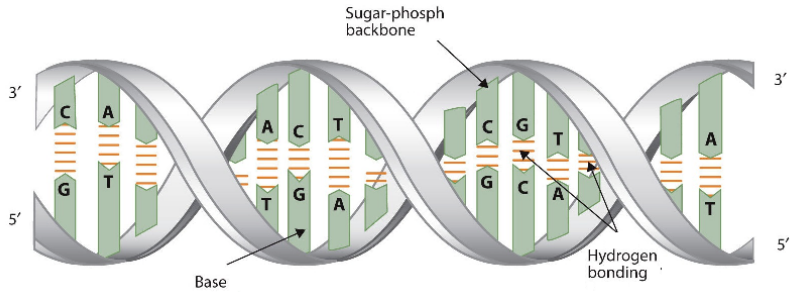


In 1950, Erwin Chargaff of Columbia University showed that the molar amount of adenine (A) in DNA was always equal to that of thymine (T). Similarly, he showed that the molar amount of guanine (G) was the same as that of cytosine (C). Chargaff's findings clearly indicate that some type of heterocyclic amine base pairing exists in the DNA structure. In double stranded DNA, the guanine (G) base on one strand can form three H-bonds with a cytosine (C) base on another strand (this is called a GC base pair). The thymine (T) base on one strand can form two H-bonds with an adenine (A) base on the other strand (this is called an AT base pair). Double-stranded DNA has a regular geometric structure with a fixed distance between the two backbones. This requires the bases pairs to consists of one base with a two-ring (bicyclic) structure (these bases are called purines) and one with a single ring structure (these bases are called pyrimidines). Hence a G and A or a T and C are not possible base pair partners.

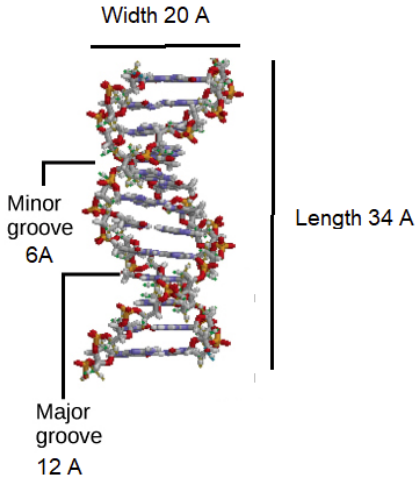


SECONDARY STRUCTURE OF DNA

The three-dimensional structure of DNA was the subject of an intensive research effort in the late 1940s to early 1950s. DNA exists as a double-stranded molecule that twists around its axis to form a helical structure,stabilized through Watson-Crick hydrogen bonding between purines and pyrimidines, and through pi-pi stacking interactions among the bases arranged in structure. helical column. Each strand is a complement to the other; the nucleotides on one strand hydrogen-bond with complementary nucleotides on the opposite strand—that is, side-by-side with the 5′ end of one chain next to the 3′ end of the other. The purine and pyrimidine bases face the inside of the helix, with guanine always opposite cytosine and adenine always opposite thymine. The double helical "twist" occurs because of the angular geometry of each bonded nucleotide.



Initial work revealed the DNA polymer had a regular repeating pattern X-ray diffraction data shows that a repeating helical pattern is 20 Angstrom units wide and occurs every 34 Angstrom units with 10 nucleotide subunits per turn. Each subunit occupies 3.4 Angstrom units which is the same amount of space occupied by a single nucleotide unit. The helix is Under most conditions, the two strands are slightly offset, which creates a 12 Angstrom major groove on one face of the double helix, and a 6 Angstrom minor groove on the other. The overall DNA polymer varies in length (number of sugar-phosphate units connected), base composition (how many of each set of bases) and sequence (the order of the bases in the backbone).



What do we mean when we say information is encoded in the DNA molecule? An organism's DNA can be compared to a book containing directions for assembling a model airplane or for knitting a sweater. Letters of the alphabet are arranged into words, and these words direct the individual to perform certain operations with specific materials. If all the directions are followed correctly, a model airplane or sweater is produced.

In DNA, the particular sequences of nucleotides along the chains encode the directions for building an organism. Just as *saw* means one thing in English and *was* means another, the sequence of bases CGT means one thing, and TGC means something different. Although there are only four letters—the four nucleotides—in the genetic code of DNA, their sequencing along the DNA strands can vary so widely that information storage is essentially unlimited.

Deoxyribonucleic acid (DNA) stores genetic information, while ribonucleic acid (RNA) is responsible for transmitting or expressing genetic information by directing the synthesis of thousands of proteins found in living organisms. But how do the nucleic acids perform these functions?

Three processes are required:

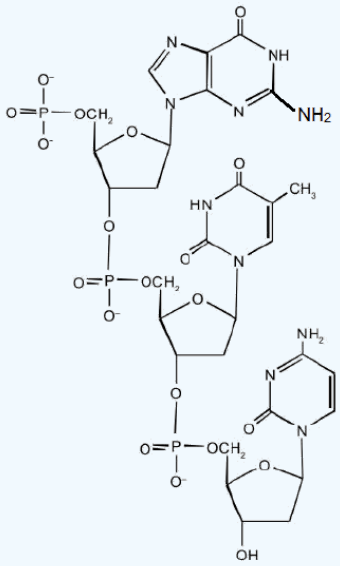
1. ***Replication***, in which new copies of DNA are made.

2. ***Transcription***, in which a segment of DNA is used to produce RNA.
3. ***Translation***, in which the information in RNA is translated into a protein sequence.

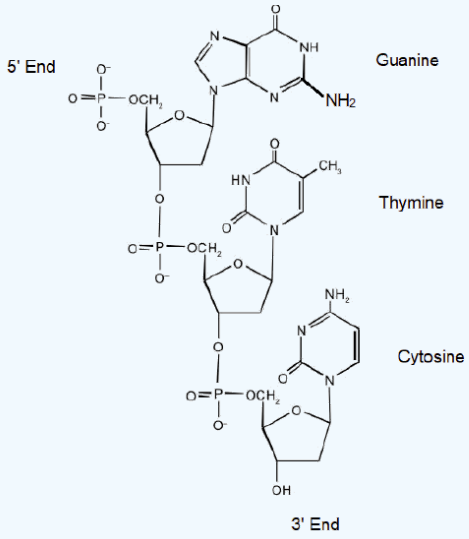
EXERCISE 28.2.1

For this short DNA segment,

a. Identify the 5′ end and the 3′ end of the molecule.
b. Circle the atoms that comprise the backbone of the nucleic acid chain.
c. Write the nucleotide sequence of this DNA segment.



Answer



EXERCISE 28.2.2

Which nitrogenous base in DNA pairs with each listed nitrogenous base?

a. Cytosine
b. Adenine
c. Guanine
d. Thymine

Answer

a. Guanine
b. Thymine
c. Cytosine
d. Adenine

EXERCISE 28.2.3

How many hydrogen bonds can form between the two strands in the short DNA segment shown below?

5′ ATGCGACTA 3′ 3′ TACGCTGAT 5′

Answer

22 (2 between each AT base pair and 3 between each GC base pair).

EXERCISE 28.2.4

A segment of one strand from a DNA molecule has the sequence 5′-TCCATGAGTTGA-3′. What is the sequence of nucleotides in the opposite, or complementary, DNA chain?

Answer

Knowing that the two strands are antiparallel and that T base pairs with A, while C base pairs with G, the sequence of the complementary strand will be 3′-AGGTACTCAACT-5′ (can also be written as TCAACTCATGGA).

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28.3: REPLICATION OF DNA

OBJECTIVES

After completing this section, you should be able to describe, very briefly, the replication of DNA.

KEY TERMS

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

- replication
- semiconservative replication

STUDY NOTES

Notice that the objective for this section requires only that you be able to describe the replication process briefly.

According to the central dogma of molecular genetics, DNA is the genetically active component of the chromosomes of a cell. That is, DNA in the cell nucleus contains all the information necessary to control synthesis of the proteins, enzymes, and other molecules which are needed as that cell grows, carries on metabolism, and eventually reproduces. Thus when a cell divides, its DNA must pass on genetic information to both daughter cells. It must somehow be able to divide into duplicate copies. This process is called **replication**. Given the complementary double strands of DNA, it is relatively easy to see how DNA as a molecule is well structured for replication, as is show in Figure 28.3.1. Each strand serves as a template for a new strand. Thus, after DNA is replicated, each new DNA double helix will have one strand from the original DNA molecule, and one newly synthesized molecule. This is referred to as **semiconservative replication**.

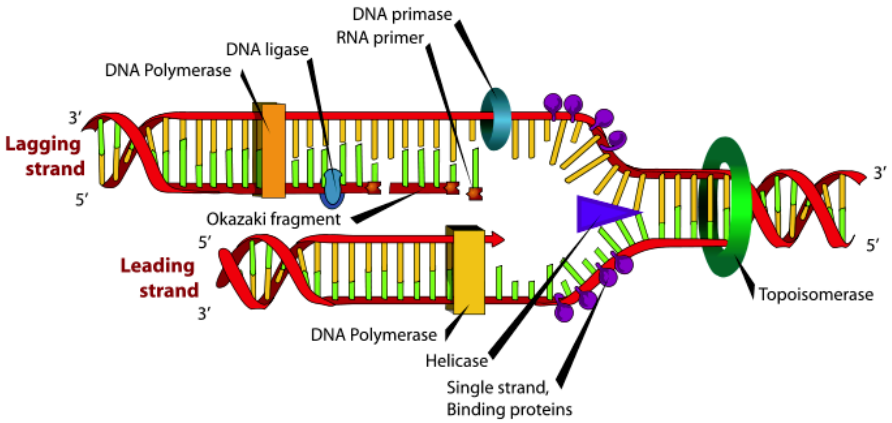

Figure 28.3.1: The replication of DNA. Replication occurs by means of partial unwinding of the two strands accompanied by synthesis of a new strand complementary to each of the originals. (CC BY 4.0; Aida Khakimova, Oleg Zolotarev, and Igor Zatsman via the Open Public Health Journal)

A rather complex mechanism exists for DNA replication, involving many different enzymes and protein factors. Let us consider some of the more important aspects of DNA replication. First, the double strand needs to be opened up to replicate each template strand. To do this, a set of proteins and enzymes bind to and open up the double helix at an origin point in the molecule. This forms **replication forks**, points where double stranded DNA opens up, allowing replication to occur. A helicase enzyme binds at the replication forks, with the function of further unwinding the DNA and allowing the replication fork to move along the double strand as DNA is replicated. Another enzyme, DNA gyrase, is also required to relieve stress on the duplex caused by unwinding the double strand. Further, single strand binding proteins are needed to prevent the single strands from reforming a double strand. Another essential enzyme in this initiation phase is primase, which creates an RNA primer on each single strand of DNA to begin replication from.

All of these initial functions are necessary to prepare the DNA for the main enzyme which builds then new strands, DNA polymerase. Multiple polymerase enzymes exist, but for the moment we will DNA polymerase III, the main DNA polymerase in *E. coli*. DNA polymerase III catalyzes the reaction by which a new nucleotide is added to a growing DNA strand. That reaction is seen in Figure 28.3.2. The DNA polymerase enzymes need a free 3' OH group in order to begin synthesizing a new strand, which explains the necessity of the RNA primer, which gives a 3'OH group for DNA polymerase III to start from.

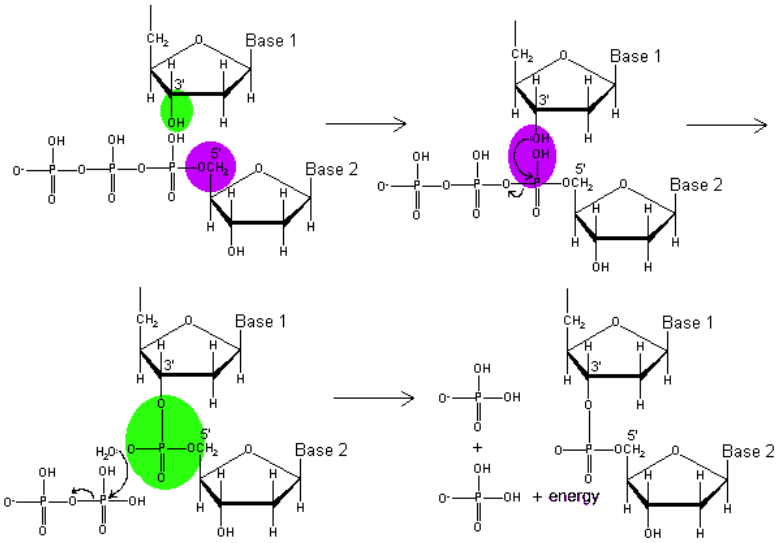

Figure 28.3.3: The polymerization of DNA nucleotides. The 3' hydroxyl group attacks the triphosphate group on the incoming nucleotide. A new phosphodiester bond is formed, and a pyrophosphate group leaves. This leaves two phosphates, the energy released from breaking down a the high energy phosphate group, and a elongated strand of DNA with a new 3' hydroxyl group to which another nucleotide may be added.
(Copyright; author via source)

This leads to another constraint on DNA polymerase III. One strand, the **leading strand** can be polymerized continuously since the new strand being created goes 5' to 3' from the replication fork, but since the original strands are anti-parallel, the other strand, the **lagging strand** is going in the wrong direction for polymerization. In this case, the polymerization reaction starts away from the replication fork and works back toward it. This means that the lagging strand is synthesized in disconnected segments, known as **Okazaki fragments**, instead of continuously. Later, another DNA polymerase, in the case of *E. coli*, DNA polymerase I, removes RNA primers and fills in the missing discontinuities. Then, *another* enzyme, DNA ligase, connects breaks between 3'OH groups and 5' phosphate groups in the newly synthesized strands that exist due to these discontinuities. While the enzymes of this process differ in eukaryotes, they fulfill similar mechanisms. Even with this complexity of this process, DNA polymerase III is able to add new nucleotides at a rate of 250-1,000 nucleotides per second.[3]

A number of advantages of the double-stranded structure held together by hydrogen bonds is evident in the process of replication. Complementary base pairing, A to T and G to C, insures that the two new DNA molecules will be the same as the original. The large number of hydrogen bonds, each of which is relatively weak, makes complete separation of the two strands unlikely, but one hydrogen bond, or even a few, can be broken rather easily. The helicase portion of the replication complex can therefore separate the two strands in much the same way that a zipper operates. Like the teeth of a zipper, hydrogen bonds provide great strength when all work together, but the proper tool can separate them one at a time.

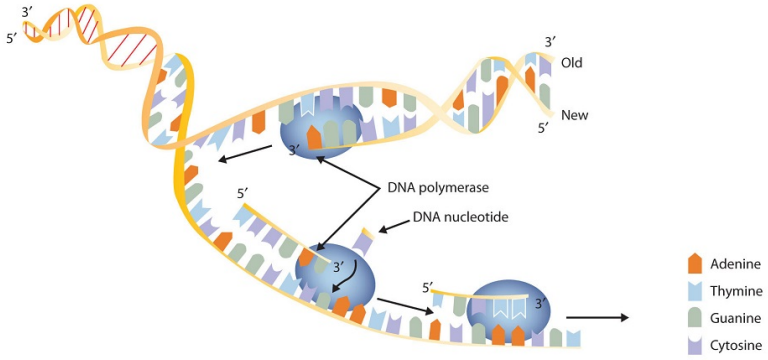

Figure 28.3.4: A Schematic Diagram of DNA Replication. DNA replication occurs by the sequential unzipping of segments of the double helix.

THE SCOPE OF THE PROBLEM OF DNA REPLICATION

The 46 chromosomes of the human genome consists of roughly 6.5 billion base pairs of DNA if one considers the full diploid genome (i.e. if you count the DNA inherited from both parents). Considering that this DNA can be copied in just a few hours shows that the rate of DNA replication is staggering.

Although DNA replication is typically a highly accurate process and proofreading DNA polymerases help to keep the error rate low (about one per 10 billion bases), mistakes still occur. In addition to errors of replication, environmental damage may also occur to the DNA. Such uncorrected errors of replication or environmental DNA damage may lead to serious consequences. Therefore, Nature has evolved several mechanisms for detecting and repairing damaged or incorrectly synthesized DNA.

✔ EXAMPLE 28.3.1

A segment of one strand from a DNA molecule has the sequence 5′-TCCATGAGTTGA-3′. What is the sequence of nucleotides in the opposite, or complementary, DNA chain?

Solution

Knowing that the two strands are antiparallel and that T base pairs with A, while C base pairs with G, the sequence of the complementary strand will be 3′-AGGTACTCAACT-5′ (can also be written as TCAACTCATGGA).

? EXERCISE 28.3.1

A segment of one strand from a DNA molecule has the sequence 5′-CCAGTGAATTGCCTAT-3′. What is the sequence of nucleotides in the opposite, or complementary, DNA chain?

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28.4: TRANSCRIPTION OF DNA

OBJECTIVES

After completing this section, you should be able to

- describe, very briefly, how RNA is synthesized in the nucleus of the cell by transcription of DNA.
- identify the important structural differences between DNA and DNA.
- given the appropriate Kekulé structures, show how uracil can form strong hydrogen bonds to adenine.
- identify the base sequence in RNA that would be complementary to a given base sequence in DNA.

KEY TERMS

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

- messenger RNA
- RNA polymerase
- ribosomal RNA
- transcription
- transfer RNA

STUDY NOTES

"Messenger RNA" (mRNA) carries the genetic information from the DNA in the nucleus to the cytoplasm where protein synthesis occurs. The code carried by mRNA is read by "transfer RNA" (tRNA) in a process called translation (see Section 28.5).

"Ribosomal RNA" (rRNA) is the term used to describe the RNA molecules which, together with proteins, make up the ribosomes on which proteins are synthesized.

Three types of RNA are formed during transcription: *messenger RNA* (mRNA), *ribosomal RNA* (rRNA), and *transfer RNA* (tRNA). These three types of RNA differ in function, size, and percentage of the total cell RNA (Table 28.4.1). mRNA makes up only a small percent of the total amount of RNA within the cell, primarily because each molecule of mRNA exists for a relatively short time; it is continuously being degraded and resynthesized. The molecular dimensions of the mRNA molecule vary according to the amount of genetic information a given molecule contains. After transcription, which takes place in the nucleus, the mRNA passes into the cytoplasm, carrying the genetic message from DNA to the ribosomes, the sites of protein synthesis. Elsewhere, we shall see how mRNA directly determines the sequence of amino acids during protein synthesis.

Table 28.4.1: Properties of Cellular RNA in Escherichia coli

Type	Function	Approximate Number of Nucleotides	Percentage of Total Cell RNA
mRNA	codes for proteins	100–6,000	~3
rRNA	component of ribosomes	120–2900	83
tRNA	adapter molecule that brings the amino acid to the ribosome	75–90	14

For the hereditary information in DNA to be useful, it must be "expressed," that is, used to direct the growth and functioning of an organism. The flow of genetic information in cells goes from DNA to mRNA to protein, by genes which specify the sequences of mRNAs, which in turn specify the sequences of proteins.

The first step in the processes that constitute DNA expression is the synthesis of RNA, by a template mechanism that is in many ways analogous to DNA replication. Because the RNA that is synthesized is a complementary copy of information contained in DNA, RNA synthesis is referred to as transcription. Transcription requires the DNA double helix to partially unwind in the region of mRNA synthesis. The region of unwinding is called a **transcription bubble**. The DNA sequence has patterns which indicate where RNA polymerase should start and end transcription. A DNA sequence at which the RNA polymerase binds to start transcription is called a **promoter**. The DNA sequence that indicates the endpoint of transcription, where the RNA polymerase should stop adding nucleotides and dissociate from the template is known as a **terminator** sequence. The promoter and terminator, thus, bracket the region of the DNA that is to be transcribed.

In bacteria, the promotor sequence contains two 6 bp region called **consensus** sequences. One sequence is centered about 10 bp upstream from the transcription start site. The second sequence at about 35 basepairs upstream from the start of transcription. The consensus sequences at -10 and -35 are necessary for recognition of the promoter region by RNA polymerase.

The DNA sequence that is transcribed to make RNA is called the antisense strand (also called template, anticoding, or transcribed strand), while the complementary sequence on the other DNA strand is called the sense strand (also called the coding or informational strand). To initiate RNA synthesis, the two DNA strands unwind at specific sites along the DNA molecule. Ribonucleotides are attracted to the uncoiling region of the DNA molecule, beginning at the 3′ end of the template strand, according to the rules of base pairing. Thymine in DNA calls for adenine in RNA, cytosine specifies guanine, guanine calls for cytosine, and adenine requires uracil. RNA polymerase—an enzyme—binds the complementary ribonucleotide and catalyzes the formation of the ester linkage between ribonucleotides, a reaction very similar to that catalyzed by DNA polymerase (Figure 28.4.1). Synthesis of the RNA strand takes place in the 5′ to 3′ direction, antiparallel to the template strand. Only a short segment of the RNA molecule is hydrogen-bonded to the template strand at any time during transcription. When transcription is completed, the RNA is released, and the DNA helix reforms. The nucleotide sequence of the RNA strand formed during transcription is identical to that of the corresponding coding strand of the DNA, except that U replaces T.

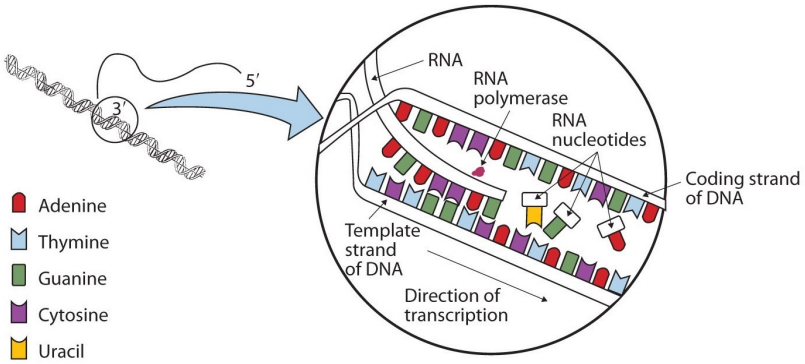

Figure 28.4.1: A Schematic Diagram of RNA Transcription from a DNA Template. The representation of RNA polymerase is proportionately much smaller than the actual molecule, which encompasses about 50 nucleotides at a time. (CC BY-SA-NC 3.0; Anonymous via LibreTexts)

The genes of eukaryotes (animals and plants) usually done have continuous segments of coding DNA. Rather they have intervening sequences of DNA (introns) within a given gene that separate coding fragments of DNA (exons). In a process called **splicing**, a primary transcript is made from the DNA, and then splicesomes cut out the introns and join the exons to form a contiguous stretch to form messenger RNA, mRNA. Once formed the mRNA leaves the nucleus is to be translated into a protein sequence..

New findings make it even more complicated to define a gene, especially if the transcripts of a "gene region" are studied. Cheng et al studied all transcripts from 10 different human chromosomes and 8 different cell lines. They found a large number of different transcripts, many of which overlapped. Splicing often occur between nonadjacent introns. Transcripts were found from both strands and were from regions containing introns and exons. Other studies found up to 5% of transcripts continued through the end of "gene" into other genes. 63% of the entire mouse genome, which is comprised of only 2% exons, is transcribed.

? EXERCISE 28.4.1

A portion of the template strand of a gene has the sequence 5′-TCCATGAGTTGA-3′. What is the sequence of nucleotides in the RNA that is formed from this template?

Answer

Four things must be remembered in answering this question: (1) the DNA strand and the RNA strand being synthesized are antiparallel; (2) RNA is synthesized in a 5′ to 3′ direction, so transcription begins at the 3′ end of the template strand; (3) ribonucleotides are used in place of deoxyribonucleotides; and (4) thymine (T) base pairs with adenine (A), A base pairs with uracil (U; in RNA), and cytosine (C) base pairs with guanine (G). The sequence is determined to be 3′-AGGUACUCAACU-5′ (can also be written as 5′-UCAACUCAUGGA-3′).

? EXERCISE 28.4.2

What would be the DNA base sequence of the coding strand required to transcribe the following RNA sequence?

5′-AUGAGCGACUUUGCGGGAUUA-3′

Answer

5′-ATGAGCGACTTTGCGGGATTA-3′.

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28.5: TRANSLATION OF RNA - PROTEIN BIOSYNTHESIS

OBJECTIVES

After completing this section, you should be able to describe, very briefly, the roles of messenger RNA and transfer RNA in the biosynthesis of proteins.

KEY TERMS

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

- anticodon
- codon
- translation

STUDY NOTES

As in the preceding section, you should not be too concerned about trying to memorize details. The objective requires you to have a general understanding of the roles played by mRNA and tRNA in the biosynthesis of proteins, and that you be able to describe this process.

After transcription, which takes place in the nucleus, the mRNA passes into the cytoplasm, carrying the genetic message from DNA to the ribosomes, the sites of protein synthesis. Ribosomes are cellular substructures where proteins are synthesized. They contain about 65% rRNA and 35% protein, held together by numerous noncovalent interactions, such as hydrogen bonding, in an overall structure consisting of two globular particles of unequal size. We turn now to the question of how the sequence of nucleotides in a molecule of ribonucleic acid (RNA) is translated into an amino acid sequence.

How can a molecule containing just 4 different nucleotides specify the sequence of the 20 amino acids that occur in proteins? If each nucleotide coded for 1 amino acid, then obviously the nucleic acids could code for only 4 amino acids. What if amino acids were coded for by groups of 2 nucleotides? There are 4^2, or 16, different combinations of 2 nucleotides (AA, AU, AC, AG, UU, and so on). Such a code is more extensive but still not adequate to code for 20 amino acids. However, if the nucleotides are arranged in groups of 3, the number of different possible combinations is 4^3, or 64. Here we have a code that is extensive enough to direct the synthesis of the primary structure of a protein molecule.

The **genetic code** can therefore be described as the identification of each group of three nucleotides and its particular amino acid. The sequence of these triplet groups in the mRNA dictates the sequence of the amino acids in the protein. Each individual three-nucleotide coding unit, as we have seen, is called a **codon**.

First base	*Second base* U	C	A	G	*Third base*
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	Stop	Stop	A
	Leu	Ser	Stop	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G

Figure 28.5.1: The Genetic Code

Early experimenters were faced with the task of determining which of the 64 possible codons stood for each of the 20 amino acids. The cracking of the genetic code was the joint accomplishment of several well-known geneticists—notably Har Khorana, Marshall Nirenberg, Philip Leder, and Severo Ochoa—from 1961 to 1964. The genetic dictionary they compiled, summarized in Figure 28.5.3, shows that 61 codons code for amino acids, and 3 codons serve as signals for the termination of polypeptide synthesis (much like the period at the end of a sentence). Notice that only methionine (AUG) and tryptophan (UGG) have single codons. All other amino acids have two or more codons.

Protein synthesis is accomplished by orderly interactions between mRNA and the other ribonucleic acids (transfer RNA [tRNA] and ribosomal RNA [rRNA]), the ribosome, and more than 100 enzymes. The mRNA formed in the nucleus during transcription is transported across the nuclear membrane into the cytoplasm to the ribosomes—carrying with it the genetic instructions. The process in which the information encoded in the mRNA is used to direct the sequencing of amino acids and thus ultimately to synthesize a protein is referred to as *translation*.

Before an amino acid can be incorporated into a polypeptide chain, it must be attached to its unique tRNA. The carboxylic acid group of the amino acid forms an ester linkage with with the 3' hydroxyl group on the riboses bonded at the 3' end of the tRNA. This crucial process requires an enzyme known as aminoacyl-tRNA synthetase (Figure 28.5.1). There is a specific aminoacyl-tRNA synthetase for each amino acid. This high degree of specificity is vital to the incorporation of the correct amino acid into a protein. After the amino acid molecule has been bound to its tRNA carrier, protein synthesis can take place.

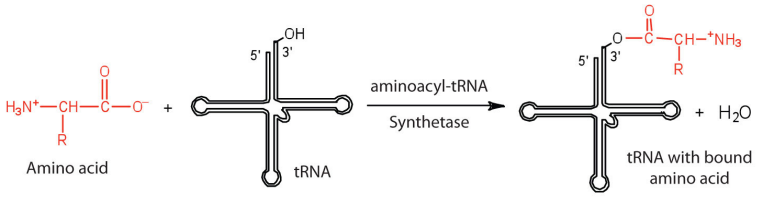


Figure 28.5.2 Binding of an Amino Acid to Its tRNA

The two-dimensional structure of a tRNA molecule is reminiscent of a cloverleaf. At one end of the tRNA molecule is the acceptor stem, where the amino acid is attached. The tRNA Molecule has three distinctive loops. One of these is called the anticodon loop which holds a sequence of three nucleotides called the **anticodon**. Each anticodon corresponds to the amino acid each is tRNA molecule is specifically designed to carry. For example, the amino acid lysine has the codon AAG, so the anticodon is UUC. Therefore, lysine would be carried by a tRNA molecule with the anticodon UUC. Each of the 20 amino acids found in proteins has at least one corresponding kind of tRNA, and most amino acids have more than one.

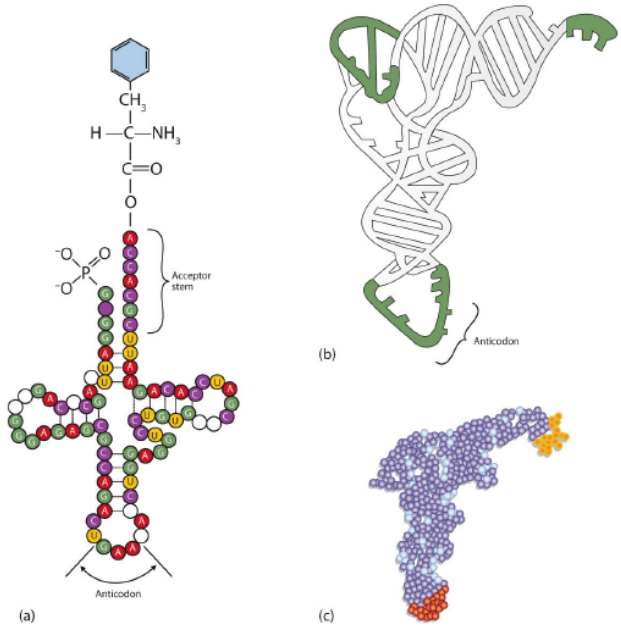
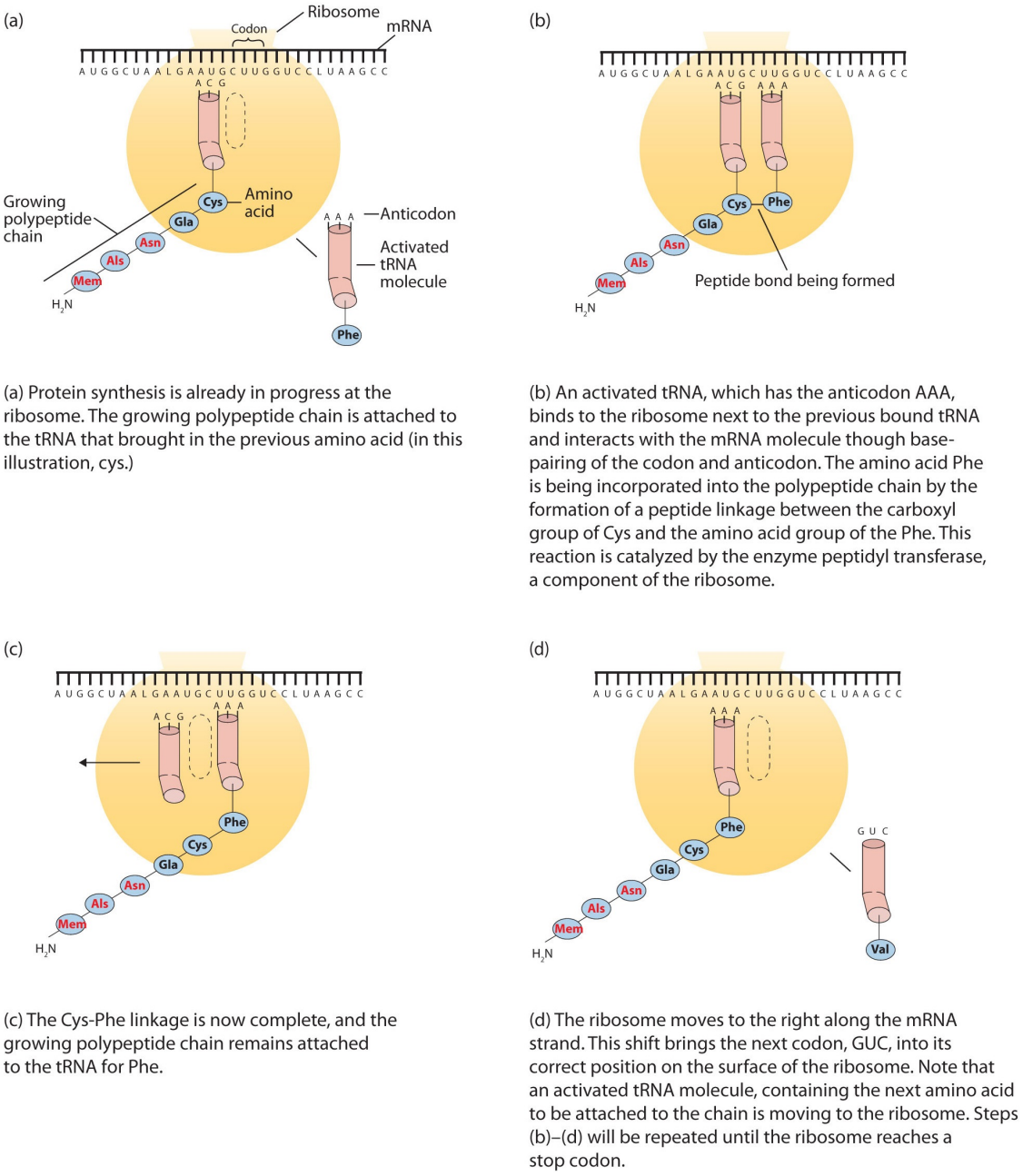


Figure 28.5.3: Transfer RNA (a) In the two-dimensional structure of a yeast tRNA molecule for phenylalanine, the amino acid binds to the acceptor stem located at the 3′ end of the tRNA primary sequence. (The nucleotides that are not specifically identified here are slightly altered analogs of the four common ribonucleotides A, U, C, and G.) (b) In the three-dimensional structure of yeast phenylalanine tRNA, note that the anticodon loop is at the bottom and the acceptor stem is at the top right. (c) This shows a space-filling model of the tRNA.

During protein synthesis the codon on the mRNA determines which kind of tRNA will add its amino acid to the growing chain. Wherever the codon AAG appears in mRNA, a UUC anticodon on a tRNA temporarily binds to the codon ect. As each different tRNA brings an amino acid into position an enzyme adds it to the growing protein chain. The protein is released from the ribosome once it is completed. Figure 28.5.2 depicts a schematic stepwise representation of this all-important process.



(a) Protein synthesis is already in progress at the ribosome. The growing polypeptide chain is attached to the tRNA that brought in the previous amino acid (in this illustration, cys.)

(b) An activated tRNA, which has the anticodon AAA, binds to the ribosome next to the previous bound tRNA and interacts with the mRNA molecule though base-pairing of the codon and anticodon. The amino acid Phe is being incorporated into the polypeptide chain by the formation of a peptide linkage between the carboxyl group of Cys and the amino acid group of the Phe. This reaction is catalyzed by the enzyme peptidyl transferase, a component of the ribosome.

(c) The Cys-Phe linkage is now complete, and the growing polypeptide chain remains attached to the tRNA for Phe.

(d) The ribosome moves to the right along the mRNA strand. This shift brings the next codon, GUC, into its correct position on the surface of the ribosome. Note that an activated tRNA molecule, containing the next amino acid to be attached to the chain is moving to the ribosome. Steps (b)–(d) will be repeated until the ribosome reaches a stop codon.

Figure 28.5.4: The Elongation Steps in Protein Synthesis

? EXERCISE 28.5.1

What are the roles of mRNA and tRNA in protein synthesis?

Answer

mRNA provides the code that determines the order of amino acids in the protein; tRNA transports the amino acids to the ribosome to incorporate into the growing protein chain.

EXERCISE 28.5.2

A portion of an mRNA molecule has the sequence 5′-AUGCCACGAGUUGAC-3′. What amino acid sequence does this code for?

Answer

Use Figure 28.5.1 to determine what amino acid each set of three nucleotides (codon) codes for. Remember that the sequence is read starting from the 5′ end and that a protein is synthesized starting with the N-terminal amino acid. The sequence 5′-AUGCCACGAGUUGAC-3′ codes for met-pro-arg-val-asp.

EXERCISE 28.5.3

Write the anticodon on tRNA that would pair with each mRNA codon.

a. 5′-UUU-3′
b. 5′-CAU-3′
c. 5′-AGC-3′
d. 5′-CCG-3′

Answer

a. 3′-AAA-5′
b. 3′-GUA-5′
c. 3′-UCG-5′
d. 3′-GGC-5′

EXERCISE 28.5.4

The peptide hormone oxytocin contains 9 amino acid units. What is the minimum number of nucleotides needed to code for this peptide?

Answer

27 nucleotides (3 nucleotides/codon)

EXERCISE 28.5.5

Determine the amino acid sequence produced from this mRNA sequence: 5′-AUGAGCGACUUUGCGGGAUUA-3′.

Answer

met-ser-asp-phe-ala-gly-leu

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28.6: DNA SEQUENCING

OBJECTIVES

After completing this section, you should be able to

- Describe briefly how DNA sequencing is carried out.

DNA sequencing determines the order of nucleotide bases within a given fragment of DNA. This information can be used to infer the RNA or protein sequence encoded by the gene, from which further inferences may be made about the gene's function and its relationship to other genes and gene products. DNA sequence information is also useful in studying the regulation of gene expression. If DNA sequencing is applied to the study of many genes, or even a whole genome, it is considered an example of genomics.

While techniques to sequence proteins have been around since the 1950s, techniques to sequence DNA were not developed until the mid-1970s, when two distinct sequencing methods were developed almost simultaneously, one by Walter Gilbert's group at Harvard University, the other by Frederick Sanger's group at Cambridge University. However, until the 1990s, the sequencing of DNA was a relatively expensive and long process. Using radiolabeled nucleotides also compounded the problem through safety concerns. With currently-available technology and automated machines, the process is cheaper, safer, and can be completed in a matter of hours. The Sanger sequencing method was used for the human genome sequencing project, which was finished its sequencing phase in 2003, but today both it and the Gilbert method have been largely replaced by better methods.

RESTRICTION ENZYMES

To be able to sequence DNA, it is first necessary to cut it into smaller fragments. What is needed is a way to cleave the DNA molecule at a few precisely-located sites so that a small set of homogeneous fragments are produced. To cut DNA at known locations, researchers use **restriction endonucleases** enzymes that have been purified from various bacterial species, and which can be purchased from various commercial sources. REs occur naturally in bacteria, where they specifically recognize short stretches of nucleotides in DNA and catalyze double-strand breaks at or near the recognition site (also known as a restriction site). These enzymes are usually named after the bacterium from which they were first isolated. For example, ***EcoRI*** and *EcoRV* are both enzymes from *E. coli*.

Restriction enzymes like EcoRI are frequently called 6-cutters, because they recognize a 6-nucleotide sequence. Assuming a random distribution of A, C, G and Ts in DNA, probability predicts that a recognition site for a 6-cutter should occur about once for every 4096 bp (4^6) in DNA. Of course, the distribution of nucleotides in DNA is not random, so the actual sizes of DNA fragments produced by EcoRI range from hundreds to many thousands of base pairs, but the mean size is close to 4000 bp. DNA fragments of this length are useful in the lab, since they long enough to contain the coding sequence for proteins and are well-resolved on agarose gels.

EcoRI recognizes the sequence G A A T T C in double stranded DNA. This recognition sequence is a palindrome with a two-fold axis of symmetry, because reading from 5' to 3' on either strand of the helix gives the same sequence. The palindromic nature of the restriction site is more obvious in the figure below. The dot in the center of the restriction site denotes the axis of symmetry. EcoRI catalyzes the hydrolysis of the phosphodiester bonds between G and A on both DNA strands. The restriction fragments generated in the reaction have short single-stranded tails at the 5'-ends. These ends are often referred to as "sticky ends," because of their ability to form hydrogen bonds with complementary DNA sequences.

Figure 28.6.1: The recognition sequence for EcoRI (blue) is cleaved by the enzyme (grey). This particular enzyme cuts DNA at a position offset from the center of the restriction site. This creates an overhanging, sticky-end. (Original-Deyholos-CC:AN)

READING DNA SEQUENCES

We will discuss one method of reading the sequence of DNA. This method, developed by Sanger won him a second Nobel prize. Sanger sequencing, also known as chain-termination sequencing, requires a single-stranded DNA template, a DNA primer, a DNA polymerase, normal deoxynucleotidetriphosphates (dNTPs), and modified nucleotides (dideoxyNTPs - ddNTP) that terminate DNA strand elongation. These chain-terminating nucleotides lack a 3′-OH group required for the formation of a phosphodiester bond between two nucleotides, causing DNA polymerase to cease extension of DNA when a ddNTP is incorporated.

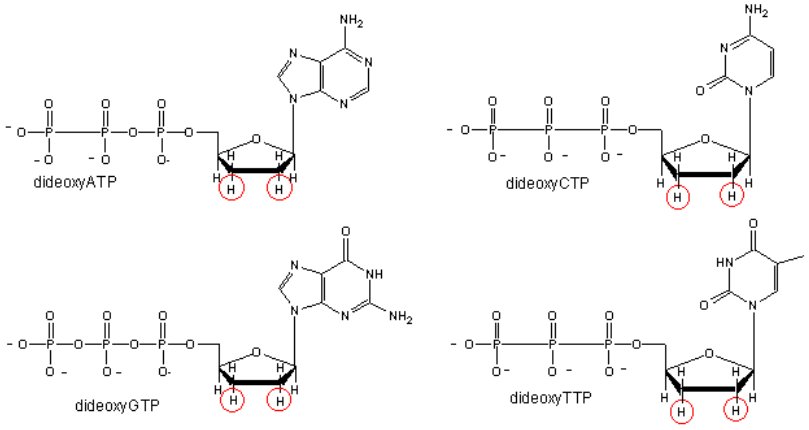

Figure 28.6.2: Didexoynucleotides

Four reaction tubes are set up, each containing the template DNA to be sequenced, a *primer* of known sequence, all four of the standard deoxynucleotides (dATP, dGTP, dCTP and dTTP), and the DNA polymerase. To each reaction is added only one of the four dideoxynucleotides (ddATP, ddGTP, ddCTP, or ddTTP) which has been fluorescently labeled. Most of the time in a Sanger sequencing reaction, DNA Polymerase will add a proper dNTP to the growing strand it is synthesizing in vitro. But at random locations, it will instead add a ddNTP. When it does, that strand will be terminated at the ddNTP just added. If enough template DNAs are included in the reaction mix, each one will have the labeled ddNTP inserted at a different random location, and there will be at least one DNA terminated at each different nucleotide along its length for as long as the in vitro reaction can take place (about 900 nucleotides under optimal conditions.)

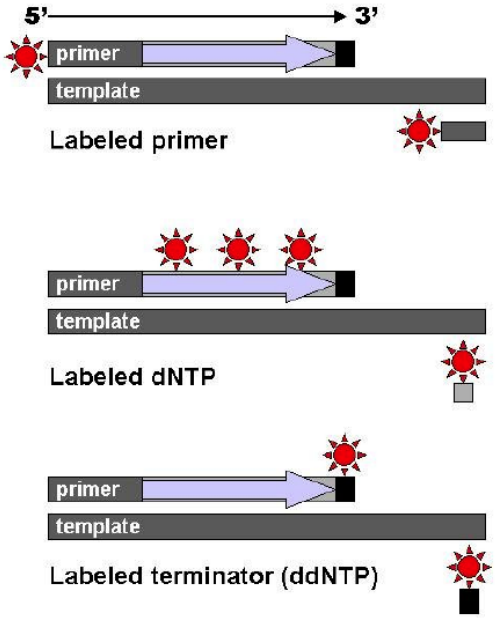

Figure 28.6.3: Sanger sequencing: Different types of Sanger sequencing, all of which depend on the sequence being stopped by a terminating dideoxynucleotide (black bars).

After the reactions are over, the newly synthesized strands can be denatured from the template, and then separated by capillary electrophoresis or other equivalent methods. Since each band differs in length by one nucleotide, and the identity of that nucleotide is known from its fluorescence, the DNA sequence can be read simply from the order of the colors in successive bands.

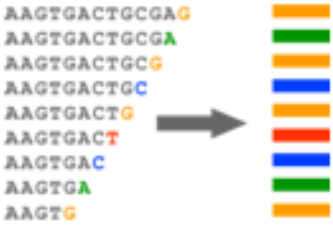

Figure 28.6.4: Fluorescently labeled products can be separated electrophoretically based on their length. (Original-Deyholos-CC:AN)

As each differently-sized fragment exits the capillary column, a laser excites the florescent tag on its terminal nucleotide. From the color of the resulting florescence, a computer can keep track of which nucleotide was present as the terminating nucleotide. The computer also keeps track of the order in which the terminating nucleotides appeared, which is the sequence of the DNA used in the original reaction. In practice, the maximum length of sequence that can be read from a single sequencing reaction is about 700 bp.

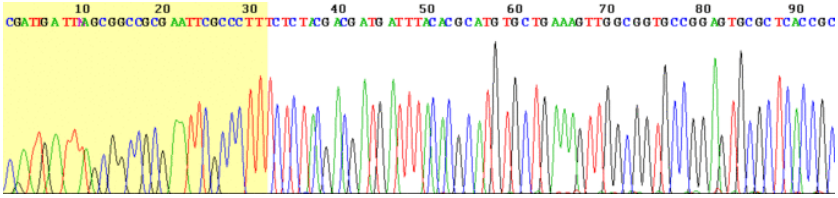

Figure 28.6.5: Chromatograph: This is an example of the output of a Sanger sequencing read using fluorescently labeled dye-terminators. The four DNA bases are represented by different colors which are interpreted by the software to give the DNA sequence above.

Scientists now know the sequence of all the 3 billion DNA base pairs in the entire human genome. This knowledge was attained by the **Human Genome Project (HGP),** a $3 billion, international scientific research project that was formally launched in 1990. The project was completed in 2003, two years ahead of its 15-year projected deadline. Determining the sequence of the billions of base pairs that make up human DNA was the main goal of the HGP. Another goal was mapping the location and determining the function of all the genes in the human genome. There are only about 20,500 genes in human beings. If modern methods were used it might bring the cost of sequencing the human genome down from the initial billion dollar range to $100.

EXAMPLE 28.6.1

You will pretend to sequence a single stranded piece of DNA as shown below. The new nucleotides are added by the enzyme DNA polymerase to the primer, GACT, in the 5' to 3' direction. You will set up 4 reaction tubes, Each tube contains all the dXTP's. In addition, add ddATP to tube 1, ddTTP to tube 2, ddCTP to tube 3, and ddGTP to tube 4. For each separate reaction mixture, determine all the possible sequences made by writing the possible sequences on one of the unfinished complementary sequences below. Cut the completed sequences from the page, determine the size of the polynucleotide sequences made, and place them as they would migrate (based on size) in the appropriate lane of a imaginary gel which you have drawn on a piece of paper. Lane 1 will contain the nucleotides made in tube 1, etc. Then draw lines under the positions of the cutout nucleotides to represent DNA bands in the gel. Read the sequence of the complementary DNA synthesized. Then write the sequence of the ssDNA that was to be sequenced.

- 5' T C A A C G A T C T G A 3' (STAND TO SEQUENCE)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)

Since the DNA fragments have no detectable color, they can not be directly visualized in the gel. Alternative methods are used. In the one described above, radiolabeled ddXTP's where used. Once the sequencing gel is run, it can be dried and the bands visualized by radioautography (also called autoradiography). A place of x-ray film is placed over the dried gel in a dark environment. The radiolabeled bands will emit radiation which will expose the x-ray film directly over the bands. The film can be developed to detect the bands. In a newer technique, the primer can be labeled with a flourescent dye. If a different dye is used for each reaction mixture, all the reaction mixtures can be run in one lane of a gel. (Actually only one reaction mix containing all the ddXTP's together need be performed.) The gel can then be scanned by a laser, which detects fluorescence from the dyes, each at a different wavelength.

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28.7: DNA SYNTHESIS

OBJECTIVES

After completing this section, you should be able to

- describe, briefly, the steps required for chemical synthesis of DNA segments.

DNA must be synthesized to study genes, the sequence of genomes, and many other studies. This occurs in two fashions, by polymerase chain reaction (PCR) and chemical synthesis. PCR is covered in Section 28.8. Here we will focus on chemical synthesis of short DNA segments, which which are called oligonucleotides. Oligonucleotide synthesis is the chemical synthesis of relatively short fragments of nucleic acids, both DNA and RNA with a defined chemical structure (sequence). The technique is extremely useful in current laboratory practice because it provides a rapid and inexpensive access to custom-made oligonucleotides of the desired sequence.

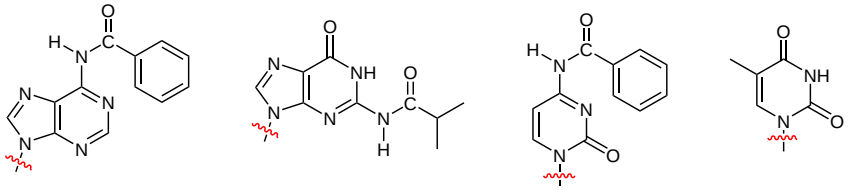
The synthesis of DNA is more difficult than peptide synthesis (Section 26-8) because of the complexity of nucleotide monomers. Commercial automated DNA synthesizers are available which allow for DNA segments to be made quickly and at a low cost. DNA synthesizers typically uses solid-phase techniques similar to the Merrifield solid-phase peptide synthesizer. Nucleotides are protected then covalently bonded to a solid support. Nucleotides are sequentially coupled to the growing oligonucleotide chain in the order required by the sequence of the product. Upon the completion of the chain assembly, the product is released from the solid phase to solution, it is then deprotected, and collected. The occurrence of side reactions sets practical limits for the length of synthetic oligonucleotides (up to about 200 nucleotide residues) because the number of errors accumulates with the length of the oligonucleotide being synthesized. Products are often isolated by HPLC to obtain the desired oligonucleotides in high purity. Typically, synthetic oligonucleotides are single-stranded DNA or RNA molecules around 15–25 bases in length.

DNA CHEMICAL SYNTHESIS

The synthesis of DNA involves five steps:

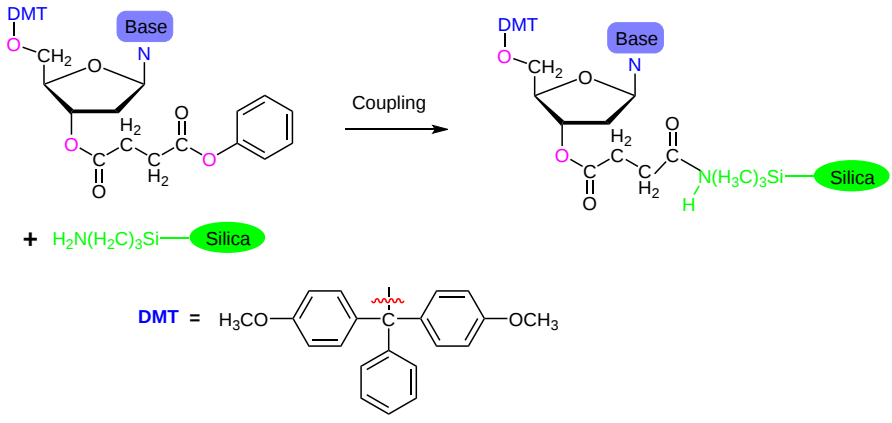
STEP 1

Nucleosides used for this synthesis are modified with a linking agent at the 3' hydroxyl group of deoxyribose. The 5' hydroxyl group of the nucleosides is protected with *p*-dimethoxytrityl (DMT) ether. The amine groups on the nucleoside's heterocyclic bases are also protected. The amines of adenine and cytosine bases are protected with benzoyl groups. Guanine's amine are protected by a isobutyryl group and thymine has no amine groups so protection is not required.



N-Protected Adenine **N-Protected Guanine** **N-Protected Cytosine** **Thymine**

The solid phase support used for DNA synthesis is commonly silica (SO_2) spheres which have been functionalized with (3-aminopropyl)triethoxysilane such that an amine group is available for reaction on the surface. A protected nucleoside is coupled to the solid phase support through an ester linkage with the 3' hydroxyl group of the nucleoside and an amide linkage with amine group from the silica surface.



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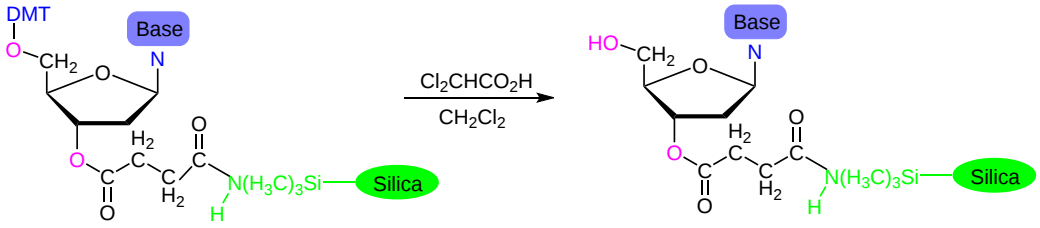
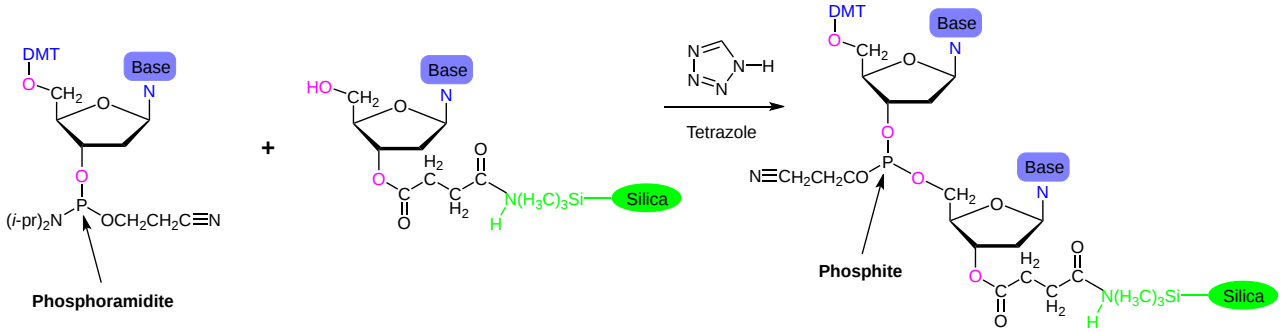
STEP 2

Reaction with with dichloroacetic acid removes the DMT protecting group from the 5' hydroxyl of the nucleoside attached to the silica surface. The *p*-dimethoxytrityl leaving group forms a relatively stable dimethoxytrityl cation which is both tertiary and benzylic. The reaction proceeds rapidly through a S_N1 mechanism.



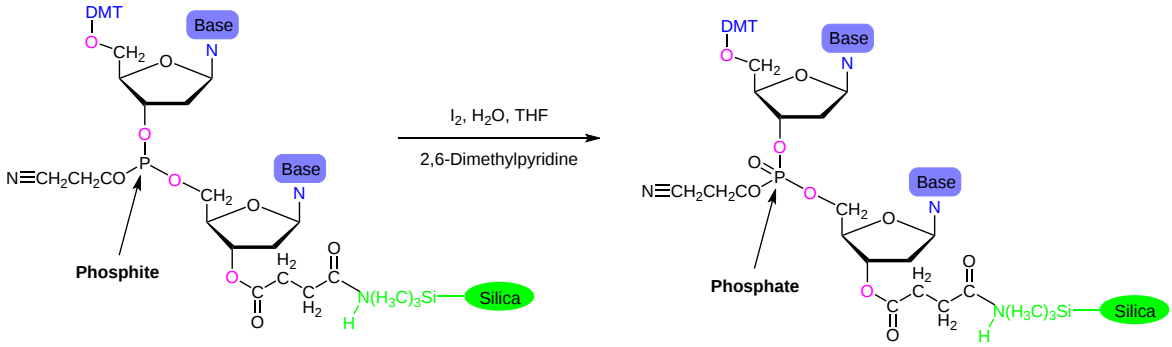
STEP 3

The nucleoside attached to the silica surface is then reacted with a protected nucleoside which has a **phosphoramidite** functional group [$R_2NP(OR)_2$] attached to the 3' hydroxyl group of its deoxyribose moiety. In addition, one of the phosphorus oxygen atoms of the phosphoramidite group is protected with a beta-cyanoethyl group (-OCH_2CH_2CN). The two nucleosides are coupled in a reaction which uses acetonitrile as a polar aprotic solvent, tetrazole as a heterocyclic amine catalyst, and produces a product with a phosphite functional group [$P(OR)_3$].



STEP 4

Next the phosphite product of the previous step is oxidized to a phosphate by reaction with iodine (I_2) along with 2,6-dimethylpyridine in aqueous tetrahydrofuran (THF). Additional nucleosides can now be added by repeating the **phosphoramidite oligodeoxynucleotide synthesis cycle** of (1) DMT deprotection, (2) phosphoramidite coupling, and (3) oxidation to a phosphite.



STEP 5

After the oligonucleotide chain of the desired sequence has been made, the final step is the removal of all the protecting groups and the linkage to silica by reaction with aqueous ammonia (NH_3).

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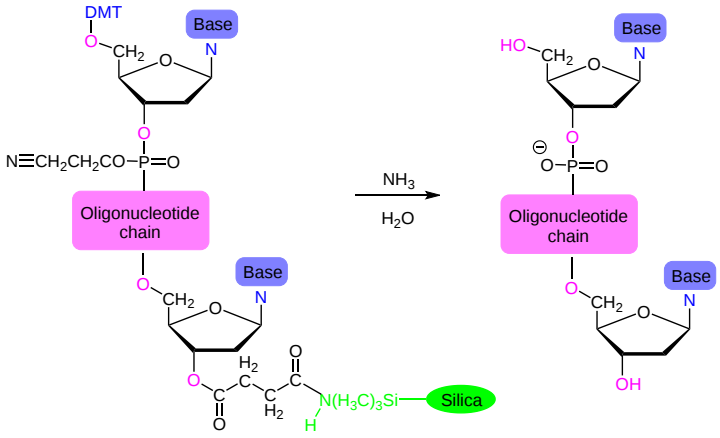
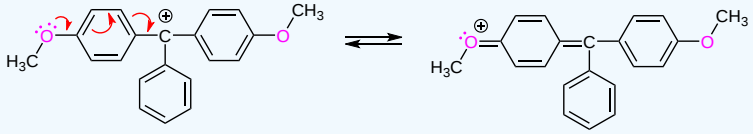


EXERCISE 28.7.1

Draw a mechanism which shows why dimethoxytrityl cation produced by the cleavage of a *p*-dimethoxytrityl protecting group is exceptionally stable.

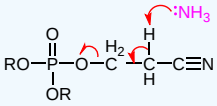
Answer



EXERCISE 28.7.2

When the beta-cyanoethyl protecting group is cleaved with aqueous ammonia, Acrylonitrile, H_2CCHCN , is also produced as a by-product. Draw a mechanism for the reaction.

Answer



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28.8: THE POLYMERASE CHAIN REACTION

OBJECTIVES

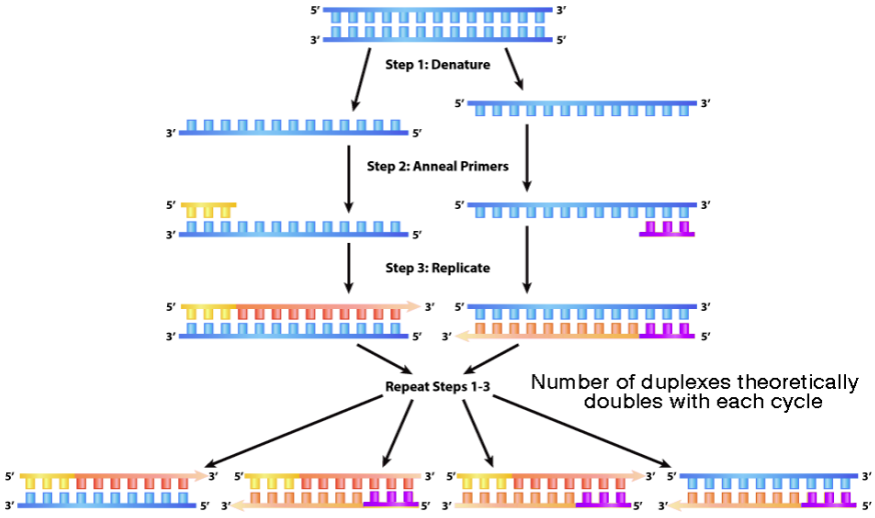
After completing this section, you should be able to

1. describe, briefly the three steps of PCR.

The polymerase chain reaction (PCR), allows one to use the power of DNA replication to amplify DNA enormously in a short period of time. As you know, cells replicate their DNA before they divide, and in doing so, double the amount of the cell's DNA. PCR essentially mimics cellular DNA replication in the test tube, repeatedly copying the target DNA over and over, to produce large quantities of the desired DNA. Kary B. Mullis was awarded a Nobel Prize in 1993 for his development of PCR, which is now the basis of innumerable research studies of gene structure, function and evolution as well as applications in criminal forensics, medical diagnostics and other commercial uses.

PCR requires a DNA fragment, some primers, which are short synthetic oligonucleotides whose sequence matches a region flanking the target sequence. All four deoxynucleotide triphosphates (dATP, dCTP, dGTP, dTTP), are added along with a heat stable DNA polymerase, **Taq**, from the organism *Thermophilus aquaticus* (which lives in hot springs).

PCR is run in a repeating cycle which involves three steps, template denaturing, primer annealing and primer extension.



TEMPLATE DENATURING

This step is the first regular cycling event and consists of heating the reaction to 94-98°C. It causes denaturing of the DNA template by disrupting the hydrogen bonds between complementary bases, yielding single-stranded DNA molecules. The Taq polymerase is heat-stable so it is not denatured by the high temperature needed to separate the DNA template strands.

PRIMER ANNEALING

Next, the solution is cooled to 50-65°C, a temperature that favors complementary DNA sequences finding each other and making base pairs, a process called **annealing**. Since the primers are present in great excess, the complementary sequences they target are readily found and base-paired to the primers. These primers direct the synthesis of DNA. Only where primer anneals to a DNA strand will replication occur, since DNA polymerases require a primer to begin synthesis of a new strand.

PRIMER EXTENSION

The temperature at this step depends on the DNA polymerase used; Taq polymerase has its optimum activity temperature at 75-80°C, and commonly a temperature of 72°C is used with this enzyme. At this step the DNA polymerase synthesizes a new DNA strand complementary to the DNA template strand by adding dNTPs that are complementary to the template in 5′ to 3′ direction, condensing the 5′-phosphate group of the dNTPs with the 3′-hydroxyl group at the end of the nascent (extending) DNA strand. On completion of this step there are two copies of the DNA template. The new DNA then be denatured to start the cycle again. Each cycle doubles the amount of DNA. Using automated equipment, each cycle of replication can be completed in less than 5 minutes. After 30 cycles, what began as a single molecule of DNA has been amplified into more than a billion copies.

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CHAPTER OVERVIEW

29: ORBITALS AND ORGANIC CHEMISTRY - PERICYCLIC REACTIONS

Pericyclic reactions are of significant synthetic importance in organic chemistry due to their high stereo- and regioselectivity, mild reaction conditions, and the formation of multiple bonds in a single step. They find applications in the synthesis of complex organic molecules, natural product synthesis, and the construction of functional materials. Understanding the principles governing pericyclic reactions is essential for synthetic chemists to design and control reactions with precision.

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29.0: Chapter Overview

Learning Objectives

- Define pericyclic reactions as concerted processes involving cyclic movement of electrons.
- Explain the Woodward-Hoffmann Rules for predicting outcomes based on molecular orbital symmetry.
- Outline subclasses like cycloadditions, electrocyclic reactions, and sigmatropic rearrangements.
- Describe how pericyclic reactions proceed through cyclic transition states and molecular orbitals.
- Provide key examples like Diels-Alder, electrocyclic ring closures, and Claisen rearrangements.
- Discuss how pericyclic reactions are used in synthesis of complex molecules and materials.

Pericyclic reactions represent a fascinating class of organic reactions characterized by the concerted movement of electrons around a cyclic array of atoms. These reactions involve a cyclic transition state where bonding changes occur with the involvement of π electrons. The term "pericyclic" stems from the Greek roots "peri," meaning around, and "cyclo," referring to cycle or ring, encapsulating the cyclic nature of these reactions.

Key features of pericyclic reactions include their stereospecificity, concertedness, and often high regio- and stereochemical control. They are governed by orbital symmetry rules, primarily the Woodward-Hoffmann rules, which provide a theoretical framework for predicting the outcome of these reactions based on the symmetry properties of the molecular orbitals involved.

Pericyclic reactions encompass several important subclasses, including:

1. **Cycloadditions**: In cycloaddition reactions, two or more unsaturated molecules combine to form a cyclic product. Diels-Alder reaction is a classic example, where a conjugated diene reacts with a dienophile to form a cyclohexene ring.
2. **Electrocyclic Reactions**: These reactions involve the reorganization of π electrons in a conjugated system to form a cyclic compound. Examples include the ring-opening and ring-closing reactions of cyclobutene and cyclohexadiene systems.
3. **Sigmatropic Rearrangements**: Sigmatropic rearrangements involve the migration of a σ-bond (a single bond) along a conjugated system. The Claisen rearrangement and the Cope rearrangement are prominent examples of sigmatropic shifts.
4. **[2+2] Cycloadditions**: These reactions involve the formation of a four-membered ring from two unsaturated reactants.

Pericyclic reactions find wide applications in organic synthesis due to their efficiency, selectivity, and the ability to form multiple bonds stereospecifically in a single step. Moreover, their predictable nature based on orbital symmetry principles makes them valuable tools for designing complex molecular architectures. Understanding and mastering pericyclic reactions are essential for synthetic chemists aiming to construct intricate organic molecules efficiently and with precision.

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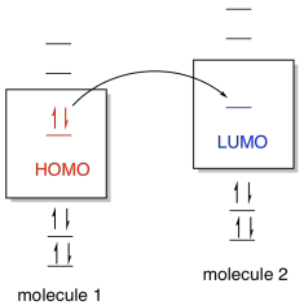
29.1: MOLECULAR ORBITALS OF CONJUGATED PI SYSTEMS

FRONTIER MOLECULAR ORBITAL THEORY

Prior to 1965, pericyclic reactions were known as "no mechanism reactions" since no one could adequately explain why reaction outcomes changed depending on whether reactants were exposed to heat or light. In 1965 Robert Burns Woodward and Roald Hoffmann used **Frontier Molecular Orbital Theory**, initially proposed by Kenichi Fukui, to develop their **Theory of Conservation of Orbital Symmetry** where outcomes of pericyclic reactions are explained by examining the **Highest Occupied Molecular Orbital (HOMO)** or **Lowest Unoccupied Molecular Orbital (LUMO)** of the reacting system. Their analysis of cycloadditions, electrocyclic reactions, and sigmatropic rearrangements is commonly referred to as the Woodward-Hoffmann Rules. A detailed analysis of three reaction types is provided in the subsequent sections of this chapter.

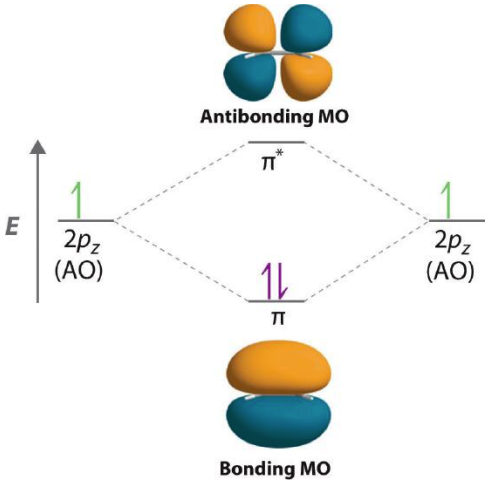
HOMO and LUMO are often referred to as **frontier orbitals** and their energy difference is termed the **HOMO–LUMO gap**. One common way of thinking about reactions in this way is through the concept of frontier orbitals. This idea says that if one species is going to donate electrons to another in order to form a new bond, then the donated electrons are most likely going to come from the highest occupied energy level. In this level, called the highest occupied molecular orbital (HOMO), the electrons are further from the nucleus and therefore less tightly held by the protons in the nucleus. The electrons would be donated, in turn, to the lowest empty energy level on the other species, called the lowest unoccupied molecular orbital (LUMO).



Molecular orbital interaction between frontier orbitals.

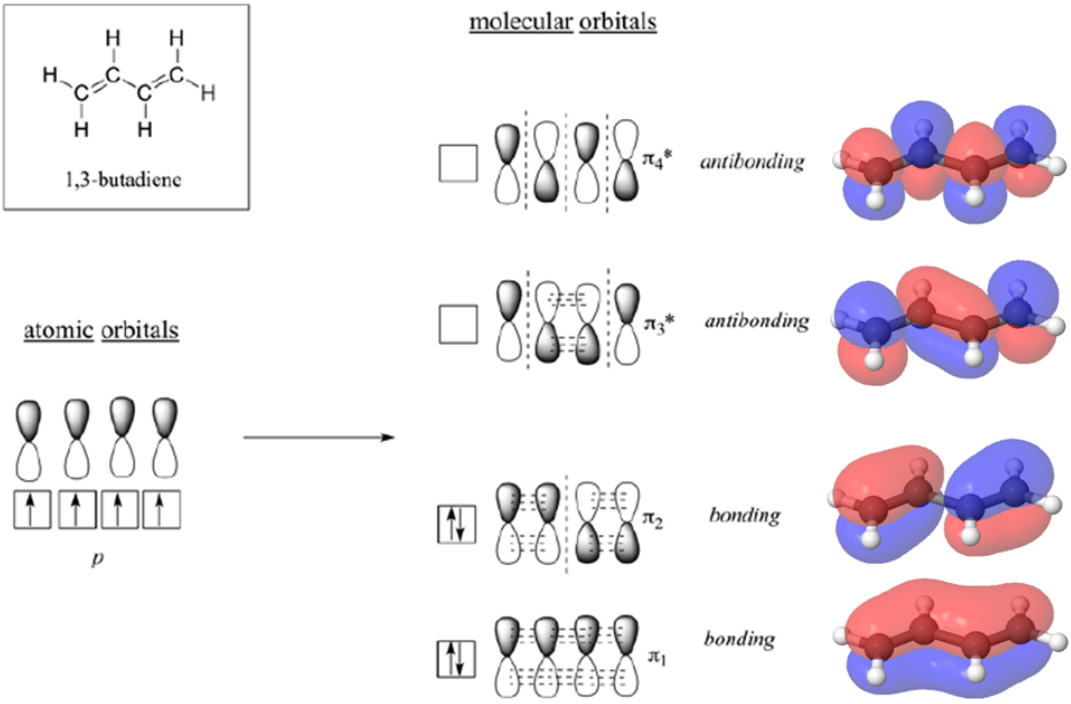
MOLECULAR ORBITALS

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.



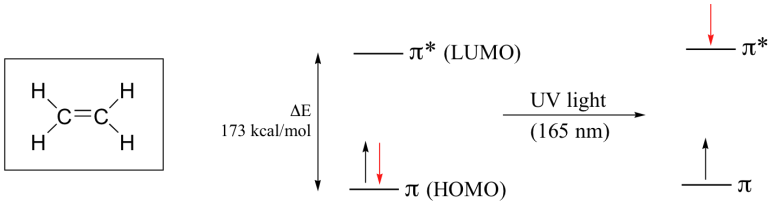
With a conjugated diene, such as 1,3-butadiene, the four *2p* atomic orbitals combine to form four pi molecular orbitals of increasing energy. Two bonding pi orbitals and two antibonding pi* orbitals. The combination of four pi molecular orbitals allow for the formation of a

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.

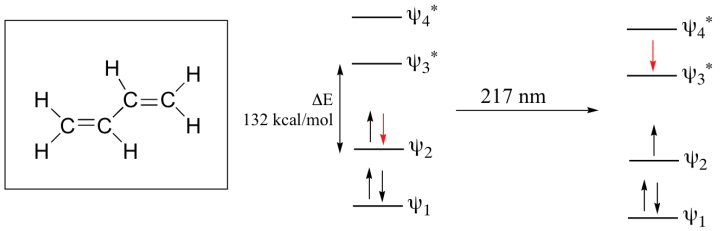


ELECTRONIC TRANSITIONS

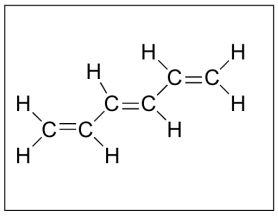
When a double-bonded molecule such as ethene (common name ethylene) absorbs 165 nm light, it undergoes a **π - π* transition**. An electron is moved from the HOMO of ethene to the LUMO placing the molecule in an **excited state**.

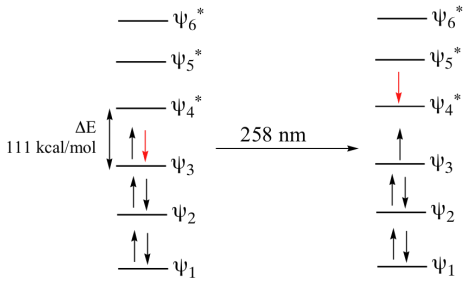


Where electronic transition becomes useful to most organic and biological chemists is in the study of molecules with conjugated pi systems. In these groups, the HOMO–LUMO gap energy gap for π -π* transitions is smaller than for isolated double bonds, and thus the wavelength absorbed is longer. The MO 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 the HOMO would be psi 2 and the LUMO would be psi 3. The HOMO-LUMO energy gap is smaller for the conjugated 1,3-butadiene system which absorbs UV light with a wavelength of 217 nm.



As conjugated pi systems become larger, the HOMO–LUMO gap 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.





WOODWARD-HOFFMANN RULES

Much of what we have said about the electronic factors controlling pericyclic reaction was formulated in the mid 1960's by the American chemists R. B. Woodward and R. Hoffmann, in terms of what came to be called the **orbital symmetry** principles, or the **Woodward-Hoffmann rules**. This is a particularly simple approach says that many details of pericyclic reactions can explained by "conservation of orbital symmetry." This requires the symmetries of the molecular orbitals of reactants to be the same as the molecular orbitals of the products for a reaction to proceed.

The original approach of Woodward and Hoffmann involved construction of an "orbital correlation diagram" to see if the lobes of the reactant molecular orbitals match phases and allow for overlap required for bonding to occur. The symmetries of the appropriate reactant and product orbitals were matched to determine whether the transformation could proceed without a symmetry imposed conversion of bonding reactant orbitals to antibonding product orbitals. If the correlation diagram indicated that the reaction could occur without encountering such a **symmetry-imposed barrier**, it was termed **symmetry allowed**. If a symmetry barrier was present, the reaction was designated **symmetry-forbidden**.

? EXERCISE 29.1.1

Using the molecular orbital diagram for 1,3,5-hexatriene determine the HOMO and LUMO for both the ground and excited state.

Answer

For the ground state the HOMO is psi 3 and LUMO is psi 4.

For the excited state the HOMO is psi 4 and LUMO is psi 5.

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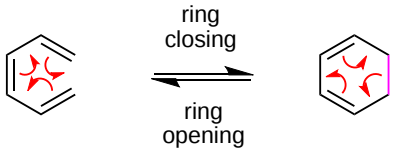
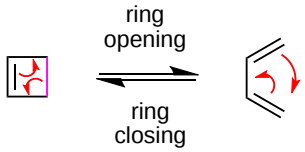
29.2: ELECTROCYCLIC REACTIONS

An electrocyclic reaction is the concerted cyclization of a conjugated π-electron system by converting one π-bond to a ring forming σ-bond. The key sigma bond must be formed at the terminus of a pi system. These reactions classified by the number of pi electrons involved. Thus, 4 pi reactions form 4 membered rings, as in a conjugated diene can being converted into a cyclobutene. Also, 6 pi reactions form 6 membered rings as in a conjugated triene can be converted into a cyclohexadiene. These reactions are often reversible with the reverse reaction may be called *electrocyclic ring opening*. Although more more pi electrons can be used, the 4 pi and 6 pi variants are by far the most common and are illustrated below with the key sigma bond highlighted in magenta.

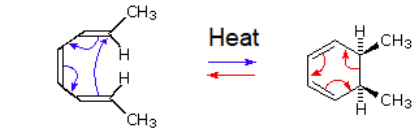


6 pi Electrocyclic Reaction



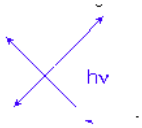
4 pi Electrocyclic Reaction

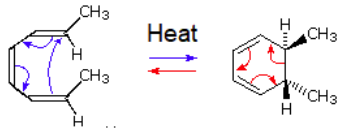
A striking feature of electrocyclic reactions that proceed by concerted mechanisms is their high degree of stereospecificity. For example, 2-*trans*, *4-cis*, *6-trans*-2,4,6-octatriene undergoes ring closure to *cis*-5,6-dimethyl-1,3-cyclohexadiene under thermal conditions i.e. when heated. Similarly the isomeric 2-*trans*, *4-cis*, *6-cis*-2,4,6-octatriene *produces trans*-5,6-dimethyl-1,3-cyclohexadiene, as noted below. However these results are completely reversed if the reaction is run under photochemical conditions (Irradiation with ultraviolet light). For example if 2-*trans*, *4-cis*, *6-cis*-2,4,6-octatriene is irradiated with UV light *cis*-5,6-dimethyl-1,3-cyclohexadiene would be produced.



2-trans, 4-cis, 6-trans-2,4,6-octatriene

cis-5,6-dimethyl-1,3-cyclohexadiene

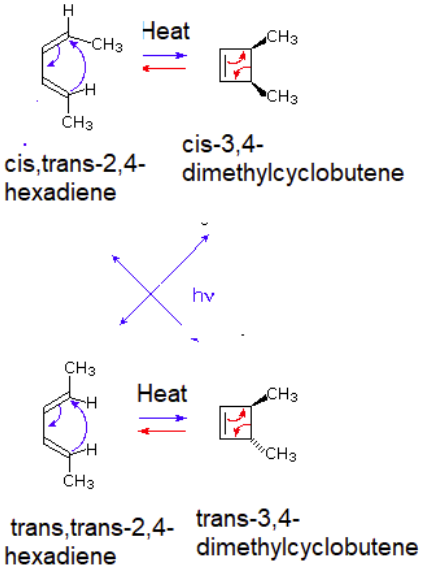




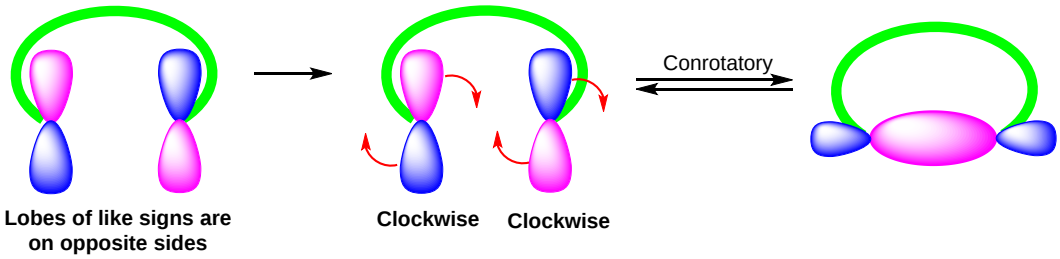
2-trans, 4-cis, 6-cis-2,4,6-octatriene

trans-5,6-dimethyl-1,3-cyclohexadiene

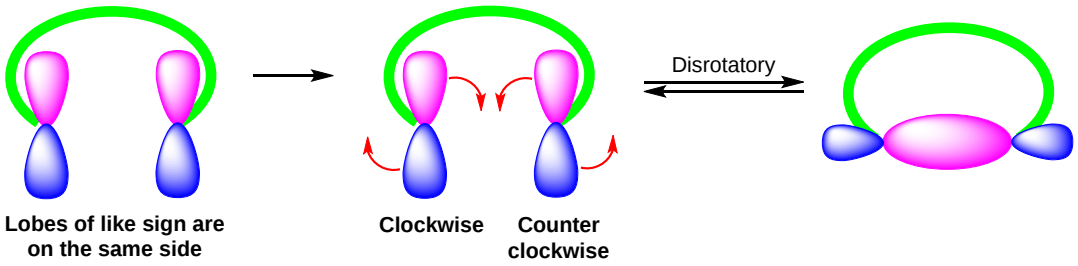
Similar results are seen with the 4 pi electrocyclic reaction of *cis*,*trans*-2,4-hexadiene being heated to exclusively form *cis*-3,4-dimethylcyclobutene and being irradiated with UV light to exclusively form *trans*-3,4-dimethylcyclobutene. Likewise, *trans*,*trans*-2,4-hexadiene forms *trans*-3,4-dimethylcyclobutene when heated and *cis*-3,4-dimethylcyclobutene when being irradiated with UV light.



The stereospecificity of electrocyclic reaction can be explained by considering the terminal lobes of the molecular orbital fo the conjugated π-electron system. For electrocyclic reactions of occur, molecular orbital lobes with the same sign from the HOMO of the molecule must rotate to form/break the key ring sigma bond. If the orbital lobes involved both rotate in the same direction (both counterclockwise or both clockwise), the process is called conrotatory. This typically occurs when orbital lobes of the same sign are on opposite sides of the molecule.



If the orbitals involved rotate in opposite directions (one clockwise and one counterclockwise), the process is called disrotatory. These differences in rotation are critically important when stereocenters are formed or broken. This typically occurs when orbital lobes of the same sign are on the same side of the molecule.



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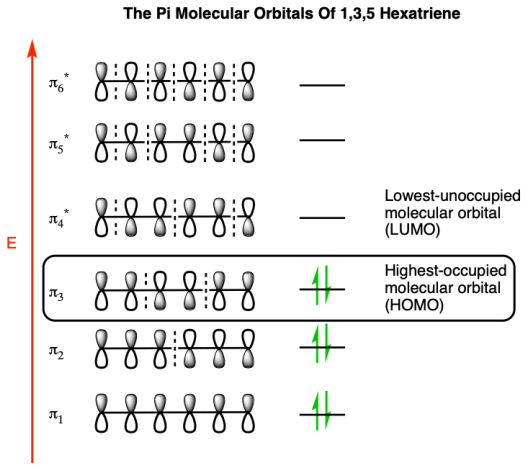
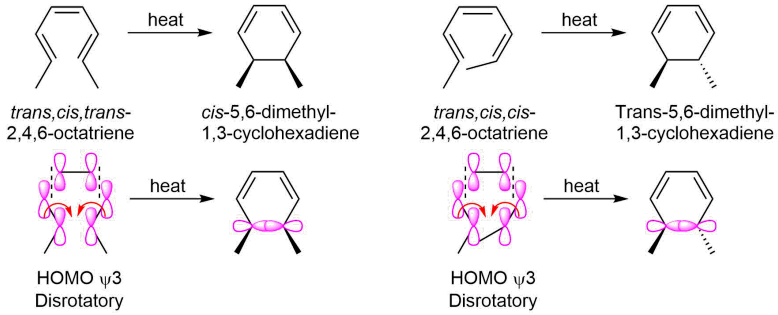
29.3: STEREOCHEMISTRY OF THERMAL ELECTROCYCLIC REACTIONS

Frontier orbital theory can be used to predict the stereochemistry of electrocyclic reactions. Electrons in the HOMO are the highest energy and therefore the most easily moved during a reaction. A molecular orbital diagram can be used to determine the orbital symmetry of a conjugated polyene's HOMO. Thermal reactions utilize the HOMO from the ground-state electron configuration of the molecular orbital diagram while photochemical reactions utilize the HOMO in the excited-state electron configuration.

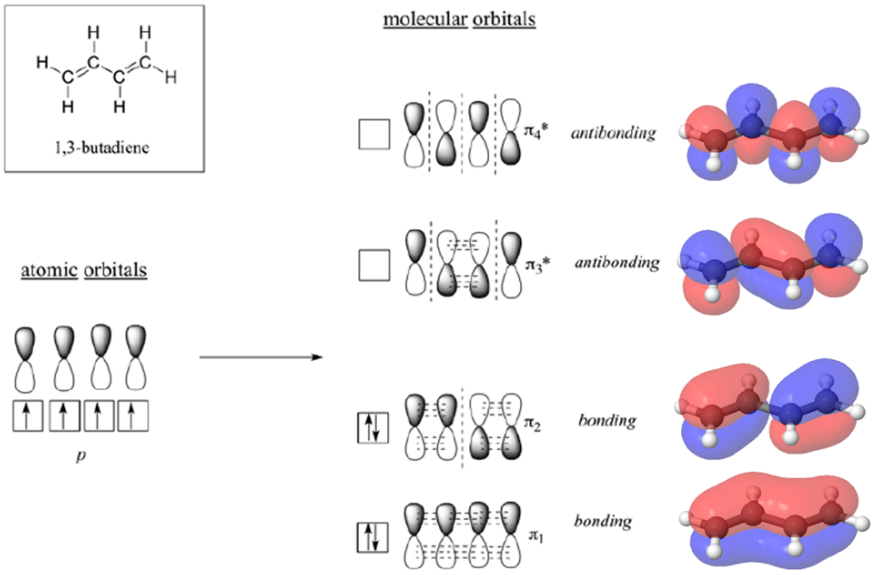
The molecular orbital of 1,3,5-hexatriene in its ground state electron configuration has psi three as its HOMO. The terminal molecular orbital lobes of the HOMO with the same sign are on the same side which predicts disrotatory ring closure under thermal conditions.



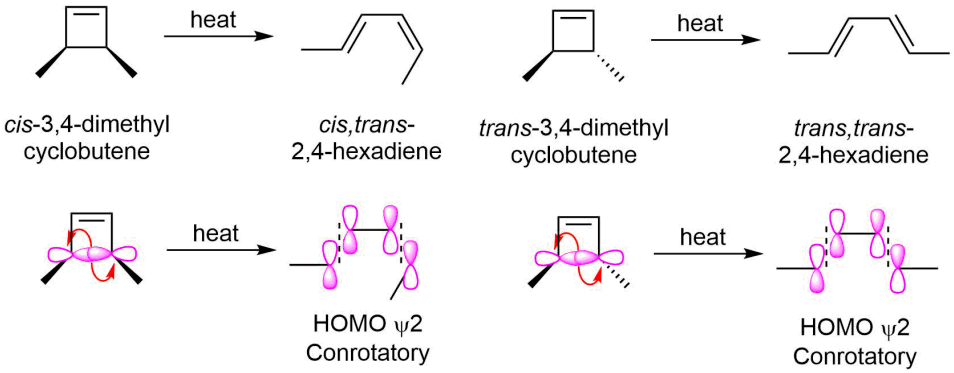
Disrotatory cyclization is observed during the electrocyclic reaction of 2,4,6-octatriene. The *trans,cis,cis*-2,4,6-octatriene isomer produces *cis*-5,6-dimethyl-1,3-cyclohexadiene as the product of thermal cyclization while the *trans,cis,cis*-2,4,6-octatriene isomer produces *trans*-5,6-dimethyl-1,3-cyclohexadiene.



The molecular orbital of a conjugated diene, such as 1,3-butadiene has psi two as the HOMO in its ground state electron configuration. The terminal molecular orbital lobes of the HOMO with the same sign are on opposite sides which predicts conrotatory ring closure under thermal conditions. However, the equilibrium of the electrocyclic reaction only allows for the ring opening to be observed.



Thus heating *cis*-3,4-dimethylcyclobutene causes the conrotatory ring opening to form *cis*,*trans*-2,4-hexadiene. Likewise, *trans*-3,4-dimethylcyclobutene forms *trans*,*trans*-2,4-hexadiene when heated.



A pattern begins to form revealing a relationship between the number of double bonds in the conjugated polyene and the rotation during electrocyclic reactions. For thermal electrocyclic reactions, polyenes with an odd number of double bonds undergo disrotation and those with an even number of double bond undergo conrotation.

? EXERCISE 29.3.1

1) The thermal electrocyclic ring opening of *trans*-3,4-dimethylcyclobutene could form *trans*,*trans*-2,4-hexadiene or *cis*,*cis*-2,4-hexadiene. However, the *trans*,*trans*-2,4-hexadiene is the isomer obtained from the reaction. Explain how it is possible to get both products and why the *trans*,*trans*-2,4-hexadiene is preferred.

2) If a conjugated tetraene were to undergo a thermal electrocylic reaction would the orbital nodes undergo con or disrotation?

Answer

1) Dienes undergo conrotation during thermal electrocyclic ring opening. Conrotation means the orbital nodes both rotate in the same direction either both clock with or both counter clockwise. If the nodes both rotate counter clockwise the *trans*,*trans*-2,4-hexadiene isomers forms. If they both rotate clockwise the *cis*,*cis*-2,4-hexadiene isomer is formed. Trans double bonds are more stable than cis due to steric strain. The *trans*,*trans*-2,4-hexadiene is perferably formed because it is more stable.

2) A tetraene has an even number of double bonds so it would be expected to undergo conrotation.

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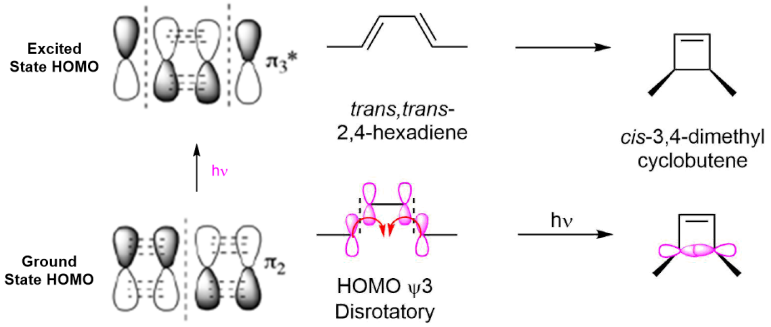
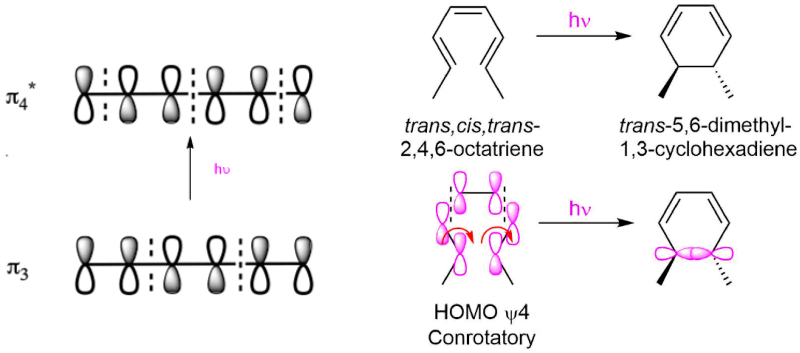
29.4: PHOTOCHEMICAL ELECTROCYCLIC REACTIONS

As discussed in **Section 30.1**, irradiation of a conjugated polyene with ultraviolet light causes an electron from the groude-state HOMO to be excited to the ground state LUMO. This creates a new higher energy HOMO in an electron configuration called the excited state. Electron excitation changes the symmetry of the new HOMO which has a corresponding effect on the reaction stereochemistry. Under photochemical reaction conditions conjugated dienes undergo disrotatory cyclization whereas under thermal conditions they underwent conrotatory cyclization. Likewise, conjugated triene undergo conrotatory photochemical cyclization while undergoing disrotatory thermal cyclization. For example, trans,trans-2,4-hexadiene undergoes conrotatory photochemical cyclization to form *cis*-3,4-dimethylcyclobutene.



The conjugated tirene, *trans*,*cis*,*trans*-2,4,6-octatriene undergoes conrotation to form *trans*-5,6-dimethyl-1,3-cyclohexadiene during photochemical cyclization.



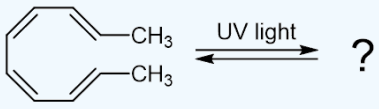
GENERALIZED STATEMENT OF WOODWARD-HOFFMANN RULES FOR ELECTROCYCLIC REACTIONS

Thermal and photochemical electrocyclic reactions always produce the opposite stereochemistry products due to the difference in symmetries in their HOMO frontier orbitals. This idea can be combined with the trend of even and odd polyenes to provide simple rules to predict the stereochemistry of electrocyclic reactions.

Number of Double Bonds	Thermal	Photochemical
Odd	Disrotatory	Conrotatory
Even	Conrotatory	Disrotatory

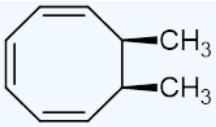
? EXERCISE 29.4.1

Would the following electrocyclic reaction be con or disrotatory? Please draw the expected product.



Answer

An even number of double bonds in photochemical conditions predicts a disrotatory reaction.



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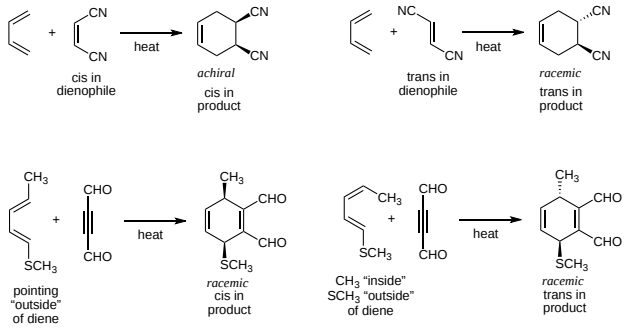
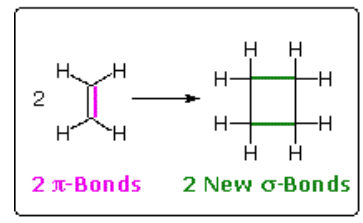
29.5: CYCLOADDITION REACTIONS

A concerted combination of two π-electron systems to form a ring of atoms having two new σ bonds and two fewer π bonds is called a **cycloaddition reaction**. The number of participating π-electrons in each component is given in brackets preceding the name of the reaction. The Diels-Alder reaction (**Section 14-4**) is the most useful cycloaddition reaction due to the ubiquity of 6-membered rings and its ability to reliably control stereochemistry in the product. In the Diels-Alder cycloaddition reaction, a conjugated diene, simply referred to as the **diene**, reacts with a double or triple bond coreactant called the **dienophile**, because it combines with (has an affinity for) the diene. The Diels-Alder reaction is a [4+2] cycloaddition (4 pi electrons from the diene and 2 pi electrons from the dienophile) that yields a functionalized 6-membered ring product. During the Diels-Alder reaction, two pi-bonds are converted to two sigma-bonds.

Due to the concerted mechanism for cycloaddition reactions, the geometry of atoms on the dienophile or the diene maintain their orientation in the product. This is a critical point for the 4 atoms (both dienophile atoms and the terminal atoms of the diene) that become sp^3 hybridized and thus are potential stereocenters in the product. (As a reminder, when chiral products are formed, we obtain a racemic mixture of enantiomers.) As highlighted below, cis dienophiles yield cis substituents in the product, while trans dienophiles yield trans product substituents. Substituents on the terminal atoms of the diene also can become stereocenters and this analysis is a little less straightforward than for dienophile substituents. The way to think about the diene substituents is whether the are pointing "outside" or "inside" the diene. These orientations are illustrated below. When groups are both pointing "outside" or "inside", we can consider them to be cis and they will end up cis in the product. When one group is pointing "outside" and one "inside", we can consider them as trans and they will be trans in the product.



Another important reaction is the [2+2] cycloaddition of two alkene containing molecules to form a 4-membered cyclobutane ring. The [2 + 2] cycloaddition of two alkenes does not occur by simply heating but can only be achieved by *irradiation* with ultraviolet light.

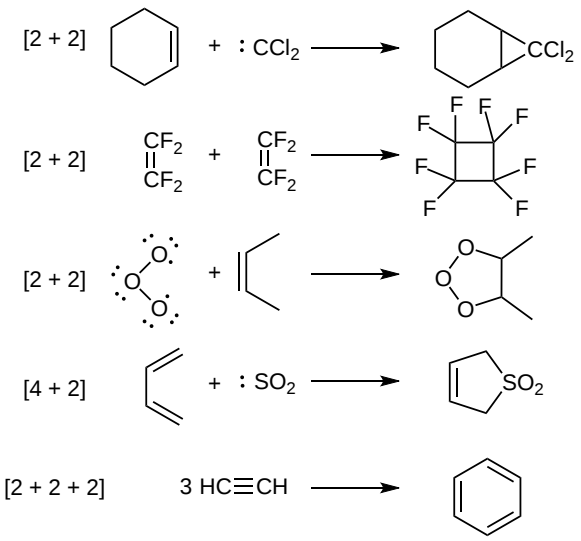


A [2+2] Cycloaddition

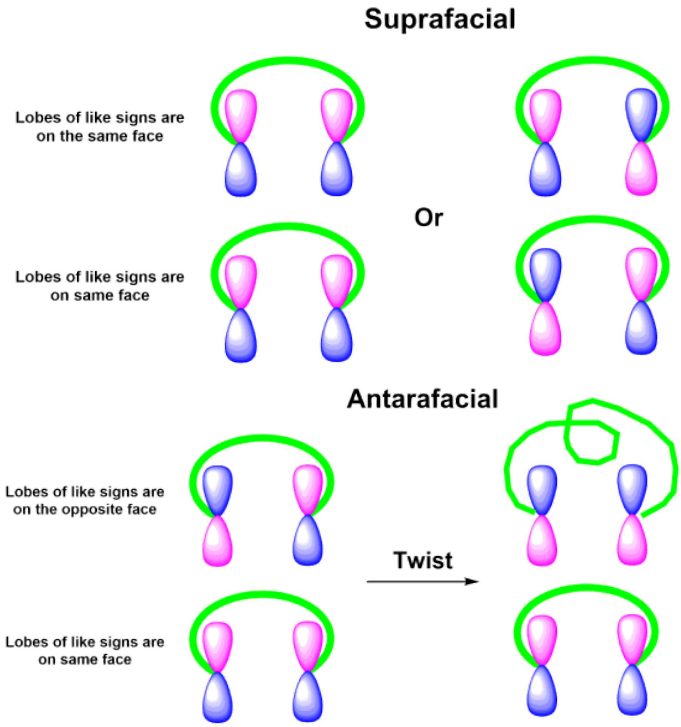
Photo [2+2] Cycloaddition

Many other cycloadditions are known, such as [2 + 2 + 2], and other types of [2 + 2], which give different size of rings. Some specific examples are shown below:

https://chem.libretexts.org/@go/page/474071



Like other pericyclic reactions, cycloadditions are determined by the orbital symmetry of the frontier orbitals of the reactants. For bonding to occur in a cycloaddition, the terminal lobes of the frontier orbitals of the two pi systems must have the correct symmetry. Correct symmetry can be obtained in two different ways. If the signs on the orbital lobes are the same on the faces of both reactants then the reaction undergoes a **suprafacial cycloaddition**. If the signs of the orbital lobes are the same on the face of one reactant but opposite on the other reactant then the reaction undergoes an **antarafacial cycloaddition**. Although both types are symmetry allowed, the fact that antarafacial cycloadditions require the twisting of a pi orbital system makes them more difficult to achieve.



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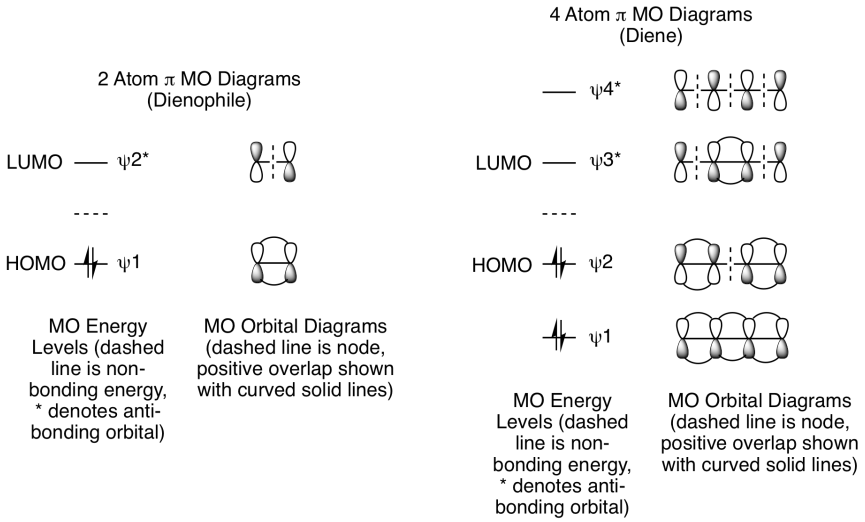
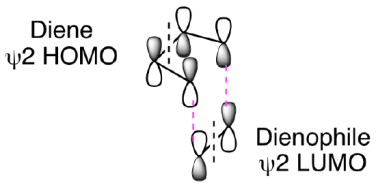
29.6: STEREOCHEMISTRY OF CYCLOADDITIONS

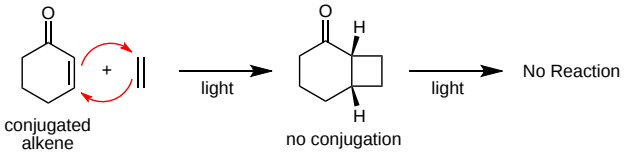
Frontier orbital theory can be used to predict if a given cycloaddition will occur with suprafacial or with antarafacial geometry. In a standard Diels-Alder reaction, bonding interactions are created when the electron containing HOMO of the diene donates electrons to the electron vacant LUMO of the other the dienophile. The dienophile has one pi bond, so it will use the pi MOs for a 2 atom system. The dienophile has 2 pi electrons which makes psi 2* its LUMO. The diene has two pi bonds, so it will use the pi MOs for a 4 atom system. The diene has has 4 pi electrons makes psi 2 its HOMO.



These MO diagrams show that the ground-state frontier orbitals of both reactants have terminal lobes with matching signs. The symmetry of these orbitals are such that bond formation will easily occur under thermal conditions with suprafacial geometry as shown below. (Note: The dashed black lines in the figure below represent nodes in the pi molecular orbitals of the diene and dienophile.) The two new sigma bonds, shown as dashed magenta lines below, are formed from constructive overlap of the terminal dienophile orbitals with the terminal orbitals of the diene.

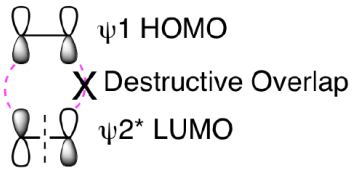


Photochemical [2+2] cycloadditions are excellent reactions for the synthesis of strained products containing 4-membered rings. One of the reaction partners must be conjugated so that it can absorb light and become an excited state molecule. These reactions produce strained 4-membered rings but are not reversible because the products lack conjugation and, thus, can't absorb light to facilitate a cycloreversion.



So, why won't this reaction happen thermally? How does our molecular orbital analysis help us understand the importance of this being a photochemical reaction? First, let's look at the orbital analysis if we tried to do a thermal [2+2] reaction. As shown below, we cannot get suprafacial overlap for both of the 2 pi reactants when trying to combine psi 1 HOMO with psi 2* LUMO. This means that it is not favorable to convert the two reactant pi bonds into two new product pi bonds.

Thermal [2+2] Reaction



No Reaction

What happens when we shine light on the reaction? Light creates an excited state molecule by promoting an electron in the HOMO to the LUMO, as shown below. This means the excited state HOMO is the ground state LUMO. We need to understand a few key points about photoreactions before doing our molecular orbital analysis. Excited state molecules are very short lived, relaxing back to the ground state very quickly. Therefore, it is practically impossible for two excited state molecules to find each other in a reaction. Instead, reactions occur between one excited state molecule and one ground state molecule. When only one molecule is conjugated, that is the molecule that will form the excited state. If both reactants are conjugated, either can form the excited state. The orbital analysis is shown below. First, we see the orbital picture when a ground state molecule absorbs light to form an excited state. Second, when we analyze the reaction, it is now psi 2* HOMO of the excited state molecule reacting with psi 2* LUMO of the ground state molecule. This gives suprafacial constructive overlap for both orbitals and the 2 reactant pi bonds can be converted into two product sigma bonds.

2 Atom π MO Diagram

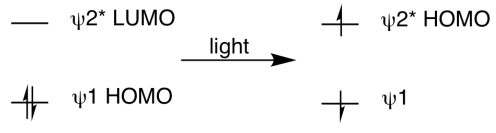
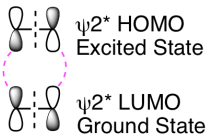


Photo [2+2] Reaction



Cycloaddition reactions can be categorized based on the total number electrons involved in the rearrangement. The [4+2] Diels-Alder reaction involves 6 electrons and takes place using a suprafacial pathway under thermal conditions. The thermal [2+2] cycloaddtion of two alkenes involves 4 electrons and must take place by antarafacial pathway. However, the pathway is reversed for photochemical [2+2] cycloaddtions which take place by a suprafacial pathway. These ideas can be generalized using the rules for cycloadditions below.

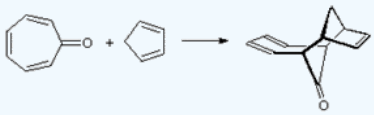
Generalized Statement of Woodward-Hoffmann Rules for Cycloadditions

Number of Electrons	Thermal	Photochemical
4n + 2	Suprafacial (Allowed)	Antarafacial (Forbidden)
4n	Antarafacial (Forbidden)	Suprafacial (Allowed)

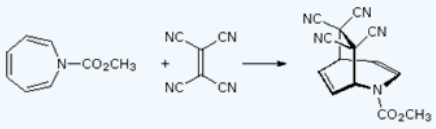
? EXERCISE 29.6.1

For the following reactions determine what type of cycloaddition is occurring, is the reaction supra or antarafacial, and would the reaction require thermal or photochemical conditions.

a)



b)



c)

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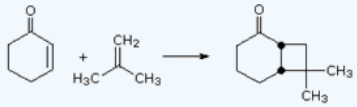

Answer

a) [6+4], suprafacial, thermal

b) [4+2], suprafacial, thermal

c) [2+2], antarafacial, photochemical

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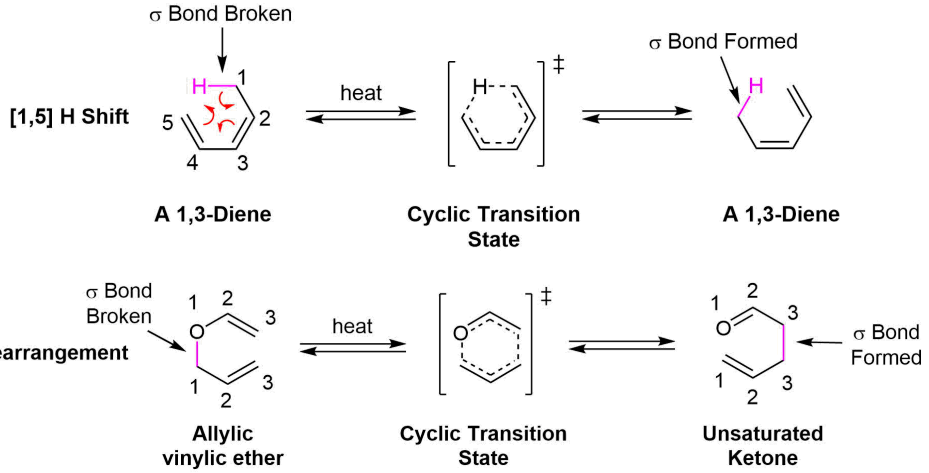
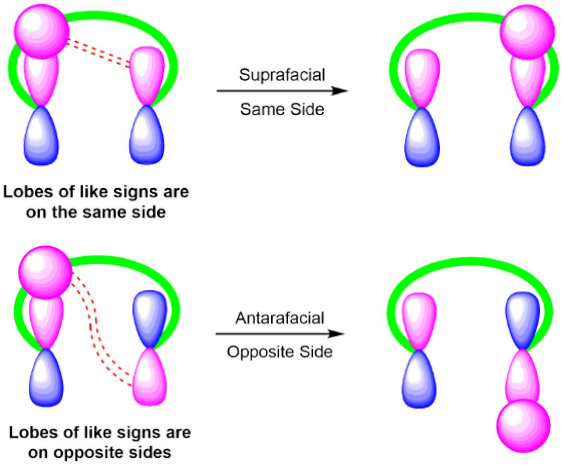
29.7: SIGMATROPIC REARRANGEMENTS

Molecular rearrangements in which a σ-bonded atom or group, flanked by one or more π-electron systems, shifts to a new location with a corresponding reorganization of the π-bonds are called **sigmatropic reactions**. The reactant and product have the same number and type of bonds, just different bond locations. These rearrangements are described by two numbers set in brackets, which refer to the position of the sigma bond in the reactant that is broken compared to the position of the sigma bond in the product that is formed. The most common examples include hydrogen shifts across a diene system (called a [1,5] H shift) and rearrangements of double allyl-type systems (called [3,3] rearrangements).

As shown in the examples below, the atoms on the sigma bond in the reactant that is broken (magenta bond) are both labeled "1", and the numbering of atoms on each side of that sigma bond continue until the atoms connected by the new sigma bond in the product (magenta) are reached. Thus, the H shift is [1,5] because the key sigma bond in both the reactant and product is to the H while the H moves from C-1 to C-5. For the [3,3] rearrangement, the broken sigma bond migrates across two allyl-type systems and forms between atoms "3" and "3" in the product. This particular example is a Claisen rearrangement since an allyl vinyl ether is transformed into a 1,4-carbonyl alkene.



The migration of a group during a sigmatropic rearrangement is controlled by the orbital symmetries of the alkenes involved. Sigmatropic rearrangements can occur on one face of the molecule (think top or bottom, like a syn addition to an alkene) which is called a **suprafacial** reaction or from one face to the other (think from top to bottom or vice versa, like an anti addition to an alkene) which is called **antarafacial**. We will explore this idea further in the next section.



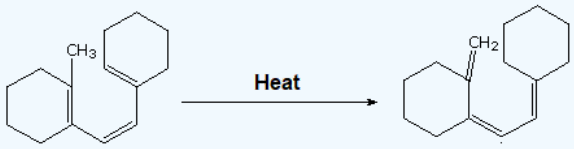
GENERALIZED STATEMENT OF WOODWARD-HOFFMANN RULES FOR SIGMATROPIC REARRANGEMENTS

Suprafacial and antarafacial sigmatropic rearrangements are considered symmetry-allowed by the Woodward-Hoffmann rules. However, suprafacial reactions are much more common. Note! These rules for sigmatropic rearrangements are the same as those given for cycloaddition reactions in **Section 30-3**.

Number of Double Bonds	Thermal	Photochemical
Odd	Suprafacial	Antarafacial
Even	Antarafacial	Suprafacial

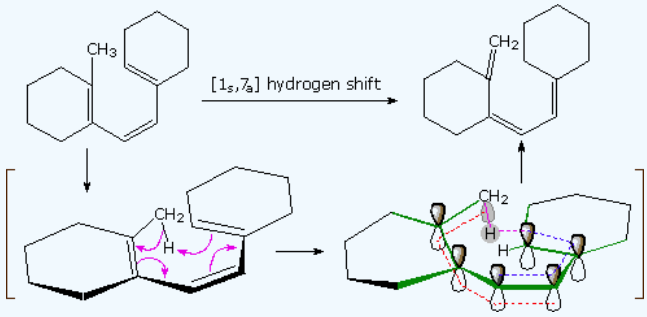
EXERCISE 29.7.1

For the following sigmatropic hydrogen shift please use braked number to describe the reaction. Predict if the hydrogen shift will be suprafacial and antarafacial. Lastly, draw in arrows to describe the mechanism for this reaction.



Answer

An example of an [1,7] hydrogen shift is shown in the following diagram. The conjugated alkene has three double bonds, which is an odd number, and the reaction is occuing under thermal conditions. This means the reaction is predicted to be suprafacial. The conjugated triene assumes a nearly planar coiled conformation in which a methyl hydrogen is oriented just above the end carbon atom of the last double bond. A [1_s,7_a] sigmatropic hydrogen shift may then take place, as described by the four curved arrows. With reference to the approximate plane of this π-electron system (defined by the green bonds), the hydrogen atom departs from the bottom face and bonds to the top face, so the transfer is antarafacial.



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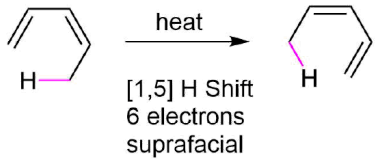
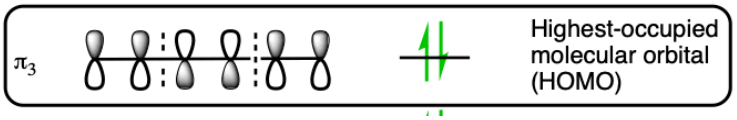
29.8: SOME EXAMPLES OF SIGMATROPIC REARRANGEMENTS

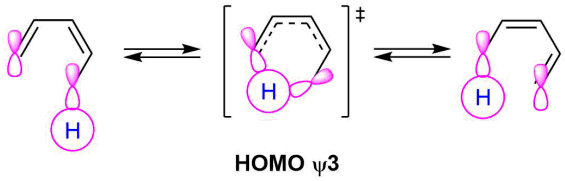
A sigmatropic rearrangement which involves a [1,5] hydrogen shift, like the one shown below illustrates, a hydrogen atom (s orbital) moving across a 5 atom system containing two conjugated double bonds. Since there are three curved arrows in the mechanism, this is a 6 pi reaction. The rules for sigmatropic rearrangements discussed in the last section predict the hydrogen atom will undergo a suprafacial shift. The C-H bond breaking and the C-H bond forming, magenta dashed lines, are both on the bottom face of the molecule's pi system.



The suprafacial nature of this reaction comes from the orbital symmetry of the HOMO from a 6 pi electron molecular orbital. The orbital lobes on the terminal ends have the same sign on the same side.

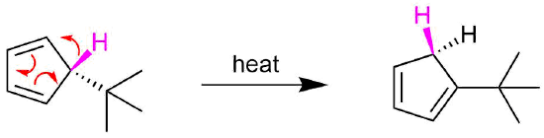


During the reaction mechanism the hydrogen atom, an s orbital, is passes from one molecular to another of the same sign on the same side of the molecule or suprafacial.



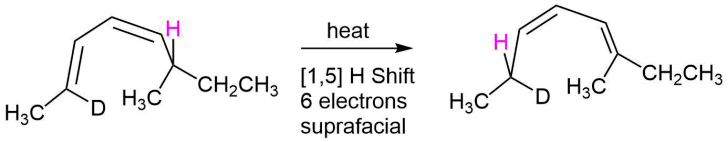
HOMO ψ3

For example, 5-*t*-butyl-1,3-cyclopentadiene easily undergoes a [1,5] suprafacial shift of a hydrogen atom under thermal conditions to yield 1-*t*-butyl-1,3-cyclopentadiene as a rearranged product.



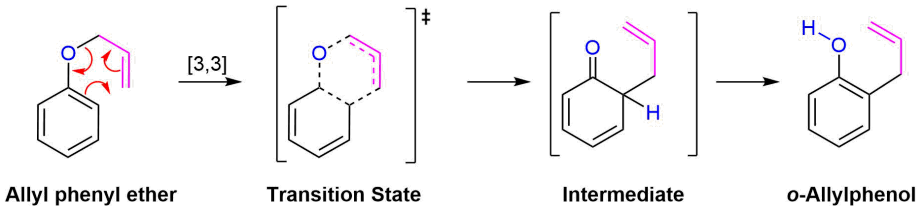
[1,5] H Shift
Suprafacial

As another example, heating S-2-deuterio-6-methyl-(2E,4Z)-2,4-octadiene undergoes a thermal [1,5] suprafacial shift of a hydrogen to produce the product, R-2-deuterio-6-methyl-(2Z,4E)-3,5-octadiene with stereochemical control.

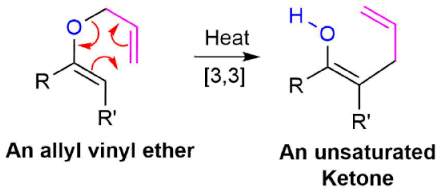


CLAISEN REARRANGEMENT

A very important example of a [3,3] sigmatropic reaction is the **Claisen rearrangement** of an allyl aryl ether or an allyl vinyl ether (**Section 18-4**). Heating an allyl aryl ether to 250 ºC causes an sigmatropic rearrangement to produce an *o*-allylphenol. 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 movement of six bonding electron.

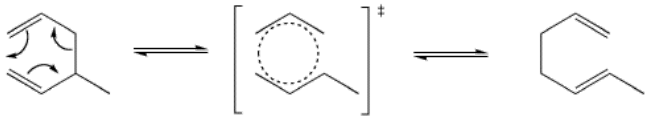


Allyl vinyl ethers can also undergo a Claisen rearrangement when heated to form gamma, delta -unsaturated ketones or aldehydes.



COPE REARRANGEMENT

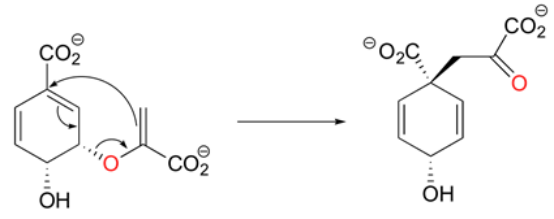
Another important example of a [3,3] sigmatropic reaction is the **cope rearrangement**. This reaction converts between isomers of a 1,5-hexadiene through a cyclic transition state.



Both Cope and Claisen rearrangements involve the movement of six electrons which means they both react by suprafacial pathways under thermal conditions. These reactions can be considered to occur due to changes in overlap between orbitals around the cyclic transition state. Two orbitals which form the sigma bond being broken tilt away from each other while two orbitals that are pi bonding tilt toward each other to from a new sigma bond. After the change there are now two p orbitals parallel to each other on the left which then form new pi bonds.

Orbital rearrangement in a Cope rearrangement

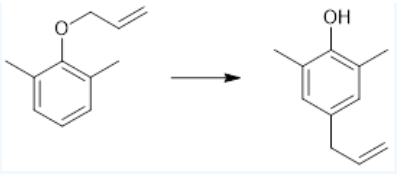
Sigmatropic rearrangements are rare in biological chemistry. One example is the chorismate mutase catalyzed Claisen rearrangement of chorismate (a allylic vinyl ether) to form prephenate. Prephenate is a precursor in the biosynthetic pathway of aromatic amino acids phenylalanine and tyrosine.



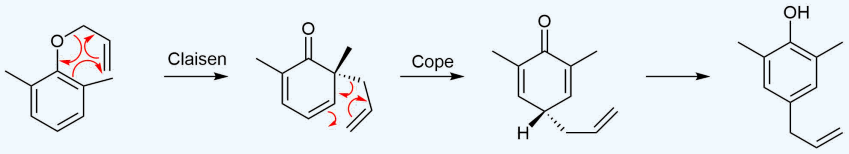
chorismate prephenate

? EXERCISE 29.8.1

A Claisen rearrangement performed in the presence of ortho-substituents exclusively leads to para-substituted rearrangement products. This occurs via a Claisen rearrangement followed by a Cope rearrangement. Draw out the intermediates formed during this transformation and the mechanisms for both rearrangements.



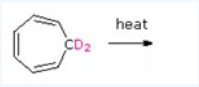
Answer



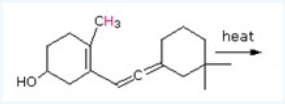
EXERCISE 29.8.2

Draw the expected products of the following [1,5] suprafacial shifts.

a)

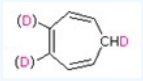


b)

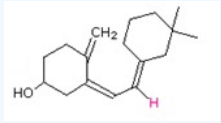


Answer

a)

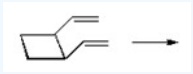


b)



EXERCISE 29.8.3

Draw the product of the following [3,3] suprafacial shifts.



Answer

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29.9: A SUMMARY OF RULES FOR PERICYCLIC REACTIONS

Before pericyclic reactions can be put to use in a predictable and controlled manner, a broad mechanistic understanding of the factors that influence these concerted transformations must be formulated. The simplest, albeit least rigorous, method for predicting the configurational path favored by a proposed pericyclic reaction is based upon a transition state electron count. In most of the earlier examples, pericyclic reactions were described by a cycle of curved arrows, each representing a pair of bonding electrons. The total number of electrons undergoing reorganization is always even, and is either a **4n+2** or **4n** number (where n is an integer). Once this electron count is made, the following table may be used for predictions. It is important to remember that going from thermal to photochemical conditions or going from 4n to 4n+2 reaction electrons changes the outcome of the reaction.

	Electron Count	**Stereochemistry**
Thermal Reactions (Ground State)	**4n + 2**	Suprafacial or Disrotatory
	4n	Antarafacial or Conrotatory
	Electron Count	**Stereochemistry**
Photochemical Reactions (Excited State)	**4n + 2**	Antarafacial or Conrotatory
	4n	Suprafacial or Disrotatory

? EXERCISE 29.9.1

Predict the stereochemistry of the following reactions:

a. The photochemical cyclization of a conjugated tetraene.
b. The thermal cyclization of a conjugated tetraene
c. A thermal [4+4] cycloaddition
d. A photochemical [2+5] cycloaddition
e. A thermal [3,5] sigmatropic rearrangement

Answer

1)a) Disrotatory

b) Conrotatory

c) Antarafacial

d) Suprafacial

e) Antarafacial

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CHAPTER OVERVIEW

30: SYNTHETIC POLYMERS

Synthetic polymer are man-made polymer that is not a biopolymer (e..g, proteins or complex carbohydrates). Synthetic polymers are mostly non-biodegradable and often synthesized from petroleum. The eight most common types of synthetic organic polymers are: Low-density polyethylene (LDPE), High-density polyethylene (HDPE), Polypropylene (PP), Polyvinyl chloride (PVC), Polystyrene (PS), Nylon, nylon 6, nylon 6,6, Teflon (Polytetrafluoroethylene) and Thermoplastic polyurethanes (TPU).

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30.0: Chapter Objectives

Learning Objectives

By the end of this chapter, students should be able to:

- Explain how synthetic polymers are formed through various polymerization reactions.
- Identify how the molecular structure of polymers influences their macroscopic properties.
- Categorize synthetic polymers based on their structure, properties, and applications.
- Describe experimental techniques used to analyze and characterize polymers.
- Examine the diverse applications of synthetic polymers in different industries.

Synthetic polymers constitute a vast class of materials that play an indispensable role in numerous aspects of modern life. These polymers are engineered in laboratories and industrial settings through chemical processes, wherein small molecules known as monomers are repetitively linked together to form long chains or networks. The resulting macromolecules exhibit a wide range of properties and functionalities tailored to specific applications, making them ubiquitous in everyday products and industrial processes.

The synthesis of synthetic polymers typically involves polymerization reactions, where monomers undergo chemical bonding to form polymer chains. This can occur through various mechanisms, including addition polymerization, condensation polymerization, and ring-opening polymerization, each yielding polymers with distinct structures and properties (Figure 30.0.1).

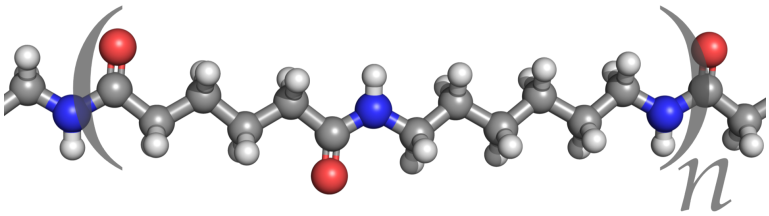

Figure 30.0.1: Nylon 6,6 chemical structure (CC BY 3.0; YassineMrabet via Wikipedia)

One of the most significant advantages of synthetic polymers is their versatility. By selecting different monomers and adjusting reaction conditions, polymer chemists can precisely control the molecular architecture, composition, and properties of the resulting polymers. This versatility enables the design of materials with tailored characteristics such as mechanical strength, flexibility, thermal stability, conductivity, and biocompatibility.

Synthetic polymers find applications across diverse industries and sectors. Plastics, for example, are ubiquitous in packaging, construction, electronics, automotive components, and consumer goods due to their lightweight, moldability, and durability. Synthetic fibers such as polyester, nylon, and acrylics are widely used in textiles, apparel, and industrial materials. Polymers also play critical roles in adhesives, coatings, biomedical implants, drug delivery systems, and advanced composites.

Understanding the structure-property relationships of synthetic polymers is essential for optimizing their performance and developing new materials with enhanced characteristics. Researchers continue to explore innovative polymerization techniques, advanced characterization methods, and sustainable alternatives to traditional polymers to address environmental concerns associated with plastic waste and pollution.

In summary, synthetic polymers represent a cornerstone of modern materials science and technology, providing tailored solutions to a myriad of societal challenges and driving innovation in various industries. Their versatility, tunable properties, and wide-ranging applications underscore their importance in shaping the world we live in today.

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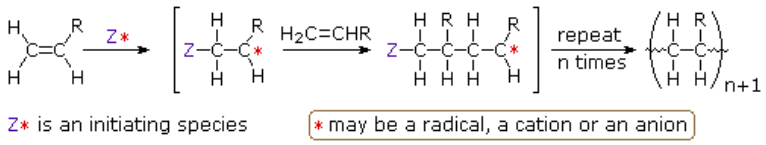
30.1: CHAIN-GROWTH POLYMERS

Polymers resulting from additions to alkenes monomers are chain-growth polymers. In these processes each addition step results in a longer chain which ends in a reactive site. The mechanism of each addition step is the same, and each addition step adds another monomer to extend the chain by one repeating unit. The most common and thermodynamically favored chemical transformations of alkenes are addition reactions. Many of these addition reactions are known to proceed in a stepwise fashion by way of reactive intermediates, and this is the mechanism followed by most polymerizations. A general diagram illustrating this assembly of linear macromolecules, which supports the name chain growth polymers, is presented here. Since a pi-bond in the monomer is converted to a sigma-bond in the polymer, the polymerization reaction is usually exothermic by 8 to 20 kcal/mol. Indeed, cases of explosively uncontrolled polymerizations have been reported.

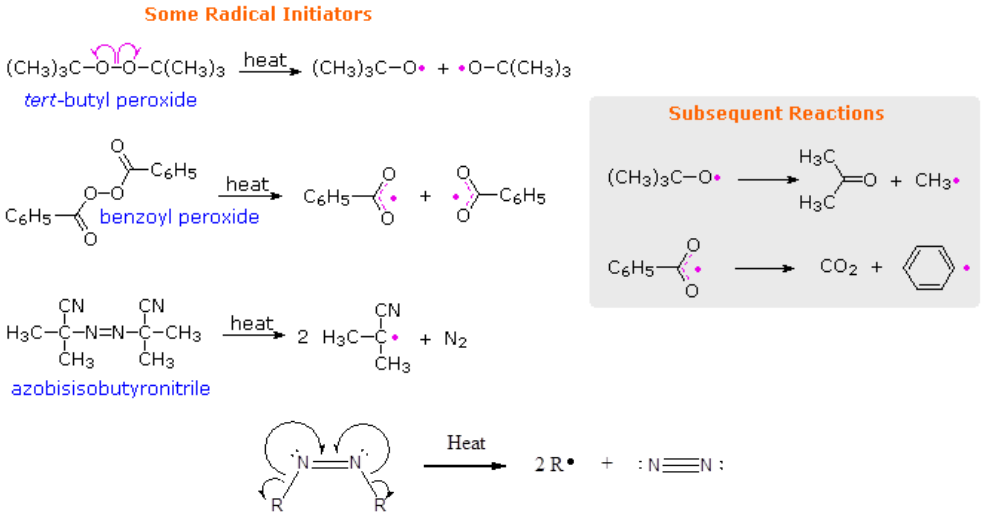


It is useful to distinguish four polymerization procedures fitting this general description.

- Radical Polymerization: The initiator is a radical, and the propagating site of reactivity (*) is a carbon radical.
- Cationic Polymerization: The initiator is an acid, and the propagating site of reactivity (*) is a carbocation.
- Anionic Polymerization: The initiator is a nucleophile, and the propagating site of reactivity (*) is a carbanion.
- Coordination Catalytic Polymerization: The initiator is a transition metal complex, and the propagating site of reactivity (*) is a terminal catalytic complex.

RADICAL CHAIN-GROWTH POLYMERIZATION

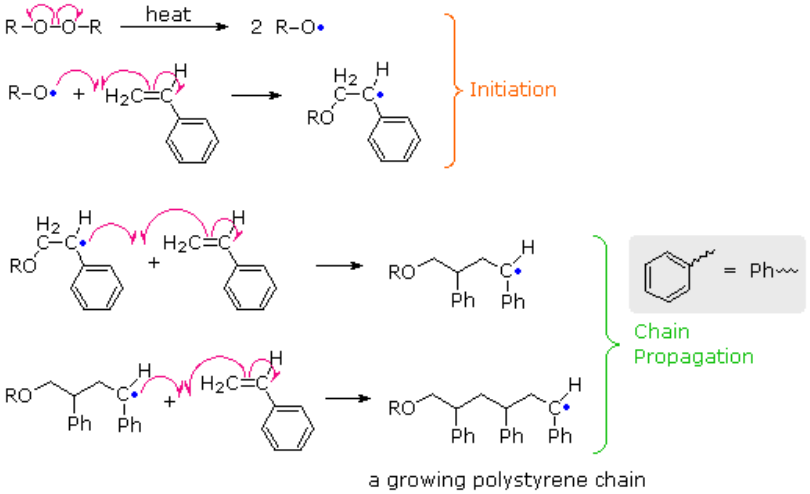
Virtually all of the monomers described above are subject to radical polymerization. Since this can be initiated by traces of oxygen or other minor impurities, pure samples of these compounds are often "stabilized" by small amounts of radical inhibitors to avoid unwanted reaction. When radical polymerization is desired, it must be started by using a radical initiator, such as a peroxide or certain azo compounds. The formulas of some common initiators, and equations showing the formation of radical species from these initiators are presented below.



By using small amounts of initiators, a wide variety of monomers can be polymerized. One example of this radical polymerization is the conversion of styrene to polystyrene, shown in the following diagram. The first two equations illustrate the initiation process, and the last two equations are examples of chain propagation. Each monomer unit adds to the growing chain in a manner that generates the most stable radical. Since carbon radicals are stabilized by substituents of many kinds, the preference for head-to-tail regioselectivity in most addition polymerizations is understandable. Because radicals are tolerant of many functional groups and solvents (including water), radical polymerizations are widely used in the chemical industry.

Each step in this polymer formation is an addition to an alkene. The mechanism is in most cases a *free radical* addition. In free radical reactions the pi pair of electrons separates. One of these electrons pairs with an electron from the attacking reagent to form a sigma bond with one of the alkene carbons. and the other electron remains attached to the other alkene carbon. (Curved arrows with only one "barb" on a point are used to follow the path of a single electron in the same way that "double-headed" arrows follow the path of an electron pair.)

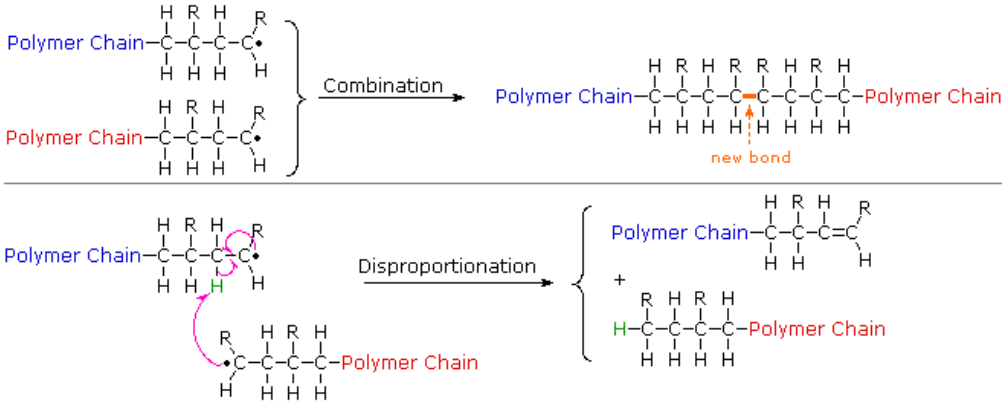
Intermediates with an unpaired electron are called free radicals, so this step can be described as adding a free radical to an alkene to lengthen the chain by two carbons and generate a new free radical. In its turn this new free radical can add to another molecule of monomer and continue the process.



a growing polystyrene chain

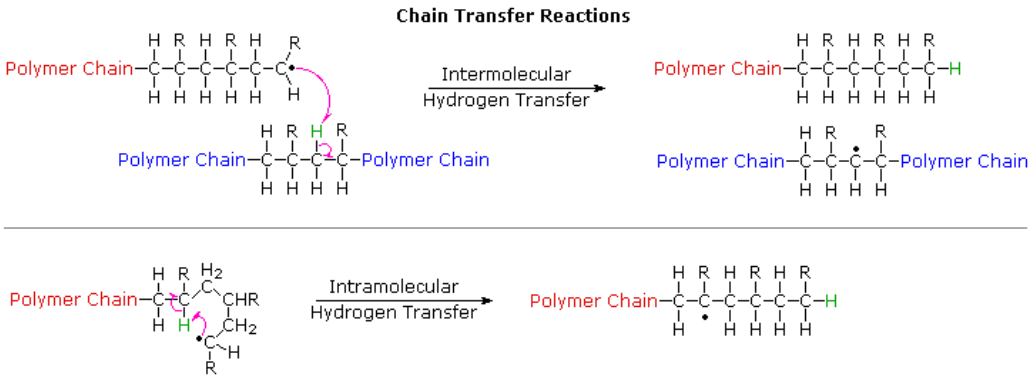
In principle, once started a radical polymerization might be expected to continue unchecked, producing a few extremely long chain polymers. In practice, larger numbers of moderately sized chains are formed, indicating that chain-terminating reactions must be taking place. The most common termination processes are Radical Combination and Disproportionation. These reactions are illustrated by the following equations. The growing polymer chains are colored blue and red, and the hydrogen atom transferred in disproportionation is colored green. Note that in both types of termination two reactive radical sites are removed by simultaneous conversion to stable product(s). Since the concentration of radical species in a polymerization reaction is small relative to other reactants (e.g. monomers, solvents and terminated chains), the rate at which these radical-radical termination reactions occurs is very small, and most growing chains achieve moderate length before termination.

Chain Termination Reactions



The relative importance of these terminations varies with the nature of the monomer undergoing polymerization. For acrylonitrile and styrene combination is the major process. However, methyl methacrylate and vinyl acetate are terminated chiefly by disproportionation.

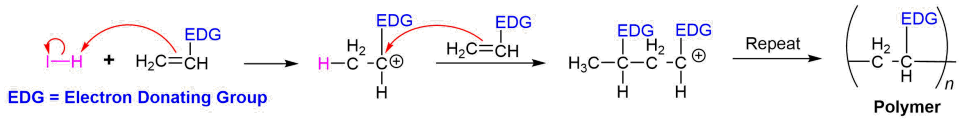
Another reaction that diverts radical chain-growth polymerizations from producing linear macromolecules is called chain transfer. As the name implies, this reaction moves a carbon radical from one location to another by an intermolecular or intramolecular hydrogen atom transfer (colored green). These possibilities are demonstrated by the following equations.



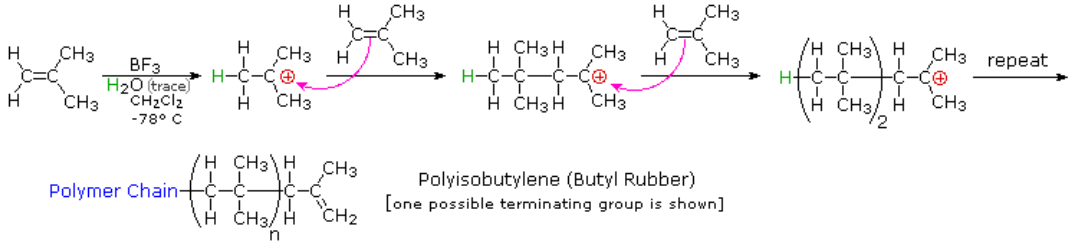
Chain transfer reactions are especially prevalent in the high pressure radical polymerization of ethylene, which is the method used to make LDPE (low density polyethylene). The 1º-radical at the end of a growing chain is converted to a more stable 2º-radical by hydrogen atom transfer. Further polymerization at the new radical site generates a side chain radical, and this may in turn lead to creation of other side chains by chain transfer reactions. As a result, the morphology of LDPE is an amorphous network of highly branched macromolecules.

CATIONIC CHAIN-GROWTH POLYMERIZATION

Cationic polymerizations are typically acid-catalyzed. Electrophilic addition of H^+ to a double bond forms a carbocation which is propagated by repeated reactions with addition alkene monomers. Alkene monomers bearing cation stabilizing groups, such as alkyl, phenyl or vinyl can be polymerized by cationic processes.

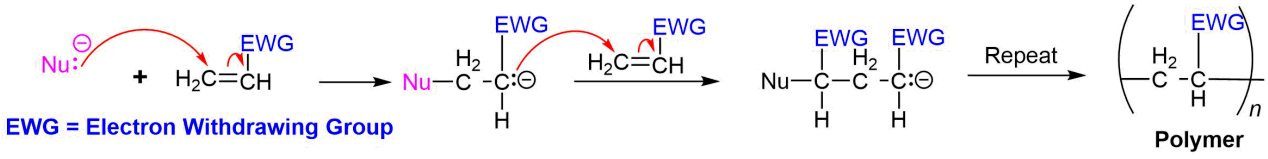


Polymerization of isobutylene (2-methylpropene) by traces of strong acids is an example of cationic polymerization. The initiation reagent cationic polymerization is commonly the Lewis acid, boron tribluoride (BF_3), along with traces of water to form the acidic $BF_3OH^-H^+$ catalyst. The polyisobutylene product is a soft rubbery solid, which is used for inner tubes. This process is similar to radical polymerization, as demonstrated by the following equations. Chain growth ceases when the terminal carbocation combines with a nucleophile or loses a proton, giving a terminal alkene (as shown here).

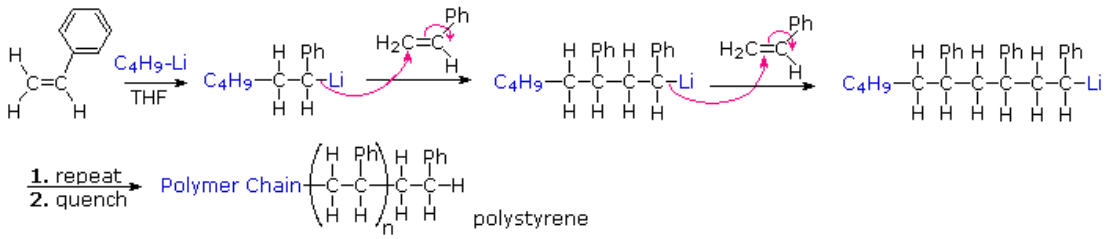


ANIONIC CHAIN-GROWTH POLYMERIZATION

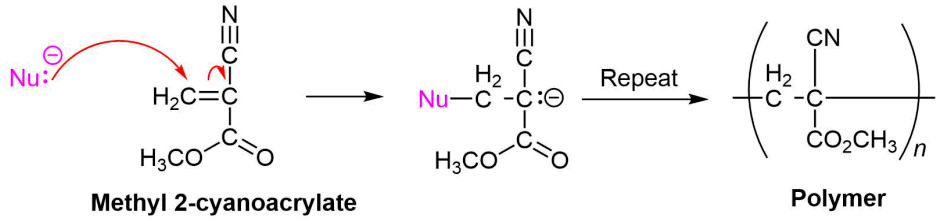
Only monomers having anion stabilizing electron-withdrawing groups (EWG) substituents, such as phenyl, cyano or carbonyl can undergo anionic polymerization.



Species that have been used to initiate anionic polymerization include alkali metals, alkali amides, alkyl lithiums and various electron sources. The fundamental reaction for anion polymerization is a conjugate nucleophilic addition (**Section 18-13**) Treatment of a cold THF solution of styrene with 0.001 equivalents of n-butyllithium causes an immediate polymerization. This is an example of anionic polymerization, the course of which is described by the following equations. Chain growth may be terminated by water or carbon dioxide, and chain transfer seldom occurs.



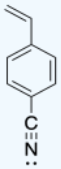
A practical application of anionic polymerization occurs in the use of superglue. This material is methyl 2-cyanoacrylate, $CH_2=C(CN)CO_2CH_3$. When exposed to water, amines or other nucleophiles, a rapid polymerization of this monomer takes place. Because the monomer has two electron withdrawing groups the polymerization particularly rapid.



Methyl 2-cyanoacrylate **Polymer**

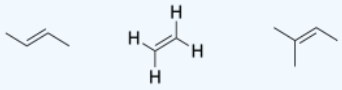
? EXERCISE 30.1.1

1) Anionic polymerization of *p*-substituted styrene proceeds very well when the substituent is an electron-withdrawing group such as nitrile. Explain the reason for the success of this approach.

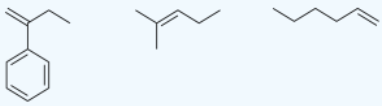


2) In each group, select the alkene monomer most suitable for cationic polymerization.

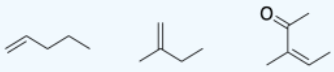
a)



b)

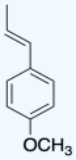


c)



3) Provide a mechanism for the formation of a protic initiator from the interaction of boron trifluoride with water.

4) Anethole in a naturally-occurring compound that has been used in cationic polymerizations. Show why anethole should be a good monomer for this method.



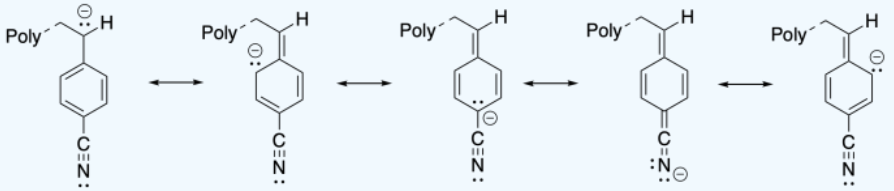
5) Show why radicals formed from the following monomers are relatively stable:

a) acrylonitrile, $CH_2=CHCN$

b) methyl acrylate, $CH_2=CHCO_2Me$

Answer

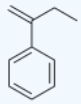
1) The additional resonance stabilization of the anion by the nitrile group makes anionic polymerization proceed smoothly.



2)

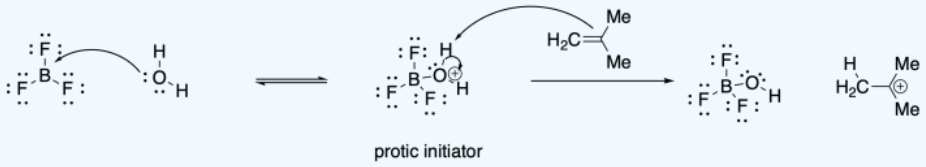
a) tertiary cation

b) tertiary cation, resonance-stabilized

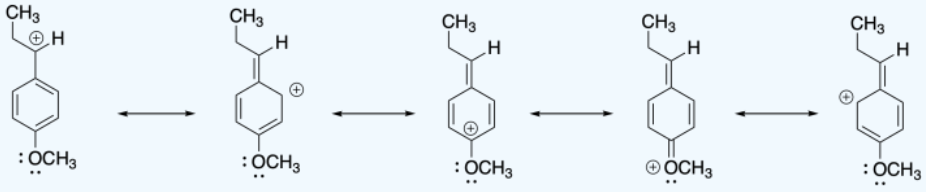


c) tertiary cation, without electron-withdrawing group

3)

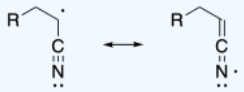


4)

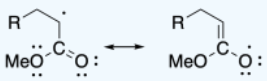


5)

a)



b)



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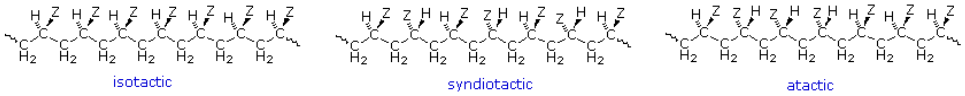
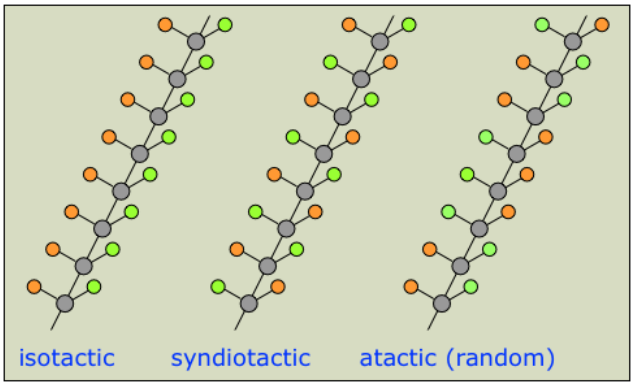
30.2: STEREOCHEMISTRY OF POLYMERIZATION - ZIEGLER-NATTA CATALYSTS

ZIEGLER-NATTA CATALYTIC POLYMERIZATION

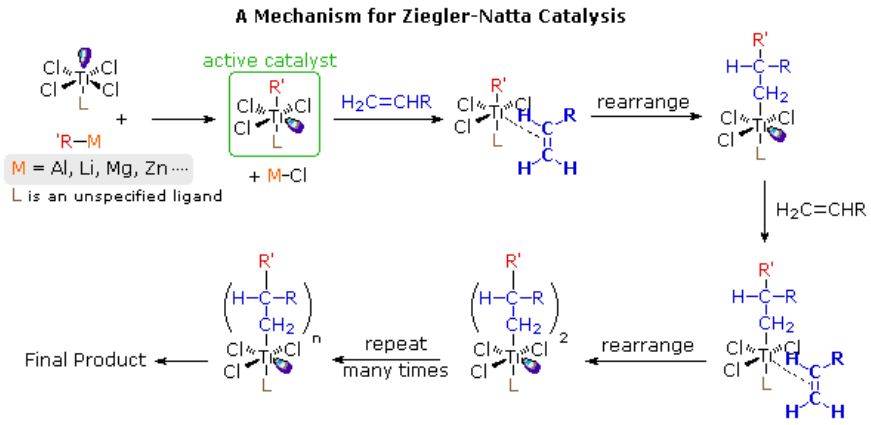
When propene is enchained into a polymer, a new chiral center is formed at every position where a methyl group branches from the backbone. Rather than trying to assign each of these chiral centers with stereochemical configurations (*R*) or (*S*), we instead describe the relative stereochemical relationships along the backbone. The term used to describe these relationships is "**tacticity**". If there is no apparent relationship between the projection of the methyl groups along the backbone, the polymer is termed "**atactic**". If the methyl groups alternate, pointing first one direction, then the other, all the way along the chain, then the polymer is termed "**syndiotactic**". If the methyl groups all project the same direction, the polymer is described as "isotactic".





An efficient and stereospecific catalytic polymerization procedure was developed by Karl Ziegler (Germany) and Giulio Natta (Italy) in the 1950's. Ziegler-Natta catalysts are prepared by reacting certain transition metal halides with organometallic reagents such as alkyl aluminum, lithium and zinc reagents. The catalyst formed by reaction of triethylaluminum with titanium tetrachloride is commonly used. Ziegler-Natta catalysts allowed for the first time, the stereochemically controlled synthesis of polymers with virtually no branching. By changing the catalyst, pure isotactic, syndiotactic, or atactic polymers could be created. For this important discovery, Ziegler and Natta received the 1963 Nobel Prize in chemistry. For example, the polymerization of ethylene, using a Ziegler-Natta catalyst produces a stronger (more crystalline) and more heat resistant product, called high-density polyethylene (HDPE), than typical radical polymerizations which produces low-density polyethlene (LDPE). HDPE is normally produced with molecular weights in the range of 200,000 to 500,000, but it can be made even higher. Polyethylene with molecular weights of three to six million is referred to as ultra-high molecular weight polyethylene, or UHMWPE. UHMWPE can be used to make fibers which are so strong they replaced Kevlar for use in bullet proof vests. Large sheets of it can be used instead of ice for skating rinks.

The following diagram presents one mechanism of the Ziegler-Natta polymerization. Formation of the Ziegler-Natta catalyst, adds an alkyl group ligand to create an organo transition metal compound with a vacant coordination site. An alkene ligand is then coordinated to the transition metal which is followed by a 1,2-insertion of the alkene into the metal-carbon bond. The insertion creates a vacant coordination site which can react with another alkene. These same elementary steps continue to occur to provide the polymerization.



EXERCISE 30.2.1

When the monomer vinylidene fluoride, $H_2C{=}CF_2$, is polymerized it does not create isotactic, syndiotactic, and atactic forms. Please explain

Answer

When vinylidene fluoride is polymerized it does not create a chiral center due to the symmetry created by the two fluorides. Chirality is necessary to create isotactic, syndiotactic, and atactic polymer forms.

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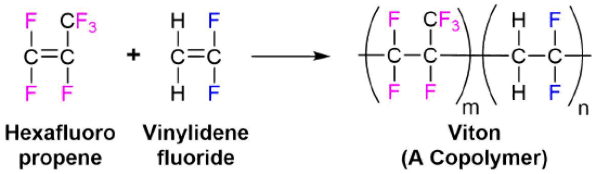
30.3: COPOLYMERS

Homopolymers are made with a single monomer and are made up of identical repeating units. Copolymers is made when two or more different monomers are polymerized together to create a polymer with variable repeating units. For example the monomers hexafluoropropene and vinylidene fluoride can be polymerized together to create the copolymer vitron which is used to create durable gaskets.

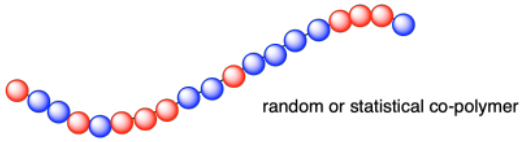


The synthesis of macromolecules composed of more than one repeating unit has been explored as a means of controlling the properties of the resulting material. In this respect, it is useful to distinguish several ways in which different monomeric units might be incorporated in a polymer. The following examples refer to a two component system, in which one monomer is designated A and the other B.

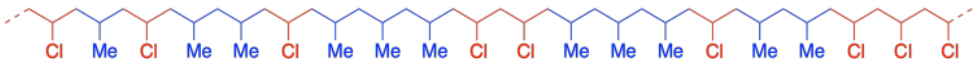
STATISTICAL COPOLYMERS

Also called random copolymers. Here the monomeric units are distributed randomly, and sometimes unevenly, in the polymer chain:

~ABBAAABAABBBABAABA~



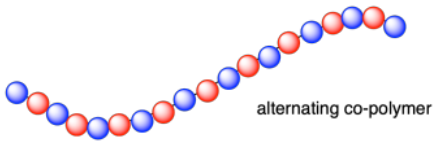
Most direct copolymerizations of equimolar mixtures of different monomers give statistical copolymers. If you take a mixture of alkenes that are capable of forming polymers and you polymerize them together, you may well get them randomly enchained into a growing polymer. For example, polymerizing propene and vinyl chloride together creates a polymer with random monmer unit.



ALTERNATING COPOLYMERS

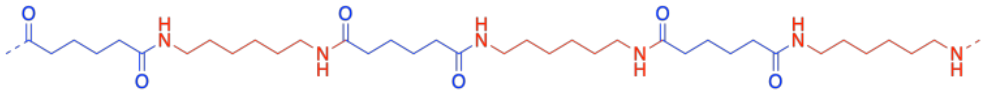
Here the monomeric units are distributed in a regular alternating fashion, with nearly equimolar amounts of each in the chain:

~ABABABABABABABAB~



Formation of alternating copolymers is favored when the monomers have different polar substituents (e.g. one electron withdrawing and the other electron donating), and both have similar reactivities toward radicals. For example, styrene and acrylonitrile copolymerize in a largely alternating fashion.

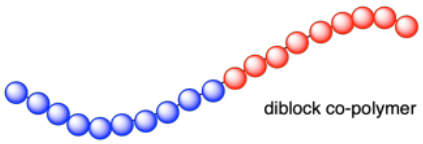
In some of the examples alternating copolymers, the chain is actually composed of two different monomers. This is the case in polyamides such as nylon-6,6, which is a chain is composed of difunctional amines alternating with difunctional carboxyloids (such as carboxylic acids or acid chlorides). Because of their complementary reactivity, the monomers have to alternate: an amine and then a carboxyloid, to form an amide, and so on. We can think of these polymers as "alternating co-polymers" because the two different monomers alternate with each other along the chain.



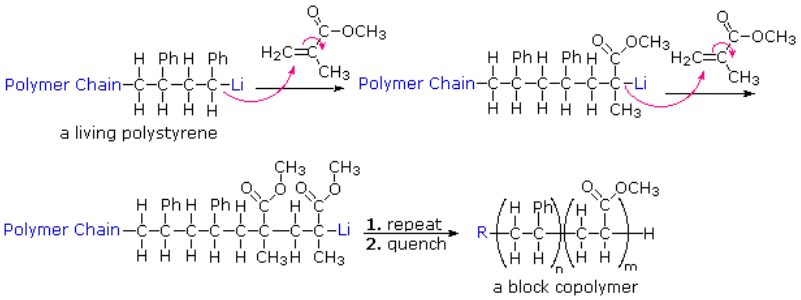
BLOCK COPOLYMERS

Instead of a mixed distribution of monomeric units, a long sequence or block of one monomer is joined to a block of the second monomer:

~AAAAA-BBBBBBB~AAAAAAA~BBB~



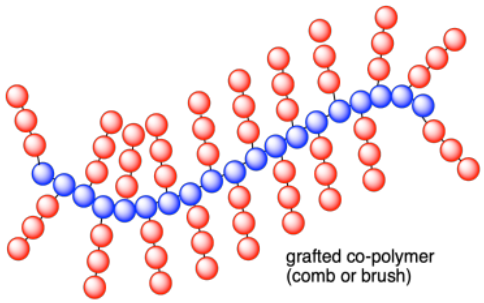
Several different techniques for preparing block copolymers have been developed, with a common example being anionic polymerization. In the anionic polymerization of styrene, a reactive site remains at the end of the chain until it is quenched. The unquenched polymer has been termed a living polymer because the polymerization can continue as long as monomer is present. If different suitable monomer, methyl methacrylate, is added the chain will continue grow by adding methyl methacrylate units and a block polymer will form. This is illustrated for in the following diagram.



GRAFT COPOLYMERS

As the name suggests, side chains of a given monomer are "grafted" to the main chain of a different monomer:

~AAAAAAA(BBBBBBB~)AAAAAAA(BBBB~)AAA~.



Graft polymers can be made in great profusion by attaching chains of one kind of polymer to the middle of another. A particularly simple but uncontrollable way of doing this is to knock groups off a polymer chain with x-ray or alpha radiation in the presence of a monomer. The polymer radicals so produced then can grow side chains made of the new monomer. A more elegant procedure is to use a photochemical reaction to dissociate groups from the polymer chains and form radicals capable of polymerization with an added monomer.

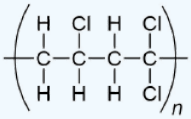
Some Useful Copolymers

Monomer A	Monomer B	Copolymer	Uses
$H_2C=CHCl$	$H_2C=CCl_2$	Saran	films & fibers
$H_2C=CHC_6H_5$	$H_2C=C-CH=CH_2$	SBR styrene butadiene rubber	tires
$H_2C=CHCN$	$H_2C=C-CH=CH_2$	Nitrile Rubber	adhesives hoses
$H_2C=C(CH_3)_2$	$H_2C=C-CH=CH_2$	Butyl Rubber	inner tubes
$F_2C=CF(CF_3)$	$H_2C=CHF$	Viton	gaskets

? EXERCISE 30.3.1

Draw the structure of an alternating segment of Saran, a copolymer of vinyl chloride (chloroethene) and vinylidene chloride (1,1-dichloroethene).

Answer



Saran

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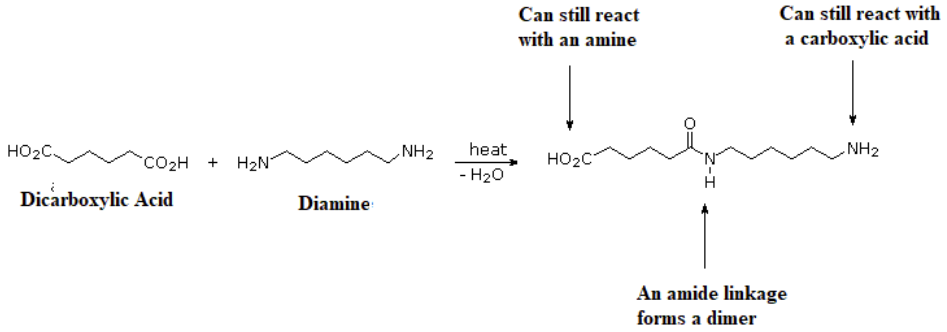
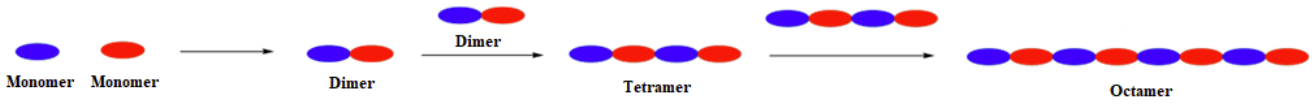
30.4: STEP-GROWTH POLYMERS

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.

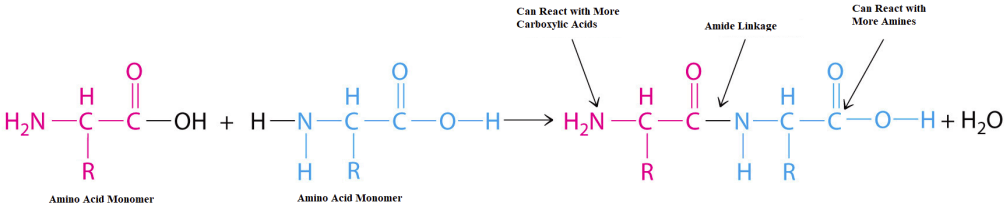


In fact the difuctionality of the monomers, allows step-growth polymers to grow in two directions at once. First, two complementary monomers react with each other to form a dimer. Assuming that monomers react at roughly similar rates, when one end of the dimer reacts again it will likely find another 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.



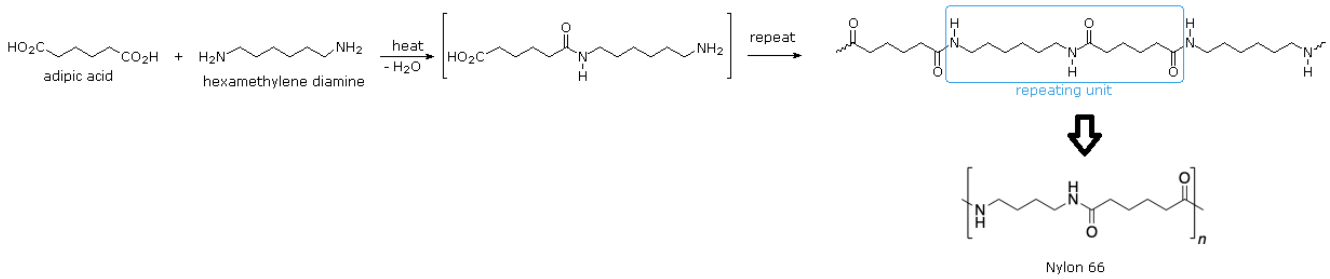
The Step-Growth Polymerization Process

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.

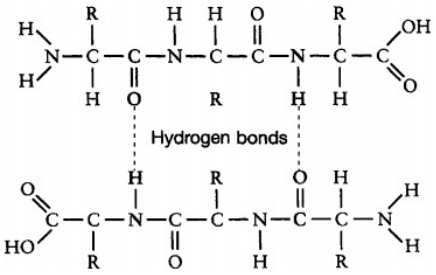


POLYAMIDES

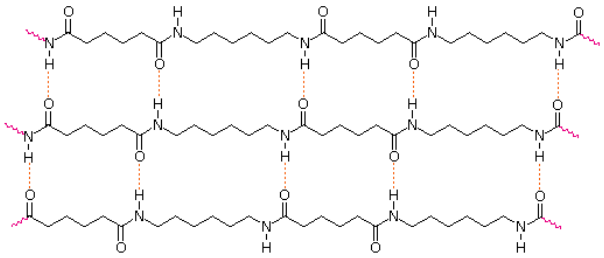
The first fully synthetic polymer fiber, nylon-6,6, was produced in 1938 by the company DuPont. The lead chemist of DuPont's work was Wallace H. Carothers, who reasoned that the properties of silk could be mimicked by constructing a polymer chain created with repeating amide bonds, just like the proteins 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.



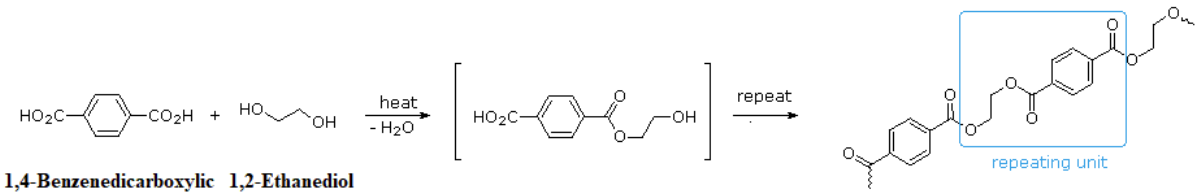
The Hydrogen Bonding between Proteins



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

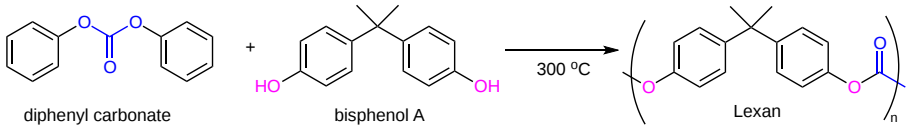
poly(ethyleneterephthalate)
(PET)
A Polyester

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 (−O−(C=O)−O−). 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.

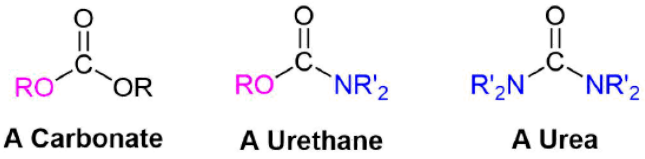
In effect, a carbonate is difunctional and can be reacted with a diol to form polymers containing repeated carbonate groups in their structure called polycarbonates. An example of a polycarbonate is the polymer, Lexan, which is created when diphenyl carbonate and bisphenol A (a diol) are reacted together.



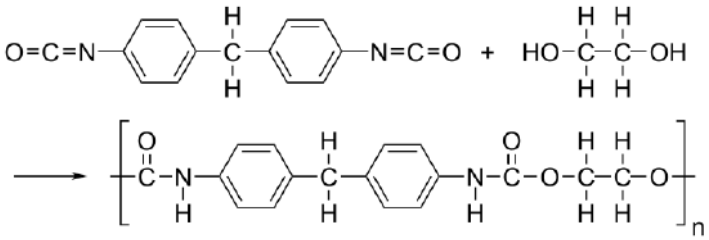
Bisphenol (BPA), primarily used to make polycarbonate, is one of the highest-volume chemicals produced in the world, with over six billion pounds made each year. Because polycarbonate is used to make plastic bottles, the lining for food cans, and the lining for beverage cans there has been much concern 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.

POLYURETHANE

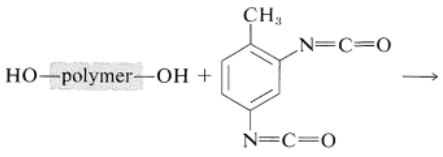
A urethane is a functional group similar to a carbonate and a urea. A urethane has an -OR and a -NR_2 group attached to the carbonyl carbon.

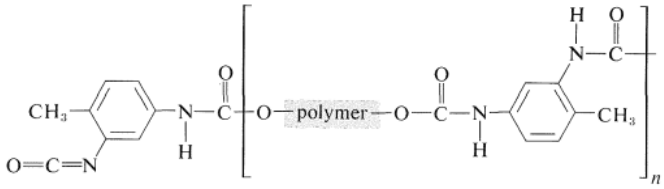


Polyurethane (**PUR** and **PU**) is a polymer composed of organic units joined by carbamate (urethane) links. Polyurethanes are produced by reacting an isocyanate containing two or more isocyanate groups per molecule ($R−(N=C=O)_n$) with a polyol containing on average two or more hydroxyl groups per molecule ($R'−(OH)_n$) in the presence of a catalyst or by activation with ultraviolet light.



The very widely used polyurethane foams can be considered to be either block polymers or copolymers. The essential ingredients are a diisocyanate and a diol. The diisocyanate most used is 2,4-diisocyano-1-methylbenzene, and the diol can be a polyether or a polyester with hydroxyl end groups. The isocyano groups react with the hydroxyl end groups to form initially an addition polymer, which has polycarbamate (polyurethane) links, and isocyano end groups:



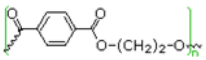
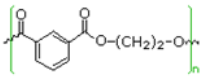
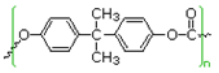
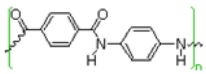
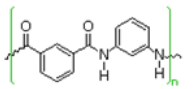


A foam is formed by addition of the proper amount of water. The water reacts with the isocyanate end groups to form carbamic acids which decarboxylate to give amine groups:

The carbon dioxide evolved is the foaming agent, and the amino groups formed at the same time extend the polymer chains by reacting with the residual isocyano end groups to form urea linkages:

Polyurethanes are used in the manufacture of high-resilience foam seating, rigid foam insulation panels, microcellular foam seals and gaskets, durable elastomeric wheels and tires (such as roller coaster, escalator, shopping cart, elevator, and skateboard wheels), automotive suspension bushings, electrical potting compounds, high performance adhesives, surface coatings and surface sealants, synthetic fibers (e.g., Spandex), carpet underlay, hard-plastic parts (e.g., for electronic instruments), condoms,[1] and hoses.

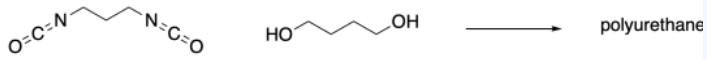
Common Step Growth Polymers

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

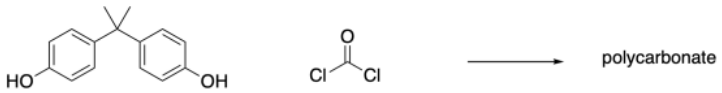
EXERCISE 30.4.1

1) The following difunctional monomers would undergo polymerization together. Show the product that results.

a)

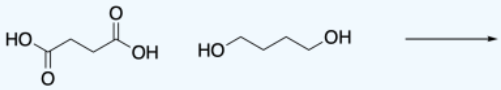


b)

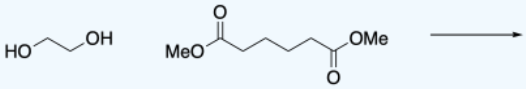


2) Provide structures of the polyesters made from the monomers as indicated.

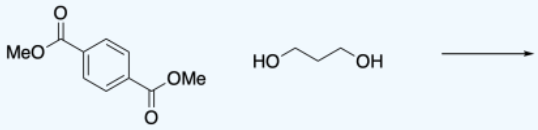
a)



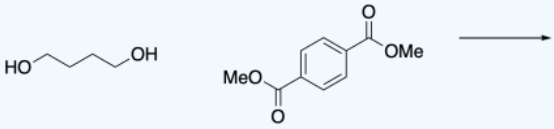
b)



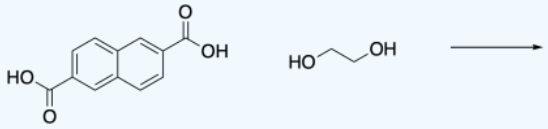
c)



d)



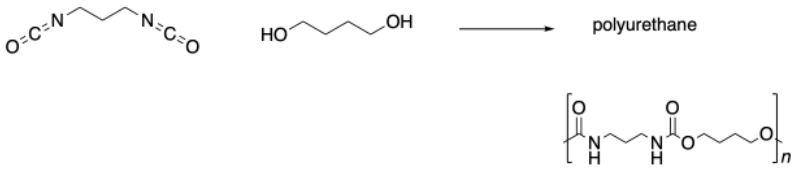
e)



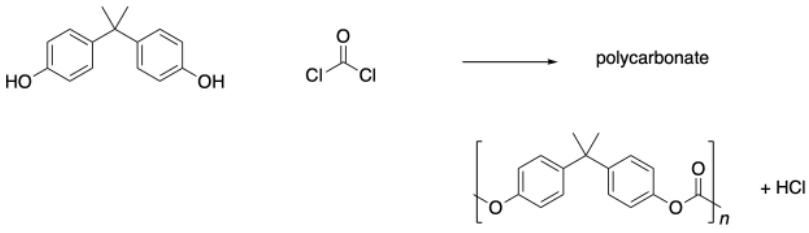
Answer

1)

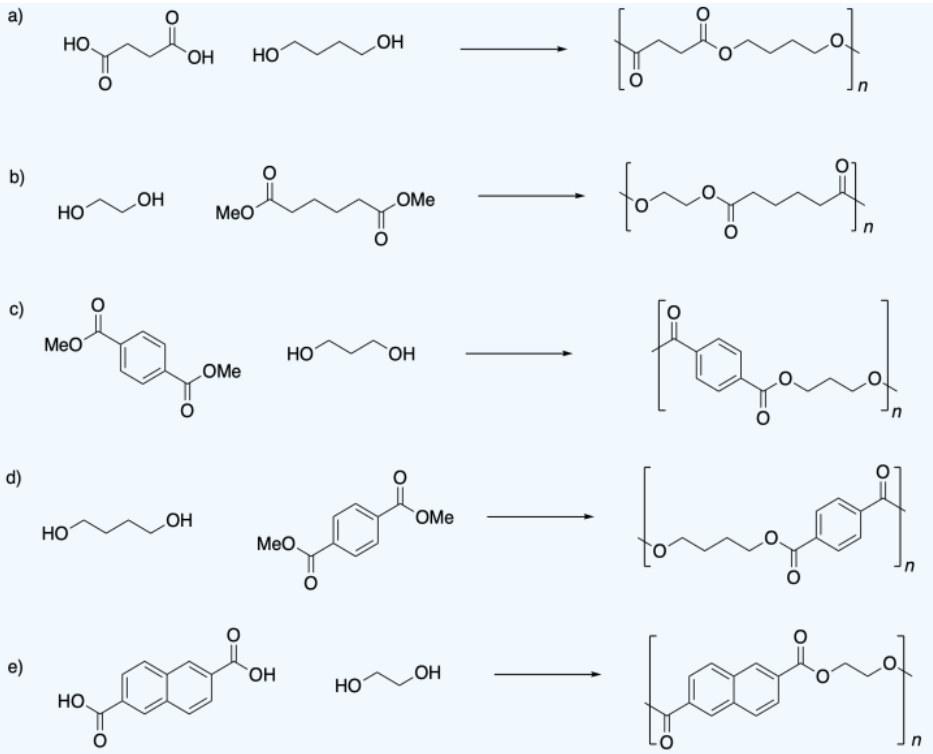
a)



b)



2)



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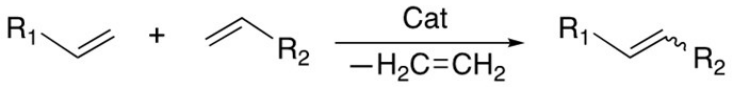
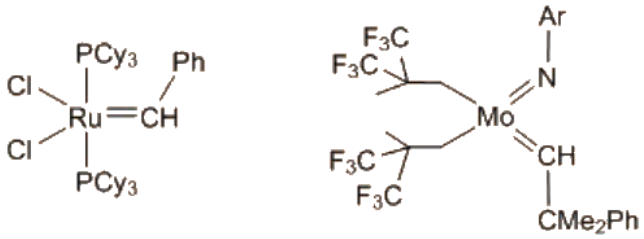
30.5: OLEFIN METATHESIS POLYMERIZATION

OLEFIN METATHESIS

The application of organometallic chemistry in homogenous catalysis is progressively increasing with the fast pace of discovery of new catalysts in the area. Alkene metathesis reactions are gaining wide popularity in synthesizing unsaturated olefinic compounds. Central to this catalysis is a metal carbene intermediate that reacts with olefins to give different olefinic compounds. When two different olefin substrates are used, the reaction is called the "cross metathesis" owing to the fact that the olefinic ends are exchanged. In a process called **olefin metathesis polymerization**, unsaturated olefinic polymers can be created by a metathesis reaction.



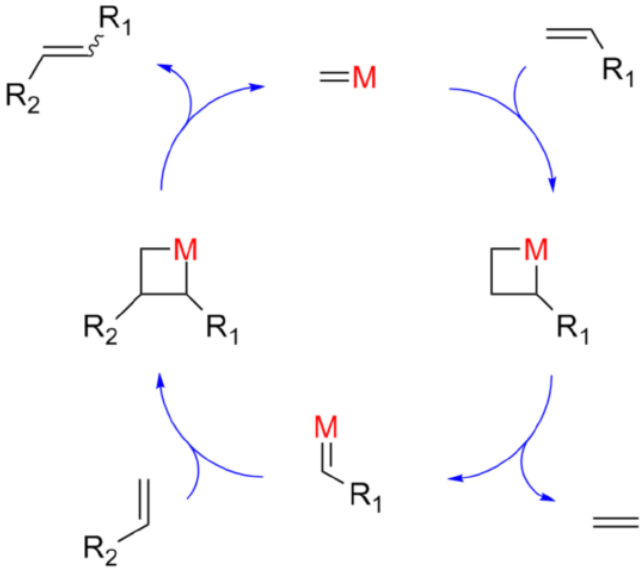
Olefin metathesis catalysts contain a metal carbon double bond with two of the most notable being are the **Grubbs Ru catalyst** and the **Schrock's Mo catalyst**.



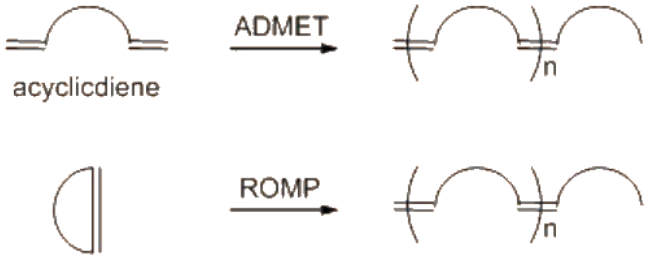
The Grubb's and the Schrock's Catalyst

MECHANISM CROSS METATHESIS

An olefin metathesis catalyst is a transition metal compound that is capable of splitting the double bond of an alkene in half and putting the two pieces together with other alkenes. The key part of an olefin metathesis catalyst is a metal-carbon double bond. That is the group that is capable of switching the ends of alkenes around with different partners. The catalyst react reversibly with an alkene to produce a 4−membered metalacyclobutane intermediate called a metallacycle. The ring promptly opens to produce a different catalyst and alkene. The reaction of this new catalyst with the second alkene produces a second metallacycle intermediate. This ring opens to produce the metathesis product and yet another form of the catalyst. The ring opening and closing continues as the reaction moves forward.



Olefin Metathesis Polymerization The variants of metathesis often used in producing polymers are: (*i*) the Acyclic Diene Metathesis (ADMET) and (*ii*) the Ring Opening Metathesis Polymerization (ROMP), both of which produce long chain polymers

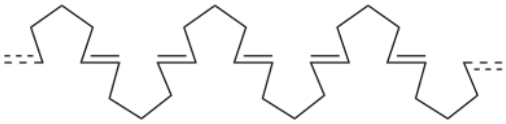


One method, called **ring-opening metathesis polymerization**, or ROMP, involves the use of a moderately strained cycloalkene, such as cyclopentene. The strain of the ring favors ring-opening, thereby driving formation of the open-chain product. The polymer that results has double bonds spaced regularly along the chain, allowing for either hydrogenation or further functionalization if desired.

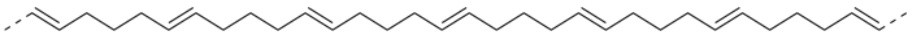
Ring-opening metathesis polymerization (ROMP) takes a cyclic alkene, splits open its double bond, and knitting it together with other cyclic alkenes to produce a long polymer chain with regularly spaced double bonds. The ring-strain of the cycloalkenes favors the open-chain product and drives the polymerization reaction forward.

During a ROMP, a cyclopentene ring is opened up at the double bond and reaches out to join with other cyclopentene rings on either side of it.

The product polymer of a ROMP using cyclopentene rings would look something like this:

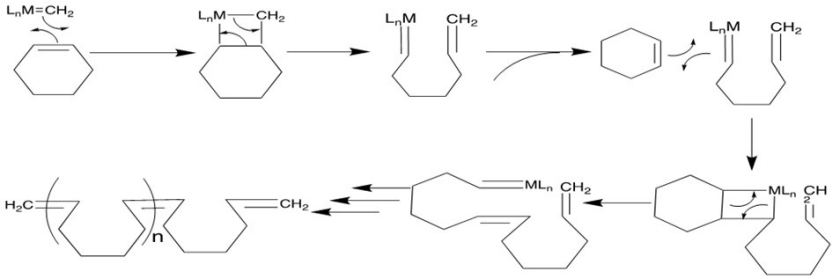


Which can draw it in an usual zig-zag conformation.

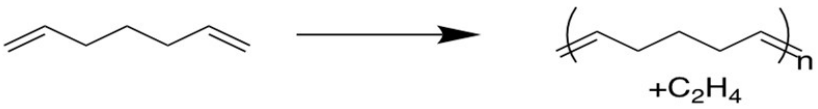


MECHANISM

The mechanism starts with a cycloalkene and a metathesis catalyst reacting to form a four-member metallacycle. Opening of the metallacycle forms a new alkene and catalyst both of which are part of the same intermediate molecule. The catalyst end of the intermediate molecule can then react with a different cycloalkene to form a new metallacycle. This process is repeated causing the polymer chain to from.



The second method is called **acyclic diene metathesis** (ADMET) which uses long open-chain substrates, which contain a double bond at both ends of the main chain, such as 1,6-heptadiene. A byproduct of the reaction, gaseous ethylene ($H_2C=CH_2$), escapes which drives the equilibrium forward.



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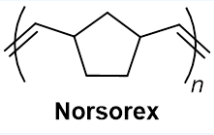
EXERCISE 30.5.1

The ring opening metathesis polymerization of norborene produces a commercial polymer called Norsore which is used a sealing material. Please draw the structure of Norsore.

Norbornene

Answer



Norsorex

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30.6: POLYMER STRUCTURE AND PHYSICAL PROPERTIES

POLYMER CRYSTALLINITY

To account for the physical differences between the different types of polymers, the nature of the aggregate macromolecular structure, or **morphology**, of each substance must be considered. Because polymer molecules are so large, they generally pack together in a non-uniform fashion, with ordered or crystalline-like regions, called **crystallites**, mixed together with disordered or amorphous domains. In some cases the entire solid may be amorphous, composed entirely of coiled and tangled macromolecular chains. Crystallinity occurs when linear polymer chains are structurally oriented in a uniform three-dimensional matrix. In the diagram on the right, crystalline domains are colored blue. Increased crystallinity is associated with an increase in rigidity, tensile strength and opacity (due to light scattering). Amorphous polymers are usually less rigid, weaker and more easily deformed. They are often transparent.

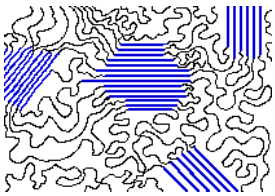


Figure 30.6.1: CSchematic diagram of crystallites (in blue) in a largely crystalline polymer.

Three factors that influence the degree of crystallinity are:

1. **Chain length:** Longer polymer chains tend to have greater van der Waals forces and increased crystallinity than do shorter chains (**Section 2-12**)
2. **Chain branching:** Polymer chains without branching can pack closely together. Lack of branching increases the crystallinity of polymers.
3. **Interchain interactions:** (Intermolecular forces and Crosslinking). Crystallinity increases as the strength of the intermolecular forces between polymer chains increases. Croslining between polymer chains tends to increase crystallinity.

The importance of the first two factors is nicely illustrated by the differences between LDPE and HDPE. As noted earlier (Section 31-2), HDPE is composed of very long unbranched hydrocarbon chains. These pack together easily in crystalline domains that alternate with amorphous segments, and the resulting material, while relatively strong and stiff, retains a degree of flexibility. In contrast, LDPE is composed of smaller and more highly branched chains which do not easily adopt crystalline structures. This material is therefore softer, weaker, less dense and more easily deformed than HDPE.

The forces between the chains in the crystallites of polyethene are the so-called **van der Waals** or **dispersion** forces, which are the same forces acting between smaller hydrocarbon molecules. Although these forces are relatively weak, they increase with the size of the molecule. Polymer chains are large enough that the van der Waals forces create a strong and stiff material.

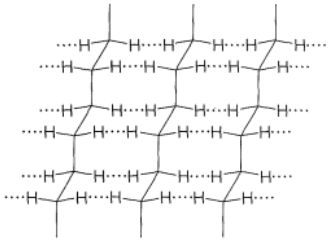


Figure 30.6.2: CRepresentation of attractive interactions between the hydrogens in a crystallite of polyethene

In other kinds of polymers, even stronger intermolecular forces can be produced by hydrogen bonding. This is especially important in the polyamides, such as the nylons, of which nylon 66 is most widely used. The increase strength of the interactions between polymer chains makes polyamides among some of the strongest polymer materials known.

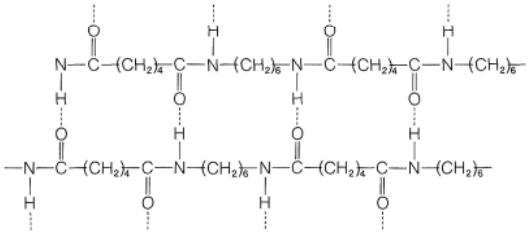


Figure 30.6.3: Possible hydrogen-bonded structure for crystallites of nylon 66, an amide-type polymer of hexanedioic acid and 1,6-hexanediamine.

Natural rubber is a completely amorphous polymer. Unfortunately, the potentially useful properties of raw latex rubber are limited by temperature dependence; however, these properties can be modified by chemical change. If the chains of rubber molecules are slightly cross-linked by sulfur atoms, a process called **vulcanization** which was discovered by Charles Goodyear in 1839, the desirable elastomeric properties of rubber are substantially improved. At 2 to 3% crosslinking a useful soft rubber, that no longer suffers stickiness and brittleness problems on heating and cooling, is obtained. At 25 to 35% crosslinking a rigid hard rubber product is formed. The following illustration shows a cross-linked section of amorphous rubber.

GLASS TRANSITION AND MELT TRANSITION TEMPERATURES

The effect of temperature on the physical properties of polymers is very important to their practical uses. At low temperatures, polymers become hard and glasslike because the motions of the segments of the polymer chains with relation to each other are slow. The approximate temperature below which glasslike behavior is apparent is called the **glass transition temperature** and is symbolized by T_g. When a polymer containing crystallites is heated, the crystallites ultimately melt, and this temperature is usually called the **melt transition temperature** and is symbolized as $T_{m.}$ As the amount of crystallinity in a polymer increases, so does T_m.

T_g often depends on the history of the sample, particularly previous heat treatment, mechanical manipulation and annealing. It is sometimes interpreted as the temperature above which significant portions of polymer chains are able to slide past each other in response to an applied force. The introduction of relatively large and stiff substituents (such as benzene rings) will interfere with this chain movement, thus increasing T_g (note polystyrene below). The introduction of small molecular compounds called **plasticizers** (discussed later in this section) into the polymer matrix increases the interchain spacing, allowing chain movement at lower temperatures. with a resulting decrease in T_g. T_m and T_g values for some common addition polymers are listed below.

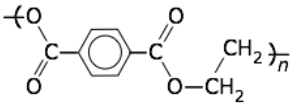
Polymer	LDPE	HDPE	PP	PVC	PS	PAN	PTFE	PMMA	Rubber
T_m (ºC)	110	130	175	180	175	>200	330	180	30
T_g (ºC)	−110	−100	−10	80	90	95	−110	105	−70

POLYMER CATEGORIES

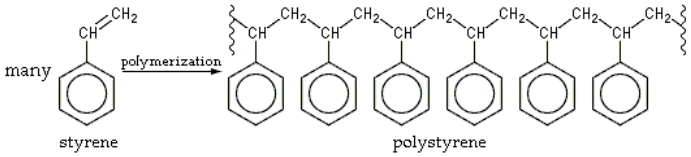
THERMOPLASTICS

Most of the polymers described in this chapter are classified as **thermoplastic**s. Plastics that soften when heated and become firm again when cooled. This is the more popular type of plastic because the heating and cooling may be repeated and the thermoplastic may be reformed. These polymers tend to have high Tg so they are hard solids at room temperature, however, above Tg they they become malleable and may be shaped, pressed into molds, spun, or cast from melts.

Polyethylene (poly(ethylene terephthalate) or PET is the most common thermoplastic . In 2017, PET made up 34% of the total plastics market with over 100 million tones of polyethylene resins being produced. PET is partially crystalline and is used to create clear plastic bottles such as 2-liter beverage bottles, milk jugs, detergent bottles, and water bottles.

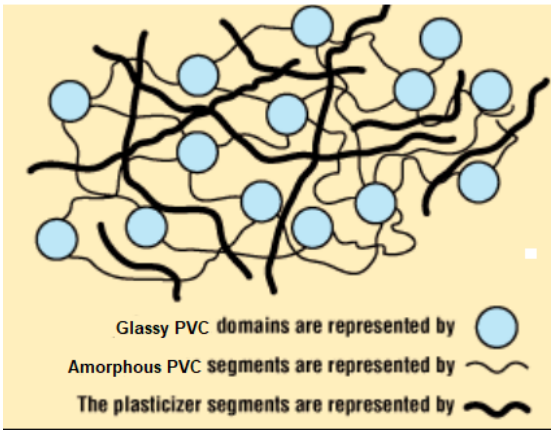


Polystyrene is also a common thermoplastic. The polymer is making it a solid but rather rather brittle at room temperature. Polystyrene is used to make hard clear plastic cups, foam cups, eating utensils, deli food containers, toy model kits, some packing popcorn.

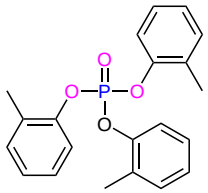


PLASTICIZERS

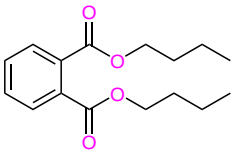
Plasticizers or **dispersants** are additives that increase the plasticity or decrease the viscosity of a material. These substances are compounded into certain types of plastics to render them more flexible by lowering the glass transition temperature. They accomplish this by taking up space between the polymer chains and acting as lubricants to enable the chains to more readily slip over each other. Many (but not all) are small enough to be diffusible and a potential source of health problems. Substantial concerns have been expressed over the safety of some plasticizers, especially because some low molecular weight ortho-phthalates have been classified as potential endocrine disruptors with some developmental toxicity reported.



Polyvinyl chloride (PVC) polymers are one of the most widely-plasticized types. PVC is usually is not very crystalline and is relatively brittle and glassy. The properties of polyvinyl chloride can be improved by blending it with substances of low volatility which tend to break down its glasslike structure. Common plasticizers used with PVC are tris-(2-methylphenyl) phosphate (tricresyl phosphate) and dibutyl benzene-1,2-dicarboxylate (dibutyl phthalate). Plasticized polyvinyl chloride is reasonably flexible and is widely used for flexible vinyl materials such as garden hoses, waterbeds, cheap shower curtains, raincoats and upholstery. The pungent oder associated with these products are a testament to the ability of plasticizers to migrate into the environment.



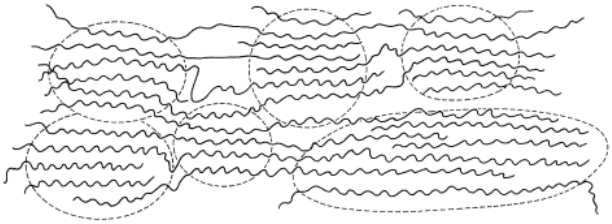
tris-(2-Methylphenyl) phosphate



Dibutyl phthalate

FIBERS

Fibers are drawn into thin threads by forcing the melted or dissolved polymer through a spinneret to generate filaments that can be woven into fabrics. Part of this process, called **cold-drawing**, the polymer material is subjected to strong stress in one direction causing the material to elongate and the crystallites to be drawn together and oriented along the direction of the applied stress. Having the crystallites in a polymer oriented with respect to one another gives the polymer a much higher tensile strength than an unoriented polymer. Polymers such as nylon, which has strong intermolecular forces, has the crystallinity required to be drawn in oriented fibers.



Schematic representation of an oriented crystalline polymer produced by drawing the polymer in the horizontal direction. The crystalline regions are enclosed with dashed lines.

Elastomers

Elastomers usually are amorphous polymers which have the ability to be stretched. The key to this elastic behavior is polymer chains with weak forces between the chains and a sufficiently irregular structure to be unstable in the crystalline state. A useful elastomer needs to have some kind of cross-linking. The important difference between an elastomer and a crystalline polymer is the size of the amorphous regions. When tension is applied and the material elongates, the chains in the amorphous regions straighten out and become more nearly parallel. The forces between the chains are too weak to maintain the crystalline state in the absence of tension. Thus when tension is released, contraction occurs and the original, amorphous polymer is produced. The entropy of the chains is more favorable in the relaxed state than in the stretched state.

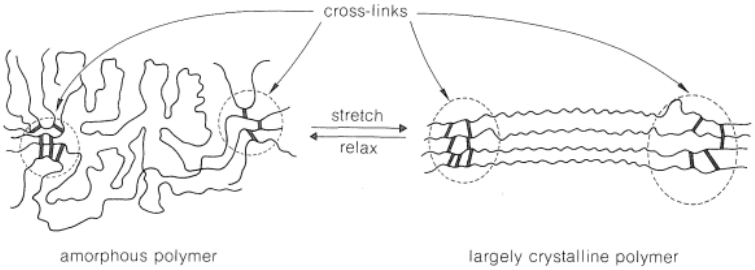
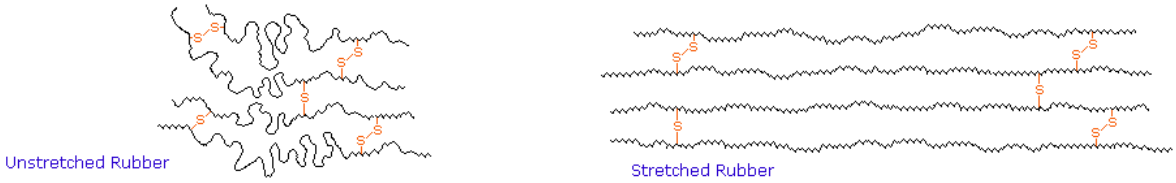
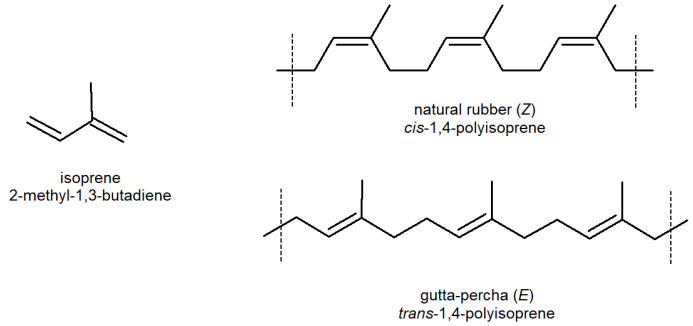


Figure 30.6.4: Schematic representation of an elastomer in relaxed and stretched configurations.

A good elastomer should not undergo plastic flow in either the stretched or relaxed state, and when stretched should have a "memory" of its relaxed state. These conditions are best achieved with natural rubber (*cis*-poly-2-methyl-1,3-butadiene, *cis*-polyisoprene) by curing (*vulcanizing*) with sulfur. Natural rubber (**Section 14-6)** is tacky and undergoes plastic flow rather readily, but when it is heated with elemental sulfur, sulfur cross-links are introduced between the chains. These cross-links reduce plastic flow and provide a reference framework for the stretched polymer to return to when it is allowed to relax. Also the double bonds in rubber all have a Z-configuration, which causes this macromolecule to adopt a kinked or coiled conformation.



However, the gutta-percha (structure above) E-isomer of rubber adopts a uniform zig-zag conformation, which produces greater crystallinity making it not an elastomer.



THERMOSETS

Thermosets are plastics that soften when heated and can be molded, but harden permanently. In a thermoset, crosslinks connect the different chains in the material, forming bridges that span from chain to chain to chain, essentially uniting the material into one big molecule. If it is one big molecule, the chains can never move completely independently of each other, and the material cannot form a new shape.

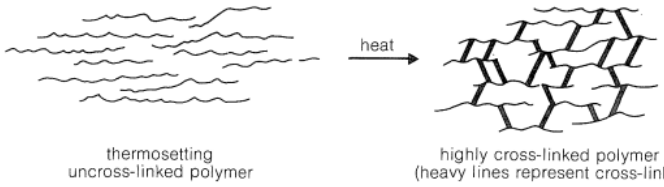
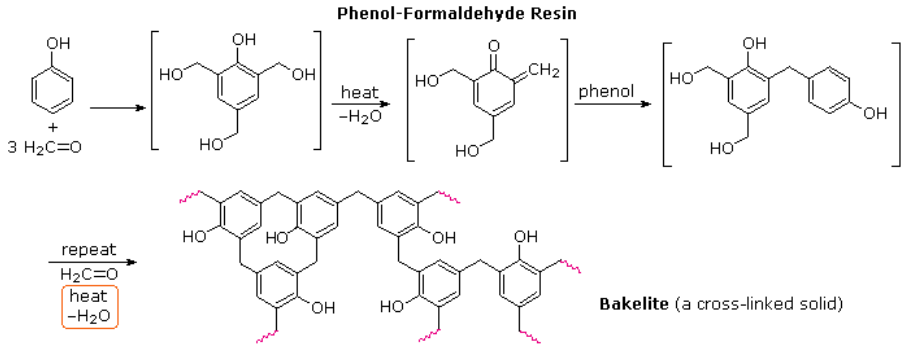


Figure 30.6.4: Schematic representation of the conversion of an uncross-linked thermosetting polymer to a highly cross-linked polymer. The cross-links are shown in a two-dimensional network, but in practice three-dimensional networks are formed.

One of the oldest known thermosetting synthetic polymers, **Bakelite**, is made by condensation of phenol with formaldehyde. During the thermoset process water is lost and many crosslinks are formed. produce (4-hydroxyphenyl)methanol. **Bakelite** was patented on December 7, 1909 and was revolutionary for its electrical nonconductivity and heat-resistant properties used in electrical insulators, radio and telephone casings and such diverse products as kitchenware, jewelry, pipe stems, and children's toys.

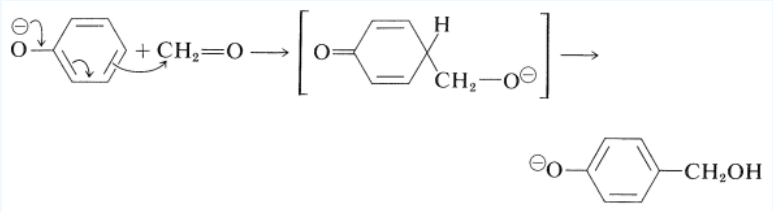


EXERCISE 30.6.1

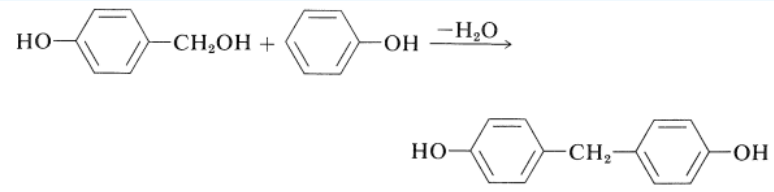
Propose a mechanism for the base-catalyzed polymerization of phenol and formaldehyde to form Bakelite.

Answer

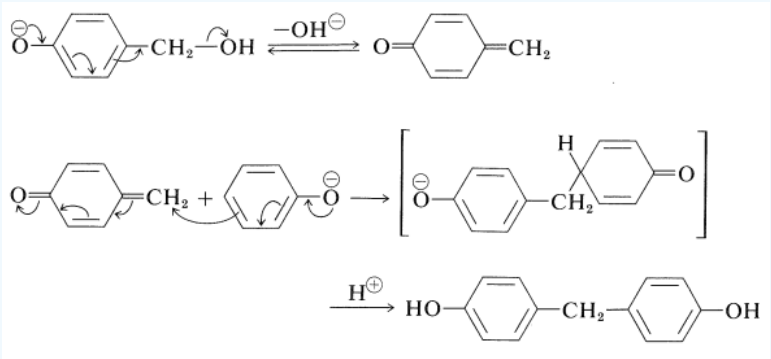
One of the oldest known thermosetting synthetic polymers is made by condensation of phenols with aldehydes using basic catalysts. The resins that are formed are known as **Bakelites**. The initial stage is the base-induced reaction of benzenol and methanal to give a (4-hydroxyphenyl)methanol, and this reaction closely resembles an aldol addition and can take place at either the 2- or the 4-position of the benzene ring:



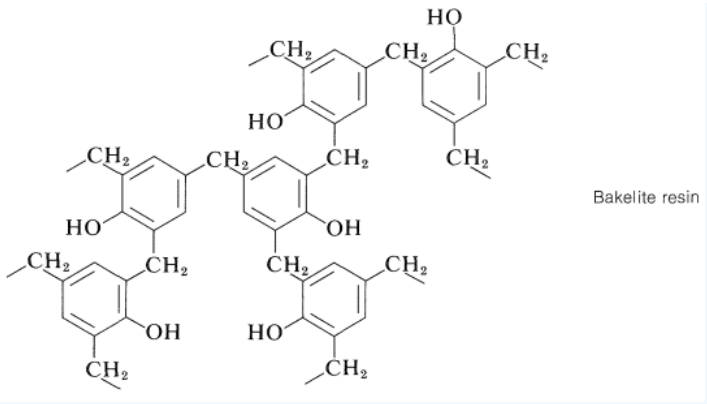
The next step in the condensation is formation of a bis(hydroxyphenyl)methane derivative, which for convenience is here taken to be the 4,4'-isomer:



This reaction is probably a Michael type of addition to a base-induced dehydration product of the (4-hydroxyphenyl)methanol:



Continuation of these reactions at the 2-, 4-, and 6-positions of the benzenol leads to the cross-linked three-dimensional Bakelite resin:



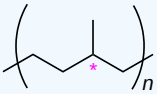
Bakelite resin

EXERCISE 30.6.2

Would you expect the catalytic hydrogenation of gutta-percha to produce a product that is syndiotactic, atactic, or isotactic?

Answer

Atactic. The methyl groups in gutta-percha lack stereochemistry because they are attached to double bond. Catalytic hydrogenation does not provide stereochemical control so H2 could attack from either side of the double bond to produce a chiral center involving the methyl group which is R or S.



Atactic

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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, $R-C\equiv C:^-$.

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, $R-C^+=O \leftrightarrow R-C\equiv O^+$. 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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