

CHE 202: ORGANIC CHEMISTRY II



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CHAPTER OVERVIEW

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- 1.1: Functional Groups in Organic Compounds
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1.1: Functional Groups in Organic Compounds

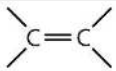
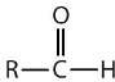
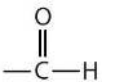
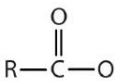
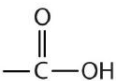
Learning Objectives

- to describe functional groups and explain why they are useful in the study of organic chemistry.

We first introduced the idea of the functional group, a specific structural arrangement of atoms or bonds that imparts a characteristic chemical reactivity to the molecule. If you understand the behavior of a particular functional group, you will know a great deal about the general properties of that class of compounds. Some common functional groups are listed in Table 1.1.1.

Last semester, we studied alkanes, alkenes, alkynes, aromatic, alcohols, thiols, ethers, and phenols. This semester, we will begin with aldehydes and ketones as our first functional groups

Table 1.1.1: Selected Organic Functional Groups

Name of Family	General Formula	Functional Group	Suffix*
alkane	RH	none	-ane
alkene	$R_2C=CR_2$		-ene
alkyne	$RC\equiv CR$	$-C\equiv C-$	-yne
alcohol	ROH	$-OH$	-ol
thiol	RSH	$-SH$	-thiol
ether	ROR	$-O-$	ether
aldehyde			-al
ketone			-one
carboxylic acid			-oic acid

*Ethers do not have a suffix in their common name; all ethers end with the word *ether*.

Summary

The functional group, a structural arrangement of atoms and/or bonds, is largely responsible for the properties of organic compound families.

Concept Review Exercises

- What is the functional group of an alkene? An alkyne?
- Does $CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$ have a functional group? Explain.

Answers

- carbon-to-carbon double bond; carbon-to-carbon triple bond
- No; it has nothing but carbon and hydrogen atoms and all single bonds.

Exercises

1. What is the functional group of 1-butanol ($\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$)?
2. What is the functional group of butyl bromide, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br}$?

Answer

1. OH

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1.2: Aldehydes and Ketones- Structure and Names

Learning Objectives

- Identify the general structure for an aldehyde and a ketone.
- Use common names to name aldehydes and ketones.
- Use the IUPAC system to name aldehydes and ketones.

The next functional group we consider, the carbonyl group, has a carbon-to-oxygen double bond.



Carbonyl groups define two related families of organic compounds: the aldehydes and the ketones.

The carbonyl group is ubiquitous in biological compounds. It is found in carbohydrates, fats, proteins, nucleic acids, hormones, and vitamins—organic compounds critical to living systems.

In a ketone, two carbon groups are attached to the carbonyl carbon atom. The following general formulas, in which R represents an alkyl group and Ar stands for an aryl group, represent ketones.



In an aldehyde, at least one of the attached groups must be a hydrogen atom. The following compounds are aldehydes:



In condensed formulas, we use CHO to identify an aldehyde rather than COH, which might be confused with an alcohol. This follows the general rule that in condensed structural formulas H comes after the atom it is attached to (usually C, N, or O).



An aldehyde

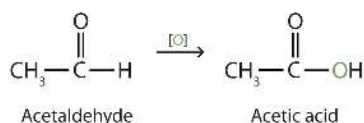
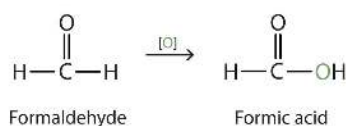


A ketone

The carbon-to-oxygen double bond is not shown but understood to be present. Because they contain the same functional group, aldehydes and ketones share many common properties, but they still differ enough to warrant their classification into two families.

Naming Aldehydes and Ketones

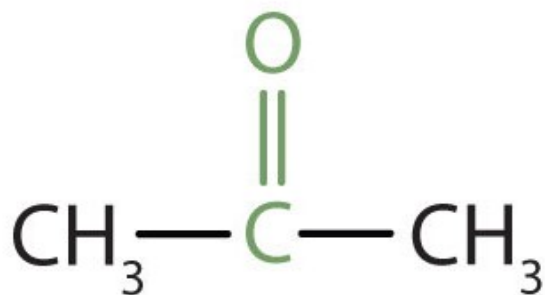
Both common and International Union of Pure and Applied Chemistry (IUPAC) names are frequently used for aldehydes and ketones, with common names predominating for the lower homologs. The common names of aldehydes are taken from the names of the acids into which the aldehydes can be converted by *oxidation*.



The stems for the common names of the first four aldehydes are as follows:

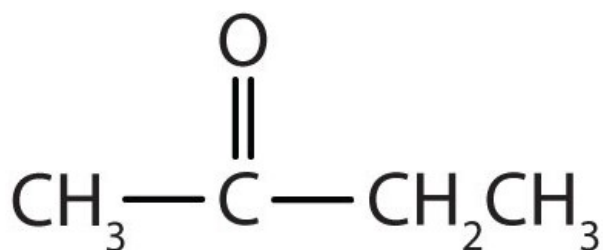
- 1 carbon atom: *form-*
- 2 carbon atoms: *acet-*
- 3 carbon atoms: *propion-*
- 4 carbon atoms: *butyr-*

Because the carbonyl group in a ketone must be attached to two carbon groups, the simplest ketone has three carbon atoms. It is widely known as *acetone*, a unique name unrelated to other common names for ketones.



Acetone

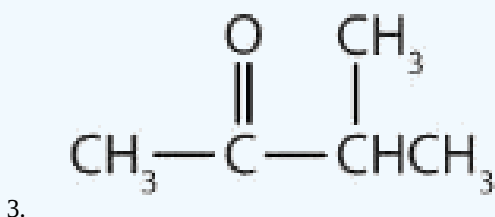
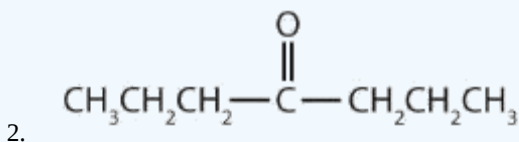
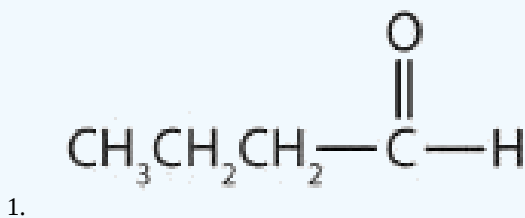
Generally, the common names of ketones consist of the names of the alkyl groups attached to the carbonyl group listed alphabetically, followed by the word *ketone*. (Note the similarity to the common name of ethers.) Another name for acetone, then, is *dimethyl ketone*. The ketone with four carbon atoms is ethyl methyl ketone.



Ethyl methyl ketone

Example 1.2.1

Classify each compound as an aldehyde or a ketone. Give the common name for each ketone.

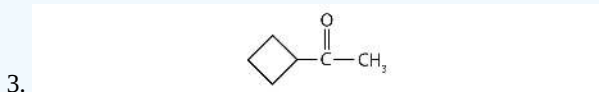
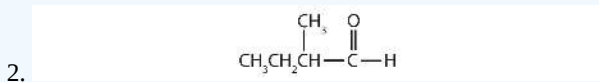
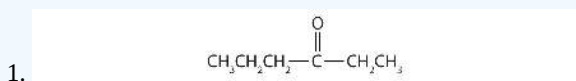


Solution

1. This compound has the carbonyl group on an end carbon atom, so it is an aldehyde.
2. This compound has the carbonyl group on an interior carbon atom, so it is a ketone. Both alkyl groups are propyl groups. The name is therefore dipropyl ketone.
3. This compound has the carbonyl group between two alkyl groups, so it is a ketone. One alkyl group has three carbon atoms and is attached by the middle carbon atom; it is an isopropyl group. A group with one carbon atom is a methyl group. The name is therefore isopropyl methyl ketone.

Exercise 1.2.1

Classify each compound as an aldehyde or a ketone. Give the common name for each ketone.



Here are some simple IUPAC rules for naming aldehydes and ketones:

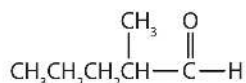
1. The stem names of aldehydes and ketones are derived from those of the parent alkanes, defined by the longest continuous chain (LCC) of carbon atoms that contains the functional group.
2. For an aldehyde, drop the *-e* from the alkane name and add the ending *-al*. Methanal is the IUPAC name for formaldehyde, and ethanal is the name for acetaldehyde.
3. For a ketone, drop the *-e* from the alkane name and add the ending *-one*. Propanone is the IUPAC name for acetone, and butanone is the name for ethyl methyl ketone.
4. To indicate the position of a substituent on an aldehyde, the carbonyl carbon atom is always considered to be C1; it is unnecessary to designate this group by number.

5. To indicate the position of a substituent on a ketone, number the chain in the manner that gives the carbonyl carbon atom the lowest possible number. In cyclic ketones, it is understood that the carbonyl carbon atom is C1.

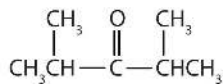
Example 1.2.2

Give the IUPAC name for each compound.

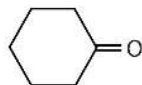
a.



b.



c.



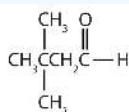
Solution

- There are five carbon atoms in the LCC. The methyl group (CH_3) is a substituent on the second carbon atom of the chain; the aldehyde carbon atom is always C1. The name is derived from pentane. Dropping the *-e* and adding the ending *-al* gives pentanal. The methyl group on the second carbon atom makes the name 2-methylpentanal.
- There are five carbon atoms in the LCC. The carbonyl carbon atom is C3, and there are methyl groups on C2 and C4. The IUPAC name is 2,4-dimethyl-3-pentanone.
- There are six carbon atoms in the ring. The compound is cyclohexanone. No number is needed to indicate the position of the carbonyl group because all six carbon atoms are equivalent.

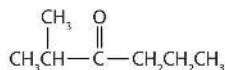
Exercise

Give the IUPAC name for each compound.

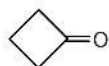
a.



b.



c.



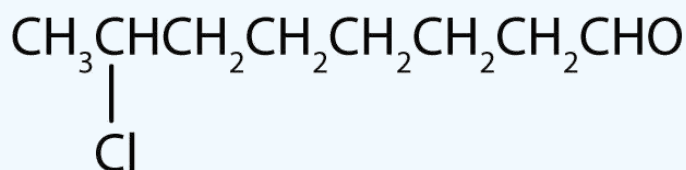
Example 1.2.3

Draw the structure for each compound.

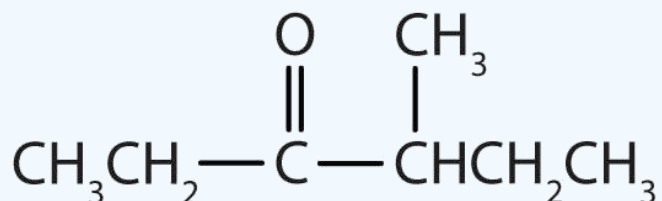
- 7-chlorooctanal
- 4-methyl-3-hexanone

Solution

- The *octan-* part of the name tells us that the LCC has eight carbon atoms. There is a chlorine (Cl) atom on the seventh carbon atom; numbering from the carbonyl group and counting the carbonyl carbon atom as C1, we place the Cl atom on the seventh carbon atom.



- b. The *hexan-* part of the name tells us that the LCC has six carbon atoms. The 3 means that the carbonyl carbon atom is C3 in this chain, and the 4 tells us that there is a methyl (CH_3) group at C4:



Exercise

Draw the structure for each compound.

- 5-bromo-3-iodoheptanal
- 5-bromo-4-ethyl-2-heptanone

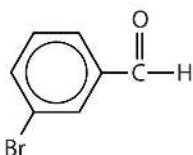
Concept Review Exercises

- Give the structure and IUPAC name for the compound that has the common name *m*-bromobenzaldehyde.
- Give the IUPAC name for glyceraldehyde, ($\text{HOCH}_2\text{CHOHCHO}$). (Hint: as a substituent, the OH group is named *hydroxy*.)

Summary

The common names of aldehydes are taken from the names of the corresponding carboxylic acids: formaldehyde, acetaldehyde, and so on. The common names of ketones, like those of ethers, consist of the names of the groups attached to the carbonyl group, followed by the word *ketone*. Stem names of aldehydes and ketones are derived from those of the parent alkanes, using an *-al* ending for an aldehydes and an *-one* ending for a ketone.

Answers

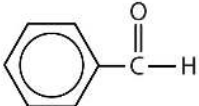


- 3-Bromobenzaldehyde
- 3-bromobenzaldehyde
- 2,3-dihydroxypropanal

Exercises

- Name each compound.



- b. $\text{CH}_3\text{CH}_2\text{CH}_2-\overset{\text{O}}{\parallel}{\text{C}}-\text{H}$
- c. $\text{CH}_3\text{CH}_2-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_2\text{CH}_3$
- d. 

2. Name each compound.

- a. $\text{CH}_3-\overset{\text{O}}{\parallel}{\text{C}}-\overset{\text{CH}_3}{\underset{|}{\text{CH}}}\text{CH}_3$
- b. $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CHO}$
- c. $\text{CH}_3\overset{\text{Br}}{\underset{|}{\text{CH}}}\text{CH}_2\text{CH}_2-\overset{\text{O}}{\parallel}{\text{C}}-\text{H}$
- d. $\text{CH}_3\text{CH}_2-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$

3. Draw the structure for each compound.

- a. butyraldehyde
- b. 2-hexanone
- c. *p*-nitrobenzaldehyde

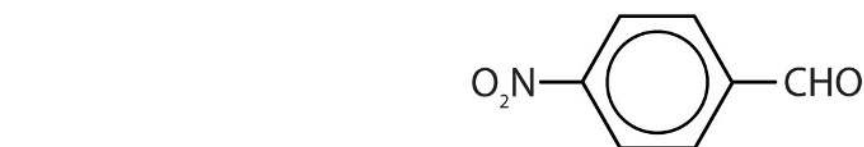
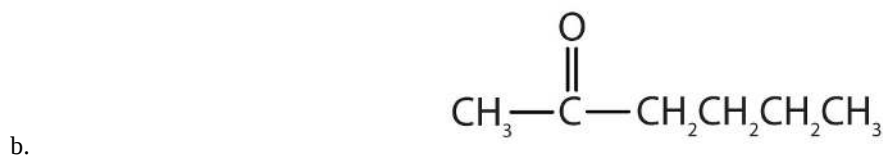
4. Draw the structure for each compound.

- a. 5-ethyloctanal
- b. 2-chloropropanal
- c. 2-hydroxy-3-pentanone

Answers

1. a. propanal or propionaldehyde
b. butanal or butyraldehyde
c. 3-pentanone or diethyl ketone
d. benzaldehyde

3. a. $\text{CH}_3\text{CH}_2\text{CH}_2\text{CHO}$



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1.3: Bonding in the Carbonyl Group

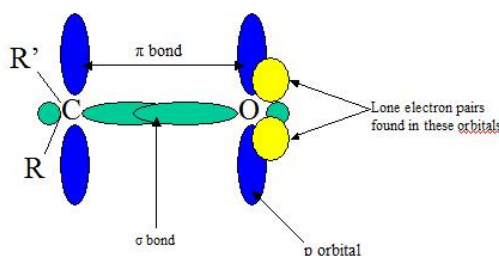
A carbonyl group is a chemically organic functional group composed of a carbon atom double-bonded to an oxygen atom $\rightarrow$ $[C=O]$. The simplest carbonyl groups are [aldehydes](#) and [ketones](#) usually attached to another carbon compound. These structures can be found in many aromatic compounds contributing to smell and taste.

Introduction

Before going into anything in depth be sure to understand that the $C=O$ entity itself is known as the "Carbonyl group" while the members of this group are called "carbonyl compounds" $\rightarrow$ $X-C=O$. The carbon and oxygen are usually sp^2 hybridized and planar.

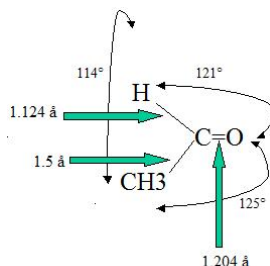
Carbonyl Group Double Bonds

The double bonds in alkenes and double bonds in carbonyl groups are VERY different in terms of reactivity. The $C=C$ is *less* reactive due to $C=O$ electronegativity attributed to the oxygen and its two lone pairs of electrons. One pair of the oxygen lone pairs are located in $2s$ while the other pair are in $2p$ orbital where its axis is directed perpendicular to the direction of the π orbitals. The Carbonyl groups properties are directly tied to its electronic structure as well as geometric positioning. For example, the electronegativity of oxygen also polarizes the π bond allowing the single bonded substituent connected to become electron withdrawing.



**Note: Both the π bonds are in phase (top and bottom blue ovals)*

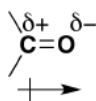
The double bond lengths of a carbonyl group is about 1.2 angstroms and the strength is about 176-179 kcal/mol). It is possible to correlate the length of a carbonyl bond with its polarity; the longer the bond meaning the lower the polarity. For example, the bond length in $C=O$ is larger in acetaldehyde than in formaldehyde (this of course takes into account the inductive effect of CH_3 in the compound).



Polarization

As discussed before, we understand that oxygen has two lone pairs of electrons hanging around. These electrons make the oxygen more electronegative than carbon. The carbon is then partially positive (electrophilic) and the oxygen partially negative (nucleophilic). The polarizability is denoted by a lowercase delta and a positive or negative superscript depending. For example, carbon would have δ^+ and oxygen δ^- . The polarization of carbonyl groups also effects the boiling point of aldehydes and ketones to be higher than those of hydrocarbons in the same amount. The larger the carbonyl compound the less soluble it is in water. If the compound exceeds six carbons it then becomes insoluble.

**For more information about carbonyl solubility, look in the "outside links" section*



**Amides are the most stable of the carbonyl couplings due to the high-resonance stabilization between nitrogen-carbon and carbon-oxygen.*

Some Carbonyl Compounds

The carbonyl group is not only present in aldehydes and ketones. Other functional groups and compounds also contain a carbonyl group as part of their structures:

Compound	Aldehyde	Ketone	Formaldehyde	Carboxylic Acid	Ester	Amide	Enone	Acyl Halide	Acid Anhydride
Structure									
General Formula	RCHO	RCOR'	CH ₂ O	RCOOH	RCOOR'	RCONR'R''	RC(O)C(R')C(R'')R'''	RCOX	(RCO) ₂ O

Nucleophile Addition to a Carbonyl Group

Just like alkenes with a C=C double bond, the carbonyl groups C=O is prone to additions reactions by nucleophilic attack. However, aldehydes and ketones are more reactive than alkenes because of carbon's partial positive charge and oxygen's partial negative charge (dipolar moment). The resonance of the carbon partial positive charge allows the negative charge on the nucleophile to attack the Carbonyl group and become a part of the structure and a positive charge (usually a proton hydrogen) attacks the oxygen. Just a reminder, the nucleophile is a good acid therefore "likes protons" so it will attack the side with a positive charge.



**Remember: due to the electronegative nature of oxygen the carbon is partially positive and oxygen is partially negative*

Let's imagine a carbonyl group reacting with a nucleophile Nu:



1 2 3

1. The Nucleophile (Nu^-) attacks the positively charged carbon and pushes one of the double bond electrons onto oxygen to give it a negative charge.
2. The Nucleophile is now a part of the carbonyl structure with a negatively charged oxygen
3. The negatively charged oxygen attacks the proton (H^+) to give the resulting product above.

Problems

1. What is the hybridization of the carbon in the C=O? the oxygen?
2. Illustrate the correct partial positive/negative or polarization of a formaldehyde.

Answers

1. sp^2 ; sp^2
2. partial positive on the carbon and partial negative on the oxygen

References

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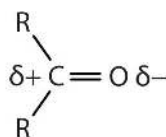
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1.4: Physical Properties of Aldehydes and Ketones

Learning Objectives

- Explain why the boiling points of aldehydes and ketones are higher than those of ethers and alkanes of similar molar masses but lower than those of comparable alcohols.
- Compare the solubilities in water of aldehydes and ketones of four or fewer carbon atoms with the solubilities of comparable alkanes and alcohols.
- Name the typical reactions that take place with aldehydes and ketones.
- Describe some of the uses of common aldehydes and ketones.

The carbon-to-oxygen double bond is quite polar, more polar than a carbon-to-oxygen single bond. The electronegative oxygen atom has a much greater attraction for the bonding electron pairs than does the carbon atom. The carbon atom has a partial positive charge, and the oxygen atom has a partial negative charge:



In aldehydes and ketones, this charge separation leads to dipole-dipole interactions that are great enough to significantly affect the boiling points. Table 1.4.1 shows that the polar single bonds in ethers have little such effect, whereas hydrogen bonding between alcohol molecules is even stronger.

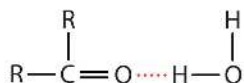
Table 1.4.1: Boiling Points of Compounds Having Similar Molar Masses but Different Types of Intermolecular Forces

Compound	Family	Molar Mass	Type of Intermolecular Forces	Boiling Point (°C)
CH ₃ CH ₂ CH ₂ CH ₃	alkane	58	dispersion only	−1
CH ₃ OCH ₂ CH ₃	ether	60	weak dipole	6
CH ₃ CH ₂ CHO	aldehyde	58	strong dipole	49
CH ₃ CH ₂ CH ₂ OH	alcohol	60	hydrogen bonding	97

Formaldehyde is a gas at room temperature. Acetaldehyde boils at 20°C; in an open vessel, it boils away in a warm room. Most other common aldehydes are liquids at room temperature.

Although the lower members of the homologous series have pungent odors, many higher aldehydes have pleasant odors and are used in perfumes and artificial flavorings. As for the ketones, acetone has a pleasant odor, but most of the higher homologs have rather bland odors.

Although aldehydes and ketones cannot hydrogen bond with themselves, the oxygen atom of the carbonyl group engages in hydrogen bonding with a water molecule, so it behaves as a *hydrogen bonding acceptor*:



The solubility of aldehydes and ketones is therefore about the same as that of alcohols and ethers. Formaldehyde, acetaldehyde, and acetone are soluble in water. As the carbon chain increases in length, solubility in water decreases. The borderline of solubility occurs at about four carbon atoms per oxygen atom. All aldehydes and ketones are soluble in organic solvents and, in general, are less dense than water.

Some Common Carbonyl Compounds

- Formaldehyde has an irritating odor. Because of its reactivity, it is difficult to handle in the gaseous state. For many uses, it is therefore dissolved in water and sold as a 37% to 40% aqueous solution called *formalin*. Formaldehyde denatures proteins, rendering them insoluble in water and resistant to bacterial decay. For this reason, formalin is used in embalming solutions and in preserving biological specimens.

Aldehydes are the active components in many other familiar substances. Large quantities of formaldehyde are used to make phenol-formaldehyde resins for gluing the wood sheets in plywood and as adhesives in other building materials. Sometimes the formaldehyde escapes from the materials and causes health problems in some people. While some people seem unaffected, others experience coughing, wheezing, eye irritation, and other symptoms.

The odor of green leaves is due in part to a carbonyl compound, cis-3-hexenal, which with related compounds is used to impart a “green” herbal odor to shampoos and other products.

Acetaldehyde is an extremely volatile, colorless liquid. It is a starting material for the preparation of many other organic compounds. Acetaldehyde is formed as a metabolite in the fermentation of sugars and in the detoxification of alcohol in the liver. Aldehydes are the active components of many other familiar materials (Figure 1.4.2).

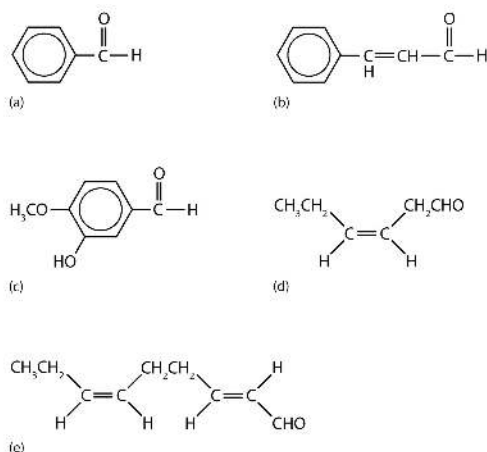


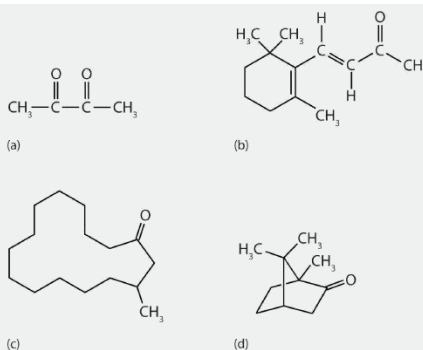
Figure 1.4.2 Some Interesting Aldehydes. (a) Benzaldehyde is an oil found in almonds; (b) cinnamaldehyde is oil of cinnamon; (c) vanillin gives vanilla its flavor; (d) *cis*-3-hexenal provides an herbal odor; and (e) *trans*-2-*cis*-6-nonadienal gives a cucumber odor.

Acetone is the simplest and most important ketone. Because it is miscible with water as well as with most organic solvents, its chief use is as an industrial solvent (for example, for paints and lacquers). It is also the chief ingredient in some brands of nail polish remover.

To Your Health: Acetone in Blood, Urine, and Breath

Acetone is formed in the human body as a by-product of lipid metabolism. Normally, acetone does not accumulate to an appreciable extent because it is oxidized to carbon dioxide and water. The normal concentration of acetone in the human body is less than 1 mg/100 mL of blood. In certain disease states, such as uncontrolled diabetes mellitus, the acetone concentration rises to higher levels. It is then excreted in the urine, where it is easily detected. In severe cases, its odor can be noted on the breath.

Ketones are also the active components of other familiar substances, some of which are noted in the accompanying figure.



Some ketones have interesting properties: (a) Butter flavoring comes from 2,3-butanedione; (b) β -ionone is responsible for the odor of violets; (c) muscone is musk oil, an ingredient in perfumes; and (d) camphor is used in some insect repellents.

Certain steroid hormones have the ketone functional group as a part of their structure. Two examples are progesterone, a hormone secreted by the ovaries that stimulates the growth of cells in the uterine wall and prepares it for attachment of a fertilized egg, and testosterone, the main male sex hormone. These and other sex hormones affect our development and our lives in fundamental ways.

Summary

The polar carbon-to-oxygen double bond causes aldehydes and ketones to have higher boiling points than those of ethers and alkanes of similar molar masses but lower than those of comparable alcohols that engage in intermolecular hydrogen bonding. Aldehydes are readily oxidized to carboxylic acids, whereas ketones resist oxidation.

Concept Review Exercises

Answers

Exercises

Answers

1. What feature of their structure makes aldehydes easier to oxidize than ketones?
2. How does the carbon-to-oxygen bond of aldehydes and ketones differ from the carbon-to-carbon bond of alkenes?
3. the H on the carbonyl carbon atom
4. The carbon-to-oxygen double bond is polar; the carbon-to-carbon double bond is nonpolar.
5. Which compound in each pair has the higher boiling point?
 - a. acetone or 2-propanol
 - b. dimethyl ether or acetaldehyde
6. Which compound in each pair has the higher boiling point?
 - a. butanal or 1-butanol
 - b. acetone or isobutane
- 7.
8.
 - a. 2-propanol
 - b. acetaldehyde
9.
 - a.
 - b.

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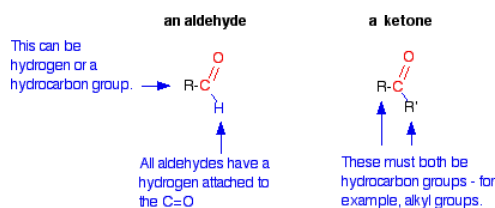
1.5: Chemical properties I- Oxidation of Aldehydes and Ketones

As mentioned earlier, aldehydes and ketones are quite reactive. They can undergo a multiplicity of reactions including additions, oxidations, and reductions. The main difference between aldehydes and ketones is based on their ability to be oxidized. This page looks at ways of distinguishing between aldehydes and ketones using oxidizing agents such as acidified potassium dichromate(VI) solution, Tollens' reagent, Fehling's solution and Benedict's solution.

Aldehydes and ketones behave differently towards oxidation

In organic chemistry, oxidation can be perceived as the loss of hydrogen atoms or the gain in oxygen atoms. The opposite definition applies to reduction (gain in hydrogen or loss in oxygen content). Common oxidizing agents in chemistry include potassium dichromate(VI) solution ($\text{K}_2\text{Cr}_2\text{O}_7$), silver nitrate (AgNO_3) solution, potassium permanganate (KMnO_4) solution, Tollens' reagent, Fehling's solution and Benedict's solution. These last three options are very common in biochemistry.

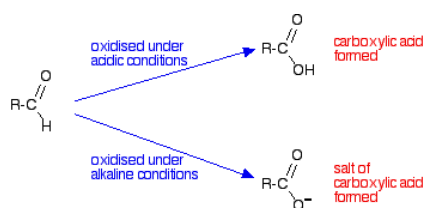
You will remember that the difference between an aldehyde and a ketone is the presence of a hydrogen atom attached to the carbon-oxygen double bond in the aldehyde. Ketones don't have that hydrogen.



The presence of that hydrogen atom makes aldehydes very easy to oxidize (i.e., they are strong reducing agents). **Because ketones do not have that particular hydrogen atom, they are resistant to oxidation.** You can easily tell the difference between an aldehyde and a ketone. Aldehydes are easily oxidized by all sorts of different oxidizing agents; ketones are not.

What is formed when aldehydes are oxidized?

It depends on whether the reaction is done under acidic or alkaline conditions. Under acidic conditions, the aldehyde is oxidized to a carboxylic acid. Under alkaline conditions, this couldn't form because it would react with the alkali. A salt is formed instead.



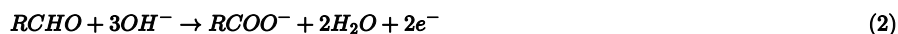
Building equations for the oxidation reactions

If you need to work out the equations for these reactions, the only reliable way of building them is to use electron-half-equations. The half-equation for the oxidation of the aldehyde obviously varies depending on whether you are doing the reaction under acidic or alkaline conditions.

Under acidic conditions:



Under alkaline conditions:



These half-equations are then combined with the half-equations from whatever oxidizing agent you are using. Examples are given in detail below.

Specific examples

In each of the following examples, we are assuming that you know that you have either an aldehyde or a ketone. There are lots of other things which could also give positive results. Assuming that you know it has to be one or the other, in each case, a ketone does nothing. Only an aldehyde gives a positive result.

Using acidified potassium dichromate(VI) solution

A small amount of potassium dichromate(VI) solution is acidified with dilute sulphuric acid and a few drops of the aldehyde or ketone are added. If nothing happens in the cold, the mixture is warmed gently for a couple of minutes - for example, in a beaker of hot water.

ketone	No change in the orange solution.
aldehyde	Orange solution turns green.

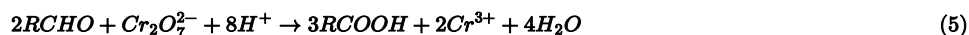
The orange dichromate(VI) ions have been reduced to green chromium(III) ions by the aldehyde. In turn the aldehyde is oxidized to the corresponding carboxylic acid. The electron-half-equation for the reduction of dichromate(VI) ions is:



Combining that with the half-equation for the oxidation of an aldehyde under acidic conditions:



... gives the overall equation:



Using Tollens' reagent (the silver mirror test)

Tollens' reagent contains the diamminesilver(I) ion, $[\text{Ag}(\text{NH}_3)_2]^+$. This is made from silver(I) nitrate solution. You add a drop of sodium hydroxide solution to give a precipitate of silver(I) oxide, and then add just enough dilute ammonia solution to redissolve the precipitate. To carry out the test, you add a few drops of the aldehyde or ketone to the freshly prepared reagent, and warm gently in a hot water bath for a few minutes.

ketone	No change in the colorless solution.
aldehyde	The colorless solution produces a grey precipitate of silver, or a silver mirror on the test tube.

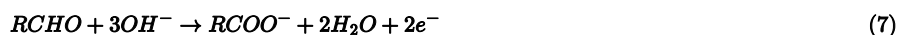


Figure 1: Tollens' test for aldehyde: left side positive (silver mirror), right side negative. Image used with permission from Wikipedia

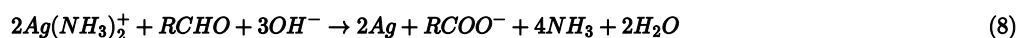
Aldehydes reduce the diamminesilver(I) ion to metallic silver. Because the solution is alkaline, the aldehyde itself is oxidized to a salt of the corresponding carboxylic acid. The electron-half-equation for the reduction of the diamminesilver(I) ions to silver is:



Combining that with the half-equation for the oxidation of an aldehyde under alkaline conditions:



gives the overall equation:



Using Fehling's solution or Benedict's solution

Fehling's solution and Benedict's solution are variants of essentially the same thing. Both contain complexed copper(II) ions in an alkaline solution.

- Fehling's solution contains copper(II) ions complexed with tartrate ions in sodium hydroxide solution. Complexing the copper(II) ions with tartrate ions prevents precipitation of copper(II) hydroxide.
- Benedict's solution contains copper(II) ions complexed with citrate ions in sodium carbonate solution. Again, complexing the copper(II) ions prevents the formation of a precipitate - this time of copper(II) carbonate.

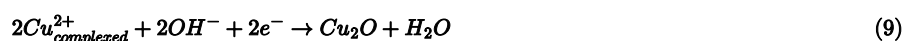
Both solutions are used in the same way. A few drops of the aldehyde or ketone are added to the reagent, and the mixture is warmed gently in a hot water bath for a few minutes.

ketone	No change in the blue solution.
aldehyde	The blue solution produces a dark red precipitate of copper(I) oxide.

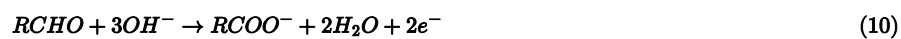


Figure 2: Fehling's test. Left side negative, right side positive. Image used with permission from Wikipedia

Aldehydes reduce the complexed copper(II) ion to copper(I) oxide. Because the solution is alkaline, the aldehyde itself is oxidized to a salt of the corresponding carboxylic acid. The equations for these reactions are always simplified to avoid having to write in the formulae for the tartrate or citrate ions in the copper complexes. The electron-half-equations for both Fehling's solution and Benedict's solution can be written as:



Combining that with the half-equation for the oxidation of an aldehyde under alkaline conditions:



to give the overall equation:



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1.6: Chemical properties II- Reactions of aldehydes and ketones with alcohols

In this organic chemistry topic, we shall see how alcohols (R-OH) add to carbonyl groups. Carbonyl groups are characterized by a carbon-oxygen double bond. The two main functional groups that consist of this carbon-oxygen double bond are [Aldehydes](#) and [Ketones](#).

Introduction

Alcohols add reversibly to aldehydes and ketones to form hemiacetals or hemiketals (*hemi*, Greek, half). This reaction can continue by adding another alcohol to form an acetal or ketal. These are important functional groups because they appear in sugars.

To achieve effective hemiacetal or acetal formation, two additional features must be implemented. First, an acid catalyst must be used because alcohol is a weak nucleophile; and second, the water produced with the acetal must be removed from the reaction by a process such as a molecular sieves or a **Dean-Stark trap**. The latter is important, since acetal formation is reversible. Whether the reaction stops at the hemiacetal or hemiketal also depends on the concentration of alcohol used in the experiment. In presence of up to 1 equivalent of alcohol, the reaction stops at the hemiacetal or hemiketal, but in presence of excess of alcohol, the reaction continues to form the acetal and ketal.

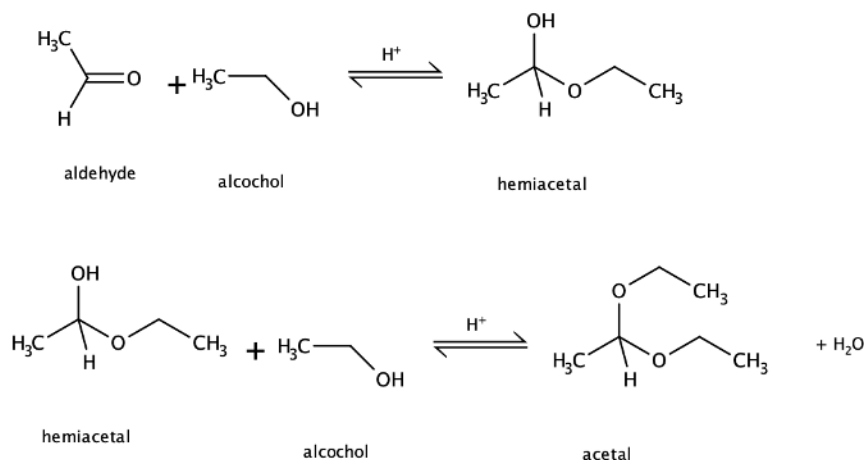
Formation of Hemiacetals and Acetals

The term ketal is used to identify the product of the reaction between alcohols and aldehydes (notice that H group from the aldehyde is retained through the reactions)

 Acetal formation 2

Figure 1. Formation of a hemiacetal and acetal from the reaction between an aldehyde and an alcohol. Notice that the reaction is reversible and requires an acid catalyst. Image by [Ryan Neff](#), [CC BY-SA 3.0](#), via Wikimedia Commons

Example: reaction between ethanal and ethanol



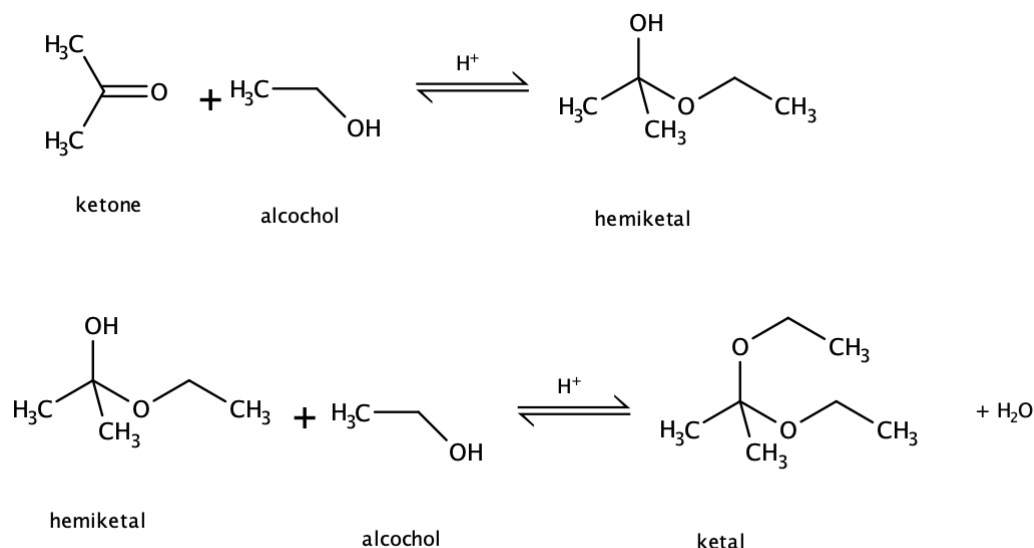
Formation of Hemiketals and ketals

The term ketal is used to identify the product of the reaction between alcohols and ketones (both R groups organic fragments rather than hydrogen)

 Ketal formation

Figure 2. Formation of a hemiketal and ketal from the reaction between a ketone and an alcohol. Notice that the reaction is reversible and requires an acid catalyst. Image by [Ryan Neff](#), [CC BY-SA 3.0](#), via Wikimedia Commons

Example: reaction between propane and ethanol



Mechanism for Hemiacetal and Acetal Formation

The mechanism shown here applies to both acetal and hemiacetal formation, but it applies to ketals and hemiketals as well.

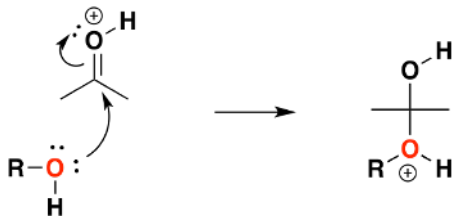
a) Formation of an hemiacetal

This reaction is an addition, in which the alcohol molecule behaves as the nucleophile

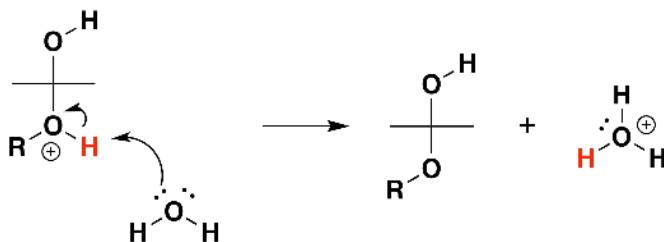
1) Protonation of the carbonyl



2) Nucleophilic attack by the alcohol



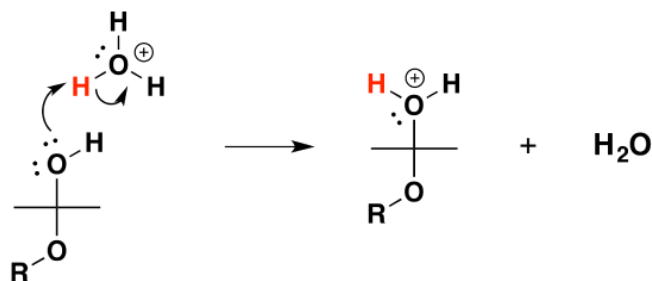
3) Deprotonation to form a hemiacetal



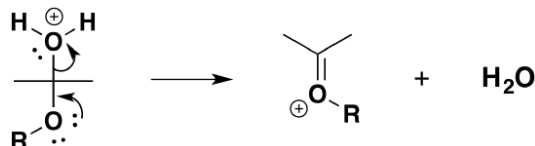
b) Formation of an acetal

This second reaction is a substitution in which the OH group is replaced by the RO- from the alcohol

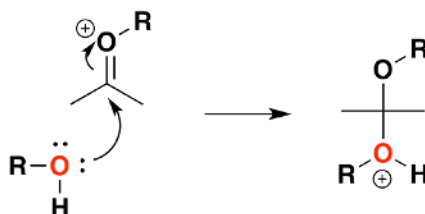
1) Protonation of the alcohol



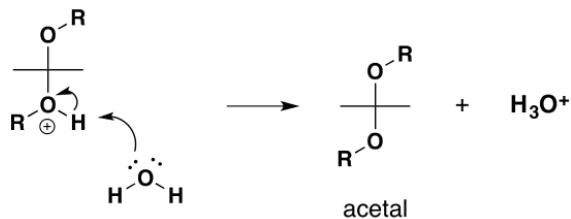
2) Removal of water



3) Nucleophilic attack by the alcohol



4) Deprotonation by water

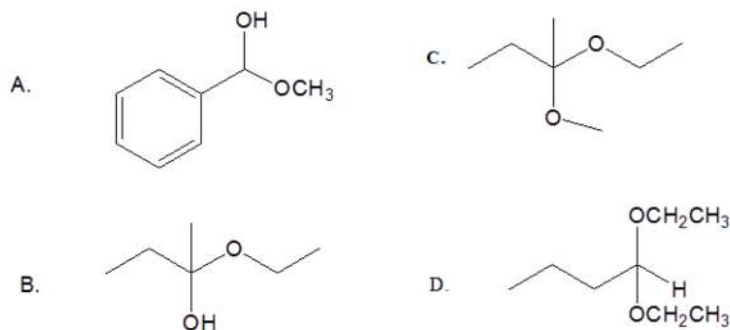


Differentiate between acetals, ketals, hemiacetal and hemiketals

The structural similarities between these functional groups might cause some difficulties when identifying whether a given structure corresponds to either one of these functional groups. However, there are some key points to consider that make identification quite easy:

- All four functional groups contain 2 oxygen atoms attached to the same sp³ carbon
- For acetals and hemiacetals, a hydrogen atom remains attached to the sp³ carbon
- For hemiacetals and hemiketals, an OH group remains attached to the sp³ carbon

Example: Identify each product as an acetal, hemiacetal, ketal, or hemiketal:

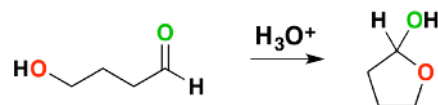


Answer:

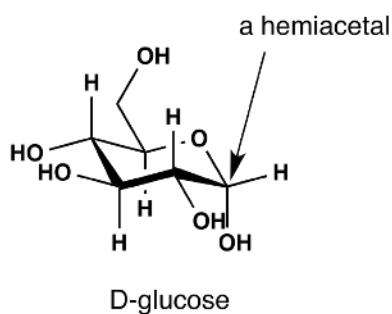
- a) There is H attached to the sp^3 carbon and an OH group. The compound is a hemiacetal
- b) There is no H attached to the sp^3 carbon and an OH group. The compound is a hemiketal
- c) There is no H attached to the sp^3 carbon and no OH group. The compound is a ketal
- d) There is H attached to the sp^3 carbon and no OH group. The compound is an acetal

Formation of Intramolecular (Cyclic) Hemiacetal and Acetals

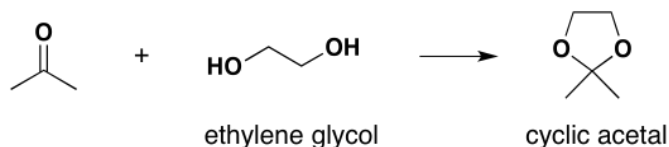
Molecules which have an alcohol and a carbonyl can undergo an intramolecular reaction to form a cyclic hemiacetal.



Intramolecular Hemiacetal formation is common in sugar chemistry. For example, the common sugar glucose exists in the cyclic manner more than 99% of the time in a mixture of aqueous solution.



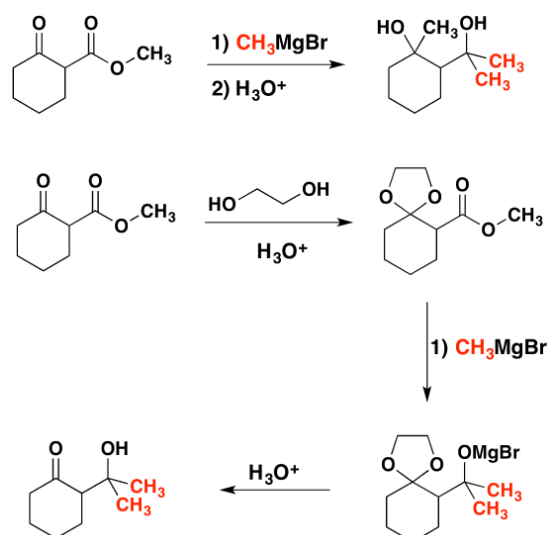
Carbonyls reacting with diol produce a cyclic acetal. A common diol used to form cyclic acetals is ethylene glycol.



Acetals as Protecting Groups

The importance of acetals as carbonyl derivatives lies chiefly in their stability and lack of reactivity in neutral to strongly basic environments. As long as they are not treated by acids, especially aqueous acid, acetals exhibit all the lack of reactivity associated with ethers in general. Among the most useful and characteristic reactions of aldehydes and ketones is their reactivity toward strongly nucleophilic (and basic) metallo-hydride, alkyl and aryl reagents. If the carbonyl functional group is converted to an acetal these powerful reagents have no effect; thus, acetals are excellent protective groups, when these irreversible addition reactions must be prevented.

In the following example we would like a [Grignard reagent](#) to react with the ester and not the ketone. This cannot be done without a protecting group because Grignard reagents react with esters and ketones.



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1. Vollhardt, K. Peter C., and Neil E. Schore. Organic Chemistry: Structure and Function. New York: W.H. Freeman and Company, 2007
2. Carey, Francis. Advanced Organic Chemistry. 5th ed. Springer, 2007.
3. [Figure 1](#) and [Figure 2](#) by [Ryan Neff](#) on Wikimedia Commons. Reused under [CC BY-SA 3.0 license](#). No changes were made.

Outside Links

- <http://en.wikipedia.org/wiki/Hemiacetal>
- <https://en.wikipedia.org/wiki/Acetal>

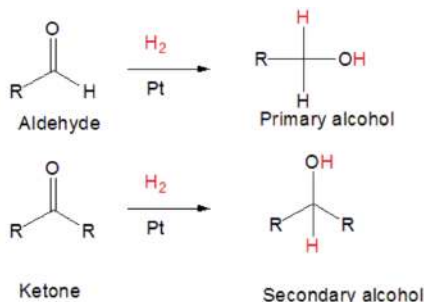
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- Ekram Alexander and Ahmed Rahim (UCD)

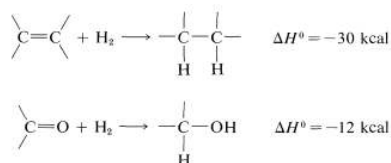
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1.7: 1.7-Chemical properties III- Catalytic Hydrogenation

The simplest large-scale procedure for reduction of aldehydes and ketones to alcohols is by catalytic hydrogenation. Catalytic hydrogenation is simultaneously an addition reaction (addition of H_2) and a reduction (gain of hydrogen). The product is an alcohol. Aldehydes produce primary alcohols, while ketones produce secondary alcohols. Tertiary alcohols cannot be obtained from aldehydes and ketones. This reaction is the opposite of oxidation.



The advantage over most other kinds of reduction is that usually the product can be obtained simply by filtration from the catalyst, then distillation. The common catalysts are nickel, palladium, or platinum. Hydrogenation of aldehyde and ketone carbonyl groups is much slower than of carbon-carbon double bonds so more strenuous conditions are required. This is not surprising, because hydrogenation of carbonyl groups is calculated to be less exothermic than that of carbon-carbon double bonds:



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1.8: Chemical properties IV- Reduction of Aldehydes and Ketones

Despite the fearsome names, the structures of the two reducing agents are very simple. In each case, there are four hydrogens ("tetrahydido") around either aluminium or boron in a negative ion (shown by the "ate" ending). The "(III)" shows the oxidation state of the aluminium or boron, and is often left out because these elements only ever show the +3 oxidation state in their compounds.

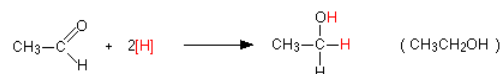
The formulae of the two compounds are ***LiAlH₄*** and ***NaBH₄***. Their structures are:



In each of the negative ions, one of the bonds is a co-ordinate covalent (dative covalent) bond using the lone pair on a hydride ion (H⁻) to form a bond with an empty orbital on the aluminium or boron.

The reduction of an aldehyde

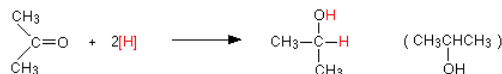
You get exactly the same organic product whether you use lithium tetrahydridoaluminate or sodium tetrahydridoborate. For example, with ethanal you get ethanol:



Notice that this is a simplified equation where [H] means "hydrogen from a reducing agent". In general terms, reduction of an aldehyde leads to a primary alcohol.

The reduction of a Ketone

Again the product is the same whichever of the two reducing agents you use. For example, with propanone you get propan-2-ol:

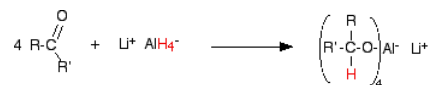


Reduction of a ketone leads to a secondary alcohol.

Using lithium tetrahydridoaluminate (lithium aluminium hydride)

Lithium tetrahydridoaluminate is much more reactive than sodium tetrahydridoborate. It reacts violently with water and alcohols, and so any reaction must exclude these common solvents. The reactions are usually carried out in solution in a carefully dried ether such as ethoxyethane (diethyl ether). The reaction happens at room temperature, and takes place in two separate stages.

In the first stage, a salt is formed containing a complex aluminium ion. The following equations show what happens if you start with a general aldehyde or ketone. R and R' can be any combination of hydrogen or alkyl groups.



The product is then treated with a dilute acid (such as dilute sulfuric acid or dilute hydrochloric acid) to release the alcohol from the complex ion.

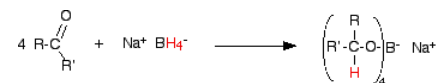


The alcohol formed can be recovered from the mixture by fractional distillation.

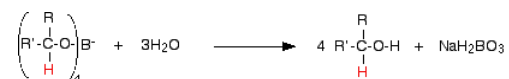
Using sodium tetrahydridoborate (sodium borohydride)

Sodium tetrahydridoborate is a more gentle (and therefore safer) reagent than lithium tetrahydridoaluminate. It can be used in solution in alcohols or even solution in water - provided the solution is alkaline. Solid sodium tetrahydridoborate is added to a solution of the aldehyde or ketone in an alcohol such as methanol, ethanol or propan-2-ol. Depending on which recipe you read, it is either heated under reflux or left for some time around room temperature. This almost certainly varies depending on the nature of the aldehyde or ketone.

At the end of this time, a complex similar to the previous one is formed.



In the second stage of the reaction, water is added and the mixture is boiled to release the alcohol from the complex.



Again, the alcohol formed can be recovered from the mixture by fractional distillation.

Contributors

- Jim Clark (Chemguide.co.uk)

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CHAPTER OVERVIEW

2: Carboxylic Acids and Esters

- 2.1: Carboxylic Acids - Structures and Nomenclature
- 2.2: Physical Properties of Carboxylic Acids
- 2.3: Chemical Properties of Carboxylic Acids I- Acidity and Salt formation
- 2.4: Chemical Properties of Carboxylic Acids II- Formation of Esters
- 2.5: Nomenclature of Esters
- 2.6: Physical Properties of Esters
- 2.7: Synthesis of Esters
- 2.8: Acid Halides for Ester Synthesis
- 2.9: Acid Anhydrides for Ester Synthesis
- 2.10: Reactions of Esters
- 2.11: Esters of Phosphoric Acid
- 2.12: Thioesters- Biological Carboxylic Acid Derivatives
- 2.13: Polyesters

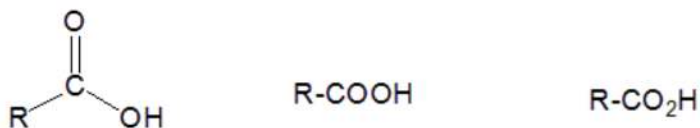
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2.1: Carboxylic Acids - Structures and Nomenclature

Learning Objectives

- Name carboxylic acids with common names.
- Name carboxylic acids according to IUPAC nomenclature.

The characteristic functional group of carboxylic acids is the carboxyl group. This group consists of a carbonyl group attached to an OH. This OH is responsible for the acidity of this type of compounds:



Different representations of the general formula for carboxylic acids. "R" represents the rest of the molecule.

Carboxylic acids occur widely in nature, often combined with alcohols or other functional groups, as in fats, oils, and waxes. They are components of many foods, medicines, and household products (Figure 2.1.1). Not surprisingly, many of them are best known by common names based on Latin and Greek words that describe their source.



Figure 2.1.1: Carboxylic Acids in the Home. Carboxylic acids occur in many common household items. (a) Vinegar contains acetic acid, (b) aspirin is acetylsalicylic acid, (c) vitamin C is ascorbic acid, (d) lemons contain citric acid, and (e) spinach contains oxalic acid. © Thinkstock

The simplest carboxylic acid, formic acid (HCOOH), was first obtained by the distillation of ants (Latin *formica*, meaning “ant”). The bites of some ants inject formic acid, and the stings of wasps and bees contain formic acid (as well as other poisonous materials).



The next higher homolog is acetic acid, which is made by fermenting cider and honey in the presence of oxygen. This fermentation produces vinegar, a solution containing 4%–10% acetic acid, plus a number of other compounds that add to its flavor. Acetic acid is probably the most familiar weak acid used in educational and industrial chemistry laboratories.



Pure acetic acid solidifies at 16.6°C, only slightly below normal room temperature. In the poorly heated laboratories of the late 19th and early 20th centuries in northern North America and Europe, acetic acid often “froze” on the storage shelf. For that reason, pure acetic acid (sometimes called concentrated acetic acid) came to be known as *glacial acetic acid*, a name that survives to this day.

The third homolog, propionic acid ($\text{CH}_3\text{CH}_2\text{COOH}$), is seldom encountered in everyday life. The fourth homolog, butyric acid ($\text{CH}_3\text{CH}_2\text{CH}_2\text{COOH}$), is one of the most foul-smelling substances imaginable. It is found in rancid butter and is one of the ingredients of body odor. By recognizing extremely small amounts of this and other chemicals, bloodhounds are able to track fugitives. Models of the first four carboxylic acids are shown in Figure 2.1.2.

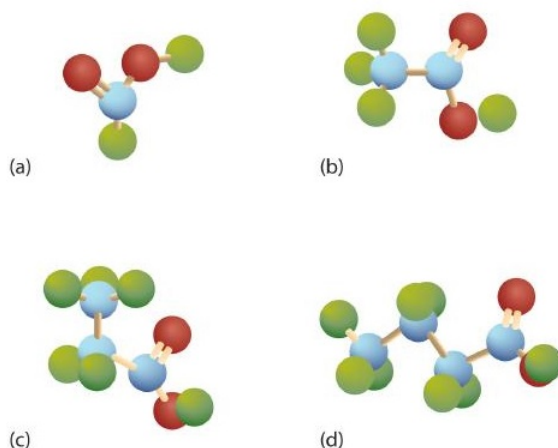
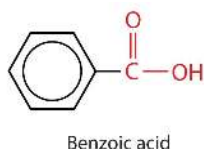


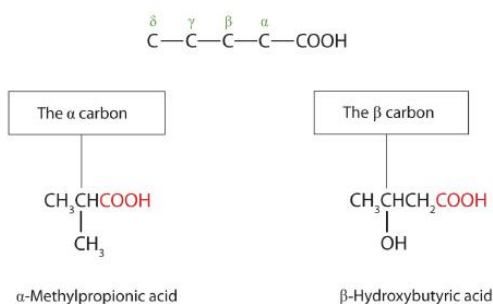
Figure 2.1.2: Ball-and-Stick Models of Carboxylic Acids. Carboxylic acids feature a carbon atom doubly bonded to an oxygen atom and also joined to an OH group. The four acids illustrated here are formic acid (a), acetic acid (b), propionic acid (c), and butyric acid (d).

The acid with the carboxyl group attached directly to a benzene ring is called benzoic acid ($\text{C}_6\text{H}_5\text{COOH}$).



Common names

The common names of carboxylic acids use the same prefixes as for the case of aldehydes, but uses Greek letters (α , β , γ , δ , and so forth), not numbers, to designate the position of substituent groups. These letters refer to the position of the carbon atom in relation to the carboxyl carbon atom.



IUPAC names

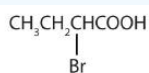
In the nomenclature system of the International Union of Pure and Applied Chemistry (IUPAC), the parent hydrocarbon is the one that corresponds to the longest continuous chain (LCC) containing the carboxyl group. The -e ending of the parent alkane is replaced by the suffix -oic and the word acid. For example, the carboxylic acid derived from pentane is pentanoic acid ($\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$). As with aldehydes, the carboxyl carbon atom is counted first; numbers are used to indicate any substituted carbon atoms in the parent chain. The position of substituents is indicated by numbers.

Greek letters are used with common names; numbers are used with IUPAC names.

Example 2.1.1

Give the common and IUPAC names for each compound.

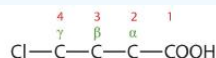
1. $\text{ClCH}_2\text{CH}_2\text{CH}_2\text{COOH}$



- 2.

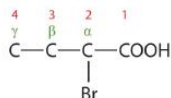
Solution

1. The LCC contains four carbon atoms; the compound is therefore named as a substituted butyric (or butanoic) acid.



The chlorine atom is attached to the γ -carbon in the common system or C4 in the IUPAC system. The compound is γ -chlorobutyric acid or 4-chlorobutanoic acid.

2. The LCC contains four carbon atoms; the compound is therefore named as a substituted butyric (or butanoic) acid.



The bromine (Br) atom is at the α -carbon in the common system or C2 in the IUPAC system. The compound is α -bromobutyric acid or 2-bromobutanoic acid.

Exercise 2.1.1

Give the IUPAC name for each compound.

- a. $\text{ClCH}_2\text{CH}_2\text{CH}_2\text{COOH}$
- b. $(\text{CH}_3)_2\text{CHCH}_2\text{CHBrCOOH}$

Example 2.1.2

Write the condensed structural formula for β -chloropropionic acid.

Solution

Propionic acid has three carbon atoms: C–C–COOH. Attach a chlorine (Cl) atom to the parent chain at the beta carbon atom, the second one from the carboxyl group: Cl–C–C–COOH. Then add enough hydrogen atoms to give each carbon atom four bonds: ClCH₂CH₂COOH.

Exercise 2.1.2

Write the condensed structural formula for 4-bromo-5-methylhexanoic acid.

Concept Review Exercises

1. What is the IUPAC name for the straight-chain carboxylic acid with six carbon atoms?
2. The straight-chain aldehyde with five carbon atoms has the common name valeraldehyde. What is the common name of the corresponding straight-chain carboxylic acid?

Answers

1. hexanoic acid
2. valeric acid

Key Takeaways

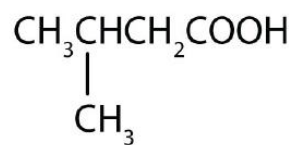
- Simple carboxylic acids are best known by common names based on Latin and Greek words that describe their source (e.g., formic acid, Latin *formica*, meaning “ant”).
- Greek letters, not numbers, designate the position of substituted acids in the common naming convention.
- IUPAC names are derived from the LCC of the parent hydrocarbon with the *-e* ending of the parent alkane replaced by the suffix *-oic* and the word *acid*.

Exercises

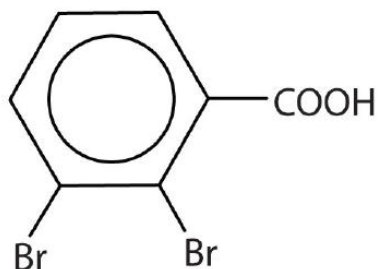
1. Draw the structure for each compound.
 - a. heptanoic acid
 - b. 3-methylbutanoic acid
 - c. 2,3-dibromobenzoic acid
 - d. β -hydroxybutyric acid
2. Draw the structure for each compound.
 - a. *o*-nitrobenzoic acid
 - b. *p*-chlorobenzoic acid
 - c. 3-chloropentanoic acid
 - d. α -chloropropionic acid
3. Name each compound with either the IUPAC name, the common name, or both.
 - a. (CH₃)₂CHCH₂COOH
 - b. (CH₃)₃CCH(CH₃)CH₂COOH
 - c. CH₂OHCH₂CH₂COOH
4. Name each compound with its IUPAC name.
 - a. CH₃(CH₂)₈COOH
 - b. (CH₃)₂CHCCl₂CH₂CH₂COOH
 - c. CH₃CHOHCH(CH₂CH₃)CHICOOH

Answers

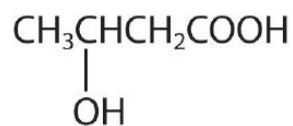
1. a. $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$



b.



c.



d.

3. a. 3-methylbutanoic acid; β -methylbutyric acid
 b. 3,4,4-trimethylpentanoic acid
 c. 4-hydroxybutanoic acid; γ -hydroxybutyric acid

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2.2: Physical Properties of Carboxylic Acids

Learning Objectives

- Compare the boiling points of carboxylic acids with alcohols of similar molar mass.
- Compare the solubilities of carboxylic acids in water with the solubilities of comparable alkanes and alcohols in water.

Many carboxylic acids are colorless liquids with disagreeable odors. The carboxylic acids with 5 to 10 carbon atoms all have “goaty” odors (explaining the odor of Limburger cheese). These acids are also produced by the action of skin bacteria on human sebum (skin oils), which accounts for the odor of poorly ventilated locker rooms. The acids with more than 10 carbon atoms are waxlike solids, and their odor diminishes with increasing molar mass and resultant decreasing volatility.

Carboxylic acids exhibit strong hydrogen bonding between molecules. They therefore have high boiling points compared to other substances of comparable molar mass. Carboxylic acids tend to have higher boiling points than water, because of their tendency to form stabilized dimers through hydrogen bonds (Figure 2.2.1). For boiling to occur, either the dimer bonds must be broken or the entire dimer arrangement must be vaporised.

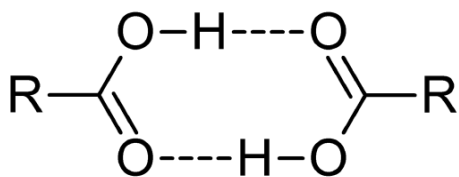


Figure 2.2.1. Carboxylic acid dimers. Image by [Mahahahaneapneap](#), Public Domain, via [Wikimedia Commons](#)

The carboxyl group readily engages in hydrogen bonding with water molecules (Figure 2.2.2) because they are both hydrogen-bond acceptors (the carbonyl $\text{C}=\text{O}$) and hydrogen-bond donors (the hydroxyl OH). The acids with one to four carbon atoms are completely miscible with water. Solubility decreases as the carbon chain length increases because dipole forces become less important and dispersion forces become more predominant. Hexanoic acid $[\text{CH}_3(\text{CH}_2)_4\text{COOH}]$ is barely soluble in water (about 1.0 g/100 g of water). Palmitic acid $[\text{CH}_3(\text{CH}_2)_{14}\text{COOH}]$, with its large nonpolar hydrocarbon component, is essentially insoluble in water. The carboxylic acids generally are soluble in such organic solvents as ethanol, toluene, and diethyl ether.

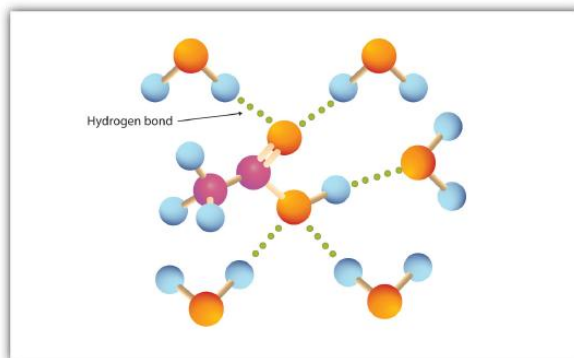


Figure 2.2.2: Hydrogen Bonding between an Acetic Acid Molecule and Water Molecules. Carboxylic acids of low molar mass are quite soluble in water.

Table 15.4.1 lists some physical properties for selected carboxylic acids. The first six are homologs. Notice that the boiling points increase with increasing molar mass, but the melting points show no regular pattern, the formation of dimers being one the reasons for this unusual behavior.

Table 2.2.1: Physical Constants of Carboxylic Acids

Condensed Structural Formula	Name of Acid	Melting Point (°C)	Boiling Point (°C)	Solubility (g/100 g of Water)
HCOOH	formic acid	8	100	miscible
CH ₃ COOH	acetic acid	17	118	miscible
CH ₃ CH ₂ COOH	propionic acid	-22	141	miscible
CH ₃ (CH ₂) ₂ COOH	butyric acid	-5	163	miscible
CH ₃ (CH ₂) ₃ COOH	valeric acid	-35	187	5
CH ₃ (CH ₂) ₄ COOH	caproic acid	-3	205	1.1
C ₆ H ₅ COOH	benzoic acid	122	249	0.29

Concept Review Exercises

- Which compound has the higher boiling point—butanoic acid (molar mass 88) or 2-pentanone (molar mass 86)? Explain.
- Would you expect butyric acid (butanoic acid) to be more or less soluble than 1-butanol in water? Explain.

Answers

- butyric acid because of hydrogen bonding (There is no intermolecular hydrogen bonding in 2-pentanone.)
- more soluble because there is more extensive hydrogen bonding

Key Takeaways

- Carboxylic acids have high boiling points compared to other substances of comparable molar mass. Boiling points increase with molar mass.
- Carboxylic acids having one to four carbon atoms are completely miscible with water. Solubility decreases with molar mass.

Exercises

- Which compound has the higher boiling point—CH₃CH₂CH₂OCH₂CH₃ or CH₃CH₂CH₂COOH? Explain.
- Which compound has the higher boiling point—CH₃CH₂CH₂CH₂CH₂OH or CH₃CH₂CH₂COOH? Explain.
- Which compound is more soluble in water—CH₃COOH or CH₃CH₂CH₂CH₃? Explain.
- Which compound is more soluble in water—CH₃CH₂COOH or CH₃CH₂CH₂CH₂CH₂COOH? Explain.

Answers

- CH₃CH₂CH₂COOH because of hydrogen bonding (There is no intermolecular hydrogen bonding with CH₃CH₂CH₂OCH₂CH₃.)
- CH₃CH₂CH₂CH₂CH₂OH because it engages in hydrogen bonding with water (There is no intermolecular hydrogen bonding with CH₃CH₂CH₂COOH.)
- CH₃COOH because it engages in hydrogen bonding with water (There is no intermolecular hydrogen bonding with CH₃CH₂CH₂CH₃.)

Attributions and citations

- Physical Properties of Carboxylic Acids. (2020, August 10). Retrieved May 22, 2021, from <https://chem.libretexts.org/@go/page/16027>
- Wikipedia contributors. (2021, May 20). Carboxylic acid. In *Wikipedia, The Free Encyclopedia*. Retrieved 16:26, May 22, 2021, from https://en.wikipedia.org/w/index.php?title=Carboxylic_acid&oldid=1024117740

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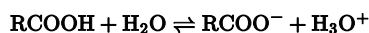
2.3: Chemical Properties of Carboxylic Acids I- Acidity and Salt formation

Learning Objectives

- Name the typical reactions that take place with carboxylic acids.
- Describe how carboxylic acids react with basic compounds.

Acidity

Water-soluble carboxylic acids ionize slightly in water to form moderately acidic solutions.

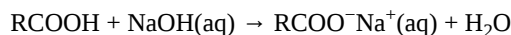


Their aqueous solutions exhibit the typical properties of acids, such as changing litmus from blue to red.

The anion formed when a carboxylic acid dissociates is called the *carboxylate* anion (RCOO^-).

Salt formation

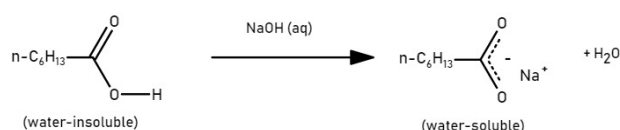
Whether soluble in water or not, carboxylic acids react with aqueous solutions of sodium hydroxide (NaOH), sodium carbonate (Na_2CO_3), and sodium bicarbonate (NaHCO_3) to form salts:



In these reactions, the carboxylic acids act like inorganic acids: they neutralize basic compounds. With solutions of sodium carbonate (Na_2CO_3) or sodium bicarbonate (NaHCO_3), they also form carbon dioxide gas:



Being ionic compounds, these salts are always soluble in water. For example, heptanoic has a low solubility in water (0.2 g/L), but its sodium salt is very soluble in water:



Water solubility of carboxylic acids compared to their salts. Image by [Fung06831](#), [CC BY-SA 4.0](#), via Wikimedia Commons

Carboxylic acid salts are named in the same manner as inorganic salts: the name of the cation is followed by the name of the organic anion. The name of the anion is obtained by dropping the *-ic* ending of the acid name and replacing it with the suffix *-ate*. This rule applies whether we are using common names or International Union of Pure and Applied Chemistry (IUPAC) names:

$\text{CH}_3\text{COO}^-\text{Li}^+$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{COO}^-\text{K}^+$	$\text{C}_6\text{H}_5\text{COO}^-\text{Na}^+$
Lithium acetate (lithium ethanoate)	Potassium butyrate (potassium butanoate)	Sodium benzoate

The salts of long-chain carboxylic acids are called soaps. We discuss the chemistry of soaps elsewhere.



Sodium palmitate (a soap)

Example 2.3.1

Write an equation for each reaction.

1. the ionization of propionic acid in water (H_2O)
2. the neutralization of propionic acid with aqueous sodium hydroxide (NaOH)

Solution

Propionic acid has three carbon atoms, so its formula is $\text{CH}_3\text{CH}_2\text{COOH}$.

1. Propionic acid ionizes in water to form a propionate ion and a hydronium (H_3O^+) ion. $\text{CH}_3\text{CH}_2\text{COOH}(\text{aq}) + \text{H}_2\text{O}(\ell) \rightarrow \text{CH}_3\text{CH}_2\text{COO}^-(\text{aq}) + \text{H}_3\text{O}^+(\text{aq})$
2. Propionic acid reacts with $\text{NaOH}(\text{aq})$ to form sodium propionate and water. $\text{CH}_3\text{CH}_2\text{COOH}(\text{aq}) + \text{NaOH}(\text{aq}) \rightarrow \text{CH}_3\text{CH}_2\text{COO}^-\text{Na}^+(\text{aq}) + \text{H}_2\text{O}(\ell)$

Exercise 2.3.1

Write an equation for each reaction.

- a. the ionization of formic acid in water
- b. the ionization of *p*-chlorobenzoic acid in water

Example 2.3.2

Write an equation for the reaction of decanoic acid with each compound.

- a. aqueous sodium hydroxide (NaOH)
- b. aqueous sodium bicarbonate (NaHCO_3)

Solution

- a. Decanoic acid has 10 carbon atoms. It reacts with NaOH to form a salt and water (H_2O). $\text{CH}_3(\text{CH}_2)_8\text{COOH} + \text{NaOH}(\text{aq}) \rightarrow \text{CH}_3(\text{CH}_2)_8\text{COO}^-\text{Na}^+(\text{aq}) + \text{H}_2\text{O}(\ell)$
- b. With NaHCO_3 , the products are a salt, H_2O , and carbon dioxide (CO_2). $\text{CH}_3(\text{CH}_2)_8\text{COOH} + \text{NaHCO}_3(\text{aq}) \rightarrow \text{CH}_3(\text{CH}_2)_8\text{COO}^-\text{Na}^+(\text{aq}) + \text{H}_2\text{O}(\ell) + \text{CO}_2(\text{g})$

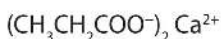
Exercise 2.3.3

Write an equation for the reaction of benzoic acid with each compound.

- a. aqueous sodium hydroxide (NaOH)
- b. aqueous sodium bicarbonate (NaHCO_3)

To Your Health: Organic Salts as Preservatives

Some organic salts are used as preservatives in food products. They prevent spoilage by inhibiting the growth of bacteria and fungi. Calcium and sodium propionate, for example, are added to processed cheese and bakery goods; sodium benzoate is added to cider, jellies, pickles, and syrups; and sodium sorbate and potassium sorbate are added to fruit juices, sauerkraut, soft drinks, and wine. Look for them on ingredient labels the next time you shop for groceries.



Calcium propionate



Potassium sorbate

Concept Review Exercises

1. How does the neutralization of a carboxylic acid differ from that of an inorganic acid? How are they similar?
2. What products are formed when a carboxylic acid is neutralized with a strong base? What additional product is formed when a carboxylic acid is neutralized with a carbonate or a bicarbonate?

Answers

1. Insoluble carboxylic acids often form soluble carboxylate salts. Both form a salt and water.
2. a carboxylate salt and water; carbon dioxide

Key Takeaways

- Soluble carboxylic acids are weak acids in aqueous solutions.
- Carboxylic acids neutralize bases to form salts.

Exercises

1. Write the equation for the ionization of $\text{CH}_3\text{CH}_2\text{CH}_2\text{COOH}$ in water.
2. Write the equation for the neutralization of $\text{CH}_3\text{CH}_2\text{CH}_2\text{COOH}$ with sodium hydroxide $[\text{NaOH}(\text{aq})]$.
3. Write the equation for the reaction of CH_3COOH with sodium carbonate $[\text{Na}_2\text{CO}_3(\text{aq})]$.
4. Write the equation for the reaction of $\text{CH}_3\text{CH}_2\text{COOH}$ with sodium bicarbonate $[\text{NaHCO}_3(\text{aq})]$.
5. Write the equation for the ionization of propionic acid in water.
6. Write the equation for the ionization of γ -chloropentanoic acid in water.
7. Write an equation for the reaction of butyric acid with each compound.
 - a. aqueous NaOH
 - b. aqueous NaHCO_3
8. Write the condensed structural formula for each compound.
 - a. potassium acetate
 - b. calcium propanoate
9. Name each compound.
 - a. $\text{CH}_3\text{CH}_2\text{CH}_2\text{COO}^-\text{Li}^+$
 - b. $\text{CH}_3\text{CH}_2\text{CH}_2\text{COO}^-\text{NH}_4^+$

Answers

1. $\text{CH}_3\text{CH}_2\text{CH}_2\text{COOH}(\text{aq}) + \text{H}_2\text{O}(\ell) \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{COO}^-(\text{aq}) + \text{H}_3\text{O}^+(\text{aq})$
3. $2\text{CH}_3\text{COOH} + \text{Na}_2\text{CO}_3(\text{aq}) \rightarrow 2\text{CH}_3\text{COO}^-\text{Na}^+(\text{aq}) + \text{H}_2\text{O}(\ell) + \text{CO}_2(\text{g})$
5. $\text{CH}_3\text{CH}_2\text{COOH}(\text{aq}) + \text{H}_2\text{O}(\ell) \rightarrow \text{CH}_3\text{CH}_2\text{COO}^-(\text{aq}) + \text{H}_3\text{O}^+(\text{aq})$
7.
 - a. $\text{CH}_3\text{CH}_2\text{CH}_2\text{COOH}(\text{aq}) + \text{NaOH}(\text{aq}) \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{COO}^-\text{Na}^+(\text{aq}) + \text{H}_2\text{O}(\ell)$
 - b. $\text{CH}_3(\text{CH}_2)_2\text{COOH} + \text{NaHCO}_3(\text{aq}) \rightarrow \text{CH}_3(\text{CH}_2)_2\text{COO}^-\text{Na}^+(\text{aq}) + \text{H}_2\text{O}(\ell) + \text{CO}_2(\text{g})$
9.
 - a. lithium butyrate (lithium butanoate)
 - b. ammonium butanoate or ammonium butyrate

Attribution and citations

- Wikipedia contributors. (2021, May 20). Carboxylic acid. In *Wikipedia, The Free Encyclopedia*. Retrieved 16:26, May 22, 2021, from https://en.wikipedia.org/w/index.php?title=Carboxylic_acid&oldid=1024117740
- Chemical Properties of Carboxylic Acids- Ionization and Neutralization. (2020, August 17). Retrieved May 22, 2021, from <https://chem.libretexts.org/@go/page/16028>

2.3: Chemical Properties of Carboxylic Acids I- Acidity and Salt formation is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

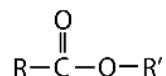
2.4: Chemical Properties of Carboxylic Acids II- Formation of Esters

Learning Objectives

- Describe the structure and properties of esters.
- Name common esters.

Formation of Esters: The Sweet Smell of RCOOR'

An **ester** is an organic compound that is a derivative of a carboxylic acid in which the hydrogen atom of the hydroxyl group has been replaced with an alkyl group. The structure is the product of a carboxylic acid (the **R**-portion) and an alcohol (the **R'**-portion). The general formula for an ester is shown below.



The **R** group can either be a hydrogen or a carbon chain. The **R'** group must be a carbon chain since a hydrogen atom would make the molecule a carboxylic acid.

Esters are produced by the reaction of acids with alcohols. For example, the ester ethyl acetate, $\text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3$, is formed when acetic acid reacts with ethanol:

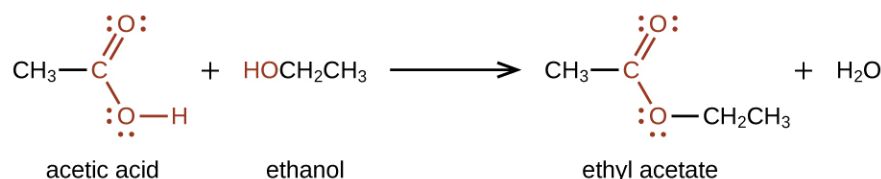


Figure 2.4.3). Once a flower or fruit has been chemically analyzed, flavor chemists can attempt to duplicate the natural odor or taste. Both natural and synthetic esters are used in perfumes and as flavoring agents.

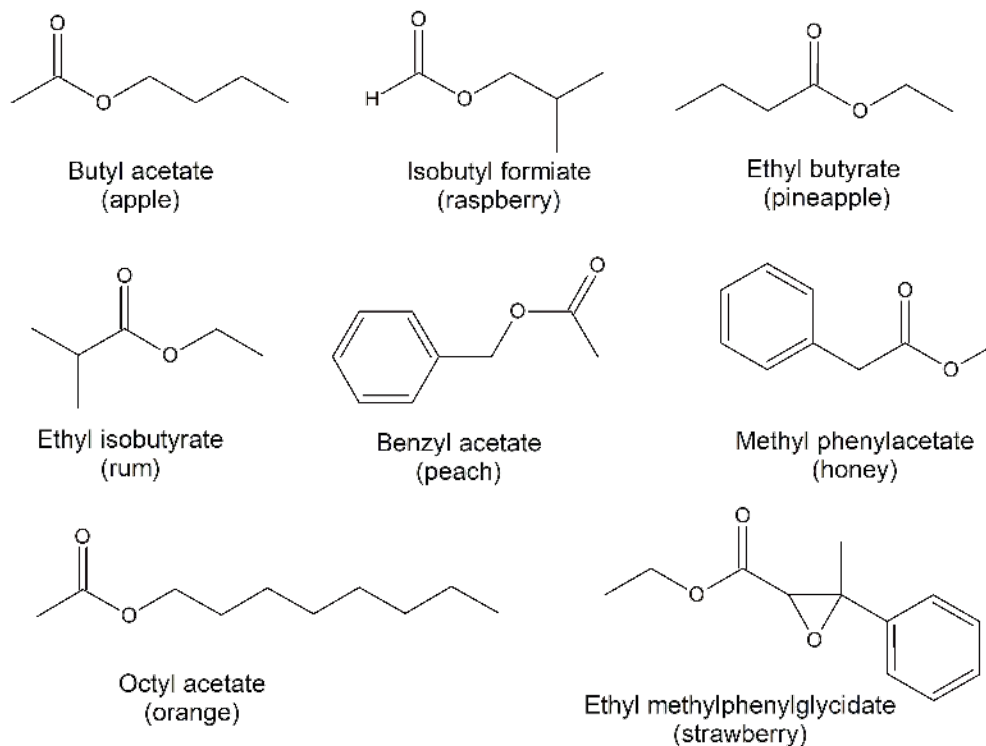


Figure 2.4.3 Esters

are responsible for the odors associated with various plants and their fruits.

Chemistry Is Everywhere: Esters, Fragrances, and Flavorings

Esters are very interesting compounds, in part because many have very pleasant odors and flavors. (Remember, never taste anything in the chemistry lab!) Many esters occur naturally and contribute to the odor of flowers and the taste of fruits. Other esters are synthesized industrially and are added to food products to improve their smell or taste; it is likely that if you eat a product whose ingredients include artificial flavorings, those flavorings are esters. Here are some esters and their uses, thanks to their odors, flavors, or both:

Ester	Tastes/Smells Like	Ester	Tastes/Smells Like
allyl hexanoate	pineapple	isobutyl formate	raspberry
benzyl acetate	pear	isobutyl acetate	pear
butyl butanoate	pineapple	methyl phenylacetate	honey
ethyl butanoate	banana	nonyl caprylate	orange
ethyl hexanoate	pineapple	pentyl acetate	apple
ethyl heptanoate	apricot	propyl ethanoate	pear
ethyl pentanoate	apple	propyl isobutyrate	rum

Finally, the **ether** functional group is an

Among the most important of the natural esters are fats (such as lard, tallow, and butter) and oils (such as linseed, cottonseed, and olive oils), which are esters of the trihydroxyl alcohol glycerine, $\text{C}_3\text{H}_5(\text{OH})_3$, with large carboxylic acids, such as palmitic acid, $\text{CH}_3(\text{CH}_2)_{14}\text{CO}_2\text{H}$, stearic acid, $\text{CH}_3(\text{CH}_2)_{16}\text{CO}_2\text{H}$, and oleic acid, $\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{CO}_2\text{H}$. Oleic acid is an unsaturated acid; it contains a $\text{C}=\text{C}$ double bond. Palmitic and stearic acids are saturated acids that contain no double or triple bonds.

Note

Fats and vegetable oils are esters of long-chain fatty acids and glycerol. Esters of phosphoric acid are of the utmost importance to life.

Esters are common solvents. Ethyl acetate is used to extract organic solutes from aqueous solutions—for example, to remove caffeine from coffee. It also is used to remove nail polish and paint. Cellulose nitrate is dissolved in ethyl acetate and butyl acetate to form lacquers. The solvent evaporates as the lacquer “dries,” leaving a thin film on the surface. High boiling esters are used as softeners (plasticizers) for brittle plastics.

Summary

- An ester has an OR group attached to the carbon atom of a carbonyl group.
- Fats and vegetable oils are esters of long-chain fatty acids and glycerol.
- Esters occur widely in nature and generally have pleasant odors and are often responsible for the characteristic fragrances of fruits and flowers.

Contributors and Attributions

- Libretext : The Basics of GOB Chemistry (Ball et al.)
- TextMap: Beginning Chemistry (Ball et al.)
- Marisa Alviar-Agnew (Sacramento City College)
- OpenSTAX
- Carboxylic Acids and Esters. (2020, August 13). Retrieved May 22, 2021, from <https://chem.libretexts.org/@go/page/153839>

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2.5: Nomenclature of Esters

Learning Objectives

- Use common names to name esters.
- Name esters according to the IUPAC system.

Esters occur widely in nature. Unlike carboxylic acids, esters generally have pleasant odors and are often responsible for the characteristic fragrances of fruits and flowers. Once a flower or fruit has been chemically analyzed, flavor chemists can attempt to duplicate the natural odor or taste. Both natural and synthetic esters are used in perfumes and as flavoring agents.

Fats and vegetable oils are esters of long-chain fatty acids and glycerol. Esters of phosphoric acid are of the utmost importance to life.

Names of Esters

Although esters are covalent compounds and salts are ionic, esters are named in a manner similar to that used for naming salts. The group name of the alkyl or aryl portion is given first and is followed by the name of the acid portion. In both common and International Union of Pure and Applied Chemistry (IUPAC) nomenclature, the *-ic* ending of the parent acid is replaced by the suffix *-ate* (Table 2.5.1). The only difference is the name used for the acid portion: the common nomenclature follows the common names used for acids, while the IUPAC nomenclature applies the official prefixes to indicate numbers of carbon atoms on the main carbon chain.

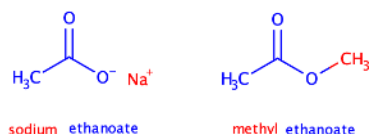
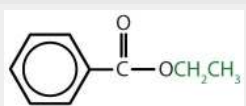


Table 2.5.1: Nomenclature of Esters

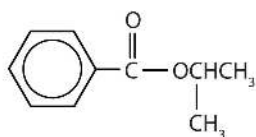
Condensed Structural Formula	Common Name	IUPAC Name
HCOOCH ₃	methyl formate	methyl methanoate
CH ₃ COOCH ₃	methyl acetate	methyl ethanoate
CH ₃ COOCH ₂ CH ₃	ethyl acetate	ethyl ethanoate
CH ₃ CH ₂ COOCH ₂ CH ₃	ethyl propionate	ethyl propanoate
CH ₃ CH ₂ CH ₂ COOCH(CH ₃) ₂	isopropyl butyrate	isopropyl butanoate
	ethyl benzoate	ethyl benzoate

Example 2.5.1

Give the common and IUPAC names for each compound.

1.





2.

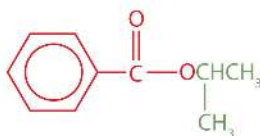
Solution

1. The alkyl group attached directly to the oxygen atom is a butyl group (in green).



The part of the molecule derived from the carboxylic acid (in red) has three carbon atoms. It is called propionate (common) or propanoate (IUPAC). The ester is therefore butyl propionate or butyl propanoate.

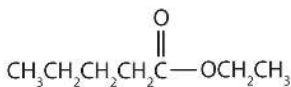
2. An alkyl group (in green) is attached directly to the oxygen atom by its middle carbon atom; it is an isopropyl group. The part derived from the acid (that is, the benzene ring and the carbonyl group, in red) is benzoate. The ester is therefore isopropyl benzoate (both the common name and the IUPAC name).



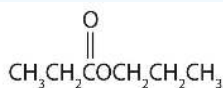
Exercise 2.5.1

Give the common and IUPAC names for each compound.

a.



b.



Example 2.5.2

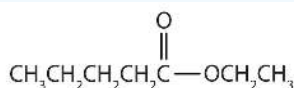
Draw the structure for ethyl pentanoate.

Solution

Start with the portion from the acid. Draw the pentanoate (five carbon atoms) group first; keeping in mind that the last carbon atom is a part of the carboxyl group.



Then attach the ethyl group to the bond that ordinarily holds the hydrogen atom in the carboxyl group.



Exercise 2.5.2

Draw the structure for phenyl pentanoate.

Concept Review Exercises

1. From what carboxylic acid and what alcohol can isopropyl hexanoate be made?
2. From what carboxylic acid and what alcohol can cyclobutyl butyrate be made?

Answers

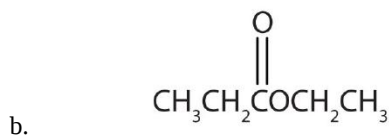
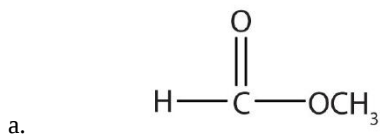
1. hexanoic acid and isopropyl alcohol
2. butyric acid and cyclobutyl alcohol

Key Takeaway

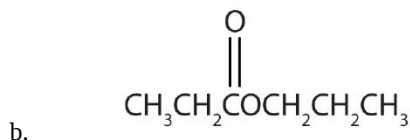
- An ester has an OR group attached to the carbon atom of a carbonyl group.

Exercises

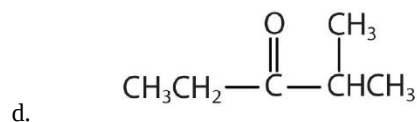
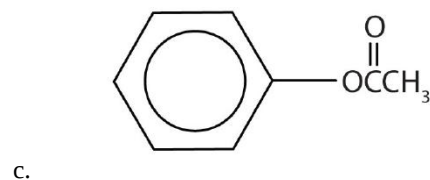
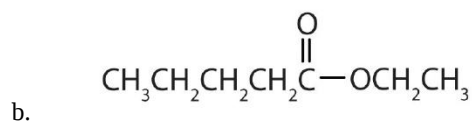
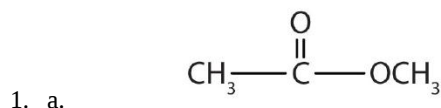
1. Draw the structure for each compound.
 - a. methyl acetate
 - b. ethyl pentanoate
 - c. phenyl acetate
 - d. isopropyl propionate
2. Draw the structure for each compound.
 - a. ethyl hexanoate
 - b. ethyl benzoate
 - c. phenyl benzoate
 - d. ethyl 3-methylhexanoate
3. Name each compound with both the common name and the IUPAC name.



4. Name each compound with both the common name and the IUPAC name.



Answers



3. a. methyl formate; methyl methanoate
b. ethyl propionate; ethyl propanoate

Citations and attributions

Esters - Structures and Names. (2020, August 17). Retrieved May 22, 2021, from <https://chem.libretexts.org/@go/page/16029>

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2.6: Physical Properties of Esters

Learning Objectives

- Compare the boiling points of esters with alcohols of similar molar mass.
- Compare the solubilities of esters in water with the solubilities of comparable alkanes and alcohols in water.

Ester molecules are polar but have no hydrogen atom attached directly to an oxygen atom. They are therefore incapable of engaging in intermolecular hydrogen bonding with one another and thus have considerably lower boiling points than their isomeric carboxylic acids counterparts. Because ester molecules can engage in hydrogen bonding with water molecules, however, esters of low molar mass are somewhat soluble in water. Borderline solubility occurs in those molecules that have three to five carbon atoms. Table 2.6.1 lists the physical properties of some common esters.

Esters are common solvents. Ethyl acetate is used to extract organic solutes from aqueous solutions—for example, to remove caffeine from coffee. It also is used to remove nail polish and paint. Cellulose nitrate is dissolved in ethyl acetate and butyl acetate to form lacquers. The solvent evaporates as the lacquer “dries,” leaving a thin film on the surface. High boiling esters are used as softeners (plasticizers) for brittle plastics.

Table 2.6.1: Physical Properties of Some Esters

Condensed Structural Formula	Name	Molar Mass	Melting Point (°C)	Boiling Point (°C)	Water solubility (grams/100 mL) at 20°C	Aroma
HCOOCH ₃	methyl formate	60	−99	32	30	
HCOOCH ₂ CH ₃	ethyl formate	74	−80	54	9	rum
CH ₃ COOCH ₃	methyl acetate	74	−98	57	25	
CH ₃ COOCH ₂ CH ₃	ethyl acetate	88	−84	77	8.3	
CH ₃ CH ₂ CH ₂ COOCH ₃	methyl butyrate	102	−85	102	1.5	apple
CH ₃ CH ₂ CH ₂ COOCH ₂ CH ₃	ethyl butyrate	116	−101	121	0.49	pineapple
CH ₃ COO(CH ₂) ₄ CH ₃	pentyl acetate	130	−71	148	0.17	pear
CH ₃ COOCH ₂ CH ₂ CH(CH ₃) ₂	isopentyl acetate	130	−79	142	0.3	banana
CH ₃ COOCH ₂ C ₆ H ₅	benzyl acetate	150	−51	215	0.31	jasmine
CH ₃ CH ₂ CH ₂ COO(CH ₂) ₄ CH ₃	pentyl butyrate	158	−73	185	0.017	apricot
CH ₃ COO(CH ₂) ₇ CH ₃	octyl acetate	172	−39	210	0.018	orange

Summary

Esters have polar bonds but do not engage in hydrogen bonding and are therefore intermediate in boiling points between the nonpolar alkanes and the alcohols, which engage in hydrogen bonding. Ester molecules can engage in hydrogen bonding with

water, so esters of low molar mass are therefore somewhat soluble in water.

Concept Review Exercises

1. Which compound has the higher boiling point— $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ or $\text{CH}_3\text{COOCH}_3$? Explain.
2. Which compound is more soluble in water—methyl butyrate or butyric acid? Explain.

Answers

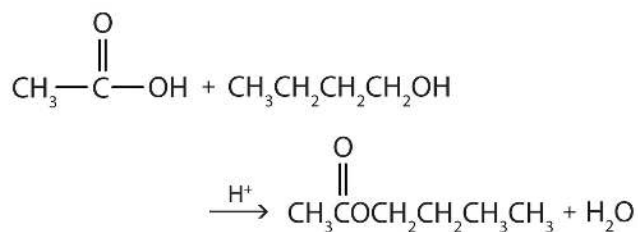
1. $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ because there is intermolecular hydrogen bonding (There is no intermolecular hydrogen bonding in $\text{CH}_3\text{COOCH}_3$.)
2. butyric acid because of hydrogen bonding with water

Exercises

1. Which compound has the higher boiling point— $\text{CH}_3\text{CH}_2\text{CH}_2\text{COOH}$ or $\text{CH}_3\text{CH}_2\text{CH}_2\text{COOCH}_3$? Explain.
2. Which compound is more soluble in water—methyl acetate or octyl acetate? Explain.

Answer

1. $\text{CH}_3\text{CH}_2\text{CH}_2\text{COOH}$ because there is intermolecular hydrogen bonding (There is no intermolecular hydrogen bonding in $\text{CH}_3\text{CH}_2\text{COOCH}_3$.)



a.

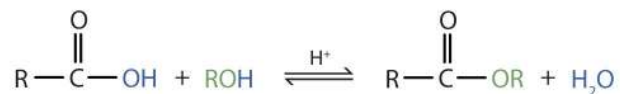
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2.7: Synthesis of Esters

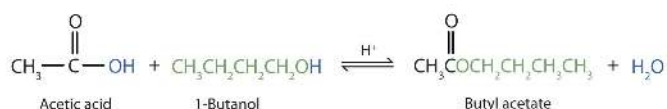
Learning Objectives

- To identify and describe the substances from which most esters are prepared.

Some esters can be prepared by esterification, a reaction in which a carboxylic acid and an alcohol, heated in the presence of a mineral acid catalyst, form an ester and water:



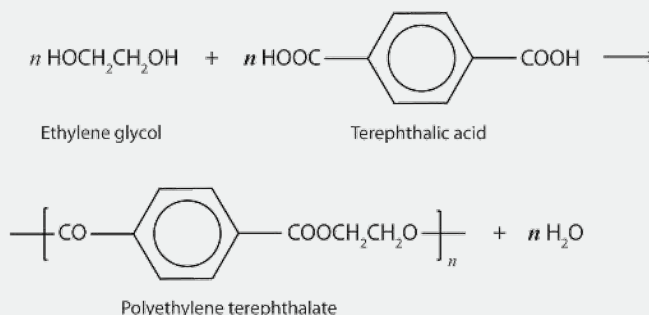
The reaction is reversible. As a specific example of an esterification reaction, butyl acetate can be made from acetic acid and 1-butanol.



A Closer Look: Condensation Polymers

A commercially important esterification reaction is condensation polymerization, in which a reaction occurs between a dicarboxylic acid and a dihydric alcohol (diol), with the elimination of water. Such a reaction yields an ester that contains a free (unreacted) carboxyl group at one end and a free alcohol group at the other end. Further condensation reactions then occur, producing polyester polymers.

The most important polyester, polyethylene terephthalate (PET), is made from terephthalic acid and ethylene glycol monomers:



Polyester molecules make excellent fibers and are used in many fabrics. A knitted polyester tube, which is biologically inert, can be used in surgery to repair or replace diseased sections of blood vessels. PET is used to make bottles for soda pop and other beverages. It is also formed into films called Mylar. When magnetically coated, Mylar tape is used in audio- and videocassettes. Synthetic arteries can be made from PET, polytetrafluoroethylene, and other polymers.

Summary

Esters are made by the reaction of a carboxylic acid with an alcohol, a process that is called esterification.

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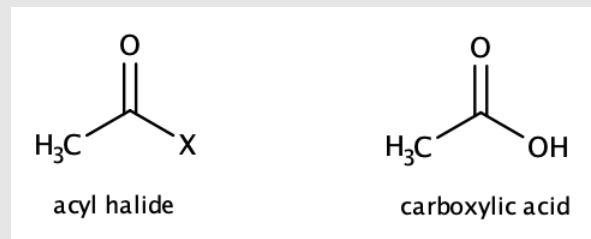
- 15.7: Preparation of Esters** by Anonymous is licensed [CC BY-NC-SA 3.0](#). Original source: <https://2012books.lardbucket.org/books/introduction-to-chemistry-general-organic-and-biological>.

2.8: Acid Halides for Ester Synthesis

Please Note: The terms "acid halide" and "acyl halide" are synonymous and are both used in this text. In biochemistry, the term "acyl" is used more frequently.

Acid Halides

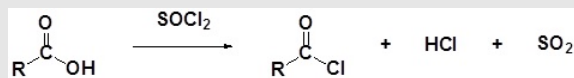
An **acyl halide** (also known as an **acid halide**) is a chemical compound derived from a carboxylic acid by replacing a hydroxyl group with a halogen:



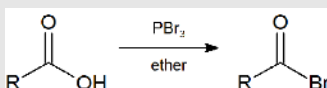
The general formula for such an acyl halide can be written **RCOX**, where R may be, for example, an alkyl group, CO is the carbonyl group, and X represents the halide, such as chloride.

Acid Halide Synthesis

Carboxylic acids react with thionyl chloride (SOCl_2) or oxalyl chloride ($\text{C}_2\text{O}_2\text{Cl}_2$) to form acid chlorides. Typically the reactions occur in the presence of a proton scavenger like pyridine to minimize unwanted side reactions. During the reaction the hydroxyl group of the carboxylic acid is converted to a chlorosulfite intermediate making it a better leaving group. The chloride anion produced during the reaction acts a nucleophile.

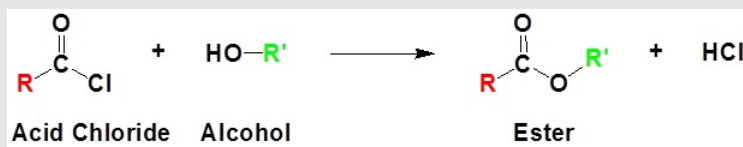


Analogous to the reactions of primary and secondary alcohols with PBr_3 to produce the corresponding alkyl bromide, acid bromides can be formed from the reaction of phosphorous tribromide with carboxylic acids.



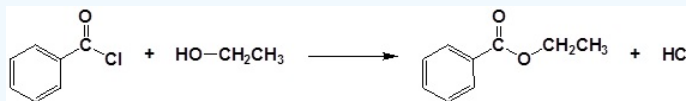
Ester Synthesis from Acyl Chlorides

Acid chlorides react with alcohols for form esters are shown in the reaction below. The benefit of using acyl chlorides instead of carboxylic acid is that the reaction becomes **irreversible**.



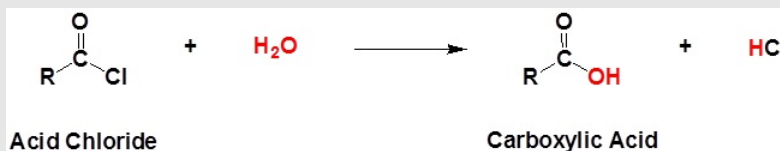
The synthesis of ethyl benzoate from benzoyl chloride and ethanol is shown as an example.

Example: Ester Synthesis from Acid Chlorides



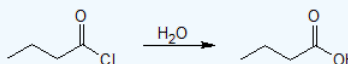
Acid Halide Hydrolysis

Acid halides are quite reactive and therefore very unstable. They react with water (even moisture) in a hydrolysis reaction as shown below:



The hydrolysis of butonyl chloride is shown below as an example.

Example: Acyl Chloride Hydrolysis



Because of this reaction, it is very important to work with glassware that has been dried, and also solvents that are free from moisture. Volatile acyl halides are lachrymatory because they can react with water at the surface of the eye producing hydrohalic and organic acids irritating to the eye. Similar problems can result if one inhales acyl halide vapors.

Contributors and Attributions

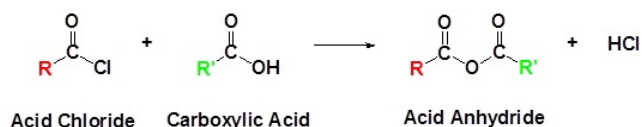
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, [Athabasca University](#))
- Prof. Steven Farmer ([Sonoma State University](#))
- Acid Halide Chemistry. (2020, May 30). Retrieved May 22, 2021, from <https://chem.libretexts.org/@go/page/45951>
- Wikipedia contributors. (2021, April 28). Acyl halide. In *Wikipedia, The Free Encyclopedia*. Retrieved 22:06, May 22, 2021, from https://en.wikipedia.org/w/index.php?title=Acyl_halide&oldid=1020318981

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2.9: Acid Anhydrides for Ester Synthesis

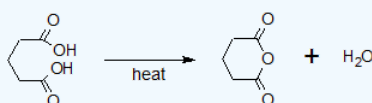
Synthesis of Acid Anhydrides

Acid chlorides react with carboxylic acids to form anhydrides as shown in the reaction below. Acid anhydrides often form when one equivalent of water is removed from two equivalents of an organic acid in a dehydration reaction:



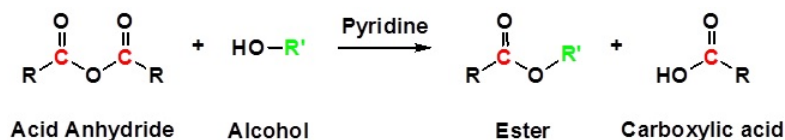
Some cyclic anhydrides can be synthesized from the corresponding dicarboxylic acid with gentle heating. The example below shows the reaction of glutaric acid to form a cyclic anhydride.

Example: Acid Anhydride Synthesis



Ester Synthesis using acid anhydrides

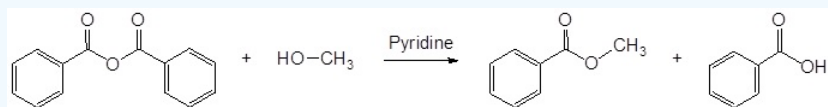
Acid anhydrides react with alcohols to produce esters as shown in the reaction below. The reactions of anhydrides frequently use pyridine as a solvent. As in the case of using acid halides, the synthesis of ester using acid anhydrides instead of carboxylic acids results in an irreversible reaction, which improves the product yield:



The presence of pyridine facilitates proton transfers during the reaction. A carboxylic acid is also produced, but is not considered a synthetic product. The ester is considered the "product of interest".

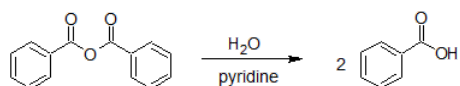
The synthesis of methyl benzoate from benzoic anhydride and methanol is shown in the example.

Example: Ester Synthesis



Acid Anhydride Hydrolysis

Acid anhydrides readily hydrolyze to carboxylic acids. In many cases, this reaction is an unwanted side reaction and steps will be taken in the lab to keep the system "dry" (aka water-free). The presence of pyridine facilitates proton transfers during the reaction. The hydrolysis reaction for benzoic anhydride is shown below.



Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, [Athabasca University](#))
- Prof. Steven Farmer ([Sonoma State University](#))
- Acid Anhydride Chemistry. (2020, May 30). Retrieved May 22, 2021, from <https://chem.libretexts.org/@go/page/45952>
- Wikipedia contributors. (2019, August 19). Acid anhydride. In *Wikipedia, The Free Encyclopedia*. Retrieved 22:13, May 22, 2021, from https://en.wikipedia.org/w/index.php?title=Acid_anhydride&oldid=911592608

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2.10: Reactions of Esters

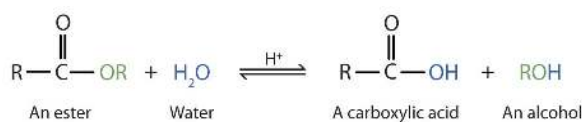
Learning Objectives

- Describe the typical reaction that takes place with esters.
- Identify the products of an acidic hydrolysis of an ester.
- Identify the products of a basic hydrolysis of an ester.

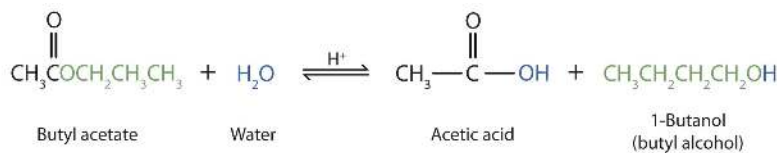
Esters hydrolysis

Esters are neutral compounds, unlike the acids from which they are formed. In typical reactions, the alkoxy (OR') group of an ester is replaced by another group. One such reaction is hydrolysis, literally "splitting with water." The hydrolysis of esters is catalyzed by either an acid or a base.

Acidic hydrolysis is simply the reverse of [esterification](#). The ester is heated with a large excess of water containing a strong-acid catalyst. Like esterification, the reaction is reversible and does not go to completion. The products are a carboxylic acid and an alcohol.



As a specific example, butyl acetate and water react to form acetic acid and 1-butanol. The reaction is reversible and does not go to completion.

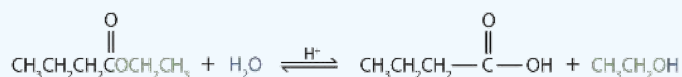


Example 2.10.1

Write an equation for the acidic hydrolysis of ethyl butyrate ($\text{CH}_3\text{CH}_2\text{CH}_2\text{COOCH}_2\text{CH}_3$) and name the products.

Solution

Remember that in acidic hydrolysis, water (HOH) splits the ester bond. The H of HOH joins to the oxygen atom in the OR part of the original ester, and the OH of HOH joins to the carbonyl carbon atom:



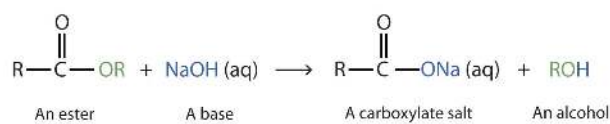
The products are butyric acid (butanoic acid) and ethanol.

Exercise 2.10.1

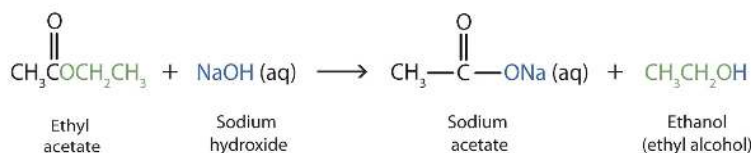
Write an equation for the acidic hydrolysis of methyl butanoate and name the products.

Basic Hydrolysis or saponification

When a base (such as sodium hydroxide [NaOH] or potassium hydroxide [KOH]) is used to hydrolyze an ester, the products are a carboxylate salt and an alcohol. Because soaps are prepared by the alkaline hydrolysis of fats and oils, alkaline hydrolysis of esters is called saponification (Latin *sapon*, meaning "soap," and *facere*, meaning "to make"). In a saponification reaction, the base is a reactant, not simply a catalyst. The reaction goes to completion:



As a specific example, ethyl acetate and NaOH react to form sodium acetate and ethanol:



The reaction is called Saponification because is the reaction used in the production of soaps. Soaps are sodium or potassium salts of long carboxylic acid called fatty acids.



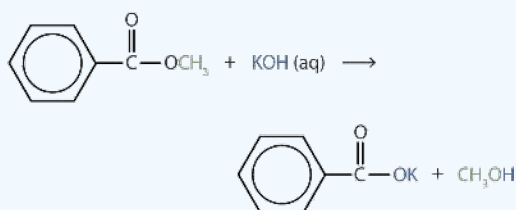
Sodium stearate, a typical ingredient found in bar soaps. Image by [Smokefoot](#), CC BY-SA 3.0, via Wikimedia Commons

Example 2.10.2

Write an equation for the hydrolysis of methyl benzoate in a potassium hydroxide solution.

Solution

In basic hydrolysis, the molecule of the base splits the ester linkage. The acid portion of the ester ends up as the *salt* of the acid (in this case, the potassium salt). The alcohol portion of the ester ends up as the free alcohol.



Exercise 2.10.2

Write the equation for the hydrolysis of ethyl propanoate in a sodium hydroxide solution.

Summary

Hydrolysis is a most important reaction of esters. Acidic hydrolysis of an ester gives a carboxylic acid and an alcohol. Basic hydrolysis of an ester gives a carboxylate salt and an alcohol.

Concept Review Exercises

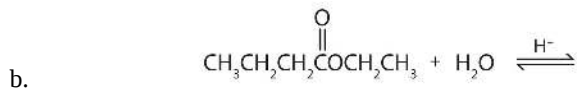
- How do acidic hydrolysis and basic hydrolysis of an ester differ in terms of
 - products obtained?
 - the extent of reaction?
- What is saponification?

Answers

- acidic hydrolysis: carboxylic acid + alcohol; basic hydrolysis: carboxylate salt + alcohol
 - basic hydrolysis: completion; acidic hydrolysis: incomplete reaction
- the basic hydrolysis of an ester

Exercises

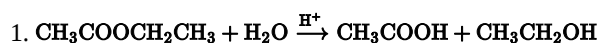
1. Write an equation for the acid-catalyzed hydrolysis of ethyl acetate.
2. Write an equation for the base-catalyzed hydrolysis of ethyl acetate.
3. Complete each equation.



4. Complete each equation.



Answers



3. a. $\text{CH}_3\text{COONa(aq)} + \text{CH}_3\text{CH}_2\text{CH}_2\text{OH}$
b. $\text{CH}_3\text{CH}_2\text{CH}_2\text{COOH} + \text{CH}_3\text{CH}_2\text{OH}$

Attributions and citations

- Hydrolysis of Esters. (2020, August 17). Retrieved May 22, 2021, from <https://chem.libretexts.org/@go/page/16031>
- Wikipedia contributors. (2021, April 16). Saponification. In *Wikipedia, The Free Encyclopedia*. Retrieved 22:24, May 22, 2021, from <https://en.wikipedia.org/w/index.php?title=Saponification&oldid=1018155674>

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- Describe phosphate esters.
- Understand why phosphate esters are important in living cells.

$$\text{CH}_3\text{CH}_2\text{O}-\overset{\overset{\text{O}}{\parallel}}{\text{P}}-\text{OH}$$

Ethyl dihydrogen phosphate

$$\text{CH}_3\text{CH}_2\text{O}-\overset{\overset{\text{O}}{\parallel}}{\text{P}}-\text{OCH}_2\text{CH}_3$$

Diethyl hydrogen phosphate

$$\text{CH}_3\text{CH}_2\text{O}-\overset{\overset{\text{O}}{\parallel}}{\text{P}}-\text{OCH}_2\text{CH}_3$$

Triethyl phosphate

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{HO}-\text{P}-\text{OH} \\ | \\ \text{OH} \end{array}$$

Phosphoric acid

$$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{HO}-\text{P}-\text{O}-\text{P}-\text{OH} \\ | \quad \quad | \\ \text{OH} \quad \text{OH} \end{array}$$

Pyrophosphoric acid

$$\begin{array}{c} \text{O} \quad \text{O} \quad \text{O} \\ \parallel \quad \parallel \quad \parallel \\ \text{HO}-\text{P}-\text{O}-\text{P}-\text{O}-\text{P}-\text{OH} \\ | \quad \quad | \quad \quad | \\ \text{OH} \quad \text{OH} \quad \text{OH} \end{array}$$

Triphosphoric acid

$$\begin{array}{c} \text{CH}_2\text{OH} \\ | \\ \text{CHOH} \\ | \\ \text{CH}_2\text{OH} \end{array} + 3 \text{HONO}_2 \longrightarrow \begin{array}{c} \text{CH}_2\text{ONO}_2 \\ | \\ \text{CHONO}_2 \\ | \\ \text{CH}_2\text{ONO}_2 \end{array} + 3 \text{H}_2\text{O}$$

Glycerol

Glycerol trinitrate
(nitroglycerin)

phosphoric acids and alcohols

Summary

Inorganic acids such as H_3PO_4 form esters. The esters of phosphoric acid are especially important in biochemistry.

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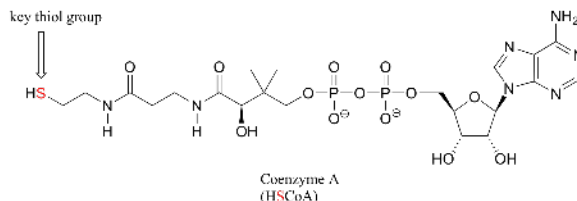
- **15.9: Esters of Phosphoric Acid** by Anonymous is licensed [CC BY-NC-SA 3.0](#). Original source: <https://2012books.lardbucket.org/books/introduction-to-chemistry-general-organic-and-biological>.

2.12: Thioesters- Biological Carboxylic Acid Derivatives

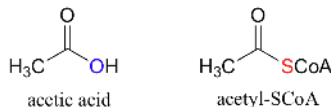
Introduction to thioesters and Coenzyme A

In the metabolism of lipids (fats and oils), thioesters are the principal form of activated carboxylate groups. They are employed as acyl carriers, assisting with the transfer of acyl groups such as fatty acids from one acyl X substrate to another.

The 'acyl X group' in a thioester is a thiol. The most important thiol compound used to make thioesters is called coenzyme A, which has the following structure:

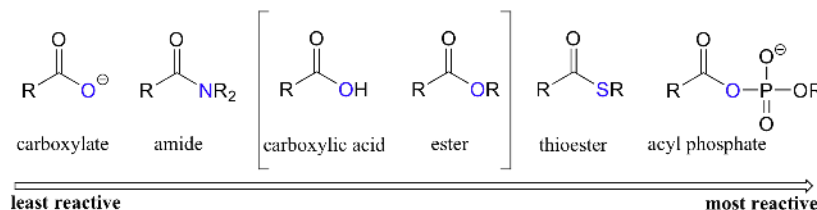


Coenzyme A is often abbreviated HSCoA, in order to emphasize that it is the thiol sulfur that provides the critical thioester linkage to acyl groups. When fuel (carbohydrate and fat) is broken down in your body, it is eventually converted to a simple two-carbon unit called acetyl CoA, which is essentially a thioester derivative of acetic acid:



Reactivity of carboxylic acids, esters thioesters and acyl phosphates

Thioesters are reactive among the biologically relevant acyl groups. However, thioesters are not as reactive as an acid chlorides or acid anhydrides. This property makes thioesters and acyl phosphates ideal reagents in biological systems, because they do not have the safety concerns related to using acid chlorides or acid anhydrides, which can only be used in the chemistry lab.



Relative reactivity of biologically relevant acyl groups

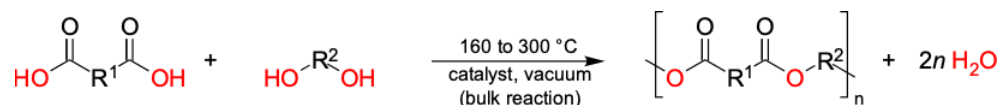
Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, [Athabasca University](#))
- Prof. Steven Farmer ([Sonoma State University](#))
- [Organic Chemistry With a Biological Emphasis](#) by Tim Soderberg (University of Minnesota, Morris)
- Thioesters: Biological Carboxylic Acid Derivatives. (2020, May 30). Retrieved May 22, 2021, from <https://chem.libretexts.org/@go/page/45956>

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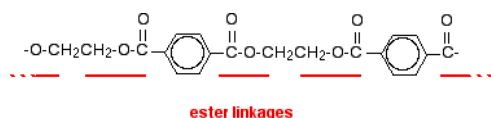
2.13: Polyesters

Polyester is a category of polymers that contain the ester functional group in every repeat unit of their main chain. The synthesis of polyesters is generally achieved by a polycondensation reaction. The general equation for the reaction of a diol with a diacid is:



General synthesis of a polyester via direct esterification. Image by [Minihaa](#), CC0, via Wikimedia Commons.

Example: poly(ethylene terephthalate) is a polyester obtained between [terephthalic acid](#) (benzene-1,4-dicarboxylic acid) and [ethylene glycol](#) (ethane-1,2-diol):



The everyday name depends on whether it is being used as a fiber or as a material for making things like bottles for soft drinks. When it is being used as a fiber to make clothes, it is often just called *polyester*. It may sometimes be known by a brand name like *Terylene*. When it is being used to make bottles, for example, it is usually called *PET*.

Making polyesters as an example of condensation polymerisation

In condensation polymerisation, when the monomers join together a small molecule gets lost. That's different from addition polymerisation which produces polymers like poly(ethene) - in that case, nothing is lost when the monomers join together. A polyester is made by a reaction involving an acid with two -COOH groups, and an alcohol with two -OH groups. In the common polyester drawn below.

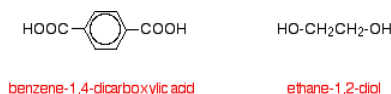
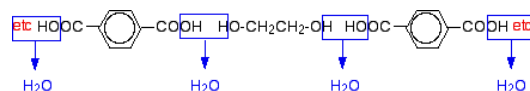
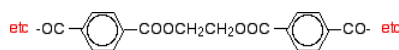


Figure: The acid is benzene-1,4-dicarboxylic acid (old name: terephthalic acid) and the alcohol is ethane-1,2-diol (old name: ethylene glycol).

Now imagine lining these up alternately and making esters with each acid group and each alcohol group, losing a molecule of water every time an ester linkage is made.

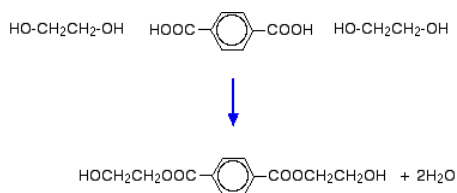


That would produce the chain shown above (although this time written without separating out the carbon-oxygen double bond - write it whichever way you like).

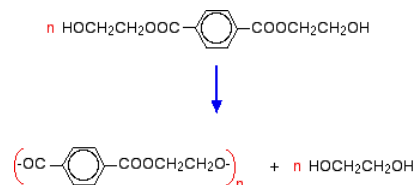


Manufacturing poly(ethylene terephthalate)

The reaction takes place in two main stages: a pre-polymerisation stage and the actual polymerisation. In the first stage, before polymerization happens, you get a fairly simple ester formed between the acid and two molecules of ethane-1,2-diol.

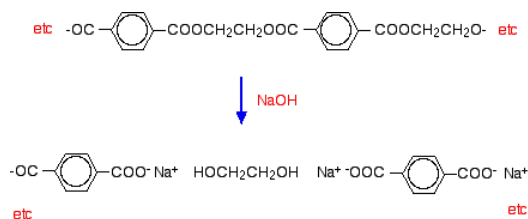


In the polymerisation stage, this is heated to a temperature of about 260°C and at a low pressure. A catalyst is needed - there are several possibilities including antimony compounds like antimony(III) oxide. The polyester forms and half of the ethane-1,2-diol is regenerated. This is removed and recycled.



Hydrolysis of polyesters

Simple esters are easily hydrolyzed by reaction with dilute acids or alkalis. Polyesters are attacked readily by alkalis, but much more slowly by dilute acids. Hydrolysis by water alone is so slow as to be completely unimportant. (You wouldn't expect your polyester fleece to fall to pieces if you went out in the rain!). If you spill dilute alkali on a fabric made from polyester, the ester linkages are broken. Ethane-1,2-diol is formed together with the salt of the carboxylic acid. Because you produce small molecules rather than the original polymer, the fibers are destroyed, and you end up with a hole! For example, if you react the polyester with sodium hydroxide solution:



Contributors

- Jim Clark (Chemguide.co.uk)

Attributions and Citations

- Polyesters. (2020, September 13). Retrieved May 22, 2021, from <https://chem.libretexts.org/@go/page/3912>
- Wikipedia contributors. (2021, May 20). Polyester. In *Wikipedia, The Free Encyclopedia*. Retrieved 22:49, May 22, 2021, from <https://en.wikipedia.org/w/index.php?title=Polyester&oldid=1024229738>

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CHAPTER OVERVIEW

3: Amines and Amides

3.1: Amines - Structures and Names

3.2: Nomenclature of Amines

3.3: Nitrogen-containing compounds in Nature

3.4: Physical Properties of Amides

3.5: Chemical Properties of Amines. Bases and Salt Formation.

3.6: Amines as Neurotransmitters

3.7: Amides- Structures and Names

3.8: Neutrality of Amides

3.9: Chemistry of Amides- Synthesis and Reactions

3.10: Polyamides

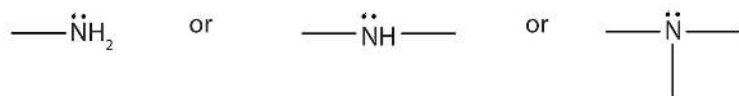
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3.1: Amines - Structures and Names

Learning Objectives

- Identify the general structure for an amine.
- Identify the functional group for amines.
- Determine the structural feature that classifies amines as primary, secondary, or tertiary.
- Use nomenclature systems to name amines.

An amine is a derivative of ammonia in which one, two, or all three hydrogen atoms are replaced by hydrocarbon groups.



Amines are classified according to the number of carbon atoms bonded directly to the nitrogen atom. A primary (1°) amine has one alkyl (or aryl) group on the nitrogen atom, a secondary (2°) amine has two, and a tertiary (3°) amine has three (Figure 3.1.1).

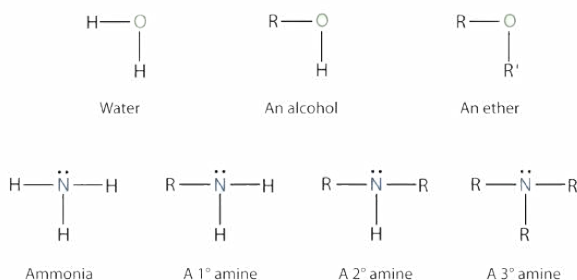
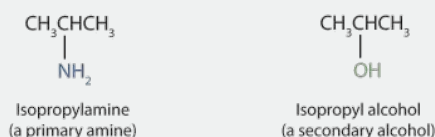


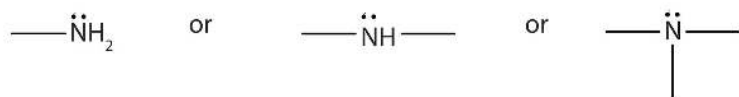
Figure 3.1.1: The Structure of Amines Compared to Water, an Alcohol, and an Ether

IMPORTANT: To classify alcohols, we look at the number of carbon atoms bonded to the *carbon atom* bearing the OH group, not the oxygen atom itself. Thus, although isopropylamine looks similar to isopropyl alcohol, the former is a *primary* amine, while the latter is a *secondary* alcohol.



Summary

An amine is a derivative of ammonia in which one, two, or all three hydrogen atoms are replaced by hydrocarbon groups. The amine functional group is as follows:



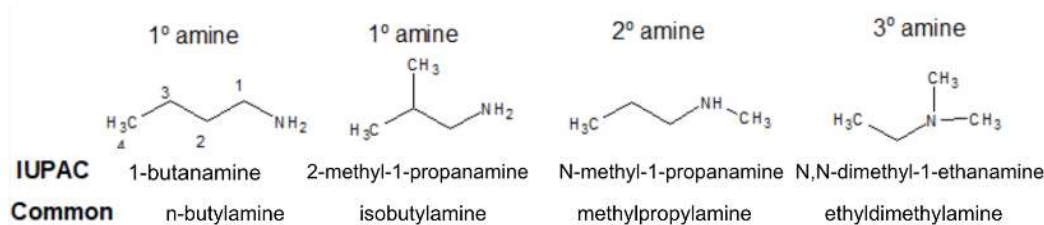
Amines are classified as primary, secondary, or tertiary by the number of hydrocarbon groups attached to the nitrogen atom.

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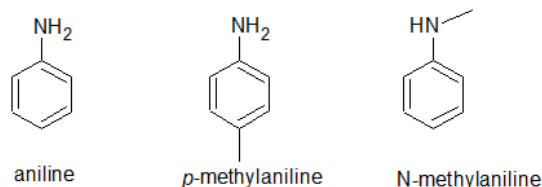
3.2: Nomenclature of Amines

Amines are derivatives of ammonia in which one or more of the hydrogens has been replaced by an alkyl or aryl group. The nomenclature of amines is complicated by the fact that several different nomenclature systems exist, and there is no clear preference for one over the others.

- The **IUPAC system** has adopted a nomenclature system in which the suffix **-amine** is attached to the root alkyl name. For 1° amines such as butanamine (first example) this is analogous to IUPAC alcohol nomenclature (-ol suffix). For 2° and 3° amines, we need to identify the longest carbon chain attached to the nitrogen atom, and that chain becomes the parent alkyl name. The other alkyl groups are designated by the prefix **N-** before the alkyl group name.
- In the **common nomenclature system** for simple amines, you must name each alkyl substituent on nitrogen in alphabetical order, followed by the suffix **-amine**. These are the names given in the last row



Aromatic amines are named as derivatives of aniline.



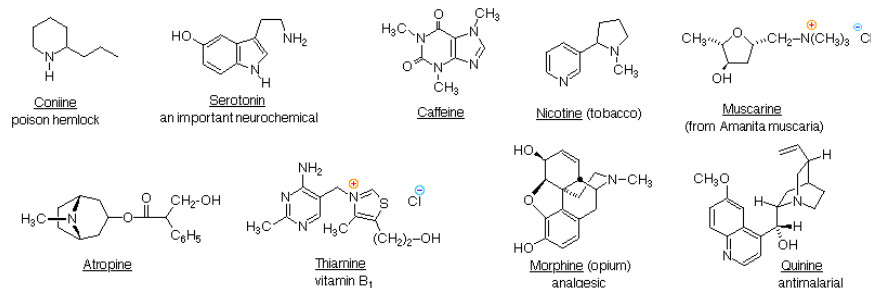
References

- William Reusch. Virtual Textbook of Organic Chemistry.

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3.3: Nitrogen-containing compounds in Nature

Nature abounds with nitrogen compounds, many of which occur in plants and are referred to as **alkaloids**. Structural formulas for some representative alkaloids and other nitrogen containing natural products are displayed below, and we can recognize many of the basic structural features listed above in their formulas. Thus, Serotonin and Thiamine are 1°-amines, Coniine is a 2°-amine, Atropine, Morphine and Quinine are 3°-amines, and Muscarine is a 4°-ammonium salt.



Nitrogen atoms that are part of aromatic rings, such as pyridine, pyrrole & imidazole, have planar configurations (sp^2 hybridization), and are not stereogenic centers. Nitrogen atoms bonded to carbonyl groups, as in caffeine, also tend to be planar. In contrast, atropine, coniine, morphine, nicotine and quinine have pyramidal nitrogen atoms in their structural formulas (think of the non-bonding electron pair as a fourth substituent on a sp^3 hybridized nitrogen). Of course, quaternary ammonium salts, such as that in muscarine, have a tetrahedral configuration. With four different substituents, such a nitrogen would be a stable stereogenic center.

Contributors

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

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3.4: Physical Properties of Amides

Learning Objectives

- Compare the boiling points of amides with alcohols of similar molar mass.
- Compare the solubilities in water of amides of five or fewer carbon atoms with the solubilities of comparable alkanes and alcohols in water.

With the exception of formamide (HCONH_2), which is a liquid, all simple amides are solids (Table 3.4.1). Primary and secondary amides can have hydrogen bonding, and therefore have high boiling points and melting points. Tertiary amides cannot hydrogen bond, so their boiling points are lower than those of similar size amides. Primary, secondary, and tertiary amines can hydrogen-bond with water, so the lower members of the series are soluble in water, with borderline solubility occurring in those that have five or six carbon atoms. Like the esters, solutions of amides in water usually are neutral—neither acidic nor basic.

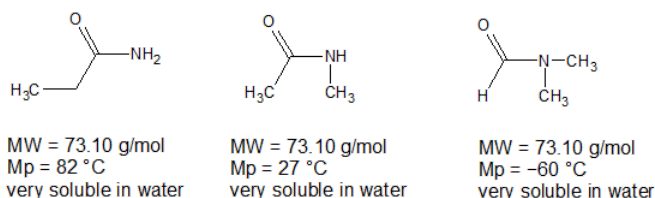


Table 3.4.1: Physical Constants of Some Unsubstituted Amides

Condensed Structural Formula	Name	Melting Point (°C)	Boiling Point (°C)	Solubility in Water
HCONH_2	formamide	2	193	soluble
CH_3CONH_2	acetamide	82	222	soluble
$\text{CH}_3\text{CH}_2\text{CONH}_2$	propionamide	81	213	soluble
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CONH}_2$	butyramide	115	216	soluble
$\text{C}_6\text{H}_5\text{CONH}_2$	benzamide	132	290	slightly soluble

The amides generally have high boiling points and melting points. These characteristics and their solubility in water result from the polar nature of the amide group and hydrogen bonding (Figure 3.4.1). (Similar hydrogen bonding plays a critical role in determining the structure and properties of proteins, deoxyribonucleic acid [DNA], ribonucleic acid [RNA], and other giant molecules so important to life processes.

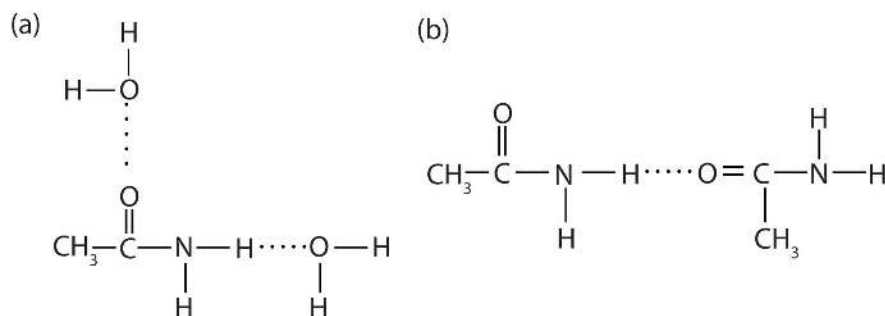


Figure 3.4.1: Hydrogen Bonding in Amides. Amide molecules can engage in hydrogen bonding with water molecules (a). Those amides with a hydrogen atom on the nitrogen atom can also engage in hydrogen bonding (b). Both hydrogen bonding networks extend in all directions.

Primary and secondary amides can have hydrogen bonding, and therefore have high boiling points and melting points. Tertiary amides cannot hydrogen bond, so their boiling points are lower than those of similar size amides

Concept Review Exercises

1. Which compound has the higher boiling point—pentanamide ($\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CONH}_2$) or propyl acetate ($\text{CH}_3\text{COOCH}_2\text{CH}_2\text{CH}_3$)? Explain.
2. Which compound is more soluble in water—propanamide ($\text{CH}_3\text{CH}_2\text{CONH}_2$) or 1-pentene ($\text{CH}_2=\text{CHCH}_2\text{CH}_2\text{CH}_3$)? Explain.

Answers

1. pentanamide because the nitrogen-to-hydrogen (N–H) and the carbon-to-oxygen double (C=O) bonds can engage in hydrogen bonding; propyl acetate cannot engage in hydrogen bonding
2. propanamide because the N–H and C=O bonds can engage in hydrogen bonding with water; 1-pentene cannot engage in hydrogen bonding with water

Key Takeaways

- Most amides are solids at room temperature; the boiling points of amides are much higher than those of alcohols of similar molar mass.
- Amides of five or fewer carbon atoms are soluble in water?.

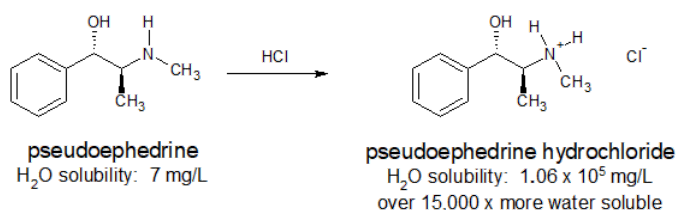
Exercises

1. Which compound has the higher boiling point—butyramide ($\text{CH}_3\text{CH}_2\text{CH}_2\text{CONH}_2$) or ethyl acetate ($\text{CH}_3\text{COOCH}_2\text{CH}_3$)? Explain.
2. Which compound has the higher boiling point—butyramide or dimethylacetamide [$\text{CH}_3\text{CON}(\text{CH}_3)_2$]? Explain.
3. Which compound is more soluble in water—acetamide (CH_3CONH_2) or 1-butene ($\text{CH}_2=\text{CHCH}_2\text{CH}_3$)? Explain.
4. Which compound is more soluble in water— $\text{CH}_3\text{CONHCH}_3$ or 2-methylbutane [$\text{CH}_3\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$]? Explain.

Answers

1. butyramide because the nitrogen-to-hydrogen (N–H) and the carbon-to-oxygen double (C=O) bonds can engage in hydrogen bonding; ethyl acetate cannot engage in hydrogen bonding
3. acetamide because the N–H and C=O bonds can engage in hydrogen bonding with water; 1-butene cannot engage in hydrogen bonding with water

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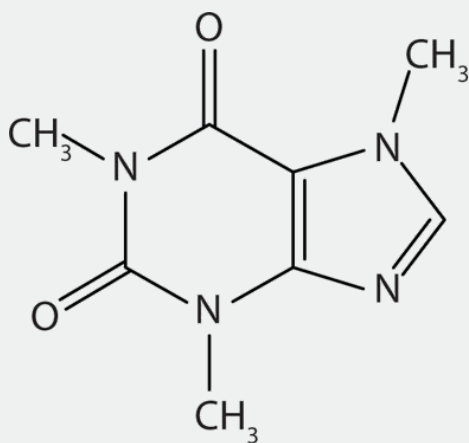
Heterocyclic Amines

Looking back at the various cyclic hydrocarbons discussed previously, we see that all the atoms in the rings of these compounds are carbon atoms. In other cyclic compounds, called **heterocyclic compounds** (Greek *heteros*, meaning “other”), nitrogen, oxygen, sulfur, or some other atom is incorporated in the ring. Many heterocyclic compounds are important in medicine and biochemistry. Some compose part of the structure of the nucleic acids, which in turn compose the genetic material of cells and direct protein synthesis.

Many heterocyclic amines occur naturally in plants. Like other amines, these compounds are basic. Such a compound is an **alkaloid**, a name that means “like alkalis.” Many alkaloids are physiologically active, including the familiar drugs caffeine, nicotine, and cocaine.

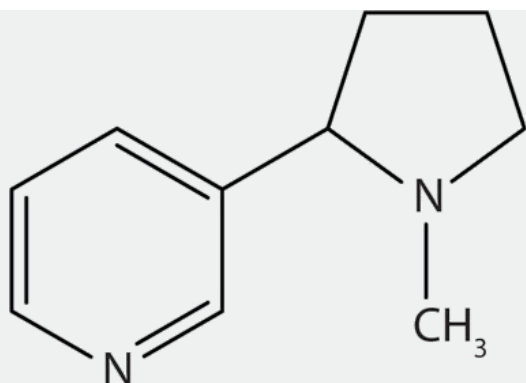
To Your Health: Three Well-Known Alkaloids

Caffeine is a stimulant found in coffee, tea, and some soft drinks. Its mechanism of action is not well understood, but it is thought to block the activity of adenosine, a heterocyclic base that acts as a neurotransmitter, a substance that carries messages across a tiny gap (synapse) from one nerve cell (neuron) to another cell. The effective dose of caffeine is about 200 mg, corresponding to about two cups of strong coffee or tea.



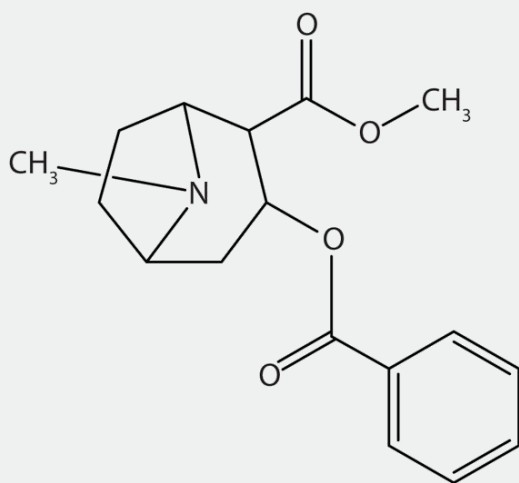
Caffeine

Nicotine acts as a stimulant by a different mechanism; it probably mimics the action of the neurotransmitter acetylcholine. People ingest this drug by smoking or chewing tobacco. Its stimulant effect seems transient, as this initial response is followed by depression. Nicotine is highly toxic to animals. It is especially deadly when injected; the lethal dose for a human is estimated to be about 50 mg. Nicotine has also been used in agriculture as a contact insecticide.



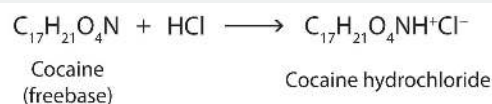
Nicotine

Cocaine acts as a stimulant by preventing nerve cells from taking up dopamine, another neurotransmitter, from the synapse. High levels of dopamine are therefore available to stimulate the pleasure centers of the brain. The enhancement of dopamine action is thought to be responsible for cocaine's "high" and its addictive properties. After the binge, dopamine is depleted in less than an hour. This leaves the user in a pleasureless state and (often) craving more cocaine.



Cocaine

Cocaine is used as the salt cocaine hydrochloride and in the form of broken lumps of the free (unneutralized) base, which is called *crack cocaine*.



Because it is soluble in water, cocaine hydrochloride is readily absorbed through the watery mucous membranes of the nose when it is snorted. Crack cocaine is more volatile than cocaine hydrochloride. It vaporizes at the temperature of a burning cigarette. When smoked, cocaine reaches the brain in 15 s.

Summary

Amines are bases; they react with acids to form salts. Salts of aniline are properly named as *ammonium* compounds. Heterocyclic amines are cyclic compounds with one or more nitrogen atoms in the ring.

Concept Review Exercises

1. Explain the basicity of amines.
2. Contrast the physical properties of amines with those of alcohols and alkanes.
3. What is a cyclic amine?

Answers

1. Amines have a lone pair of electrons on the nitrogen atom and can thus act as proton acceptors (bases).
2. The solubilities of amines are similar to those of alcohols; the boiling points of primary and secondary amines are similar to those of alcohols; the boiling points of tertiary amines, which cannot engage in hydrogen bonding because they do not have a hydrogen atom on the nitrogen atom, are comparable to those of alkanes.
3. Cyclic amines are ring compounds with nitrogen atoms in the ring.

Exercises

1. What salt is formed in each reaction? Write its condensed structural formula and its name.
 - a. $\text{CH}_3\text{NH}_2(\text{aq}) + \text{HBr}(\text{aq}) \rightarrow$
 - b. $\text{CH}_3\text{NHCH}_3(\text{aq}) + \text{HNO}_3(\text{aq}) \rightarrow$
2. What salt is formed in each reaction? Draw its structure.



a.



b.

Answer

1. a. $\text{CH}_3\text{NH}_3^+\text{Br}^-(\text{aq})$ methylammonium bromide
 b. $[\text{CH}_3\text{NH}_2\text{CH}_3]^+\text{NO}_3^-(\text{aq})$ dimethylammonium nitrate

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3.6: Amines as Neurotransmitters

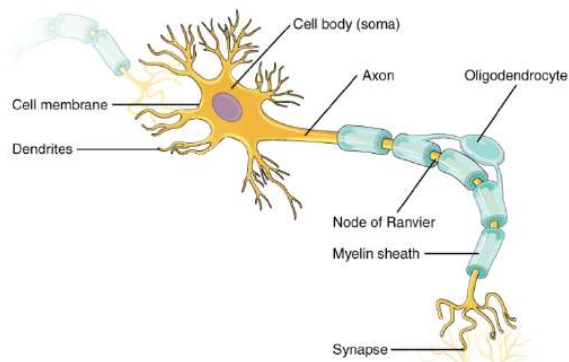
Learning Objectives

- Describe how neurotransmitters work.

Amines have powerful biological functions. Many amines act as neurotransmitter and psychoactive drugs. These molecules generally produce their effects by affecting brain chemistry, which in turn may cause changes in a person's mood, thinking, perception, and/or behavior. Each molecule tends to have a specific action on one or more neurotransmitters or neurotransmitter receptors in the brain. Generally, they act as either agonists or antagonists.

- Agonists** are drugs that increase the activity of particular neurotransmitters. They might act by promoting the synthesis of the neurotransmitters, reducing their reuptake from synapses, or mimicking their action by binding to receptors for the neurotransmitters.
- Antagonists** are drugs that decrease the activity of particular neurotransmitters. They might act by interfering with the synthesis of the neurotransmitters or by blocking their receptors so the neurotransmitters cannot bind to them.

Chemistry of the Nervous System



The brain and the rest of the nervous system are composed of many different types of cells, but the primary functional unit is a cell called the neuron (nerve cell). All sensations, movements, thoughts, memories, and feelings are the result of signals that pass through neurons. Neurons consist of three parts (Figure

3.6.2). The cell body

contains the nucleus, where most of the molecules that the neuron needs to survive and function are manufactured.

Dendrites

extend out from the cell body like the branches of a tree and receive messages from other nerve cells. Signals then pass from the dendrites through the cell body and may travel away from the cell body down an

axon

to another neuron, a muscle cell, or cells in some other organ.

Figure 3.6.2 Parts of a neuron.

Scientists have learned a great deal about neurons by studying the synapse—the place where a signal passes from the neuron to another cell. When the signal reaches the end of the axon it stimulates the release of tiny **sacs**. These sacs release chemicals called neurotransmitters into the **synapse** (Figure 3.6.3). The neurotransmitters cross the synapse and attach to **receptors** on the neighboring cell. These receptors can change the properties of the receiving cell. If the receiving cell is also a neuron, the signal can continue the transmission to the next cell.

Neurotransmitters

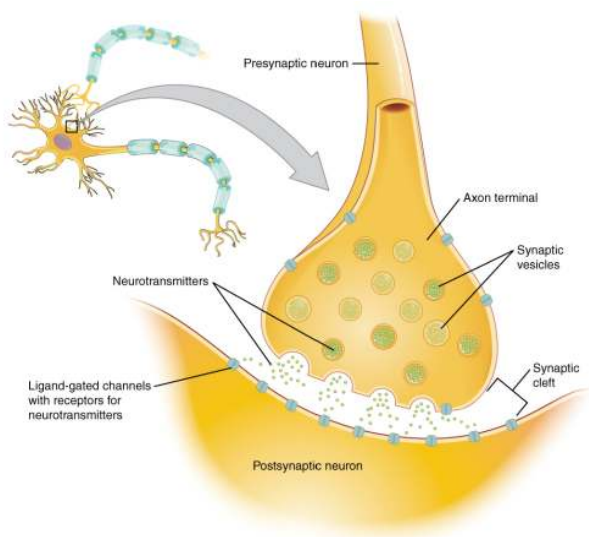
Neurotransmitters are that enable . It is a type of chemical messenger which transmits signals across a , such as a , from one (nerve cell) to another "target" neuron.

Figure 3.6.3 *The synapse.* The synapse is a connection between a neuron and its target cell (which is not necessarily a neuron).

Biochemical Theories of Brain Diseases

The only direct action of a neurotransmitter is to activate a receptor. Therefore, the effects of a neurotransmitter system depend on the connections of the neurons that use the transmitter, and the chemical properties of the receptors that the transmitter binds to. An understanding of the functions of neurotransmitters (Table 3.6.1) gives us a better idea of how an imbalance of these substances could contribute to certain brain disorders.

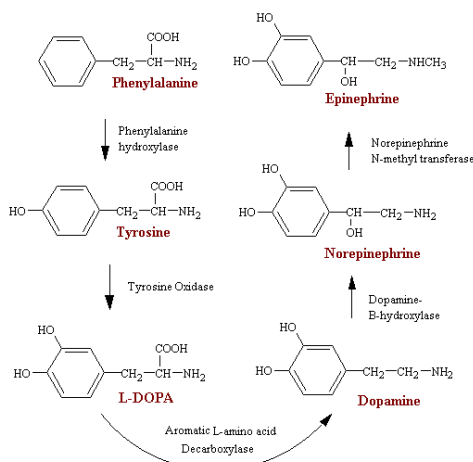
Strong imbalances or disruptions to neurotransmitter systems have been associated with many diseases and mental disorders. These include Parkinson's, depression, insomnia, Attention Deficit Hyperactivity Disorder (ADHD), anxiety, memory loss, dramatic changes in weight and addictions. Chronic physical or emotional stress can be a contributor to neurotransmitter system changes. Genetics also plays a role in neurotransmitter activities. Apart from recreational use, medications that directly and indirectly interact one or more transmitter or its receptor are commonly prescribed for psychiatric and psychological issues. Notably, drugs interacting with and are prescribed to patients with problems such as depression and anxiety—though the notion that there is much solid medical evidence to support such interventions has been widely criticized.



Monoamine Neurotransmitters: Serotonin, Dopamine, Epinephrine, and Norepinephrine

Monoamine neurotransmitters are and that contain one group connected to an ring by a two-carbon chain (such as $-\text{CH}_2-\text{CH}_2-$). Examples are , , norepinephrine and .

All monoamines are derived from aromatic like , , and by the action of . They are deactivated in the body by the enzymes known as which clip off the amine group.



astrocytes, a chemical which maintains neuron integrity and provides neurons with trophic support.

Figures 3.6.4 and 3.6.5.

On top an L-tryptophan molecule with an arrow down to a 5-HTP molecule. Tryptophan hydroxylase catalyses this reaction with help of O₂ and tetrahydrobiopterin, which becomes water and dihydrobiopterin. From the 5-HTP molecule goes an arrow down to a serotonin molecule. Aromatic L-amino acid decarboxylase or 5-Hydroxytryptophan decarboxylase catalyses this reaction with help of pyridoxal phosphate. From the serotonin molecule goes an arrow to a 5-HIAA molecule at the bottom of the image. Monoamine oxidase catalyses this reaction, in the process O₂ and water is consumed, and ammonia and hydrogen peroxide is produced.

Figure 3.6.4 The biosynthesis of dopamine, epinephrine, and norepinephrine.

Figure 3.6.5 The biosynthesis of serotonin.

Barbiturates

Barbiturates are CNS depressants and are similar, in many ways, to the depressant effects of alcohol. To date, there are about 2,500 derivatives of barbituric acid of which only 15 are used medically. The first barbiturate was synthesized from barbituric acid in 1864.

The original use of barbiturates was to replace drugs such as opiates, bromides, and alcohol to induce sleep. Barbiturates are effective as , , and , but have physical and psychological potential as well as potential among other possible adverse effects. They have largely been replaced by (discussed below) and ("Z-drugs") in routine medical practice, particularly in the treatment of anxiety and insomnia, due to the significantly lower risk of addiction and the lack of an for barbiturate overdose. Despite this, barbiturates are still in use for various purposes: in , , treatment of acute or , , and .

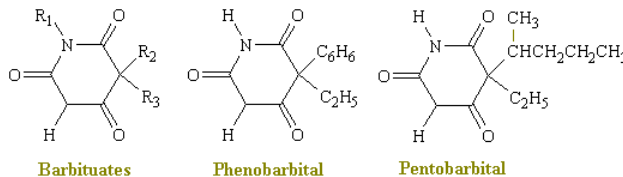


Figure 3.6.9 Barbiturates.

Some symptoms of an overdose typically include sluggishness, incoordination, difficulty in thinking, slowness of speech, faulty judgement, drowsiness, shallow breathing, staggering, and, in severe cases, coma or death. The lethal dosage of barbiturates varies greatly with tolerance and from one individual to another.

Barbiturates in overdose with other CNS (central nervous system) depressants (e.g. alcohol, opiates, benzodiazepines) are even more dangerous due to additive CNS and respiratory depressant effects. In the case of benzodiazepines, not only do they have additive effects, barbiturates also increase the binding affinity of the benzodiazepine binding site, leading to exaggerated benzodiazepine effects. (ex. If a benzodiazepine increases the frequency of channel opening by 300%, and a barbiturate increases the duration of their opening by 300%, then the combined effects of the drugs increase the channels overall function by 900%, not 600%).

Anti-anxiety Agents

Anti-anxiety medications help reduce the symptoms of anxiety, such as panic attacks, or extreme fear and worry.

The most common anti-anxiety medications are called benzodiazepines. **Benzodiazepines** can treat generalized anxiety disorder. In the case of panic disorder or social phobia (social anxiety disorder), benzodiazepines are usually second-line treatments, behind SSRIs or other antidepressants. Benzodiazepines used to treat anxiety disorders include, clonazepam (Klonopin), alprazolam (Niravam), and lorazepam (Ativan and Lorazepam Intensol).

Short half-life (or short-acting) benzodiazepines (such as Lorazepam) and beta-blockers are used to treat the short-term symptoms of anxiety. Beta-blockers help manage physical symptoms of anxiety, such as trembling, rapid heartbeat, and sweating that people with phobias (an overwhelming and unreasonable fear of an object or situation, such as public speaking) experience in difficult

situations. Taking these medications for a short period of time can help the person keep physical symptoms under control and can be used “as needed” to reduce acute anxiety.

Antipsychotic medicines are primarily used to manage psychosis. The word “psychosis” is used to describe conditions that affect the mind, and in which there has been some loss of contact with reality, often including delusions (false, fixed beliefs) or hallucinations (hearing or seeing things that are not really there). It can be a symptom of a physical condition such as drug abuse or a mental disorder such as schizophrenia, bipolar disorder, or very severe depression (also known as “psychotic depression”).

Antipsychotic medications are often used in combination with other medications to treat delirium, dementia, and mental health conditions, including:

- Attention-Deficit Hyperactivity Disorder (ADHD)
- Severe Depression
- Eating Disorders
- Post-traumatic Stress Disorder (PTSD)
- Obsessive Compulsive Disorder (OCD)
- Generalized Anxiety Disorder

Antipsychotic medicines do not cure these conditions. They are used to help relieve symptoms and improve quality of life.

Older or first-generation antipsychotic medications are also called conventional “typical” antipsychotics or “neuroleptics”. Some of the common typical antipsychotics include, chlorpromazine (Promapar and Thorazine), haloperidol (Haldol), perphenazine (Trilafon), and fluphenazine (Permitil and Prolixin). **Chlorpromazine** was discovered in 1950 and was the first antipsychotic. It is on the , the most effective and safe medicines needed in a . Its introduction has been labeled as one of the great advances in the .

Chlorpromazine (CPZ), is marketed under the **Thorazine** and **Largactil**. It is primarily used to treat such as . Other uses include the treatment of , , and , anxiety before surgery, and that do not improve following other measures. It can be given by mouth, by , or . Common side effects include , , dry mouth, , and increased weight. Serious side effects may include the potentially permanent movement disorder , , and . In older people with psychosis as a result of it may increase the risk of death. It is unclear if it is safe for use in . Chlorpromazine is in the class. Its mechanism of action is not entirely clear but believed to be related to its ability as a .

Newer or second generation medications are called “**atypical**” **antipsychotics**. The atypical antipsychotics (AAP; also known as second generation antipsychotics (SGAs)) are a group of drugs (antipsychotic drugs in general are also known as major and neuroleptics, although the latter is usually reserved for the) largely introduced after the 1970s and used to treat psychiatric conditions. Some atypical antipsychotics have received regulatory approval (e.g. by the of the , the of , the of the) for , , , and as an in . Some of the common atypical antipsychotics include risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel), ziprasidone (Geodon), aripiprazole (Abilify), paliperidone (Invega), and lurasidone (Latuda). The atypical antipsychotics have found favor among clinicians and are now considered to be for schizophrenia and are gradually replacing the .

According to a 2013 research review by the Agency for Healthcare Research and Quality, typical and atypical antipsychotics both work to treat symptoms of schizophrenia and the manic phase of bipolar disorder. Several atypical antipsychotics have a “broader spectrum” of action than the older medications, and are used for treating bipolar depression or depression that has not responded to an antidepressant medication alone.

Older antidepressant medications include tricyclics, tetracyclics, and monoamine oxidase inhibitors (MAOIs). All tricyclic antidepressants in current use in the U.S. potentiate the actions of biogenic amines in the CNS by blocking its re-uptake at nerve terminals. However, the potency and selectivity for the inhibition of the uptake of norepinephrine, serotonin, and dopamine vary greatly among the agents. For some people, tricyclics, tetracyclics, or MAOIs may be the best medications.

The most popular types of antidepressants are called **selective serotonin reuptake inhibitors (SSRIs)** see examples on Figure 3.6.10 . Examples of SSRIs include fluoxetine (Prozac), citalopram (Celexa), sertraline (Zoloft), paroxetine (Brisdelle, Paxil, Pexeva), and escitalopram (Lexapro). Prozac is the most famous drug in this class. In 2016 it was the 29th most prescribed medication in the United States with more than 23 million prescriptions. Clomipramine, fluoxetine (Prozac), sertraline and paroxetine selectively block the reuptake of serotonin, thereby increasing the levels of serotonin in the central nervous system. Some of the newer, SSRIs (e.g., clomipramine) have been useful in the treatment of obsessive-compulsive disorders.

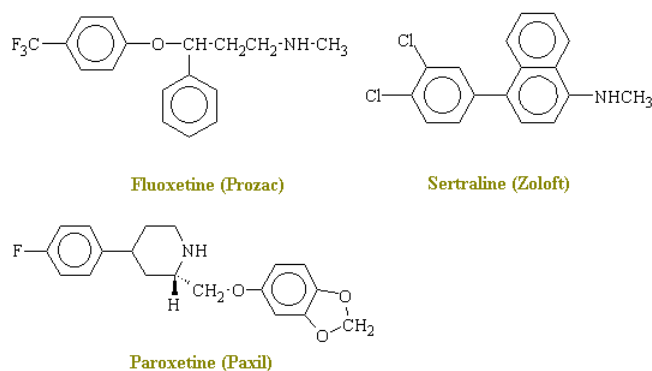


Figure 3.6.10 Examples of SSRIs.

Other types of antidepressants are **serotonin and norepinephrine reuptake inhibitors (SNRIs)**. SNRIs are similar to SSRIs and include venlafaxine (Effexor) and duloxetine (Cymbalta).

Another antidepressant that is commonly used is **bupropion** (Aplenzin, Wellbutrin, Wellbutrin SR, Wellbutrin XL). Bupropion is a third type of antidepressant which works differently than either SSRIs or SNRIs. Bupropion is also used to treat seasonal affective disorder and to help people stop smoking.

SSRIs, SNRIs, and bupropion are popular because they do not cause as many side effects as older classes of antidepressants, and seem to help a broader group of depressive and anxiety disorders.

Cocaine, Caffeine, and Nicotine

Cocaine, also known as **coke**, is a strong most frequently used as a . It is commonly , inhaled as smoke, or dissolved and injected into a . Mental effects may include , an , or . Physical symptoms may include a , sweating, and . High doses can result in very or . Effects begin within seconds to minutes of use and last between five and ninety minutes. Cocaine has a small number of accepted medical uses such as and decreasing bleeding during nasal surgery.

Cocaine is due to its effect on the in the brain. After a short period of use, there is a high risk that will occur. Its use also increases the risk of , , lung problems in those who smoke it, , and . Cocaine sold on the street is commonly mixed with , cornstarch, , or sugar, which can result in additional toxicity. Following repeated doses a person may have and be very physically tired. Cocaine acts by

Caffeine is a (CNS) of the . Caffeine is a stimulant compound belonging to the class of chemicals naturally found in , , and (to a lesser degree) or . It is included in many , as well as a larger amount in . Caffeine is the world's most widely used psychoactive drug and by far the most common stimulant. In North America, 90% of adults consume caffeine daily. A few jurisdictions restrict its sale and use. Caffeine is also included in some medications, usually for the purpose of enhancing the effect of the primary ingredient, or reducing one of its side-effects (especially drowsiness). Tablets containing standardized doses of caffeine are also widely available.

Caffeine's mechanism of action differs from many stimulants, as it produces stimulant effects by inhibiting adenosine receptors. Adenosine receptors are thought to be a large driver of drowsiness and sleep, and their action increases with extended wakefulness. Caffeine (in coffee), theophylline (in tea) and theobromine (in chocolate) share in common several pharmacological actions of therapeutic interest. They stimulate the central nervous system, act on the kidney to produce diuresis, stimulate cardiac muscle, and relax smooth muscle, notably bronchial muscle. From the figure below, we can see that the methylxanthines have a structure which is very similar to adenine (the amino group in adenosine).

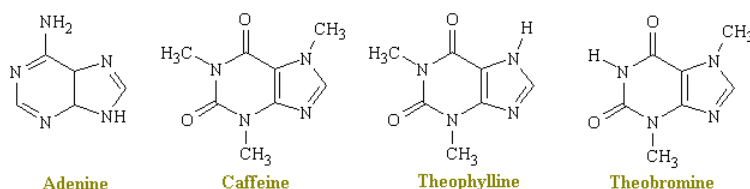


Figure 3.6.11 Adenine and other molecules with similar structures.

is the active chemical constituent in , which is available in many forms, including , , and aids such as , , and . Nicotine is used widely throughout the world for its stimulating and relaxing effects. Nicotine exerts its effects through the agonism of , resulting in multiple downstream effects such as increase in activity of dopaminergic neurons in the midbrain , as well as the decreased expression of in the brain. Nicotine is addictive and dependence forming.

Hallucinogens and Dissociative Drugs



feeling sensations that seem real but are not. While the exact mechanisms by which hallucinogens and dissociative drugs cause their effects are not yet clearly understood, research suggests that they work at least partially by temporarily disrupting communication between neurotransmitter systems throughout the brain and spinal cord that regulate mood, sensory perception, sleep, hunger, body temperature, sexual behavior, and muscle control.

Figure 3.6.12 Psilocybin mushrooms, LSD, and Salvia divinorum

are commonly used hallucinogenic and dissociative compounds.

Classic Hallucinogens

LSD (d-lysergic acid diethylamide)—also known as acid, blotter, doses, hits, microdots, sugar cubes, trips, tabs, or window panes—is one of the most potent mood and perception-altering hallucinogenic drugs. It is a clear or white, odorless, water-soluble material synthesized from lysergic acid, a compound derived from a rye fungus. LSD is initially produced in crystalline form, which can then be used to produce tablets known as “microdots” or thin squares of gelatin called “window panes.” It can also be diluted with water or alcohol and sold in liquid form. The most common form, however, is LSD-soaked paper punched into small individual squares, known as “blotters.”

Psilocybin (4-phosphoryloxyN, N-dimethyltryptamine)—also known as magic mushrooms, shrooms, boomers, or little smoke—is extracted from certain types of mushrooms found in tropical and subtropical regions of South America, Mexico, and the United States. In the past, psilocybin was ingested during religious ceremonies by indigenous cultures from Mexico and Central America. Psilocybin can either be dried or fresh and eaten raw, mixed with food, or brewed into a tea, and produces similar effects to LSD.

Peyote (Mescaline)—also known as buttons, cactus, and mesc—is a small, spineless cactus with mescaline as its main ingredient. It has been used by natives in northern Mexico and the southwestern United States as a part of religious ceremonies. The top, or “crown,” of the peyote cactus has disc-shaped buttons that are cut out, dried, and usually chewed or soaked in water to produce an intoxicating liquid. Because the extract is so bitter, some users prepare a tea by boiling the plant for several hours. Mescaline can also be produced through chemical synthesis.

DMT (Dimethyltryptamine)—also known as Dimitri—is a powerful hallucinogenic chemical found naturally occurring in some Amazonian plant species (see “Ayahuasca”) and also synthesized in the laboratory. Synthetic DMT usually takes the form of a white crystalline powder and is typically vaporized or smoked in a pipe. Ayahuasca—also known as hoasca, aya, and yagé—is a hallucinogenic brew made from one of several Amazonian plants containing DMT (the primary psychoactive ingredient) along with a vine containing a natural alkaloid that prevents the normal breakdown of DMT in the digestive tract. Ayahuasca tea has traditionally been used for healing and religious purposes in indigenous South American cultures, mainly in the Amazon region.

Dissociative Drugs

PCP (Phencyclidine)—also known as ozone, rocket fuel, love boat, hog, embalming fluid, or superweed—was originally developed in the 1950s as a general anesthetic for surgery. While it can be found in a variety of forms, including tablets or capsules, it is usually sold as a liquid or powder. PCP can be snorted, smoked, injected, or swallowed. It is sometimes smoked after being sprinkled on marijuana, tobacco, or parsley.

Ketamine—also known as K, Special K, or cat Valium—is a dissociative currently used as an anesthetic for humans as well as animals. Much of the ketamine sold on the street has been diverted from veterinary offices. Although it is manufactured as an injectable liquid, ketamine is generally evaporated to form a powder that is snorted or compressed into pills for illicit use. Because ketamine is odorless and tasteless and has amnesia-inducing properties, it is sometimes added to drinks to facilitate sexual assault. 2 NIDA Research Report Series Common Hallucinogens and Dissociative Drugs *In this report, the term “hallucinogen” will refer to the classic hallucinogenic drugs LSD and Psilocybin.

DXM (Dextromethorphan)—also known as robo—is a cough suppressant and expectorant ingredient in some over-the-counter (OTC) cold and cough medications that are often abused by adolescents and young adults. The most common sources of abused DXM are “extra-strength” cough syrup, which typically contains around 15 milligrams of DXM per teaspoon, and pills and gel capsules, which typically contain 15 milligrams of DXM per pill. OTC medications that contain DXM often also contain antihistamines and decongestants.

Salvia divinorum—also known as diviner’s sage, Maria Pastora, Sally-D, or magic mint—is a psychoactive plant common to southern Mexico and Central and South America. Salvia is typically ingested by chewing fresh leaves or by drinking their extracted juices. The dried leaves of salvia can also be smoked or vaporized and inhaled.

Short-Term General Effects of Hallucinogens Sensory Effects

- Hallucinations, including seeing, hearing, touching, or smelling things in a distorted way or perceiving things that do not exist
- Intensified feelings and sensory experiences (brighter colors, sharper sounds)
- Mixed senses (“seeing” sounds or “hearing” colors)
- Changes in sense or perception of time (time goes by slowly) Physical Effects
- Increased energy and heart rate
- Nausea

Summary

- Neurotransmitters are that enable . It is a type of chemical messenger which transmits signals across a , such as a , from one (nerve cell) to another “target” neuron, , or .
- Strong imbalances or disruptions to neurotransmitter systems have been associated with many diseases and mental disorders.
- Psychoactive drugs are substances that change the function of the brain and result in alterations of mood, thinking, perception, and/or behavior. They include prescription medications such as opioid painkillers, legal substances such as nicotine and alcohol, and illegal drugs such as LSD and heroin.
- Psychoactive drugs are divided into different classes according to their pharmacological effects. They include stimulants, depressants, anxiolytics, euphorants, hallucinogens, and empathogens. Many psychoactive drugs have multiple effects so they may be placed in more than one class.
- Psychoactive drugs generally produce their effects by affecting brain chemistry. Generally, they act either as agonists, which enhance the activity of particular neurotransmitters; or as antagonists, which decrease the activity of particular neurotransmitters.
- Psychoactive drugs are used for various purposes, including medical, ritual, and recreational purposes.
- Misuse of psychoactive drugs may lead to addiction, which is compulsive use of a drug despite negative consequences such use may entail. Sustained use of an addictive drug may produce physical or psychological dependence on the drug. Rehabilitation typically involves psychotherapy and sometimes the temporary use of other psychoactive drugs.

Sources

NIH National Institute of Neurological Disorder and Stroke (NIDS)

NIH National Institute of Mental Health

NIH National Institute on Drug Abuse

Wikipedia

Contributors and Attributions

- Libertext: Human Biology (Wakim and Grewal)
- [Edward B. Walker \(Weber State University\)](#)
- Charles Ophardt, Professor Emeritus, Elmhurst College; [Virtual Chembook](#)
- Psychology OPENSTAX
- [Marisa Alviar-Agnew \(Sacramento City College\)](#)
- Drugs and the Mind. (2020, August 13). Retrieved May 23, 2021, from <https://chem.libretexts.org/@go/page/153917>

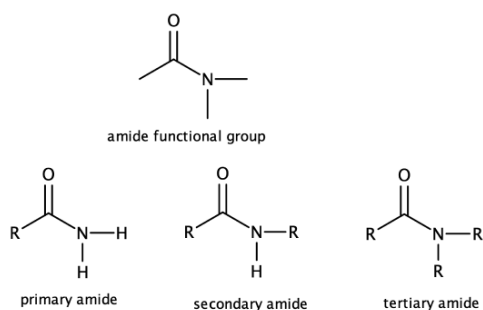
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3.7: Amides- Structures and Names

Learning Objectives

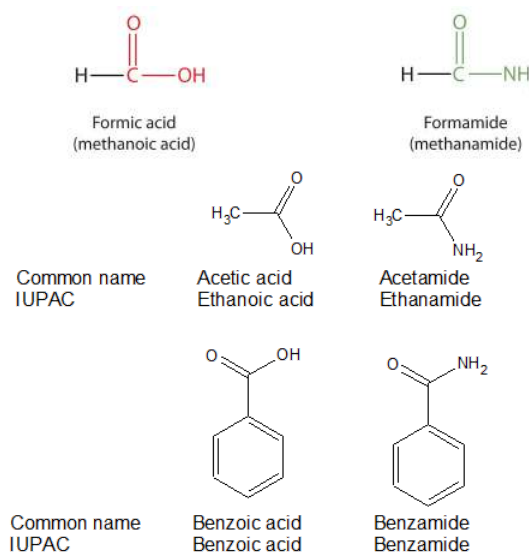
- Identify the general structure for an amide.
- Identify the functional group for an amide.
- Name amides with common names.
- Name amides according to the IUPAC system.

The amide functional group has an nitrogen atom attached to a carbonyl carbon atom. If the two remaining bonds on the nitrogen atom are attached to hydrogen atoms, the compound is a *simple amide*. If one or both of the two remaining bonds on the atom are attached to alkyl or aryl groups, the compound is a *substituted amide*.



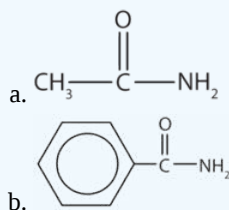
The carbonyl carbon-to-nitrogen bond is called an *amide linkage*. This bond is quite stable and is found in the repeating units of protein molecules, where it is called a *peptide linkage*.

Simple, primary amides are named as derivatives of carboxylic acids. The *-oic* ending of the International Union of Pure and Applied Chemistry (IUPAC) name of the carboxylic acid is replaced with the suffix *-amide*. In the common nomenclature system, the *-ic* ending from the common name of the carboxylic acid is replaced with the suffix **-amide**. The additional nitrogen substituents in secondary and tertiary amides are designated by the prefix *N-* before the group name, just like in the case of amines:



Example 3.7.1

Name each compound with the common name, the IUPAC name, or both.



Solution

- a. This amide has two carbon atoms and is thus derived from acetic acid. The OH of acetic acid is replaced by an NH_2 group. The *-ic* from *acetic* (or *-oic* from ethanoic) is dropped, and *-amide* is added to give *acetamide* (or ethanamide in the IUPAC system).
- b. This amide is derived from benzoic acid. The *-oic* is dropped, and *-amide* is added to give benzamide.

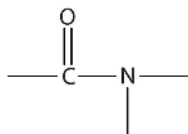
Exercise 3.7.1

Name each compound with the common name, the IUPAC name, or both.



Key Takeaways

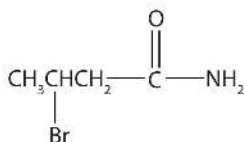
- Amides have a general structure in which a nitrogen atom is bonded to a carbonyl carbon atom.
- The functional group for an amide is as follows:



- In names for amides, the *-ic acid* of the common name or the *-oic* ending of the IUPAC for the corresponding carboxylic acid is replaced by *-amide*.

Concept Review Exercises

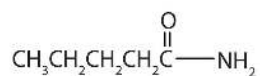
- Name this compound with the common name and the IUPAC name.



- Draw the structural formulae for pentanamide.

Answers

- β -bromobutyramide (3-bromobutanamide)



2.

Exercises

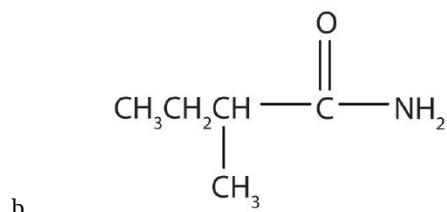
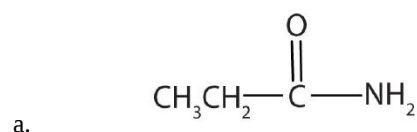
1. Draw the structure for each compound.

- formamide
- hexanamide

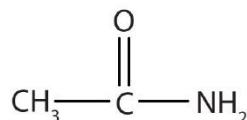
2. Draw the structure for each compound.

- propionamide
- butanamide

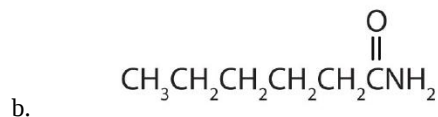
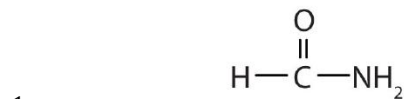
3. Name each compound with the common name, the IUPAC name, or both.



4. Name the compound.



Answers



- propionamide (propanamide)
 - α -methylbutyramide (2-methylbutanamide)

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3.8: Neutrality of Amides

Amides are **neutral** compounds -- in contrast to their seemingly close relatives, the **amines**, which are basic. The amide linkage is **planar** -- even though we normally show the C-N connected by a single bond, which should provide free rotation. Figure 1 below shows this common drawing of an amide.

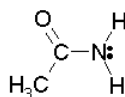


Figure 1. An amide; usual representation. The amide shown here, and in Figure 2, is the primary amide from ethanoic acid (acetic acid); the amide is called ethanamide (acetamide).

To help understand these properties, we need to look at a more complex -- but better -- representation of the amide structure. This is shown in Figure 2:

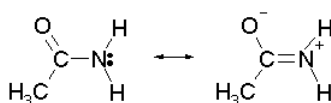


Figure 2. Resonance structures for an amide. Remember that the molecule does not actually switch between these structures. Instead, the actual structure is somewhere in between the structures shown. It can be thought of as some average of these structures.

Why is this resonance system better? A qualitative argument is that the O, which is very electronegative, draws electrons toward it. In this case, it draws electrons from the lone pair of the N. Note that in the right hand form, the electrons of the N lone pair have moved in to the double bond (giving the N a + charge), and electrons of the C=O double bond have moved out to the O (giving it a - charge).

The resonance system shown in Figure 2 is based on measurements of the properties of amides. That is, detailed study of amides shows that the properties are better explained by Figure 2 than by Figure 1. As examples:

- The bond length measured for amides is about half way between that typical for C-N single bonds and C=N double bonds. This is easily explained by the resonance system shown in Figure 2, which suggests that the actual bond between C and N is about a 1 1/2 bond.
- A double bonded structure, or a structure with a substantial contribution of double bonding, would be expected to be planar, without free rotation about the C-N bond. This fits with observation.
- The left hand structure in Figure 2 might look like it would accept an H⁺ on the N, thus acting as a base. However, the right hand structure has no lone pair, and even has a positive charge on the N. These features argue against the N being basic. A resonance system with a substantial contribution of the right hand structure would not be expected to be basic.

Contributors

- >Robert Bruner (<http://bbruner.org>)

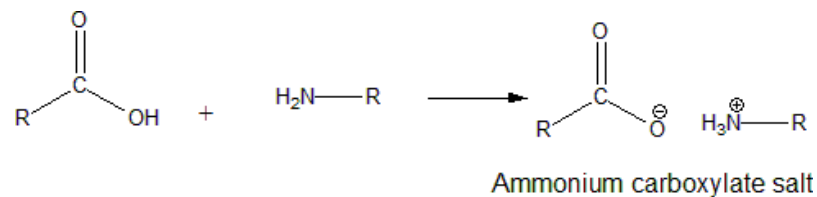
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3.9: Chemistry of Amides- Synthesis and Reactions

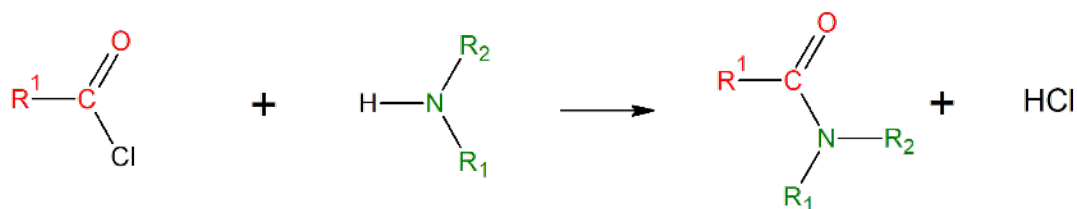
Synthesis of Amides

Direct reaction of a carboxylic acid with an amine does not produce an amide, but a salt.



Therefore, we need to use **acyl chlorides** or **anhydrides** as an alternative.

Acid chlorides react with ammonia, 1° amines and 2° amines to form amides

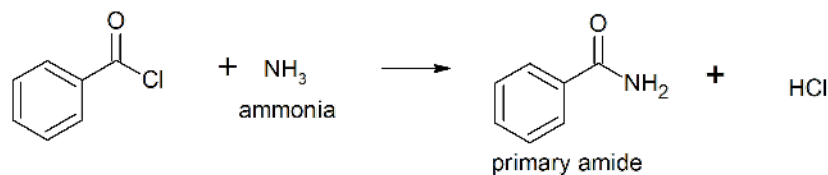


Acid Anhydrides react with ammonia, 1° amines and 2° amines to form amides

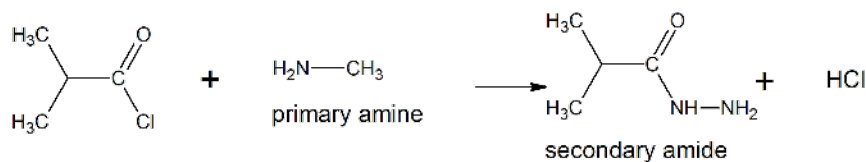


Examples

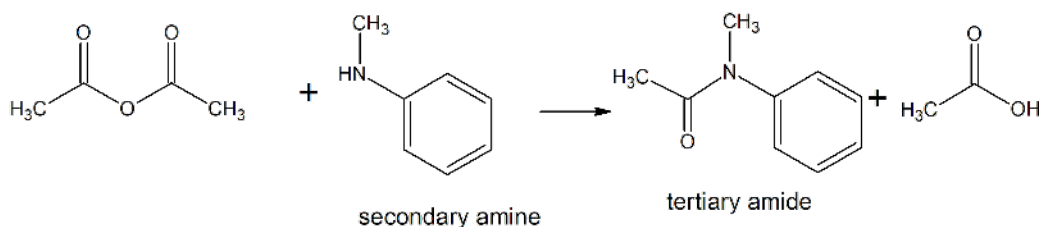
1. Formation of a primary amide:



2. Formation of a secondary amide:



3. Formation of a tertiary amide:

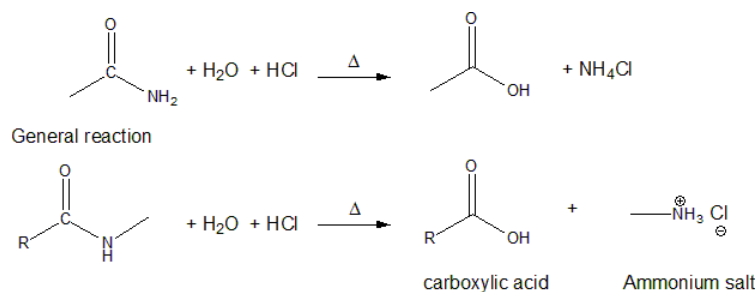


Tertiary amines cannot form amides due to the lack of H atom that can be replaced by the acyl group

Chemical properties of Amides

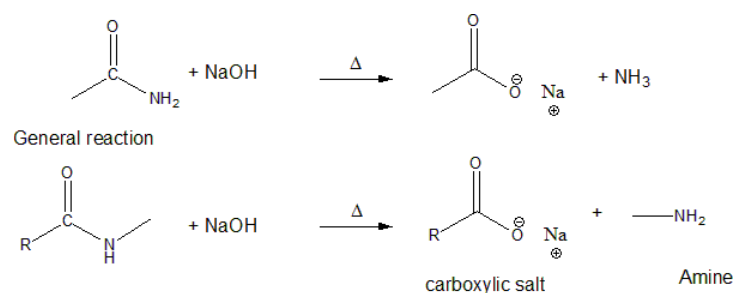
Hydrolysis under acidic conditions

Taking acetamide (ethanamide) as a typical amide. If acetamide is heated with a dilute acid (such as dilute hydrochloric acid), acetic acid is formed together with ammonium ions. So, if you were using hydrochloric acid, the final solution would contain ammonium chloride and acetic acid.



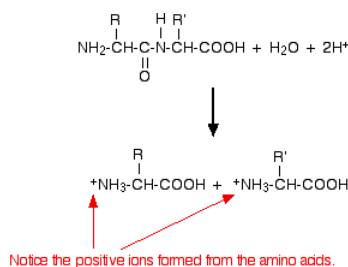
Hydrolysis under alkaline conditions

Also, if acetamide is heated with sodium hydroxide solution, ammonia gas is given off and you are left with a solution containing sodium acetate.



Peptide hydrolysis

Peptide hydrolysis of proteins is amide hydrolysis. What biologists and biochemists call a peptide link (in proteins, for example) is what chemists call an amide link. Apply either hydrolysis reaction above to the dipeptide below to produce two amino acids. The amines in the products are shown in their protonated form because this hydrolysis reaction was performed under acidic conditions.



Contributors and Attributions

- [Dr. Dietmar Kennepohl](#) FCIC (Professor of Chemistry, [Athabasca University](#))
- Prof. Steven Farmer ([Sonoma State University](#))
- Jim Clark ([Chemguide.co.uk](#))

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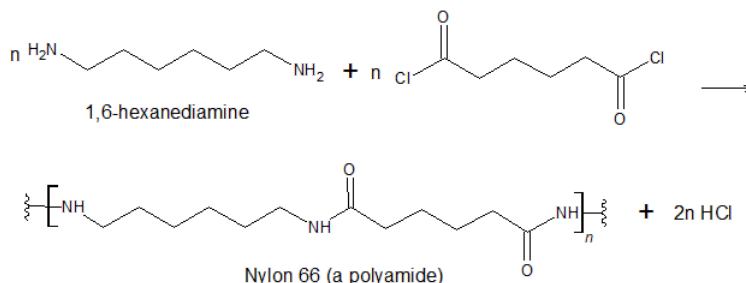
3.10: Polyamides

Learning Objectives

- To describe the preparation procedure for polyamides.

Polyamides

Just as the reaction of a diol and a diacid forms a polyester, the reaction of a diacid chloride and a diamine yields a polyamide. The two difunctional monomers often employed are the acyl chloride of adipic acid and 1,6-hexanediamine. The monomers condense by splitting out HCl to form a new product, which is still difunctional and thus can react further to yield a polyamide polymer.



Some polyamides are known as *nylons*. Nylons are among the most widely used synthetic fibers—for example, they are used in ropes, sails, carpets, clothing, tires, brushes, and parachutes. They also can be molded into blocks for use in electrical equipment, gears, bearings, and valves.

Key Takeaway

- Polyamides are prepared by the reaction of a dicarboxylic acid chloride with an diamine.

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CHAPTER OVERVIEW

4: Substitution and Elimination reactions

- 4.1: Alkyl Halides - Structure and Physical Properties
- 4.2: Common Sources of Alkyl Halides
- 4.3: Reactions of Alkyl Halides- Substitution and Elimination
- 4.4: Characteristic of the SN2 Reaction
- 4.5: Factors affecting the SN2 Reaction
- 4.6: Characteristic of the SN1 Reaction
- 4.7: Factors Affecting the SN1 Reaction
- 4.8: Comparison of SN1 and SN2 Reactions
- 4.9: Characteristics of the E2 Reaction
- 4.10: Zaitsev's Rule
- 4.11: Characteristics of the E1 Reaction
- 4.12: Comparison of E1 and E2 Reactions
- 4.13: Competition between substitution and elimination

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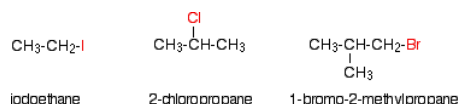
4.1: Alkyl Halides - Structure and Physical Properties

Learning Objective

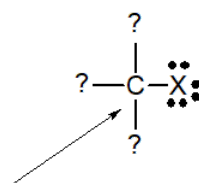
- classify alkyl halides
- predict relative boiling points and solubility of alkyl halides

Introduction

Alkyl halides are also known as haloalkanes. Alkyl halides are compounds in which one or more hydrogen atoms in an alkane have been replaced by halogen atoms (fluorine, chlorine, bromine or iodine). We will only look at compounds containing one halogen atom like the compounds below.



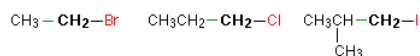
Alkyl halides fall into different classes depending on how the halogen atom is positioned on the chain of carbon atoms. Alkyl halides can be classified as primary, secondary, or tertiary. The chemical reactivity of alkyl halides is frequently discussed using alkyl halide classifications to help discern patterns and trends. Because the neutral bonding pattern for halogens is one bond and three lone pairs, the carbon and halogen always share a single bond. Alkyl halide classification is determined by the bonding pattern of the carbon atom bonded to the halogen as shown in the diagram below.



Alkyl halide classification is determined by the carbon bonded to the halogen.

Primary alkyl halides

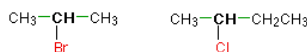
In a primary (1°) haloalkane, the carbon bonded to the halogen atom is only attached to one other alkyl group. Some examples of primary alkyl halides include the compounds below.



Notice that it doesn't matter how complicated the attached alkyl group is. In each case there is only one linkage to an alkyl group from the CH_2 group holding the halogen. There is an exception to this: CH_3Br and the other methyl halides are often counted as primary alkyl halides even though there are **no** alkyl groups attached to the carbon with the halogen on it.

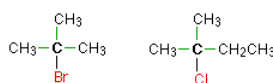
Secondary alkyl halides

In a secondary (2°) haloalkane, the carbon bonded with the halogen atom is joined directly to two other alkyl groups that can be the same or different. Some examples of secondary alkyl halides include the compounds below.



Tertiary alkyl halides

In a tertiary (3°) haloalkane, the carbon atom holding the halogen is attached directly to three alkyl groups, which may be any combination of same or different. Some examples of tertiary alkyl halides include the compounds below.



Nomenclature

Many organic compounds are closely related to the alkanes and this similarity is incorporated into many common names. The reactions of alkanes with halogens produce halogenated hydrocarbons, compounds in which one or more hydrogen atoms of a hydrocarbon have been replaced by halogen atoms: The replacement of only one hydrogen atom gives an alkyl halide (or haloalkane). The *common names* of alkyl halides consist of two parts: the name of the alkyl group plus the stem of the name of the halogen, with the ending *-ide*. In the IUPAC system, alkyl halides are named as substituted alkanes.

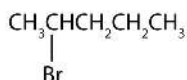
			
Common	ethyl chloride	isopropyl bromide	n-butyl iodide
IUPAC	chloroethane	2-bromopropane	1-iodobutane

Examples

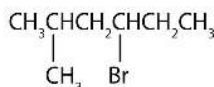
Give the common and IUPAC names for each compound.

- $\text{CH}_3\text{CH}_2\text{CH}_2\text{Br}$
- $(\text{CH}_3)_2\text{CHCl}$
- Give the IUPAC name for each compound.

a)



b)

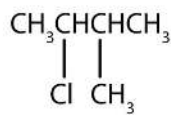


SolutionS

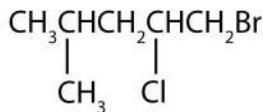
- The alkyl group ($\text{CH}_3\text{CH}_2\text{CH}_2-$) is a propyl group, and the halogen is bromine (Br). The common name is therefore propyl bromide. For the IUPAC name, the prefix for bromine (bromo) is combined with the name for a three-carbon chain (propane), preceded by a number identifying the carbon atom to which the Br atom is attached, so the IUPAC name is 1-bromopropane.
- The alkyl group $[(\text{CH}_3)_2\text{CH}-]$ has three carbon atoms, with a chlorine (Cl) atom attached to the middle carbon atom. The alkyl group is therefore isopropyl, and the common name of the compound is isopropyl chloride. For the IUPAC name, the Cl atom (prefix *chloro-*) attached to the middle (second) carbon atom of a propane chain results in 2-chloropropane.
- a) The parent alkane has five carbon atoms in the longest continuous chain; it is pentane. A bromo (Br) group is attached to the second carbon atom of the chain. The IUPAC name is 2-bromopentane.
b) The parent alkane is hexane. Methyl (CH_3) and bromo (Br) groups are attached to the second and fourth carbon atoms, respectively. Listing the substituents in alphabetical order gives the name 4-bromo-2-methylhexane.

Exercise

- Give common and IUPAC names for each compound.
 - $\text{CH}_3\text{CH}_2\text{I}$
 - $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{F}$
- Give the IUPAC name for each compound.
 -



b)



Answer

1. a) ethyl iodide and iodoethane, respectively; Note the IUPAC name does not need a locator number because there is only one possible structure with two carbons and one iodine.
- b) butyl fluoride and 1-fluorobutane
2. a) 2-chloro-2-methylbutane
- b) 1-bromo-2-chloro-4-methylpentane

Halogens and the Character of the Carbon-Halogen Bond

With respect to electronegativity, halogens are more electronegative than carbons. This results in a carbon-halogen bond that is polarized. As shown in the image below, carbon atom has a partial positive charge, while the halogen has a partial negative charge.

The Polar C-X Bond



The following image shows the relationship between the halogens and electronegativity. Notice, as we move up the periodic table from iodine to fluorine, electronegativity increases.

Electronegativity $\text{I} < \text{Br} < \text{Cl} < \text{F}$

The following image shows the relationships between bond length, bond strength, and molecular size. As we progress down the periodic table from fluorine to iodine, molecular size increases. As a result, we also see an increase in bond length. Conversely, as molecular size increases and we get longer bonds, the strength of those bonds decreases.

Bond length	C-F	<	C-Cl	<	C-Br	<	C-I
Bond strength	C-I	<	C-Br	<	C-Cl	<	C-F
Molecular size	F	<	Cl	<	Br	<	I

Haloalkanes Have Higher Boiling Points than Alkanes

When comparing alkanes and haloalkanes, we will see that haloalkanes have higher boiling points than alkanes containing the same number of carbons. London dispersion forces are the first of two types of forces that contribute to this physical property. You might recall from general chemistry that London dispersion forces increase with molecular surface area. In comparing haloalkanes with alkanes, haloalkanes exhibit an increase in surface area due to the substitution of a halogen for hydrogen. The increase in surface area leads to an increase in London dispersion forces, which then results in a higher boiling point.

Dipole-dipole interaction is the second type of force that contributes to a higher boiling point. As you may recall, this type of interaction is a coulombic attraction between the partial positive and partial negative charges that exist between carbon-halogen

bonds on separate haloalkane molecules. Similar to London dispersion forces, dipole-dipole interactions establish a higher boiling point for haloalkanes in comparison to alkanes with the same number of carbons.

Dipole-Dipole Interaction



The table below illustrates how boiling points are affected by some of these properties. Notice that the boiling point increases when hydrogen is replaced by a halogen, a consequence of the increase in molecular size, as well as an increase in both London dispersion forces and dipole-dipole attractions. The boiling point also increases as a result of increasing the size of the halogen, as well as increasing the size of the carbon chain.

Boiling Points of Haloalkanes (°C)						
R	X =	H	F	Cl	Br	I
CH ₃		-161.7	-78.4	-24.2	3.6	42.4
CH ₃ CH ₂		-88.6	-37.7	12.3	38.4	72.3
CH ₃ (CH ₂) ₂		-42.1	-2.5	46.6	71.0	102.5
CH ₃ (CH ₂) ₃		-0.5	32.5	78.4	101.6	130.5
CH ₃ (CH ₂) ₄		36.1	62.8	107.8	129.6	157.0
CH ₃ (CH ₂) ₇		125.7	142.0	182.0	200.3	225.5

Solubility

Solubility in water

Alkyl halides have little to no solubility in water in spite of the polar carbon-halogen bond. The attraction between the alkyl halide molecules is stronger than the attraction between the alkyl halide and water. Alkyl halides have little to no solubility in water, but be aware of densities. Polyhalogenated alkanes such as dichloromethane can have densities greater than water.

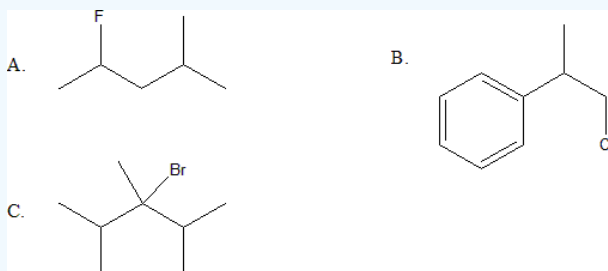
Solubility in organic solvents

Alkyl halides are soluble in most organic solvents. The London Dispersion forces play a dominant role in solubility.

Exercises

Exercise

3. Classify (primary, secondary or tertiary) and give the IUPAC name for the following organohalides:



4. Classify each alkyl halide as primary, secondary, or tertiary:

- 1-Chloro-3,3-dimethylpentane
- 1-chloro-4-isopropylcyclohexane
- 3-bromo-3-ethylhexane

5. Predict the solvent with great alkyl halide solubility.

- water or hexane
- water or 1-octanol

c) water or benzene

d) water or acetone

Solutions

3.

a) secondary; 2-fluoro-4-methylpentane

b) primary; 1-chloro-2-methyl-2-phenylethane

c) tertiary, 3-bromo-2,3,4-trimethylpentane

4. (A) primary; (B) secondary (C) tertiary

5. a) hexane

b) benzene

c) 1-octanol

d) acetone

Alkyl halides have little to no solubility in water, but be aware of densities. Polyhalogenated alkanes can have densities greater than water.

Contributors and Attributions

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- Jim Clark ([Chemguide.co.uk](#))
- Rachael Curtis (UC Davis)

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4.2: Common Sources of Alkyl Halides

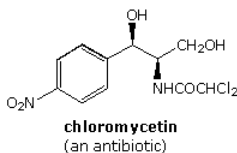
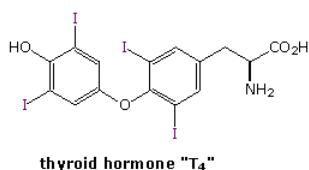
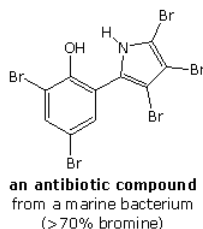
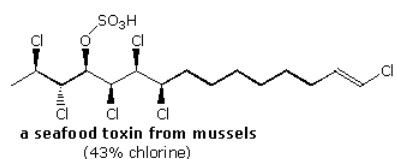
Learning Objective

- Discuss the common uses of alkyl halides

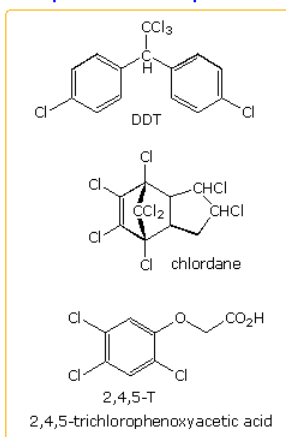
Halogen containing organic compounds are relatively rare in terrestrial plants and animals. The thyroid hormones T_3 and T_4 are exceptions; as is fluoroacetate, the toxic agent in the South African shrub *Dichapetalum cymosum*, known as "gifblaar". However, the halogen rich environment of the ocean has produced many interesting natural products incorporating large amounts of halogen. Some examples are shown below.

The ocean is the largest known source for atmospheric methyl bromide and methyl iodide. Furthermore, the ocean is also estimated to supply 10-20% of atmospheric methyl chloride, with other significant contributions coming from biomass burning, salt marshes and wood-rotting fungi. Many subsequent chemical and biological processes produce poly-halogenated methanes.

Naturally Occurring Compounds



Synthetic Compounds



Synthetic organic halogen compounds are readily available by direct halogenation of hydrocarbons and by addition reactions to alkenes and alkynes. Many of these have proven useful as intermediates in traditional synthetic processes. Some halogen compounds, shown in the box, have been used as pesticides, but their persistence in the environment, once applied, has led to restrictions, including banning, of their use in developed countries. Because DDT is a cheap and effective mosquito control agent, underdeveloped countries in Africa and Latin America have experienced a dramatic increase in malaria deaths following its removal, and arguments are made for returning it to limited use. 2,4,5-T and 2,4-D are common herbicides that are sold by most garden stores. Other organic halogen compounds that have been implicated in environmental damage include the polychloro- and polybromo-biphenyls (PCBs and PBBs), used as heat transfer fluids and fire retardants; and freons (e.g. CCl_2F_2 and other chlorofluorocarbons) used as refrigeration gases and fire extinguishing agents.

Alkyl halides provide nice examples for learning about two very important organic reaction mechanism types: nucleophilic substitution and beta-elimination. In learning about these mechanisms in the context of alkyl halide reactivity, we will also learn some very fundamental ideas about three main players in many organic reactions: nucleophiles, electrophiles, and leaving groups. We'll start with an overview of the substitution and elimination reactions which alkyl halides undergo.

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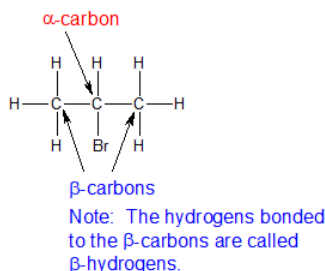
4.3: Reactions of Alkyl Halides- Substitution and Elimination

Learning Objective

- apply the alpha and beta labels to alkyl halides for substitution and elimination reactions - refer to section 7.4

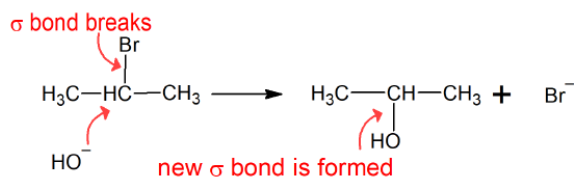
Alkyl Halide Structure and Reaction Language

The carbon bonded to a halide is called the alpha-carbon. The carbons bonded to the alpha-carbon are called beta-carbons. Carbon atoms further removed from the alpha carbon are named by continuing the Greek alphabet (alpha, beta, gamma, delta, etc). In discussing the reactions of alkyl halides, it can be effective to use the alpha- and beta- labels. The structure for 2-bromopropane is used below to illustrate the application of these terms.

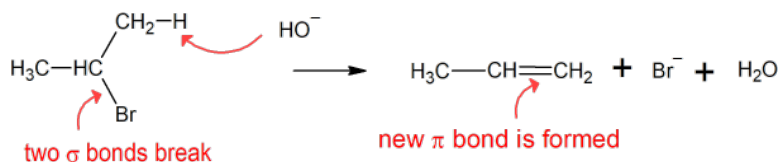


The Reactions - Nucleophilic Substitution and Elimination

Alkyl halides can undergo two major types of reactions - substitution and/or elimination. The substitution reaction is called a Nucleophilic Substitution reaction because the electrophilic alkyl halide forms a new bond with the nucleophile which substitutes for (replaces) the halogen at the alpha-carbon. Because carbon can only form four bonds, the halogen must leave and is called the "Leaving Group". Alkyl halides are excellent electrophiles because halogens share a polar bond with carbon, are polarizable, and form relatively stable leaving groups as halide anions. During a substitution reaction, one sigma bond breaks, and another sigma bond is formed. In the example below, 2-bromopropane is converted into 2-propanol in a substitution reaction.



Alkyl halides can also undergo elimination reactions in the presence of strong bases. The elimination of a beta-hydrogen (hydrogen on a carbon vicinal to the alkyl halide carbon) and the halide produces a carbon-carbon double bond to form an alkene. During an elimination reaction, two sigma bonds break, and a pi bond is formed. In the example below, 2-bromopropane has undergone an elimination reaction to give an alkene - propene.



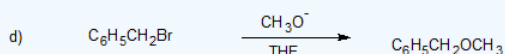
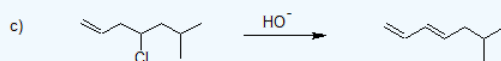
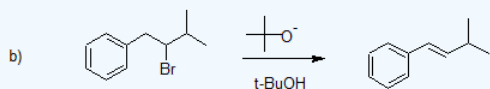
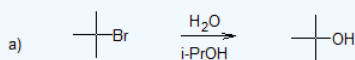
What decides whether you get substitution or elimination?

In the examples above, the reagents were the same for both substitution and elimination - the halogenoalkane and either sodium or potassium hydroxide solution. In all cases, you will get a mixture of both reactions happening - some substitution and some elimination. The product distribution depends on a number of factors. These factors will be explored in the remaining sections of this chapter. Depending on the structure of the alkyl halide, reagent type, reaction conditions, some reactions will only undergo

only one pathway - substitution or elimination. While other alkyl halides will always produce a mixture of substitution and elimination products like the example above. The goal of efficient multiple-step synthetic pathways is to maximize the formation of a single product during each step. The reaction conditions explored in this chapter will be useful for future reactions we will study and learn.

Exercise

1. Classify the following reactions as "Substitutions" or "Eliminations".



Answer

1. a) substitution
- b) elimination
- c) elimination
- d) substitution

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Jim Clark (Chemguide.co.uk)

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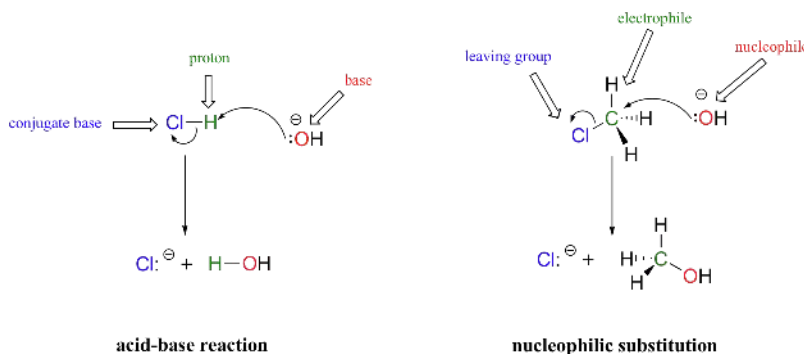
4.4: Characteristic of the S_N2 Reaction

Learning Objectives

- determine the rate law & predict the mechanism based on its rate equation or reaction data for S_N2 reactions
- propose mechanisms for S_N2 reactions
- draw and interpret Reaction Energy Diagrams for S_N2 reactions

Introduction

In many ways, the proton transfer process of a Brønsted-Lowry acid-base reaction can be thought of as simply a special kind of nucleophilic substitution reaction, one in which the electrophile is a hydrogen rather than a carbon.



In both reaction types, we are looking at very similar players: an electron-rich species (the nucleophile/base) reacts with an electron-poor species (the electrophile/proton), driving off the leaving group/conjugate base.

In the next few sections, we are going to be discussing some general aspects of nucleophilic substitution reactions, and in doing so it will simplify things greatly if we can use some abbreviations and generalizations before we dive into real examples.

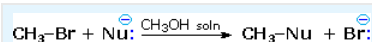
What is a nucleophile (Nu)?

Instead of showing a specific nucleophile like hydroxide, we will simply refer to the nucleophilic reactant as 'Nu'. Nucleophilic functional groups are those which have electron-rich atoms able to donate a pair of electrons to form a new covalent bond. Nucleophiles can be negatively charged and some that are neutral molecules with lone pair electrons. In both laboratory and biological organic chemistry, the most relevant nucleophilic atoms are oxygen, nitrogen, and sulfur, and the most common nucleophilic functional groups are water, alcohols, phenols, amines, thiols, and occasionally carboxylates.

When thinking about nucleophiles, the first thing to recognize is that, for the most part, the same quality of 'electron-richness' that makes a something nucleophilic also makes it basic: *nucleophiles can be bases, and bases can be nucleophiles*. It should not be surprising, then, that most of the trends in basicity that we have already discussed also apply to nucleophilicity.

Some confusion in distinguishing basicity (base strength) and nucleophilicity (nucleophile strength) is inevitable. Since basicity is a less troublesome concept; it is convenient to start with it. Basicity refers to the ability of a base to accept a proton. Basicity may be related to the pK_a of the corresponding conjugate acid, as shown below. The strongest bases have the weakest conjugate acids and vice versa.

Nucleophilicity is a more complex property. It commonly refers to the rate of substitution reactions at the halogen-bearing **carbon atom** of a reference alkyl halide, such as CH₃-Br. Thus the nucleophilicity of the Nu:⁽⁻⁾ reactant in the following substitution reaction varies as shown in the chart below:



Nucleophilicity: CH₃CO₂⁽⁻⁾ < Cl⁽⁻⁾ < Br⁽⁻⁾ < N₃⁽⁻⁾ < CH₃O⁽⁻⁾ < CN⁽⁻⁾ < I⁽⁻⁾ < CH₃S⁽⁻⁾

What is a Leaving Group (X or LG)?

In a similar fashion, we will call the leaving group 'X' for halogens as is customary. For other reactions, it will be more accurate to abbreviate the leaving group as "LG". The context of the reaction will dictate the abbreviation. Leaving groups are sometimes negatively charged, sometimes neutral, and sometimes positively charged. Therefore, in this general picture we will not include a charge designation on the 'X' or 'LG' species. In referring to the comparison between acid-base chemistry and substitution reactions, the stability of the leaving group is evaluated the same way we evaluate the stability of conjugate bases.

When comparing the reactivity of electrophiles that vary only in their leaving groups, then leaving group stability plays a dominant role. The electrophile with the more stable leaving group will be favored. The lower the electron density of the leaving group, the more stable it is. Neutral leaving groups are favored over charged leaving groups. When comparing charged leaving groups, apply the concepts used to determine the relative stability of conjugate bases:

- 1) identity or identities of the atom(s) holding the charge
- 2) delocalization of the charge via resonance
- 3) inductive effects
- 4) orbital hybridization

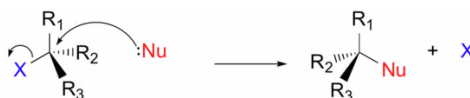
What is an Electrophile (E) or the Substrate (S)?

An electrophile accepts electrons, so it is a species that contains a carbon atom with electron deficiency. Electrophiles (E) are sometimes protonated and sometimes neutral. Electrophiles can also be called "Substrates". Electrophilicity of alkyl halides comes from the polar carbon-halogen bond.

Since nucleophiles, leaving groups, and electrons may be charged or neutral, we will not include charges on 'Nu' or 'X' (or 'LG') or 'E'.

We will generalize the three other groups bonded on the electrophilic alpha-carbon as R_1 , R_2 , and R_3 : these symbols could represent hydrogens as well as alkyl groups. Finally, in order to keep figures from becoming too crowded, we will use in most cases the line structure convention in which the central, electrophilic carbon is not drawn out as a 'C'.

Here, then, is the generalized picture of a nucleophilic substitution reaction:



Alkyl halides are good substrates for nucleophilic substitution, due to the electrophilicity of the carbon atom attached to the halogen. The common halogens being fluorine, chlorine, bromine and iodine. With the exception of iodine, these halogens have electronegativities significantly greater than carbon. Consequently, this functional group is polarized so that the carbon is electrophilic and the halogen is nucleophilic. Two characteristics other than electronegativity also have an important influence on the chemical behavior of these compounds. The first of these is covalent bond strength. The strongest of the carbon-halogen covalent bonds is that to fluorine. Because of this, **alkyl fluorides and fluorocarbons in general are chemically and thermodynamically quite stable**, and do not share any of the reactivity patterns shown by the other alkyl halides. The second factor to be considered is the relative stability of the corresponding halide anions, which is likely the form in which these electronegative atoms will be replaced. This stability may be estimated from the relative acidities of the H-X acids, assuming that the strongest acid releases the most stable conjugate base (halide anion). With the exception of HF ($pK_a = 3.2$), all the hydrohalic acids are very strong, small differences being in the direction $HCl < HBr < HI$.

Exercise

1. Since everything is relative in chemistry, one reaction's nucleophile can be another reaction's leaving group. Some functional groups can only react as a nucleophile or electrophile, while other functional groups can react as either a nucleophile or electrophile depending on the reaction conditions. Classify the following compounds as nucleophiles, electrophiles, or leaving groups. More than one answer may be possible.

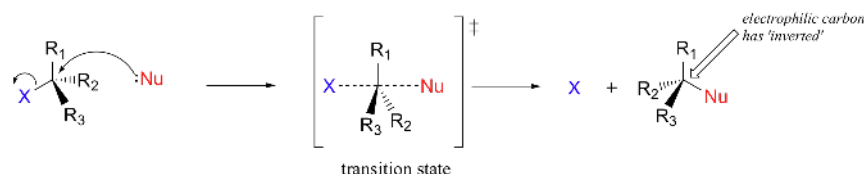
- a) bromoethane
- b) hydroxide
- c) water
- d) chlorocyclohexane
- e) ethanol
- f) bromide

Answer

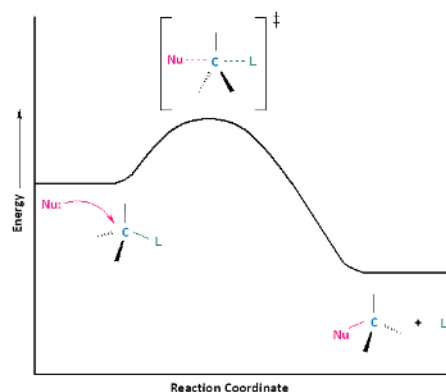
- a) electrophile (Alkyl halides are always electrophiles - one reason they are an o-chem student's best friend.)
- b) strong nucleophile
- c) weak nucleophile and good leaving group
- d) electrophile (Alkyl halides are always electrophiles - one reason they are an o-chem student's best friend.)
- e) weak nucleophile, a poor electrophile without clever chemistry (stay tuned for future chapters), good leaving group
- f) good nucleophile and a good leaving group

The S_N2 mechanism

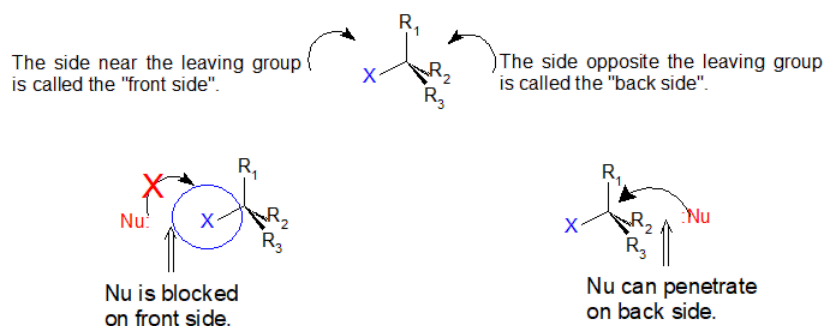
There are two mechanistic models for how an alkyl halide can undergo nucleophilic substitution, S_N2 and S_N1. The S_N2 reaction takes place in a single step with bond-forming and bond-breaking occurring simultaneously. (In all figures in this section, 'X' indicates a halogen substituent).



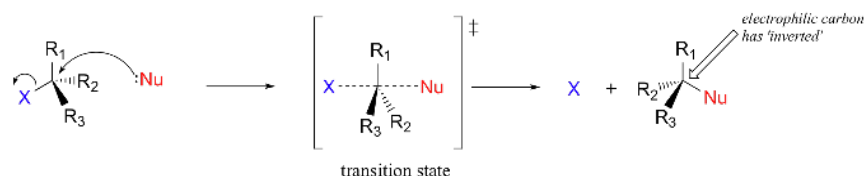
This is called an 'S_N2' mechanism. In the term S_N2, S stands for 'substitution', the subscript N stands for 'nucleophilic', and the number 2 refers to the fact that it is a **bimolecular reaction**: the overall rate depends on a step in which two separate molecules (the nucleophile and the electrophile) collide. A potential energy diagram for this reaction shows the transition state (TS) as the highest point on the pathway from reactants to products.



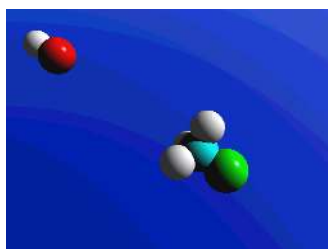
If you look carefully at the progress of the S_N2 reaction, you will realize something very important about the outcome. The nucleophile, being an electron-rich species, must react with the electrophilic carbon from the *back side* relative to the location of the leaving group. Approach from the front side simply doesn't work: the electron rich, leaving group blocks the way with electrostatic repulsion and steric hindrance.



The result of this backside penetration is that the stereochemical configuration at the central carbon *inverts* as the reaction proceeds. In a sense, the molecule is turned inside out. At the transition state, the electrophilic carbon and the three 'R' substituents all lie on the same plane.

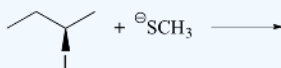


What this means is that S_N2 reactions are inherently stereoselective: when the substitution takes place at a stereocenter, we can confidently predict the stereochemical configuration of the product. Below is an animation illustrating the principles we have just learned, showing the S_N2 reaction between hydroxide ion and methyl iodide. Notice how backside attack by the hydroxide nucleophile results in inversion at the tetrahedral carbon electrophile.



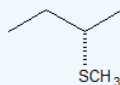
Exercise

2. Predict the structure of the product in this S_N2 reaction. Be sure to specify stereochemistry.



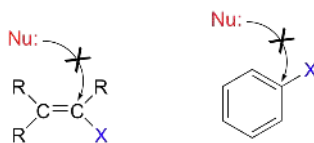
Solution

2.



S_N2 Reactions Occur at sp^3 Carbons with a Leaving Group

One more important point must be made before continuing: nucleophilic substitutions as a rule occur at sp^3 -hybridized carbons bonded to a leaving group. S_N2 reactions cannot occur where the leaving group is attached to an sp^2 -hybridized carbon:



Bonds on sp^2 -hybridized carbons are inherently shorter and stronger than bonds on sp^3 -hybridized carbons, meaning that it is harder to break the C-X bond in these substrates. S_N2 reactions of this type are unlikely also because the (hypothetical) electrophilic carbon is protected from nucleophilic attack by electron density in the p bond.

Exercise

3. Predict which alkyl halides can undergo a S_N2 reaction.

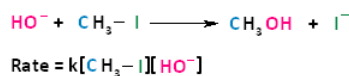
- a) C_6H_5Br
- b) $CH_3CH_2CH_2Br$
- c) CH_2CHBr
- d) $CH_3CH_2CH_2CHBrCH_3$

Solutions

- 3.
- a) No, sp^2 carbon
 - b) Yes, primary alkyl halide
 - c) No, sp^2 carbon
 - d) Yes, secondary alkyl halide

S_N2 Reaction Kinetics

In the term S_N2 , the S stands for substitution, the N stands for nucleophilic, and the number two stands for bimolecular, meaning there are two molecules involved in the rate determining step. The rate of bimolecular nucleophilic substitution reactions depends on the concentration of both the haloalkane and the nucleophile. To understand how the rate depends on the concentrations of both the haloalkane and the nucleophile, let us look at the following example. The hydroxide ion is the nucleophile and methyl iodide is the haloalkane.



If we were to double the concentration of either the haloalkane or the nucleophile, we can see that the rate of the reaction would proceed twice as fast as the initial rate.

$$\begin{aligned}\text{Rate}_1 &= k[\text{CH}_3\text{I}][\text{HO}^-] \\ \text{Rate}_2 &= 2k[\text{CH}_3\text{I}][\text{HO}^-] \\ \text{Rate}_2 &= 2\text{Rate}_1\end{aligned}$$

If we were to double the concentration of both the haloalkane and the nucleophile, we can see that the rate of the reaction would proceed four times as fast as the initial rate.

$$\begin{aligned}\text{Rate}_1 &= k[\text{CH}_3\text{I}][\text{HO}^-] \\ \text{Rate}_2 &= 4k[\text{CH}_3\text{I}][\text{HO}^-] \\ \text{Rate}_2 &= 4\text{Rate}_1\end{aligned}$$

The bimolecular nucleophilic substitution reaction follows second-order kinetics; that is, the rate of the reaction depends on the concentration of two first-order reactants. In the case of bimolecular nucleophilic substitution, these two reactants are the haloalkane and the nucleophile. For further clarification on reaction kinetics, the following links may facilitate your understanding of rate laws, rate constants, and second-order kinetics

Exercise

4. The reaction below follows the SN2 mechanism.



- Write the rate law for this reaction.
- Determine the value of the rate coefficient, k , if the initial concentrations are 0.01 M CH_3Cl , 0.01 M NaOH , and the initial reaction rate is 6×10^{-10} M/s.
- Calculate the initial reaction rate if the initial reactant concentrations are changed to 0.02 M CH_3Cl and 0.0005 M NaOH .

Solutions

4.

a) $\text{rate} = k[\text{CH}_3\text{Cl}][\text{OH}^-]$

b) substitute the data into the rate expression above and apply algebra to solve for k

$$k = 6 \times 10^{-6} \text{ Lmol}^{-1}\text{s}^{-1}$$

c) Using the rate law above, substitute the value for k from the previous question along with the new concentrations to determine the new initial rate.

$$\text{rate} = 6 \times 10^{-10} \text{ M/s}$$

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, [Athabasca University](#))
- Prof. Steven Farmer ([Sonoma State University](#))
- William Reusch, Professor Emeritus ([Michigan State U.](#)), [Virtual Textbook of Organic Chemistry](#)
- [Organic Chemistry With a Biological Emphasis](#) by Tim Soderberg (University of Minnesota, Morris)

- The S_N2 Reaction. (2020, May 30). Retrieved May 23, 2021, from <https://chem.libretexts.org/@go/page/45173>

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4.5: Factors affecting the SN2 Reaction

Learning Objective

- determine the rate law & predict the mechanism based on its rate equation or reaction data for S_N2 reactions
- predict the products and specify the reagents for S_N2 reactions with stereochemistry
- propose mechanisms for S_N2 reactions
- draw and interpret Reaction Energy Diagrams for S_N2 reactions

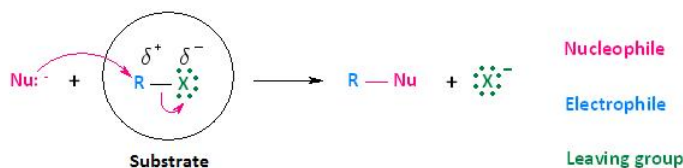
Bimolecular nucleophilic substitution (S_N2) reactions are **concerted**, meaning they are a **one step process**. The bond-making between the nucleophile and the electrophilic carbon occurs at the same time as the bond-breaking between the electrophilic carbon and the halogen.

In order of decreasing importance, the factors impacting S_N2 reaction pathways are

- 1) structure of the alkyl halide
- 2) strength of the nucleophile
- 3) stability of the leaving group
- 4) type of solvent.

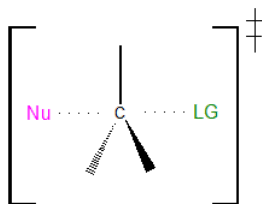
Structure of the alkyl halide (Substrate) and S_N2 Reaction Rates

Bimolecular nucleophilic substitution (S_N2) reactions are **concerted**, meaning they are a **one step process**. The bond-making between the nucleophile and the electrophilic carbon occurs at the same time as the bond-breaking between the electrophilic carbon and the halogen.



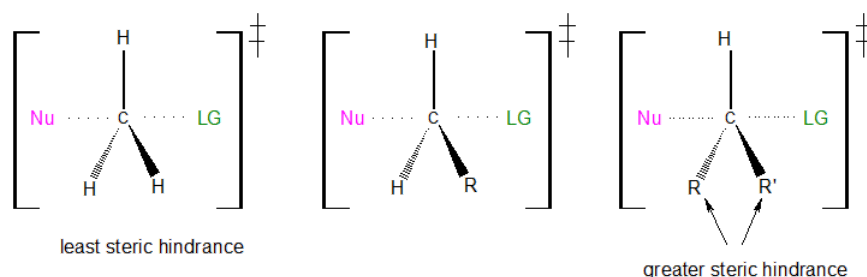
The S_N2 transition state is very crowded with a total of five groups around the electrophilic center, the nucleophile, the leaving group, and three substituents.

S_N2 Transition State



If each of the three substituents in this transition state were small hydrogen atoms, as illustrated in the first example below, there would be little steric repulsion between the incoming nucleophile and the electrophilic center, thereby increasing the ease at which the nucleophilic substitution reaction can occur. Remember, for the S_N2 reaction to occur, the nucleophile must be able to overlap orbitals with the electrophilic carbon center, resulting in the expulsion of the leaving group. If one of the hydrogens, however, were replaced with an R group, such as a methyl or ethyl group, there would be an increase in steric repulsion with the incoming nucleophile. If two of the hydrogens were replaced by R groups, there would be an even greater increase in steric repulsion with the incoming nucleophile.

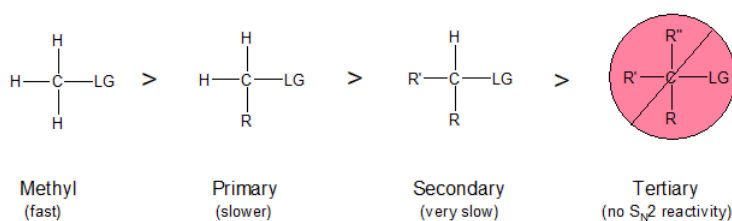
Alkyl Halide Structure and the S_N2 Transition State



How does steric hindrance affect the rate at which an S_N2 reaction will occur? As each hydrogen is replaced by an R group, the rate of reaction is significantly diminished. This is because the addition of one or two R groups shields the backside of the electrophilic carbon impeding nucleophilic penetration.

The diagram below illustrates this concept, showing that electrophilic carbons attached to three hydrogen atoms results in faster nucleophilic substitution reactions, in comparison to primary and secondary haloalkanes, which result in nucleophilic substitution reactions that occur at slower or much slower rates, respectively. Notice that a tertiary haloalkane, that which has three R groups attached, does not undergo nucleophilic substitution reactions at all. The addition of a third R group to this molecule creates a carbon that is entirely blocked.

Alkyl Halide Structure and S_N2 Relative Reactivity



Substitutes on Neighboring Carbons Slow Nucleophilic Substitution Reactions

Previously we learned that adding R groups to the electrophilic carbon results in nucleophilic substitution reactions that occur at a slower rate. What if R groups are added to neighboring carbons? It turns out that the addition of substitutes on neighboring carbons will slow nucleophilic substitution reactions as well.

In the example below, 2-methyl-1-bromopropane differs from 1-bromopropane in that it has a methyl group attached to the carbon that neighbors the electrophilic carbon. The addition of this methyl group results in a significant decrease in the rate of a nucleophilic substitution reaction.



If R groups were added to carbons farther away from the electrophilic carbon, we would still see a decrease in the reaction rate. However, branching at carbons farther away from the electrophilic carbon would have a much smaller effect.

Strength of the Nucleophile (Nucleophilicity)

In the S_N2 reaction, the rate determining step for the reaction is the attack of the nucleophile to the substrate. Therefore, S_N2 is easier to perform for stronger nucleophiles. There are predictable periodic trends in nucleophilicity. More electronegative elements hold their electrons more tightly, and are less able to donate them to form a new bond. For example, thiols (R-SH) are more nucleophilic than alcohols (R-OH) because oxygen has a higher electronegativity than sulfur. Also, negatively charged species are

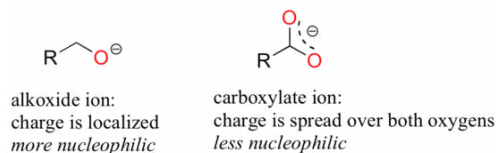
more nucleophilic than neutral molecules. For example methoxide anion CH_3O^- is more nucleophilic than methanol CH_3OH . Table 4.5.1 shows a list of common nucleophiles and their relative nucleophilicity.

Table 4.5.1 Some common nucleophiles and their relative nucleophilicity.

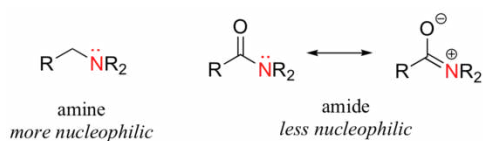
Weak Nucleophiles	Strong nucleophiles
H_2O water R-OH alcohols R-SH thiols NH_3 ammonia R-NH_2 amines R-COOH carboxylic acids R-CONH_2 amides	HO^- hydroxide R-O^- alkoxide R-S^- thiolate NH_2^- Azanide R-NH^- R-COO^- carboxylate CN^- cyanide N_3^- azide R^- carbanions X^- halides

Resonance effects on nucleophilicity

Resonance effects also come into play when comparing the inherent nucleophilicity of different molecules. The reasoning involved is the same as that which we used to understand resonance effects on basicity. If the electron lone pair on a heteroatom is delocalized by resonance, it is inherently less reactive - meaning less nucleophilic, and also less basic. An alkoxide ion, for example, is more nucleophilic and more basic than a carboxylate group, even though in both cases the nucleophilic atom is a negatively charged oxygen. In the alkoxide, the negative charge is localized on a single oxygen, while in the carboxylate the charge is delocalized over two oxygen atoms by resonance.



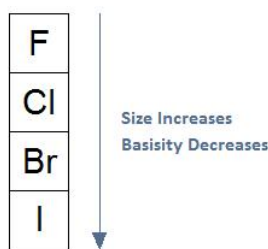
The nitrogen atom on an amide is less nucleophilic than the nitrogen of an amine, due to the resonance stabilization of the nitrogen lone pair provided by the amide carbonyl group.



The leaving group

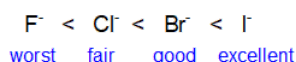
The more stable the leaving group, the lower the transition state energy, the lower the activation energy, the faster the reaction rate. Evaluating leaving group stability is analogous to determining relative acidity by evaluating conjugate base stability. The considerations are the same: identity of the atom(s) and relative position on the periodic table, resonance delocalization, and electronegativity. Orbital hybridization is rarely relevant.

As Size Increases, Basicity Decreases, Leaving Group Stability Increases: In general, if we move from the top of the periodic table to the bottom of the periodic table as shown in the diagram below, the size of an atom will increase. As size increases, basicity will decrease, meaning a species will be less likely to act as a base; that is, the species will be less likely to share its electrons.



When evaluating halogens as leaving groups, the same trend is significant. Fluoride has the highest electron density and is considered the worst leaving group to the point of no reactivity. As move down the column, the leaving groups have lower electron density and greater stability with iodide considered an excellent leaving group.

Leaving Group Comparison



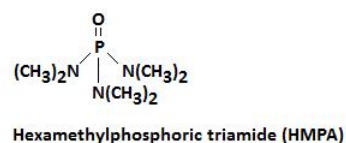
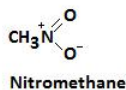
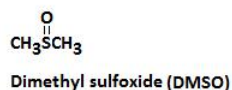
slower reaction and requires a catalyst to overcome the alkoxides as poor leaving groups. The details of these two reactions will be studied in greater detail later in this text.

Solvent Effects on an S_N2 reaction

The rate of an S_N2 reaction is significantly influenced by the solvent in which the reaction takes place. The use of protic solvents (those, such as water or alcohols, with hydrogen-bond donating capability) decreases the power of the nucleophile through strong solvation. WE can view the nucleophile as being locked in a solvent cage through the strong hydrogen-bond interactions between solvent protons and the reactive lone pairs on the nucleophile. A less powerful nucleophile in turn means a slower S_N2 reaction.

S_N2 reactions are faster in **polar, aprotic solvents**: those that lack hydrogen-bond donating capability. Below are several polar aprotic solvents that are commonly used in the laboratory:

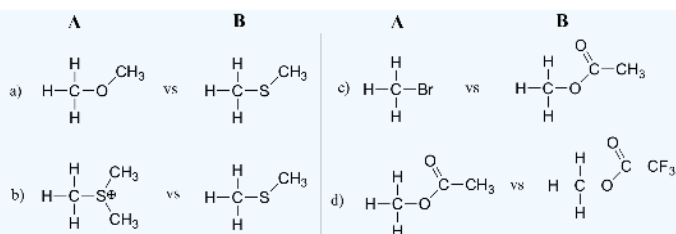
Polar Aprotic Solvents



These aprotic solvents are polar but, because they do not form hydrogen bonds with the anionic nucleophile, there is a relatively weak interaction between the aprotic solvent and the nucleophile. By using an aprotic solvent we can raise the reactivity of the nucleophile.

Example

In each pair (A and B) below, which electrophile would be expected to react more rapidly in an S_N2 reaction with the thiol group of cysteine as the common nucleophile?



Explanations to explain differences in chemical reactivity need to discuss structural and/or electrostatic differences between the reactants

a) Cpd B b/c it has a more stable leaving group.

The larger atomic size of S relative to O means the sulfide (CH_3S^-) will have a lower electron density than the alkoxide (CH_3O^-).

b) Cpd A b/c it has a more stable leaving group.

The neutral leaving group, $(\text{CH}_3)_2\text{S}$, is more stable than the charged sulfide leaving group (CH_3S^-).

c) Cpd B b/c the leaving group is resonance stabilized delocalizing the negative charge over two oxygen atoms. d) Cpd B b/c the leaving group has inductive electron withdrawal stabilization from the three fluorine atoms in addition to the resonance stabilization.

Exercise

1. What product(s) do you expect from the reaction of 1-bromopentane with each of the following reagents in an $\text{S}_{\text{N}}2$ reaction?

a) KI

b) NaOH

c) $\text{CH}_3\text{C}\equiv\text{C}-\text{Li}$

d) NH_3

2. Which in the following pairs is a better nucleophile?

a) $(\text{CH}_3\text{CH}_2)_2\text{N}^-$ or $(\text{CH}_3\text{CH}_2)_2\text{NH}$

b) $(\text{CH}_3\text{CH}_2)_3\text{N}$ or $(\text{CH}_3\text{CH}_2)_3\text{B}$

c) H_2O or H_2S

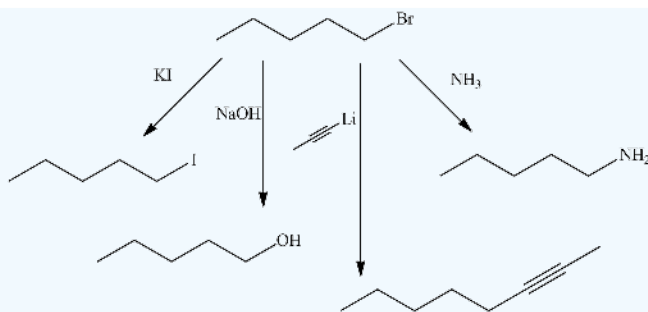
3. Order the following in increasing reactivity for an $\text{S}_{\text{N}}2$ reaction.

$\text{CH}_3\text{CH}_2\text{Br}$ $\text{CH}_3\text{CH}_2\text{OTos}$ $(\text{CH}_3\text{CH}_2)_3\text{CCl}$ $(\text{CH}_3\text{CH}_2)_2\text{CHCl}$

4. Solvents benzene, ether, chloroform are non-polar and not strongly polar solvents. What effects do these solvents have on an $\text{S}_{\text{N}}2$ reaction?

Answer

1. (a) - (d)



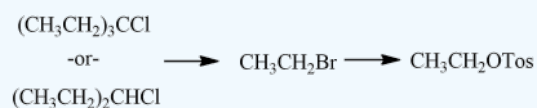
2.

a) $(\text{CH}_3\text{CH}_2)_2\text{N}^-$ as there is a charge present on the nitrogen.

b) $(\text{CH}_3\text{CH}_2)_3\text{N}$ because a lone pair of electrons is present.

c) H_2O as oxygen is more electronegative.

3.



4. They will decrease the reactivity of the reaction.

Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Jim Clark (Chemguide.co.uk)
- Characteristics of the $\text{S}_\text{N}2$ Reaction. (2020, May 30). Retrieved May 23, 2021, from <https://chem.libretexts.org/@go/page/45174>

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4.6: Characteristic of the SN1 Reaction

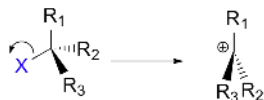
Learning Objective

- determine the rate law & predict the mechanism based on its rate equation or reaction data for S_N1 reactions
- predict the products and specify the reagents for S_N1 reactions with stereochemistry
- propose mechanisms for S_N1 reactions
- draw and interpret Reaction Energy Diagrams for S_N1 reactions

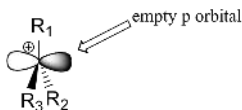
The S_N1 mechanism with Stereochemistry

As mentioned earlier, There are two possible mechanism for how an alkyl halide can undergo nucleophilic substitution, S_N2 and S_N1. The S_N2 reaction takes place in a single step with bond-forming and bond-breaking occurring simultaneously and we have described it in the previous section. A second model for a nucleophilic substitution reaction is called the '**dissociative**' or '**S_N1**' mechanism. In many examples of S_N1 reactions, the nucleophile is the solvent, so this mechanism can also be called "solvolysis". In this model, the nucleophilic substitution occurs in two steps:

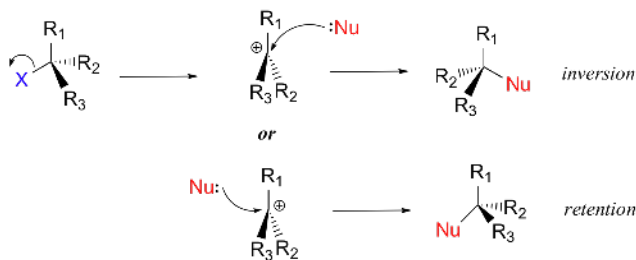
Step 1: In the S_N1 mechanism, the carbocation forms when the C-X bond breaks *first*, before the nucleophile approaches



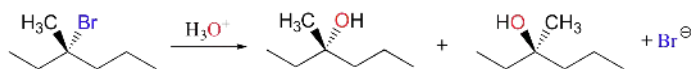
The carbocation has a central carbon with only three bonds and bears a formal charge of +1. Recall that a carbocation should be pictured as sp^2 hybridized, with trigonal planar geometry. Perpendicular to the plane formed by the three sp^2 hybrid orbitals is an empty, unhybridized p orbital.



Step 2: The nucleophile reacts with the empty, 'electron hungry' p orbital of the carbocation to form a new bond and return the carbon to tetrahedral geometry. Because of this trigonal planar geometry, the nucleophile can approach the carbocation from either lobe of the empty p orbital (aka either side of the carbocation). This means that about half the time the product has the same stereochemical configuration as the starting material (retention of configuration), and about half the time the stereochemistry has been inverted. In other words, *racemization* of the product occurs during S_N1 reactions if the electrophilic carbon is chiral. If the intermediate from a chiral alkyl halide survives long enough to encounter a random environment, the products are expected to be racemic (a 50:50 mixture of enantiomers). On the other hand, if the departing halide anion temporarily blocks the front side, or if a nucleophile is oriented selectively at one or the other face, then the substitution might occur with predominant inversion or even retention of configuration.



As an example, the tertiary alkyl bromide below, (S)-3-bromo-3-methylhexane, would be expected to form a racemic mix of R- and S-3-methyl-3-hexanol after an S_N1 reaction with water as the nucleophile.

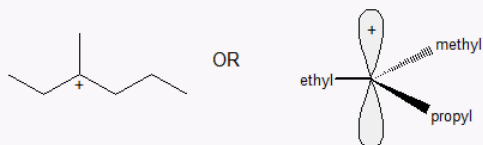


Exercise

1. Draw the structure of the intermediate in the two-step nucleophilic substitution reaction (S_N1) above.

Solution

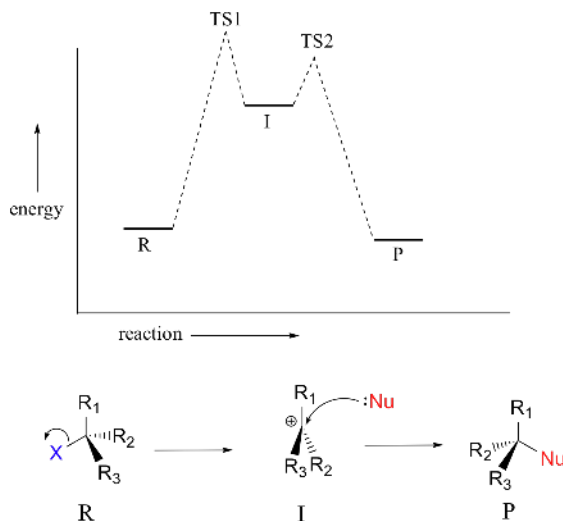
1.



When interpreting bond-line structures, it is useful to visualize the electronic structure with an unhybridized, empty p orbital extending perpendicular to the alkyl groups.

The S_N1 Reaction Energy Diagram

The S_N1 reaction is an example of a two-step reaction with a reaction intermediate. Evaluating reactive intermediates is a very important skill in the study of organic reaction mechanisms. Many important organic reactions do not occur in a single step; rather, they are the sum of two or more discrete bond-forming / bond-breaking steps, and involve transient intermediate species that go on to react very quickly. In the S_N1 reaction, the carbocation species is a reaction intermediate. A potential energy diagram for an S_N1 reaction shows that the carbocation intermediate can be visualized as a kind of valley in the path of the reaction, higher in energy than both the reactant and product but lower in energy than the two transition states.

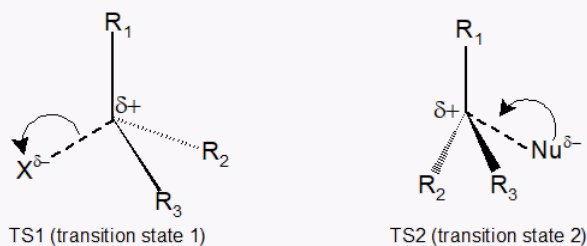


Exercise

2. Draw structures representing transition state 1 (TS1) and transition state 2 (TS2) in the reaction above. Use the solid/dash wedge convention to show three dimensions.

Solution

2.

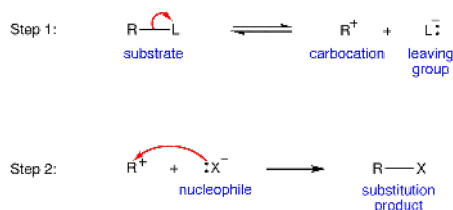


S_N1 Reaction Kinetics

In the first step of an S_N1 mechanism, two charged species are formed from a neutral molecule. This step is much the slower of the two steps, and is therefore rate-determining. In the reaction energy diagram, the activation energy for the first step is higher than that for the second step indicating that the S_N1 reaction has *first order* kinetics because the rate determining step involves one molecule splitting apart, not two molecules colliding. It is important to remember that first order refers to the rate law expression where the generic term substrate is used to describe the alkyl halide.

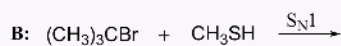
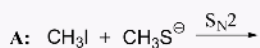
$$\text{rate} = k [\text{substrate}]$$

Because an S_N1 reaction is first order overall the concentration of the nucleophile does not affect the rate. The implication is that the nucleophile does not participate in the rate limiting step or any prior steps, which suggests that the first step is the rate limiting step. Since the nucleophile is not involved in the rate-limiting first step, the nature of the nucleophile does not affect the rate of an S_N1 reaction.

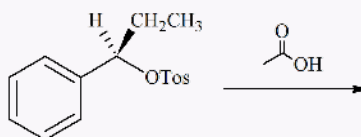


Exercise

3. Consider two nucleophilic substitutions that occur uncatalyzed in solution. Assume that reaction A is S_N2, and reaction B is S_N1. Predict, in each case, what would happen to the rate of the reaction if the concentration of the nucleophile were doubled, while all other conditions remained constant.



4. Give the products of the following S_N1 reaction. Show stereochemistry.

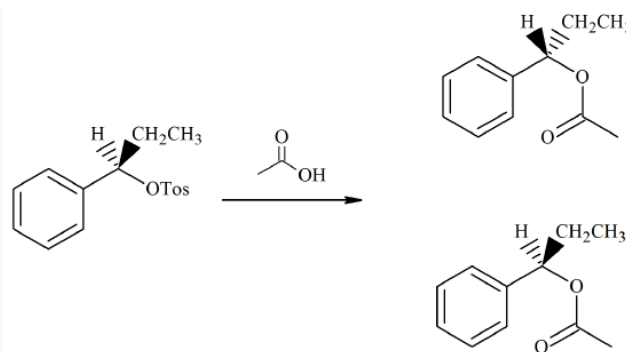


Solution

3. For Reaction A, the rate law is $\text{rate} = k[\text{CH}_3\text{I}][\text{CH}_3\text{S}^-]$. Therefore, if the concentration of the nucleophile, CH_3S^- , is doubled and the concentration of the alkyl halide remains the same, then the reaction rate will double.

For Reaction B, the rate law is $\text{rate} = k[(\text{CH}_3)_3\text{CBr}]$. Therefore, if the concentration of the nucleophile, CH_3SH , is doubled and the concentration of the alkyl halide remains the same, then reaction rate stays the same.

4.



Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, [Athabasca University](#))
- Prof. Steven Farmer ([Sonoma State University](#))
- William Reusch, Professor Emeritus ([Michigan State U.](#)), [Virtual Textbook of Organic Chemistry](#)
- [Organic Chemistry With a Biological Emphasis](#) by Tim Soderberg (University of Minnesota, Morris)
- Jim Clark ([Chemguide.co.uk](#))
- The S_N1 Reaction. (2020, May 30). Retrieved May 23, 2021, from <https://chem.libretexts.org/@go/page/45178>

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4.7: Factors Affecting the S_N1 Reaction

Learning Objective

- determine the rate law & predict the mechanism based on its rate equation or reaction data for S_N1 reactions
- predict the products and specify the reagents for S_N1 reactions with stereochemistry
- propose mechanisms for S_N1 reactions
- draw and interpret Reaction Energy Diagrams for S_N1 reactions

In order of decreasing importance, the factors impacting S_N1 reaction pathways are

1. structure of the alkyl halide
2. stability of the leaving group
3. type of solvent.

The unimolecular transition state of the S_N1 pathway means that structure of the alkyl halide and stability of the leaving group are the primary considerations. Alkyl halides that can ionize to form stable carbocations are more reactive via the S_N1 mechanism. Because carbocation stability is the primary energetic consideration, stabilization of the carbocation via solvation is also an important consideration.

Alkyl Halide Structure

Alkyl halides that can ionize to form stable carbocations are more reactive via the S_N1 mechanism. The stability order for carbocation is as follows:

 Carbocation Stability Trend

Carbocation stability order: 3° > 2° > 1° > methyl. Image by [Alatleephillips](#), CC BY-SA 4.0, via Wikimedia Commons

That order means that a tertiary alkyl halide is more reactive towards S_N1 compared to secondary and primary alkyl halides respective. Methyl halides almost never react via an S_N1 mechanism. Notice that this reactivity order is the exact opposite of S_N2 reactions.

Effects of Leaving Group

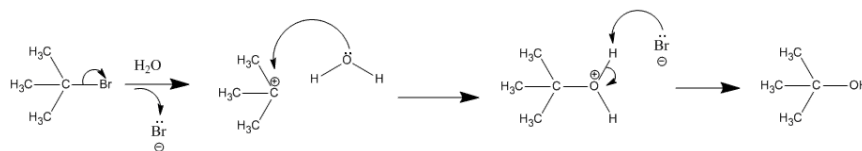
An S_N1 reaction also speeds up with a good leaving group. This is because the leaving group is involved in the rate-determining step. A good leaving group wants to leave so it breaks the C-Leaving Group bond faster. Once the bond breaks, the carbocation is formed and the faster the carbocation is formed, the faster the nucleophile can come in and the faster the reaction will be completed.

A good leaving group is a weak base because weak bases can hold the charge. They're happy to leave with both electrons and in order for the leaving group to leave, it needs to be able to accept electrons. Strong bases, on the other hand, donate electrons which is why they can't be good leaving groups. As you go from left to right on the periodic table, electron donating ability decreases and thus ability to be a good leaving group increases. Halides are an example of a good leaving group whos leaving-group ability increases as you go down the column.



Solvent Effects on the S_N1 Reaction

To facilitate the formation of ions, a polar solvent is needed. In the case of S_N1 reactions, polar protic solvents speed up the rate of S_N1 reactions because the polar solvent helps stabilize the transition state and carbocation intermediate. Since the carbocation is unstable, anything that can stabilize this even a little will speed up the reaction. Polar aprotic solvents have a dipole moment, but their hydrogen is not highly polarized.

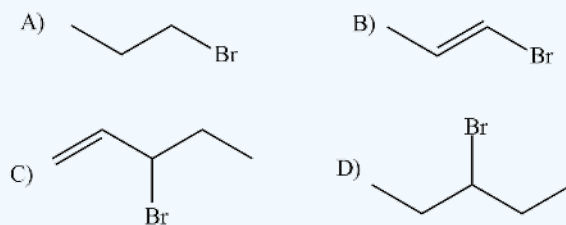


Effects of Nucleophile

The strength of the nucleophile does not affect the reaction rate of S_N1 because the nucleophile is not involved in the rate-determining step. Therefore, weak nucleophiles tend to favor S_N1 mechanism. Typical S_N1 reactions take place where the solvent is the nucleophile. Examples: H_2O , alcohols (ROH), CH_3CN , etc.

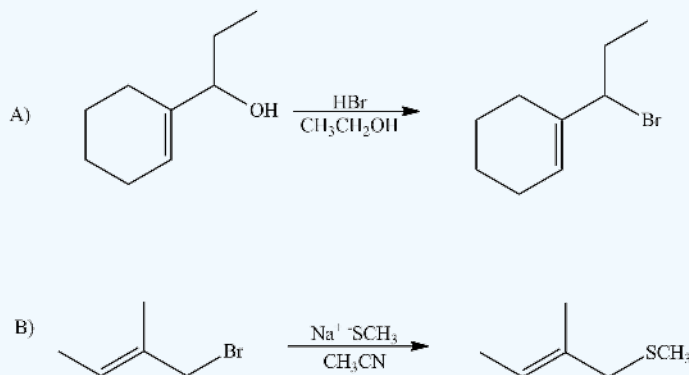
Exercises

1. Rank the following by increasing reactivity in an S_N1 reaction.



2. 3-bromo-1-pentene and 1-bromo-2-pentene undergo S_N1 reaction at almost the same rate, but one is a secondary halide while the other is a primary halide. Explain why this is.

3. Label the following reactions as most likely occurring by an S_N1 or S_N2 mechanism. Suggest why.

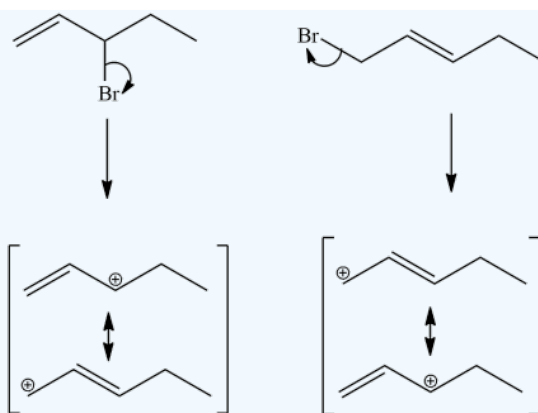


Answers

1. Consider the stability of the intermediate, the carbocation.

A < D < B < C (most reactive)

2. They have the same intermediates when you look at the resonance forms.



3. A – S_N1 *poor leaving group, protic solvent, secondary cation intermediate

B – S_N2 *good leaving group, polar solvent, primary position.

Citations and attributions

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

Characteristics of the S_N1 Reaction. (2020, May 30). Retrieved May 23, 2021, from <https://chem.libretexts.org/@go/page/45179>

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4.8: Comparison of S_N1 and S_N2 Reactions

Learning Objective

- distinguish 1st or 2nd order substitution reactions

Predicting S_N1 vs. S_N2 mechanisms

When considering whether a nucleophilic substitution is likely to occur via an S_N1 or S_N2 mechanism, we really need to consider three factors:

1) **The electrophile:** when the leaving group is attached to a methyl group or a primary carbon, an S_N2 mechanism is favored (here the electrophile is unhindered by surrounded groups, and any carbocation intermediate would be high-energy and thus unlikely). When the leaving group is attached to a tertiary carbon, a carbocation intermediate will be relatively stable and thus an S_N1 mechanism is favored. These patterns of reactivity of summarized below.

Alkyl Halide Structure	Possible Substitution Reactions
methyl and primary	S _N 2 only
secondary	S _N 2 and S _N 1
tertiary	S _N 1 only
primary and secondary benzylic and allylic	S _N 2 and S _N 1

2) **The nucleophile:** powerful nucleophiles, especially those with negative charges, favor the S_N2 mechanism. Weaker nucleophiles such as water or alcohols favor the S_N1 mechanism.

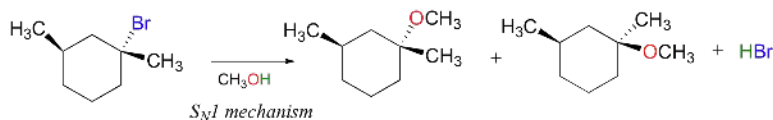
3) **The solvent:** Polar aprotic solvents favor the S_N2 mechanism by enhancing the reactivity of the nucleophile. Polar protic solvents favor the S_N1 mechanism by stabilizing the transition state and carbocation intermediate. S_N1 reactions are called solvolysis reactions when the solvent is the nucleophile.

These patterns of reactivity are summarized in the table below.

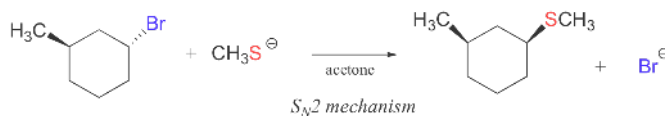
Comparison between S_N2 and S_N1 Reactions

Reaction Parameter	S _N 2	S _N 1
alkyl halide structure	methyl > primary > secondary >>>> tertiary	tertiary > secondary >>>> primary > methyl
nucleophile	high concentration of a strong nucleophile	poor nucleophile (often the solvent)
mechanism	1-step	2-step
rate limiting step	bimolecular transition state	carbocation formation
rate law	rate = k[R-X][Nu]	rate = k[R-X]
stereochemistry	inversion of configuration	mixed configuration
solvent	polar aprotic	polar protic

For example, the reaction below has a tertiary alkyl bromide as the electrophile, a weak nucleophile, and a polar protic solvent (we'll assume that methanol is the solvent). Thus we'd confidently predict an S_N1 reaction mechanism. Because substitution occurs at a chiral carbon, we can also predict that the reaction will proceed with racemization.

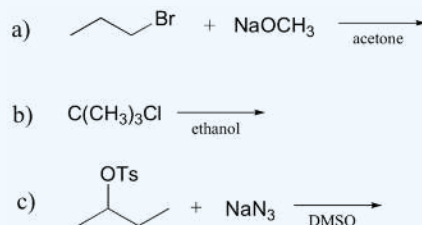


In the reaction below, on the other hand, the electrophile is a secondary alkyl bromide – with these, both S_N1 and S_N2 mechanisms are possible, depending on the nucleophile and the solvent. In this example, the nucleophile (a thiolate anion) is strong, and a polar aprotic solvent is used – so the S_N2 mechanism is heavily favored. The reaction is expected to proceed with inversion of configuration.



Exercise

1. Determine whether each substitution reaction shown below is likely to proceed by an S_N1 or S_N2 mechanism and explain your reasoning.



Answer

- a) S_N2 b/c primary alkyl halide with a strong nucleophile in a polar aprotic solvent.
- b) S_N1 b/c tertiary alkyl halide with a weak nucleophile that is also the solvent (solvolysis).
- c) S_N2 b/c secondary alkyl halides favor this mechanism when reacted with a strong nucleophile (and weak base) in a polar aprotic solvent.

Attributions and citations

Comparison of S_N1 and S_N2 Reactions. (2020, May 30). Retrieved May 23, 2021, from <https://chem.libretexts.org/@go/page/45181>

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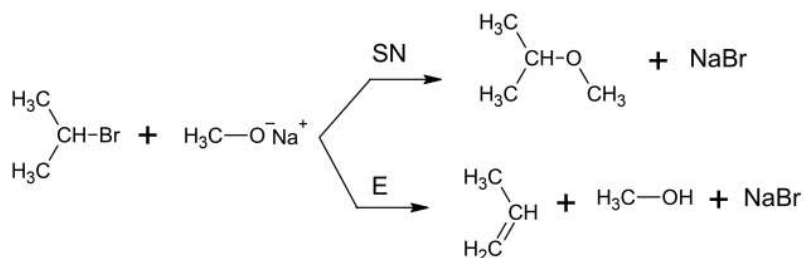
4.9: Characteristics of the E2 Reaction

Learning Objective

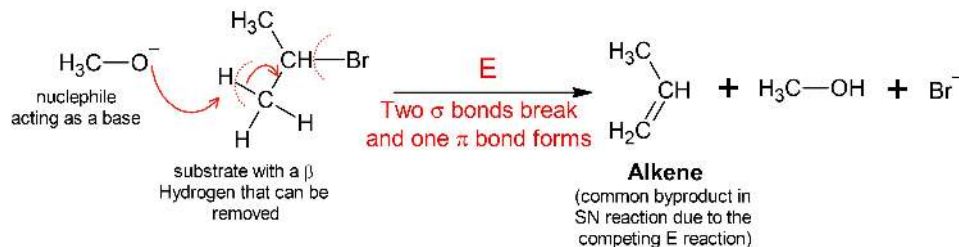
- determine the rate law & predict the mechanism based on its rate equation or reaction data for E2 reactions
- predict the products and specify the reagents for E2 reactions with stereochemistry
- propose mechanisms for E2 reactions
- draw and interpret Reaction Energy Diagrams for E2 reactions

Elimination vs Substitution reactions

When an alkyl halide has a beta hydrogen, two competing reactions are possible: substitution or elimination. The symbol E is used to designate an elimination process.



Elimination reactions are possible because nucleophiles are also bases (they can capture a H⁺).

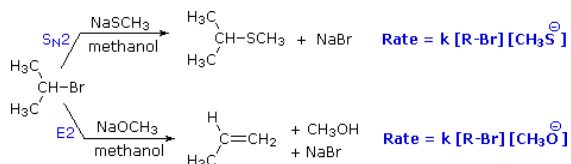


There are two main mechanisms for elimination reactions, designated E2 or E1.

Introduction to E2

E2 reactions are typically seen with secondary and tertiary alkyl halides, but a hindered base is necessary with a primary halide. The mechanism by which it occurs is a single step **concerted** reaction with one transition state. The rate at which this mechanism occurs is second order kinetics, and depends on both the base and alkyl halide. A good leaving group is required because it is involved in the rate determining step. The leaving groups must be coplanar in order to form a pi bond; carbons go from sp^3 to sp^2 hybridization states.

To get a clearer picture of the interplay of these factors involved in a reaction between a nucleophile/base and an alkyl halide, consider the reaction of a 2°-alkyl halide, isopropyl bromide, with two different nucleophiles. In one pathway, a methanethiolate nucleophile substitutes for bromine in an $\text{S}_{\text{N}}2$ reaction. In the other (bottom) pathway, methoxide ion acts as a base (rather than as a nucleophile) in an elimination reaction. As we will soon see, the mechanism of this reaction is single-step, and is referred to as the E2 mechanism.



In order of decreasing importance, the factors impacting E2 reaction pathways are

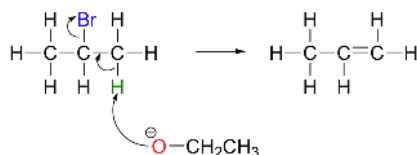
- 1) structure of the alkyl halide

- 2) strength of the base
- 3) stability of the leaving group
- 4) type of solvent.

The bimolecular transition state of the E2 pathway means that orientation of the base and leaving group are a primary consideration. Both the base and leaving group are electron rich and electrostatically repel each other forcing an anti-coplanar orientation between the base and leaving group. The structure of the alkyl halide must assume the orientation for an anti-coplanar transition state. The strength of the base will also influence the reaction along with the stability of the leaving group. Solvents play a very minor role in E2 pathway.

General Reaction

Below is a mechanistic diagram of an elimination reaction by the E2 pathway:



In this reaction, ethoxide ($\text{CH}_3\text{CH}_2\text{O}^-$) represents the base and Br represents a leaving group, typically a halogen. There is one transition state that shows the concerted reaction for the base attracting the hydrogen and the halogen taking the electrons from the bond.

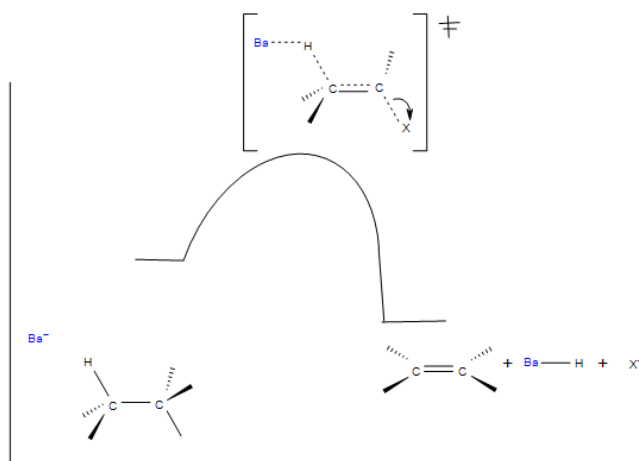
An E2 reaction has certain requirements to proceed:

- A strong base is necessary especially necessary for primary alkyl halides. Secondary and tertiary primary halides will proceed with E2 in the presence of a base (OH^- , RO^- , R_2N^-)
- Both leaving groups should be on the same plane, this allows the double bond to form in the reaction. In the reaction above you can see both leaving groups are in the plane of the carbons.
- Follows Zaitsev's rule, the most substituted alkene is usually the major product.
-

E2 Reaction Coordinate

In the reaction energy diagram below, the base is represented as Ba^- . The bimolecular transition state determines the overall reaction rate. It is important to note the anti-coplanar orientation of the base and the leaving group. Both the base and leaving group are electron rich and electrostatically repel each other forcing an anti-coplanar orientation between the base and leaving group.

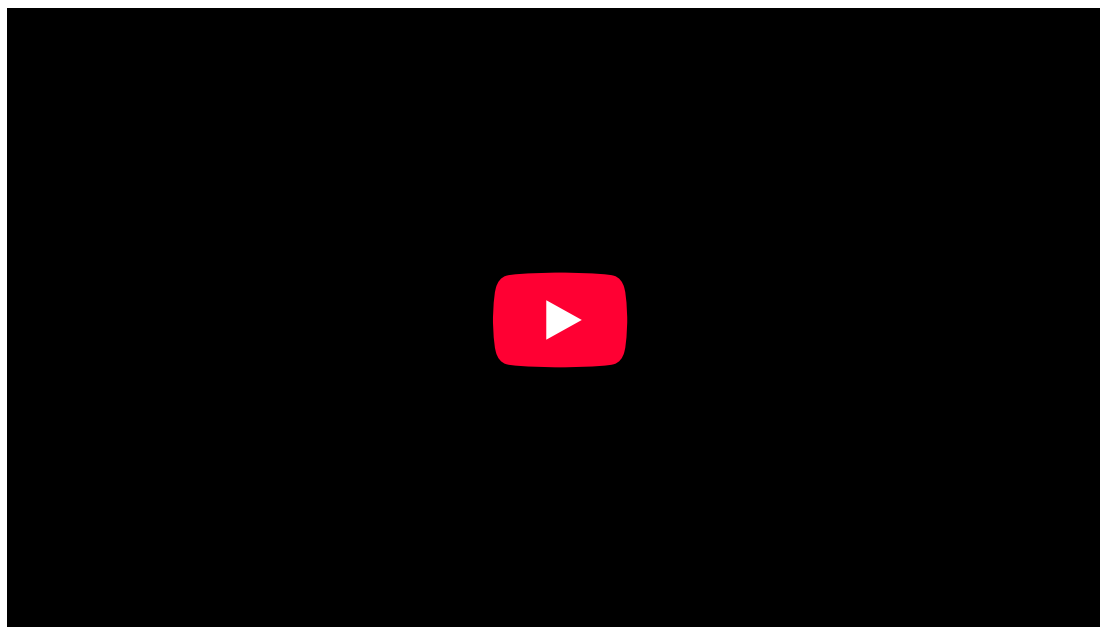
anti-coplanar transition state



The Leaving Group Effect in E₂ Reactions

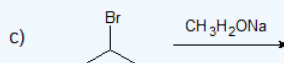
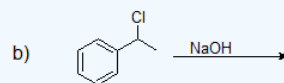
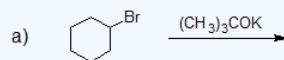
As Size Increases, The Electron Density Decrease, The Ability of the Leaving Group to Leave Increases: Here we revisit the effect size has on basicity. If we move down the periodic table, size increases. With an increase in size, basicity decreases, and the ability of the leaving group to leave increases. The relationship among the following halogens, unlike the previous example, is true to what we will see in upcoming reaction mechanisms.





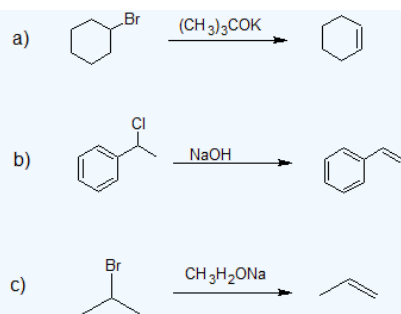
Exercise

1. Ignoring the alkene stereochemistry show the elimination product(s) of the following compounds.



Answer

1.



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

- Layne A. Morsch (University of Illinois Springfield)
- Characteristics of the E2 Reaction. (2020, May 30). Retrieved May 23, 2021, from <https://chem.libretexts.org/@go/page/111924>

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4.10: Zaitsev's Rule

Learning Objective

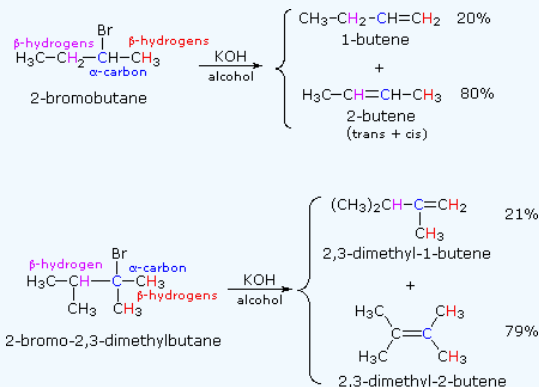
- use Zaitsev's rule to predict major and minor products of elimination reactions

Zaitsev's Rule and Regioselectivity

The prefix "regio" indicates the interaction of reactants during bond making and/or bond breaking occurs preferentially by one orientation. Because the beta-carbons of an alkyl halide may not be equivalent, there can be more than one possible elimination product. Zaitsev's Rule can be used to predict the regiochemistry of elimination reactions.

Zaitsev's or Saytzev's (anglicized spelling) rule is an empirical rule used to predict regioselectivity of beta-elimination reactions occurring via the E1 or E2 mechanisms. It states that in a regioselective E1 or E2 reaction the major product is the more stable alkene with the more highly substituted double bond as shown in the example below.

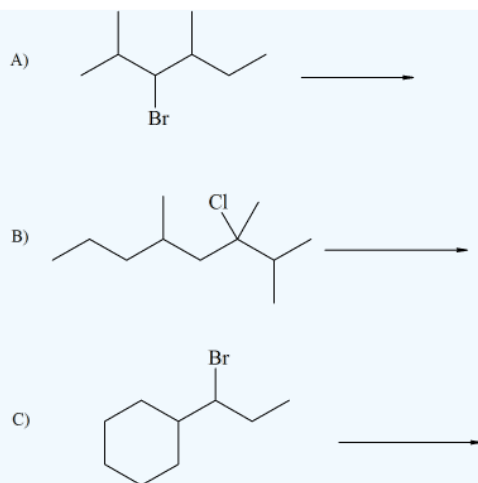
If two or more structurally distinct groups of beta-hydrogens are present in a given reactant, then several constitutionally isomeric alkenes may be formed by an E2 elimination. This situation is illustrated by the 2-bromobutane and 2-bromo-2,3-dimethylbutane elimination examples given below.



By using the strongly basic hydroxide nucleophile, we direct these reactions toward elimination. In both cases there are two different sets of beta-hydrogens available to the elimination reaction (these are colored red and magenta and the alpha carbon is blue). If the rate of each possible elimination was the same, we might expect the amounts of the isomeric elimination products to reflect the number of hydrogens that could participate in that reaction. For example, since there are three 1°-hydrogens (red) and two 2°-hydrogens (magenta) on beta-carbons in 2-bromobutane, statistics would suggest a 3:2 ratio of 1-butene and 2-butene in the products. This is not observed, and the latter predominates by 4:1. This departure from statistical expectation is even more pronounced in the second example, where there are six 1°-beta-hydrogens compared with one 3°-hydrogen. These results point to a strong regioselectivity favoring the more highly substituted product double bond, an empirical statement generally called the **Zaitsev Rule**.

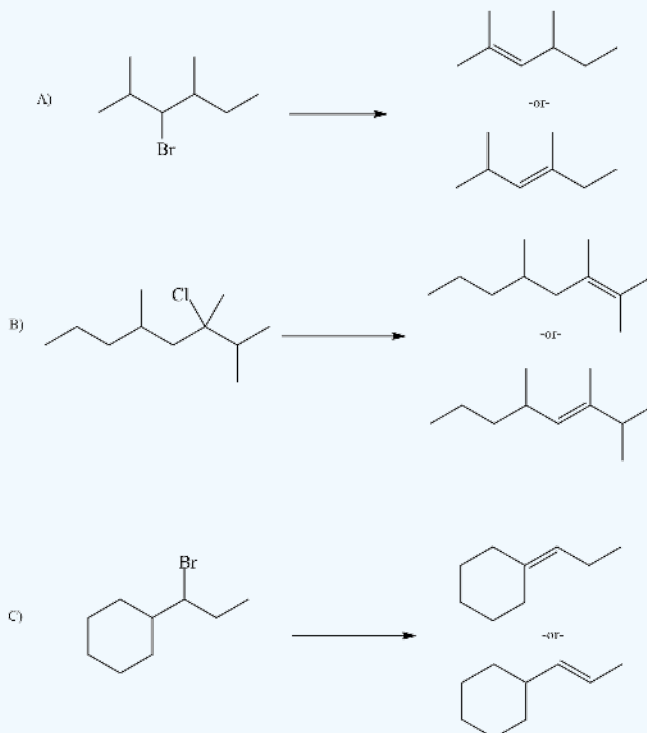
Exercise

- Ignoring the alkene stereochemistry show the elimination product(s) of the following compounds:



Answer

1.



Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, [Athabasca University](#))
- Prof. Steven Farmer ([Sonoma State University](#))
- William Reusch, Professor Emeritus ([Michigan State U.](#)), [Virtual Textbook of Organic Chemistry](#)
- [Organic Chemistry With a Biological Emphasis](#) by Tim Soderberg (University of Minnesota, Morris)

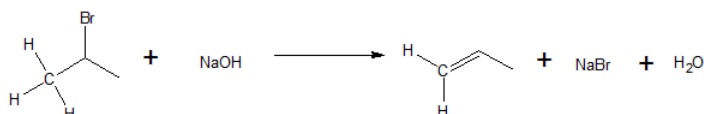
4.11: Characteristics of the E1 Reaction

Learning Objective

- determine the rate law & predict the mechanism based on its rate equation or reaction data for E1 reactions
- predict the products and specify the reagents for E1 reactions with stereochemistry
- propose mechanisms for E1 reactions
- draw and interpret Reaction Energy Diagrams for E1 reactions

General Reaction

Unimolecular Elimination (E1) is a reaction in which loss of the leaving group followed by removal of the beta-hydrogen results in the formation of a double bond.



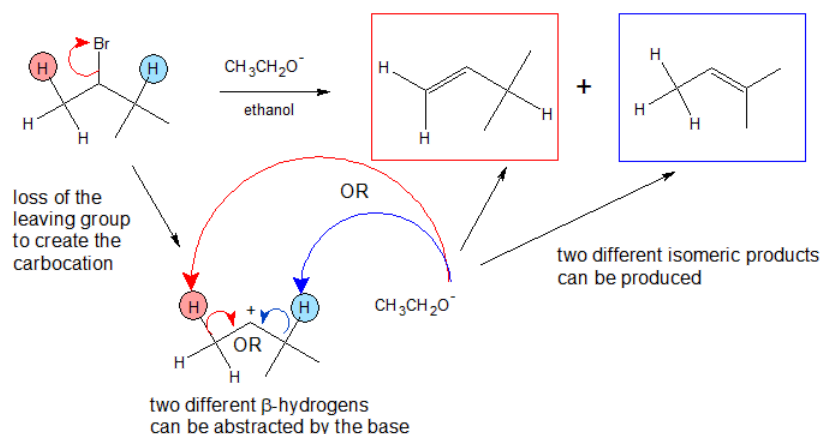
It is similar to a unimolecular nucleophilic substitution reaction (S_N1) in various ways. One being the formation of a carbocation intermediate as the rate determining (slow) step, hence the name unimolecular. Alkyl halides that can ionize to form stable carbocations are more reactive via the E1 mechanism. Because carbocation stability is the primary energetic consideration, stabilization of the carbocation via solvation is also an important consideration. Because carbocations are highly reactive, the strength of the base is not important and weak bases can be used. Since S_N1 and E1 reactions behave similarly, they often compete against each other. Many times, both these reactions will occur simultaneously to form different products from a single reaction. However, one can be favored over another through thermodynamic control. Heating the reaction favors elimination over substitution.

In order of decreasing importance, the factors impacting E1 reaction pathways are

- 1) structure of the alkyl halide
- 2) stability of the carbocation
- 3) type of solvent
- 4) strength of the base.

Mechanism for Alkyl Halides

As can be seen in the E1 mechanism below, the preliminary step is the leaving group (LG) leaving on its own. Because it takes the electrons in the bond along with it, the carbon that was attached to it loses its electron, making it a carbocation. Once it becomes a carbocation, a Lewis Base (B⁻) deprotonates the intermediate carbocation at the beta position, which then donates its electrons to the neighboring C-C bond to form a double bond. Unlike E2 reactions, which require the proton to be *anti* to the leaving group, E1 reactions only require a neighboring hydrogen. This is due to the fact that the leaving group has already left the molecule. The final product is an alkene along with the HB byproduct and leaving group salt.



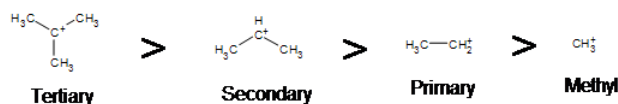
Once again, we see the two steps of the E1 mechanism.

1. A base deprotonates a beta carbon to form a pi bond.

In this case we see a mixture of products rather than one discrete one. This is the case because the carbocation has two nearby carbons that are capable of being deprotonated, but that only one forms a major product (more stable).

Reactivity

Due to the fact that E1 reactions create a carbocation intermediate, rules present in $\text{S}_{\text{N}}1$ reactions still apply.



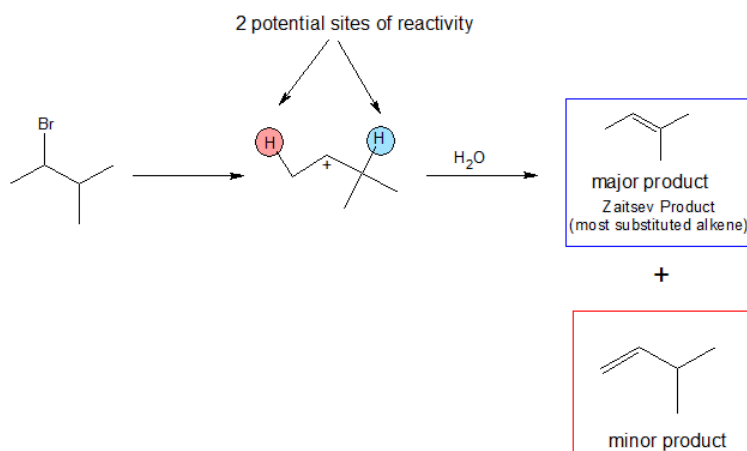
As expected, tertiary carbocations are favored over secondary, primary and methyl's. This is due to the phenomena of hyperconjugation, which essentially allows a nearby C-C or C-H bond to interact with the p orbital of the carbon to bring the electrons down to a lower energy state. Thus, this has a stabilizing effect on the molecule as a whole. In general, primary and methyl carbocations do not proceed through the E1 pathway for this reason, unless there is a means of carbocation rearrangement to move the positive charge to a nearby carbon. Secondary and Tertiary carbons form more stable carbocations, thus this formation occurs quite rapidly.

Secondary carbocations can be subject to the E2 reaction pathway, but this generally occurs in the presence of a good / strong base. Adding a weak base to the reaction disfavors E2, essentially pushing towards the E1 pathway. In many instances, solvolysis occurs rather than using a base to deprotonate. This means heat is added to the solution, and the solvent itself deprotonates a hydrogen. The medium can effect the pathway of the reaction as well. Polar protic solvents may be used to hinder nucleophiles, thus disfavoring E2 / $\text{S}_{\text{N}}2$ from occurring.

Regiochemistry & Stereochemistry of the E1 Reaction

The E1 reaction is regiospecific because it follows Zaitsev's rule that states the more substituted alkene is the major product. This infers that the hydrogen on the most substituted carbon is the most probable to be deprotonated, thus allowing for the most substituted alkene to be formed.

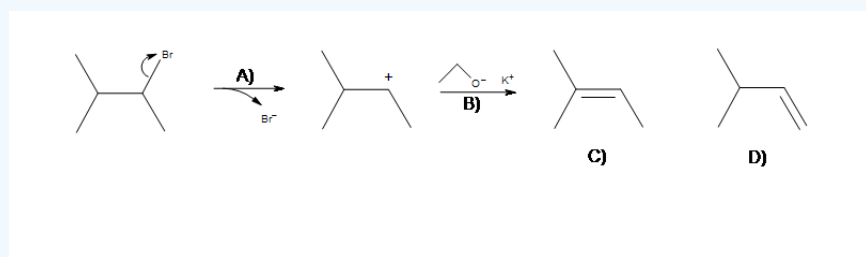
Unlike E2 reactions, the E1 reaction is not stereospecific. Thus, a hydrogen is not required to be anti-coplanar to the leaving group because the leaving group is gone. In the mechanism below, we can see two possible pathways for the reaction. Either one leads to a plausible resultant product, however, only one forms a major product. As stated by [Zaitsev's rule](#), deprotonation of the most substituted carbon results in the most substituted alkene. This then becomes the most stable product due to hyperconjugation, and is also more common than the minor product.



Exercises

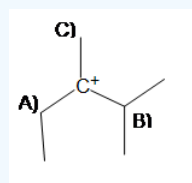
1. Which of these steps is the rate determining step (A or B)?

What is the major product formed (C or D)?

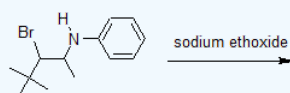


2. In order to produce the most stable alkene product, from which carbon should the base deprotonate (A, B, or C)?

If the carbocation were to rearrange, on which carbon would the positive charge go onto without sacrificing stability (A, B, or C)?



3) Predict the major product of the following reaction.



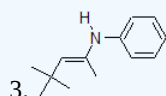
4) (True or False) – There is no way of controlling the product ratio of E1 / S_N1 reactions.

5) Explain why the presence of a weak base / nucleophile favors E1 reactions over E2.

Answer

1. A , C

2. B, B



4. False - They can be thermodynamically controlled to favor a certain product over another.
5. By definition, an E1 reaction is a Unimolecular Elimination reaction. This means the only rate determining step is that of the dissociation of the leaving group to form a carbocation. Since E2 is bimolecular and the nucleophilic attack is part of the rate determining step, a weak base/nucleophile disfavors it and ultimately allows E1 to dominate. (Don't forget about S_N1 which still pertains to this reaction simultaneously).

Outside Links

- E1 reaction background: http://en.Wikipedia.org/wiki/E1_elimination

Outside Sources

1. McMurry, J., Simanek, E. Fundamentals of Organic Chemistry, 6th edition. Cengage Learning, 2007.

Contributors

- Satish Balasubramanian

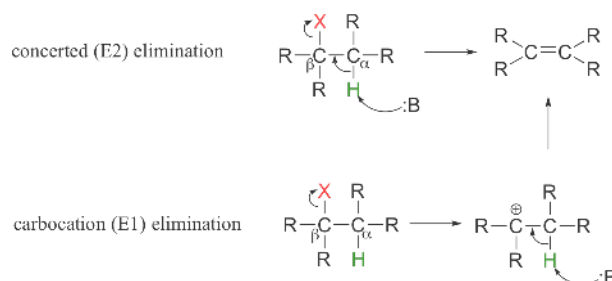
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4.12: Comparison of E1 and E2 Reactions

Learning Objective

- distinguish 1st or 2nd order elimination reactions

Elimination reactions of alkyl halides can occur via the bimolecular E2 mechanism or unimolecular E1 mechanism as shown in the diagram below.



Comparing E1 and E2 mechanisms

When considering whether an elimination reaction is likely to occur via an E1 or E2 mechanism, we really need to consider three factors:

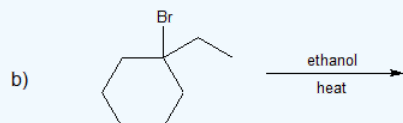
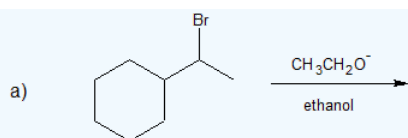
- The base:** strong bases favor the E2 mechanism, whereas, E1 mechanisms only require a weak base.
- The solvent:** good ionizing solvents (polar protic) favor the E1 mechanism by stabilizing the carbocation intermediate.
- The alkyl halide:** primary alkyl halides have the only structure useful in distinguishing between the E2 and E1 pathways. Since primary carbocations do not form, only the E2 mechanism is possible.

Ultimately, whether the elimination mechanism is E1 or E2 is not very important, since the product is the same alkene. We need to remember, however, that Zaitsev's rule always determines the most likely alkene to be formed.

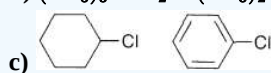
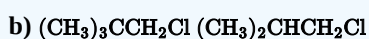
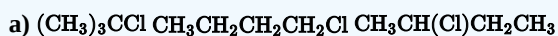
Reaction Parameter	E2	E1
alkyl halide structure	tertiary > secondary > primary	tertiary > secondary >>>> primary
nucleophile	high concentration of a strong base	weak base
mechanism	1-step	2-step
rate limiting step	bimolecular transition state	carbocation formation
rate law	rate = $k[\text{R-X}][\text{Base}]$	rate = $k[\text{R-X}]$
solvent	not important	polar protic

Exercises

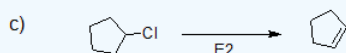
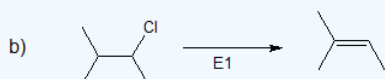
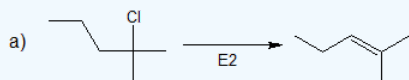
- Predict the dominant elimination mechanism (E1 or E2) for each reaction below. Explain your reasoning.



2. Which one of the following groups of compounds would eliminate **HCl** most readily on reaction with potassium hydroxide? Explain your reasoning, draw the bond-line structure and give the IUPAC name of the product.

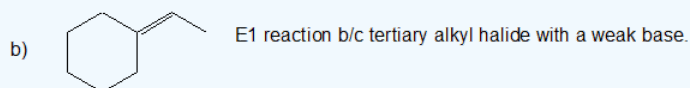
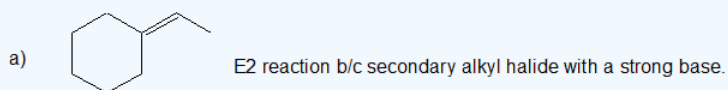


3. Specify the reaction conditions to favor the indicated elimination mechanism.



Answer

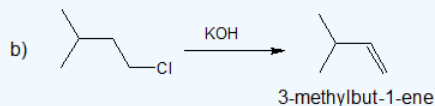
1.



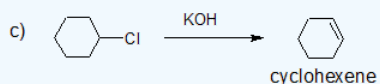
2.



t-butyl chloride will react faster b/c it is a tertiary alkyl halide reacting with a strong base via the E2 mechanism.



1-chloro-3-methyl butane will react faster since both reactants are primary alkyl halides and the reaction conditions favor the E2 mechanism, the reactant with less steric hindrance at the beta-hydrogen will react faster.



The alkyl halide b/c aryl halides cannot undergo elimination reactions under these conditions.

3. a) strong base, such as hydroxide, an alkoxide, or equivalent

b) water or alcohol or equivalent weak base with heat

c) strong base, such as hydroxide, an alkoxide, or equivalent

Citations and attributions

Comparison of E1 and E2 Reactions. (2020, May 30). Retrieved May 23, 2021, from <https://chem.libretexts.org/@go/page/45186>
Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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4.13: Competition between substitution and elimination

Having discussed the many factors that influence nucleophilic substitution and elimination reactions of alkyl halides, we must now consider the practical problem of predicting the most likely outcome when a given alkyl halide is reacted with a given nucleophile. As we noted earlier, several variables must be considered, **the most important being the structure of the alkyl group and the nature of the nucleophilic reactant**. In general, in order for an S_N1 or $E1$ reaction to occur, the relevant carbocation intermediate must be relatively stable. Strong nucleophiles favor substitution, and strong bases, especially strong hindered bases (such as tert-butoxide) favor elimination.

The nature of the halogen substituent on the alkyl halide is usually not very significant if it is Cl, Br or I. In cases where both S_N2 and $E2$ reactions compete, chlorides generally give more elimination than do iodides, since the greater electronegativity of chlorine increases the acidity of beta-hydrogens. Indeed, although alkyl fluorides are relatively unreactive, when reactions with basic nucleophiles are forced, elimination occurs (note the high electronegativity of fluorine).

The following table summarizes the expected outcome of alkyl halide reactions with nucleophiles. It is assumed that the alkyl halides have one or more beta-hydrogens, making elimination possible; and that low dielectric solvents (e.g. acetone, ethanol, tetrahydrofuran & ethyl acetate) are used. When a very polar solvent would significantly influence the reaction this is noted in red. Remember that halogens bonded to sp^2 or sp hybridized carbon atoms do not normally undergo substitution or elimination reactions with nucleophilic reagents.

The most important aspect to remember is that substitution and elimination reactions compete with each other, and in most cases, a mixture of different products is obtained. By changing the experimental condition (mainly the nucleophile and solvent), we can favor the formation of substitution or elimination products

Nucleophile	Anionic Nucleophiles (Weak Bases: I^- , Br^- , SCN^- , N_3^- , $CH_3CO_2^-$, RS^- , CN^- etc.) pK_a 's from -9 to 10 (left to right)	Anionic Nucleophiles (Strong Bases: HO^- , RO^-) pK_a 's > 15	Neutral Nucleophiles (H_2O , ROH , RSH , R_3N) pK_a 's ranging from -2 to 11

Contributors

4.13.2

Competition between substitution and elimination. (2020, September 13). Retrieved May 23, 2021, from <https://chem.libretexts.org/@go/page/14800>

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CHAPTER OVERVIEW

5: Structural Determination I

- 5.1: Prelude to Structure Determination I
- 5.2: Molecular Formulas and Empirical Formulas
- 5.3: Mass Spectrometry
- 5.4: Introduction to molecular spectroscopy
- 5.5: Ultraviolet and visible spectroscopy
- 5.6: Effect of Conjugation
- 5.7: Conjugation, Color, and the Chemistry of Vision
- 5.8: Infrared spectroscopy

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5.1: Prelude to Structure Determination I

Structural determination of organic structures

Paclitaxel, sold under the brand name Taxol® among others, is a chemotherapy medication used to treat a number of types of cancer. Paclitaxel was first isolated in 1971 from the Pacific yew and approved for medical use in 1993. Its chemical structure is quite complex, with several functional groups and a total of 11 stereogenic centers. How do chemists determine the structure of such complex molecules?



Chemical structure of Paclitaxel, sold under the brand name Taxol®. Image by Calvero., Public domain, via Wikimedia Commons

In the next two chapters of this text, we have focused our efforts on learning about the structure of organic compounds. Now that we know what organic molecules look like, we can begin to address, in the next two chapters, the question of how we get this knowledge in the first place. How are chemists able to draw with confidence the bonding arrangements in organic molecules, even simple ones such as acetone or ethanol? How was James Martin at Orion Analytical able to identify the chemical structure of the pigment compound responsible for the 'funky yellow color' in the forged William Aiken Walker painting?

This chapter is devoted to three very important techniques used by chemists to learn about the structures of organic molecules. First, we will learn how elemental analysis and mass spectrometry can provide us with information about the mass of a molecule as well as the mass of fragments into which the molecule has been broken. Then, we will begin our investigation of molecular spectroscopy, which is the study of how electromagnetic radiation at different wavelengths interacts in different ways with molecules - and how these interactions can be quantified, analyzed, and interpreted to gain information about molecular structure. After a brief overview of the properties of light and the elements of a molecular spectroscopy experiment, we will consider ultraviolet-visible (UV-vis) spectroscopy, with which chemists gain information about conjugated pi-bonding systems in organic molecules. Among other applications, we will see how information from UV-vis spectroscopy can be used to measure the concentration of biomolecules compounds in solution. Then we will move to a discussion of infrared (IR) spectroscopy, the key technique to learn about functional groups present in an organic compound. T

Looking ahead, next chapter will be devoted to nuclear magnetic resonance (NMR) spectroscopy, where we use ultra-strong magnets and radiofrequency radiation to learn about the electronic environment of individual atoms in a molecule and use this information to determine the atom-to-atom bonding arrangement. For most organic chemists, NMR is one of the most powerful analytical tools available in terms of the wealth of detailed information it can provide about the structure of a molecule.

Attributions and citations

Prelude to Structure Determination I. (2020, September 17). Retrieved May 24, 2021, from <https://chem.libretexts.org/@go/page/234529>

Wikipedia contributors. (2021, May 10). Paclitaxel. In *Wikipedia, The Free Encyclopedia*. Retrieved 14:15, May 24, 2021, from <https://en.wikipedia.org/w/index.php?title=Paclitaxel&oldid=1022502529>

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5.2: Molecular Formulas and Empirical Formulas

Learning objective

- Determine the empirical and molecular formulas from combustion data

Empirical and Molecular formulas

Molecular formulas tell you how many atoms of each element are in a compound, and empirical formulas tell you the simplest or most reduced ratio of elements in a compound. If a compound's molecular formula cannot be reduced anymore, then the empirical formula is the same as the molecular formula. Combustion analysis can determine the empirical formula of a compound, but cannot determine the molecular formula (other techniques can though). Once known, the molecular formula can be calculated from the empirical formula.

Empirical Formulas

An empirical formula tells us the relative ratios of different atoms in a compound. The ratios hold true on the *molar* level as well. Thus, H_2O is composed of two atoms of hydrogen and 1 atom of oxygen. Likewise, **1.0 mole of H_2O** is composed of **2.0 moles of hydrogen** and **1.0 mole of oxygen**. We can also work backwards from molar ratios since *if we know the molar amounts of each element in a compound we can determine the empirical formula*.

Example 5.2.1: Mercury Chloride

Mercury forms a compound with chlorine that is 73.9% mercury and 26.1% chlorine by mass. What is the empirical formula?

Let's say we had a 100 gram sample of this compound. The sample would therefore contain 73.9 grams of mercury and 26.1 grams of chlorine. How many moles of each atom do the individual masses represent?

For Mercury:

$$(73.9 \text{ g}) \times \left(\frac{1 \text{ mol}}{200.59 \text{ g}} \right) = 0.368 \text{ moles} \quad (5.2.1)$$

For Chlorine:

$$(26.1 \text{ g}) \times \left(\frac{1 \text{ mol}}{35.45 \text{ g}} \right) = 0.736 \text{ mol} \quad (5.2.2)$$

What is the molar ratio between the two elements?

$$\frac{0.736 \text{ mol Cl}}{0.368 \text{ mol Hg}} = 2.0 \quad (5.2.3)$$

Thus, we have twice as many moles (i.e. atoms) of Cl as Hg. The empirical formula would thus be (remember to list cation first, anion last):

Combustion Analysis in a CHNS analyzer

One of the most common ways to determine the elemental composition of an unknown hydrocarbon is an analytical procedure called combustion analysis. A small, carefully weighed sample of an unknown compound that may contain carbon, hydrogen, nitrogen, and/or sulfur is burned in an oxygen atmosphere, and the quantities of the resulting gaseous products (CO_2 , H_2O , N_2 , and SO_2 , respectively) are determined by one of several possible methods. This procedure is usually performed in a **CHNS Analyzer** (also known as a carbon-hydrogen, nitrogen, and sulfur analyzer, Figure \(\backslash(\backslash\text{PageIndex}\{1\}\backslash)\)). These analyzers are capable of handling a wide variety of sample types, including solids, liquids, volatile and viscous samples.

The general procedure used in combustion analysis is outlined schematically in Figure 5.2.2 and a typical combustion analysis is illustrated in Examples 5.2.1. Since this methodology requires that O_2 must be added externally to burn the sample, the content of O in the organic compound cannot be measured directly. Therefore, it must be calculated by subtracting the mass of any other

elements from the total mass of sample. Example 1 shows an example of how to calculate a empirical formula from a combustion analysis. Other elements, such as metals, can be determined by other methods.

Elementar modern elemental analyzer 2011

Figure \(\PageIndex{1}\): Combustion analysis apparatus . Image by [MaRufaru82](#), [CC BY-SA 4.0](#), via Wikimedia Commons

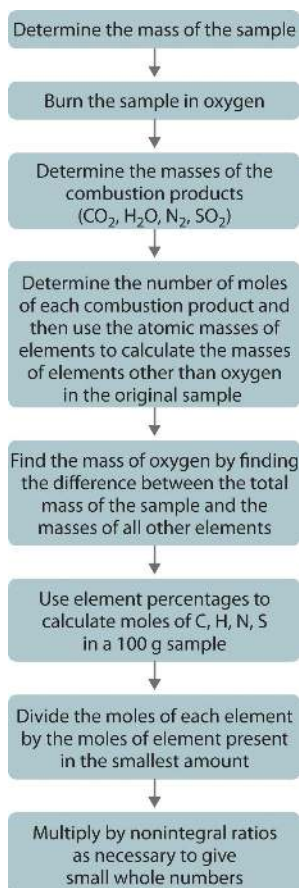


Figure 5.2.2: Steps for Obtaining an Empirical Formula from Combustion Analysis

Example 5.2.1: Combustion of Isopropyl Alcohol

What is the empirical formula for isopropyl alcohol (which contains only C, H and O) if the combustion of a 0.255 grams isopropyl alcohol sample produces 0.561 grams of CO₂ and 0.306 grams of H₂O?

Solution

From this information quantitate the amount of C and H in the sample.

$$(0.561 \text{ g CO}_2) \left(\frac{1 \text{ mol CO}_2}{44.0 \text{ g CO}_2} \right) = 0.0128 \text{ mol CO}_2 \quad (5.2.4)$$

Since one mole of CO₂ is made up of one mole of C and two moles of O, if we have 0.0128 moles of CO₂ in our sample, then we know we have 0.0128 moles of C in the sample. How many grams of C is this?

$$(0.0128 \cancel{\text{ mol C}}) \left(\frac{12.011 \text{ g C}}{1 \cancel{\text{ mol C}}} \right) = 0.154 \text{ g C} \quad (5.2.5)$$

How about the hydrogen?

$$(0.306 \cancel{\text{ g H}_2\text{O}}) \left(\frac{1 \text{ mol H}_2\text{O}}{18.0 \cancel{\text{ g H}_2\text{O}}} \right) = 0.017 \text{ mol H}_2\text{O} \quad (5.2.6)$$

Since one mole of H₂O is made up of one mole of oxygen and **two** moles of hydrogen, if we have 0.017 moles of H₂O, then we have 2*(0.017) = 0.034 moles of hydrogen. Since hydrogen is about 1 gram/mole, we must have **0.034 grams of hydrogen** in our original sample.

When we add our carbon and hydrogen together we get:

$$0.154 \text{ grams (C)} + 0.034 \text{ grams (H)} = \mathbf{0.188 \text{ grams}}$$

But we know we combusted 0.255 grams of isopropyl alcohol. The 'missing' mass must be from the oxygen atoms in the isopropyl alcohol:

$$0.255 \text{ grams} - 0.188 \text{ grams} = 0.067 \text{ grams oxygen}$$

This much oxygen is how many moles?

$$(0.067 \cancel{\text{ g O}}) \left(\frac{1 \text{ mol O}}{15.994 \cancel{\text{ g O}}} \right) = 0.0042 \text{ mol O} \quad (5.2.7)$$

Overall therefore, we have:

- 0.0128 moles Carbon
- 0.0340 moles Hydrogen
- 0.0042 moles Oxygen

Divide by the smallest molar amount to normalize:

- C = 3.05 atoms
- H = 8.1 atoms
- O = 1 atom

Within experimental error, the most likely empirical formula for propanol would be **C₃H₈O**

Molecular Formula from Empirical Formula

The chemical formula for a compound obtained by composition analysis is always the empirical formula. We can obtain the chemical formula from the empirical formula if we know the molecular weight of the compound. The chemical formula will always be some *integer multiple* of the empirical formula (i.e. integer multiples of the subscripts of the empirical formula). The general flow for this approach is shown in Figure 5.2.3 and demonstrated in Example 5.2.2.

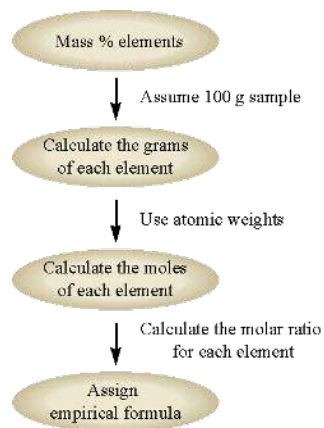


Figure 5.2.3: The general flow chart for solving empirical formulas from known mass percentages.

Example 5.2.2: Ascorbic Acid

Vitamin C (ascorbic acid) contains 40.92 % C, 4.58 % H, and 54.50 % O, by mass. The experimentally determined molecular mass is 176 amu. What is the empirical and chemical formula for ascorbic acid?

Solution

Consider an arbitrary amount of 100 grams of ascorbic acid, so we would have:

- 40.92 grams C
- 4.58 grams H
- 54.50 grams O

This would give us how many moles of each element?

- Carbon

$$(40.92 \text{ g C}) \times \left(\frac{1 \text{ mol C}}{12.011 \text{ g C}} \right) = 3.407 \text{ mol C} \quad (5.2.8)$$

- Hydrogen

$$(4.58 \text{ g H}) \times \left(\frac{1 \text{ mol H}}{1.008 \text{ g H}} \right) = 4.544 \text{ mol H} \quad (5.2.9)$$

- Oxygen

$$(54.50 \text{ g O}) \times \left(\frac{1 \text{ mol O}}{15.999 \text{ g O}} \right) = 3.406 \text{ mol O} \quad (5.2.10)$$

Determine the simplest whole number ratio by dividing by the smallest molar amount (3.406 moles in this case - see oxygen):

- Carbon

$$C = \frac{3.407 \text{ mol}}{3.406 \text{ mol}} \approx 1.0 \quad (5.2.11)$$

- Hydrogen

$$C = \frac{4.544 \text{ mol}}{3.406 \text{ mol}} = 1.0 \quad (5.2.12)$$

- Oxygen

$$C = \frac{3.406 \text{ mol}}{3.406 \text{ mol}} = 1.0 \quad (5.2.13)$$

The relative molar amounts of carbon and oxygen appear to be equal, but the relative molar amount of hydrogen is higher. Since we cannot have "fractional" atoms in a compound, we need to normalize the relative amount of hydrogen to be equal to an integer. 1.333 would appear to be 1 and 1/3, so if we multiply the relative amounts of each atom by '3', we should be able to get integer values for each atom.

$$\text{C} = (1.0) \cdot 3 = 3$$

$$\text{H} = (1.333) \cdot 3 = 4$$

$$\text{O} = (1.0) \cdot 3 = 3$$

or



This is our *empirical formula* for ascorbic acid.

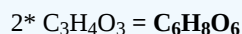
What about the chemical formula? We are told that the experimentally determined molecular mass is **176 amu**. What is the molecular mass of our empirical formula?

$$(3 \cdot 12.011) + (4 \cdot 1.008) + (3 \cdot 15.999) = 88.062 \text{ amu}$$

The molecular mass from our empirical formula is significantly lower than the experimentally determined value. What is the ratio between the two values?

$$(176 \text{ amu} / 88.062 \text{ amu}) = 2.0$$

Thus, it would appear that our empirical formula is essentially one half the mass of the actual molecular mass. If we multiplied our empirical formula by '2', then the molecular mass would be correct. Thus, the actual molecular formula is:



Exercise 1

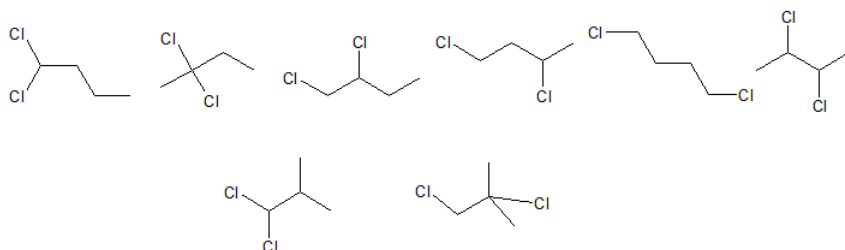
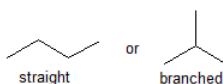
Elemental analysis of an organic compound indicates its composition to be 37.82% carbon, 6.36% hydrogen, and 55.82% chlorine.

- What is the empirical formula for this compound?
- Mass spectral analysis indicates a molar mass of 129 g/mol. What is the molecular formula for this compound?
- Draw all the possible bond-line structures with this molecular formula.

Solutions to Exercise 1

- $\text{C}_2\text{H}_5\text{Cl}$ with a molar mass of 64.5 g/mol
- $\text{C}_4\text{H}_{10}\text{Cl}_2$
- There are 8 possible structures with the molecular formula $\text{C}_4\text{H}_{10}\text{Cl}_2$. It can help to start with the different carbon backbones and then systematically add any branches (substituents).

For $C_2H_{10}Cl_2$, there are two ways to bond the carbon atoms.



Molecular Formula from Empirical Formula

The chemical formula for a compound obtained by composition analysis is always the empirical formula. We can obtain the chemical formula from the empirical formula if we know the molecular weight of the compound. The chemical formula will always be some *integer multiple* of the empirical formula (i.e. integer multiples of the subscripts of the empirical formula). The general flow for this approach is shown in Figure 5.2.1 and demonstrated in Example 5.2.2.

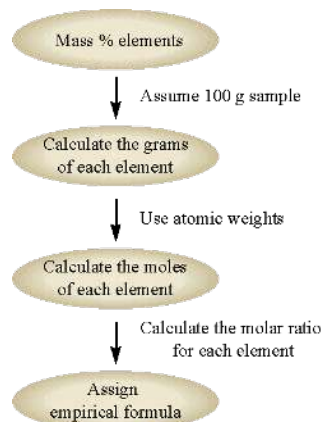


Figure 5.2.1: The general flow chart for solving empirical formulas from known mass percentages.

Contributors and Attributions

- Mike Blaber (Florida State University)
- Molecular Formulas and Empirical Formulas (Review). (2020, May 30). Retrieved May 24, 2021, from <https://chem.libretexts.org/@go/page/44636>
- Wikipedia contributors. (2021, April 15). CHN analyzer. In *Wikipedia, The Free Encyclopedia*. Retrieved 14:43, May 24, 2021, from https://en.wikipedia.org/w/index.php?title=CHN_analyzer&oldid=1018003336

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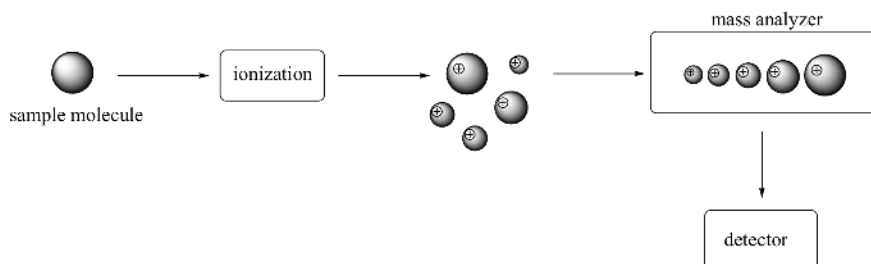
5.3: Mass Spectrometry

Mass spectrometry (MS) is a powerful analytical technique widely used by chemists, biologists, medical researchers, and environmental and forensic scientists, among others. With MS, we are looking at the molecular mass of a molecule, or of different fragments of that molecule.

The basics of a mass spectrometry experiment

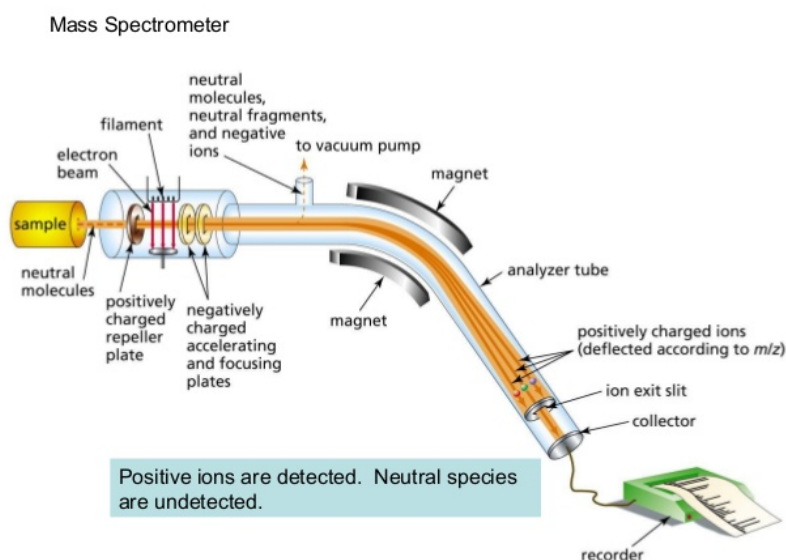
There are many different types of MS instruments, but they all have the same three essential components. First, there is an ionization source, where the molecule is given a positive electrical charge, either by removing an electron or by adding a proton. Depending on the ionization method used, the ionized molecule may or may not break apart into a population of smaller fragments. In the figure below, some of the sample molecules remain whole, while others fragment into smaller pieces.

Next in line there is a mass analyzer, where the cationic fragments are separated according to their mass.



Finally, there is a detector, which detects and quantifies the separated ions.

One of the more common types of MS techniques used in the organic laboratory is **electron ionization**. In the ionization source, the sample molecule is bombarded by a high-energy electron beam, which has the effect of knocking a valence electron off of the molecule to form a **radical cation**. Because a great deal of energy is transferred by this bombardment process, the radical cation quickly begins to break up into smaller fragments, some of which are positively charged and some of which are neutral. The neutral fragments are either adsorbed onto the walls of the chamber or are removed by a vacuum source. In the mass analyzer component, the positively charged fragments and any remaining unfragmented **molecular ions** are accelerated down a tube by an electric field.

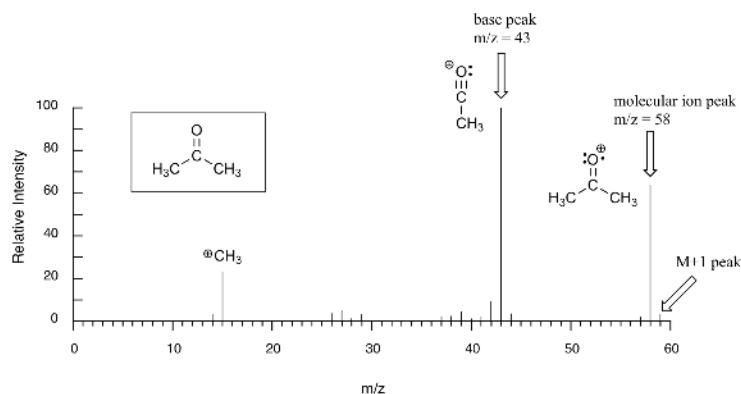


(Image from [Wikipedia Commons](#))

This tube is curved, and the ions are deflected by a strong magnetic field. Ions of different mass to charge (m/z) ratios are deflected to a different extent, resulting in a 'sorting' of ions by mass (virtually all ions have charges of $z = +1$, so sorting by the mass to charge ratio is the same thing as sorting by mass). A detector at the end of the curved flight tube records and quantifies the sorted ions.

Looking at mass spectra

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

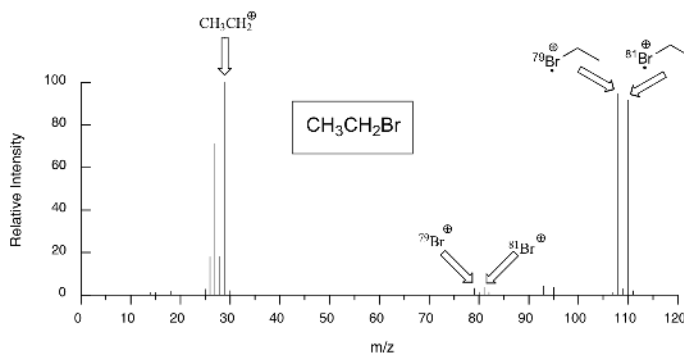


The sample is acetone. On the horizontal axis is the value for m/z (as we stated above, the charge z is almost always $+1$, so in practice this is the same as mass). On the vertical axis is the relative abundance of each ion detected. On this scale, the most abundant ion, called the **base peak**, is set to 100%, and all other peaks are recorded relative to this value. For acetone, the base peak is at $m/z = 43$ - we will discuss the formation of this fragment a bit later. The molecular weight of acetone is 58, so we can identify the peak at $m/z = 58$ as that corresponding to the **molecular ion peak**, or **parent peak**.

Isotopic distribution

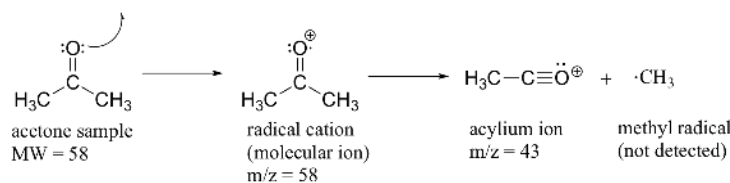
Notice that there is a small peak at $m/z = 59$: this is referred to as the **M+1 peak**. How can there be an ion that has a greater mass than the molecular ion? Simple: a small fraction - about 1.1% - of all carbon atoms in nature are actually the ^{13}C rather than the ^{12}C isotope. The ^{13}C isotope is, of course, heavier than ^{12}C by 1 mass unit. In addition, about 0.015% of all hydrogen atoms are actually deuterium, the ^2H isotope. So the M+1 peak represents those few acetone molecules in the sample which contained either a ^{13}C or ^2H .

Molecules with lots of oxygen atoms sometimes show a small **M+2 peak** (2 m/z units greater than the parent peak) in their mass spectra, due to the presence of a small amount of ^{18}O (the most abundant isotope of oxygen is ^{16}O). Because there are two abundant isotopes of both chlorine (about 75% ^{35}Cl and 25% ^{37}Cl) and bromine (about 50% ^{79}Br and 50% ^{81}Br), chlorinated and brominated compounds have very large and recognizable M+2 peaks. Fragments containing both isotopes of Br can be seen in the mass spectrum of ethyl bromide:

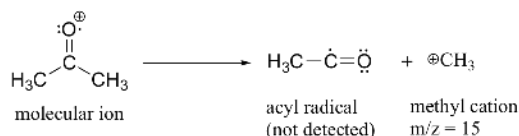


Fragmentation patterns

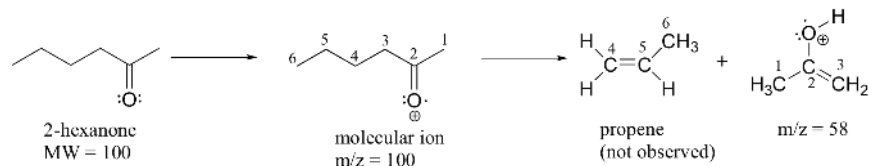
Much of the utility in electron-ionization MS comes from the fact that the radical cations generated in the electron-bombardment process tend to fragment in predictable ways. Detailed analysis of the typical fragmentation patterns of different functional groups is beyond the scope of this text, but it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



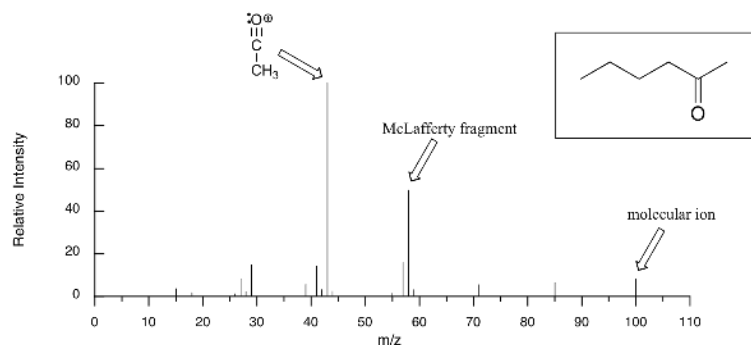
After the parent peak and the base peak, the next largest peak, at a relative abundance of 23%, is at $m/z = 15$. This, as you might expect, is the result of formation of a methyl cation, in addition to an acyl radical (which is neutral and not detected).



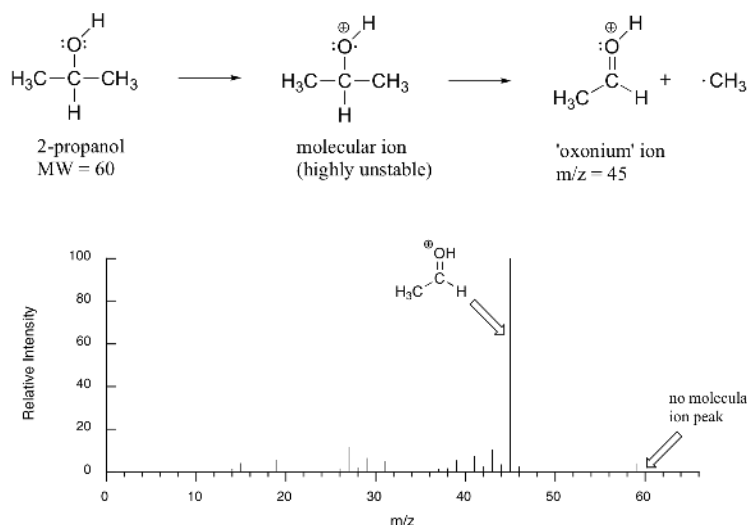
A common fragmentation pattern for larger carbonyl compounds is called the **McLafferty rearrangement**:



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



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



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

You can see many more actual examples of mass spectra in the [Spectral Database for Organic Compounds](#)

Exercise 4.1

Using the fragmentation patterns for acetone as a guide, predict the signals that you would find in the mass spectra of:

a) 2-butanone; b) 3-hexanone; c) cyclopentanone.

Exercise 4.2

Predict some signals that you would expect to see in a mass spectrum of 2-chloropropane.

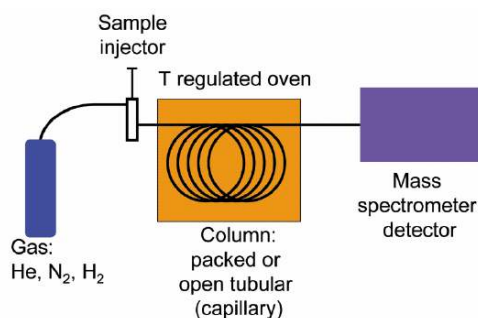
Exercise 4.3

The mass spectrum of an aldehyde shows a parent peak at $m/z = 58$ and a base peak at $m/z = 29$. Propose a structure, and identify the two species whose m/z values were listed.

Solutions

Gas Chromatography - Mass Spectrometry

Quite often, mass spectrometry is used in conjunction with a separation technique called gas chromatography (GC). The combined GC-MS procedure is very useful when dealing with a sample that is a mixture of two or more different compounds, because the various compounds are separated from one another before being subjected individually to MS analysis. We will not go into the details of gas chromatography here, although if you are taking an organic laboratory course you might well get a chance to try your hand at GC, and you will almost certainly be exposed to the conceptually analogous techniques of thin layer and column chromatography. Suffice it to say that in GC, a very small amount of a liquid sample is vaporized, injected into a long, coiled metal column, and pushed through the column by helium gas. Along the way, different compounds in the sample stick to the walls of the column to different extents, and thus travel at different speeds and emerge separately from the end of the column. In GC-MS, each purified compound is sent directly from the end of GC column into the MS instrument, so in the end we get a separate mass spectrum for each of the compounds in the original mixed sample. Because a compound's MS spectrum is a very reliable and reproducible 'fingerprint', we can instruct the instrument to search an MS database and identify each compound in the sample.



Gas chromatography-mass spectrometry (GC-MS) schematic

(Image from [Wikipedia](#) by K. Murray)

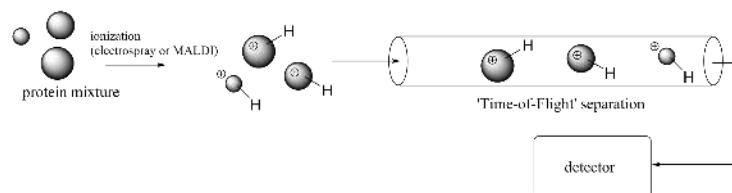
The extremely high sensitivity of modern GC-MS instrumentation makes it possible to detect and identify very small trace amounts of organic compounds. GC-MS is being used increasingly by environmental chemists to detect the presence of harmful organic contaminants in food and water samples. Airport security screeners also use high-speed GC-MS instruments to look for residue from bomb-making chemicals on checked luggage.

Mass spectrometry of proteins - applications in proteomics

Electron ionization mass spectrometry is generally not very useful for analyzing biomolecules: their high polarity makes it difficult to get them into the vapor phase, the first step in EIMS. Mass spectrometry of biomolecules has undergone a revolution over the past few decades, with many new ionization and separation techniques being developed. Generally, the strategy for biomolecule analysis involves **soft ionization**, in which much less energy (compared to techniques such as EIMS) is imparted to the molecule being analyzed during the ionization process. Usually, soft ionization involves adding protons rather than removing electrons: the cations formed in this way are significantly less energetic than the radical cations formed by removal of an electron. The result of soft ionization is that little or no fragmentation occurs, so the mass being measured is that of an intact molecule. Typically, large biomolecules are digested into smaller pieces using chemical or enzymatic methods, then their masses determined by 'soft' MS.

New developments in soft ionization MS technology have made it easier to detect and identify proteins that are present in very small quantities in biological samples. In **electrospray ionization** (ESI), the protein sample, in solution, is sprayed into a tube and the molecules are induced by an electric field to pick up extra protons from the solvent. Another common 'soft ionization' method is 'matrix-assisted laser desorption ionization' (MALDI). Here, the protein sample is adsorbed onto a solid matrix, and protonation is achieved with a laser.

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



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

Soft ionization mass spectrometry has become in recent years an increasingly important tool in the field of **proteomics**. Traditionally, protein biochemists tend to study the structure and function of individual proteins. Proteomics researchers, in contrast, want to learn more about how large numbers of proteins in a living system interact with each other, and how they respond to changes in the state of the organism. One important subfield of proteomics is the search for protein 'biomarkers' for human

disease: in other words, proteins which are present in greater quantities in the tissues of a sick person than in a healthy person. Detection in a healthy person of a known biomarker for a disease such as diabetes or cancer could provide doctors with an early warning that the patient may be especially susceptible to the disease, so that preventive measures could be taken to prevent or delay onset.

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

Contributors and Attributions

- [Organic Chemistry With a Biological Emphasis](#) by [Tim Soderberg](#) (University of Minnesota, Morris)
- Mass Spectrometry. (2021, March 16). Retrieved May 24, 2021, from <https://chem.libretexts.org/@go/page/106509>

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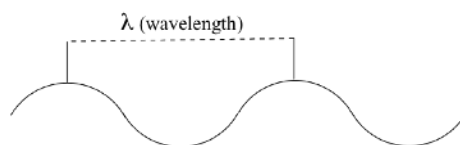
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5.4: Introduction to molecular spectroscopy

The electromagnetic spectrum

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

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



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

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

$$E = \frac{hc}{\lambda} \quad (4.1.1)$$

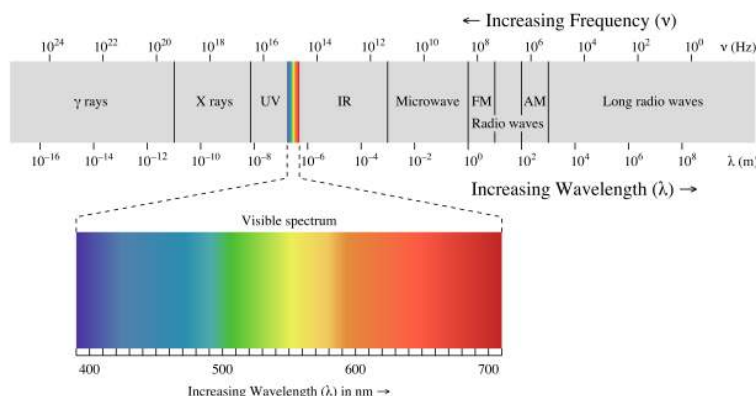
where E is energy in kJ/mol, λ (the Greek letter *lambda*) is wavelength in meters, c is 3.00×10^8 m/s (the speed of light), and h is 3.99×10^{-13} kJ·s·mol⁻¹, a number known as **Planck’s constant**.

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

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

$$\lambda\nu = c \quad (4.1.2)$$

where ν (the Greek letter ‘nu’) is frequency in s⁻¹. Visible red light with a wavelength of 700 nm, for example, has a frequency of 4.29×10^{14} Hz, and an energy of 40.9 kcal per mole of photons. The full range of electromagnetic radiation wavelengths is referred to as the **electromagnetic spectrum**.



(Image from [Wikipedia commons](#))

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

? Exercise 4.4

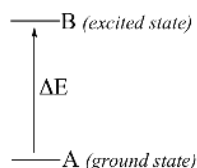
Visible light has a wavelength range of about 400-700 nm. What is the corresponding frequency range? What is the corresponding energy range, in kJ/mol of photons?

Solutions

Overview of a molecular spectroscopy experiment

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

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



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

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

Contributors and Attributions

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

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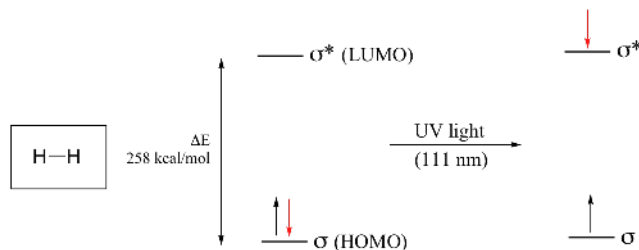
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5.5: Ultraviolet and visible spectroscopy

While interaction with infrared light causes molecules to undergo vibrational transitions, the shorter wavelength, higher energy radiation in the UV (200-400 nm) and visible (400-700 nm) range of the electromagnetic spectrum causes many organic molecules to undergo **electronic transitions**. What this means is that when the energy from UV or visible light is absorbed by a molecule, one of its electrons jumps from a lower energy to a higher energy molecular orbital.

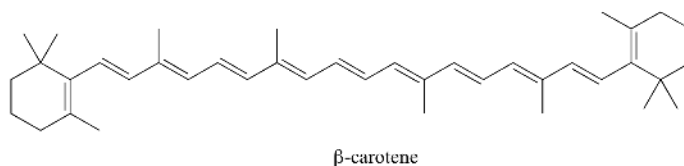
Electronic transitions

As you may recall from CHE 103, electrons in atoms are occupying atomic orbitals. Analogously, electrons in a molecule are occupying molecular orbitals. These orbitals are called HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital). In molecules, electrons can transition from HOMO to LUMO:



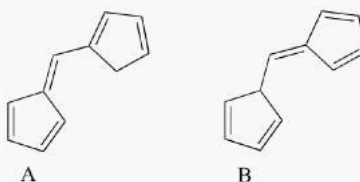
If the molecule is exposed to light of a wavelength with energy equal to ΔE , the HOMO-LUMO energy gap, this wavelength will be absorbed and the energy used to bump one of the electrons from the HOMO to the LUMO. For some molecules, these electron transitions occur in the UV-visible region of the electromagnetic spectrum. Molecules or parts of molecules that absorb light strongly in the UV-vis region are called **chromophores**. These electronic transitions Where UV-vis spectroscopy becomes useful to most organic and biological chemists is in the study of molecules with conjugated π systems.

In molecules with extended pi systems, the HOMO-LUMO energy gap becomes so small that absorption occurs in the visible rather than the UV region of the electromagnetic spectrum. Beta-carotene, with its system of 11 conjugated double bonds, absorbs light with wavelengths in the blue region of the visible spectrum while allowing other visible wavelengths – mainly those in the red-yellow region - to be transmitted. This is why carrots are orange.



Exercise 4.9: What is the energy of the photons (in kJ/mol) of light with wavelength of 470 nm, the λ_{max} of b-carotene?

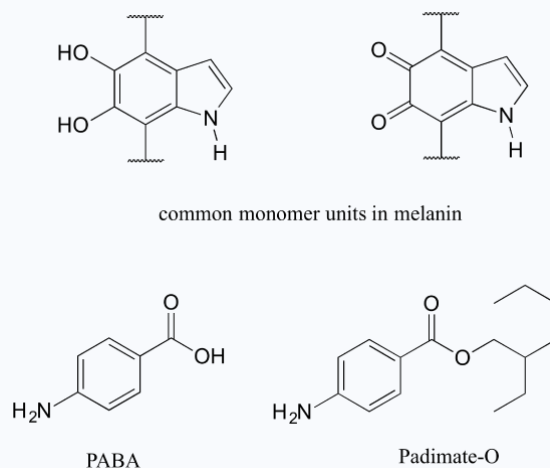
Exercise 4.10: Which of the following molecules would you expect absorb at a longer wavelength in the UV region of the electromagnetic spectrum? Explain your answer.



[Solutions](#)

Protecting yourself from sunburn

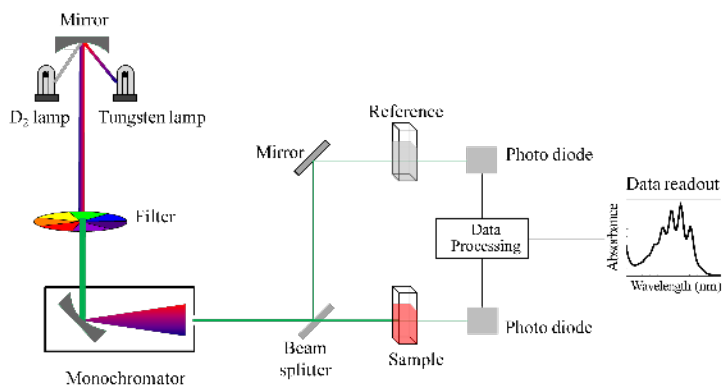
Human skin can be damaged by exposure to ultraviolet light from the sun. We naturally produce a pigment, called melanin, which protects the skin by absorbing much of the ultraviolet radiation. Melanin is a complex polymer, two of the most common monomers units of which are shown below.



Overexposure to the sun is still dangerous, because there is a limit to how much radiation our melanin can absorb. Most commercial sunscreens claim to offer additional protection from both UV-A and UV-B radiation: UV-A refers to wavelengths between 315-400 nm, UV-B to shorter, more harmful wavelengths between 280-315 nm. PABA (*para*-aminobenzoic acid) was used in sunscreens in the past, but its relatively high polarity meant that it was not very soluble in oily lotions, and it tended to rinse away when swimming. Many sunscreens today contain, among other active ingredients, a more hydrophobic derivative of PABA called Padimate O.

Looking at UV-vis spectra

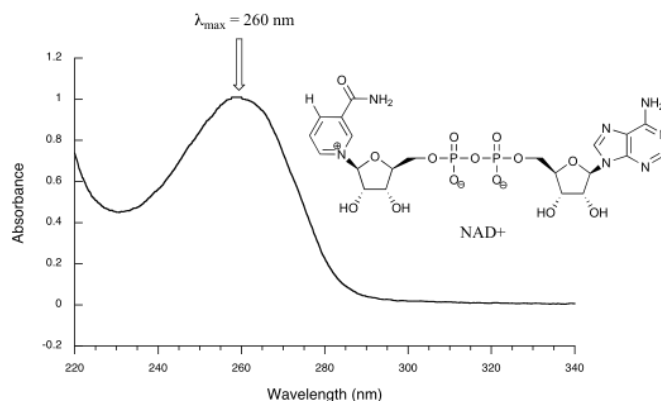
We have been talking in general terms about how molecules absorb UV and visible light – now let's look at some actual examples of data from a UV-vis absorbance spectrophotometer. The basic setup is the same as for IR spectroscopy: radiation with a range of wavelengths is directed through a sample of interest, and a detector records which wavelengths were absorbed and to what extent the absorption occurred.



Schematic for a UV-Vis spectrophotometer

(Image from [Wikipedia Commons](#))

Below is the absorbance spectrum of an important biological molecule called nicotinamide adenine dinucleotide, abbreviated NAD⁺. This compound absorbs light in the UV range due to the presence of conjugated pi-bonding systems.



Wavelength values on the x-axis are generally measured in nanometers (nm). Peaks in UV spectra tend to be quite broad, often spanning well over 20 nm at half-maximal height. Typically, there are two things that we look for and record from a UV-Vis spectrum. The first is λ_{max} , which is the wavelength at maximal light absorbance. As you can see, NAD⁺ has $\lambda_{\text{max}} = 260 \text{ nm}$. We also want to record how much light is absorbed at λ_{max} . Here we use a unitless number called **absorbance**, abbreviated 'A'. To calculate absorbance at a given wavelength, the computer in the spectrophotometer simply takes the intensity of light at that wavelength *before* it passes through the sample (I_0), divides this value by the intensity of the same wavelength *after* it passes through the sample (I), then takes the $\log_{10}$ of that number:

$$A = \log \frac{I_0}{I} \quad (4.3.1)$$

You can see that the absorbance value at 260 nm (A_{260}) is about 1.0 in this spectrum.

Exercise 4.11: Express $A = 1.0$ in terms of percent transmittance (%T, the unit usually used in IR spectroscopy (and sometimes in UV-vis as well)).

[Solutions](#)

Kahn Academy video tutorials on UV-Vis spectroscopy

Contributors

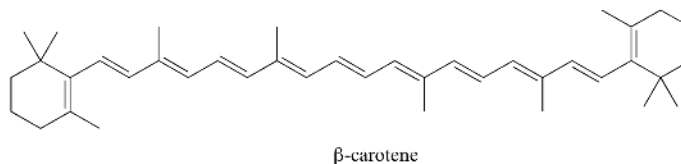
- [Organic Chemistry With a Biological Emphasis](#) by [Tim Soderberg](#) (University of Minnesota, Morris)

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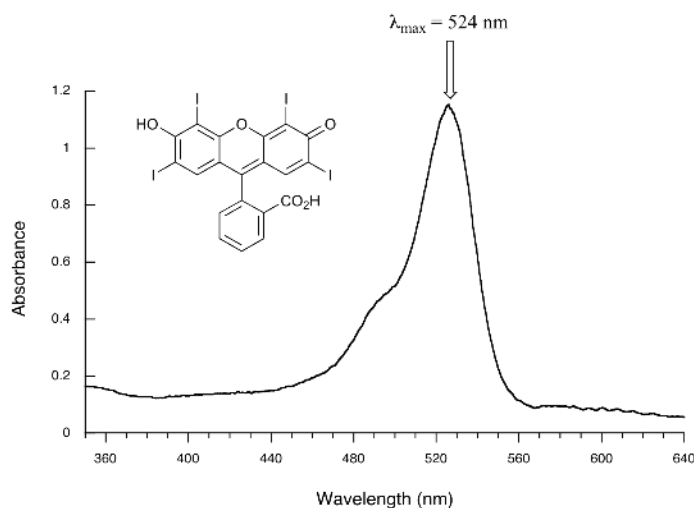
5.6: Effect of Conjugation

Conjugated systems or conjugated molecules contains an alternation of single and double bonds. For example, beta-carotene represents a conjugate system with 11 conjugated double bonds. Beta-carotene absorbs light with wavelengths in the blue region of the visible spectrum while allowing other visible wavelengths – mainly those in the red-yellow region - to be transmitted. This is why carrots are orange.



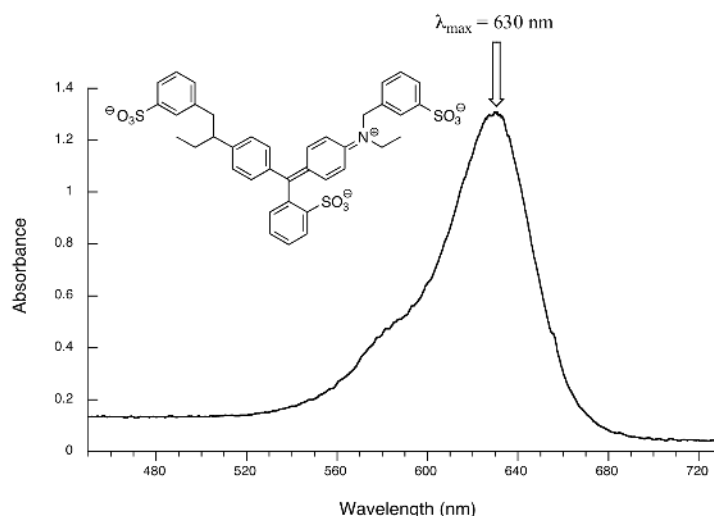
To understand the effect of conjugation, let's compare two typical food colorings. Food coloring Red #3 (less conjugated) and Blue #1 (more conjugated)

Here is the absorbance spectrum of the common food coloring Red #3:



Here, we see that the extended system of conjugated pi bonds causes the molecule to absorb light in the visible range. Because the λ_{max} of 524 nm falls within the green region of the spectrum, the compound appears red to our eyes.

Now, take a look at the spectrum of another food coloring, Blue #1:



Here, maximum absorbance is at 630 nm, in the orange range of the visible spectrum, and the compound appears blue.

We can observe that the more conjugation present in a molecule, the higher the maximum absorbance (λ_{max}) values. We say that the λ_{max} shifts towards longer wavelengths (lower energies, red shift). At the same time, the absorbance becomes more intense (higher values on the Y-axis).

Applications of UV spectroscopy in organic and biological chemistry

UV-vis spectroscopy has many different applications in organic and biological chemistry. One of the most basic of these applications is the use of the **Beer - Lambert Law** to determine the concentration of a chromophore. You most likely have performed a Beer – Lambert experiment in a previous chemistry lab. The law is simply an application of the observation that, within certain ranges, the absorbance of a chromophore at a given wavelength varies in a linear fashion with its concentration: the higher the concentration of the molecule, the greater its absorbance. If we divide the observed value of A at λ_{max} by the concentration of the sample (c , in mol/L), we obtain the **molar absorptivity**, or **extinction coefficient** (ϵ), which is a characteristic value for a given compound.

$$\epsilon = A/c$$

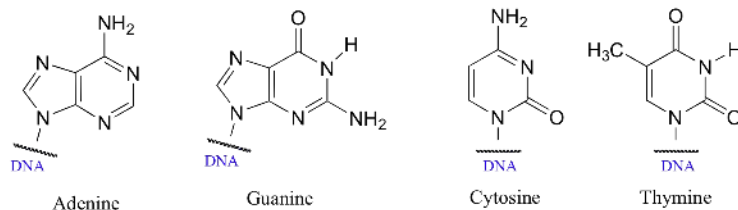
The absorbance will also depend, of course, on the **path length** - in other words, the distance that the beam of light travels through the sample. In most cases, sample holders are designed so that the path length is equal to 1 cm, so the units for molar absorptivity are $\text{mol} \cdot \text{L}^{-1} \cdot \text{cm}^{-1}$. If we look up the value of ϵ for our compound at λ_{max} , and we measure absorbance at this wavelength, we can easily calculate the concentration of our sample. As an example, for NAD^+ the literature value of ϵ at 260 nm is $18,000 \text{ mol} \cdot \text{L}^{-1} \cdot \text{cm}^{-1}$. In our NAD^+ spectrum we observed $A_{260} = 1.0$, so using equation 4.4 and solving for concentration we find that our sample is $5.6 \times 10^{-5} \text{ M}$.

Template:ExampleStart

The literature value of ϵ for 1,3-pentadiene in hexane is $26,000 \text{ mol} \cdot \text{L}^{-1} \cdot \text{cm}^{-1}$ at its maximum absorbance at 224 nm. You prepare a sample and take a UV spectrum, finding that $A_{224} = 0.850$. What is the concentration of your sample?

Template:ExampleEnd

The bases of DNA and RNA are good chromophores:



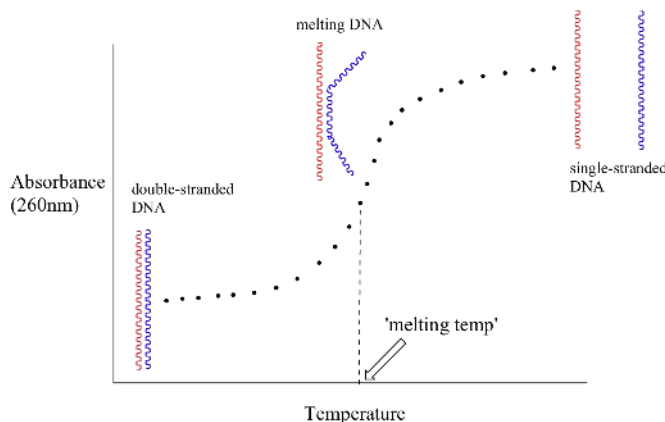
Biochemists and molecular biologists often determine the concentration of a DNA sample by assuming an average value of $\epsilon = 0.020 \text{ ng}^{-1} \times \text{mL}$ for double-stranded DNA at its λ_{max} of 260 nm (notice that concentration in this application is expressed in mass/volume rather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

Template:ExampleStart

50 mL of an aqueous sample of double stranded DNA is dissolved in 950 mL of water. This diluted solution has a maximal absorbance of 0.326 at 260 nm. What is the concentration of the original (more concentrated) DNA sample, expressed in mg/mL?

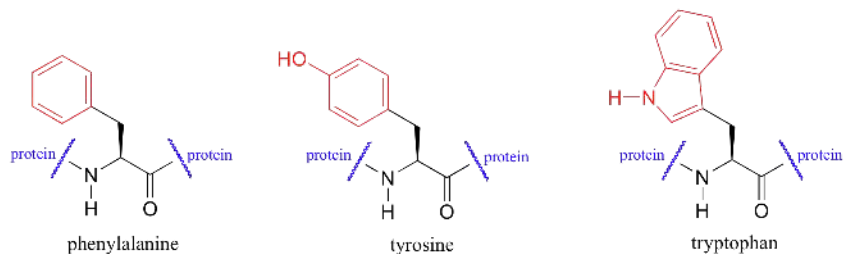
Template:ExampleEnd

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



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

Proteins absorb light in the UV range due to the presence of the aromatic amino acids tryptophan, phenylalanine, and tyrosine, all of which are chromophores.



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

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5.7: Conjugation, Color, and the Chemistry of Vision

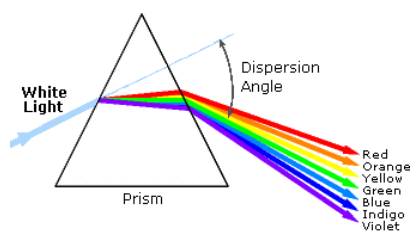
Objectives

After completing this section, you should be able to

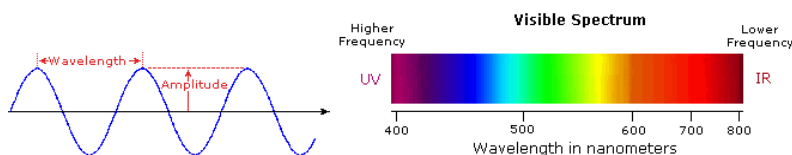
1. explain why some organic compounds have different colors based on compound structure and our perception of light.
2. state the relationship between frequency of light absorbed and the extent of conjugation in an extended pi electron system.

Introduction

An obvious difference between certain compounds is their color. Thus, quinone is yellow; chlorophyll is green; and aspirin is colorless. In this respect the human eye is functioning as a spectrometer analyzing the light reflected from the surface of a solid or passing through a liquid. Although we see sunlight (or white light) as uniform or homogeneous in color, it is actually composed of a broad range of radiation wavelengths in the ultraviolet (UV), visible and infrared (IR) portions of the spectrum. As shown on the image below, the component colors of the visible portion can be separated by passing sunlight through a prism, which acts to bend the light in differing degrees according to wavelength.

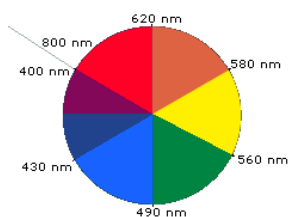


Visible wavelengths cover a range from approximately 400 to 800 nm. The longest visible wavelength is red and the shortest is violet. The wavelengths of what we perceive as particular colors in the visible portion of the spectrum are displayed and listed below.



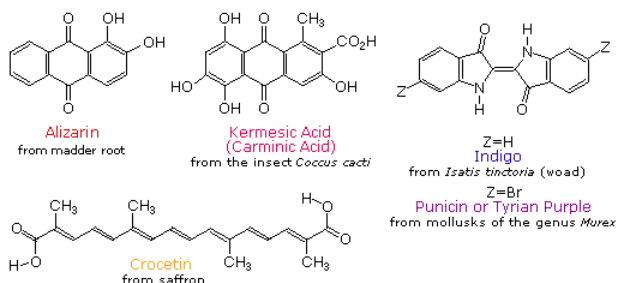
- **Violet:** 400 - 420 nm
- **Indigo:** 420 - 440 nm
- **Blue:** 440 - 490 nm
- **Green:** 490 - 570 nm
- **Yellow:** 570 - 585 nm
- **Orange:** 585 - 620 nm
- **Red:** 620 - 780 nm

When white light passes through or is reflected by a colored substance, a characteristic portion of the mixed wavelengths is absorbed. The remaining light will then assume the complementary color to the wavelength(s) absorbed. This relationship is demonstrated by the color wheel shown below. Here, complementary colors are diametrically opposite each other. Thus, absorption of violet (400-440 nm) light renders a substance yellow, and absorption of 490-560 nm (green) light makes it red. Green is unique in that it can be created by absorption close to 400 nm as well as absorption near 800 nm.

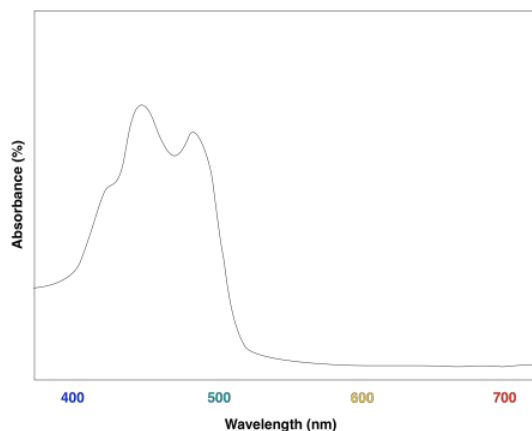
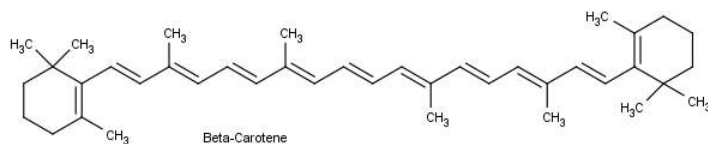


Early humans valued colored pigments, and used them for decorative purposes. Many of these were inorganic minerals, but several important organic dyes were also known. These included the crimson pigment, kermesic acid, the blue dye, indigo, and the yellow saffron pigment, crocetin. A rare dibromo-indigo derivative, punicin, was used to color the robes of the royal and wealthy. A common feature of all these colored compounds, displayed below, is a system of **extensively conjugated π -electrons**.

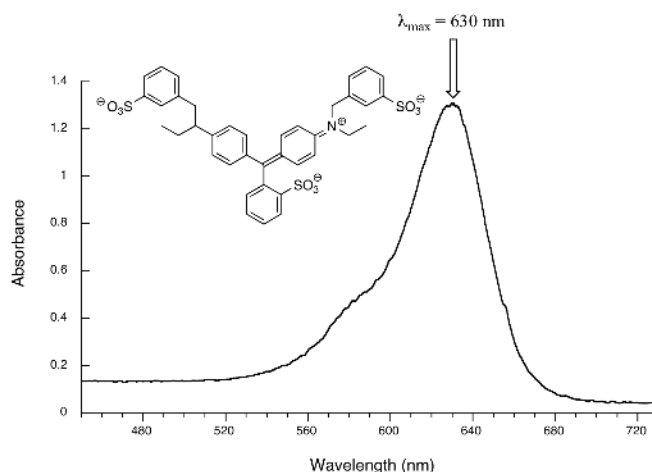
Some Natural Organic Pigments



By understanding visible light, complementary colors, and adsorption the color of organic compounds can be understood. Beta-carotene, a compound found in carrots, is a deep orange color. Beta-carotene has 11 conjugated double bonds which places its λ_{max} at 455 nm which is within the blue region of the visible spectrum. The Beta-carotene compound absorbs blue from white light so it appears orange which is the the complementary color of blue.



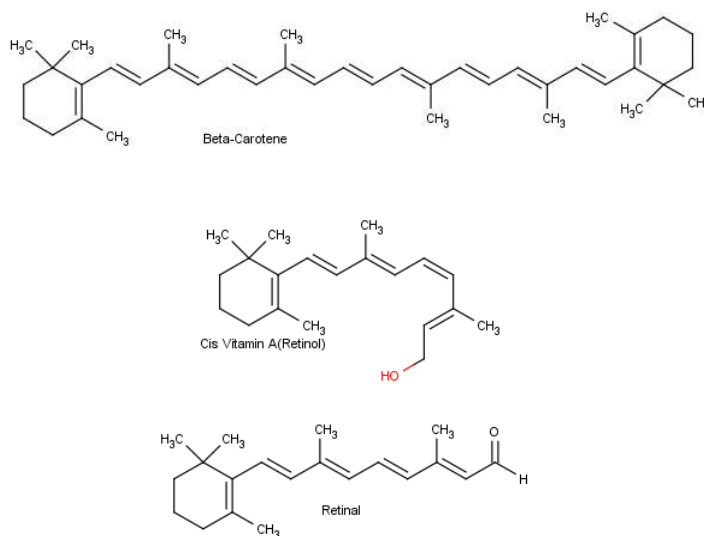
Another example is seen in the absorption spectrum of another food coloring, Blue #1:



Blue #1 absorbs at a λ_{max} at 630 nm which is the color red in the visible spectrum. Blue is the complementary color of red.

Mechanism of Vision

Conjugation is also important in light sensitive compounds used for vision. Beta carotene, found in carrots and other natural products is cleaved into the liver and converted into Vitamin A, also known as retinol. Vitamin A is critical for vision because it is needed by the retina of eye. Retinol can be oxidized to an aldehyde called retinal which is also important for vision.

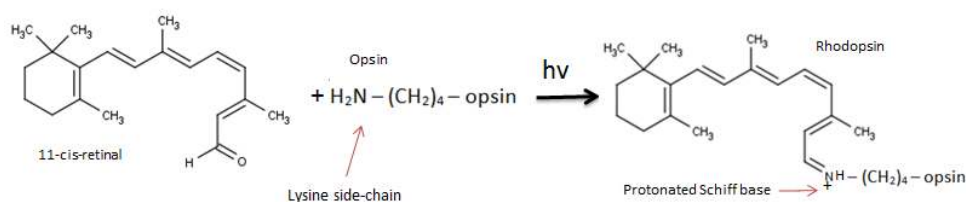


The eye is an extraordinarily sensitive instrument. Although its wavelength response is restricted to 400-800 nm, but its degree of sensitivity is such that a fully dark-adapted eye can clearly detect objects in light so dim as to correspond to a light input over the retina of only about 10,000 quanta per second - one light quantum per three minutes per receptor cell in the retina!

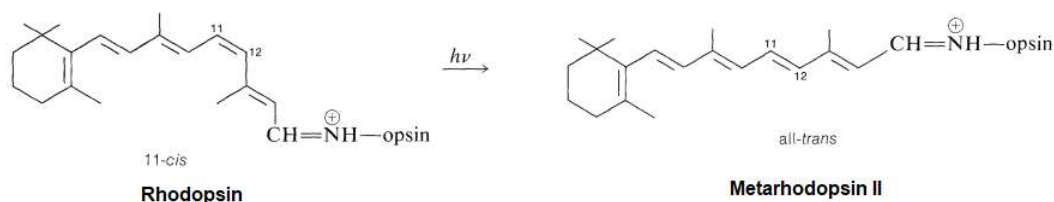
The retina is made up of two kinds of light-sensitive (photoreceptor) cells, known as rods and cones. The rods are the more sensitive and are responsible for vision in dim light. The cones are much fewer in number than the rods and provide detail and color vision in good light. The part of the retina that corresponds to the center of the visual field contains only cones. A red pigment called **rhodopsin** is the photosensitive substance in the rod cells of the retina. It absorbs most strongly in the blue-green region of the visible spectrum ($\lambda_{\text{max}} = 500\text{nm}$) and is essentially unaffected by the far-red end of the spectrum. Cone vision appears to involve a different pigment called **iodopsin**, which absorbs farther toward the red than does rhodopsin.

Rhodopsin, is made up of a protein (opsin) and retinal. Opsin does not absorb visible light, but when it is bonded with 11-cis-retinal to form rhodopsin, the new molecule has a very broad absorption band in the visible region of the spectrum. Rhodopsin is formed

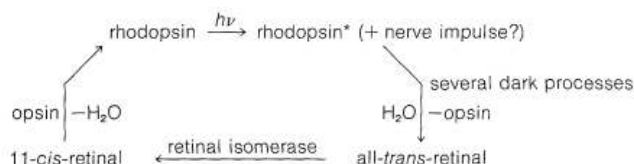
by an imine (Schiff base) functional group formed between the aldehyde group of the retinal and the side-chain amino function of a lysine unit of opsin.



Opsin itself is colorless, whereas 11-cis-retinal absorbs strongly at 370 nm. The combination of opsin with 11-cis-retinal produces a remarkable shift of λ_{max} to longer wavelengths (430 nm to 620 nm, depending on the species). Light striking the retina changes the color of rhodopsin from red to yellow. The primary photochemical event in this process was established by G. Wald (Nobel Laureate in Physiology and Medicine, 1967), who showed that light absorption led to a change of configuration about the C₁₁-C₁₂ double bond of the retinal moiety of rhodopsin from *cis* to *trans* to form a compound called metarhodopsin II. The new form of trans-retinal does not fit as well into the opsin protein, and so a series of geometry changes in the protein begins. As the protein changes its geometry, it initiates a cascade of biochemical reactions that result in changes in charge so that a large potential difference builds up across the neuron membranes. This potential difference is passed along to an adjoining nerve cell as an electrical impulse. The nerve cell carries this impulse to the brain, where the visual information is interpreted.

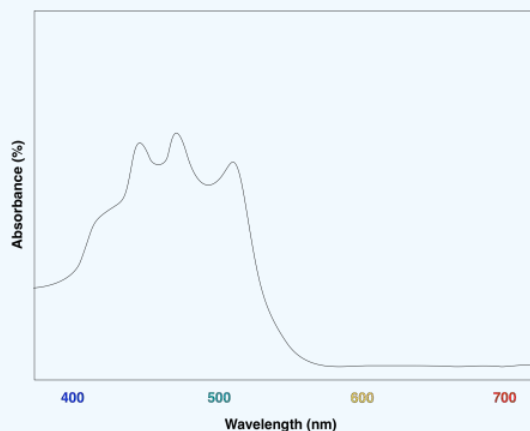


Metarhodopsin II can then be recycled back to rhodopsin by first cleaving to form all-*trans*-retinal and the isomerization back to 11-*cis*-retinal by the enzyme retinal isomerase. Finally, 11-*cis*-retinal is once again coupled with opsin to form rhodopsin.



? Exercise 5.7.1

Lycopene is conjugated compound found in tomatoes. What colors correspond to the UV-Vis absorption maxima of lycopene? What color do we see when we look at lycopene?



Answer

The absorption maxima of lycopene are regions of blue and green in the visible spectrum. Lycopene would be expected to appear orange and red.

? Exercise 5.7.2

Asprin has a λ_{max} of 220 nm. Briefly explain why Asprin appears white.

Answer

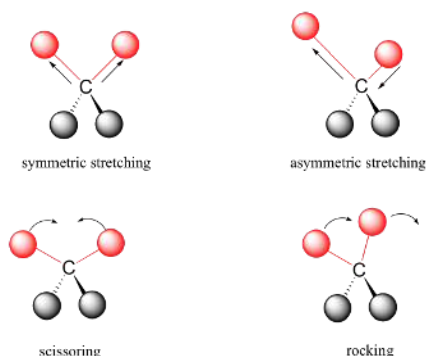
Asprin absorbs in the ultraviolet portion of the electromagnetic spectrum. Asprin cannot remove any colors from white light by absorption so the compound itself appears white. Many compounds with a relatively small amount of conjugation appear white because they only absorb in the ultraviolet and not the visible region.

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5.8: Infrared spectroscopy

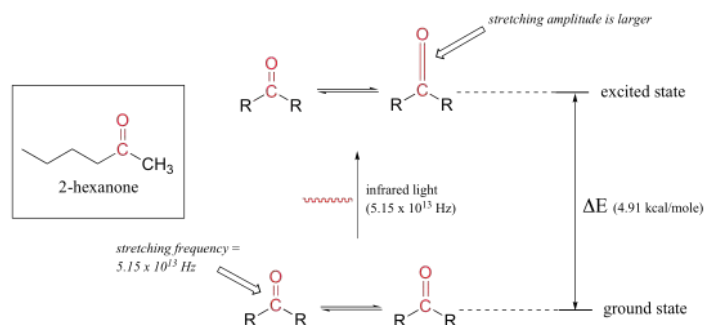
Covalent bonds in organic molecules are not rigid sticks – rather, they behave more like springs. At room temperature, organic molecules are always in motion, as their bonds stretch, bend, and twist. These complex vibrations can be broken down mathematically into individual **vibrational modes**, a few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



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

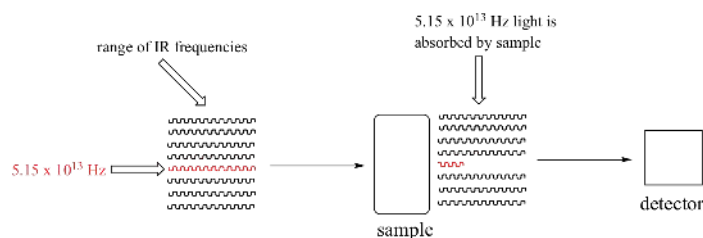
Let's take 2-hexanone as an example. Picture the carbonyl bond of the ketone group as a spring that is constantly bouncing back and forth, stretching and compressing, pushing the carbon and oxygen atoms further apart and then pulling them together. This is the **stretching mode** of the carbonyl bond.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

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



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

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



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

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

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

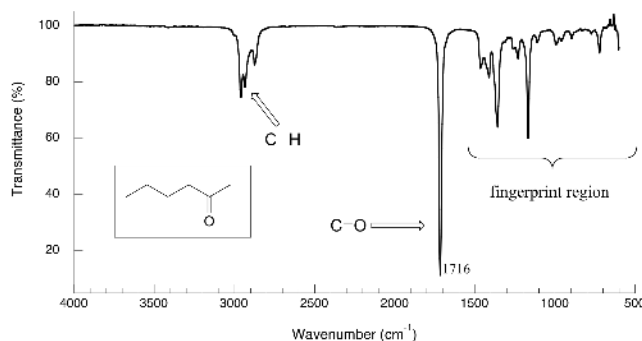
Some bonds absorb infrared light more strongly than others, and some bonds do not absorb at all. *In order for a vibrational mode to absorb infrared light, it must result in a periodic change in the dipole moment of the molecule.* Such vibrations are said to be **infrared active**. In general, the greater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

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



infrared-inactive double and triple bonds

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



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

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

Exercise 4.5

Express the wavenumber value of 3000 cm^{-1} in terms of wavelength (in meter units) frequency (in Hz), and associated energy (in kJ/mol).

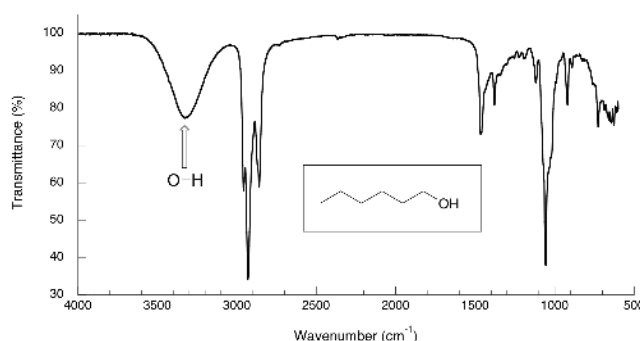
Solutions

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

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

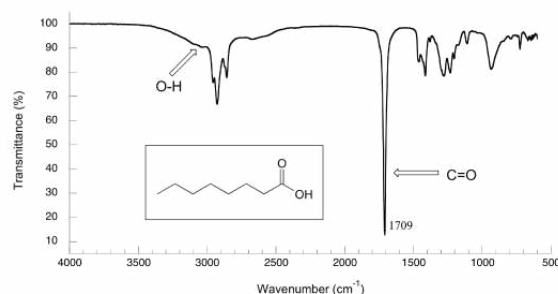
You will notice that there are many additional peaks in this spectrum in the longer-wavelength $400\text{--}1400\text{ cm}^{-1}$ region. This part of the spectrum is called the **fingerprint region**. While it is usually very difficult to pick out any specific functional group identifications from this region, it does, nevertheless, contain valuable information. The reason for this is suggested by the name: just like a human fingerprint, the pattern of absorbance peaks in the fingerprint region is unique to every molecule, meaning that the data from an unknown sample can be compared to the IR spectra of known standards in order to make a positive identification. It was the IR fingerprint region of the suspicious yellow paint that allowed for its identification as a pigment that could not possibly have been used by the purported artist, William Aiken Walker.

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



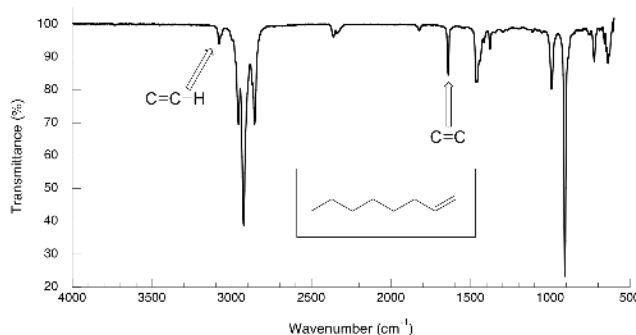
As you can see, the carbonyl peak is gone, and in its place is a very broad ‘mountain’ centered at about 3400 cm^{-1} . This signal is characteristic of the O-H stretching mode of alcohols, and is a dead giveaway for the presence of an alcohol group. The breadth of this signal is a consequence of hydrogen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

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



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

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



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

You can see many more examples of IR spectra in the [Spectral Database for Organic Compounds](#)

? Exercise 4.6

Explain how you could use the C-C and C-H stretching frequencies in IR spectra to distinguish between four constitutional isomers: 1,2-dimethylcyclohexene, 1,3-octadiene, 3-octyne, and 1-octyne.

Exercise 4.7

Using the online Spectral Database for Organic Compounds, look up IR spectra for the following compounds, and identify absorbance bands corresponding to those listed in the table above. List actual frequencies for each signal to the nearest cm⁻¹ unit, using the information in tables provided on the site.

- 1-methylcyclohexanol
- 4-methylcyclohexene
- 1-hexyne
- 2-hexyne

e) 3-hexyne-2,5-diol

Exercise 4.8

A carbon-carbon single bond absorbs in the fingerprint region, and we have already seen the characteristic absorption wavelengths of carbon-carbon double and triple bonds. Rationalize the trend in wavelengths. (*Hint* - remember, we are thinking of bonds as springs, and looking at the frequency at which they 'bounce').

Solutions

It is possible to identify other functional groups such as amines and ethers, but the characteristic peaks for these groups are considerably more subtle and/or variable, and often are overlapped with peaks from the fingerprint region. For this reason, we will limit our discussion here to the most easily recognized functional groups, which are summarized in table 1 in the tables section at the end of the text.

As you can imagine, obtaining an IR spectrum for a compound will not allow us to figure out the complete structure of even a simple molecule, unless we happen to have a reference spectrum for comparison. In conjunction with other analytical methods, however, IR spectroscopy can prove to be a very valuable tool, given the information it provides about the presence or absence of key functional groups. IR can also be a quick and convenient way for a chemist to check to see if a reaction has proceeded as planned. If we were to run a reaction in which we wished to convert cyclohexanone to cyclohexanol, for example, a quick comparison of the IR spectra of starting compound and product would tell us if we had successfully converted the ketone group to an alcohol (this type of reaction is discussed in detail in chapter 15).

[Khan Academy video tutorials on infrared spectroscopy](#)

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CHAPTER OVERVIEW

6: Structural Determination II

- 6.1: Nuclear Magnetic Resonance Spectroscopy
- 6.2: The Nature of NMR Absorptions
- 6.3: Chemical Shifts in ^1H NMR Spectroscopy
- 6.4: Integration of ^1H NMR Absorptions- Proton Counting
- 6.5: Spin-Spin Splitting in ^1H NMR Spectra
- 6.6: ^1H NMR Spectroscopy and Proton Equivalence
- 6.7: General Characteristics of ^{13}C NMR Spectroscopy
- 6.8: Principles of ^{13}C NMR Spectroscopy

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6.1: Nuclear Magnetic Resonance Spectroscopy

Objectives

After completing this section, you should be able to

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

Key Terms

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

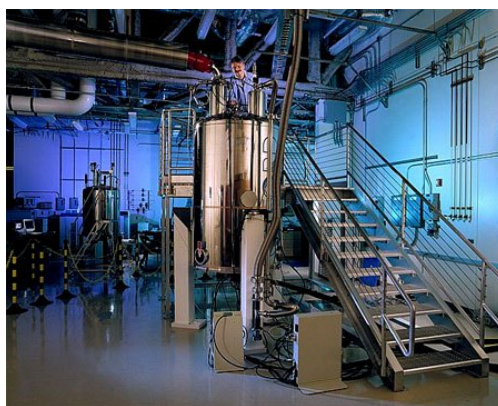
- resonance

Study Notes

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

Introduction

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



NMR Spectrometer

In the absence of an external magnetic field the direction of the spin of the nuclei will be randomly oriented (see figure below left). However, when a sample of these nuclei is placed in an external magnetic field, the nuclear spins will adopt specific orientations much as a compass needle responds to the Earth's magnetic field and aligns with it. Two possible orientations are possible, with the external field (*i.e.* parallel to and in the same direction as the external field) or against the field (*i.e.* antiparallel to the external field). Nuclei in line with the magnetic field have a slightly lower energy than those aligned against the magnetic field ($\uparrow\downarrow E$). The difference in energy depends on the intensity of the applied magnetic field B_0 .

See figure below right.

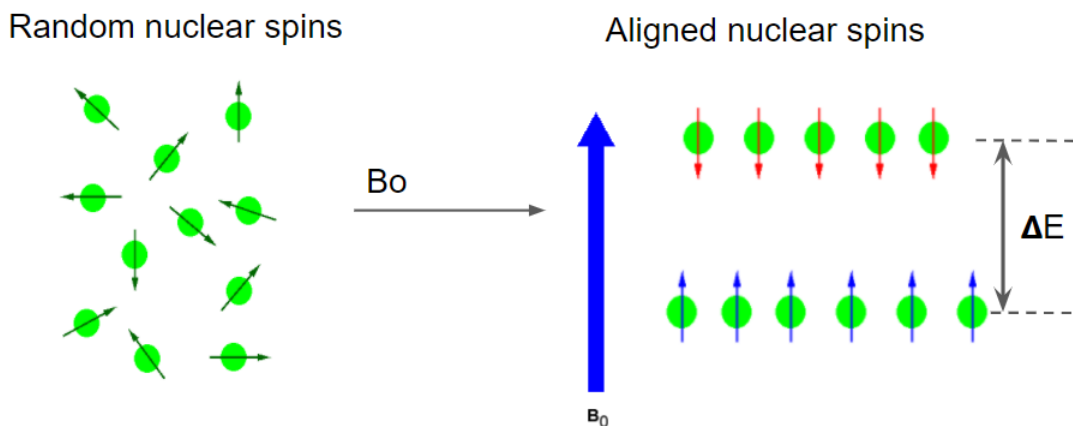
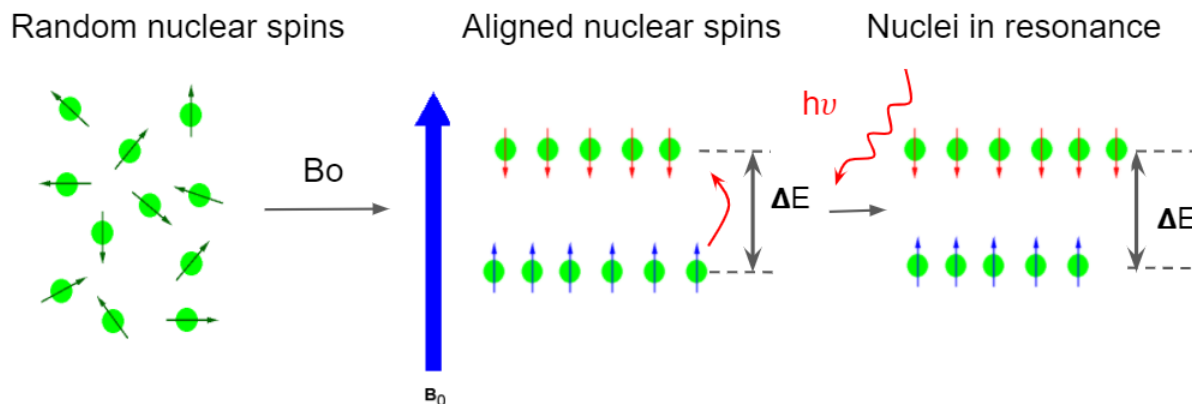
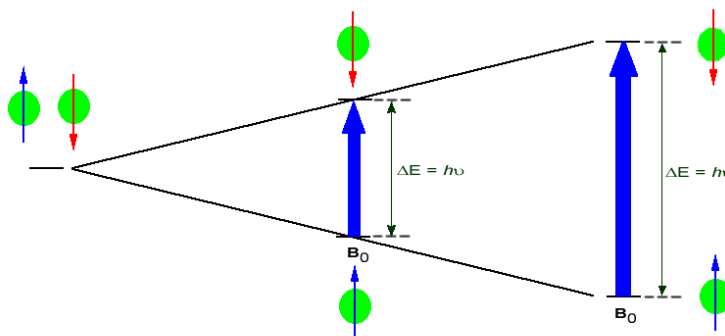


Figure 1: (Left) Random nuclear spin without an external magnetic field. (Right) Ordered nuclear spin in an external magnetic field

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



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



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

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

Exercise

13.1 Nuclear Magnetic Resonance Spectroscopy

13.1 Exercises

Questions

Q13.1.1

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

Q13.1.2

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

Solutions

S13.1.1

$$E = h\nu$$

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

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

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

S13.1.2

$$E = h\nu$$

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

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

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

Contributors and Attributions

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Dr. Richard Spinney (The Ohio State University)

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6.2: The Nature of NMR Absorptions

Objectives

After completing this section, you should be able to

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

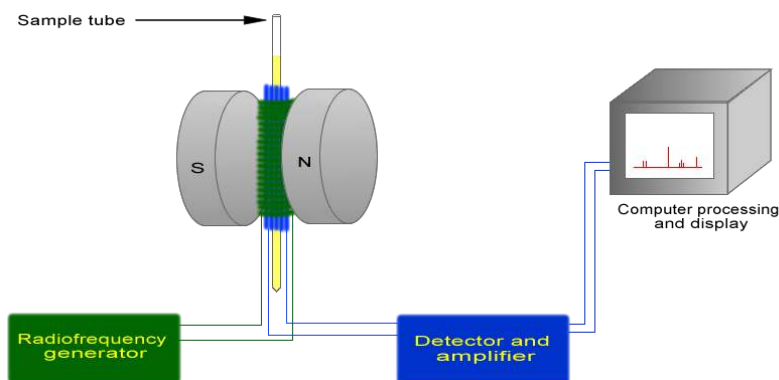
Study Notes

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

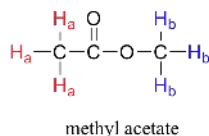
Methyl acetate has a very simple ^1H NMR spectrum, because there is no proton-proton coupling, and therefore no splitting of the signals. In later sections, we discuss splitting patterns in ^1H NMR spectra and how they help a chemist determine the structure of organic compounds.

The basics of an NMR experiment

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



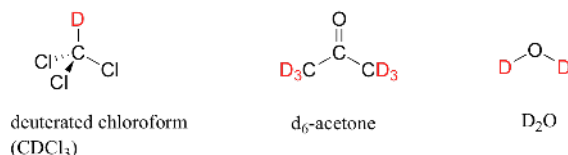
Given that **chemically nonequivalent protons have different resonance frequencies** in the same applied magnetic field, we can see how NMR spectroscopy can provide us with useful information about the structure of an organic molecule. A full explanation of how a modern NMR instrument functions is beyond the scope of this text, but in very simple terms, here is what happens. First, a sample compound (we'll use methyl acetate) is placed inside a very strong applied magnetic field (B_0).



At first, the magnetic moments of (slightly more than) half of the protons are aligned with B_0 , and half are aligned against B_0 . Then, the sample is hit with electromagnetic radiation in the radio frequency range. The two specific frequencies which match the

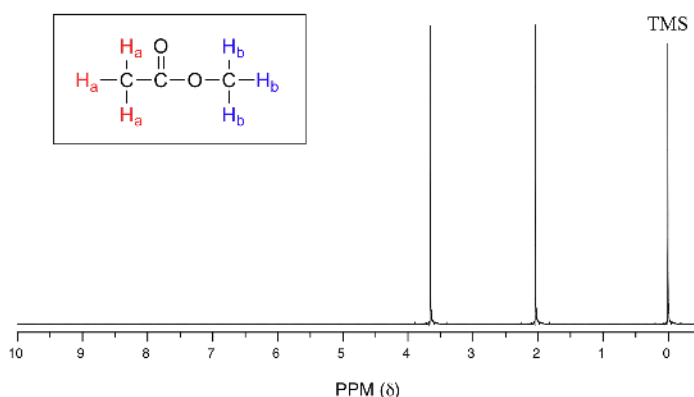
resonance frequencies for H_a and H_b protons to 'flip' so that they are now aligned *against* B_0 . In doing so, the protons absorb radiation at the two resonance frequencies. The NMR instrument records which frequencies were absorbed, as well as the intensity of each absorbance.

In most cases, a sample being analyzed by NMR is in solution. If we use a common laboratory solvent (diethyl ether, acetone, dichloromethane, ethanol, water, etc.) to dissolve our NMR sample, however, we run into a problem – there many more solvent protons in solution than there are sample protons, so the signals from the sample protons will be overwhelmed. To get around this problem, we use special NMR solvents in which all protons have been replaced by deuterium. Recall that deuterium is NMR-active, but its resonance frequency is very different from that of protons, and thus it is 'invisible' in ^1H -NMR. Some common NMR solvents are shown below.

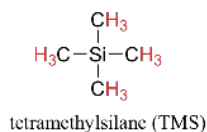


The Chemical Shift

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



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



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

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

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

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

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

Example

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

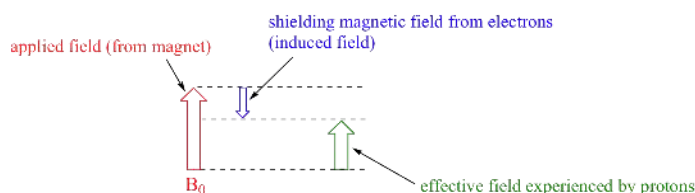
- What is its chemical shift, expressed in Hz, in a 300 MHz instrument? On a 200 MHz instrument?
- What is its resonance frequency, expressed in Hz, in a 300 MHz instrument? On a 200 MHz instrument?

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

Solution

Diamagnetic shielding and deshielding

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

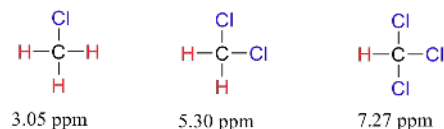


Therefore, their resonance frequency is slightly lower than what it would be if they did not have electrons nearby to shield them.

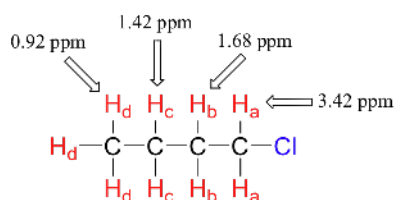
Now consider methyl fluoride, CH_3F , in which the protons have a chemical shift of 4.26 ppm, significantly higher than that of methane. This is caused by something called the **deshielding effect**. Because fluorine is more electronegative than carbon, it pulls valence electrons away from the carbon,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



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



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



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

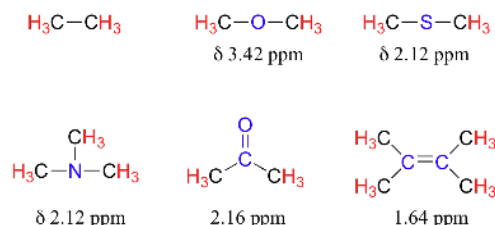
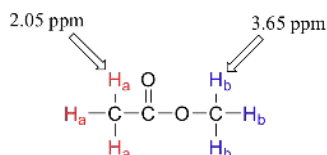


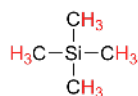
Table 2 lists typical chemical shift values for protons in different chemical environments.

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



Finally, a note on the use of TMS as a standard in NMR spectroscopy: one of the main reasons why the TMS proton signal was chosen as a zero-point is that the TMS protons are highly shielded: silicon is slightly *less* electronegative than carbon, and therefore

donates some additional shielding electron density. Very few organic molecules contain protons with chemical shifts that are negative relative to TMS.



Exercise

Questions

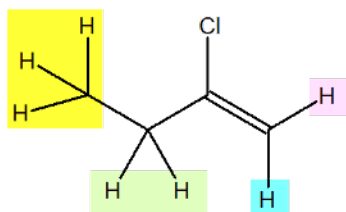
Q13.2.1

2-chlorobutene shows 4 different hydrogen signals. Explain why this is.

Solutions

S13.2.1

The same colors represent the same signal. 4 different colors for 4 different signals. The hydrogen on the alkene would give two different signals.



Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, [Athabasca University](#))
- Prof. Steven Farmer ([Sonoma State University](#))
- [Organic Chemistry With a Biological Emphasis](#) by Tim Soderberg (University of Minnesota, Morris)

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6.3: Chemical Shifts in ^1H NMR Spectroscopy

Objectives

After completing this section, you should be able to

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

Study Notes

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

^1H NMR Chemical Shifts

Chemical shift is associated with the chemical environment of a nuclei. Tetramethylsilane [$\text{TMS}; (\text{CH}_3)_4\text{Si}$] is generally used for standard to determine chemical shift of compounds: $\delta_{\text{TMS}} = 0\text{ppm}$. In other words, frequencies for chemicals are measured for a ^1H or ^{13}C nucleus of a sample from the ^1H or ^{13}C resonance of TMS. It is important to understand trend of chemical shift in terms of NMR interpretation. The proton NMR chemical shift is affected by nearness to electronegative atoms (O, N, halogen.) and unsaturated groups ($\text{C}=\text{C}$, $\text{C}=\text{O}$, aromatic). Electronegative groups move to the downfield (left; increase in ppm). Unsaturated groups shift to downfield (left) when affecting nucleus is in the plane of the unsaturation, but reverse shift takes place in the regions above and below this plane. ^1H chemical shift plays a role in identifying many functional groups. Figure 1. indicates important example to figure out the functional groups.

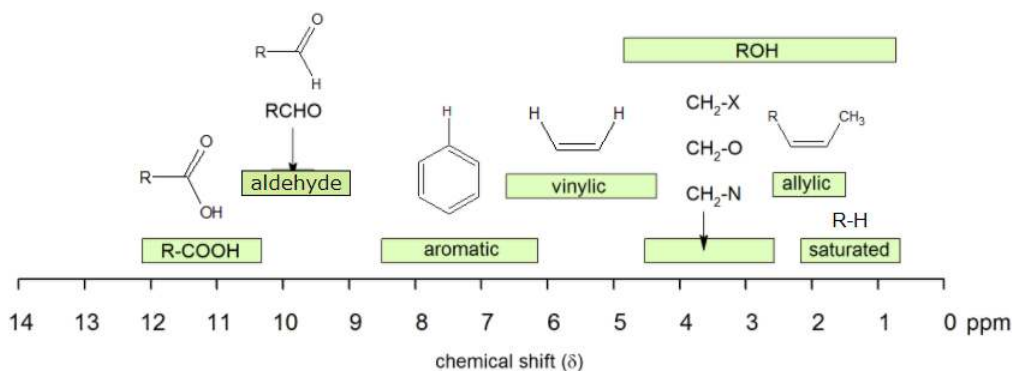


Figure 1. ^1H chemical shift ranges for organic compounds

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

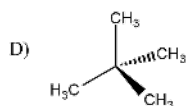
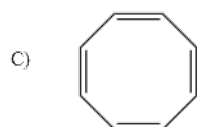
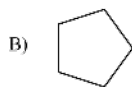
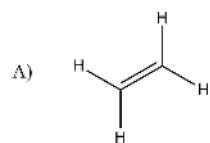
Hydrogen type (Ar= aromatic ring)	Chemical shift (ppm)
RCH_3	0.9 - 1.0
RCH_2R	1.2 - 1.7
R_3CH	1.5 - 2.0
	2.0 - 2.3
$\begin{array}{c} \text{R} \quad \text{CH}_3 \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{R} \quad \text{R} \end{array}$	1.5 - 1.8
RNH_2	1 - 3
ArCH_3	2.2 - 2.4
$\text{R}-\text{C}\equiv\text{C}-\text{H}$	2.3 - 3.0
ROCH_3	3.7 - 3.9
$\begin{array}{c} \text{O} \\ \\ \text{R}-\text{C}-\text{O}-\text{CH}_3 \end{array}$	3.7 - 3.9
ROH	1 - 5
$\begin{array}{c} \text{R} \quad \text{H} \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{R} \quad \text{R} \end{array}$	3.7 - 6.5
$\begin{array}{c} \text{O} \\ \\ \text{R}-\text{C}-\text{N}-\text{R} \\ \\ \text{H} \end{array}$	5 - 9
ArH	6.0 - 8.7
$\begin{array}{c} \text{O} \\ \\ \text{R}-\text{C}-\text{H} \end{array}$	9.5 - 10.0
$\begin{array}{c} \text{O} \\ \\ \text{R}-\text{C}-\text{OH} \end{array}$	10 - 13

Exercise

Questions

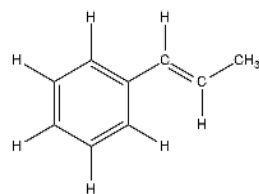
Q13.9.1

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



Q13.9.2

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



Solutions

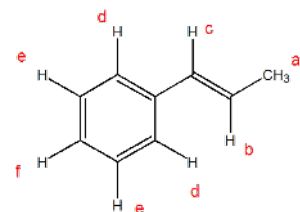
S13.9.1

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

S13.9.2

There are 6 different protons in this molecule

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



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6.4: Integration of ^1H NMR Absorptions- Proton Counting

Objectives

After completing this section, you should be able to

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

Study Notes

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

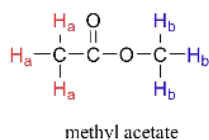
In practice, we do not have to measure these areas ourselves: it is all done electronically by the spectrometer, and an integration curve is superimposed on the rest of the spectrum. The integration curve appears as a series of steps, with the height of each step being proportional to the area of the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

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

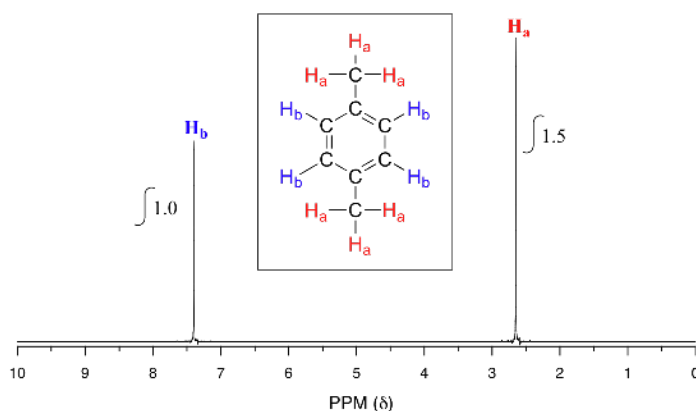
Signal integration in NMR (Nuclear Magnetic Resonance) spectroscopy is crucial for quantifying the relative number of nuclei contributing to each signal in the spectrum. This process involves measuring the area under each peak in the NMR spectrum, which directly correlates to the abundance of the corresponding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

Signal Integration

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



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



This molecule has two sets of protons: the six methyl (H_a) protons and the four aromatic (H_b) protons. When we instruct the instrument to integrate the areas under the two signals, we find that the area under the peak at 2.6 ppm is 1.5 times greater than the area under the peak at 7.4 ppm, which is the case with 6 methyl protons and 4 aromatic protons. This (along with the actual chemical shift values, which we'll discuss soon) tells us which set of protons corresponds to which NMR signal.

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

✓ Example 6.4.1

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

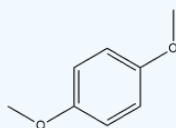
✓ Example 6.4.2

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

[Solutions](#)

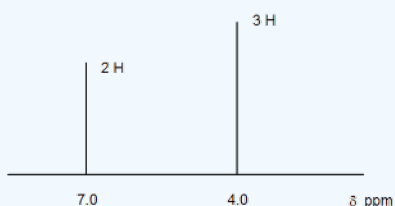
? Exercise 6.4.1

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



Answer

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



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6.5: Spin-Spin Splitting in ^1H NMR Spectra

Objectives

After completing this section, you should be able to

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

Key Terms

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

- coupling constant
- multiplet
- quartet
- triplet
- doublet

Study Notes

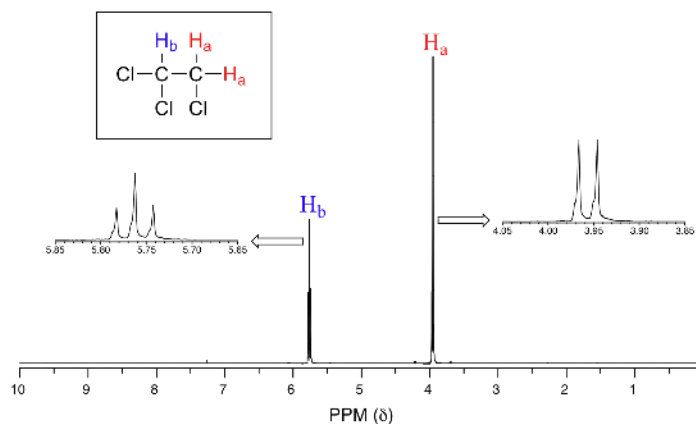
From what we have learned about ^1H NMR spectra so far, we might predict that the spectrum of 1,1,2-trichloroethane, $\text{CHCl}_2\text{CH}_2\text{Cl}$, would consist of two peaks—one, at about 2.5–4.0 δ , expected for CH_2 -halogen compounds and one shifted downfield because of the presence of an additional electronegative chlorine atom on the second carbon. However, when we look at the spectrum it appears to be much more complex. True, we see absorptions in the regions we predicted, but these absorptions appear as a group of two peaks (a *doublet*) and a group of three peaks (a *triplet*). This complication, which may be disturbing to a student who longs for the simple life, is in fact very useful to the organic chemist, and adds greatly to the power of NMR spectroscopy as a tool for the elucidation of chemical structures. The split peaks (*multiplets*) arise because the magnetic field experienced by the protons of one group is influenced by the spin arrangements of the protons in an adjacent group.

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

The source of spin-spin coupling

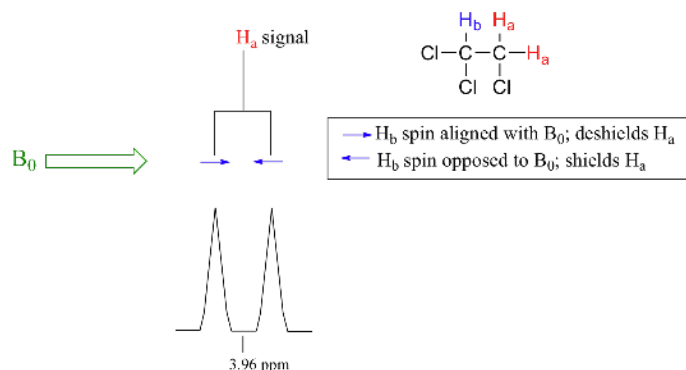
The ^1H -NMR spectra that we have seen so far (of methyl acetate and *para*-xylene) are somewhat unusual in the sense that in both of these molecules, each set of protons generates a single NMR signal. In fact, the ^1H -NMR spectra of most organic molecules contain proton signals that are 'split' into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

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

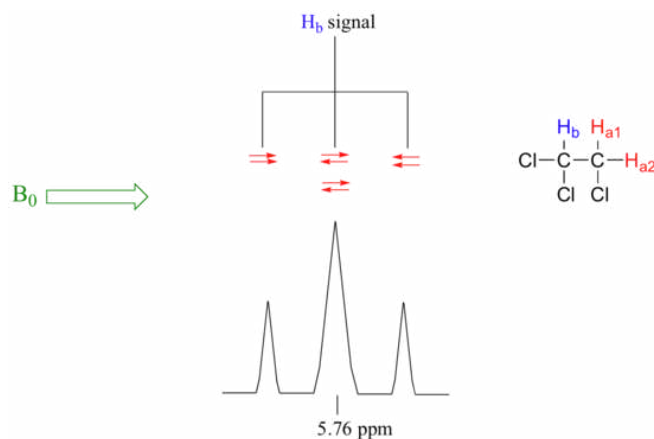


The signal at 3.96 ppm, corresponding to the two H_a protons, is split into two subpeaks of equal height (and area) – this is referred to as a **doublet**. The H_b signal at 5.76 ppm, on the other hand, is split into three sub-peaks, with the middle peak higher than the two outside peaks - if we were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

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

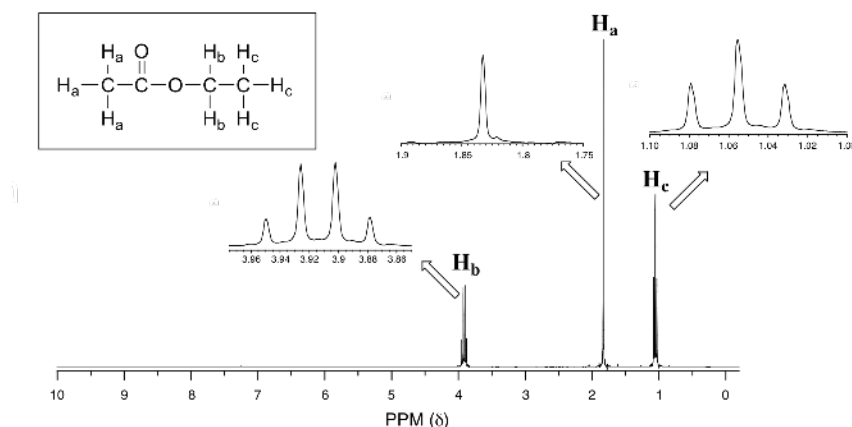


Now, let's think about the H_b signal. The magnetic environment experienced by H_b is influenced by the fields of both neighboring H_a protons, which we will call H_{a1} and H_{a2} . There are four possibilities here, each of which is equally probable. First, the magnetic fields of both H_{a1} and H_{a2}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



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

Now, consider the spectrum for ethyl acetate:



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

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

Example 13.11.1

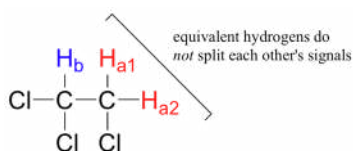
- Explain, using left and right arrows to illustrate the possible combinations of nuclear spin states for the H_c hydrogens, why the H_b signal in ethyl acetate is split into a quartet.
- The integration ratio of doublets is 1:1, and of triplets is 1:2:1. What is the integration ratio of the H_b quartet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

Solution

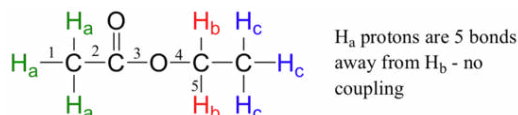
By now, you probably have recognized the pattern which is usually referred to as the **$n + 1$ rule**: if a set of hydrogens has n neighboring, non-equivalent hydrogens, it will be split into $n + 1$ subpeaks. Thus the two H_b hydrogens in ethyl acetate split the H_c signal into a triplet, and the three H_c hydrogens split the H_b signal into a quartet. This is very useful information if we are trying to determine the structure of an unknown molecule: if we see a triplet signal, we know that the corresponding hydrogen or set of

hydrogens has two `neighbors`. When we begin to determine structures of unknown compounds using ^1H -NMR spectral data, it will become more apparent how this kind of information can be used.

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

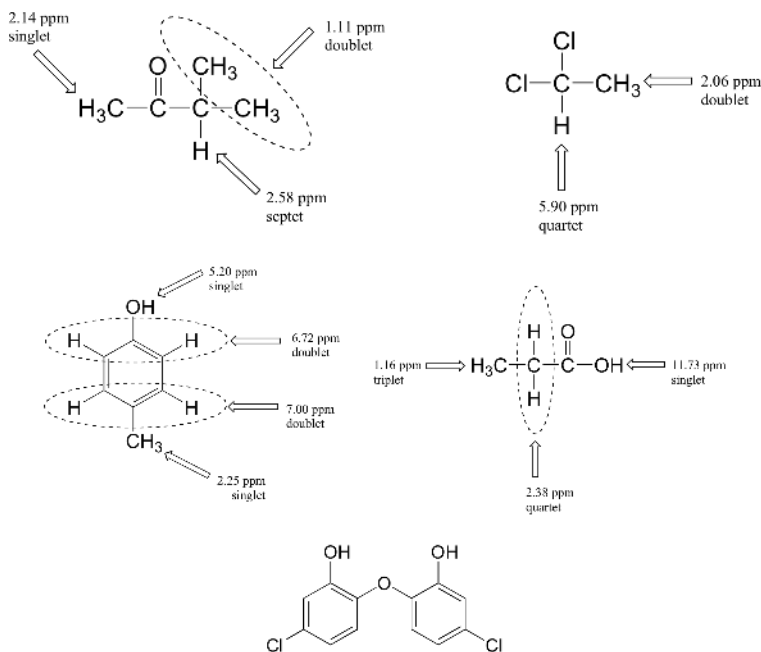


Second, splitting occurs primarily between hydrogens that are separated by three bonds. This is why the H_a hydrogens in ethyl acetate form a singlet– the nearest hydrogen neighbors are five bonds away, too far for coupling to occur.



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

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



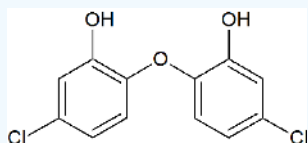
Multiplicity Patterns in Proton NMR

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

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

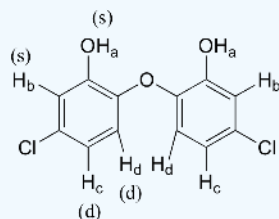
Example 13.11.2

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



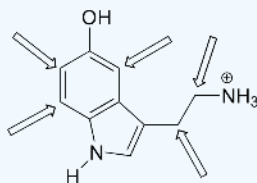
Answer

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



Example 13.11.3

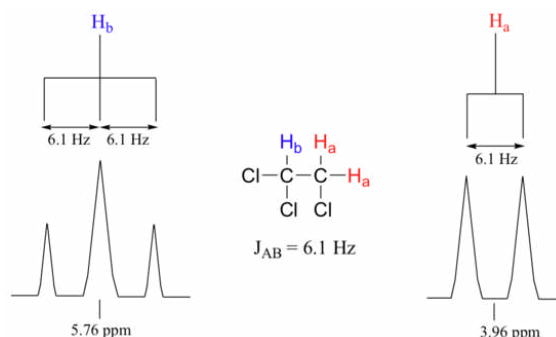
Predict the splitting pattern for the ^1H -NMR signals corresponding to the protons at the locations indicated by arrows (the structure is that of the neurotransmitter serotonin).



Solutions

Coupling constants

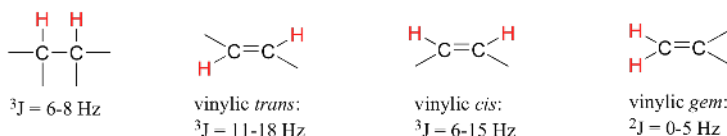
Chemists quantify the spin-spin coupling effect using something called the **coupling constant**, which is abbreviated with the capital letter J . The coupling constant is simply the difference, expressed in Hz, between two adjacent sub-peaks in a split signal. For our doublet in the 1,1,2-trichloroethane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



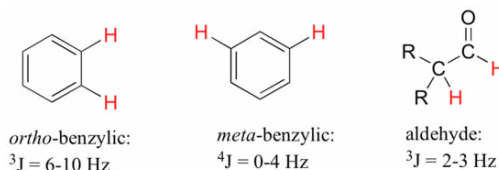
The superscript 3 tells us that this is a three-bond coupling interaction, and the a-b subscript tells us that we are talking about coupling between H_a and H_b . Unlike the chemical shift value, *the coupling constant, expressed in Hz, is the same regardless of the applied field strength of the NMR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

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

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



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



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

Exercise

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

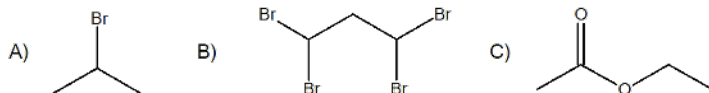
13.11 Spin-Spin Splitting in ^1H NMR Spectra

13.11 Exercises

Questions

Q13.11.1

Predict the splitting patterns of the following molecules:



Q13.11.2

Draw the following according to the criteria given.

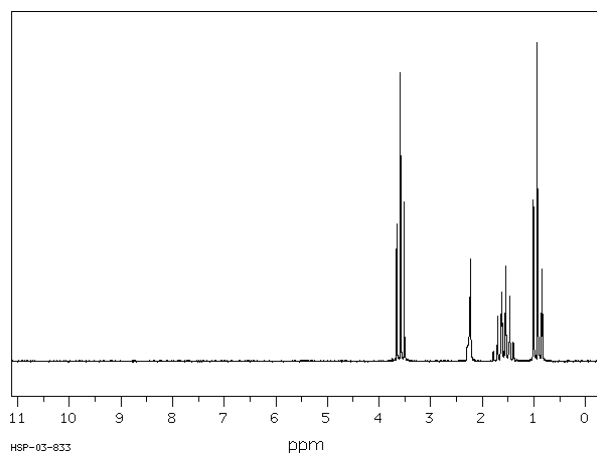
A. $\text{C}_3\text{H}_5\text{O}$; two triplet, 1 doublet

B. $\text{C}_4\text{H}_8\text{O}_2$; three singlets

C. C_5H_{12} ; one singlet

Q13.11.3

The following spectrum is for $\text{C}_3\text{H}_8\text{O}$. Determine the structure.



A triplet; B singlet; C sextet; D triplet

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

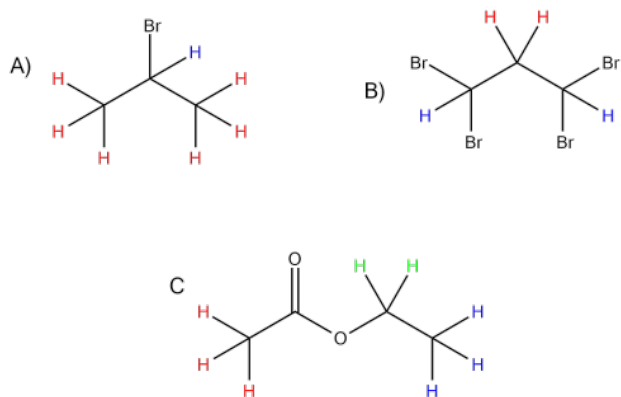
Solutions

S13.11.1

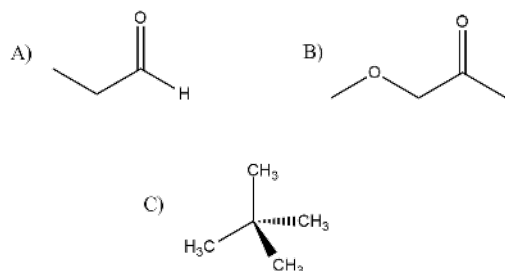
A. H: Doublet, H: Septet

B. H: Doublet, H: Triplet

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

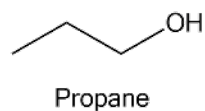


S13.11.2



These are just some drawings, more may be possible.

S13.11.3



Contributors and Attributions

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- Prof. Steven Farmer ([Sonoma State University](#))
- [Organic Chemistry With a Biological Emphasis](#) by [Tim Soderberg](#) (University of Minnesota, Morris)
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6.5: Spin-Spin Splitting in ^1H NMR Spectra is shared under a [not declared](#) license and was authored, remixed, and/or curated by LibreTexts.

6.6: ^1H NMR Spectroscopy and Proton Equivalence

Objectives

After completing this section, you should be able to

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

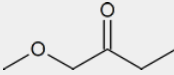
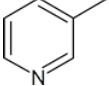
Key Terms

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

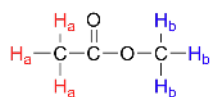
- diastereotopic
- enantiotopic
- homotopic

Study Notes

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

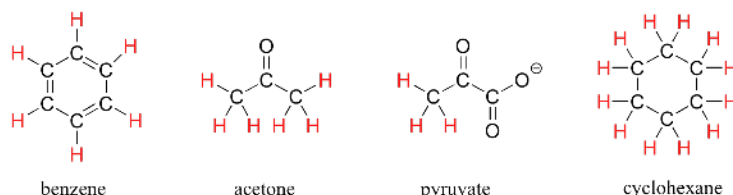
Structure	Number of Signals	Ratio of Signals	
<chem>CH3OCH2CH2Br</chem>	3	A : B : C	3 : 2 : 2
	1		
	3	A : B : C	2 : 2 : 6 (or 1 : 1 : 3)
	3	A : B : C	2 : 4 : 2 (or 1 : 2 : 1)
	4	A : B : C : D	3 : 2 : 2 : 3
	5	A : B : C : D : E	3 : 1 : 1 : 1 : 1

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

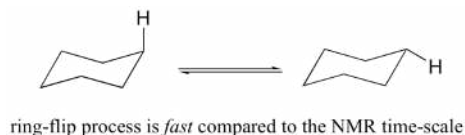


On the other hand, the three H_a protons are all in the same electronic environment, and are chemically equivalent to one another. They have identical resonance frequencies. The same can be said for the three H_b protons. These protons are considered to be homotopic. Homotopic protons are chemically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

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

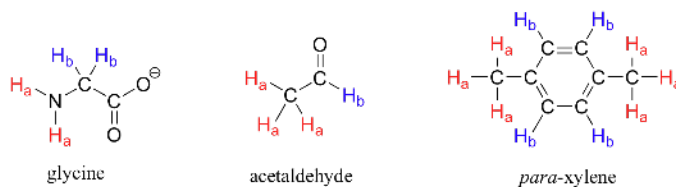


You might expect that the equatorial and axial hydrogens in cyclohexane would be non-equivalent, and would have different resonance frequencies. In fact, an axial hydrogen is in a different electronic environment than an equatorial hydrogen. Remember, though, that the molecule rotates rapidly between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



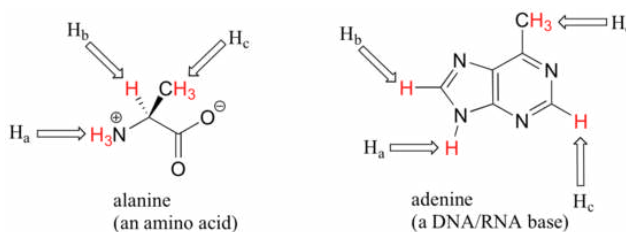
In this sense, NMR is like a camera that takes photographs of a rapidly moving object with a slow shutter speed - the result is a blurred image. In NMR terms, this means that all 12 protons in cyclohexane are equivalent.

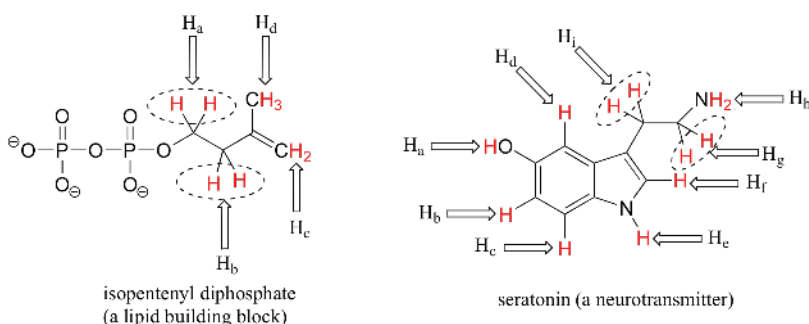
Each the molecules in the next figure contains *two* sets of protons, just like our previous example of methyl acetate, and again in each case the resonance frequency of the H_a protons will be different from that of the H_b protons.



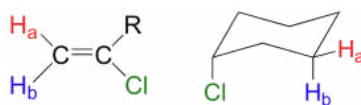
Notice how the symmetry of *para*-xylene results in there being only two different sets of protons.

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

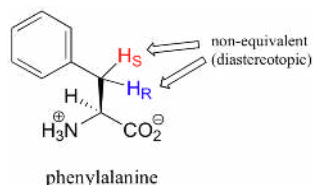




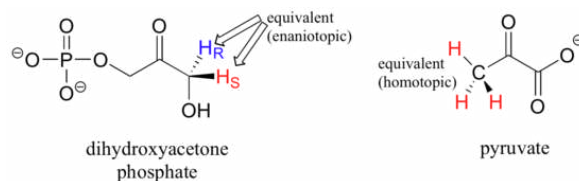
When stereochemistry is taken into account, the issue of equivalence vs nonequivalence in NMR starts to get a little more complicated. It should be fairly intuitive that hydrogens on different sides of asymmetric ring structures and double bonds are in different electronic environments, and thus are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



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

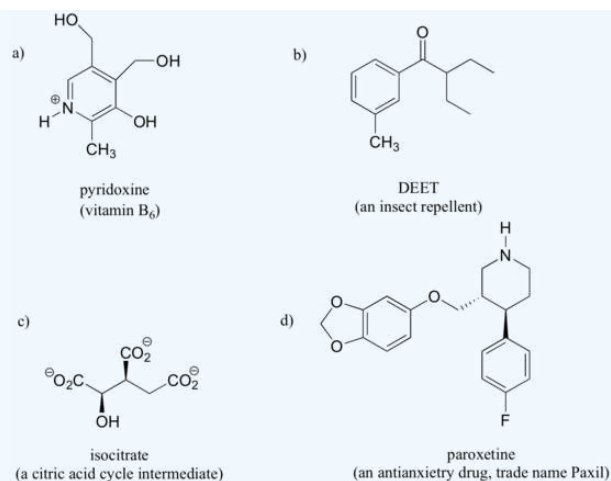


However, enantiotopic and homotopic hydrogens are chemically equivalent. To determine if protons are homotopic or enantiotopic, you can do a thought experiment by replacing one H with X followed by the other H by X. In pyruvate below, if you replace any of the Hs with an X, then you would get the same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



✓ Example 13.6.1

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



Solution

? Exercise 6.6.1

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

- $\text{CH}_3\text{CH}_2\text{CH}_2\text{Br}$
- $\text{CH}_3\text{OCH}_2\text{C}(\text{CH}_3)_3$
- Ethyl Benzene
- 2-methyl-1-hexene

Answer

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

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6.7: General Characteristics of ^{13}C NMR Spectroscopy

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

Signal strength in ^{13}C -NMR spectroscopy

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

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

Contributors and Attributions

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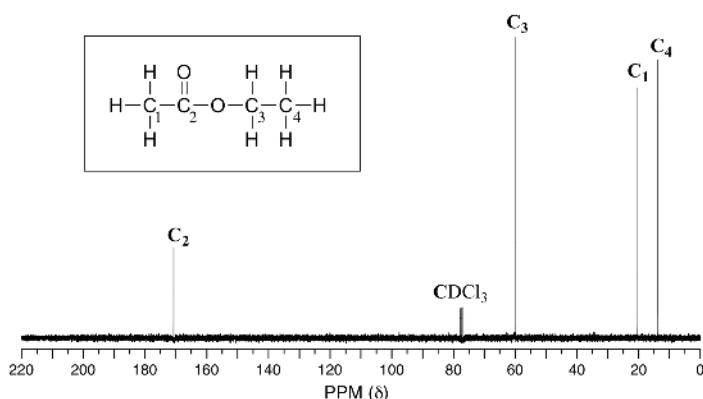
6.7: General Characteristics of ^{13}C NMR Spectroscopy is shared under a [not declared](#) license and was authored, remixed, and/or curated by LibreTexts.

6.8: Principles of ^{13}C NMR Spectroscopy

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

Number of signals in ^{13}C -NMR spectroscopy

In analogy to ^1H NMR, ^{13}C NMR can be used to obtain information about the C-C skeleton in an organic compound. The number of signals in a ^{13}C NMR spectrum is related to the number of nonequivalent carbons in the chemical structure of the compound. For example, the ^{13}C NMR spectrum of ethyl acetate shows four signals, one for each of the nonequivalent carbons.



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

Example

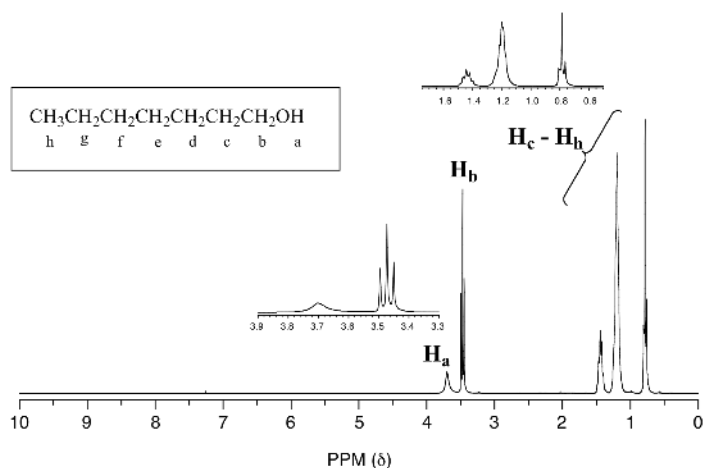
How many sets of non-equivalent carbons are there in:

- toluene
- 2-pentanone
- para-xylene

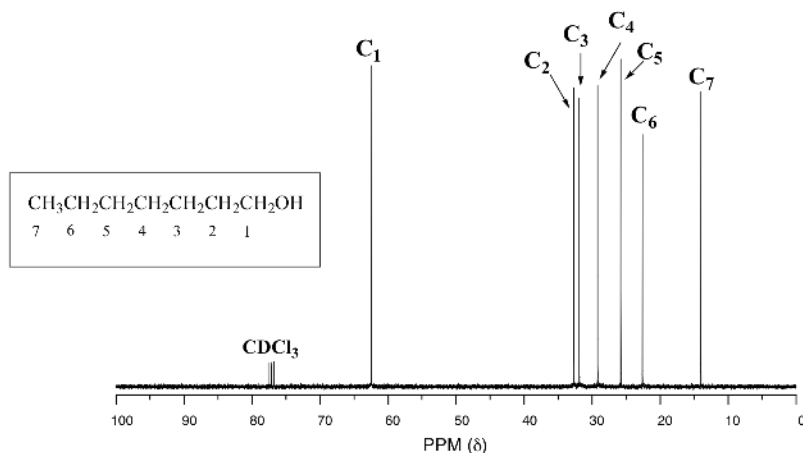
Solution

^{13}C NMR Spectral window

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



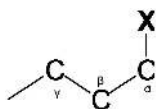
In the ^{13}C spectrum of the same molecule, however, we can easily distinguish each carbon signal, and we know from this data that our sample has seven non-equivalent carbons. (Notice also that, as we would expect, the chemical shifts of the carbons get progressively smaller as they get farther away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



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

^{13}C NMR Chemical Shifts for functional groups

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



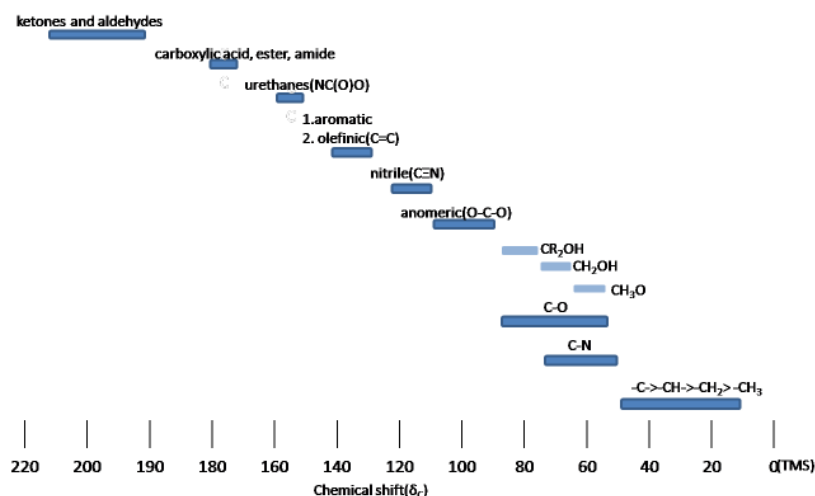


Figure 13.11.1: ^{13}C Chemical shift range for organic compound

^{13}C NMR Chemical Shifts Intensity

Unlike ^1H -NMR signals, the area under a ^{13}C -NMR signal cannot be used to determine the number of carbons to which it corresponds. This is because the signals for some types of carbons are inherently weaker than for other types – peaks corresponding to carbonyl carbons, for example, are much smaller than those for methyl or methylene (CH_2) peaks. Peak integration is generally not useful in ^{13}C -NMR spectroscopy, and therefore, the most useful information provided by the ^{13}C -NMR spectrum is the number and chemical shift of the signals, but no integration or multiplicity of signals.

Contributors and Attributions

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- Layne Morsch (University of Illinois Springfield)

6.8: Principles of ^{13}C NMR Spectroscopy is shared under a [not declared](#) license and was authored, remixed, and/or curated by LibreTexts.

CHAPTER OVERVIEW

7: Organic Chemistry of Drugs

- 7.1: Drug Definition and Activity
- 7.2: Therapeutic index
- 7.3: The phases of Drug Action
- 7.4: Drug discovery and development
- 7.5: Molecular Modification
- 7.6: FDA Drug Approval Process
- 7.7: Drugs and Infectious Diseases

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7.1: Drug Definition and Activity

A very broad definition of a drug would include "all chemicals other than food that affect living processes." A more concise definition of a drug is any substance that has an effect when ingested or introduced into the body. If the effect helps the body, the drug is a medicine. If a drug causes a harmful effect on the body, the drug is a poison. Any drug can be a medicine and a poison depending on its concentration (dose) and the metabolic conditions of the person taking the drug.

Drug effect

It is important to distinguish between actions of drugs and their effects. Actions of drugs are the biochemical physiological mechanisms by which the chemical produces a response in living organisms. The effect is the observable consequence of a drug action. For example, the action of penicillin is to interfere with cell wall synthesis in bacteria and the effect is the death of the bacteria.

One major problem of pharmacology is that no drug produces a single effect. The primary effect is the desired (beneficial) therapeutic effect. Secondary effects are all other effects besides the desired effect which may be either beneficial or harmful. **The key is to regulate the drug dose to maximize the beneficial effects and minimize the non-desired side effects.**

The biological effects observed after a drug has been administered are the result of an interaction between that chemical and some part of the organism. Mechanisms of drug action can be viewed from different perspectives, namely, the site of action and the general nature of the drug-cell interaction.

Drug Classification

Drugs can be classified according to various criteria including chemical structure or pharmacological action. The preferred classification is the latter one which may be divided into main groups as follows:

1. Chemotherapeutic agents - used to cure infectious diseases and cancer. (Sulfa drugs, Antibiotics)
2. Pharmacodynamic agents - used in non-infectious diseases (Cholinergic, Adrenergic, Hallucinogenic, Sedatives)
3. Miscellaneous agents (Narcotic Analgesics, Local Anesthetics)

Unfortunately, there is no connection between chemical structure and pharmacological activity. Drugs with similar chemical structure might have very different pharmacological activity. For example, cortisol is a steroid drug used to regulate the body's anti-inflammatory processes. Ibuprofen is another drug used in anti-inflammatory processes. However, both drugs have very different chemical structures.



Cortisol, a steroid drug used to regulate the body's anti-inflammatory processes. Image by NEUROtiker, Public domain, via [Wikimedia Commons](#)



Ibuprofen, a non-steroid drug used to regulate the body's anti-inflammatory processes. Image by Benjah-bmm27, Public domain, via [Wikimedia Commons](#).

Drug Names

Drugs have three or more names including a: chemical name, brand or trade name, and generic or common name. The chemical name is assigned according to rules of nomenclature of chemical compounds. The brand name is always capitalized and is selected by the manufacturer. The generic name refers to a common established name irrespective of its manufacturer.

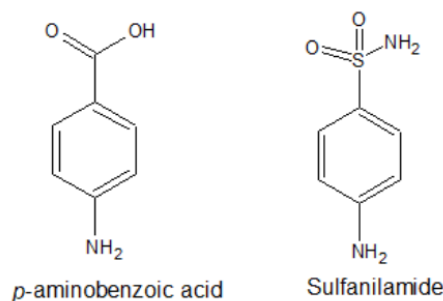
In most cases, a drug bearing a generic name is equivalent to the same drug with a brand name. However, this equivalency is not always true. Although drugs are chemically equivalent, different manufacturing processes may cause differences in pharmacological action. Several differences may be crystal size or form, isomers, crystal hydration, purity-(type and number of impurities), vehicles, binders, coatings, dissolution rate, and storage stability.

Mode of Drug Action

Drugs act within the cell by modifying normal biochemical reactions. There are three main mechanisms of drug action:

Drug-Receptor Inhibition (antagonist drugs)

Drugs can act within the cell by blocking the substrate binding to an enzyme or receptor. Because these drugs prevent an enzyme from performing its function, the drug is called an antagonist. Enzyme inhibition may be reversible or nonreversible; competitive or non-competitive. For example, the antibiotic drug **sulfanilamide** competitively binds to the enzyme in the dihydropteroate synthase (DHPS) active site by mimicking the substrate **para-aminobenzoic acid** (PABA). This prevents the substrate itself from binding which halts the production of folic acid, an essential nutrient for bacteria.



Drug-Receptor Activation (agonist drugs)

Drugs can act within the cell by binding to specific receptors located on the cell membrane. The binding of the drug to the receptor triggers an intracellular response. Some receptor sites have been identified with specific parts of proteins and nucleic acids. In most cases, the chemical nature of the receptor site remains obscure. For example, the drug Morphine binds to opioid receptors (inhibitory G protein-coupled proteins). After binding to its receptors, an internal cellular response is triggered. Activation of the inhibitory G protein-coupled proteins produces analgesia and respiratory depression.

Non-specific Interactions

Some drugs act exclusively by physical means outside of cells, without involving a drug-receptor interaction. These extracellular sites include external surfaces of the skin and gastrointestinal tract. Neutralization of stomach acid by antacids is a good example.

 Agonist & Antagonist

Difference between Agonist and Antagonist drugs. Image by [Dolleyj](#), CC BY-SA 3.0, via [Wikimedia Commons](#)

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7.2: Therapeutic index

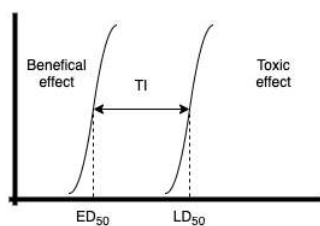
Therapeutic index

The therapeutic index (TI; also referred to as therapeutic ratio) is a quantitative measurement of the relative safety of a drug. It is a comparison of the amount of a therapeutic agent that causes the therapeutic effect to the amount that causes toxicity.

TI is determined in animals as the lethal dose of a drug for 50% of the population (LD_{50}) divided by the minimum effective dose for 50% of the population (ED_{50}):

$$\text{Therapeutic Index (TI)} = LD_{50} / ED_{50}$$

A higher therapeutic index is preferable to a lower one: a patient would have to take a much higher dose of such a drug to reach the toxic threshold than the dose taken to elicit the therapeutic effect.



The related terms therapeutic window or safety window refer to a range of doses which optimize between efficacy and toxicity, achieving the greatest therapeutic benefit without resulting in unacceptable side-effects or toxicity.

Range of therapeutic indices

The therapeutic index varies widely among substances, even within a related group.

For instance, the opioid painkiller remifentanyl is very forgiving, offering a therapeutic index of 33,000:1, while Diazepam, a benzodiazepine sedative-hypnotic and skeletal muscle relaxant, has a less forgiving therapeutic index of 100:1. Morphine is even less so with a therapeutic index of 70.

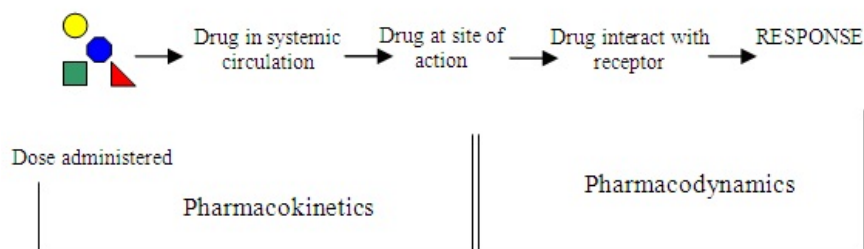
Sources

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7.3: The phases of Drug Action

The ability of a drug to carry its metabolic action (response) depends on two general phases. One phase is the ability of the drug to reach its site of action (receptor) in a particular cell. This process begins with the administration of the drug, its absorption, distribution, metabolism, and excretion through the body. This phase of drug action is called **pharmacokinetics**. Once at its action site, the ability of the drug to bind to the receptor depends on the chemical interactions between the chemical groups in the receptor and the drug (drug-receptor affinity). This phase of drug action is called **pharmacodynamics**. In order for a drug to be effective, it needs to exhibit acceptable pharmacokinetic and pharmacodynamic properties.



Pharmacokinetics and Pharmacodynamic stages of Drug Action. Image by [Jorge Guerra Pires](#), CC BY-SA 4.0, via [Wikimedia Commons](#)

A. Pharmacokinetics

Pharmacokinetics deals with the absorption, distribution, biotransformation (metabolization), and excretion of drugs. These factors, coupled with dosage, determine the concentration of a drug at its sites of action and, hence, the intensity of its effects as a function of time. Many basic principles of biochemistry and enzymology and the physical and chemical principles that govern the active and passive transfer and the distribution of substances across biological membranes are readily applied to the understanding of this important aspect of medicinal chemistry.

Drug Absorption:

Absorption occurs after drugs enter the body and travel from the site of administration into the body's circulation. Medications can enter the body through various routes of administration:

- oral (swallowing an aspirin tablet)
- enteral (administering to the GI tract such as via a NG tube)
- rectal (administering an acetaminophen [Tylenol] suppository)
- inhalation (breathing in medication from an inhaler)
- intramuscular (getting a flu shot in the deltoid muscle)
- subcutaneous (injecting insulin into the fat tissue beneath the skin)
- transdermal (wearing a nicotine patch)

Different factors, such as the chemical structure of the drug, the type of cellular tissue at the administration site, local pH, concentration (dosage), and the formulation of the drug (tablet, capsule, liquid, cream, etc) can affect the ability of the drug to enter the body.

Drug Distribution

Distribution is the process by which medication is distributed throughout the body. The distribution of a drug throughout the body is dependent on common factors such as blood flow, plasma protein binding, lipid solubility, the blood-brain barrier, and the placental barrier. Other factors include capillary permeability, differences between blood/tissue, and volume of distribution.

The bloodstream carries medications to their destinations in the body. Once the drug is in the bloodstream, a portion of it may exist as free drug, dissolved in plasma water. Some of the drug will be reversibly taken up by red cells, and some will be reversibly bound to plasma proteins. For many drugs, the bound forms can account for 95-98% of the total. This is important because it is the free drug that traverses cell membranes and produces the desired effect. It is also important because a protein-bound drug can act as a reservoir that releases the drug slowly and thus prolongs its action. With drug distribution, it is important to consider both the amount of free drug that is readily available to tissues, as well as the potential drug reserve that may be released over time.

Drug Metabolism

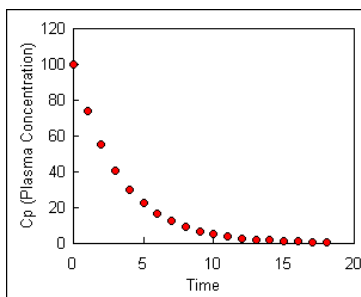
Once a drug has been absorbed and distributed in the body, it will then be broken down by a process known as metabolism. The breakdown of a drug molecule usually involves enzymes present in the liver. Many of the products of enzymatic breakdown, which are called metabolites, are less chemically active than the original molecule. Metabolites are usually more water-soluble than the parental drug and therefore easier to excrete in the urine.

Drug Excretion or Elimination

Drugs are eliminated from the body either unchanged or as metabolites. Most of the excretion is done by filtration at the kidneys, where a portion of the drug undergoes reabsorption back into the bloodstream, and the remainder is excreted in the urine. The liver also excretes byproducts and waste into the bile. Excretory organs eliminate polar compounds more efficiently than substances with high lipid solubility. Lipid-soluble drugs are thus not readily eliminated until they are metabolized to more polar compounds.

The kidney is the most important organ for elimination of drugs and their metabolites. Substances excreted in the feces are mainly unabsorbed orally ingested drugs or metabolites excreted in the bile and not reabsorbed from the intestinal tract. Excretion of drugs in milk is important not because of the amounts eliminated but because the excreted drugs are potential sources of unwanted pharmacological effects in the nursing infant. Pulmonary excretion is important mainly for the elimination of anesthetic gases and vapors: occasionally, small quantities of other drugs or metabolites are excreted by this route.

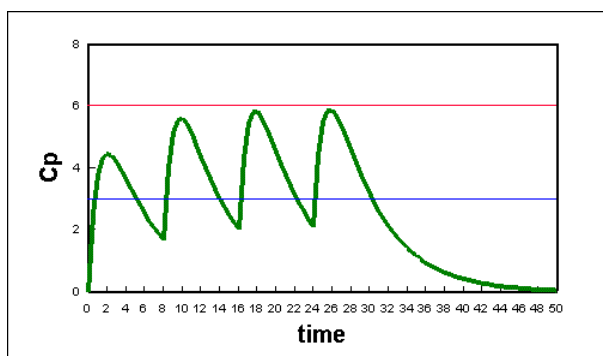
Drug elimination follows first-order kinetics. To illustrate first order kinetics we might consider what would happen if we were instantly inject (with an IV) a person with a drug, collect blood samples at various times and measure the plasma concentrations C_p of the drug. We might see a steady decrease in concentration as the drug is eliminated, as shown in the figure below.



Drug dosage and concentration

because of the pharmacokinetic phases, the plasma concentration (C_p) of a drug is not constant. As a drug is absorbed, metabolized, and eliminated, we see an onset, a peak and a duration of its effect. The plot below shows the effects of multiple doses

given at different time intervals. Using a graph such as this, doctors can coordinate drug doses with proper time intervals in order to will keep drug concentrations at their optimum levels (between the blue and red lines, the therapeutic window)



Plot of plasma concentration (Cp) due to multiple doses of a hypothetical drug.
Each dose was the same quantity of drug administrated every 8 hours

B. Pharmacodynamics: interaction of drugs with their sites of action

While there are several types of exceptions, the effects of most drugs result from their interaction with functional macromolecular components of the organism. Such interaction alters the function of the pertinent cellular component and thereby initiates the series of biochemical and physiological changes that are characteristic of the response to the drug. The term receptor is used to denote the component of the organism with which the chemical agent interacts. By virtue of interactions with such receptors, drugs do not create effects but merely modulate ongoing function. Thus, drugs cannot impart a new function to a cell.

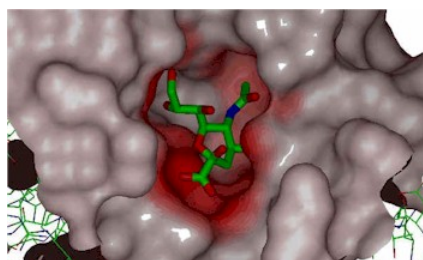


Figure. - hypothetical drug in receptor site.

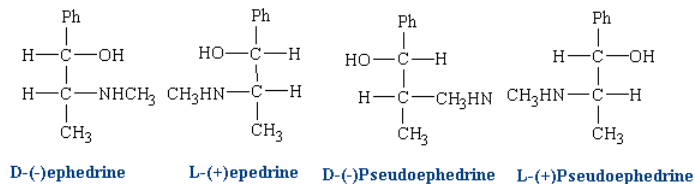
Structure-Activity

The affinity of a drug for a specific macromolecular component of the cell and its intrinsic activity are intimately related to its chemical structure. The relationship is frequently quite stringent, and relatively minor modifications in the drug molecule, particularly such subtle changes as stereochemistry, may result in major changes in pharmacological properties. Exploitation of structure-activity relationships has on many occasions led to the synthesis of valuable therapeutic agents. Since changes in molecular configuration need to alter all actions and effects of a drug equally, it is sometimes possible to develop a congener with a more favorable ratio of therapeutic to toxic effects, enhanced selectivity among different cells or tissues, or more acceptable secondary characteristics than those of the parent drug. In addition, effective therapeutic agents have been fashioned by developing structurally related competitive antagonists of other drugs or of endogenous substances known to be important in biochemical or physiological function. Minor modifications of structure can also have profound effects on the pharmacokinetic properties of drugs.

Key factors to consider in the structure of a drug are its polarity and molecular shape (stereochemistry).

Stereochemistry

Enantomerism can be produced by sp^3 hybridized carbon atoms. Because free rotation about the chiral carbon is not possible, two stable forms of the molecule can exist. A molecule with two nonidentical asymmetric centers can exist as ($2^2 = 4$) four stereo isomers. Interaction with biological receptors can differ greatly between two enantiomers, even to the point of no binding. There are numerous examples among drug molecules where only one isomer exhibits the desired pharmacology. Some isomers may even cause side effects or entirely different effects than its mirror image.



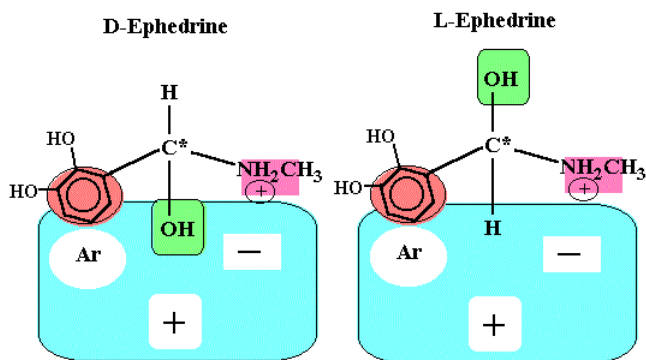
Ephedrine has two chiral centers and four isomers:

Different isomers can be used in different cases depending on the desired effect. Clinically, D(-) ephedrine is used to a large extent as an anti-asthmatic and, formerly, as a presser amine to restore low blood pressure as a result of trauma. L(+) pseudo-ephedrine is used primarily as a nasal decongestant.

Potencies of the Ephedrines

Isomer	Relative activity
D(-) Pseudoephedrine	1
L(+) Pseudoephedrine	7
L(+) Ephedrine	11
D(-) Ephedrine	36

If the biological receptor has at least three binding sites, the receptor easily can differentiate enantiomers (see figures below). The R(-)isomer has three points of interaction and is held in the conformation shown to maximize binding energy, whereas, the S(+)isomer can have only two sites of interaction.



It should be noted that the structure of alpha and beta adrenergic receptors are not entirely known. Also we should not forget that there is also enantioselectivity with respect to pharmacokinetics, such as absorption, distribution, metabolism, and excretion.

Polarity

The affinity of a drug for its receptor is determined by the type and intensity of intermolecular forces between the functional groups present in the drug molecule and the amino acids in the receptors (most receptors are proteins). Hydrogen-bonding, dipole-dipole interactions, London Dispersion Forces, ion-dipole, etc., all contribute to increase the interactions between drug and receptor and

increase the physiological response of the drug. At the same time, the presence of polar groups in the drug tend to increase water solubility and reduce the ability of a drug to permeate through the blood-brain barrier, while non-polar groups tend to increase lipid solubility and permeability to the blood-brain barrier

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7.4: Drug discovery and development

Drug discovery is the process by which new candidate medications are discovered. Historically, drug discovery was based on natural products extracted from plants and animals. More recently, chemical libraries of synthetic small molecules are used. Usually, the development process begins with the discovery of a **lead compound** that exhibits the desired biological activity likely to be useful. Afterwards, organic chemists perform studies of structure-activity relationship (SAR) to synthesize derivatives of the lead compound with optimized pharmacokinetic or pharmacodynamic properties. These derivatives are called **analogues**.

The process of drug discovery and development is a very demanding process that requires the collaborative effort of scientists, governments, and pharmaceutical corporations. The cost of discovering, optimizing, testing and putting a new drug in the market is estimated to be 1.8 billion USD. To be allowed to come to market, drugs must undergo several successful phases of clinical trials, and pass through a new drug approval process, called the New Drug Application in the United States.



Schematic diagram of drug discovery cycle. Image by [Boghog](#), CC BY-SA 4.0, via [Wikimedia Commons](#)

Lead compound

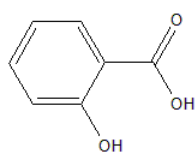
Lead compound is a chemical compound that has pharmacological or biological activity likely to be therapeutically useful, but may nevertheless have suboptimal structure that requires modification to fit better to the target. Lead drugs offer the prospect of being followed by back-up compounds called **analogs**. Its chemical structure serves as a starting point for chemical modifications in order to improve potency, selectivity, or pharmacokinetic parameters. Furthermore, newly invented pharmacologically active moieties may have poor drug-likeness and may require chemical modification to become drug-like enough to be tested biologically or clinically.

Analog

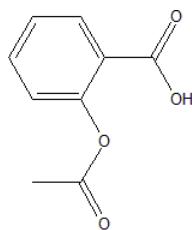
A structural analog, also known as a chemical analog or simply an analog, is a compound having a structure similar to that of another compound, but differing from it in respect to a certain component. It can differ in one or more atoms, functional groups, or substructures, which are replaced with other atoms, groups, or substructures. A structural analog can be imagined to be formed, at least theoretically, from the other compound.

Despite a high chemical similarity, structural analogs are not necessarily functional analogs and can have very different physical, chemical, biochemical, or pharmacological properties. In drug discovery either a large series of structural analogs of an initial lead compound are created and tested as part of a structure-activity relationship study or a database is screened for structural analogs of a lead compound.

Figure 1. Example of a lead compound (salicylic acid) and its analog (acetylsalicylic acid)



Salicylic acid



Acetyl salicylic acid (aspirin)

Pharmacophore

A **pharmacophore** is an abstract description of molecular features that are necessary for molecular recognition of a ligand by a biological macromolecule. IUPAC defines a pharmacophore to be "an ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target and to trigger (or block) its biological response". A pharmacophore region of a drug is responsible for its biological action, and this model explains how structurally diverse ligands can bind to a common receptor site.

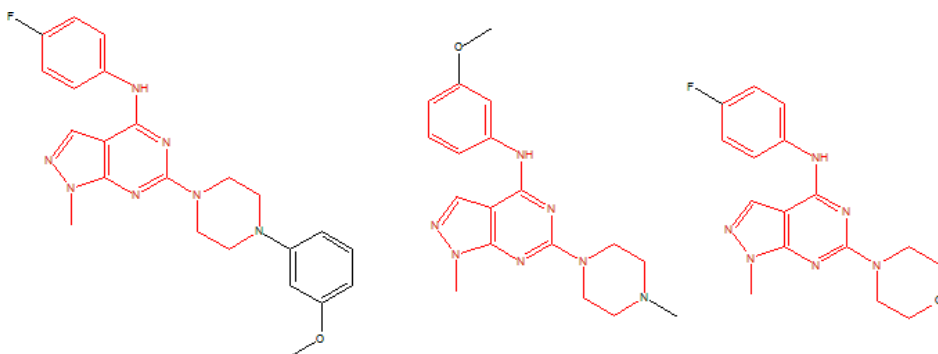


Figure 2. Examples of pyrimidine derivatives used as potential drugs in the treatment of a number of conditions including obesity, psychiatric disorders, sexual dysfunction, and urinary incontinence. The pharmacophore region of each molecule is indicated in red.

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7.5: Molecular Modification

Once a lead compound or a pharmacophore structure with the desired pharmacological effect has been identified, organic chemists can introduce modifications in the chemical structure of the lead compound with the goal of improving the pharmacokinetics or pharmacodynamics of a drug candidate. These evolved structures are known as **analogs**. There are two important factors that organic chemist must consider when modifying the chemical structure of a drug candidate which are

The effect of the chemical modification on **polarity** and **solubility**

The effect of the chemical modification on **molecular shape** and **flexibility**

Molecular shape and flexibility

The presence of flexible or rigid groups can affect the molecular shape and therefore the ability of the drug to bind a specific ligand in the body. For example, the introduction of **unsaturated groups** and **ring systems** generate **more structurally rigid** analog than aliphatic systems. Figure 1 shows the structure of dopamine and a more structurally rigid analog.

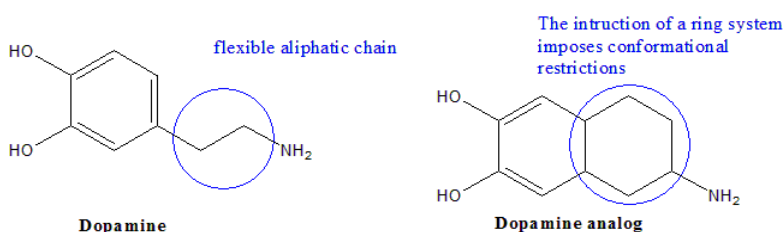


Figure 1. Dopamine and an analog with fewer possible conformations due to the ring

The biological effects induced by changes in the molecular flexibility are difficult to predict. Every single new analog needs to be retested in order to determine its pharmacological properties, and compare them with the lead compound. A more rigid molecule tends to create a stronger binding to its biological target (receptor). However, when the target receptor has a more flexible binding site, increasing molecular rigidity might decrease the ability of the drug to enter this site.

Polarity and Flexibility

The relative solubility of a drug in both aqueous and non-polar media plays a major role in the ability of the body to absorb and transport the active molecule to its action site. Most of the time, the drug must be hydrophilic enough to be able transported in the blood, but also lipophilic enough to travel through a membrane.

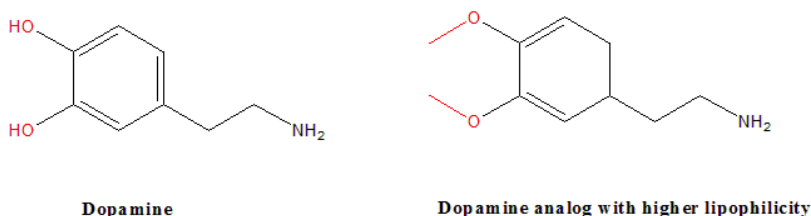


Figure 2. Increased lipophilicity of a dopamine analog by methylation of phenol groups.

We must consider that polarity (and therefore solubility in polar and non-polar media) is a synergistic effect, and it is the combined effect of functional groups and molecular geometry that will determine the polarity of a drug candidate. However, there are certain tendencies that are summarized in table 1.

Molecular modifications that increase hydrophilicity	Molecular modifications that increase lipophilicity
-OH -NH₂ -COOH -SO₃H - salt formation	-CH₃ -C(CH₃)₃ -F, -Cl, -I - phenyl -COOR (ester)

As in the case of molecular shape, the introduction of additional functional groups and substituents (chemical modifications) may alter the biological effect of the drug. Every new analog needs to be tested in order to determine its new pharmacological properties (pharmacokinetics and pharmacodynamics).

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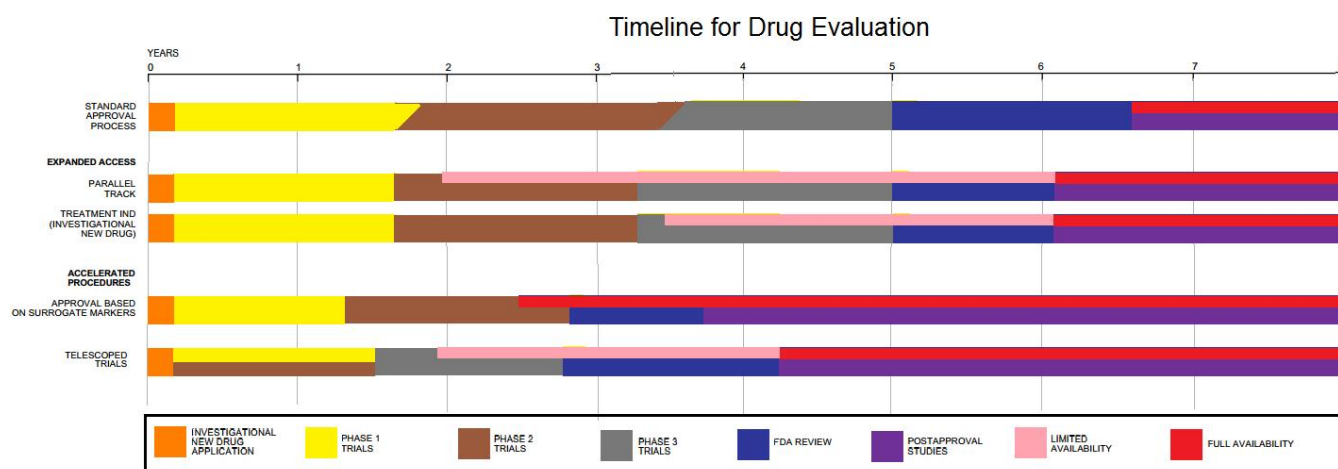
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7.6: FDA Drug Approval Process

Before an investigational new drug (IND) can even be tested on humans, extensive pre-clinical research must be conducted. This includes first identifying potential drug candidates:

- Sometimes a drug is discovered purely by serendipity,
- Other times natural products produced by microorganisms are screened for antifungal, antibiotic, antiviral, or antitumor activity.
- Another approach is to use computer modeling to design drugs that will interact effectively with a particular receptor in the body—for example, DNA or a specific enzyme.
- Once an active compound or a target has been identified, many new compounds—hundreds, even thousands—are synthesized. These hundreds or thousands of compounds are then usually screened *in vitro* (generally, using cell cultures in a Petri dish—that is, outside the living organism). The most active compounds are then screened *in vivo* (using animal assays). The drug candidate is tested on at least two different species of animals (one rodent and one non-rodent) because drugs do not always affect different species the same way. (For example, cisplatin was tested on both mice and dogs.) Both short- and long-term testing is conducted on animals. Short-term testing lasts from 2 weeks to 3 months and is designed to examine the metabolism and toxicity of the drug candidate. Long-term testing lasts from a few weeks to several years and is done to see whether long-term use of the drug will lead to cancer or birth defects.

After the completion of pre-clinical research, the FDA meets with the sponsor of the drug (usually a pharmaceutical company—in the case of cisplatin, Bristol-Myers), and the sponsor submits data demonstrating that the drug candidate is both biologically active and safe for administration to humans. After these meetings, the sponsor submits the drug candidate as an IND, and clinical testing can begin. The purpose of clinical research is to determine the safety and efficacy of the IND for the treatment of a particular disease or condition in humans. Clinical research is divided into three phases in the normal course of testing. (Certain drugs are placed in an accelerated development and review process; this will not be discussed here, but is described more fully on the FDA website on the new drug development process



- Phase 1 clinical studies represent the first time that an IND is tested on humans—generally, healthy volunteers, but sometimes patients (the latter was the case with phase 1 clinical studies of cisplatin). The purpose of these studies is to determine the metabolism, structure-reactivity relationships, mechanism of action, and side effects of the drug in humans. If possible, phase 1 studies are used to ascertain the efficacy of the drug. Phase 1 studies are usually conducted on 20 to 80 subjects.
- The purpose of phase 2 clinical trials is to determine the efficacy of a drug to treat patients with a specific disease or condition, as well as common short-term side effects or risks. These studies are conducted on a larger scale than phase 1 studies and typically involve several hundred patients.
- Phase 3 clinical trials provide more information about the efficacy and safety of the drug and allow scientists to extrapolate the results of clinical studies to the general population. Phase 3 studies generally involve several hundred to several thousand

people.

There are several checks and balances in the process of clinical trials; among them is the use of institutional review boards (IRBs) and advisory committees. IRBs are designed to protect the rights and welfare of people participating in clinical trials both before and during the trials. IRBs comprise at least five experts and lay people with a variety of backgrounds to provide a complete review of clinical proceedings. In addition, the CDER uses advisory committees comprising various experts in order to obtain outside opinions and advice about a new drug, a new indication for a previously approved drug, labeling information about a drug, guidelines for developing particular kinds of drugs, or the adequacy of safety and efficacy data. The sponsor of a drug makes a formal application to the FDA to approve a new drug for use in the United States by submitting a new drug application (NDA). An NDA must include results and analyses from tests of the drug on both animals and humans, as well as a description of how the drug was manufactured. The NDA must provide enough information for FDA reviewers to make several critical decisions, including whether the drug is safe and efficacious and whether its benefits outweigh its risks, whether the drug's labeling information is appropriate, and whether the manufacturing methods used to obtain the drug are adequate for ensuring the purity and integrity of the drug. The process of developing and testing a new drug is a lengthy one. The FDA estimates that it takes a little over 8 years to test a drug—including early laboratory and animal testing—before the final approval for use by the general public.

Inside the FDA—Vocabulary CDER: Center for Drug Evaluation and Research FDA: Food and Drug Administration IND: Investigational New Drug IRB: Institutional Review Board NDA: New Drug Application

Sources

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CHAPTER OVERVIEW

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8.3: Polyethylene - From the Battle of Britain to Bread Bags

8.4: Addition Polymerization - One One One ... Gives One!

8.5: Condensation Polymers

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8.7: Properties of Polymers

8.8: Plastics and the Environment

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8.1: Prelude

Polymers are substances made up of recurring structural units, each of which can be regarded as derived from a specific compound called a **monomer**. The number of monomeric units usually is large and variable, each sample of a given polymer being characteristically a mixture of molecules with different molecular weights. The range of molecular weights is sometimes quite narrow, but is more often very broad. The concept of polymers being mixtures of molecules with long chains of atoms connected to one another seems simple and logical today, but was not accepted until the 1930's when the results of the extensive work of H. Staudinger, who received the Nobel Prize in Chemistry in 1953, finally became appreciated. Prior to Staudinger's work, polymers were believed to be colloidal aggregates of small molecules with quite nonspecific chemical structures.

The adoption of definite chemical structures for polymers has had far-reaching practical applications, because it has led to an understanding of how and why the physical and chemical properties of polymers change with the nature of the monomers from which they are synthesized. This means that to a very considerable degree the properties of a polymer can be tailored to particular practical applications. Much of the emphasis in this chapter will be on how the properties of polymers can be related to their structures. This is appropriate because we already have given considerable attention in previous chapters to methods of synthesis of monomers and polymers, as well as to the mechanisms of polymerization reactions.

The special technical importance of polymers can be judged by the fact that half of the professional organic chemists employed by industry in the United States are engaged in research or development related to polymers.

Contributors and Attributions

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8.2: Polymerization - Making Big Ones Out of Little Ones

Learning Objectives

- Define the terms *monomer* and *polymer*.
- Know the different types of natural polymers.

A **polymer** is a large molecule, or macromolecule, composed of many repeated subunits. The term "polymer" derives from the Greek word *polus* (meaning "many, much") and *meros* (meaning "part"), and refers to a molecule whose structure is composed of multiple repeating units, from which originates a characteristic of high relative molecular mass and attendant properties. As shown schematically in Figure 8.2.1.

Due to their broad range of properties, both synthetic and natural polymers play essential and ubiquitous roles in everyday life. Polymers range from familiar synthetic plastics such as polystyrene to natural biopolymers such as DNA and proteins that are fundamental to biological structure and function. Polymers, both natural and synthetic, are created via polymerization of many small molecules, known as monomers. Their consequently large molecular mass relative to small molecule compounds produces unique physical properties, including toughness, viscoelasticity, and a tendency to form glasses and semicrystalline structures rather than crystals. The terms polymer and resin are often synonymous with plastic.

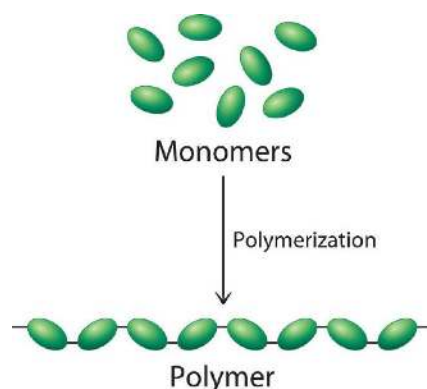
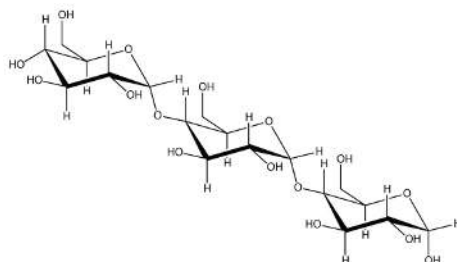


Figure 8.2.1 Polymer formation during a polymerization reaction, a large number of monomers become connected by covalent bonds to form a single long molecule, a polymer.

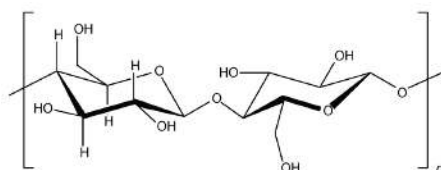
Natural Polymers

Some very important biological materials are polymers. Of the three major food groups, polymers are represented in two: proteins and carbohydrates. **Proteins** are polymers of amino acids, which are monomers that have an amine functional group and a carboxylic acid functional group. Proteins play a crucial role in living organisms.

Linking hundreds of glucose molecules together makes a relatively common material known as *starch*:



Starch is an important source of energy in the human diet. Note how individual glucose units are joined together. They can also be joined together in another way, like this:



This polymer is known as *cellulose*. **Cellulose** is a major component in the cell walls of plants. Curiously, despite the similarity in the building blocks, some animals (such as humans) cannot digest cellulose; those animals that can digest cellulose typically rely on symbiotic bacteria in the digestive tract for the actual digestion. Animals do not have the proper enzymes to break apart the glucose units in cellulose, so it passes through the digestive tract and is considered *dietary fiber*.

Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are also polymers, composed of long, three-part chains consisting of phosphate groups, sugars with 5 C atoms (ribose or deoxyribose), and N-containing rings referred to as bases. Each combination of the three parts is called a nucleotide; DNA and RNA are essentially polymers of nucleotides that have rather complicated but intriguing structures (**Figure 8.2.2 - Nucleotides**). DNA is the fundamental material in chromosomes and is directly responsible for heredity, while RNA is an essential substance in protein synthesis.

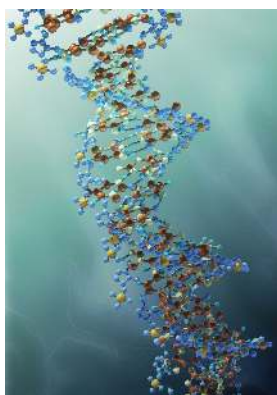


Figure 8.2.2 Nucleotides © Thinkstock

The DNA in our cells is a polymer of nucleotides, each of which is composed of a phosphate group, a sugar, and a N-containing base

The above mentioned biopolymers (polymers produced by living organisms) are discussed further in Chapter 16.

Celluloid: Billiard Balls

Celluloids are a class of compounds created from nitrocellulose (partially nitrated cellulose) and camphor, with added dyes and other agents. Generally considered the first thermoplastic, it was first created as Parkesinein (by Alexander Parkes of Birmingham England) in 1856 and as Xylonite in 1869. In the 1860s, an American, John Wesley Hyatt, acquired Parkes's patent and began experimenting with cellulose nitrate with the intention of manufacturing billiard balls, which until that time were made from ivory. In the 1870s the modified plastic was registered as "celluloid".

The main use was in movie and photography film industries, which used only celluloid film stock prior to the adoption of acetate safety film in the 1950s. Celluloid is highly flammable, difficult and expensive to produce and no longer widely used; its most common uses today are in table tennis balls, musical instruments, and guitar picks.

Bakelite (sometimes spelled **Baekelite**) or **polyoxybenzylmethyleneglycolanhydride** was the first plastic made from synthetic components. It is a thermosetting phenol formaldehyde resin, formed from a condensation reaction of phenol with formaldehyde. It was developed by the Belgian-American chemist Leo Baekeland in Yonkers, New York, in 1907.

Bakelite was patented on December 7, 1909. The creation of a synthetic plastic was revolutionary for its electrical non conductivity and heat-resistant properties in electrical insulators, radio and telephone casings and such diverse products as kitchenware, jewelry, pipe stems, children's toys, and firearms.



Video 8.2.2 Polymers Crash Course

Summary

- Polymers are giant molecules that consist of long chains of units called monomers connected by covalent bonds.
- Polymerization is the process of linking monomers together to form a polymer.
- Plastic is the general term for polymers made from synthetic materials.
- Several important biological polymers include proteins, starch, cellulose, DNA and RNA.

Contributors and Attributions

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8.3: Polyethylene - From the Battle of Britain to Bread Bags

Learning Objectives

- List the different types of polyethylene.
- Differentiate between thermolastic and thermosetting polymers.

Polyethylene was first synthesized by the German chemist Hans von Pechmann, who prepared it by accident in 1898. Industrial production of low-density polyethylene (LDPE) began in 1939 in England. Because polyethylene was found to have very low-loss properties at very high frequency radio waves, commercial distribution in Britain was suspended on the outbreak of World War II in order to produce insulation for UHF (ultra high frequency) and SHF (super high frequency) cables of radar sets.

Polyethylene or **polythene** is the most common plastic. As of 2017, over 100 million tonnes of polyethylene resins are produced annually, accounting for 34% of the total plastics market. Its primary use is in packaging (plastic bags, plastic films, geomembranes, containers including bottles, etc.). Many kinds of polyethylene are known, with most having the chemical formula $(C_2H_4)_n$. PE is usually a mixture of similar polymers of ethylene with various values of n .

Polymers based on skeletons with only carbon are all synthetic. Let's begin by looking at polyethylene Figure 8.3.1. It is the simplest polymer, consisting of random-length (but generally very long) chains made up of two-carbon units.

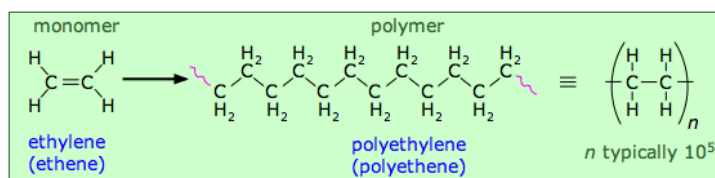


Figure 8.3.1 Polyethylene.

You will notice some "fuzziness" in the way that the polyethylene structures are represented above. The squiggly lines at the ends of the long structure indicate that the same pattern extends indefinitely. The more compact notation on the right shows the minimal repeating unit enclosed in brackets overprinted with a dash; this means the same thing and is the preferred way of depicting polymer structures.

Types of Polyethylene

Most of synthetic polymers are formed from ethylene. The relative lengths of the chains and any branches control the properties of polyethylene. The most important polymer grades with regard to volume are High density polyethylene (HDPE) Low density polyethylene (LDPE), and Linear low density polyethylene (LLDPE).

HDPE (High density polyethylene) is defined by a density of greater or equal to 0.941 g/cm^3 . HDPE has a low degree of branching. The mostly linear molecules pack together well, so intermolecular forces are stronger than in highly branched polymers. HDPE has high tensile strength. It is used in products and packaging such as milk jugs, detergent bottles, butter tubs, garbage containers, and water pipes. One-third of all toys are manufactured from HDPE. In 2007, the global HDPE consumption reached a volume of more than 30 million tons.

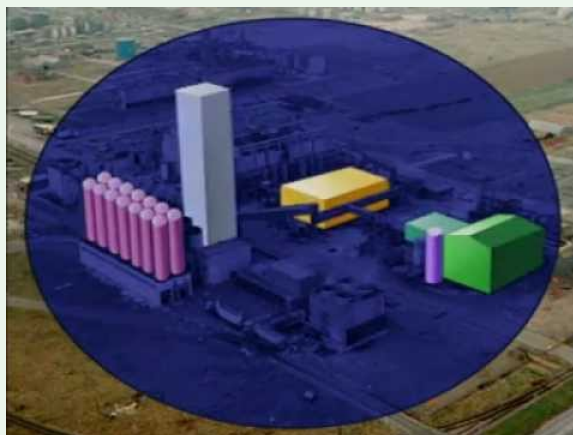
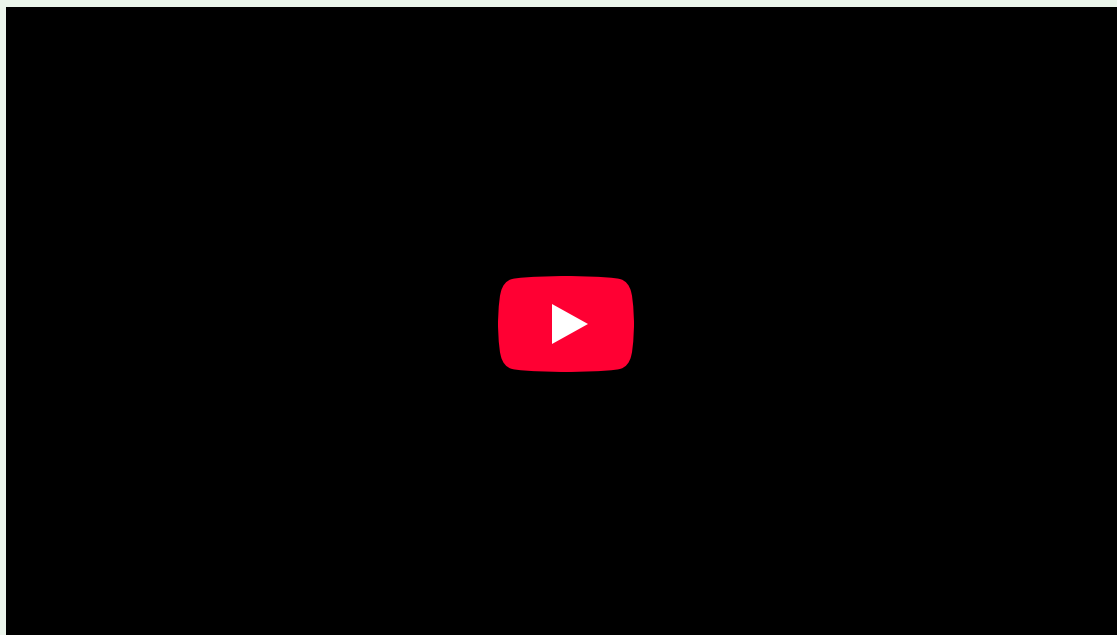
LDPE (Low density polyethylene) is defined by a density range of $0.910\text{--}0.940 \text{ g/cm}^3$. LDPE has a high degree of short- and long-chain branching, which means that the chains do not pack into the crystal structure as well. It has, therefore, less strong intermolecular forces as the instantaneous-dipole induced-dipole attraction is less. This results in a lower tensile strength and increased ductility. The high degree of branching with long chains gives molten LDPE unique and desirable flow properties. LDPE is used for both rigid containers and plastic film applications such as plastic bags and film wrap. In 2013, the global LDPE market had a volume of almost US\$33 billion.

LLDPE (Linear low density polyethylene) is defined by a density range of $0.915\text{--}0.925 \text{ g/cm}^3$. LLDPE is a substantially linear polymer with significant numbers of short branches. LLDPE has higher tensile strength than LDPE, and it exhibits higher impact and puncture resistance than LDPE. Lower thickness (gauge) films can be blown, compared with LDPE, with better environmental stress-cracking resistance, but is not as easy to process. LLDPE is used in packaging, particularly film for bags and sheets. Lower

thickness may be used compared to LDPE. It is used for cable coverings, toys, lids, buckets, containers, and pipe. While other applications are available, LLDPE is used predominantly in film applications due to its toughness, flexibility, and relative transparency. Product examples range from agricultural films, Saran wrap, and bubble wrap, to multilayer and composite films. In 2013, the world LLDPE market reached a volume of US\$40 billion.

Figure 8.3.2 A pill box presented to a technician at Imperial Chemical Industries (ICI) in Northwich, England in 1936 made from the first pound of polyethylene.

Polyethylene Production



Video 8.3.1 The commercial production of Polyethylene (polyethene). from the [Royal Society of Chemistry](#)

Thermoplastic and Thermosetting Polymers

Polymers can be classified by their physical response to heating. Polyethylene is a thermoplastic; however, it can become a thermoset plastic when modified (such as cross-linked polyethylene). **Thermoplastics** are plastics that soften when heated and become firm again when cooled. This is the more popular type of plastic because the heating and cooling may be repeated and the thermoplastic may be reformed.

Thermosets are plastics that soften when heated and can be molded, but harden permanently. They will decompose when reheated. An example is Bakelite, which is used in toasters, handles for pots and pans, dishes, electrical outlets and billiard balls.

Summary

Polyethylene is the long chain polymer formed from ethylene (ethene) monomers.

Polyethylene can be classified as HDPE, LDPE, and LLDPE based on how close the polymer chains pack together affecting its density.

Polymers can be classified as thermoplastics (can be reformed after repeated heating) or thermosets (harden permanently) based on their physical response to heating.

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8.4: Addition Polymerization - One One One ... Gives One!

10.03: Addition Polymerization - One One One ... Gives One

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8.5: Condensation Polymers

Learning Objectives

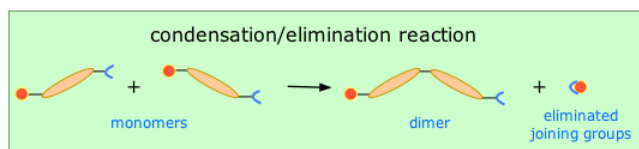
- Know the difference between addition and condensation polymerization.
- Know the properties and uses of common synthetic condensation polymers.

A large number of important and useful polymeric materials are not formed by addition polymerization, but proceed instead by conventional functional group transformations of polyfunctional reactants. These polymerizations often (but not always) occur with loss of a small byproduct, such as water, and generally (but not always) combine two different components in an alternating structure. The polyester Dacron and the polyamide Nylon 66, shown here, are two examples of synthetic condensation polymers, also known as step-growth polymers. In contrast to addition polymerization, most of which grow by carbon-carbon bond formation, step-growth polymers generally grow by carbon-heteroatom bond formation (C-O & C-N in Dacron & Nylon respectively). Although polymers of this kind might be considered to be alternating copolymers, the repeating monomeric unit is usually defined as a combined moiety.

Examples of naturally occurring condensation polymers are cellulose, starch, the polypeptide chains of proteins, and poly(β -hydroxybutyric acid), a polyester synthesized in large quantity by certain soil and water bacteria.

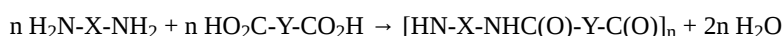
Nylon and Other Polyamides

Condensation polymerization (also known as *step-growth*) requires that the monomers possess two or more kinds of functional groups that are able to react with each other in such a way that parts of these groups combine to form a small molecule (often H₂O) which is eliminated from the two pieces. The now-empty bonding positions on the two monomers can then join together.

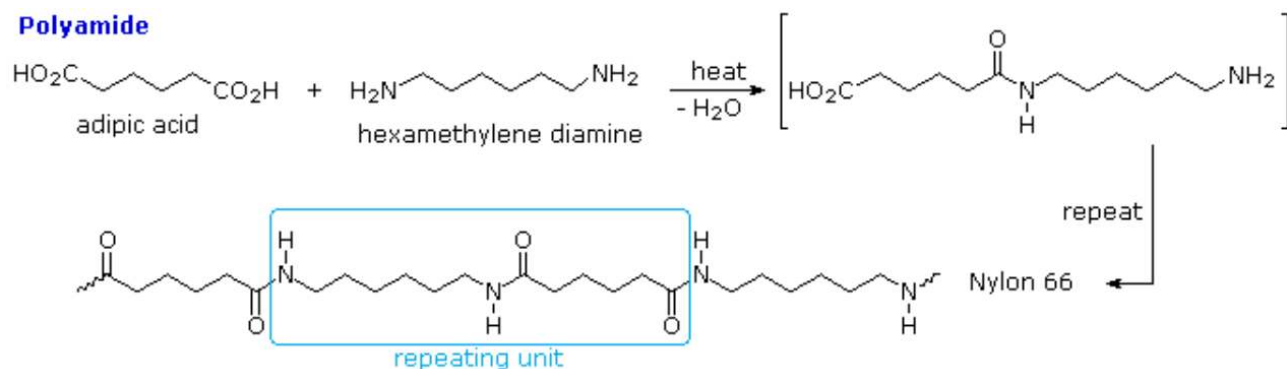


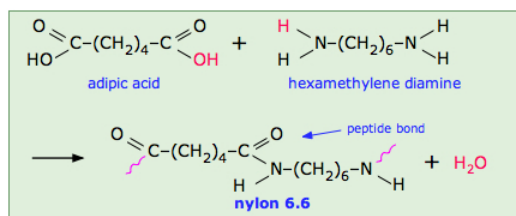
One important class of condensation polymers are polyamides. They arise from the reaction of carboxylic acid and an amine. Examples include nylons and proteins.

When prepared from diamines and dicarboxylic acids, e.g. the production of nylon 66, the polymerization produces two molecules of water per repeat unit:



Polyamide





Note that the monomeric units that make up the polymer are not identical with the starting components.

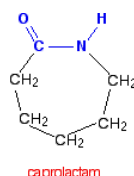
Nylon is a thermoplastic silky material that can be melt-processed into fibers, films, or shapes.¹² It is made of repeating units linked by amide links similar to the peptide bonds in proteins. Nylon polymers can be mixed with a wide variety of additives to achieve many different property variations. Nylon polymers have found significant commercial applications in fabric and fibers (apparel, flooring and rubber reinforcement), in shapes (molded parts for cars, electrical equipment, etc.), and in films (mostly for food packaging).

Figure 8.5.1 Wallace H. Carothers

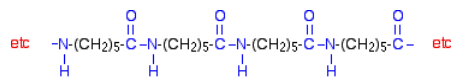
Nylon was the first commercially successful synthetic thermoplastic polymer. DuPont began its research project in 1927. The first example of nylon (nylon 6,6) was produced using diamines on February 28, 1935, by Wallace Hume Carothers (Figure 8.5.1) at DuPont's research facility at the DuPont Experimental Station. In response to Carothers' work, Paul Schlack at IG Farben developed nylon 6, a different molecule based on caprolactam, on January 29, 1938.¹⁰

Nylon was first used commercially in a nylon-bristled toothbrush in 1938, followed more famously in women's stockings or "nylons" which were shown at the 1939 New York World's Fair and first sold commercially in 1940. During World War II, almost all nylon production was diverted to the military for use in parachutes and parachute cord. Wartime uses of nylon and other plastics greatly increased the market for the new materials.

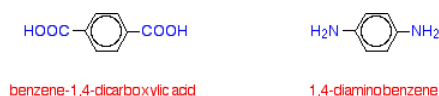
Other polyamides of practical use include nylon 6 and kevlar. Nylon-6 is made from a monomer called caprolactam.



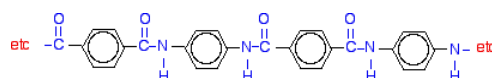
Notice that this already contains an amide link. When this molecule polymerizes, the ring opens, and the molecules join up in a continuous chain. Nylon 6 fibers are tough, possessing high tensile strength, as well as elasticity and lustre. They are wrinkleproof and highly resistant to abrasion and chemicals such as acids and alkalis. The fibers can absorb up to 2.4% of water, although this lowers tensile strength.



Kevlar is similar in structure to nylon-6,6 except that instead of the amide links joining chains of carbon atoms together, they join benzene rings. The two monomers are benzene-1,4-dicarboxylic acid and 1,4-diaminobenzene.



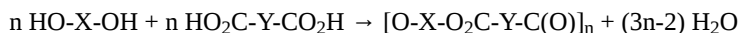
If you line these up and remove water between the -COOH and -NH₂ groups in the same way as we did with nylon-6,6, you get the structure of Kevlar:



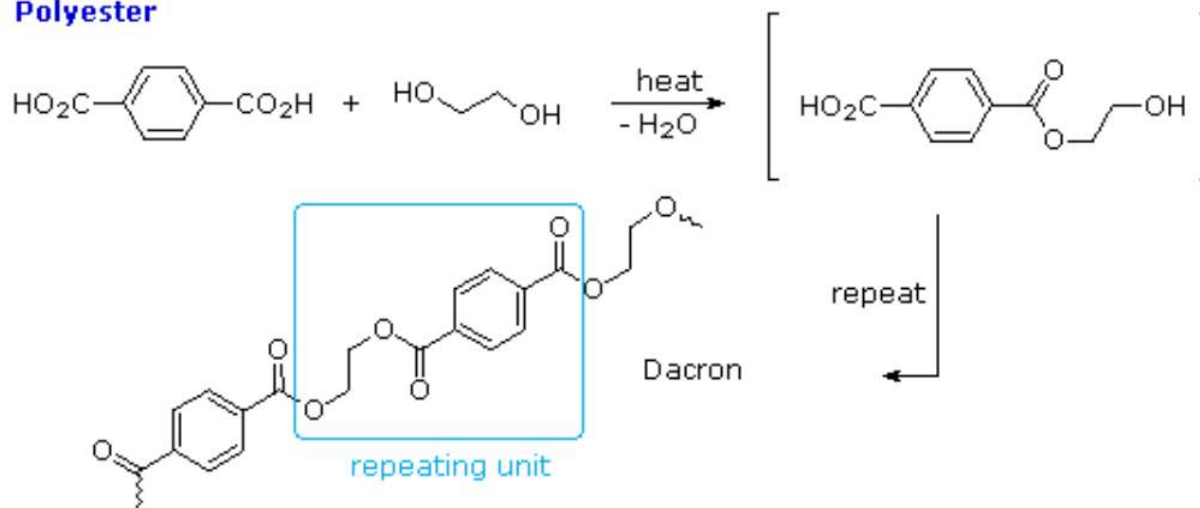
Kevlar is a very strong material - about five times as strong as steel, weight for weight. It is used in bulletproof vests, in composites for boat construction, in lightweight mountaineering ropes, and for lightweight skis and racquets - amongst many other things.

Polyethylene Terephthalate and Other Polyesters

One important class of condensation polymers are polyesters. They arise from the reaction of carboxylic acid and an alcohol. Examples include polyesters, e.g. polyethyleneterephthalate:



Polyester



Polyethylene terephthalate (sometimes written poly(ethylene terephthalate)), commonly abbreviated **PET**, **PETE**, or the obsolete PETP or PET-P, is the most common thermoplastic polymer resin of the polyester family and is used in fibres for clothing, containers for liquids and foods, thermoforming for manufacturing, and in combination with glass fibre for engineering resins.

It may also be referred to by the brand names **Terylene** in the UK, **Lavsan** in Russia and the former Soviet Union, and **Dacron** in the US.

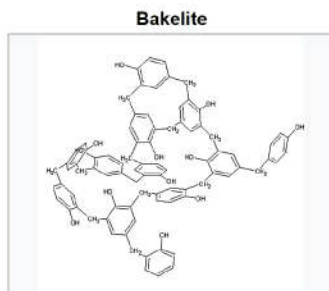
The majority of the world's PET production is for synthetic fibres (in excess of 60%), with bottle production accounting for about 30% of global demand. In the context of textile applications, PET is referred to by its common name, polyester, whereas the acronym *PET* is generally used in relation to packaging. Polyester makes up about 18% of world polymer production and is the fourth-most-produced polymer after polyethylene (PE), polypropylene (PP) and polyvinyl chloride (PVC).

Phenol-Formaldehyde and Related Resins

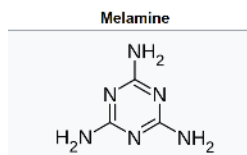
Bakelite was patented on December 7, 1909. The creation of a synthetic plastic was revolutionary for its electrical nonconductivity and heat-resistant properties in electrical insulators, radio and telephone casings and such diverse products as kitchenware, jewelry, pipe stems, children's toys, and firearms.

In recent years the "retro" appeal of old Bakelite products has made them collectible.

Bakelite was designated a National Historic Chemical Landmark on November 9, 1993, by the American Chemical Society in recognition of its significance as the world's first synthetic plastic.



Melamine /¹mɛləˈmiːn/ ( About this sound [listen](#)) is an organic compound with the formula $C_3H_6N_6$. This white solid is a trimer of cyanamide, with a 1,3,5-triazine skeleton. Like cyanamide, it contains 67% nitrogen by mass, and its derivatives have fire retardant properties due to its release of nitrogen gas when burned or charred. Melamine can be combined with formaldehyde and other agents to produce melamine resins. Such resins are characteristically durable thermosetting plastic used in high pressure decorative laminates such as Formica, melamine dinnerware, laminate flooring, and dry erase boards. Melamine foam is used as insulation, soundproofing material and in polymeric cleaning products, such as Magic Eraser.



Other Condensation Polymers

Polycarbonates (PC) are a group of thermoplastic polymers containing carbonate groups in their chemical structures. Polycarbonates used in engineering are strong, tough materials, and some grades are optically transparent. They are easily worked, molded, and thermoformed. Because of these properties, polycarbonates find many applications. Polycarbonates received their name because they are polymers containing carbonate groups ($-O-(C=O)-O-$). A balance of useful features, including temperature resistance, impact resistance and optical properties, positions polycarbonates between commodity plastics and engineering plastics.

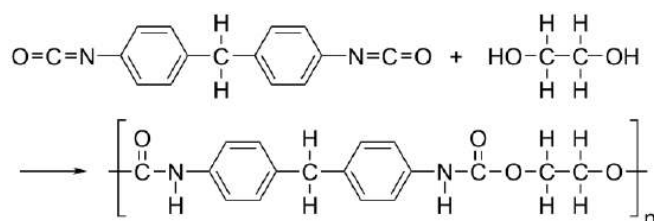
The main polycarbonate material is produced by the reaction of bisphenol A (BPA) and phosgene $COCl_2$. The overall reaction can be written as follows:



Polycarbonate is mainly used for electronic applications that capitalize on its collective safety features. Being a good electrical insulator and having heat-resistant and flame-retardant properties. The second largest consumer of polycarbonates is the construction industry, e.g. for domelights, flat or curved glazing, and sound walls, which all use extruded flat solid or multiwall sheet, or corrugated sheet. A major application of polycarbonate is the production of Compact Discs, DVDs, and Blu-ray Discs.

Polyurethane (PUR and PU) is a polymer composed of organic units joined by carbamate (urethane) links. While most polyurethanes are thermosetting polymers that do not melt when heated, thermoplastic polyurethanes are also available.

Polyurethanes are in the class of compounds called **reaction polymers**, which include epoxies, unsaturated polyesters, and phenolics. 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.



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, and hoses.

Figure 8.5.2 A polyurethane foam sponge.

Health and Safety

Fully reacted polyurethane polymer is chemically **inert**. No exposure limits have been established in the U.S. by OSHA (Occupational Safety and Health Administration) or ACGIH (American Conference of Governmental Industrial Hygienists). It is not regulated by OSHA for carcinogenicity.

Figure 8.5.3 Open-flame test. Top, untreated polyurethane foam burns vigorously. Bottom, with fire-retardant treatment.

Polyurethane polymer is a combustible solid and can be ignited if exposed to an open flame. Decomposition from fire can produce significant amounts of carbon monoxide and hydrogen cyanide, in addition to nitrogen oxides, isocyanates, and other toxic products. Because of the flammability of the material, it has to be treated with flame retardants (at least in case of furniture), almost all of which are considered harmful. California later issued Technical Bulletin 117 2013 which allowed most polyurethane foam to pass flammability tests without the use of flame retardants. Green Science Policy Institute states: "Although the new standard can be met without flame retardants, it does NOT ban their use. Consumers who wish to reduce household exposure to flame retardants can look for a TB117-2013 tag on furniture, and verify with retailers that products do not contain flame retardants."

Liquid resin blends and isocyanates may contain hazardous or regulated components. Isocyanates are known skin and respiratory sensitizers. Additionally, amines, glycols, and phosphate present in spray polyurethane foams present risks.

Exposure to chemicals that may be emitted during or after application of polyurethane spray foam (such as isocyanates) are harmful to human health and therefore special precautions are required during and after this process.

In the United States, additional health and safety information can be found through organizations such as the Polyurethane Manufacturers Association (PMA) and the Center for the Polyurethanes Industry (CPI), as well as from polyurethane system and raw material manufacturers. Regulatory information can be found in the Code of Federal Regulations Title 21 (Food and Drugs) and Title 40 (Protection of the Environment). In Europe, health and safety information is available from ISOPA, the European Diisocyanate and Polyol Producers Association.

Epoxy is either any of the basic components or the cured end products of **epoxy resins**, as well as a colloquial name for the epoxide functional group. Epoxy resins, also known as **polyepoxides**, are a class of reactive prepolymers and polymers which contain epoxide groups.

Epoxy resins may be reacted (cross-linked) either with themselves through catalytic homopolymerisation, or with a wide range of co-reactants including polyfunctional amines, acids (and acid anhydrides), phenols, alcohols and thiols (usually called mercaptans). These co-reactants are often referred to as hardeners or curatives, and the cross-linking reaction is commonly referred to as curing. The structure of bisphenol-A diglycidyl ether epoxy resin is shown below: n denotes the number of polymerized subunits and is typically in the range from 0 to 25



Figure 8.5.4 Bisphenol-A diglycidyl ether epoxy.

Reaction of polyepoxides with themselves or with polyfunctional hardeners forms a thermosetting polymer, often with favorable mechanical properties and high thermal and chemical resistance. Epoxy has a wide range of applications, including metal coatings, use in electronics/electrical components/LEDs, high tension electrical insulators, paint brush manufacturing, fiber-reinforced plastic materials and structural adhesives. Epoxy is sometimes used as a glue (see image at right).

Figure 8.5.5 A 5-minute epoxy glue.

Composite Materials

A **composite material** (also called a **composition material** or shortened to **composite**, which is the common name) is a material made from two or more constituent materials with significantly different physical or chemical properties that, when combined, produce a material with characteristics different from the individual components. Composite materials are generally used for buildings, bridges, and structures such as boat hulls, swimming pool panels, racing car bodies, shower stalls, bathtubs, storage tanks, imitation granite and cultured marble sinks and countertops.

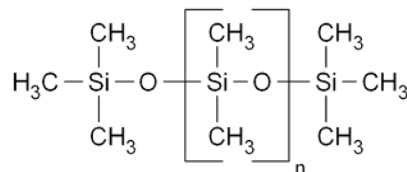
Composites are made up of individual materials referred to as constituent materials. There are two main categories of constituent materials: **matrix** (binder) and **reinforcement**. At least one portion of each type is required. The matrix material surrounds and supports the reinforcement materials by maintaining their relative positions. The reinforcements impart their special mechanical and physical properties to enhance the matrix properties. A synergism produces material properties unavailable from the individual constituent materials, while the wide variety of matrix and strengthening materials allows the designer of the product or structure to choose an optimum combination. Many commercially produced composites use a polymer matrix material often called a resin solution. There are many different polymers available depending upon the starting raw ingredients. There are several broad categories, each with numerous variations. The most common are known as polyester, vinyl ester, epoxy, phenolic, polyimide, polyamide, polypropylene, PEEK (polyether ether ketone), and others. Common fibres used for reinforcement include glass fibres, carbon fibres, cellulose (wood/paper fibre and straw) and high strength polymers for example aramid. Silicon carbide fibers are used for some high temperature applications.

One of the most common and familiar composite is fibreglass, in which small glass fibre are embedded within a polymeric material (normally an epoxy or polyester). The glass e is relatively strong and stiff (but also brittle), whereas the polymer is ductile (but also weak and flexible). Thus the resulting fibreglass is relatively stiff, strong, flexible, and ductile.

Figure 8.5.6 Glass reinforcements used for fiberglass are supplied in different physical forms, microspheres, chopped or woven.

Silicones

Silicones, also known as **polysiloxanes**, are polymers that include any synthetic compound made up of repeating units of siloxane. Silicones consist of an inorganic silicon-oxygen backbone chain ($\cdots\text{Si-O-Si-O-Si-O}\cdots$) with organic side groups attached to the silicon atoms. Silicones have in general the chemical formula $[\text{R}_2\text{SiO}]_n$, where R is an organic group such as an alkyl (methyl, ethyl) or phenyl group. A silicone polymer tha consist of repeated units of dimethyl silicone is shown below.



They are typically heat-resistant and either liquid or rubber-like. Silicones are used in many products. Ullmann's Encyclopedia of Industrial Chemistry lists the following major categories of application: Electrical (e.g., insulation), electronics (e.g., coatings), household (e.g., sealants and cooking utensils), automobile (e.g., gaskets), aeroplane (e.g., seals), office machines (e.g., keyboard pads), medicine and dentistry (e.g., tooth impression molds), textiles and paper (e.g., coatings). For these applications, an estimated 400,000 tonnes of silicones were produced in 1991.

Figure 8.5.7 Soup ladle and pasta ladle made of silicone.

Silicone vs Silicon

Silicone is often confused with silicon, but they are distinct substances. Silicon is a chemical element, a hard dark-grey semiconducting metalloid which in its crystalline form is used to make integrated circuits ("electronic chips") and solar cells. Silicones are compounds that contain silicon, carbon, hydrogen, oxygen, and perhaps other kinds of atoms as well, and have very different physical and chemical properties.

Summary

- Condensation polymerization (also known as *step-growth*) requires that the monomers possess two or more kinds of functional groups that are able to react with each other in such a way that parts of these groups combine to form a small molecule (often H_2O) which is eliminated from the two pieces. The now-empty bonding positions on the two monomers can then join together .
- Examples of natural condensation polymers include cellulose, starch, and polypeptide chains of proteins.

- Several synthetic condensation polymers discussed include nylon, kevlar, polyester, Bakelite, Melamine, polycarbonates, polyurethanes, epoxies.
- Synthetic condensation polymers have a wide array of household, industrial, commercial, and medical uses and applications.

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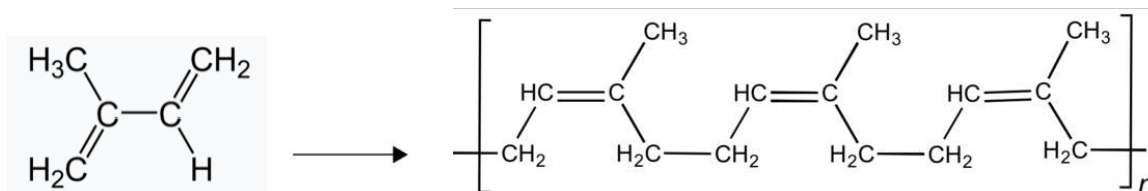
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8.6: Natural Rubber and Other Elastomers

Learning Objectives

- Know the properties of rubber.
- Describe the process of vulcanization.

Natural rubber, also called **India rubber** or *caoutchouc*, as initially produced, consists of polymers of the organic compound isoprene, with minor impurities of other organic compounds, plus water. Thailand and Indonesia are two of the leading rubber producers. Forms of polyisoprene that are used as natural rubbers are classified as elastomers.



Isoprene Polyisoprene (rubber)

Currently, rubber is harvested mainly in the form of the latex from the rubber tree or others. The latex is a sticky, milky colloid drawn off by making incisions in the bark and collecting the fluid in vessels in a process called "tapping". The latex then is refined into rubber ready for commercial processing. In major areas, latex is allowed to coagulate in the collection cup. The coagulated lumps are collected and processed into dry forms for marketing.

Natural rubber is used extensively in many applications and products, either alone or in combination with other materials. In most of its useful forms, it has a large stretch ratio and high resilience, and is extremely waterproof.

Vulcanization

In 1832–1834 Nathaniel Hayward and Friedrich Ludersdorf discovered that rubber treated with sulfur lost its stickiness. It is likely Hayward shared his discovery with Charles Goodyear, possibly inspiring him to make the discovery of vulcanization. Thomas Hancock (1786–1865), a scientist and engineer, was the first to patent vulcanization of rubber. He was awarded a British patent on May 21, 1845. Three weeks later, on June 15, 1845, Charles Goodyear was awarded a patent in the United States. It was Hancock's friend William Brockedon who coined term 'vulcanization'. Goodyear claimed that he had discovered vulcanization earlier, in 1839.

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

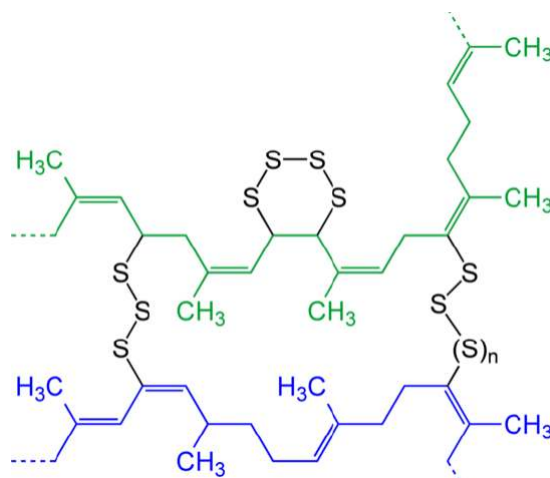


Figure \(\backslash \text{PageIndex}\{1\}\) General representation of the chemical structure of vulcanized natural rubber showing the crosslinking of two polymer chains (**blue** and **green**) with sulfur ($n = 0, 1, 2, 3 \dots$).

Synthetic Rubber

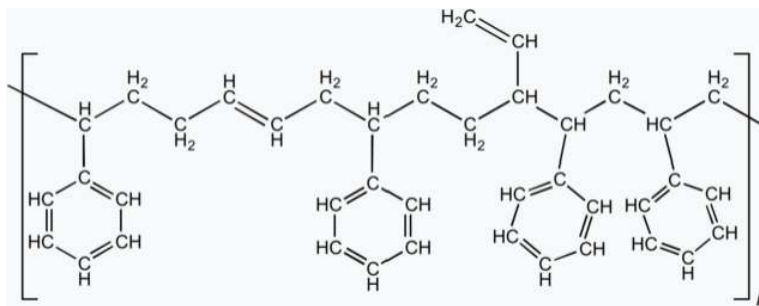
The expanded use of bicycles, and particularly their pneumatic tires, starting in the 1880s, created increased demand for rubber. In 1909 a team headed by Fritz Hofmann, working at the Bayer laboratory in Germany, succeeded in polymerizing isoprene, the first synthetic rubber. A synthetic rubber is any artificial elastomer. These are mainly polymers synthesized from petroleum by products.

Polybutadiene rubber is a polymer formed from the polymerization of the monomer 1,3-butadiene. Polybutadiene has a high resistance to wear and is used especially in the manufacture of tires, which consumes about 70% of the production. Another 25% is used as an additive to improve the toughness (impact resistance) of plastics such as polystyrene and acrylonitrile butadiene styrene (ABS). Polybutadiene rubber accounted for about a quarter of total global consumption of synthetic rubbers in 2012. It is also used to manufacture golf balls, various elastic objects and to coat or encapsulate electronic assemblies, offering high electrical resistivity.

Neoprene (also **polychloroprene** or **pc-rubber**) is a family of synthetic rubbers that are produced by polymerization of chloroprene. Neoprene exhibits good chemical stability and maintains flexibility over a wide temperature range. Neoprene is sold either as solid rubber or in latex form and is used in a wide variety of applications, such as laptop sleeves, orthopaedic braces (wrist, knee, etc.), electrical insulation, liquid and sheet applied elastomeric membranes or flashings, and automotive fan belts. Neoprene is produced by free-radical polymerization of chloroprene. In commercial production, this polymer is prepared by free radical emulsion polymerization. Polymerization is initiated using potassium persulfate. Bifunctional nucleophiles, metal oxides (e.g. zinc oxide), and thioureas are used to crosslink individual polymer strands.

Free radical production of neoprene.png

Styrene-butadiene or **styrene-butadiene rubber (SBR)** describe families of synthetic rubbers derived from styrene and butadiene (the version developed by Goodyear is called **Neolite**). These materials have good abrasion resistance and good aging stability when protected by additives. In 2012, more than 5.4 million tonnes of SBR were processed worldwide. About 50% of car tires are made from various types of SBR.



It is a commodity material which competes with natural rubber. The elastomer is used widely in pneumatic tires. Other uses include shoe heels and soles, gaskets, and even chewing gum.

Polymers in Paints

Polymers are one of the key components of modern paints that function as binders. The binder is the film-forming component of paint. It is the only component that is always present among all the various types of formulations. The binder imparts properties such as gloss, durability, flexibility, and toughness. Binders include synthetic or natural resins such as alkyds, acrylics, vinyl-acrylics, vinyl acetate/ethylene (VAE), polyurethanes, polyesters, melamine resins, epoxy, or siloxanes or oils.

Summary

The many uses of natural rubber has led to development and manufacture of synthetic rubber.

Sulfur vulcanization is a chemical process for converting natural rubber or related polymers into more durable materials by heating them with sulfur or other equivalent curatives or accelerators.

Three examples of synthetic rubber used in various applications are polybutadiene, polychloroprene (Neoprene), and styrene-butadiene rubber (SBR)

Contributors and Attributions

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- Wikipedia

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8.7: Properties of Polymers

Learning Objectives

- Know the properties of polymers based on their molecular and intermolecular structures.
- Know the relationship between degree of crystallinity to physical properties of polymers.

The physical properties of a polymer such as its strength and flexibility depend on:

- *chain length* - in general, the longer the chains the stronger the polymer;
- *side groups* - polar side groups (including those that lead to hydrogen bonding) give stronger attraction between polymer chains, making the polymer stronger;
- *branching* - straight, unbranched chains can pack together more closely than highly branched chains, giving polymers that have higher density, are more crystalline and therefore stronger;
- *cross-linking* - if polymer chains are linked together extensively by covalent bonds, the polymer is harder and more difficult to melt.

Crystalline and Amorphous Polymers

When applied to polymers, the term *crystalline* has a somewhat ambiguous usage. A synthetic polymer may be loosely described as crystalline if it contains regions of three-dimensional ordering on atomic (rather than macromolecular) length scales, usually arising from intramolecular folding and/or stacking of adjacent chains. Synthetic polymers may consist of both crystalline and amorphous regions; the degree of crystallinity may be expressed in terms of a weight fraction or volume fraction of crystalline material. Few synthetic polymers are entirely crystalline. The crystallinity of polymers is characterized by their degree of crystallinity, ranging from zero for a completely non-crystalline polymer to one for a theoretical completely crystalline polymer. Polymers with microcrystalline regions are generally tougher (can be bent more without breaking) and more impact-resistant than totally amorphous polymers. Polymers with a degree of crystallinity approaching zero or one will tend to be transparent, while polymers with intermediate degrees of crystallinity will tend to be opaque due to light scattering by crystalline or glassy regions. For many polymers, reduced crystallinity may also be associated with increased transparency.

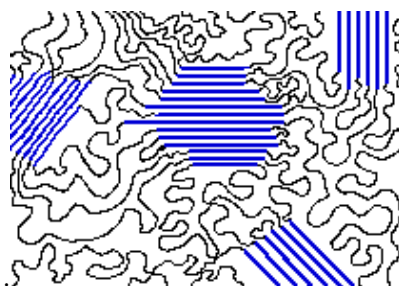


Figure 8.7.1 The crystalline parts of this polymer are shown in blue.

Depending on the degree of crystallinity, there will be a higher temperature, the *melting point* t_m , at which the crystalline regions come apart and the material becomes a viscous liquid. Such liquids can easily be injected into molds to manufacture objects of various shapes, or extruded into sheets or fibers. Other polymers (generally those that are highly cross-linked) do not melt at all; these are known as *thermosets*. If they are to be made into molded objects, the polymerization reaction must take place within the molds — a far more complicated process. About 20% of the commercially-produced polymers are thermosets; the remainder are thermoplastics.

The Glass Transition Temperature

In some polymers (known as *thermoplastics*) there is a fairly definite softening point that is observed when the thermal kinetic energy becomes high enough to allow internal rotation to occur within the bonds and to allow the individual molecules to slide independently of their neighbors, thus rendering them more flexible and deformable. This defines the *glass transition temperature* t_g . Hard plastics like polystyrene and poly(methyl methacrylate) are used well below their glass transition temperatures, i.e., when

they are in their glassy state. Their T_g values are well above room temperature, both at around 100 °C (212 °F). Rubber elastomers like polyisoprene and polyisobutylene are used above their T_g , that is, in the rubbery state, where they are soft and flexible.

Fiber Formation

Bill Pittendreich, DuPont, and other individuals and corporations worked diligently during the first few months of World War II to find a way to replace Asian silk and hemp with nylon in parachutes. It was also used to make tires, tents, ropes, ponchos, and other military supplies. It was even used in the production of a high-grade paper for U.S. currency. At the outset of the war, cotton accounted for more than 80% of all fibers used and manufactured, and wool fibers accounted for nearly all of the rest. By August 1945, manufactured fibers had taken a market share of 25%, at the expense of n. After the war, e of shortages of both silk and nylon, nylon parachute material was sometimes repurposed to make dresses. Nylon 6 and 66 fibers are used in carpet manufacture. Nylon is one kind of fibers used in tire cord. Herman E. Schroeder pioneered application of nylon in tires.

Figure 8.7.2 Blue nylon fabric ball gown by Emma Domb, Science History Institute.

Fabrics woven or knitted from polyester thread or yarn are used extensively in apparel and home furnishings, from shirts and pants to jackets and hats, bed sheets, blankets, upholstered ure and computer mouse mats. Industrial polyester fibers, yarns and ropes are used in car tire reinforcements, fabrics for conveyor belts, safety belts, coated fabrics and plastic reinforcements with high-energy absorption. Polyester fiber is used as cushioning and insulating material in pillows, comforters and upholstery padding. Polyester fabrics are highly stain-resistant—in fact, the only class of dyes which *can* be used to alter the color of polyester fabric are what are known as disperse dyes.

Figure 8.7.3 Stretching polyester fabric.

Acrylic fibers are synthetic fibers made from a polymer (polyacrylonitrile) with an average molecular weight of -100,000, about 1900 monomer units. For a fiber to be called "acrylic" in the US, the polymer must contain at least 85% acrylonitrile monomer. Typical comonomers are vinyl acetate or methyl acrylate. DuPont created the first acrylic fibers in 1941 and trademarked them under the name **Orlon**. It was first developed in the mid-1940s but was not produced in large quantities until the 1950s. Strong and warm, acrylic fiber is often used for sweaters and tracksuits and as linings for boots and gloves, as well as in furnishing fabrics and carpets. It is manufactured as a filament, then cut into short staple lengths similar to wool hairs, and spun into yarn.

Modacrylic is a modified acrylic fiber that contains at least 35% and at most 85% acrylonitrile monomer. The comonomers vinyl chloride, vinylidene chloride or vinyl bromide used in modacrylic give the fiber flame retardant properties. End-uses of modacrylic include faux fur, wigs, hair extensions and protective clothing.

Microfiber (or **microfibre**) is synthetic fiber finer than one denier or decitex/thread, having a diameter of less than ten micrometres. This is smaller than the diameter of a strand of silk (which is approximately one denier), which is itself about 1/5 the diameter of a human hair.



Figure 8.7.4 Close-up view of microfiber (left) and microfiber household cloth (right).

The most common types of microfibers are made from polyesters, polyamides (e.g., nylon, Kevlar, Nomex, tregamide), or a conjugation of polyester, polyamide, and polypropylene. Microfiber is used to make mats, knits, and weaves for apparel, upholstery, industrial filters, and cleaning products. The shape, size, and combinations of synthetic fibers are selected for specific characteristics, including softness, toughness, absorption, water repellency, electrostatics, and filtering capabilities.

Environmental and Safety Issues

Microfiber textiles tend to be flammable if manufactured from hydrocarbons (polyester) or carbohydrates (cellulose) and emit toxic gases when burning, more so if aromatic (PET, PS, ABS) or treated with halogenated flame retardants and azo dyes. Their polyester and nylon stock are made from petrochemicals, which are not a renewable resource and are not biodegradable. However, if made out of polypropylene, they are recyclable (Prolen).

For most cleaning applications they are designed for repeated use rather than being discarded after use. An exception to this is the precise cleaning of optical components where a wet cloth is drawn once across the object and must not be used again as the debris collected are now embedded in the cloth and may scratch the optical surface.

Microfiber that is made from petrochemicals includes polyester and nylon which are not biodegradable. However, microfiber made from polypropylene can be recyclable. Microfiber products may also have the potential of entering the oceanic water supply and food chain similar to other microplastics. Synthetic clothing made of microfibers that are washed can release materials and travel to local wastewater treatment plants, contributing to plastic pollution in water. Fibers retained in wastewater treatment sludge (biosolids) that are land-applied can persist in soils.

There are environmental concerns about this product entering the oceanic food chain similar to other microplastics. A study by the clothing brand Patagonia and University of California, Santa Barbara, found that when synthetic jackets made of microfibers are washed, on average 1.7 grams (0.060 oz) of microfibers are released from the washing machine. These microfibers then travel to local wastewater treatment plants, where up to 40% of them enter into rivers, lakes, and oceans where they contribute to the overall plastic pollution. Microfibers account for 85% of man-made debris found on shorelines worldwide.

However, no pesticides are used for producing synthetic fibers (in comparison to cotton). If these products are made of polypropylene yarn, the yarn is dope-dyed; i.e. no water is used for dyeing (as with cotton, where thousands of liters of water become contaminated).

Summary

- The physical properties of a polymer such as its strength and flexibility depend on chain length, side groups present, branching, and cross-linking.
- Synthetic polymers may consist of both crystalline (more ordered, crystal-like) and amorphous (less ordered) regions; the degree of crystallinity may be expressed in terms of a weight fraction or volume fraction of crystalline material.
- The crystallinity of polymers is characterized by their degree of crystallinity, ranging from zero for a completely non-crystalline polymer to one for a theoretical completely crystalline polymer. Polymers with microcrystalline regions are generally tougher (can be bent more without breaking) and more impact-resistant than totally amorphous polymers.
- Due to their chemical structure, nylon, polyester, and acrylic fibers have physical properties that are comparable or even superior to natural fibers. Thus, many of these fibers have a variety of uses and have replaced natural fibers in various products.

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8.8: Plastics and the Environment

Learning Objectives

- Know the problems associated with plastics.
- Identify the type of polymer associated with each recycling number.
- Know the different plastic recycling processes.

Problems with Plastics

Due to their low cost, ease of manufacture, versatility, and imperviousness to water, plastics are used in a multitude of products of different scale, including paper clips and spacecraft. They have prevailed over traditional materials, such as wood, stone, horn and bone, leather, metal, glass, and ceramic, in some products previously left to natural materials. However, there are numerous problems encountered with plastic use.

Small-molecule release

Many kinds of polymers contain small molecules — either unreacted monomers, or substances specifically added (plasticizers, uv absorbers, flame retardants, etc.) to modify their properties. Many of these smaller molecules are able to diffuse through the material and be released into any liquid or air in contact with the plastic — and eventually into the aquatic environment. Those that are used for building materials (in mobile homes, for example) can build up in closed environments and contribute to indoor air pollution.

Residual monomer

Formation of long polymer chains is a complicated and somewhat random process that is never perfectly stoichiometric. It is therefore not uncommon for some unreacted monomer to remain in the finished product. Some of these monomers, such as formaldehyde, styrene (from polystyrene, including polystyrene foam food take-out containers), vinyl chloride, and bisphenol-A (from polycarbonates) are known carcinogens. Although there is little evidence that the small quantities that diffuse into the air or leach out into fluids pose a quantifiable health risk, people are understandably reluctant to tolerate these exposures, and public policy is gradually beginning to regulate them.

Perfluorooctanoic acid (PFOA), the monomer from which Teflon is made, has been the subject of a 2004 lawsuit against a DuPont factory that contaminated groundwater. Small amounts of PFOA have been detected in gaseous emissions from hot fluorocarbon products.

Decomposition products

Most commonly-used polymers are not readily biodegradable, particularly under the anaerobic conditions of most landfills. And what decomposition does occur will combine with rainwater to form *leachates* that can contaminate nearby streams and groundwater supplies. Partial photodecomposition, initiated by exposure to sunlight, is a more likely long-term fate for exposed plastics, resulting in tiny broken-up fragments. Many of these materials are less dense than seawater, and once they enter the oceans through coastal sewage outfalls or from marine vessel wastes, they tend to remain there indefinitely.

Open burning of polymeric materials containing chlorine (polyvinyl chloride, for example) is known to release compounds such as dioxins that persist in the environment. Incineration under the right conditions can effectively eliminate this hazard. Disposed products containing **fluorocarbons** (Teflon-coated ware, some personal-care, waterproofing and anti-stick materials) break down into perfluorooctane sulfonate which has been shown to damage aquatic animals.

Hazards to animals

There are two general types of hazards that polymers can introduce into the aquatic environment. One of these relates to the release of small molecules that act as hormone disrupters as described above. It is well established that small aquatic animals such as fish are being seriously affected by such substances in many rivers and estuarine systems, but details of the sources and identities of these molecules have not been identified. One confounding factor is the release of sewage water containing human birth-control drugs (which have a feminizing effect on sexual development) into many waterways.

The other hazard relates to pieces of plastic waste that aquatic animals mistake for food or become entangled in (Figure 8.8.1) .



Figure 8.8.1 A plastic bag (probably mistaken for a jellyfish, the sea turtle's only food) cannot be regurgitated and leads to intestinal blockage and a slow death (left) remains of an albatross that mistook bits of plastic junk for food (right).

These dangers occur throughout the ocean, but are greatly accentuated in regions known as gyres. These are regions of the ocean in which a combination of ocean currents drives permanent vortices that tend to collect and concentrate floating materials. The most notorious of these are the Great Pacific Gyres that have accumulated astounding quantities of plastic waste.



Recycling

The huge quantity (one estimate is 10^8 metric tons per year) of plastic materials produced for consumer and industrial use has created a gigantic problem of what to do with plastic waste which is difficult to incinerate safely and which, being largely non-biodegradable, threatens to overwhelm the capacity of landfills. An additional consideration is that *de novo* production most of the major polymers consumes non-renewable hydrocarbon resources.



Figure 8.8.2 Plastic water bottles present a special recycling problem because of their widespread use in away-from-home locations.

Plastics recycling has become a major industry, greatly aided by enlightened trash management policies in the major developed nations. However, it is plagued with some special problems of its own:

- Recycling is only profitable when there is a market for the regenerated material. Such markets vary with the economic cycle (they practically disappeared during the recession that commenced in 2008.)
- The energy-related costs of collecting and transporting plastic waste, and especially of processing it for re-use, are frequently the deciding factor in assessing the practicability of recycling.
- Collection of plastic wastes from diverse sources and locations and their transport to processing centers consumes energy and presents numerous operational problems.
- Most recycling processes are optimized for particular classes of polymers. The diversity of plastic types necessitates their separation into different waste streams — usually requiring manual (i.e., low-cost) labor. This in turn encourages shipment of these wastes to low-wage countries, thus reducing the availability of recycled materials in the countries in which the plastics originated.

Some of the major recycling processes include

- Thermal decomposition processes that can accommodate mixed kinds of plastics and render them into fuel oil, but the large inputs of energy they require have been a problem.
- A very small number of condensation polymers can be depolymerized so that the monomers can be recovered and re-used.
- Thermopolymers can be melted and pelletized, but those of widely differing types must be treated separately to avoid incompatibility problems.
- Thermosets are usually shredded and used as filler material in recycled thermopolymers.

Other processes

A process has also been developed in which many kinds of plastic can be used as a carbon source in the recycling of scrap steel. There is also a possibility of mixed recycling of different plastics, which does not require their separation. It is called compatibilization and requires use of special chemical bridging agents compatibilizers. It can help to keep the quality of recycled material and to skip often expensive and inefficient preliminary scanning of waste plastics streams and their separation/purification.

Figure 8.8.3 Plastic or other polymer compatibilization.

Recycled Plastics

Seven groups of plastic polymers, each with specific properties, are used worldwide for packaging applications (see Table 8.8.1). Each group of plastic polymer can be identified by its plastic identification code (PIC), usually a number or a letter abbreviation. For instance, low-density polyethylene can be identified by the number "4" or the letters "LDPE". The PIC appears inside a three-chasing-arrow recycling symbol. The symbol is used to indicate whether the plastic can be recycled into new products.

The PIC was introduced by the Society of the Plastics Industry, Inc., to provide a uniform system for the identification of various polymer types and to help recycling companies separate various plastics for reprocessing. Manufacturers of plastic products are required to use PIC labels in some countries/regions and can voluntarily mark their products with the PIC where there are no requirements. Consumers can identify the plastic types based on the codes usually found at the base or at the side of the plastic products, including food/chemical packaging and containers.



Not all categories are accepted by all local recycling authorities, so residents need to be informed about which kinds should be placed in recycling containers and which should be combined with ordinary trash.

Table 8.8.1 The Major Groups of Plastic Polymers. Source: Wikipedia

Plastic identification code	Type of plastic polymer	Properties	Common packaging applications	Melting temperatures (°C)
	Polyethylene terephthalate(PET, PETE)	Clarity, strength, toughness, barrier to gas and moisture.	Soft drink, water and salad dressing bottles; peanut butter and jam jars; ice cream cone lids; small consumer electronics	T _m = 250
	High-density polyethylene(HDPE)	Stiffness, strength, toughness, resistance to moisture, permeability to gas	Water pipes , Gas & Fire Pipelines , Electrical & Communications conduit, hula hoop rings, five gallon buckets, milk, juice and water bottles; grocery bags, some shampoo/toiletry bottles	T _m = 130
	Polyvinyl chloride(PVC)	Versatility, ease of blending, strength, toughness.	Blister packaging for non-food items; cling films for non-food use. May be used for food packaging with the addition of the plasticisers needed to make natively rigid PVC flexible. Non-packaging uses are electrical cable insulation; rigid piping; vinyl records.	T _m = 240
	Low-density polyethylene(LDPE)	Ease of processing, strength, toughness, flexibility, ease of sealing, barrier to moisture	Frozen food bags; squeezable bottles, e.g. honey, mustard; cling films; flexible container lids	T _m = 120
	Polypropylene(PP)	Strength, toughness, resistance to heat, chemicals, grease and oil, versatile, barrier to moisture.	Reusable microwaveable ware; kitchenware; yogurt containers; margarine tubs; microwaveable disposable take-away containers; disposable cups; soft drink bottle caps; plates.	T _m = 173
	Polystyrene(PS)	Versatility, clarity, easily formed	Egg cartons; packing peanuts; disposable cups, plates, trays and cutlery; disposable take-away containers	T _m = 240

	Other (often polycarbonate or ABS)	Dependent on polymers or combination of polymers	Beverage bottles, baby milk bottles. Non-packaging uses for polycarbonate, compact discs, "unbreakable" glazing, electronic apparatus housing, lenses (including sunglasses), prescription glasses, automotive headlamps, riot shields, instrument panels.	Polycarbonate: $T_m = 225$
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Tire Recycling

The large number of rubber tires that are disposed of, together with the increasing reluctance of landfills to accept them, has stimulated considerable innovation in the re-use of this material, especially in the construction industry.

Plastics and Fire Hazards

The term *fire (or flame)-retardant* as applied to organic (i.e., containing carbon) materials, is intended to refer to *reduced* fire hazard, as all will burn under certain circumstances. Fabric flammability is an important textile issue, especially for stage drapery that will be used in a public space such as a school, theatre or special event venue. In the United States, Federal regulations require that drapery fabrics used in such spaces be certified as flame or fire-retardant. For draperies and other fabrics used in public places, this is known as the NFPA 701 Test, which follows standards developed by the National Fire Protection Association (NFPA). Although all fabrics will burn, some are naturally more resistant to fire than others. Those that are more flammable can have their fire resistance drastically improved by treatment with fire-retardant chemicals. Inherently flame-retardant fabrics such as polyester are commonly used for flame retardant curtain fabrics.

The deaths in fiery crashes of race car drivers Fireball Roberts at Charlotte, and Eddie Sachs and Dave MacDonald at Indianapolis in 1964 led to the use of flame-resistant ics such as Nomex. Nomex and related aramid polymers are related to nylon, but have aromatic backbones, and hence are more rigid and more durable. Nomex is an example of a *meta* variant of the aramids (Kevlar is a *para* aramid). Unlike Kevlar, Nomex strands cannot align during filament polymerization and has less strength. However, it has excellent thermal, chemical, and radiation resistance for a polymer material.

A Nomex hood is a common piece of racing and firefighting equipment. It is placed on the head on top of a firefighter's face mask. The hood protects the portions of the head not covered by the helmet and face mask from the intense heat of the fire.

Figure 8.8.4 A firefighter in Toronto, Canada wears a Nomex hood in 2007.

Wildland firefighters wear Nomex shirts and trousers as part of their personal protective equipment during wildfire suppression activities.

Racing car drivers wear driving suits constructed of Nomex and or other fire retardant materials, along with Nomex gloves, long underwear, balaclavas, socks, helmet lining and shoes, to protect them in the event of a fire.

Military pilots and aircrew wear flight suits made of over 92 percent Nomex to protect them from the possibility of cockpit fires and other mishaps. Recently, troops riding in ground vehicles have also begun wearing Nomex. Kevlar thread is often used to hold the fabric together at seams.

Military tank drivers also typically use Nomex hoods as protection against fire.

Plasticizers and Pollution

Plasticizers (UK: **plasticisers**) 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.

Polyvinyl chloride polymers are one of the most widely-plasticized types, and the odors often associated with flexible vinyl materials such as garden hoses, waterbeds, cheap shower curtains, raincoats and upholstery are testament to their ability to migrate into the environment.

The well-known "new car smell" is largely due to plasticizer release from upholstery and internal trim.

According to 2014 data, the total global market for plasticizers was 8.4 million metric tonnes including 1.3 million metric tonnes in Europe.

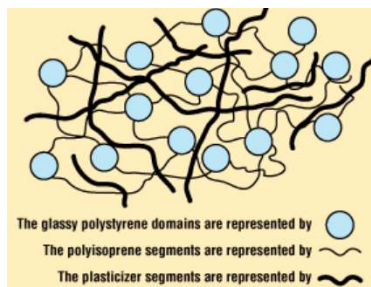


Figure 8.8.5 Shares of global plasticizer consumption in 2014 (8 million metric tons).

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.

Summary

- Plastics are found everywhere due to its low cost, versatility, ease of use etc.
- Plastics pose a threat to the environment due to residual or degradation products that contribute to air and water pollution.
- Plastics hazards to animals and marine life as these living creatures mistake them for food.
- Plastic polymers are classified into seven groups for recycling purposes.

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