INTRODUCTION TO ORGANIC AND BIOCHEMISTRY



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Introduction to Organic and Biochemistry

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CHAPTER OVERVIEW

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1.1: Organic Chemistry

Learning Objectives

- To recognize the composition and properties typical of organic and inorganic compounds.

Scientists of the 18th and early 19th centuries studied compounds obtained from plants and animals and labeled them *organic* because they were isolated from "organized" (living) systems. Compounds isolated from nonliving systems, such as rocks and ores, the atmosphere, and the oceans, were labeled *inorganic*. For many years, scientists thought organic compounds could be made by only living organisms because they possessed a vital force found only in living systems. The vital force theory began to decline in 1828, when the German chemist Friedrich Wöhler synthesized urea from inorganic starting materials. He reacted silver cyanate ($AgOCN$) and ammonium chloride (NH_4Cl), expecting to get ammonium cyanate (NH_4OCN). What he expected is described by the following equation.

$$AgOCN + NH_4Cl \rightarrow AgCl + NH_4OCN$$

However, when heated, ammonium cyanate continues to react and rearranges into urea (NH_2CONH_2), a well-known organic material readily isolated from urine.

$$NH_4OCN \longrightarrow NH_2CONH_2$$

This observation led to a series of experiments in which a wide variety of organic compounds were made from inorganic starting materials. The vital force theory gradually went away as chemists learned that they could make many organic compounds in the laboratory. Today organic chemistry is the study of the chemistry of the carbon compounds, and inorganic chemistry is the study of the chemistry of all other elements. It may seem strange that we divide chemistry into two branches—one that considers compounds of only one element and one that covers the 100-plus remaining elements. However, this division seems more reasonable when we consider that of tens of millions of compounds that have been characterized, the overwhelming majority are carbon compounds.

> The word *organic* has different meanings. Organic fertilizer, such as cow manure, is organic in the original sense; it is derived from living organisms. Organic foods generally are foods grown without synthetic pesticides or fertilizers. Organic chemistry is the chemistry of compounds of carbon.

Carbon is unique among the other elements in that its atoms can form stable covalent bonds with each other and with atoms of other elements in a multitude of variations. The resulting molecules can contain from one to millions of carbon atoms. We previously surveyed organic chemistry by dividing its compounds into families based on functional groups. We begin with the simplest members of a family and then move on to molecules that are organic in the original sense—that is, they are made by and found in living organisms. These complex molecules (all containing carbon) determine the forms and functions of living systems and are the subject of biochemistry.

Organic compounds, like inorganic compounds, obey all the natural laws. Often there is no clear distinction in the chemical or physical properties among organic and inorganic molecules. Nevertheless, it is useful to compare typical members of each class, as in Table **1.1.1**.

Table **1.1.1**: General Contrasting Properties and Examples of Organic and Inorganic Compounds

Organic	Hexane		Inorganic	NaCl
low melting points	−95°C		high melting points	801°C
low boiling points	69°C		high boiling points	1,413°C
low solubility in water; high solubility in nonpolar solvents	insoluble in water; soluble in gasoline		greater solubility in water; low solubility in nonpolar solvents	soluble in water; insoluble in gasoline
flammable	highly flammable		nonflammable	nonflammable
aqueous solutions do not conduct electricity	nonconductive		aqueous solutions conduct electricity	conductive in aqueous solution
exhibit covalent bonding	covalent bonds		exhibit ionic bonding	ionic bonds

Keep in mind, however, that there are exceptions to every category in this table. To further illustrate typical differences among organic and inorganic compounds, Table **1.1.1** also lists properties of the inorganic compound sodium chloride (common table salt, NaCl) and the organic compound hexane (C_6H_{14}), a solvent that is used to extract soybean oil from soybeans (among other uses). Many compounds can be classified as organic or inorganic by the presence or absence of certain typical properties, as illustrated in Table **1.1.1**.

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1.2: Families of Organic Molecules - Functional Groups

Learning Objectives

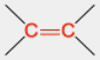
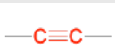
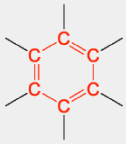
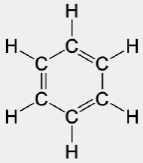
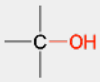
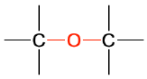
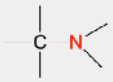
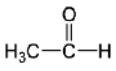
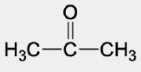
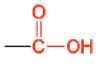
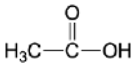
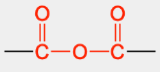
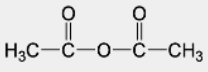
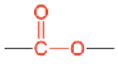
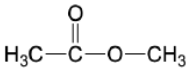
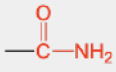
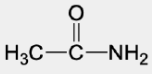
- Identify and describe functional groups in organic molecules.

Organic molecules can be classified into *families* based on structural similarities. Within a family, molecules have similar physical behavior and often have predictable chemical reactivity. The structural components differentiating different organic families involve specific arrangements of atoms or bonds, called **functional groups**. If you understand the behavior of a particular functional group, you can describe the general properties of that class of compounds.

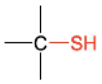
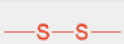
The simplest organic compounds are in the **alkane** family and contain only carbon–carbon and carbon–hydrogen *single* bonds but do not have any specific functional group. Hydrocarbons containing at least one carbon–carbon double bond, (denoted C=C), are in the **alkene** family. **Alkynes** have at least one carbon–carbon triple bond (C≡C). Both carbon–carbon double bonds and triple bonds chemically react in specific ways that differ from reactions of alkanes and each other, making these specific functional groups.

In the next few chapters, we will learn more about additional functional groups that are made up of atoms or groups of atoms attached to hydrocarbons. Being able to recognize different functional groups will help to understand and describe common medications and biomolecules such as amino acids, carbohydrates, and fats. Table 1.2.1 and Figure 1.2.1 below list several of the functional groups to become familiar with as you learn about organic chemistry.

Table 1.2.1: Organic Families and Functional Groups

Family Name	Functional Group Structure	Simple Example Structure	Simple Example Name	Name Suffix
alkane	none	$CH_3CH_2CH_3$	propane	*-ane*
alkene		$H_2C{=}CH_2$	ethene (ethylene)	*-ene*
alkyne		$HC{\equiv}CH$	ethyne (acetylene)	*-yne*
aromatic			benzene	none
alkyl halide	 (X = F, Cl, Br, I)	CH_3CH_2Cl	chloroethane	none
alcohol		CH_3CH_2OH	ethanol	*-ol*
ether		$CH_3CH_2{-}O{-}CH_2CH_3$	diethyl ether	none*
amine		$CH_3CH_2NH_2$	ethylamine	*-amine*
aldehyde			ethanal	*-al*
ketone			propanone (acetone)	*-one*
carboxylic acid			ethanoic acid (acetic acid)	*-oic acid*
anhydride			acetic anhydride	none
ester			methyl ethanoate (methyl acetate)	*-ate*
amide			acetamide	*-amide*

Atoms and bonds in red indicate the functional group. Bonds not specified are attached to R groups (carbons and hydrogens).
*Ethers do not have a suffix in their common name; all ethers end with the word *ether*.

Family Name	Functional Group Structure	Simple Example Structure	Simple Example Name	Name Suffix
thiol		CH_3CH_2SH	ethanethiol	*-thiol*
disulfide		$CH_3S–SCH_3$	dimethyl disulfide	none
sulfide		$CH_3CH_2SCH_3$	ethyl methyl sulfide	none

Atoms and bonds in red indicate the functional group. Bonds not specified are attached to R groups (carbons and hydrogens).
*Ethers do not have a suffix in their common name; all ethers end with the word *ether*.

Organic-Functional-Groups-2016_24ee.pdfOrganic-Functional-Groups-2016.pdf

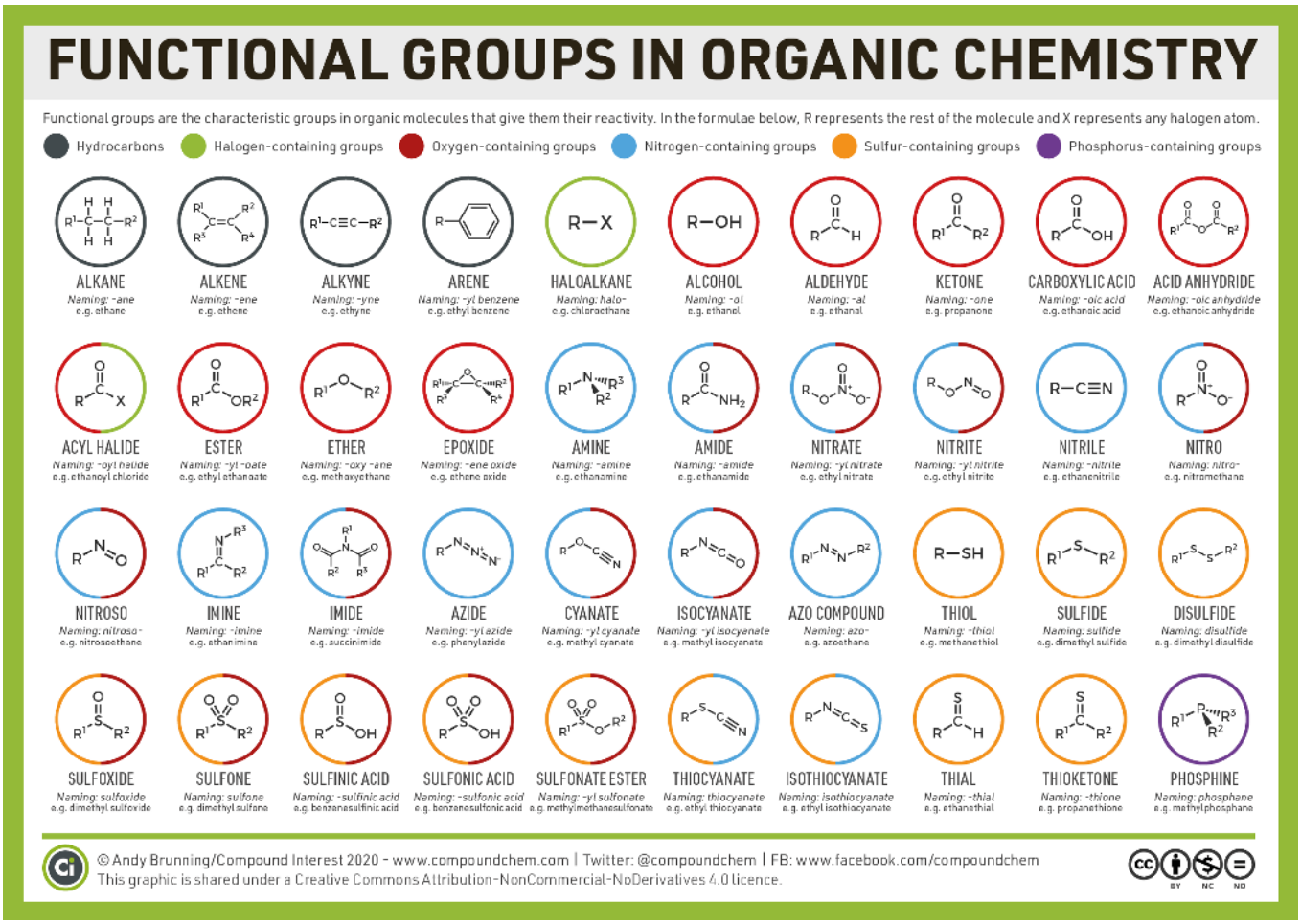


Figure **1.2.1**: Functional groups in organic chemistry. (CC BY-NC-ND, CompoundChem.com).

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1.3: Branched-Chain Alkanes

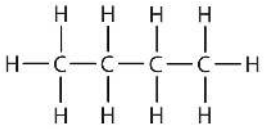
Learning Objectives

- To learn how alkane molecules can have branched chains and recognize compounds that are isomers.

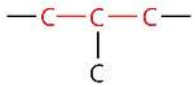
We can write the structure of butane (C_4H_{10}) by stringing four carbon atoms in a row,

–C–C–C–C–

and then adding enough hydrogen atoms to give each carbon atom four bonds:



The compound butane has this structure, but there is another way to put 4 carbon atoms and 10 hydrogen atoms together. Place 3 of the carbon atoms in a row and then branch the fourth one off the middle carbon atom:



Now we add enough hydrogen atoms to give each carbon four bonds.

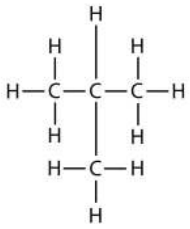


Figure **1.3.1**).

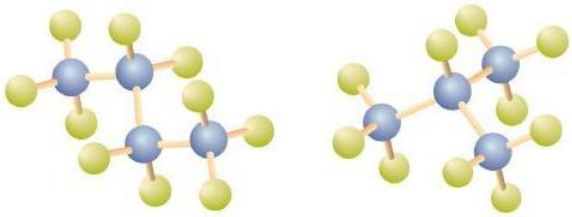
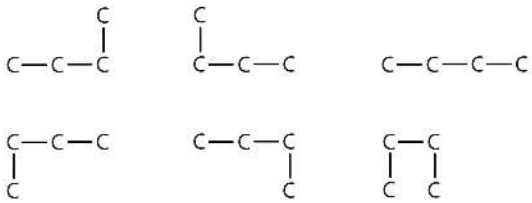


Figure **1.3.1**: Butane and Isobutane. The ball-and-stick models of these two compounds show them to be isomers; both have the molecular formula C_4H_{10}.

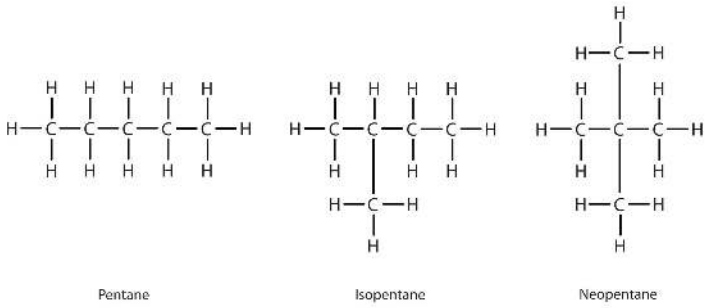
Notice that C_4H_{10} is depicted with a bent chain in Figure **1.3.1**. The four-carbon chain may be bent in various ways because the groups can rotate freely about the C–C bonds. However, this rotation does not change the identity of the compound. It is important to realize that bending a chain does *not* change the identity of the compound; all of the following represent the same compound, butane:



The structure of isobutane shows a continuous chain of three carbon atoms only, with the fourth attached as a branch off the middle carbon atom of the continuous chain, which is different from the structures of butane (compare the two structures in Figure **1.3.1**.

Unlike C_4H_{10}, the compounds methane (CH_4), ethane (C_2H_6), and propane (C_3H_8) do not exist in isomeric forms because there is only one way to arrange the atoms in each formula so that each carbon atom has four bonds.

Next beyond C_4H_{10} in the homologous series is pentane. Each compound has the same molecular formula: C_5H_{12}. (Table 12.1.1 from the previous section has a column identifying the number of possible isomers for the first 10 straight-chain alkanes.) The compound at the far left is pentane because it has all five carbon atoms in a continuous chain. The compound in the middle is isopentane; like isobutane, it has a one CH_3 branch off the second carbon atom of the continuous chain. The compound at the far right, discovered after the other two, was named neopentane (from the Greek *neos*, meaning "new"). Although all three have the same molecular formula, they have different properties, including boiling points: pentane, 36.1°C; isopentane, 27.7°C; and neopentane, 9.5°C.



A continuous (unbranched) chain of carbon atoms is often called a *straight chain* even though the tetrahedral arrangement about each carbon gives it a zigzag shape. Straight-chain alkanes are sometimes called *normal alkanes*, and their names are given the prefix *n*-. For example, butane is called *n*-butane. We will not use that prefix here because it is not a part of the system established by the International Union of Pure and Applied Chemistry.

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1.4: Condensed Structural and Line-Angle Formulas

Learning Objectives

- Write condensed structural formulas for alkanes given complete structural formulas.
- Draw line-angle formulas given structural formulas.

We use several kinds of formulas to describe organic compounds. A *molecular formula* shows only the kinds and numbers of atoms in a molecule. For example, the molecular formula C_4H_{10} tells us there are 4 carbon atoms and 10 hydrogen atoms in a molecule, but it doesn't distinguish between butane and isobutane. A structural formula shows all the carbon and hydrogen atoms and the bonds attaching them. Thus, structural formulas identify the specific isomers by showing the order of attachment of the various atoms.

Unfortunately, structural formulas are difficult to type/write and take up a lot of space. Chemists often use condensed structural formulas to alleviate these problems. The condensed formulas show hydrogen atoms right next to the carbon atoms to which they are attached, as illustrated for butane:



The ultimate condensed formula is a line-angle formula, in which carbon atoms are implied at the corners and ends of lines, and each carbon atom is understood to be attached to enough hydrogen atoms to give each carbon atom four bonds. For example, we can represent pentane ($CH_3CH_2CH_2CH_2CH_3$) and isopentane [$(CH_3)_2CHCH_2CH_3$] as follows:



Pentane Isopentane

Parentheses in condensed structural formulas indicate that the enclosed grouping of atoms is attached to the adjacent carbon atom.

Key Takeaways

- Condensed chemical formulas show the hydrogen atoms (or other atoms or groups) right next to the carbon atoms to which they are attached.
- Line-angle formulas imply a carbon atom at the corners and ends of lines. Each carbon atom is understood to be attached to enough hydrogen atoms to give each carbon atom four bonds.

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1.5: IUPAC Nomenclature

Learning Objectives

- To name alkanes by the IUPAC system and write formulas for alkanes given IUPAC names

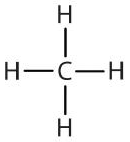
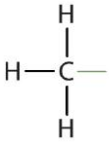
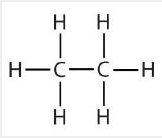
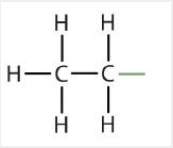
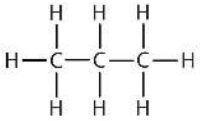
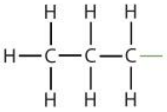
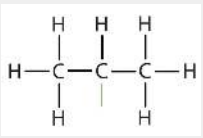
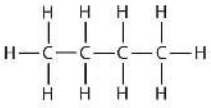
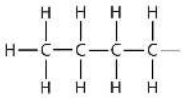
As noted in previously, the number of isomers increases rapidly as the number of carbon atoms increases. There are 3 pentanes, 5 hexanes, 9 heptanes, and 18 octanes. It would be difficult to assign unique individual names that we could remember. A systematic way of naming hydrocarbons and other organic compounds has been devised by the International Union of Pure and Applied Chemistry (IUPAC). These rules, used worldwide, are known as the IUPAC System of Nomenclature. (Some of the names we used earlier, such as isobutane, isopentane, and neopentane, do not follow these rules and are called *common names*.) A stem name (Table **1.5.1**) indicates the number of carbon atoms in the longest continuous chain (LCC). Atoms or groups attached to this carbon chain, called *substituents*, are then named, with their positions indicated by numbers. For now, we will consider only those substituents called alkyl groups.

Table **1.5.1**: Stems That Indicate the Number of Carbon Atoms in Organic Molecules

Stem	Number
meth-	1
eth-	2
prop-	3
but-	4
pent-	5
hex-	6
hept-	7
oct-	8
non-	9
dec-	10

An alkyl group is a group of atoms that results when one hydrogen atom is removed from an alkane. The group is named by replacing the *-ane* suffix of the parent hydrocarbon with *-yl*. For example, the -CH_3 group derived from methane (CH_4) results from subtracting one hydrogen atom and is called a *methyl group*. The alkyl groups we will use most frequently are listed in Table **1.5.2**. Alkyl groups are not independent molecules; they are parts of molecules that we consider as a unit to name compounds systematically.

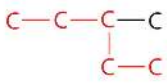
Table **1.5.2**: Common Alkyl Groups

Parent Alkane		Alkyl Group		Condensed Structural Formula
methane		methyl		$CH_3–$
ethane		ethyl		$CH_3CH_2–$
propane		propyl		$CH_3CH_2CH_2–$
		isopropyl		$(CH_3)_2CH–$
butane		butyl*		$CH_3CH_2CH_2CH_2–$

*There are four butyl groups, two derived from butane and two from isobutane. We will introduce the other three where appropriate.

Simplified IUPAC rules for naming alkanes are as follows (demonstrated in Example **1.5.1**).

1. **Name alkanes according to the LCC (longest continuous chain) of carbon atoms in the molecule (rather than the total number of carbon atoms).** This LCC, considered the parent chain, determines the base name, to which we add the suffix *-ane* to indicate that the molecule is an alkane.
2. **If the hydrocarbon is branched, number the carbon atoms of the LCC.** Numbers are assigned in the direction that gives the lowest numbers to the carbon atoms with attached substituents. Hyphens are used to separate numbers from the names of substituents; commas separate numbers from each other. (The LCC need not be written in a straight line; for example, the LCC in the following has five carbon atoms.)

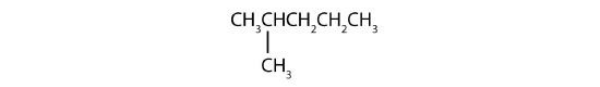
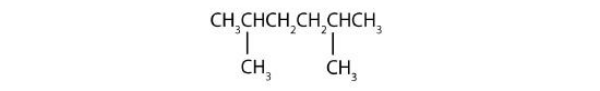
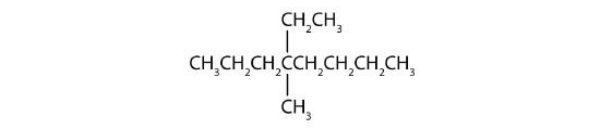


3. **Place the names of the substituent groups in alphabetical order before the name of the parent compound.** If the same alkyl group appears more than once, the numbers of all the carbon atoms to which it is attached are expressed. If the same group appears more than once on the same carbon atom, the number of that carbon atom is repeated as many times as the group appears. Moreover, the number of identical groups is indicated by the Greek prefixes *di-*, *tri-*, *tetra-*, and so on. These prefixes are *not* considered in determining the alphabetical order of the substituents. For example, ethyl is listed before dimethyl; the di- is simply ignored. The last alkyl group named is prefixed to the name of the parent alkane to form one word.

When these rules are followed, every unique compound receives its own exclusive name. The rules enable us to not only name a compound from a given structure but also draw a structure from a given name. The best way to learn how to use the IUPAC system is to put it to work, not just memorize the rules. It's easier than it looks.

Example 1.5.1

Name each compound.

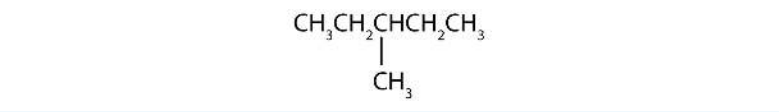
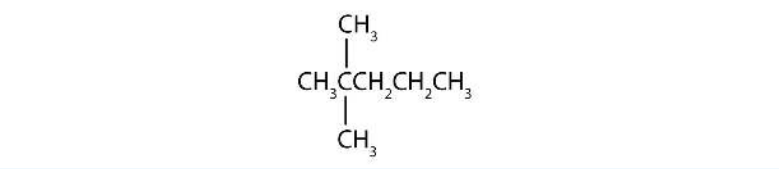
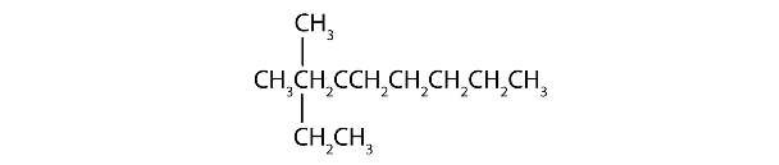
1. 
2. 
3. 

Solution

1. The LCC has five carbon atoms, and so the parent compound is pentane (rule 1). There is a methyl group (rule 2) attached to the second carbon atom of the pentane chain. The name is therefore 2-methylpentane.
2. The LCC has six carbon atoms, so the parent compound is hexne (rule 1). Methyl groups (rule 2) are attached to the second and fifth carbon atoms. The name is 2,5-dimethylhexane.
3. The LCC has eight carbon atoms, so the parent compound is octane (rule 1). There are methyl and ethyl groups (rule 2), both attached to the fourth carbon atom (counting from the *right* gives this carbon atom a lower number; rule 3). The correct name is thus 4-ethyl-4-methyloctane.

Exercise 1.5.1

Name each compound.

1. 
2. 
3. 

Example 1.5.2

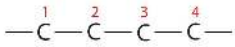
Draw the structure for each compound.

a. 2,3-dimethylbutane
b. 4-ethyl-2-methylheptane

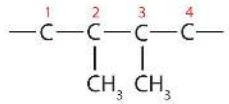
Solution a

In drawing structures, always start with the parent chain.

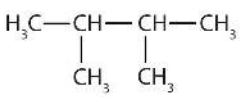
The parent chain is butane, indicating four carbon atoms in the LCC.



Then add the groups at their proper positions. You can number the parent chain from either direction as long as you are consistent; just don't change directions before the structure is done. The name indicates two methyl (CH_3) groups, one on the second carbon atom and one on the third.

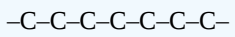


Finally, fill in all the hydrogen atoms, keeping in mind that each carbon atom must have four bonds.

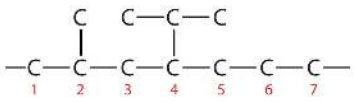


Solution b

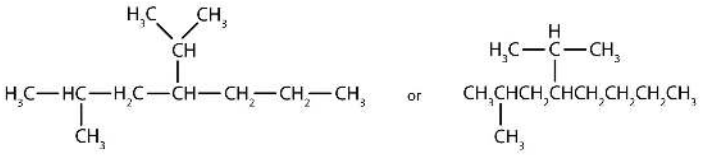
The parent chain is heptane in this case, indicating seven carbon atoms in the LCC.



Adding the groups at their proper positions gives



Filling in all the hydrogen atoms gives the following condensed structural formulas:



Note that the bonds (dashes) can be shown or not; sometimes they are needed for spacing.

? Exercise 1.5.2

Draw the structure for each compound.

a. 4-ethyloctane
b. 3-ethyl-2-methylpentane
c. 3,3,5-trimethylheptane

Key Takeaway

- Alkanes have both common names and systematic names, specified by IUPAC.

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1.6: Cycloalkanes

Learning Objectives

- To name cycloalkanes given their formulas and write formulas for these compounds given their names.

The hydrocarbons we have encountered so far have been composed of molecules with open-ended chains of carbon atoms. When a chain contains three or more carbon atoms, the atoms can join to form *ring* or *cyclic* structures. The simplest of these cyclic hydrocarbons has the formula C_3H_6. Each carbon atom has two hydrogen atoms attached (Figure **1.6.1**) and is called cyclopropane.

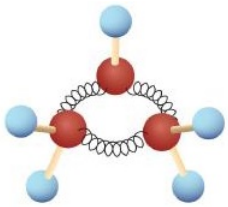
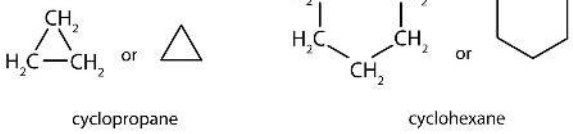


Figure **1.6.1**: Ball-and-Spring Model of Cyclopropane. The springs are bent to join the carbon atoms.

To Your Health: Cyclopropane as an Anesthetic

With its boiling point of −33°C, cyclopropane is a gas at room temperature. It is also a potent, quick-acting anesthetic with few undesirable side effects in the body. It is no longer used in surgery, however, because it forms explosive mixtures with air at nearly all concentrations.

The cycloalkanes—cyclic hydrocarbons with only single bonds—are named by adding the prefix *cyclo-* to the name of the open-chain compound having the same number of carbon atoms as there are in the ring. Thus the name for the cyclic compound C_4H_8 is cyclobutane. The carbon atoms in cyclic compounds can be represented by *line-angle formulas* that result in regular geometric figures. Keep in mind, however, that each corner of the geometric figure represents a carbon atom plus as many hydrogen atoms as needed to give each carbon atom four bonds.



Some cyclic compounds have substituent groups attached. Example **1.6.1** interprets the name of a cycloalkane with a single substituent group.

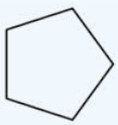
Example 1.6.1

Draw the structure for each compound.

a. cyclopentane
b. methylcyclobutane

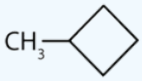
Solution a

The name *cyclopentane* indicates a cyclic (cyclo) alkane with five (pent-) carbon atoms. It can be represented as a pentagon.



Solution b

The name *methylcyclobutane* indicates a cyclic alkane with four (but-) carbon atoms in the cyclic part. It can be represented as a square with a CH_3 group attached.



? Exercise 1.6.1

Draw the structure for each compound.

a. cycloheptane
b. ethylcyclohexane

The properties of cyclic hydrocarbons are generally quite similar to those of the corresponding open-chain compounds. So cycloalkanes (with the exception of cyclopropane, which has a highly strained ring) act very much like noncyclic alkanes. Cyclic structures containing five or six carbon atoms, such as cyclopentane and cyclohexane, are particularly stable. We will see later that some carbohydrates (sugars) form five- or six-membered rings in solution.

The cyclopropane ring is strained because the C–C–C angles are 60°, and the preferred (tetrahedral) bond angle is 109.5°. (This strain is readily evident when you try to build a ball-and-stick model of cyclopropane; see Figure **1.6.1**.) Cyclopentane and cyclohexane rings have little strain because the C–C–C angles are near the preferred angles.

Key Takeaway

- Many organic compounds have cyclic structures.

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1.7: Halogenated Hydrocarbons

Learning Objectives

- To name halogenated hydrocarbons given formulas and write formulas for these compounds given names.

Many organic compounds are closely related to the alkanes. As we noted previously, alkanes react with halogens to produce halogenated hydrocarbons, the simplest of which have a single halogen atom substituted for a hydrogen atom of the alkane. Even more closely related are the cycloalkanes, compounds in which the carbon atoms are joined in a ring, or cyclic fashion.

The reactions of alkanes with halogens produce halogenated hydrocarbons, compounds in which one or more hydrogen atoms of a hydrocarbon have been replaced by halogen atoms:



The replacement of only one hydrogen atom gives an alkyl halide (or haloalkane). The *common names* of alkyl halides consist of two parts: the name of the alkyl group plus the stem of the name of the halogen, with the ending *-ide*. The IUPAC system uses the name of the parent alkane with a prefix indicating the halogen substituents, preceded by number indicating the substituent's location. The prefixes are *fluoro-*, *chloro-*, *bromo-*, and *iodo-*. Thus CH_3CH_2Cl has the common name ethyl chloride and the IUPAC name chloroethane. Alkyl halides with simple alkyl groups (one to four carbon atoms) are often called by common names. Those with a larger number of carbon atoms are usually given IUPAC names.

Example 1.7.1

Give the common and IUPAC names for each compound.

a. $CH_3CH_2CH_2Br$
b. $(CH_3)_2CHCl$

Solution

a. The alkyl group ($CH_3CH_2CH_2$–) is a propyl group, and the halogen is bromine (Br). The common name is therefore propyl bromide. For the IUPAC name, the prefix for bromine (bromo) is combined with the name for a three-carbon chain (propane), preceded by a number identifying the carbon atom to which the Br atom is attached, so the IUPAC name is 1-bromopropane.
b. The alkyl group [$(CH_3)_2CH$–] has three carbon atoms, with a chlorine (Cl) atom attached to the middle carbon atom. The alkyl group is therefore isopropyl, and the common name of the compound is isopropyl chloride. For the IUPAC name, the Cl atom (prefix *chloro-*) attached to the middle (second) carbon atom of a propane chain results in 2-chloropropane.

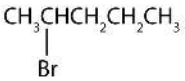
Exercise 1.7.1

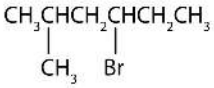
Give common and IUPAC names for each compound.

a. CH_3CH_2I
b. $CH_3CH_2CH_2CH_2F$

Example 1.7.2

Give the IUPAC name for each compound.

1. 

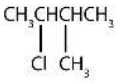
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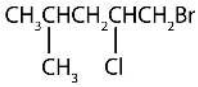
Solution

1. The parent alkane has five carbon atoms in the longest continuous chain; it is pentane. A bromo (Br) group is attached to the second carbon atom of the chain. The IUPAC name is 2-bromopentane.
2. The parent alkane is hexane. Methyl ($CH_{3)}$ and bromo (Br) groups are attached to the second and fourth carbon atoms, respectively. Listing the substituents in alphabetical order gives the name 4-bromo-2-methylhexane.

? Exercise 1.7.2

Give the IUPAC name for each compound.

a. 

b. 

A wide variety of interesting and often useful compounds have one or more halogen atoms per molecule. For example, methane (CH_4) can react with chlorine (Cl_2), replacing one, two, three, or all four hydrogen atoms with Cl atoms. Several halogenated products derived from methane and ethane (CH_3CH_3) are listed in Table **1.7.1**, along with some of their uses.

Table **1.7.1**: Some Halogenated Hydrocarbons

Formula	Common Name	IUPAC Name	Some Important Uses
Derived from CH_4			
CH_3Cl	methyl chloride	chloromethane	refrigerant; the manufacture of silicones, methyl cellulose, and synthetic rubber
CH_2Cl_2	methylene chloride	dichloromethane	laboratory and industrial solvent
$CHCl_3$	chloroform	trichloromethane	industrial solvent
CCl_4	carbon tetrachloride	tetrachloromethane	dry-cleaning solvent and fire extinguishers (but no longer recommended for use)
$CBrF_3$	halon-1301	bromotrifluoromethane	fire extinguisher systems
CCl_3F	chlorofluorocarbon-11 (CFC-11)	trichlorofluoromethane	foaming plastics
CCl_2F_2	chlorofluorocarbon-12 (CFC-12)	dichlorodifluoromethane	refrigerant
Derived from CH_3CH_3			
CH_3CH_2Cl	ethyl chloride	chloroethane	local anesthetic
$ClCH_2CH_2Cl$	ethylene dichloride	1,2-dichloroethane	solvent for rubber
CCl_3CH_3	methylchloroform	1,1,1-trichloroethane	solvent for cleaning computer chips and molds for shaping plastics

To Your Health: Halogenated Hydrocarbons

Once widely used in consumer products, many chlorinated hydrocarbons are suspected carcinogens (cancer-causing substances) and also are known to cause severe liver damage. An example is carbon tetrachloride (CCl_4), once used as a dry-cleaning solvent and in fire extinguishers but no longer recommended for either use. Even in small amounts, its vapor can cause serious illness if exposure is prolonged. Moreover, it reacts with water at high temperatures to form deadly phosgene ($COCl_2$) gas, which makes the use of CCl_4 in fire extinguishers particularly dangerous.

Ethyl chloride, in contrast, is used as an external local anesthetic. When sprayed on the skin, it evaporates quickly, cooling the area enough to make it insensitive to pain. It can also be used as an emergency general anesthetic.

Bromine-containing compounds are widely used in fire extinguishers and as fire retardants on clothing and other materials. Because they too are toxic and have adverse effects on the environment, scientists are engaged in designing safer substitutes for them, as for many other halogenated compounds.

To Your Health: Chlorofluorocarbons and the Ozone Layer

Alkanes substituted with both fluorine (F) and chlorine (Cl) atoms have been used as the dispersing gases in aerosol cans, as foaming agents for plastics, and as refrigerants. Two of the best known of these chlorofluorocarbons (CFCs) are listed in Table **1.7.1**.

Chlorofluorocarbons contribute to the greenhouse effect in the lower atmosphere. They also diffuse into the stratosphere, where they are broken down by ultraviolet (UV) radiation to release Cl atoms. These in turn break down the ozone (O_3) molecules that protect Earth from harmful UV radiation. Worldwide action has reduced the use of CFCs and related compounds. The CFCs and other Cl- or bromine (Br)-containing ozone-destroying compounds are being replaced with more benign substances. Hydrofluorocarbons (HFCs), such as CH_2FCF_3, which have no Cl or Br to form radicals, are one alternative. Another is

hydrochlorofluorocarbons (HCFCs), such as $CHCl_2CF_3$. HCFC molecules break down more readily in the troposphere, and fewer ozone-destroying molecules reach the stratosphere.

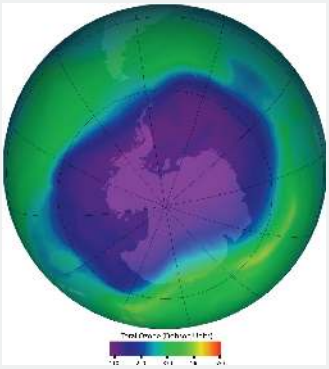


Figure **1.7.1**: Ozone in the upper atmosphere shields Earth's surface from UV radiation from the sun, which can cause skin cancer in humans and is also harmful to other animals and to some plants. Ozone "holes" in the upper atmosphere (the gray, pink, and purple areas at the center) are large areas of substantial ozone depletion. They occur mainly over Antarctica from late August through early October and fill in about mid-November. Ozone depletion has also been noted over the Arctic regions. The largest ozone hole ever observed occurred on 24 September 2006. Source: Image courtesy of NASA, Ozone watch (opens in new window) [ozonewatch.gsfc.nasa.gov].

Key Takeaway

- The replacement of an hydrogen atom on an alkane by a halogen atom—F, Cl, Br, or I—forms a halogenated compound.

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1.8: Physical Properties of Alkanes

Learning Objectives

- To identify the physical properties of alkanes and describe trends in these properties.

Because alkanes have relatively predictable physical properties and undergo relatively few chemical reactions other than combustion, they serve as a basis of comparison for the properties of many other organic compound families. Let's consider their physical properties first.

Table **1.8.1** describes some of the properties of some of the first 10 straight-chain alkanes. Because alkane molecules are nonpolar, they are insoluble in water, which is a polar solvent, but are soluble in nonpolar and slightly polar solvents. Consequently, alkanes themselves are commonly used as solvents for organic substances of low polarity, such as fats, oils, and waxes. Nearly all alkanes have densities less than 1.0 g/mL and are therefore less dense than water (the density of H_2O is 1.00 g/mL at 20°C). These properties explain why oil and grease do not mix with water but rather float on its surface.

Table **1.8.1**: Physical Properties of Some Alkanes

Molecular Name	Formula	Melting Point (°C)	Boiling Point (°C)	Density (20°C)*	Physical State (at 20°C)
methane	CH_4	–182	–164	0.668 g/L	gas
ethane	C_2H_6	–183	–89	1.265 g/L	gas
propane	C_3H_8	–190	–42	1.867 g/L	gas
butane	C_4H_{10}	–138	–1	2.493 g/L	gas
pentane	C_5H_{12}	–130	36	0.626 g/mL	liquid
hexane	C_6H_{14}	–95	69	0.659 g/mL	liquid
octane	C_8H_{18}	–57	125	0.703 g/mL	liquid
decane	$C_{10}H_{22}$	–30	174	0.730 g/mL	liquid

*Note the change in units going from gases (grams per liter) to liquids (grams per milliliter). Gas densities are at 1 atm pressure.



Figure 1.8.1: Oil Spills. Crude oil coats the water's surface in the Gulf of Mexico after the *Deepwater Horizon* oil rig sank following an explosion. The leak was a mile below the surface, making it difficult to estimate the size of the spill. One liter of oil can create a slick 2.5 hectares (6.3 acres) in size. This and similar spills provide a reminder that hydrocarbons and water don't mix. Source: Photo courtesy of NASA Goddard / MODIS Rapid Response Team, NASA.gov, Topics, Earth Features, Oil Spill(opens in new window) [www.nasa.gov].

Looking Closer: Gas Densities and Fire Hazards

Table 1.8.1 indicates that the first four members of the alkane series are gases at ordinary temperatures. Natural gas is composed chiefly of methane, which has a density of about 0.67 g/L. The density of air is about 1.29 g/L. Because natural gas is less dense than air, it rises. When a natural-gas leak is detected and shut off in a room, the gas can be removed by opening an upper window. On the other hand, bottled gas can be either propane (density 1.88 g/L) or butanes (a mixture of butane and isobutane; density about 2.5 g/L). Both are much heavier than air (density 1.2 g/L). If bottled gas escapes into a building, it collects near the floor. This presents a much more serious fire hazard than a natural-gas leak because it is more difficult to rid the room of the heavier gas.

Also shown in Table 1.8.1 are the boiling points of the straight-chain alkanes increase with increasing molar mass. This general rule holds true for the straight-chain homologs of all organic compound families. Larger molecules have greater surface areas and consequently interact more strongly; more energy is therefore required to separate them. For a given molar mass, the boiling points of alkanes are relatively low because these nonpolar molecules have only weak dispersion forces to hold them together in the liquid state.

Looking Closer: An Alkane Basis for Properties of Other Compounds

An understanding of the physical properties of the alkanes is important in that petroleum and natural gas and the many products derived from them—gasoline, bottled gas, solvents, plastics, and more—are composed primarily of alkanes. This understanding is also vital because it is the basis for describing the properties of other organic and biological compound families. For example, large portions of the structures of lipids consist of nonpolar alkyl groups. Lipids include the dietary fats and fatlike compounds called phospholipids and sphingolipids that serve as structural components of living tissues. These compounds have both polar and nonpolar groups, enabling them to bridge the gap between water-soluble and water-insoluble phases. This characteristic is essential for the selective permeability of cell membranes.

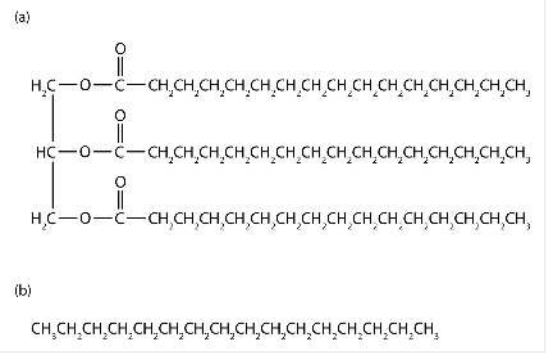


Figure 1.8.2: Tripalmitin (a), a typical fat molecule, has long hydrocarbon chains typical of most lipids. Compare these chains to hexadecane (b), an alkane with 16 carbon atoms

Key Takeaway

- Alkanes are nonpolar compounds that are low boiling and insoluble in water.

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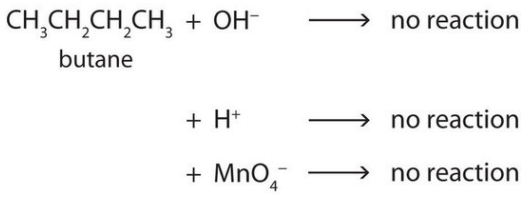
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1.9: Chemical Properties of Alkanes

Learning Objectives

- To identify the main chemical properties of alkanes.

Alkane molecules are nonpolar and therefore generally do not react with ionic compounds such as most laboratory acids, bases, oxidizing agents, or reducing agents. Consider butane as an example:



Butane plus O H superscript negative sign yields no reaction. There is also no reaction of butane with H superscript positive sign and Mn O subscript 4 superscript negative sign.

Neither positive ions nor negative ions are attracted to a nonpolar molecule. In fact, the alkanes undergo so few reactions that they are sometimes called *paraffins*, from the Latin *parum affinis*, meaning "little affinity."

Two important reactions that the alkanes do undergo are combustion and halogenation. Nothing happens when alkanes are merely mixed with oxygen (O_2) at room temperature, but when a flame or spark provides the activation energy, a highly exothermic combustion reaction proceeds vigorously. For methane (CH_4), the reaction is as follows:

$$CH_4 + 2\,O_2 \rightarrow CO_2 + 2\,H_2O + \text{heat}$$

If the reactants are adequately mixed and there is sufficient oxygen, the only products are carbon dioxide (CO_2), water (H_2O), and heat—heat for cooking foods, heating homes, and drying clothes. Because conditions are rarely ideal, however, other products are frequently formed. When the oxygen supply is limited, carbon monoxide (CO) is a by-product:

$$2\,CH_4 + 3\,O_2 \rightarrow 2\,CO + 4\,H_2O$$

This reaction is responsible for dozens of deaths each year from unventilated or improperly adjusted gas heaters. (Similar reactions with similar results occur with kerosene heaters.)

Alkanes also react with the halogens chlorine (Cl_2) and bromine (Br_2) in the presence of ultraviolet light or at high temperatures to yield chlorinated and brominated alkanes. For example, chlorine reacts with excess methane (CH_4) to give methyl chloride (CH_3Cl).

$$CH_4 + Cl_2 \rightarrow CH_3Cl + HCl$$

With more chlorine, a mixture of products is obtained: CH_3Cl, CH_2Cl_2, $CHCl_3$, and CCl_4. Fluorine (F_2), the lightest halogen, combines explosively with most hydrocarbons. Iodine (I_2) is relatively unreactive. Fluorinated and iodinated alkanes are produced by indirect methods.

Key Takeaway

- Alkanes react with oxygen (combustion) and with halogens (halogenation).

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CHAPTER OVERVIEW

2: Unsaturated and Aromatic Hydrocarbons

Our modern society is based to a large degree on the chemicals we discuss in this chapter. Most are made from petroleum. Alkanes—saturated hydrocarbons—have relatively few important chemical properties other than that they undergo combustion and react with halogens. Unsaturated hydrocarbons—hydrocarbons with double or triple bonds—on the other hand, are quite reactive. In fact, they serve as building blocks for many familiar plastics—polyethylene, vinyl plastics, acrylics—and other important synthetic materials (e.g., alcohols, antifreeze, and detergents). Aromatic hydrocarbons have formulas that can be drawn as cyclic alkenes, making them appear unsaturated, but their structure and properties are generally quite different, so they are not considered to be alkenes. Aromatic compounds serve as the basis for many drugs, antiseptics, explosives, solvents, and plastics (e.g., polyesters and polystyrene). The two simplest unsaturated compounds—ethylene (ethene) and acetylene (ethyne)—were once used as anesthetics and were introduced to the medical field in 1924. However, it was discovered that acetylene forms explosive mixtures with air, so its medical use was abandoned in 1925. Ethylene was thought to be safer, but it too was implicated in numerous lethal fires and explosions during anesthesia. Even so, it remained an important anesthetic into the 1960s, when it was replaced by nonflammable anesthetics such as halothane ($CHBrClCF_3$).

2.1: Prelude to Unsaturated and Aromatic Hydrocarbons
2.2: Alkenes- Structures and Names
2.3: Cis-Trans Isomers (Geometric Isomers)
2.4: Physical Properties of Alkenes
2.5: Chemical Properties of Alkenes
2.6: Electrophilic addition reactions
2.7: Polymers
2.8: Alkynes
2.9: Aromatic Compounds- Benzene
2.10: Structure and Nomenclature of Aromatic Compounds

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2.1: Prelude to Unsaturated and Aromatic Hydrocarbons

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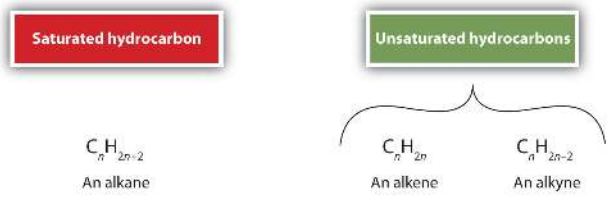
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2.2: Alkenes- Structures and Names

Learning Objectives

- To name alkenes given formulas and write formulas for alkenes given names.

As noted before, alkenes are hydrocarbons with carbon-to-carbon double bonds ($R_2C{=}CR_2$) and alkynes are hydrocarbons with carbon-to-carbon triple bonds (R–C≡C–R). Collectively, they are called unsaturated hydrocarbons because they have fewer hydrogen atoms than does an alkane with the same number of carbon atoms, as is indicated in the following general formulas:

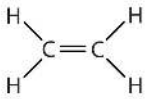


Some representative alkenes—their names, structures, and physical properties—are given in Table **2.2.1**.

Table **2.2.1**: Physical Properties of Some Selected Alkenes

IUPAC Name	Molecular Formula	Condensed Structural Formula	Melting Point (°C)	Boiling Point (°C)
ethene	C_2H_4	$CH_2{=}CH_2$	–169	–104
propene	C_3H_6	$CH_2{=}CHCH_3$	–185	–47
1-butene	C_4H_8	$CH_2{=}CHCH_2CH_3$	–185	–6
1-pentene	C_5H_{10}	$CH_2{=}CH(CH_2)_2CH_3$	–138	30
1-hexene	C_6H_{12}	$CH_2{=}CH(CH_2)_3CH_3$	–140	63
1-heptene	C_7H_{14}	$CH_2{=}CH(CH_2)_4CH_3$	–119	94
1-octene	C_8H_{16}	$CH_2{=}CH(CH_2)_5CH_3$	–102	121

We used only condensed structural formulas in Table **2.2.1**. Thus, $CH_2{=}CH_2$ stands for



The double bond is shared by the two carbons and does not involve the hydrogen atoms, although the condensed formula does not make this point obvious. Note that the molecular formula for ethene is C_2H_4, whereas that for ethane is C_2H_6.

The first two alkenes in Table **2.2.1**, ethene and propene, are most often called by their common names—ethylene and propylene, respectively (Figure **2.2.1**). Ethylene is a major commercial chemical. The US chemical industry produces about 25 billion kilograms of ethylene annually, more than any other synthetic organic chemical. More than half of this ethylene goes into the manufacture of polyethylene, one of the most familiar plastics. Propylene is also an important industrial chemical. It is converted to plastics, isopropyl alcohol, and a variety of other products.

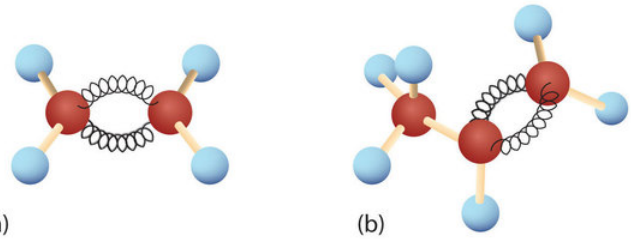
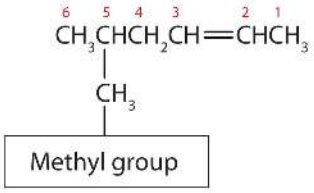


Figure **2.2.1**: Ethene and Propene. The ball-and-spring models of ethene/ethylene (a) and propene/propylene (b) show their respective shapes, especially bond angles.

Although there is only one alkene with the formula C_2H_4 (ethene) and only one with the formula C_3H_6 (propene), there are several alkenes with the formula C_4H_8.

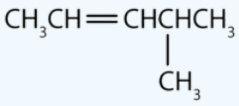
Here are some basic rules for naming alkenes from the International Union of Pure and Applied Chemistry (IUPAC):

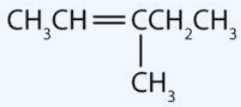
1. The longest chain of carbon atoms *containing the double bond* is considered the parent chain. It is named using the same stem as the alkane having the same number of carbon atoms but ends in *-ene* to identify it as an alkene. Thus the compound CH_2=$CHCH_3$ is *propene*.
2. If there are four or more carbon atoms in a chain, we must indicate the position of the double bond. The carbons atoms are numbered so that the first of the two that are doubly bonded is given the lower of the two possible numbers.The compound CH_3CH=$CHCH_2CH_3$, for example, has the double bond between the second and third carbon atoms. Its name is 2-pentene (not 3-pentene).
3. Substituent groups are named as with alkanes, and their position is indicated by a number. Thus, the structure below is 5-methyl-2-hexene. Note that the numbering of the parent chain is always done in such a way as to give the double bond the lowest number, even if that causes a substituent to have a higher number. *The double bond always has priority in numbering.*



Example 2.2.1

Name each compound.

a. 

b. 

Solution

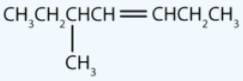
a. The longest chain containing the double bond has five carbon atoms, so the compound is a *pentene* (rule 1). To give the first carbon atom of the double bond the lowest number (rule 2), we number from the left, so the compound is a 2-pentene. There is a methyl group on the fourth carbon atom (rule 3), so the compound's name is 4-methyl-2-pentene.

b. The longest chain containing the double bond has five carbon atoms, so the parent compound is a *pentene* (rule 1). To give the first carbon atom of the double bond the lowest number (rule 2), we number from the left, so the compound is a 2-pentene. There is a methyl group on the third carbon atom (rule 3), so the compound's name is 3-methyl-2-pentene.

Exercise 2.2.1

Name each compound.

a. $CH_3CH_2CH_2CH_2CH_2CH{=}CHCH_3$

b. 

Answer

Just as there are cycloalkanes, there are *cycloalkenes*. These compounds are named like alkenes, but with the prefix *cyclo-* attached to the beginning of the parent alkene name.

Example 2.2.2

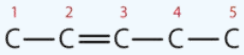
Draw the structure for each compound.

a. 3-methyl-2-pentene
b. cyclohexene

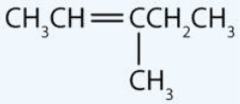
Solution

a.

First write the parent chain of five carbon atoms: C–C–C–C–C. Then add the double bond between the second and third carbon atoms:

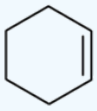


Now place the methyl group on the third carbon atom and add enough hydrogen atoms to give each carbon atom a total of four bonds.



b

First, consider what each of the three parts of the name means. *Cyclo* means a ring compound, *hex* means 6 carbon atoms, and *-ene* means a double bond.



Exercise 2.2.2

Draw the structure for each compound.

a. 2-ethyl-1-hexene
b. cyclopentene

Key Takeaway

- Alkenes are hydrocarbons with a carbon-to-carbon double bond.

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2.3: Cis-Trans Isomers (Geometric Isomers)

Learning Objectives

- Recognize that alkenes that can exist as cis-trans isomers.
- Classify isomers as cis or trans.
- Draw structures for cis-trans isomers given their names.

There is free rotation about the carbon-to-carbon single bonds (C–C) in alkanes. In contrast, the structure of alkenes requires that the carbon atoms of a double bond and the two atoms bonded to each carbon atom all lie in a single plane, and that each doubly bonded carbon atom lies in the center of a triangle. This part of the molecule's structure is rigid; rotation about doubly bonded carbon atoms is *not* possible without rupturing the bond. Look at the two chlorinated hydrocarbons in Figure **2.3.1**.

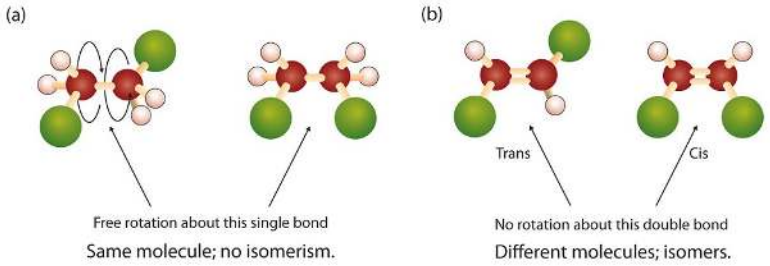


Figure **2.3.1**: *Rotation about Bonds. In 1,2-dichloroethane (a), free rotation about the C–C bond allows the two structures to be interconverted by a twist of one end relative to the other. In 1,2-dichloroethene (b), restricted rotation about the double bond means that the relative positions of substituent groups above or below the double bond are significant.*

In 1,2-dichloroethane (part (a) of Figure **2.3.1**), there is free rotation about the C–C bond. The two models shown represent exactly the same molecule; they are *not* isomers. You can draw structural formulas that look different, but if you bear in mind the possibility of this free rotation about single bonds, you should recognize that these two structures represent the same molecule:



In 1,2-dichloroethene (Figure **2.3.1***b*), however, restricted rotation about the double bond means that the relative positions of substituent groups above or below the double bond become significant. This leads to a special kind of isomerism. The isomer in which the two chlorine (Cl) atoms lie on the same side of the molecule is called the cis isomer (Latin *cis*, meaning "on this side") and is named cis-1,2-dichloroethene. The isomer with the two Cl atoms on opposite sides of the molecule is the trans isomer (Latin *trans*, meaning "across") and is named *trans*-1,2-dichloroethene. These two compounds are cis-trans isomers (or geometric isomers), compounds that have different configurations (groups permanently in different places in space) because of the presence of a rigid structure in their molecule.

Consider the alkene with the condensed structural formula $CH_3CH{=}CHCH_3$. We could name it 2-butene, but there are actually two such compounds; the double bond results in cis-trans isomerism (Figure **2.3.2**).

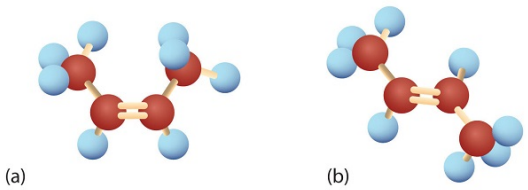


Figure **2.3.2**: Ball-and-Spring Models of (a) Cis-2-Butene and (b) Trans-2-Butene. Cis-trans isomers have different physical, chemical, and physiological properties.

Cis-2-butene has both methyl groups on the same side of the molecule. *Trans*-2-butene has the methyl groups on opposite sides of the molecule. Their structural formulas are as follows:



***Figure* 2.3.3**: *Models of (left) Cis-2-Butene and (right) Trans-2-Butene.*

Note, however, that the presence of a double bond does **not** necessarily lead to cis-trans isomerism (Figure **2.3.4**). We can draw two *seemingly* different propenes:



***Figure* 2.3.4**: *Different views of the propene molecule (flip vertically). These are not isomers.*

However, these two structures are not really different from each other. If you could pick up either molecule from the page and flip it over top to bottom, you would see that the two formulas are identical. Thus there are two requirements for cis-trans isomerism:

1. Rotation must be restricted in the molecule.
2. There must be **two nonidentical groups** on **each** doubly bonded carbon atom.

In these propene structures, the second requirement for cis-trans isomerism is not fulfilled. One of the doubly bonded carbon atoms does have two different groups attached, but the rules require that *both* carbon atoms have two different groups. In general, the following statements hold true in cis-trans isomerism:

- Alkenes with a $C{=}CH_2$ unit do not exist as cis-trans isomers.
- Alkenes with a $C{=}CR_2$ unit, where the two R groups are the same, do not exist as cis-trans isomers.
- Alkenes of the type R–CH=CH–R can exist as cis and trans isomers; cis if the two R groups are on the same side of the carbon-to-carbon double bond, and trans if the two R groups are on opposite sides of the carbon-to-carbon double bond.

Advanced Note: E/Z Isomerization

If a molecule has a C=C bond with one non-hydrogen group attached to each of the carbons, cis/trans nomenclature descried above is enough to describe it. However, if you have three different groups (or four), then the cis/trans approach is insufficient to describe the different isomers, since we do not know which two of the three groups are being described. For example, if you have a C=C bond, with a methyl group and a bromine on one carbon , and an ethyl group on the other, it is neither trans nor cis, since it is not clear whether the ethyl group is trans to the bromine or the methyl. This is addressed with a more advanced E,Z Convention [E] [E] [E] discussed elsewhere.

Cis-trans isomerism also occurs in cyclic compounds. In ring structures, groups are unable to rotate about any of the ring carbon–carbon bonds. Therefore, groups can be either on the same side of the ring (cis) or on opposite sides of the ring (trans). For our purposes here, we represent all cycloalkanes as planar structures, and we indicate the positions of the groups, either above or below the plane of the ring.



Example 2.3.1

Which compounds can exist as cis-trans (geometric) isomers? Draw them.

1. CHCl=CHBr
2. CH_2=$CBrCH_3$
3. $(CH_3)_2C$=$CHCH_2CH_3$
4. CH_3CH=$CHCH_2CH_3$

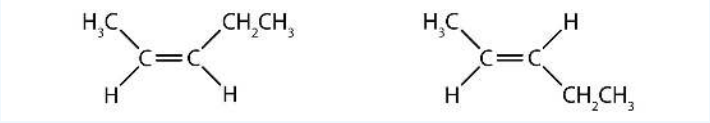
Solution

All four structures have a double bond and thus meet rule 1 for cis-trans isomerism.

1. This compound meets rule 2; it has two nonidentical groups on *each* carbon atom (H and Cl on one and H and Br on the other). It exists as both cis and trans isomers:

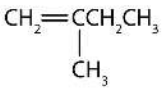


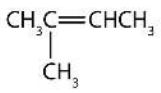
2. This compound has two hydrogen atoms on one of its doubly bonded carbon atoms; it fails rule 2 and does not exist as cis and trans isomers.
3. This compound has two methyl (CH_3) groups on one of its doubly bonded carbon atoms. It fails rule 2 and does not exist as cis and trans isomers.
4. This compound meets rule 2; it has two nonidentical groups on *each* carbon atom and exists as both cis and trans isomers:



Exercise 2.3.1

Which compounds can exist as cis-trans isomers? Draw them.

a. CH_2=$CHCH_2CH_2CH_3$
b. CH_3CH=$CHCH_2CH_3$
c. CH_3CH_2CH=$CHCH_2CH_3$
d. 

e. 

Key Takeaway

- Cis-trans (geometric) isomerism exists when there is restricted rotation in a molecule and there are two nonidentical groups on *each* doubly bonded carbon atom.

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2.4: Physical Properties of Alkenes

Learning Objectives

- To identify the physical properties of alkenes and describe trends in these properties.

The physical properties of alkenes are similar to those of the alkanes. The table at the start of the chapter shows that the boiling points of straight-chain alkenes increase with increasing molar mass, just as with alkanes. For molecules with the same number of carbon atoms and the same general shape, the boiling points usually differ only slightly, just as we would expect for substances whose molar mass differs by only 2 u (equivalent to two hydrogen atoms). Like other hydrocarbons, the alkenes are insoluble in water but soluble in organic solvents.

Looking Closer: Environmental Note

Alkenes occur widely in nature. Ripening fruits and vegetables give off ethylene, which triggers further ripening. Fruit processors artificially introduce ethylene to hasten the ripening process; exposure to as little as 0.1 mg of ethylene for 24 h can ripen 1 kg of tomatoes. Unfortunately, this process does not exactly duplicate the ripening process, and tomatoes picked green and treated this way don't taste much like vine-ripened tomatoes fresh from the garden.



The bright red color of tomatoes is due to lycopene—a polyene.

Other alkenes that occur in nature include 1-octene, a constituent of lemon oil, and octadecene ($C_{18}H_{36}$) found in fish liver. Dienes (two double bonds) and polyenes (three or more double bonds) are also common. Butadiene (CH_2=CHCH=CH_2) is found in coffee. Lycopene and the carotenes are isomeric polyenes ($C_{40}H_{56}$) that give the attractive red, orange, and yellow colors to watermelons, tomatoes, carrots, and other fruits and vegetables. Vitamin A, essential to good vision, is derived from a carotene. The world would be a much less colorful place without alkenes.

Key Takeaway

- The physical properties of alkenes are much like those of the alkanes: their boiling points increase with increasing molar mass, and they are insoluble in water.

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2.5: Chemical Properties of Alkenes

Learning Objectives

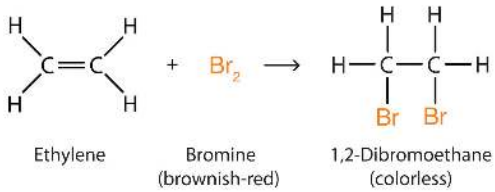
- To write equations for the addition reactions of alkenes with hydrogen, halogens, and water

Alkenes are valued mainly for addition reactions, in which one of the bonds in the double bond is broken. Each of the carbon atoms in the bond can then attach another atom or group while remaining joined to each other by a single bond. Perhaps the simplest addition reaction is hydrogenation—a reaction with hydrogen (H_2) in the presence of a catalyst such as nickel (Ni) or platinum (Pt).

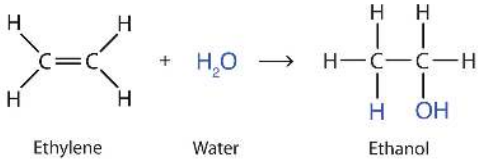


The product is an alkane having the same carbon skeleton as the alkene.

Alkenes also readily undergo halogenation—the addition of halogens. Indeed, the reaction with bromine (Br_2) can be used to test for alkenes. Bromine solutions are brownish red. When we add a Br_2 solution to an alkene, the color of the solution disappears because the alkene reacts with the bromine:



Another important addition reaction is that between an alkene and water to form an alcohol. This reaction, called hydration, requires a catalyst—usually a strong acid, such as sulfuric acid (H_2SO_4):



The hydration reaction is discussed later, where we deal with this reaction in the synthesis of alcohols.

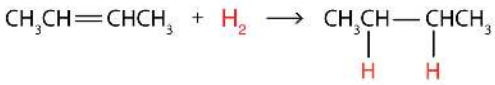
Example 2.5.1

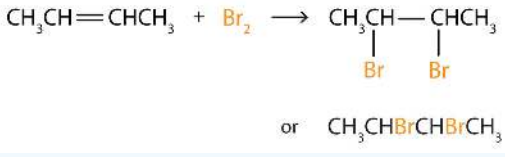
Write the equation for the reaction between $CH_3CH{=}CHCH_3$ and each substance.

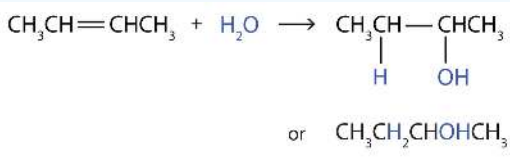
a. H_2 (Ni catalyst)
b. Br_2
c. H_2O (H_2SO_4 catalyst)

Solution

In each reaction, the reagent adds across the double bond.

a. 

b. 

c. 

? Exercise 2.5.1

Write the equation for each reaction.

a. $CH_3CH_2CH{=}CH_2$ with H_2 (Ni catalyst)
b. $CH_3CH{=}CH_2$ with Cl_2
c. $CH_3CH_2CH{=}CHCH_2CH_3$ with H_2O (H_2SO_4 catalyst)

Key Takeaway

- Alkenes undergo addition reactions, adding such substances as hydrogen, bromine, and water across the carbon-to-carbon double bond.

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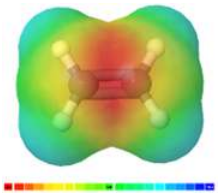
2.6: Electrophilic addition reactions

Learning Objectives

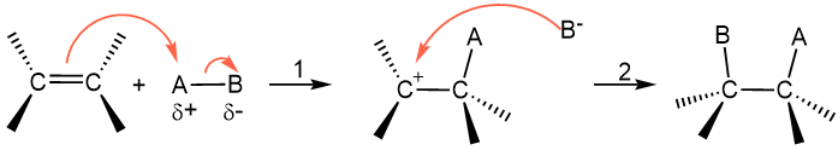
- Draw an electrophilic addition mechanism with curly arrows showing the movement of electrons.
- Apply the electrophilic addition to reactions of alkenes and alkynes with halogen acids and water.
- Define the concepts: regioselectivity, stereoselective and stereospecific reactions, and tautomerism with examples of electrophilic addition relations of alkenes and alkynes.

Electrophilic addition mechanism

The π-bond of alkenes distributes electrons above and below the σ-bond that creates a local electron-rich ($\delta-$) region, as shown by red color region in the following electrostatic potential map of ethene.



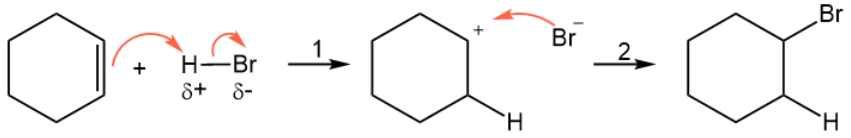
Therefore, the alkenes are nucleophiles ($\delta-$) attracted to electrophiles ($\delta+$) and capable of donating their π-electrons to make a bond with them, as shown in the following reaction mechanism.



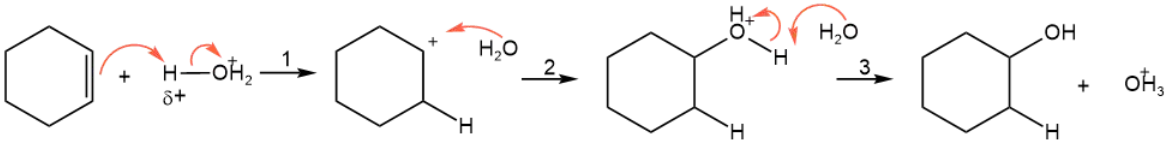
In first step of this mechanism, π-bond acts as an incoming nucleophile making a σ-bond with the electrophilic $\delta+$ end of the polar reagent $\overset{\delta+}{\mathbf{A}}\text{-}\overset{\delta-}{\mathbf{B}}$ while the ($\overset{\delta-}{\mathbf{B}}$) acts as a leaving group, leaving as a nucleophile $\mathbf{B}^-$. One of the π-bonded carbon that receives the electrophile $\overset{\delta+}{\mathbf{A}}$ becomes sp^3 hybridized, and the other carbon stays sp^2 hybridized with an empty p-orbital as a carbocation. In the second step, the nucleophile ($\mathbf{B}^-$) attacks the electrophilic carbocation and makes a new bond. As a result, the reagent $\mathbf{A}-\mathbf{B}$ add to the $\mathbf{C}=\mathbf{C}$-bond. Since the process begins with the addition of an electrophile $\overset{\delta+}{\mathbf{A}}$, it is called an electrophilic addition reaction.

Examples of electrophilic addition reactions of alkenes

Halogen acids ($\overset{\delta+}{\mathbf{H}}\text{-}\overset{\delta-}{\mathbf{Cl}}$, $\overset{\delta+}{\mathbf{H}}\text{-}\overset{\delta-}{\mathbf{Br}}$, and $\overset{\delta+}{\mathbf{H}}\text{-}\overset{\delta-}{\mathbf{I}}$) are among many reagents that add to alkenes by electrophilic addition mechanism, as shown in the following example.



Water ($\mathbf{H_2O}$) has more polar $\overset{\delta+}{\mathbf{H}}\text{-}\overset{\delta-}{\mathbf{O}}$ bonds than the halogen acids, but $-\mathbf{OH}$ is a bad leaving group and usually do not act as a leaving group. The bad leaving $-\mathbf{OH}$ is first converted to a good leaving $-\overset{+}{\mathbf{O}}\mathbf{H_2}$ by adding stronger acid like sulfuric acid ($\mathbf{H_2SO_4}$) in the water. Then, the hydronium ion ($\mathbf{H}-\overset{+}{\mathbf{O}}\mathbf{H_2}$) enters the first step of the electrophilic addition reaction, as shown below.

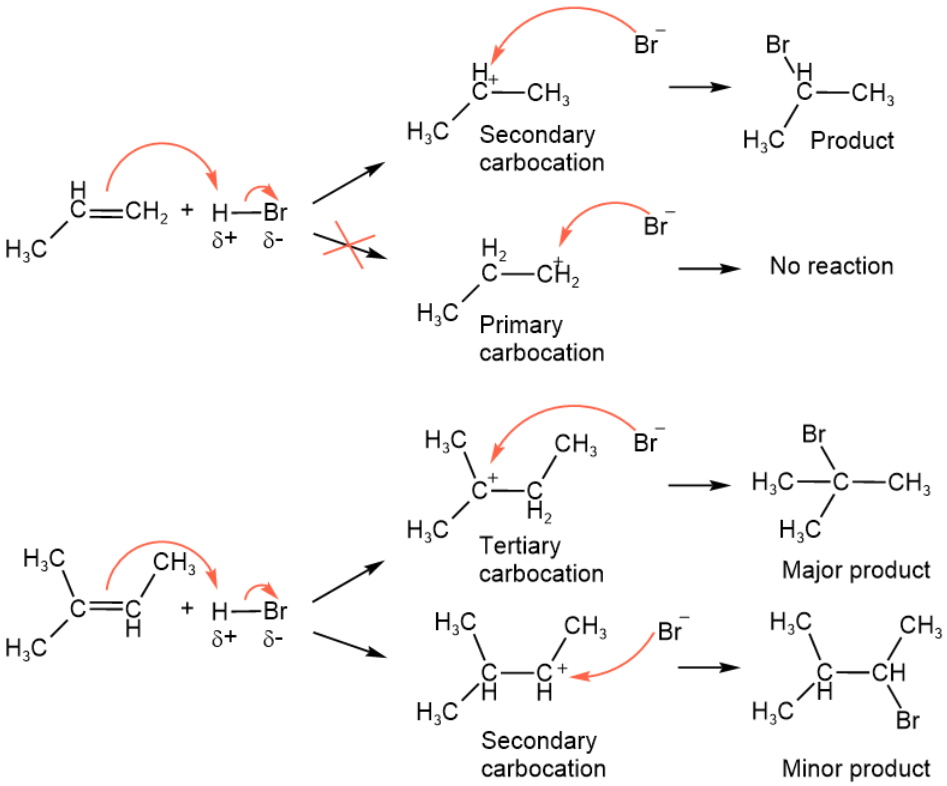


H_2O acts as an incoming nucleophile in step#2, another water molecule removes its acidic proton in step#3. This reaction is called hydration of alkene because the result is the addition of a water molecule $\overset{\delta+}{H}\text{-}\overset{\delta-}{OH}$ to a C=C-bond of an alkene.

Sulfuric acid is used as an acid catalyst because its conjugate base HSO_4^- is a poor nucleophile. H_2O is also a poor nucleophile, but being in higher concentration wins the completion in step#2. Even if HSO_4^- add to the carbocation in the second step, it is substituted by H_2O under the reaction conditions.

Regioselectivity of electrophilic addition reactions

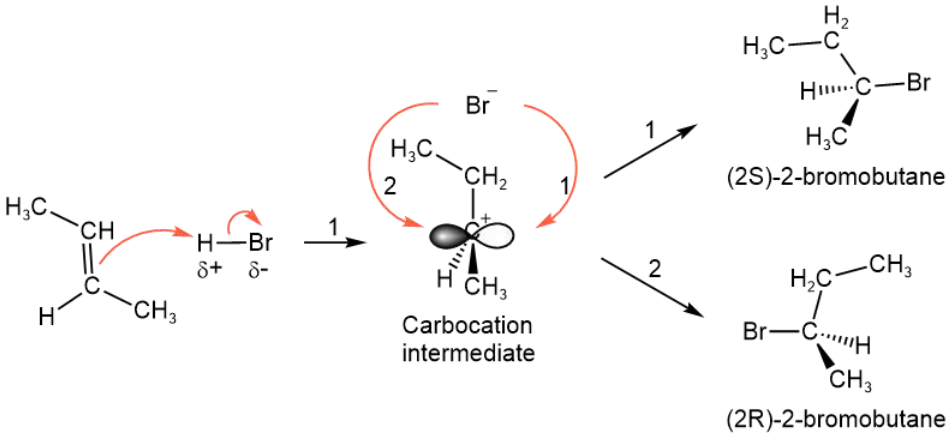
In the cases of unsymmetrical alkenes, two constitutional isomers are possible, but one is produced exclusively or as a major product. The reason is that the two potential carbonation intermediates have unequal stability. The stability of carbocations increases in this order: $\xrightarrow{\text{primary } (R\overset{+}{C}H_2) < \text{secondary } (R_2\overset{+}{C}H) < \text{tertiary } (R_3\overset{+}{C})}$. The following examples show that the more stable carbocation is formed exclusively or predominantly when there is a choice.



Chemical reactions in which two constitutional isomers are possible, but one is formed exclusively or predominantly are called **regioselective reactions**. Electrophilic additions are regioselective reactions.

Stereoselectivity of electrophilic addition reactions

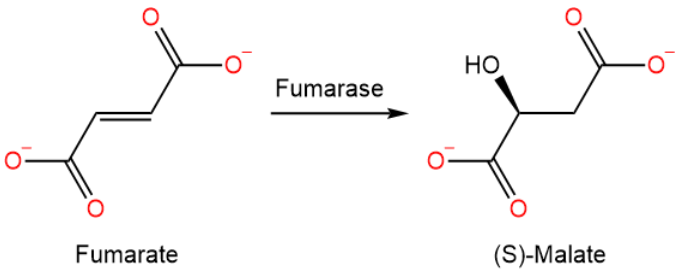
When reactants and catalysts are achiral, but the product is chiral, it is produced equally in both (R) and (S) configurations. For example, the carbocation intermediate in electrophilic addition reactions is trigonal planer. The nucleophile can attack it from either side with about equal probability resulting in a racemic mixture, as illustrated in the following example.



However, suppose one of the reactants or the catalyst is chiral and a pure enantiomer. In that case, one of the enantiomers (R or S) is usually formed exclusively or as a major product. Enzymes in biochemical systems are chiral catalysts that usually produce one enantiomer exclusively.

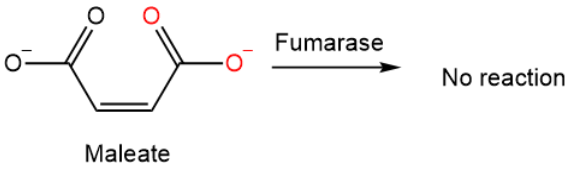
> Chemical reactions that produce one stereoisomer exclusively or preferentially relative to the others are called **stereoselective reactions**.

Enzyme-catalyzed reactions are stereoselective reactions. For example, hydration fumarate, catalyzed by an enzyme fumarase, produces (S)-malate, as shown below.



The R-enantiomer is not produced in the above reaction.

Enzymes usually also react with one stereoisomer in the reactant exclusively. For example, fumarase catalyzes the hydration of fumarate but does not react with its enantiomer maleate, as illustrated below.



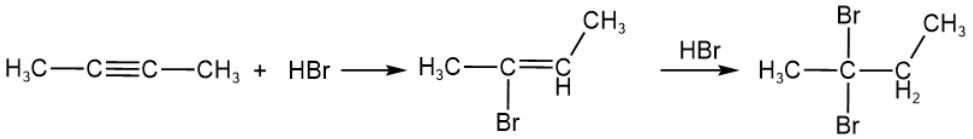
> Chemical reactions that preferentially react with one stereoisomer among reactant and preferentially produce one stereoisomer in the products are called **stereospecific reactions**.

Enzyme-catalyzed reactions are often stereospecific reactions. For example, the fumarase enzyme selectively reacts with fumarate (and not with its stereoisomer maleate) and selectively produces (S)-malate (and not its stereoisomer (R)-malate).

Electrophilic addition reactions of alkynes

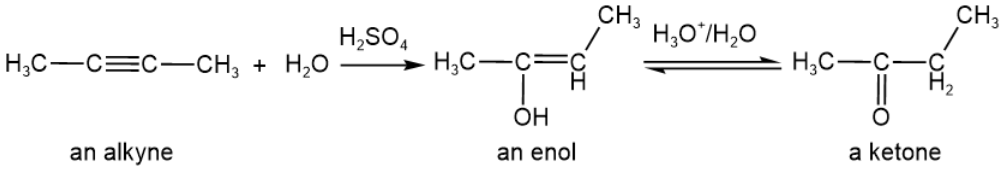
Alkynes have a triple C≡C-bond, i.e., one σ-bond and two π-bonds. The electrophilic addition reactions happen on π-bonds of alkynes. If the reagent is in a one-to-one mole ratio, it adds to one of the π-bonds. If the reagent is in excess, a second addition

reaction happens on the product of the first addition, as shown below.



In step#2, the nucleophile (\(\ce{Br} in this case) adds to the carbon carrying the nucleophile of step#1. This is because the carbonation intermediate of step#2 is stabilized by resonance with the lone pair of electrons on the nucleophile added in the first step.

Hydration of alkyne follows the same step#1 as for alkenes, but the intermediate enol containing **C=C** and **–OH** together exists in equilibrium with its structural isomer ketone, as shown in the following example.



> **Tautomers** are constitutional isomers that are readily interconvertible. **Tauomerization** is the chemical reaction that interconverts the tautomers.

Enol and its isomer ketone, e.g., but-2-ene-2-ol and but-2-one in the above example, are called **tautomers,** and the equilibrium between the two in step#2 of the above reaction is **tautomerization**.

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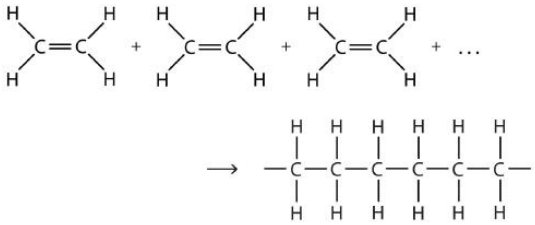
2.7: Polymers

Learning Objectives

- To draw structures for monomers that can undergo addition polymerization and for four-monomer-unit sections of an addition polymer.

The most important commercial reactions of alkenes are *polymerizations*, reactions in which small molecules, referred to in general as monomers (from the Greek *monos*, meaning “one,” and *meros*, meaning “parts”), are assembled into giant molecules referred to as polymers (from the Greek *poly*, meaning “many,” and *meros*, meaning “parts”). A polymer is as different from its monomer as a long strand of spaghetti is from a tiny speck of flour. For example, polyethylene, the familiar waxy material used to make plastic bags, is made from the monomer ethylene—a gas.

There are two general types of polymerization reactions: addition polymerization and condensation polymerization. In addition polymerization, the monomers add to one another in such a way that the polymer contains all the atoms of the starting monomers. Ethylene molecules are joined together in long chains. The polymerization can be represented by the reaction of a few monomer units:



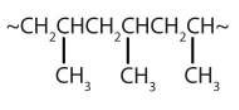
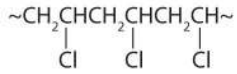
The bond lines extending at the ends in the formula of the product indicate that the structure extends for many units in each direction. Notice that all the atoms—two carbon atoms and four hydrogen atoms—of each monomer molecule are incorporated into the polymer structure. Because displays such as the one above are cumbersome, the polymerization is often abbreviated as follows:

$$n\mathrm{CH_2{=}CH_2} \rightarrow \text{-}\mathrm{CH_2CH_2}\text{-}_n$$

> Many natural materials—such as proteins, cellulose and starch, and complex silicate minerals—are polymers. Artificial fibers, films, plastics, semisolid resins, and rubbers are also polymers. More than half the compounds produced by the chemical industry are synthetic polymers.

Some common addition polymers are listed in Table **2.7.1**. Note that all the monomers have carbon-to-carbon double bonds. Many polymers are mundane (e.g., plastic bags, food wrap, toys, and tableware), but there are also polymers that conduct electricity, have amazing adhesive properties, or are stronger than steel but much lighter in weight.

Table **2.7.1***: Some Addition Polymers*

Monomer	Polymer	Polymer Name	Some Uses
$CH_2=CH_2$	$\sim CH_2CH_2CH_2CH_2CH_2CH_2\sim$	polyethylene	plastic bags, bottles, toys, electrical insulation
$CH_2=CHCH_3$		polypropylene	carpeting, bottles, luggage, exercise clothing
$CH_2=CHCl$		polyvinyl chloride	bags for intravenous solutions, pipes, tubing, floor coverings
$CF_2=CF_2$	$\sim CF_2CF_2CF_2CF_2CF_2CF_2\sim$	polytetrafluoroethylene	nonstick coatings, electrical insulation

Medical Uses of Polymers

An interesting use of polymers is the replacement of diseased, worn out, or missing parts in the body. For example, about a 250,000 hip joints and 500,000 knees are replaced in US hospitals each year. The artificial ball-and-socket hip joints are made of a special steel (the ball) and plastic (the socket). People crippled by arthritis or injuries gain freedom of movement and relief from pain. Patients with heart and circulatory problems can be helped by replacing worn out heart valves with parts based on synthetic polymers. These are only a few of the many biomedical uses of polymers.

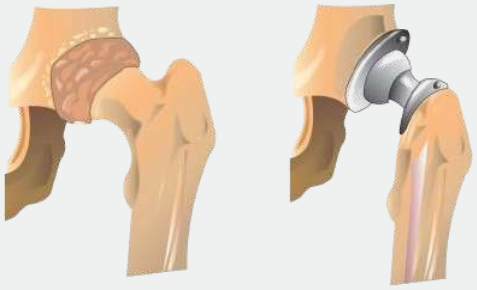


Figure **2.7.1**: Hip Joint Replacement. Synthetic polymers are an important part of a hip joint replacement. The hip is much like a ball-and-socket joint, and total hip replacements mimic this with a metal ball that fits in a plastic cup.

Key Takeaway

- Molecules having carbon-to-carbon double bonds can undergo addition polymerization.

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2.8: Alkynes

Learning Objectives

- Describe the general physical and chemical properties of alkynes.
- Name alkynes given formulas and write formulas for alkynes given names.

The simplest alkyne—a hydrocarbon with carbon-to-carbon triple bond—has the molecular formula C_2H_2 and is known by its common name—acetylene (Figure **2.8.1**). Its structure is H–C≡C–H.

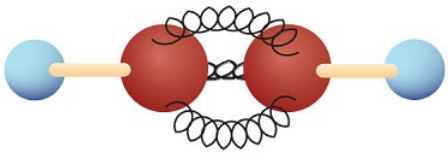


Figure **2.8.1**: Ball-and-Spring Model of Acetylene. Acetylene (ethyne) is the simplest member of the alkyne family.

Acetylene is used in oxyacetylene torches for cutting and welding metals. The flame from such a torch can be very hot. Most acetylene, however, is converted to chemical intermediates that are used to make vinyl and acrylic plastics, fibers, resins, and a variety of other products.

Alkynes are similar to alkenes in both physical and chemical properties. For example, alkynes undergo many of the typical addition reactions of alkenes. The International Union of Pure and Applied Chemistry (IUPAC) names for alkynes parallel those of alkenes, except that the family ending is *-yne* rather than *-ene*. The IUPAC name for acetylene is ethyne. The names of other alkynes are illustrated in the following exercises.

Key Takeaway

- Alkynes are hydrocarbons with carbon-to-carbon triple bonds and properties much like those of alkenes.

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2.9: Aromatic Compounds- Benzene

Learning Objectives

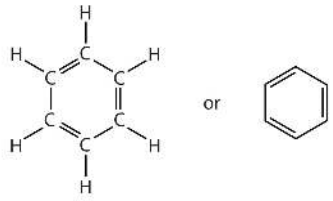
- To describe the bonding in benzene and the way typical reactions of benzene differ from those of the alkenes.

Next we consider a class of hydrocarbons with molecular formulas like those of unsaturated hydrocarbons, but which, unlike the alkenes, do not readily undergo addition reactions. These compounds comprise a distinct class, called aromatic hydrocarbons, with unique structures and properties. We start with the simplest of these compounds. Benzene (C_6H_6) is of great commercial importance, but it also has noteworthy health effects.

The formula C_6H_6 seems to indicate that benzene has a high degree of unsaturation. (Hexane, the saturated hydrocarbon with six carbon atoms has the formula C_6H_{14}—eight more hydrogen atoms than benzene.) However, despite the seeming low level of saturation, benzene is rather unreactive. It does not, for example, react readily with bromine, which, is a test for unsaturation.

Benzene is a liquid that smells like gasoline, boils at 80°C, and freezes at 5.5°C. It is the aromatic hydrocarbon produced in the largest volume. It was formerly used to decaffeinate coffee and was a significant component of many consumer products, such as paint strippers, rubber cements, and home dry-cleaning spot removers. It was removed from many product formulations in the 1950s, but others continued to use benzene in products until the 1970s when it was associated with leukemia deaths. Benzene is still important in industry as a precursor in the production of plastics (such as Styrofoam and nylon), drugs, detergents, synthetic rubber, pesticides, and dyes. It is used as a solvent for such things as cleaning and maintaining printing equipment and for adhesives such as those used to attach soles to shoes. Benzene is a natural constituent of petroleum products, but because it is a known carcinogen, its use as an additive in gasoline is now limited.

To explain the surprising properties of benzene, chemists suppose the molecule has a cyclic, hexagonal, planar structure of six carbon atoms with one hydrogen atom bonded to each. We can write a structure with alternate single and double bonds, either as a full structural formula or as a line-angle formula:



However, these structures do not explain the unique properties of benzene. Furthermore, experimental evidence indicates that all the carbon-to-carbon bonds in benzene are equivalent, and the molecule is unusually stable. Chemists often represent benzene as a hexagon with an inscribed circle:



The inner circle indicates that the valence electrons are shared equally by all six carbon atoms (that is, the electrons are *delocalized*, or spread out, over all the carbon atoms). It is understood that each corner of the hexagon is occupied by one carbon atom, and each carbon atom has one hydrogen atom attached to it. Any other atom or groups of atoms substituted for a hydrogen atom must be shown bonded to a particular corner of the hexagon. We use this modern symbolism, but many scientists still use the earlier structure with alternate double and single bonds.

To Your Health: Benzene and Us

Most of the benzene used commercially comes from petroleum. It is employed as a starting material for the production of detergents, drugs, dyes, insecticides, and plastics. Once widely used as an organic solvent, benzene is now known to have both short- and long-term toxic effects. The inhalation of large concentrations can cause nausea and even death due to respiratory or heart failure, while repeated exposure leads to a progressive disease in which the ability of the bone marrow to make new blood cells is eventually destroyed. This results in a condition called *aplastic anemia*, in which there is a decrease in the numbers of both the red and white blood cells.

Key Takeaway

- Aromatic hydrocarbons appear to be unsaturated, but they have a special type of bonding and do not undergo addition reactions.

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2.10: Structure and Nomenclature of Aromatic Compounds

Learning Objectives

- Recognize aromatic compounds from structural formulas.
- Name aromatic compounds given formulas.
- Write formulas for aromatic compounds given their names.

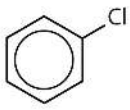
Historically, benzene-like substances were called aromatic hydrocarbons because they had distinctive aromas. Today, an aromatic compound is any compound that contains a benzene ring or has certain benzene-like properties (but not necessarily a strong aroma). You can recognize the aromatic compounds in this text by the presence of one or more benzene rings in their structure. Some representative aromatic compounds and their uses are listed in Table **2.10.1**, where the benzene ring is represented as C_6H_5.

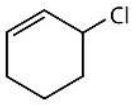
Table **2.10.1**: Some Representative Aromatic Compounds

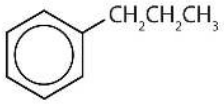
Name	Structure	Typical Uses
aniline	$C_6H_5–NH_2$	starting material for the synthesis of dyes, drugs, resins, varnishes, perfumes; solvent; vulcanizing rubber
benzoic acid	$C_6H_5–COOH$	food preservative; starting material for the synthesis of dyes and other organic compounds; curing of tobacco
bromobenzene	$C_6H_5–Br$	starting material for the synthesis of many other aromatic compounds; solvent; motor oil additive
nitrobenzene	$C_6H_5–NO_2$	starting material for the synthesis of aniline; solvent for cellulose nitrate; in soaps and shoe polish
phenol	$C_6H_5–OH$	disinfectant; starting material for the synthesis of resins, drugs, and other organic compounds
toluene	$C_6H_5–CH_3$	solvent; gasoline octane booster; starting material for the synthesis of benzoic acid, benzaldehyde, and many other organic compounds

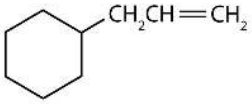
Example 2.10.1

Which compounds are aromatic?

1. 

2. 

3. 

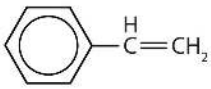
4. 

Solution

1. The compound has a benzene ring (with a chlorine atom substituted for one of the hydrogen atoms); it is aromatic.
2. The compound is cyclic, but it does not have a benzene ring; it is not aromatic.
3. The compound has a benzene ring (with a propyl group substituted for one of the hydrogen atoms); it is aromatic.
4. The compound is cyclic, but it does not have a benzene ring; it is not aromatic.

? Exercise 2.10.1

Which compounds are aromatic?

1. 

2. 

3. 

In the International Union of Pure and Applied Chemistry (IUPAC) system, aromatic hydrocarbons are named as derivatives of benzene. Figure 2.10.1 shows four examples. In these structures, it is immaterial whether the single substituent is written at the top, side, or bottom of the ring: a hexagon is symmetrical, and therefore all positions are equivalent.

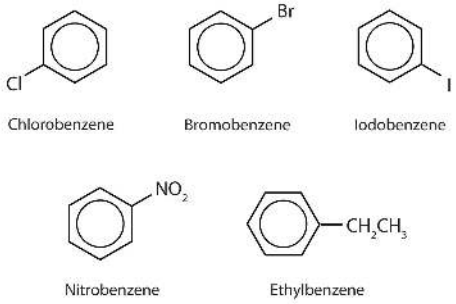


Figure 2.10.1: Some Benzene Derivatives. These compounds are named in the usual way with the group that replaces a hydrogen atom named as a substituent group: Cl as chloro, Br as bromo, I as iodo, NO_2 as nitro, and CH_3CH_2 as ethyl.

Although some compounds are referred to exclusively by IUPAC names, some are more frequently denoted by common names, as is indicated in Table 2.10.1.



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When there is more than one substituent, the corners of the hexagon are no longer equivalent, so we must designate the relative positions. There are three possible disubstituted benzenes, and we can use numbers to distinguish them (Figure **2.10.2**). We start numbering at the carbon atom to which one of the groups is attached and count toward the carbon atom that bears the other substituent group by the shortest path.

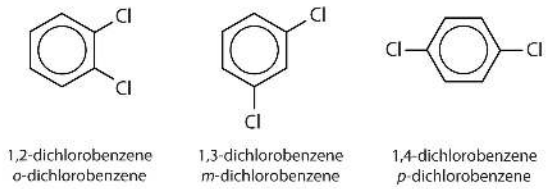
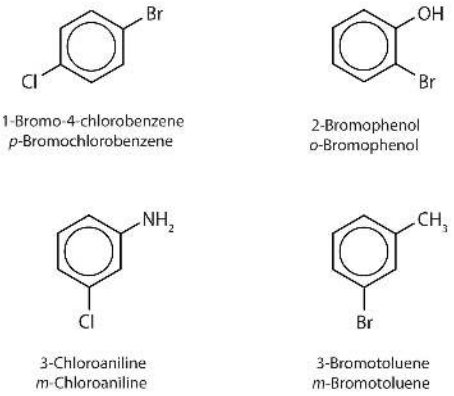


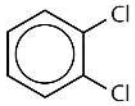
Figure **2.10.2**: The Three Isomeric Dichlorobenzenes

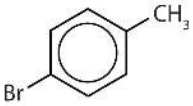
In Figure **2.10.2**, common names are also used: the prefix *ortho* (*o*-) for 1,2-disubstitution, *meta* (*m*-) for 1,3-disubstitution, and *para* (*p*-) for 1,4-disubstitution. The substituent names are listed in alphabetical order. The first substituent is given the lowest number. When a common name is used, the carbon atom that bears the group responsible for the name is given the number 1:

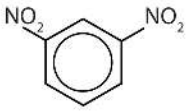


Example 2.10.2

Name each compound using both the common name and the IUPAC name.

1. 

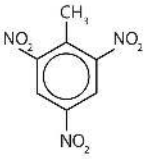
2. 

3. 

Solution

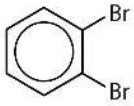
1. The benzene ring has two chlorine atoms (dichloro) in the first and second positions. The compound is *o*-dichlorobenzene or 1,2-dichlorobenzene.
2. The benzene ring has a methyl (CH_3) group. The compound is therefore named as a derivative of toluene. The bromine atom is on the fourth carbon atom, counting from the methyl group. The compound is *p*-bromotoluene or 4-bromotoluene.
3. The benzene ring has two nitro (NO_2) groups in the first and third positions. It is *m*-dinitrobenzene or 1,3-dinitrobenzene.

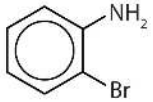
4. Note: The nitro (NO_2) group is a common substituent in aromatic compounds. Many nitro compounds are explosive, most notably 2,4,6-trinitrotoluene (TNT).

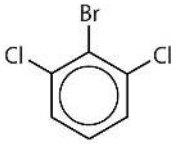


? Exercise 2.10.2

Name each compound using both the common name and the IUPAC name.

1. 

2. 

3. 

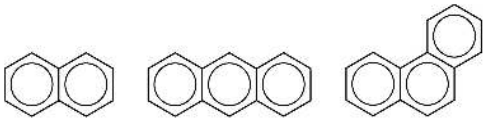
- Sometimes an aromatic group is found as a substituent bonded to a nonaromatic entity or to another aromatic ring. The group of atoms remaining when a hydrogen atom is removed from an aromatic compound is called an aryl group. The most common aryl group is derived from benzene (C_6H_6) by removing one hydrogen atom (C_6H_5) and is called a *phenyl* group, from *pheno*, an old name for benzene.



Phenyl group 2-Phenylheptane

Polycyclic Aromatic Hydrocarbons

Some common aromatic hydrocarbons consist of fused benzene rings—rings that share a common side. These compounds are called polycyclic aromatic hydrocarbons (PAHs).



Naphthalene Anthracene Phenanthrene

The three examples shown here are colorless, crystalline solids generally obtained from coal tar. Naphthalene has a pungent odor and is used in mothballs. Anthracene is used in the manufacture of certain dyes. Steroids, a large group of naturally occurring substances, contain the phenanthrene structure.

To Your Health: Polycyclic Aromatic Hydrocarbons and Cancer

The intense heating required for distilling coal tar results in the formation of PAHs. For many years, it has been known that workers in coal-tar refineries are susceptible to a type of skin cancer known as tar cancer. Investigations have shown that a number of PAHs

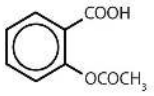
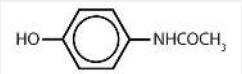
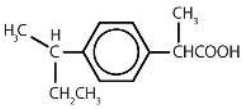
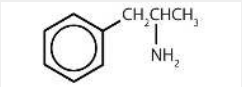
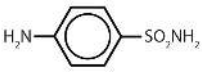
are carcinogens. One of the most active carcinogenic compounds, benzopyrene, occurs in coal tar and has also been isolated from cigarette smoke, automobile exhaust gases, and charcoal-broiled steaks. It is estimated that more than 1,000 t of benzopyrene are emitted into the air over the United States each year. Only a few milligrams of benzopyrene per kilogram of body weight are required to induce cancer in experimental animals.

Biologically Important Compounds with Benzene Rings

Substances containing the benzene ring are common in both animals and plants, although they are more abundant in the latter. Plants can synthesize the benzene ring from carbon dioxide, water, and inorganic materials. Animals cannot synthesize it, but they are dependent on certain aromatic compounds for survival and therefore must obtain them from food. Phenylalanine, tyrosine, and tryptophan (essential amino acids) and vitamins K, B_2 (riboflavin), and B_9 (folic acid) all contain the benzene ring. Many important drugs, a few of which are shown in Table **2.10.2**, also feature a benzene ring.

> So far we have studied only aromatic compounds with carbon-containing rings. However, many cyclic compounds have an element other than carbon atoms in the ring. These compounds, called *heterocyclic compounds*, are discussed later. Some of these are heterocyclic aromatic compounds.

Table **2.10.2**: Some Drugs That Contain a Benzene Ring

Name	Structure
aspirin	
acetaminophen	
ibuprofen	
amphetamine	
sulfanilamide	

Key Takeaway

- Aromatic compounds contain a benzene ring or have certain benzene-like properties; for our purposes, you can recognize aromatic compounds by the presence of one or more benzene rings in their structure.

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CHAPTER OVERVIEW

3: Alcohols, Ethers, Thiols, and Related Molecules

3.1: Organic Compounds with Functional Groups
3.2: Alcohols - Nomenclature and Classification
3.3: Phenols
3.4: Names and Properties of Ethers
3.5: Thiols and Sulfides
3.6: Intermolecular Forces- The Forces that Hold Condensed Phases Together
3.7: Properties of Alcohols and Phenols
3.8: Reactions that Form Alcohols
3.9: Nucleophilic substitution and elimination reactions

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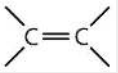
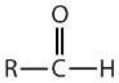
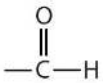
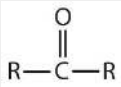
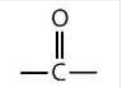
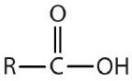
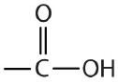
3.1: Organic Compounds with Functional Groups

Learning Objectives

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

Previously, we considered several kinds of hydrocarbons. Now we examine some of the many organic compounds that contain functional groups. 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. In this chapter, we make a brief yet systematic study of some of organic compound families. Each family is based on a common, simple functional group that contains an oxygen atom or a nitrogen atom. Some common functional groups are listed in Table **3.1.1**.

Table **3.1.1**: Selected Organic Functional Groups

Name of Family	General Formula	Functional Group	Suffix*
alkane	RH	none	*-ane*
alkene	$R_2C{=}CR_2$		*-ene*
alkyne	RC≡CR	–C≡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.

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3.2: Alcohols - Nomenclature and Classification

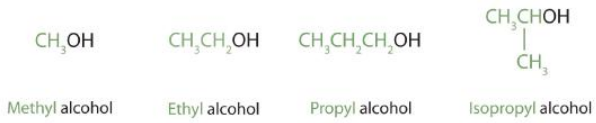
Learning Objectives

- Identify the general structure for an alcohol.
- Identify the structural feature that classifies alcohols as primary, secondary, or tertiary.
- Name alcohols with both common names and IUPAC names

An alcohol is an organic compound with a hydroxyl (OH) functional group on an aliphatic carbon atom. Because OH is the functional group of all alcohols, we often represent alcohols by the general formula ROH, where R is an alkyl group. Alcohols are common in nature. Most people are familiar with ethyl alcohol (ethanol), the active ingredient in alcoholic beverages, but this compound is only one of a family of organic compounds known as alcohols. The family also includes such familiar substances as cholesterol and the carbohydrates. Methanol (CH_3OH) and ethanol (CH_3CH_2OH) are the first two members of the homologous series of alcohols.

Nomenclature of Alcohols

Alcohols with one to four carbon atoms are frequently called by common names, in which the name of the alkyl group is followed by the word *alcohol*:



Structural formula of methyl alcohol, ethyl alcohol, propyl alcohol, and isopropyl alcohol with the methyl, ethyl propyl, and isopropyl groups highlighted in green.

According to the International Union of Pure and Applied Chemistry (IUPAC), alcohols are named by changing the ending of the parent alkane name to *-ol*. Here are some basic IUPAC rules for naming alcohols:

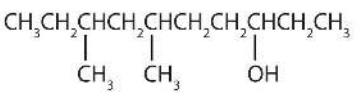
1. The longest continuous chain (LCC) of carbon atoms containing the OH group is taken as the parent compound—an alkane with the same number of carbon atoms. The chain is numbered from the end nearest the OH group.
2. The number that indicates the position of the OH group is prefixed to the name of the parent hydrocarbon, and the *-e* ending of the parent alkane is replaced by the suffix *-ol*. (In cyclic alcohols, the carbon atom bearing the OH group is designated C1, but the 1 is not used in the name.) Substituents are named and numbered as in alkanes.
3. If more than one OH group appears in the same molecule (polyhydroxy alcohols), suffixes such as *-diol* and *-triol* are used. In these cases, the *-e* ending of the parent alkane is retained.

Figure **3.2.1** shows some examples of the application of these rules.

Structures of 2 methylbutan-2-ol, 3 5-dimethylhexan-1-ol, 6 methylheptan-3-ol, 2 bromo 5 chlorocyclopentanol are shown to highlight rules 1 and 2. 1 2 ethanediol and propane 1 2 3 triol are shown to highlight rule 3
Figure **3.2.1**: IUPAC Rules for Alcohols. The names and structures of some alcohols demonstrate the use of IUPAC rules.

Example 3.2.1

Give the IUPAC name for each compound.

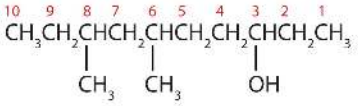
a. 

From left to right, there are ten carbon on the alkane straight chain with methyl groups emerging from carbon 3 and 5 and a hydroxyl group on carbon 8.

- $HOCH_2CH_2CH_2CH_2CH_2OH$

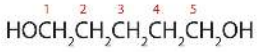
Solution

a. Ten carbon atoms in the LCC makes the compound a derivative of decane (rule 1), and the OH on the third carbon atom makes it a 3-decanol (rule 2).



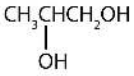
The carbon atoms are numbered from the end closest to the OH group. That fixes the two methyl (CH_3) groups at the sixth and eighth positions. The name is 6,8-dimethyl-3-decanol (not 3,5-dimethyl-8-decanol).

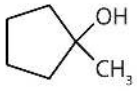
b. Five carbon atoms in the LCC make the compound a derivative of pentane. Two OH groups on the first and fifth carbon atoms make the compound a diol and give the name 1,5-pentanediol (rule 3).



? Exercise 3.2.1

Give the IUPAC name for each compound.

a. 

- 

✔ Example 3.2.2

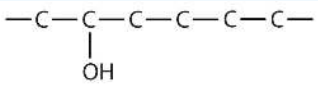
Draw the structure for each compound.

a. 2-hexanol
b. 3-methyl-2-pentanol

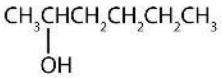
Solution

a. The ending *-ol* indicates an alcohol (the OH functional group), and the *hex-* stem tells us that there are six carbon atoms in the LCC. We start by drawing a chain of six carbon atoms: –C–C–C–C–C–C–.

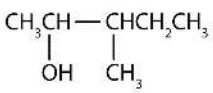
The 2 indicates that the OH group is attached to the second carbon atom.



Finally, we add enough hydrogen atoms to give each carbon atom four bonds.



- The numbers indicate that there is a methyl (CH_3) group on the third carbon atom and an OH group on the second carbon atom.



? Exercise 3.2.2

Draw the structure for each compound.

a. 3-heptanol

- 2-methyl-3-hexanol

Classification of Alcohols

Some of the properties of alcohols depend on the number of carbon atoms attached to the specific carbon atom that is attached to the OH group. Alcohols can be grouped into three classes on this basis.

- A primary (1°) alcohol is one in which the carbon atom (in red) with the OH group is attached to *one* other carbon atom (in blue). Its general formula is RCH_2OH.



- A secondary (2°) alcohol is one in which the carbon atom (in red) with the OH group is attached to *two* other carbon atoms (in blue). Its general formula is R_2CHOH.



- A tertiary (3°) alcohol is one in which the carbon atom (in red) with the OH group is attached to *three* other carbon atoms (in blue). Its general formula is R_3COH.

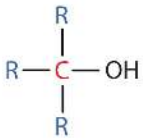
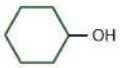


Table **3.2.1** names and classifies some of the simpler alcohols. Some of the common names reflect a compound's classification as secondary (*sec*-) or tertiary (*tert*-). These designations are not used in the IUPAC nomenclature system for alcohols. Note that there are four butyl alcohols in the table, corresponding to the four butyl groups: the butyl group ($CH_3CH_2CH_2CH_2$) discussed before, and three others:



Table **3.2.1**: Classification and Nomenclature of Some Alcohols

Condensed Structural Formula	Class of Alcohol	Common Name	IUPAC Name
CH_3OH	—	methyl alcohol	methanol
CH_3CH_2OH	primary	ethyl alcohol	ethanol
$CH_3CH_2CH_2OH$	primary	propyl alcohol	1-propanol
$(CH_3)_2CHOH$	secondary	isopropyl alcohol	2-propanol
$CH_3CH_2CH_2CH_2OH$	primary	butyl alcohol	1-butanol
$CH_3CH_2CHOHCH_3$	secondary	*sec*-butyl alcohol	2-butanol
$(CH_3)_2CHCH_2OH$	primary	isobutyl alcohol	2-methyl-1-propanol
$(CH_3)_3COH$	tertiary	*tert*-butyl alcohol	2-methyl-2-propanol
	secondary	cyclohexyl alcohol	cyclohexanol

Summary

In the IUPAC system, alcohols are named by changing the ending of the parent alkane name to *-ol*. Alcohols are classified according to the number of carbon atoms attached to the carbon atom that is attached to the OH group.

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3.3: Phenols

Learning Objectives

- To describe the structure and uses of some phenols

Compounds in which an OH group is attached directly to an aromatic ring are designated ArOH and called phenols. Phenols differ from alcohols in that they are slightly acidic in water. They react with aqueous sodium hydroxide (NaOH) to form salts.

$$\mathrm{ArOH\,(aq) + NaOH\,(aq) \rightarrow ArONa\,(aq) + H_2O}$$

The parent compound, C_6H_5OH, is itself called phenol. (An old name, emphasizing its slight acidity, was *carbolic acid*.) Phenol is a white crystalline compound that has a distinctive ("hospital smell") odor.

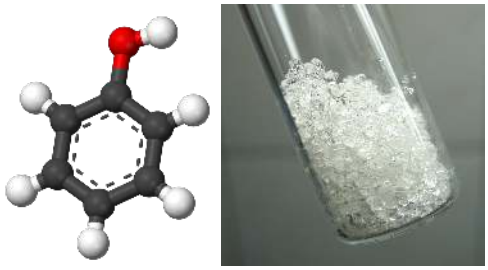


Figure 3.3.1: (Left) Structure of Phenol (right) Approximately two grams of phenol in glass vial. from Wikipedia

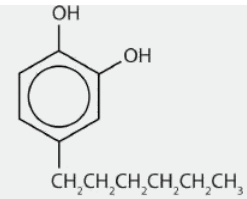
To Your Health: Phenols and Us

Phenols are widely used as antiseptics (substances that kill microorganisms on living tissue) and as disinfectants (substances intended to kill microorganisms on inanimate objects such as furniture or floors). The first widely used antiseptic was phenol. Joseph Lister used it for antiseptic surgery in 1867. Phenol is toxic to humans, however, and can cause severe burns when applied to the skin. In the bloodstream, it is a systemic poison—that is, one that is carried to and affects all parts of the body. Its severe side effects led to searches for safer antiseptics, a number of which have been found.



An operation in 1753, painted by Gaspare Traversi, of a surgery before antiseptics were used.

One safer phenolic antiseptic is 4-hexylresorcinol (4-hexyl-1,3-dihydroxybenzene; resorcinol is the common name for 1,3-dihydroxybenzene, and 4-hexylresorcinol has a hexyl group on the fourth carbon atom of the resorcinol ring). It is much more powerful than phenol as a germicide and has fewer undesirable side effects. Indeed, it is safe enough to be used as the active ingredient in some mouthwashes and throat lozenges.



The compound 4-hexylresorcinol is mild enough to be used as the active ingredient in antiseptic preparations for use on the skin.

The compound 4-hexylresorcinol is mild enough to be used as the active ingredient in antiseptic preparations for use on the skin.

Summary

Phenols are compounds in which an OH group is attached directly to an aromatic ring. Many phenols are used as antiseptics.

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3.4: NAMES AND PROPERTIES OF ETHERS

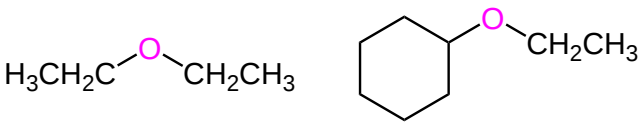
OBJECTIVES

After completing this section, you should be able to

1. write two acceptable names for a simple dialkyl ether, given its Kekulé, shorthand or condensed structure.
2. name a complicated ether by the IUPAC system, given its Kekulé, shorthand or condensed structure.
3. draw the Kekulé, condensed or shorthand structure of an ether, given an acceptable name.
4. explain why the boiling point of an ether is generally higher than that of an alkane of similar molecular mass.

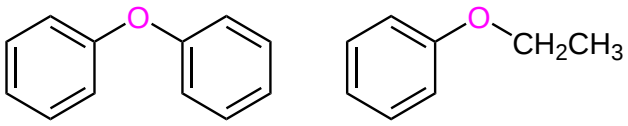
STRUCTURE OF ETHERS

Ethers are a class of organic compounds that contain an sp^3 hybridized oxygen between two alkyl groups and have the formula R-O-R'. These compounds are used in dyes, perfumes, oils, waxes and other industrial uses. Aliphatic ethers have no aryl groups directly attached to the ether oxygen.



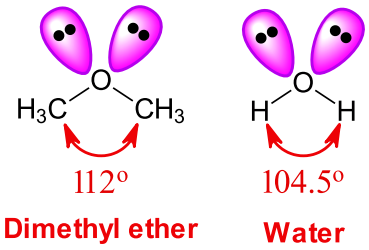
Examples of Aliphatic Ethers

Aromatic ethers have at least one aryl ring directly attached to the ether oxygen. In aryl ethers, the lone pair electrons on oxygen are conjugated with the aromatic ring which significantly changes the properties of the ether.

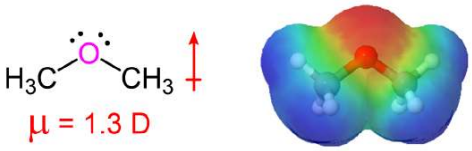


Example of Aromatic Ethers

The sp^3 hybridization of oxygen gives ethers roughly the same geometry as alcohols and water. The R-O-R' bond angle is close to what is expected in a tetrahedral geometry. The bond angle of dimethyl ether is 112° which is larger than the H-O-H bond angle in water (104.5°) due to the steric repulsion of the methyl groups.



The presence of an electronegative oxygen atom gives ethers a small dipole moment with the electron density primarily on oxygen (red and orange in the electrostatic potential map).



COMPARISONS OF PHYSICAL PROPERTIES OF ALCOHOLS AND ETHERS

Ethers, unlike alcohols, have no hydrogen atom on the oxygen atom (that is, no OH group). Therefore, there is no intermolecular hydrogen bonding between ether molecules, which makes their boiling points much lower than an alcohol with similar mass. Despite the presence of a

small dipole moment, ethers have boiling points that are about the same as alkanes of comparable molar mass. (Table 18.1.1).

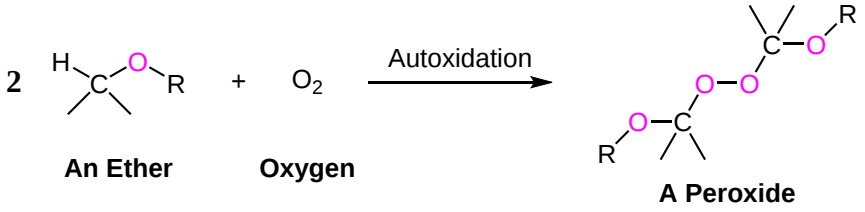
Table 18.1.1 : Comparison of Boiling Points of Alkanes, Alcohols, and Ethers

Condensed Structural Formula	Name	Molar Mass	Boiling Point (°C)	Intermolecular Hydrogen Bonding in Pure Liquid?
$CH_3CH_2CH_3$	propane	44	–42	no
CH_3OCH_3	dimethyl ether	46	–25	no
CH_3CH_2OH	ethyl alcohol	46	78	yes
$CH_3CH_2CH_2CH_2CH_3$	pentane	72	36	no
$CH_3CH_2OCH_2CH_3$	diethyl ether	74	35	no
$CH_3CH_2CH_2CH_2OH$	butyl alcohol	74	117	yes

Ether molecules do have an oxygen atom, however, and engage in hydrogen bonding with water molecules. Consequently, an ether has about the same solubility in water as the alcohol that is isomeric with it. For example, dimethyl ether and ethanol (both having the molecular formula C_2H_6O) are completely soluble in water, whereas diethyl ether and 1-butanol (both $C_4H_{10}O$) are barely soluble in water (8 g/100 mL of water).

PEROXIDE FORMATION

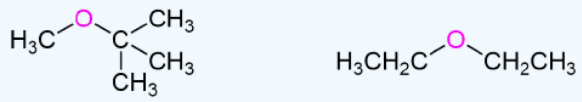
Many ethers can react with oxygen to form explosive peroxide compounds n a free radical process called autoxidation. For this reason ethers should not be stored for long periods of time and should not be stored in glass bottles. The danger is particularly acute when ether solutions are distilled to near dryness. The hydroperoxides can become more concentrated during a distillation because they tend to have a slightly higher boiling point than the corresponding ether. Before performing an ether distillation great care should be taken to test for the presence of peroxides.



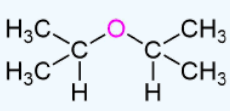
NAMING ETHERS

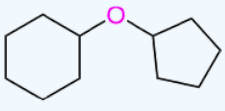
When no other functional group is present, simple ethers are often given common functional class names. Both alkyl groups attached to the oxygen atom are named as substituents (in alphabetical order) and then the word *ether* is added. The common names for alkyl substituents discussed in **Section 3.3** are often used.

EXAMPLE 18.1.1


Methyl *tert*-butyl ether

Diethyl ether


Diisopropyl ether

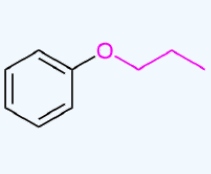

Cyclohexyl cyclopentyl ether

IUPAC nomenclature for ethers should be used for complicated ethers, compounds with more than one ether linkage, and compounds where other functional groups are present with an ether. In these cases, an RO group of the ether is named as an alkoxy substituent. Common alkoxy substituents are given names derived from their alkyl component. The suffix *-yl* is replaced with *-oxy*. (Table 18.1.2):

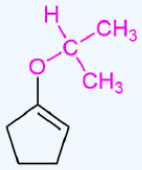
Table 18.1.2 : Common Alkyl and Alkoxy Groups

Alkyl Group	Name	Alkoxy Group	Name
CH_3–	Methyl	CH_3O–	Methoxy
CH_3CH_2–	Ethyl	CH_3CH_2O–	Ethoxy
$(CH_3)_2CH$–	Isopropyl	$(CH_3)_2CHO$–	Isopropoxy
$(CH_3)_3C$–	tert-Butyl	$(CH_3)_3CO$–	tert-Butoxy
C_6H_5–	Phenyl	C_6H_5O–	Phenoxy

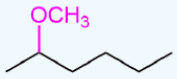
EXAMPLE 18.1.2



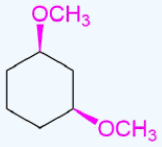
Propoxybenzene



1-Isopropoxycyclopentene



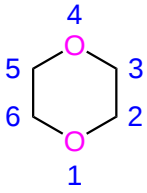
2-Methoxyhexane



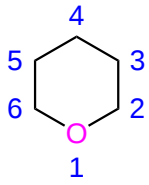
***Cis*-1,3-Dimethoxycyclohexane**

CYCLIC ETHERS

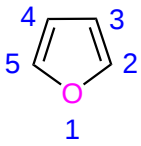
Cyclic ethers are a type of heterocycle with one or more oxygens located in the ring. Many cyclic ethers have common names and are often used as solvents due to their inert nature. These ring structures are also found in many biological molecules such as sugars and DNA. The rings are numbered so that an oxygen gets position 1.



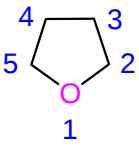
Dioxane



Tetrahydropyran

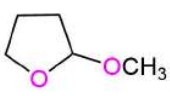


Furan

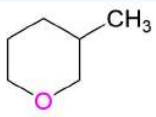


Tetrahydrofuran

EXAMPLE 18.1.3



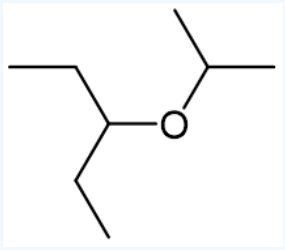
2-Methoxytetrahydrofuran



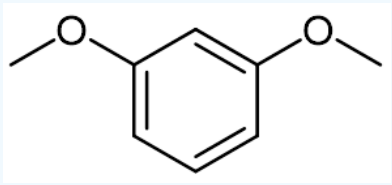
3-Methyltetrahydropyran

EXERCISE 18.1.1

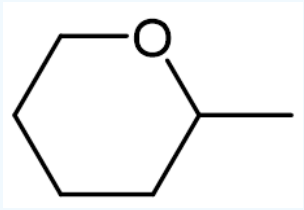
Name the following ethers:



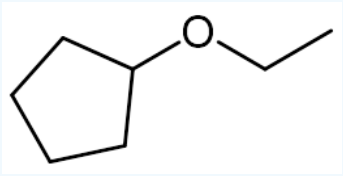
b)



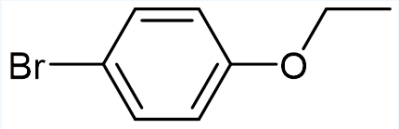
c)



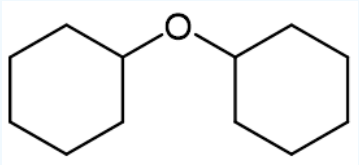
d)



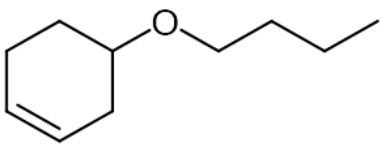
e)



f)



g)



Answers

a) 3-Isopropoxypentane

b) 1,3-Dimethoxybenzene

c) 2-Methyltetrahydropyran

d) Cyclopentyl ethyl ether

e) 4-Bromo-1-ethoxybenzene

f) Dicyclohexyl ether

g) 4-Butoxycyclohexene

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3.5: THIOLS AND SULFIDES

OBJECTIVES

After completing this section, you should be able to

1. a. write the IUPAC name of a thiol, given its Kekulé, condensed or shorthand structure.
   b. draw the structure of a thiol, given its IUPAC name.
   c. write an equation to represent the formation of a thiol by the reaction of hydrosulfide anion with an alkyl halide.
   d. write an equation to illustrate the preparation of a thiol by the reaction of thiourea with an alkyl halide.
2. write an equation to show the interconversion between thiols and disulfides.
3. a. write the name of a sulfide, given its structure.
   b. draw the structure of a sulfide, given its name.
   c. write an equation showing how a sulfide may be prepared by the reaction of a thiolate anion on an alkyl halide.
   d. identify the product from the reaction of a given alkyl halide with a given thiolate anion.
   e. identify the reagents necessary to prepare a given sulfide.
   f. write an equation to illustrate the formation of a trialkylsulfonium salt from a sulfide and an alkyl halide.

KEY TERMS

Note: All of these terms are defined in the "Study Notes," below.

- disulfide
- mercapto group
- (organic) sulfide
- sulfone
- sulfoxide
- thiol
- thiolate anion
- trialkylsulfonium ion (trialkylsulfonium salt)

STUDY NOTES

The chemistry of sulfur-containing organic compounds is often omitted from introductory organic chemistry courses. However, we have included a short section on these compounds, not for the sake of increasing the amount of material to be digested, but because much of the chemistry of these substances can be predicted from a knowledge of their oxygen-containing analogues.

A thiol is a compound which contains an SH functional group. The SH group itself is called a mercapto group. A disulfide is a compound containing an S-S linkage.

(Organic) sulfides have the structure R-S-R′, and are therefore the sulfur analogues of ethers. The nomenclature of sulfides can be easily understood if one understands the nomenclature of the corresponding ethers. Notice that the term "thio" is also used in inorganic chemistry. For example, SO_4^{2-} is the sulfate ion; while $S_2O_3^{2-}$, in which one of the oxygen atoms of a sulfate ion has been replaced by a sulfur atom, is called thiosulfate. Thiolate anions, RS^-, are analogous to alkoxy anions, RO^-. Thiolate anions are better nucleophiles than are alkoxy anions.

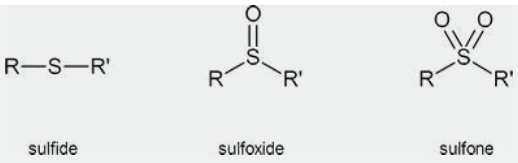
If you have trouble understanding why trialkylsulfonium ions are formed, think of them as being somewhat similar to the hydronium ions that are formed by protonating water:



hydronium ion trialkylsulfonium ion

Later we shall see examples of tetraalkylammonium ions, R_4N^+, which again may be regarded as being similar to hydronium ions.

Sulfoxides and sulfones are obtained by oxidizing organic sulfides. You need not memorize the methods used to carry out these oxidations.



sulfide sulfoxide sulfone

Table 18.1, below, provides a quick comparison of oxygen-containing and sulfur-containing organic compounds.

Table **3.5.1**: Comparison of compounds containing oxygen and sulfur

Oxygen-containing Compound	Sulfur Analogue
ether, R-O-R′	sulfide, R-S-R′
alkoxy anion, RO^-	thiolate anion, RS^-
alcohol, ROH	thiol, RSH
hydroxy group, OH^-	mercapto group, SH^-
peroxide, R-O-O-R′	disulfide, R-S-S-R′

Note that when we name thiols, we include the “e” of the alkane name. Thus, CH_3CH_2SH is called “ethanethiol,” not “ethanthiol.”

Thiols and sulfides are the "sulfur equivalent" of alcohols and ethers. You can replace the oxygen atom of an alcohol with a sulfur atom to make a thiol; similarly, you can replace the oxygen atom in an ether with S to make the corresponding alkyl sulfide. This is because thiols contain the C-S-H functional group, while sulfides contain the C-S-C group.

OXIDATION STATES OF SULFUR COMPOUNDS

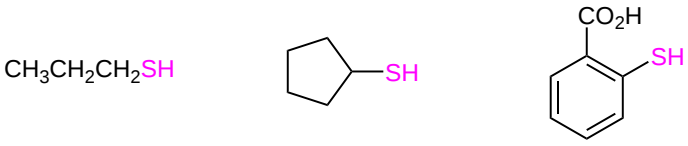
Oxygen assumes only two oxidation states in its organic compounds (–1 in peroxides and –2 in other compounds). Sulfur, on the other hand, is found in oxidation states ranging from –2 to +6, as shown in the following table (some simple inorganic compounds are displayed in orange).

Sulfur Oxidation States in Organic Compounds

-2	-1	0	+2	+4	+6
H_2S R–S–H thiols R–S–R sulfides R–S(+)(R)–R sulfonium ions	R–S–S–R disulfides	S elemental R–S(=O)–R sulfoxides R–S–OH sulfenic acids	R–S(=O)(=O)–R sulfones R–S(=O)–OH sulfinic acids	SO_2 R–S(=O)(=O)–OH sulfonic acids R-O–S(=O)–O-R sulfite esters	SO_3 R-O–S(=O)(=O)–O-R sulfate esters

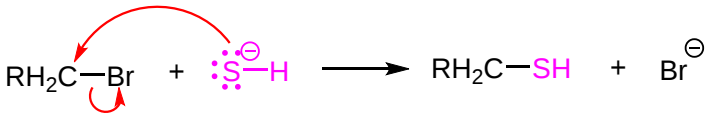
THIOLS

Thiols are often called “mercaptans,” a reference to the Latin term mercurium captans (capturing mercury), since the -SH group forms strong bonds with mercury and its ions. Thiols are analogous to alcohols. Thiols are weakly acidic (pK_a ~ 10) and are much stronger acids than alcohols (pKa ~ 16). However, thiols usually do not form hydrogen bonds due to the sulfur atom not have sufficient electronegativity. Thiols named using the same rules as alcohols except the parent chain is named as alkane with the suffix -thiol added. As a substituent the -SH group is called a **mercapto** group.



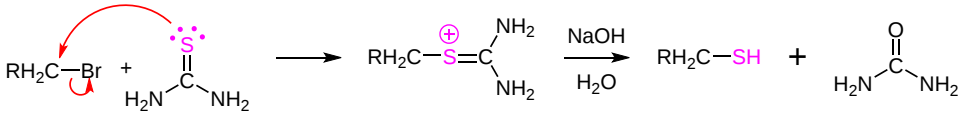
Propanethiol **Cyclopentanethiol** ***o*-Mercaptobenzoic acid**

Thiols are usually prepared by using the hydrosulfide anion (-SH) as a nucleophile in an S_N2 reaction with alkyl halides.



Hydrosulfide ion **Thiol**

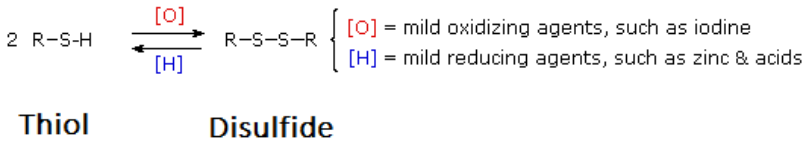
One problem with this reaction is that the thiol product can deprotonate and undergo a second S_N2 reaction with an additional alkyl halide to produce a sulfide side product. This problem can be solved by using thiourea, $(NH_2)_2C{=}S$, as the nucleophile. The S_N2 reaction first produces an alkyl isothiourea salt as an intermediate. This salt is then hydrolyzed to form the thiol by a reaction with aqueous base.



Thiourea **Thiol** **Urea**

DISULFIDES

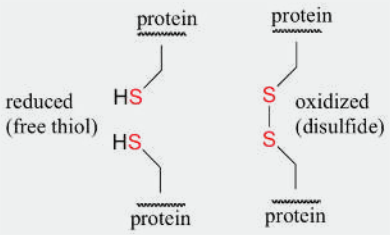
Thiols (R-S-H) can be oxidized to form disulfides (R-S-S-R') through reaction with Br_2 or I_2. Note, an equivalent oxidation of alcohols (R-O-H) to peroxides (R-O-O-R') is not normally observed. The reasons for this different behavior becomes clear when looking at bond strengths. The S–S single bond in disulfides is nearly twice as strong as the O–O bond in peroxides. Also, the O–H bond in alcohols is more than 25 kcal/mole stronger than the S–H bond in thiols. Thus, thermodynamics favors disulfide formation over peroxide. Disulfides can easily be reduced back to a thiols through reaction with zinc and acid.



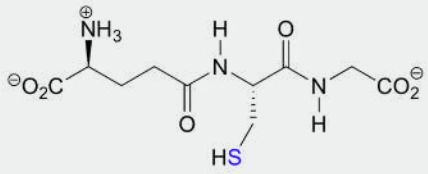
Thiol **Disulfide**

DISULFIDE BRIDGES IN PROTEINS

Disulfide (sulfur-sulfur) linkages between two cysteine residues are an integral component of the three-dimensional structure of many proteins. The interconversion between thiols and disulfide groups is a redox reaction: the thiol is the reduced state, and the disulfide is the oxidized state.

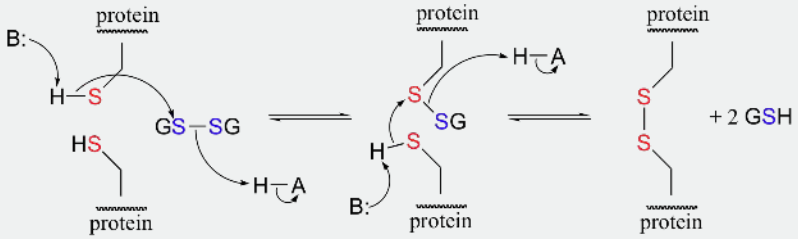


Notice that in the oxidized (disulfide) state, each sulfur atom has lost a bond to hydrogen and gained a bond to a sulfur - this is why the disulfide state is considered to be oxidized relative to the thiol state. The redox agent that mediates the formation and degradation of disulfide bridges in most proteins is glutathione, a versatile coenzyme. Recall that the important functional group in glutathione is the thiol, highlighted in blue in the figure below. In its reduced (free thiol) form, glutathione is abbreviated 'GSH'.



Glutathione (GSH)

In its oxidized form, glutathione exists as a dimer of two molecules linked by a disulfide group, and is abbreviated 'GSSG'. A new disulfide in a protein forms via a 'disulfide exchange' reaction with GSSG, a process that can be described as a combination of two S_N2-like attacks. The end result is that a new cysteine-cysteine disulfide forms at the expense of the disulfide in GSSG.



In its reduced (thiol) state, glutathione can reduce disulfides bridges in proteins through the reverse of the above reaction.

SULFIDES

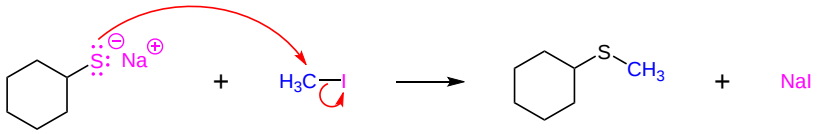
Sulfides are named using the same rules as ethers except *sulfide* is used in the place of *ether*. For more complex substances, alkylthio is used in place of alkoxy.



Diethyl sulfide **Ethyl phenyl sulfide** **3-(Methylthio)cyclopentene**

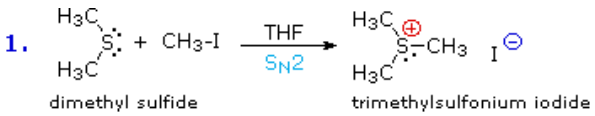
Sulfur analogs of ethers are called **sulfides**. Sulfides are less common than thiols as naturally occurring compounds. However, sulfides—especially disulfides (C-S-S-C)—have important biological functions, mainly in reducing agents (antioxidants).

Since thiols are weakly acidic their conjugate bases, called thiolate ions, can be easily formed through reaction with a strong base such as NaH. Thiolates have proven to be excellent nucleophiles and easily undergo S_N2 reactions with primary and secondary alkyl halides to form sulfides. The reaction is analogous to the Williamson ether synthesis previously discussed in this chapter (**Section 18-2**)



Cyclohexanethiolate **Cyclohexyl methyl sulfide**

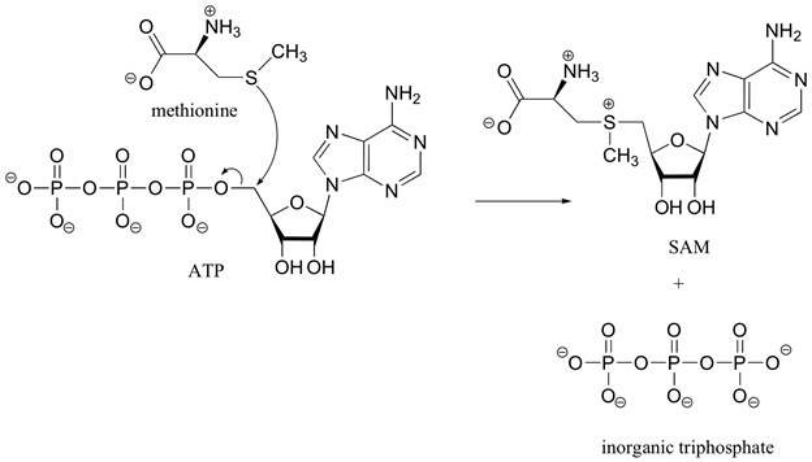
The chemical behavior of sulfides contrasts with that of ethers in some important ways. Because sulfur's valence electrons involve 3P orbitals they are further away and less tightly held than the valence electrons on oxygen which involve 2P orbitals. This makes the nucleophilicity of sulfur atoms much greater than that of oxygen, leading to a number of interesting and useful electrophilic substitutions of sulfur that are not normally observed for oxygen. For instance, sulfides, unlike ethers, easily react with primary alkyl halides through an S_N2 mechanism to give ternary sulfonium ions (R_3S^+) in the same manner that 3º-amines can be alkylated to form quaternary ammonium salts. Although equivalent oxonium salts of ethers are known, they are only prepared under extreme conditions, and are exceptionally reactive.



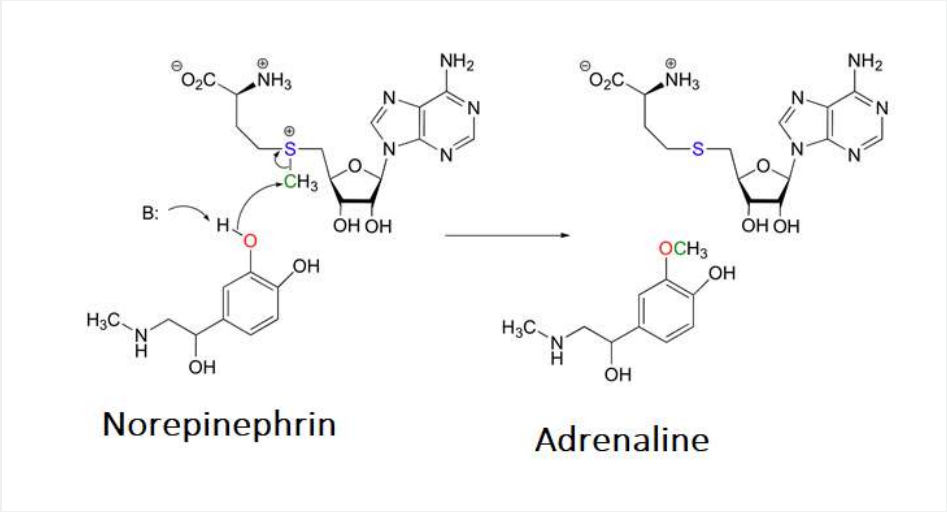
dimethyl sulfide trimethylsulfonium iodide

BIOLOGICAL SULFONIUM ION FORMATION

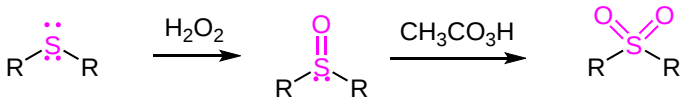
In biological systems the sulfonium ion, *S*-adenosylmethionine (SAM), is formed by a S_N2 reaction between the nucleophilic sulfur atom of the amino acid methionine and the electrophilic methene (CH_2) carbon of adenosine triphosphate (ATP). This reaction is unusually in that the triphosphate ion is removed from ATP as a leaving group. In most cases biological nucleophiles attack an electrophilic phosphorus on ATP causing a diphosphate ion to be removed as the leaving group.



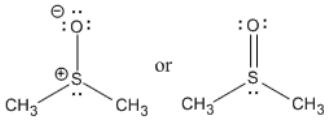
The sulfonium ion in SAM is an effective methylating agent. Through an S_N2 reaction, biological nucleophiles can attack the electrophilic methyl group bonded to the positively charged sulfonium ion and cause the removal of a neutral sulfide as a leaving group. An example of this reaction is the catechol-O-methyltransferase catalyzed O-methylation of norepinephrin by SAM to produce adrenaline.



Sulfides can be easily oxidized. Reacting a sulfide with hydrogen peroxide, H_2O_2, as room temperature produces a sulfoxide (R_2SO). The oxidation can be continued by reaction with a peroxyacid, such as peracetic acid (CH_3CO_3H), to produce the sulfone (R_2SO_2).



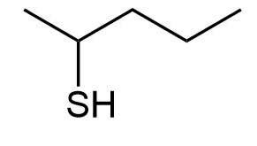
A common example of a sulfoxide is the solvent dimethyl sulfoxide (DMSO). DMSO is considered a polar aprotic solvent.



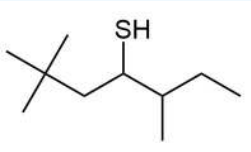
EXERCISE 3.5.1

Give IUPAC names the following compounds:

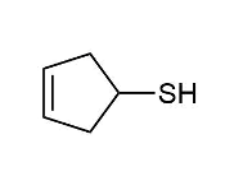
a)



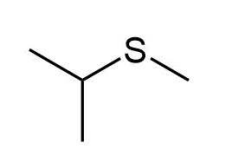
b)



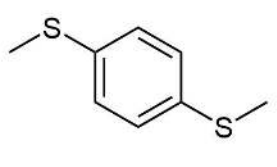
c)



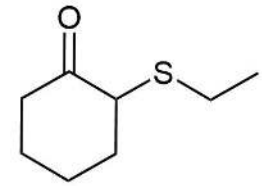
d)



e)



f)



Answer

a) 2-Pentanethiol

b) 2,2,5-Trimethyl-4-heptanethiol

c) 3-Cyclopentene-1-thiol

d) Methyl isopropyl sulfide

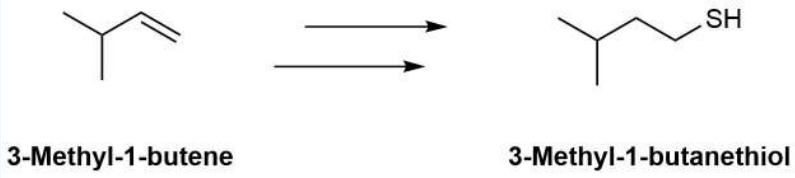
e) *p*-Di(methylthio)benzene

f) 2-(Ethylthio)cyclohexanone

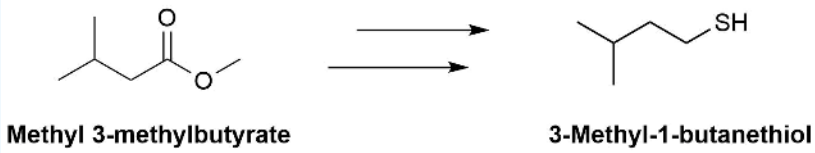
? EXERCISE 3.5.2

The molecule 3-methyl-1-butanethiol has been shown to be one of the components of skunk spray. How would make the following conversions?

a)



b)



Answers

a) 1) HBr & Peroxides, 2) $(NH_2)_2C=S$, 3) NaOH & H_2O

b) 1) $LiAlH_4$, 2) PBr_3, 3) $(NH_2)_2C=S$, 4) NaOH & H_2O

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3.6: Intermolecular Forces- The Forces that Hold Condensed Phases Together

Learning Objectives

- To describe the intermolecular forces in liquids.

The properties of liquids are intermediate between those of gases and solids, but are more similar to solids. In contrast to *intra*molecular forces, such as the covalent bonds that hold atoms together in molecules and polyatomic ions, *inter*molecular forces hold molecules together in a liquid or solid. Intermolecular forces are generally much weaker than covalent bonds. For example, it requires 927 kJ to overcome the intramolecular forces and break both O–H bonds in 1 mol of water, but it takes only about 41 kJ to overcome the intermolecular attractions and convert 1 mol of liquid water to water vapor at 100°C. (Despite this seemingly low value, the intermolecular forces in liquid water are among the strongest such forces known!) Given the large difference in the strengths of intra- and intermolecular forces, changes between the solid, liquid, and gaseous states almost invariably occur for molecular substances *without breaking covalent bonds*.

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

Intermolecular forces determine bulk properties, such as the melting points of solids and the boiling points of liquids. Liquids boil when the molecules have enough thermal energy to overcome the intermolecular attractive forces that hold them together, thereby forming bubbles of vapor within the liquid. Similarly, solids melt when the molecules acquire enough thermal energy to overcome the intermolecular forces that lock them into place in the solid.

Intermolecular forces are electrostatic in nature; that is, they arise from the interaction between positively and negatively charged species. Like covalent and ionic bonds, intermolecular interactions are the sum of both attractive and repulsive components. Because electrostatic interactions fall off rapidly with increasing distance between molecules, intermolecular interactions are most important for solids and liquids, where the molecules are close together. These interactions become important for gases only at very high pressures, where they are responsible for the observed deviations from the ideal gas law at high pressures.

In this section, we explicitly consider three kinds of intermolecular interactions. There are two additional types of electrostatic interaction that you are already familiar with: the ion–ion interactions that are responsible for ionic bonding, and the ion–dipole interactions that occur when ionic substances dissolve in a polar substance such as water. The first two are often described collectively as van der Waals forces.

Dipole–Dipole Interactions

Polar covalent bonds behave as if the bonded atoms have localized fractional charges that are equal but opposite (i.e., the two bonded atoms generate a *dipole*). If the structure of a molecule is such that the individual bond dipoles do not cancel one another, then the molecule has a net dipole moment. Molecules with net dipole moments tend to align themselves so that the positive end of one dipole is near the negative end of another and vice versa, as shown in Figure **3.6.1***a*.

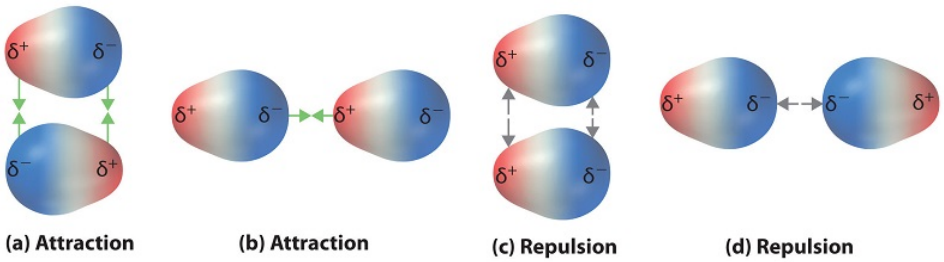


Figure **3.6.1**: Attractive and Repulsive Dipole–Dipole Interactions. (a and b) Molecular orientations in which the positive end of one dipole (δ^+) is near the negative end of another (δ^-) (and vice versa) produce attractive interactions. (c and d) Molecular orientations that juxtapose the positive or negative ends of the dipoles on adjacent molecules produce repulsive interactions. (CC BY-SA-NC; anonymous)

These arrangements are more stable than arrangements in which two positive or two negative ends are adjacent (Figure **3.6.1***c*). Hence dipole–dipole interactions, such as those in Figure **3.6.1***b*, are *attractive intermolecular interactions*, whereas those in Figure **3.6.1***d* are *repulsive intermolecular interactions*. Because molecules in a liquid move freely and continuously, molecules always experience both attractive and repulsive dipole–dipole interactions simultaneously, as shown in Figure **3.6.2**. On average, however, the attractive interactions dominate.

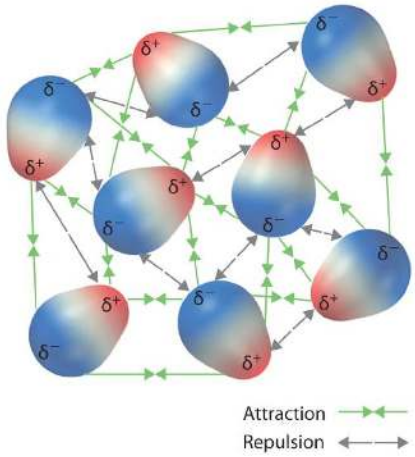


Figure **3.6.2**: Both attractive and repulsive dipole–dipole interactions occur in a liquid sample with many molecules. (CC BY-SA-NC; anonymous)

The green arrows pointing towards each other represent attraction. The gray arrows pointing away from each other represent repulsion

Because each end of a dipole possesses only a fraction of the charge of an electron, dipole–dipole interactions are substantially weaker than the interactions between two ions, each of which has a charge of at least ±1, or between a dipole and an ion, in which one of the species has at least a full positive or negative charge. In addition, the attractive interaction between dipoles falls off much more rapidly with increasing distance than do the ion–ion interactions. Recall that the attractive energy between two ions is proportional to $1/r$, where r is the distance between the ions. Doubling the distance ($r \rightarrow 2r$) decreases the attractive energy by one-half. In contrast, the energy of the interaction of two dipoles is proportional to $1/r^3$, so doubling the distance between the dipoles decreases the strength of the interaction by 2^3, or 8-fold. Thus a substance such as **HCl**, which is partially held together by dipole–dipole interactions, is a gas at room temperature and 1 atm pressure. Conversely, **NaCl**, which is held together by interionic interactions, is a high-melting-point solid. Within a series of compounds of similar molar mass, the strength of the intermolecular interactions increases as the dipole moment of the molecules increases, as shown in Table **3.6.1**.

Table **3.6.1**: Relationships Between the Dipole Moment and the Boiling Point for Organic Compounds of Similar Molar Mass

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

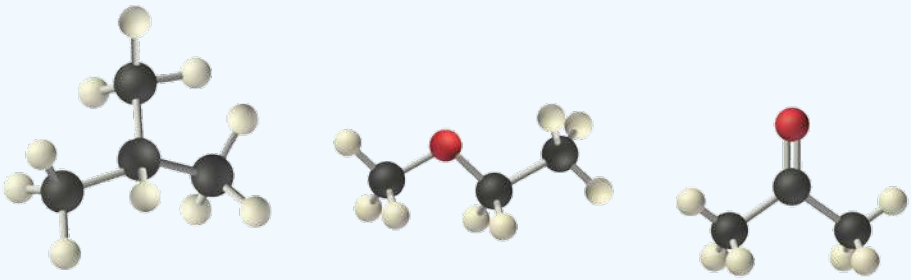
> *The attractive energy between two ions is proportional to 1/r, whereas the attractive energy between two dipoles is proportional to 1/r6.*



Video Discussing Dipole Intermolecular Forces. Source: Dipole Intermolecular Force, YouTube(opens in new window) [youtu.be]

Example 3.6.1

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



2-Methylpropane Ethyl methyl ether Acetone

Given: compounds.

Asked for: order of increasing boiling points.

Strategy:

Compare the molar masses and the polarities of the compounds. Compounds with higher molar masses and that are polar will have the highest boiling points.

Solution:

The three compounds have essentially the same molar mass (58–60 g/mol), so we must look at differences in polarity to predict the strength of the intermolecular dipole–dipole interactions and thus the boiling points of the compounds.

The first compound, 2-methylpropane, contains only C–H bonds, which are not very polar because C and H have similar electronegativities. It should therefore have a very small (but nonzero) dipole moment and a very low boiling point.

Ethyl methyl ether has a structure similar to H_2O; it contains two polar C–O single bonds oriented at about a 109° angle to each other, in addition to relatively nonpolar C–H bonds. As a result, the C–O bond dipoles partially reinforce one another and generate a significant dipole moment that should give a moderately high boiling point.

Acetone contains a polar C=O double bond oriented at about 120° to two methyl groups with nonpolar C–H bonds. The C–O bond dipole therefore corresponds to the molecular dipole, which should result in both a rather large dipole moment and a high boiling point.

Thus we predict the following order of boiling points:

2-methylpropane < ethyl methyl ether < acetone

This result is in good agreement with the actual data: 2-methylpropane, boiling point = −11.7°C, and the dipole moment (μ) = 0.13 D; methyl ethyl ether, boiling point = 7.4°C and μ = 1.17 D; acetone, boiling point = 56.1°C and μ = 2.88 D.

? Exercise 3.6.1

Arrange carbon tetrafluoride (CF_4), ethyl methyl sulfide ($CH_3SC_2H_5$), dimethyl sulfoxide [$(CH_3)_2S{=}O$], and 2-methylbutane [isopentane, $(CH_3)_2CHCH_2CH_3$] in order of decreasing boiling points.

Answer

dimethyl sulfoxide (boiling point = 189.9°C) > ethyl methyl sulfide (boiling point = 67°C) > 2-methylbutane (boiling point = 27.8°C) > carbon tetrafluoride (boiling point = −128°C)

London Dispersion Forces

Thus far, we have considered only interactions between polar molecules. Other factors must be considered to explain why many nonpolar molecules, such as bromine, benzene, and hexane, are liquids at room temperature; why others, such as iodine and naphthalene, are solids. Even the noble gases can be liquefied or solidified at low temperatures, high pressures, or both (Table **3.6.2**).

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

Table **3.6.2**: Normal Melting and Boiling Points of Some Elements and Nonpolar Compounds

Substance	Molar Mass (g/mol)	Melting Point (°C)	Boiling Point (°C)
Ar	40	−189.4	−185.9
Xe	131	−111.8	−108.1
N_2	28	−210	−195.8
O_2	32	−218.8	−183.0
F_2	38	−219.7	−188.1
I_2	254	113.7	184.4
CH_4	16	−182.5	−161.5

Consider a pair of adjacent He atoms, for example. On average, the two electrons in each He atom are uniformly distributed around the nucleus. Because the electrons are in constant motion, however, their distribution in one atom is likely to be asymmetrical at any given instant, resulting in an instantaneous dipole moment. As shown in part (a) in Figure **3.6.3**, the instantaneous dipole moment on one atom can interact with the electrons in an adjacent atom, pulling them toward the positive end of the instantaneous dipole or repelling them from the negative end. The net effect is that the first atom causes the temporary formation of a dipole, called an induced dipole, in the second. Interactions between these temporary dipoles cause atoms to be attracted to one another. These attractive interactions are weak and fall off rapidly with increasing distance. London was able to show with quantum mechanics that the attractive energy between molecules due to temporary dipole–induced dipole interactions falls off as $1/r^6$. Doubling the distance therefore decreases the attractive energy by 2^6, or 64-fold.

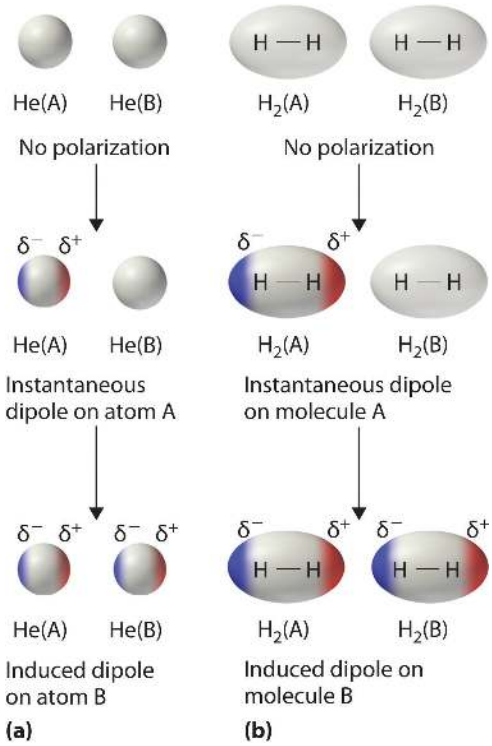


Figure **3.6.3**: Instantaneous Dipole Moments. The formation of an instantaneous dipole moment on one He atom (a) or an H_2 molecule (b) results in the formation of an induced dipole on an adjacent atom or molecule.

Instantaneous dipole–induced dipole interactions between nonpolar molecules can produce intermolecular attractions just as they produce interatomic attractions in monatomic substances like Xe. This effect, illustrated for two H_2 molecules in part (b) in Figure **3.6.3**, tends to become more pronounced as atomic and molecular masses increase (Table **3.6.2**). For example, Xe boils at −108.1°C, whereas He boils at −269°C. The reason for this trend is that the strength of London dispersion forces is related to the ease with which the electron distribution in a given atom can be perturbed. In small atoms such as He, the two 1*s* electrons are held close to the nucleus in a very small volume, and electron–electron repulsions are strong enough to prevent significant asymmetry in their distribution. In larger atoms such as Xe, however, the outer electrons are much less strongly attracted to the nucleus because of filled intervening shells. As a result, it is relatively easy to temporarily deform the electron distribution to generate an instantaneous or induced dipole. The ease of deformation of the electron distribution in an atom or molecule is called its polarizability. Because the electron distribution is more easily perturbed in large, heavy species than in small, light species, we say that heavier substances tend to be much more *polarizable* than lighter ones.

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

The polarizability of a substance also determines how it interacts with ions and species that possess permanent dipoles. Thus, London dispersion forces are responsible for the general trend toward higher boiling points with increased molecular mass and greater surface area in a homologous series of compounds, such as the alkanes (part (a) in Figure **3.6.4**). The strengths of London dispersion forces also depend significantly on molecular shape because shape determines how much of one molecule can interact with its neighboring molecules at any given time. For example, part (b) in Figure **3.6.4** shows 2,2-dimethylpropane (neopentane) and *n*-pentane, both of which have the empirical formula C_5H_{12}. Neopentane is almost spherical, with a small surface area for intermolecular interactions, whereas *n*-pentane has an extended conformation that enables it to come into close contact with other *n*-pentane molecules. As a result, the boiling point of neopentane (9.5°C) is more than 25°C lower than the boiling point of *n*-pentane (36.1°C).

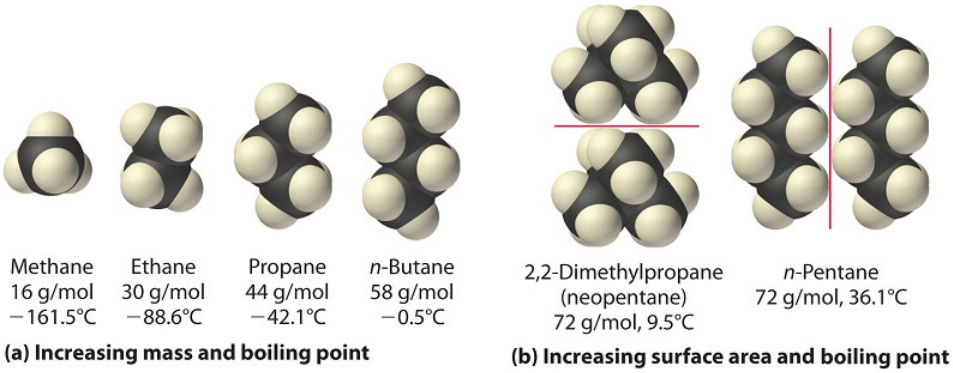


Figure **3.6.4**: Mass and Surface Area Affect the Strength of London Dispersion Forces. (a) In this series of four simple alkanes, larger molecules have stronger London forces between them than smaller molecules do, and consequently have higher boiling points. (b) Linear *n*-pentane molecules have a larger surface area and stronger intermolecular forces than spherical neopentane molecules. As a result, neopentane is a gas at room temperature, whereas *n*-pentane is a volatile liquid.

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



Video Discussing London/Dispersion Intermolecular Forces. Source: Dispersion Intermolecular Force, YouTube(opens in new window) [youtu.be]

Example 3.6.2

Arrange *n*-butane, propane, 2-methylpropane [isobutene, $(CH_3)_2CHCH_3$], and *n*-pentane in order of increasing boiling points.

Given: compounds

Asked for: order of increasing boiling points

Strategy:

Determine the intermolecular forces in the compounds, and then arrange the compounds according to the strength of those forces. The substance with the weakest forces will have the lowest boiling point.

Solution:

The four compounds are alkanes and nonpolar, so London dispersion forces are the only important intermolecular forces. These forces are generally stronger with increasing molecular mass, so propane should have the lowest boiling point and *n*-pentane should have the highest, with the two butane isomers falling in between. Of the two butane isomers, 2-methylpropane is more compact, and *n*-butane has the more extended shape. Consequently, we expect intermolecular interactions for *n*-butane

to be stronger due to its larger surface area, resulting in a higher boiling point. The overall order is thus as follows, with actual boiling points in parentheses: propane (−42.1°C) < 2-methylpropane (−11.7°C) < *n*-butane (−0.5°C) < *n*-pentane (36.1°C).

? Exercise 3.6.2

Arrange GeH_4, $SiCl_4$, SiH_4, CH_4, and $GeCl_4$ in order of decreasing boiling points.

Answer

$GeCl_4$ (87°C) > $SiCl_4$ (57.6°C) > GeH_4 (−88.5°C) > SiH_4 (−111.8°C) > CH_4 (−161°C)

Hydrogen Bonds

Molecules with hydrogen atoms bonded to electronegative atoms such as O, N, and F (and to a much lesser extent, Cl and S) tend to exhibit unusually strong intermolecular interactions. These result in much higher boiling points than are observed for substances in which London dispersion forces dominate, as illustrated for the covalent hydrides of elements of groups 14–17 in Figure **3.6.5**. Methane and its heavier congeners in group 14 form a series whose boiling points increase smoothly with increasing molar mass. This is the expected trend in nonpolar molecules, for which London dispersion forces are the exclusive intermolecular forces. In contrast, the hydrides of the lightest members of groups 15–17 have boiling points that are more than 100°C greater than predicted on the basis of their molar masses. The effect is most dramatic for water: if we extend the straight line connecting the points for H_2Te and H_2Se to the line for period 2, we obtain an estimated boiling point of −130°C for water! Imagine the implications for life on Earth if water boiled at −130°C rather than 100°C.

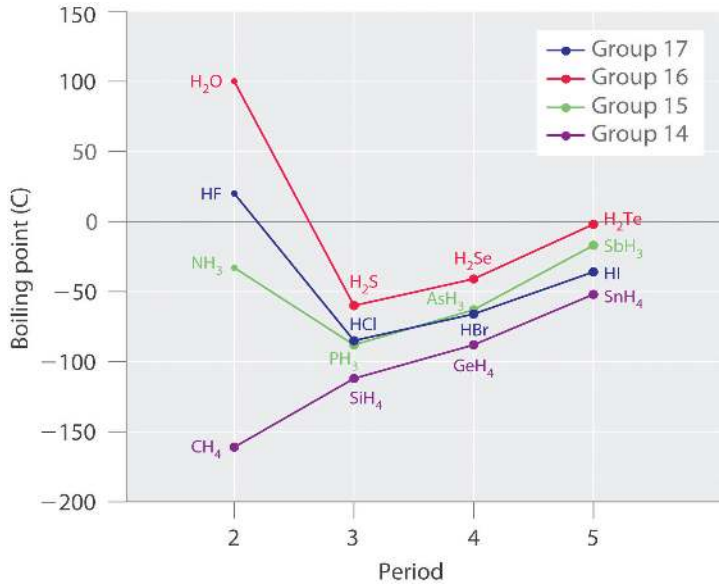


Figure **3.6.5**: The Effects of Hydrogen Bonding on Boiling Points. These plots of the boiling points of the covalent hydrides of the elements of groups 14–17 show that the boiling points of the lightest members of each series for which hydrogen bonding is possible (HF, NH_3, and H_2O) are anomalously high for compounds with such low molecular masses.

Group 14 is in purple, group 15 is in green, group 16 is red, and group 17 is blue. Graph of boiling point against period.

Why do strong intermolecular forces produce such anomalously high boiling points and other unusual properties, such as high enthalpies of vaporization and high melting points? The answer lies in the highly polar nature of the bonds between hydrogen and very electronegative elements such as O, N, and F. The large difference in electronegativity results in a large partial positive charge on hydrogen and a correspondingly large partial negative charge on the O, N, or F atom. Consequently, H–O, H–N, and H–F bonds have very large bond dipoles that can interact strongly with one another. Because a hydrogen atom is so small, these dipoles can also approach one another more closely than most other dipoles. The combination of large bond dipoles and short dipole–dipole distances results in very strong dipole–dipole interactions called hydrogen bonds, as shown for ice in Figure **3.6.6**. A hydrogen bond is usually indicated by a dotted line between the hydrogen atom attached to O, N, or F (the *hydrogen bond donor*) and the atom that has the lone pair of electrons (the *hydrogen bond acceptor*). Because each water molecule contains two hydrogen atoms and two

lone pairs, a tetrahedral arrangement maximizes the number of hydrogen bonds that can be formed. In the structure of ice, each oxygen atom is surrounded by a distorted tetrahedron of hydrogen atoms that form bridges to the oxygen atoms of adjacent water molecules. The bridging hydrogen atoms are *not* equidistant from the two oxygen atoms they connect, however. Instead, each hydrogen atom is 101 pm from one oxygen and 174 pm from the other. In contrast, each oxygen atom is bonded to two H atoms at the shorter distance and two at the longer distance, corresponding to two O–H covalent bonds and two O···H hydrogen bonds from adjacent water molecules, respectively. The resulting open, cagelike structure of ice means that the solid is actually slightly less dense than the liquid, which explains why ice floats on water, rather than sinks.

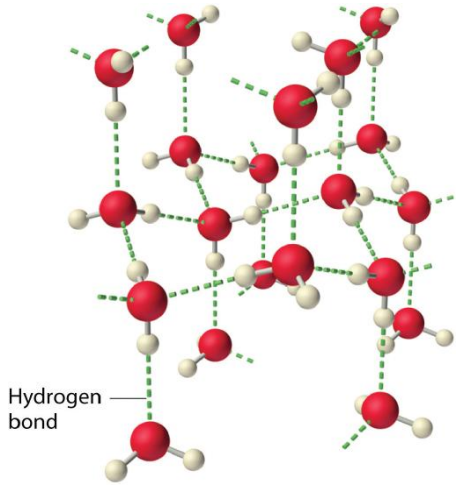
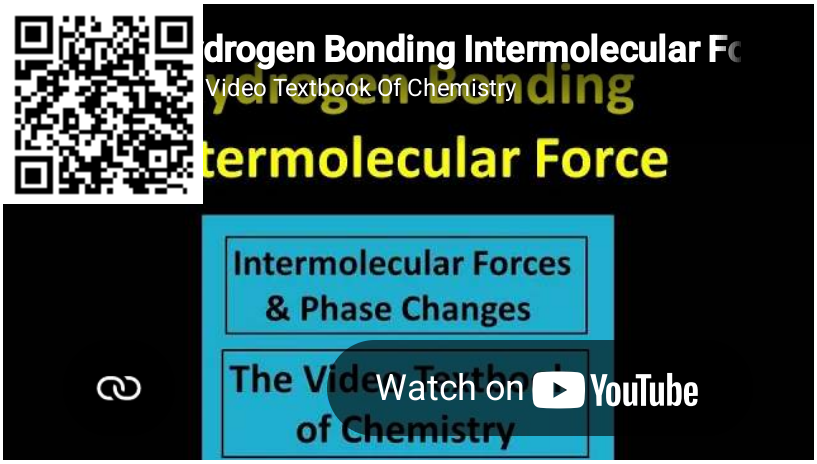


Figure **3.6.6**: The Hydrogen-Bonded Structure of Ice

Each water molecule accepts two hydrogen bonds from two other water molecules and donates two hydrogen atoms to form hydrogen bonds with two more water molecules, producing an open, cage like structure. The structure of liquid water is very similar, but in the liquid, the hydrogen bonds are continually broken and formed because of rapid molecular motion.

> *Hydrogen bond formation requires both a hydrogen bond donor and a hydrogen bond acceptor.*

Because ice is less dense than liquid water, rivers, lakes, and oceans freeze from the top down. In fact, the ice forms a protective surface layer that insulates the rest of the water, allowing fish and other organisms to survive in the lower levels of a frozen lake or sea. If ice were denser than the liquid, the ice formed at the surface in cold weather would sink as fast as it formed. Bodies of water would freeze from the bottom up, which would be lethal for most aquatic creatures. The expansion of water when freezing also explains why automobile or boat engines must be protected by “antifreeze” and why unprotected pipes in houses break if they are allowed to freeze.



Video Discussing Hydrogen Bonding Intermolecular Forces. Source: Hydrogen Bonding Intermolecular Force, YouTube(opens in new window) [youtu.be]

Example 3.6.3

Considering CH_3OH, C_2H_6, Xe, and $(CH_3)_3N$, which can form hydrogen bonds with themselves? Draw the hydrogen-bonded structures.

Given: compounds

Asked for: formation of hydrogen bonds and structure

Strategy:

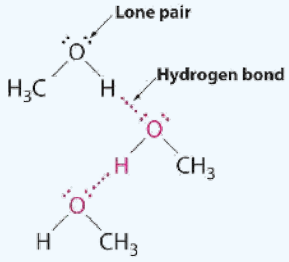
A. Identify the compounds with a hydrogen atom attached to O, N, or F. These are likely to be able to act as hydrogen bond donors.

B. Of the compounds that can act as hydrogen bond donors, identify those that also contain lone pairs of electrons, which allow them to be hydrogen bond acceptors. If a substance is both a hydrogen donor and a hydrogen bond acceptor, draw a structure showing the hydrogen bonding.

Solution:

A. Of the species listed, xenon (Xe), ethane (C_2H_6), and trimethylamine [$(CH_3)_3N$] do not contain a hydrogen atom attached to O, N, or F; hence they cannot act as hydrogen bond donors.

B. The one compound that can act as a hydrogen bond donor, methanol (CH_3OH), contains both a hydrogen atom attached to O (making it a hydrogen bond donor) and two lone pairs of electrons on O (making it a hydrogen bond acceptor); methanol can thus form hydrogen bonds by acting as either a hydrogen bond donor or a hydrogen bond acceptor. The hydrogen-bonded structure of methanol is as follows:



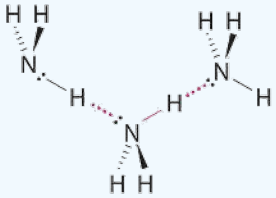
Hydrogen bonding in methanol

Exercise 3.6.3

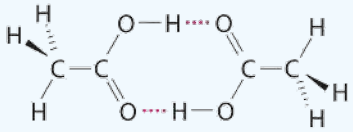
Considering CH_3CO_2H, $(CH_3)_3N$, NH_3, and CH_3F, which can form hydrogen bonds with themselves? Draw the hydrogen-bonded structures.

Answer

CH_3CO_2H and NH_3;



Hydrogen bonding in ammonia



Hydrogen bonding in acetic acid

Hydrogen bonding in ammonia between nitrogen and hydrogen. hydrogen bonding in acetic acid is between oxygen and hydrogen.

Although hydrogen bonds are significantly weaker than covalent bonds, with typical dissociation energies of only 15–25 kJ/mol, they have a significant influence on the physical properties of a compound. Compounds such as HF can form only two hydrogen

bonds at a time as can, on average, pure liquid NH_3. Consequently, even though their molecular masses are similar to that of water, their boiling points are significantly lower than the boiling point of water, which forms *four* hydrogen bonds at a time.

Example 3.6.4: Buckyballs

Arrange C_{60} (buckminsterfullerene, which has a cage structure), NaCl, He, Ar, and N_2O in order of increasing boiling points.

Given: compounds.

Asked for: order of increasing boiling points.

Strategy:

Identify the intermolecular forces in each compound and then arrange the compounds according to the strength of those forces. The substance with the weakest forces will have the lowest boiling point.

Solution

Electrostatic interactions are strongest for an ionic compound, so we expect NaCl to have the highest boiling point. To predict the relative boiling points of the other compounds, we must consider their polarity (for dipole–dipole interactions), their ability to form hydrogen bonds, and their molar mass (for London dispersion forces). Helium is nonpolar and by far the lightest, so it should have the lowest boiling point. Argon and N_2O have very similar molar masses (40 and 44 g/mol, respectively), but N_2O is polar while Ar is not. Consequently, N_2O should have a higher boiling point. A C_{60} molecule is nonpolar, but its molar mass is 720 g/mol, much greater than that of Ar or N_2O. Because the boiling points of nonpolar substances increase rapidly with molecular mass, C_{60} should boil at a higher temperature than the other nonionic substances. The predicted order is thus as follows, with actual boiling points in parentheses:

$$\text{He } (-269^\circ\text{C}) < \text{Ar } (-185.7^\circ\text{C}) < N_2O\ (-88.5^\circ\text{C}) < C_{60}\ (>280^\circ\text{C}) < \text{NaCl } (1465^\circ\text{C}).$$

Exercise 3.6.4

Arrange 2,4-dimethylheptane, Ne, CS_2, Cl_2, and KBr in order of decreasing boiling points.

Answer

KBr (1435°C) > 2,4-dimethylheptane (132.9°C) > CS_2 (46.6°C) > Cl_2 (−34.6°C) > Ne (−246°C)

Example 3.6.5

Identify the most significant intermolecular force in each substance.

a. C_3H_8
b. CH_3OH
c. H_2S

Solution

a. Although C–H bonds are polar, they are only minimally polar. The most significant intermolecular force for this substance would be dispersion forces.
b. This molecule has an H atom bonded to an O atom, so it will experience hydrogen bonding.
c. Although this molecule does not experience hydrogen bonding, the Lewis electron dot diagram and VSEPR indicate that it is bent, so it has a permanent dipole. The most significant force in this substance is dipole-dipole interaction.

Exercise 3.6.6

Identify the most significant intermolecular force in each substance.

a. HF
b. HCl

Answer a

hydrogen bonding

Answer b

dipole-dipole interactions

Summary

Intermolecular forces are electrostatic in nature and include van der Waals forces and hydrogen bonds. Molecules in liquids are held to other molecules by intermolecular interactions, which are weaker than the intramolecular interactions that hold the atoms together within molecules and polyatomic ions. Transitions between the solid and liquid, or the liquid and gas phases, are due to changes in intermolecular interactions, but do not affect intramolecular interactions. The three major types of intermolecular interactions are dipole–dipole interactions, London dispersion forces (these two are often referred to collectively as **van der Waals forces**), and hydrogen bonds. **Dipole–dipole interactions** arise from the electrostatic interactions of the positive and negative ends of molecules with permanent dipole moments; their strength is proportional to the magnitude of the dipole moment and to $1/r^3$, where r is the distance between dipoles. **London dispersion forces** are due to the formation of **instantaneous dipole moments** in polar or nonpolar molecules as a result of short-lived fluctuations of electron charge distribution, which in turn cause the temporary formation of an **induced dipole** in adjacent molecules; their energy falls off as $1/r^6$. Larger atoms tend to be more **polarizable** than smaller ones, because their outer electrons are less tightly bound and are therefore more easily perturbed. **Hydrogen bonds** are especially strong dipole–dipole interactions between molecules that have hydrogen bonded to a highly electronegative atom, such as O, N, or F. The resulting partially positively charged H atom on one molecule (the *hydrogen bond donor*) can interact strongly with a lone pair of electrons of a partially negatively charged O, N, or F atom on adjacent molecules (the *hydrogen bond acceptor*). Because of strong O···H hydrogen bonding between water molecules, water has an unusually high boiling point, and ice has an open, cage like structure that is less dense than liquid water.

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3.7: PROPERTIES OF ALCOHOLS AND PHENOLS

OBJECTIVES

After completing this section, you should be able to

1. explain why the boiling points of alcohols and phenols are much higher than those of alkanes, ethers, etc., of similar molecular mass.
2. discuss the factors that are believed to determine the acidity of alcohols and phenols.
3. list a given series of alcohols or phenols in order of increasing or decreasing acidity.
4. explain the difference in acidity between two given alcohols or phenols.
5. explain why phenols are more acidic than alcohols.
6. explain, in terms of inductive and resonance effects, why a given substituted phenol is more or less acidic than phenol itself.
7. write equations for the reactions of given alcohols and phenols with strong bases, such as sodium hydride and sodium amide.

KEY TERMS

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

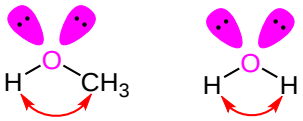
- acid ionization constant (K_a)
- alkoxide ion (RO^-)
- phenoxide ion (ArO^-)

STUDY NOTES

You may wish to review the concept of hydrogen bonding, which should have been discussed in your first-year general chemistry course.

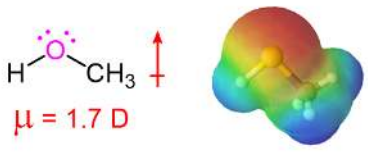
BOILING POINTS OF ALCOHOLS

The oxygen in alcohols and phenols is sp^3 hybridized which gives the roughly the same tetrahedral geometry as water. The bond angle of methanol (108.5 º) is slightly less than the tetrahedral value mainly due to the presence of its lone pair electrons.



108.5 º **Methanol** 104.5 º **Water**

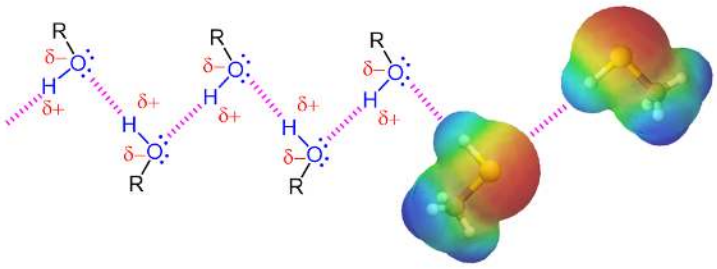
The presence of a highly electronegative oxygen confers a measure of polar character to alcohols. Much of the electron density of an alcohol is drawn towards the oxygen, giving alcohols a relatively high dipole momeny (1.7 D for Methanol).



The Dipole Moment of Methanol

Alcohols contain an extremely polar covalent O-H bond. The electrons in this bond are strongly drawn towards the oxygen giving it a partial negative charge (delta-) while the electrons are drawn away from the hydrogen giving is a partial positive charge (delta+). The polar character of this bond leads to an interaction between alcohol molecules where the positively polarized hydrogen of one alcohol molecule is attracted to the lone pair electrons on the electronegative oxygen atom of a different alcohol molecule. This creates a type of intramolecular attraction is called “hydrogen bonding.” Although the strength of such attractions are much less than most conventional chemical bonds, they are still significant (about 5 to 10 kcal per bond). For an alcohol to vaporize, these intramolecular hydrogen bonding attractions must be

broken making alcohols substantially less volatile, have higher boiling points, and greater water solubility than molecules with a similar molecular weight (Table **3.7.1**). An example of this is seen when comparing 1-propanol (MW = 60.1), Chloroethane (MW = 64.5), and butane (MW = 58.1) which have boiling points of 94.7 ^{o}C, 12.3 ^{o}C, and -1 ^{o}C respectively.



A Representation of Hydrogen Bonding in Alcohols

This table shows that alcohols (in blue) have higher boiling points than haloalkanes and alkanes with the equivalent molecular weight. It also shows that the boiling points of alcohols increase with the number of carbon atoms.

Table **3.7.1**: Physical Properties of Selected Alcohols, Haloalkanes, and Alkanes

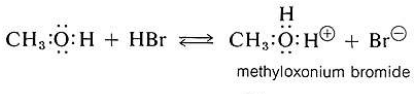
Compound	IUPAC Name	Molecular Weight (g/mol)	Melting Point (^{o}C)	Boiling Point (^{o}C)
CH_3OH	Methanol	32.0	-97.8	65.0
CH_3Cl	Chloromethane	50.5	-97.7	-24.2
CH_3CH_2OH	Ethanol	46.1	-114.7	78.5
$CH_3CH_2CH_2CH_3$	Butane	58.1	-140.	-1
$CH_3CH_2CH_2OH$	1-Propanol	60.1	-126.5	97.4
CH_3CH_2Cl	Chloroethane	64.5	-136.4	12.3
$CH_3CH_2CH_2CH_2CH_3$	Pentane	72.2	-130	36.3
$CH_3CH_2CH_2CH_2OH$	1-Butanol	74.1	-89.5	117.3
$CH_3(CH_2)_4OH$	1-Pentanol	88.1	-79	138

SOLUBILITY OF ALCOHOLS IN WATER

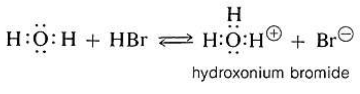
Alcohols and water have the ability to form hydrogen bonds with one another which tends to make the two liquids miscible. Small alcohols are completely soluble in water; mixing the two in any proportion generates a single solution. However, solubility decreases as the length of the hydrocarbon chain in the alcohol increases. At four carbon atoms and beyond, the decrease in solubility is noticeable; a two-layered substance may appear in a test tube when the two are mixed.

BASIC PROPERTIES OF ALCOHOLS

Alcohols are weak bases similar in strength to water and can accept protons from strong acids to form the conjugate acid called oxonium ions (ROH_2^+). An example is the reaction of methanol with hydrogen bromide to give methyloxonium bromide, which is analogous to the formation of hydroxonium bromide from the reaction of hydrogen bromide and water:



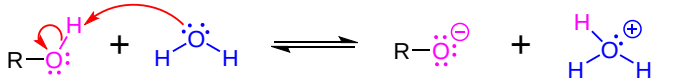
methyloxonium bromide



hydroxonium bromide

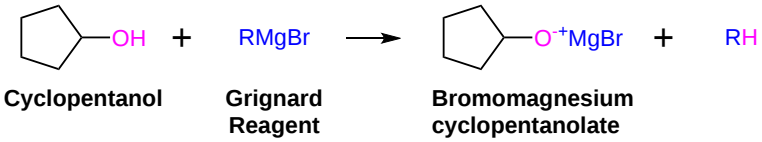
ACIDIC PROPERTIES OF ALCOHOLS

Alcohols, like water, are both weak bases and weak acids. In aqueous solutions, alcohols dissociate slightly by donating a hydrogen to water. This creates the alcohol's conjugate base, called an alkoxide ion (RO^-), along with hydronium (H_3O^+). The acid ionization constant (K_a) of ethanol is about 10^{-18}, which is slightly less than that of water. Alcohols, such as ethanol, can be deprotonated to form its conjugate base by reaction with a stronger base, such as sodium amide ($NaNH_2$), sodium hydride (NaH), or Grignard reagents (RMgBr). Alkoxides can also be formed using sodium or potassium metal which reacts vigorously but controllably with alcohols.



Alcohol **Alkoxide** **Hydronium**

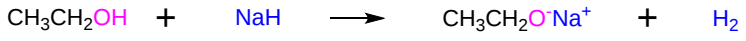
Once created, alkoxides act as bases and are often used as reagents in organic chemistry. Alkoxide's systematic names are based of the corresponding alcohol with the suffix *-ate* added. For example, ethanol becomes ethanolate. They are named systematically by adding the *-ate* suffix to the name of the alcohol. Methanol becomes methanolate, for instance. Common names are often used for small alkoxides. Common names are generated as: (Name of the positive counter ion) (Prefix for the parent chain + oxide). Example: ethanol becomes ethoxide.



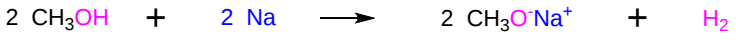
Cyclopentanol **Grignard Reagent** **Bromomagnesium cyclopentanolate**



***tert*-Butyl Alcohol (2-Methyl-2-propanol)** **Sodium Amide** **Sodium *tert*-Butoxide (Sodium 2-Methyl-2-proanolate)**



Ethanol **Sodium Hydride** **Sodum Ethoxide (Sodium ethanolate)**



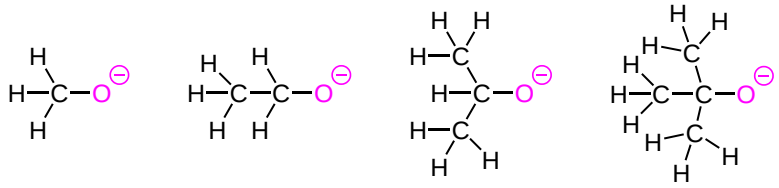
Methanol **Sodium** **Sodium methoxide (Sodium methanolate)**

As discussed in Section 2.8, the strength of an acid in water can be expressed either by its K_a or its pK_a. Compounds with a lower K_a and a higher pK_a are considered less acidic than compound with a higher K_a and a lower pK_a.

$$K_a = \frac{[A^-][H_3O^+]}{[HA]} \tag{3.7.1}$$

$$pK_a = -\log K_a$$

In general, alcohols in aqueous solution are slightly less acidic than water. The order of acidity of various liquid alcohols generally is water > primary > secondary > tertiary ROH. By this we mean that the pK_a is increased as R is changed from primary to secondary to tertiary; therefore, *tert*-butyl alcohol is less acidic than ethanol. This trend is explained by the importance of solvation in equilibrium. In solution, the larger alkoxide ions, are less well solvated than the smaller ions, because fewer solvent molecules can be accommodated around the negatively charged oxygen in the larger ions. Acidity of alcohols therefore decreases as the size of the conjugate base increases. This trend can be clearly seen when comparing alkoxide size to the pKa of the corresponding alcohol listed in Table **3.7.2**.



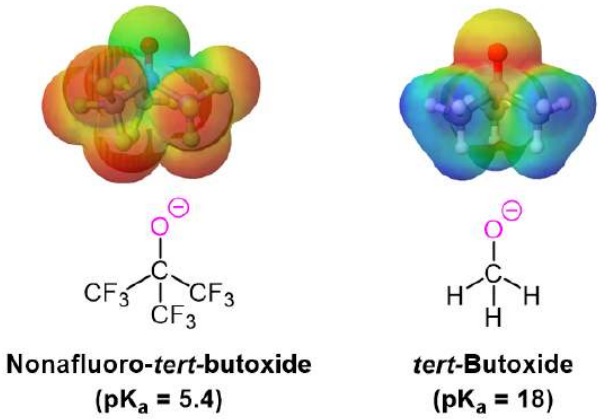
Methoxide **Ethoxide** **Isopropoxide** ***tert*-Butoxide**

$$ROH + OH^- \rightleftharpoons RO^- + HOH$$

Table **3.7.2**: The pKa's of various alcohols

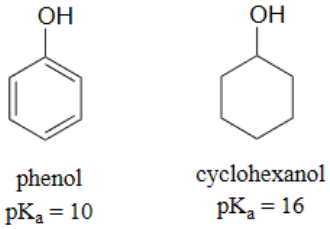
R	Name	pK_{a1}
H	water	14.0
CH_3	methanol	15.5
CH_3CH_2	ethanol	15.9
$(CH_3)_2CH$	propan-2-ol (isopropyl alcohol)	16.5
$(CH_3)_3C$	2-methylpropan-2-ol (*tert*-butanol)	17
C_6H_5 (phenyl)	phenol	9.95

The addition of an electron-withdrawing group, such as an electronegative halogen, can increase the acid strength of an alcohol by stabilizing its alkoxide conjugate base through induction (Section 2.10). The electron-withdrawing group helps to spread out the electron density of the alkoxide's negative charge, which has a stabilizing effect. The inductive effect is cumulative such that the acid strength of an alcohol becomes stronger (Lower pK_a) as the number of halogens increases. The presence of nine fluorines in nonafluoro-*tert*-butyl alcohol decreases its pK_a to 5.4 which is significantly more acidic than *tert*-butyl alcohol (pK_a = 18). The electron-withdrawing effect of the fluorines is clearly seen when comparing the electrostatic potential maps of the corresponding alkoxides. In *tert*-butoxide the molecule's electron density is firmly centered around the oxygen as shown by the orange/yellow color. In nonafluoro-*tert*-butoxide the molecule's electron density is almost completely removed from the oxygen and shifted to the fluorines.

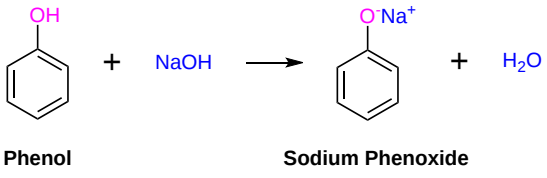


ACIDITY OF PHENOL

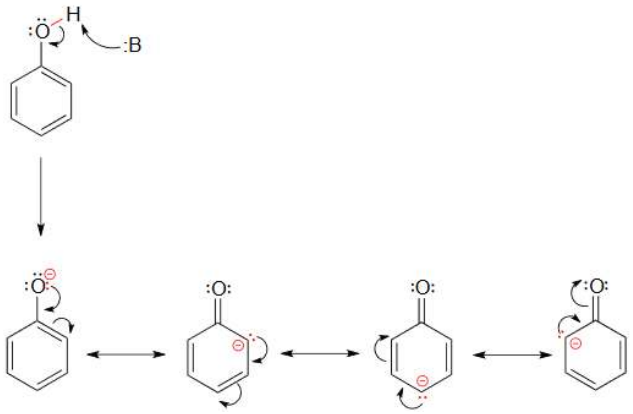
Another method for increasing acidity is through stabilizing a conjugate base through resonance effects. An excellent example of this effect is shown through phenol being roughly a million times more acidic than cyclohexanol.



Phenol is acidic enough to be deprotonated by weaker bases, such as sodium hydroxide (NaOH), to form the phenoxide ion.

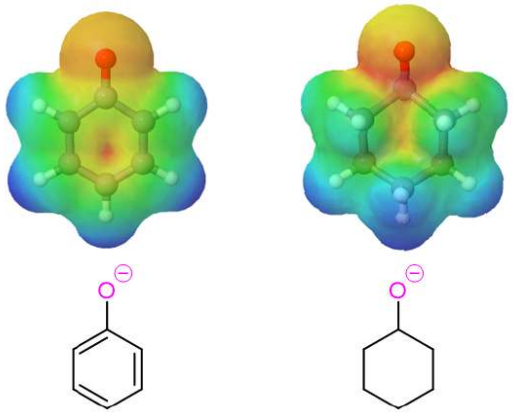


The increased acidity of phenol is caused by the negative charge and a set of lone pair electrons from the phenoxide's oxygen atom being delocalized by resonance to three different carbons on the aromatic ring. As a result, the negative charge is no longer entirely localized on the oxygen, but is spread throughout the whole ion allowing it to be highly stabilized.



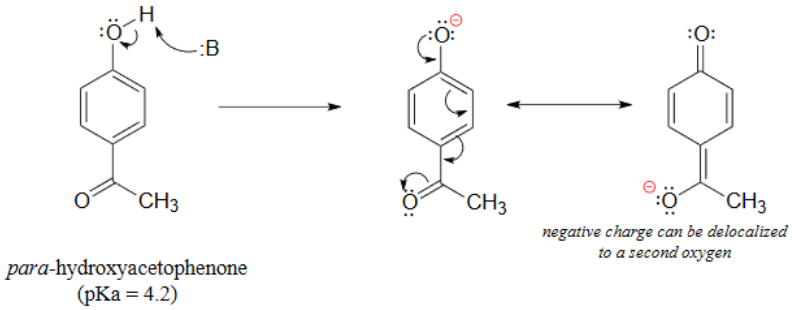
Although these are all minor resonance contributors (negative charge is placed on a carbon rather than the more electronegative oxygen), they nonetheless have a significant effect on the acidity of the phenolic proton. Essentially, the benzene ring is acting as an electron-withdrawing group by resonance.

The electrostatic potential maps below compare the phenoxide ion to an unconjugated alkoxide. The negative charge of the phenoxide ion, show as a yellow/orange color, is delocalized from oxygen into the aromatic ring (seen by the growing red color in the phenoxide ring).



ACIDITY OF SUBSTITUTED PHENOLS

Phenolic acidity is further enhanced by the presence of an additional electron-withdrawing substituent, such as a nitro or carbonyl, on the aromatic ring. For the conjugate base of the phenol derivative below, an additional resonance contributor can be drawn in which the negative formal charge is placed on the carbonyl oxygen.



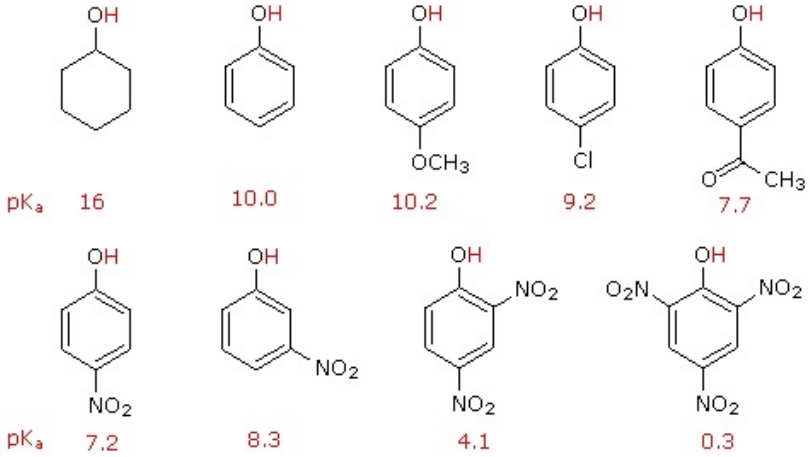
para-hydroxyacetophenone
(pKa = 4.2)

Now the negative charge on the conjugate base can be spread out over two oxygens (in addition to three aromatic carbons). The phenol acid therefore has a pK_a similar to that of a carboxylic acid, where the negative charge on the conjugate base is also delocalized to two oxygen

atoms. The ketone group on the aromatic ring is acting as an electron withdrawing group and 'pulling' electron density towards itself, through both inductive and resonance effects.

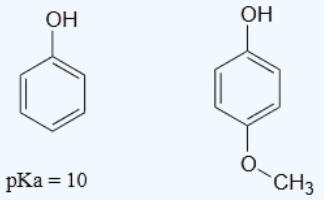
It is noteworthy that the influence of a nitro substituent is over ten times stronger in the *para*-location than it is meta, despite the fact that the latter position is closer to the hydroxyl group. This occurs since nitro groups at the meta position cannot accept the negative charge through resonance. Furthermore additional nitro groups have an additive influence if they are positioned *ortho* or *para* locations to the hydroxide. The trinitro compound shown at the lower right is a very strong acid called picric acid.

Lastly, if an electron donating group is attached to aromatic ring, as in *p*-methoxyphenol, the phenoxide ion is destabilized which causes a decrease in acidity in the corresponding phenol.



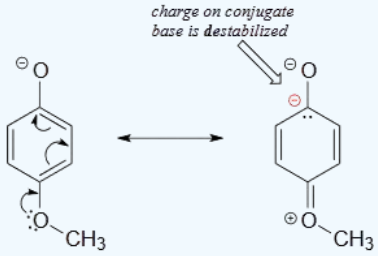
WORKED EXAMPLE 3.7.1

Using resonance structures, please explain why 4-methoxyphenol is less acidic than phenol.



Answer

The methoxy group is an electron-donating group by resonance. A resonance contributor can be drawn in which a formal negative charge is placed on the carbon adjacent to the negatively-charged phenolate oxygen.

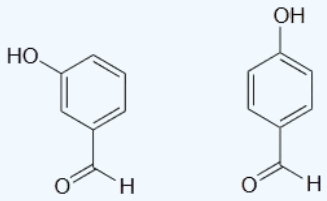


Because of like-charge repulsion, this destabilizes the negative charge on the phenolate oxygen, making the corresponding phenol less acidic.

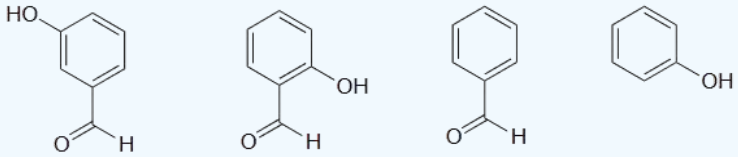
EXERCISE 3.7.1

1.

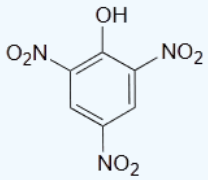
The position of the electron-withdrawing substituent relative to the phenol hydroxyl is very important in terms of its effect on acidity. Which of the two substituted phenols below is more acidic? Use resonance drawings to explain your answer.



2) Rank the four compounds below from most acidic to least.



3) Use a resonance argument to explain why picric acid has such a low pKa.



picric acid
pKa = 0.25

4) Predict which compound of each pair is more soluble in water and explain your reasoning.

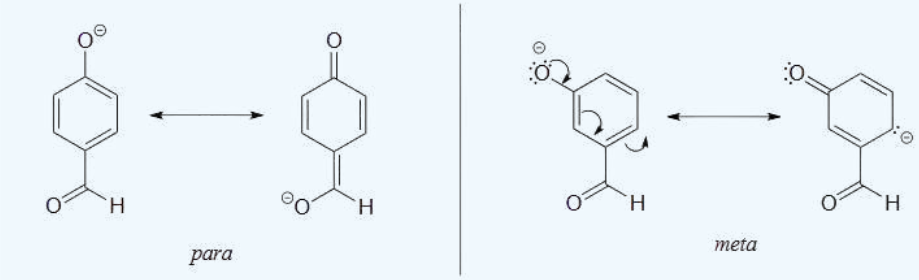
a. Butan-1-ol or pentan-1-ol
b. Phenol or cyclohexanol
c. Octan-1,3-diol or octan-1-ol
d. 1-Chlorohexane or hexan-1-ol

5) Predict which compound has the higher boiling point and explain your reasoning.

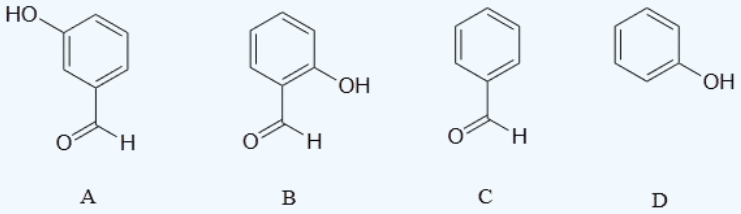
a. Water or ethanol
b. Butan-1-ol or octan-1-ol
c. Hexan-2-ol or hexan-2-one

Answer

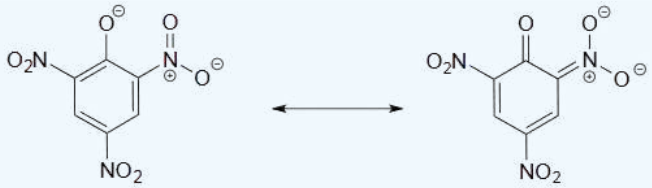
1) The para-subsituted phenol is more acidic, because the negative charge on the conjugate base can be delocalized to the aldehyde oxygen. This is not possible when the aldehyde group is in the meta position



2) Compound B is the strongest acid due to electron-withdrawing resonance effects-the negative charge on the conjugate base can be delocalized to the aldehyde oxygen. Compound A is the 2nd strongest acid -while the negative charge on the conjugate base cannot be delocalized to the aldehyde oxygen due to the *meta*-position, the aldehyde none the less has a stabilizing, electron-withdrawing inductive effect. Compound D is ranked #3 -it is phenol, and does not have any electron-withdrawing substituents on the ring as do B and A. Compound C is the least acidic -neither the phenyl group nor the aldehyde are even slightly acidic.



3) The negative charge on the conjugate base of picric acid can be delocalized to oxygen atoms on all threeof the nitro groups. One such resonance contributor is shown below. This extensive delocalization means that the conjugate base is very stable, and the conjugate acid is thus a very strong acid.



4)

a. Butan-1-ol is more soluble in water because it has a smaller hydrophobic region compared to pentan-1-ol, allowing butan-1-ol to interact with water better.
b. Phenol is more soluble in water than cyclohexanol because of the more polar character of its ring. phenol is able to interact with water better than cyclohexanol due to the conjugated pi-system of electrons in its ring, which which gives it a more ionic character.
c. Octan-1,3-diol is more soluble in water as it has two hydroxy groups, allowing it to form more hydrogen bonds and interact with water better than octan-1-ol.
d. Hexan-1-ol is more soluble in water as it can hydrogen bond compared to alkyl halides, such as 1-chlorohexane, which are insoluble in water.

5)

a. Water has a higher boiling point compared to ethanol as it participates in more hydrogen bonding with other water molecules, thus requiring more energy to break the intermolecular attractions between water molecules.
b. Octan-1-ol has the higher boiling point compared to butan-1-ol. Both alcohols can H-bond, however the longer hydrophobic carbon chain tail of octan-1-ol experiences more van der Waal interactions compared to the shorter hydrophobic region of butan-1-ol leading to a higher boiling point.
c. Since hexan-1-ol can H-bond, it has a higher boiling point than hexan-2-one, which cannot H-bond.

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3.8: Reactions that Form Alcohols

Learning Objectives

- To describe how to prepare alcohols from alkenes

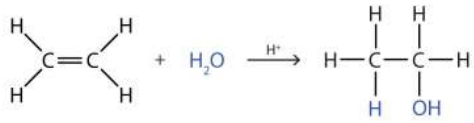
Methanol is prepared by combining hydrogen gas and carbon monoxide at high temperatures and pressures in the presence of a catalyst composed of zinc oxide (ZnO) and chromium oxide (Cr_2O_3) catalyst:

$$2H_2 + CO \xrightarrow[ZnO,\ Cr_2O_3]{200\ atm,\ 350°C} CH_3OH$$

Methanol is an important solvent and is used as an automotive fuel, either as the pure liquid—as in some racing cars—or as an additive in gasoline.

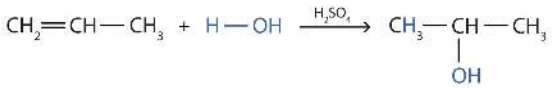
> *Nearly 2 billion gallons of methanol are produced each year in the United States by the catalytic reduction of carbon monoxide with hydrogen gas.*

Many simple alcohols are made by the hydration of alkenes. Ethanol is made by the hydration of ethylene in the presence of a catalyst such as sulfuric acid (H_2SO_4).



Ethylene Water Ethanol

In a similar manner, isopropyl alcohol is produced by the addition of water to propene (propylene).



Propylene Isopropyl alcohol (2-propanol)

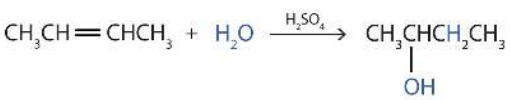
Additional Exercise **3.8.1** describes how to use a generalization called Markovnikov's rule to predict the results when the addition of water to an alcohol has two possible products.

Example 3.8.1

Write the equation for the reaction of 2-butene with water to form 2-butanol. Indicate that sulfuric acid is used as a catalyst.

Solution

First write the condensed structural formula of 2-butene and indicate that it reacts with water. Then write the condensed structural formula of 2-butanol after the reaction arrow to indicate that it is the product. Finally, write the formula for the catalyst above the arrow.



Exercise 3.8.1

Write the equation for the reaction of cyclopentene with water to form cyclopentanol. Indicate that phosphoric acid (H_3PO_4) is used as a catalyst.

> *Many OH compounds in living systems are formed by alkene hydration. Here is an example that occurs in the Krebs cycle: fumarate is hydrated to form malate.*
>
> $$^-OOCCH{=}CHCOO^- + HOH \overset{\text{enzyme}}{\rightleftharpoons} {}^-OOCCH_2CHOHCOO^-$$

In addition to its preparation from ethylene, ethanol is made by the fermentation of sugars or starch from various sources (potatoes, corn, wheat, rice, etc.). Fermentation is catalyzed by enzymes found in yeast and proceeds by an elaborate multistep mechanism. We can represent the overall process as follows:

$$(C_6H_{10}O_5)_x \xrightarrow{\text{enzymes}} C_6H_{12}O_6 \xrightarrow{\text{enzymes}} 2CH_3CH_2OH + 2CO_2$$

Starch — Glucose — Ethanol

To Your Health: The Physiological Effects of Alcohols

Methanol is quite poisonous to humans. Ingestion of as little as 15 mL of methanol can cause blindness, and 30 mL (1 oz) can cause death. However, the usual fatal dose is 100 to 150 mL. The main reason for methanol's toxicity is that we have liver enzymes that catalyze its oxidation to formaldehyde, the simplest member of the aldehyde family:

$$CH_3OH \xrightarrow{\text{liver enzymes}} H{-}\overset{\overset{O}{\|}}{C}{-}H$$

Methanol — Formaldehyde

Formaldehyde reacts rapidly with the components of cells, coagulating proteins in much the same way that cooking coagulates an egg. This property of formaldehyde accounts for much of the toxicity of methanol.

Organic and biochemical equations are frequently written showing only the organic reactants and products. In this way, we focus attention on the organic starting material and product, rather than on balancing complicated equations.

Ethanol is oxidized in the liver to acetaldehyde:

$$CH_3CH_2OH \xrightarrow{\text{liver enzymes}} CH_3{-}\overset{\overset{O}{\|}}{C}{-}H$$

Ethanol — Acetaldehyde

The acetaldehyde is in turn oxidized to acetic acid ($HC_2H_3O_2$), a normal constituent of cells, which is then oxidized to carbon dioxide and water. Even so, ethanol is potentially toxic to humans. The rapid ingestion of 1 pt (about 500 mL) of pure ethanol would kill most people, and acute ethanol poisoning kills several hundred people each year—often those engaged in some sort of drinking contest. Ethanol freely crosses into the brain, where it depresses the respiratory control center, resulting in failure of the respiratory muscles in the lungs and hence suffocation. Ethanol is believed to act on nerve cell membranes, causing a diminution in speech, thought, cognition, and judgment.

Rubbing alcohol is usually a 70% aqueous solution of isopropyl alcohol. It has a high vapor pressure, and its rapid evaporation from the skin produces a cooling effect. It is toxic when ingested but, compared to methanol, is less readily absorbed through the skin.

Summary

Many alcohols are made by the hydration of alkenes. Ethanol can be made by the fermentation of sugars or starch from various sources.

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3.9: Nucleophilic substitution and elimination reactions

Learning Objectives

- Identify nucleophiles and electrophiles, their similarities, and differences from acids and bases.
- Understand S_N2, E2, S_N1, or E1 reaction mechanisms, factors that affect them, and conditions that dictate which one will take place.
- Learn some examples of S_N2, E2, S_N1, and E1 reactions of alcohols, ethers, amines, and thiols.

Nucleophile and electrophile

Nucleophile is a neutral or anionic specie that can donate a lone pair or π bonding electrons to make a covalent bond.

Examples of nucleophile are negative or partial negative ($\delta-$) atoms with lone pair or π bond in the following $H_3N:$, $H_2O:$, $HO:^-$, and $H_2C{=}CH_2$.

Electrophile is an electron-deficient atom of a neutral or cationic species that can receive an electron pair to make a covalent bond.

Examples of electrophile are positive charge or partial positive ($\delta+$) charge $C's$ or $H's$ in the following species: $(CH_3)_3\overset{+}{C}$, $\overset{\delta+}{C}H_3\text{-}\overset{\delta-}{Cl}$, $(CH_3)_2\overset{\delta+}{C}{=}\overset{\delta-}{O}$, and $\overset{\delta+}{H}\text{-}\overset{\delta-}{Cl}$.

Differences between nucleophile-electrophile and acid-base

The base is a substance that donates a pair of electrons to a proton to make a covalent bond. So, a base is a sub-class of nucleophiles and an acidic proton is a subclass of electrophiles. Acid-base reactions are fast reactions. In acid-base reactions, emphasis is on thermodynamic, specifically on the equilibrium constant K quantified in terms of pKa, i.e., smaller the pKa means larger K and stronger acid. Nucleophiles donate electrons to an electron-deficient carbon or some atom usually other than a proton. Emphasis in nucleophilic-electrophilic reaction is on the kinetics, a good nucleophile reacts faster and a poor nucleophile reacts slower.

Similarities and differences in nucleophilicity and basicity

The similarity is that the stronger bases are stronger nucleophiles when compared within the same row of the periodic table. For example, basicity follows the order $\overrightarrow{HO^- < NH_2^- < F^-}$ and their nucleophilicity follows the same order. Similarly, anionic species, e.g., NH_2^-, HO^- and RO^- are stronger bases and good nucleophiles compared to the corresponding neutral species of the same element, i.e., NH_3, H_2O and ROH.

The difference is that the basicity and nucleophilicity are affected differently when comparing atoms of different rows. For example, hydride ion (H^-) from the 1st row is a stronger base but a poor nucleophile. the opposite is true for the 3rd-row and higher elements, e.g., SH^-, Cl^-, Br^-. and I^- are week bases but usually good nucleophiles. Unlike basicity, nucleophilicity is affected by steric factors and solvents. Most of these differences are related to the fact that in acid-base reactions, the electron recipient is the 1s orbital of a proton, and in nucleophilic-electophilic reactions, the electron recipient is 2s, 2p, or larger orbital of carbon or some other element. The details of these factors are out of the scope of this book. Base strength is described as stronger or weak, and nucleophilic strength is described as good or poor.

Nucleophilic substitution mechanisms

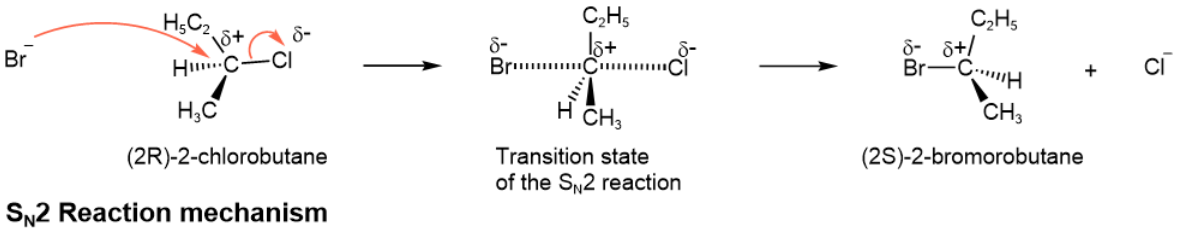
In a nucleophilic substitution reaction, a nucleophile ($Nu:^-$) attacks and makes a covalent bond with $\delta+$ atom of the target molecule, called **substrate** ($\overset{\delta+}{R}\text{-}\overset{\delta-}{X}$). The polar bond of the target molecule breaks heterolytically, leaving the bonding electrons with the more electronegative end called **leaving group** ($X:^-$), as shown in the following generalized reaction.

$$\mathrm{Nu:^- + \overset{\delta+}{R}-\overset{\delta-}{X} \longrightarrow \overset{\delta+}{R}-\overset{\delta-}{Nu} + X:^-}$$

Since one nucleophile, i.e., $\mathrm{Nu:^-}$, replaces another nucleophile, i.e., $\mathrm{X:^-}$ on the substrate, it is called a **nucleophilic substitution reaction**. The nucleophilic substitution reactions are based on the fact the incoming nucleophile has a stronger tendency to make a covalent bond with the electrophilic center than the leaving group. In other words, the incoming nucleophile is stronger and the leaving group is a weaker nucleophile. Mechanisms of the nucleophilic substitution reactions are described below.

Nucleophilic substitution bimolecular (S_N2)

One mechanism for nucleophilic substitution reaction is concerted bond-making and breaking in a single step, as shown below.



S_N2 Reaction mechanism

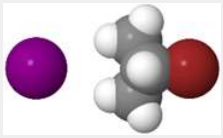
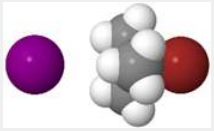
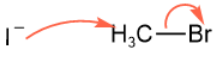
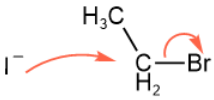
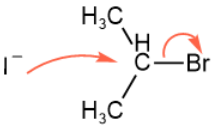
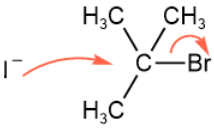
The incoming nucleophile approaches the electrophilic $\overset{\delta+}{C}$ from the side opposite to the leaving group. The incoming nucleophile starts making the bond and the leaving group starts breaking the bond simultaneously. The other three groups pointing away from the leaving group, start moving to the other side, away from the incoming nucleophile. In the transition state, the three groups acquire a trigonal planar arrangement perpendicular to the bond being broken and formed. This reaction mechanism is called S_N2, where S is for substitution, N is for nucleophilic, and 2 is for bimolecular.

- If the electrophilic $\overset{\delta+}{C}$ is a chiral center, its configuration is inverted in the product of S_N2 reaction.
- This elementary step of S_N2 reaction involves two reactants in its rate-determining step, the incoming nucleophile, and the substrate, and it is a bimolecular reaction.

The rate of an S_N2 reaction is directly proportional to the substrate concentration and the nucleophile concentration. The rate depends on the substrate's structure, the nature of the leaving group, the nature of the nucleophile, and the solvent, as described next.

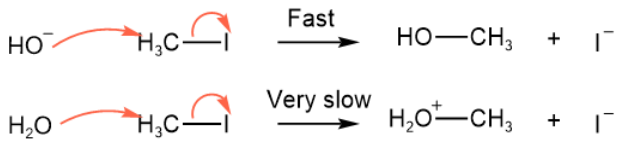
Effect of the structure of the substrate

The rate follows the following order with respect to the nature of the electrophilic $\overset{\delta+}{C}$: $\mathbf{\xleftarrow{\text{methyl > primary > secondary > tertiary}}}$. The steric hindrance posted by the substrate to the nucleophile explains it, which follows the same order, as illustrated below.

Type of electrophile carbon	Methyl	Primary	Secondary	Tertiary
Model				
Structures with mechanism arrows	 bromomethane	 bromoethane (primary)	 2-bromopropane (secondary)	 2-bromo-2-methyl-propane (tertiary)
The relative S_N2 reaction rate	145	1	0.008	no reaction

Effect of the nucleophile

Good nucleophiles react faster. Particularly, anionic nucleophiles, like $\mathbf{HO^-}$ or $\mathbf{RO^-}$ are employed for S_N2 as they react much faster than their corresponding neutral counterparts, i.e., $\mathbf{H_2O}$ or $\mathbf{ROH}$, as shown in the following example.



Effect of the leaving group

Leaving group propensity has a trend opposite to the basicity of the leaving group, i.e., good leaving groups are weaker bases. For example, the basicity of halide ions follows this order: $\overleftarrow{\mathbf{F^- > Cl^- > Br^- > I^-}}$ but the rate of reaction of alkyl halides, under the same conditions, follows the opposite trend, i.e., $\overrightarrow{\mathbf{R{-}F < R{-}Cl < R{-}Br < R{-}I}}$. The effect of the leaving group on the rate of the reaction is shown in the following table.

Reaction	Relative rate
$\mathbf{HO^- + RCH_2{-}F \longrightarrow RCH_2{-}OH + F^-}$	1
$\mathbf{HO^- + RCH_2{-}Cl \longrightarrow RCH_2{-}OH + Cl^-}$	200
$\mathbf{HO^- + RCH_2{-}Br \longrightarrow RCH_2{-}OH + Br^-}$	10,000
$\mathbf{HO^- + RCH_2{-}I \longrightarrow RCH_2{-}OH + I^-}$	30,000

Effect of the solvent

The solvent is needed to dissolve both the substrate and the nucleophile. The substrate is a polar compound like $\mathbf{\overset{\delta+}{C}H_3{-}\overset{\delta-}{Br}}$ and the nucleophile is usually in the form of an ionic solid like $\mathbf{Na^+OH^-}$ or $\mathbf{CH_3O^-Na^+}$. Nonpolar solvents do not work because polar and ionic substances do not dissolve in nonpolar solvents. Polar solvents can dissolve polar and ionic compounds. Polar solvents fall into two categories:

- **polar protic** solvent that have an acidic proton like water ($\mathbf{H_2O}$) and methanol ($\mathbf{CH_3{-}OH}$), and
- **polar aprotic** like acetone ($\mathbf{(CH_3)_2\overset{\delta+}{C}{=}\overset{\delta-}{O}}$) and dimethylsulfoxide ($\mathbf{(CH_3)_2\overset{\delta+}{S}{=}\overset{\delta-}{O}}$ }\)) which do not have an acidic proton. Their $\delta+$ end is at the center of the molecule, surrounded by bulky groups.

Polar protic solvent dissolves ionic compounds by ion-dipole interactions forming a layer of solvent around cation and anion. They are not suitable for S_N2 reactionas the solvent layer prevents nucleophiles from approaching electrophilic $\overset{\delta+}{C}$.

Aprotic solvents dissolve the ionic compound by the ion-dipole interaction but leave the anion, i.e., nucleophile, almost free. This is because the anion is prevented from approaching the $\delta+$ pole of the solvent due to steric hindrance, as illustrated in Figure **3.9.1**. Recall that electrostatic force is inversely proportional to the square of the distance between the +ve charge and the -ve charge, i.e., the longer the distance, the weaker the force.

Polar aprotic solvents are suitable for S_N2 reaction as the nucleophiles are relatively free to approach electrophilic $\overset{\delta+}{C}$ of the substrate.

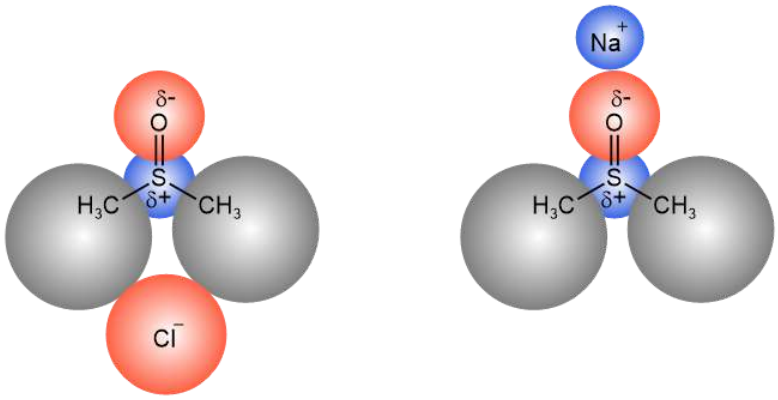


Figure 3.9.1: Illustration of dissolution of Na^+Cl^- in dimethylsulfoxide ($(CH_3)_2\overset{\delta+}{S}=\overset{\delta-}{O}$ }\)). The aprotic solvent dissolves ionic compounds by making strong ion-dipole interaction with the cation but leaves the anion relatively free as it is prevented by steric hindrance from approaching the \(\delta{+} pole of the solvent molecule.

Examples of S_N2 reactions

Alkyl halides are derived from alkanes by free radical reactions. The alkyl halides are then converted to a number of other classes of organic compounds by S_N2 reaction, e.g., ethyl bromide can be converted to:

alcohol: $CH_3CH_2Br + OH^- \longrightarrow CH_3CH_2OH + Br^-$,

a thiol: $CH_3CH_2Br + HS^- \longrightarrow CH_3CH_2SH + Br^-$,

an ether: $CH_3CH_2Br + CH_3CH_2O^- \longrightarrow CH_3CH_2OCH_2CH_3 + Br^-$,

a thioether: $CH_3CH_2Br + CH_3CH_2S^- \longrightarrow CH_3CH_2SCH_2CH_3 + Br^-$,

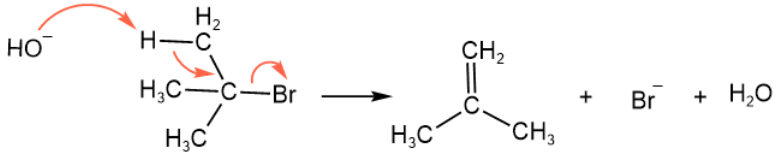
an amine: $CH_3CH_2Br + {}^-NH_2 \longrightarrow CH_3CH_2NH_2 + Br^-$,

a nitrile: $CH_3CH_2Br + {}^-C{\equiv}N \longrightarrow CH_3CH_2C{\equiv}N + Br^-$, and

and an alkyne: $CH_3CH_2Br + {}^-C{\equiv}CCH_3 \longrightarrow CH_3CH_2C{\equiv}CCH_3 + Br^-$.

Elimination bimolecular (E2)

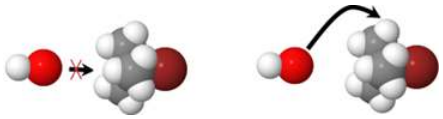
Recall that the C connected to a functional group is αC, and the one adjacent to it is βC. Also, recall that $\overset{\delta+}{H}-\overset{\delta-}{Br}$ is a strong acid because the acidic polar leaves electron on elecronegative Br. Similarly, protons on βC are acidic because they can send the bonding electrons to Br through the following mechanism.



Nucleophiles are bases at the same time. The base HO^- attacks βH, the H–C bonding electrons establish a π-bond between αC and βC, and the αC let go the leaving group Br^-. Since a βH is eliminated along with the leaving group, This reaction mechanism is called β-elimination. It is a bimolecular reaction because of two species involved in this elementary step: the base and the substrate. This specific β-elimination is called **elimination bimolecular (E2)**, where E stands for elimination and 2 for bimolecular.

S_N2 vs. E2

S_N2 and E2 reactions compete because the same reagent is nucleophile in S_N2 and base in the E2 reaction. However, the effect of the structure of the substrate is opposite in S_N2 and E2. The structure of substrate affects S_N2 in this order: $\overleftarrow{\text{methyl} > \text{primary} > \text{secondary} > \text{tertiary}}$. Tertiary substrates do not react by S_N2 mechanics because the nucleophile is prevented from approaching αC by steric hindrance. However, βH is still exposed and easily approachable by the base, as shown below.



Further, E2 is facilitated by lowering steric crowding around the αC. Therefore, tertiary substrates yield E2 product under the S_N2 conditions. The steric crowding around αC of secondary substrates is less than tertiary. So, E2 and S_N2 compete, and elimination and substation products are formed from the secondary substrates. There is no steric crowding in the case of primary or methyl substrates. So, S_N2 dominated over E2, and substitution product is formed almost exclusively in the case of primary and methyl substrates. The effect of the structure of the substrate on E2 reaction is in this order: $\overrightarrow{\text{methyl} < \text{primary} < \text{secondary} < \text{tertiary}}$, which is the opposite of S_N2. E2 reactions synthesize alkenes from alkyl halides, as in the above example, and form similar functional groups that will be described later.

Substitution nucleophilic unimolecular S_N1

Ionic compounds like Na^+Cl^- dissociate into ions in polar protic solvents like H_2O better than in polar aprotic solvents like. This is because unlike polar aprotic solvents solvating only cations, polar protic solvents solvent both cations and anions. Polar covalent bonded compounds like $\overset{\delta+}{H}-\overset{\delta-}{Br}$ also dissociate in polar portic solvent by the same mechanism. Polar organic compounds like $H_3\overset{\delta+}{C}-\overset{\delta-}{Br}$ have less tendency to dissociate. However, if the substrate is tertiary like $(H_3C)_3\overset{\delta+}{C}-\overset{\delta-}{Br}$, the effect of steric crowding on αC and the dissociation ability of the polar protic solvent together are strong enough to dissociate polar organic compounds, as in 1st step of the mechanism shown in Figure 3.9.2.

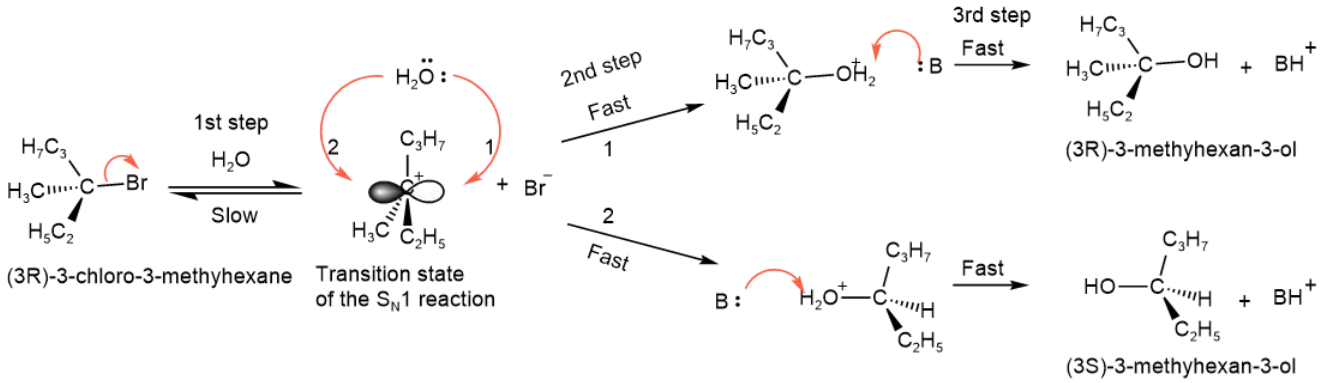


Figure 3.9.2: S_N1 reaction mechanism illustrated. (Copyright; Public domain)

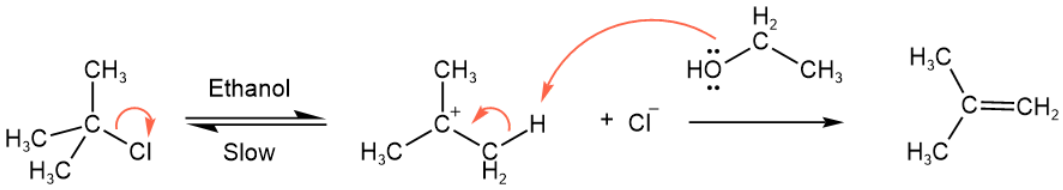
The carbonation produced in the 1st step, e.g., $(H_3C)_3C^+$ in this case, is a strong electrophile and reacts with any nucleophile around, including solvent molecules, e.g., (H_2O in this case. Since the 2nd step in non-selective, the solvent wins over any other nucleophile in the system because of its higher concentration. The neutral nucleophile becomes a cationic group in the product of the 2nd step, e.g., $R{-}OH_2^+$ in this case. The strong acid like $R{-}OH_2^+$ donates its proton to any base ($:B$) in the medium, including the solvent, e.g., H_2O in this case.

The overall reaction is substitution nucleophilic. The overall reaction is unimolecular proportional to the substrate concentration in the 1st step. So, this mechanism is called substitution nucleophilic unimolecular S_N1, where S stands for substitution, N or nucleophilic, and 1 for unimolecular.

- S_N1 is unimolecular.
- The carbonation intermediate is trigonal planar and the nucleophile can attack it from either side to make a new covalent bond. Therefore, if S_N1 reaction happens on a chiral carbon, around 50% of the product retains the configuration of the reactant, and the other 50% has the inverted configuration, i.e., **the product is a racemic mixture**.
- S_N1 Reaction takes place on tertiary alkyl halides. Secondary and primary alkyl halides do not undergo S_N1 reactions.

Elimination unimolecular (E1)

The carbocation formed in S_N1 reaction has acidic protons on β**C** because the electrons left on the conjugate base are stabilized as a π-bond, as in the mechanism shown below.



This mechanism eliminates a leaving group and a proton β to the leaving group. The 1st step, which is the rate-determining step, is unimolecular. This mechanism is called elimination unimolecular (E1), where E stands for elimination and 1 for unimolecular. E1 always competes with S_N1 because they have a common first step.

What decides the reaction will happen by S_N2, E2, S_N1, or E1 mechanism?

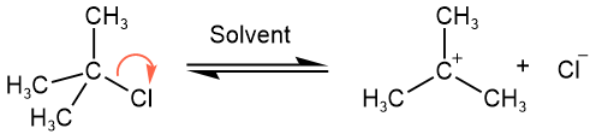
All of the S_N2, E2, S_N1, or E1 involve two nucleophiles, an incoming nucleophile and a leaving group which is a nucleophile attached to the substrate. Incoming nucleophile substitutes the leaving group in substitution reactions and eliminates β**H** and the leaving group in elimination reactions. The question is what decides which mechanism the reaction will follow? This section addresses the answers to this question. The solvent and the nucleophile determine S_N2 or S_N1 condition.

> Strong nucleophiles, usually anionic like $\mathbf{HO^-}$, $\mathbf{RO^-}$, and polar aprotic solvent like acetone ($\mathbf{(CH_3)_2C{=}O}$) or dimethylsulfoxide ($\mathbf{(CH_3)_2S{=}O}$) define **S_N2 and E2 condition**.

The substrate dictates S_N2, E2, or both will happen: S_N2 happens on the primary or methyl substrate, E2 happens on the tertiary substrate, and both happen simultaneously on a secondary substrate. S_N2 and E2 reactions do not take place in polar protic solvents.

> Polar protic solvents like water ($\mathbf{H_2O}$) or methanol ($\mathbf{CH_3{-}OH}$) and neutral nucleophiles like $\mathbf{H_2O}$, $\mathbf{ROH}$ define **S_N1 and E1 condition**.

Anionic nucleophiles can not exist in protic sovlents due to acid-base neutralization reactions between them. Neutral species are poor nucleophiles but are OK in S_N1 or E1 reactions because they are not involved in the rate-determining step. The following data on the dissociation rate of tertiary butyl chloride shows the effect of polar protic solvent on the rate-determining step of S_N1 and E1 reactions.



Solvent	Polarity (Dielectric constant)	Protic or aprotic	Relative rate
Water ($\mathbf{H_2O}$)	78	Polar protic	40
Ethanol ($\mathbf{CH_3CH_2{-}OH}$)	24	Polar protic	1
Acetone ($\mathbf{(CH_3)_2C{=}O}$	21	Polar aprotic	0.005

S_N1 and E1 usually compete as both have the same rate-determining step. Tertiary substrate easily react by S_N1 and E1 mechanism. Secondary substrate may or may not take place by S_N1 and E1. For example, secondary alkyl halides do not react, but secondary alcohols and ethers react by S_N1 and E1. Primary substrates usually do not react by S_N1 and E1 mechanisms.

Effect of leaving group on S_N2, E2, S_N1, and E1 mechanisms

Recall that the stronger the acid, the weaker the conjugate base, and voice versa. For example, **HI** is a strong acid and $\mathbf{I^-}$ is a weak base, while **HF** is a weak acid and $\mathbf{F^-}$ is a strong base. In other words, strong bases do not tend to protons, and weak bases easily leave protons in acid-base reactions. The same applies to leaving groups in S_N2, E2, S_N1, and E1 reactions.

> Strong bases are poor leaving groups, and weak bases are good leaving groups in S_N2, E2, S_N1, and E1 reactions.

The basicity and hence the leaving propensity of leaving groups follows these trends:

1. Basicity decreases from top to bottom in a group of periodic table. For example, the base strength of halides follows this order: $\overleftarrow{\mathbf{F^- > Cl^- > Br^- > I^-}}$. Leaving propensity follows the opposite trend i.e., **–I** is the best-leaving group, while **–F** is the worst leaving group. **–F** does not act as a leaving group.
2. Basicity decreases from right to left in a row of the periodic table. For example, the base strength of 2nd row elements follows this order: $\overleftarrow{\mathbf{F^- < OH^- < NH_2^- < CH_3^-}}$. Leaving propensity follows the opposite trend, i.e., $\mathbf{-OH}$ $\mathbf{-NH_2}$. $\mathbf{-CH_3}$ are the worst leaving group than **–F** and do not act as leaving group.
3. Basicity decreases upon protonation in the cases of amphoteric species. For example, $\mathbf{H_2O}$ is a weaker base than $\mathbf{OH^-}$. That is why, $\mathbf{-OH}$ is not a leaving group, but $\mathbf{-\overset{+}{O}H_2}$ is a good leaving group that leaves as a weak base $\mathbf{H_2O}$.

Nucleophilic substitution and elimination reactions of alcohols, ethers, amines, and sulfur compounds

Reactions of alcohols

Substitution reactions

The **O** of an alcohol (**R–OH**) is protonated by a strong acid to convert it from not leaving group ((**–OH**) to a good leaving group (($\mathbf{-\overset{+}{O}H_2}$). The protonated alcohols under go S_N1 or E1 reactions, except when the substrate is primary. that undergoes S_N2 or E2 reactions. For example, primary, secondary, and tertiary alcohols undergo nucleophilic substitution with **HCl**, **HBr**, or **HI** as shown below.

$$\mathbf{(CH_3)_3C{-}OH + HBr \rightleftharpoons (CH_3)_3C{-}\overset{+}{O}H_2 + Br^- \xrightarrow{\Delta} (CH_3)_3C{-}Br + H_2O} \text{ by } S_N1 \text{ mechanism}$$

$$\mathbf{(CH_3)_2CH{-}OH + HBr \rightleftharpoons (CH_3)_2CH{-}\overset{+}{O}H_2 + Br^- \xrightarrow{\Delta} (CH_3)_2CH{-}Br + H_2O} \text{ by } S_N1 \text{ mechanism}$$

$$\mathbf{CH_3CH_2{-}OH + HBr \rightleftharpoons CH_3CH_2{-}\overset{+}{O}H_2 + Br^- \xrightarrow{\Delta} CH_3CH_2{-}Br + H_2O} \text{ by } S_N2 \text{ mechanism}$$

Elimination reactions may compete with substitution reactions described above, but the alkene products of elimination add **HCl**, **HBr**, or **HI** and end in the same final product as the substitution products. These reactions of alkens will be described in a later section.

Elimination reactions

Inorder to perform elimination reactions, the **O** of alcohols (**R–OH**) is protonated by sulfuric acid ($\mathbf{H_2SO_4}$) in water solution. The conjugate base of sulfuric, i.e., $\mathbf{[HSO_4]^-}$ is a weak nucleophile and does not cause the substitution reaction. Water is a nucleophile, but its creation does not change the intermediate. However, water acts as a base picking up $\beta\mathbf{H}$, causing elimination reactions, as shown below.

$$\mathbf{(CH_3)_3C{-}OH \overset{H_2SO_4+H_2O}{\rightleftharpoons} (CH_3)_3C{-}\overset{+}{O}H_2 \xrightarrow{\Delta^+ HSO_4^- + H_2O} (CH_3)_2C{=}CH_2 + H_2O} \text{ by E1 mechanism}$$

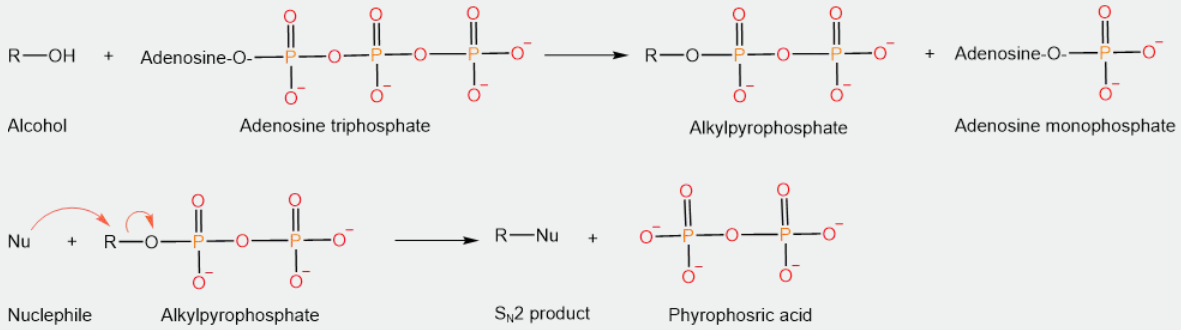
$$\mathbf{(CH_3)_2CH{-}OH \overset{H_2SO_4+H_2O}{\rightleftharpoons} (CH_3)_2CH{-}\overset{+}{O}H_2 \xrightarrow{\Delta^+ HSO_4^- + H_2O} CH_3CH{=}CH_2 + H_2O} \text{ by E1 mechanism}$$

$$\mathbf{CH_3CH_2{-}OH \overset{H_2SO_4+H_2O}{\rightleftharpoons} CH_3CH_2{-}\overset{+}{O}H_2 \xrightarrow{\Delta^+ HSO_4^- + H_2O} CH_2{=}CH_2 + H_2O} \text{ by E2 mechanism}$$

These reactions are called dehydration of alcohols that convert alcohols to alkenes.

Activating alcohols in biochemical systems

Alcohols are common intermediates in biochemical reactions. However, unlike in a chemical laboratory, strong acids like \(\ce{HBr}) or \(\ce(H2SO4) needed to activate alcohol groups do not survive under physiological conditions. Phosphoric acid and its anhydrides, i.e., pyrophosphoric acid and triphosphoric acids are weak acids and their conjugate bases, i.e., phosphate, pyrophosphate, and triphosphate, are weak bases and good leaving groups. Therefore, biological systems convert alcohols into phosphate or pyrophaste esters by reacting with adenosine triphosphate (ATP). It allows them to participate in the nucleophilic substitution reactions under physiological conditions as shown below.



Reactions of ethers

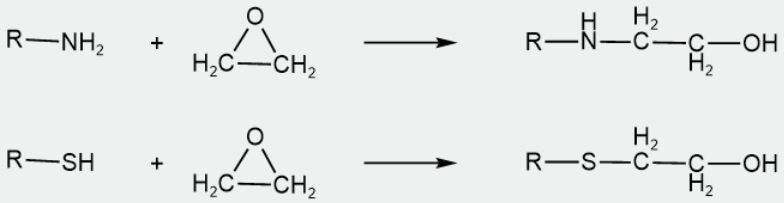
Like alcohols, the $\mathbf{O}$ of ethers ($\mathbf{R{-}O{-}R'}$) is protonated by a strong acid to convert it from not leaving group (($\mathbf{{-}OR'}$) to a good leaving group (($\mathbf{{-}\overset{+}{O}HR}$). For example, ethers undergo nucleophilic substitution reactions with $\mathbf{HCl}$, $\mathbf{HBr}$, or $\mathbf{HI}$ producing alcohols and an alkyl halides, as shown below.

$$\mathbf{(CH_3)_3C{-}O{-}C(CH_3)_3 + HBr \rightleftharpoons (CH_3)_3C{-}\overset{+}{O}HC(CH_3)_3 + Br^- \xrightarrow{\Delta} (CH_3)_3C{-}Br + (CH_3)_3C{-}OH}$$ by S_N1 mechanism

$$\mathbf{CH_3CH_2{-}O{-}CH_3 + HBr \rightleftharpoons CH_3CH_2{-}\overset{+}{O}HCH_3 + Br^- \xrightarrow{\Delta} CH_3CH_2{-}OH + CH_3{-}Br}$$ by S_N2 mechanism

Ethylene oxide: A sterilant based on S_N2 reactions

Ethylene oxide is a three-membered cyclic ether. It is a colorless gas with a boiling point of 11 ^oC. The $\mathbf{C{-}O}$ bonds in ethylene oxide are unstable due to angle strain. Therefore, the ether groups in ethylene oxide act as excellent leaving groups because angle strain is released. Ethylene oxide reacts fast by S_N2 mechanism with amino ($\mathbf{{-}NH_2}$) and sulfhydryl ($\mathbf{{-}SH}$) groups that are commonly present in biochemicals, as shown below.



These reactions modify the biochemicals, leading to the death of microorganisms. Ethylene oxide is used as a fumigant in foods and textiles and to sterilize surgical instruments in hospitals.

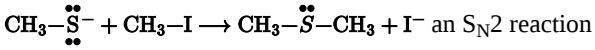
Reactions of amines

Amine $\mathbf{{-}NH_2}$ and also its protonated form $\mathbf{{-}NH_3^+}$ are poor as leaving groups and do not act as leaving groups. However, amines are good nucleophiles and act as incoming nucleophiles in various reactions, e.g., in S_N2 reactions with alkyl halides, as shown below.

$$\mathbf{CH_3CH_2{-}Br + CH_3{-}NH_2 \longrightarrow CH_3CH_2{-}\overset{+}{N}H_2{-}CH_2CH_3 + Br^-}$$ an S_N2 reaction

Reactions of thiols

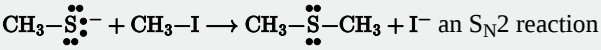
Thiolate ion is a good nucleophile for S_N2 reactions as shown in the following example.



$$CH_3{-}\ddot{S}^- + CH_3{-}I \longrightarrow CH_3{-}\ddot{S}{-}CH_3 + I^-$$ an S_N2 reaction

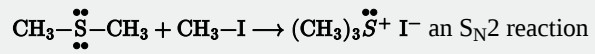
Methylating agent in lab and in biochemical systems

Methyl ($\overset{\delta+}{C}H_3\text{-}\overset{\delta-}{X}$) is the best electrophilic site, and iodide ($-I$) is the best-leaving group that makes methyliodide ($\overset{\delta+}{C}H_3\text{-}\overset{\delta-}{I}$) the best substrate for methylating any nucleophile in an S_N2 reactions, as shown in the following examples.



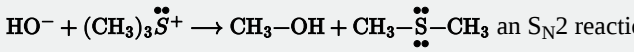
$$CH_3{-}\ddot{S}^- + CH_3{-}I \longrightarrow CH_3{-}\ddot{S}{-}CH_3 + I^-$$ an S_N2 reaction

Sulfur is a larger atom that can accommodate three alkyl groups. Therefore, dimethyl sulfide produced in the above reaction can be methylated one more time, producing a solfonium salt, as shown below.



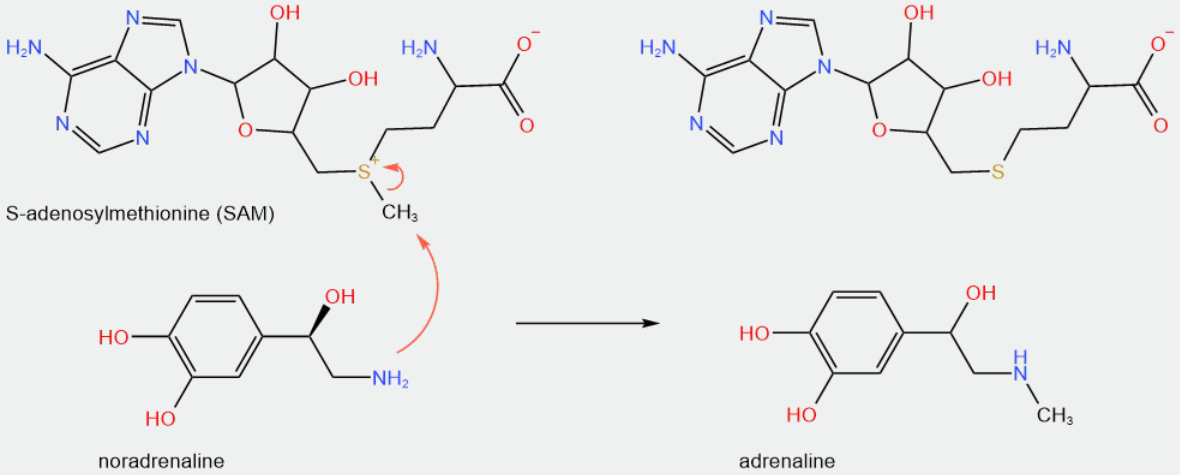
$$CH_3{-}\ddot{S}{-}CH_3 + CH_3{-}I \longrightarrow (CH_3)_3\ddot{S}^+\ I^-$$ an S_N2 reaction

Dimethyl sulfide ($(CH_3)_2\ddot{S}^+$-) is an excellent leaving group that makes trimethylsulfonium ion ($(CH_3)_3\ddot{S}^+$) an excellent methylating agent, as shown in an example below.



$$HO^- + (CH_3)_3\ddot{S}^+ \longrightarrow CH_3{-}OH + CH_3{-}\ddot{S}{-}CH_3$$ an S_N2 reaction

methyliodide ($H_3C{-}I$) is a common methylating agent in laboratory,- but it is not available in biological systems. S-adenosylmethionine (SAM), which is similar to trimethylsulfonium ion ($(CH_3)_3\ddot{S}^+$) is a common methylating agent in biological systems, as shown in an example below.



In the above example of a biochemical reaction, noradrenaline hormone is converted into a more potent adrenaline hormone by methylation reaction using SAM as a methylating agent.

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CHAPTER OVERVIEW

4: Aldehydes and Ketones

4.1: The Carbonyl Group
4.2: Naming Aldehydes and Ketones
4.3: Properties of Aldehydes and Ketones
4.4: Some Common Aldehydes and Ketones
4.5: Oxidation of Aldehydes
4.6: Reduction of Aldehydes and Ketones
4.7: Addition of Alcohols - Hemiacetals and Acetals

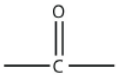
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4.1: The Carbonyl Group

Learning Objective

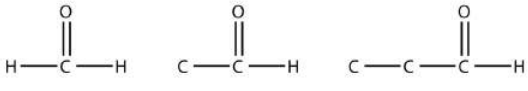
- Identify the aldehyde and ketone functional groups.

There are other functional groups that contain O atoms. Before we introduce them, we define the **carbonyl group**, which is formed when an O atom and a C atom are joined by a double bond:



The other two bonds on the C atom are attached to other atoms. It is the identities of these other atoms that define what specific type of compound an organic molecule is.

If one bond of the carbonyl group is made to an H atom, then the molecule is classified as an **aldehyde** (If there are two H atoms, there is only 1 C atom). When naming aldehydes, the main chain of C atoms must include the carbon in the carbonyl group, which is numbered as position 1 in the carbon chain. The parent name of the hydrocarbon is used, but the suffix *-al* is appended. (Do not confuse *-al* with *-ol*, which is the suffix used for alcohols.) So we have



Methanal has a common name with which you may be familiar: formaldehyde. The main thing to note about aldehydes is that the carbonyl group is at the *end* of a carbon chain.

A carbonyl group in the middle of a carbon chain implies that both remaining bonds of the carbonyl group are made to C atoms. This type of molecule is called a **ketone.** Despite the fact that aldehydes and ketones have the same carbonyl group, they have different chemical and physical properties and are properly grouped as two different types of compounds. The smallest ketone has three C atoms in it. When naming a ketone, we take the name of the parent hydrocarbon and change the suffix to *-one*:



The common name for propanone is acetone. With larger ketones, we must use a number to indicate the position of the carbonyl group, much like a number is used with alkenes and alkynes:



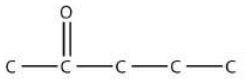
There is another way to name ketones: name the alkyl groups that are attached to the carbonyl group and add the word *ketone* to the name. So propanone can also be called dimethyl ketone, while 2-butanone is called methyl ethyl ketone.

Example 4.1.1

Draw the structure of 2-pentanone.

Solution

This molecule has five C atoms in a chain, with the carbonyl group on the second C atom. Its structure is as follows:



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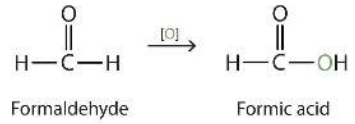
- **16.5: Other Oxygen-Containing Functional Groups** by Anonymous is licensed CC BY-NC-SA 3.0. Original source: https://2012books.lardbucket.org/books/beginning-chemistry.

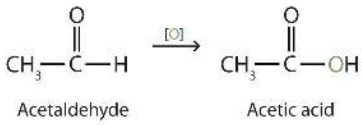
4.2: Naming Aldehydes and Ketones

Learning Objectives

- Use the IUPAC system to name and draw 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*.

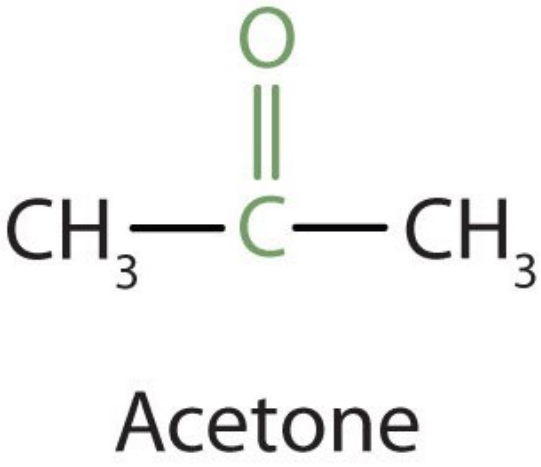




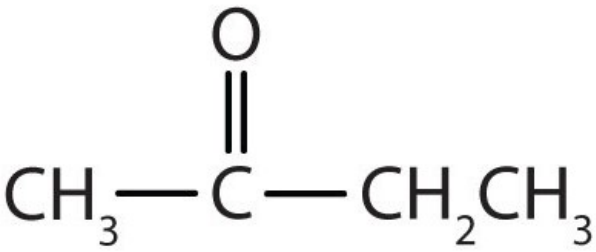
The stems for the common names of the first four aldehydes are as follows:

- 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.



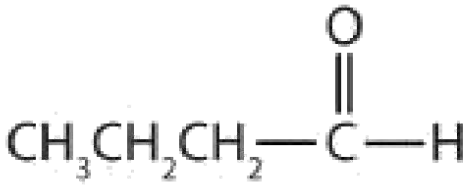
Generally, the common names of ketones consist of the names of the groups attached to the carbonyl group, followed by the word *ketone*. (Note the similarity to the naming of ethers.) Another name for acetone, then, is *dimethyl ketone*. The ketone with four carbon atoms is ethyl methyl ketone.

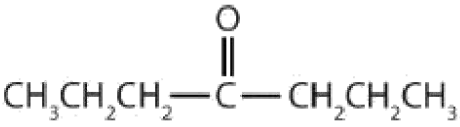


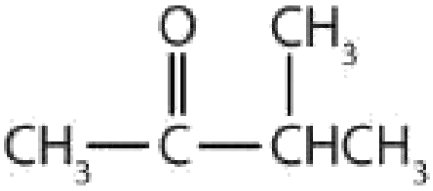
Ethyl methyl ketone

Example 4.2.1

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

1. 

- 

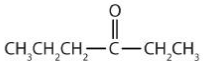
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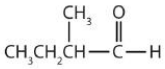
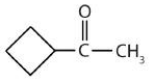
Solution

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 4.2.1

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

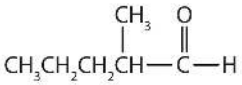
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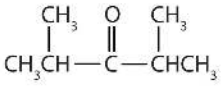
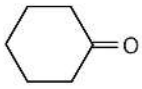
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Here are some simple IUPAC rules for naming aldehydes and ketones:

Example 4.2.2

Give the IUPAC name for each compound.

a. 

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- 

Solution

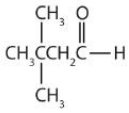
a. There are five carbon atoms in the LCC. The methyl group (CH_3) is a substituent on the second carbon atom of the chain; the aldehyde carbon atom is always C1. The name is derived from pentane. Dropping the *-e* and adding the ending *-al* gives pentanal. The methyl group on the second carbon atom makes the name 2-methylpentanal.

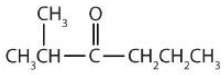
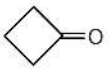
b. There are five carbon atoms in the LCC. The carbonyl carbon atom is C3, and there are methyl groups on C2 and C4. The IUPAC name is 2,4-dimethyl-3-pentanone.

c. 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. 

- 
- 

Example 4.2.3

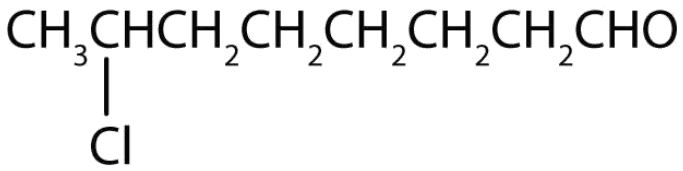
Draw the structure for each compound.

a. 7-chlorooctanal

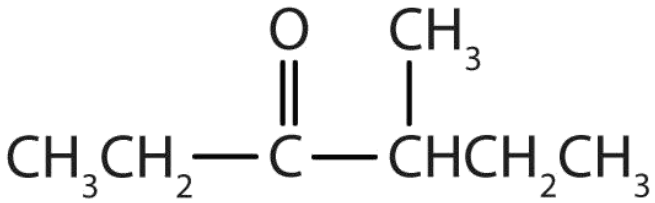
b. 4-methyl–3-hexanone

Solution

a. 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.



- 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.

a. 5-bromo-3-iodoheptanal
b. 5-bromo-4-ethyl-2-heptanone

Concept Review Exercises

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.

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.
6. Give the structure and IUPAC name for the compound that has the common name *m*-bromobenzaldehyde.
7. Give the IUPAC name for glyceraldehyde, ($HOCH_2CHOHCHO$). (Hint: as a substituent, the OH group is named *hydroxy*.)

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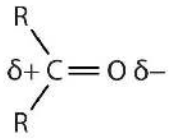
- **14.9: Aldehydes and Ketones- Structure and Names** by Anonymous is licensed CC BY-NC-SA 3.0. Original source: https://2012books.lardbucket.org/books/introduction-to-chemistry-general-organic-and-biological.

4.3: 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 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 **4.3.1** shows that the polar single bonds in ethers have little such effect, whereas hydrogen bonding between alcohol molecules is even stronger.

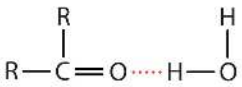
Table **4.3.1**: Boiling Points of Compounds Having Similar Molar Masses but Different Types of Intermolecular Forces

Compound	Family	Molar Mass	Type of Intermolecular Forces	Boiling Point (°C)
$CH_3CH_2CH_2CH_3$	alkane	58	dispersion only	–1
$CH_3OCH_2CH_3$	ether	60	weak dipole	6
CH_3CH_2CHO	aldehyde	58	strong dipole	49
$CH_3CH_2CH_2OH$	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.

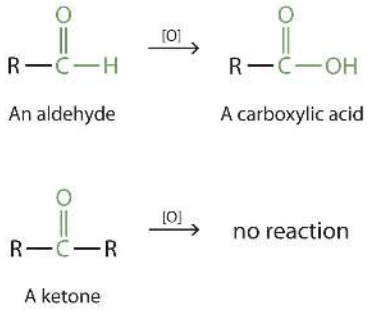
The oxygen atom of the carbonyl group engages in hydrogen bonding with a water molecule.



The solubility of aldehydes 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.

Oxidation of Aldehydes and Ketones

Aldehydes and ketones are much alike in many of their reactions, owing to the presence of the carbonyl functional group in both. They differ greatly, however, in one most important type of reaction: oxidation. Aldehydes are readily oxidized to carboxylic acids, whereas ketones resist oxidation.



The aldehydes are, in fact, among the most easily oxidized of organic compounds. They are oxidized by oxygen (O_2) in air to carboxylic acids.

$$2RCHO + O_2 \rightarrow 2RCOOH \tag{4.3.1}$$

The ease of oxidation helps chemists identify aldehydes. A sufficiently mild oxidizing agent can distinguish aldehydes not only from ketones but also from alcohols. Tollens' reagent, for example, is an alkaline solution of silver (Ag^+) ion complexed with ammonia (NH_3), which keeps the Ag^+ ion in solution.

$$H_3N—Ag^+—NH_3 \tag{4.3.2}$$

When Tollens' reagent oxidizes an aldehyde, the Ag^+ ion is reduced to free silver (Ag).



Deposited on a clean glass surface, the silver produces a mirror (Figure 4.3.1). Ordinary ketones do not react with Tollens' reagent.



Figure 4.3.1: Aldehyde Reactions. A reaction related to the Tollens' reaction is often used to silver mirrors. These ornaments were silvered by such a reaction. Glucose, a simple sugar with an aldehyde functional group, is used as the reducing agent. Source: Photo courtesy of Krebs Glas Lauscha, commons.wikimedia.org/wiki/File:Silvering.jpg.

Although ketones resist oxidation by ordinary laboratory oxidizing agents, they undergo combustion, as do aldehydes.

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.

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4.4: Some Common Aldehydes and Ketones

Learning Objectives

- Objective 1
- Objective 2

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 **4.4.2**).

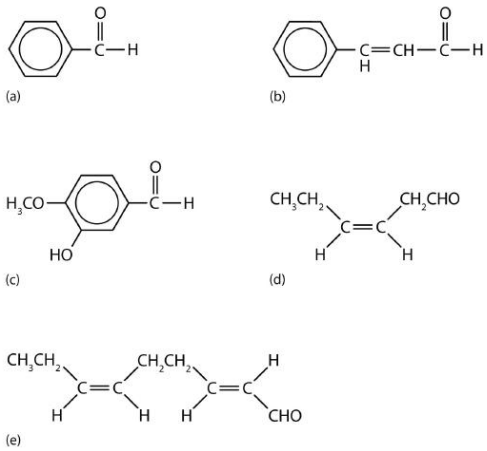


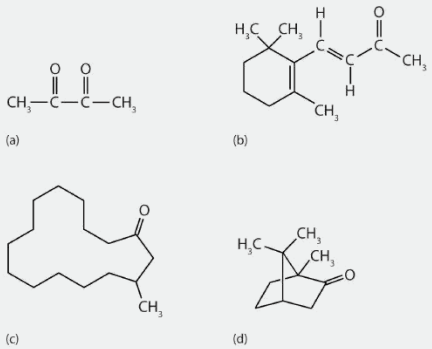
Figure **4.4.2** Some Interesting Aldehydes. (a) Benzaldehyde is an oil found in almonds; (b) cinnamaldehyde is oil of cinnamon; (c) vanillin gives vanilla its flavor; (d) *cis*-3-hexenal provides an herbal odor; and (e) *trans*-2-*cis*-6-nonadienal gives a cucumber odor.

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.

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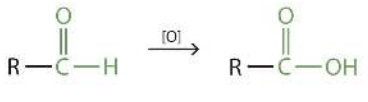
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4.5: Oxidation of Aldehydes

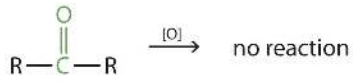
Learning Objectives

- Objective 1
- Objective 2
-

ldehydes and ketones are much alike in many of their reactions, owing to the presence of the carbonyl functional group in both. They differ greatly, however, in one most important type of reaction: oxidation. Aldehydes are readily oxidized to carboxylic acids, whereas ketones resist oxidation.



An aldehyde A carboxylic acid



A ketone

The aldehydes are, in fact, among the most easily oxidized of organic compounds. They are oxidized by oxygen (O_2) in air to carboxylic acids.

$$2RCHO + O_2 \rightarrow 2RCOOH \tag{4.5.1}$$

The ease of oxidation helps chemists identify aldehydes. A sufficiently mild oxidizing agent can distinguish aldehydes not only from ketones but also from alcohols. Tollens' reagent, for example, is an alkaline solution of silver (Ag^+) ion complexed with ammonia (NH_3), which keeps the Ag^+ ion in solution.

$$H_3N—Ag^+—NH_3 \tag{4.5.2}$$

When Tollens' reagent oxidizes an aldehyde, the Ag^+ ion is reduced to free silver (Ag).

$$RCHO(aq) + 2Ag(NH_3)_2^+(aq) + 3OH^-(aq) \longrightarrow$$

An aldehyde

$$RCOO^-(aq) + 2Ag(s) + 4\,NH_3(aq) + 2H_2O$$

Free silver

Deposited on a clean glass surface, the silver produces a mirror (Figure **4.5.1**). Ordinary ketones do not react with Tollens' reagent.



Figure **4.5.1**: Aldehyde Reactions. A reaction related to the Tollens' reaction is often used to silver mirrors. These ornaments were silvered by such a reaction. Glucose, a simple sugar with an aldehyde functional group, is used as the reducing agent. Source: Photo courtesy of Krebs Glas Lauscha, commons.wikimedia.org/wiki/File:Silvering.jpg.

Although ketones resist oxidation by ordinary laboratory oxidizing agents, they undergo combustion, as do aldehydes.

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4.6: Reduction of Aldehydes and Ketones



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4.7: Addition of Alcohols - Hemiacetals and Acetals



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CHAPTER OVERVIEW

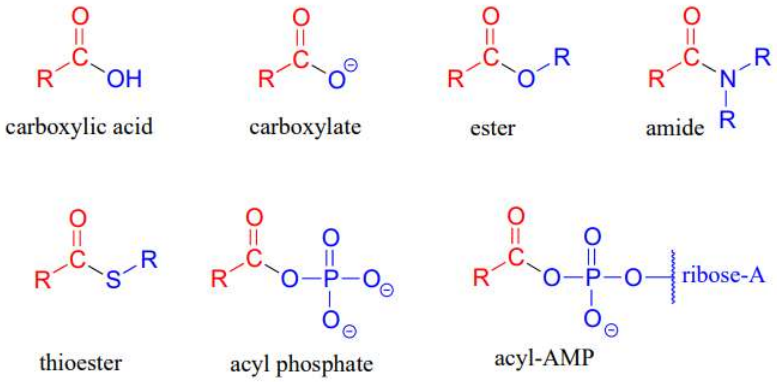
5: Carboxylic Acids and their Derivatives

5.1: Carboxylic Acid Derivatives
5.2: Nomenclature of Carboxylic Acids
5.3: Physical Properties of Carboxylic Acids
5.4: Nomenclature of Esters
5.5: Properties of Esters
5.6: Acidity of Carboxylic Acids
5.7: The Nucleophilic Acyl Substitution Mechanism
5.8: Reactions of Carboxylic Acids - Ester and Amide Formation

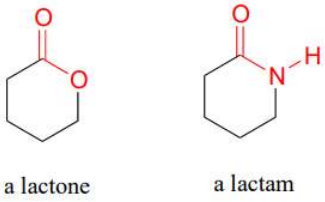
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5.1: Carboxylic Acid Derivatives

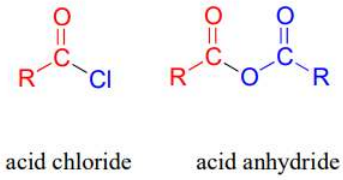
The functional groups at the heart of this chapter are called **carboxylic acid derivatives**: they include carboxylic acids themselves, carboxylates (deprotonated carboxylic acids), amides, esters, thioesters, and acyl phosphates.



Cyclic esters and amides are referred to as **lactones** and **lactams**, respectively.



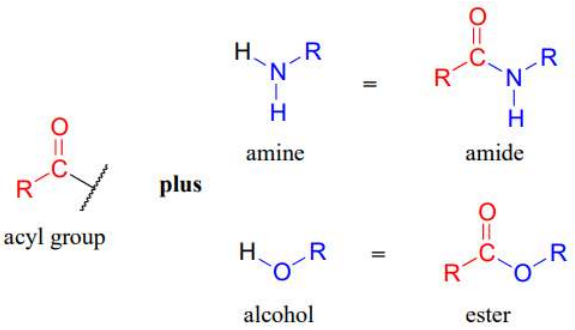
Carboxylic acid anyhydrides and acid chlorides, which also fall under the carboxylic acid derivative category, are not generally found in biomolecules but are useful intermediates in laboratory synthesis. They are discussed in a section on laboratory reactions at the end of this chapter.



Carboxylic acid derivatives can be distinguished from aldehydes and ketones by the presence of a group containing an electronegative heteroatom - usually oxygen, nitrogen, or sulfur – bonded directly to the carbonyl carbon. You can think of a carboxylic acid derivative as having two sides. One side is the acyl group, which is the carbonyl plus the attached alkyl (R) group. In the specific cases where R is a hydrogen or methyl, chemists use the terms formyl and acetyl group, respectively. One the other side is the heteroatom-linked group: in this text, we will sometimes refer to this component as the ‘acyl X' group (this, however, is not a standard term in organic chemistry).



Notice that the acyl X groups are simply deprotonated forms of other functional groups linked to the acyl group: in an amide, for example, the acyl X group is an amine, while in an ester the acyl X group is an alcohol.



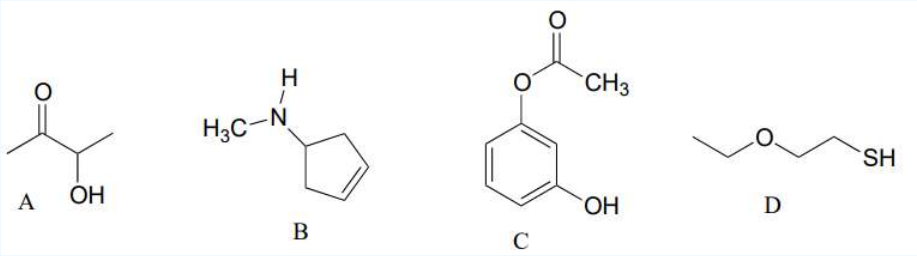
Exercise 11.2.1

What is the 'acyl X' group in:

a. an acid anhydride?
b. a thioester?
c. a carboxylic acid?
d. an acyl phosphate?

Exercise 11.2.2

Draw the structures indicated:

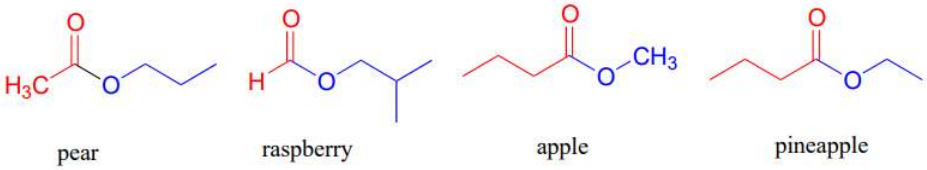


a. compound A after is has been acetylated (ie. an acetyl group added)
b. compound B after it has been formylated
c. compound C after it has been formylated
d. Compound D after it has been acetylated

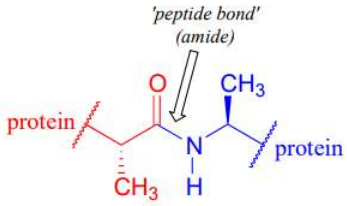
'Fatty acid' molecules such as stearate are carboxylates with long carbon chains for acyl groups.



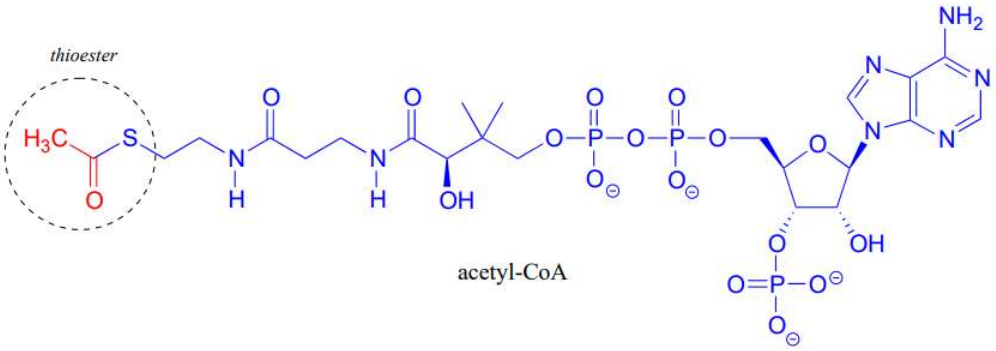
The aromas of many fruits come from small ester-containing molecules:



The 'peptide bonds' that link amino acids together in proteins are amides.



Acetyl-Coenzyme A, a very important two carbon (acetyl group) 'building block' molecule in metabolism, is characterized by reactions at its thioester functional group:

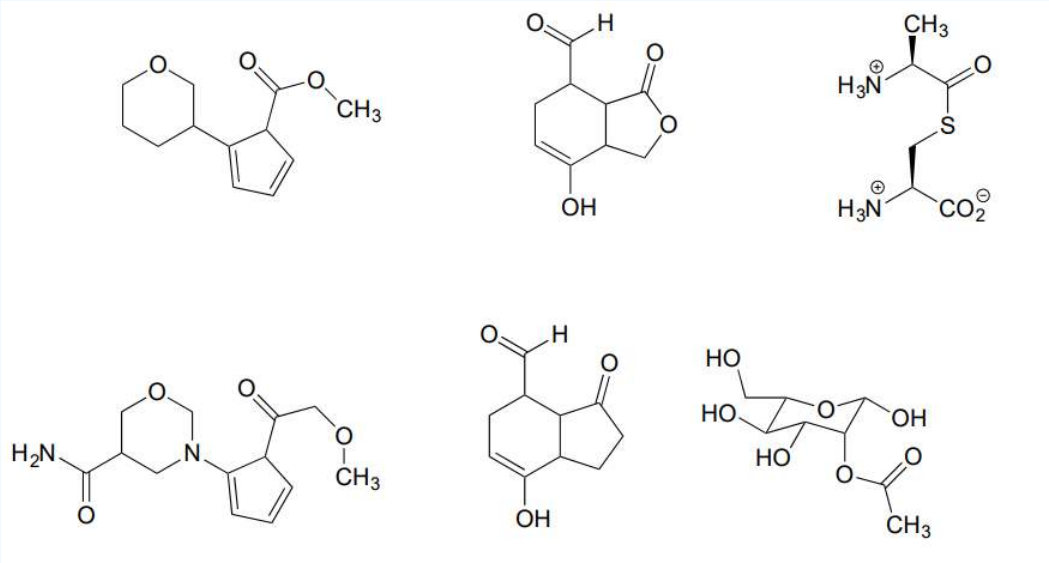


? Exercise 11.2.3

There are two amide groups in acetyl-CoA: identify them.

? Exercise 11.2.4

Name all carboxylic acid derivative groups in the molecules below.



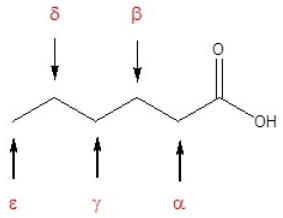
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5.2: Nomenclature of Carboxylic Acids

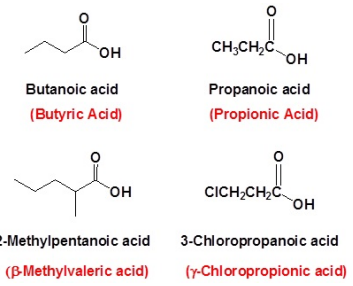
The IUPAC system of nomenclature assigns a characteristic suffix to these classes. The **–e** ending is removed from the name of the parent chain and is replaced **-anoic acid**. Since a carboxylic acid group must always lie at the end of a carbon chain, it is always is given the #1 location position in numbering and it is not necessary to include it in the name.

Many carboxylic acids are called by the common names. These names were chosen by chemists to usually describe a source of where the compound is found. In common names of aldehydes, carbon atoms near the carboxyl group are often designated by Greek letters. The atom adjacent to the carbonyl function is alpha, the next removed is beta and so on.



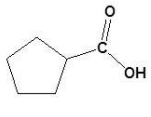
Formula	Common Name	Source	IUPAC Name	Melting Point	Boiling Point
HCO_2H	formic acid	ants (L. formica)	methanoic acid	8.4 ºC	101 ºC
CH_3CO_2H	acetic acid	vinegar (L. acetum)	ethanoic acid	16.6 ºC	118 ºC
$CH_3CH_2CO_2H$	propionic acid	milk (Gk. protus prion)	propanoic acid	-20.8 ºC	141 ºC
$CH_3(CH_2)_2CO_2H$	butyric acid	butter (L. butyrum)	butanoic acid	-5.5 ºC	164 ºC
$CH_3(CH_2)_3CO_2H$	valeric acid	valerian root	pentanoic acid	-34.5 ºC	186 ºC
$CH_3(CH_2)_4CO_2H$	caproic acid	goats (L. caper)	hexanoic acid	-4.0 ºC	205 ºC
$CH_3(CH_2)_5CO_2H$	enanthic acid	vines (Gk. oenanthe)	heptanoic acid	-7.5 ºC	223 ºC
$CH_3(CH_2)_6CO_2H$	caprylic acid	goats (L. caper)	octanoic acid	16.3 ºC	239 ºC
$CH_3(CH_2)_7CO_2H$	pelargonic acid	pelargonium (an herb)	nonanoic acid	12.0 ºC	253 ºC
$CH_3(CH_2)_8CO_2H$	capric acid	goats (L. caper)	decanoic acid	31.0 ºC	219 ºC

Example (Common Names Are in Red)

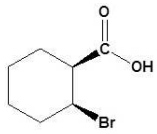


Naming carboxyl groups added to a ring

When a carboxyl group is added to a ring the suffix **-carboxylic acid** is added to the name of the cyclic compound. The ring carbon attached to the carboxyl group is given the #1 location number.



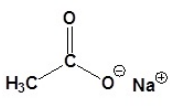
Cyclopentanecarboxylic acid



Cis-2-Bromocyclohexanecarboxylic acid

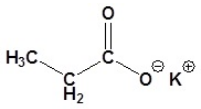
Naming carboxylates

Salts of carboxylic acids are named by writing the name of the cation followed by the name of the acid with the **–ic acid** ending replaced by an **–ate** ending. This is true for both the IUPAC and Common nomenclature systems.



Sodium ethanoate

(Sodium Acetate)

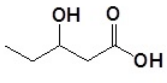


Potassium Propanoate

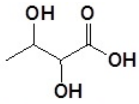
(Potassium propionate)

Naming carboxylic acids which contain other functional groups

Carboxylic acids are given the highest nomenclature priority by the IUPAC system. This means that the carboxyl group is given the lowest possible location number and the appropriate nomenclature suffix is included. In the case of molecules containing carboxylic acid and alcohol functional groups the OH is named as a hydroxyl substituent. However, the **l** in hydroxyl is generally removed.

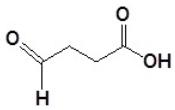


3-Hydroxypentanoic acid

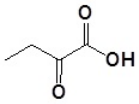


2,3-Dihydroxybutanoic acid

In the case of molecules containing a carboxylic acid and aldehydes and/or ketones functional groups the carbonyl is named as a "Oxo" substituent.

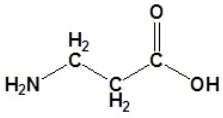


4-Oxobutanoic acid

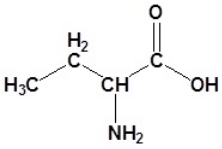


2-Oxobutanoic acid

In the case of molecules containing a carboxylic acid an amine functional group the amine is named as an "amino" substituent.



3-Aminopropanoic acid

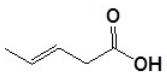


2-Aminobutanoic acid

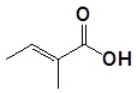
When carboxylic acids are included with an alkene the following order is followed:

(Location number of the alkene)-(Prefix name for the longest carbon chain minus the -ane ending)-(an –enoic acid ending to indicate the presence of an alkene and carboxylic acid)

Remember that the carboxylic acid has priority so it should get the lowest possible location number. Also, remember that cis/tran or E/Z nomenclature for the alkene needs to be included if necessary.



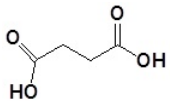
Trans-3-pentenoic acid



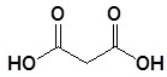
(E)-2-Methyl-2-butenoic acid

Naming dicarboxylic acids

For dicarboxylic acids the location numbers for both carboxyl groups are omitted because both functional groups are expected to occupy the ends of the parent chain. The ending **–dioic acid** is added to the end of the parent chain.



Butanedioic acid



Propanedioic acid

Contributors

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

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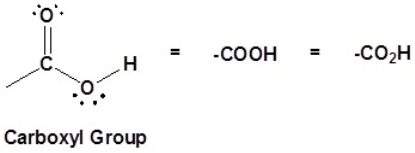
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5.3: Physical Properties of Carboxylic Acids

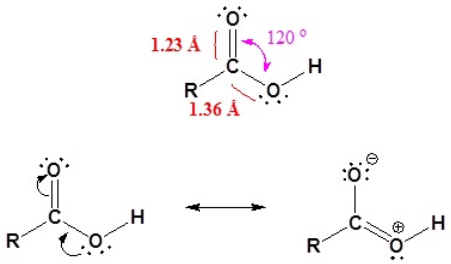
Structure of the carboxyl acid group

Carboxylic acids are organic compounds which incorporate a carboxyl functional group, CO_2H. The name carboxyl comes from the fact that a carbonyl and a hydroxyl group are attached to the same carbon.



Carboxyl Group

The carbon and oxygen in the carbonyl are both sp2 hybridized which give a carbonyl group a basic trigonal shape. The hydroxyl oxygen is also sp2 hybridized which allows one of its lone pair electrons to conjugate with the pi system of the carbonyl group. This make the carboxyl group planar an can represented with the following resonance structure.



Major Contributor Minor Contributor

Carboxylic acids are named such because they can donate a hydrogen to produce a carboxylate ion. The factors which affect the acidity of carboxylic acids will be discussed later.



Carboxylic acid Carboxylate ion

Physical Properties of Some Carboxylic Acids

Formula	Common Name	Source	IUPAC Name	Melting Point	Boiling Point
HCO_2H	formic acid	ants (L. formica)	methanoic acid	8.4 ºC	101 ºC
CH_3CO_2H	acetic acid	vinegar (L. acetum)	ethanoic acid	16.6 ºC	118 ºC
$CH_3CH_2CO_2H$	propionic acid	milk (Gk. protus prion)	propanoic acid	-20.8 ºC	141 ºC
$CH_3(CH_2)_2CO_2H$	butyric acid	butter (L. butyrum)	butanoic acid	-5.5 ºC	164 ºC
$CH_3(CH_2)_3CO_2H$	valeric acid	valerian root	pentanoic acid	-34.5 ºC	186 ºC
$CH_3(CH_2)_4CO_2H$	caproic acid	goats (L. caper)	hexanoic acid	-4.0 ºC	205 ºC
$CH_3(CH_2)_5CO_2H$	enanthic acid	vines (Gk. oenanthe)	heptanoic acid	-7.5 ºC	223 ºC
$CH_3(CH_2)_6CO_2H$	caprylic acid	goats (L. caper)	octanoic acid	16.3 ºC	239 ºC
$CH_3(CH_2)_7CO_2H$	pelargonic acid	pelargonium (an herb)	nonanoic acid	12.0 ºC	253 ºC
$CH_3(CH_2)_8CO_2H$	capric acid	goats (L. caper)	decanoic acid	31.0 ºC	219 ºC

Saturated			Unsaturated		
Formula	Common Name	Melting Point	Formula	Common Name	Melting Point
$CH_3(CH_2)_{10}CO_2H$	lauric acid	45 ºC	$CH_3(CH_2)_5CH{=}CH(CH_2)_7CO_2H$	palmitoleic acid	0 ºC
$CH_3(CH_2)_{12}CO_2H$	myristic acid	55 ºC	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$	oleic acid	13 ºC
$CH_3(CH_2)_{14}CO_2H$	palmitic acid	63 ºC	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$	linoleic acid	-5 ºC
$CH_3(CH_2)_{16}CO_2H$	stearic acid	69 ºC	$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$	linolenic acid	-11 ºC
$CH_3(CH_2)_{18}CO_2H$	arachidic acid	76 ºC	$CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2CO_2H$	arachidonic acid	-49 ºC

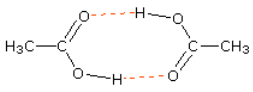
The table at the beginning of this page gave the melting and boiling points for a homologous group of carboxylic acids having from one to ten carbon atoms. The boiling points increased with size in a regular manner, but the melting points did not. Unbranched acids made up of an even number of carbon atoms have melting points higher than the odd numbered homologs having one more or one less carbon. This reflects differences in intermolecular attractive forces in the crystalline state. In the table of fatty acids we see that the presence of a cis-double bond significantly lowers the melting point of a compound. Thus, palmitoleic acid melts over 60º lower than palmitic acid, and similar decreases occur for the C_{18} and C_{20} compounds. Again, changes in crystal packing and intermolecular forces are responsible.

The factors that influence the relative boiling points and water solubilities of various types of compounds were discussed earlier. In general, dipolar attractive forces between molecules act to increase the boiling point of a given compound, with hydrogen bonds being an extreme example. Hydrogen bonding is also a major factor in the water solubility of covalent compounds To refresh your understanding of these principles Click Here. The following table lists a few examples of these properties for some similar sized polar compounds (the non-polar hydrocarbon hexane is provided for comparison).

Physical Properties of Some Organic Compounds

Formula	IUPAC Name	Molecular Weight	Boiling Point	Water Solubility
$CH_3(CH_2)_2CO_2H$	butanoic acid	88	164 ºC	very soluble
$CH_3(CH_2)_4OH$	1-pentanol	88	138 ºC	slightly soluble
$CH_3(CH_2)_3CHO$	pentanal	86	103 ºC	slightly soluble
$CH_3CO_2C_2H_5$	ethyl ethanoate	88	77 ºC	moderately soluble
$CH_3CH_2CO_2CH_3$	methyl propanoate	88	80 ºC	slightly soluble
$CH_3(CH_2)_2CONH_2$	butanamide	87	216 ºC	soluble
$CH_3CON(CH_3)_2$	N,N-dimethylethanamide	87	165 ºC	very soluble
$CH_3(CH_2)_4NH_2$	1-aminobutane	87	103 ºC	very soluble
$CH_3(CH_2)_3CN$	pentanenitrile	83	140 ºC	slightly soluble
$CH_3(CH_2)_4CH_3$	hexane	86	69 ºC	insoluble

The first five entries all have oxygen functional groups, and the relatively high boiling points of the first two is clearly due to hydrogen bonding. Carboxylic acids have exceptionally high boiling points, due in large part to dimeric associations involving two hydrogen bonds. A structural formula for the dimer of acetic acid is shown here. When the mouse pointer passes over the drawing, an electron cloud diagram will appear. The high boiling points of the amides and nitriles are due in large part to strong dipole attractions, supplemented in some cases by hydrogen bonding.



Acidity of Carboxylic Acids

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

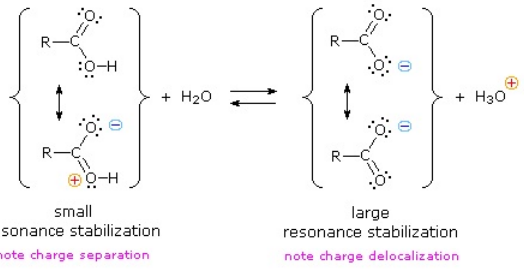
Compound	pK_a	Compound	pK_a
HCO_2H	3.75	$CH_3CH_2CH_2CO_2H$	4.82
CH_3CO_2H	4.74	$ClCH_2CH_2CH_2CO_2H$	4.53
FCH_2CO_2H	2.65	$CH_3CHClCH_2CO_2H$	4.05
$ClCH_2CO_2H$	2.85	$CH_3CH_2CHClCO_2H$	2.89
$BrCH_2CO_2H$	2.90	$C_6H_5CO_2H$	4.20
ICH_2CO_2H	3.10	$p\text{-}O_2NC_6H_4CO_2H$	3.45
Cl_3CCO_2H	0.77	$p\text{-}CH_3OC_6H_4CO_2H$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

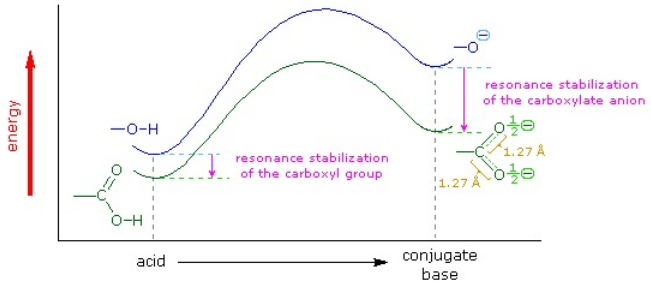
Why should the presence of a carbonyl group adjacent to a hydroxyl group have such a profound effect on the acidity of the hydroxyl proton? To answer this question we must return to the nature of acid-base equilibria and the definition of pK_a , illustrated by the general equations given below. These relationships were described in an previous section of this text.

$$H\text{–}A + H_2O \rightleftharpoons H_3O^{\oplus} + A:^{\ominus} \qquad K_{eq} = \frac{[H_3O^{\oplus}]\,[A:^{\ominus}]}{[HA]\,[H_2O]}$$

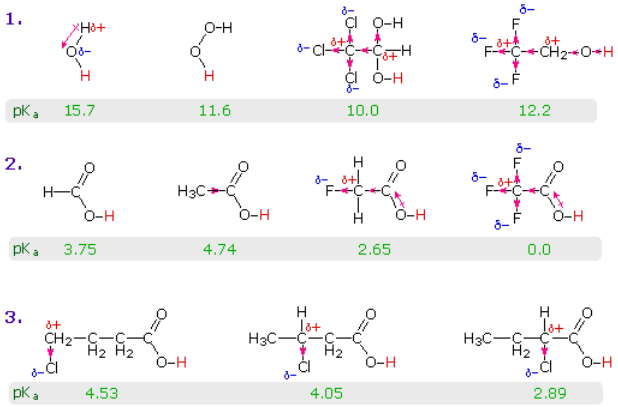
$$K_a = \frac{[H_3O^{\oplus}]\,[A:^{\ominus}]}{[HA]} \qquad pK_a = -\log K_a = \log\left(\frac{1}{K_a}\right)$$

We know that an equilibrium favors the thermodynamically more stable side, and that the magnitude of the equilibrium constant reflects the energy difference between the components of each side. In an acid base equilibrium the equilibrium always favors the weaker acid and base (these are the more stable components). Water is the standard base used for pK_a measurements; consequently, anything that stabilizes the conjugate base ($A:^{(-)}$) of an acid will necessarily make that acid (H–A) stronger and shift the equilibrium to the right. Both the carboxyl group and the carboxylate anion are stabilized by resonance, but the stabilization of the anion is much greater than that of the neutral function, as shown in the following diagram. In the carboxylate anion the two contributing structures have equal weight in the hybrid, and the C–O bonds are of equal length (between a double and a single bond). This stabilization leads to a markedly increased acidity, as illustrated by the energy diagram displayed by clicking the "Toggle Display" button.





The resonance effect described here is undoubtedly the major contributor to the exceptional acidity of carboxylic acids. However, inductive effects also play a role. For example, alcohols have pK_a's of 16 or greater but their acidity is increased by electron withdrawing substituents on the alkyl group. The following diagram illustrates this factor for several simple inorganic and organic compounds (row #1), and shows how inductive electron withdrawal may also increase the acidity of carboxylic acids (rows #2 & 3). The acidic hydrogen is colored red in all examples.



Water is less acidic than hydrogen peroxide because hydrogen is less electronegative than oxygen, and the covalent bond joining these atoms is polarized in the manner shown. Alcohols are slightly less acidic than water, due to the poor electronegativity of carbon, but chloral hydrate, $Cl_3CCH(OH)_2$, and 2,2,2,-trifluoroethanol are significantly more acidic than water, due to inductive electron withdrawal by the electronegative halogens (and the second oxygen in chloral hydrate). In the case of carboxylic acids, if the electrophilic character of the carbonyl carbon is decreased the acidity of the carboxylic acid will also decrease. Similarly, an increase in its electrophilicity will increase the acidity of the acid. Acetic acid is ten times weaker an acid than formic acid (first two entries in the second row), confirming the electron donating character of an alkyl group relative to hydrogen, as noted earlier in a discussion of carbocation stability. Electronegative substituents increase acidity by inductive electron withdrawal. As expected, the higher the electronegativity of the substituent the greater the increase in acidity (F > Cl > Br > I), and the closer the substituent is to the carboxyl group the greater is its effect (isomers in the 3rd row). Substituents also influence the acidity of benzoic acid derivatives, but resonance effects compete with inductive effects. The methoxy group is electron donating and the nitro group is electron withdrawing (last three entries in the table of pK_a values).

For additional information about substituent effects on the acidity of carboxylic acids Click Here

Vinylagous Acids

Compounds in which an enolic hydroxyl group is conjugated with a carbonyl group also show enhanced acidity. To see examples of such compounds Click Here

Contributors

Prof. Steven Farmer (Sonoma State University)

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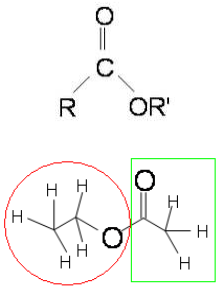
- **Physical Properties of Carboxylic Acids** is licensed CC BY-NC-SA 4.0.

5.4: Nomenclature of Esters

Esters are known for their distinctive odors and are commonly used for food aroma and fragrances. The general formula of an ester is RCOOR'.

Introduction

Esters are formed through reactions between an acid and an alcohol with the elimination of water. An example of this is the reaction of acetic acid with an alcohol, which yields an acetic ester and water.

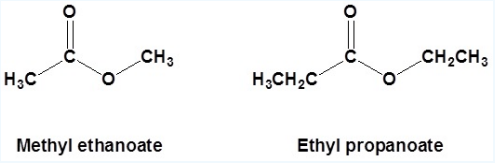


The part enclosed by the red circle represents the ethyl group from the alcohol and the part enclosed by the green rectangle represents the acetate group from the acid.

Esters can be named using a few steps

Esters are named as if the alkyl chain from the alcohol is a substituent. No number is assigned to this alkyl chain. This is followed by the name of the parent chain from the carboxylic acid part of the ester with an **–e** remove and replaced with the ending **–oate**.

Example



Esters are formed through reactions between an acid and an alcohol with the elimination of water. An example

1. First, identify the oxygen that is part of the continuous chain and bonded to carbon on both sides. (On one side of this oxygen there will be a carbonyl present but on the other side there won't be.)

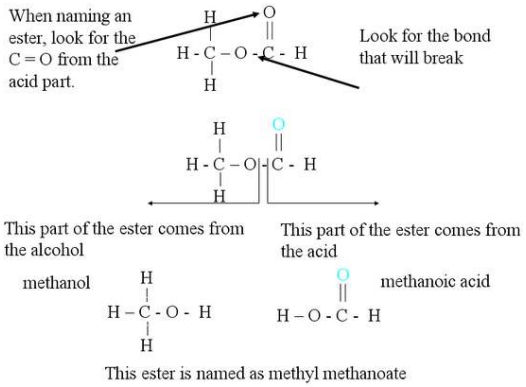


2. Second, begin numbering the carbon chains on either side of the oxygen identified in step 1.

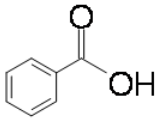


3. Next, use this format: [alkyl on side further from the carbonyl] (space) [alkane on the side with the carbonyl] - (In this case: [methyl] [methane])

4. Finally, change the ending of the alkane on the same side as the carbonyl from -e to -oate. (In this case: methyl methanoate)

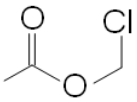


When an ester group is attached to a ring, the ester is named as a substituent on the ring.

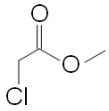


Benzenecarboxylic acid (Benzoic acid)

Other substituents that exist on either side of the ester are named in the same way as they are on regular alkane chains. The only thing you must make sure of is placing the substituent name on the part of the name that corresponds to the side of the ester that it is on.



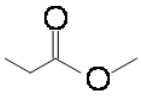
1-chloromethyl ethanoate



methyl 2-chloroethanoate

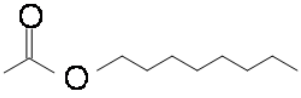
$$CH_3COOCH_2CH_3$$

methyl propanoate



$$CH_3COOCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$$

octyl ethanoate



References

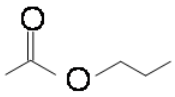
1. Leigh, G. J., H. Favre, and Val Metanomski. Principles of Chemical Nomenclature A Guide to Iupac Recommendations (IUPAC Chemical Data Series). Malden: Blackwell Science, 1998.
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Outside Links

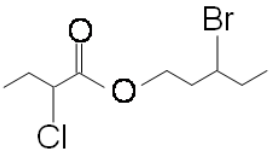
- http://en.Wikipedia.org/wiki/Esters
- http://en.Wikipedia.org/wiki/IUPAC_n...emistry#Esters

Problems

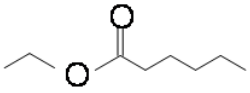
Name the following:



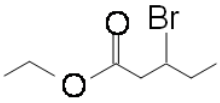
Answer: propyl ethanoate



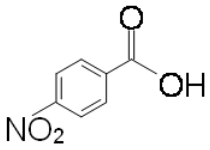
Answer: 3-bromopentyl 2-chlorobutanoate



Answer: ethyl hexanoate



Answer: ethyl 3-bromopentanoate



Answer: 4-nitrobenzenecarboxylic acid or

4-nitrobenzoic acid

Contributors

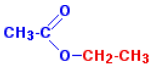
- Prof. Steven Farmer (Sonoma State University)

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5.5: Properties of Esters

Esters are derived from carboxylic acids. A carboxylic acid contains the -COOH group, and in an ester the hydrogen in this group is replaced by a hydrocarbon group. This could be an alkyl group like methyl or ethyl, or one containing a benzene ring such as a phenyl or benzyl group. The most commonly discussed ester is ethyl ethanoate. In this case, the hydrogen in the -COOH group has been replaced by an ethyl group. The formula for ethyl ethanoate is:

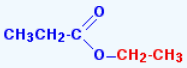


ethyl ethanoate

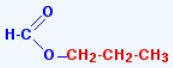
Notice that the ester is named the opposite way around from the way the formula is written. The "ethanoate" bit comes from ethanoic acid. The "ethyl" bit comes from the ethyl group replacing the hydrogen.

Example

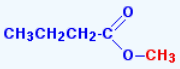
In each case, be sure that you can see how the names and formulae relate to each other.



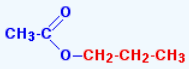
ethyl propanoate



propyl methanoate



methyl butanoate



propyl ethanoate

Notice that the acid is named by counting up the total number of carbon atoms in the chain - including the carbonyl carbon. So, for example, CH_3CH_2COOH is propanoic acid, and CH_3CH_2COO is the propanoate group.

Fats and oils

Animal and vegetable fats and oils are composed of long-chain, complicated esters. The physical differences observed between a fat (like butter) and an oil (like sunflower oil) are due to differences in melting points of the mixture of esters they contain. If the melting point of the substance is below room temperature, it will be a liquid - an oil. If the melting point is above room temperature, it will be a solid - a fat. The causes of the differences in melting points are discussed below.

Fats and oils as big esters

Esters can be made from carboxylic acids and alcohols. This is discussed in detail on another page; in general terms, the two combine together, losing a molecule of water in the process. Consider a very simple ester such as ethyl ethanoate. The figure below shows its formation from ethanoic acid and ethanol.

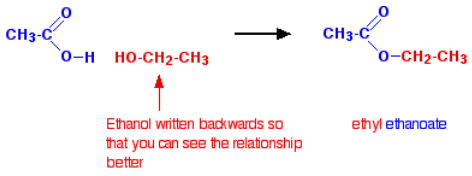
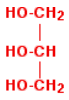
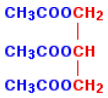


Figure: The diagram shows the relationship between the ethanoic acid, the ethanol and the ester. This is not intended to be a full equation. Water, of course, is also produced.

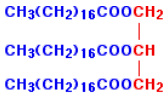
The same process can be carried out for more complicated alcohols. The diagram below shows the structure of propane-1,2,3-triol (commonly known as glycerol).



Just as with the ethanol in the previous equation, I've drawn this back-to-front to make the next diagrams clearer. Normally, it is drawn with the -OH groups on the right-hand side. By the esterification process shown above, three ethanoate groups can be formed.



Lengthening each carbon chain creates a triglyceride, otherwise known as a fat.

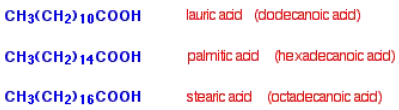


The acid $CH_3(CH_2)_{16}COOH$ is called octadecanoic acid, frequently referred to by its common name, stearic acid. The full name for the ester of this with propane-1,2,3-triol is propane-1,2,3-triyl trioctadecanoate, unsurprisingly known by by its common name of glyceryl tristearate.

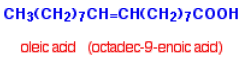
Saturated and unsaturated fats and oils

If the fat or oil is saturated, the acid from which it is derived has no carbon-carbon double bonds in its chain. Stearic acid is a saturated acid; therefore glyceryl tristearate is a saturated fat. If the acid has just one carbon-carbon double bond somewhere in the chain, it is called mono-unsaturated. If it has more than one carbon-carbon double bond, it is polyunsaturated.

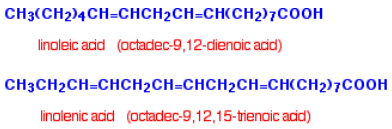
The acids below are saturated acids, and will therefore form saturated fats and oils:



Oleic acid is a typical mono-unsaturated acid:



Linoleic and linolenic acids are typical polyunsaturated acids.



Physical properties

Boiling points

Small esters have boiling points which are similar to those of aldehydes and ketones with the same number of carbon atoms. Esters, like aldehydes and ketones, are polar molecules and so have dipole-dipole interactions as well as van der Waals dispersion forces. However, they do not form ester-ester hydrogen bonds, so their boiling points are significantly lower than those of an acid with the same number of carbon atoms.

molecule	type	boiling point (°C)
$CH_3COOCH_2CH_3$	ester	77.1
$CH_3CH_2CH_2COOH$	carboxylic acid	164

Solubility in water

Small esters are fairly soluble in water but solubility decreases with increasing chain length, as shown below:

ester	formula	solubility (g per 100 g of water)
ethyl methanoate	$HCOOCH_2CH_3$	10.5
ethyl ethanoate	$CH_3COOCH_2CH_3$	8.7
ethyl propanoate	$CH_3CH_2COOCH_2CH_3$	1.7

The reason for this trend in solubility is that although esters cannot hydrogen bond with each other, they can hydrogen bond with water molecules. One of the partially-positive hydrogen atoms in a water molecule can be sufficiently attracted to one of the lone pairs on one of the oxygen atoms in an ester, forming a hydrogen bond. Dispersion forces and dipole-dipole attractions are also present.

Forming these intermolecular attractions releases some of the energy needed to solvate the ester. As chain length increases, the hydrocarbon portion forces itself between water molecules, breaking the relatively strong hydrogen bonds between water molecules without offering an energetic compensation; furthermore, the water molecules are forced into an ordered alignment along the chain, decreasing the entropy in the system. This makes the process thermodynamically less favorable, and so solubility decreases.

The physical properties of fats and oils

Solubility in water

Fats and oils are not water soluble. The chain lengths are so great that far too many hydrogen bonds between water molecules must be broken; this is not an energetically profitable arrangement.

Melting point

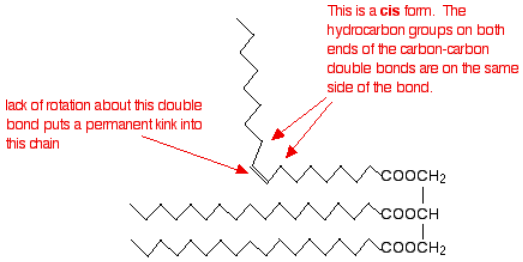
Melting points determine whether the substance is a fat (a solid at room temperature) or an oil (a liquid at room temperature). Fats normally contain saturated chains. These allow more effective van der Waals dispersion forces between the molecules: more energy is required to separate the chains, increasing the melting point.

A greater number of double bonds, or degree of unsaturation, in the molecules results in a lower melting point, because the van der Waals forces are less effective. The efficacy of van derWaals forces depends on the ability of molecules to pack closely together. The presence of carbon-carbon double bonds in the chains disrupts otherwise tidy packing. Here is a simplified diagram of a saturated fat:

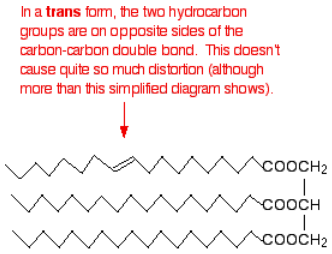


The hydrocarbon chains are, of course, in constant motion in the liquid, but it is possible for them to lie tidily when the substance solidifies. If the chains in one molecule can lie tidily, that means that neighboring molecules can get close. That increases the attractions between one molecule and its neighbors and so increases the melting point.

Unsaturated fats and oils have at least one carbon-carbon double bond in at least one chain. Rotation about a carbon-carbon double bond is constrained, locking a permanent kink into the chain. This makes packing molecules close together more difficult. If the chains cannot pack well, the van der Waals forces will be less effective. This effect is much stronger for molecules in which the hydrocarbon chains at either end of the double bond are arranged *cis*- to each other, as shown in the figure below:



In the *trans*- conformation, the effect is not as marked. It is, however, rather more than the diagram below suggests because of the changes in bond angles around the double bond compared with the rest of the chain.



Trans-fats and oils have higher melting points than their corresponding *cis*- conformations because the packing is not interrupted to the same degree. Naturally occurring unsaturated fats and oils tend to adopt the *cis*- conformations.

Contributors

- Jim Clark (Chemguide.co.uk)

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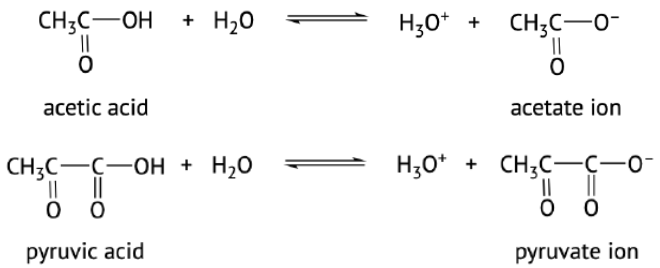
5.6: Acidity of Carboxylic Acids

Learning Objectives

- Define pK_a and use it to determine acidity of different carboxylic acids.
- Describe the reactions between carboxylic acids and strong bases.

Ionization of Carboxylic Acids

Carboxylic acids are named such because they tend to be more acidic than other functional groups in organic chemistry. In dilute aqueous solutions, they act as *weak acids* that partially dissociate to produce the corresponding **carboxylate anion** and hydronium cation (H_3O^+). Carboxylate anions are named by replacing the *-ic acid* ending from the carboxylic acid with *-ate*, see examples below.



The extent of dissociation of these weak acids in water is described by K_a values. Remember that a compound with a smaller K_a value will be a weaker acid.

$$RCOOH + H_2O \rightleftharpoons RCOO^- + H_3O^+ \; K_a = \frac{[RCOO^-][H_3O^+]}{[RCOOH]}$$

When comparing the acidity of organic and biomolecules, it is useful (and more preferable) to use pK_a values instead of K_a values, which are calculated by taking the negative log of K_a: $pK_a = -\log K_a$. When using the pK_a scale, it is important to know that *weaker acids* have *larger* and more positive pK_a values, this is opposite of K_a values. The pK_a values of some typical carboxylic acids are listed in Table **5.6.1**. (Remember that pK_a is a log expression, which means that every 1 pK_a unit represents a 10-fold change in acidity.)

Table **5.6.1**: Comparisons of Carboxylic Acid K_a and pK_a Values

Name	Compound	K_a	pK_a
formic acid	HCOOH	1.8×10^{-4}	3.74
acetic acid	CH_3COOH	1.8×10^{-5}	4.74
propanoic acid	CH_3CH_2COOH	1.3×10^{-5}	4.89
butanoic acid	$CH_3CH_2CH_2COOH$	1.5×10^{-5}	4.82
chloroacetic acid	$ClCH_2COOH$	1.4×10^{-3}	2.85
trichloroacetic acid	Cl_3CCOOH	2.3×10^{-1}	0.64
hexanoic acid	$CH_3(CH_2)_4COOH$	1.3×10^{-5}	4.89
benzoic acid	C_6H_5COOH	6.5×10^{-5}	4.19
oxalic acid	HOOCCOOH	5.4×10^{-2}	1.27
	$^-OOCCOOH$	5.2×10^{-5}	4.28
glutaric acid	$HOOC(CH_2)_3COOH$	4.5×10^{-5}	4.35
	$^-OOC(CH_2)_3COOH$	3.8×10^{-6}	5.42

Neutralization of Carboxylic Acids

Carboxylic acids will react with bases such as sodium hydroxide (NaOH), sodium carbonate (Na_2CO_3), and sodium bicarbonate ($NaHCO_3$) to form water and a **carboxylic acid salt**:

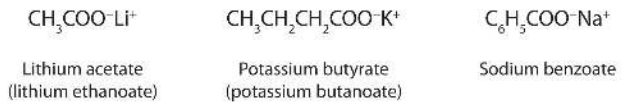
$$RCOOH + NaOH(aq) \rightarrow RCOO^-Na^+(aq) + H_2O$$

$$2RCOOH + Na_2CO_3(aq) \rightarrow 2RCOO^-Na^+(aq) + H_2O + CO_2(g)$$

$$RCOOH + NaHCO_3(aq) \rightarrow RCOO^-Na^+(aq) + H_2O + CO_2(g)$$

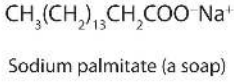
In these reactions, the carboxylic acids act like inorganic acids: they neutralize basic compounds. With solutions of carbonate (CO_3^{2-}) and bicarbonate (HCO_3^-) ions, they also form carbon dioxide gas.

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:



Note

The salts of long-chain carboxylic acids are called soaps.



Example 5.6.1

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 CH_2CH_2COOH.

1. Propionic acid ionizes in water to form a propionate ion and a hydronium (H_3O^+) ion. $CH_3CH_2COOH(aq) + H_2O(\ell) \rightarrow CH_3CH_2COO^-(aq) + H_3O^+(aq)$
2. Propionic acid reacts with NaOH(aq) to form sodium propionate and water. $CH_3CH_2COOH(aq) + NaOH(aq) \rightarrow CH_3CH_2COO^-Na^+(aq) + H_2O(\ell)$

? Exercise 5.6.1

Write an equation for each reaction.

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

✓ Example 5.6.2

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

a. aqueous sodium hydoxide (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). $CH_3(CH_2)_8COOH + NaOH(aq) \rightarrow CH_3(CH_2)_8COO^-Na^+(aq) + H_2O(\ell)$
b. With $NaHCO_3$, the products are a salt, H_2O, and carbon dioxide (CO_2). $CH_3(CH_2)_8COOH + NaHCO_3(aq) \rightarrow CH_3(CH_2)_8COO^-Na^+(aq) + H_2O(\ell) + CO_2(g)$

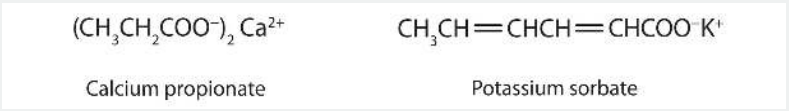
? Exercise 5.6.3

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

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

Note 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.



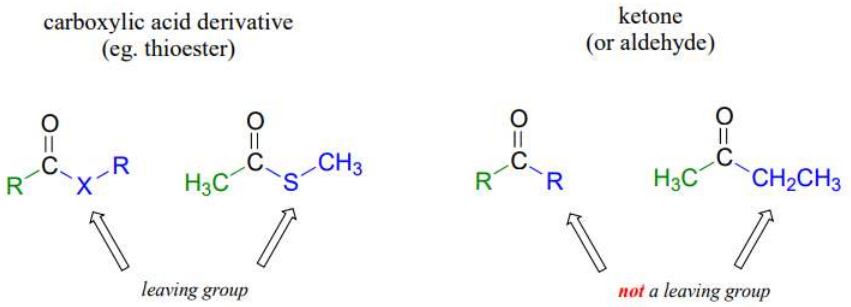
Calcium propionate — Potassium sorbate

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5.7: The Nucleophilic Acyl Substitution Mechanism

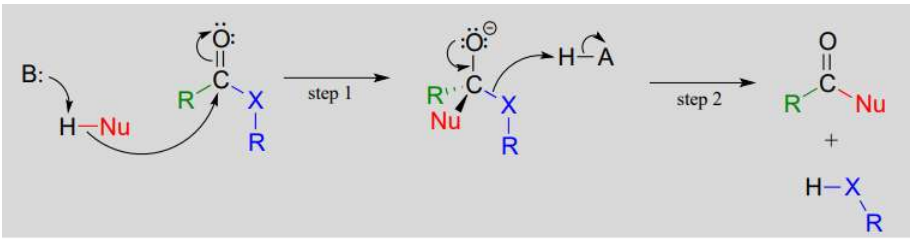
The fact that one of the atoms adjacent to the carbonyl carbon in carboxylic acid derivatives is an electronegative heteroatom – rather than a carbon like in ketones or a hydrogen like in aldehydes - is critical to understanding the reactivity of carboxylic acid derivatives. The most significant difference between a ketone/aldehyde and a carboxylic acid derivative is that the latter has a potential leaving group - what we are calling the 'acyl X group' - bonded to the carbonyl carbon.



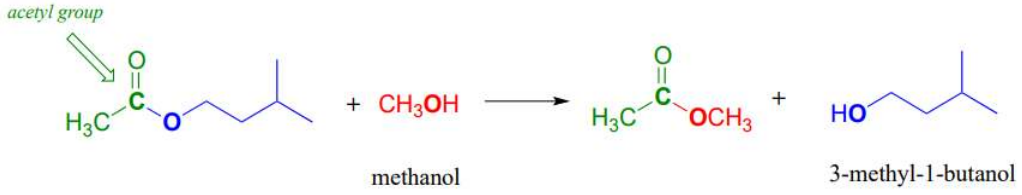
As a result, carboxylic acid derivatives undergo nucleophilic acyl substitution reactions, rather than nucleophilic additions like ketones and aldehydes.

A nucleophilic acyl substitution reaction starts with nucleophilic attack at the carbonyl, leading to a tetrahedral intermediate (step 1 below). In step 2, the tetrahedral intermediate collapses and the acyl X group is expelled, usually accepting a proton from an enzymatic acid in the process.

Mechanism for a nucleophilic acyl substitution reaction:



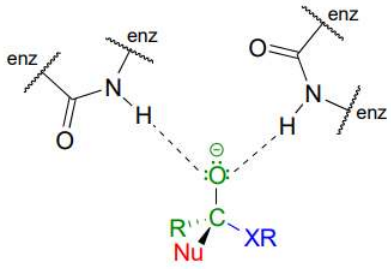
Notice that in the product, the nucleophile becomes the new acyl X group. This is why this reaction type is called a nucleophilic acyl substitution: one acyl X group is substituted for another. For example, in the reaction below, one alcohol 'X group' (methanol), substitutes for by another alcohol 'X group' (3-methyl-1-butanol) as one ester is converted to another.



Another way of looking at this reaction is to picture the acyl group being transferred from one acyl X group to another: in the example above, the acetyl group (in green) is transferred from 3-methyl-1-butanol (blue) to methanol (red). For this reason, nucleophilic acyl substitutions are also commonly referred to as acyl transfer reactions.

Enzymes catalyzing nucleophilic acyl substitution reactions have evolved ways to stabilize the negatively charged, tetrahedral intermediate, thus lowering the activation energy of the first, rate-determining step (nucleophilic attack). The late transition state of the first step resembles the tetrahedral intermediate that results: recall from chapter 6 that the Hammond postulate tells us that anything that stabilizes the tetrahedral intermediate will also stabilize the transition state. In many cases, for example, enzymatic amino acid residues are positioned in the active site so as to provide stabilizing hydrogen bond donating interactions with the

negatively-charged oxygen. This arrangement is sometimes referred to in the biochemistry literature as an oxanion hole. The figure below shows a tetrahedral intermediate stabilized by hydrogen bond donation from two main chain (amide) nitrogen atoms.



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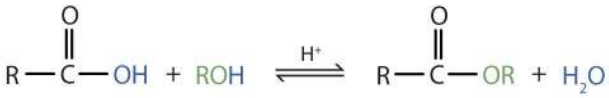
5.8: Reactions of Carboxylic Acids - Ester and Amide Formation

Learning Objectives

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

Carboxylic acids will react with alcohols and amines following a similar pattern. In both cases, the –OH group of the carboxylic acid will be replaced by a different group to form either an ester or an amide, with water formed as a by-product. When the reaction involves an alcohol, the –OH of the acid is replaced by the –OR' of the alcohol. When the reaction involves an amine, the –OH of the acid is replaced by the $–NH_2$, or –NHR', or $–NR'_2$ of the amine.

Ester formation

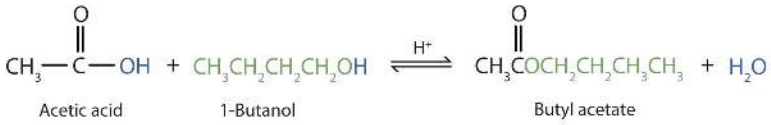


Amide formation



Esterification

Esters are prepared by **esterification**, a reaction in which a carboxylic acid and an alcohol are heated in the presence of an acid catalyst:

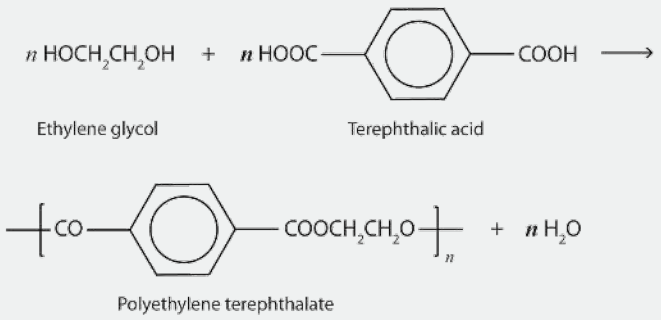


The reaction is reversible and will reach equilibrium with approximately equivalent amounts of reactants and products. Using excess amounts of alcohol and continuously removing a product, can drive the reaction towards the product side as per LeChatelier's principle.

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.

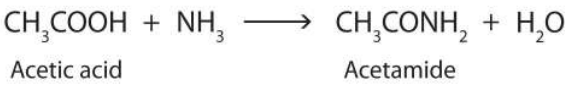
The most important polyester, polyethylene terephthalate (PET), is made from terephthalic acid and ethylene glycol monomers:



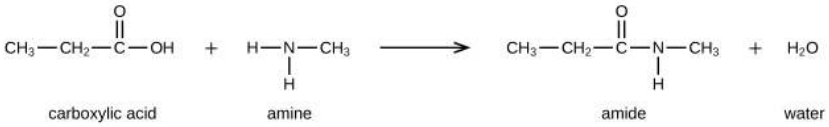
Polyester molecules make excellent fibers and are used in many fabrics. A knitted polyester tube, which is biologically inert, can be used in surgery to repair or replace diseased sections of blood vessels. PET is used to make bottles for soda pop and other beverages. It is also formed into films called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

Amide Formation

When a carboxylic acid reacts with ammonia (NH_3) a *primary amide* is formed:



When a carboxylic acid reacts with primary or secondary amines, secondary or tertiary amides are produced, respectively.



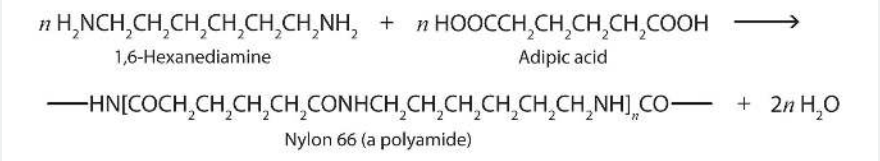
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Tertiary amines do not have a hydrogen attached to the nitrogen and therefore do not form amides when mixed with carboxylic acids. However, an acid-base reaction does occur with the amine accepting a proton (acts as a base) and the carboxylic acid donating a proton. In this case the ammonium and carboxylate salts are formed:

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Note Polyamides

Just as the reaction of a diol and a diacid forms a polyester, the reaction of a diacid and a diamine yields a polyamide. The two difunctional monomers often employed are adipic acid and 1,6-hexanediamine. The monomers condense by splitting out water 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.

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CHAPTER OVERVIEW

6: Amines and Amides

6.1: Amines - Structures and Names
6.2: Physical Properties of Amines
6.3: Amines as Bases
6.4: Amides- Structures and Names
6.5: Physical Properties of Amides
6.6: Chemistry of Amides

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6.1: 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.

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 **6.1.1**).

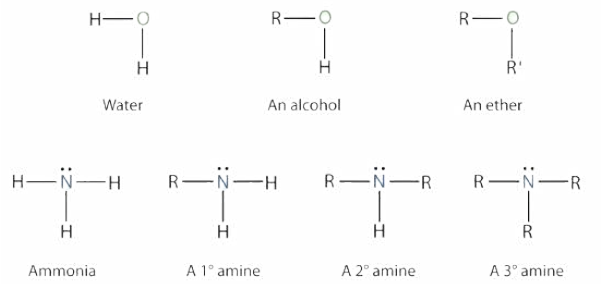


Figure **6.1.1**: The Structure of Amines Compared to Water, an Alcohol, and an Ether

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.



The common names for simple aliphatic amines consist of an alphabetic list of alkyl groups attached to the nitrogen atom, followed by the suffix *-amine*. (Systematic names are often used by some chemists.) The amino group (NH_2) is named as a substituent in more complicated amines, such as those that incorporate other functional groups or in which the alkyl groups cannot be simply named.

Example 6.1.1

Name and classify each compound.

a. $CH_3CH_2CH_2NH_2$

b. 

c. $CH_3CH_2NHCH_2CH_3$

d. $CH_3CH_2CH_2NHCH_3$

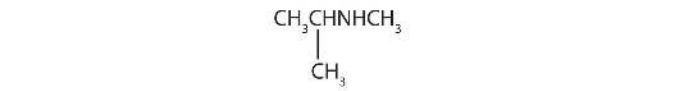
Solution

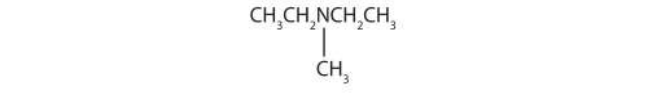
a. There is only one alkyl group attached to the nitrogen atom, so the amine is primary. A group of three carbon atoms (a propyl group) is attached to the NH_2 group through an end carbon atom, so the name is propylamine.

b. There are two methyl groups and one ethyl group on the nitrogen atom. The compound is ethyldimethylamine, a tertiary amine.
c. There are two ethyl groups attached to the nitrogen atom; the amine is secondary, so the compound is diethylamine.
d. The nitrogen atom has a methyl group and a propyl group, so the compound is methylpropylamine, a secondary amine.

Exercise 6.1.1

Name and classify each compound.

a. 

b. 

c. $CH_3CH_2CH_2CH_2NH_2$
d. $CH_3CH_2CH_2NHCH_2CH_2\ CH_3$

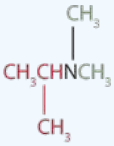
Example 6.1.2

Draw the structure for each compound and classify.

a. isopropyldimethylamine
b. dipropylamine

Solution

a. The name indicates that there are an isopropyl group (in red) and two methyl groups (in green) attached to the nitrogen atom; the amine is tertiary.



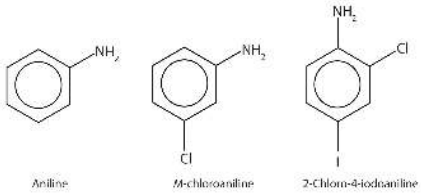
b. The name indicates that there are two propyl groups attached to the nitrogen atom; the amine is secondary. (The third bond on the nitrogen atom goes to a hydrogen atom.) $CH_3CH_2CH_2NHCH_2CH_2CH_3$

Exercise 6.1.2

Draw the structure for each compound and classify.

a. ethylisopropylamine
b. diethylpropylamine

The primary amine in which the nitrogen atom is attached directly to a benzene ring has a special name—**aniline**. Aryl amines are named as derivatives of aniline.

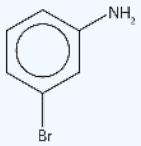


Aniline *M*-chloroaniline 2-Chloro-4-iodoaniline

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Example 6.1.3

Name this compound.

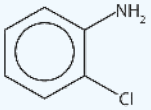


Solution

The benzene ring with an amino (NH_2) group is aniline. The compound is named as a derivative of aniline: 3-bromoaniline or *m*-bromoaniline.

Exercise 6.1.3

Name this compound.

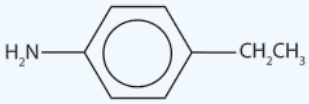


Example 6.1.4

Draw the structure for *p*-ethylaniline and classify.

Solution

The compound is a derivative of aniline. It is a primary amine having an ethyl group located *para* to the amino (NH_2) group.



Exercise 6.1.4

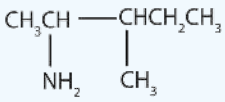
Draw the structure for *p*-isopropylaniline and classify.

Example 6.1.5

Draw the structure for 2-amino-3-methylpentane.

Solution

Always start with the parent compound: draw the pentane chain. Then attach a methyl group at the third carbon atom and an amino group at the second carbon atom.



Exercise 6.1.5

Draw the structure for 2-amino-3-ethyl-1-chloroheptane.

Ammonium (NH_4^+) ions, in which one or more hydrogen atoms are replaced with alkyl groups, are named in a manner analogous to that used for simple amines. The alkyl groups are named as substituents, and the parent species is regarded as the NH_4^+ ion. For example, $CH_3NH_3^+$ is the methylammonium ion. The ion formed from aniline ($C_6H_5NH_3^+$) is called the anilinium ion.

Example 6.1.6

Name each ion.

a. $CH_3NH_3^+$
b. $(CH_3)_2NH_2^+$
c. $(CH_3)_3NH^+$
d. $(CH_3)_4N^+$

Solution

The ions have one, two, three, and four methyl (CH_3) groups attached to a nitrogen atom. Their names are as follows:

a. methylammonium ion
b. dimethylammonium ion
c. trimethylammonium ion
d. tetramethylammonium ion

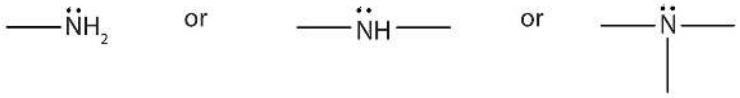
Exercise 6.1.6

Name each ion.

a. $CH_3CH_2NH_3^+$
b. $(CH_3CH_2)_3NH^+$
c. $(CH_3CH_2CH_2)_2NH_2^+$
d. $(CH_3CH_2CH_2CH_2)_4N^+$

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. Amines are named by naming the alkyl groups attached to the nitrogen atom, followed by the suffix *-amine*.

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6.2: Physical Properties of Amines

Learning Objectives

- Explain why the boiling points of primary and secondary amines are higher than those of alkanes or ethers of similar molar mass but are lower than those of alcohols.
- Compare the boiling points of tertiary amines with alcohols, alkanes, and ethers of similar molar mass.
- Compare the solubilities in water of amines of five or fewer carbon atoms with the solubilities of comparable alkanes and alcohols in water.

Primary and secondary amines have hydrogen atoms bonded to an nitrogen atom and are therefore capable of hydrogen bonding (part (a) of Figure **6.2.1**), although not as strongly as alcohol molecules (which have hydrogen atoms bonded to an oxygen atom, which is more electronegative than nitrogen). These amines boil at higher temperatures than alkanes but at lower temperatures than alcohols of comparable molar mass. For example, compare the boiling point of methylamine (CH_3NH_2; −6°C) with those of ethane (CH_3CH_3; −89°C) and methanol (CH_3OH; 65°C). Tertiary amines have no hydrogen atom bonded to the nitrogen atom and so cannot participate in intermolecular hydrogen bonding. They have boiling points comparable to those of ethers (Table **6.2.1**).

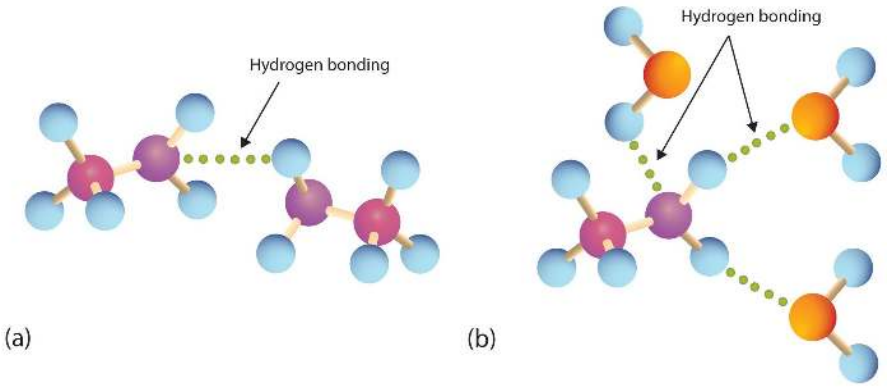


Figure **6.2.1**: Hydrogen Bonding. (a) Amine molecules are associated through hydrogen bonding. (b) An amine molecule can form a hydrogen bond with water molecules.

Table **6.2.1**: Physical Properties of Some Amines and Comparable Oxygen-Containing Compounds

Name	Condensed Structural Formula	Class	Molar Mass	Boiling Point (°C)	Solubility at 25°C (g/100 g Water)
butylamine	$CH_3CH_2CH_2CH_2NH_2$	1°	73	78	miscible
diethylamine	$(CH_3CH_2)_2NH$	2°	73	55	miscible
butyl alcohol	$CH_3CH_2CH_2CH_2OH$	—	74	118	8
dipropylamine	$(CH_3CH_2CH_2)_2NH$	2°	101	111	4
triethylamine	$(CH_3CH_2)_3N$	3°	101	90	14
dipropyl ether	$(CH_3CH_2CH_2)_2O$	—	102	91	0.25

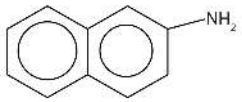
All three classes of amines can engage in hydrogen bonding with water (Figure **6.2.1***b*). Amines of low molar mass are quite soluble in water; the borderline of solubility in water is at five or six carbon atoms.

To Your Health: Amines in Death and Life

Amines have “interesting” odors. The simple ones smell very much like ammonia. Higher aliphatic amines smell like decaying fish. Or perhaps we should put it the other way around: Decaying fish give off odorous amines. The stench of rotting fish is due in part to two diamines: putrescine and cadaverine. They arise from the decarboxylation of ornithine and lysine, respectively, amino acids that are found in animal cells.

$$HOCH_2CH_2OH$$

Aromatic amines generally are quite toxic. They are readily absorbed through the skin, and workers must exercise caution when handling these compounds. Several aromatic amines, including β-naphthylamine, are potent carcinogens.



Key Takeaways

- Primary and secondary amines have higher boiling points than those of alkanes or ethers of similar molar mass because they can engage in intermolecular hydrogen bonding. Their boiling points are lower than those of alcohols because alcohol molecules have hydrogen atoms bonded to an oxygen atom, which is more electronegative.
- The boiling points of tertiary amines, which cannot engage in hydrogen bonding because they have no hydrogen atom on the nitrogen atom, are comparable to those of alkanes and ethers of similar molar mass.
- Because all three classes of amines can engage in hydrogen bonding with water, amines of low molar mass are quite soluble in water.

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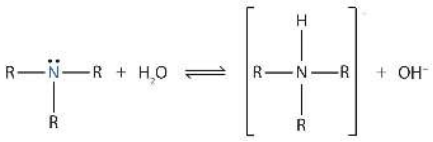
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6.3: Amines as Bases

Learning Objectives

- Name the typical reactions that take place with amines.
- Describe heterocyclic amines.

Recall that ammonia (NH_3) acts as a base because the nitrogen atom has a lone pair of electrons that can accept a proton. Amines also have a lone electron pair on their nitrogen atoms and can accept a proton from water to form substituted ammonium (NH_4^+) ions and hydroxide (OH^-) ions:



As a specific example, methylamine reacts with water to form the methylammonium ion and the OH^- ion.

$$\underset{\text{Methylamine}}{CH_3NH_2(aq)} + H_2O \rightleftharpoons \underset{\text{Methylammonium ion}}{CH_3NH_3^+(aq)} + OH^-(aq)$$

Nearly all amines, including those that are not very soluble in water, will react with strong acids to form salts soluble in water.

$$\underset{\text{Octylamine (insoluble)}}{CH_3(CH_2)_6NH_2(l)} + HNO_3(aq) \longrightarrow \underset{\text{Octylammonium nitrate (soluble)}}{CH_3(CH_2)_6NH_3{}^+NO_3^-(aq)}$$

Amine salts are named like other salts: the name of the cation is followed by the name of the anion.

Example 6.3.1

What are the formulas of the acid and base that react to form $[CH_3NH_2CH_2CH_3]^+CH_3COO^-$?

Solution

The cation has two groups—methyl and ethyl—attached to the nitrogen atom. It comes from ethylmethylamine ($CH_3NHCH_2CH_3$). The anion is the acetate ion. It comes from acetic acid (CH_3COOH).

Exercise 6.3.1

What are the formulas of the acid and base that react to form $\mathbf{(CH_3CH_2CH_2)_3NH^+I^-}$?

To Your Health: Amine Salts as Drugs

Salts of aniline are properly named as *anilinium* compounds, but an older system, still in use for naming drugs, identifies the salt of aniline and hydrochloric acid as “aniline hydrochloride.” These compounds are ionic—they are salts—and the properties of the compounds (solubility, for example) are those characteristic of salts. Many drugs that are amines are converted to hydrochloride salts to increase their solubility in aqueous solution.

Heterocyclic Amines

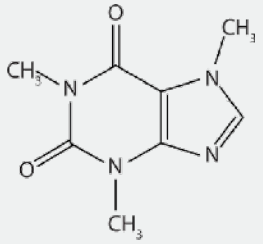
Looking back at the various cyclic hydrocarbons discussed previously, we see that all the atoms in the rings of these compounds are carbon atoms. In other cyclic compounds, called **heterocyclic compounds** (Greek *heteros*, meaning “other”), nitrogen, oxygen, sulfur, or some other atom is incorporated 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.

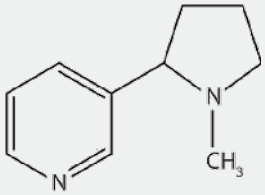
To Your Health: Three Well-Known Alkaloids

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.



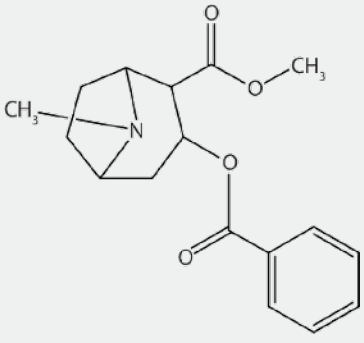
Caffeine

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*.

$$\underbrace{C_{17}H_{21}O_4N}_{\text{cocaine (freebase)}} + HCl \longrightarrow \text{munder}$$

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 *anilinium* compounds, but an older system is used to name drugs: the salts of amine drugs and hydrochloric acid are called “hydrochlorides.” Heterocyclic amines are cyclic compounds with one or more nitrogen atoms in the ring.

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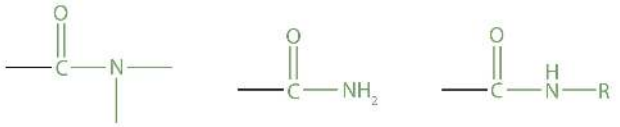
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6.4: Amides- Structures and Names

Learning Objectives

- Identify the general structure for an amide.
- Identify the functional group for an amide.
- Names 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 amide group | A simple amide | 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*.

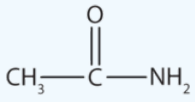
Simple amides are named as derivatives of carboxylic acids. The *-ic* ending of the common name or the *-oic* ending of the International Union of Pure and Applied Chemistry (IUPAC) name of the carboxylic acid is replaced with the suffix *-amide*.

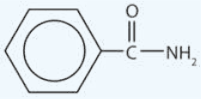


Formic acid (methanoic acid) | Formamide (methanamide)

Example 6.4.1

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

a. 

b. 

Solution

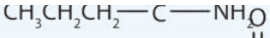
a. This amide has two carbon atoms and is thus derived from acetic acid. The OH of acetic acid is replaced by an NH_2 group. The *-ic* from *acetic* (or *-oic* from ethanoic) is dropped, and *-amide* is added to give *acetamide* (or ethanamide in the IUPAC system).

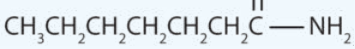
b. This amide is derived from benzoic acid. The *-oic* is dropped, and *-amide* is added to give benzamide.

Exercise 6.4.1

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

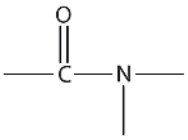


a. 

b. 

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*.

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6.5: 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 **6.5.1**). 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 **6.5.1**: *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
$CH_3CH_2CONH_2$	propionamide	81	213	soluble
$CH_3CH_2CH_2CONH_2$	butyramide	115	216	soluble
$C_6H_5CONH_2$	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 **6.5.1**). (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.

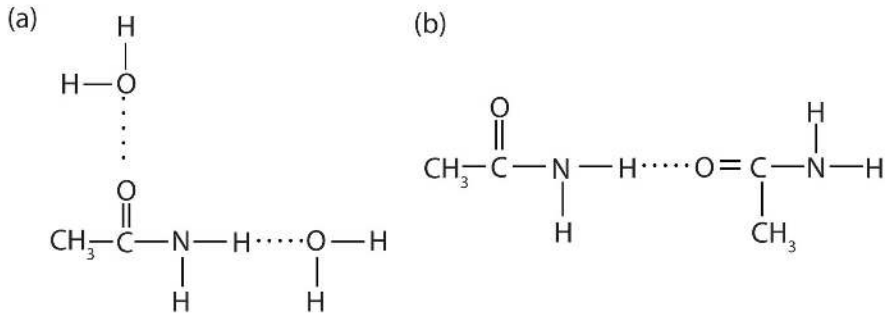


Figure **6.5.1**: Hydrogen Bonding in Amides. Amide molecules can engage in hydrogen bonding with water molecules (a). Those amides with a hydrogen atom on the nitrogen atom can also engage in hydrogen bonding (b). Both hydrogen bonding networks extend in all directions.

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?.

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6.6: CHEMISTRY OF AMIDES

OBJECTIVES

After completing this section, you should be able to

1. write an equation to describe the preparation of an amide from an acid chloride.
2. identify the amide linkage as the basic unit from which all proteins are made, and hence recognize the importance of the amide linkage to biologists and biochemists.
3. write detailed mechanisms for the acidic and basic hydrolysis of amides.
4. write an equation to describe the reduction of an amide to an amine.
5. write a detailed mechanism for the reduction of an amide to an amine.
6. identify the product formed when a given amide is reduced with lithium aluminum hydride.
7. identify the amide, the reagents, or both, necessary to prepare a given amine by direct reduction.
8. identify lactams as being cyclic amides which undergo hydrolysis and reduction in a manner analogous to that of their acyclic counterparts.

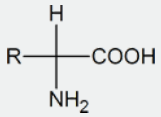
KEY TERMS

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

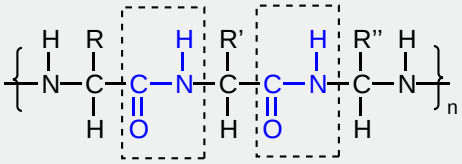
- lactam

STUDY NOTES

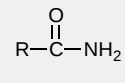
When we talk about amino acids, we are generally referring to *α*-amino acids; that is, compounds in which an amino (NH_2) group and a carboxyl group are attached to the same carbon atom:



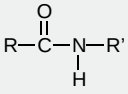
Notice that such compounds contain a chiral carbon atom (unless R = H, which is glycine). Proteins can be considered to consist of amino acid residues joined by amide (or peptide) links. These peptide links consist of exactly the same structural units that we find in *N*-substituted primary amides.



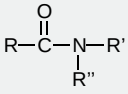
peptide (amide) links



primary amide

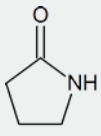


N—substituted primary amide

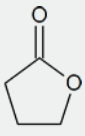


N, *N*—disubstituted primary amide

A lactam is a cyclic amide, in the same way that a lactone is a cyclic ester:

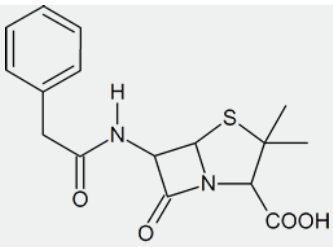


a lactam



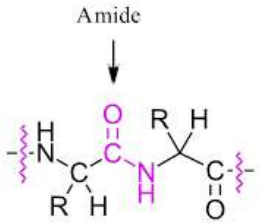
a lactone

Among the most important molecules that contain lactam rings are the penicillins:



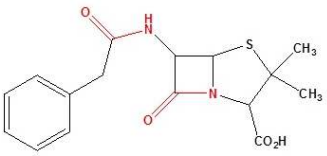
penicillin G (benzylpenicillin)

The amide functional group is extremely important for biological molecules because amides make up the backbone of proteins. Proteins are actually polymers of amino acids, linked by amide groups known as peptide bonds. Proteins (polymers of ~40 amino acids or more) and peptides (shorter polymers) are formed when the amino group of one amino acid monomer reacts with the carboxylate carbon of another amino acid to form an amide linkage, which in protein terminology is a **peptide bond**. The individual amino acids within a peptide or protein are called **amino acid residues**.

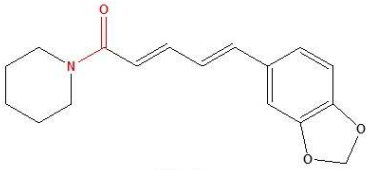


Protein Backbone

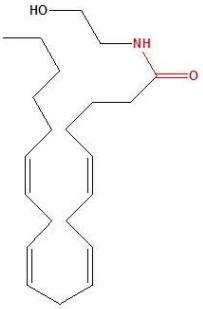
Compounds containing amides have a wide range of biological activity and include penicillin G an antibiotic, piperine which is responsible for the pungent flavor of black pepper, and anandamide which provides some of the pleasurable sensations gained from eating chocolate.



Penicillin G
(An Antibiotic)



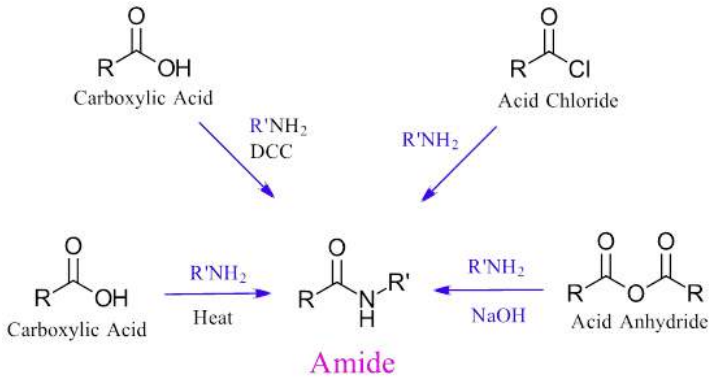
Piperine
(From Black Pepper)



Anandamide
(From Chocolate)

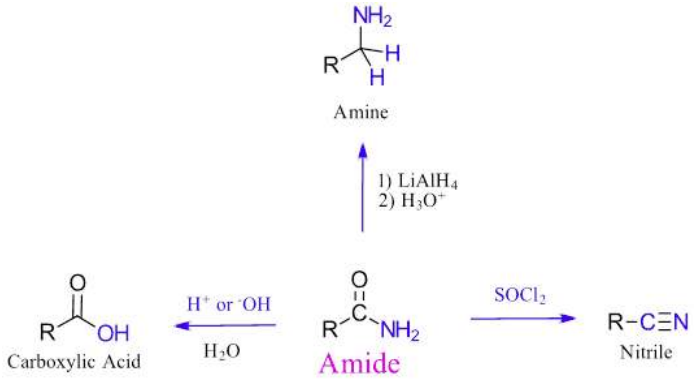
PREPARATION OF AMIDES

Amides are most commonly prepared though the reaction of an acid chloride with ammonia, a 1º amine, or 2º amine. In an analogous reaction, an amide can be prepared through the reaction of a carboxylic acid and an amine using a coupling agent such as DCC. Simple amides can be prepared by reacting an acid anhydride with an amine. Lastly, amides can be formed through the direct reaction of a carboxylic acid and an amine. However, this reaction is rarely used because the conditions are relatively severe.



REACTIONS OF AMIDES

Amides are relatively unreactive towards nucleophilic acyl substitutions due to the poor leaving group ability of its nitrogen containing Y group. Despite this, amides can react with water under acidic or basic conditions to create a carboxylic acid through nucleophilic acyl substitution. Reaction of primary amides with thionyl chloride ($SOCl_2$) creates nitriles. Hydride reduction using $LiAlH_4$ causes the carbonyl oxygen of the amide to eliminate as a leaving group creating the corresponding amine.



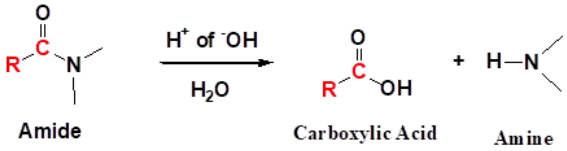
Lactams, cyclic amides, are affected by these reactions in the same fashion as acyclic amides.



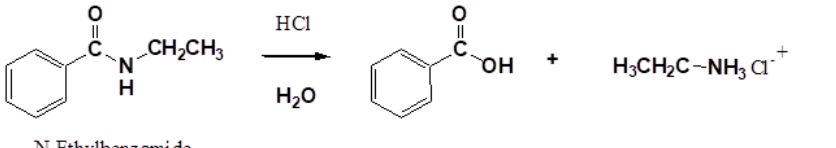
CONVERSION OF AMIDES TO CARBOXYLIC ACIDS: HYDROLYSIS

Amides can be hydrolyzed into a carboxylic acid and ammonia or an amine by heating in an acidic or basic aqueous solution. In both cases, acid-base reactions occurring with the products make the overall reaction irreversible. Under acidic conditions the amine produced by the reaction is protonated to form a non-nucleophilic ammonium compound. Under basic conditions the carboxylic acid produced by the reaction is deprotonated to a non-electrophilic carboxylate.

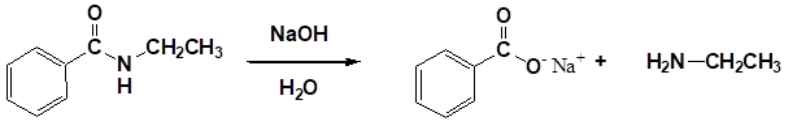
GENERAL REACTION



EXAMPLES



N-Ethylbenzamide — Benzoic Acid — Ethyl Ammonium Chloride

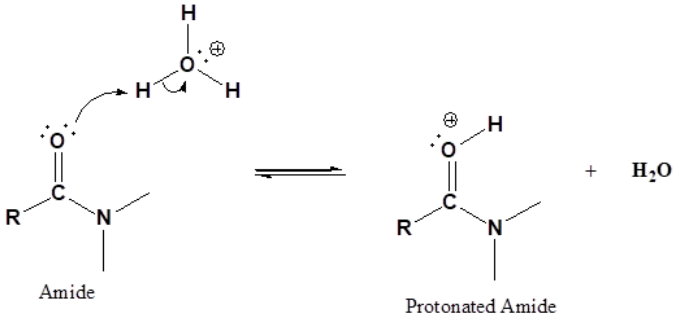


N-Ethylbenzamide — Sodium Benzoate — Ethyl Amine

MECHANISM UNDER ACIDIC CONDITIONS

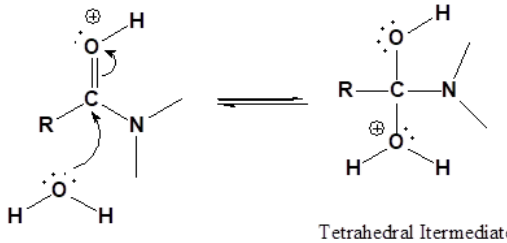
Protonation of the amide increases the electrophilicity of the carbonyl carbon allowing water to add causing formation of a tetrahedral oxonium intermediate. Next a proton is transferred to the amide nitrogen giving it a positive charge and increasing its ability to act as a leaving group. Reforming the carbonyl double bond causes the elimination of an amine as a leaving group, creating a protonated carboxylic acid. In the last step of the mechanism, the produced amine acts as a base, removing a hydrogen, to form a carboxylic acid and an ammonium compound. This final deprotonation step essentially removes the amine from the equilibrium which drives the reaction towards completion. Since the amine is no longer part of the equilibrium, the reaction is effectively irreversible.

1) Protonation of the carbonyl



Amide — Protonated Amide

2) Nucleophilic attack by water

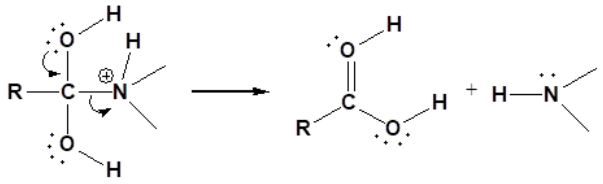


Tetrahedral Itermediate

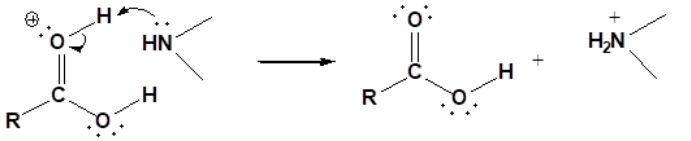
3) Proton transfer



4) Leaving group removal



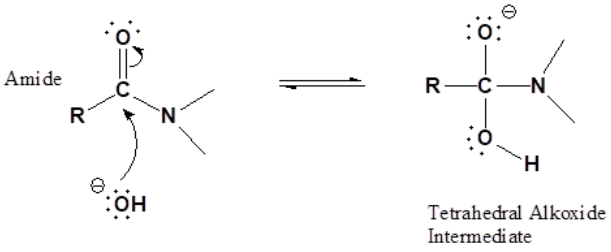
5) Deprotonation



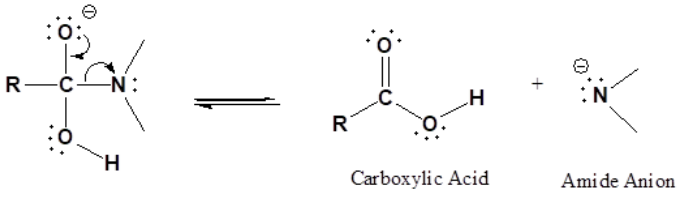
MECHANISM UNDER BASIC CONDITIONS

The base-promoted hydrolysis of an amide follows the typical nucleophilic acyl substitution mechanism. A full equivalent of hydroxide anion is used, so the reaction is called base-promoted and not base catalyzed. The mechanism of basic amide hydrolysis begins with the nucleophilic addition of a hydroxide ion at the carbonyl carbon creating a tetrahedral alkoxide intermediate. The carbonyl bond is reformed along with the elimination of an amide ion (-NHR) leaving group (note this is a different use of the word amide meaning an amine anion), forming a carboxylic acid. In the last step, the amide ion deprotonates the carboxylic acid to form a carboxylate salt and an amine as products. This final deprotonation step essentially removes the carboxylic acid from the equilibrium which drives the reaction towards completion. Since the carboxylic acid is no longer part of the equilibrium, the reaction is effectively irreversible.

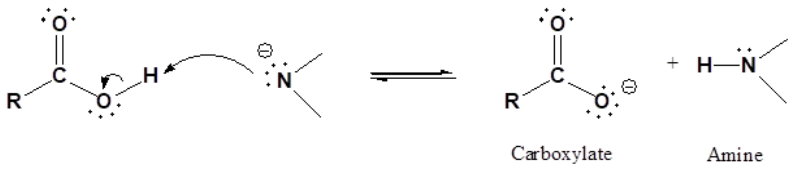
1) Nucleophilic attack by hydroxide



2) Leaving group removal

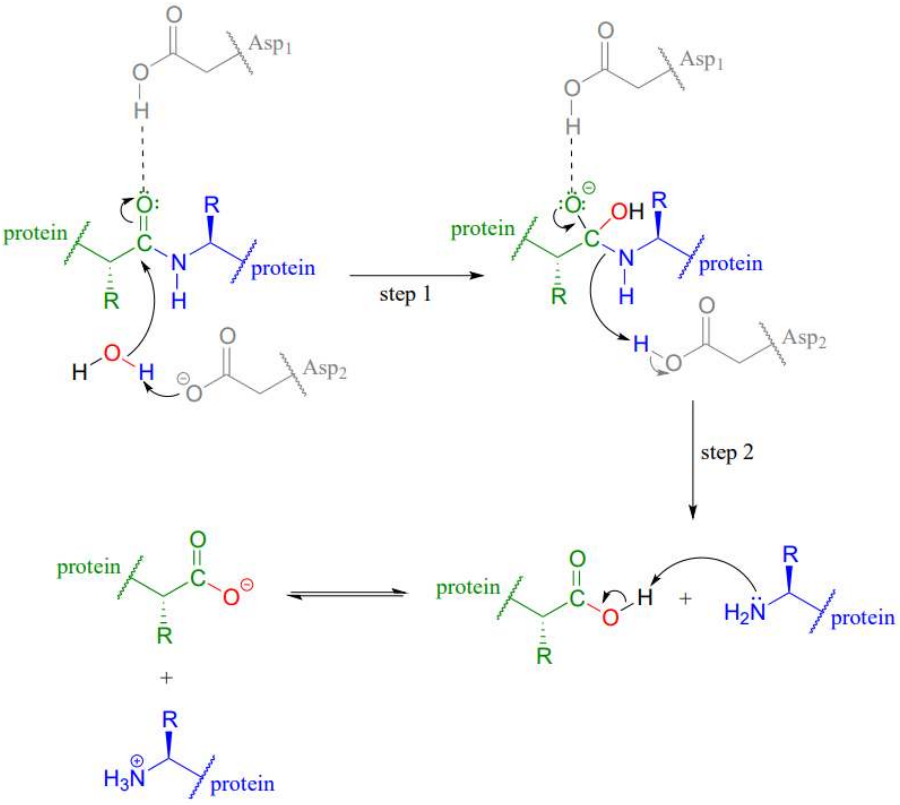


3) Deprotonation



HYDROLYSIS OF PROTEINS

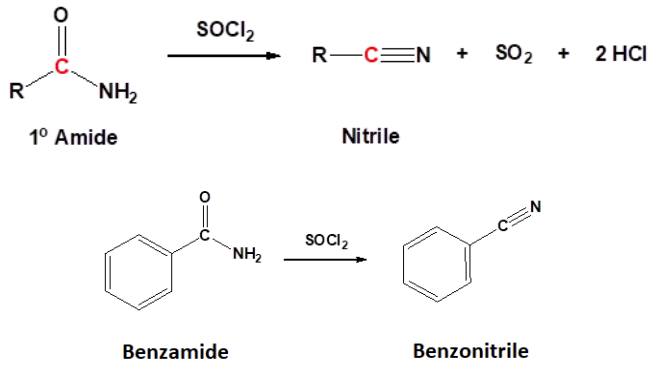
Hydrolysis of amide bonds is the first step in the metabolism of dietary proteins. Protein hydrolysis is catalyzed by protease enzymes (abbreviated Asp_1 and Asp_2 in the figure below). The mechanisms starts with the nucleophilic acyl substitution by water while breaking the amide C-N bond. This produces a protein fragment with an amine and another with a carboxylic acid. The amine fragment will deprotonate the carboxylic acid forming the carboxylate and ammonium fragments.



CONVERSION OF 1^{O} AMIDES TO NITRILES: DEHYDRATION

1º Amides can be converted into a nitrile through reaction with thionyl chloride ($SOCl_2$). Sulfurdioxide (SO_2) and hydrochloric acid are produced as byproducts.

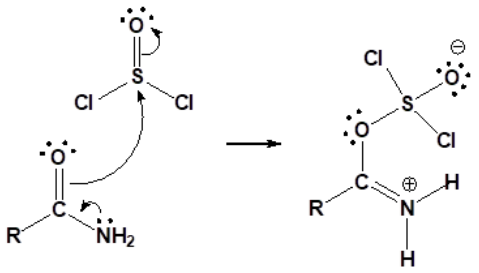
GENERAL REACTION



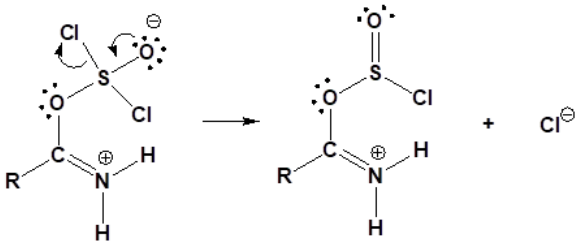
MECHANISM FOR THE CONVERSION OF A 1^{O} AMIDE TO A NITRILE

During the first step of the mechanism, the amide acts as a nucleophile and attacks the electrophilic sulfur of thionyl chloride, pushing the pi electrons of the S=O bond onto oxygen. Removal of a chloride anion as a leaving group allows the sulfoxide S=O bond to reform creating a protonated imine chlorosulfite. Deprotonation forms an imine chlorosulfite intermediate. A second deprotonation eliminates the chlorosulfite leaving group as sulfur dioxide and a chloride anion and forms the C-N triple bond of the nitrile product.

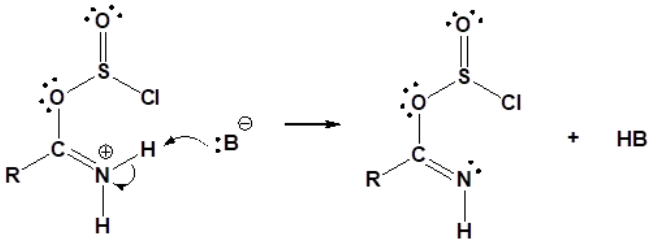
1) Nucleophilic attach on thionyl chloride



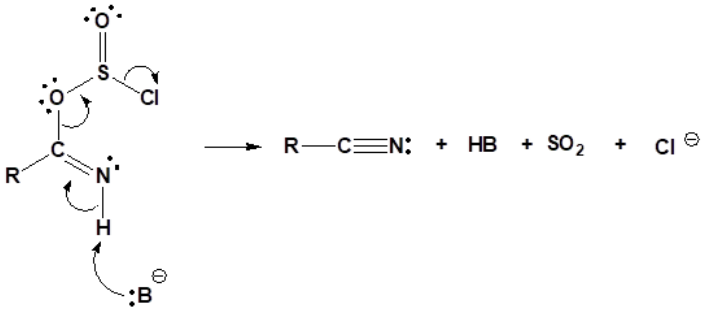
2) Leaving group removal



3) Deprotonation



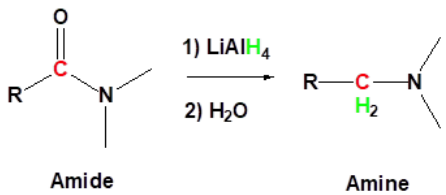
4) Leaving group removal



CONVERSION OF AMIDES TO 1^{O}, 2^{O} OR 3^{O} AMINES: HYDRIDE REDUCTION

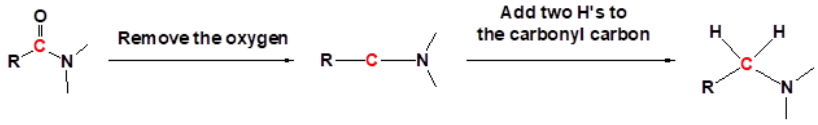
Amides are reduced to amines by treatment with $LiAlH_4$, and this has proven to be one of the most general methods for preparing all classes of amines (1º, 2º & 3º). Due to the nitrogen in the Y group of amides, the outcome of $LiAlH_4$ reductions is distinctly different than for esters since amide anions are poorer leaving groups than alkoxide anions. Furthermore, oxygen forms especially strong bonds to aluminum. During this reaction the carbonyl oxygen of the amide is removed as a leaving group and not the nitrogen containing Y group. Removal of the leaving group allows for a formation of a C=N iminium bond which can accept a second addition of a hydride nucleophile to form the amine.

GENERAL REACTION

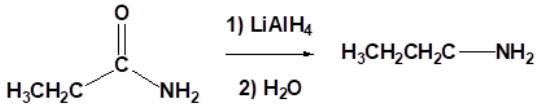


PREDICTING THE PRODUCTS OF A HYDRIDE REDUCTION

There are two major changes in bonding during this reaction: 1) The C=O carbonyl is removed from the starting material 2) Two hydride nucleophiles are added to what was the carbonyl carbon of the amide.

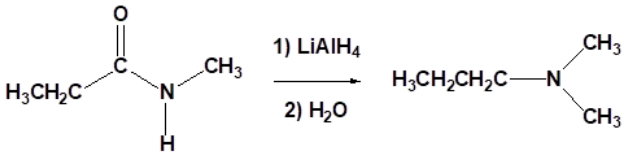


EXAMPLE

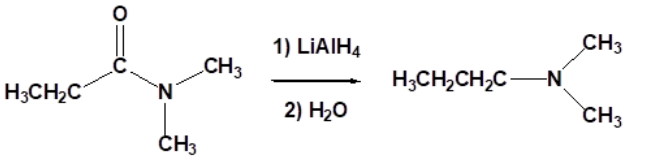


Propanamide — Propyl Amine

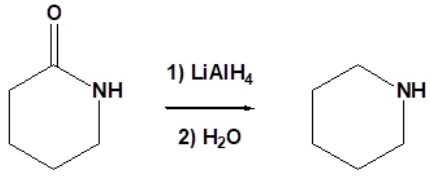
Alkyl groups attached to the nitrogen do not affect the reaction.



N-Methylpropanamide — N-Methylpropylamine



N,N-Dimethylpropanamide — N,N-Dimethylpropylamine

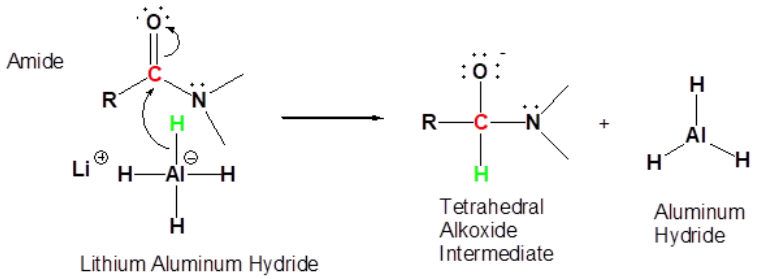


δ-Valerolactam — Piperidine

MECHANISM FOR THE HYDRIDE REDUCTION OF AN AMIDE TO FORM AN AMINE

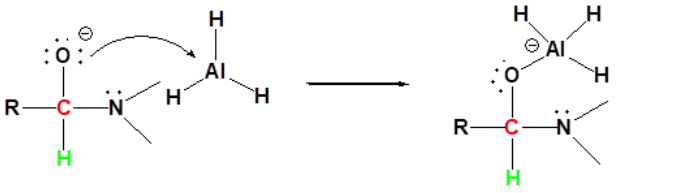
Addition of a hydride nucleophile to the carbonyl carbon of the amide produces a tetrahedral alkoxide intermediate. A Lewis acid-base interaction occurs between the alkoxide (Lewis Base) and AlH_3 (Lewis acid) forming a complex with an O-Al bond. The nitrogen lone pair forms a double bond with the previous carbonyl carbon ejecting a metal oxide species (e.g. $[H3Al–O]^{2–}$) as a leaving group, and while forming an iminium double bond. Addition of a second equivalent of hydride nucleophile to the iminium carbon produces an amine.

1) Nucleophilic attack by the hydride

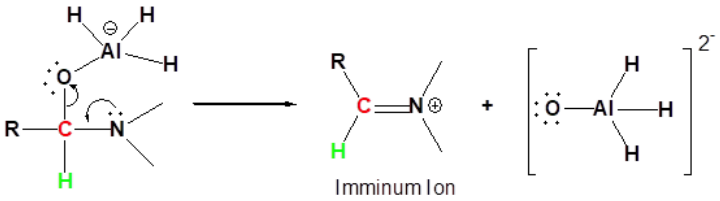


Lithium Aluminum Hydride — Tetrahedral Alkoxide Intermediate — Aluminum Hydride

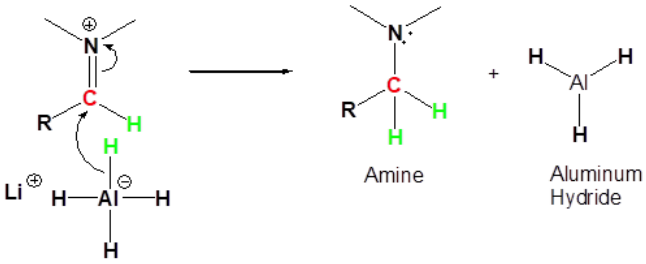
2) Complex formation



3) Leaving group removal

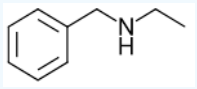


4) Nucleophilic attach by the hydride



? EXAMPLE 6.6.1

How could the following molecule be synthesized using an aminolysis of an acid chloride?



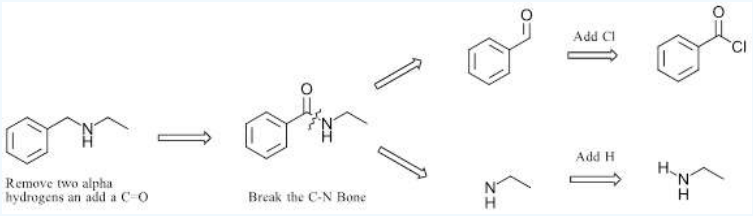
Answer

One of the preferred methods for making amines is through a nucleophilic acyl substitution using an acid chloride and amine to form an amide. The amide is then reduced to the amine during a hydride reduction with $LiAlH_4$.

In the first step of retrosynthetic analysis, one of the carbons alpha to the amine nitrogen is converted to a carbonyl thus creating an amide intermediate. The key bond formed during this pathway is the C-N sigma bond between the carbonyl carbon and the nitrogen created during amide formation. Breaking this bond separated the target molecule into the two starting materials for the pathway. The carbonyl carbon gains a –Cl to become an acid chloride and the nitrogen fragment gains an H to become a 1º amine. In the forward reaction pathway, the acid chloride and the 1º amine are linked to from an amide in the first step of the reaction. Subsequent hydride reduction of the amide using $LiAlH_4$ produces the amine target molecule.

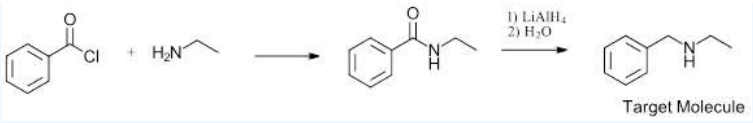
The target molecule has two alpha carbons which could possibly be converted to a carbonyl. This allows there to be two possible synthetic pathways.

Pathway 1

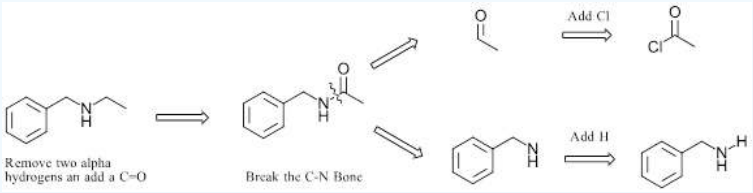


Solution 1

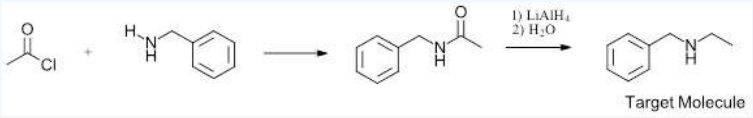
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Pathway 2



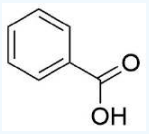
Solution 2



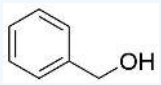
EXERCISE 6.6.1

1) How would you prepare the following compounds from N-Propypl benzamide?

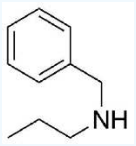
(a)



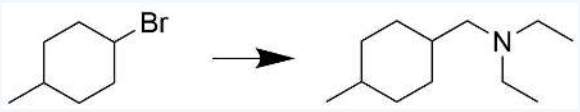
(b)



(c)



2) Propose a synthesis pathway for the following conversion:



Answer

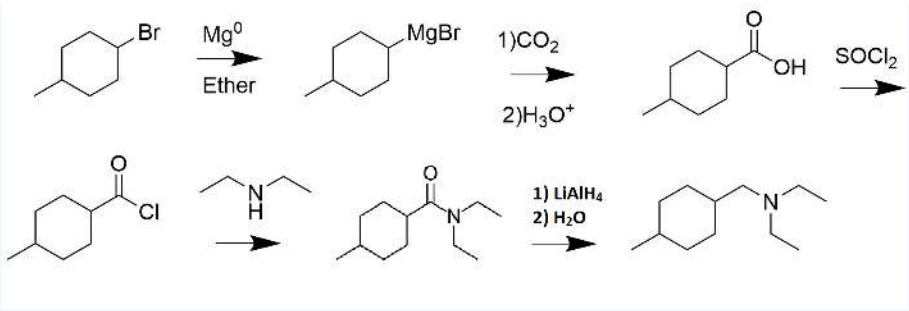
1) (a) NaOH, H_2O

(b) NaOH, H_2O, then $LiAlH_4$

(c) $LiAlH_4$

2)

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CHAPTER OVERVIEW

7: Carbohydrates

7.1: What are carbohydrates
7.2: General class names and Common names of monosaccharides
7.3: Cyclic structures of monosaccharides
7.4: Reactions of monosaccharides
7.5: Disaccharides
7.6: Oligosaccharides
7.7: Polysaccharides

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7.1: What are carbohydrates

Learning Objectives

- Define carbohydrates, monosaccharides, polysaccharides, and write their general formulas.
- Draw and interpret fisher projections of monosaccharides.

What are carbohydrates

Carbohydrates are primary energy storage compounds, e.g., glucose ($C_6H_{12}O_6$) synthesized by using carbon dioxide (CO_2) from the air, water (H_2O) from the soil, and energy from sunlight, along with the release of oxygen (O_2), as illustrated in Figure 7.1.1.

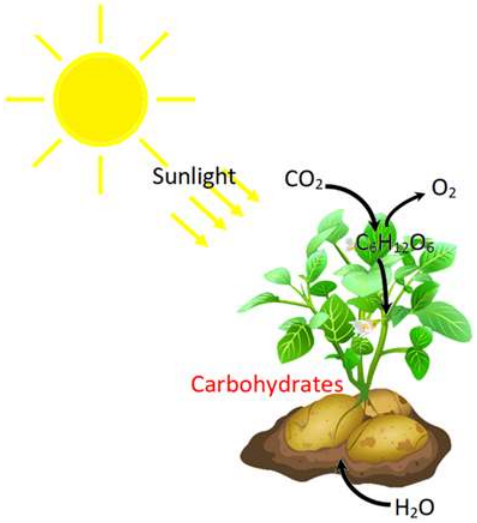


Figure 7.1.1: Illustration of photosynthesis by plants. (Copyright; Public domain)

Oxidation of carbohydrates, e.g., the reverse of the photosynthesis reaction, release energy that plant and animals use for activities. Carbohydrates are the support structure material in plants, e.g., cell-wall and wood, shell material of crustaceans, and connective tissues in animals.

Glucose is a polyhydroxy aldehyde, and fructose, i.e., another carbohydrate found in honey, is a polyhydroxy ketone, as illustrated in Figure 7.1.2.

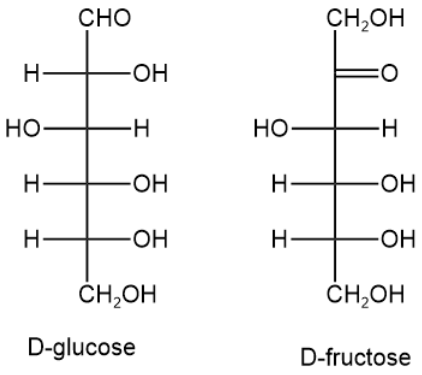


Figure 7.1.2: Fisher projections of D-glucose and D-fructose. (Copyright; Public domain)

Carbohydrates

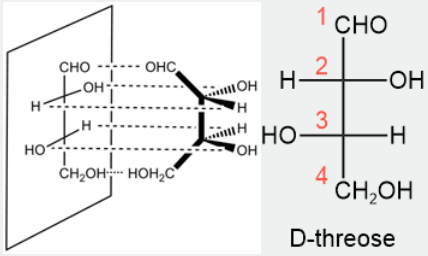
Carbohydrates are polyhydroxy aldehydes, polyhydroxy ketones, or other compounds that hydrolyze to polyhydroxy aldehydes or polyhydroxy ketones.

The general formula of simple carbohydrates is $C_nH_{2n}O_n$, which can also be written as $C_n \cdot (H_2O)_n$ which is the origin of the name carbohydrates, i.e., hydrates of carbon.

Fisher projections

Fisher projections are two-dimensional representations of molecules for showing the configuration of chiral centers:

- the chiral center is in the plane of the page,
- horizontal lines represent bonds projecting toward the viewers,
- and vertical lines represent bonds projecting away from the viewer.
- The parent C chain is placed on the vertical line, with the most oxidized C, i.e., the C=O in carbohydrates, at the top or near the top end, and the numbering starts from the top most C, as illustrated in Figure 7.1.2.



(a) (b)

Figure 7.1.2: Illustration of creating a Fisher projection (a) and numbering the C chain of carbohydrates using D-threose as an example. (Copyright: (a) Olion17, Public domain, via Wikimedia Commons, (b) Public domain)

Monosaccharides and polysaccharides

Monosaccharides

Simple carbohydrates that can not be hydrolyzed to more simple ones are called **monosaccharides**. For example, D-glucose, D-fructose, and D-threose shown in previous figures are monosaccharides.

Polysaccharides

Linear or branched chain polymers comprised of monosaccharide repeat units (monomers) are called **polysaccharides**. For example, starch is a polysaccharide with a D-glucose monomer, illustrated in Figure 7.1.3.

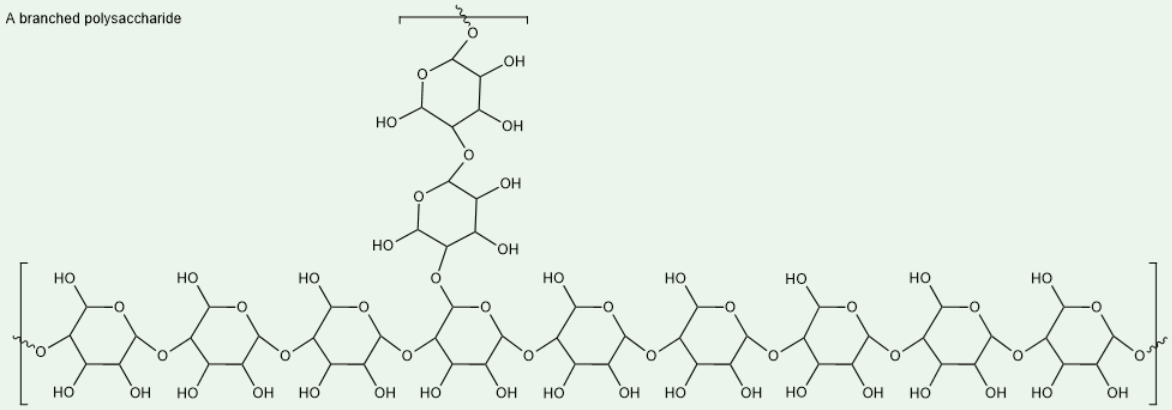
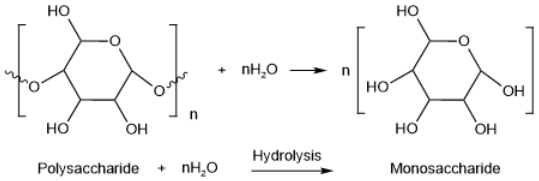


Figure 7.1.3: General structural formula of a starch -a polysaccharide D-glucose. (Copyright; Public domain)

Polysaccharides hydrolyze to monosaccharides, as illustrated in the following general hydrolysis reaction.



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7.2: General class names and Common names of monosaccharides

Learning Objectives

- Assign and interpret class names of monosaccharides.
- Assign D/L stereodescriptors to the common names and define epimers.
- Draw structure from the name and vice versa for important monosaccharides, including D-ribose, D-glucose, D-mannose, and D-galactose.

General class names of monosaccharides

Monosaccharides are either polyhydroxy aldehydes that take *aldo* as prefixes or polyhydroxy ketones that take *keto* as prefixes in their general name. The general formula of monosaccharides is $C_nH_{2n}O_n$ where n can be 3, 4, 5, 6, 7, or 8 representing triose, tetrose, pentose, hexose, heptose, or octose, respectively, in the general name. For example, D-glucose belongs to aldohexose, where the aldo- prefix tells it is an aldehyde, -hex- in the middle of the name tells it has six C's, and -ose suffix denotes it is a carbohydrate. D-fructose belongs to ketohexose, i.e., it is a monosaccharide with a ketone group and six C's. D-glyceraldehyde is an aldotriose, i.e., a monosaccharide with an aldehyde group and three C's.

Common names of monosaccharides

Common names are specific for each monosaccharide. All C's in a monosaccharide are chiral centers except the two terminal C's and the C of ketone group if it is a ketose. The absolute configuration of the **penultimate** C, i.e., the second-last C, is explicitly expressed by D- or L-stereochemical descriptors and the absolute configuration of all other chiral centers is implicit in the common name of the monosaccharide. There is one set of common names for all D-isomers, and their mirror images (enantiomers) have the same common name with D- replaced with L-. For example, D-glyceraldehyde and L-glyceraldehyde, D-glucose, and L-glucose are enantiomer pairs shown in Figure 7.2.1.

D/L Stereochemical descriptors

If the –OH group on the second-last carbon (penultimate C or the second C from the bottom end) in Fisher projection of a monosaccharide is on the right side, it is assigned D- and if it is on the left side, it is assigned L-configuration. Monosaccharides that are enantiomer pairs have the same common name, but D- is replaced with L- or vice versa. For example, D-glyceraldehyde and L-glyceraldehyde, D-glucose and L-glucose enantiomer pairs are shown in Figure 7.2.1. with the penultimate C defining D- or L-configuration shown in red color.

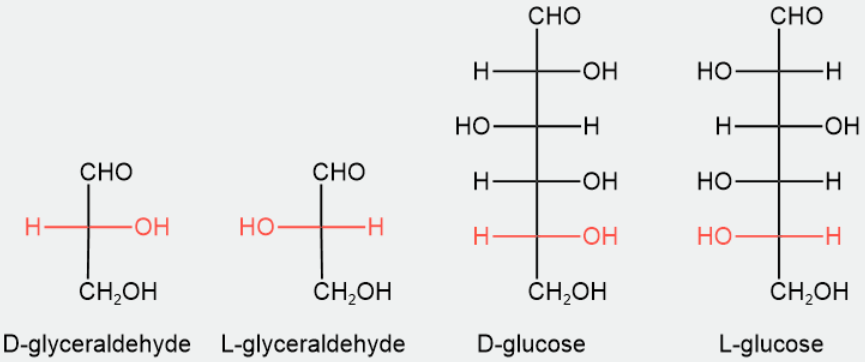


Figure 7.2.1: Assigning D- or L-configuration based on orientation of Extra close brace or missing open brace on penultimate C in Fisher projection. (Copyright; Public domain)

D-configuration of monosaccharides is commonly found in nature. The D/L stereodescriptors do not indicate the rotation of the plane polarized light, i.e., the enantiomer's dextro/levo rotatory nature. However, if one enantiomer is dextro (d-), the other is levo (l-) to the same degree, and vice versa.

The structures as Fisher projections and common names of D-aldoses are shown in Figure **7.2.2**. and those of D-ketoses are shown in Figure **7.2.3**. These are the most common monosaccharides found in nature.

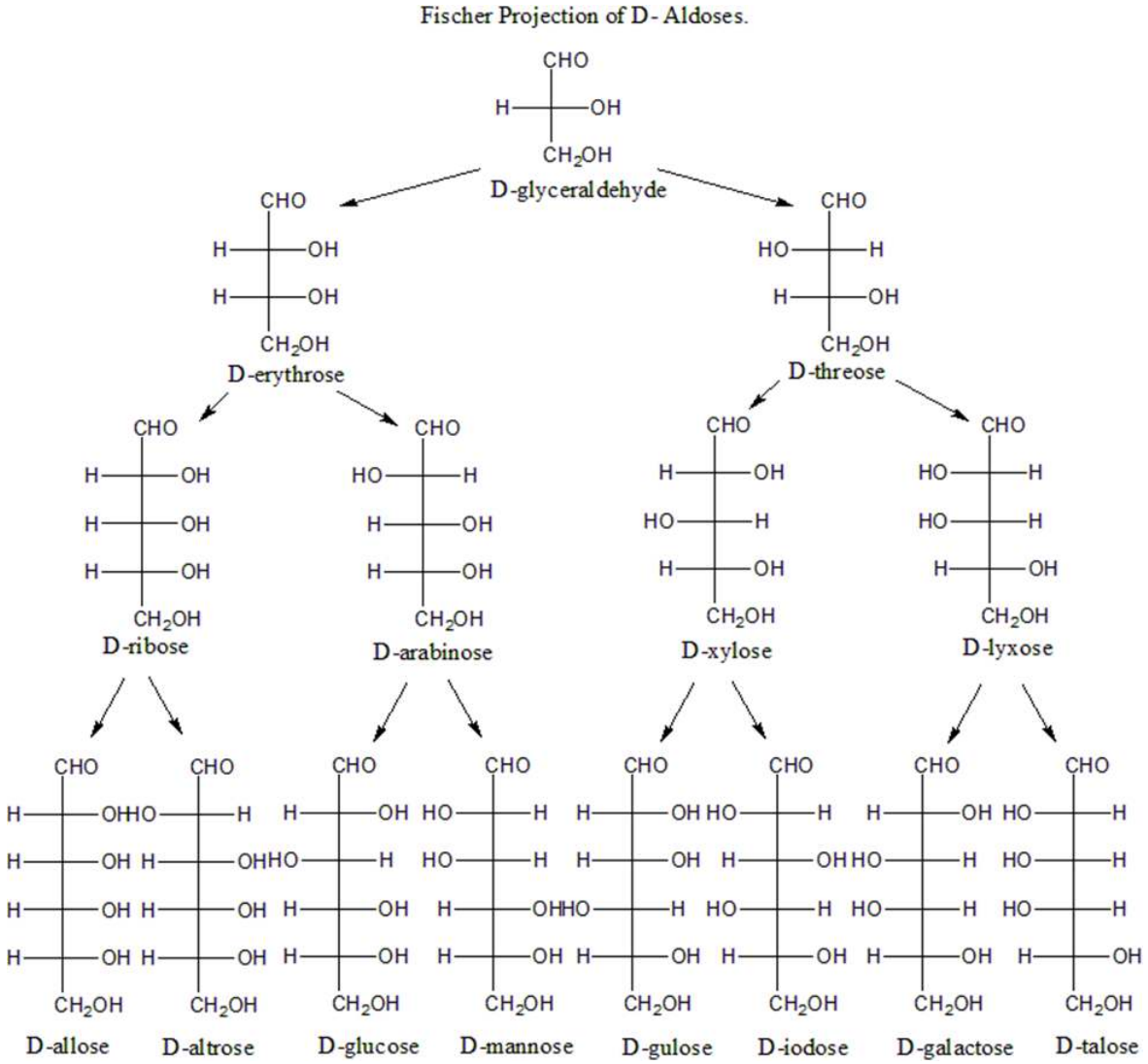


Figure **7.2.2**: Fisher projections and common names of D-aldoses. (Copyright; Dineshts, Public domain, via Wikimedia Commons)

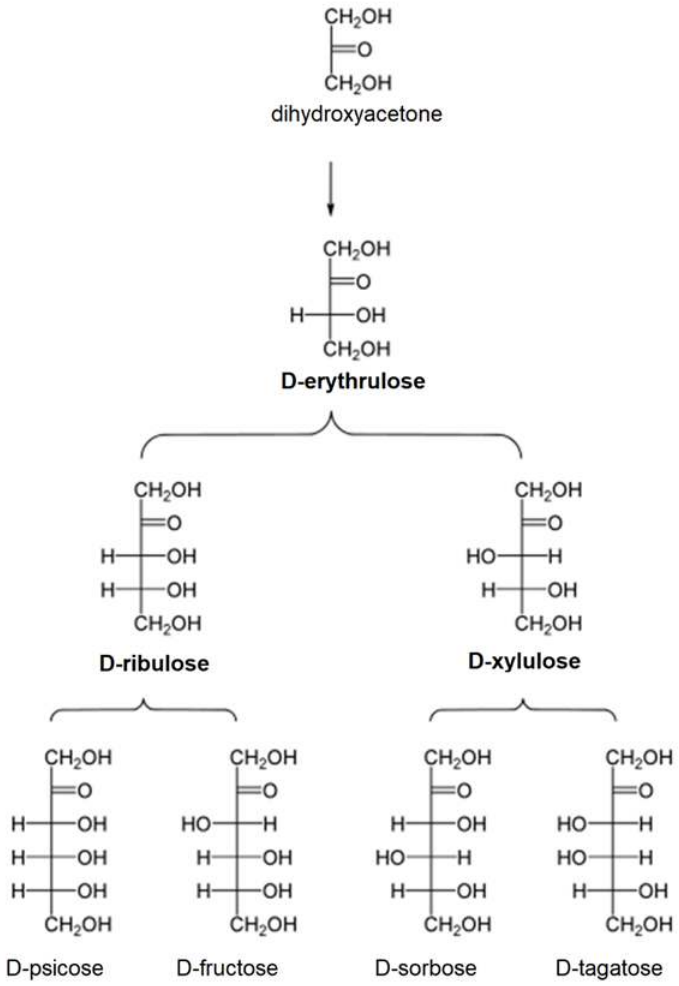


Figure 7.2.3: Fisher projections and common names of D-ketoses. (Copyright;modified from: Yikrazuul, Public domain, via Wikimedia Commons)

Some important monosaccharides

D-Glucose is the most abundant monosaccharide in nature. Plants produce it in a photosynthesis process. D-Galactose and D-mannose are two important diastereomers of D-glucose that differ from D-glucose in the configuration of only one chiral center.

Epimers

Epimers are diastereomers that differ in absolute configuration of only one chiral center. For example, D-galactose configuration is different from D-glucose only at C#4, i.e., D-galactose is a C4-epimer of D-glucose. Similarly, D-mannose is C 2-epimer of D-glucose.

D-Fructose is another important monosaccharide that differs at C#1 and C#2 from glucose. That is, the C=O is an aldehyde group at C#1 in D-glucose, but it is a ketone at C#2 in D-fructose. Fisher projections of D-glucose, D-galactose, D-mannose, and D-fructose are shown in Figure 7.2.4. with the differences from D-glucose highlighted by red-color fonts. D-ribose is another important monosaccharide present in RNA.

Drawing structures of important monosaccharides

D-ribose is aldopentose, i.e., an aldehyde with five C's. All chiral C's have −OH groups oriented towards the right in the Fisher projection. D-allose is aldohexose with the same structural features as D-ribose, i.e., all chiral C's have −OH groups oriented towards the right in the Fisher projection. D-glucose is C3 epimer of D-allose. The other three important monosaccharides can be

drawn by relating them to D-glucose, i.e., D-galactose is a C4 epimer, D-mannose is a C2 epimer of D-glucose, and D-fructose has a ketone group at C2 in the place of aldehyde group of D-glucose at C1.

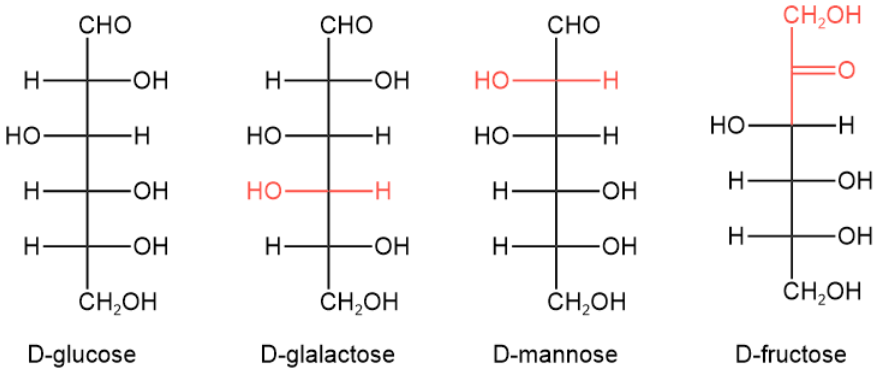


Figure 7.2.4: Fisher projections of four important monosaccharides with their differences from D-glucose highlighted by red-color fonts. (Copyright; Public domain)

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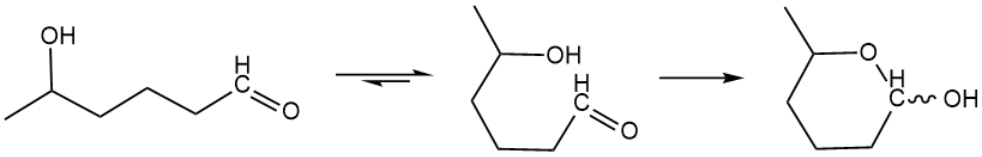
7.3: Cyclic structures of monosaccharides

Learning Objectives

- Draw and inter-convert open-chain and cyclic hemiacetal forms of compounds containing carbonyl and alcohol groups in the same molecule.
- Convert Fisher projections to Howarth projections and to chair conformation in the cases of pyranose forms of monosaccharides.
- Define Howarth projection, anomeric carbon, α and β configuration of the anomeric carbon, furanose, and pyranose forms, and mutarotation of monosaccharides.

Cyclic hemiacetal

Alcohol ($\mathbf{R–OH}$) and a carbonyl ($\mathbf{C=O}$) groups react with each other and form a hemiacetal group. The hemiacetals are usually unstable and revert to the reactants. However, suppose the alcohol and the carbonyl groups are on the same molecule and can react to form a five- or six-member cyclic hemiacetal. The product is more stable than the reactants, as shown in the following example reaction.



5-hydroxyhexanal (Linear conformation) | 5-hydroxyhexanal (Cyclic conformation) | A cyclic hemiacetal (Racemic mixture)

Note that the hemiacetal $\mathbf{C}$ is a new chiral center that is produced as a racemic mixture, which is represented by a wavy line in the $\mathbf{–OH}$ group. Monosaccharides are polyhydroxy aldehydes or polyhydroxy ketones that often exist as hemiacetal as the dominant form in equilibrium with the open-chain form, as described in the next section.

Fisher projections to Haworth projections

Fisher projections represent the open-chain forms of monosaccharides where the $\mathbf{C}$-chain is a vertical line. Hemiacetals are five or six-member ring structures represented by pentagon or hexagon shapes.

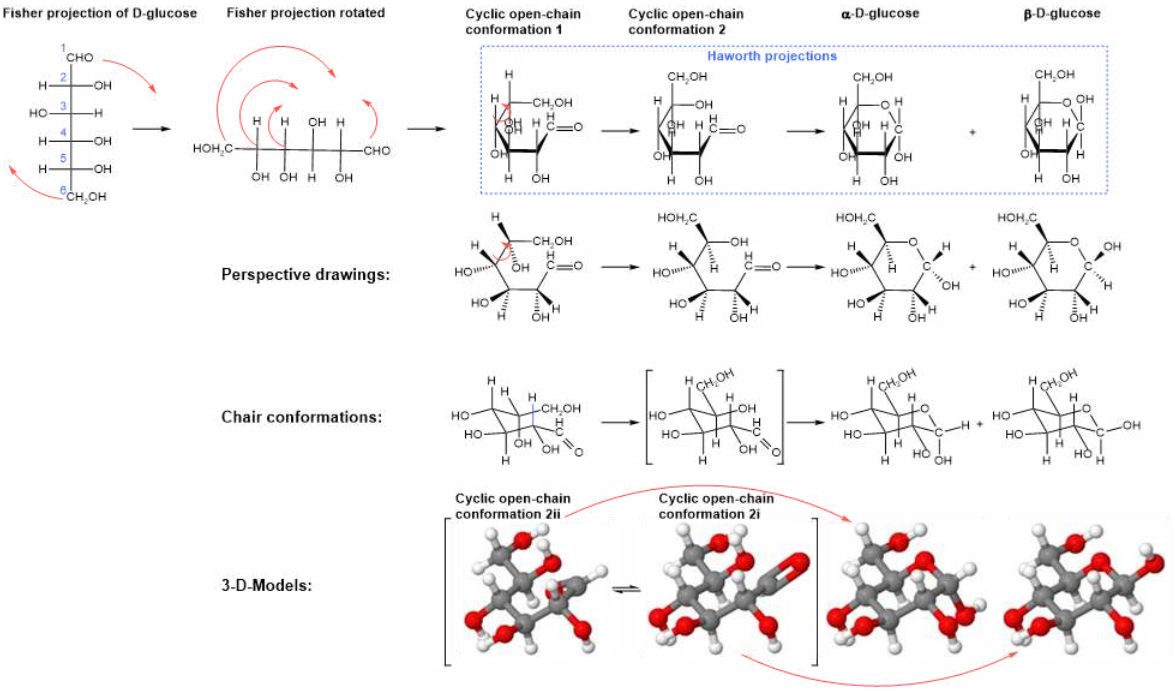


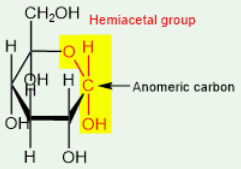
Figure **7.3.1**: Fisher projections to Haworth projections explained. Follow the movement of atoms or rotations around single bonds, represented by curvy arrows in red color (Copyright; Public domain)

Figure **7.3.1** explains the steps to re-draw Fisher projection in cyclic conformation.

1. Rotate the Fisher projection by 90^o clockwise from vertical to horizontal orientation. The groups on the left of Fisher's projection end up above, and those to the right end below in the horizontal orientation.
2. Move **C′s**#1, 4, 5, and 6 up by 60^o each to arrive at the cyclic open-chain conformation#1.
3. Rotate the **C**4-**C**5 bond by 60^o counterclock wise to bring the **C**#5**–OH** group in the cycle of **C′s** and **C**#6 pointing above, i.e., cyclic conformation#1 in Figure **7.3.1**.
4. **C**#5**–OH** and a carbonyl (**C=O**) of **C**#1 react to produce the hemiacetal group with the new **–OH** group on **C**#1 either pointing away from the hemiacetal **O**, i.e., α- or point towards the hemiacetal **O**, i.e., β-orientation in the cyclic hemiacetal.

Anomeric C

Anomeric C is the **C** of carbonyl (**C=O**) group in the open chain conformation that becomes the **C** of the hemiacetal group in the cyclic structure of a monosaccharide. For example, **C**#1 of D-glucose is the anomeric **C**, as highlighted in the figure on the right.

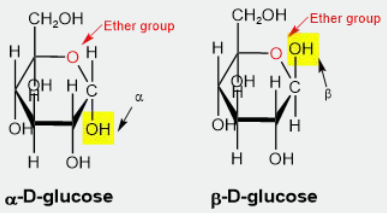


Haworth projection

Haworth projection is five or six-membered cyclic hemiacetals of monosaccharides, presented as pentagon or hexagon shape. It is viewed through its edge perpendicular to the plane of the page, such that the anomeric **C** s the right corner in the plane of the page and ether group (**R–O–R**) is the top right corner in the rear, as shown in the figure on the right. Bold lines usually show the ring bonds toward the viewer (above the page) and those below the page (away from the viewer) as solid lines. Bonds outside the ring are shown as solid lines pointing above or below it.

Assigning α- or β- to the cyclic structures of monosaccharides

Conversion of monosaccharides from open chain to cyclic hemiacetal produced a new chiral center at the anomeric **C**. It is a mixture of two conformations: the **–OH** group on anomeric **C** going away from the ether (**R–O–R**) group is α- and towards it is β-configuration, as illustrated in the figure on the right with the help of D-glucose example.



D-Fructose exists in five-membered and six-membered hemiacetal forms, as shown in Figure **7.3.2**.

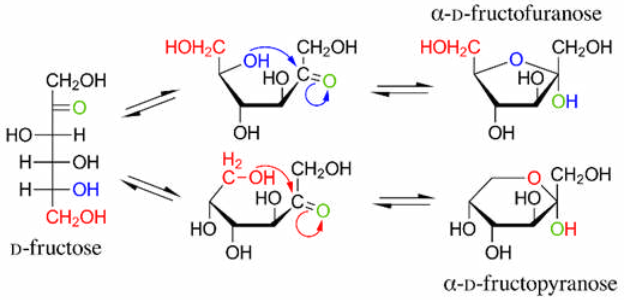
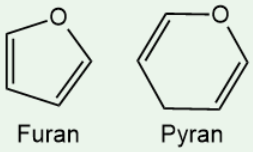


Figure **7.3.2**: Equilibrium reaction between the acyclic and the cyclic hemiketal forms of D-fructose (note: hemiacetal group from a ketone is called hemiketal. α-forms of the hemiketal are shown and the corresponding β-forms are not shown in this figure). (Copyright; Vaccinationist, Public domain, via Wikimedia Commons)

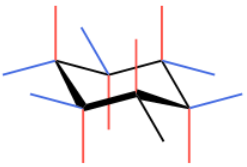
Furanose and pyranose forms of monosaccharides

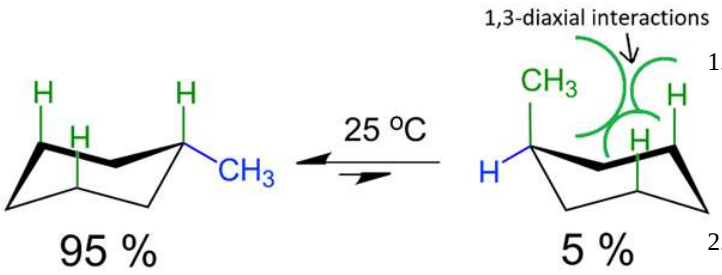
Furanose is a five-membered, and **pyranose** is a six-membered cyclic hemiacetal of monosaccharide. These names originate from the names of cyclic ethers, furan, and pyran, shown in the figure on the right. Based on this nomenclature, the class name of α-D-Glucose is α-D-glucopyranose and of β-D-glucose is β-D-glucopyranose. D-Fructose exists in pyranose and furanose forms, as shown in Figure **7.3.2**.



Chair conformations of pyranose forms

Haworth projections assume a flat ring structure. It is close to the structure of furanose forms (five-membered rings), but pyranose forms (six-membered rings) exist in chair conformations. The figure on the right shows a chair conformation of a six-membered cyclic structure. The points to note are the following.





1. Each **C** has two bonds (shown in black) in the cycle, one axial bond (shown in red) pointing along the axis of the cycle and one equatorial bond (shown in blue) pointing approximately along the equator of the cycle.
2. The axial bonds point in opposite directions, up and down, on neighboring **C′**. The same applies to equatorial bonds.
3. Bulky group, i.e., any group other than **–H**, is more stable at the equatorial than axial position because of steric strain (push away) from the other two axial positions on the same face of the ring., as illustrated in the figure on the left.

How to draw chair conformations of monosaccharides

Alpha (α) and axial start with the letter *a*. Remember α- means an axial **–OH** at anomeric **C** in the case of pyranose chair conformation.

Since α–OH is axial, β–OH is equatorial at anomeric C. The Howarth projection of β-D-glucose in the figure on the right shows that the bulky groups alternate between up and down positions on C#1 to C#5. It means all of them are either axial or equatorial. Since β–OH is equatorial, all bulky groups in β-D-glucose are equatorial, as shown in Figure 7.3.3.

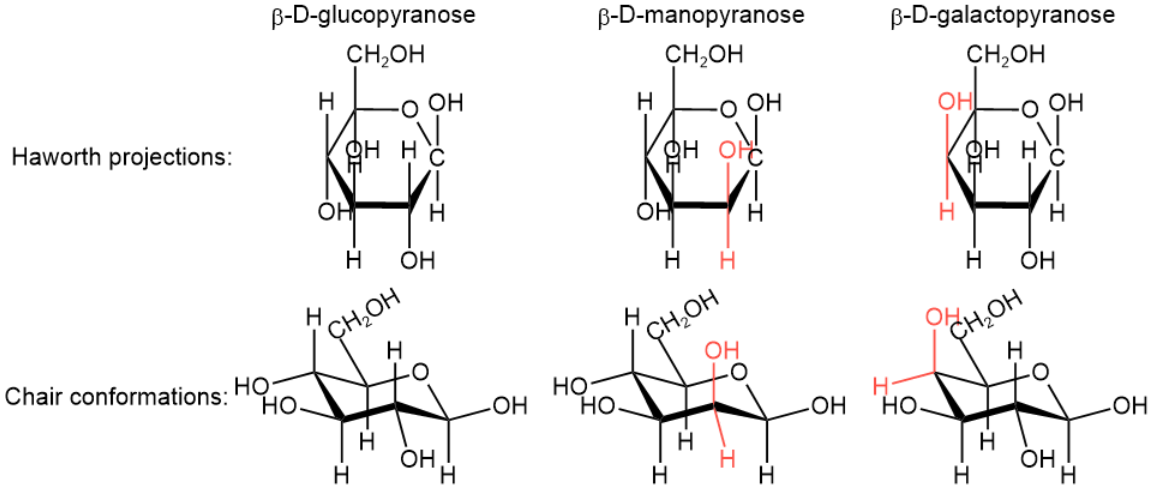


Figure 7.3.3: Haworth projections and the corresponding chair conformations of β-D-glucopyranose, β-D-manopyranose, and β-D-galactopyranose with the differences form β-D-glucopyranose shown in red color. The corresponding α forms (not shown) have *ce–OH* on C#1 (right-most) on axial positions . (Copyright; Public domain)

After learning how to draw β-D-glucopyranose, the other monosaccharides can be drawn easily based on the knowledge of the difference from β-D-glucopyranose. For example, β-D-manopyranose is C#2 epimer, β-D-galactopyranose is C#4 epimer, and their α forms have an axial –OH at anomeric C, as shown in Figure 7.3.3.

Mutarotation

D-Glucose is a chiral compound. A freshly prepared aqueous solution of β-D-glucopyranose has a specific rotation of +112.2. A freshly prepared solution of α-D-glucopyranose has a specific rotation of +18.7. However, the specific rotation of β-D-glucopyranose and α-D-glucopyranose gradually changes to +52.5. This is because the open chain and the two cyclic forms establish equilibrium in the solution, as illustrated in Figure 7.3.4.

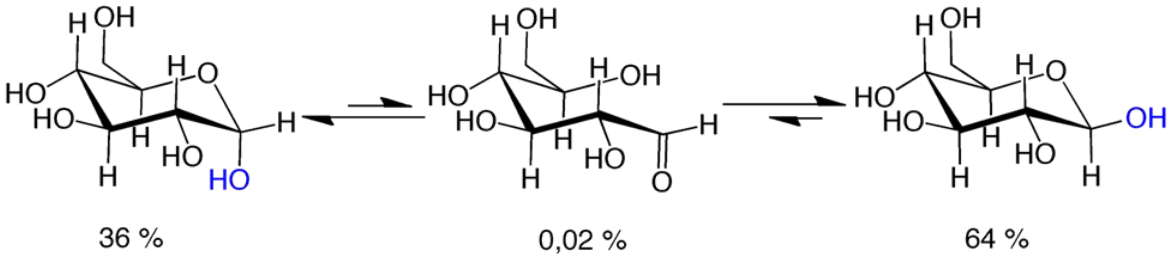


Figure 7.3.4: Equilibrium between three forms of D-glucose: open-chain D-glucose in the middle, β-D-glucopyranose on the right, and α-D-glucopyranose on the left side, with their % ratios shown below the structure. (Copyright; Jü, CC0, via Wikimedia Commons)

Open chain and the two cyclic forms of D-glucose exist in equilibrium in solution where β-D-glucose has all bulky group in equatorial position is the most stable, α-D-glucose with one bulky group in axial position is the second most stable and, and open chain for is the least stable, as reflected by their proportions at equilibrium shown in Figure 7.3.4.

> Mutarotation is the change in the optical rotation of carbohydrate solution over time due to the change in the composition of different compound forms to achieve equilibrium composition.

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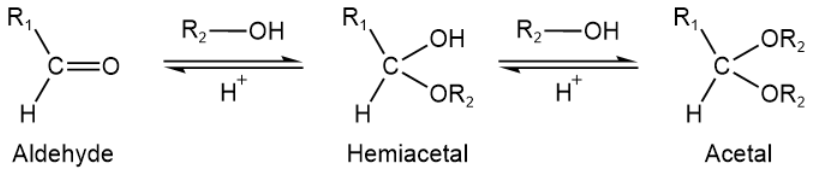
7.4: Reactions of monosaccharides

Learning Objectives

- Write and understand chemical reactions of monosaccharides, including conversion of cyclic hemiacetal to glycosides and N-glycosides, oxidation of open-chain aldehyde form to aldonic acids, and reduction to alditols.
- Define reducing sugars with the examples of D-glucose and D-fructose.

Glycosidic bond formation

Aldehydes and ketones react with alcohols to form hemiacetals. If the alcohol reagent is in excess, a second molecule of the alcohol reacts and converts hemiacetal to acetal. Acetals can be isolated. Acetals convert to alcohol and the aldehyde or ketone when their aqueous solution is acidified, as shown in the general reaction below.



Cyclic (pyranose and furanose) forms of monosaccharides are hemiacetals that react with alcohols to form acetals.

Glycosides are the acetals of monosaccharides. The glucose formed by a reaction with alcohol is also called **O-glycoside**.

For example, β-D-glucopyranose reacts with methanol to form glycosides, shown in Figure **7.4.1**.

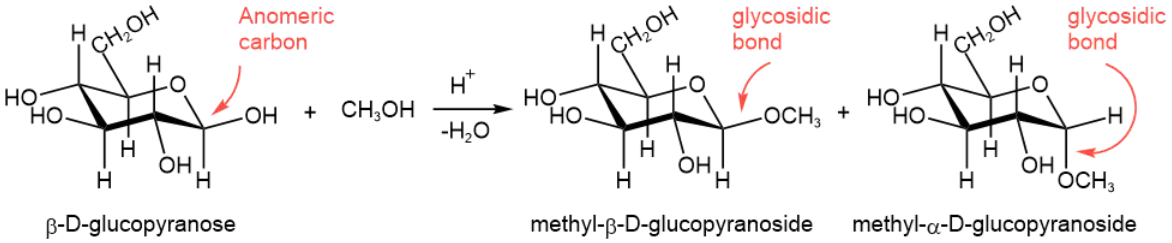


Figure **7.4.1**: Conversion of β-D-glucopyranose to its methyl glycosides. Mixture of α and β glycosides is produced, irrespective of whether the reactant is α or β form of the carbohydrate.(Copyright; Public domain)

Glycoside and glycosidic bond

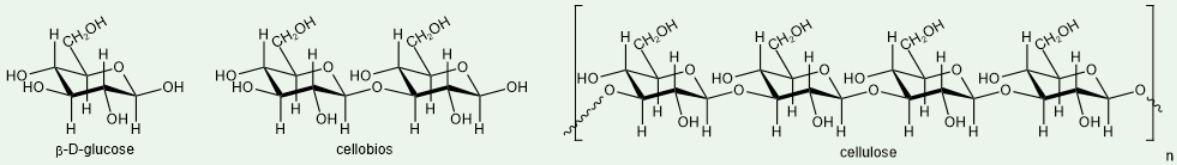
An acetal of a monosaccharide is a glycoside. The bond between anomeric **C** to the new ether **–OR** group in the glycoside is called the glycosidic bond. Anomeric **C** and glycosidic bonds are indicated by red arrows in Figure **7.4.1**.

Glycoside is named by replacing the last e of the carbohydrate name with ide and adding the name of the alkyl part of the new ether **–OR** group as a prefix separated by a hyphen. other For example, β-D-glucopyranose reacts with methanol to form methyl-β-D-glucopyranoside and methyl-α-D-glucopyranoside, as shown in Figure **7.4.1**.

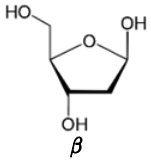
Since monosaccharides have many alcohol groups, two monosaccharides can react with each to form a glycoside, called a **disaccharide**, three can form a **trisaccharide**, and many can form a **polysaccharide**. The di-, tri-, and polysaccharides can be hydrolyzed to monosaccharides in an acidic aqueous solution.

Monosaccharide, disaccharide, oligosaccharide, and polysaccharide

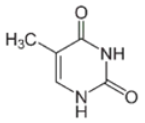
A carbohydrate that can not be hydrolyzed to a simpler carbohydrate is a **monosaccharide**, e.g., D-glucose. A glycoside of two monosaccharides is a **disaccharide**, e.g., cellobiose. A glycoside of three to ten monosaccharides is an **oligosaccharide**, e.g., a fragment of cellulose. A glycoside of more than ten monosaccharides is a **polysaccharide**, e.g., cellulose. The figure below illustrates the structures of D-glucose -a monosaccharide; cellobiose -a disaccharide; and cellulose, -a polysaccharide.



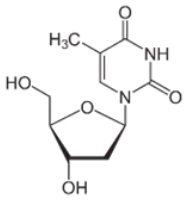
Amines react with hemiacetals forms of monosaccharides the same way as alcohols and produce N-glycosides. For example, β-D-2-deoxyribose reacts with thymine and produced an N-glycoside called deoxythymidine, a part of a monomer of DNA molecule, as shown in the figure below.



-D-2-Deoxyribose (a monosaccharide)



Thymine (an amine)



Doxythymidine (an N-glycoside)

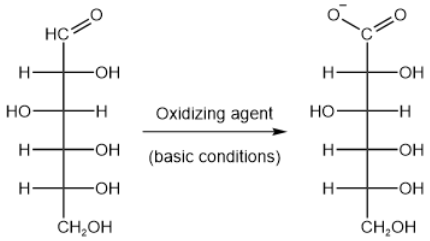
Exceptions to the general formula of carbohydrates

The general formula of carbohydrates is $C_m(H_2O)_n$, and usually for monosaccharides m is equal to n, i.e., $C\cdot_n(H_2O)_n$ or $C_nH_{2n}O_n$. However, there are exceptions.

- Carbohydrates do not necessarily conform to this formula. For example, β-D-2-Deoxyribose $C_5H_{10}O_4$ has less $O's$ than what is dictated by the general formula.
- Compounds following this general formula are not necessarily always carbohydrates. For example, acetic acid $C_2H_4O_2$ follows the general formula, but it is not a carbohydrate.

Oxidation to aldonic acids

Aldehydes are oxidized by a variety of reagents to carboxylic acids. Similarly, the aldehyde group ($-CHO$) of the open-chain form of aldoses is oxidized to a carboxylic acid ($-COOH$) group by oxygen O_2 in the presence of enzymes called oxidases. The acid is named by replacing the suffix -ose of the class name aldose with -onic acid. For example, D-glucose is oxidized to D-gluconic acid. Since, $-COOH$ exists in ionized ($-COO^-$) form, the suffix -onic acid is replaced with -onate for the ionized form. For example, D-glucose is oxidized to D-gluconate, as shown in the figure below.



D-glucose D-gluconate

Reducing sugars

A carbohydrate that reacts with a mild oxidizing agent under alkaline conditions to form an aldonic acid (or aldonate anion in physiological conditions) is called a reducing sugar. For example, D-glucose is a reducing sugar, as shown in the figure above. The carbohydrate reduces the oxidizing agent.

Common reagents used to test the presence of a reducing sugar include Tollen's reagent in which Ag^+ is reduced to Ag that forms a silver mirror on the glass, and Benedict's reagent in which Cu^{2+} is reduced to Cu^+ that forms red color precipitate Cu_2O, as shown in Figure **7.4.2**.

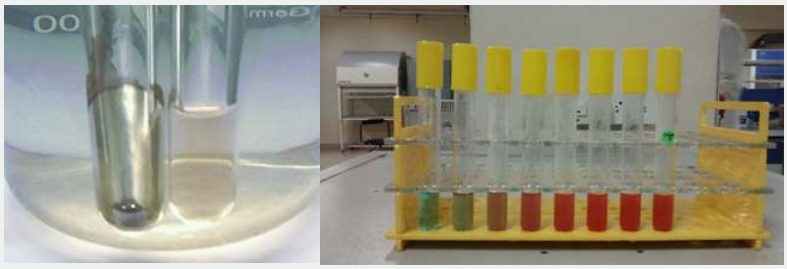
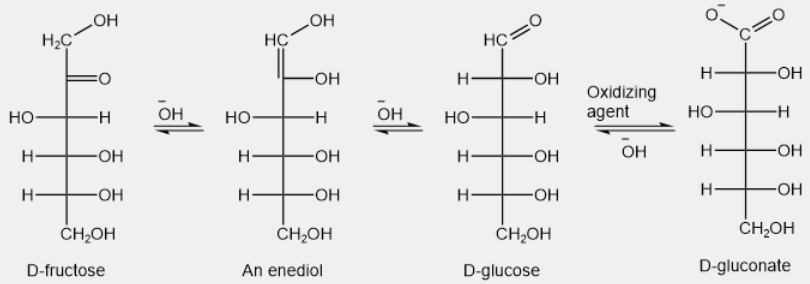


Figure **7.4.2**: Tests for reducing sugars: silver mirror test forming silver mirror as a positive test (left) and Benedict's test forming red color precipitate as a positive test (right). (Copyright; silver mirror test: K1954, Public domain, via Wikimedia Commons, Benedict's test: Psgs123xyz at English Wikipedia, CC0, via Wikimedia Commons)

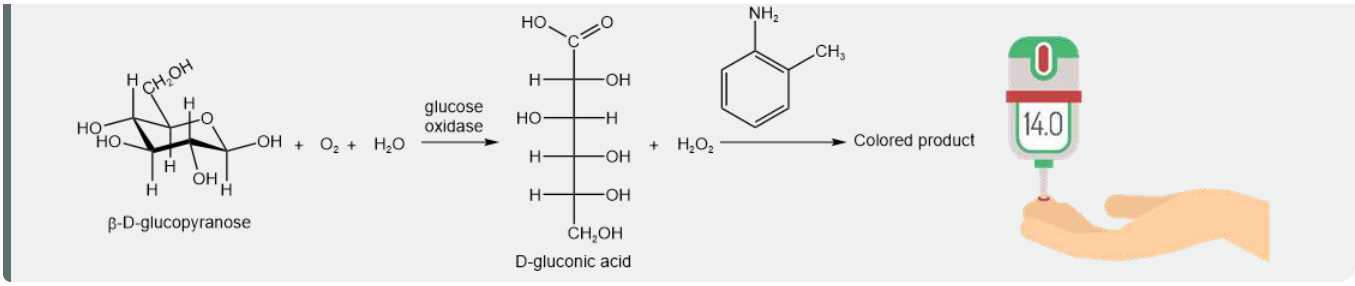
Although open-chain form is in small concentration at equilibrium, it is continuously formed from the hemiacetal forms as the oxidation reaction removes it. The 2-ketoses are also reducing sugars. This is because 2-ketoses exist in equilibrium with the corresponding aldoses under the basic conditions. The aldose form is the actual reducing agent in this mixture. For example, D-fructose is a reducing sugar. D-fructose exists in equilibrium with D-glucose in basic conditions, where D-glucose is the reducing agent, as illustrated in the figure below.



Diabetes and blood-sugar test

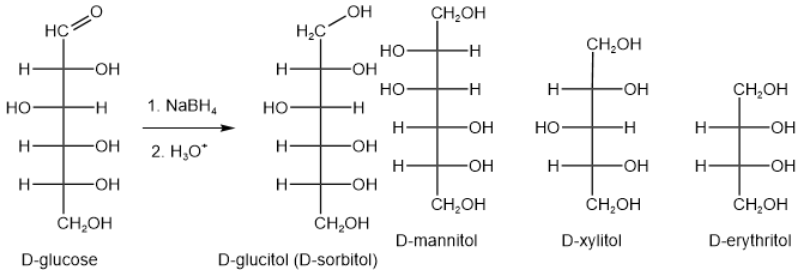
D-Glucose is also called blood sugar, as it is normally present in blood at about 70 mg/dL to 130 mg/dL. It may rise up to 140 mg/dL after eating food, but it returns to the normal range in healthy persons. Enzyme insulin controls blood sugar. If blood glucose control is not functioning properly, the blood glucose may stay higher than normal -a condition called hyperglycemia or diabetes; or it may stay below the normal level -a condition called hypoglycemia.

Blood glucose is usually tested based on enzyme-catalyzed reactions. Glucose oxidase enzyme oxidizes β-D-glucose using O_2 to D-gluconate and hydrogen peroxide H_2O_2. α-D-glucose does not react directly, but it converts to β-D-glucose as the latter is consumed. A second enzyme, peroxidase, causes H_2O_2 to react with 2-methylaniline and produces a colored product that is monitored to measure blood glucose, as illustrated in the figure below.



Reduction to alditols

Aldehydes are reduced to alcohols by a variety of reducing agents. Aldoses in the open-chain form are reduced by reducing agents like sodium borohydride ($NaBH_4$), H_2 in the presence of **Pt**, **Pd**, or **Ni**. Oxidases enzymes are reducing agents in biochemical systems. Although open-chain aldehyde form is in small concentration in the equilibrium mixture, cyclic hemiacetal forms convert to open-chain form as the latter is consumed. The product alcohol is named by replacing -ose suffix of the aldose name with -itol. For example, D-glucose is reduced to D-glucitol, as shown below.



D-glucitol is found in berries, cherries, plums, pears, seaweed, and algae. It is commonly known as D-sorbitol and is a sugar substitute for diabetes. Other alditol examples include D-erythritol, D-mannitol, and D-xylitol. D-xylitol is used in cereals, sugarless candies, and gums.

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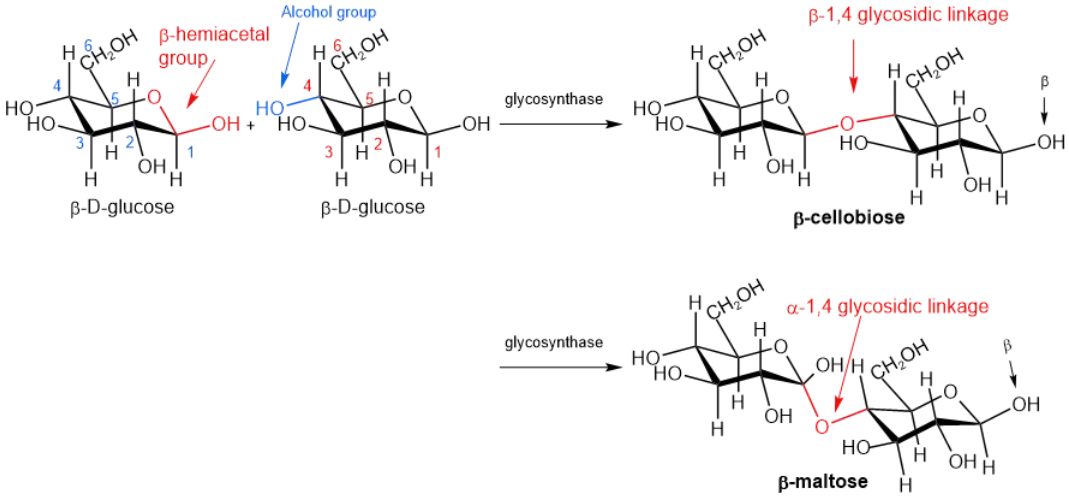
7.5: Disaccharides

Learning Objectives

- Be able to draw and name the glycosidic linkage in disaccharides.
- Know common disaccharides' structures, sources, and properties, including maltose, cellobiose, lactose, and sucrose.

Nomenclature of glycosidic linkage

Disaccharides are glycosides of two monosaccharides. Glycosidic linkage is formed by a reaction between the hemiacetal group of one monosaccharide and an alcohol group of the other, as illustrated in the figure below.

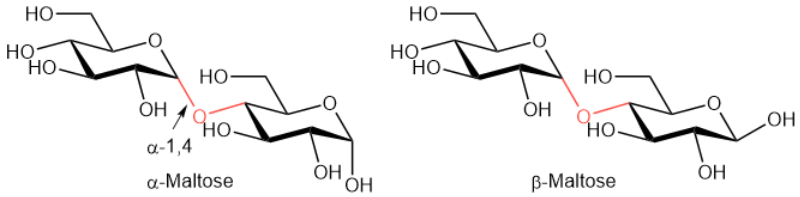


The glycosidic linkage is named by listing the number of the **C's** linked, separated by a comma. In the case of an anomeric carbon, ***α*/*β*** orientation is also indicated, separated by a hyphen from the number of the anomeric carbon. For example, *β*-cellobiose is linked by *β*-1,4 glycosidic linkage and *β*-maltose by ***α***-1,4 glycosidic linkage. The *β* in the name *β*-cellobiose and *β*-maltose indicates the orientation of the free hemiacetal group in the second saccharide unit. It is not related to the orientation of the glycosidic linkage, as indicated by the black arrow in the figure. *β*-Cellobiose and *β*-maltose are configurational isomers having different physical and chemical properties.

Examples of disaccharides include maltose, cellobiose, lactose, and sucrose, described next.

Maltose

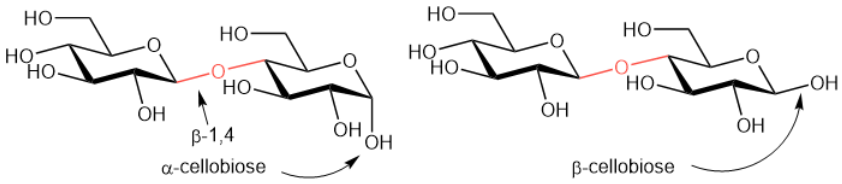
Maltose is a disaccharide of two D-glucose units connected through ***α***-1,4-glycosidic linkage, as shown below.



The second D-glucose unit with free hemiacetal group can be either in ***α***- or *β*-configuration, as indicated by ***α*/*β*** prefix to the name. An aqueous solution exists in equilibrium between ***α***, *β*, and open-chain aldose forms. Since common oxidizing agents can reduce the open-chain aldose form, maltose is a reducing sugar. Maltose is found in the juice of sprouted barley grains and other grains.

Cellobiose

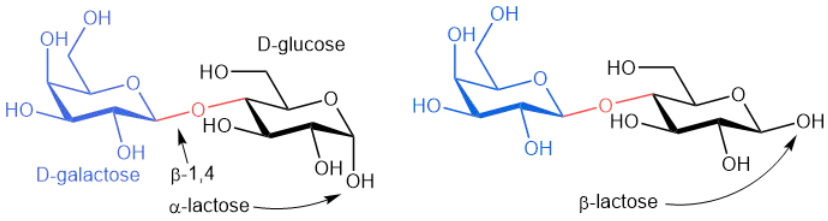
Cellobiose is a disaccharide of two D-glucose units connected by *β*-1,4-glycosidic linkage, as shown below. Hemiacetal forms of cellobiose are shown below.



Cellulobiose is a reducing sugar because, like maltose, the D-glucose unit with free hemiacetal group can exist in α, β, or open-chain aldose forms in solution. Cellobiose is obtained by hydrolysis of cellulose.

Lactose

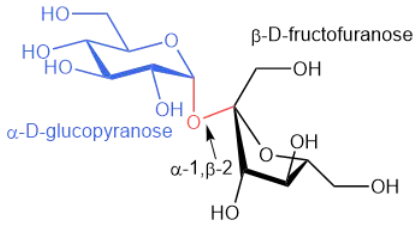
Lactose is a disaccharide of D-galactose joined by β-1,4-glycosidic linkage with D-glucose, as shown below.



Lactose is a reducing sugar because, like maltose, the D-glucose unit with free hemiacetal group can exist in α, β, or open-chain aldose forms in solution. Lactose is present in milk, up to 5% to 8% in human milk and 4% to 6% in cow milk. Lactase is the enzyme that hydrolysis lactose in the digestion process. Many adults develop lactose intolerance due to a lack of or insufficient lactase production. Without lactase, lactose enters the colon undigested and is fermented by bacteria causing bloating and abdominal cramps. Therefore, some products that use lactose also add lactase to avoid the problem.

Sucrose

Sucrose is a disaccharide of D-glucose (in pyranose form) and D-fructose (in furanose form) joined by α-1,β-2-glycosidic linkage, as shown below.



Sucrose

Both anomeric C,s in the glycosidic linkage can not exist in open-chain aldose or ketose forms. Therefore, sucrose is a non-reducing sugar. Sucrose is commonly used as table sugar. It is the most abundant disaccharide found in sugar cane and sugar beats.

Relative sweetness

Monosaccharides and disaccharides are sweet, but sweetness varies. Fructose is the sweetest monosaccharide, and lactose is the least sweet, as shown in Table 1. Honey is a mixture of fructose and glucose and has a sweetness about the same as table sugar (sucrose). Relative sweetness in the table is based on the results of a group of people tasting and ranking them in order of taste relative to sucrose (table sugar), rated 1. Some artificial sweeteners listed in the table are commonly used as sugar-substitute in diet foods.

Table 1: Relative sweetness of some carbohydrates and artificial sweeteners (Based on the results of a group of people tasting and ranking them in order of taste relative to sucrose (table sugar) rated 1 as reference).

Carbohydrates	Sweetness relative to sucrose	Sugar alcohols	Sweetness relative to sucrose	Artificial sweeteners	Sweetness relative to sucrose
Fructose	1.74	Xylitol	1.00	Advantame	2,000
Sucrose (table sugar)	1.00	Maltitol	0.80	Saccharin	450
Honey	0.97	Sorbitol	0.60	Acesulfame-K	200
Glucose	0.74			Aspartame	180
Maltose	0.33			Stevia	150
Galactose	0.65			Sucralose	60
Lactose	0.16				

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7.6: Oligosaccharides

Learning Objectives

- Differentiate between blood types based on the oligosaccharides attached to the red blood cell surface and blood compatibility related to the blood type.

Oligosaccharides are polymers containing a small number, typically three to ten of monosaccharides. Oligosaccharides include dextrins which are microbial breakdown products of long polysaccharides like starch or cellulose and other glycans linked to lipids or proteins through N- or O-glycosidic bonds. The primary role of the last class is cell recognition and cell adhesion. For example, oligosaccharides attached to red-blood cells define the blood type A, B, AB, or O, depending on the linked oligosaccharides, as described next.

A, B, AB, or O blood types

The membrane of animal plasma cells typically has oligosaccharides comprising 4 to 17 monosaccharides attached to them. Their purpose is cell recognition, i.e., if there is a foreign cell or an object in the biochemical system, it is identified through the surface oligosaccharides and either destroyed or flagged for destruction by the body's immune system. For example, red blood cells have different types based on the oligosaccharides attached to their cell membrane, as shown in Figure 7.6.1.

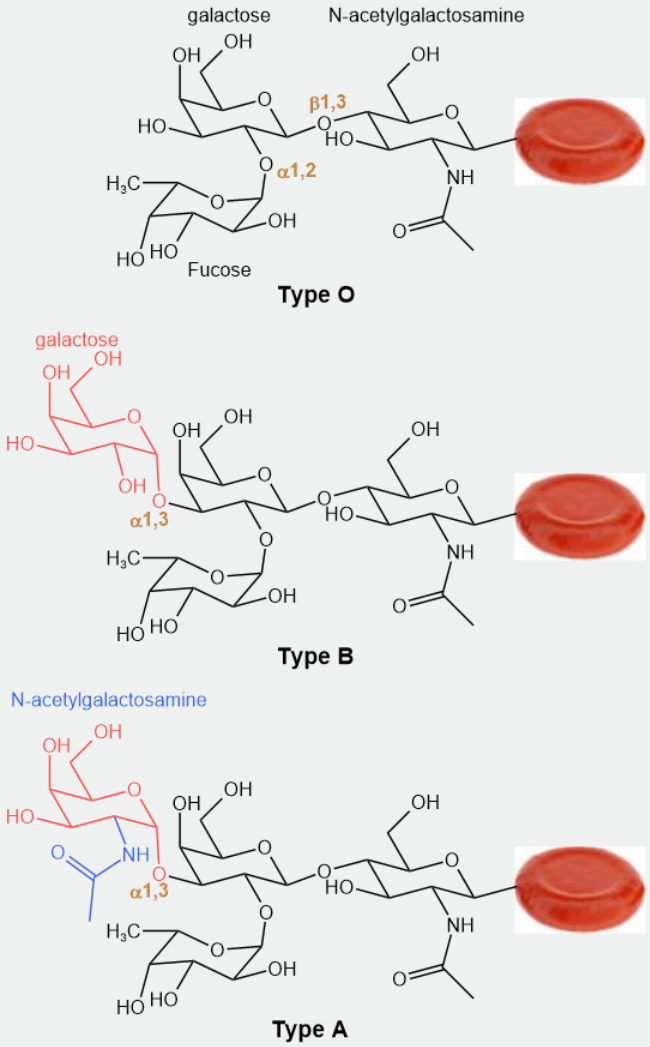


Figure 7.6.1: Oligosaccharide structures of blood type O, type B, and type A. Type AB has type A + type B in it. (Copyright; Public domain)

Blood type O has a combination of N-acetylgalactoseamine-galactose-Fucose. This combination is present in all other blood types also. So, Blood type O is not recognized as foreign in any blood type. A person with blood type O can donate blood to every type, i.e., type O is a universal donor. Any class other than type O has some additional monosaccharide attached which is recognized as foreign by blood type O. So, a person with blood type O can accept only type O blood.

Blood type B has an additional monosaccharide, i.e., galactose attached to galactose of type O oligosaccharide. Type B can receive blood from type O or type B and donate to type B or type AB, as shown in Figure **7.6.2**.

Blood type A has an additional monosaccharide, N-acetyl galactosamine, attached to galactose of type O oligosaccharide. Type A can receive blood from type O or type A and can donate to type A or type A.B

Blood type AB has a mix of type A and type B. Type AB can accept all types, i.e., it is a universal recipient but can donate only to type AB.

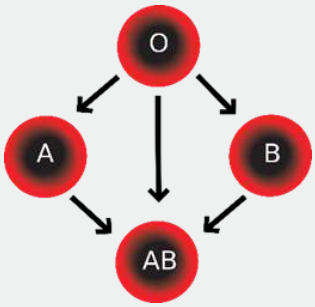


Figure **7.6.2**: Diagram showing the blood group compatibility for transfusion purposes. (Copyright; InvictaHOG, Public domain, via Wikimedia Commons)

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7.7: Polysaccharides

Learning Objectives

- Learn the structures and some characteristics of polysaccharides, including starches, cellulose, and chitin.

Polysaccharides are long polymers from ten to thousands of monosaccharides joined by glycosidic linkages. The most abundant polysaccharides are starch, glycogen, cellulose, and chitin. Except for chitin, all others are composed of D-glucose. Chitin is composed of a modified form of glucose. These are described next.

Starch

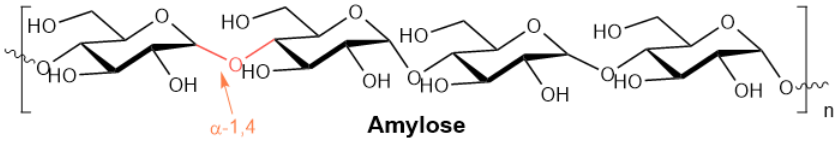
Starch is a storage form of D-glucose in plants. It is found in potatoes, beans, rice, wheat, and other grains and roots, as illustrated in Figure **7.7.1**. Starch is a mixture of two forms, 20% to 25% amylose and 75 to 80% amylopectin.



Figure **7.7.1**: Starch food: Sindhi Biryani is a delicious Dish of Sindh. (Copyright; Miansari66, Public domain, via Wikimedia Commons)

Amylose

Amylose is an unbranched chain of up to 4,000 D-glucose units joined by α-1,4-glycosidic linkage, as shown below.



Amylose

The orientation of bonds with α-1,4-glycosidic linkage makes the amylose chain exist in a helical structure, as shown in Figure **7.7.2**, that allows water molecules to access and establish hydrogen bonds with **–OH** groups. Starch is a water-soluble polymer. It can dissolve in water due to extensive hydrogen bonding with the water molecules when mixed with water.

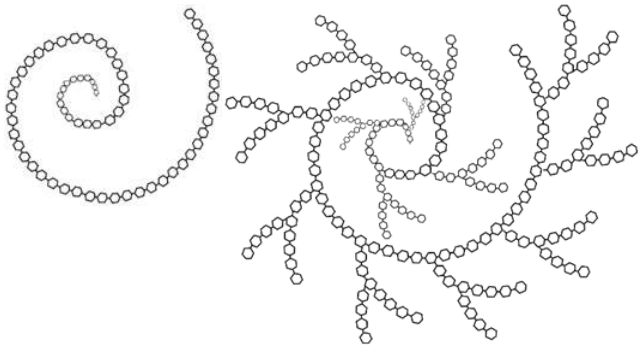
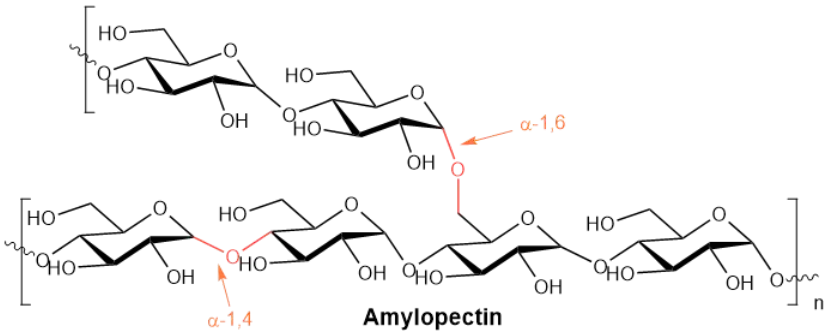


Figure **7.7.2**: Illustration of a spiral structure of amylose (left) and branched helical structure of amylopectin (right). (Copyright; modified the free download from: https://www.hiclipart.com/free-trans...lumuh/download)

Amylopectin

Amylopectin is a branched chain polymer of D-glucose, as shown below.



The main chain comprises 10,000 D-glucose units joined by α-1,4-glycosidic linkage. The main chain exists in the form of a helix. Branches originate at every 24 to 30 unit intervals on the main chain connected to the main chain by a α-1,6-glycosidic linkage, as shown in Figure **7.7.2**. This helix with branches going outwards makes amylopectin more accessible to water for hydrogen bonding and easier to digest.

Glycogen

Glycogen is an energy-storage polysaccharide in animals with the same structure as amylopectin. it has up to 10^6 D-glucose units joined by α-1,4-glycosidic linkages and branching through α-1,6-glycosidic linkages. The main difference from amylopectin is that glycogen has more frequent branching at 10 to 15 D-glucose units interval, as illustrated in Figure **7.7.3**. More branching makes it more soluble in water and easier to hydrolyze multiple D-glucose units from the ends of branches, when the body needs D-glucose.

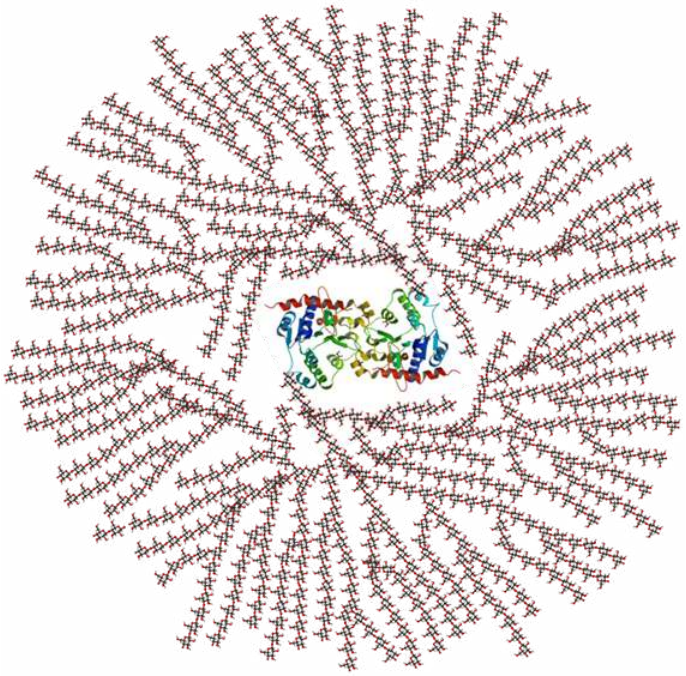


Figure **7.7.3**: A 2-D cross-sectional view of glycogen -A core glycogen protein surrounded by branches of glucose units. (Copyright; Mikael Häggström. Public domain, via Wikimedia Commons)

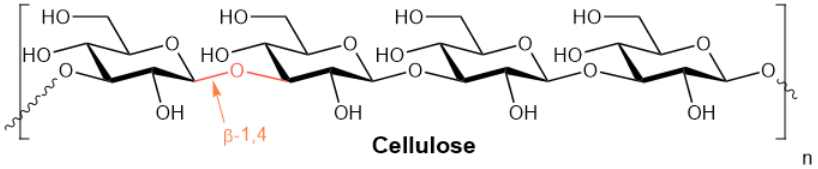
Cellulose

Cellulose is the most abundant polysaccharide in nature that makes up about 50% of the cell wall of plant cells. Cotton, shown in Figure **7.7.4**, is almost pure cellulose.



Figure **7.7.4**: Cellulse: Cotton is almost pure cellulose. (Copyright; United States Department of Agriculture, Public domain via Wikimedia Common)

Cellulose is a linear polysaccharide of about 2200 D-glucose units joined by β-1,4-glycosidic linkage, as shown below.



The β-1,4-glycosidic linkage allowes glucose units to adopt a linear structure with intra-molecule hydrogen bonding. The linear polymer packs nicely with inter-molecular hydrogen bonding and the London-dispersion forces, as shown in Figure **7.7.5**. It gives cellulose its mechanical strength and makes it insoluble in water. Due to the extensive inter- and intra-molecular hydrogen bonding within cellulose, water can not establish enough hydrogen-bonds to dissolve it.

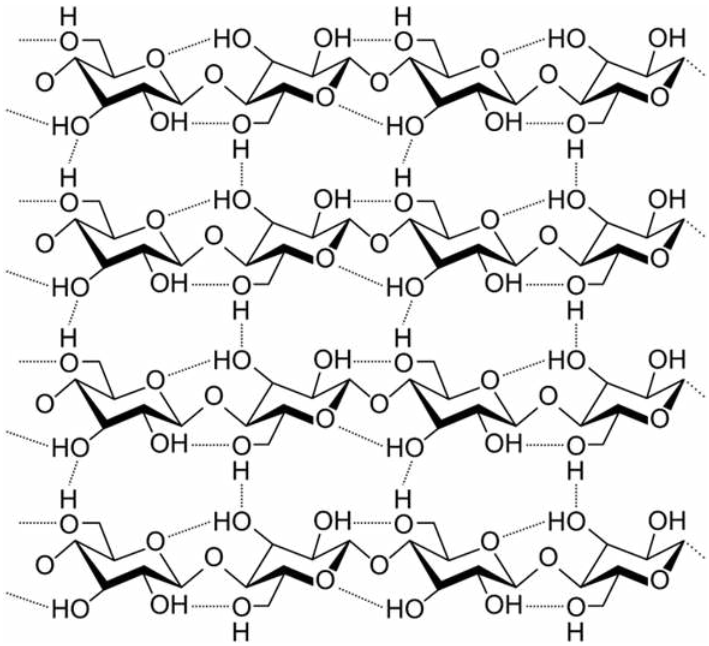


Figure **7.7.5**: Illustration of linear chains of cellulose polymer with intra- and inter-molecular hydrogen bonding shown by dotted lines. (Copyright; Laghi.l, CC BY-SA 3.0, via Wikimedia Commons)

Animals have α-glucosidase enzymes that allow them to hydrolyze starch and glycogen to D-glucose, but they do not have β-glucosidase enzymes needed to hydrolyze cellulose. Grazing animals and termite host bacteria in their stomach that have the β-glucosidase enzymes. Therefore, grazing animals and termites can digest cellulose.

Chitin

Chitin is the second most abundant polysaccharide, second only to cellulose. It is found in the exoskeleton of crustaceans and insects, as shown in Figure **7.7.6**.



Figure **7.7.6**: Blue crab, an example of chitin in the exoskeleton of crustaceans and insets. (Copyright; Blue Crab. USEPA Environmental-Protection-Agency, Public domain, via Wikimedia Commons)

Chitin has the same structure as cellulose except that it is composed of N-acetylglucosamine, an amide derivative of D-glucose, in place of D-glucose in cellulose, as illustrated below Figure **7.7.7**.

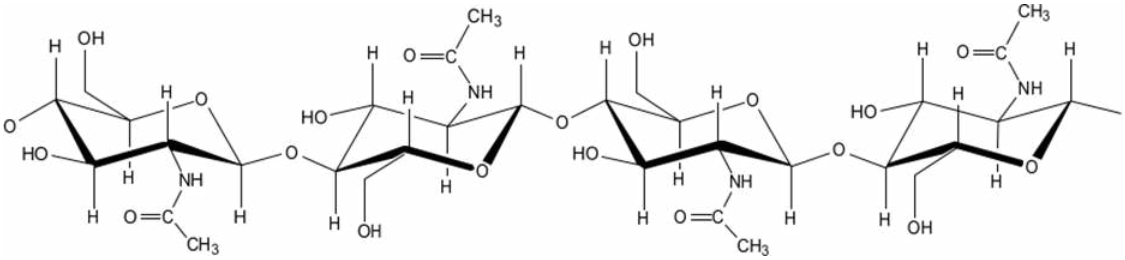


Figure **7.7.7**: Structure of chitin. (Copyright; Ronny Flores, Public domain, via Wikimedia Commons)

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CHAPTER OVERVIEW

8: Lipids

8.1: What are lipids?
8.2: Fatty acyls
8.3: Glycerolipids
8.4: Glycerophospholipids
8.5: Sphingolipids
8.6: Saccharolipids, polyketides, and prenols
8.7: Sterols
8.8: Cell membrane

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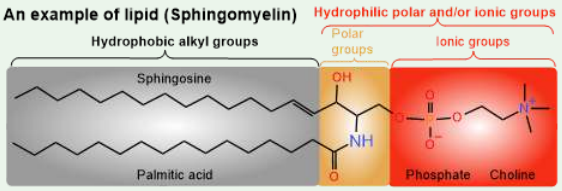
8.1: What are lipids?

Learning Objectives

- Define lipids and understand the basic characteristics of their structural components.

Lipids

Lipids can be defined as hydrophobic or amphiphilic biochemicals, where **hydrophobic** means water-hating or non-polar and **amphiphilic** means having both **hydrophilic**, i.e., water-loving or polar and **lipophilic**, i.e., fat-loving or non-polar components within the same molecule, but overall water insoluble.



Lipids have a long alkyl group that imparts hydrophobic or lipophilic character to the lipids and, usually, a polar and/or ionic group that is a hydrophilic component of the molecule, as illustrated in the figure on the right.

Lipids are a diverse group of biomolecules, including waxes, fats, fat-soluble vitamins (such as vitamins A, D, E, and K), phospholipids, steroids, terpenes, and others. They have a common property of being water insoluble. They can be dissolved in nonpolar solvents like ether or chloroform. Lipids have different functions in living things, including energy storage, signaling, hormonal activities, acting as structural components of cell membranes, etc.

Classification of lipids

Lipids are divided into eight categories: 1) fatty acyls; 2) glycerolipids; 3) glycerophospholipids; 4) sphingolipids; 5) saccharolipids; 6) polyketides; 7) steroids; and 8) prenol lipids. Six of the lipid categories are illustrated in Figure 8.1.1.

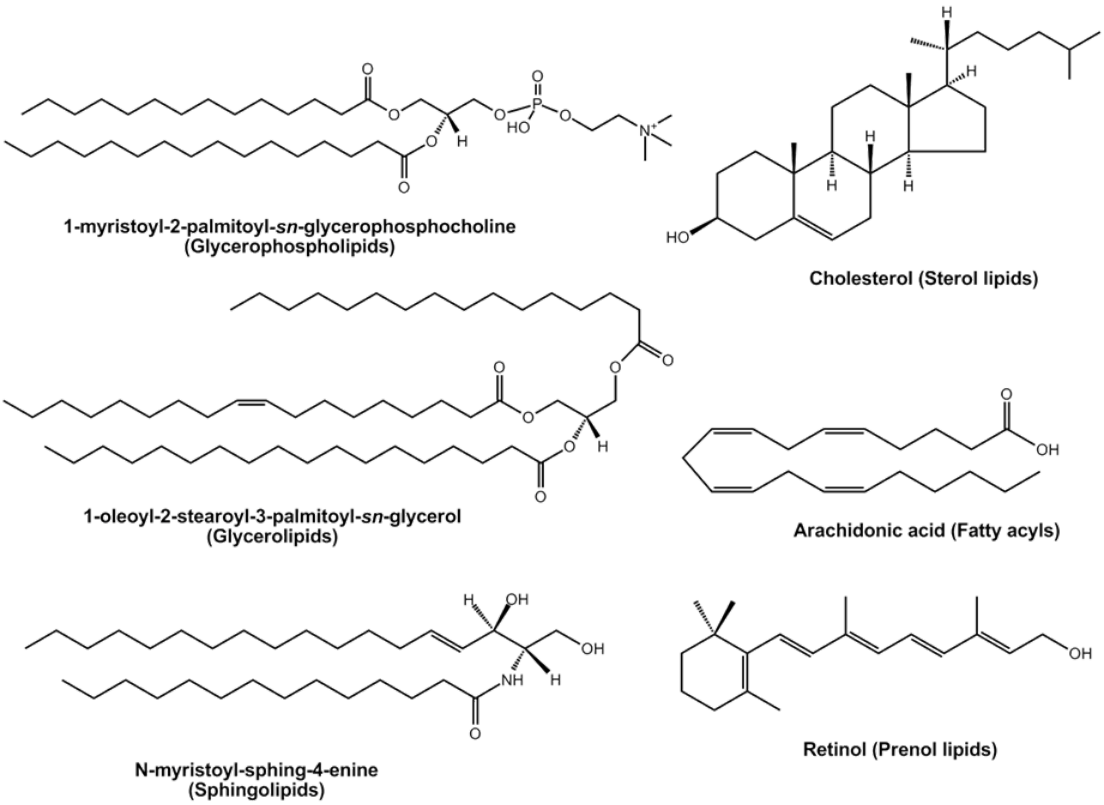
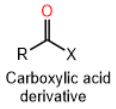
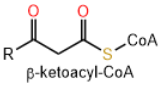


Figure 8.1.1: Examples of some lipid categories. (Copyright; Lmaps, GFDL 1.2, via Wikimedia Commons)



Carboxylic acid derivative

Five lipid categories contain long alkyl chain carboxylic acids or carboxylic acid derivatives. These include fatty acyls, glycerolipids, glycerophospholipids, sphingolipids, and saccharolipids. Polyketides are derived from condensation reactions of β-ketoacyl subunits. Steroids and prenols are derived from condensation reactions of isoprene subunits. These categories of lipids are described in the following sections.



β-ketoacyl-CoA


Isoprene

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8.2: Fatty acyls

Learning Objectives

- Understand the basic structural features of fatty acids, the notations reflecting them, and their relationship to the melting points and health effects.
- Define essential fatty acids, omega fatty acids, and their importance.
- Understand the basic structure features, nomenclature, and functions of prostaglandins.
- Understand the structures and uses of important waxes.

Fatty acyls are a group of lipids that contain a fatty acid or its derivative.

Fatty acids

Fatty acids

Fatty acids are carboxylic acids with an alkyl chain that is usually unbranched and containing an even number of C′s, usually between 8 to 20 C′s.

Figure 8.2.1 shows some examples of fatty acids that have 18 C′s in the chain. Carboxylic acid group (−COOH is hydrophilic, and the alkyl chain is hydrophobic, making fatty acids amphiphilic. The hydrophobic property of the long alkyl chain dominates, making fatty acids insoluble in water.

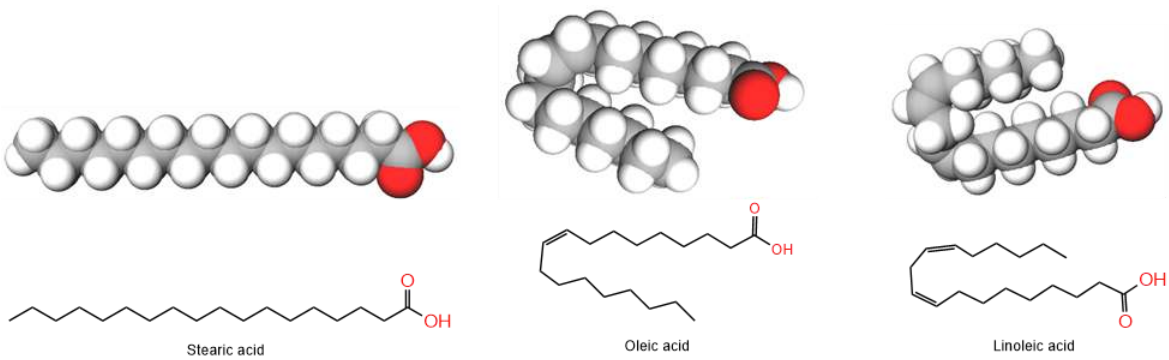


Figure 8.2.1: Examples of fatty acids: a saturated steric acid (18:0), a monounsaturated oleic acid (18:1), and a polyunsaturated linoleic acid (18:2). Skeletal formulas are shown with the corresponding space-filling model shown on the top of each of the skeletal formula. (Copyright; Public domain)

Unsaturated, monounsaturated, and polyunsaturated fatty acids

- The alkyl chain can be saturated with all C−C σ-bonds, called **saturated fatty acid (SFA)**, e.g., steric acid;
- or may contain some double bonds (C=C), called **unsaturated fatty acid (USFA)**., e.g., oleic acid and linoleic acid Figure 8.2.1.
  - The unsaturated fatty acid may have one C=C bond called **monounsaturated fatty acid (MUFA)**, e.g., oleic acid;
  - or more than one C=C bonds called **polyunsaturated fatty acid (PUFA)**, e.g., linoleic acid.

Notations for and labelling C′s in fatty acids

Short notations

Carboxylic acids are usually referred to by their trivial names. **Short notation** is used to indicate # of C′s:# of C=C bonds, e.g., steric acid Figure 8.2.1 is 18:0 meaning eighteen carbons and zero double bonds. Similarly, oleic acid is 18:1 meaning eighteen carbons and one double bond, and linoleic acid is 8:2 meaning eighteen carbons and two double bonds.

Labelling C′s

Systematic IUPAC nomenclature starts numbers from carbonyl-carbon (**C=O**) as shown in Figure **8.2.2**, red numbers. Trivial nomenclature uses Greek alphabets starting from **C**#2 as α, next one as β, than γ, and so on, as shown in Figure **8.2.2**, black numbers. **IUPAC short** notation shows the position labels of the double bonds' first **C′s** in a bracket, separated by commas, next to the regular short notation. The numbering begins from (**−COOH** end. For example, steric acid 18:0, i.e., eighteen carbons and zero double bonds, oleic acid is 18:1(9), i.e., eighteen carbons and one double bond at **C**# 9, and linoleic acid is 18:2(9, 12), i.e., eighteen carbons and bonds, one at **C**# 9 and the other at **C**# 12.

Omega-minus (ω-#) labeling

In omega-minus (ω-#) labeling the last **C**, i.e., the **−CH₃** at the end opposite to carboxyl (**−COOH**) group is labeled ω-1, the **C** next to it as ω-2, than ω-3 and so on, as as shown in Figure **8.2.2**, in blue fonts. Recall that ω is the last alphabet in Greek, so, ω-1 is the last carbon. **The "omega-#"** (ω-#) label is usually used to refer to the position of the first **C** of the first **C=C** bond from the ω-end, i.e., from the **−CH₃** end, opposite to the **−COOH** end. For example, α-linolenic acid in Figure **8.2.2** is an ω-3 fatty acid.

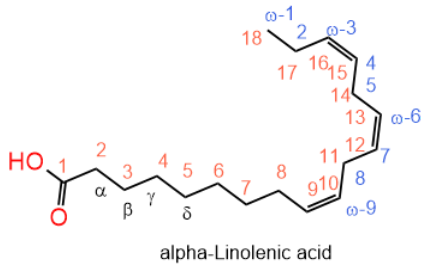


Figure **8.2.2**: Labelling of **C′s** in fatty acids: systematic IUPAC numbers are in red, nonsystematic Greek letter labels are in black, and omega-minus (ω-#) are in blue. (Copyright; Public domain)

Table 1 lists common fatty acids with their IUPAC short notations, ω-#, and melting points.

Table 1: Some of the common fatty acids

Common name	Condensed formula	IUPAC notation*	Melting point (°C)	ω-#	Found in
Saturated fatty acids					
Caprylic acid	$CH_3(CH_2)_6COOH$	8:0	17		Milk
Capric acid	$CH_3(CH_2)_8COOH$	10:0	32		Coconut
Lauric acid	$CH_3(CH_2)_{10}COOH$	12:0	44		Coconut
Myristic acid	$CH_3(CH_2)_{12}COOH$	14:0	55		Nutmeg
Palmitic acid	$CH_3(CH_2)_{14}COOH$	16:0	63		Palm
Stearic acid	$CH_3(CH_2)_{16}COOH$	18:0	69		Animal fat
Arachidic acid	$CH_3(CH_2)_{18}COOH$	20:0	75		Corn
Monounsaturated fatty acids					
Myristoleic acid	$CH_3(CH_2)_3\mathbf{CH=CH}(CH_2)_7COOH$	14:1(9)	0	ω−5	Butter
Oleic acid	$CH_3(CH_2)_7\mathbf{CH=CH}(CH_2)_7COOH$	18:1(9)	14	ω-9	Olives, pecan, grapeseed
Elaidic acid	$CH_3(CH_2)_7\mathbf{CH=CH}(CH_2)_7COOH$	18:1(9t)	45	ω-9	Milk
Erucic acid	$CH_3(CH_2)_7\mathbf{CH=CH}(CH_2)_{11}COOH$	22:1(13)	34	ω-9	Rapeseed
Polyunsaturated fatty acids					
Linoleic acid	$CH_3(CH_2)_4\mathbf{CH=CH}CH_2\mathbf{CH=CH}(CH_2)_7COOH$	18:2(9,12)	-5	ω−6	Soybean, safflower, sunflower
α-Linolenic acid	$CH_3CH_2\mathbf{CH=CH}CH_2\mathbf{CH=CH}CH_2\mathbf{CH=CH}(CH_2)_7COOH$	18:3(9,12,15)	-11	ω−3	Corn
Arachidonic acid	$CH_3(CH_2)_4\mathbf{CH=CH}CH_2\mathbf{CH=CH}CH_2\mathbf{CH=CH}CH_2\mathbf{CH=CH}(CH_2)_3COOH$	20:4(5,8,11,14)	-50	ω−6	Meat, eggs, fish
Eicosapentaenoic acid	$CH_3CH_2\mathbf{CH=CH}CH_2\mathbf{CH=CH}CH_2\mathbf{CH=CH}CH_2\mathbf{CH=CH}CH_2\mathbf{CH=CH}(CH_2)_3COOH$	20:5(5,8,11,14,17)	-65	ω−3	Fish
Docosahexaenoic acid	$CH_3CH_3\mathbf{CH=CH}CH_2\mathbf{CH=CH}CH_2\mathbf{CH=CH}CH_2\mathbf{CH=CH}CH_2\mathbf{CH=CH}CH_2\mathbf{CH=CH}(CH_2)_2COOH$	22:6(4,7,10,13,16,19)	-44	ω−3	Fish

* IUPAC notation shows Numbers of **C's**:number of double bonds(position of *cis*-double bond, except when there is symbol t for *trans*-

Common name	Condensed formula	IUPAC notation*	Melting point (°C)	ω-#	Found in
configuration)					

Essential fatty acids

α-Linolenic acid (18:3(9,12,15)) -an ω−3 fatty acid, and linoleic acid (18:2(9,12)) - an ω−6 fatty acid are **essential fatty acids (EFAs)** because humans and other animals cannot synthesize them. They must be included in the diet as they are needed for good health. Although eicosapentaenoic acid (20:5(5,8,11,14,17)) and docosahexaenoic acid (22:6(4,7,10,13,16,19)), called **long-chain unsaturated fatty acids**, can be synthesized from α-linolenic acid, the conversion efficiency is low, and it is recommended that these should also be included in the diet. Arachidonic acid (20:4(5,8,11,14)) is another long-chain unsaturated fatty acid that can be synthesized from linoleic acid.

Shapes and physical properties of fatty acids

Shapes

The saturated fatty acids are cylindrical that pack nicely in the solid state with a large contact area between the molecules. The double bonds in unsaturated fatty acids are usually in the *cis* configuration. A *cis*-**C=C** introduces a kink in the structure that does not let molecules pack with a large contact area between neighboring molecules, as illustrated in Figure **8.2.3**. Some unsaturated fatty acids have *trans*-double bonds and are cylindrical, like saturated fatty acids, but they are rare.

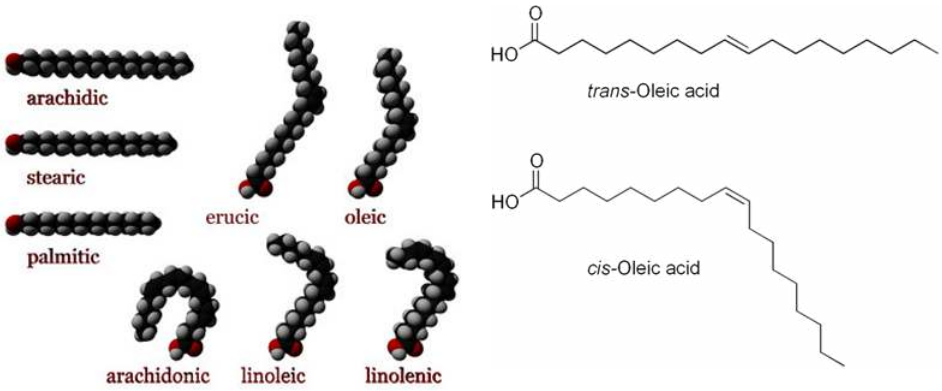


Figure **8.2.3**: Three-dimensional representations of several fatty acids. Saturated fatty acids (arachidic 20:0, steric acid 18:0. palmitic acid 16:0) are cylindrical. Unsaturated ones (erucic 21:1, oleic 18:1, arachidonic 20:4, linoleic 18:2, and linolenic (18:3) are typically bent unless they have a trans configuration (Copyright: Automated conversion, CC BY-SA 3.0, via Wikimedia Commons), right: Oleic acid and its trans isomer (Copyright: Edgar181, Public domain, via Wikimedia Commons)

Melting points

The melting point of fatty acids is affected by two factors, as shown in Table 1:

1. an increase in the number of **C's** increases the melting point because it increases London dispersion forces holding the molecules together, and
2. the presence of *cis*-**C=C** bond decreases the melting point due to the kink in the structure that reduces the contact area between molecules and, consequently, London dispersion forces are less.

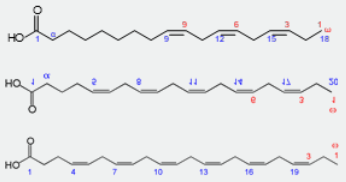
Fats containing saturated fatty acids are considered unhealthy as they tend to deposit in arteries forming plaque, i.e., atherosclerosis. It can lead to high blood pressure, rupture of arteries, or heart attack. Saturated fatty acids are more common in animal fats, while unsaturated fatty acids, considered healthier, are more common in vegetable oils.

It has been observed that people from Alaska eat more unsaturated fats and have a low occurrence of atherosclerosis and heart attack. Fats in Alaskan food is primarily from fish, such as salmon, tuna, and herring, as shown in Figure **8.2.4**. Vegetable oils

have higher contents of ω-6 fatty acids, such as linoleic acid and arachidonic acid. Fish oil mainly contains ω-3 fatty acids, such as linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid.



salmon tuna herring



ω-3 fatty acids in fish

Figure **8.2.4**: Three common fish in the diet of people of Alaska and three common ω-3 fatty acids found in the fish: linolenic acid (top), eicosapentaenoic acid (middle), and docosahexaenoic acid (bottom). (Copyright: Public domain).

Prostaglandins

Prostaglandins are lipids containing 20 **C's** that are derived from arachidonic acid (20:4(5, 8, 11, 14)) and act like hormones. They are found in small concentrations in almost all body tissues and cells. Their activities include blood pressure regulation, blood clotting, inflammation, gastric secretions, kidney functions, and reproductive activities. They are usually short-lived and produced locally where they perform their function.

Prostaglandins synthesis

Prostaglandins synthesis starts from arachidonic acid using enzymes like cyclooxygenase (COX-1 and COX-2) and prostaglandin synthase, like PGE-synthase and PGF-synthase, as illustrated in Figure **8.2.5**. The prostaglandins have a five-membered ring and two side chains. The prostaglandin PGG_2 is synthesized from arachidonate and quickly converts to PGH_2. PGH_2 regulates constriction and dilation of blood vessels and stimulates platelet aggregation. PGH_2 converts to PGE_2 and PGF_2 which induce labor by stimulating uterine contraction. PGF_2 also lowers blood pressure by relaxing smooth muscle cells in blood vessels. PGH_2 is also a precursor of several other Prostaglandins and related biomolecules.

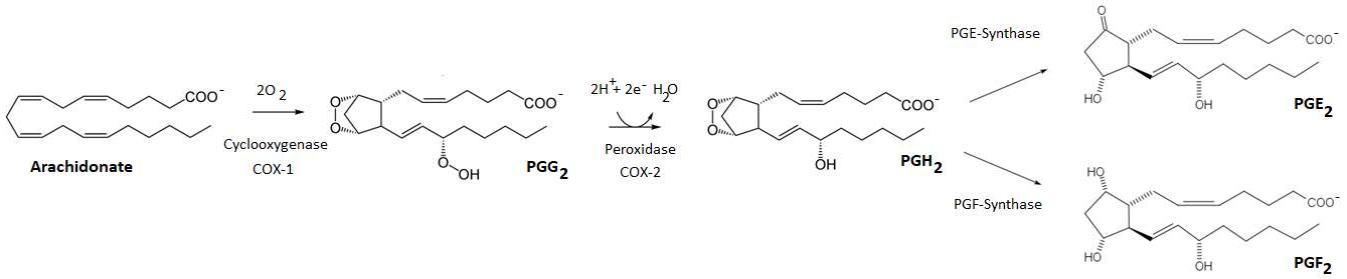


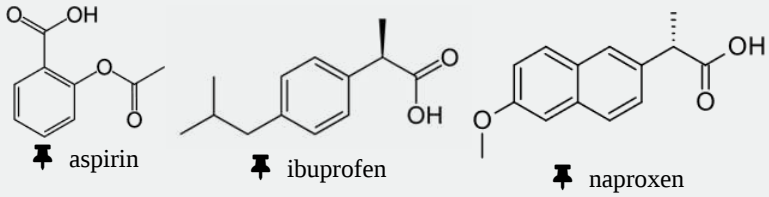
Figure **8.2.5**: Synthesis of some prostaglandins from arachidonate. (Copyright; Public domain)

Prostaglandins names

The names of prostaglandins are abbreviated as three letters followed by a subscript, where the first two letters, i.e., PG, stands for prostaglandin, the 3rd letter indicates the substitution pattern, and the subscript tells the number of **C=C** bonds in the side chains. For example, the 3rd letter G has endoperoxide in the ring and a hydroperoxide group at **C's** 15, H has endoperoxide in the ring, and a hydroxyl group at **C's** 15, E has a β-hydroxyketone, and F has a 1,3-diol groups in the ring. The subscript 2 shows two **C=C** bonds in the side chains. The letter E in PGE_2 also indicates that it is soluble in ether and F in PGF_2 indicates it is soluble in phosphate buffer.

Nonsteroidal anti-inflammatory drugs (NSAIDs) action on prostaglandin synthesis

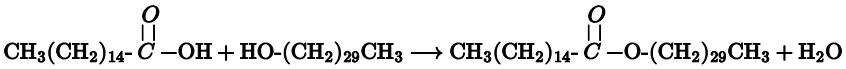
When tissues are injured, arachidonic acid is converted into prostaglandins that cause inflammation and pain. Nonsteroidal anti-inflammatory drugs, like aspirin, ibuprofen, and naproxen, shown below, inhibit the conversion of arachidonic acid into prostaglandins. Ibuprofen and naproxen inhibit the cyclooxygenase (COX) enzyme by binding with it. Aspirin deactivates the cyclooxygenase (COX) by transferring an acetyl group to the hydroxyl group of the active site of the cyclooxygenase. Care must be taken using NSAIDs as their long-term use can cause gastrointestinal, liver, or kidney damage.

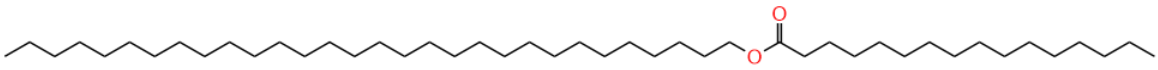


aspirin ibuprofen naproxen

Waxes

Lipid waxes are esters of one long-chain fatty acid with unbranched long-chain alcohol containing 14 to 30 **C's** per chain. For example, myricyl palmitate found in beeswax can be obtained by the esterification of palmitic acid and myricyl alcohol:





Functions of waxes

Waxes form a waterproof coating on plants' leaves, fruits, and stems to minimize water evaporation and protect against parasites. Examples include palm trees and jojoba wax from jojoba bushes. The wax coating on animals' skin, fur, and feathers protects water birds from water wetting and rainwater and shelters them from rainwater. Bees use wax to construct protection and housing for honey, as illustrated below. Sperm whales use spermaceti wax in their heads as a part of their eco analysis, i.e., navigation system.



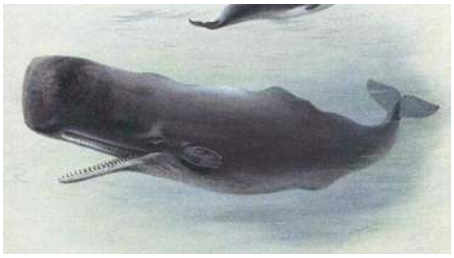
Honeycomb made of beeswax:



Carnauba wax coating on palm tree leaves:



Jojoba wax on leaves and fruits of jojoba bush:



Sperm whale has spermaceti wax in the head as a part of their eco-analysis syterm:

Figure 8.2.1: Examples of waxes, their uses, and formulas (Copyright: Public domain).

Beeswax and carnauba wax protective coatings on cars, furniture, floors, etc. Jojoba wax and spermaceti are used to make candles and cosmetics. A mixture of waxes obtained from wool is used in lotions for face and skin softening.

Petroleum waxes and earwax

Petroleum-derived waxes or paraffin are also called waxes, but they are not esters but mixtures of long-chain hydrocarbons. Earwax is a mixture of glycerol esters, cholesterol, phospholipids, etc., from dead skin and secretions of cerumen glands. Like other lipid waxes, it protects the ear canal against bacteria, fungi, and water. Excess earwax can cause blockage in the ear canal and hearing loss.

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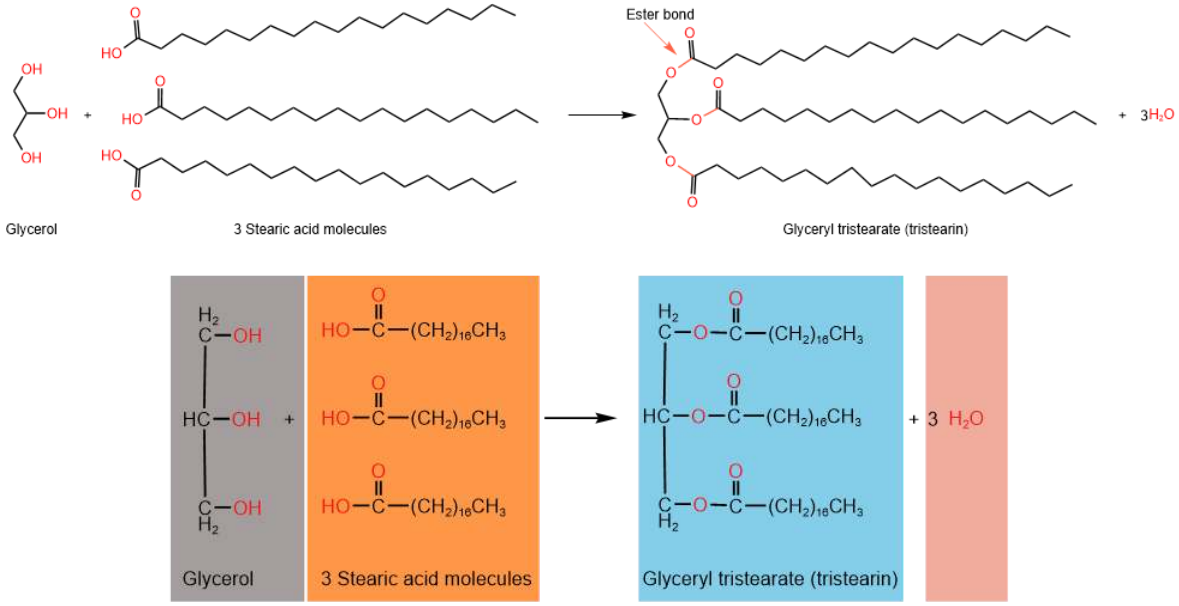
8.3: Glycerolipids

Learning Objectives

- Define glycerolipids and triglycerides and understand their structures.
- Understand the difference in composition and properties of fats and oils and their primary role as energy storage molecules.
- Understand the chemical properties of fats and oils, including hydrolysis, saponification, and partial or complete hydrogenation.

What is a glycerolipid?

Glycerolipids have two components: propane-1,2,3-triol, also called glycerol, and one, two, or three fatty acids. Recall that a condensation reaction between an alcohol and a carboxylic acid forms an ester by eliminating a water molecule. The following example shows the reaction of glycerol with three molecules of stearic acid, creating a triester.

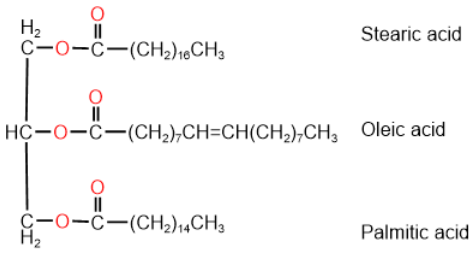


A mono-, di-, or tri-ester of glycerol is called glycerolipid.

The name of a glycerolipid begins with glyceryl and is followed by carboxylate. For example, the triester of glycerol shown above is glyceryl tristearate, which is commonly known as tristearin.

Glycerolipids that are triesters of glycerol with three fatty acids are called **triacylglycerol** or **triglycerides**. For example, glyceryl tristearate shown above is a triglyceride.

Triglycerides may be esters of three molecules of the same fatty acids, e.g., tristearin. Still, often the triglycerides found in nature are esters of two or three different fatty acids. Fatty acids usually found in fats and vegetable oils include lauric, myristic, palmitic, stearic, oleic, linoleic, and linolenic acids. An example of a mixed triglyceride of stearic, oleic, and palmitic acid is shown below.



A mixed triacylglycerol

Fats and oils

Fats and oils are triglycerides used as energy storage molecules in animals and plants.

Energy storage is essential for hibernating animals that live in icy environments. They have plenty of food available during summer but no food and below-freezing temperatures in winter. They eat plants, seeds, and nuts and accumulate fat that becomes their energy source when hibernating in winter. For example, the polar bear shown on the right can accumulate up to 14 kg of fat per week in summer when the food is plenty and uses it as an energy source when the animal hibernates for 4 to 7 months in winter.



Although glycogen is a quick energy source, fats and oils are more energy dense for two reasons:

- first, fats and oils are in a more reduced form than glycogen and release more energy per mass upon oxidation, and
- second, glycogen is hydrophilic and absorbs water, increasing its mass.

Physical properties of fats and oils

Pure fats and oils are colorless, odorless, and tasteless. The color, taste, and odor associated with butter -an animal fat, and olive oil -a vegetable oil, is due to a small number of other substances mixed with the triglycerides.

Fats come from animal sources, such as meat, whole milk, lard, butter, and cheese. Vegetable oils come from plant sources, e.g., soybeans, peanuts, sunflowers, etc.

Fats are usually solid at room temperature because they have a higher proportion of long-chain unsaturated fatty acids with higher melting points, e.g., lard and butter shown in Figure **8.3.1**. **Vegetable oils are usually liquid** at room temperature because they contain more unsaturated or short-chain saturated fatty acids.



Figure **8.3.1**: Butter -a fat that is semisolid, and olive oil -a vegetable oil liquid at room temperature. (Copyright:Butter: Renee Comet (National Cancer Institute), Public domain, via Wikimedia Commons, Olive oil: Roberta Sorge robertina, CC0, via Wikimedia Commons)

For example, canola oil, safflower oil, flaxseed oil, sunflower oil, corn oil, olive oil, soyabean oil, peanut oil, and cottonseed oil are vegetable oils that are liquid at room temperature and have a higher proportion of unsaturated fatty acids as shown in Figure **8.3.2**. Palm and coconut oils are vegetable oils with a higher balance of saturated fatty acids. Still, they are liquid at room temperature because they have short-chain saturated fatty acids. For example, coconut mainly comprises lauric acid (12:0), a short-chain fatty acid.

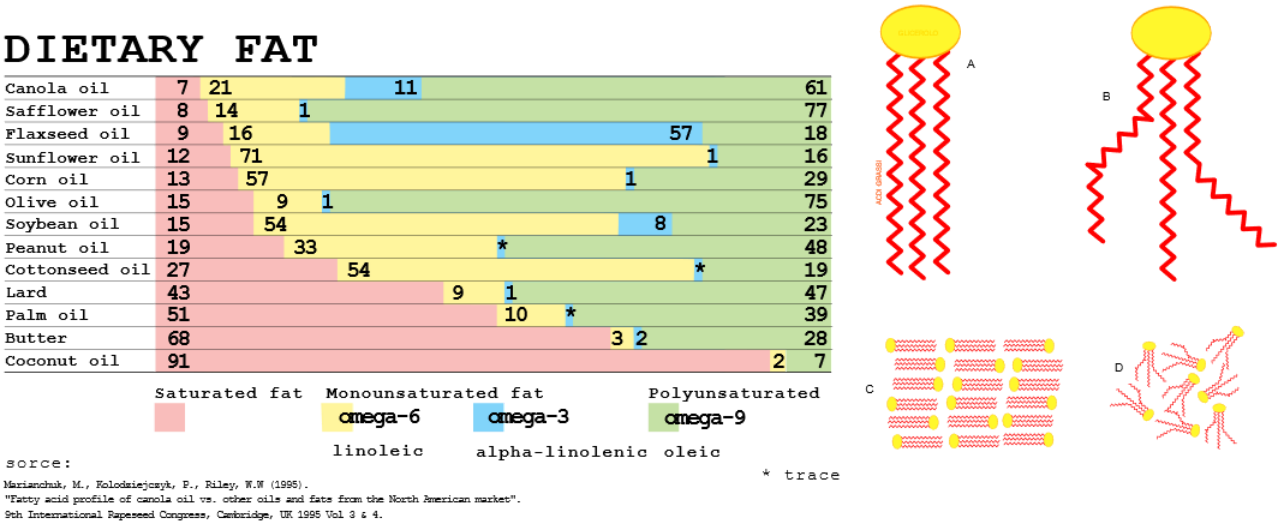


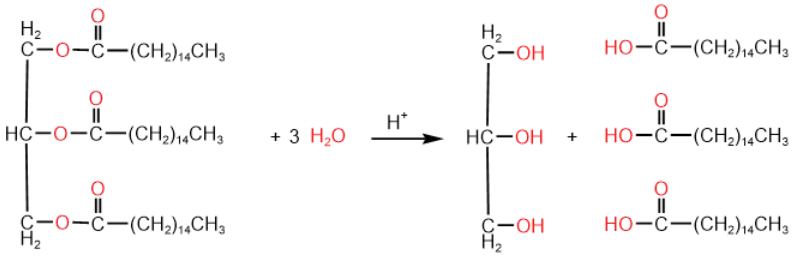
Figure **8.3.2**: Right: Proportion of saturated, monounsaturated, and polyunsaturated fatty acids in fats (lard and butter) and vegetable oils. (Copyright; Diamboroid, CC BY-SA 4.0, via Wikimedia Commons). Left: Saturated triglyceride (top left) and unsaturated (top right). The drawing below shows how packing is easier in saturated triglycerides, so they tend to be solid at room temperature. (Copyright; AGeremia, CC BY 3.0, via Wikimedia Commons)

Chemical properties of fats and oils

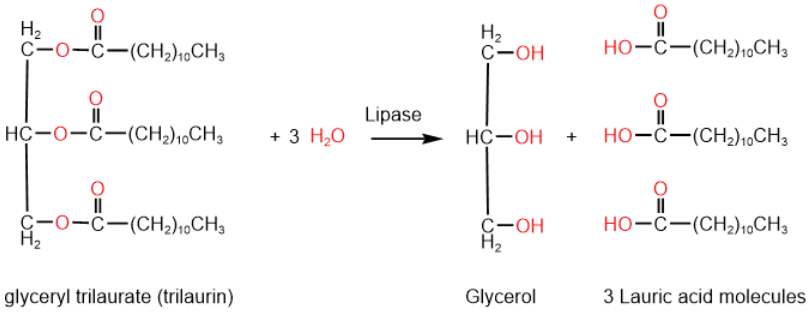
Three important reactions of triglycerides are hydrolysis by water in the presence of acid or lipase enzyme, saponification, i.e., base-promoted hydrolysis, and hydrogenation of double bonds in the fatty acids.

Hydrolysis

Easters are hydrolyzed (split) by water in the presence of an acid catalyst into alcohol and carboxylic acid. The same reaction happens with triglycerides, i.e., fats and vegetable oils—for example, tripalmitin hydrolyzes into glycerol and three palmitic acid molecules, as shown below.



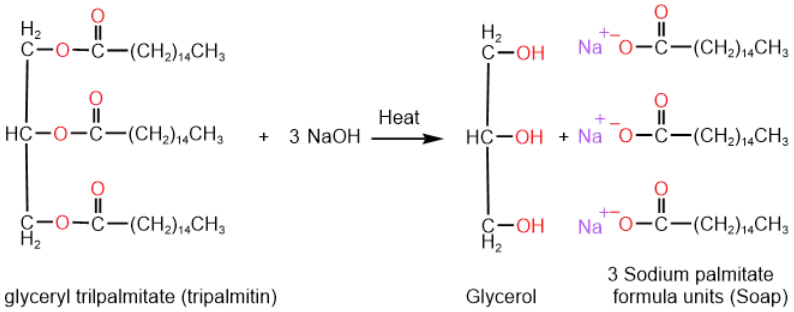
Lipase enzymes do the same reaction during the digestion of triglycerides, e.g., trilaurin is hydrolyzed by lipase to glycerol and three molecules of lauric acid, as shown in the reaction below.



The digestion of lipids starts in the mouth with lingual lipases secreted by glands in the tongue and continues in the stomach with lingual and gastric lipases. Glycerol in the hydrolysis product is soluble in water, but fatty acids are not. Fatty acids are emulsified in the stomach and later mixed with bile and pancreatic juice to continue the process of digestion.

Saponification

Saponification is base-promoted hydrolysis of triglycerides that produces glycerol and salts of the fatty acids, a soap, as shown below for the case of saponification of tripalmitin.





Different varieties of soaps are shown in the figure on the right. Sodium salts of fatty acids make hard soaps, while potassium salts make soft soaps. Three of the most common soaps are sodium stearate, oleate, and linoleate. Salts of saturated fatty acids make rigid, and those of polyunsaturated fatty acids make soft soap. Perfumes are added for scent and dyes for color, sand is added in scouring soap, and the air is blown into the soap to make it float on water.

Hydrogenation

Alkenes add $\mathbf{H_2}$ and covert to alkane in the presence of $\mathbf{Ni}$, $\mathbf{Pt}$, or $\mathbf{Pd}$ catalyst. The same reaction happens with the $\mathbf{C{=}C}$ in unsaturated fatty acids found in triglycerides. The conversion of unsaturated fatty acids to saturated fatty acids increases the melting point of triglycerides. Therefore, vegetable oils with more unsaturated fatty acids become semisolid or solid after partial or complete hydrogenation, as illustrated by the reaction in Figure **8.3.3**. Hydrogenation of vegetable oils is a commercial process to convert vegetable oils to semisolid products like margarine and shortening.

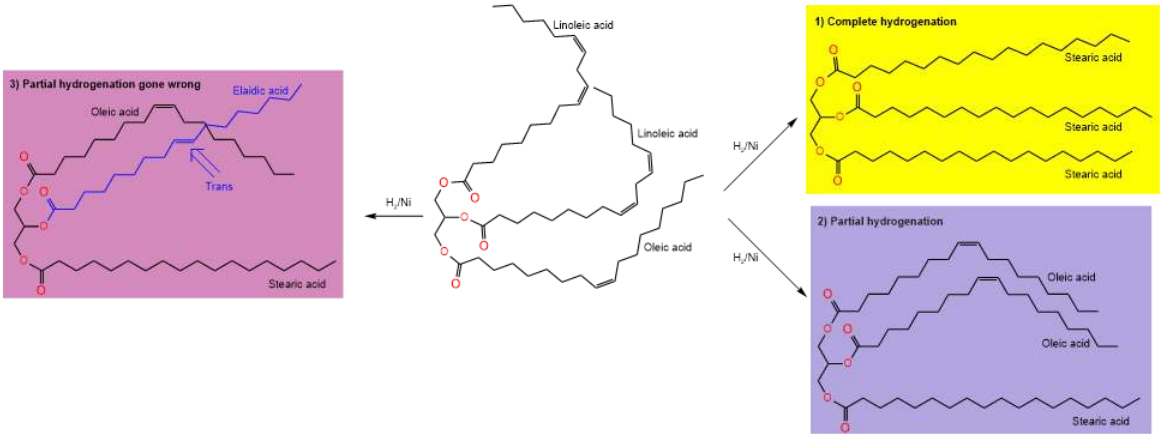


Figure **8.3.3**: Hydrogenation of unsaturated fatty acids in vegetable oils: 1) complete hydrogenation, 2) partial hydrogenation, 3) partial hydrogenation that results in conversion of some *cis*-C=C bonds to *trans*-C=C bonds that are undesirable. (Copyright; Public domain)

The driving force for the industrial process of hydrogenation of vegetable oils is that margarine or shortenings are used as cheaper alternatives to butter with a longer shelf-life. Complete hydrogenation of vegetable oils converts them into hard margarine. Often partial hydrogenation is performed as the partially hydrogenated product is semisolid and mimics butter better than hard shortening. Dyes and flavors are mixed with it to mimic butter's color, taste, and odor.

Unwanted trans-fatty acids are by-products of the hydrogenation of vegetable oils.

Like all other processed food products, hydrogenated vegetable oil products are associated with health problems. Partial hydrogenation converts some of the *cis*-C=C bonds to *trans*-C=C bonds, as illustrated in Figure **8.3.3**. *Trans*-C=C bonds are rare in some fatty acids. Research reports indicate that trans-fatty acids affect blood cholesterol like unsaturated fatty acids. Research reports also indicated that trans-fatty acids increase the level of low-density lipids (LDL), considered bad cholesterol, and decrease the level of high-density lipids (HDL), regarded as good cholesterol. Health organizations force the manufacturers to show the trans-fatty acid contents on the product labels. They are trying to educate the consumers about trans-fatty acids, as shown in Figure **8.3.4** from U.S. Food and Drug Administration.



Figure **8.3.4**: A variety of processed foods—including the frozen, canned, and baked goods shown—contain *trans* fat. The amount per serving is listed on the Nutrition Facts label. Including partially hydrogenated oil in the list of ingredients is another indication that *trans* fat is present. (Copyright; The U.S. Food and Drug Administration, Public domain, via Wikimedia Commons)

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8.4: Glycerophospholipids

Learning Objectives

- Define glycerophospholipids and understand the structural features that allow them to organize into lipid bilayers.
- Understand the classification of glycerophospholipids and their role in infant respiratory distress syndrome.

What are glycerophospholipids?

Glycerophospholipids are triesters of propane-1,2,3-triol (glycerol): 1st and 2nd ester bonds with fatty acids, and the 3rd ester bond with phosphate, as illustrated in Figure **8.4.1**. The phosphate group is often a diester: an ester with the primary alcohol of glycerol and 2nd ester bond with a small molecule, such as choline, ethanolamine, serine, or inositol.

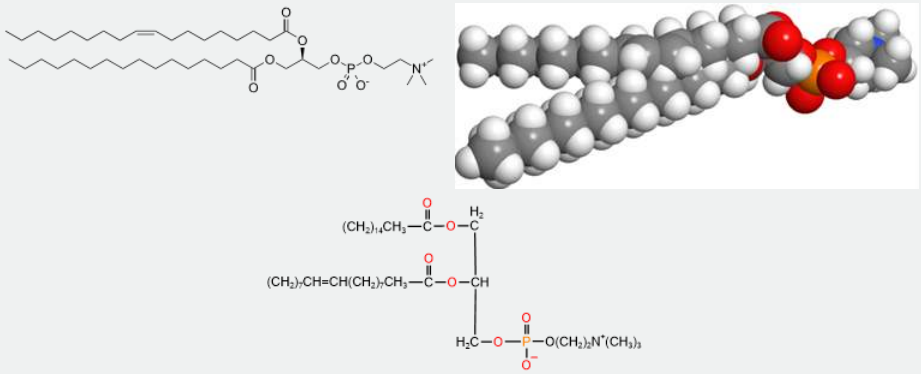
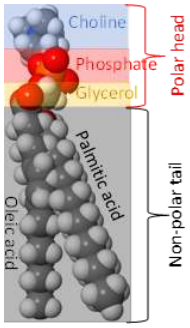


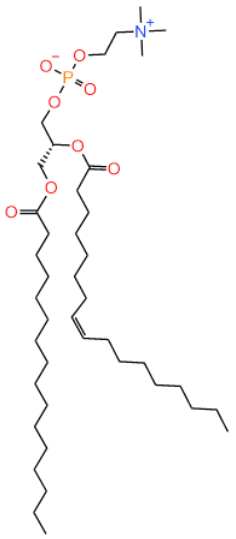
Figure **8.4.1**: Chemical structure of a phospholipid (1-palmitoyl-2-oleoylphosphatidylcholine): skeletal formula (left); space filling model showing **C's** gray, **O's** red, **N** blue, and **P** orange (middle); and condensed formula (right). (Copyright: Public domain).



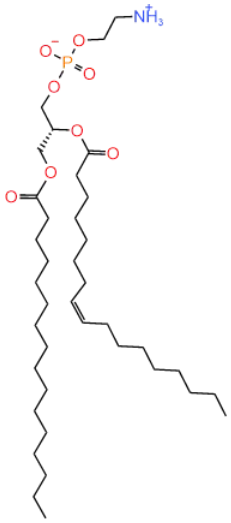
Phospholipids have two hydrophobic tails, which are the hydrocarbon groups of two fatty acids and a polar head comprising of ester groups with fatty acids, phosphate having a -ve charge, and often also have a +ve charge on the nitrogen of the small molecule attached with the phosphite, as shown in the figure on the right. The 1st fatty acid attached to the primary alcohol group is usually a saturated fatty acid, and the 2nd fatty acid attached to the secondary alcohol group of glycerol is usually an unsaturated fatty acid.

Classes of glycerophospholipids

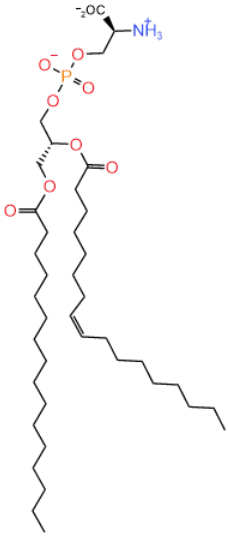
The glycerol esterified with two fatty acids and one phosphoric acid is also called **phosphatidyl**. Phosphatidyls with phosphate esterified with choline are called **phosphatidylcholines** (**lecithin**). Phosphatidyl esterified with ethanolamine, or sometimes with serine, are called phosphatidylethanolamines or phosphatidylserine (common name cephalins). Another category is phosphatidylinositols with inositol-esterified phosphate, as shown in Figure **8.4.2**.



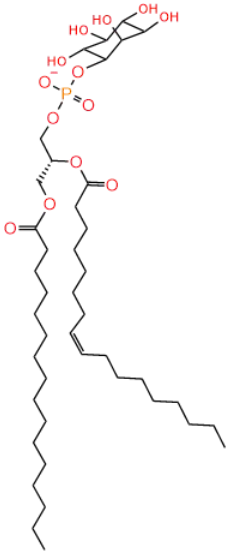
1-palmitoyl-2-oleoyl phosphatidylcholine (a lecithin)



1-palmitoyl-2-oleoyl phosphatidylethanolamine (a cephalin)



1-palmitoyl-2-oleoyl phosphatidylserine (a cephalin)



1-palmitoyl-2-oleoyl phosphatidylinositol

Figure **8.4.2**: Major categories of glycerophospholipids. (Copyright; Public domain)

Lipid bilayer

Recall the general solubility rule "like dissolves like". Oil droplets that are nonpolar floating on the surface of the water, which is polar, ultimately coalesce, making bigger droplets. Glycerophospholipids are amphiphilic, having an overall cylindrical shape with nonpolar tails of fatty acid chains and polar heads of ester groups on the glycerol part and ionic groups on phosphate and amine groups. Glycerophospholipids form a bilayer in the watery environment of living things based on the principle "like dissolves like", as illustrated in Figure **8.4.3**.

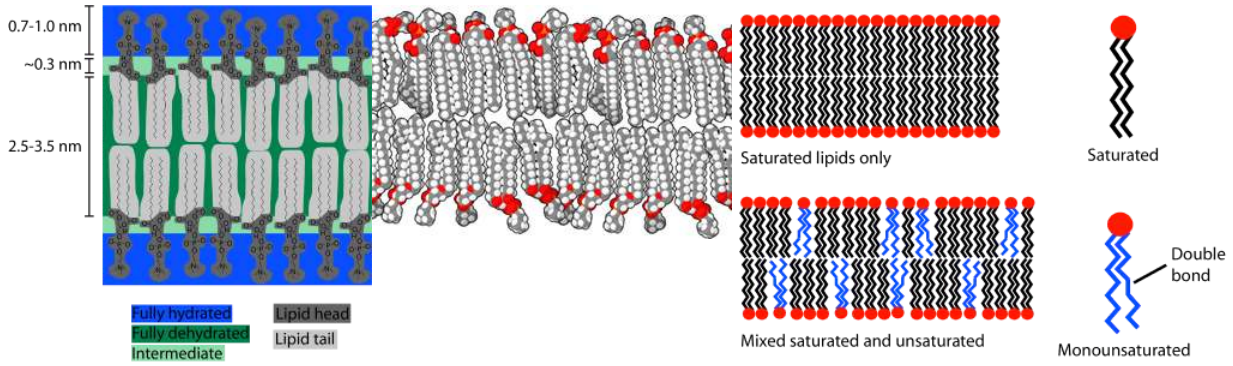


Figure 8.4.3: Lipid bilayer cross-section of phosphatidylcholine as a model phospholipid: illustration of hydrophilic and hydrophobic layers in contact with water on the interior and exterior of cells (left, Copyright: MDougM, Public domain, via Wikimedia Commons), simulation of fluid nature of the lipid bilayer (middle, Bensaccount, Public domain, via Wikimedia Commons), and illustration of the control of fluidity of the bilayer based on the proportion of unsaturated/saturated fatty acids (right, Copyright: MDougM, Public domain, via Wikimedia Commons).

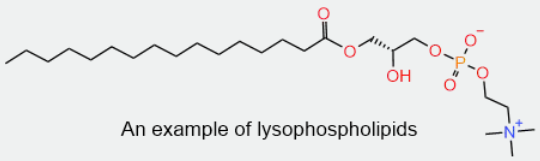
The hydrophobic tails of fatty acids form the interior of the bilayer, and the hydrophilic polar heads make the outer layers in contact with water. The molecules are in a fluid (dynamic) state due to thermal energy (Figure 8.4.3 middle) but held together by intermolecular interactions: dipole-dipole interaction in the polar heads and London dispersion forces in the hydrophobic tails. Saturated fatty acids pack tightly together, making a rigid bilayer. However, adding unsaturated fatty acids with kinks makes the packaging lose, resulting in a more fluid bilayer, as illustrated in Figure 8.4.3 right.

The glycerophospholipid bilayer is a significant component of the cell membrane, the membranes around the nucleus, and some cell organelles. The hydrophobic nature of the interior of the bilayer becomes a barrier to the movement of ions and water in and out of the cell. Still, the bilayer's fluid nature allows the diffusion process to move some particles across the membrane. Other components of the cell membrane, such as cholesterol, adjust the rigidity, and proteins control the movement of particles in and out of the cell as needed. The structure of cell membranes is described in a later section.



Snake wrangler demonstrating how his venom flows from fangs at certain movement. (Copyright: Usman Ahmad from Pakistan, CC BY-SA 2.0, via Wikimedia Commons)

Snake venom

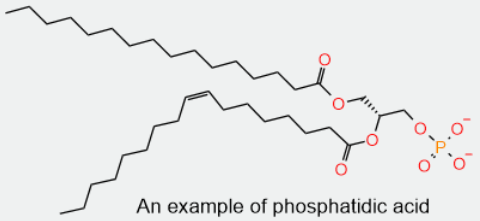


Snakes inject their venom through fangs when they bite their prey, as shown in the figure on the right. The venom of eastern diamondback rattlesnakes and Indian cobra contains phospholipase enzymes that catalyze the hydrolysis of fatty acid on the secondary hydroxyl group of glycerol. The resulting phospholipids with one less carboxylate group, called lysophospholipids, is no more cylindrical molecule and do not fit correctly in the lipid-bilayer, causing the red blood cell membrane to rupture. This poses a significant health risk and may kill humans. The structure of the lysophospholipid example is shown in the figure on the left.

Infant respiratory distress syndrome (IRDS)

In the breathing process, the exchange of O_2 and CO_2 takes place in air sacs called alveoli within the lungs, as illustrated in Figure 8.4.4. Pulmonary surfactants, composed of a mixture of lecithin and sphingomyelin lipids, are released into the lungs of newborn babies that reduce the surface tension and ease the inflation of alveoli. Lecithins are mixtures of glycerophospholipids, including phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, phosphatidylserine (shown in Figure 8.4.2) and phosphatidic acid shown in the figure on the right.

In the cases of premature birth, before 28 weeks of gestation, the level of the surfactant is insufficient, causing the air sacs to collapse and have to reopen with each breathing, a condition called **infant respiratory distress syndrome**. This makes breathing difficult, may damage the alveoli, and lead to hypoxia and acidosis due to less oxygen inhalation and less carbon dioxide exhalation.


An example of phosphatidic acid

The lecithin to sphingomyelin ratio in mature fetal lungs is ~2.5, the ratio 2.4 to 1.6 poses a low risk, and less than 1.5 poses a high risk of infant respiratory distress syndrome. Treatment includes steroids given to the mother or infant to assist the development of lungs, the application of surfactants, and the use of a ventilator to help breathing.

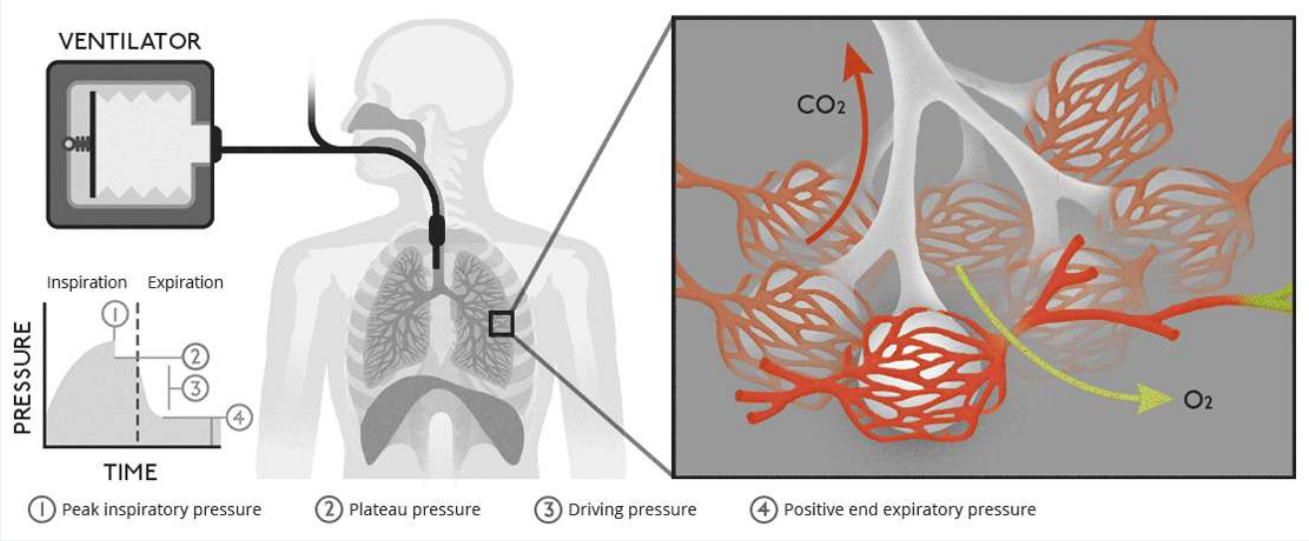


Figure 8.4.4: Illustration of the inflation of alveoli with air pressure in the lugs during inhalation accompanied by the exchange of O_2 and CO_2, and assistance of the process by a ventilator. (Copyright; Eleanor Lutz, CC0, via Wikimedia Commons)

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8.5: Sphingolipids

Learning Objectives

- Define and understand the structure of sphingolipids, their subclasses, and their role in the nervous system.
- Understand the role of sphingolipids in multiple sclerosis.

Sphingolipids and their subclasses

Sphingolipids are a class of lipids having a sphingoid base that is a set of aliphatic amino alcohols, including **sphingosine,** shown in Figure **8.5.1**. When the amino (**$-NH_2$** group is attached to a fatty acid by an amide bond, it is called **ceramide**. When the primary alcohol of ceramide is linked to a phosphorylcholine or phosphorylethanolamine group, it is called **sphingomyelin**. When the primary alcohol of ceramide is bound to glucose or galactose by a glycosidic bond, it is called **cerebroside**. When a glycosidic bond connects the primary alcohol of ceramide to an oligosaccharide with one or more sialic acids, it is called **ganglioside**.

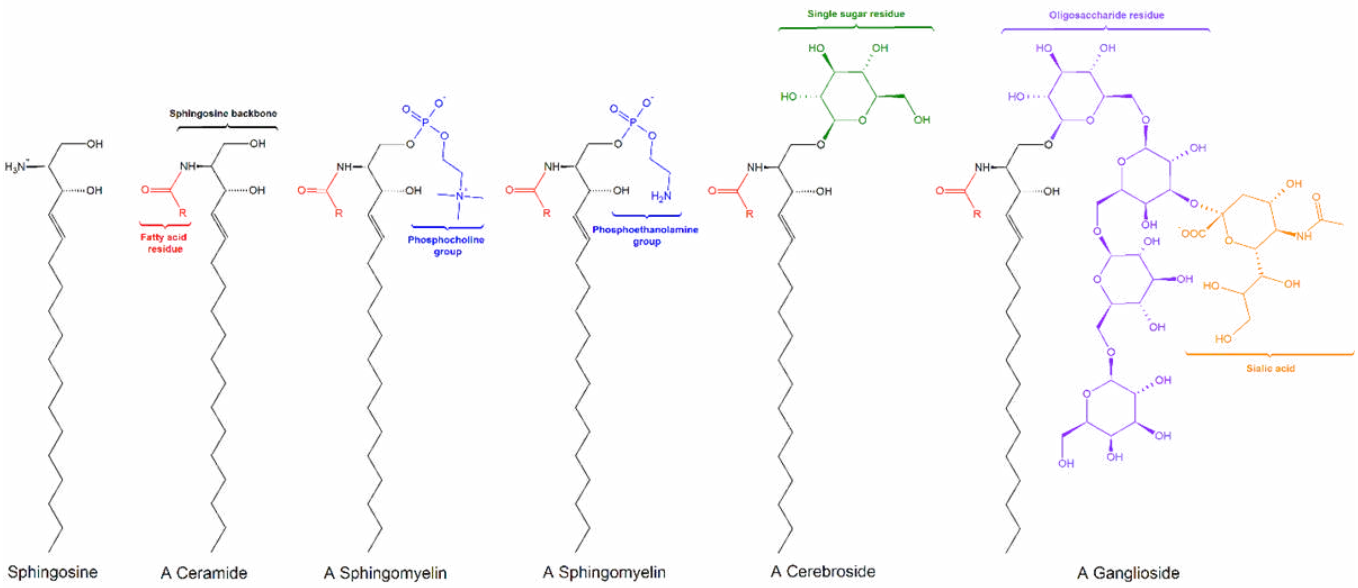


Figure **8.5.1**: General structures of sphingolipids. (Copyright; LHcheM, CC BY-SA 3.0, via Wikimedia Commons)

Figure **8.5.2** illustrates two examples of sphingomyelin. Like glycerophospholipids, these sphingolipids are an essential component of the lipid bilayer. Mainly, they are abundant in the brain and nerves. They are abundant in the white matter of myelin sheath, i.e., a coating surrounding the nerve cells. Myelin sheath increases the speed of nerve impulses and is essential in protecting nerve cells, signal transduction, and cell recognition.

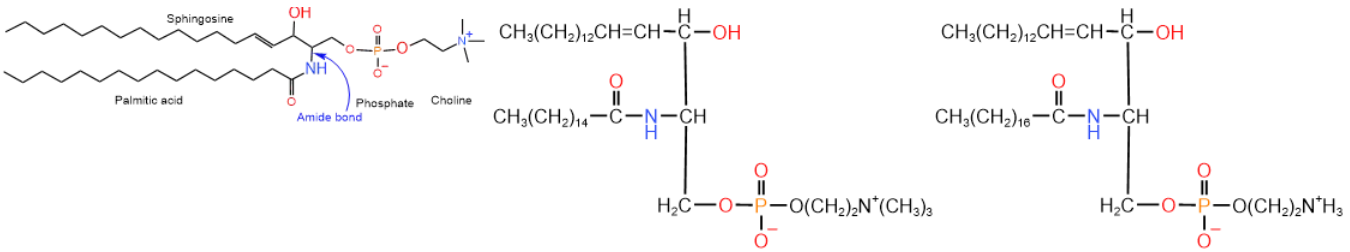


Figure **8.5.2**: Two examples of sphingomyelin: one containing palmitic acid and choline (right -a skeletal formula, and middle -a condensed formula) and the other containing stearic acid and ethanolamine (right). (Copyright: Public domain).

Multiple sclerosis

Multiple sclerosis is a nervous system disease in which the myelin sheaths wrapped around axons of nerve cells are damaged, as illustrated in Figure **8.5.3**. Symptoms are related to the retardation of signal conduction by the nerves that, in turn, reduces sensation, coordination, movement, cognition, muscle weakness, blindness, and other functions involving nerves. The severity

of the effects depends on the amount of damage. Studies indicate that vitamin D may lessen the severity of the disease. Nearly 1 million people in the US and about 2.8 million worldwide have multiple sclerosis.

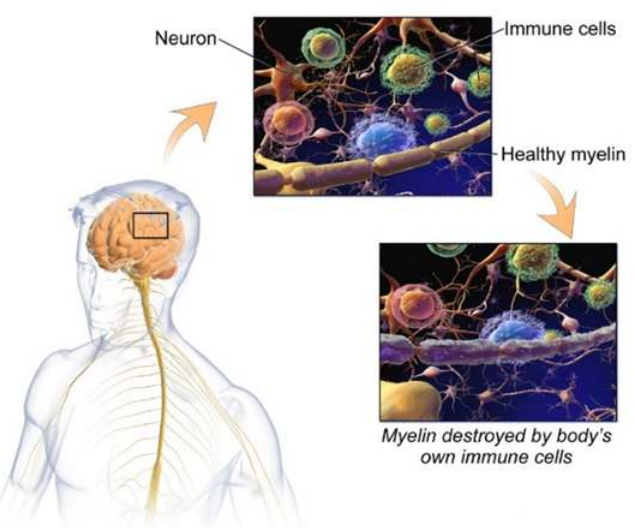


Figure **8.5.3**: Multiple sclerosis is currently thought to be a disease in which autoimmune cells attack the nervous system, destroying myelin. (Copyright; BruceBlaus, CC BY-SA 4.0, via Wikimedia Commons)

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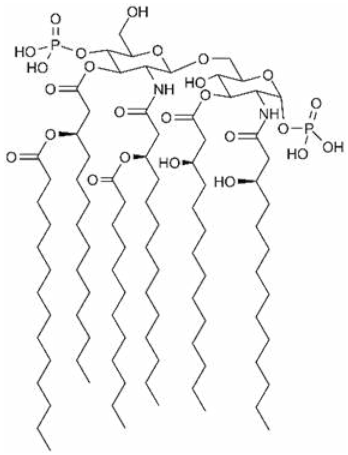
8.6: Saccharolipids, polyketides, and prenols

Learning Objectives

- Define and understand the basic structural features of saccharolipids, polyketides, and prenols.
- Define mono-, sesqui-, di-, and tri-terpenes and recognize isoprene units in terpenes, terpenoids, and steroids.

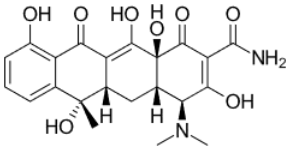
Saccharolipids

Saccharolipids are fatty acids linked to a saccharide (carbohydrate) backbone by linkages other than glycosidic linkages. They are compatible with membrane bilayers. For example, saccharolipid lipid A found in E. Coli is shown in the figure on the right.

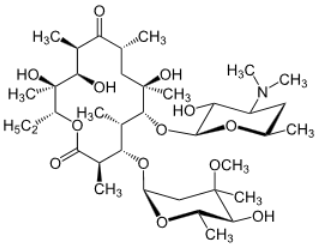


Polyketides

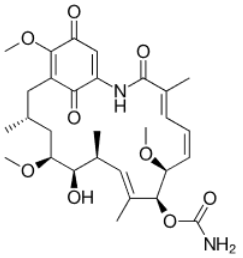
Polyketides are a broad class of natural products derived from β-polyketones, i.e., compounds containing $[-\overset{O}{\overset{\|}{C}}-CH_2-]_n$ repeat units in their backbone or their reduced forms, such as $[-\overset{OH}{\overset{|}{C}}-CH_2-]_n$, and $[-CH_2-CH_2-]_n$. Polyketides are important in the pharmaceutical industry. They are used as antimicrobial, antiparasitic, and anticancer agents; some are toxins. About 20% of the top-selling medicines are polyketides. Some examples of medically important polyketide products are shown below.



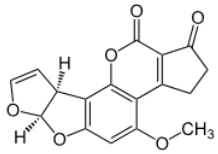
Tetracycline -an antibiotic



Erythromycin A -an antibiotic



Geldanamycin -an antitumor antibiotic



Aflatoxin B1 -an aflatoxin

Prenols

Prenols are synthesized from five-carbon isoprene precursors: isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP), as shown in Figure **8.6.1** (left). The five-carbon skeleton of isoprene units in these products can often be easily distinguished, as shown in by different color sections of some examples in Figure **8.6.1** (right). Since they contain a multiple of five **C′s** in their skeleton, they are also classified as monoterpens (10 **C′s**), sesquiterpenes (15 **C′s**), diterpenes (20 **C′s**), triterpenes ((30 **C′s**), and tetraterpenes (40 **C′s**). Terpenoids are modified terpenes that contain additional functional groups, usually oxygen functional groups as those shown in **8.6.1** (right).

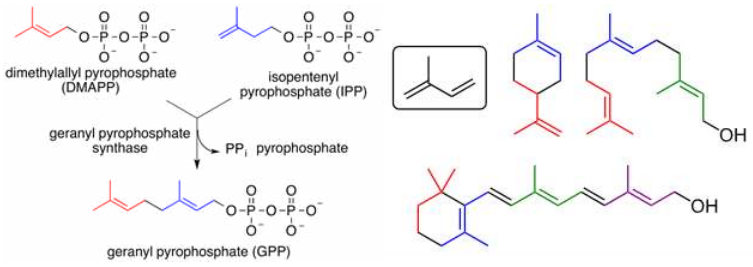


Figure **8.6.1**: Dimethylallyl pyrophosphate (DMAPP) and isopentenyl pyrophosphate (IPP) condense to produce geranyl pyrophosphate, a precursor to all terpenes and terpenoids (left, Copyright; Andrew Murkin, CC0, via Wikimedia Commons) and structure of Isoprene, limonene, farnesol, and retinol, respectively, showing isoprene skeleton in these products in different color sections (right, Copyright; Calvero., Public domain, via Wikimedia Commons)

.

Steroids -other lipids described later are derived from triterpene squalene, as illustrated in Figure 8.6.2.

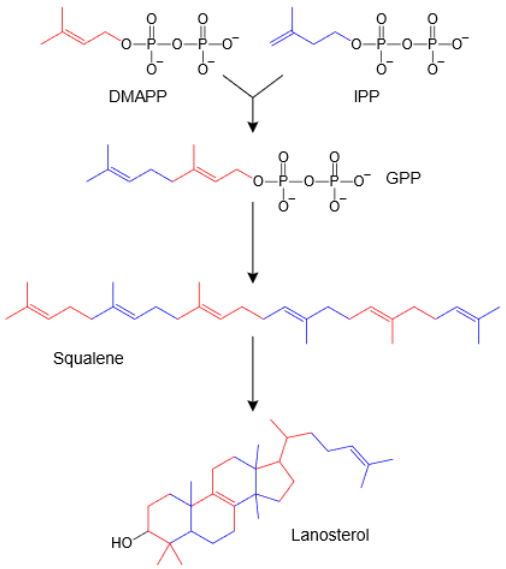


Figure 8.6.2: A simplified scheme for steroid biosynthesis via terpenoid intermediates: isopentenyl pyrophosphate (IPP), dimethylallyl pyrophosphate (DMAPP), geranyl pyrophosphate (GPP) and squalene. (Copyright; Fvasconcellos, original by Tim Vickers, Public domain, via Wikimedia Commons)

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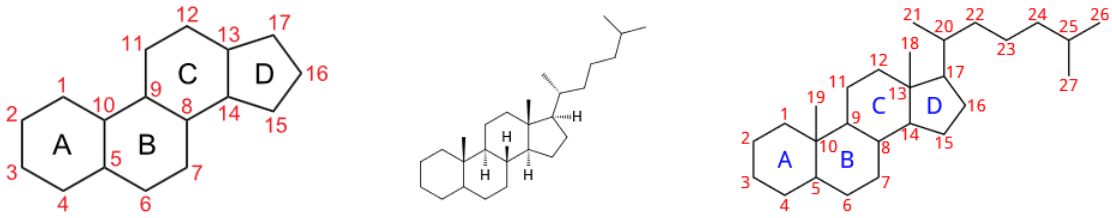
8.7: Sterols

Learning Objectives

- Understand the core structure of steroids and sterols.
- Understand the structural features of cholesterol, its production, consumption, transport, and medical problems.
- Understand bile acids' structure features, their functions, and medical problems.
- Understand the structural features of steroid hormones, functions, abuses, and medical problems.

What are steroids?

Steroids are biologically active compounds that have a core structure composed of four fused rings in a specific configuration: three six-membered rings designated A, B, and C and one five-membered ring D, as Figure 8.7.1 right. Gonane has this core structure of steroids. Other steroids have gonane skeletons with some groups attached. For example, cholestane has methyl groups at positions 10 and 13 and an aliphatic chain at position 17. Cholesterol has the structure of cholestane. It is a biomarker found in rocks and petroleum deposits.



Gonane or sterane with C's numbered

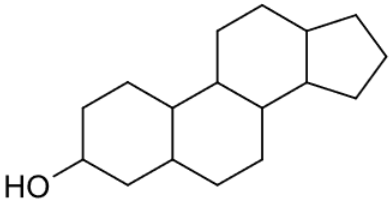
Cholestan with stereochemistry shown

cholestan with C's numbered

Figure 8.7.1: Steroid core structure represented by gonane with C labels shown and cholestane that has the C skeleton of cholestrol with C labels. (Copyright; Public domain)

What are sterols?

Sterols are organic compounds derived from gonane with H #3 replaced with an alcohol (–OH) group. The sterols are a sub-class of steroids. The simplest sterol is the alcohol gonane shown in the figure on the right. Other sterols have other groups attached to the gonane structure.



Cholesterol

Cholesterol is the most abundant sterol found in animals. It is a structural component of animal cell membranes, a precursor for steroid hormones, bile acids, and vitamin D. Cholesterol has the C skeleton of cholestane, with an –OH group at position #3 and a C=C bond at position 5 and 6, as shown in Figure 8.7.2.

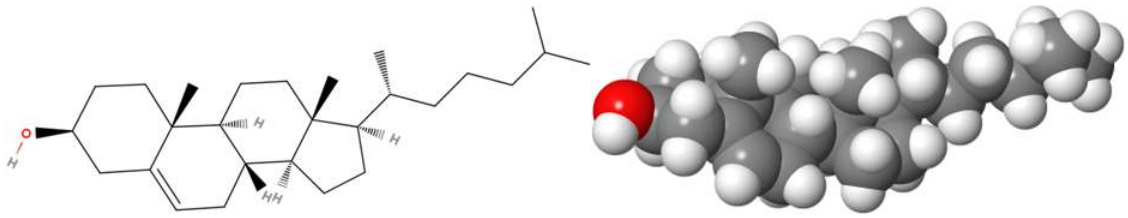


Figure 8.7.2: Structure of cholesterol (left) and space-filling model of cholesterol: hydrophilic head, i.e., –OH group (O is read and H is white) and hydrophobic tail of tetracyclic rings and an alkyl side chain (C'sare gray and H's are white). (Copyright; Public domain)

Cholesterol sources and consumption

Cholesterol is biosynthesized from lanosterol, which, in turn, is synthesized from squalene, as described in the previous section. Cholesterol is synthesized in the liver using fats, proteins, and carbohydrates as raw materials. An average human weighing 68 kg

synthesizes about 1000 mg of cholesterol daily. Food is also a source of cholesterol intake, as shown in the figure on the right. Typically about 307 mg of cholesterol intake is through food per day in the US. The liver reduces cholesterol production to adjust for the intake from food sources.

Cholesterol is amphiphilic like phospholipids and sphingolipids, with $-OH$ as a polar head and cholestane structure as a hydrophobic tail. The cholesterol molecule is stiff due to restricted movements around $C-C$ bonds locked in the cyclic structure.

Cholesterol contents of foods

Foods	Cholesterol (mg/100 g)
Beef brain	3100
Egg yolk	1085
Egg	373
Lamb kidney	337
Pork liver	301
Butter	215
Lobster	200
Shrimp	125
Light whipping cream	111
Yellow cheese	108
Beef	90
Chicken	88
ChPork	80
Fish	70
Yogurt	13
Egg whites	0
Fruits	0
Grains	0
Nuts	0

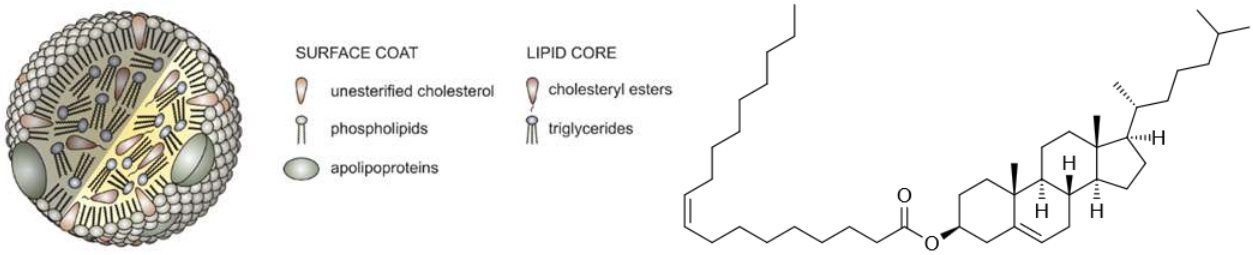
> Cholesterol is used in the cell membrane to impart rigidity to the ring -the higher the proportion of cholesterol in the cell membrane, the more rigid the membrane.

Usually, cholesterol is 30% of the cell membrane. It is involved in signaling and is found in the brain, plasma membrane, and myelin sheath of nerve cells. Cholesterol is a precursor to vitamin D and steroid hormones, including corticosteroids, such as cortisol and aldosterone, and sex hormones, such as progesterone, estrogens, and testosterone.

The liver recycles the excess cholesterol by converting it into bile acids stored in the gallbladder and excreted into the digestive tract. Bile acids emulsify fats in the food, which helps digest the food. About 50% of the excreted cholesterol is re-absorbed into the bloodstream by the small intestine.

Transport of cholesterol

Cholesterol is insoluble in water like other lipids. It is transported by the blood, which is water rich medium. Like soap carries greases in water during washing, lipoprotein transport glycerolipids and cholesterol in the body. The lipoproteins exist as particles suspended in blood. Glycerides and cholesteryl esters are in the core, and phospholipids, proteins (apolipoprotein), and cholesterol form the outer layer having their hydrophobic parts oriented outwards in contact with water, as illustrated in Figure **8.7.3**.



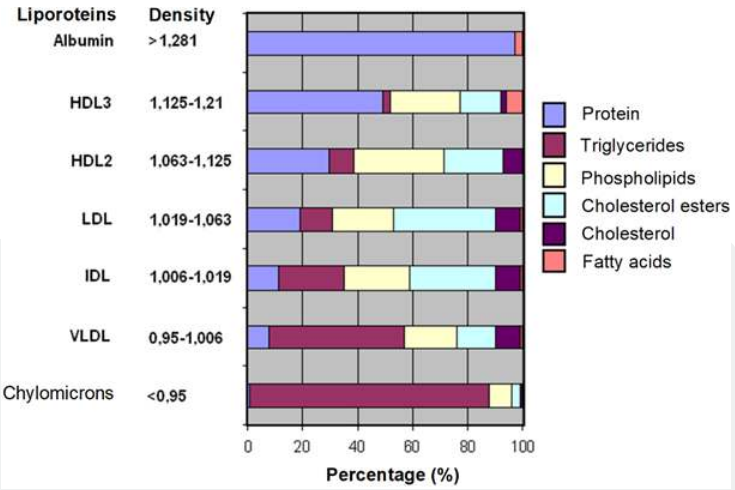
High-density lipoprotein (HDL) Cholesterol oleate

Figure **8.7.3**: High-density lipoprotein (HDL), as an example lipoprotein particles, are composed of a lipid core containing cholesteryl esters and triglycerides, and a surface coat of phospholipids, unesterified cholesterol, and apolipoprotein (left, copyright: AntiSense, CC BY-SA 3.0, via Wikimedia Commons) and cholesterol oleate as an example of cholesteryl ester (right, Public domain)

Lipoproteins are classified based on their density, as shown in the figure on the right (*Copyright: Modified from İnfoCan at Turkish Wikipedia., FAL, via Wikimedia Commons, Public domain*). Their density is based on the proportion of proteins in them -the higher the proportion of proteins, the higher the density. They also have roles in the transportation process of cholesterol and lipids:

- **Chylomicrons** – Transport triglycerides from the small intestine to the liver.
- **Very low-density lipoproteins** (VLDL) - transport newly synthesized triglycerides from the liver to the fatty tissues.
- **Intermediate-density lipoproteins** (IDL) are between VLDL and LDL in density. They are not usually seen in the blood.

- **Low-density lipoproteins** (LDL) - carry cholesterol from the liver to other tissues. They are also sometimes referred to as "**bad cholesterol**."
- **High-density lipoproteins** (HDL) - collect cholesterol from other tissues and return it to the liver. They are sometimes referred to as "**good cholesterol**."



Atherosclerosis and heart attack

Excessive fats and cholesterol in the body are associated with diabetes; cancers of the breast, pancreas, and colon; heart attack; and stroke. Lipoproteins transport cholesterol and fats in the body. LDLs transport cholesterol from the liver to the cells where they are needed, and HDLs transport surplus cholesterol back to the liver, where it is converted to other steroids and bile acids. If the LDL level is too high, some cholesterol is deposited in the artery as plagues, as shown in Figure 8.7.4. That is why LDLs are sometimes called **bad cholesterol**. The plaque causes inflammation and death of the tissue in that area and restricts blood flow. It may lead to a heart attack if the blood flow to the heart is inadequate or a stroke if the blood flow to the brain is insufficient.

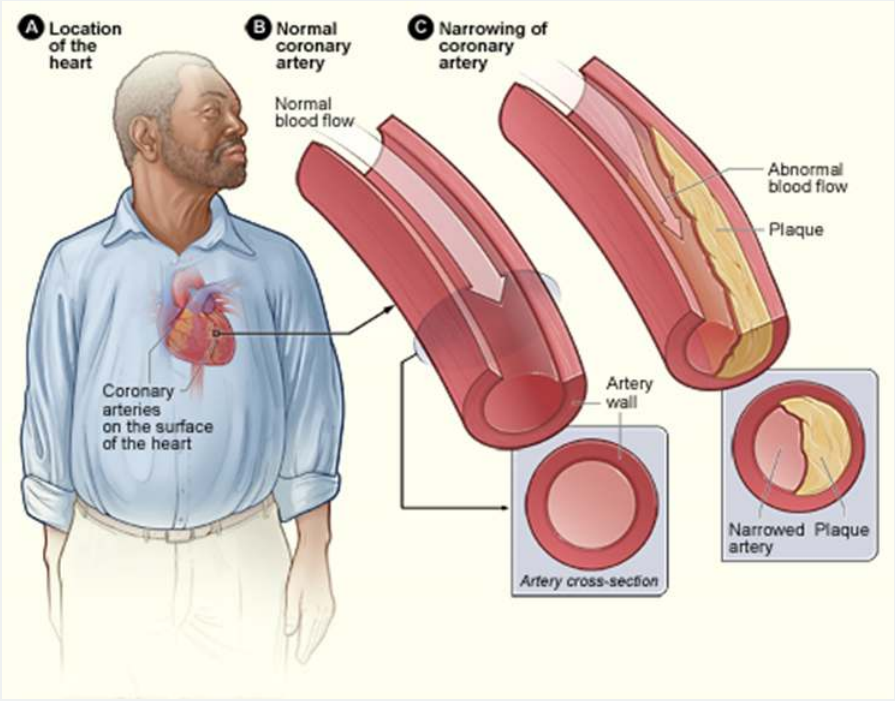


Figure 8.7.4: Figure A shows the location of the heart in the body. Figure B shows a normal coronary artery with normal blood flow. The inset image shows a cross-section of a normal coronary artery. Figure C shows a coronary artery narrowed by plaque. The buildup of plaque limits the flow of oxygen-rich blood through the artery. The inset image shows a cross-section of the plaque-narrowed artery. (Copyright; National Heart Lung and Blood Insitute (NIH), Public domain, via Wikimedia Commons)

Since HDLs transport the surplus cholesterol back to the liver for recycling and avoid plaque formation, HDLs are also called good cholesterol. The HDL levels must be sufficiently high to prevent a heart attack. A lipid panel test is prescribed to assess

the risk of a heart attack. It measures the levels of total cholesterol, LDLs, HDLs, and triglycerides in the blood. The normal levels are the following.

Total cholesterol	About 150 mg/dL, less is better
LDL ("bad") cholesterol	About 100 mg/dL, less is better
HDL ("good") cholesterol	At least 40 mg/dL in men and 50 mg/dL in women; higher is better
Triglycerides	Less than 150 mg/dL, less is better

Bile salts

Bile salts are synthesized from cholesterol in the liver. First, additional **–OH** groups are incorporated, and the alkyl side chain is shortened and oxidized to a carboxylic acid (**–COOH**) group. Then the **–COOH** group is esterified with either glycine or taurine that imparts a negative charge group, as illustrated in Figure **8.7.5**.

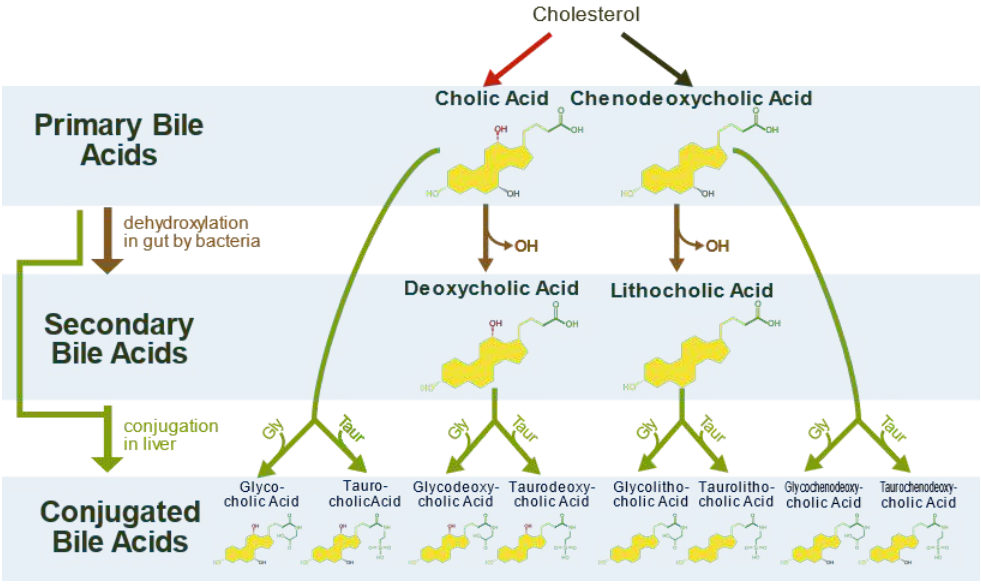


Figure **8.7.5**: Synthesis of the 12 bile acids in human bile from cholesterol. (Copyright; Mcstrother, CC BY 3.0, via Wikimedia Commons)

Bile salts act like soaps with an ionic head and the remaining hydrophobic part. They are stored in the gallbladder and released into the small intestine, where they emulsify fats, i.e., convert the larger fat drops into smaller droplets, just like greases and dirt are emulsified by soaps. The smaller droplets have a larger surface area, increasing the fats' reaction rate with the pancreatic lipase enzymes, as illustrated in Figure **8.7.6**.

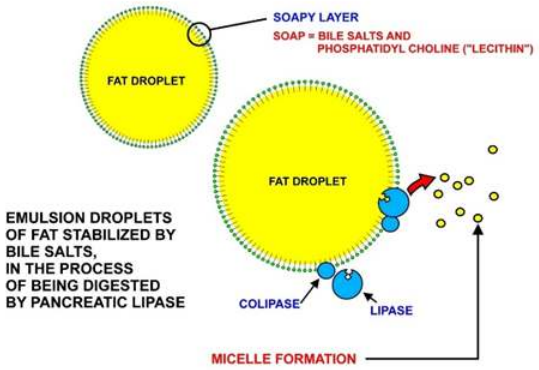


Figure 8.7.6: Dietary fats are emulsified in the duodenum by soaps in bile salts and phospholipids, which pancreatic lipase can attack. (Copyright; Cruithne9, CC BY-SA 4.0, via Wikimedia Commons)

Since bile salts are excreted with the feces, they remove cholesterol in two ways: 1) they are themselves the products of cholesterol, and 2) they dissolve cholesterol in the form of bile salt-cholesterol particles that are eliminated.

Gallstones and jaundice

When a large amount of cholesterol accumulates in the gallbladder, it turns into solid particles, i.e., gallstones. The gallstones are almost 100% cholesterol with a small amount of calcium salts, glycerophospholipids, and fatty acids. Small gallstones pass through the bile duct and enter the duodenum, i.e., the initial part of the small intestine, and are excreted. However, large gallstones may get stuck in the bile duct and cause pain, as illustrated in Figure 8.7.7. If a gallstone block the bile duct, the bile can not be excreted. Then the bile pigment, known as bilirubin, will back up into the liver and be passed via blood. It causes jaundice which gives a yellow color to the skin and whiteness to the eyes.



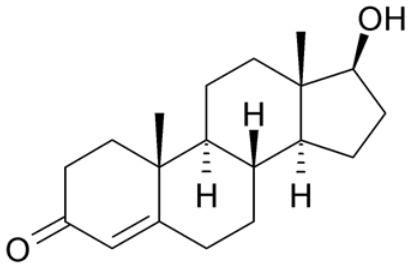
Figure 8.7.7: Illustration of gallstones blocking the bile duct that causes pain and jaundice. (Copyright; BruceBlaus, CC BY-SA 4.0, via Wikimedia Commons)

Steroid hormones

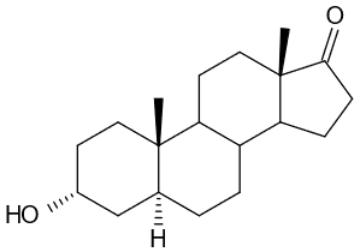
Steroid hormones have structural similarities with cholesterol and are derived from it. Two significant subclasses of steroid hormones are sex and adrenocortical hormones, described in the following sections.

Sex hormones

The male sex hormones are called androgens which include testosterone and androsterone. The female sex hormones are estrogens, e.g., estradiol and estrone, and progestins, e.g., progesterone. These five of the most essential sex hormones are shown in the figure below. All five are present in males and females, but androgens are produced more in males, and estrogens and progestins are produced more in females.

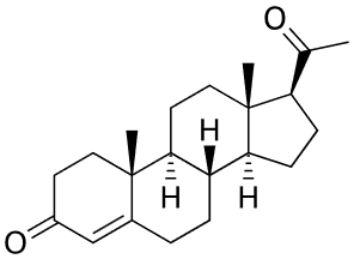


Testosterone

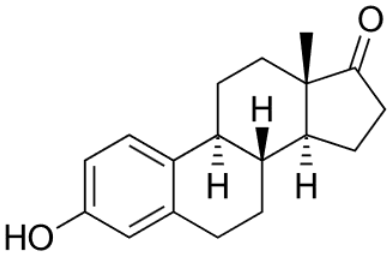


Androsterone

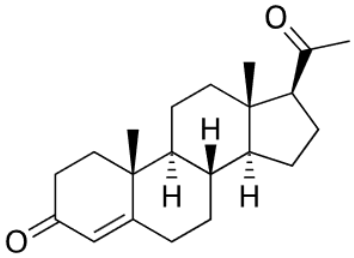
Male sex hormones (androgens)



Estradiol



Estrone



Progesterone

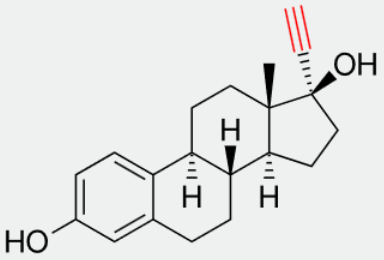
Female sex hormones

Functions of sex hormones

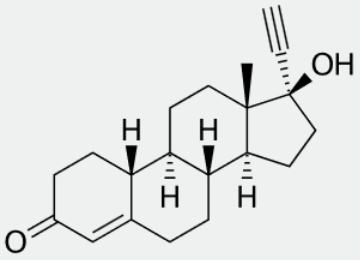
Testosterone and androsterone are the most potent male sex hormones. They control the development of male secondary sex characteristics, which include the growth of muscles, facial hair, maturation of sex organs, and sperms. Estrogens and progestins control the development of female secondary sex characteristics. Estrogens increase the size of the uterus, deposit fat in the breasts, and broaden the pelvis of females. Progestins prepare the uterus for nurturing the fertilized egg. If the egg is not fertilized, the levels of estrogens and progestins drop sharply, and menstruation begins.

Birth control

The release of estrogens and progestins during pregnancy prevents ovulation. This is mimicked by synthetic estrogens, such as ethynyl estradiol, and synthetic progestins, such as norethindrone, shown below, used in birth control formulations. As with the use of any steroid hormones, there are risks associated with synthetic hormones for birth control, including weight gain and a greater chance of forming blood clots.



Ethynyl estradiol

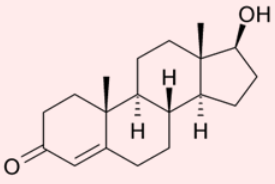


Norethindrone

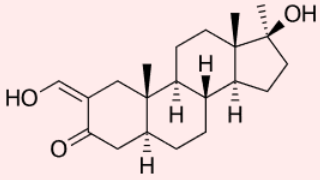
Synthetic estrogens used in birth control

Anabolic steroids

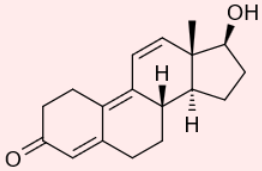
One physiological function of testosterone is increasing muscle mass and decreasing body fat. Several synthetic equivalents, called anabolic steroids, have been developed for use as **appearance and performance-enhancing drugs**, as shown in the figure below. Although there are some benefits of anabolic steroids, their harmful effects are numerous and outweigh their benefits. They may not produce a euphoric high but develop substance use disorder. They can cause early heart attacks, strokes, kidney failure, liver tumors, make pimples pop up, hair fallout, grow breasts, and reduced testicles in males, grow beards in females, and cause extreme mood changes that may lead to committing suicide. Some of these harmful effects are related to the changes in cholesterol levels, causing an increase in low-density lipoprotein (bad cholesterol), a decrease in high-density lipoprotein (good cholesterol), high blood pressure, and liver damage. The harmful effects are long-lasting and may be irreversible.



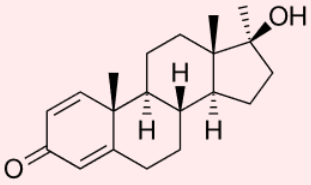
Testosterone



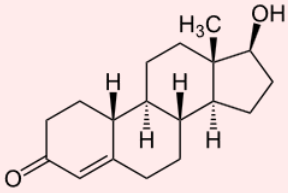
Oxymetholone



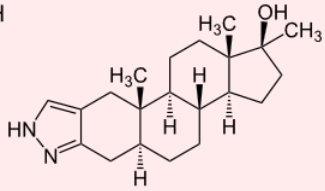
Trenbolone



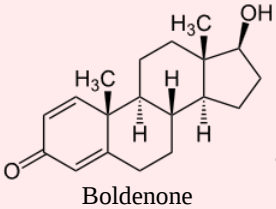
Methandrostenolone



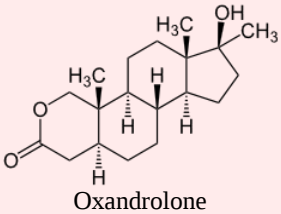
Nandrolone



Stanozolol



Boldenone

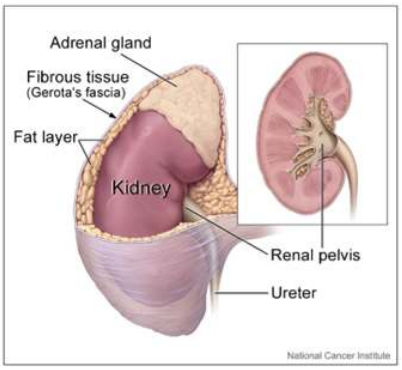


Oxandrolone

Anabolic steroids that are most commonly encountered by United States law enforcement

Adrenocortical hormones

Adrenocortical hormones are produced by adrenal glands on the top of the kidneys, as shown in the figure on the right (*Copyright; Alan Hoofring (Illustrator), Public domain, via Wikimedia Commons*). There are two major subclasses: **mineralocorticoids** which regulate $\mathbf{Na^+}$ and $\mathbf{K^+}$ ions, and **glucocorticoids** which control carbohydrate metabolism.



Mineralocorticoid

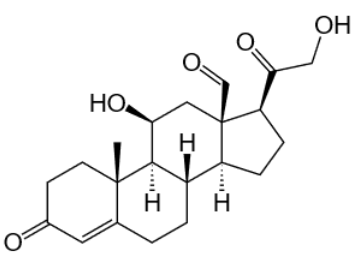
Aldosterone is an important mineralocorticoid that enhances the reabsorption of $\mathbf{Na^+}$ and $\mathbf{K^+}$ ions in the kidney tubules. The control of $\mathbf{Na^+}$ and $\mathbf{K^+}$ concentrations controls water absorption and swelling of tissues.

glucocorticoid

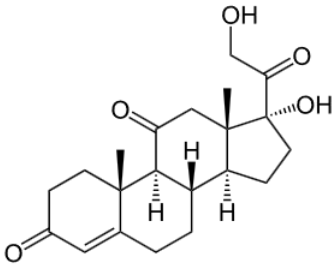
Cortisone is a glucocorticoid that increases blood glucose levels and glycogen synthesis in the liver. Cortisol is another glucocorticoid released under stress to increase blood glucose levels at the expense of the metabolism of carbohydrates, fats, and

proteins.

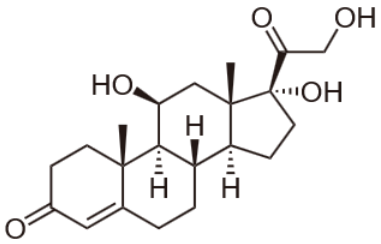
These hormones or their synthetic derivative, such as prednisone, shown below, are used to reduce inflammation, asthma, and arthritis. As with the use of steroids in general, health problems can result if these steroids are used for the long term.



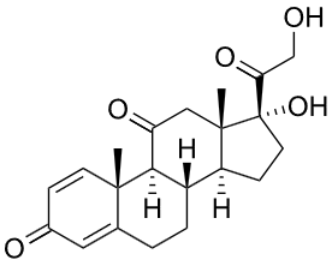
Aldosterone



Cortisone



Cortisol



Prednisone (a synthetic corticoid)

Adrenocortical hormones and their synthetic derivative

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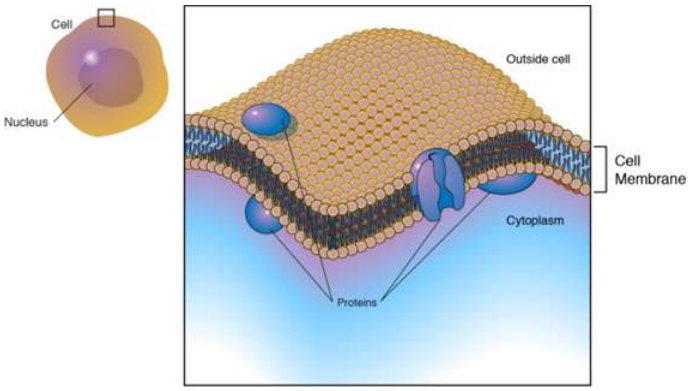
8.8: Cell membrane

Learning Objectives

- Define and understand the composition of the cell membrane and how the composition adjusts the fluidity fo the membrane.
- Understand three modes of transport through the cell membrane: diffusion, facilitated transport, and active transport.

What is a cell membrane?

The cell membrane, also known as the plasma membrane, cytoplasmic membrane, and plasmalemma, is a lipid bilayer with proteins dispersed in it that separates the cell interior from the extracellular space, as illustrated in the figure on the right (*Copyright; National Human Genome Research Institute, Public domain*).



Composition of the cell membrane

A cell membrane is a complex structure with several components, as shown in Figure 8.8.1. and described here.

- Phospholipid bilayer that has polar heads on the outside in contact with water and nonpolar tails inside the bilayer. Unsaturated fatty acids in the lipid hydrophobic tails increase the membrane fluidity -the more proportion of unsaturated fatty acids, the higher the fluidity.
- Cholesterol interspersed between phospholipids controls the rigidity of the membrane -the more the proportion of cholesterol, the more rigid the membrane.
- Two types of proteins: integral proteins that span the membrane and serve as transporters of species, and peripheral proteins that are loosely attached to the outer side of the membrane that act as enzymes to facilitate the interaction with the cell's environment.
- Glycoproteins and glycolipids have carbohydrate oligomers attached to the outer lipid layer and serve the purpose of cell-to-cell recognition.

The cell membrane controls the movement of substances in and out of the cells and organelles. It is selectively permeable to ions and organic molecules. It plays a role in cell adhesion, cell signaling, and attachment surface for the cytoskeleton to shape the cells and attach to the extracellular matrix to hold them together in tissues.

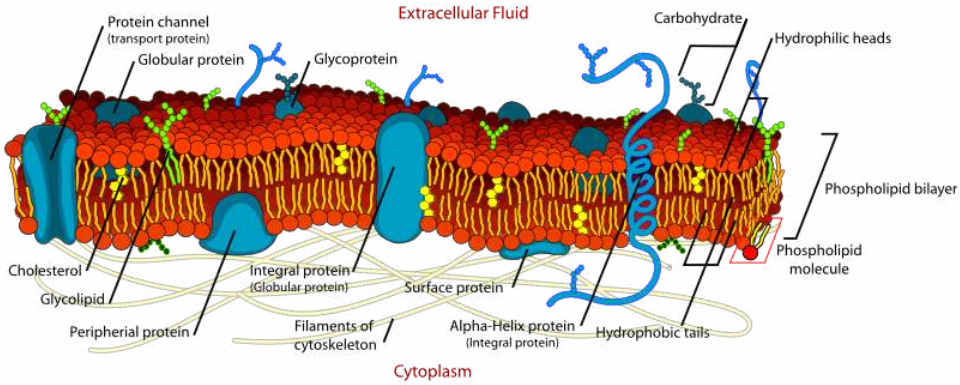


Figure 8.8.1: A detailed cell membrane structure. (Copyright; LadyofHats, Public domain, via Wikimedia Commons)

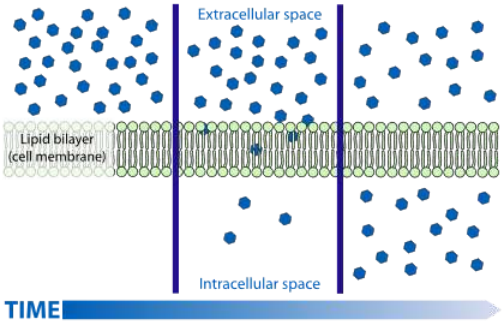
Transport through the cell membrane

The cell membrane is a partition between intracellular and extracellular spaces. Still, some substances needed by the cell need to enter, and some products or wastes need to exit the cell. The cell membrane allows a selective movement of substances in and out

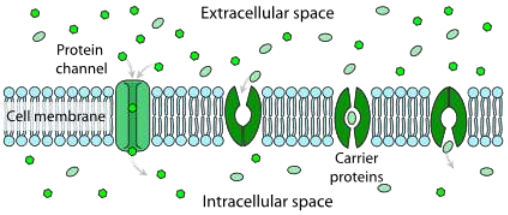
of the cell in several ways.

Diffusion (passive) transport

The molecules in the lipid bilayer are vibrating due to thermal energy. Therefore, some molecules, such as O_2, CO_2, urea, water, etc., can move across the membrane from a higher concentration region to a lower concentration region through the process of diffusion, as illustrated in Figure 8.8.2 left.



Diffusion or passive transport



Facilitated transport through protein channels or carrier protein

Figure 8.8.2: Illustration of diffusion and facilitated transport across the cell membrane. (Copyright; LadyofHats, Public domain, via Wikimedia Commons)

Facilitated transport

Integral proteins form channels through which certain substances can diffuse more rapidly than by simple diffusion. The proteins have a channel size that matches the substance's size or changes the shape to adjust to the size of the substance that needs to be selectively transported through the facilitated transport, as illustrated in Figure 8.8.2 right. Particularly, water-soluble substances such as chloride ion (Cl^-), bicarbonate ion HCO_3^-, and glucose molecules do not move fast enough through simple diffusion and are transported by the facilitate transport process to meet the need of the cells.

Active transport

Sometimes substances need to be moved against the concentration gradient. It takes place at the expense of energy in the form of ATP, just like pumping substances at the cost of electricity in everyday life. For example, K^+ concentration is greater inside the cell, and that of Na^+ is greater outside the cell. In the conduction of nerve impulses and contraction of muscles, K^+ moves into the cell, and Na^+ moves out of the cell by active transport process, as illustrated in Figure 8.8.3.

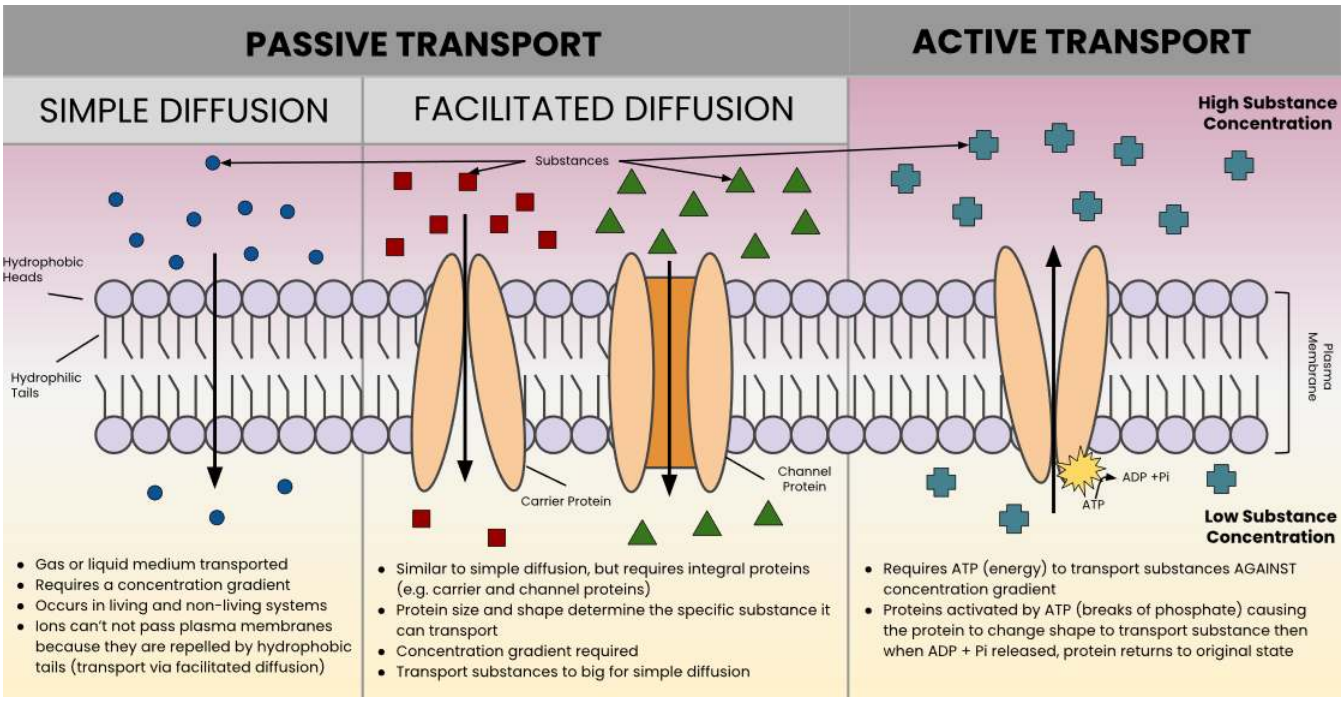


Figure **8.8.3**: Comparison of membrane transport methods: passive transport, which includes simple and facilitated diffusion, and active transport, which takes place at the expense of energy. (Copyright; LSumi, CC BY-SA 4.0, via Wikimedia Commons)

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CHAPTER OVERVIEW

9: Amino Acids, Proteins, and Enzymes

Proteins may be defined as compounds of high molar mass consisting largely or entirely of chains of amino acids. Their masses range from several thousand to several million daltons (Da). In addition to carbon, hydrogen, and oxygen atoms, all proteins contain nitrogen and sulfur atoms, and many also contain phosphorus atoms and traces of other elements. Proteins serve a variety of roles in living organisms and are often classified by these biological roles. Muscle tissue is largely protein, as are skin and hair. Proteins are present in the blood, in the brain, and even in tooth enamel. Each type of cell in our bodies makes its own specialized proteins, as well as proteins common to all or most cells. We begin our study of proteins by looking at the properties and reactions of amino acids, which is followed by a discussion of how amino acids link covalently to form peptides and proteins. We end the chapter with a discussion of enzymes—the proteins that act as catalysts in the body.

9.1: Prelude to Amino Acids, Proteins, and Enzymes
9.2: Properties of Amino Acids
9.3: Reactions of Amino Acids
9.4: Peptides
9.5: Proteins
9.6: Enzymes
9.7: Enzyme Action
9.8: Enzyme Activity
9.9: Enzyme Inhibition
9.10: Enzyme Cofactors and Vitamins

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9.1: Prelude to Amino Acids, Proteins, and Enzymes

The 1923 Nobel Prize in Medicine or Physiology was awarded to Frederick Grant Banting and John James Richard Macleod for their discovery of the protein *insulin*. In 1958, the Nobel Prize in Chemistry was awarded to Frederick Sanger for his discoveries concerning the structure of proteins and, in particular, the structure of insulin. What is so important about insulin that two Nobel Prizes have been awarded for work on this protein?

Insulin is a hormone that is synthesized in the pancreas. Insulin stimulates the transport of glucose into cells throughout the body and the storage of glucose as glycogen. People with diabetes do not produce insulin or use it properly. The isolation of insulin in 1921 led to the first effective treatment for these individuals.



Figure **9.1.1**: Insulin pump, showing an infusion set loaded into spring-loaded insertion device. A reservoir is attached to the infusion set (shown here removed from the pump). (Public Domain; User:David-i98).

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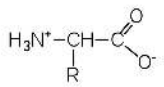
9.2: Properties of Amino Acids

Learning Objectives

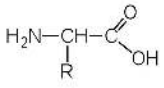
- To recognize amino acids and classify them based on the characteristics of their side chains.

The proteins in all living species, from bacteria to humans, are constructed from the same set of 20 amino acids, so called because each contains an amino group attached to a carboxylic acid. The amino acids in proteins are α-amino acids, which means the amino group is attached to the α-carbon of the carboxylic acid. Humans can synthesize only about half of the needed amino acids; the remainder must be obtained from the diet and are known as essential amino acids. However, two additional amino acids have been found in limited quantities in proteins: Selenocysteine was discovered in 1986, while pyrrolysine was discovered in 2002.

The amino acids are colorless, nonvolatile, crystalline solids, melting and decomposing at temperatures above 200°C. These melting temperatures are more like those of inorganic salts than those of amines or organic acids and indicate that the structures of the amino acids in the solid state and in neutral solution are best represented as having both a negatively charged group and a positively charged group. Such a species is known as a zwitterion.



α-Amino acid drawn as a zwitterion



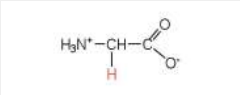
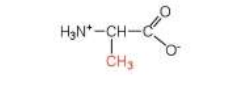
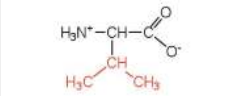
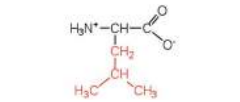
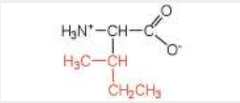
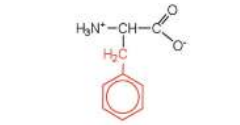
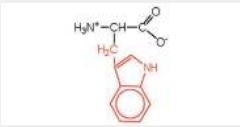
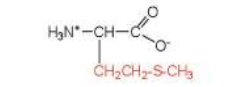
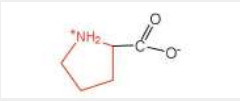
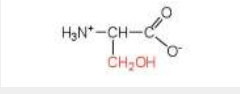
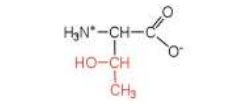
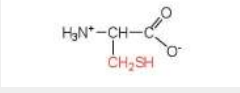
α-Amino acid drawn as an uncharged molecule; not an accurate respresentation of amino acid structure

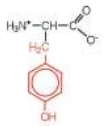
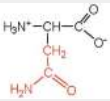
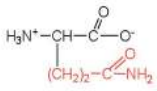
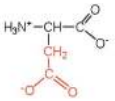
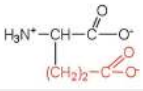
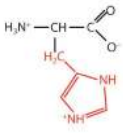
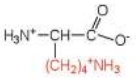
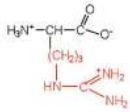
Classification

In addition to the amino and carboxyl groups, amino acids have a side chain or R group attached to the α-carbon. Each amino acid has unique characteristics arising from the size, shape, solubility, and ionization properties of its R group. As a result, the side chains of amino acids exert a profound effect on the structure and biological activity of proteins. Although amino acids can be classified in various ways, one common approach is to classify them according to whether the functional group on the side chain at neutral pH is nonpolar, polar but uncharged, negatively charged, or positively charged. The structures and names of the 20 amino acids, their one- and three-letter abbreviations, and some of their distinctive features are given in Table **9.2.1**.

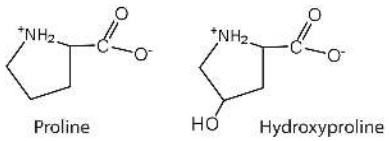
Table **9.2.1**: Common Amino Acids Found in Proteins

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Common Name	Abbreviation	Structural Formula (at pH 6)	Molar Mass	Distinctive Feature
Amino acids with a nonpolar R group				
glycine	gly (G)		75	the only amino acid lacking a chiral carbon
alanine	ala (A)		89	—
valine	val (V)		117	a branched-chain amino acid
leucine	leu (L)		131	a branched-chain amino acid
isoleucine	ile (I)		131	an essential amino acid because most animals cannot synthesize branched-chain amino acids
phenylalanine	phe (F)		165	also classified as an aromatic amino acid
tryptophan	trp (W)		204	also classified as an aromatic amino acid
methionine	met (M)		149	side chain functions as a methyl group donor
proline	pro (P)		115	contains a secondary amine group; referred to as an *α-imino acid*
Amino acids with a polar but neutral R group				
serine	ser (S)		105	found at the active site of many enzymes
threonine	thr (T)		119	named for its similarity to the sugar threose
cysteine	cys (C)		121	oxidation of two cysteine molecules yields *cystine*

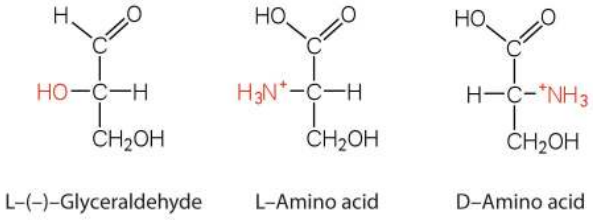
Common Name	Abbreviation	Structural Formula (at pH 6)	Molar Mass	Distinctive Feature
tyrosine	tyr (Y)		181	also classified as an aromatic amino acid
asparagine	asn (N)		132	the amide of aspartic acid
glutamine	gln (Q)		146	the amide of glutamic acid
Amino acids with a negatively charged R group				
aspartic acid	asp (D)		132	carboxyl groups are ionized at physiological pH; also known as aspartate
glutamic acid	glu (E)		146	carboxyl groups are ionized at physiological pH; also known as glutamate
Amino acids with a positively charged R group				
histidine	his (H)		155	the only amino acid whose R group has a pK_a (6.0) near physiological pH
lysine	lys (K)		147	—
arginine	arg (R)		175	almost as strong a base as sodium hydroxide

The first amino acid to be isolated was asparagine in 1806. It was obtained from protein found in asparagus juice (hence the name). Glycine, the major amino acid found in gelatin, was named for its sweet taste (Greek *glykys*, meaning “sweet”). In some cases an amino acid found in a protein is actually a derivative of one of the common 20 amino acids (one such derivative is hydroxyproline). The modification occurs *after* the amino acid has been assembled into a protein.



Configuration

Notice in Table 9.2.1 that glycine is the only amino acid whose α-carbon is *not* chiral. Therefore, with the exception of glycine, the amino acids could theoretically exist in either the D- or the L-enantiomeric form and rotate plane-polarized light. As with sugars, chemists used L-glyceraldehyde as the reference compound for the assignment of absolute configuration to amino acids. Its structure closely resembles an amino acid structure except that in the latter, an amino group takes the place of the OH group on the chiral carbon of the L-glyceraldehyde and a carboxylic acid replaces the aldehyde. Modern stereochemistry assignments using the Cahn-Ingold-Prelog priority rules used ubiquitously in chemistry show that all of the naturally occurring chiral amino acids are S except Cys which is R.



We learned that all naturally occurring sugars belong to the D series. It is interesting, therefore, that nearly all known plant and animal proteins are composed entirely of L-amino acids. However, certain bacteria contain D-amino acids in their cell walls, and several antibiotics (e.g., actinomycin D and the gramicidins) contain varying amounts of D-leucine, D-phenylalanine, and D-valine.

Summary

Amino acids can be classified based on the characteristics of their distinctive side chains as nonpolar, polar but uncharged, negatively charged, or positively charged. The amino acids found in proteins are L-amino acids.

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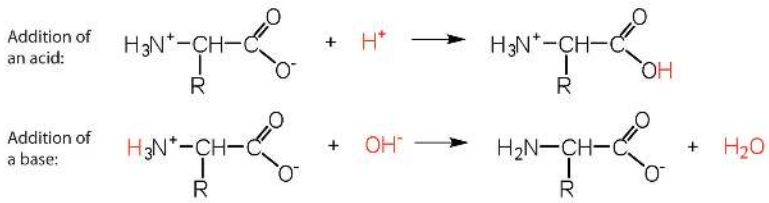
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9.3: Reactions of Amino Acids

Learning Objectives

- To explain how an amino acid can act as both an acid and a base.

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

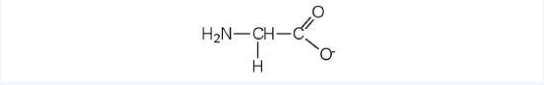


Example 9.3.1

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

Solution

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



- The acid adds H^+ to the carboxylate group.



Exercise 9.3.1

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

The particular pH at which a given amino acid exists in solution as a zwitterion is called the isoelectric point (pI). At its pI, the positive and negative charges on the amino acid balance, and the molecule as a whole is electrically neutral. The amino acids whose side chains are always neutral have isoelectric points ranging from 5.0 to 6.5. The basic amino acids (which have positively charged side chains at neutral pH) have relatively high examples. Acidic amino acids (which have negatively charged side chains at neutral pH) have quite low examples (Table 9.3.1).

Table 9.3.1: ExampIes of Some Representative Amino Acids

Amino Acid	Classification	pI
alanine	nonpolar	6.0
valine	nonpolar	6.0
serine	polar, uncharged	5.7
threonine	polar, uncharged	6.5
arginine	positively charged (basic)	10.8
histidine	positively charged (basic)	7.6
lysine	positively charged (basic)	9.8
aspartic acid	negatively charged (acidic)	3.0
glutamic acid	negatively charged (acidic)	3.2

Amino acids undergo reactions characteristic of carboxylic acids and amines. The reactivity of these functional groups is particularly important in linking amino acids together to form peptides and proteins, as you will see later in this chapter. Simple chemical tests that are used to detect amino acids take advantage of the reactivity of these functional groups. An example is the ninhydrin test in which the amine functional group of α-amino acids reacts with ninhydrin to form purple-colored compounds. Ninhydrin is used to detect fingerprints because it reacts with amino acids from the proteins in skin cells transferred to the surface by the individual leaving the fingerprint.



Ninhydrin



Summary

Amino acids can act as both an acid and a base due to the presence of the amino and carboxyl functional groups. The pH at which a given amino acid exists in solution as a zwitterion is called the *isoelectric point* (pI).

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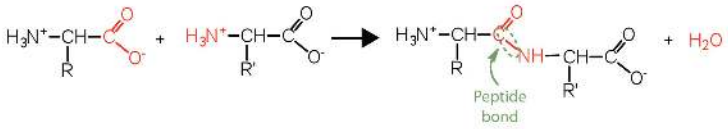
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9.4: Peptides

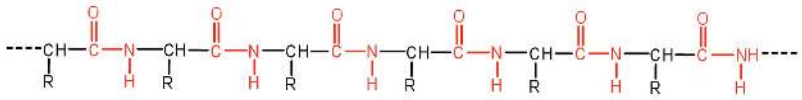
Learning Objectives

- Explain how a peptide is formed from individual amino acids.
- Explain why the sequence of amino acids in a protein is important.

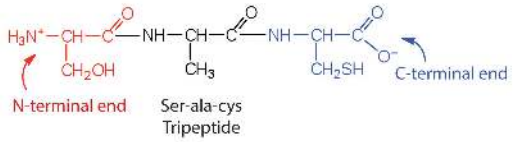
Two or more amino acids can join together into chains called peptides. Previously, we discussed the reaction between ammonia and a carboxylic acid to form an amide. In a similar reaction, the amino group on one amino acid molecule reacts with the carboxyl group on another, releasing a molecule of water and forming an amide linkage:



An amide bond joining two amino acid units is called a peptide bond. Note that the product molecule still has a reactive amino group on the left and a reactive carboxyl group on the right. These can react with additional amino acids to lengthen the peptide. The process can continue until thousands of units have joined, resulting in large proteins.



A chain consisting of only two amino acid units is called a *dipeptide*; a chain consisting of three is a *tripeptide*. By convention, peptide and protein structures are depicted with the amino acid whose amino group is free (the N-terminal end) on the left and the amino acid with a free carboxyl group (the C-terminal end) to the right.



The general term *peptide* refers to an amino acid chain of unspecified length. However, chains of about 50 amino acids or more are usually called proteins or polypeptides. In its physiologically active form, a protein may be composed of one or more polypeptide chains.

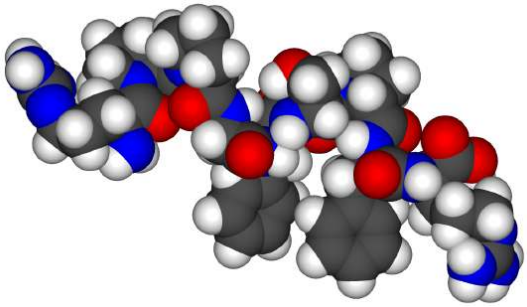


Figure **9.4.1**: Space-filling model of bradykinin. (Public Domain; Fvasconcellos)

For peptides and proteins to be physiologically active, it is not enough that they incorporate certain amounts of specific amino acids. The order, or *sequence*, in which the amino acids are connected is also of critical importance. Bradykinin is a nine-amino acid peptide (Figure **9.4.1**) produced in the blood that has the following amino acid sequence:

arg-pro-pro-gly-phe-ser-pro-phe-arg

This peptide lowers blood pressure, stimulates smooth muscle tissue, increases capillary permeability, and causes pain. When the order of amino acids in bradykinin is reversed,

arg-phe-pro-ser-phe-gly-pro-pro-arg

the peptide resulting from this synthesis shows none of the activity of bradykinin.

Just as millions of different words are spelled with our 26-letter English alphabet, millions of different proteins are made with the 20 common amino acids. However, just as the English alphabet can be used to write gibberish, amino acids can be put together in the *wrong sequence* to produce nonfunctional proteins. Although the correct sequence is ordinarily of utmost importance, it is not always absolutely required. Just as you can sometimes make sense of incorrectly spelled English words, a protein with a small percentage of “incorrect” amino acids may continue to function. However, it rarely functions as well as a protein having the correct sequence. There are also instances in which seemingly minor errors of sequence have disastrous effects. For example, in some people, every molecule of hemoglobin (a protein in the blood that transports oxygen) has a single incorrect amino acid unit out of about 300 (a single valine replaces a glutamic acid). That “minor” error is responsible for sickle cell anemia, an inherited condition that usually is fatal.

Summary

The amino group of one amino acid can react with the carboxyl group on another amino acid to form a peptide bond that links the two amino acids together. Additional amino acids can be added on through the formation of addition peptide (amide) bonds. A sequence of amino acids in a peptide or protein is written with the N-terminal amino acid first and the C-terminal amino acid at the end (writing left to right).

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9.5: Proteins

Learning Objectives

- Describe the four levels of protein structure.
- Identify the types of attractive interactions that hold proteins in their most stable three-dimensional structure.
- Explain what happens when proteins are denatured.
- Identify how a protein can be denatured.

Each of the thousands of naturally occurring proteins has its own characteristic amino acid composition and sequence that result in a unique three-dimensional shape. Since the 1950s, scientists have determined the amino acid sequences and three-dimensional conformation of numerous proteins and thus obtained important clues on how each protein performs its specific function in the body.

Proteins are compounds of high molar mass consisting largely or entirely of chains of amino acids. Because of their great complexity, protein molecules cannot be classified on the basis of specific structural similarities, as carbohydrates and lipids are categorized. The two major structural classifications of proteins are based on far more general qualities: whether the protein is (1) fiberlike and insoluble or (2) globular and soluble. Some proteins, such as those that compose hair, skin, muscles, and connective tissue, are fiberlike. These fibrous proteins are insoluble in water and usually serve structural, connective, and protective functions. Examples of fibrous proteins are keratins, collagens, myosins, and elastins. Hair and the outer layer of skin are composed of keratin. Connective tissues contain collagen. Myosins are muscle proteins and are capable of contraction and extension. Elastins are found in ligaments and the elastic tissue of artery walls.

Globular proteins, the other major class, are soluble in aqueous media. In these proteins, the chains are folded so that the molecule as a whole is roughly spherical. Familiar examples include egg albumin from egg whites and serum albumin in blood. Serum albumin plays a major role in transporting fatty acids and maintaining a proper balance of osmotic pressures in the body. Hemoglobin and myoglobin, which are important for binding oxygen, are also globular proteins.

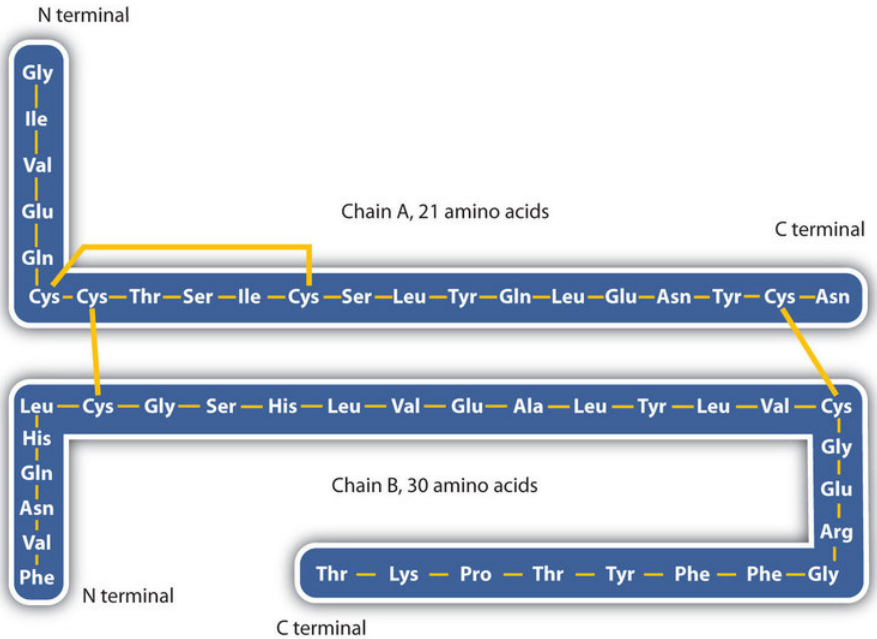


Figure **9.5.1**: Primary Structure of Human Insulin. Human insulin, whose amino acid sequence is shown here, is a hormone that is required for the proper metabolism of glucose.

Levels of Protein Structure

The structure of proteins is generally described as having four organizational levels. The first of these is the primary structure, which is the number and sequence of amino acids in a protein's polypeptide chain or chains, beginning with the free amino group

and maintained by the peptide bonds connecting each amino acid to the next. The primary structure of insulin, composed of 51 amino acids, is shown in Figure **9.5.1**.

A protein molecule is not a random tangle of polypeptide chains. Instead, the chains are arranged in unique but specific conformations. The term secondary structure refers to the fixed arrangement of the polypeptide backbone. On the basis of X ray studies, Linus Pauling and Robert Corey postulated that certain proteins or portions of proteins twist into a spiral or a helix. This helix is stabilized by *intrachain* hydrogen bonding between the carbonyl oxygen atom of one amino acid and the amide hydrogen atom four amino acids up the chain (located on the next turn of the helix) and is known as a right-handed α-helix. X ray data indicate that this helix makes one turn for every 3.6 amino acids, and the side chains of these amino acids project outward from the coiled backbone (Figure **9.5.2**). The α-keratins, found in hair and wool, are exclusively α-helical in conformation. Some proteins, such as gamma globulin, chymotrypsin, and cytochrome c, have little or no helical structure. Others, such as hemoglobin and myoglobin, are helical in certain regions but not in others.

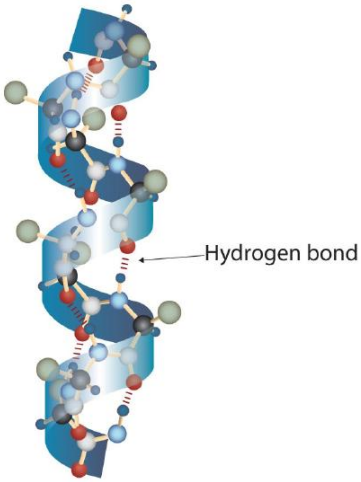


Figure **9.5.2** A Ball-and-Stick Model of an α-Helix. This ball-and-stick model shows the intrachain hydrogen bonding between carbonyl oxygen atoms and amide hydrogen atoms. Each turn of the helix spans 3.6 amino acids. Note that the side chains (represented as green spheres) point out from the helix.

Another common type of secondary structure, called the *β-pleated sheet conformation*, is a sheetlike arrangement in which two or more extended polypeptide chains (or separate regions on the same chain) are aligned side by side. The aligned segments can run either parallel or antiparallel—that is, the N-terminals can face in the same direction on adjacent chains or in different directions—and are connected by *interchain* hydrogen bonding (Figure **9.5.3**). The β-pleated sheet is particularly important in structural proteins, such as silk fibroin. It is also seen in portions of many enzymes, such as carboxypeptidase A and lysozyme.

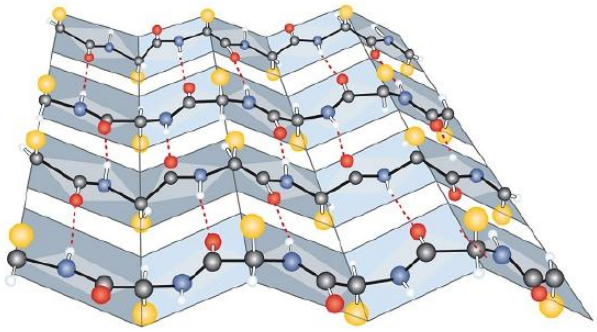


Figure **9.5.3**: A Ball-and-Stick Model of the β-Pleated Sheet Structure in Proteins. The side chains extend above or below the sheet and alternate along the chain. The protein chains are held together by interchain hydrogen bonding.

Tertiary structure refers to the unique three-dimensional shape of the protein as a whole, which results from the folding and bending of the protein backbone. The tertiary structure is intimately tied to the proper biochemical functioning of the protein. Figure **9.5.4** shows a depiction of the three-dimensional structure of insulin.

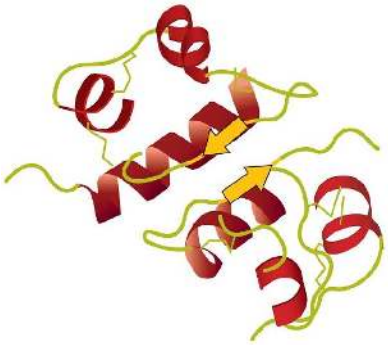
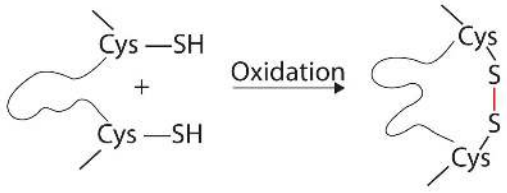


Figure 9.5.4: A Ribbon Model of the Three-Dimensional Structure of Insulin. The spiral regions represent sections of the polypeptide chain that have an α-helical structure, while the broad arrows represent β-pleated sheet structures.

Four major types of attractive interactions determine the shape and stability of the tertiary structure of proteins. You studied several of them previously.

1. Ionic bonding. Ionic bonds result from electrostatic attractions between positively and negatively charged side chains of amino acids. For example, the mutual attraction between an aspartic acid carboxylate ion and a lysine ammonium ion helps to maintain a particular folded area of a protein (part (a) of Figure 9.5.5).
2. Hydrogen bonding. Hydrogen bonding forms between a highly electronegative oxygen atom or a nitrogen atom and a hydrogen atom attached to another oxygen atom or a nitrogen atom, such as those found in polar amino acid side chains. Hydrogen bonding (as well as ionic attractions) is extremely important in both the intra- and intermolecular interactions of proteins (part (b) of Figure 9.5.5).
3. Disulfide linkages. Two cysteine amino acid units may be brought close together as the protein molecule folds. Subsequent oxidation and linkage of the sulfur atoms in the highly reactive sulfhydryl (SH) groups leads to the formation of cystine (part (c) of Figure 9.5.5). Intrachain disulfide linkages are found in many proteins, including insulin (yellow bars in Figure 9.5.1) and have a strong stabilizing effect on the tertiary structure.



4. Dispersion forces. Dispersion forces arise when a normally nonpolar atom becomes momentarily polar due to an uneven distribution of electrons, leading to an instantaneous dipole that induces a shift of electrons in a neighboring nonpolar atom. Dispersion forces are weak but can be important when other types of interactions are either missing or minimal (part (d) of Figure 9.5.5). This is the case with fibroin, the major protein in silk, in which a high proportion of amino acids in the protein have nonpolar side chains. The term *hydrophobic interaction* is often misused as a synonym for dispersion forces. Hydrophobic interactions arise because water molecules engage in hydrogen bonding with other water molecules (or groups in proteins capable of hydrogen bonding). Because nonpolar groups cannot engage in hydrogen bonding, the protein folds in such a way that these groups are buried in the interior part of the protein structure, minimizing their contact with water.

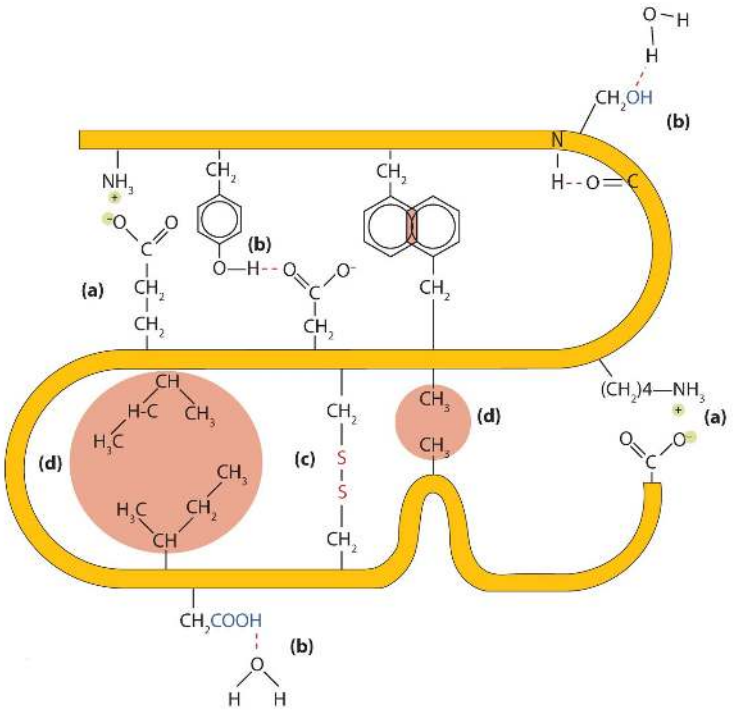


Figure 9.5.5: Tertiary Protein Structure Interactions. Four interactions stabilize the tertiary structure of a protein: (a) ionic bonding, (b) hydrogen bonding, (c) disulfide linkages, and (d) dispersion forces.

When a protein contains more than one polypeptide chain, each chain is called a *subunit*. The arrangement of multiple subunits represents a fourth level of structure, the quaternary structure of a protein. Hemoglobin, with four polypeptide chains or subunits, is the most frequently cited example of a protein having quaternary structure (Figure 9.5.6). The quaternary structure of a protein is produced and stabilized by the same kinds of interactions that produce and maintain the tertiary structure. A schematic representation of the four levels of protein structure is in Figure 9.5.7.

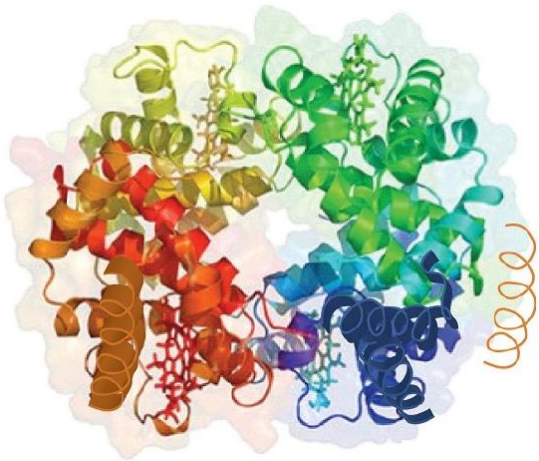


Figure 9.5.6 The Quaternary Structure of Hemoglobin. Hemoglobin is a protein that transports oxygen throughout the body.

Source: Image from the RCSB PDB (www.pdb.org(opens in new window)) of PDB ID 1I3D (R.D. Kidd, H.M. Baker, A.J. Mathews, T. Brittain, E.N. Baker (2001) Oligomerization and ligand binding in a homotetrameric hemoglobin: two high-resolution crystal structures of hemoglobin Bart's (gamma(4)), a marker for alpha-thalassemia. Protein Sci. 1739–1749).

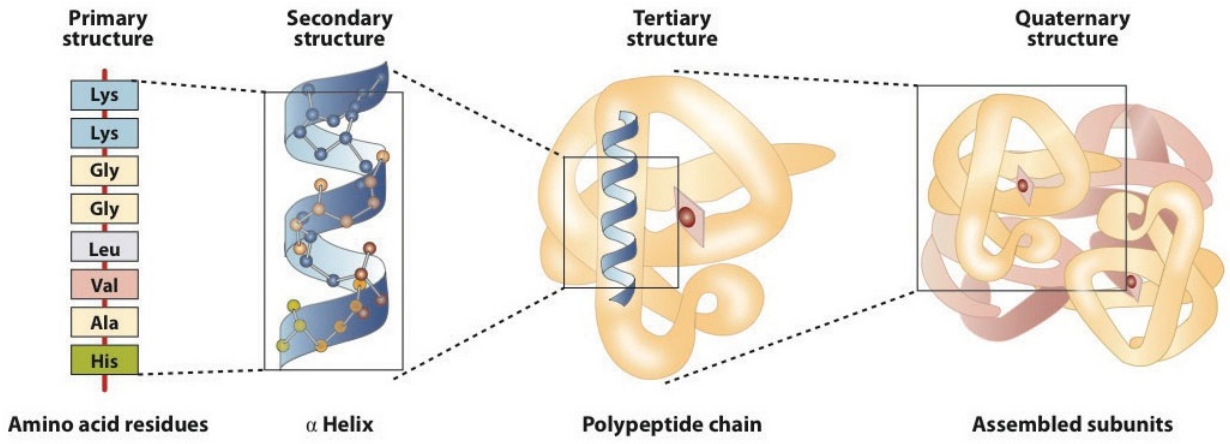


Figure **9.5.7**: Levels of Structure in Proteins

The *primary structure* consists of the specific amino acid sequence. The resulting peptide chain can twist into an α-helix, which is one type of *secondary structure*. This helical segment is incorporated into the *tertiary structure* of the folded polypeptide chain. The single polypeptide chain is a subunit that constitutes the *quaternary structure* of a protein, such as hemoglobin that has four polypeptide chains.

Denaturation of Proteins

The highly organized structures of proteins are truly masterworks of chemical architecture. But highly organized structures tend to have a certain delicacy, and this is true of proteins. Denaturation is the term used for any change in the three-dimensional structure of a protein that renders it incapable of performing its assigned function. A denatured protein cannot do its job. (Sometimes denaturation is equated with the precipitation or coagulation of a protein; our definition is a bit broader.) A wide variety of reagents and conditions, such as heat, organic compounds, pH changes, and heavy metal ions can cause protein denaturation (Figure **9.5.1**).

Figure **9.5.1**: Protein Denaturation Methods

Method	Effect on Protein Structure
Heat above 50°C or ultraviolet (UV) radiation	Heat or UV radiation supplies kinetic energy to protein molecules, causing their atoms to vibrate more rapidly and disrupting relatively weak hydrogen bonding and dispersion forces.
Use of organic compounds, such as ethyl alcohol	These compounds are capable of engaging in intermolecular hydrogen bonding with protein molecules, disrupting intramolecular hydrogen bonding within the protein.
Salts of heavy metal ions, such as mercury, silver, and lead	These ions form strong bonds with the carboxylate anions of the acidic amino acids or SH groups of cysteine, disrupting ionic bonds and disulfide linkages.
Alkaloid reagents, such as tannic acid (used in tanning leather)	These reagents combine with positively charged amino groups in proteins to disrupt ionic bonds.

Anyone who has fried an egg has observed denaturation. The clear egg white turns opaque as the albumin denatures and coagulates. No one has yet reversed that process. However, given the proper circumstances and enough time, a protein that has unfolded under sufficiently gentle conditions can refold and may again exhibit biological activity (Figure **9.5.8**). Such evidence suggests that, at least for these proteins, the primary structure determines the secondary and tertiary structure. A given sequence of amino acids seems to adopt its particular three-dimensional arrangement naturally if conditions are right.

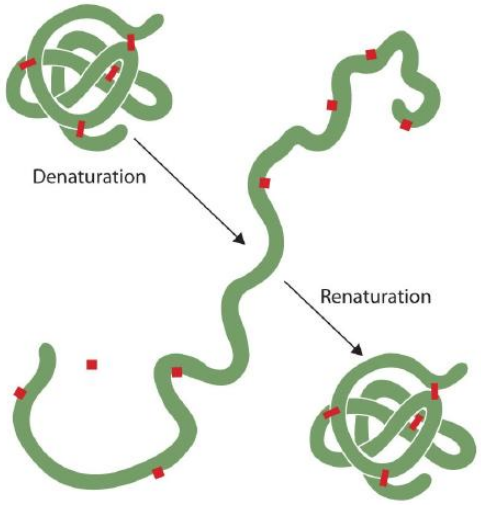


Figure 9.5.8: Denaturation and Renaturation of a Protein. The denaturation (unfolding) and renaturation (refolding) of a protein is depicted. The red boxes represent stabilizing interactions, such as disulfide linkages, hydrogen bonding, and/or ionic bonds.

The primary structures of proteins are quite sturdy. In general, fairly vigorous conditions are needed to hydrolyze peptide bonds. At the secondary through quaternary levels, however, proteins are quite vulnerable to attack, though they vary in their vulnerability to denaturation. The delicately folded globular proteins are much easier to denature than are the tough, fibrous proteins of hair and skin.

Summary

Proteins can be divided into two categories: fibrous, which tend to be insoluble in water, and globular, which are more soluble in water. A protein may have up to four levels of structure. The primary structure consists of the specific amino acid sequence. The resulting peptide chain can form an α-helix or β-pleated sheet (or local structures not as easily categorized), which is known as secondary structure. These segments of secondary structure are incorporated into the tertiary structure of the folded polypeptide chain. The quaternary structure describes the arrangements of subunits in a protein that contains more than one subunit. Four major types of attractive interactions determine the shape and stability of the folded protein: ionic bonding, hydrogen bonding, disulfide linkages, and dispersion forces. A wide variety of reagents and conditions can cause a protein to unfold or denature.

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9.6: Enzymes

Learning Objectives

- Explain the functions of enzymes.
- Explain how enzymes are classified and named.

A catalyst is any substance that increases the *rate* or speed of a chemical reaction without being changed or consumed in the reaction. Enzymes are biological catalysts, and nearly all of them are proteins. The reaction rates attained by enzymes are truly amazing. In their presence, reactions occur at rates that are a million (10^6) or more times faster than would be attainable in their absence. What is even more amazing is that enzymes perform this function at body temperature (~37°C) and physiological pH (pH ~7), rather than at the conditions that are typically necessary to increase reaction rates (high temperature or pressure, the use of strong oxidizing or reducing agents or strong acids or bases, or a combination of any of these). In addition, enzymes are highly specific in their action; that is, each enzyme catalyzes only one type of reaction in only one compound or a group of structurally related compounds. The compound or compounds on which an enzyme acts are known as its substrates.

Hundreds of enzymes have been purified and studied in an effort to understand how they work so effectively and with such specificity. The resulting knowledge has been used to design drugs that inhibit or activate particular enzymes. An example is the intensive research to improve the treatment of or find a cure for acquired immunodeficiency syndrome (AIDS). AIDS is caused by the human immunodeficiency virus (HIV). Researchers are studying the enzymes produced by this virus and are developing drugs intended to block the action of those enzymes without interfering with enzymes produced by the human body. Several of these drugs have now been approved for use by AIDS patients.

Table **9.6.1**: Classes of Enzymes

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

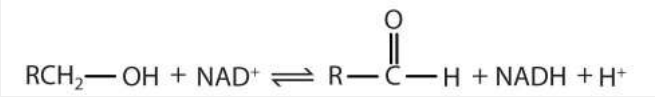
The first enzymes to be discovered were named according to their source or method of discovery. The enzyme *pepsin*, which aids in the hydrolysis of proteins, is found in the digestive juices of the stomach (Greek *pepsis*, meaning “digestion”). *Papain*, another

enzyme that hydrolyzes protein (in fact, it is used in meat tenderizers), is isolated from papayas. As more enzymes were discovered, chemists recognized the need for a more systematic and chemically informative identification scheme. In the current numbering and naming scheme, under the oversight of the Nomenclature Commission of the International Union of Biochemistry, enzymes are arranged into six groups according to the general type of reaction they catalyze (Table **9.6.1**), with subgroups and secondary subgroups that specify the reaction more precisely.

Figure* 9.6.1*: *Structure of the alcohol dehydrogenase protein (E.C.1.1.1.1) (EE ISOZYME) complexed wtih nicotinamide adenini dinulceotide (NAD) and zinc (PDB: 1CDO).*

Each enzyme is assigned a four-digit number, preceded by the prefix EC—for enzyme classification—that indicates its group, subgroup, and so forth. This is demonstrated in Table **9.6.2** for alcohol dehydrogenase. Each enzyme is also given a name consisting of the root of the name of its substrate or substrates and the *-ase* suffix. Thus urease is the enzyme that catalyzes the hydrolysis of urea.

Table **9.6.2**: Assignment of an Enzyme Classification Number

Alcohol Dehydrogenase: EC 1.1.1.1	
The first digit indicates that this enzyme is an oxidoreductase; that is, an enzyme that catalyzes an oxidation-reduction reaction. The second digit indicates that this oxidoreductase catalyzes a reaction involving a primary or secondary alcohol. The third digit indicates that either the coenzyme NAD^+ or $NADP^+$ is required for this reaction.	
The fourth digit indicates that this was the first enzyme isolated, characterized, and named using this system of nomenclature.	
The systematic name for this enzyme is *alcohol:NAD^+ oxidoreductase*, while the recommended or common name is alcohol dehydrogenase.	
Reaction catalyzed:	

Summary

An enzyme is a biological catalyst, a substance that increases the rate of a chemical reaction without being changed or consumed in the reaction. A systematic process is used to name and classify enzymes.

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9.7: Enzyme Action

Learning Objectives

- To describe the interaction between an enzyme and its substrate.

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

$$S + E \rightarrow E\text{–}S \tag{9.7.1}$$

$$E\text{–}S \rightarrow P + E \tag{9.7.2}$$

Hydrogen bonding and other electrostatic interactions hold the enzyme and substrate together in the complex. The structural features or functional groups on the enzyme that participate in these interactions are located in a cleft or pocket on the enzyme surface. This pocket, where the enzyme combines with the substrate and transforms the substrate to product is called the active site of the enzyme (Figure 9.7.1).

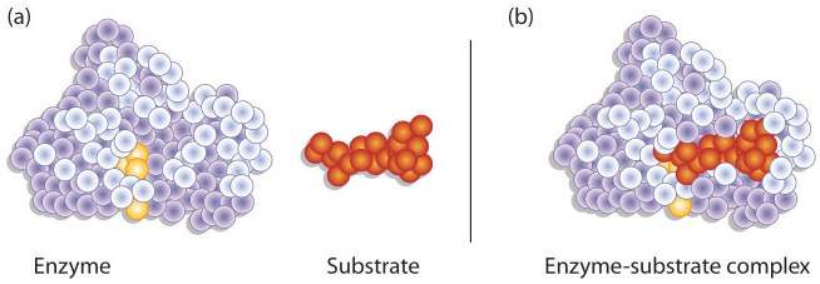


Figure 9.7.1: Substrate Binding to the Active Site of an Enzyme. The enzyme dihydrofolate reductase is shown with one of its substrates: $NADP^+$ (a) unbound and (b) bound. The $NADP^+$ (shown in red) binds to a pocket that is complementary to it in shape and ionic properties.

The active site of an enzyme possesses a unique conformation (including correctly positioned bonding groups) that is complementary to the structure of the substrate, so that the enzyme and substrate molecules fit together in much the same manner as a key fits into a tumbler lock. In fact, an early model describing the formation of the enzyme-substrate complex was called the lock-and-key model (Figure 9.7.2). This model portrayed the enzyme as conformationally rigid and able to bond only to substrates that exactly fit the active site.

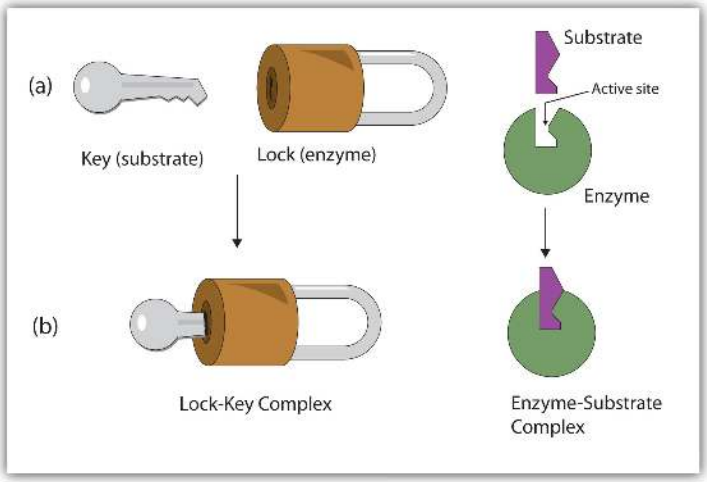


Figure **9.7.2**: The Lock-and-Key Model of Enzyme Action. (a) Because the substrate and the active site of the enzyme have complementary structures and bonding groups, they fit together as a key fits a lock. (b) The catalytic reaction occurs while the two are bonded together in the enzyme-substrate complex.

Working out the precise three-dimensional structures of numerous enzymes has enabled chemists to refine the original lock-and-key model of enzyme actions. They discovered that the binding of a substrate often leads to a large conformational change in the enzyme, as well as to changes in the structure of the substrate or substrates. The current theory, known as the induced-fit model, says that enzymes can undergo a change in conformation when they bind substrate molecules, and the active site has a shape complementary to that of the substrate only *after* the substrate is bound, as shown for hexokinase in Figure **9.7.3**. After catalysis, the enzyme resumes its original structure.

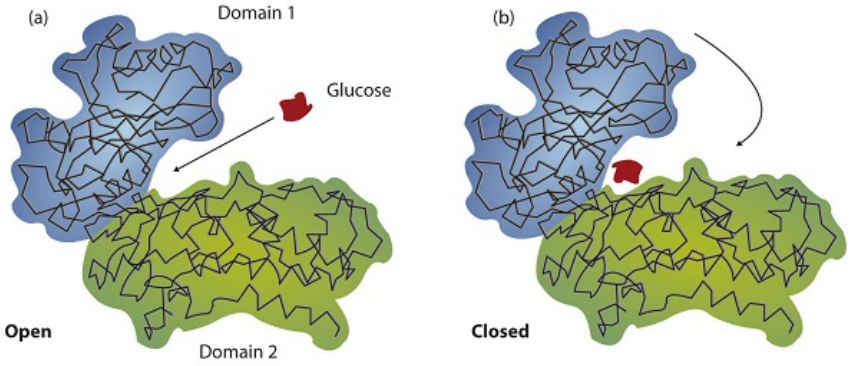


Figure **9.7.3**: The Induced-Fit Model of Enzyme Action. (a) The enzyme hexokinase without its substrate (glucose, shown in red) is bound to the active site. (b) The enzyme conformation changes dramatically when the substrate binds to it, resulting in additional interactions between hexokinase and glucose.

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

✔ Example 9.7.1

a. What type of interaction would occur between an OH group present on a substrate molecule and a functional group in the active site of an enzyme?

b. Suggest an amino acid whose side chain might be in the active site of an enzyme and form the type of interaction you just identified.

Solution

a. An OH group would most likely engage in hydrogen bonding with an appropriate functional group present in the active site of an enzyme.

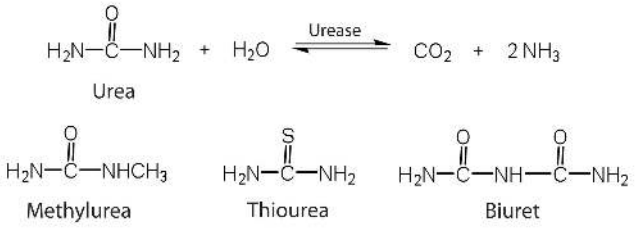
b. Several amino acid side chains would be able to engage in hydrogen bonding with an OH group. One example would be asparagine, which has an amide functional group.

? Exercise 9.7.1

a. What type of interaction would occur between an COO^- group present on a substrate molecule and a functional group in the active site of an enzyme?

b. Suggest an amino acid whose side chain might be in the active site of an enzyme and form the type of interaction you just identified.

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



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

Summary

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

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9.8: Enzyme Activity

Learning Objectives

- To describe how pH, temperature, and the concentration of an enzyme and its substrate influence enzyme activity.

The single most important property of enzymes is the ability to increase the rates of reactions occurring in living organisms, a property known as *catalytic activity*. Because most enzymes are proteins, their activity is affected by factors that disrupt protein structure, as well as by factors that affect catalysts in general. Factors that disrupt protein structure include temperature and pH; factors that affect catalysts in general include reactant or substrate concentration and catalyst or enzyme concentration. The activity of an enzyme can be measured by monitoring either the rate at which a substrate disappears or the rate at which a product forms.

Concentration of Substrate

In the presence of a given amount of enzyme, the rate of an enzymatic reaction increases as the substrate concentration increases until a limiting rate is reached, after which further increase in the substrate concentration produces no significant change in the reaction rate (part (a) of Figure **9.8.1**). At this point, so much substrate is present that essentially all of the enzyme active sites have substrate bound to them. In other words, the enzyme molecules are saturated with substrate. The excess substrate molecules cannot react until the substrate already bound to the enzymes has reacted and been released (or been released without reacting).

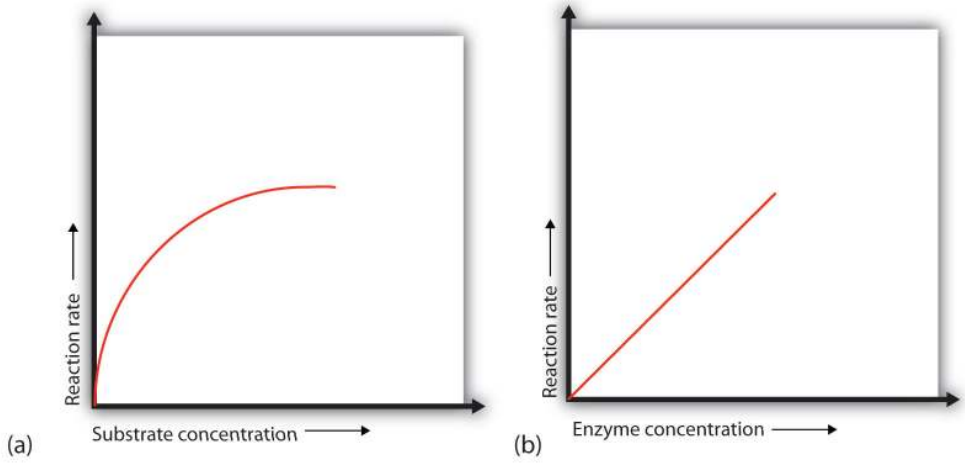


Figure **9.8.1**: Concentration versus Reaction Rate. (a) This graph shows the effect of substrate concentration on the rate of a reaction that is catalyzed by a fixed amount of enzyme. (b) This graph shows the effect of enzyme concentration on the reaction rate at a constant level of substrate.

Let's consider an analogy. Ten taxis (enzyme molecules) are waiting at a taxi stand to take people (substrate) on a 10-minute trip to a concert hall, one passenger at a time. If only 5 people are present at the stand, the rate of their arrival at the concert hall is 5 people in 10 minutes. If the number of people at the stand is increased to 10, the rate increases to 10 arrivals in 10 minutes. With 20 people at the stand, the rate would still be 10 arrivals in 10 minutes. The taxis have been "saturated." If the taxis could carry 2 or 3 passengers each, the same principle would apply. The rate would simply be higher (20 or 30 people in 10 minutes) before it leveled off.

Concentration of Enzyme

When the concentration of the enzyme is significantly lower than the concentration of the substrate (as when the number of taxis is far lower than the number of waiting passengers), the rate of an enzyme-catalyzed reaction is directly dependent on the enzyme concentration (part (b) of Figure **9.8.1**). This is true for any catalyst; the reaction rate increases as the concentration of the catalyst is increased.

Temperature

A general rule of thumb for most chemical reactions is that a temperature rise of 10°C approximately doubles the reaction rate. To some extent, this rule holds for all enzymatic reactions. After a certain point, however, an increase in temperature causes a decrease in the reaction rate, due to denaturation of the protein structure and disruption of the active site (part (a) of Figure **9.8.2**). For many proteins, denaturation occurs between 45°C and 55°C. Furthermore, even though an enzyme may appear to have a maximum reaction rate between 40°C and 50°C, most biochemical reactions are carried out at lower temperatures because enzymes are not stable at these higher temperatures and will denature after a few minutes.

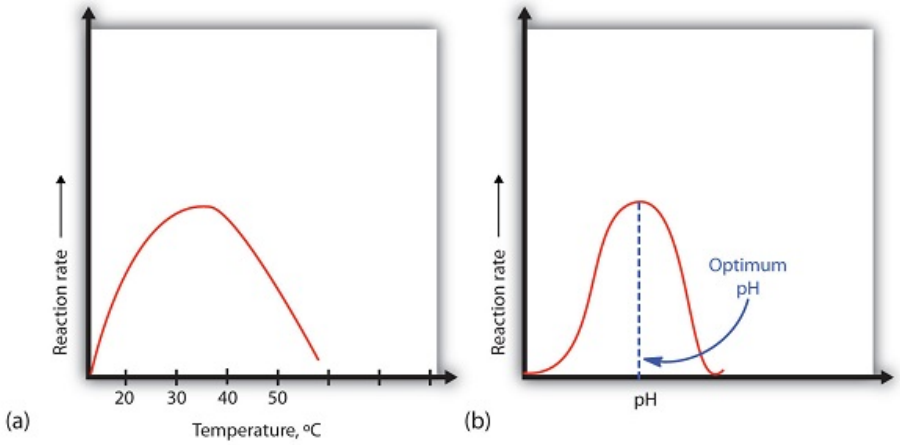


Figure **9.8.2**: Temperature and pH versus Concentration. (a) This graph depicts the effect of temperature on the rate of a reaction that is catalyzed by a fixed amount of enzyme. (b) This graph depicts the effect of pH on the rate of a reaction that is catalyzed by a fixed amount of enzyme.

At 0°C and 100°C, the rate of enzyme-catalyzed reactions is nearly zero. This fact has several practical applications. We sterilize objects by placing them in boiling water, which denatures the enzymes of any bacteria that may be in or on them. We preserve our food by refrigerating or freezing it, which slows enzyme activity. When animals go into hibernation in winter, their body temperature drops, decreasing the rates of their metabolic processes to levels that can be maintained by the amount of energy stored in the fat reserves in the animals' tissues.

Hydrogen Ion Concentration (pH)

Because most enzymes are proteins, they are sensitive to changes in the hydrogen ion concentration or pH. Enzymes may be denatured by extreme levels of hydrogen ions (whether high or low); *any* change in pH, even a small one, alters the degree of ionization of an enzyme's acidic and basic side groups and the substrate components as well. Ionizable side groups located in the active site must have a certain charge for the enzyme to bind its substrate. Neutralization of even one of these charges alters an enzyme's catalytic activity.

An enzyme exhibits maximum activity over the narrow pH range in which a molecule exists in its properly charged form. The median value of this pH range is called the optimum pH of the enzyme (part (b) of Figure **9.8.2**). With the notable exception of gastric juice (the fluids secreted in the stomach), most body fluids have pH values between 6 and 8. Not surprisingly, most enzymes exhibit optimal activity in this pH range. However, a few enzymes have optimum pH values outside this range. For example, the optimum pH for pepsin, an enzyme that is active in the stomach, is 2.0.

Summary

Initially, an increase in substrate concentration leads to an increase in the rate of an enzyme-catalyzed reaction. As the enzyme molecules become saturated with substrate, this increase in reaction rate levels off. The rate of an enzyme-catalyzed reaction increases with an increase in the concentration of an enzyme. At low temperatures, an increase in temperature increases the rate of an enzyme-catalyzed reaction. At higher temperatures, the protein is denatured, and the rate of the reaction dramatically decreases. An enzyme has an optimum pH range in which it exhibits maximum activity.

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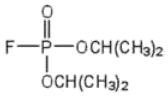
9.9: Enzyme Inhibition

Learning Objectives

- Explain what an enzyme inhibitor is.
- Distinguish between reversible and irreversible inhibitors.
- Distinguish between competitive and noncompetitive inhibitors.

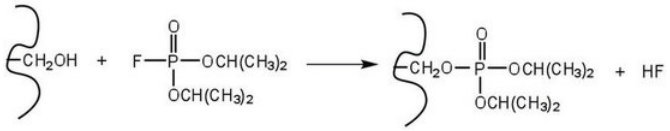
Previously, we noted that enzymes are inactivated at high temperatures and by changes in pH. These are nonspecific factors that would inactivate any enzyme. The activity of enzymes can also be regulated by more specific inhibitors. Many compounds are poisons because they bind covalently to particular enzymes or kinds of enzymes and inactivate them (Table **9.9.1**).

Table **9.9.1**: Poisons as Enzyme Inhibitors

Poison	Formula	Example of Enzyme Inhibited	Action
arsenate	AsO_4^{3-}	glyceraldehyde 3-phosphate dehydrogenase	substitutes for phosphate
iodoacetate	ICH_2COO^-	triose phosphate dehydrogenase	binds to cysteine **SH** group
diisopropylfluoro-phosphate (DIFP; a nerve poison)		acetylcholinesterase	binds to serine **OH** group

Irreversible Inhibition: Poisons

An irreversible inhibitor inactivates an enzyme by bonding covalently to a particular group at the active site. The inhibitor-enzyme bond is so strong that the inhibition cannot be reversed by the addition of excess substrate. The nerve gases, especially Diisopropyl fluorophosphate (DIFP), irreversibly inhibit biological systems by forming an enzyme-inhibitor complex with a specific OH group of serine situated at the active sites of certain enzymes. The peptidases trypsin and chymotrypsin contain serine groups at the active site and are inhibited by DIFP.



Reversible Inhibition

A reversible inhibitor inactivates an enzyme through noncovalent, more easily reversed, interactions. Unlike an irreversible inhibitor, a reversible inhibitor can dissociate from the enzyme. Reversible inhibitors include competitive inhibitors and noncompetitive inhibitors. (There are additional types of reversible inhibitors.) A competitive inhibitor is any compound that bears a structural resemblance to a particular substrate and thus competes with that substrate for binding at the active site of an enzyme. The inhibitor is not acted on by the enzyme but does prevent the substrate from approaching the active site.

The degree to which a competitive inhibitor interferes with an enzyme's activity depends on the relative concentrations of the substrate and the inhibitor. If the inhibitor is present in relatively large quantities, it will initially block most of the active sites. But because the binding is reversible, some substrate molecules will eventually bind to the active site and be converted to product. Increasing the substrate concentration promotes displacement of the inhibitor from the active site. Competitive inhibition can be completely reversed by adding substrate so that it reaches a much higher concentration than that of the inhibitor.

Studies of competitive inhibition have provided helpful information about certain enzyme-substrate complexes and the interactions of specific groups at the active sites. As a result, pharmaceutical companies have synthesized drugs that competitively inhibit metabolic processes in bacteria and certain cancer cells. Many drugs are competitive inhibitors of specific enzymes.

A classic example of competitive inhibition is the effect of malonate on the enzyme activity of succinate dehydrogenase (Figure 9.9.1). Malonate and succinate are the anions of dicarboxylic acids and contain three and four carbon atoms, respectively. The malonate molecule binds to the active site because the spacing of its carboxyl groups is not greatly different from that of succinate. However, no catalytic reaction occurs because malonate does not have a CH_2CH_2 group to convert to CH=CH. This reaction will also be discussed in connection with the Krebs cycle and energy production.

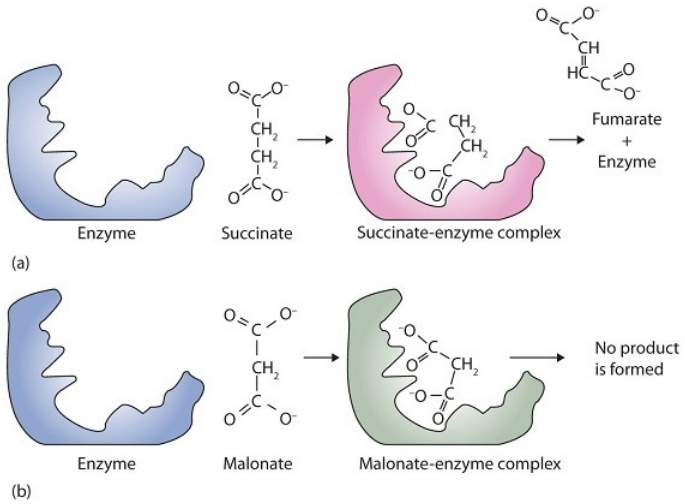


Figure 9.9.1: Competitive Inhibition. (a) Succinate binds to the enzyme succinate dehydrogenase. A dehydrogenation reaction occurs, and the product—fumarate—is released from the enzyme. (b) Malonate also binds to the active site of succinate dehydrogenase. In this case, however, no subsequent reaction occurs while malonate remains bound to the enzyme.

To Your Health: Penicillin

Chemotherapy is the strategic use of chemicals (that is, drugs) to destroy infectious microorganisms or cancer cells without causing excessive damage to the other, healthy cells of the host. From bacteria to humans, the metabolic pathways of all living organisms are quite similar, so the search for safe and effective chemotherapeutic agents is a formidable task. Many well-established chemotherapeutic drugs function by inhibiting a critical enzyme in the cells of the invading organism.

An *antibiotic* is a compound that kills bacteria; it may come from a natural source such as molds or be synthesized with a structure analogous to a naturally occurring antibacterial compound. Antibiotics constitute no well-defined class of chemically related substances, but many of them work by effectively inhibiting a variety of enzymes essential to bacterial growth.

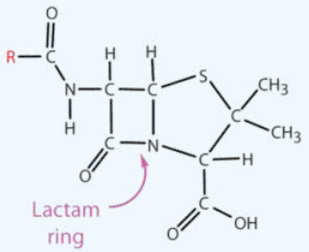
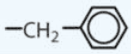
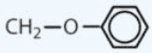
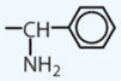
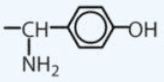
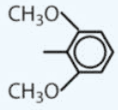
Penicillin, one of the most widely used antibiotics in the world, was fortuitously discovered by Alexander Fleming in 1928, when he noticed antibacterial properties in a mold growing on a bacterial culture plate. In 1938, Ernst Chain and Howard Florey began an intensive effort to isolate penicillin from the mold and study its properties. The large quantities of penicillin needed for this research became available through development of a corn-based nutrient medium that the mold loved and through the discovery of a higher-yielding strain of mold at a United States Department of Agriculture research center near Peoria, Illinois. Even so, it was not until 1944 that large quantities of penicillin were being produced and made available for the treatment of bacterial infections.

Penicillin functions by interfering with the synthesis of cell walls of reproducing bacteria. It does so by inhibiting an enzyme—transpeptidase—that catalyzes the last step in bacterial cell-wall biosynthesis. The defective walls cause bacterial cells to burst. Human cells are not affected because they have cell membranes, not cell walls.

Several naturally occurring penicillins have been isolated. They are distinguished by different R groups connected to a common structure: a four-member cyclic amide (called a lactam ring) fused to a five-member ring. The addition of appropriate organic compounds to the culture medium leads to the production of the different kinds of penicillin.

The penicillins are effective against gram-positive bacteria (bacteria capable of being stained by Gram's stain) and a few gram-negative bacteria (including the intestinal bacterium *Escherichia coli*). They are effective in the treatment of diphtheria, gonorrhea, pneumonia, syphilis, many pus infections, and certain types of boils. Penicillin G was the earliest penicillin to be used on a wide scale. However, it cannot be administered orally because it is quite unstable; the acidic pH of the stomach

converts it to an inactive derivative. The major oral penicillins—penicillin V, ampicillin, and amoxicillin—on the other hand, are acid stable.

Penicillin Structure	R Group	Drug Name
		penicillin G
		penicillin V
		ampicillin
		amoxicillin
		methicillin

Some strains of bacteria become resistant to penicillin through a mutation that allows them to synthesize an enzyme—penicillinase—that breaks the antibiotic down (by cleavage of the amide linkage in the lactam ring). To combat these strains, scientists have synthesized penicillin analogs (such as methicillin) that are not inactivated by penicillinase.

Some people (perhaps 5% of the population) are allergic to penicillin and therefore must be treated with other antibiotics. Their allergic reaction can be so severe that a fatal coma may occur if penicillin is inadvertently administered to them. Fortunately, several other antibiotics have been discovered. Most, including aureomycin and streptomycin, are the products of microbial synthesis. Others, such as the semisynthetic penicillins and tetracyclines, are made by chemical modifications of antibiotics; and some, like chloramphenicol, are manufactured entirely by chemical synthesis. They are as effective as penicillin in destroying infectious microorganisms. Many of these antibiotics exert their effects by blocking protein synthesis in microorganisms.

Initially, antibiotics were considered miracle drugs, substantially reducing the number of deaths from blood poisoning, pneumonia, and other infectious diseases. Some seven decades ago, a person with a major infection almost always died. Today, such deaths are rare. Seven decades ago, pneumonia was a dreaded killer of people of all ages. Today, it kills only the very old or those ill from other causes. Antibiotics have indeed worked miracles in our time, but even miracle drugs have limitations. Not long after the drugs were first used, disease organisms began to develop strains resistant to them. In a race to stay ahead of resistant bacterial strains, scientists continue to seek new antibiotics. The penicillins have now been partially displaced by related compounds, such as the cephalosporins and vancomycin. Unfortunately, some strains of bacteria have already shown resistance to these antibiotics.

Some reversible inhibitors are noncompetitive. A noncompetitive inhibitor can combine with either the free enzyme or the enzyme-substrate complex because its binding site on the enzyme is distinct from the active site. Binding of this kind of inhibitor alters the three-dimensional conformation of the enzyme, changing the configuration of the active site with one of two results. Either the enzyme-substrate complex does not form at its normal rate, or, once formed, it does not yield products at the normal rate. Because the inhibitor does not structurally resemble the substrate, the addition of excess substrate does *not* reverse the inhibitory effect.

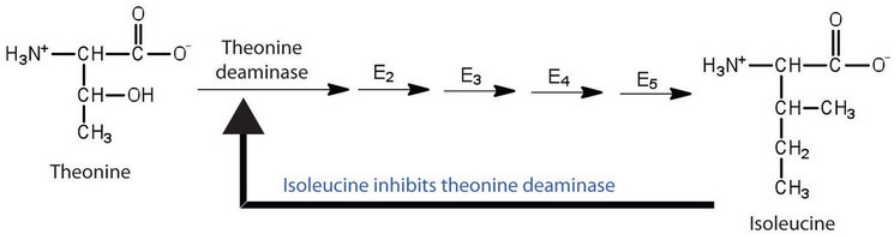


Figure **9.9.2**: Feedback Inhibition of Threonine Deaminase by Isoleucine. Threonine deaminase is the first enzyme in the conversion of threonine to isoleucine. Isoleucine inhibits threonine deaminase through feedback inhibition.

Feedback inhibition is a normal biochemical process that makes use of noncompetitive inhibitors to control some enzymatic activity. In this process, the final product inhibits the enzyme that catalyzes the first step in a series of reactions. Feedback inhibition is used to regulate the synthesis of many amino acids. For example, bacteria synthesize isoleucine from threonine in a series of five enzyme-catalyzed steps. As the concentration of isoleucine increases, some of it binds as a noncompetitive inhibitor to the first enzyme of the series (threonine deaminase), thus bringing about a decrease in the amount of isoleucine being formed (Figure **9.9.2**).

Summary

An irreversible inhibitor inactivates an enzyme by bonding covalently to a particular group at the active site. A reversible inhibitor inactivates an enzyme through noncovalent, reversible interactions. A competitive inhibitor competes with the substrate for binding at the active site of the enzyme. A noncompetitive inhibitor binds at a site distinct from the active site.

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9.10: Enzyme Cofactors and Vitamins

Learning Objectives

- To explain why vitamins are necessary in the diet.

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

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

Table **9.10.1**: Fat-Soluble Vitamins and Physiological Functions

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

Because organisms differ in their synthetic abilities, a substance that is a vitamin for one species may not be so for another. Over the past 100 years, scientists have identified and isolated 13 vitamins required in the human diet and have divided them into two broad categories: the *fat-soluble vitamins*, which include vitamins A, D, E, and K, and the *water-soluble vitamins*, which are the B complex vitamins and vitamin C. All fat-soluble vitamins contain a high proportion of hydrocarbon structural components. There are one or two oxygen atoms present, but the compounds as a whole are nonpolar. In contrast, water-soluble vitamins contain large numbers of electronegative oxygen and nitrogen atoms, which can engage in hydrogen bonding with water. Most water-soluble vitamins act as coenzymes or are required for the synthesis of coenzymes. The fat-soluble vitamins are important for a variety of physiological functions. The key vitamins and their functions are found in Tables **9.10.1** and **9.10.2**.

Table **9.10.2**: Water-Soluble Vitamins and Physiological Functions

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

Vitamins C and E, as well as the provitamin β-carotene can act as antioxidants in the body. Antioxidants prevent damage from free radicals, which are molecules that are highly reactive because they have unpaired electrons. Free radicals are formed not only through metabolic reactions involving oxygen but also by such environmental factors as radiation and pollution.

> *β-carotene is known as a provitamin because it can be converted to vitamin A in the body.*

Free radicals react most commonly react with lipoproteins and unsaturated fatty acids in cell membranes, removing an electron from those molecules and thus generating a new free radical. The process becomes a chain reaction that finally leads to the oxidative degradation of the affected compounds. Antioxidants react with free radicals to stop these chain reactions by forming a more stable molecule or, in the case of vitamin E, a free radical that is much less reactive (vitamin E is converted back to its original form through interaction with vitamin C).

Summary

Vitamins are organic compounds that are essential in very small amounts for the maintenance of normal metabolism. Vitamins are divided into two broad categories: fat-soluble vitamins and water-soluble vitamins. Most water-soluble vitamins are needed for the formation of coenzymes, which are organic molecules needed by some enzymes for catalytic activity.

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CHAPTER OVERVIEW

10: Nucleic Acids

The blueprint for the reproduction and the maintenance of each organism is found in the nuclei of its cells, concentrated in elongated, threadlike structures called chromosomes. These complex structures, consisting of DNA and proteins, contain the basic units of heredity, called genes. The number of chromosomes (and genes) varies with each species. Human body cells have 23 pairs of chromosomes having 20,000–40,000 different genes.

Sperm and egg cells contain only a single copy of each chromosome; that is, they contain only one member of each chromosome pair. Thus, in sexual reproduction, the entire complement of chromosomes is achieved only when an egg and sperm combine. A new individual receives half its hereditary material from each parent. Calling the unit of heredity a “gene” merely gives it a name. But what really are genes and how is the information they contain expressed? One definition of a gene is that it is a segment of DNA that constitutes the code for a specific polypeptide. If genes are segments of DNA, we need to learn more about the structure and physiological function of DNA. We begin by looking at the small molecules needed to form DNA and RNA (ribonucleic acid)—the nucleotides.

10.1: Prelude to Nucleic Acids
10.2: Nucleotides
10.3: Nucleic Acid Structure
10.4: Replication and Expression of Genetic Information
10.5: Protein Synthesis and the Genetic Code
10.6: Mutations and Genetic Diseases
10.7: Viruses
10.E: Nucleic Acids (Exercises)
10.S: Nucleic Acids (Summary)

Template:HideTOC

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10.1: Prelude to Nucleic Acids

Following the initial isolation of insulin in 1921, diabetic patients could be treated with insulin obtained from the pancreases of cattle and pigs. Unfortunately, some patients developed an allergic reaction to this insulin because its amino acid sequence was not identical to that of human insulin. In the 1970s, an intense research effort began that eventually led to the production of genetically engineered human insulin—the first genetically engineered product to be approved for medical use. To accomplish this feat, researchers first had to determine how insulin is made in the body and then find a way of causing the same process to occur in nonhuman organisms, such as bacteria or yeast cells. Many aspects of these discoveries are presented in this chapter on nucleic acids.



Figure **10.1.1**: A vial of insulin. It has been given a trade name, Actrapid, by the manufacturer. (Public Domain; Mr Hyde).

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10.2: Nucleotides

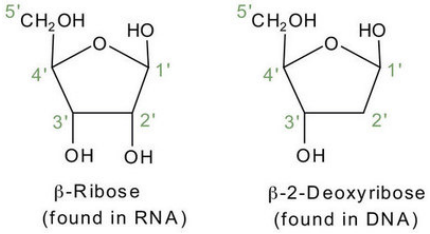
Learning Objectives

- To identify the different molecules that combine to form nucleotides.

The repeating, or monomer, units that are linked together to form nucleic acids are known as nucleotides. The deoxyribonucleic acid (DNA) of a typical mammalian cell contains about 3×10^9 nucleotides. Nucleotides can be further broken down to phosphoric acid (H_3PO_4), a pentose sugar (a sugar with five carbon atoms), and a nitrogenous base (a base containing nitrogen atoms).

$$\text{nucleic acids} \xrightarrow[\text{down into}]{\text{can be broken}} \text{nucleotides} \xrightarrow[\text{down into}]{\text{can be broken}} H_3PO_4 + \text{nitrogen base} + \text{pentose sugar}$$

If the pentose sugar is ribose, the nucleotide is more specifically referred to as a *ribonucleotide*, and the resulting nucleic acid is ribonucleic acid (RNA). If the sugar is 2-deoxyribose, the nucleotide is a *deoxyribonucleotide*, and the nucleic acid is DNA.



The nitrogenous bases found in nucleotides are classified as pyrimidines or purines. Pyrimidines are heterocyclic amines with two nitrogen atoms in a six-member ring and include uracil, thymine, and cytosine. Purines are heterocyclic amines consisting of a pyrimidine ring fused to a five-member ring with two nitrogen atoms. Adenine and guanine are the major purines found in nucleic acids (Figure **10.2.1**).

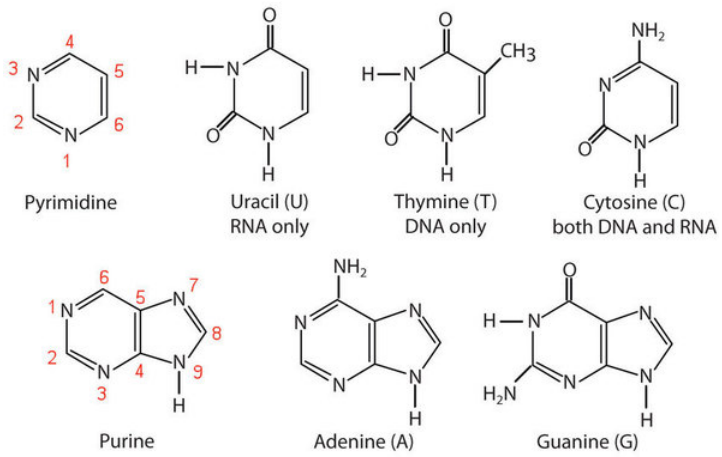


Figure **10.2.1**: The Nitrogenous Bases Found in DNA and RNA

The formation of a bond between C1′ of the pentose sugar and N1 of the pyrimidine base or N9 of the purine base joins the pentose sugar to the nitrogenous base. In the formation of this bond, a molecule of water is removed. Table **10.2.1** summarizes the similarities and differences in the composition of nucleotides in DNA and RNA.

> The numbering convention is that primed numbers designate the atoms of the pentose ring, and unprimed numbers designate the atoms of the purine or pyrimidine ring.

Table **10.2.1**: Composition of Nucleotides in DNA and RNA

Composition	DNA	RNA
purine bases	adenine and guanine	adenine and guanine
pyrimidine bases	cytosine and thymine	cytosine and uracil
pentose sugar	2-deoxyribose	ribose
inorganic acid	phosphoric acid (H_3PO_4)	H_3PO_4

The names and structures of the major ribonucleotides and one of the deoxyribonucleotides are given in Figure **10.2.2**.

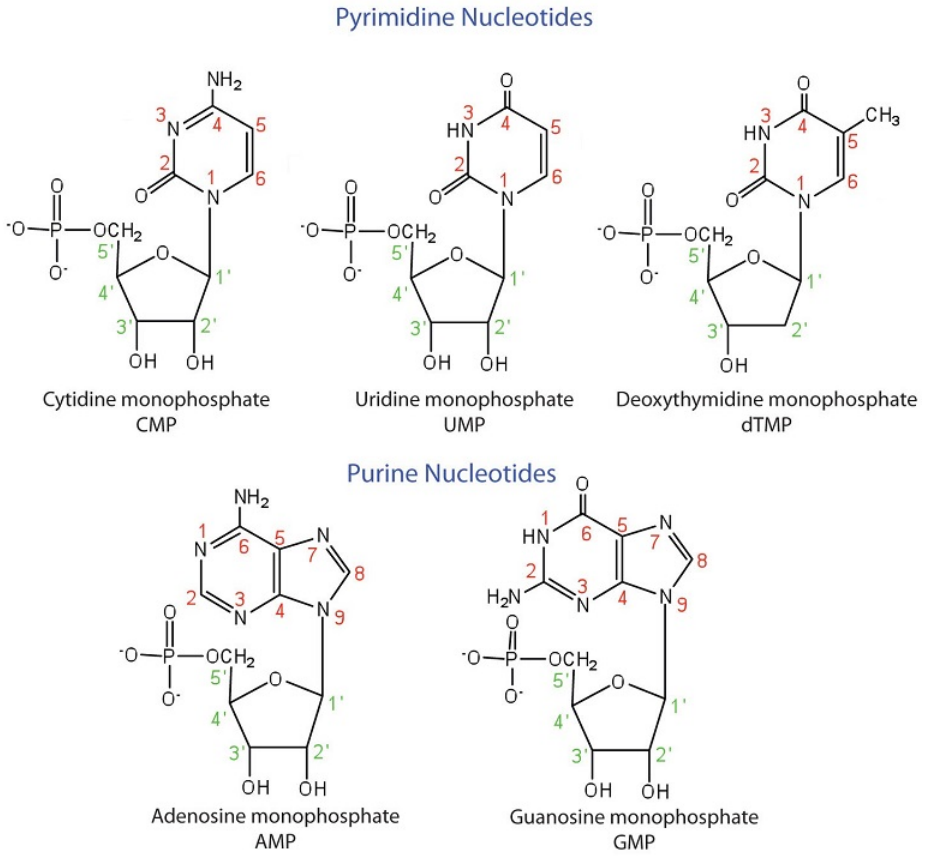


Figure **10.2.2**: The Pyrimidine and Purine Nucleotides

Apart from being the monomer units of DNA and RNA, the nucleotides and some of their derivatives have other functions as well. Adenosine diphosphate (ADP) and adenosine triphosphate (ATP), shown in Figure **10.2.3**, have a role in cell metabolism. Moreover, a number of coenzymes, including flavin adenine dinucleotide (FAD), nicotinamide adenine dinucleotide (NAD^+), and coenzyme A, contain adenine nucleotides as structural components.

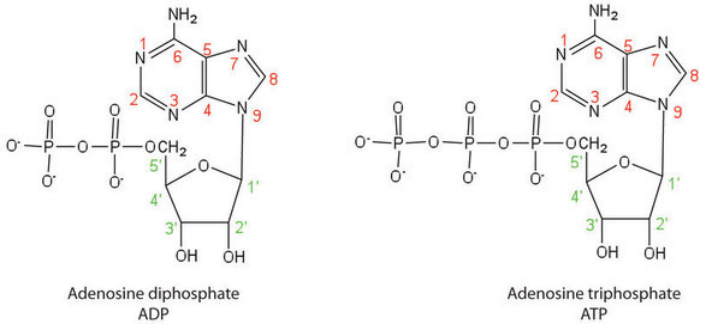


Figure **10.2.3**: Structures of Two Important Adenine-Containing Nucleotides

Summary

Nucleotides are composed of phosphoric acid, a pentose sugar (ribose or deoxyribose), and a nitrogen-containing base (adenine, cytosine, guanine, thymine, or uracil). Ribonucleotides contain ribose, while deoxyribonucleotides contain deoxyribose.

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10.3: Nucleic Acid Structure

Skills to Develop

- Identify the two types of nucleic acids and the function of each type.
- Describe how nucleotides are linked together to form nucleic acids.
- Describe the secondary structure of DNA and the importance of complementary base pairing.

Nucleic acids are large polymers formed by linking nucleotides together and are found in every cell. Deoxyribonucleic acid (DNA) is the nucleic acid that stores genetic information. If all the DNA in a typical mammalian cell were stretched out end to end, it would extend more than 2 m. Ribonucleic acid (RNA) is the nucleic acid responsible for using the genetic information encoded in DNA to produce the thousands of proteins found in living organisms.

Primary Structure of Nucleic Acids

Nucleotides are joined together through the phosphate group of one nucleotide connecting in an ester linkage to the OH group on the third carbon atom of the sugar unit of a second nucleotide. This unit joins to a third nucleotide, and the process is repeated to produce a long nucleic acid chain (Figure **10.3.1**). The backbone of the chain consists of alternating phosphate and sugar units (2-deoxyribose in DNA and ribose in RNA). The purine and pyrimidine bases branch off this backbone.

> *Each phosphate group has one acidic hydrogen atom that is ionized at physiological pH. This is why these compounds are known as nucleic acids.*

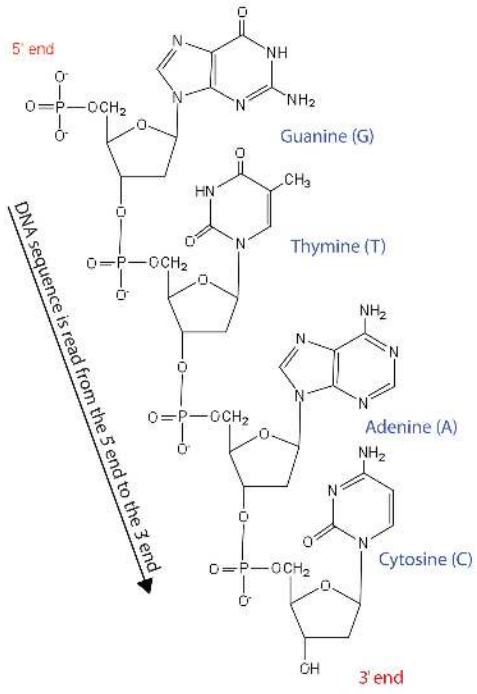


***Figure* 10.3.1** *Structure of a Segment of DNA. A similar segment of RNA would have OH groups on each C2', and uracil would replace thymine.*

Like proteins, nucleic acids have a primary structure that is defined as the sequence of their nucleotides. Unlike proteins, which have 20 different kinds of amino acids, there are only 4 different kinds of nucleotides in nucleic acids. For amino acid sequences in proteins, the convention is to write the amino acids in order starting with the N-terminal amino acid. In writing nucleotide sequences for nucleic acids, the convention is to write the nucleotides (usually using the one-letter abbreviations for the bases, shown in Figure **10.3.1**) starting with the nucleotide having a free phosphate group, which is known as the 5′ end, and indicate the nucleotides in order. For DNA, a lowercase *d* is often written in front of the sequence to indicate that the monomers are

deoxyribonucleotides. The final nucleotide has a free OH group on the 3′ carbon atom and is called the *3′ end*. The sequence of nucleotides in the DNA segment shown in Figure **10.3.1** would be written 5′-dG-dT-dA-dC-3′, which is often further abbreviated to dGTAC or just GTAC.

Secondary Structure of DNA

The three-dimensional structure of DNA was the subject of an intensive research effort in the late 1940s to early 1950s. Initial work revealed that the polymer had a regular repeating structure. In 1950, Erwin Chargaff of Columbia University showed that the molar amount of adenine (A) in DNA was always equal to that of thymine (T). Similarly, he showed that the molar amount of guanine (G) was the same as that of cytosine (C). Chargaff drew no conclusions from his work, but others soon did.

At Cambridge University in 1953, James D. Watson and Francis Crick announced that they had a model for the secondary structure of DNA. Using the information from Chargaff's experiments (as well as other experiments) and data from the X ray studies of Rosalind Franklin (which involved sophisticated chemistry, physics, and mathematics), Watson and Crick worked with models that were not unlike a child's construction set and finally concluded that DNA is composed of two nucleic acid chains running antiparallel to one another—that is, side-by-side with the 5′ end of one chain next to the 3′ end of the other. Moreover, as their model showed, the two chains are twisted to form a double helix—a structure that can be compared to a spiral staircase, with the phosphate and sugar groups (the backbone of the nucleic acid polymer) representing the outside edges of the staircase. The purine and pyrimidine bases face the inside of the helix, with guanine always opposite cytosine and adenine always opposite thymine. These specific base pairs, referred to as complementary bases, are the steps, or treads, in our staircase analogy (Figure **10.3.2**).

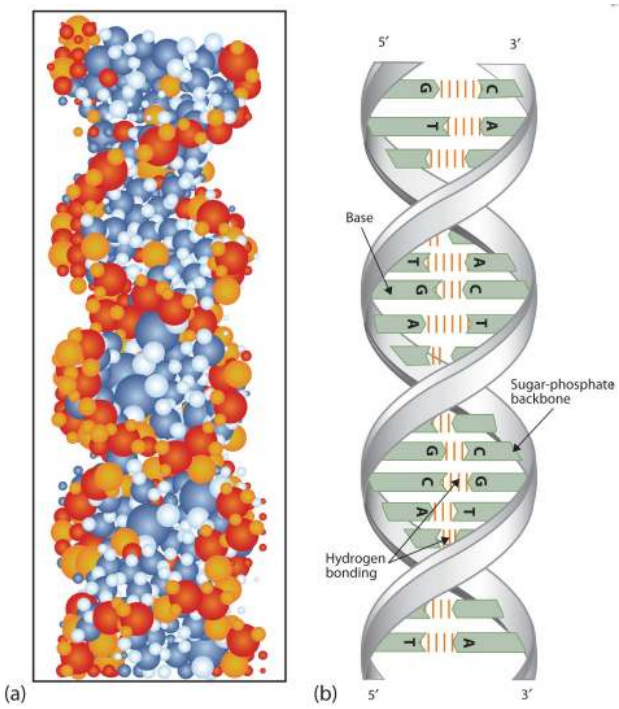


***Figure* 10.3.2** *DNA Double Helix. (a) This represents a computer-generated model of the DNA double helix. (b) This represents a schematic representation of the double helix, showing the complementary bases.*

The structure proposed by Watson and Crick provided clues to the mechanisms by which cells are able to divide into two identical, functioning daughter cells; how genetic data are passed to new generations; and even how proteins are built to required specifications. All these abilities depend on the pairing of complementary bases. Figure **10.3.3** shows the two sets of base pairs and illustrates two things. First, a pyrimidine is paired with a purine in each case, so that the long dimensions of both pairs are identical (1.08 nm).

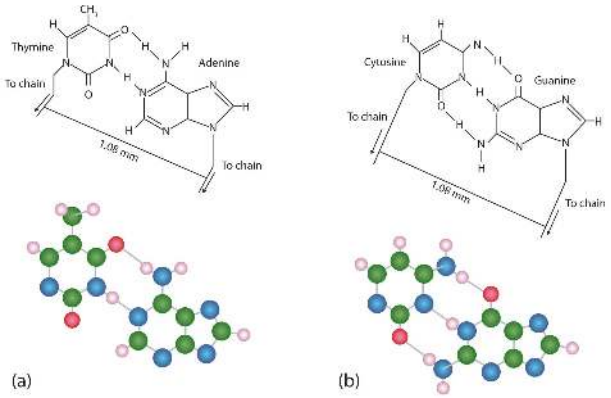


***Figure* 10.3.3** *Complementary Base Pairing. Complementary bases engage in hydrogen bonding with one another: (a) thymine and adenine; (b) cytosine and guanine.*

If two pyrimidines were paired or two purines were paired, the two pyrimidines would take up less space than a purine and a pyrimidine, and the two purines would take up more space, as illustrated in Figure **10.3.4**. If these pairings were ever to occur, the structure of DNA would be like a staircase made with stairs of different widths. For the two strands of the double helix to fit neatly, a pyrimidine must always be paired with a purine. The second thing you should notice in Figure **10.3.3** is that the correct pairing enables formation of three instances of hydrogen bonding between guanine and cytosine and two between adenine and thymine. The additive contribution of this hydrogen bonding imparts great stability to the DNA double helix.

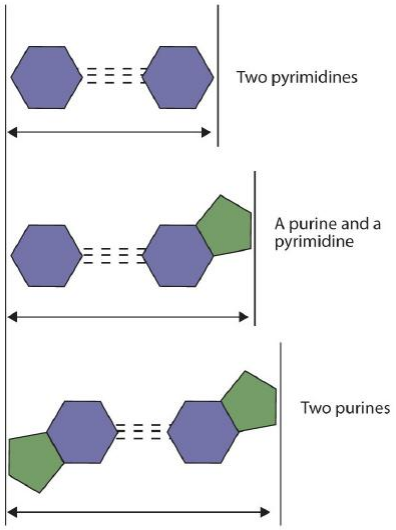


***Figure* 10.3.4** *Difference in Widths of Possible Base Pairs*

Summary

- DNA is the nucleic acid that stores genetic information. RNA is the nucleic acid responsible for using the genetic information in DNA to produce proteins.
- Nucleotides are joined together to form nucleic acids through the phosphate group of one nucleotide connecting in an ester linkage to the OH group on the third carbon atom of the sugar unit of a second nucleotide.
- Nucleic acid sequences are written starting with the nucleotide having a free phosphate group (the 5′ end).
- Two DNA strands link together in an antiparallel direction and are twisted to form a double helix. The nitrogenous bases face the inside of the helix. Guanine is always opposite cytosine, and adenine is always opposite thymine.

Concept Review Exercises

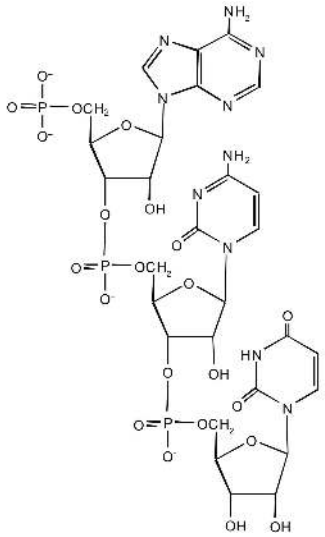
1.
   a. Name the two kinds of nucleic acids.
   b. Which type of nucleic acid stores genetic information in the cell?
2. What are complementary bases?
3. Why is it structurally important that a purine base always pair with a pyrimidine base in the DNA double helix?

Answers

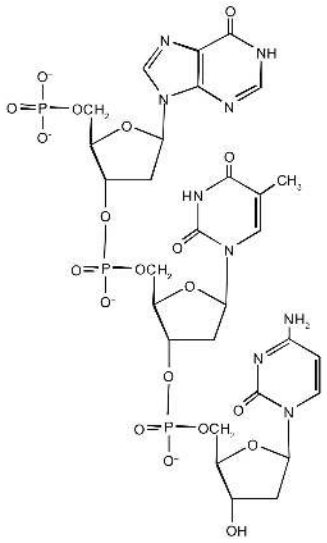
1.
   a. deoxyribonucleic acid (DNA) and ribonucleic acid (RNA)
   b. DNA
2. the specific base pairings in the DNA double helix in which guanine is paired with cytosine and adenine is paired with thymine
3. The width of the DNA double helix is kept at a constant width, rather than narrowing (if two pyrimidines were across from each other) or widening (if two purines were across from each other).

Exercises

1. For this short RNA segment,
   a. identify the 5′ end and the 3′ end of the molecule.
   b. circle the atoms that comprise the backbone of the nucleic acid chain.
   c. write the nucleotide sequence of this RNA segment.



2. For this short DNA segment,
   a. identify the 5′ end and the 3′ end of the molecule.
   b. circle the atoms that comprise the backbone of the nucleic acid chain.
   c. write the nucleotide sequence of this DNA segment.



3. Which nitrogenous base in DNA pairs with each nitrogenous base?

   a. cytosine
   b. adenine
   c. guanine
   d. thymine

4. Which nitrogenous base in RNA pairs with each nitrogenous base?

   a. cytosine
   b. adenine
   c. guanine
   d. thymine

5. How many hydrogen bonds can form between the two strands in the short DNA segment shown below?

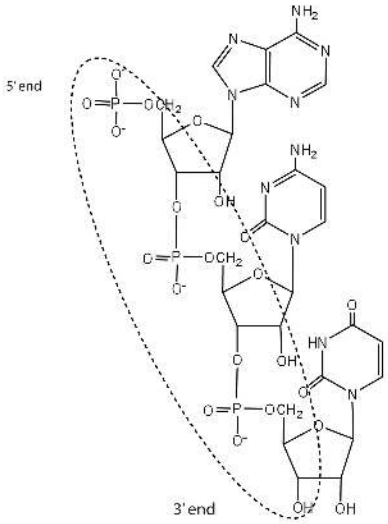
   5′ ATGCGACTA 3′ 3′ TACGCTGAT 5′

6. How many hydrogen bonds can form between the two strands in the short DNA segment shown below?

   5′ CGATGAGCC 3′ 3′ GCTACTCGG 5′

Answers

1.



c. ACU

3.

a. guanine
b. thymine
c. cytosine
d. adenine

5. 22 (2 between each AT base pair and 3 between each GC base pair)

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10.4: Replication and Expression of Genetic Information

Learning Objectives

- Describe how a new copy of DNA is synthesized.
- Describe how RNA is synthesized from DNA.
- Identify the different types of RNA and the function of each type of RNA.

We previously stated that deoxyribonucleic acid (DNA) stores genetic information, while ribonucleic acid (RNA) is responsible for transmitting or expressing genetic information by directing the synthesis of thousands of proteins found in living organisms. But how do the nucleic acids perform these functions? Three processes are required: (1) *replication*, in which new copies of DNA are made; (2) *transcription*, in which a segment of DNA is used to produce RNA; and (3) *translation*, in which the information in RNA is translated into a protein sequence.

Replication

New cells are continuously forming in the body through the process of cell division. For this to happen, the DNA in a dividing cell must be copied in a process known as replication. The complementary base pairing of the double helix provides a ready model for how genetic replication occurs. If the two chains of the double helix are pulled apart, disrupting the hydrogen bonding between base pairs, each chain can act as a *template*, or pattern, for the synthesis of a new complementary DNA chain.

The nucleus contains all the necessary enzymes, proteins, and nucleotides required for this synthesis. A short segment of DNA is "unzipped," so that the two strands in the segment are separated to serve as templates for new DNA. DNA polymerase, an enzyme, recognizes each base in a template strand and matches it to the complementary base in a free nucleotide. The enzyme then catalyzes the formation of an ester bond between the 5′ phosphate group of the nucleotide and the 3′ OH end of the new, growing DNA chain. In this way, each strand of the original DNA molecule is used to produce a duplicate of its former partner (Figure 10.4.1). Whatever information was encoded in the original DNA double helix is now contained in each replicate helix. When the cell divides, each daughter cell gets one of these replicates and thus all of the information that was originally possessed by the parent cell.

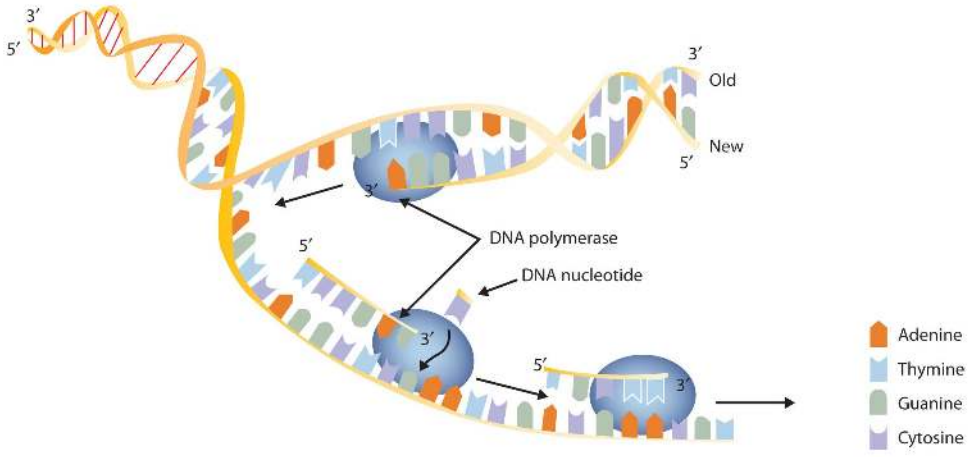


Figure 10.4.1: A Schematic Diagram of DNA Replication. DNA replication occurs by the sequential unzipping of segments of the double helix. Each new nucleotide is brought into position by DNA polymerase and is added to the growing strand by the formation of a phosphate ester bond. Thus, two double helixes form from one, and each consists of one old strand and one new strand, an outcome called *semiconservative replications*. (This representation is simplified; many more proteins are involved in replication.)

Example 10.4.1

A segment of one strand from a DNA molecule has the sequence 5′-TCCATGAGTTGA-3′. What is the sequence of nucleotides in the opposite, or complementary, DNA chain?

Solution

Knowing that the two strands are antiparallel and that T base pairs with A, while C base pairs with G, the sequence of the complementary strand will be 3′-AGGTACTCAACT-5′ (can also be written as TCAACTCATGGA).

? Exercise 10.4.1

A segment of one strand from a DNA molecule has the sequence 5′-CCAGTGAATTGCCTAT-3′. What is the sequence of nucleotides in the opposite, or complementary, DNA chain?

What do we mean when we say information is encoded in the DNA molecule? An organism's DNA can be compared to a book containing directions for assembling a model airplane or for knitting a sweater. Letters of the alphabet are arranged into words, and these words direct the individual to perform certain operations with specific materials. If all the directions are followed correctly, a model airplane or sweater is produced.

In DNA, the particular sequences of nucleotides along the chains encode the directions for building an organism. Just as *saw* means one thing in English and *was* means another, the sequence of bases CGT means one thing, and TGC means something different. Although there are only four letters—the four nucleotides—in the genetic code of DNA, their sequencing along the DNA strands can vary so widely that information storage is essentially unlimited.

Transcription

For the hereditary information in DNA to be useful, it must be "expressed," that is, used to direct the growth and functioning of an organism. The first step in the processes that constitute DNA expression is the synthesis of RNA, by a template mechanism that is in many ways analogous to DNA replication. Because the RNA that is synthesized is a complementary copy of information contained in DNA, RNA synthesis is referred to as transcription. There are three key differences between replication and transcription:

1. RNA molecules are much shorter than DNA molecules; only a portion of one DNA strand is copied or transcribed to make an RNA molecule.
2. RNA is built from ribonucleotides rather than deoxyribonucleotides.
3. The newly synthesized RNA strand does not remain associated with the DNA sequence it was transcribed from.

The DNA sequence that is transcribed to make RNA is called the *template strand*, while the complementary sequence on the other DNA strand is called the *coding* or *informational strand*. To initiate RNA synthesis, the two DNA strands unwind at specific sites along the DNA molecule. Ribonucleotides are attracted to the uncoiling region of the DNA molecule, beginning at the 3′ end of the template strand, according to the rules of base pairing. Thymine in DNA calls for adenine in RNA, cytosine specifies guanine, guanine calls for cytosine, and adenine requires uracil. RNA polymerase—an enzyme—binds the complementary ribonucleotide and catalyzes the formation of the ester linkage between ribonucleotides, a reaction very similar to that catalyzed by DNA polymerase (Figure **10.4.2**). Synthesis of the RNA strand takes place in the 5′ to 3′ direction, antiparallel to the template strand. Only a short segment of the RNA molecule is hydrogen-bonded to the template strand at any time during transcription. When transcription is completed, the RNA is released, and the DNA helix reforms. The nucleotide sequence of the RNA strand formed during transcription is identical to that of the corresponding coding strand of the DNA, except that U replaces T.

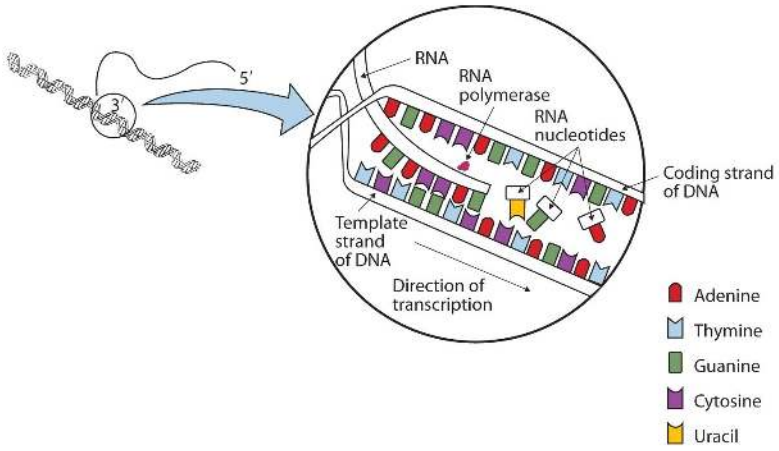


Figure 10.4.2: A Schematic Diagram of RNA Transcription from a DNA Template. The representation of RNA polymerase is proportionately much smaller than the actual molecule, which encompasses about 50 nucleotides at a time.

Example 10.4.2

A portion of the template strand of a gene has the sequence 5′-TCCATGAGTTGA-3′. What is the sequence of nucleotides in the RNA that is formed from this template?

Solution

Four things must be remembered in answering this question: (1) the DNA strand and the RNA strand being synthesized are antiparallel; (2) RNA is synthesized in a 5′ to 3′ direction, so transcription begins at the 3′ end of the template strand; (3) ribonucleotides are used in place of deoxyribonucleotides; and (4) thymine (T) base pairs with adenine (A), A base pairs with uracil (U; in RNA), and cytosine (C) base pairs with guanine (G). The sequence is determined to be 3′-AGGUACUCAACU-5′ (can also be written as 5′-UCAACUCAUGGA-3′).

Exercise 10.4.2

A portion of the template strand of a gene has the sequence 5′-CCAGTGAATTGCCTAT-3′. What is the sequence of nucleotides in the RNA that is formed from this template?

Three types of RNA are formed during transcription: *messenger RNA* (mRNA), *ribosomal RNA* (rRNA), and *transfer RNA* (tRNA). These three types of RNA differ in function, size, and percentage of the total cell RNA (Table 10.4.1). mRNA makes up only a small percent of the total amount of RNA within the cell, primarily because each molecule of mRNA exists for a relatively short time; it is continuously being degraded and resynthesized. The molecular dimensions of the mRNA molecule vary according to the amount of genetic information a given molecule contains. After transcription, which takes place in the nucleus, the mRNA passes into the cytoplasm, carrying the genetic message from DNA to the ribosomes, the sites of protein synthesis. Elsewhere, we shall see how mRNA directly determines the sequence of amino acids during protein synthesis.

Table 10.4.1: Properties of Cellular RNA in Escherichia coli

Type	Function	Approximate Number of Nucleotides	Percentage of Total Cell RNA
mRNA	codes for proteins	100–6,000	~3
rRNA	component of ribosomes	120–2900	83
tRNA	adapter molecule that brings the amino acid to the ribosome	75–90	14

Ribosomes are cellular substructures where proteins are synthesized. They contain about 65% rRNA and 35% protein, held together by numerous noncovalent interactions, such as hydrogen bonding, in an overall structure consisting of two globular particles of unequal size.

Molecules of tRNA, which bring amino acids (one at a time) to the ribosomes for the construction of proteins, differ from one another in the kinds of amino acid each is specifically designed to carry. A set of three nucleotides, known as a codon, on the mRNA determines which kind of tRNA will add its amino acid to the growing chain. Each of the 20 amino acids found in proteins has at least one corresponding kind of tRNA, and most amino acids have more than one.

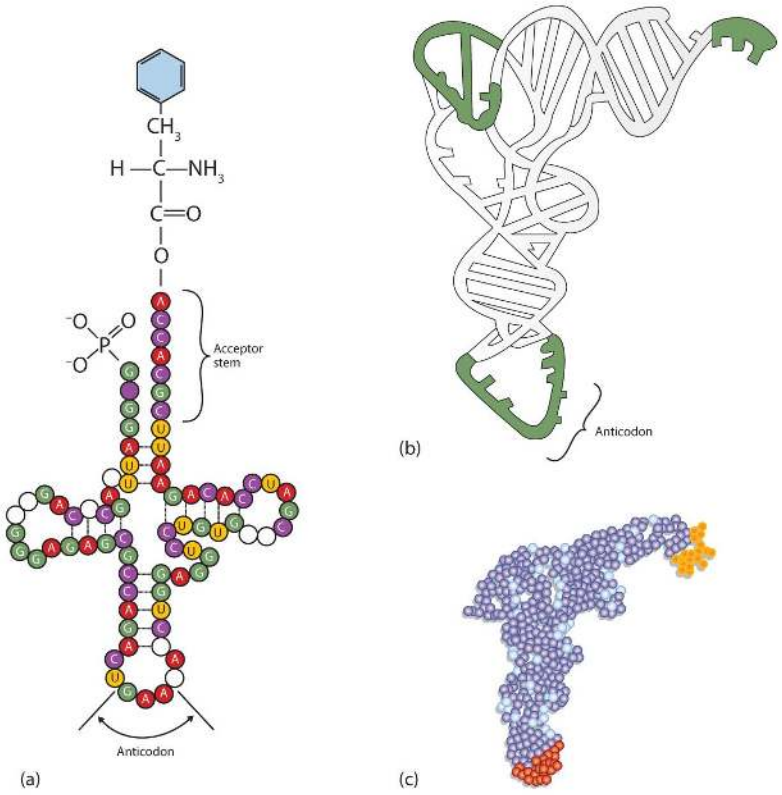


Figure 10.4.3: Transfer RNA. (a) In the two-dimensional structure of a yeast tRNA molecule for phenylalanine, the amino acid binds to the acceptor stem located at the 3′ end of the tRNA primary sequence. (The nucleotides that are not specifically identified here are slightly altered analogs of the four common ribonucleotides A, U, C, and G.) (b) In the three-dimensional structure of yeast phenylalanine tRNA, note that the anticodon loop is at the bottom and the acceptor stem is at the top right. (c) This shows a space-filling model of the tRNA.

The two-dimensional structure of a tRNA molecule has three distinctive loops, reminiscent of a cloverleaf (Figure 10.4.3). On one loop is a sequence of three nucleotides that varies for each kind of tRNA. This triplet, called the anticodon, is complementary to and pairs with the codon on the mRNA. At the opposite end of the molecule is the acceptor stem, where the amino acid is attached.

Summary

- In DNA replication, each strand of the original DNA serves as a template for the synthesis of a complementary strand.
- DNA polymerase is the primary enzyme needed for replication.
- In transcription, a segment of DNA serves as a template for the synthesis of an RNA sequence.
- RNA polymerase is the primary enzyme needed for transcription.
- Three types of RNA are formed during transcription: mRNA, rRNA, and tRNA.

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10.5: Protein Synthesis and the Genetic Code

Learning Objectives

- describe the characteristics of the genetic code.
- describe how a protein is synthesized from mRNA.

One of the definitions of a gene is as follows: a segment of deoxyribonucleic acid (DNA) carrying the code for a specific polypeptide. Each molecule of messenger RNA (mRNA) is a transcribed copy of a gene that is used by a cell for synthesizing a polypeptide chain. If a protein contains two or more different polypeptide chains, each chain is coded by a different gene. We turn now to the question of how the sequence of nucleotides in a molecule of ribonucleic acid (RNA) is translated into an amino acid sequence.

How can a molecule containing just 4 different nucleotides specify the sequence of the 20 amino acids that occur in proteins? If each nucleotide coded for 1 amino acid, then obviously the nucleic acids could code for only 4 amino acids. What if amino acids were coded for by groups of 2 nucleotides? There are 4^2, or 16, different combinations of 2 nucleotides (AA, AU, AC, AG, UU, and so on). Such a code is more extensive but still not adequate to code for 20 amino acids. However, if the nucleotides are arranged in groups of 3, the number of different possible combinations is 4^3, or 64. Here we have a code that is extensive enough to direct the synthesis of the primary structure of a protein molecule.



***Video**: NDSU Virtual Cell Animations project animation "Translation". For more information, see VCell, NDSU(opens in new window) [vcell.ndsu.nodak.edu]*

The genetic code can therefore be described as the identification of each group of three nucleotides and its particular amino acid. The sequence of these triplet groups in the mRNA dictates the sequence of the amino acids in the protein. Each individual three-nucleotide coding unit, as we have seen, is called a *codon*.

Protein synthesis is accomplished by orderly interactions between mRNA and the other ribonucleic acids (transfer RNA [tRNA] and ribosomal RNA [rRNA]), the ribosome, and more than 100 enzymes. The mRNA formed in the nucleus during transcription is transported across the nuclear membrane into the cytoplasm to the ribosomes—carrying with it the genetic instructions. The process in which the information encoded in the mRNA is used to direct the sequencing of amino acids and thus ultimately to synthesize a protein is referred to as translation.

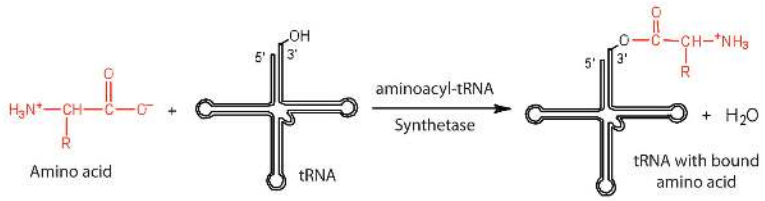


Figure 10.5.1: Binding of an Amino Acid to Its tRNA

Before an amino acid can be incorporated into a polypeptide chain, it must be attached to its unique tRNA. This crucial process requires an enzyme known as aminoacyl-tRNA synthetase (Figure 10.5.1). There is a specific aminoacyl-tRNA synthetase for each amino acid. This high degree of specificity is vital to the incorporation of the correct amino acid into a protein. After the amino acid molecule has been bound to its tRNA carrier, protein synthesis can take place. Figure 10.5.2 depicts a schematic stepwise representation of this all-important process.

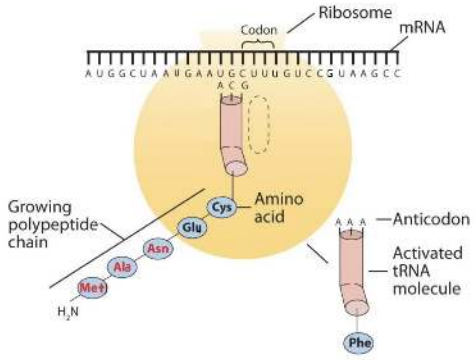


Figure 10.5.2a: The Elongation Steps in Protein Synthesis - Protein synthesis is already in progress at the ribosome. The growing polypeptide chain is attached to the tRNA that brought in the previous amino acid (in this illustration, cys.)

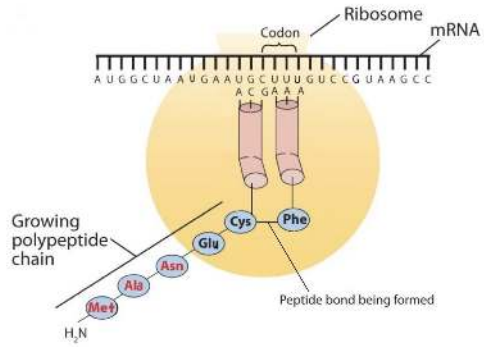


Figure 10.5.2b: The Elongation Steps in Protein Synthesis - An activated tRNA, which has the anticodon AAA, binds to the ribosome next to the previous bound tRNA and interacts with the mRNA molecule though basepairing of the codon and anticodon. The amino acid Phe is being incorporated into the polypeptide chain by the formation of a peptide linkage between the carboxyl group of Cys and the amino acid group of the Phe. This reaction is catalyzed by the enzyme peptidyl transferase, a component of the ribosome.

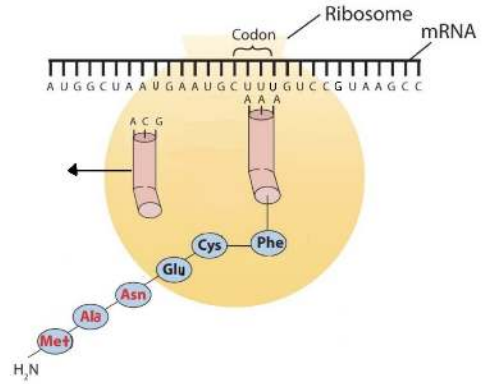


Figure 10.5.2*c*: The Elongation Steps in Protein Synthesis - The Cys-Phe linkage is now complete, and the growing polypeptide chain remains attached to the tRNA for Phe.

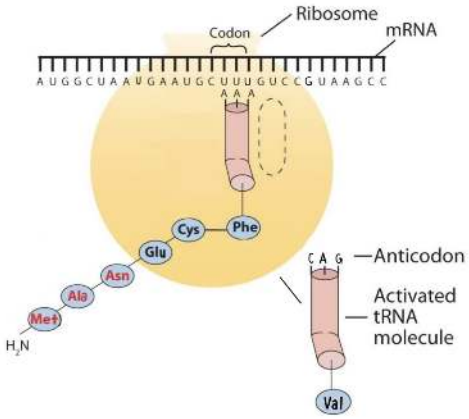


Figure 10.5.2*d*: The Elongation Steps in Protein Synthesis - The ribosome moves to the right along the mRNA strand. This shift brings the next codon, GUC, into its correct position on the surface of the ribosome. Note that an activated tRNA molecule, containing the next amino acid to be attached to the chain is moving to the ribosome. Steps (b)-(d) will be repeated until the ribosome reaches a stop codon.

Early experimenters were faced with the task of determining which of the 64 possible codons stood for each of the 20 amino acids. The cracking of the genetic code was the joint accomplishment of several well-known geneticists—notably Har Khorana, Marshall Nirenberg, Philip Leder, and Severo Ochoa—from 1961 to 1964. The genetic dictionary they compiled, summarized in Figure 10.5.3, shows that 61 codons code for amino acids, and 3 codons serve as signals for the termination of polypeptide synthesis (much like the period at the end of a sentence). Notice that only methionine (AUG) and tryptophan (UGG) have single codons. All other amino acids have two or more codons.

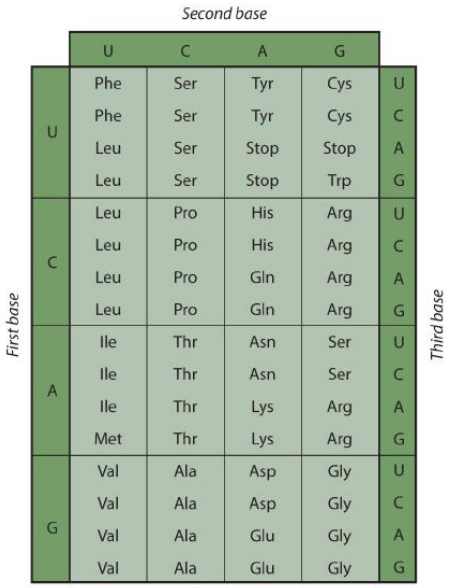


Figure **10.5.3**: The Genetic Code

Example 10.5.1: Using the Genetic Code

A portion of an mRNA molecule has the sequence 5′-AUGCCACGAGUUGAC-3′. What amino acid sequence does this code for?

Solution

Use Figure **10.5.3** to determine what amino acid each set of three nucleotides (codon) codes for. Remember that the sequence is read starting from the 5′ end and that a protein is synthesized starting with the N-terminal amino acid. The sequence 5′-AUGCCACGAGUUGAC-3′ codes for met-pro-arg-val-asp.

Exercise 10.5.4

A portion of an RNA molecule has the sequence 5′-AUGCUGAAUUGCGUAGGA-3′. What amino acid sequence does this code for?

Further experimentation threw much light on the nature of the genetic code, as follows:

1. The code is virtually universal; animal, plant, and bacterial cells use the same codons to specify each amino acid (with a few exceptions).
2. The code is “degenerate”; in all but two cases (methionine and tryptophan), more than one triplet codes for a given amino acid.
3. The first two bases of each codon are most significant; the third base often varies. This suggests that a change in the third base by a mutation may still permit the correct incorporation of a given amino acid into a protein. The third base is sometimes called the “wobble” base.
4. The code is continuous and nonoverlapping; there are *no* nucleotides between codons, and adjacent codons do not overlap.
5. The three termination codons are read by special proteins called release factors, which signal the end of the translation process.
6. The codon AUG codes for methionine and is also the initiation codon. Thus methionine is the first amino acid in each newly synthesized polypeptide. This first amino acid is usually removed enzymatically before the polypeptide chain is completed; the vast majority of polypeptides do not begin with methionine.

Summary

In translation, the information in mRNA directs the order of amino acids in protein synthesis. A set of three nucleotides (codon) codes for a specific amino acid.

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10.6: Mutations and Genetic Diseases

Learning Objectives

- To describe the causes of genetic mutations and how they lead to genetic diseases.

We have seen that the sequence of nucleotides in a cell's deoxyribonucleic acid (DNA) is what ultimately determines the sequence of amino acids in proteins made by the cell and thus is critical for the proper functioning of the cell. On rare occasions, however, the nucleotide sequence in DNA may be modified either spontaneously (by errors during replication, occurring approximately once for every 10 billion nucleotides) or from exposure to heat, radiation, or certain chemicals. Any chemical or physical change that alters the nucleotide sequence in DNA is called a mutation. When a mutation occurs in an egg or sperm cell that then produces a living organism, it will be inherited by all the offspring of that organism.

Common types of mutations include **substitution** (a different nucleotide is substituted), **insertion** (the addition of a new nucleotide), and **deletion** (the loss of a nucleotide). These changes within DNA are called point mutations because only one nucleotide is substituted, added, or deleted (Figure **10.6.1**). Because an insertion or deletion results in a frame-shift that changes the reading of subsequent codons and, therefore, alters the entire amino acid sequence that follows the mutation, insertions and deletions are usually more harmful than a substitution in which only a single amino acid is altered.

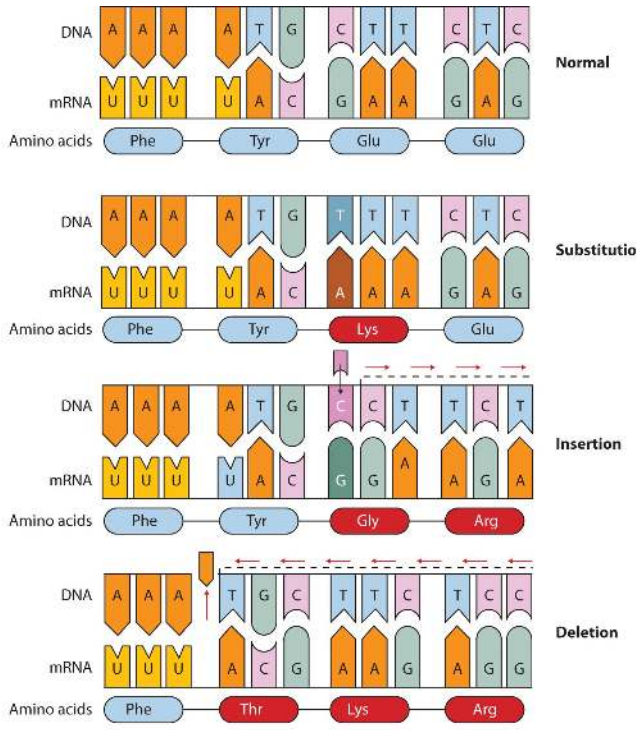


Figure **10.6.1**: Three Types of Point Mutations

The chemical or physical agents that cause mutations are called mutagens. Examples of physical mutagens are ultraviolet (UV) and gamma radiation. Radiation exerts its mutagenic effect either directly or by creating free radicals that in turn have mutagenic effects. Radiation and free radicals can lead to the formation of bonds between nitrogenous bases in DNA. For example, exposure to UV light can result in the formation of a covalent bond between two adjacent thymines on a DNA strand, producing a thymine dimer (Figure **10.6.2**). If not repaired, the dimer prevents the formation of the double helix at the point where it occurs. The genetic disease *xeroderma pigmentosum* is caused by a lack of the enzyme that cuts out the thymine dimers in damaged DNA. Individuals affected by this condition are abnormally sensitive to light and are more prone to skin cancer than normal individuals.

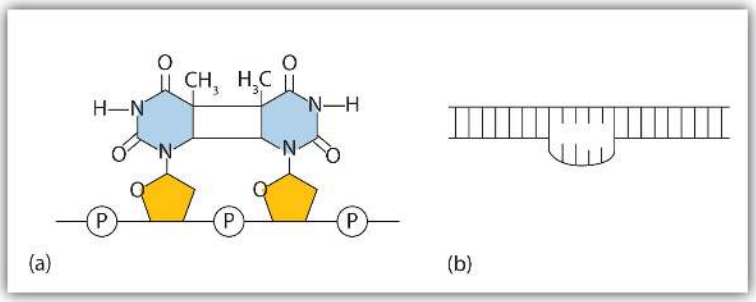


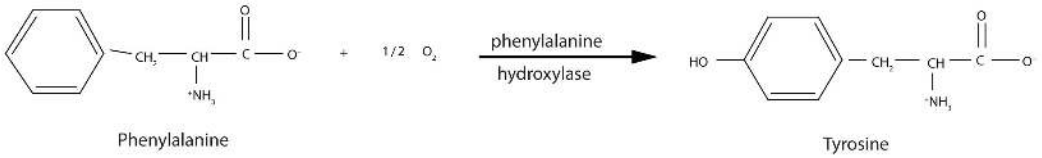
Figure **10.6.2**: An Example of Radiation Damage to DNA. (a) The thymine dimer is formed by the action of UV light. (b) When a defect in the double strand is produced by the thymine dimer, this defect temporarily stops DNA replication, but the dimer can be removed, and the region can be repaired by an enzyme repair system.

Sometimes gene mutations are beneficial, but most of them are detrimental. For example, if a point mutation occurs at a crucial position in a DNA sequence, the affected protein will lack biological activity, perhaps resulting in the death of a cell. In such cases the altered DNA sequence is lost and will not be copied into daughter cells. Nonlethal mutations in an egg or sperm cell may lead to metabolic abnormalities or hereditary diseases. Such diseases are called *inborn errors of metabolism* or genetic diseases. A partial listing of genetic diseases is presented in Figure **10.6.1**, and two specific diseases are discussed in the following sections. In most cases, the defective gene results in a failure to synthesize a particular enzyme.

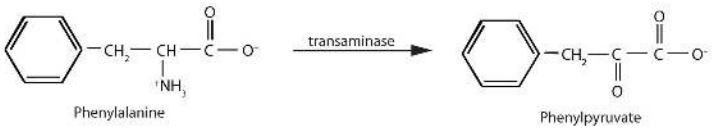
Figure **10.6.1**: Some Representative Genetic Diseases in Humans and the Protein or Enzyme Responsible

Disease	Responsible Protein or Enzyme
alkaptonuria	homogentisic acid oxidase
galactosemia	galactose 1-phosphate uridyl transferase, galactokinase, or UDP galactose epimerase
Gaucher disease	glucocerebrosidase
gout and Lesch-Nyhan syndrome	hypoxanthine-guanine phosphoribosyl transferase
hemophilia	antihemophilic factor (factor VIII) or Christmas factor (factor IX)
homocystinuria	cystathionine synthetase
maple syrup urine disease	branched chain α-keto acid dehydrogenase complex
McArdle syndrome	muscle phosphorylase
Niemann-Pick disease	sphingomyelinase
phenylketonuria (PKU)	phenylalanine hydroxylase
sickle cell anemia	hemoglobin
Tay-Sachs disease	hexosaminidase A
tyrosinemia	fumarylacetoacetate hydrolase or tyrosine aminotransferase
von Gierke disease	glucose 6-phosphatase
Wilson disease	Wilson disease protein

PKU results from the absence of the enzyme phenylalanine hydroxylase. Without this enzyme, a person cannot convert phenylalanine to tyrosine, which is the precursor of the neurotransmitters dopamine and norepinephrine as well as the skin pigment melanin.



When this reaction cannot occur, phenylalanine accumulates and is then converted to higher than normal quantities of phenylpyruvate. The disease acquired its name from the high levels of phenylpyruvate (a phenyl ketone) in urine. Excessive amounts of phenylpyruvate impair normal brain development, which causes severe mental retardation.



PKU may be diagnosed by assaying a sample of blood or urine for phenylalanine or one of its metabolites. Medical authorities recommend testing every newborn's blood for phenylalanine within 24 h to 3 weeks after birth. If the condition is detected, mental retardation can be prevented by immediately placing the infant on a diet containing little or no phenylalanine. Because phenylalanine is plentiful in naturally produced proteins, the low-phenylalanine diet depends on a synthetic protein substitute plus very small measured amounts of naturally produced foods. Before dietary treatment was introduced in the early 1960s, severe mental retardation was a common outcome for children with PKU. Prior to the 1960s, 85% of patients with PKU had an intelligence quotient (IQ) less than 40, and 37% had IQ scores below 10. Since the introduction of dietary treatments, however, over 95% of children with PKU have developed normal or near-normal intelligence. The incidence of PKU in newborns is about 1 in 12,000 in North America.

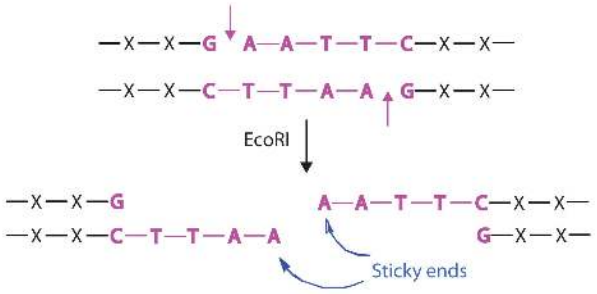
> *Every state in the United States has mandated that screening for PKU be provided to all newborns.*

Several genetic diseases are collectively categorized as *lipid-storage diseases*. Lipids are constantly being synthesized and broken down in the body, so if the enzymes that catalyze lipid degradation are missing, the lipids tend to accumulate and cause a variety of medical problems. When a genetic mutation occurs in the gene for the enzyme hexosaminidase A, for example, gangliosides cannot be degraded but accumulate in brain tissue, causing the ganglion cells of the brain to become greatly enlarged and nonfunctional. This genetic disease, known as *Tay-Sachs disease*, leads to a regression in development, dementia, paralysis, and blindness, with death usually occurring before the age of three. There is currently no treatment, but Tay-Sachs disease can be diagnosed in a fetus by assaying the amniotic fluid (amniocentesis) for hexosaminidase A. A blood test can identify Tay-Sachs carriers—people who inherit a defective gene from only one rather than both parents—because they produce only half the normal amount of hexosaminidase A, although they do not exhibit symptoms of the disease.

Looking Closer: Recombinant DNA Technology

More than 3,000 human diseases have been shown to have a genetic component, caused or in some way modulated by the person's genetic composition. Moreover, in the last decade or so, researchers have succeeded in identifying many of the genes and even mutations that are responsible for specific genetic diseases. Now scientists have found ways of identifying and isolating genes that have specific biological functions and placing those genes in another organism, such as a bacterium, which can be easily grown in culture. With these techniques, known as *recombinant DNA technology*, the ability to cure many serious genetic diseases appears to be within our grasp.

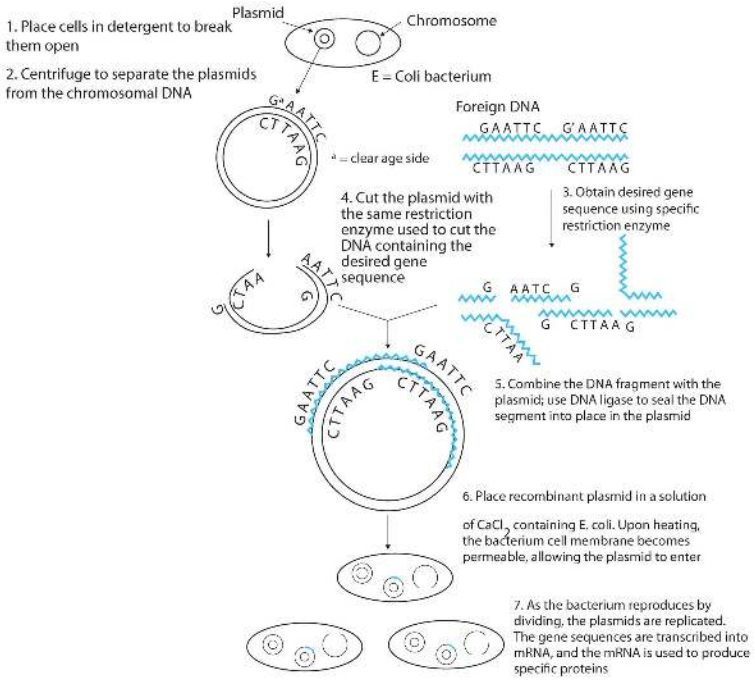
Isolating the specific gene or genes that cause a particular genetic disease is a monumental task. One reason for the difficulty is the enormous amount of a cell's DNA, only a minute portion of which contains the gene sequence. Thus, the first task is to obtain smaller pieces of DNA that can be more easily handled. Fortunately, researchers are able to use *restriction enzymes* (also known as restriction endonucleases), discovered in 1970, which are enzymes that cut DNA at specific, known nucleotide sequences, yielding DNA fragments of shorter length. For example, the restriction enzyme *EcoRI* recognizes the nucleotide sequence shown here and cuts both DNA strands as indicated:



Once a DNA strand has been fragmented, it must be cloned; that is, multiple identical copies of each DNA fragment are produced to make sure there are sufficient amounts of each to detect and manipulate in the laboratory. Cloning is accomplished by inserting the individual DNA fragments into phages (bacterial viruses) that can enter bacterial cells and be replicated. When a bacterial cell infected by the modified phage is placed in an appropriate culture medium, it forms a colony of cells, all containing copies of the original DNA fragment. This technique is used to produce many bacterial colonies, each containing a different DNA fragment. The result is a *DNA library*, a collection of bacterial colonies that together contain the entire genome of a particular organism.

The next task is to screen the DNA library to determine which bacterial colony (or colonies) has incorporated the DNA fragment containing the desired gene. A short piece of DNA, known as a *hybridization probe*, which has a nucleotide sequence complementary to a known sequence in the gene, is synthesized, and a radioactive phosphate group is added to it as a "tag." You might be wondering how researchers are able to prepare such a probe if the gene has not yet been isolated. One way is to use a segment of the desired gene isolated from another organism. An alternative method depends on knowing all or part of the amino acid sequence of the protein produced by the gene of interest: the amino acid sequence is used to produce an approximate genetic code for the gene, and this nucleotide sequence is then produced synthetically. (The amino acid sequence used is carefully chosen to include, if possible, many amino acids such as methionine and tryptophan, which have only a single codon each.)

After a probe identifies a colony containing the desired gene, the DNA fragment is clipped out, again using restriction enzymes, and spliced into another replicating entity, usually a plasmid. *Plasmids* are tiny mini-chromosomes found in many bacteria, such as *Escherichia coli* (*E. coli*). A recombined plasmid would then be inserted into the host organism (usually the bacterium *E. coli*), where it would go to work to produce the desired protein.



Proponents of recombinant DNA research are excited about its great potential benefits. An example is the production of human growth hormone, which is used to treat children who fail to grow properly. Formerly, human growth hormone was available only in tiny amounts obtained from cadavers. Now it is readily available through recombinant DNA technology. Another gene that has been cloned is the gene for epidermal growth factor, which stimulates the growth of skin cells and can be used to speed the healing of burns and other skin wounds. Recombinant techniques are also a powerful research tool, providing enormous aid to scientists as they map and sequence genes and determine the functions of different segments of an organism's DNA.

In addition to advancements in the ongoing treatment of genetic diseases, recombinant DNA technology may actually lead to cures. When appropriate genes are successfully inserted into *E. coli*, the bacteria can become miniature pharmaceutical factories, producing great quantities of insulin for people with diabetes, clotting factor for people with hemophilia, missing enzymes, hormones, vitamins, antibodies, vaccines, and so on. Recent accomplishments include the production in *E. coli* of recombinant DNA molecules containing synthetic genes for tissue plasminogen activator, a clot-dissolving enzyme that can rescue heart attack victims, as well as the production of vaccines against hepatitis B (humans) and hoof-and-mouth disease (cattle).

Scientists have used other bacteria besides *E. coli* in gene-splicing experiments and also yeast and fungi. Plant molecular biologists use a bacterial plasmid to introduce genes for several foreign proteins (including animal proteins) into plants. The bacterium is *Agrobacterium tumefaciens*, which can cause tumors in many plants, but which can be treated so that its tumor-causing ability is eliminated. One practical application of its plasmids would be to enhance a plant's nutritional value by transferring into it the gene necessary for the synthesis of an amino acid in which the plant is normally deficient (for example, transferring the gene for methionine synthesis into pinto beans, which normally do not synthesize high levels of methionine).

> Restriction enzymes have been isolated from a number of bacteria and are named after the bacterium of origin. *EcoRI* is a restriction enzyme obtained from the R strain of *E. coli*. The roman numeral I indicates that it was the first restriction enzyme obtained from this strain of bacteria.

Summary

- The nucleotide sequence in DNA may be modified either spontaneously or from exposure to heat, radiation, or certain chemicals and can lead to mutations.
- Mutagens are the chemical or physical agents that cause mutations.
- Genetic diseases are hereditary diseases that occur because of a mutation in a critical gene.

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10.7: Viruses

Learning Objectives

- To explain how viruses reproduce in cells.

Viruses are visible only under an electron microscope. They come in a variety of shapes, ranging from spherical to rod shaped. The fact that they contain either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA)—*but never both*—allows them to be divided into two major classes: DNA viruses and RNA viruses (Figure **10.7.1**).

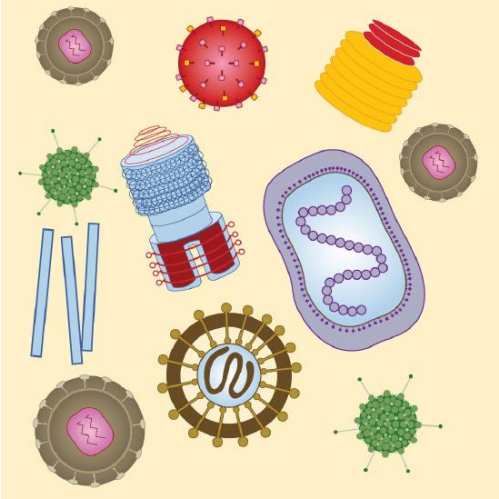


Figure **10.7.1**: Viruses. Viruses come in a variety of shapes that are determined by their protein coats.

Most *RNA viruses* use their nucleic acids in much the same way as the DNA viruses, penetrating a host cell and inducing it to replicate the viral RNA and synthesize viral proteins. The new RNA strands and viral proteins are then assembled into new viruses. Some RNA viruses, however, called retroviruses (Figure **10.7.2**), synthesize DNA in the host cell, in a process that is the reverse of the DNA-to-RNA transcription that normally occurs in cells. The synthesis of DNA from an RNA template is catalyzed by the enzyme reverse transcriptase.

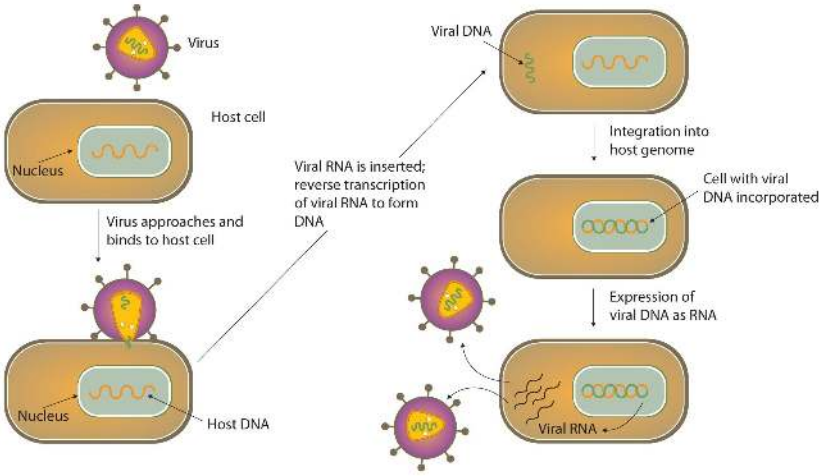
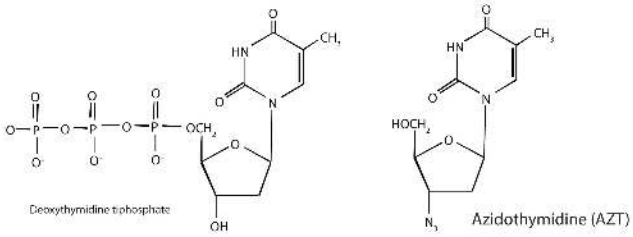
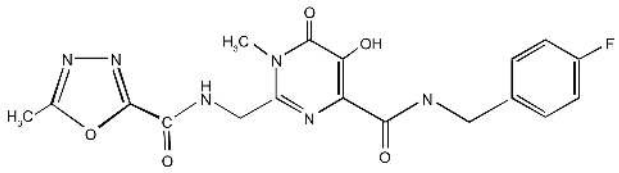


Figure **10.7.2**: Life Cycle of a Retrovirus

In 1987, **azidothymidine** (AZT, also known as zidovudine or the brand name Retrovir) became the first drug approved for the treatment of AIDS. It works by binding to reverse transcriptase in place of deoxythymidine triphosphate, after which, because AZT does not have a 3′OH group, further replication is blocked. In the past 10 years, several other drugs have been approved that also act by inhibiting the viral reverse transcriptase.



Raltegravir (Isentress) is a newer anti-AIDS drug that was approved by the FDA in October 2007. This drug inhibits the integrase enzyme that is needed to integrate the HIV DNA into cellular DNA, an essential step in the production of more HIV particles.



A major problem in treating HIV infections is that the virus can become resistant to any of these drugs. One way to combat the problem has been to administer a “cocktail” of drugs, typically a combination of two reverse transcriptase inhibitors along with a protease inhibitor. These treatments can significantly reduce the amount of HIV in an infected person.

Career Focus: Genetics Counselor

A genetics counselor works with individuals and families who have birth defects or genetic disorders or a family history of a disease, such as cancer, with a genetic link. A genetics counselor may work in a variety of health-care settings (such as a hospital) to obtain family medical and reproductive histories; explain how genetic conditions are inherited; explain the causes, diagnosis, and care of these conditions; interpret the results of genetic tests; and aid the individual or family in making decisions regarding genetic diseases or conditions. A certified genetics counselor must obtain a master’s degree from an accredited program. Applicants to these graduate programs usually have an undergraduate degree in biology, psychology, or genetics.



Photo courtesy of the United States National Institutes for Health, commons.wikimedia.org/wiki/File:Geneticcounseling.jpg.

Summary

Viruses are very small infectious agents that contain either DNA or RNA as their genetic material. The human immunodeficiency virus (HIV) causes acquired immunodeficiency syndrome (AIDS).

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10.E: Nucleic Acids (Exercises)

19.1: Nucleotides

Concept Review Exercises

1. Identify the three molecules needed to form the nucleotides in each nucleic acid.
   a. DNA
   b. RNA
2. Classify each compound as a pentose sugar, a purine, or a pyrimidine.
   a. adenine
   b. guanine
   c. deoxyribose
   d. thymine
   e. ribose
   f. cytosine

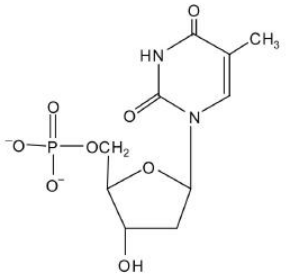
Answers

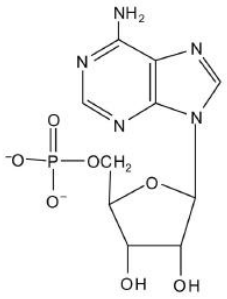
1. a. nitrogenous base (adenine, guanine, cytosine, and thymine), 2-deoxyribose, and H_3PO_4
   b. nitrogenous base (adenine, guanine, cytosine, and uracil), ribose, and H_3PO_4
2. a. purine
   b. purine
   c. pentose sugar
   d. pyrimidine
   e. pentose sugar
   f. pyrimidine

Exercises

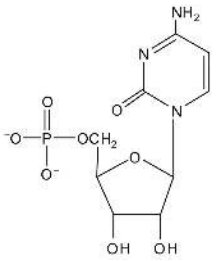
1. What is the sugar unit in each nucleic acid?
   a. RNA
   b. DNA
2. Identify the major nitrogenous bases in each nucleic acid.
   a. DNA
   b. RNA
3. For each structure, circle the sugar unit and identify the nucleotide as a ribonucleotide or a deoxyribonucleotide.

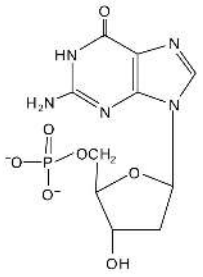
   a.



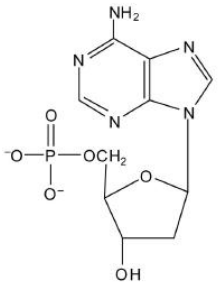
b. 

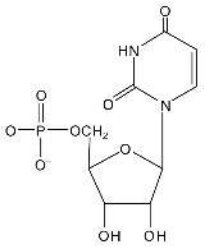
4. For each structure, circle the sugar unit and identify the nucleotide as a ribonucleotide or a deoxyribonucleotide.

a. 

b. 

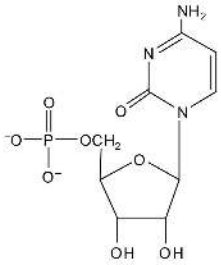
5. For each structure, circle the nitrogenous base and identify it as a purine or pyrimidine.

a. 

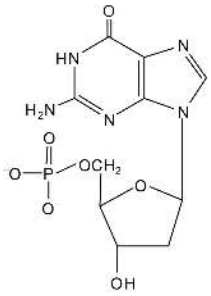
b. 

6. For each structure, circle the nitrogenous base and identify it as a purine or pyrimidine.

a.



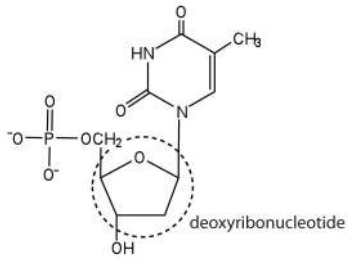
b.



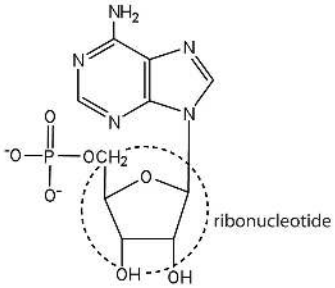
Answers

1. a. ribose
   b. deoxyribose

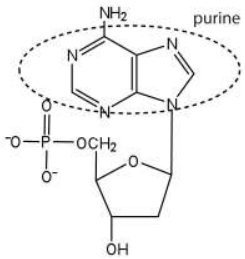
3. a.



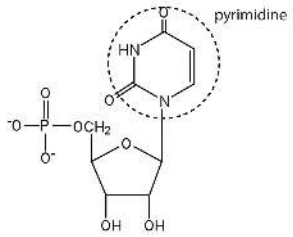
b.



a.



b.



19.2: Nucleic Acid Structure

Concept Review Exercises

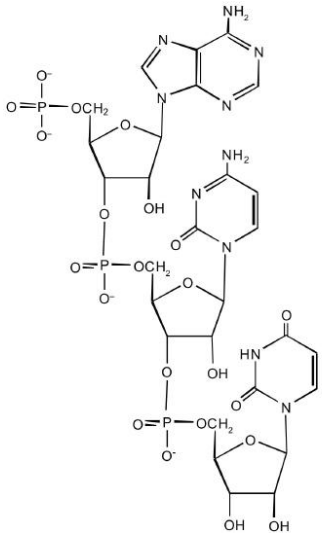
1. a. Name the two kinds of nucleic acids.
   b. Which type of nucleic acid stores genetic information in the cell?
2. What are complementary bases?
3. Why is it structurally important that a purine base always pair with a pyrimidine base in the DNA double helix?

Answers

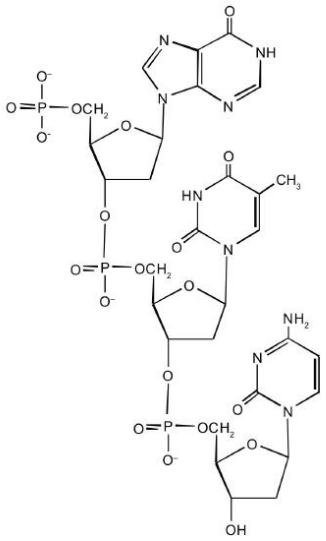
1. a. deoxyribonucleic acid (DNA) and ribonucleic acid (RNA)
   b. DNA
2. the specific base pairings in the DNA double helix in which guanine is paired with cytosine and adenine is paired with thymine
3. The width of the DNA double helix is kept at a constant width, rather than narrowing (if two pyrimidines were across from each other) or widening (if two purines were across from each other).

Exercises

1. For this short RNA segment,
   a. identify the 5′ end and the 3′ end of the molecule.
   b. circle the atoms that comprise the backbone of the nucleic acid chain.
   c. write the nucleotide sequence of this RNA segment.



2. For this short DNA segment,
   a. identify the 5′ end and the 3′ end of the molecule.
   b. circle the atoms that comprise the backbone of the nucleic acid chain.
   c. write the nucleotide sequence of this DNA segment.

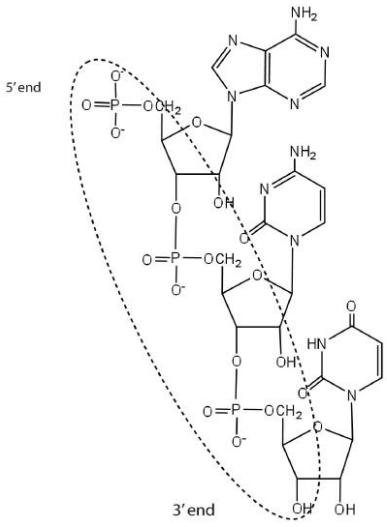


3. Which nitrogenous base in DNA pairs with each nitrogenous base?
    a. cytosine
    b. adenine
    c. guanine
    d. thymine
4. Which nitrogenous base in RNA pairs with each nitrogenous base?
    a. cytosine
    b. adenine
    c. guanine
    d. thymine
5. How many hydrogen bonds can form between the two strands in the short DNA segment shown below?

    5′ ATGCGACTA 3′ 3′ TACGCTGAT 5′
6. How many hydrogen bonds can form between the two strands in the short DNA segment shown below?

    5′ CGATGAGCC 3′ 3′ GCTACTCGG 5′

Answers

1. 

    c. ACU

3. a. guanine
   b. thymine
   c. cytosine
   d. adenine

5. 22 (2 between each AT base pair and 3 between each GC base pair)

19.3: Replication and Expression of Genetic Information

Concept Review Exercises

1. In DNA replication, a parent DNA molecule produces two daughter molecules. What is the fate of each strand of the parent DNA double helix?
2. What is the role of DNA in transcription? What is produced in transcription?
3. Which type of RNA contains the codon? Which type of RNA contains the anticodon?

Answers

1. Each strand of the parent DNA double helix remains associated with the newly synthesized DNA strand.
2. DNA serves as a template for the synthesis of an RNA strand (the product of transcription).
3. codon: mRNA; anticodon: tRNA

Exercises

1. Describe how replication and transcription are similar.
2. Describe how replication and transcription differ.
3. A portion of the coding strand for a given gene has the sequence 5′-ATGAGCGACTTTGCGGGATTA-3′.
   a. What is the sequence of complementary template strand?
   b. What is the sequence of the mRNA that would be produced during transcription from this segment of DNA?
4. A portion of the coding strand for a given gene has the sequence 5′-ATGGCAATCCTCAAACGCTGT-3′.
   a. What is the sequence of complementary template strand?
   b. What is the sequence of the mRNA that would be produced during transcription from this segment of DNA?

Answers

1. Both processes require a template from which a complementary strand is synthesized.

3.

a. 3′-TACTCGCTGAAACGCCCTAAT-5′
b. 5′-AUGAGCGACUUUGCGGGAUUA-3′

19.4: Protein Synthesis and the Genetic Code

Concept Review Exercises

1. What are the roles of mRNA and tRNA in protein synthesis?
2. What is the initiation codon?
3. What are the termination codons and how are they recognized?

Answers

1. mRNA provides the code that determines the order of amino acids in the protein; tRNA transports the amino acids to the ribosome to incorporate into the growing protein chain.
2. AUG
3. UAA, UAG, and UGA; they are recognized by special proteins called release factors, which signal the end of the translation process.

Exercises

1. Write the anticodon on tRNA that would pair with each mRNA codon.
   a. 5′-UUU-3′
   b. 5′-CAU-3′
   c. 5′-AGC-3′
   d. 5′-CCG-3′
2. Write the codon on mRNA that would pair with each tRNA anticodon.
   a. 5′-UUG-3′
   b. 5′-GAA-3′
   c. 5′-UCC-3′
   d. 5′-CAC-3′
3. The peptide hormone oxytocin contains 9 amino acid units. What is the minimum number of nucleotides needed to code for this peptide?
4. Myoglobin, a protein that stores oxygen in muscle cells, has been purified from a number of organisms. The protein from a sperm whale is composed of 153 amino acid units. What is the minimum number of nucleotides that must be present in the mRNA that codes for this protein?
5. Use Figure **10.*E*.3** to identify the amino acids carried by each tRNA molecule in Exercise 1.
6. Use Figure **10.*E*.3** to identify the amino acids carried by each tRNA molecule in Exercise 2.
7. Use Figure **10.*E*.3** to determine the amino acid sequence produced from this mRNA sequence: 5′-AUGAGCGACUUUGCGGGAUUA-3′.
8. Use Figure **10.*E*.3** to determine the amino acid sequence produced from this mRNA sequence: 5′-AUGGCAAUCCUCAAACGCUGU-3′

Answers

1. a. 3′-AAA-5′
   b. 3′-GUA-5′
   c. 3′-UCG-5′
   d. 3′-GGC-5′
3. 27 nucleotides (3 nucleotides/codon)
5. 1a: phenyalanine; 1b: histidine; 1c: serine; 1d: proline
7. met-ser-asp-phe-ala-gly-leu

19.5: Mutations and Genetic Diseases

Concept Review Exercises

1. a. What effect can UV radiation have on DNA?
   b. Is UV radiation an example of a physical mutagen or a chemical mutagen?
2. a. What causes PKU?
   b. How is PKU detected and treated?

Answers

1. a. It can lead to the formation of a covalent bond between two adjacent thymines on a DNA strand, producing a thymine dimer.
   b. physical mutagen
2. a. the absence of the enzyme phenylalanine hydroxylase
   b. PKU is diagnosed by assaying a sample of blood or urine for phenylalanine or one of its metabolites; treatment calls for an individual to be placed on a diet containing little or no phenylalanine.

Exercises

1. A portion of the coding strand of a gene was found to have the sequence 5′-ATGAGCGACTTTCGCCCATTA-3′. A mutation occurred in the gene, making the sequence 5′-ATGAGCGACCTTCGCCCATTA-3′.
   a. Identify the mutation as a substitution, an insertion, or a deletion.
   b. What effect would the mutation have on the amino acid sequence of the protein obtained from this mutated gene (use Figure 19.14)?
2. A portion of the coding strand of a gene was found to have the sequence 5′-ATGGCAATCCTCAAACGCTGT-3′. A mutation occurred in the gene, making the sequence 5′-ATGGCAATCCTCAACGCTGT-3′.
   a. Identify the mutation as a substitution, an insertion, or a deletion.
   b. What effect would the mutation have on the amino acid sequence of the protein obtained from this mutated gene (use Figure 19.14)?
3. a. What is a mutagen?
   b. Give two examples of mutagens.
4. For each genetic disease, indicate which enzyme is lacking or defective and the characteristic symptoms of the disease.
   a. PKU
   b. Tay-Sachs disease

Answers

1. a. substitution
   b. Phenylalanine (UUU) would be replaced with leucine (CUU).
3. a. a chemical or physical agent that can cause a mutation
   b. UV radiation and gamma radiation (answers will vary)

19.6: Viruses

Questions

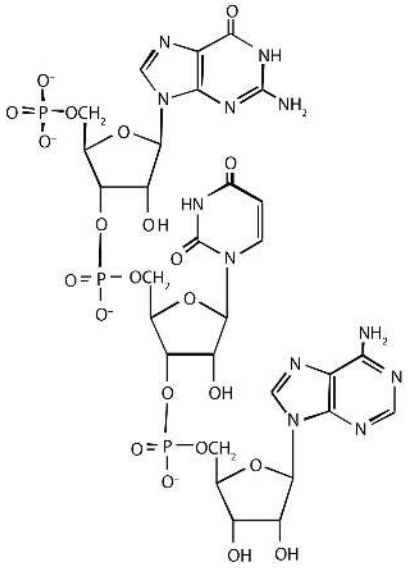
1. Describe the general structure of a virus.
2. How does a DNA virus differ from an RNA virus?
3. Why is HIV known as a retrovirus?
4. Describe how a DNA virus invades and destroys a cell.
5. a. Describe how an RNA virus invades and destroys a cell.
   b. How does this differ from a DNA virus?
6. What HIV enzyme does AZT inhibit?
7. What HIV enzyme does raltegravir inhibit?

Answers

1. A virus consists of a central core of nucleic acid enclosed in a protective shell of proteins. There may be lipid or carbohydrate molecules on the surface.
2. A DNA virus has DNA as its genetic material, while an RNA virus has RNA as its genetic material.
3. In a cell, a retrovirus synthesizes a DNA copy of its RNA genetic material.
4. The DNA virus enters a host cell and induces the cell to replicate the viral DNA and produce viral proteins. These proteins and DNA assemble into new viruses that are released by the host cell, which may die in the process.
5. -
6. reverse transcriptase
7. -

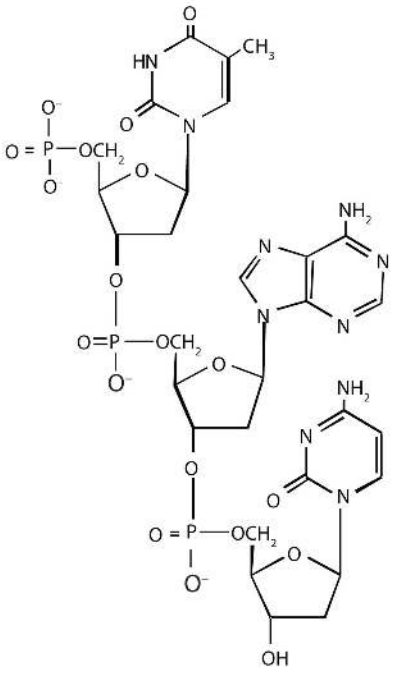
Additional Exercises

1. For this nucleic acid segment,



   a. classify this segment as RNA or DNA and justify your choice.
   b. determine the sequence of this segment, labeling the 5′ and 3′ ends.

2. For this nucleic acid segment,



   a. classify this segment as RNA or DNA and justify your choice.
   b. determine the sequence of this segment, labeling the 5′ and 3′ ends.

3. One of the key pieces of information that Watson and Crick used in determining the secondary structure of DNA came from experiments done by E. Chargaff, in which he studied the nucleotide composition of DNA from many different species. Chargaff noted that the molar quantity of A was always approximately equal to the molar quantity of T, and the molar quantity of C was always approximately equal to the molar quantity of G. How were Chargaff's results explained by the structural model of DNA proposed by Watson and Crick?

4. Suppose Chargaff (see Exercise 3) had used RNA instead of DNA. Would his results have been the same; that is, would the molar quantity of A approximately equal the molar quantity of T? Explain.
5. In the DNA segment

   5′-ATGAGGCATGAGACG-3′ (coding strand) 3′-TACTCCGTACTCTGC-5′ (template strand)

   a. What products would be formed from the segment's replication?
   b. Write the mRNA sequence that would be obtained from the segment's transcription.
   c. What is the amino acid sequence of the peptide produced from the mRNA in Exercise 5b?
6. In the DNA segment

   5′-ATGACGGTTTACTAAGCC-3′ (coding strand) 3′-TACTGCCAAATGATTCGG-5′ (template strand)

   a. What products would be formed from the segment's replication?
   b. Write the mRNA sequence that would be obtained from the segment's transcription.
   c. What is the amino acid sequence of the peptide produced from the mRNA in Exercise 6b?
7. A hypothetical protein has a molar mass of 23,300 Da. Assume that the average molar mass of an amino acid is 120.

   a. How many amino acids are present in this hypothetical protein?
   b. What is the minimum number of codons present in the mRNA that codes for this protein?
   c. What is the minimum number of nucleotides needed to code for this protein?
8. Bradykinin is a potent peptide hormone composed of nine amino acids that lowers blood pressure.

   a. The amino acid sequence for bradykinin is arg-pro-pro-gly-phe-ser-pro-phe-arg. Postulate a base sequence in the mRNA that would direct the synthesis of this hormone. Include an initiation codon and a termination codon.
   b. What is the nucleotide sequence of the DNA that codes for this mRNA?
9. A particular DNA coding segment is ACGTTAGCCCCAGCT.

   a. Write the sequence of nucleotides in the corresponding mRNA.
   b. Determine the amino acid sequence formed from the mRNA in Exercise 9a during translation.
   c. What amino acid sequence results from each of the following mutations?

      a. replacement of the underlined guanine by adenine
      b. insertion of thymine immediately after the underlined guanine
      c. deletion of the underlined guanine
10. A particular DNA coding segment is TACGACGTAACAAGC.

    a. Write the sequence of nucleotides in the corresponding mRNA.
    b. Determine the amino acid sequence formed from the mRNA in Exercise 10a during translation.
    c. What amino acid sequence results from each of the following mutations?

       a. replacement of the underlined guanine by adenine
       b. replacement of the underlined adenine by thymine
11. Two possible point mutations are the substitution of lysine for leucine *or* the substitution of serine for threonine. Which is likely to be more serious and why?
12. Two possible point mutations are the substitution of valine for leucine *or* the substitution of glutamic acid for histidine. Which is likely to be more serious and why?

Answers

1.

   a. RNA; the sugar is ribose, rather than deoxyribose
   b. 5′-GUA-3′

3. In the DNA structure, because guanine (G) is always paired with cytosine (C) and adenine (A) is always paired with thymine (T), you would expect to have equal amounts of each.

5.

a. Each strand would be replicated, resulting in two double-stranded segments.
b. 5′-AUGAGGCAUGAGACG-3′
c. met-arg-his-glu-thr

7.

a. 194
b. 194
c. 582

9.

a. 5′-ACGUUAGCCCCAGCU-3′
b. thr-leu-ala-pro-ala
c. a. thr-leu-thr-pro-ala
   b. thr-leu-val-pro-ser
   c. thr-leu-pro-gin

11. substitution of lysine for leucine because you are changing from an amino acid with a nonpolar side chain to one that has a positively charged side chain; both serine and threonine, on the other hand, have polar side chains containing the OH group.

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10.S: Nucleic Acids (Summary)

To ensure that you understand the material in this chapter, you should review the meanings of the bold terms in the following summary and ask yourself how they relate to the topics in the chapter.

A cell's hereditary information is encoded in **chromosomes** in the cell's nucleus. Each chromosome is composed of proteins and **deoxyribonucleic acid (DNA)**. The chromosomes contain smaller hereditary units called **genes,** which are relatively short segments of DNA. The hereditary information is expressed or used through the synthesis of **ribonucleic acid (RNA)**. Both **nucleic acids**—DNA and RNA—are polymers composed of monomers known as **nucleotides**, which in turn consist of phosphoric acid (H_3PO_4), a nitrogenous base, and a pentose sugar.

The two types of *nitrogenous bases* most important in nucleic acids are **purines**—adenine (A) and guanine (G)—and **pyrimidines**—cytosine (C), thymine (T), and uracil (U). DNA contains the nitrogenous bases adenine, cytosine, guanine, and thymine, while the bases in RNA are adenine, cytosine, guanine, and uracil. The sugar in the nucleotides of RNA is ribose; the one in DNA is 2-deoxyribose. The sequence of nucleotides in a nucleic acid defines the primary structure of the molecule.

RNA is a single-chain nucleic acid, whereas DNA possesses two nucleic-acid chains intertwined in a secondary structure called a **double helix**. The sugar-phosphate backbone forms the outside the double helix, with the purine and pyrimidine bases tucked inside. Hydrogen bonding between **complementary bases** holds the two strands of the double helix together; A always pairs with T and C always pairs with G.

Cell growth requires **replication**, or reproduction of the cell's DNA. The double helix unwinds, and hydrogen bonding between complementary bases breaks so that there are two single strands of DNA, and each strand is a *template* for the synthesis of a new strand. For protein synthesis, three types of RNA are needed: *messenger RNA* (mRNA), *ribosomal RNA* (rRNA), and *transfer RNA* (tRNA). All are made from a DNA template by a process called **transcription**. The double helix uncoils, and ribonucleotides base-pair to the deoxyribonucleotides on one DNA strand; however, RNA is produced using *uracil* rather than thymine. Once the RNA is formed, it dissociates from the template and leaves the nucleus, and the DNA double helix reforms.

Translation is the process in which proteins are synthesized from the information in mRNA. It occurs at structures called **ribosomes**, which are located outside the nucleus and are composed of rRNA and protein. The 64 possible three-nucleotide combinations of the 4 nucleotides of DNA constitute the **genetic code** that dictates the sequence in which amino acids are joined to make proteins. Each three-nucleotide sequence on mRNA is a **codon**. Each kind of tRNA molecule binds a specific amino acid and has a site containing a three-nucleotide sequence called an **anticodon**.

The general term for any change in the genetic code in an organism's DNA is **mutation**. A change in which a single base is substituted, inserted, or deleted is a **point mutation**. The chemical and/or physical agents that cause mutations are called **mutagens**. Diseases that occur due to mutations in critical DNA sequences are referred to as **genetic diseases**.

Viruses are infectious agents composed of a tightly packed central core of nucleic acids enclosed by a protective shell of proteins. Viruses contain either DNA or RNA as their genetic material but not both. Some RNA viruses, called **retroviruses**, synthesize DNA in the host cell from their RNA genome. The human immunodeficiency virus (HIV) causes acquired immunodeficiency syndrome (AIDS).

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CHAPTER OVERVIEW

11: Energy Metabolism

Metabolism is the set of life-sustaining chemical transformations within the cells of living organisms. The three main purposes of metabolism are the conversion of food/fuel to energy to run cellular processes, the conversion of food/fuel to building blocks for proteins, lipids, nucleic acids, and some carbohydrates, and the elimination of nitrogenous wastes. These enzyme-catalyzed reactions allow organisms to grow and reproduce, maintain their structures, and respond to their environments. Metabolism is usually divided into two categories: **catabolism**, the breaking down of organic matter, for example, by cellular respiration, and **anabolism**, the building up of components of cells such as proteins and nucleic acids. Usually, breaking down releases energy and building up consumes energy.

11.1: Prelude to Energy Metabolism
11.2: ATP- the Universal Energy Currency
11.3: Stage I of Catabolism
11.4: Overview of Stage II of Catabolism
11.5: Stage III of Catabolism
11.6: Stage II of Carbohydrate Catabolism
11.7: Stage II of Lipid Catabolism
11.8: Stage II of Protein Catabolism
11.E: Energy Metabolism (Exercises)
11.S: Energy Metabolism (Summary)

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11.1: Prelude to Energy Metabolism

The discovery of the link between insulin and diabetes led to a period of intense research aimed at understanding exactly how insulin works in the body to regulate glucose levels. Hormones in general act by binding to some protein, known as the hormone's receptor, thus initiating a series of events that lead to a desired outcome. In the early 1970s, the insulin receptor was purified, and researchers began to study what happens after insulin binds to its receptor and how those events are linked to the uptake and metabolism of glucose in cells.

The insulin receptor is located in the cell membrane and consists of four polypeptide chains: two identical chains called α chains and two identical chains called β chains. The α chains, positioned on the outer surface of the membrane, consist of 735 amino acids each and contain the binding site for insulin. The β chains are integral membrane proteins, each composed of 620 amino acids. The binding of insulin to its receptor stimulates the β chains to catalyze the addition of phosphate groups to the specific side chains of tyrosine (referred to as phosphorylation) in the β chains and other cell proteins, leading to the activation of reactions that metabolize glucose. In this chapter we will look at the pathway that breaks down glucose—in response to activation by insulin—for the purpose of providing energy for the cell.

GLmol

Figure **11.1.1**: Model of the Structure of the Insulin Receptor (PDB code 4ZXB).

Life requires energy. Animals, for example, require heat energy to maintain body temperature, mechanical energy to move their limbs, and chemical energy to synthesize the compounds needed by their cells. Living cells remain organized and functioning properly only through a continual supply of energy. But only specific forms of energy can be used. Supplying a plant with energy by holding it in a flame will not prolong its life. On the other hand, a green plant is able to absorb radiant energy from the sun, the most abundant source of energy for life on the earth. Plants use this energy first to form glucose and then to make other carbohydrates, as well as lipids and proteins. Unlike plants, animals cannot directly use the sun's energy to synthesize new compounds. They must eat plants or other animals to get carbohydrates, fats, and proteins and the chemical energy stored in them. Once digested and transported to the cells, the nutrient molecules can be used in either of two ways: as building blocks for making new cell parts or repairing old ones or "burned" for energy.

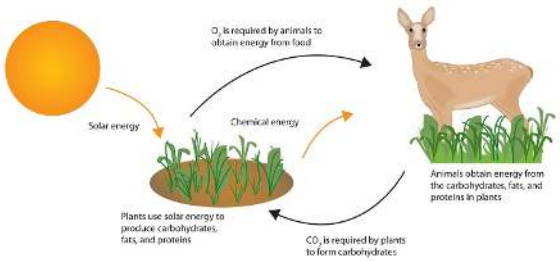


Figure **11.1.2**: Some Energy Transformations in Living Systems. Plants and animals exist in a cycle; each requires products of the other.

The thousands of coordinated chemical reactions that keep cells alive are referred to collectively as **metabolism**. In general, metabolic reactions are divided into two classes: the breaking down of molecules to obtain energy is **catabolism**, and the building of new molecules needed by living systems is **anabolism**.

Definition: Metabolite

Any chemical compound that participates in a metabolic reaction is a *metabolite*.

Most of the energy required by animals is generated from lipids and carbohydrates. These fuels must be oxidized, or "burned," for the energy to be released. The oxidation process ultimately converts the lipid or carbohydrate to carbon dioxide (CO_2) and water (H_2O).

Carbohydrate:

$$C_6H_{12}O_6 + 6\,O_2 \longrightarrow 6\,CO_2 + 6\,H_2O + 670\,\text{kcal}$$

Lipid:

$$C_{16}H_{32}O_2 + 23\,O_2 \longrightarrow 16\,CO_2 + 16\,H_2O + 2{,}385\,\text{kcal}$$

These two equations summarize the biological combustion of a carbohydrate and a lipid by the cell through respiration. **Respiration** is the collective name for all metabolic processes in which gaseous oxygen is used to oxidize organic matter to carbon dioxide, water, and energy.

Like the combustion of the common fuels we burn in our homes and cars (wood, coal, gasoline), respiration uses oxygen from the air to break down complex organic substances to carbon dioxide and water. But the energy released in the burning of wood is manifested entirely in the form of heat, and excess heat energy is not only useless but also injurious to the living cell. Living organisms instead conserve much of the energy respiration releases by channeling it into a series of stepwise reactions that produce adenosine triphosphate (ATP) or other compounds that ultimately lead to the synthesis of ATP. The remainder of the energy is released as heat and manifested as body temperature.

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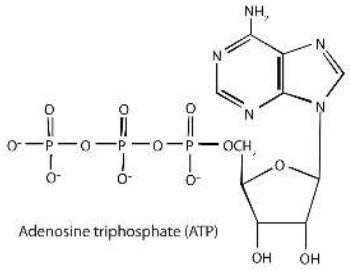
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11.2: ATP- the Universal Energy Currency

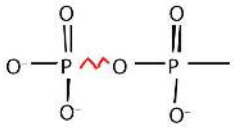
Learning Objectives

- To describe the importance of ATP as a source of energy in living organisms.

Adenosine triphosphate (ATP), a nucleotide composed of adenine, ribose, and three phosphate groups, is perhaps the most important of the so-called energy-rich compounds in a cell. Its concentration in the cell varies from 0.5 to 2.5 mg/mL of cell fluid.



Energy-rich compounds are substances having particular structural features that lead to a release of energy after hydrolysis. As a result, these compounds are able to supply energy for biochemical processes that require energy. The structural feature important in ATP is the phosphoric acid anhydride, or pyrophosphate, linkage:



The pyrophosphate bond, symbolized by a squiggle (~), is hydrolyzed when ATP is converted to adenosine diphosphate (ADP). In this hydrolysis reaction, the products contain less energy than the reactants; there is a release of energy (> 7 kcal/mol). One reason for the amount of energy released is that hydrolysis relieves the electron-electron repulsions experienced by the negatively charged phosphate groups when they are bonded to each other (Figure 20.1.1).

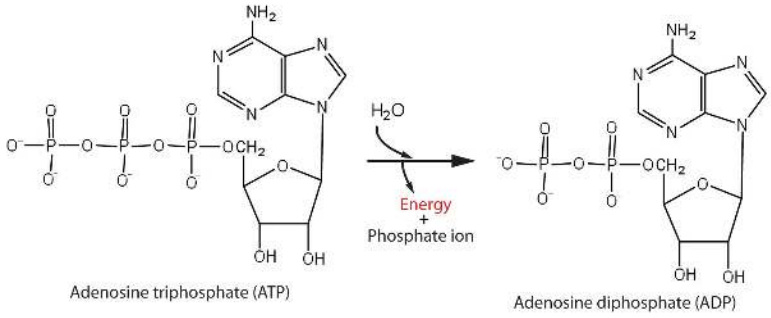


Figure **11.2.1**: Hydrolysis of ATP to Form ADP

Energy is released because the products (ADP and phosphate ion) have less energy than the reactants [ATP and water (H_2O)].

The general equation for ATP hydrolysis is as follows:

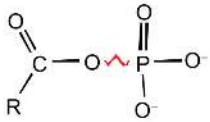
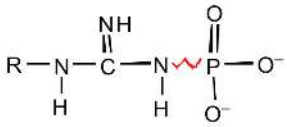
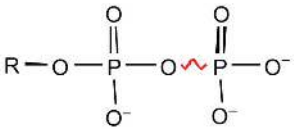
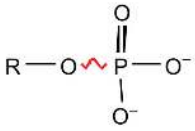
$$ATP + H_2O \rightarrow ADP + P_i + 7.4\ kcal/mol$$

If the hydrolysis of ATP releases energy, its synthesis (from ADP) requires energy. In the cell, ATP is produced by those processes that supply energy to the organism (absorption of radiant energy from the sun in green plants and breakdown of food in animals), and it is hydrolyzed by those processes that require energy (the syntheses of carbohydrates, lipids, proteins; the transmission of nerve impulses; muscle contractions). In fact, ATP is the principal medium of energy exchange in biological systems. Many scientists call it the energy currency of cells.

> *P_i is the symbol for the inorganic phosphate anions $H_2PO_4^-$ and HPO_4^{2-}.*

ATP is not the only high-energy compound needed for metabolism. Several others are listed in Table **11.2.1**. Notice, however, that the energy released when ATP is hydrolyzed is approximately midway between those of the high-energy and the low-energy phosphate compounds. This means that the hydrolysis of ATP can provide energy for the phosphorylation of the compounds below it in the table. For example, the hydrolysis of ATP provides sufficient energy for the phosphorylation of glucose to form glucose 1-phosphate. By the same token, the hydrolysis of compounds, such as creatine phosphate, that appear *above* ATP in the table can provide the energy needed to resynthesize ATP from ADP.

Table **11.2.1**: Energy Released by Hydrolysis of Some Phosphate Compounds

Type	Example	Energy Released (kcal/mol)
acyl phosphate 	1,3-bisphosphoglycerate (BPG)	−11.8
	acetyl phosphate	−11.3
guanidine phosphates 	creatine phosphate	−10.3
	arginine phosphate	−9.1
pyrophosphates 	$PP_{i*} \rightarrow 2P_i$	−7.8
	$ATP \rightarrow AMP + PP_i$	−7.7
	$ATP \rightarrow ADP + P_i$	−7.5
	$ADP \rightarrow AMP + P_i$	−7.5
sugar phosphates 	glucose 1-phosphate	−5.0
	fructose 6-phosphate	−3.8
	$AMP \rightarrow$ adenosine $+ P_i$	−3.4
	glucose 6-phosphate	−3.3
	glycerol 3-phosphate	−2.2

*PP_i is the pyrophosphate ion.

Summary

The hydrolysis of ATP releases energy that can be used for cellular processes that require energy.

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11.3: Stage I of Catabolism

Learning Objectives

- To describe how carbohydrates, fats, and proteins are broken down during digestion.

We have said that animals obtain chemical energy from the food—carbohydrates, fats, and proteins—they eat through reactions defined collectively as *catabolism*. We can think of catabolism as occurring in three stages (Figure **11.3.1**). In stage I, carbohydrates, fats, and proteins are broken down into their individual monomer units: carbohydrates into simple sugars, fats into fatty acids and glycerol, and proteins into amino acids. One part of stage I of catabolism is the breakdown of food molecules by hydrolysis reactions into the individual monomer units—which occurs in the mouth, stomach, and small intestine—and is referred to as digestion.

In stage II, these monomer units (or building blocks) are further broken down through different reaction pathways, one of which produces ATP, to form a common end product that can then be used in stage III to produce even more ATP. In this chapter, we will look at each stage of catabolism—as an overview and in detail.

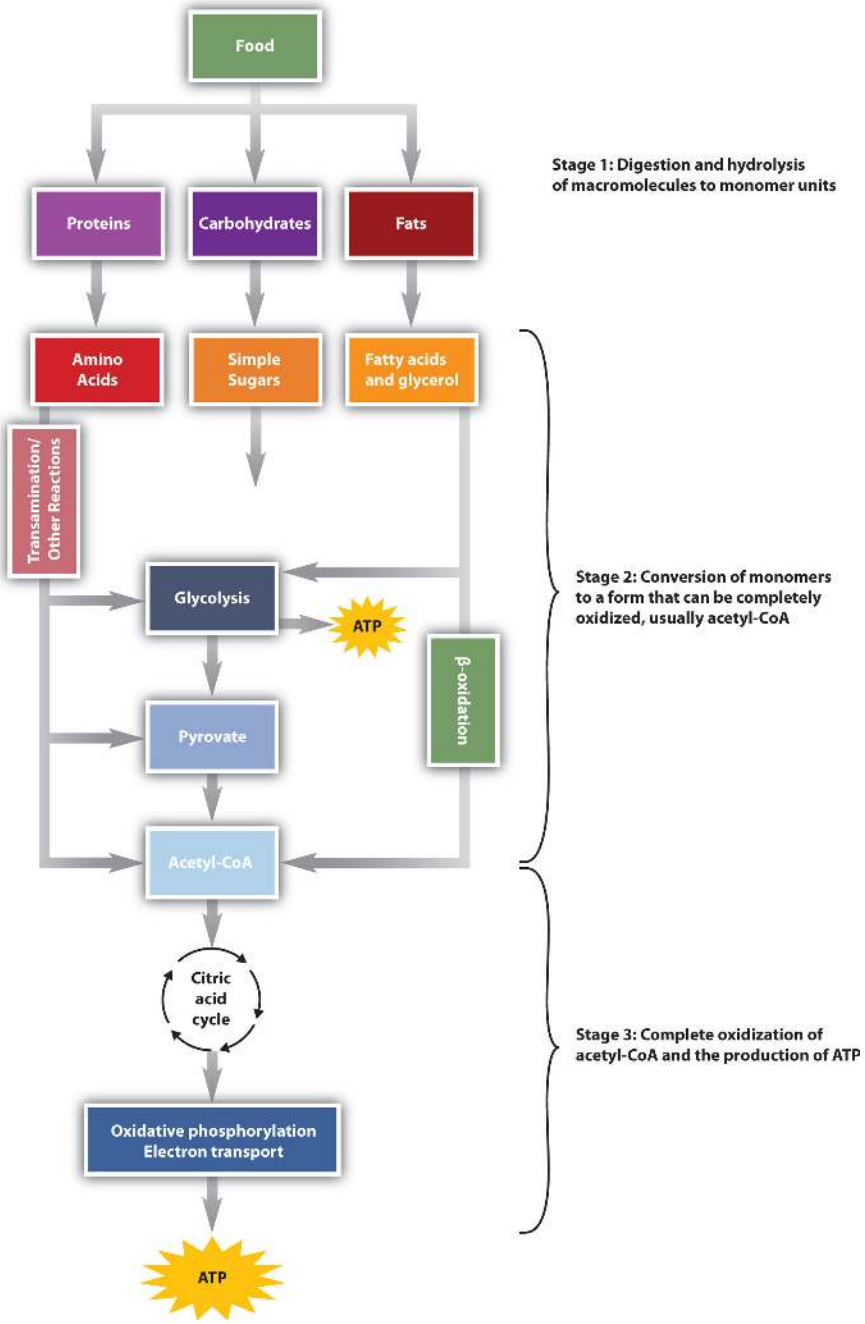


Figure 11.3.1: Energy Conversions

The conversion of food into cellular energy (as ATP) occurs in three stages.

Digestion of Carbohydrates

Carbohydrate digestion begins in the mouth (Figure **11.3.2**) where salivary α-amylase attacks the α-glycosidic linkages in starch, the main carbohydrate ingested by humans. Cleavage of the glycosidic linkages produces a mixture of dextrins, maltose, and glucose. The α-amylase mixed into the food remains active as the food passes through the esophagus, but it is rapidly inactivated in the acidic environment of the stomach.

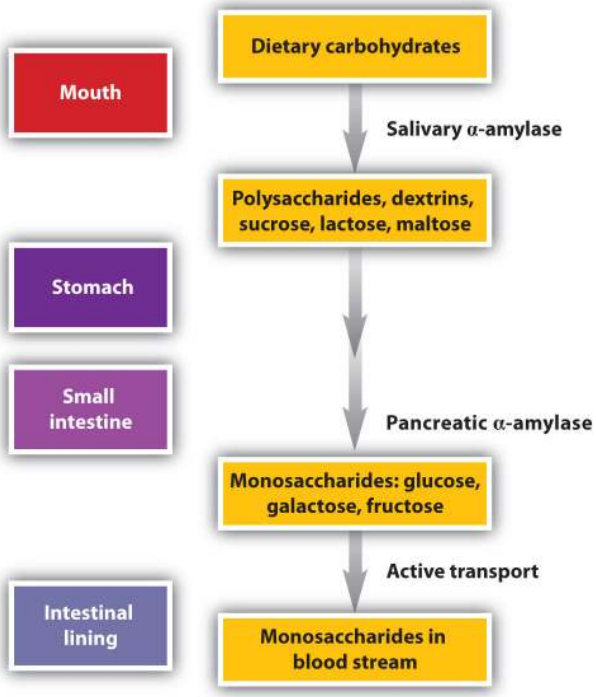


Figure **11.3.2**: The Principal Events and Sites of Carbohydrate Digestion

The primary site of carbohydrate digestion is the small intestine. The secretion of α-amylase in the small intestine converts any remaining starch molecules, as well as the dextrins, to maltose. Maltose is then cleaved into two glucose molecules by maltase. Disaccharides such as sucrose and lactose are not digested until they reach the small intestine, where they are acted on by sucrase and lactase, respectively. The major products of the complete hydrolysis of disaccharides and polysaccharides are three monosaccharide units: glucose, fructose, and galactose. These are absorbed through the wall of the small intestine into the bloodstream.

Digestion of Proteins

Protein digestion begins in the stomach (Figure **11.3.3**), where the action of gastric juice hydrolyzes about 10% of the peptide bonds. Gastric juice is a mixture of water (more than 99%), inorganic ions, hydrochloric acid, and various enzymes and other proteins.

> The pain of a gastric ulcer is at least partially due to irritation of the ulcerated tissue by acidic gastric juice.

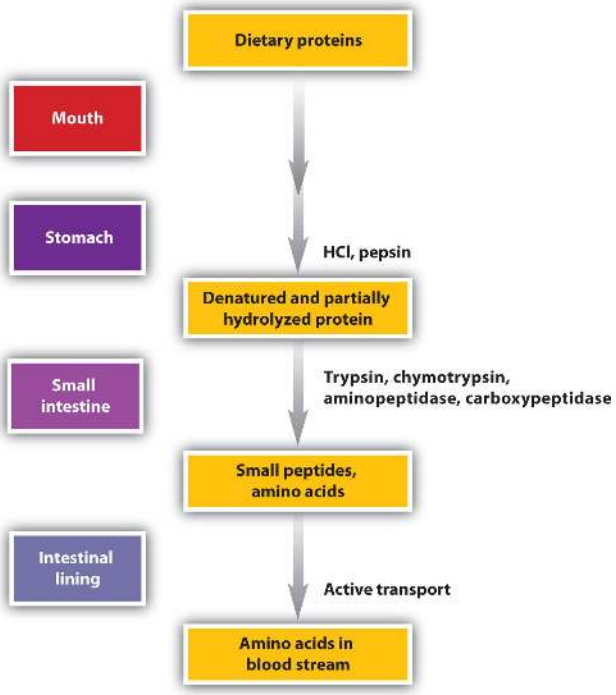


Figure **11.3.3**: The Principal Events and Sites of Protein Digestion

The hydrochloric acid (HCl) in gastric juice is secreted by glands in the stomach lining. The pH of freshly secreted gastric juice is about 1.0, but the contents of the stomach may raise the pH to between 1.5 and 2.5. HCl helps to denature food proteins; that is, it unfolds the protein molecules to expose their chains to more efficient enzyme action. The principal digestive component of gastric juice is pepsinogen, an inactive enzyme produced in cells located in the stomach wall. When food enters the stomach after a period of fasting, pepsinogen is converted to its active form—pepsin—in a series of steps initiated by the drop in pH. Pepsin catalyzes the hydrolysis of peptide linkages within protein molecules. It has a fairly broad specificity but acts preferentially on linkages involving the aromatic amino acids tryptophan, tyrosine, and phenylalanine, as well as methionine and leucine.

Protein digestion is completed in the small intestine. Pancreatic juice, carried from the pancreas via the pancreatic duct, contains inactive enzymes such as trypsinogen and chymotrypsinogen. They are activated in the small intestine as follows (Figure **11.3.4**): The intestinal mucosal cells secrete the proteolytic enzyme enteropeptidase, which converts trypsinogen to trypsin; trypsin then activates chymotrypsinogen to chymotrypsin (and also completes the activation of trypsinogen). Both of these active enzymes catalyze the hydrolysis of peptide bonds in protein chains. Chymotrypsin preferentially attacks peptide bonds involving the carboxyl groups of the aromatic amino acids (phenylalanine, tryptophan, and tyrosine). Trypsin attacks peptide bonds involving the carboxyl groups of the basic amino acids (lysine and arginine). Pancreatic juice also contains procarboxypeptidase, which is cleaved by trypsin to carboxypeptidase. The latter is an enzyme that catalyzes the hydrolysis of peptide linkages at the free carboxyl end of the peptide chain, resulting in the stepwise liberation of free amino acids from the carboxyl end of the polypeptide.

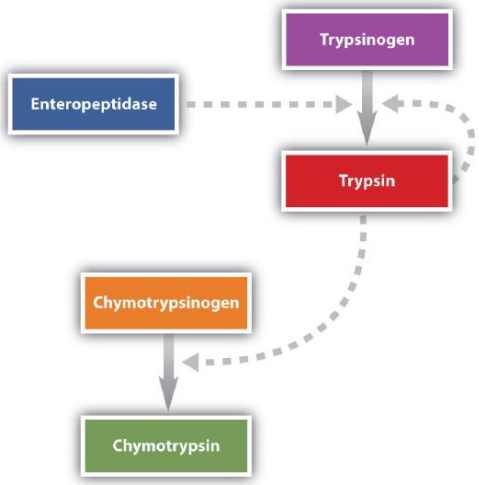


Figure **11.3.4**: Activation of Some Pancreatic Enzymes in the Small Intestine

Aminopeptidases in the intestinal juice remove amino acids from the N-terminal end of peptides and proteins possessing a free amino group. Figure **11.3.5** illustrates the specificity of these protein-digesting enzymes. The amino acids that are released by protein digestion are absorbed across the intestinal wall into the circulatory system, where they can be used for protein synthesis.

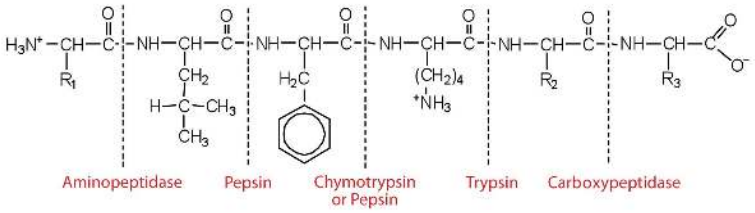


Figure **11.3.5**: Hydrolysis of a Peptide by Several Peptidases

This diagram illustrates where in a peptide the different peptidases we have discussed would catalyze hydrolysis the peptide bonds.

Digestion of Lipids

Lipid digestion begins in the upper portion of the small intestine (Figure **11.3.6**). A hormone secreted in this region stimulates the gallbladder to discharge bile into the duodenum. The principal constituents of bile are the bile salts, which emulsify large, water-insoluble lipid droplets, disrupting some of the hydrophobic interactions holding the lipid molecules together and suspending the resulting smaller globules (micelles) in the aqueous digestive medium. These changes greatly increase the surface area of the lipid particles, allowing for more intimate contact with the lipases and thus rapid digestion of the fats. Another hormone promotes the secretion of pancreatic juice, which contains these enzymes.

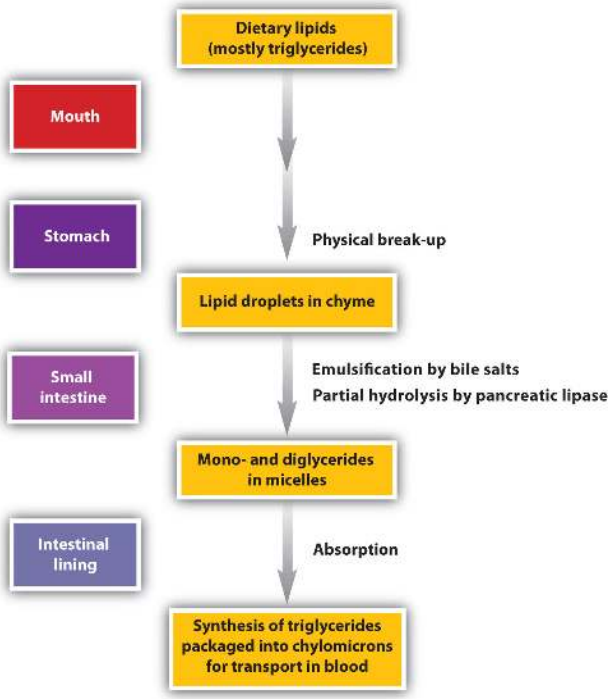
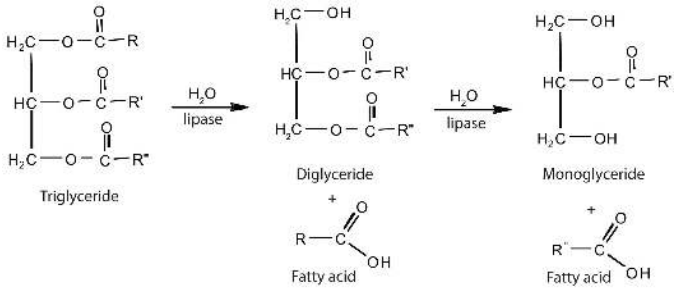


Figure **11.3.6**: The Principal Events and Sites of Lipid (Primarily Triglyceride) Digestion

The lipases in pancreatic juice catalyze the digestion of triglycerides first to diglycerides and then to 2-monoglycerides and fatty acids:



The monoglycerides and fatty acids cross the intestinal lining into the bloodstream, where they are resynthesized into triglycerides and transported as lipoprotein complexes known as chylomicrons. Phospholipids and cholesteryl esters undergo similar hydrolysis in the small intestine, and their component molecules are also absorbed through the intestinal lining.

The further metabolism of monosaccharides, fatty acids, and amino acids released in stage I of catabolism occurs in stages II and III of catabolism.

Summary

During digestion, carbohydrates are broken down into monosaccharides, proteins are broken down into amino acids, and triglycerides are broken down into glycerol and fatty acids. Most of the digestion reactions occur in the small intestine.

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11.4: Overview of Stage II of Catabolism

Learning Objectives

- To describe the role of acetyl-CoA in metabolism.

A metabolic pathway is a series of biochemical reactions by which an organism converts a given reactant to a specific end product. There are specific metabolic pathways—which are different for carbohydrates, triglycerides, and proteins—that break down the products of stage I of catabolism (monosaccharides, fatty acids, and amino acids) to produce a common end product, acetyl-coenzyme A (acetyl-CoA) in stage II of catabolism.

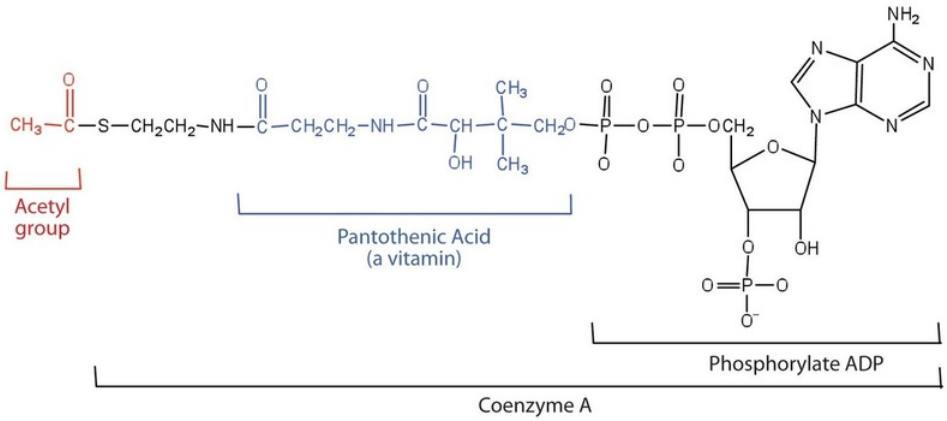


Figure **11.4.1**: The Structure of Acetyl-Coenzyme A (Acetyl-CoA)

Acetyl-CoA is shown in Figure **11.4.1**. The acetyl unit, derived (as we will see) from the breakdown of carbohydrates, lipids, and proteins, is attached to coenzyme A, making the acetyl unit more reactive. Acetyl-CoA is used in a myriad of biochemical pathways. For example, it may be used as the starting material for the biosynthesis of lipids (such as triglycerides, phospholipids, or cholesterol and other steroids). Most importantly for energy generation, it may enter the citric acid cycle and be oxidized to produce energy, if energy is needed and oxygen is available. The various fates or uses of acetyl-CoA are summarized in Figure **11.4.1**.

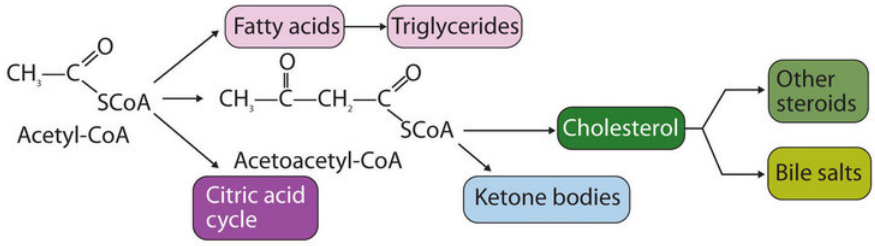


Figure **11.4.2**: Cell Chemistry. Acetyl-CoA plays a variety of roles in cell chemistry.

Glycolysis

Glycolysis is the catabolic process in which glucose is converted into pyruvate via ten enzymatic steps. There are three regulatory steps, each of which is highly regulated that are separated into two phases:

1. the "priming phase" because it requires an input of energy in the form of 2 ATPs per glucose molecule and
2. the "pay off phase" because energy is released in the form of 4 ATPs, 2 per glyceraldehyde molecule.

The end result of Glycolysis is two new pyruvate molecules which can then be fed into the Citric Acid cycle (also known as the Kreb's Cycle) if oxygen is present, or can be reduced to lactate or ethanol in the absence of of oxygen using a process known as fermentation.



Video **11.4.1**: Glycolysis: An Overview. Glycolysis is a series of 10 reactions that converts sugars, like glucose, into 3-carbon molecules called pyruvate. This animation provides an overview of the energy consumed and produced by the pathway. NDSU VCell Production's animation; for more information please see Vcell, NDSU(opens in new window) [vcell.ndsu.edu].

Glycolysis occurs within almost all living cells and is the primary source of Acetyl-CoA, which is the molecule responsible for the majority of energy output under aerobic conditions. The structures of Glycolysis intermediates can be found in Figure **11.4.3**.

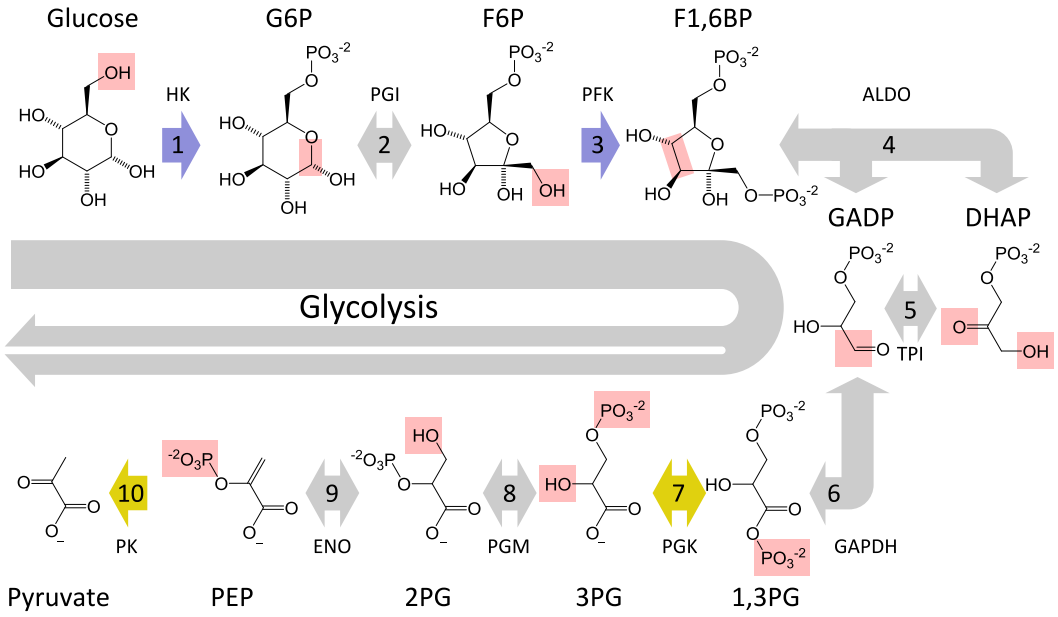


Figure **11.4.3**: Glycolysis pathway. (CC BY-SA 4.0; International; Thomas Shafee via Wikipedia)

Phase 1: The "Priming Step"

The first phase of Glycolysis requires an input of energy in the form of ATP (adenosine triphosphate).

1. alpha-D-Glucose is phosphorolated at the 6 carbon by ATP via the enzyme Hexokinase (Class: Transferase) to yield alpha-D-Glucose-6-phosphate (G-6-P). This is a regulatory step which is negatively regulated by the presence of glucose-6-phosphate.
2. alpha-D-Glucose-6-phosphate is then converted into D-Fructose-6-phosphate (F-6-P) by Phosphoglucoisomerase (Class: Isomerase)
3. D-Fructose-6-phosphate is once again phosphorolated this time at the 1 carbon position by ATP via the enzyme Phosphofructokinase (Class: Transferase) to yield D-Fructose-1,6-bisphosphate (FBP). This is the committed step of glycolysis because of its large ΔG value.
4. D-Fructose-1,6-bisphosphate is then cleaved into two, three carbon molecules; Dihydroxyacetone phosphate (DHAP) and D-Glyceraldehyde-3-phosphate (G-3-P) by the enzyme Fructose bisphosphate aldolase (Class: Lyase)

5. Because the next portion of Glycolysis requires the molecule D-Glyceraldehyde-3-phosphate to continue Dihydroxyacetone phosphate is converted into D-Glyceraldehyde-3-phosphate by the enzyme Triose phosphate isomerase (Class: Isomerase)

Phase 2: The "Pay Off Step"

The second phase of Glycolysis where 4 molecules of ATP are produced per molecule of glucose. Enzymes appear in red:

1. D-Glyceraldehyde-3-phosphate is phosphorolated at the 1 carbon by the enzyme Glyceraldehyde-3-phosphate dehodrogenase to yield the high energy molecule 1,3-Bisphosphoglycerate (BPG)
2. ADP is then phosphorolated at the expense of 1,3-Bisphosphoglycerate by the enzyme Phosphoglycerate kinase (Class: Transferase) to yield ATP and 3-Phosphoglycerate (3-PG)
3. 3-Phosphoglycerate is then converted into 2-Phosphoglycerate by Phosphoglycerate mutase in preparation to yield another high energy molecule
4. 2-Phosphoglycerate is then converted to phosphoenolpyruvate (PEP) by Enolase. H_2O, potassium, and magnesium are all released as a result.
5. ADP is once again phosphorolated, this time at the expense of PEP by the enzyme pyruvate kinase to yield another molecule of ATP and and pyruvate. This step is regulated by the energy in the cell. The higher the energy of the cell the more inhibited pyruvate kinase becomes. Indicators of high energy levels within the cell are high concentrations of ATP, Acetyl-CoA, Alanine, and cAMP.

Because Glucose is split to yield two molecules of D-Glyceraldehyde-3-phosphate, each step in the "Pay Off" phase occurs twice per molecule of glucose.

Beta-Oxidation

The best source of energy for eukaryotic organisms are fats. Glucose offers a ratio 6.3 moles of ATP per carbon while saturated fatty acids offer 8.1 ATP per carbon. Also the complete oxidation of fats yields enormous amounts of water for those organisms that do not have adequate access to drinkable water. Camels and killer whales are good example of this, they obtain their water requirements from the complete oxidation of fats.



Video **11.4.2**: Fatty acid metabolism / beta oxidation / β-Oxidation

There are four distinct stages in the oxidation of fatty acids. Fatty acid degradation takes place within the mitochondria and requires the help of several different enzymes. In order for fatty acids to enter the mitochondria the assistance of two carrier proteins is required, Carnitine acyltransferase I and II. It is also interesting to note the similarities between the four steps of beta-oxidation and the later four steps of the TCA cycle.

Entry into Beta-oxidation

Most fats stored in eukaryotic organisms are stored as triglycerides as seen below. In order to enter into beta-oxidation bonds must be broken usually with the use of a Lipase. The end result of these broken bonds are a glycerol molecule and three fatty acids in the case of triglycerides. Other lipids are capable of being degraded as well.

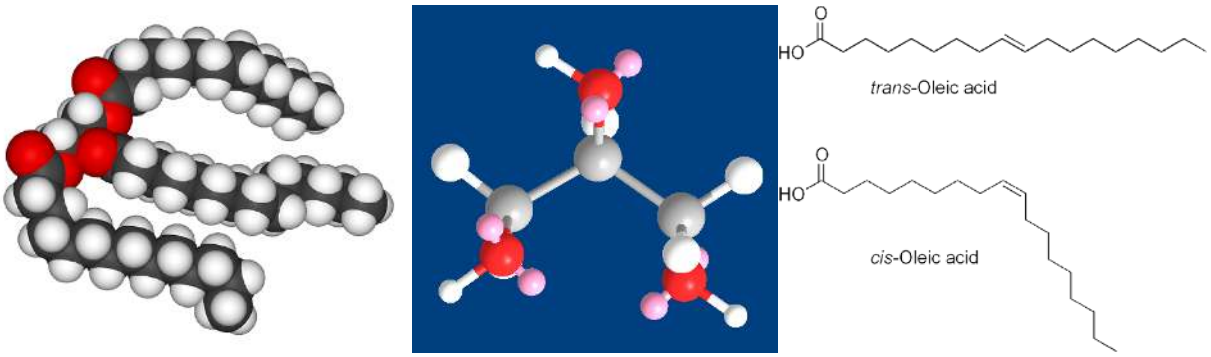


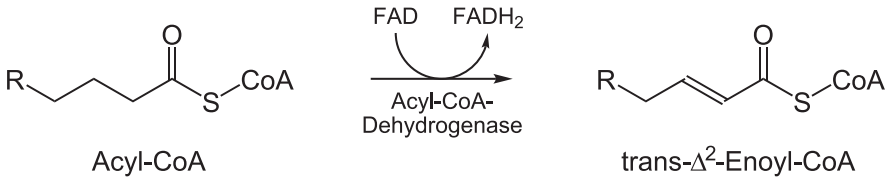
Figure **11.4.4**: Key molecules in beta-oxidation: (left) A triglyceride molecule, (middle) Glycerol, (right) Fatty Acids (unsaturated)

Activation Step

- Once the triglycerides are broken down into glycerol and fatty acids they must be activated before they can enter into the mitochondria and proceed on with beta-oxidation. This is done by Acyl-CoA synthetase to yield fatty acyl-CoA.
- After the fatty acid has been acylated it is now ready to enter into the mitochondria.
- There are two carrier proteins (Carnitine acyltransferase I and II), one located on the outer membrane and one on the inner membrane of the mitochondria. Both are required for entry of the Acyl-CoA into the mitochondria.
- Once inside the mitochondria the fatty acyl-CoA can enter into beta-oxidation.

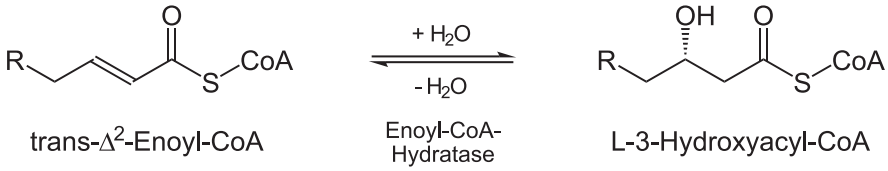
Oxidation Step

A fatty acyl-CoA is oxidized by Acyl-CoA dehydrogenase to yield a trans alkene. This is done with the aid of an [FAD] prosthetic group.



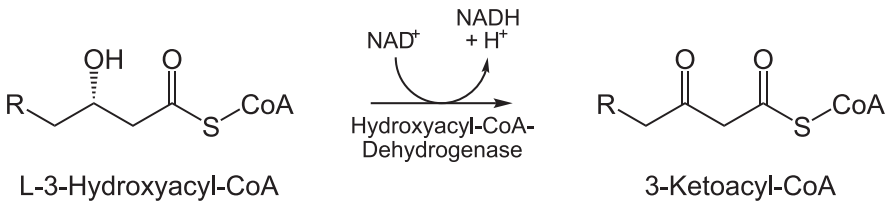
Hydration Step

The trans alkene is then hydrated with the help of Enoyl-CoA hydratase



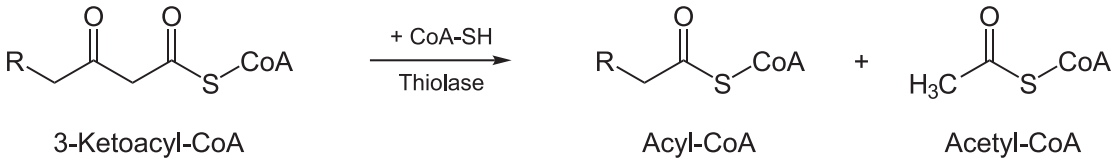
Oxidation Step

The alcohol of the hydroxyacly-CoA is then oxidized by NAD^+ to a carbonyl with the help of Hydroxyacyl-CoA dehydrogenase. NAD^+ is used to oxidize the alcohol rather then [FAD] because NAD^+ is capable of the alcohol while [FAD] is not.



Cleavage

Finally acetyl-CoA is cleaved off with the help of Thiolase to yield an Acyl-CoA that is two carbons shorter than before. The cleaved acetyl-CoA can then enter into the TCA and ETC because it is already within the mitochondria.



3-Ketoacyl-CoA | Acyl-CoA | Acetyl-CoA

Summary

Acetyl-CoA is formed from the breakdown of carbohydrates, lipids, and proteins. It is used in many biochemical pathways.

References

1. Garrett, H., Reginald and Charles Grisham. Biochemistry. Boston: Twayne Publishers, 2008.
2. Raven, Peter. Biology. Boston: Twayne Publishers, 2005.

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11.5: Stage III of Catabolism

Learning Objectives

- Describe the reactions of the citric acid cycle.
- Describe the function of the citric acid cycle and identify the products produced.
- Describe the role of the electron transport chain in energy metabolism.
- Describe the role of oxidative phosphorylation in energy metabolism.

The acetyl group enters a cyclic sequence of reactions known collectively as the citric acid cycle (or Krebs cycle or tricarboxylic acid [TCA] cycle). The cyclical design of this complex series of reactions, which bring about the oxidation of the acetyl group of acetyl-CoA to carbon dioxide and water, was first proposed by Hans Krebs in 1937. (He was awarded the 1953 Nobel Prize in Physiology or Medicine.) Acetyl-CoA's entrance into the citric acid cycle is the beginning of stage III of catabolism. The citric acid cycle produces adenosine triphosphate (ATP), reduced nicotinamide adenine dinucleotide (NADH), reduced flavin adenine dinucleotide ($FADH_2$), and metabolic intermediates for the synthesis of needed compounds.

Steps of the Citric Acid Cycle

At first glance, the citric acid cycle appears rather complex (Figure **11.5.1**). All the reactions, however, are familiar types in organic chemistry: hydration, oxidation, decarboxylation, and hydrolysis. Each reaction of the citric acid cycle is numbered, and in Figure **11.5.1**, the two acetyl carbon atoms are highlighted in red. Each intermediate in the cycle is a carboxylic acid, existing as an anion at physiological pH. All the reactions occur within the mitochondria, which are small organelles within the cells of plants and animals.

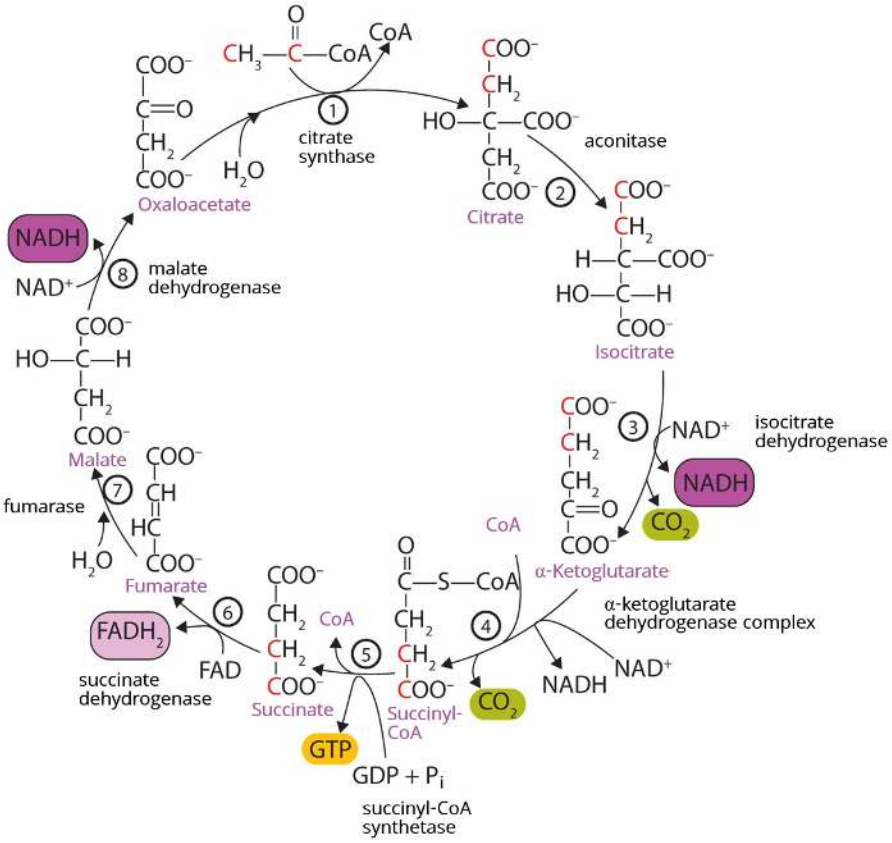


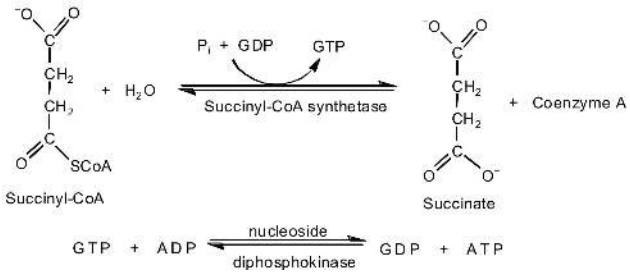
Figure **11.5.1**: Reactions of the Citric Acid Cycle

1. In the first step, acetyl-CoA enters the citric acid cycle, and the acetyl group is transferred onto oxaloacetate, yielding citrate. Note that this step releases coenzyme A. The reaction is catalyzed by *citrate synthase*.

2. In the next step, *aconitase* catalyzes the isomerization of citrate to isocitrate. In this reaction, a tertiary alcohol, which cannot be oxidized, is converted to a secondary alcohol, which can be oxidized in the next step.
3. Isocitrate then undergoes a reaction known as oxidative decarboxylation because the alcohol is oxidized and the molecule is shortened by one carbon atom with the release of carbon dioxide (decarboxylation). The reaction is catalyzed by *isocitrate dehydrogenase*, and the product of the reaction is α-ketoglutarate. An important reaction linked to this is the reduction of the coenzyme nicotinamide adenine dinucleotide (NAD^+) to NADH. The NADH is ultimately reoxidized, and the energy released is used in the synthesis of ATP, as we shall see.
4. The fourth step is another oxidative decarboxylation. This time α-ketoglutarate is converted to succinyl-CoA, and another molecule of NAD^+ is reduced to NADH. The *α-ketoglutarate dehydrogenase complex* catalyzes this reaction. This is the only irreversible reaction in the citric acid cycle. As such, it prevents the cycle from operating in the reverse direction, in which acetyl-CoA would be synthesized from carbon dioxide.

> So far, in the first four steps, two carbon atoms have entered the cycle as an acetyl group, and two carbon atoms have been released as molecules of carbon dioxide. The remaining reactions of the citric acid cycle use the four carbon atoms of the succinyl group to resynthesize a molecule of oxaloacetate, which is the compound needed to combine with an incoming acetyl group and begin another round of the cycle.

In the fifth reaction, the energy released by the hydrolysis of the high-energy thioester bond of succinyl-CoA is used to form guanosine triphosphate (GTP) from guanosine diphosphate (GDP) and inorganic phosphate in a reaction catalyzed by *succinyl-CoA synthetase*. This step is the only reaction in the citric acid cycle that directly forms a high-energy phosphate compound. GTP can readily transfer its terminal phosphate group to adenosine diphosphate (ADP) to generate ATP in the presence of *nucleoside diphosphokinase*.



Succinate dehydrogenase then catalyzes the removal of two hydrogen atoms from succinate, forming fumarate. This oxidation-reduction reaction uses flavin adenine dinucleotide (FAD), rather than NAD^+, as the oxidizing agent. Succinate dehydrogenase is the only enzyme of the citric acid cycle located within the inner mitochondrial membrane. We will see soon the importance of this.

In the following step, a molecule of water is added to the double bond of fumarate to form L-malate in a reaction catalyzed by *fumarase*.

One revolution of the cycle is completed with the oxidation of L-malate to oxaloacetate, brought about by *malate dehydrogenase*. This is the third oxidation-reduction reaction that uses NAD^+ as the oxidizing agent. Oxaloacetate can accept an acetyl group from acetyl-CoA, allowing the cycle to begin again.



Video: "The Citric Acid Cycle: An Overview". In the matrix of the mitochondrion, the Citric Acid Cycle uses Acetyl CoA molecules to produce energy through eight chemical reactions. This animation provides an overview of the pathway and its products. NDSU VCell Production's animation; for more information please see Vcell, NDSU, Animations(opens in new window) [vcell.ndsu.edu].

Cellular Respiration

Respiration can be defined as the process by which cells oxidize organic molecules in the presence of gaseous oxygen to produce carbon dioxide, water, and energy in the form of ATP. We have seen that two carbon atoms enter the citric acid cycle from acetyl-CoA (step 1), and two different carbon atoms exit the cycle as carbon dioxide (steps 3 and 4). Yet nowhere in our discussion of the citric acid cycle have we indicated how oxygen is used. Recall, however, that in the four oxidation-reduction steps occurring in the citric acid cycle, the coenzyme NAD^+ or FAD is reduced to NADH or $FADH_2$, respectively. *Oxygen is needed to reoxidize these coenzymes*. Recall, too, that very little ATP is obtained directly from the citric acid cycle. Instead, oxygen participation and significant ATP production occur subsequent to the citric acid cycle, in two pathways that are closely linked: electron transport and oxidative phosphorylation.

All the enzymes and coenzymes for the citric acid cycle, the reoxidation of NADH and $FADH_2$, and the production of ATP are located in the mitochondria, which are small, oval organelles with double membranes, often referred to as the “power plants” of the cell (Figure **11.5.2**). A cell may contain 100–5,000 mitochondria, depending on its function, and the mitochondria can reproduce themselves if the energy requirements of the cell increase.

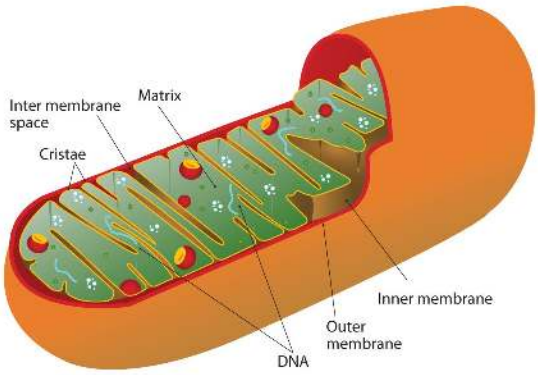


Figure **11.5.2**: Respiration

Cellular respiration occurs in the mitochondria

Figure **11.5.2** shows the mitochondrion’s two membranes: *outer* and *inner*. The inner membrane is extensively folded into a series of internal ridges called *cristae*. Thus there are two compartments in mitochondria: the *intermembrane space*, which lies between the membranes, and the *matrix*, which lies inside the inner membrane. The outer membrane is permeable, whereas the inner membrane is impermeable to most molecules and ions, although water, oxygen, and carbon dioxide can freely penetrate both membranes. The matrix contains all the enzymes of the citric acid cycle with the exception of succinate dehydrogenase, which is

embedded in the inner membrane. The enzymes that are needed for the reoxidation of NADH and $FADH_2$ and ATP production are also located in the inner membrane. They are arranged in specific positions so that they function in a manner analogous to a bucket brigade. This highly organized sequence of oxidation-reduction enzymes is known as the electron transport chain (or respiratory chain).

Electron Transport

Figure **11.5.3** illustrates the organization of the electron transport chain. The components of the chain are organized into four complexes designated I, II, III, and IV. Each complex contains several enzymes, other proteins, and metal ions. The metal ions can be reduced and then oxidized repeatedly as electrons are passed from one component to the next. Recall that a compound is reduced when it gains electrons or hydrogen atoms and is oxidized when it loses electrons or hydrogen atoms.

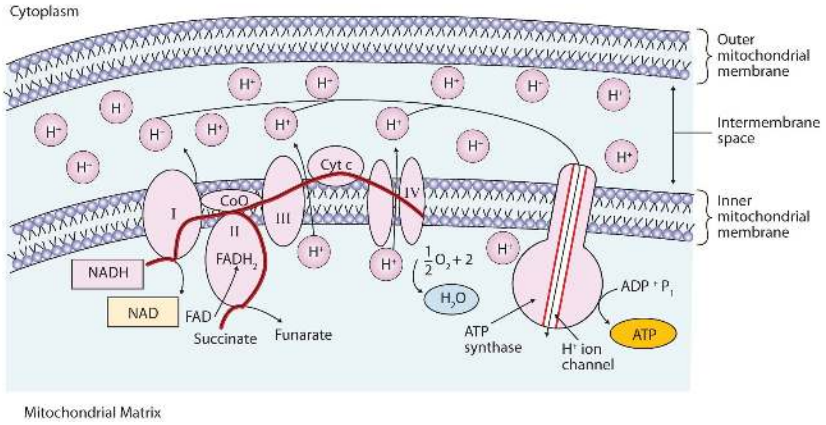
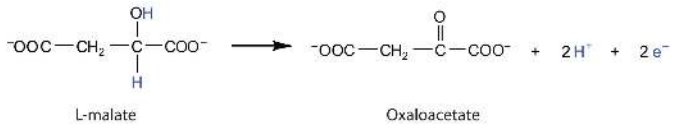


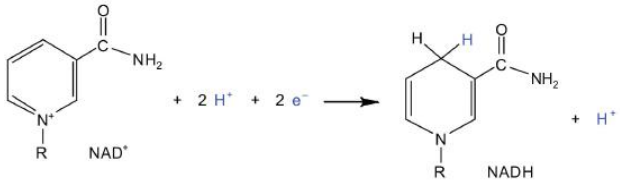
Figure **11.5.3**: The Mitochondrial Electron Transport Chain and ATP Synthase. The red line shows the path of electrons.

Electrons can enter the electron transport chain through either complex I or II. We will look first at electrons entering at complex I. These electrons come from NADH, which is formed in three reactions of the citric acid cycle. Let's use step 8 as an example, the reaction in which L-malate is oxidized to oxaloacetate and NAD^+ is reduced to NADH. This reaction can be divided into two half reactions:

- *Oxidation half-reaction*:



- *Reduction half-reaction*:

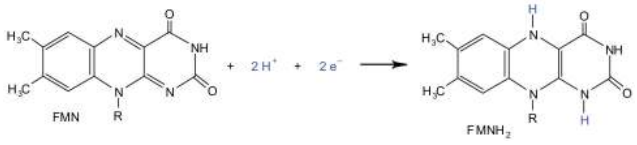


In the oxidation half-reaction, two hydrogen (H^+) ions and two electrons are removed from the substrate. In the reduction half-reaction, the NAD^+ molecule accepts both of those electrons and one of the H^+ ions. The other H^+ ion is transported from the matrix, across the inner mitochondrial membrane, and into the intermembrane space. The NADH diffuses through the matrix and is bound by complex I of the electron transport chain. In the complex, the coenzyme flavin mononucleotide (FMN) accepts both electrons from NADH. By passing the electrons along, NADH is oxidized back to NAD^+ and FMN is reduced to $FMNH_2$ (reduced form of flavin mononucleotide). Again, the reaction can be illustrated by dividing it into its respective half-reactions.

- *Oxidation half-reaction*:

$$NADH + H^+ \longrightarrow NAD^+ + 2H^+ + 2e^-$$

- *Reduction half-reaction*:



Complex I contains several proteins that have iron-sulfur (Fe·S) centers. The electrons that reduced FMN to $FMNH_2$ are now transferred to these proteins. The iron ions in the Fe·S centers are in the Fe(III) form at first, but by accepting an electron, each ion is reduced to the Fe(II) form. Because each Fe·S center can transfer only one electron, two centers are needed to accept the two electrons that will regenerate FMN.

- *Oxidation half-reaction*:

$$\mathbf{FMNH_2 \longrightarrow FMN + 2H^+ + 2e^-}$$

- *Reduction half-reaction*:

$$\mathbf{2\,Fe(III)\cdot S + 2e^- \longrightarrow 2\,Fe(II)\cdot S}$$

Electrons from $FADH_2$, formed in step 6 of the citric acid cycle, enter the electron transport chain through complex II. Succinate dehydrogenase, the enzyme in the citric acid cycle that catalyzes the formation of $FADH_2$ from FAD is part of complex II. The electrons from $FADH_2$ are then transferred to an Fe·S protein.

- *Oxidation half-reaction*:

$$\mathbf{FADH_2 \longrightarrow FAD + 2H^+ + 2e^-}$$

- *Reduction half-reaction*:

$$\mathbf{2\,Fe(III)\cdot S + 2e^- \longrightarrow 2\,Fe(II)\cdot S}$$

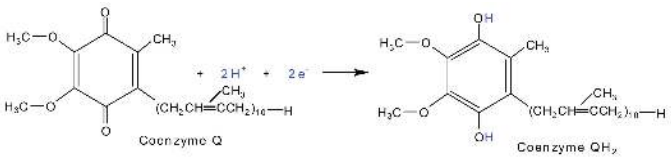
Electrons from complexes I and II are then transferred from the $\mathbf{Fe\cdot S}$ protein to coenzyme Q (CoQ), a mobile electron carrier that acts as the electron shuttle between complexes I or II and complex III.

> *Coenzyme Q is also called ubiquinone because it is ubiquitous in living systems.*

- *Oxidation half-reaction*:

$$\mathbf{2\,Fe(II)\cdot S \longrightarrow 2\,Fe(III)\cdot S + 2e^-}$$

- *Reduction half-reaction*:



Complexes III and IV include several iron-containing proteins known as cytochromes. The iron in these enzymes is located in substructures known as iron porphyrins (Figure **11.5.4**). Like the Fe·S centers, the characteristic feature of the cytochromes is the ability of their iron atoms to exist as either Fe(II) or Fe(III). Thus, each cytochrome in its oxidized form—Fe(III)—can accept one electron and be reduced to the Fe(II) form. This change in oxidation state is reversible, so the reduced form can donate its electron to the next cytochrome, and so on. Complex III contains cytochromes b and c, as well as Fe·S proteins, with cytochrome c acting as the electron shuttle between complex III and IV. Complex IV contains cytochromes a and a_3 in an enzyme known as *cytochrome oxidase*. This enzyme has the ability to transfer electrons to molecular oxygen, the last electron acceptor in the chain of electron transport reactions. In this final step, water (H_2O) is formed.

- *Oxidation half-reaction*:

$$4\,\text{Cyt}\ \ a_3\text{-Fe(II)} \longrightarrow 4\,\text{Cyt}\ \ a_3\text{-Fe(III)} + 4\,e^-$$

- *Reduction half-reaction*:

$$O_2 + 4\,H^+ + 4\,e^- \longrightarrow 2\,H_2O$$

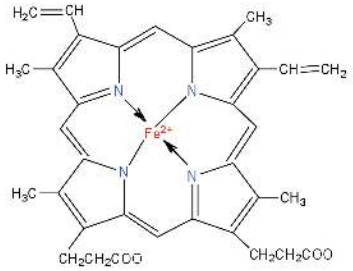


Figure **11.5.4**: An Iron Porphyrin. Iron porphyrins are present in cytochromes as well as in myoglobin and hemoglobin.



Video: Cellular Respiration (Electron Transport Chain). Cellular respiration occurs in the mitochondria and provides both animals and plants with the energy needed to power other cellular processes. This section covers the electron transport chain.NDSU Virtual Cell Animations Project animation; ror more information please see Vcell, NDSU, Animations(opens in new window) [vcell.ndsu.edu]

Oxidative Phosphorylation

Each intermediate compound in the electron transport chain is reduced by the addition of one or two electrons in one reaction and then subsequently restored to its original form by delivering the electron(s) to the next compound along the chain. The successive electron transfers result in energy production. But how is this energy used for the synthesis of ATP? The process that links ATP synthesis to the operation of the electron transport chain is referred to as oxidative phosphorylation.

Electron transport is tightly coupled to oxidative phosphorylation. The coenzymes NADH and $FADH_2$ are oxidized by the respiratory chain *only* if ADP is simultaneously phosphorylated to ATP. The currently accepted model explaining how these two processes are linked is known as the *chemiosmotic hypothesis*, which was proposed by Peter Mitchell, resulting in Mitchell being awarded the 1978 Nobel Prize in Chemistry.

Looking again at Figure **11.5.3**, we see that as electrons are being transferred through the electron transport chain, hydrogen (H^+) ions are being transported across the inner mitochondrial membrane from the matrix to the intermembrane space. The concentration of H^+ is already higher in the intermembrane space than in the matrix, so energy is required to transport the additional H^+ there. This energy comes from the electron transfer reactions in the electron transport chain. But how does the extreme difference in H^+ concentration then lead to ATP synthesis? The buildup of H^+ ions in the intermembrane space results in an H^+ ion gradient that is a large energy source, like water behind a dam (because, given the opportunity, the protons will flow out of the intermembrane space and into the less concentrated matrix). Current research indicates that the flow of H^+ down this concentration gradient through a

fifth enzyme complex, known as ATP synthase, leads to a change in the structure of the synthase, causing the synthesis and release of ATP.

In cells that are using energy, the turnover of ATP is very high, so these cells contain high levels of ADP. They must therefore consume large quantities of oxygen continuously, so as to have the energy necessary to phosphorylate ADP to form ATP. Consider, for example, that resting skeletal muscles use about 30% of a resting adult's oxygen consumption, but when the same muscles are working strenuously, they account for almost 90% of the total oxygen consumption of the organism.

Experiment has shown that 2.5–3 ATP molecules are formed for every molecule of NADH oxidized in the electron transport chain, and 1.5–2 ATP molecules are formed for every molecule of $FADH_2$ oxidized. Table **11.5.1** summarizes the theoretical maximum yield of ATP produced by the complete oxidation of 1 mol of acetyl-CoA through the sequential action of the citric acid cycle, the electron transport chain, and oxidative phosphorylation.

Table **11.5.1**: Maximum Yield of ATP from the Complete Oxidation of 1 Mol of Acetyl-CoA

Reaction	Comments	Yield of ATP (moles)
Isocitrate → α-ketoglutarate + CO_2	produces 1 mol NADH	
α-ketoglutarate → succinyl-CoA + CO_2	produces 1 mol NADH	
Succinyl-CoA → succinate	produces 1 mol GTP	+1
Succinate → fumarate	produces 1 mol $FADH_2$	
Malate → oxaloacetate	produces 1 mol NADH	
1 $FADH_2$ from the citric acid cycle	yields 2 mol ATP	+2
3 NADH from the citric acid cycle	yields 3 mol ATP/NADH	+9
Net yield of ATP:		+12

Key Takeaways

- The acetyl group of acetyl-CoA enters the citric acid cycle. For each acetyl-CoA that enters the citric acid cycle, 2 molecules of carbon dioxide, 3 molecules of NADH, 1 molecule of ATP, and 1 molecule of $FADH_2$ are produced.
- The reduced coenzymes (NADH and $FADH_2$) produced by the citric acid cycle are reoxidized by the reactions of the electron transport chain. This series of reactions also produces a pH gradient across the inner mitochondrial membrane.
- The pH gradient produced by the electron transport chain drives the synthesis of ATP from ADP. For each NADH reoxidized, 2.5–3 molecules of ATP are produced; for each $FADH_2$ reoxidized, 1.5–2 molecules of ATP are produced.

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11.6: Stage II of Carbohydrate Catabolism

Learning Objectives

- Describe the function of glycolysis and identify its major products.
- Describe how the presence or absence of oxygen determines what happens to the pyruvate and the NADH that are produced in glycolysis.
- Determine the amount of ATP produced by the oxidation of glucose in the presence and absence of oxygen.

In stage II of catabolism, the metabolic pathway known as glycolysis converts glucose into two molecules of pyruvate (a three-carbon compound with three carbon atoms) with the corresponding production of adenosine triphosphate (ATP). The individual reactions in glycolysis were determined during the first part of the 20th century. It was the first metabolic pathway to be elucidated, in part because the participating enzymes are found in soluble form in the cell and are readily isolated and purified. The pathway is structured so that the product of one enzyme-catalyzed reaction becomes the substrate of the next. The transfer of intermediates from one enzyme to the next occurs by diffusion.

Steps in Glycolysis

The 10 reactions of glycolysis, summarized in Figures **11.6.1** and **11.6.2**, can be divided into two phases. In the first 5 reactions—phase I—glucose is broken down into two molecules of glyceraldehyde 3-phosphate. In the last five reactions—phase II—each glyceraldehyde 3-phosphate is converted into pyruvate, and ATP is generated. Notice that all the intermediates in glycolysis are phosphorylated and contain either six or three carbon atoms.

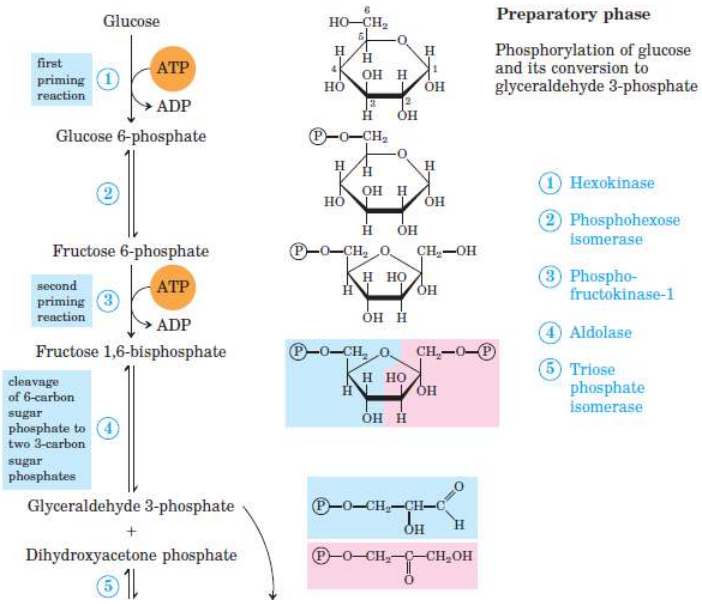


Figure **11.6.1**: Phase 1 (preparatory phase) of Glycolysis

- When glucose enters a cell, it is immediately phosphorylated to form glucose 6-phosphate, in the first reaction of phase I. The phosphate donor in this reaction is ATP, and the enzyme—which requires magnesium ions for its activity—is *hexokinase*. In this reaction, ATP is being used rather than being synthesized. The presence of such a reaction in a catabolic pathway that is supposed to *generate* energy may surprise you. However, in addition to activating the glucose molecule, this initial reaction is essentially irreversible, an added benefit that keeps the overall process moving in the right direction. Furthermore, the addition of the negatively charged phosphate group prevents the intermediates formed in glycolysis from diffusing through the cell membrane, as neutral molecules such as glucose can do.
- In the next reaction, *phosphoglucose isomerase* catalyzes the isomerization of glucose 6-phosphate to fructose 6-phosphate. This reaction is important because it creates a primary alcohol, which can be readily phosphorylated.

- The subsequent phosphorylation of fructose 6-phosphate to form fructose 1,6-bisphosphate is catalyzed by *phosphofructokinase*, which requires magnesium ions for activity. ATP is again the phosphate donor.
- Fructose 1,6-bisphosphate is enzymatically cleaved by *aldolase* to form two triose phosphates: dihydroxyacetone phosphate and glyceraldehyde 3-phosphate.
- Isomerization of dihydroxyacetone phosphate into a second molecule of glyceraldehyde 3-phosphate is the final step in phase I. The enzyme catalyzing this reaction is *triose phosphate isomerase*.

When a molecule contains two phosphate groups on different carbon atoms, the convention is to use the prefix *bis*. When the two phosphate groups are bonded to each other on the same carbon atom (for example, adenosine diphosphate [ADP]), the prefix is *di*.

In steps 4 and 5, aldolase and triose phosphate isomerase effectively convert one molecule of fructose 1,6-bisphosphate into *two* molecules of glyceraldehyde 3-phosphate. Thus, phase I of glycolysis requires energy in the form of two molecules of ATP and releases none of the energy stored in glucose.

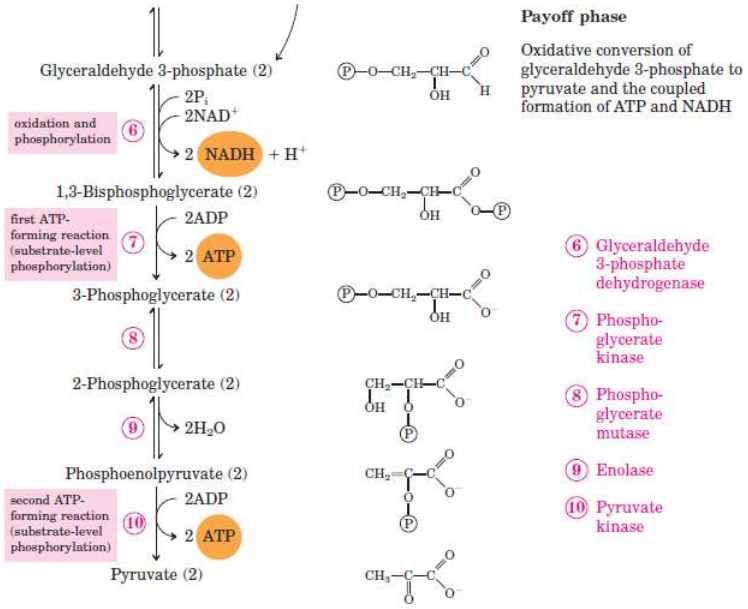


Figure **11.6.2**: Phase 2 (payoff phase) of Glycolysis

In the initial step of phase II (Figure **11.6.2**), glyceraldehyde 3-phosphate is both oxidized and phosphorylated in a reaction catalyzed by *glyceraldehyde-3-phosphate dehydrogenase*, an enzyme that requires nicotinamide adenine dinucleotide (NAD^+) as the oxidizing agent and inorganic phosphate as the phosphate donor. In the reaction, NAD^+ is reduced to reduced nicotinamide adenine dinucleotide (NADH), and 1,3-bisphosphoglycerate (BPG) is formed.

- BPG has a high-energy phosphate bond (Table **11.6.1**) joining a phosphate group to C1. This phosphate group is now transferred directly to a molecule of ADP, thus forming ATP and 3-phosphoglycerate. The enzyme that catalyzes the reaction is **phosphoglycerate kinase**, which, like all other kinases, requires magnesium ions to function. This is the first reaction to produce ATP in the pathway. Because the ATP is formed by a direct transfer of a phosphate group from a metabolite to ADP—that is, from one substrate to another—the process is referred to as substrate-level phosphorylation, to distinguish it from the *oxidative phosphorylation* discussed in Section 20.4.
- In the next reaction, the phosphate group on 3-phosphoglycerate is transferred from the OH group of C3 to the OH group of C2, forming 2-phosphoglycerate in a reaction catalyzed by *phosphoglyceromutase*.
- A dehydration reaction, catalyzed by *enolase*, forms phosphoenolpyruvate (PEP), another compound possessing a high-energy phosphate group.

- The final step is irreversible and is the second reaction in which substrate-level phosphorylation occurs. The phosphate group of PEP is transferred to ADP, with one molecule of ATP being produced per molecule of PEP. The reaction is catalyzed by *pyruvate kinase*, which requires both magnesium and potassium ions to be active.

Table **11.6.1**: Maximum Yield of ATP from the Complete Oxidation of 1 Mol of Glucose

Reaction	Comments	Yield of ATP (moles)
glucose → glucose 6-phosphate	consumes 1 mol ATP	−1
fructose 6-phosphate → fructose 1,6-bisphosphate	consumes 1 mol ATP	−1
glyceraldehyde 3-phosphate → BPG	produces 2 mol of cytoplasmic NADH	
BPG → 3-phosphoglycerate	produces 2 mol ATP	+2
phosphoenolpyruvate → pyruvate	produces 2 mol ATP	+2
pyruvate → acetyl-CoA + CO_2	produces 2 mol NADH	
isocitrate → α-ketoglutarate + CO_2	produces 2 mol NADH	
α-ketoglutarate → succinyl-CoA + CO_2	produces 2 mol NADH	
succinyl-CoA → succinate	produces 2 mol GTP	+2
succinate → fumarate	produces 2 mol $FADH_2$	
malate → oxaloacetate	produces 2 mol NADH	
2 cytoplasmic NADH from glycolysis	yields 2–3 mol ATP per NADH (depending on tissue)	+4 to +6
2 NADH from the oxidation of pyruvate	yields 3 mol ATP per NADH	+6
2 $FADH_2$ from the citric acid cycle	yields 2 ATP per $FADH_2$	+4
3 NADH from the citric acid cycle	yields 3 ATP per NADH	+18
Net yield of ATP:		+36 to +38

In phase II, two molecules of glyceraldehyde 3-phosphate are converted to two molecules of pyruvate, along with the production of four molecules of ATP and two molecules of NADH.

To Your Health: Diabetes

Although medical science has made significant progress against diabetes , it continues to be a major health threat. Some of the serious complications of diabetes are as follows:

- It is the leading cause of lower limb amputations in the United States.
- It is the leading cause of blindness in adults over age 20.
- It is the leading cause of kidney failure.
- It increases the risk of having a heart attack or stroke by two to four times.

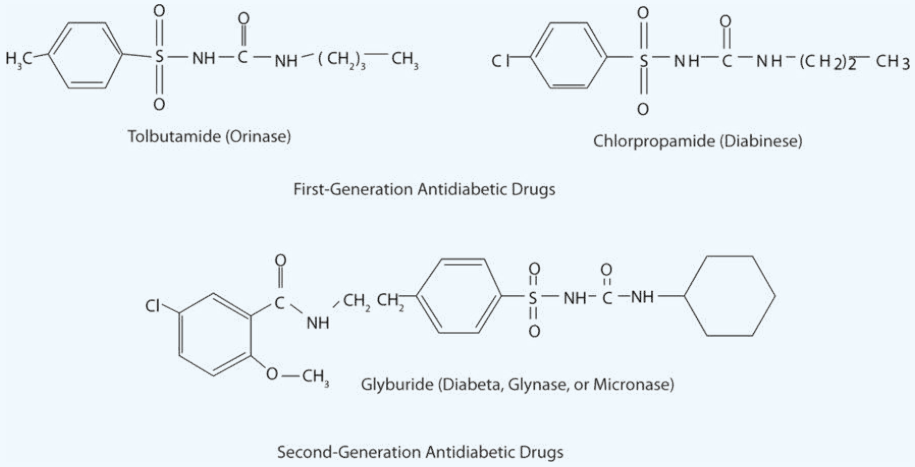
Because a person with diabetes is unable to use glucose properly, excessive quantities accumulate in the blood and the urine. Other characteristic symptoms are constant hunger, weight loss, extreme thirst, and frequent urination because the kidneys excrete large amounts of water in an attempt to remove excess sugar from the blood.

There are two types of diabetes. In immune-mediated diabetes, insufficient amounts of insulin are produced. This type of diabetes develops early in life and is also known as *Type 1 diabetes*, as well as insulin-dependent or juvenile-onset diabetes.

Symptoms are rapidly reversed by the administration of insulin, and Type 1 diabetics can lead active lives provided they receive insulin as needed. Because insulin is a protein that is readily digested in the small intestine, it cannot be taken orally and must be injected at least once a day.

In Type 1 diabetes, insulin-producing cells of the pancreas are destroyed by the body's immune system. Researchers are still trying to find out why. Meanwhile, they have developed a simple blood test capable of predicting who will develop Type 1 diabetes several years before the disease becomes apparent. The blood test reveals the presence of antibodies that destroy the body's insulin-producing cells.

Type 2 diabetes, also known as noninsulin-dependent or adult-onset diabetes, is by far the more common, representing about 95% of diagnosed diabetic cases. (This translates to about 16 million Americans.) Type 2 diabetics usually produce sufficient amounts of insulin, but either the insulin-producing cells in the pancreas do not release enough of it, or it is not used properly because of defective insulin receptors or a lack of insulin receptors on the target cells. In many of these people, the disease can be controlled with a combination of diet and exercise alone. For some people who are overweight, losing weight is sufficient to bring their blood sugar level into the normal range, after which medication is not required if they exercise regularly and eat wisely.



Those who require medication may use oral antidiabetic drugs that stimulate the islet cells to secrete insulin. First-generation antidiabetic drugs stimulated the release of insulin. Newer second-generation drugs, such as glyburide, do as well, but they also increase the sensitivity of cell receptors to insulin. Some individuals with Type 2 diabetes do not produce enough insulin and thus do not respond to these oral medications; they must use insulin. In both Type 1 and Type 2 diabetes, the blood sugar level must be carefully monitored and adjustments made in diet or medication to keep the level as normal as possible (70–120 mg/dL).

Metabolism of Pyruvate

The presence or absence of oxygen determines the fates of the pyruvate and the NADH produced in glycolysis. When plenty of oxygen is available, pyruvate is completely oxidized to carbon dioxide, with the release of much greater amounts of ATP through the combined actions of the citric acid cycle, the electron transport chain, and oxidative phosphorylation. However, in the absence of oxygen (that is, under anaerobic conditions), the fate of pyruvate is different in different organisms. In vertebrates, pyruvate is converted to lactate, while other organisms, such as yeast, convert pyruvate to ethanol and carbon dioxide. These possible fates of pyruvate are summarized in Figure **11.6.2**. The conversion to lactate or ethanol under anaerobic conditions allows for the reoxidation of NADH to NAD^+ in the absence of oxygen.

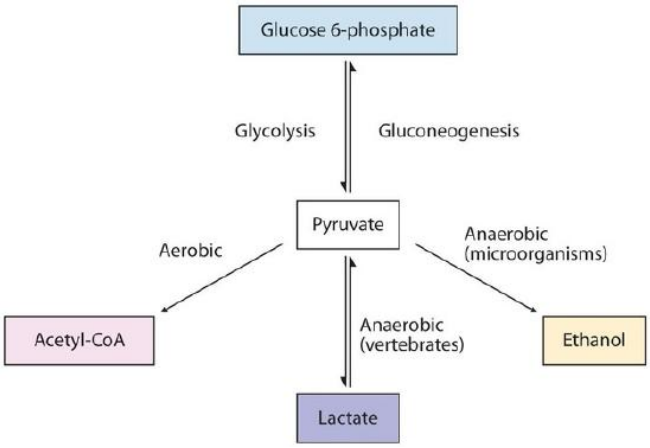


Figure 11.6.2: Metabolic Fates of Pyruvate

ATP Yield from Glycolysis

The net energy yield from anaerobic glucose metabolism can readily be calculated in moles of ATP. In the initial phosphorylation of glucose (step 1), 1 mol of ATP is expended, along with another in the phosphorylation of fructose 6-phosphate (step 3). In step 7, 2 mol of BPG (recall that 2 mol of 1,3-BPG are formed for each mole of glucose) are converted to 2 mol of 3-phosphoglycerate, and 2 mol of ATP are produced. In step 10, 2 mol of pyruvate and 2 mol of ATP are formed per mole of glucose.

For every mole of glucose degraded, 2 mol of ATP are initially consumed and 4 mol of ATP are ultimately produced. The net production of ATP is thus 2 mol for each mole of glucose converted to lactate or ethanol. If 7.4 kcal of energy is conserved per mole of ATP produced, and the total amount of energy that can theoretically be obtained from the complete oxidation of 1 mol of glucose is 670 kcal (as stated in the chapter introduction), the energy conserved in the anaerobic catabolism of glucose to two molecules of lactate (or ethanol) is as follows:

$$\frac{2 \times 7.4\ \text{kcal}}{670\ \text{kcal}} \times 100 = 2.2\%$$

Thus anaerobic cells extract only a very small fraction of the total energy of the glucose molecule.

Contrast this result with the amount of energy obtained when glucose is completely oxidized to carbon dioxide and water through glycolysis, the citric acid cycle, the electron transport chain, and oxidative phosphorylation as summarized in Table 11.6.1. Note the indication in the table that a variable amount of ATP is synthesized, depending on the tissue, from the NADH formed in the cytoplasm during glycolysis. This is because NADH is not transported into the inner mitochondrial membrane where the enzymes for the electron transport chain are located. Instead, brain and muscle cells use a transport mechanism that passes electrons from the cytoplasmic NADH through the membrane to flavin adenine dinucleotide (FAD) molecules inside the mitochondria, forming reduced flavin adenine dinucleotide ($FADH_2$), which then feeds the electrons into the electron transport chain. This route lowers the yield of ATP to 1.5–2 molecules of ATP, rather than the usual 2.5–3 molecules. A more efficient transport system is found in liver, heart, and kidney cells where the formation of one cytoplasmic NADH molecule results in the formation of one mitochondrial NADH molecule, which leads to the formation of 2.5–3 molecules of ATP.The total amount of energy conserved in the aerobic catabolism of glucose in the liver is as follows:

$$\frac{38 \times 7.4\ \text{kcal}}{670\ \text{kcal}} \times 100 = 42\%$$

Conservation of 42% of the total energy released compares favorably with the efficiency of any machine. In comparison, automobiles are only about 20%–25% efficient in using the energy released by the combustion of gasoline.

As indicated earlier, the 58% of released energy that is not conserved enters the surroundings (that is, the cell) as heat that helps to maintain body temperature. If we are exercising strenuously and our metabolism speeds up to provide the energy needed for muscle contraction, more heat is produced. We begin to perspire to dissipate some of that heat. As the perspiration evaporates, the excess heat is carried away from the body by the departing water vapor.

Summary

- The monosaccharide glucose is broken down through a series of enzyme-catalyzed reactions known as glycolysis.
- For each molecule of glucose that is broken down, two molecules of pyruvate, two molecules of ATP, and two molecules of NADH are produced.
- In the absence of oxygen, pyruvate is converted to lactate, and NADH is reoxidized to NAD+. In the presence of oxygen, pyruvate is converted to acetyl-CoA and then enters the citric acid cycle.
- More ATP can be formed from the breakdown of glucose when oxygen is present.

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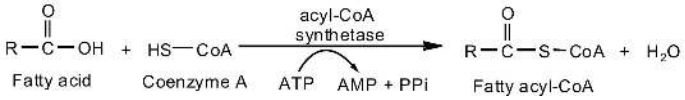
11.7: Stage II of Lipid Catabolism

Learning Objectives

- To describe the reactions needed to completely oxidize a fatty acid to carbon dioxide and water.

Like glucose, the fatty acids released in the digestion of triglycerides and other lipids are broken down in a series of sequential reactions accompanied by the gradual release of usable energy. Some of these reactions are oxidative and require nicotinamide adenine dinucleotide (NAD^+) and flavin adenine dinucleotide (FAD). The enzymes that participate in fatty acid catabolism are located in the mitochondria, along with the enzymes of the citric acid cycle, the electron transport chain, and oxidative phosphorylation. This localization of enzymes in the mitochondria is of the utmost importance because it facilitates efficient utilization of energy stored in fatty acids and other molecules.

Fatty acid oxidation is initiated on the outer mitochondrial membrane. There the fatty acids, which like carbohydrates are relatively inert, must first be activated by conversion to an energy-rich fatty acid derivative of coenzyme A called *fatty acyl-coenzyme A* (CoA). The activation is catalyzed by *acyl-CoA synthetase*. For each molecule of fatty acid activated, one molecule of coenzyme A and one molecule of adenosine triphosphate (ATP) are used, equaling a net utilization of the two high-energy bonds in one ATP molecule (which is therefore converted to adenosine monophosphate [AMP] rather than adenosine diphosphate [ADP]):



The fatty acyl-CoA diffuses to the inner mitochondrial membrane, where it combines with a carrier molecule known as carnitine in a reaction catalyzed by *carnitine acyltransferase*. The acyl-carnitine derivative is transported into the mitochondrial matrix and converted back to the fatty acyl-CoA.

Steps in the β-Oxidation of Fatty Acids

Further oxidation of the fatty acyl-CoA occurs in the mitochondrial matrix via a sequence of four reactions known collectively as β-oxidation because the β-carbon undergoes successive oxidations in the progressive removal of two carbon atoms from the carboxyl end of the fatty acyl-CoA (Figure 11.7.1).

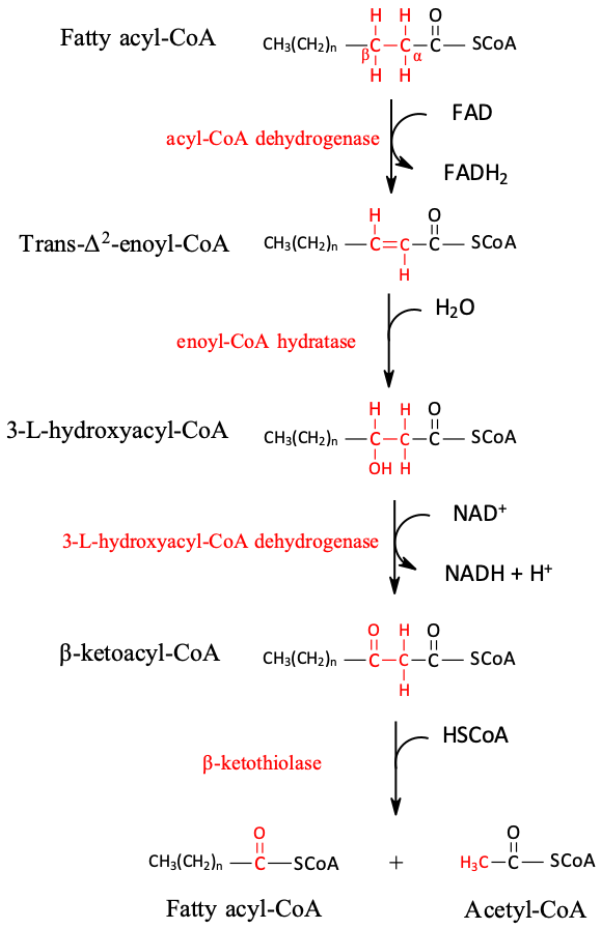


Figure **11.7.1**: Fatty Acid Oxidation. The fatty acyl-CoA formed in the final step becomes the substrate for the first step in the next round of β-oxidation. β-oxidation continues until two acetyl-CoA molecules are produced in the final step.

The first step in the catabolism of fatty acids is the formation of an alkene in an oxidation reaction catalyzed by *acyl-CoA dehydrogenase*. In this reaction, the coenzyme FAD accepts two hydrogen atoms from the acyl-CoA, one from the α-carbon and one from the β-carbon, forming reduced flavin adenine dinucleotide ($FADH_2$).

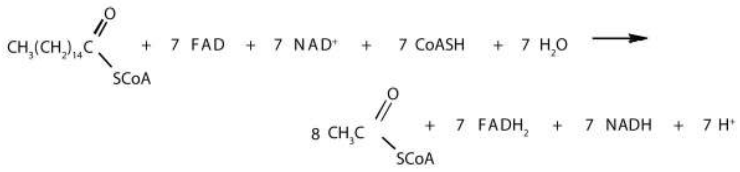
> The $FADH_2$ is reoxidized back to FAD via the electron transport chain that supplies energy to form 1.5–2 molecules of ATP.

Next, the *trans*-alkene is hydrated to form a secondary alcohol in a reaction catalyzed by *enoyl-CoA hydratase*. The enzyme forms only the L-isomer.

The secondary alcohol is then oxidized to a ketone by *β-hydroxyacyl-CoA dehydrogenase*, with NAD^+ acting as the oxidizing agent. The reoxidation of each molecule of NADH to NAD^+ by the electron transport chain furnishes 2.5–3 molecules of ATP.

The final reaction is cleavage of the β-ketoacyl-CoA by a molecule of coenzyme A. The products are acetyl-CoA and a fatty acyl-CoA that has been shortened by two carbon atoms. The reaction is catalyzed by *thiolase*.

The shortened fatty acyl-CoA is then degraded by repetitions of these four steps, each time releasing a molecule of acetyl-CoA. The overall equation for the β-oxidation of palmitoyl-CoA (16 carbon atoms) is as follows:

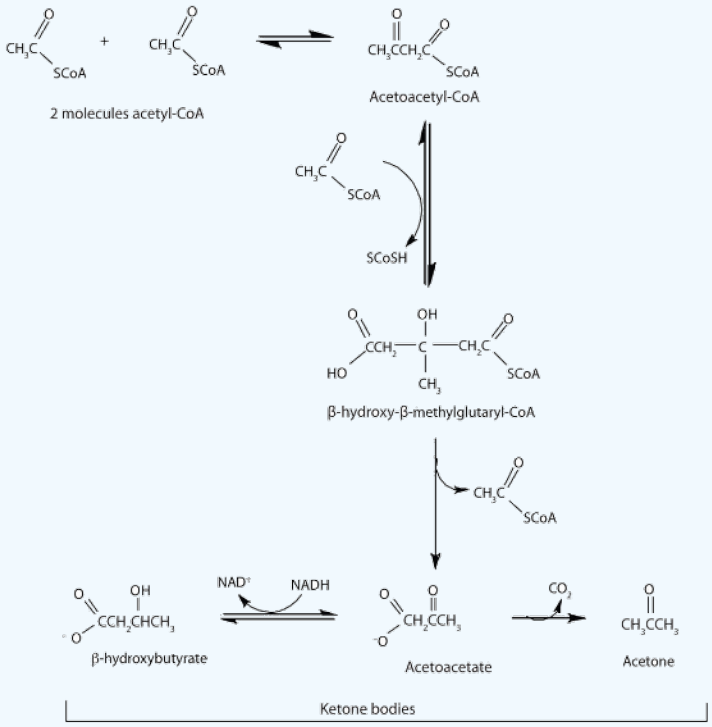


> *Because each shortened fatty acyl-CoA cycles back to the beginning of the pathway, β-oxidation is sometimes referred to as the fatty acid spiral.*

The fate of the acetyl-CoA obtained from fatty acid oxidation depends on the needs of an organism. It may enter the citric acid cycle and be oxidized to produce energy, it may be used for the formation of water-soluble derivatives known as ketone bodies, or it may serve as the starting material for the synthesis of fatty acids. For more information about the citric acid cycle, see Section 20.4.

Looking Closer: Ketone Bodies

In the liver, most of the acetyl-CoA obtained from fatty acid oxidation is oxidized by the citric acid cycle. However, some of the acetyl-CoA is used to synthesize a group of compounds known as *ketone bodies*: acetoacetate, β-hydroxybutyrate, and acetone. Two acetyl-CoA molecules combine, in a reversal of the final step of β-oxidation, to produce acetoacetyl-CoA. The acetoacetyl-CoA reacts with another molecule of acetyl-CoA and water to form β-hydroxy-β-methylglutaryl-CoA, which is then cleaved to acetoacetate and acetyl-CoA. Most of the acetoacetate is reduced to β-hydroxybutyrate, while a small amount is decarboxylated to carbon dioxide and acetone.



The acetoacetate and β-hydroxybutyrate synthesized by the liver are released into the blood for use as a metabolic fuel (to be converted back to acetyl-CoA) by other tissues, particularly the kidney and the heart. Thus, during prolonged starvation, ketone bodies provide about 70% of the energy requirements of the brain. Under normal conditions, the kidneys excrete about 20 mg of ketone bodies each day, and the blood levels are maintained at about 1 mg of ketone bodies per 100 mL of blood.

In starvation, diabetes mellitus, and certain other physiological conditions in which cells do not receive sufficient amounts of carbohydrate, the rate of fatty acid oxidation increases to provide energy. This leads to an increase in the concentration of acetyl-CoA. The increased acetyl-CoA cannot be oxidized by the citric acid cycle because of a decrease in the concentration of oxaloacetate, which is diverted to glucose synthesis. In response, the rate of ketone body formation in the liver increases further, to a level much higher than can be used by other tissues. The excess ketone bodies accumulate in the blood and the urine, a condition referred to as *ketosis*. When the acetone in the blood reaches the lungs, its volatility causes it to be expelled in the breath. The sweet smell of acetone, a characteristic of ketosis, is frequently noticed on the breath of severely diabetic patients.

Because two of the three kinds of ketone bodies are weak acids, their presence in the blood in excessive amounts overwhelms the blood buffers and causes a marked decrease in blood pH (to 6.9 from a normal value of 7.4). This decrease in pH leads to a serious condition known as *acidosis*. One of the effects of acidosis is a decrease in the ability of hemoglobin to transport oxygen in the blood. In moderate to severe acidosis, breathing becomes labored and very painful. The body also loses fluids and becomes dehydrated as the kidneys attempt to get rid of the acids by eliminating large quantities of water. The lowered oxygen supply and dehydration lead to depression; even mild acidosis leads to lethargy, loss of appetite, and a generally run-down feeling. Untreated patients may go into a coma. At that point, prompt treatment is necessary if the person's life is to be saved.

ATP Yield from Fatty Acid Oxidation

The amount of ATP obtained from fatty acid oxidation depends on the size of the fatty acid being oxidized. For our purposes here. we'll study palmitic acid, a saturated fatty acid with 16 carbon atoms, as a typical fatty acid in the human diet. Calculating its energy yield provides a model for determining the ATP yield of all other fatty acids.

The breakdown by an organism of 1 mol of palmitic acid requires 1 mol of ATP (for activation) and forms 8 mol of acetyl-CoA. Recall from Table 20.4.1 that each mole of acetyl-CoA metabolized by the citric acid cycle yields 10 mol of ATP. The complete degradation of 1 mol of palmitic acid requires the β-oxidation reactions to be repeated seven times. Thus, 7 mol of NADH and 7 mol of $FADH_2$ are produced. Reoxidation of these compounds through respiration yields 2.5–3 and 1.5–2 mol of ATP, respectively. The energy calculations can be summarized as follows:

ATP Yield from Fatty Acid Oxidation

1 mol of ATP is split to AMP and $2P_i$	−2 ATP
8 mol of acetyl-CoA formed (8 × 12)	96 ATP
7 mol of $FADH_2$ formed (7 × 2)	14 ATP
7 mol of NADH formed (7 × 3)	21 ATP
Total	129 ATP

> *The number of times β-oxidation is repeated for a fatty acid containing n carbon atoms is n/2 – 1 because the final turn yields two acetyl-CoA molecules.*

The combustion of 1 mol of palmitic acid releases a considerable amount of energy:

$$C_{16}H_{32}O_2 + 23O_2 \rightarrow 16CO_2 + 16H_2O + 2,340\ kcal$$

The percentage of this energy that is conserved by the cell in the form of ATP is as follows:

$$\frac{\text{energy conserved}}{\text{total energy available}} \times 100 = \frac{(129\ \text{ATP})(7.4\ \text{kcal/ATP})}{2,340\ \text{kcal}} \times 100 = 41\%$$

The efficiency of fatty acid metabolism is comparable to that of carbohydrate metabolism, which we calculated to be 42%. For more information about the efficiency of fatty acid metabolism, see II of Carbohydrate Catabolism" data-cke-saved-href="/Bookshelves/Introductory_Chemistry/Basics_of_General_Organic_and_Biological_Chemistry_(Ball_et_al.)/20:_Energy_Metabolism/20.05:_Stage_II_of_Carbohydrate_Catabolism" href="/Bookshelves/Introductory_Chemistry/Basics_of_General_Organic_and_Biological_Chemistry_(Ball_et_al.)/20:_Energy_Metabolism/20.05:_Stage_II_of_Carbohydrate_Catabolism" data-quail-id="91">Section 20.5.

> *The oxidation of fatty acids produces large quantities of water. This water, which sustains migratory birds and animals (such as the camel) for long periods of time.*

Summary

- Fatty acids, obtained from the breakdown of triglycerides and other lipids, are oxidized through a series of reactions known as β-oxidation.
- In each round of β-oxidation, 1 molecule of acetyl-CoA, 1 molecule of NADH, and 1 molecule of $FADH_2$ are produced.
- The acetyl-CoA, NADH, and $FADH_2$ are used in the citric acid cycle, the electron transport chain, and oxidative phosphorylation to produce ATP.

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11.8: Stage II of Protein Catabolism

Learning Objectives

- To describe how excess amino acids are degraded.

The liver is the principal site of amino acid metabolism, but other tissues, such as the kidney, the small intestine, muscles, and adipose tissue, take part. Generally, the first step in the breakdown of amino acids is the separation of the amino group from the carbon skeleton, usually by a transamination reaction. The carbon skeletons resulting from the deaminated amino acids are used to form either glucose or fats, or they are converted to a metabolic intermediate that can be oxidized by the citric acid cycle. The latter alternative, amino acid catabolism, is more likely to occur when glucose levels are low—for example, when a person is fasting or starving.

Transamination

Transamination is an exchange of functional groups between any amino acid (except lysine, proline, and threonine) and an α-keto acid. The amino group is usually transferred to the keto carbon atom of pyruvate, oxaloacetate, or α-ketoglutarate, converting the α-keto acid to alanine, aspartate, or glutamate, respectively. Transamination reactions are catalyzed by specific transaminases (also called aminotransferases), which require pyridoxal phosphate as a coenzyme.

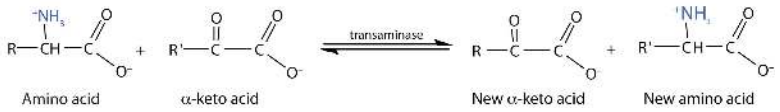


Figure 11.8.1).

> *In an α-keto acid, the carbonyl or keto group is located on the carbon atom adjacent to the carboxyl group of the acid.*

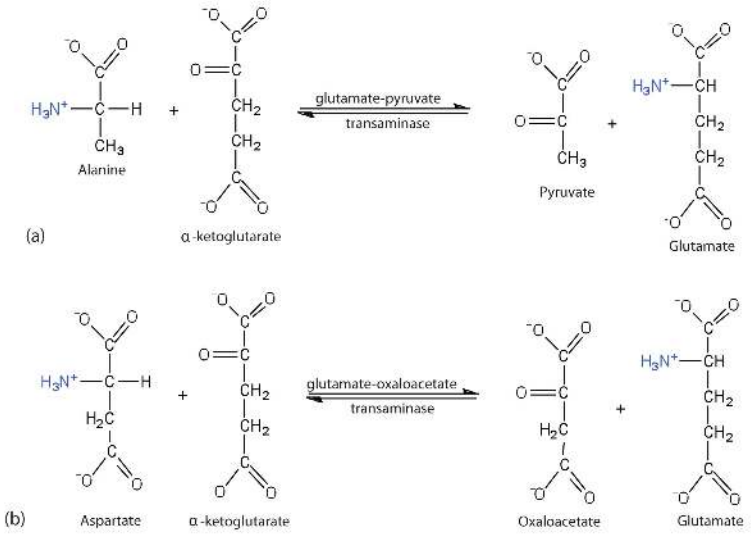
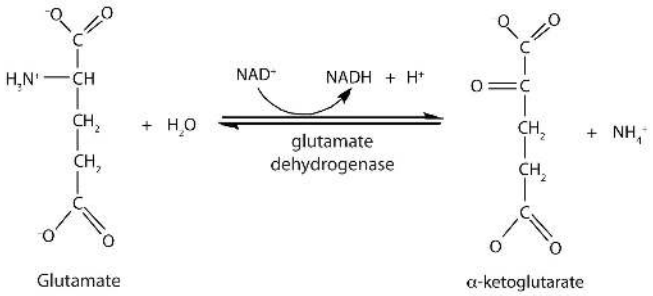


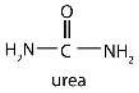
Figure 11.8.1: Two Transamination Reactions. In both reactions, the final acceptor of the amino group is α-ketoglutarate, and the final product is glutamate.

Oxidative Deamination

In the breakdown of amino acids for energy, the final acceptor of the α-amino group is α-ketoglutarate, forming glutamate. Glutamate can then undergooxidative deamination, in which it loses its amino group as an ammonium (NH_4^+) ion and is oxidized back to α-ketoglutarate (ready to accept another amino group):



This reaction occurs primarily in liver mitochondria. Most of the NH_4^+ ion formed by oxidative deamination of glutamate is converted to urea and excreted in the urine in a series of reactions known as the **urea cycle**.



The synthesis of glutamate occurs in animal cells by reversing the reaction catalyzed by glutamate dehydrogenase. For this reaction nicotinamide adenine dinucleotide phosphate (NADPH) acts as the reducing agent. The synthesis of glutamate is significant because it is one of the few reactions in animals that can incorporate inorganic nitrogen (NH_4^+) into an α-keto acid to form an amino acid. The amino group can then be passed on through transamination reactions, to produce other amino acids from the appropriate α-keto acids.

The Fate of the Carbon Skeleton

Any amino acid can be converted into an intermediate of the citric acid cycle. Once the amino group is removed, usually by transamination, the α-keto acid that remains is catabolized by a pathway unique to that acid and consisting of one or more reactions. For example, phenylalanine undergoes a series of six reactions before it splits into fumarate and acetoacetate. Fumarate is an intermediate in the citric acid cycle, while acetoacetate must be converted to acetoacetyl-coenzyme A (CoA) and then to acetyl-CoA before it enters the citric acid cycle.

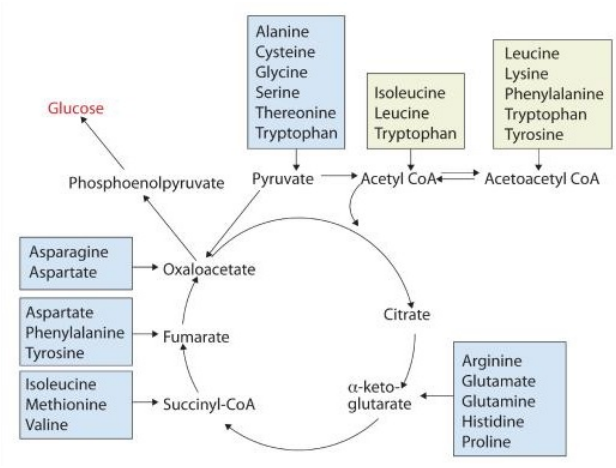


Figure **11.8.2**: Fates of the Carbon Skeletons of Amino Acids

Those amino acids that can form any of the intermediates of carbohydrate metabolism can subsequently be converted to glucose via a metabolic pathway known as gluconeogenesis. These amino acids are called glucogenic amino acids. Amino acids that are converted to acetoacetyl-CoA or acetyl-CoA, which can be used for the synthesis of ketone bodies but not glucose, are called ketogenic amino acids. Some amino acids fall into both categories. Leucine and lysine are the only amino acids that are exclusively ketogenic. Figure **11.8.2** summarizes the ultimate fates of the carbon skeletons of the 20 amino acids.

Career Focus: Exercise Physiologist

An exercise physiologist works with individuals who have or wish to prevent developing a wide variety of chronic diseases, such as diabetes, in which exercise has been shown to be beneficial. Each individual must be referred by a licensed physician. An exercise physiologist works in a variety of settings, such as a hospital or in a wellness program at a commercial business, to design and monitor individual exercise plans. A registered clinical exercise physiologist must have an undergraduate degree in exercise physiology or a related degree. Some job opportunities require a master's degree in exercise physiology or a related degree.



Ergospirometry laboratory for the measurement of metabolic changes during a graded exercise test on a treadmill. from Wikipedia.

Summary

Generally the first step in the breakdown of amino acids is the removal of the amino group, usually through a reaction known as transamination. The carbon skeletons of the amino acids undergo further reactions to form compounds that can either be used for the synthesis of glucose or the synthesis of ketone bodies.

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11.E: Energy Metabolism (Exercises)

20.1: ATP- the Universal Energy Currency

Concept Review Exercise

1. Why is ATP referred to as the energy currency of the cell?

Answer

1. ATP is the principal molecule involved in energy exchange reactions in biological systems.

Exercises

1. How do ATP and ADP differ in structure?
2. Why does the hydrolysis of ATP to ADP involve the release of energy?
3. Identify whether each compound would be classified as a high-energy phosphate compound.
   a. ATP
   b. glucose 6-phosphate
   c. creatine phosphate
4. Identify whether each compound would be classified as a high-energy phosphate compound.
   a. ADP
   b. AMP
   c. glucose 1-phosphate

Answers

1. ATP has a triphosphate group attached, while ADP has only a diphosphate group attached.

3. a. yes
   b. no
   c. yes

20.2: Stage I of Catabolism

Concept Review Exercises

1. Distinguish between each pair of compounds.
   a. pepsin and pepsinogen
   b. chymotrypsin and trypsin
   c. aminopeptidase and carboxypeptidase
2. What are the primary end products of each form of digestion?
   a. carbohydrate digestion
   b. lipid digestion
   c. protein digestion
3. In what section of the digestive tract does most of the carbohydrate, lipid, and protein digestion take place?

Answers

1. a. Pepsinogen is an inactive form of pepsin; pepsin is the active form of the enzyme.
   b. Both enzymes catalyze the hydrolysis of peptide bonds. Chymotrypsin catalyzes the hydrolysis of peptide bonds following aromatic amino acids, while trypsin catalyzes the hydrolysis of peptide bonds following lysine and arginine.
   c. Aminopeptidase catalyzes the hydrolysis of amino acids from the N-terminal end of a protein, while carboxypeptidase catalyzes the hydrolysis of amino acids from the C-terminal end of a protein.
2. a. glucose, fructose, and galactose

b. monoglycerides and fatty acids
c. amino acids

3. the small intestine

Exercises

1. What are the products of digestion (or stage I of catabolism)?
2. What is the general type of reaction used in digestion?
3. Give the site of action and the function of each enzyme.
   a. chymotrypsin
   b. lactase
   c. pepsin
   d. maltase
4. Give the site of action and the function of each enzyme.
   a. α-amylase
   b. trypsin
   c. sucrase
   d. aminopeptidase
5. a. What is the meaning of the following statement? “Bile salts act to emulsify lipids in the small intestine.”
   b. Why is emulsification important?
6. Using chemical equations, describe the chemical changes that triglycerides undergo during digestion.
7. What are the expected products from the enzymatic action of chymotrypsin on each amino acid segment?
   a. gly-ala-phe-thr-leu
   b. ala-ile-tyr-ser-arg
   c. val-trp-arg-leu-cys
8. What are the expected products from the enzymatic action of trypsin on each amino acid segment?
   a. leu-thr-glu-lys-ala
   b. phe-arg-ala-leu-val
   c. ala-arg-glu-trp-lys

Answers

1. proteins: amino acids; carbohydrates: monosaccharides; fats: fatty acids and glycerol
3. a. Chymotrypsin is found in the small intestine and catalyzes the hydrolysis of peptide bonds following aromatic amino acids.
   b. Lactase is found in the small intestine and catalyzes the hydrolysis of lactose.
   c. Pepsin is found in the stomach and catalyzes the hydrolysis of peptide bonds, primarily those that occur after aromatic amino acids.
   d. Maltase is found in the small intestine and catalyzes the hydrolysis of maltose.
5. a. Bile salts aid in digestion by dispersing lipids throughout the aqueous solution in the small intestine.
   b. Emulsification is important because lipids are not soluble in water; it breaks lipids up into smaller particles that can be more readily hydrolyzed by lipases.
7. a. gly-ala-phe and thr-leu
   b. ala-ile-tyr and ser-arg
   c. val-trp and arg-leu-cys

20.3: Overview of Stage II of Catabolism

Concept Review Exercises

1. What is a metabolic pathway?
2. What vitamin is required to make coenzyme A?
3. What is the net yield of Glycolysis as far as ATP?
4. Name the enzymes that are key regulatory sites in Glycolysis.
5. Why are the enzymes in the previous question targets for regulation?
6. Why is the priming phase necessary?
7. Draw the entire pathway for glycolysis including enzymes, reactants and products for each step.
8. Where does beta-oxidation occur?
9. What is the average net yield of ATP per carbon?
10. Where exactly is water formed during the process of fatty acid degradation? (Hint: H_2O is formed when when the one of the products of beta-oxidation is passed through another of the metabolic pathways)
11. During the process of beta-oxidation, why is it that [FAD] is used to oxidize an alkane to an alkene while NAD^+ is used to oxidize an alchol to a carbonyl
12. Draw out the entire process of the degradation of a triglyceride, include enzymes and products and reactants for each step.

Answers

1. A metabolic pathway is a series of biochemical reactions by which an organism converts a given reactant to a specific end product.
2. pantothenic acid

20.4: Stage III of Catabolism

Concept Review Exercises

1. What is the main function of the citric acid cycle?
2. Two carbon atoms are fed into the citric acid cycle as acetyl-CoA. In what form are two carbon atoms removed from the cycle?
3. What are mitochondria and what is their function in the cell?

Answers

1. the complete oxidation of carbon atoms to carbon dioxide and the formation of a high-energy phosphate compound, energy rich reduced coenzymes (NADH and $FADH_2$), and metabolic intermediates for the synthesis of other compounds
2. as carbon dioxide
3. Mitochondria are small organelles with a double membrane that contain the enzymes and other molecules needed for the production of most of the ATP needed by the body.

Exercises

1. Replace each question mark with the correct compound.
   a. $\text{?} \xrightarrow{\text{aconitase}} \text{isocitrate}$
   b. $\text{?} + \text{?} \xrightarrow{\text{citrate synthase}} \text{citrate} + \text{coenzyme A}$
   c. $\text{fumarate} \xrightarrow{\text{fumarase}} \text{?}$
   d. $\text{isocitrate} + \text{NAD}^+ \xrightarrow{\text{?}} \alpha\text{-ketoglurate} + \text{NADH} + \text{CO}_2$

2. Replace each question mark with the correct compound.

   a. $\text{malate} + \text{NAD}^+ \xrightarrow{?} \text{oxaloacetate} + \text{NADH}$

   b. $? + ? \xrightarrow{\text{nucleoside diphosphokinase}} \text{GDP} + \text{ATP}$

   c. $\text{succinyl-CoA} \xrightarrow{\text{succinyl-CoA synthetase}} ? + ?$

   d. $\text{succinate} + \text{FAD} \xrightarrow{\text{succinate dehydrogenase}} ? + \text{FADH}_2$

3. From the reactions in Exercises 1 and 2, select the equation(s) by number and letter in which each type of reaction occurs.

   a. isomerization

   b. hydration

   c. synthesis

4. From the reactions in Exercises 1 and 2, select the equation(s) by number and letter in which each type of reaction occurs.

   a. oxidation

   b. decarboxylation

   c. phosphorylation

5. What similar role do coenzyme Q and cytochrome c serve in the electron transport chain?

6. What is the electron acceptor at the end of the electron transport chain? To what product is this compound reduced?

7. What is the function of the cytochromes in the electron transport chain?

8. a. What is meant by this statement? “Electron transport is tightly coupled to oxidative phosphorylation.”

   b. How are electron transport and oxidative phosphorylation coupled or linked?

Answers

1. a. citrate

   b. oxaloacetate + acetyl-CoA

   c. malate

   d. α-ketoglutarate hydrogenase complex

3. a. reaction in 1a

   b. reaction in 1c

   c. reaction in 1b

5. Both molecules serve as electron shuttles between the complexes of the electron transport chain.

7. Cytochromes are proteins in the electron transport chain and serve as one-electron carriers.

20.5: Stage II of Carbohydrate Catabolism

- ### Concept Review Exercises

  1. In glycolysis, how many molecules of pyruvate are produced from one molecule of glucose?

  2. In vertebrates, what happens to pyruvate when

     a. plenty of oxygen is available?

     b. oxygen supplies are limited?

  3. In anaerobic glycolysis, how many molecules of ATP are produced from one molecule of glucose?

  #### Answers

  1. two

  2. a. Pyruvate is completely oxidized to carbon dioxide.

     b. Pyruvate is reduced to lactate, allowing for the reoxidation of NADH to NAD^+.

  3. There is a net production of two molecules of ATP.

Exercises

1. Replace each question mark with the correct compound.

   a. $\text{fructose 1, 6-bisphosphate} \xrightarrow{\text{aldolase}} ? + ?$

   b. $? + \text{ADP} \xrightarrow{\text{pyruvate kinase}} \text{pyruvate} + \text{ATP}$

   c. $\text{dihydroxyacetone phosphate} \xrightarrow{?} \text{glyceraldehyde 3-phosphate}$

   d. $\text{glucose} + \text{ATP} \xrightarrow{\text{hexokinase}} ? + \text{ADP}$

2. Replace each question mark with the correct compound.

   a. $\text{fructose 6-phosphate} + \text{ATP} \xrightarrow{?} \text{fructose 1, 6-bisphosphate} + \text{ADP}$

   b. $? \xrightarrow{\text{phosphoglucose isomerase}} \text{fructose 6-phosphate}$

   c. $\text{glyceraldehyde 3-phosphate} + \text{NAD}^+ + \text{P}_\text{i} \xrightarrow{?} \text{1, 3-bisphosphoglycerate} + \text{NADH}$

   d. $\text{3-phosphoglycerate} \xrightarrow{\text{phosphoglyceromutase}} ?$

3. From the reactions in Exercises 1 and 2, select the equation(s) by number and letter in which each type of reaction occurs.

   a. hydrolysis of a high-energy phosphate compound

   b. synthesis of ATP

4. From the reactions in Exercises 1 and 2, select the equation(s) by number and letter in which each type of reaction occurs.

   a. isomerization

   b. oxidation

5. What coenzyme is needed as an oxidizing agent in glycolysis?

6. Calculate

   a. the *total* number of molecules of ATP produced for each molecule of glucose converted to pyruvate in glycolysis.

   b. the number of molecules of ATP hydrolyzed in phase I of glycolysis.

   c. the *net* ATP production from glycolysis alone.

7. How is the NADH produced in glycolysis reoxidized when oxygen supplies are limited in

   a. muscle cells?

   b. yeast?

8. a. Calculate the number of moles of ATP produced by the aerobic oxidation of 1 mol of glucose in a liver cell.

   b. Of the total calculated in Exercise 9a, determine the number of moles of ATP produced in each process.

      a. glycolysis alone

      b. the citric acid cycle

      c. the electron transport chain and oxidative phosphorylation

Answers

1. a. glyceraldehyde 3-phosphate + dihydroxyacetone phosphate

   b. phosphoenolpyruvate

   c. triose phosphate isomerase

   d. glucose 6-phosphate

3. a. reactions 1b, 1d, and 2a

   b. reaction 1b

5. NAD^+

7. a. Pyruvate is reduced to lactate, and NADH is reoxidized to NAD^+.

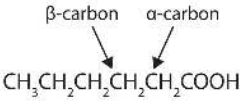
   b. Pyruvate is converted to ethanol and carbon dioxide, and NADH is reoxidized to NAD^+.

20.6: Stage II of Lipid Catabolism

- ### Concept Review Exercises

1. How are fatty acids activated prior to being transported into the mitochondria and oxidized?
2. Draw the structure of hexanoic (caproic) acid and identify the α-carbon and the β-carbon.

Answers

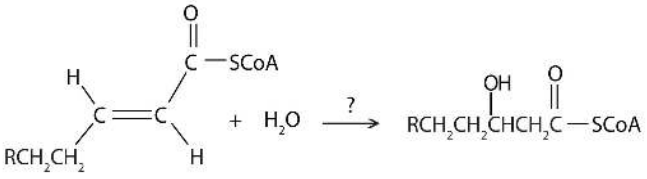
1. They react with CoA to form fatty acyl-CoA molecules.
2. 

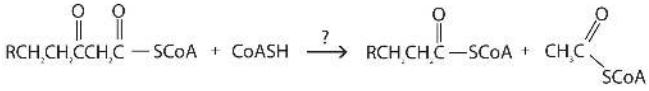
Key Takeaways

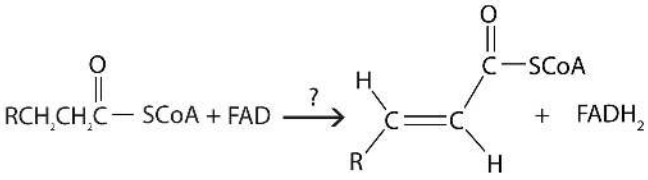
- Fatty acids, obtained from the breakdown of triglycerides and other lipids, are oxidized through a series of reactions known as β-oxidation.
- In each round of β-oxidation, 1 molecule of acetyl-CoA, 1 molecule of NADH, and 1 molecule of $FADH_2$ are produced.
- The acetyl-CoA, NADH, and $FADH_2$ are used in the citric acid cycle, the electron transport chain, and oxidative phosphorylation to produce ATP.

Exercises

1. For each reaction found in β-oxidation, identify the enzyme that catalyzes the reaction and classify the reaction as oxidation-reduction, hydration, or cleavage.

a. 

b. 

c. 

2. What are the products of β-oxidation?
3. How many rounds of β-oxidation are necessary to metabolize lauric acid (a saturated fatty acid with 12 carbon atoms)?
4. How many rounds of β-oxidation are necessary to metabolize arachidic acid (a saturated fatty acid with 20 carbon atoms)?
5. When myristic acid (a saturated fatty acid with 14 carbon atoms) is completely oxidized by β-oxidation, how many molecules of each are formed?
   a. acetyl-CoA
   b. $FADH_2$
   c. NADH
6. When stearic acid (a saturated fatty acid with 18 carbon atoms) is completely oxidized by β-oxidation, how many molecules of each are formed?
   a. acetyl-CoA

b. $FADH_2$

c. NADH

7. What is the net yield of ATP from the complete oxidation, in a liver cell, of one molecule of myristic acid?
8. What is the net yield of ATP from the complete oxidation, in a liver cell, of one molecule of stearic acid?

Answers

1. a. enoyl-CoA hydratase; hydration

   b. thiolase; cleavage

   c. acyl-CoA dehydrogenase; oxidation-reduction

3. five rounds
5. a. 7 molecules

   b. 6 molecules

   c. 6 molecules

7. 112 molecules

20.7: Stage II of Protein Catabolism

Concept Review Exercises

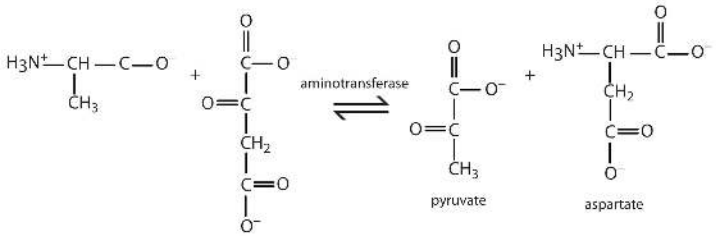
1. a. Write the equation for the transamination reaction between alanine and oxaloacetate.

   b. Name the two products that are formed.

2. What is the purpose of oxidative deamination?

Answers

1. a.



   b. pyruvate and aspartate

2. Oxidative deamination provides a reaction in which the amino group [as the ammonium (NH_4^+) ion] is removed from a molecule, not simply transferred from one molecule to another. Most of the NH_4^+ ion is converted to urea and excreted from the body.

Exercises

1. Write the equation for the transamination reaction between valine and pyruvate.
2. Write the equation for the transamination reaction between phenylalanine and oxaloacetate.
3. What products are formed in the oxidative deamination of glutamate?
4. Determine if each amino acid is glucogenic, ketogenic, or both.

   a. phenylalanine

   b. leucine

   c. serine

5. Determine if each amino acid is glucogenic, ketogenic, or both.

   a. asparagine

   b. tyrosine

   c. valine

Answers



1.

3. α-ketoglutarate, NADH, and NH_4^+

5. a. glucogenic
   b. both
   c. glucogenic

Additional Exercises

1. Hydrolysis of which compound—arginine phosphate or glucose 6-phosphate—would provide enough energy for the phosphorylation of ATP? Why?
2. If a cracker, which is rich in starch, is chewed for a long time, it begins to develop a sweet, sugary taste. Why?
3. Indicate where each enzymes would cleave the short peptide ala-ser-met-val-phe-gly-cys-lys-asp-leu.

   a. aminopeptidase
   b. chymotrypsin

4. Indicate where each enzymes would cleave the short peptide ala-ser-met-val-phe-gly-cys-lys-asp-leu.

   a. trypsin
   b. carboxypeptidase

5. If the methyl carbon atom of acetyl-CoA is labeled, where does the label appear after the acetyl-CoA goes through one round of the citric acid cycle?
6. If the carbonyl carbon atom of acetyl-CoA is labeled, where does the label appear after the acetyl-CoA goes through one round of the citric acid cycle?
7. The average adult consumes about 65 g of fructose daily (either as the free sugar or from the breakdown of sucrose). In the liver, fructose is first phosphorylated to fructose 1-phosphate, which is then split into dihydroxyacetone phosphate and glyceraldehyde. Glyceraldehyde is then phosphorylated to glyceraldehyde 3-phosphate, with ATP as the phosphate group donor. Write the equations (using structural formulas) for these three steps. Indicate the type of enzyme that catalyzes each step.
8. What critical role is played by both BPG and PEP in glycolysis?
9. How is the NADH produced in glycolysis reoxidized when oxygen supplies are abundant?
10. When a triglyceride is hydrolyzed to form three fatty acids and glycerol, the glycerol can be converted to glycerol 3-phosphate and then oxidized to form dihydroxyacetone phosphate, an intermediate of glycolysis. (In this reaction, NAD^+ is reduced to NADH.) If you assume that there is sufficient oxygen to completely oxidize the pyruvate formed from dihydroxyacetone phosphate, what is the maximum amount of ATP formed from the complete oxidation of 1 mol of glycerol?
11. How is the $FADH_2$ from β-oxidation converted back to FAD?
12. If 1 mol of alanine is converted to pyruvate in a muscle cell (through transamination) and the pyruvate is then metabolized via the citric acid cycle, the electron transport chain, and oxidative phosphorylation, how many moles of ATP are produced?
13. If the essential amino acid leucine (2-amino-4-methylpentanoic acid) is lacking in the diet, an α-keto acid can substitute for it. Give the structure of the α-keto acid and the probable reaction used to form leucine from this α-keto acid.

Answers

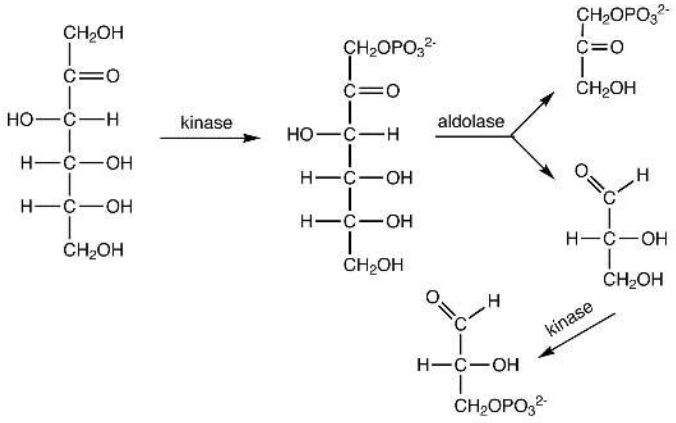
1. The hydrolysis of arginine phosphate releases more energy than is needed for the synthesis of ATP, while hydrolysis of glucose 6-phosphate does not.

3.

a. The enzyme will cleave off amino acids one at a time beginning with alanine (the N-terminal end).
b. following phenylalanine

5. Half of the label will be on the second carbon atom of oxaloacetate, while the other half will be on the third carbon atom.

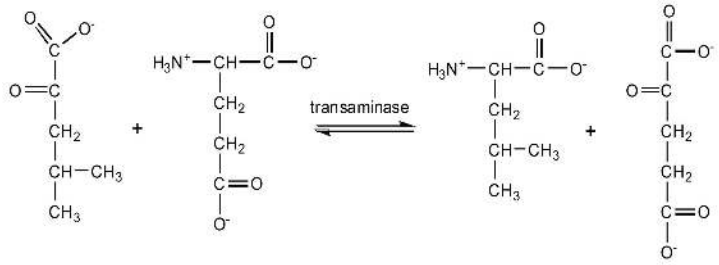
7.



9. When oxygen is abundant, NADH is reoxidized through the reactions of the electron transport chain.

11. $FADH_2$ is reoxidized back to FAD via the electron transport chain.

13.



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11.S: Energy Metabolism (Summary)

To ensure that you understand the material in this chapter, you should review the meanings of the bold terms in the following summary and ask yourself how they relate to the topics in the chapter.

Metabolism is the general term for all chemical reactions in living organisms. The two types of metabolism are **catabolism**—those reactions in which complex molecules (carbohydrates, lipids, and proteins) are broken down to simpler ones with the concomitant release of energy—and **anabolism**—those reactions that consume energy to build complex molecules. Metabolism is studied by looking at individual **metabolic pathways**, which are a series of biochemical reactions in which a given reactant is converted to a desired end product.

The oxidation of fuel molecules (primarily carbohydrates and lipids), a process called **respiration**, is the source of energy used by cells. Catabolic reactions release energy from food molecules and use some of that energy for the synthesis of *adenosine triphosphate* (ATP); anabolic reactions use the energy in ATP to create new compounds. Catabolism can be divided into three stages. In stage I, carbohydrates, lipids, and proteins are broken down into their individual monomer units—simple sugars, fatty acids, and amino acids, respectively. In stage II, these monomer units are broken down by specific metabolic pathways to form a common end product *acetyl-coenzyme A* (CoA). In stage III, acetyl-CoA is completely oxidized to form carbon dioxide and water, and ATP is produced.

The **digestion** of carbohydrates begins in the mouth as α-amylase breaks glycosidic linkages in carbohydrate molecules. Essentially no carbohydrate digestion occurs in the stomach, and food particles pass through to the small intestine, where α-amylase and intestinal enzymes convert complex carbohydrate molecules (starches) to monosaccharides. The monosaccharides then pass through the lining of the small intestine and into the bloodstream for transport to all body cells.

Protein digestion begins in the stomach as pepsinogen in **gastric juice** is converted to pepsin, the enzyme that hydrolyzes peptide bonds. The partially digested protein then passes to the small intestine, where the remainder of protein digestion takes place through the action of several enzymes. The resulting amino acids cross the intestinal wall into the blood and are carried to the liver.

Lipid digestion begins in the small intestine. Bile salts emulsify the lipid molecules, and then lipases hydrolyze them to fatty acids and monoglycerides. The hydrolysis products pass through the intestine and are repackaged for transport in the bloodstream.

In cells that are operating aerobically, acetyl-CoA produced in stage II of catabolism is oxidized to carbon dioxide. The **citric acid cycle** describes this oxidation, which takes place with the formation of the coenzymes reduced nicotinamide adenine dinucleotide (NADH) and reduced flavin adenine dinucleotide ($FADH_2$). The sequence of reactions needed to oxidize these coenzymes and transfer the resulting electrons to oxygen is called the **electron transport chain**, or the **respiratory chain**. The compounds responsible for this series of oxidation-reduction reactions include proteins known as **cytochromes**, Fe·S proteins, and other molecules that ultimately result in the reduction of molecular oxygen to water. Every time a compound with two carbon atoms is oxidized in the citric acid cycle, a respiratory chain compound accepts the electrons lost in the oxidation (and so is reduced) and then passes them on to the next metabolite in the chain. The energy released by the electron transport chain is used to transport hydrogen (H^+) ions from the mitochondrial matrix to the intermembrane space. The flow of H^+ back through ATP synthase leads to the synthesis and release of ATP from adenosine diphosphate (ADP) and inorganic phosphate ions (P_i) in a process known as **oxidative phosphorylation**. Electron transport and oxidative phosphorylation are tightly coupled to each other. The enzymes and intermediates of the citric acid cycle, the electron transport chain, and oxidative phosphorylation are located in organelles called **mitochondria**.

The oxidation of carbohydrates is the source of over 50% of the energy used by cells. Glucose is oxidized to two molecules of pyruvate through a series of reactions known as **glycolysis**. Some of the energy released in these reactions is conserved by the formation of ATP from ADP. Glycolysis can be divided into two phases: phase I consists of the first five reactions and requires energy to “prime” the glucose molecule for phase II, the last five reactions in which ATP is produced through **substrate-level phosphorylation**.

The pyruvate produced by glycolysis has several possible fates, depending on the organism and whether or not oxygen is present. In animal cells, pyruvate can be further oxidized to acetyl-CoA and then to carbon dioxide (through the citric acid cycle) if oxygen supplies are sufficient. When oxygen supplies are insufficient, pyruvate is reduced to lactate. In yeast and other microorganisms, pyruvate is not converted to lactate in the absence of oxygen but instead is converted to ethanol and carbon dioxide.

The amount of ATP formed by the oxidation of glucose depends on whether or not oxygen is present. If oxygen is present, glucose is oxidized to carbon dioxide, and 36–38 ATP molecules are produced for each glucose molecule oxidized, using the combined pathways of glycolysis, the citric acid cycle, the electron transport chain, and oxidative phosphorylation. Thus, approximately 42% of the energy released by the complete oxidation of glucose is conserved by the synthesis of ATP. In the absence of oxygen, only 2 molecules of ATP are formed for each molecule of glucose converted to lactate (2 molecules), and the amount of energy conserved is much less (2%).

Fatty acids, released by the degradation of triglycerides and other lipids, are converted to fatty acyl-CoA, transported into the mitochondria, and oxidized by repeated cycling through a sequence of four reactions known as **β-oxidation**. In each round of β-oxidation, the fatty acyl-CoA is shortened by two carbon atoms as one molecule of acetyl-CoA is formed. The final round of β-oxidation, once the chain has been shortened to four carbon atoms, forms two molecules of acetyl-CoA. β-oxidation also forms the reduced coenzymes $FADH_2$ and NADH, whose reoxidation through the electron transport chain and oxidative phosphorylation leads to the synthesis of ATP. The efficiency of fatty acid oxidation in the human body is approximately 41%.

Amino acids from the breakdown of proteins can be catabolized to provide energy. Amino acids whose carbon skeletons are converted to intermediates that can be converted to glucose through gluconeogenesis are known as **glucogenic amino acids**. Amino acids whose carbon skeletons are broken down to compounds used to form ketone bodies are known as **ketogenic amino acids**.

The first step in amino acid catabolism is separation of the amino group from the carbon skeleton. In a **transamination**, the amino acid gives its NH_2 to pyruvate, α-ketoglutarate, or oxaloacetate. The products of this reaction are a new amino acid and an α-keto acid containing the carbon skeleton of the original amino acid. Pyruvate is transaminated to alanine, α-ketoglutarate to glutamate, and oxaloacetate to aspartate. The amino groups used to form alanine and aspartate are ultimately transferred to α-ketoglutarate, forming glutamate. The glutamate then undergoes **oxidative deamination** to yield α-ketoglutarate and ammonia.

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