INTRODUCTORY BIOCHEMISTRY



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Introductory Biochemistry

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Licensing

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CHAPTER OVERVIEW

1: Organic Chemistry - Alkanes and Halogenated Hydrocarbons

We begin our study of organic chemistry with the alkanes, compounds containing only two elements, carbon and hydrogen, and having only single bonds. There are several other kinds of hydrocarbons, distinguished by the types of bonding between carbon atoms and by the properties that result from that bonding. We will first examine hydrocarbons with double bonds, with triple bonds, and with a special kind of bonding called aromaticity. Then we will study some compounds considered to be derived from hydrocarbons by replacing one or more hydrogen atoms with an oxygen-containing group. Finally, we focuse on organic acids and bases, after which we will be ready to look at the chemistry of life itself—biochemistry—in the remaining five chapters.

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1.1: Prelude to Organic Chemistry - Alkanes and Halogenated Hydrocarbons

Hydrocarbons are the simplest organic compounds, but they have interesting physiological effects. These effects depend on the size of the hydrocarbon molecules and where on or in the body they are applied. Alkanes of low molar mass—those with from 1 to approximately 10 or so carbon atoms—are gases or light liquids that act as anesthetics. Inhaling ("sniffing") these hydrocarbons in gasoline or aerosol propellants for their intoxicating effect is a major health problem that can lead to liver, kidney, or brain damage or to immediate death by asphyxiation by excluding oxygen.

Swallowed, liquid alkanes do little harm while in the stomach. In the lungs, however, they cause "chemical" pneumonia by dissolving fatlike molecules from cell membranes in the tiny air sacs (alveoli). The lungs become unable to expel fluids, just as in pneumonia caused by bacteria or viruses. People who swallow gasoline or other liquid alkane mixtures should not be made to vomit, as this would increase the chance of getting alkanes into the lungs. (There is no home-treatment antidote for gasoline poisoning; call a poison control center.)



Figure **1.1.1**: Butane is a hydrocarbon with the formula C_4H_{10} and is a gas at room temperature and atmospheric pressure. Under excess pressures, it can be liquidized like the fuel shown in this butane lighters. (CC BY-SA 3.0 Unported; Frank Vincentz via Wikipedia)

Liquid alkanes with approximately 5–16 carbon atoms per molecule wash away natural skin oils and cause drying and chapping of the skin, while heavier liquid alkanes (those with approximately 17 or more carbon atoms per molecule) act as emollients (skin softeners). Such alkane mixtures as mineral oil and petroleum jelly can be applied as a protective film. Water and aqueous solutions such as urine will not dissolve such a film, which explains why petroleum jelly protects a baby's tender skin from diaper rash.

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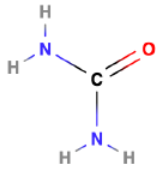
1.2: Organic Chemistry

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.

$$AgOCN + NH_4Cl \rightarrow AgCl + NH_4OCN \tag{1.2.1}$$



Instead, he found the product to be urea (NH_2CONH_2 or), a well-known organic material readily isolated from urine. This result 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 **1.2.1**.

Table **1.2.1**: 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 **1.2.1** 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 **1.2.1**.

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1.3: Branched-Chain Alkanes

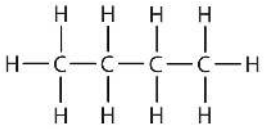
Learning Objectives

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

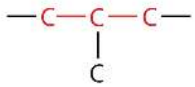
We can write the structure of butane (C_4H_{10}) by stringing four carbon atoms in a row,

–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.

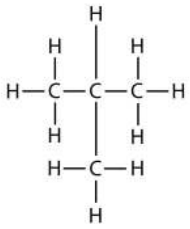


Figure **1.3.1**).

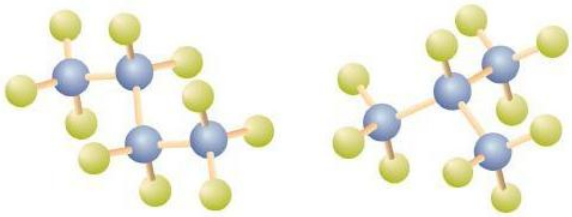
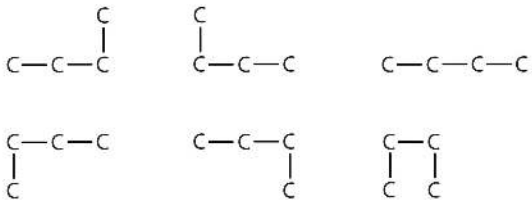


Figure **1.3.1**: Butane and Isobutane. The ball-and-stick models of these two compounds show them to be isomers; both have the molecular formula C_4H_{10}.

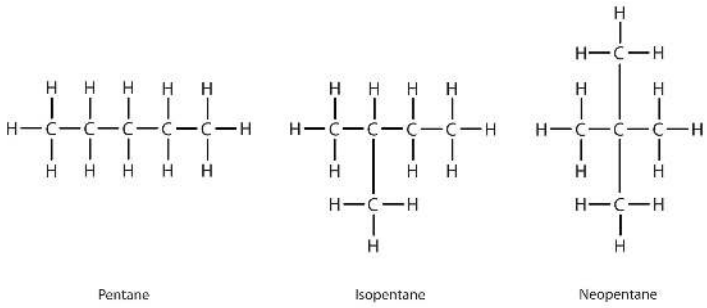
Notice that C_4H_{10} is depicted with a bent chain in Figure **1.3.1**. The four-carbon chain may be bent in various ways because the groups can rotate freely about the C–C bonds. However, this rotation does not change the identity of the compound. It is important to realize that bending a chain does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

Learning Objectives

- To identify and name simple (straight-chain) alkanes given formulas and write formulas for straight-chain alkanes given their names.

We begin our study of organic chemistry with the hydrocarbons, the simplest organic compounds, which are composed of carbon and hydrogen atoms only. As we noted, there are several different kinds of hydrocarbons. They are distinguished by the types of bonding between carbon atoms and the properties that result from that bonding. Hydrocarbons with only carbon-to-carbon single bonds (C–C) and existing as a continuous chain of carbon atoms also bonded to hydrogen atoms are called alkanes (or saturated hydrocarbons). *Saturated*, in this case, means that each carbon atom is bonded to four other atoms (hydrogen or carbon)—the most possible; there are no double or triple bonds in the molecules.

> The word *saturated* has the same meaning for hydrocarbons as it does for the dietary fats and oils: the molecule has no carbon-to-carbon double bonds (C=C).

We previously introduced the three simplest alkanes—methane (CH_4), ethane (C_2H_6), and propane (C_3H_8) and they are shown again in Figure **1.4.1**.

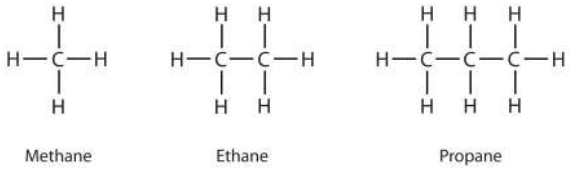


Figure **1.4.1**: The Three Simplest Alkanes

The flat representations shown do not accurately portray bond angles or molecular geometry. Methane has a tetrahedral shape that chemists often portray with wedges indicating bonds coming out toward you and dashed lines indicating bonds that go back away from you. An ordinary solid line indicates a bond in the plane of the page. Recall that the VSEPR theory correctly predicts a tetrahedral shape for the methane molecule (Figure **1.4.2**).

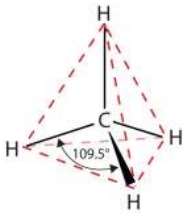


Figure **1.4.2**: The Tetrahedral Methane Molecule

Methane (CH_4), ethane (C_2H_6), and propane (C_3H_8) are the beginning of a series of compounds in which any two members in a sequence differ by one carbon atom and two hydrogen atoms—namely, a CH_2 unit. The first 10 members of this series are given in Table **1.4.1**.

Table **1.4.1**: The First 10 Straight-Chain Alkanes

Name	Molecular Formula (C_nH_{2n+2})	Condensed Structural Formula	Number of Possible Isomers
methane	CH_4	CH_4	—
ethane	C_2H_6	CH_3CH_3	—
propane	C_3H_8	$CH_3CH_2CH_3$	—
butane	C_4H_{10}	$CH_3CH_2CH_2CH_3$	2
pentane	C_5H_{12}	$CH_3CH_2CH_2CH_2CH_3$	3
hexane	C_6H_{14}	$CH_3CH_2CH_2CH_2CH_2CH_3$	5
heptane	C_7H_{16}	$CH_3CH_2CH_2CH_2CH_2CH_2CH_3$	9
octane	C_8H_{18}	$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_3$	18
nonane	C_9H_{20}	$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$	35
decane	$C_{10}H_{22}$	$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$	75

Consider the series in Figure **1.4.3**. The sequence starts with C_3H_8, and a CH_2 unit is added in each step moving up the series. Any family of compounds in which adjacent members differ from each other by a definite factor (here a CH_2 group) is called a homologous series. The members of such a series, called *homologs*, have properties that vary in a regular and predictable manner. The principle of *homology* gives organization to organic chemistry in much the same way that the periodic table gives organization to inorganic chemistry. Instead of a bewildering array of individual carbon compounds, we can study a few members of a homologous series and from them deduce some of the properties of other compounds in the series.

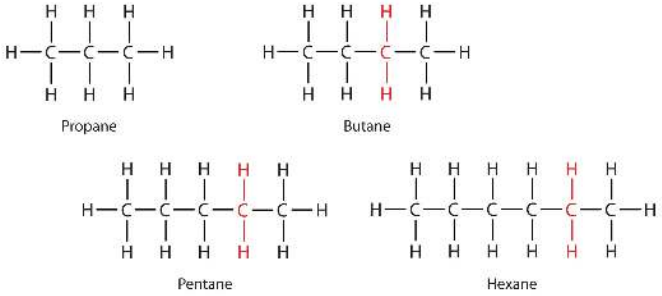


Figure **1.4.3**: Members of a Homologous Series. Each succeeding formula incorporates one carbon atom and two hydrogen atoms more than the previous formula.

The principle of homology allows us to write a general formula for alkanes: C_nH_{2n+2}. Using this formula, we can write a molecular formula for any alkane with a given number of carbon atoms. For example, an alkane with eight carbon atoms has the molecular formula $C_8H_{(2\times 8)+2} = C_8H_{18}$.

Key Takeaway

- Simple alkanes exist as a homologous series, in which adjacent members differ by a CH_2 unit.

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1.5: 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:



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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1.6: IUPAC Nomenclature

Learning Objectives

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

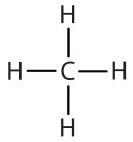
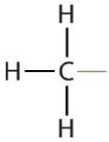
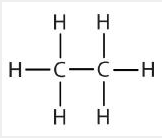
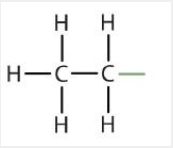
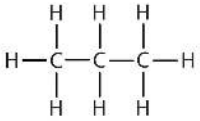
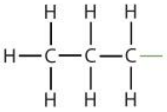
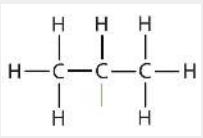
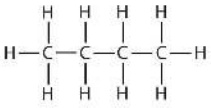
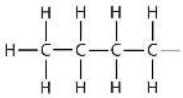
As noted in previously, the number of isomers increases rapidly as the number of carbon atoms increases. There are 3 pentanes, 5 hexanes, 9 heptanes, and 18 octanes. It would be difficult to assign unique individual names that we could remember. A systematic way of naming hydrocarbons and other organic 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 **1.6.1**) 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 **1.6.1**: 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 **1.6.2**. Alkyl groups are not independent molecules; they are parts of molecules that we consider as a unit to name compounds systematically.

Table **1.6.2**: Common Alkyl Groups

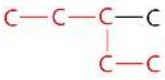
Parent Alkane		Alkyl Group		Condensed Structural Formula
methane		methyl		$CH_3–$
ethane		ethyl		$CH_3CH_2–$
propane		propyl		$CH_3CH_2CH_2–$
		isopropyl		$(CH_3)_2CH–$
butane		butyl*		$CH_3CH_2CH_2CH_2–$

*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 **1.6.1**).

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.)

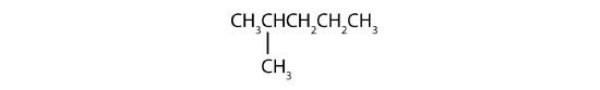


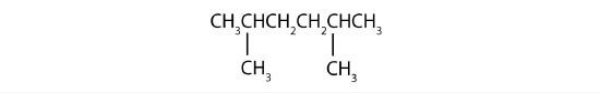
3. **Place the names of the substituent groups in alphabetical order before the name of the parent compound.** If the same alkyl group appears more than once, the numbers of all the carbon atoms to which it is attached are expressed. If the same group appears more than once on the same carbon atom, the 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.

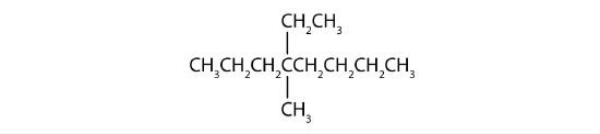
When these rules are followed, every unique compound receives its own exclusive name. The rules enable us to not only name a compound from a given structure but also draw a structure from a given name. The best way to learn how to use the IUPAC system is to put it to work, not just memorize the rules.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

Example 1.6.1

Name each compound.

1. 

2. 

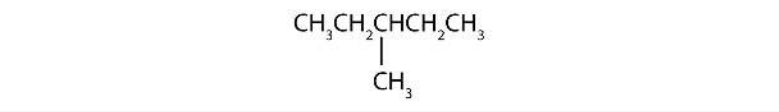
3. 

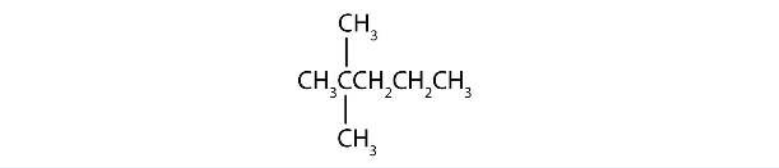
Solution

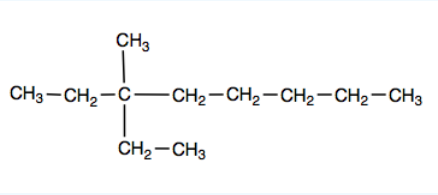
1. The LCC has five carbon atoms, and so the parent compound is pentane (rule 1). There is a methyl group (rule 2) attached to the second carbon atom of the pentane chain. The name is therefore 2-methylpentane.
2. The LCC has six carbon atoms, so the parent compound is hexane (rule 1). Methyl groups (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 1.6.1

Name each compound.

1. 

2. 

3. 

Example 1.6.2

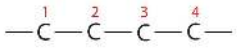
Draw the structure for each compound.

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

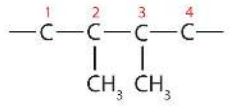
Solution

In drawing structures, always start with the parent chain.

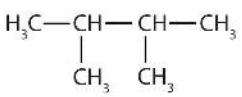
a. The parent chain is butane, indicating four carbon atoms in the LCC.



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.

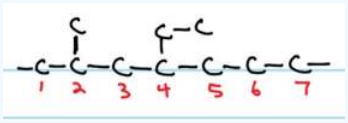


Finally, fill in all the hydrogen atoms, keeping in mind that each carbon atom must have four bonds.

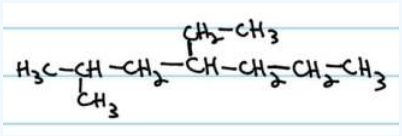


b. The parent chain is heptane in this case, indicating seven carbon atoms in the LCC. –C–C–C–C–C–C–C–

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 1.6.2

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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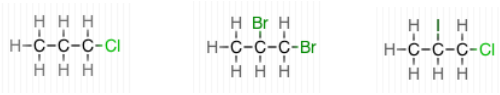
1.7: Halogenated Hydrocarbons

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:

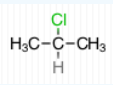


The replacement of only one hydrogen atom gives an alkyl halide (or haloalkane). The *common names* of alkyl halides consist of two parts: the name of the alkyl group plus the stem of the name of the halogen, with the ending *-ide*. The IUPAC system uses the name of the parent alkane with a prefix indicating 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 IUPAC names for each compound.

a. $CH_3CH_2CH_2Br$

b. 

Solution

a. The molecule is a propane with a halogen bromine (Br). 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 molecule is a propane with a halogen chlorine (Cl) atom attached to the middle carbon atom. 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

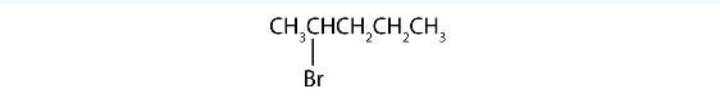
Give the IUPAC names for each compound.

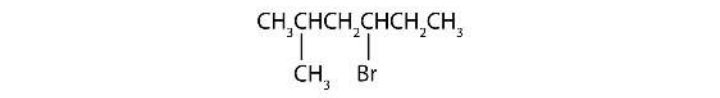
a. CH_3CH_2I

b. $CH_3CH_2CH_2CH_2F$

Example 1.7.2

Give the IUPAC name for each compound.

1. 

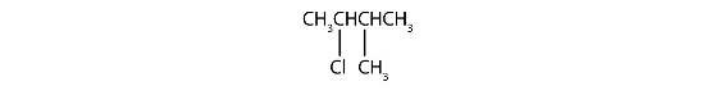
2. 

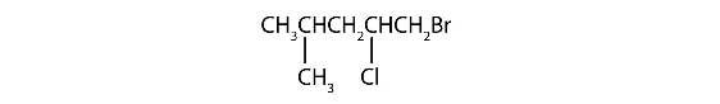
Solution

1. The parent alkane has five carbon atoms in the longest continuous chain; it is pentane. A bromo (Br) group is attached to the second carbon atom of the chain. The IUPAC name is 2-bromopentane.
2. The parent alkane is hexane. Methyl (CH_3) and bromo (Br) groups are attached to the second and fourth carbon atoms, respectively. Listing the substituents in alphabetical order gives the name 4-bromo-2-methylhexane.

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.

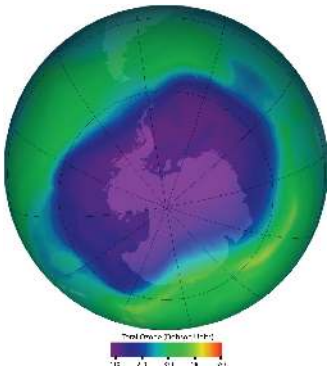
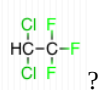


Figure **1.7.1**: Ozone in the upper atmosphere shields Earth's surface from UV radiation from the sun, which can cause skin cancer in humans and is also harmful to other animals and to some plants. Ozone "holes" in the upper atmosphere (the gray, pink, and purple areas at the center) are large areas 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, http://ozonewatch.gsfc.nasa.gov/daily.php?date=2006-09-24.

Concept Review Exercises

1. What is the IUPAC name for the HFC that has the formula  ?(Hint: you must use a number to indicate the location of each substituent F atom.)

2. What is the IUPAC name for the HCFC that has the formula  ?

Answers

1. 1,1,1,2-tetrafluoroethane
2. 2,2-dichloro-1,1,1-trifluoroethane

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: 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 1.8.1) and is called cyclopropane.

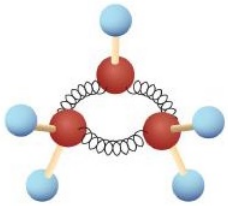
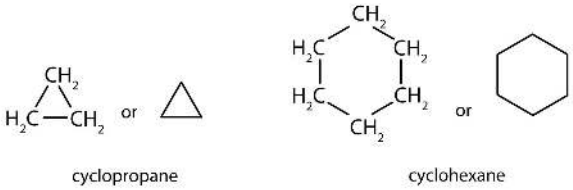


Figure 1.8.1: Ball-and-Spring Model of Cyclopropane. The springs are bent to join the carbon atoms.

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 1.8.1 interprets the name of a cycloalkane with a single substituent group.

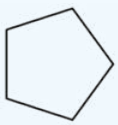
Example 1.8.1

Draw the structure for each compound.

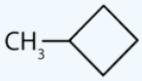
a. cyclopentane
b. methylcyclobutane

Solution

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



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 1.8.1

Draw the structure for each compound.

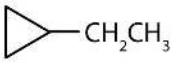
a. cycloheptane
b. ethylcyclohexane

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 1.8.1.) Cyclopentane and cyclohexane rings have little strain because the C–C–C angles are near the preferred angles.

Concept Review Exercises

1. What is the molecular formula of cyclooctane?
2. What is the IUPAC name for this compound?



Answers

1. C_8H_{16}
2. ethylcyclopropane

Key Takeaway

- Many organic compounds have cyclic structures.

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1.9: 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 **1.9.1** 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 **1.9.1**: 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 **1.9.1**: 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, http://www.nasa.gov/topics/earth/features/oilspill/oil-20100519a.html.

Looking Closer: Gas Densities and Fire Hazards

Table **1.9.1** 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 **1.9.1** 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.

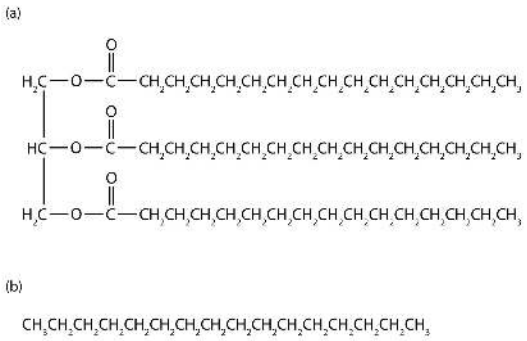


Figure **1.9.2**: Tripalmitin (a), a typical fat molecule, has long hydrocarbon chains typical of most lipids. Compare these chains to hexadecane (b), an alkane with 16 carbon atoms.

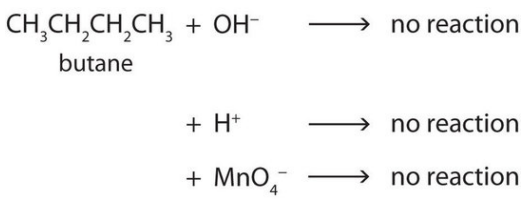
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1.10: Chemical Properties of Alkanes

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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1.11: Organic Chemistry

Learning Objectives

- Define *organic chemistry*.
- Identify organic molecules as alkanes, alkenes, alkynes, alcohols, or carboxylic acids.

When methane was mentioned previously, we described it as the simplest organic compound. In this section, we introduce organic chemistry more formally. Organic chemistry is the study of the chemistry of carbon compounds. Carbon is singled out because it has a chemical diversity unrivaled by any other chemical element. Its diversity is based on the following:

- Carbon atoms bond reasonably strongly with other carbon atoms.
- Carbon atoms bond reasonably strongly with atoms of other elements.
- Carbon atoms make a large number of covalent bonds (four).

Curiously, elemental carbon is not particularly abundant. It does not even appear in the list of the most common elements in Earth's crust. Nevertheless, all living things consist of organic compounds. Most organic chemicals are covalent compounds, which is why we introduce organic chemistry here. By convention, compounds containing carbonate ions and bicarbonate ions, as well as carbon dioxide and carbon monoxide, are not considered part of organic chemistry, even though they contain carbon.

Alkanes

The simplest organic compounds are the **hydrocarbons**, compounds composed of carbon and hydrogen atoms only. Some hydrocarbons have only single bonds and appear as a chain (which can be a straight chain or can have branches) of carbon atoms also bonded to hydrogen atoms. These hydrocarbons are called **alkanes (saturated hydrocarbons)**. Each alkane has a characteristic, systematic name depending on the number of carbon atoms in the molecule. These names consist of a stem that indicates the number of carbon atoms in the chain plus the ending -ane. The stem meth- means one carbon atom, so methane is an alkane with one carbon atom. Similarly, the stem eth- means two carbon atoms; ethane is an alkane with two carbon atoms. Continuing, the stem prop- means three carbon atoms, so propane is an alkane with three carbon atoms. The stem but- means four carbon atoms; butane is an alkane with four carbon atoms. Figure 1.11.1 gives the Lewis structures, condensed structural formulas and molecular formulas of the four simplest alkanes. In the **condensed structural formula**, the covalent bonds are understood to exist between each carbon and the hydrogens associated with it, as well as between carbon atoms.

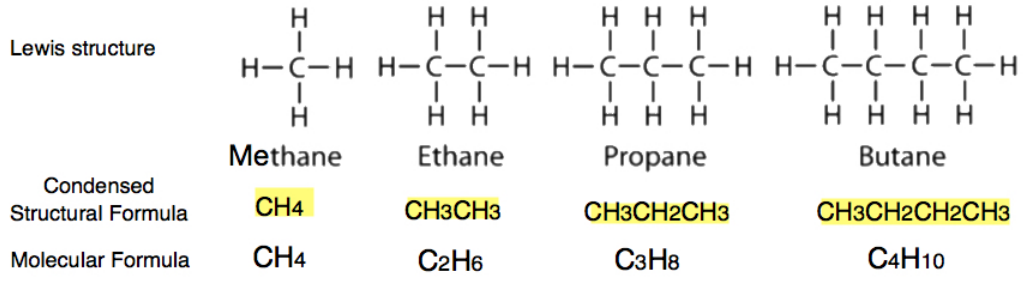


Figure 1.11.1: Formulas and Molecular Models of the Four Simplest Alkanes. The four smallest alkanes are methane, ethane, propane and butane.

Alkenes

Some hydrocarbons have one or more carbon–carbon double bonds (denoted C=C). These hydrocarbons are called alkenes. Figure 1.11.2 shows the formulas and the molecular models of the two simplest alkenes. Note that the names of alkenes have the same stem as the alkane with the same number of carbon atoms in its chain but have the ending *-ene*. Thus, ethene is an alkene with two carbon atoms per molecule, and propene is a compound with three carbon atoms and one double bond.

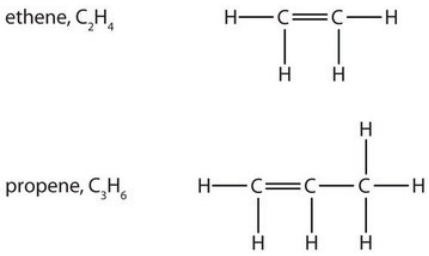
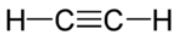


Figure **1.11.2**: Formulas and Molecular Models of the Two Simplest Alkenes. Ethene is commonly called ethylene, while propene is commonly called propylene.

Alkynes

Alkynes are hydrocarbons with a carbon–carbon triple bond (denoted C≡C) as part of their carbon skeleton. Below is the formula and the molecular model of the simplest alkyne and its systematic name. Its common name is acetylene. Its chemical formula is $\mathbf{C_2H_2}$.



Ethyne

The names for alkynes have the same stems as for alkanes but with the ending *-yne*.

To Your Health: Saturated and Unsaturated Fats

Hydrocarbons are not the only compounds that can have carbon–carbon double bonds. A group of compounds called fats can have them as well, and their presence or absence in the human diet is becoming increasingly correlated with health issues.

Fats are combinations of long-chain organic compounds (fatty acids) and glycerol ($C_3H_8O_3$). (For more information on fats, see Chapter 17) The long carbon chains can have either all single bonds, in which case the fat is classified as *saturated*, or one or more double bonds, in which case it is a *monounsaturated* or a *polyunsaturated* fat, respectively. Saturated fats are typically solids at room temperature; beef fat (tallow) is one example. Mono- or polyunsaturated fats are likely to be liquids at room temperature and are often called oils. Olive oil, flaxseed oil, and many fish oils are mono- or polyunsaturated fats.

Studies have linked higher amounts of saturated fats in people's diets with a greater likelihood of developing heart disease, high cholesterol, and other diet-related diseases. In contrast, increases in unsaturated fats (either mono- or polyunsaturated) have been linked to a lower incidence of certain diseases. Thus, there have been an increasing number of recommendations by government bodies and health associations to decrease the proportion of saturated fat and increase the proportion of unsaturated fat in the diet. Most of these organizations also recommend decreasing the total amount of fat in the diet.

Recently, certain fats called trans fats have been implicated in the presence of heart disease. These are fats from animal sources and are also produced when liquid oils are exposed to partial hydrogenation, an industrial process that increases their saturation. Trans fats are used in many prepared and fried foods. Because they bring with them the health risks that naturally occurring saturated fats do, there has been some effort to better quantify the presence of trans fats in food products. US law now requires that food labels list the amount of trans fat in each serving.

Since the early 1900's, the US Department of Agriculture has been providing science-based dietary guidelines for the public. The most current version is the MyPlate illustration that gives a simple, visual picture of how much of what kind of foods make up a good, balanced diet. It recommends minimizing daily intake of sugars, the "bad fats", trans and saturated fat, and sodium. "Good fats", unsaturated fats or oils, are not considered a food group but do contain essential nutrients and therefore are included as part of a healthy eating pattern. The difference as simple as the difference between a single and double carbon–carbon bond, good and bad fats, can have a significant impact on health.



MyPlate is a reminder that everything you eat and drink matters. Source: Image courtesy of the USDA, www.mypyramid.gov/downloads/MiniPoster.pdf.

Functional Groups

The carbon–carbon double and triple bonds are examples of functional groups in organic chemistry. A functional group is a specific structural arrangement of atoms or bonds that imparts a characteristic chemical reactivity to a molecule. Alkanes have no functional group. A carbon–carbon double bond is considered a functional group because carbon–carbon double bonds chemically react in specific ways that differ from reactions of alkanes (for example, under certain circumstances, alkenes react with water); a carbon–carbon triple bond also undergoes certain specific chemical reactions. In the remainder of this section, we introduce two other common functional groups.

If an OH group (also called a hydroxyl group) is substituted for a hydrogen atom in a hydrocarbon molecule, the compound is an alcohol. Alcohols are named using the parent hydrocarbon name but with the final *-e* dropped and the suffix *-ol* attached. The two simplest alcohols are methanol and ethanol. Figure **1.11.4** shows their formulas along with a molecular model of each.

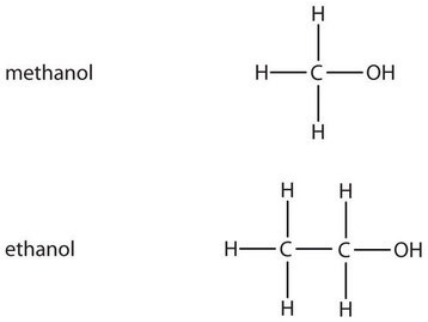


Figure **1.11.4**: The Two Simplest Organic Alcohol Compounds. Alcohols have an OH functional group in the molecule.

Cholesterol, described in the chapter-opening essay, has an alcohol functional group, as its name implies.

Alcohol

Ethanol (also called ethyl alcohol) is the alcohol in alcoholic beverages. Other alcohols include methanol (or methyl alcohol), which is used as a solvent and a cleaner, and isopropyl alcohol (or rubbing alcohol), which is used as a medicinal disinfectant. Neither methanol nor isopropyl alcohol should be ingested, as they are toxic even in small quantities.

Another important family of organic compounds has a carboxyl group, in which a carbon atom is double-bonded to an oxygen atom and to an OH group. Compounds with a carboxyl functional group are called carboxylic acids, and their names end in *-oic acid*. Figure **1.11.5** shows the formulas and the molecular models of the two simplest carboxylic acids, perhaps best known by the common names formic acid and acetic acid. The carboxyl group is sometimes written in molecules as COOH.

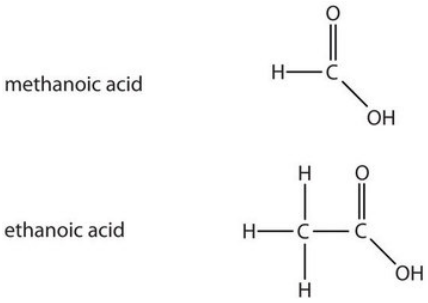


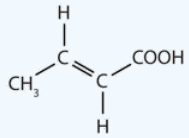
Figure **1.11.5**: The Two Smallest Organic Acids. The two smallest carboxylic acids are formic acid (found in the stingers of ants) and acetic acid (found in vinegar).

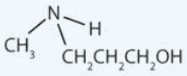
The condensed structures of methanoic acid and ethanoic acid are **HCOOH** and **CH_3COOH**, respectively.

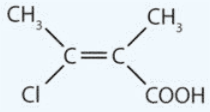
Many organic compounds are considerably more complex than the examples described here. Many compounds, such as cholesterol discussed in the chapter-opening essay, contain more than one functional group. The formal names can also be quite complex.

Example 1.11.1

Identify the functional group(s) in each molecule as a double bond, a triple bond, an alcohol, or a carboxyl.

a. 

b. 

c. 

d. **$CH_3CH_2CH_2CH_2OH$**

Answer a

This molecule has a double bond and a carboxyl functional group.

Answer b

This molecule has an alcohol functional group.

Answer c

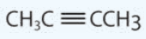
This molecule has a carbon-carbon double bond and a carboxyl functional group.

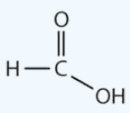
Answer d

This molecule has an alcohol functional group.

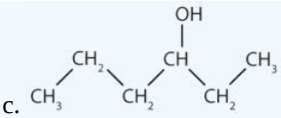
Exercise 1.11.1

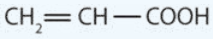
Identify the functional group(s) in each molecule as a double bond, a triple bond, an alcohol, or a carboxyl.

a. 

b. 

https://chem.libretexts.org/@go/page/306586

c. 

d. 

Answer a:

triple bond (alkyne)

Answer b:

carboxyl group

Answer c:

alcohol group

Answer d:

double bond (alkene) and carboxyl group

Career Focus: Forensic Chemist

The main job of a forensic chemist is to identify unknown materials and their origins. Although forensic chemists are most closely associated in the public mind with crime labs, they are employed in pursuits as diverse as tracing evolutionary patterns in living organisms, identifying environmental contaminants, and determining the origin of manufactured chemicals.

In a crime lab, the forensic chemist has the job of identifying the evidence so that a crime can be solved. The unknown samples may consist of almost anything—for example, paint chips, blood, glass, cloth fibers, drugs, or human remains. The forensic chemist subjects them to a variety of chemical and instrumental tests to discover what the samples are. Sometimes these samples are extremely small, but sophisticated forensic labs have state-of-the-art equipment capable of identifying the smallest amount of unknown sample.

Another aspect of a forensic chemist's job is testifying in court. Judges and juries need to be informed about the results of forensic analyses, and it is the forensic chemist's job to explain those results. Good public-speaking skills, along with a broad background in chemistry, are necessary to be a successful forensic chemist.

Key Takeaways

- Organic chemistry is the study of the chemistry of carbon compounds.
- Organic molecules can be classified according to the types of elements and bonds in the molecules.

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1.12: Organic Chemistry- Alkanes and Halogenated Hydrocarbons (Summary)

To ensure that you understand the material in this chapter, you should review the meanings of the following bold terms in the summary and ask yourself how they relate to the topics in the chapter.

Organic chemistry is the chemistry of carbon compounds, and **inorganic chemistry** is the chemistry of all the other elements. Carbon atoms can form stable covalent bonds with other carbon atoms and with atoms of other elements, and this property allows the formation the tens of millions of organic compounds. **Hydrocarbons** contain only hydrogen and carbon atoms.

Hydrocarbons in which each carbon atom is bonded to four other atoms are called **alkanes** or **saturated hydrocarbons**. They have the general formula C_nH_{2n+2}. Any given alkane differs from the next one in a series by a CH_2 unit. Any family of compounds in which adjacent members differ from each other by a definite factor is called a **homologous series**.

Carbon atoms in alkanes can form straight chains or branched chains. Two or more compounds having the same molecular formula but different structural formulas are **isomers** of each other. There are no isomeric forms for the three smallest alkanes; beginning with C_4H_{10}, all other alkanes have isomeric forms.

A **structural formula** shows all the carbon and hydrogen atoms and how they are attached to one another. A **condensed structural formula** shows the hydrogen atoms right next to the carbon atoms to which they are attached. A **line-angle formula** is a formula in which carbon atoms are implied 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.

The **IUPAC System of Nomenclature** provides rules for naming organic compounds. An **alkyl group** is a unit formed by removing one hydrogen atom from an alkane.

The physical properties of alkanes reflect the fact that alkane molecules are nonpolar. Alkanes are insoluble in water and less dense than water.

Alkanes are generally unreactive toward laboratory acids, bases, oxidizing agents, and reducing agents. They do burn (undergo **combustion reactions**).

Alkanes react with halogens by substituting one or more halogen atoms for hydrogen atoms to form **halogenated hydrocarbons**. An **alkyl halide (haloalkane)** is a compound resulting from the replacement of a hydrogen atom of an alkane with a halogen atom.

Cycloalkanes are hydrocarbons whose molecules are closed rings rather than straight or branched chains. A **cyclic hydrocarbon** is a hydrocarbon with a ring of carbon atoms

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1.13: Organic Chemistry- Alkanes and Halogenated Hydrocarbons (Exercises)

12.1: Organic Chemistry

Concept Review Exercises

1. Classify each compound as organic or inorganic.
    a. C_3H_8O
    b. $CaCl_2$
    c. $Cr(NH_3)_3Cl_3$
    d. $C_{30}H_{48}O_3N$
2. Which compound is likely organic and which is likely inorganic?
    a. a flammable compound that boils at 80°C and is insoluble in water
    b. a compound that does not burn, melts at 630°C, and is soluble in water
3. Classify each compound as organic or inorganic.
    a. C_6H_{10}
    b. $CoCl_2$
    c. $C_{12}H_{22}O_{11}$
4. Classify each compound as organic or inorganic.
    a. CH_3NH_2
    b. $NaNH_2$
    c. $Cu(NH_3)_6Cl_2$
5. Which member of each pair has a higher melting point?
    a. CH_3OH and NaOH
    b. CH_3Cl and KCl
6. Which member of each pair has a higher melting point?
    a. C_2H_6 and $CoCl_2$
    b. CH_4 and LiH

Answers

1. a. organic
    b. inorganic
    c. inorganic
    d. organic
2.
    a. organic
    b. inorganic
3. a. organic b. inorganic c. organic
4.
5.
    a. NaOH
    b. KCl

12.3: Branched-Chain Alkanes

Concept Review Exercises

1. In alkanes, can there be a two-carbon branch off the second carbon atom of a four-carbon chain? Explain.
2. A student is asked to write structural formulas for two different hydrocarbons having the molecular formula C_5H_{12}. She writes one formula with all five carbon atoms in a horizontal line and the other with four carbon atoms in a line, with a CH_3 group extending down from the first attached to the third carbon atom. Do these structural formulas represent different molecular formulas? Explain why or why not.

Answers

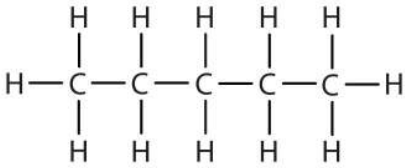
1. No; the branch would make the longest continuous chain of five carbon atoms.
2. No; both are five-carbon continuous chains.

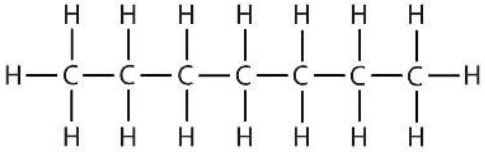
Key Takeaway

- Alkanes with four or more carbon atoms can exist in isomeric forms.

Exercises

1. Briefly identify the important distinctions between a straight-chain alkane and a branched-chain alkane.
2. How are butane and isobutane related? How do they differ?
3. Name each compound.

a. 

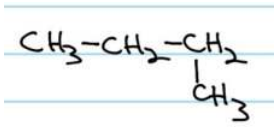
b. 

4. Write the structural formula for each compound.

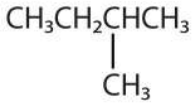
   a. hexane
   b. octane

5. Indicate whether the structures in each set represent the same compound or isomers.

   a. $CH_3CH_2CH_2CH_3$ and



   b. $CH_3CH_2CH_2CH_2CH_3$ and



Answers

1. Straight-chain alkanes and branched-chain alkanes have different properties as well as different structures.

3.

a. pentane
b. heptane

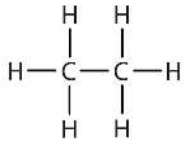
5.

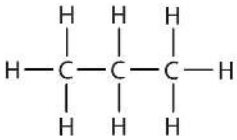
a. not isomers, same compound
b. yes, isomers

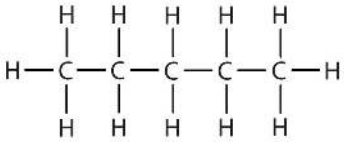
12.4: Condensed Structural and Line-Angle Formulas

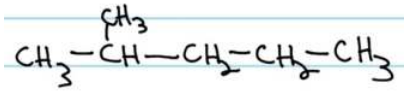
Exercises

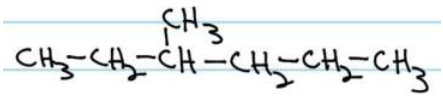
1. Write the condensed structural formula for each structural formula.

a. 

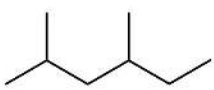
b. 

c. 

2. A condensed structural formula for isohexane can be written as  . Draw the line-angle formula for isohexane.

3. Draw a line-angle formula for the compound 

4. Give the condensed structural formula for the compound represented by this line-angle formula:



Answers

1.

a. CH_3CH_3
b. $CH_3CH_2CH_3$

c. $CH_3CH_2CH_2CH_2CH_3$

3. 

12.5: IUPAC Nomenclature

Concept Review Exercises

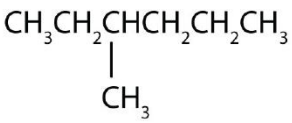
1. What is a CH_3 group called when it is attached to a chain of carbon atoms—a substituent or a functional group?
2. Which type of name uses numbers to locate substituents—common names or IUPAC names?

Answers

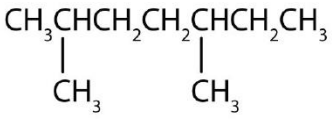
1. substituent
2. IUPAC names

Exercises

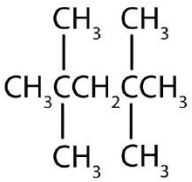
1. Briefly identify the important distinctions between an alkane and an alkyl group.
2. How many carbon atoms are present in each molecule?
   a. 2-methylbutane
   b. 3-ethylpentane
3. How many carbon atoms are present in each molecule?
   a. 2,3-dimethylbutane
   b. 3-ethyl-2-methylheptane
4. Draw the condensed structure for each compound.
   a. 3-methylpentane
   b. 2,2,5-trimethylhexane
   c. 4-ethyl-3-methyloctane
5. Draw the condensed structure for each compound.
   a. 2-methylpentane
   b. 4-ethyl-2-methylhexane
   c. 2,2,3,3-tetramethylbutane
6. Name each compound according to the IUPAC system.

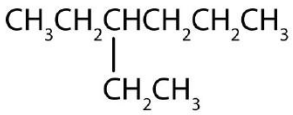


a.

b. 

7. Name each compound according to the IUPAC system.

a. 

b. 

8. What is a substituent? How is the location of a substituent indicated in the IUPAC system?

9. Briefly identify the important distinctions between a common name and an IUPAC name.

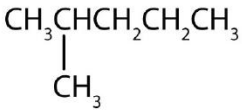
Answers

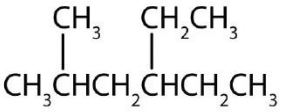
1. An alkane is a molecule; an alkyl group is not an independent molecule but rather a part of a molecule that we consider as a unit.

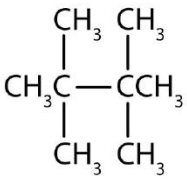
3.

a. 6
b. 10

5.

a. 

b. 

c. 

7.

a. 2,2,4,4-tetramethylpentane
b. 3-ethylhexane

9. Common names are widely used but not very systematic; IUPAC names identify a parent compound and name other groups as substituents.

12.6: Physical Properties of Alkanes

12.7: Chemical Properties of Alkanes

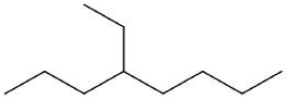
12.8: Halogenated Hydrocarbons

12.9: Cycloalkanes

12.10: Chapter Summary

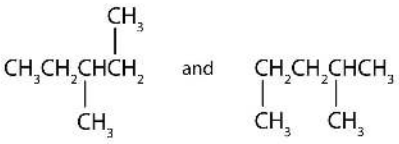
Additional Exercises

1. You find an unlabeled jar containing a solid that melts at 48°C. It ignites readily and burns readily. The substance is insoluble in water and floats on the surface. Is the substance likely to be organic or inorganic?
2. Give the molecular formulas for methylcyclopentane, 2-methylpentane, and cyclohexane. Which are isomers?
3. What is wrong with each name? (Hint: first write the structure *as if* it were correct.) Give the correct name for each compound.
   a. 2-dimethylpropane
   b. 2,3,3-trimethylbutane
   c. 2,4-diethylpentane
   d. 3,4-dimethyl-5-propylhexane
4. What is the danger in swallowing a liquid alkane?
5. Distinguish between lighter and heavier liquid alkanes in terms of their effects on the skin.
6. Following is the line formula for an alkane. Draw its condensed structure and give its name.



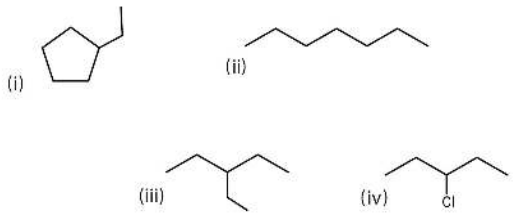
7. Write equations for the complete combustion of each compound.
   a. propane (a bottled gas fuel)
   b. octane (a typical hydrocarbon in gasoline).
8. Skip
9. Draw the structures for the five isomeric hexanes (C_6H_{14}). Name each by the IUPAC system.
10. Indicate whether the structures in each set represent the same compound or isomers.

a. 

b. 

c. 

11. Consider the line-angle formulas shown here and answer the questions.



a. Which pair of formulas represents isomers? Draw each structure as condensed.
b. Which formula represents an alkyl halide? Name the compound and write its condensed structural formula.
c. Which formula represents a cyclic alkane? Name the compound and draw its structure.
d. What is the molecular formula of the compound represented by (i)?

Answers

1. organic

3.

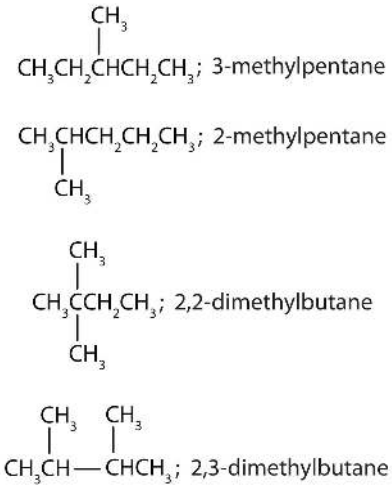
a. Two numbers are needed to indicate two substituents; 2,2-dimethylpropane.
b. The lowest possible numbers were not used; 2,2,3-trimethylbutane.
c. An ethyl substituent is not possible on the second carbon atom; 3,5-dimethylheptane.
d. A propyl substituent is not possible on the fifth carbon atom; 3,4,5-trimethyloctane.

5. Lighter alkanes wash away protective skin oils; heavier alkanes form a protective layer.

7.

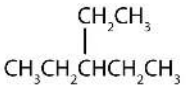
a. $C_3H_8 + 5O_2 \rightarrow 3CO_2 + 4H_2O$
b. $2C_8H_{18} + 25O_2 \rightarrow 16CO_2 + 18H_2O$

9. $CH_3CH_2CH_2CH_2CH_2CH_3$; hexane

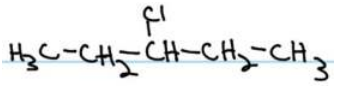


11.

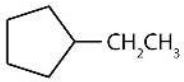
a. ii and iii; $CH_3CH_2CH_2CH_2CH_2CH_2CH_3$ and



b. iv; 3-chloropentane;



c. i; ethylcyclopentane;



d. C_7H_{14}

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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: Polymers
2.7: Alkynes
2.8: Aromatic Compounds- Benzene
2.9: Structure and Nomenclature of Aromatic Compounds
2.E: Unsaturated and Aromatic Hydrocarbons (Exercises)
2.S: Unsaturated and Aromatic Hydrocarbons (Summary)

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2.1: Prelude to Unsaturated and Aromatic Hydrocarbons

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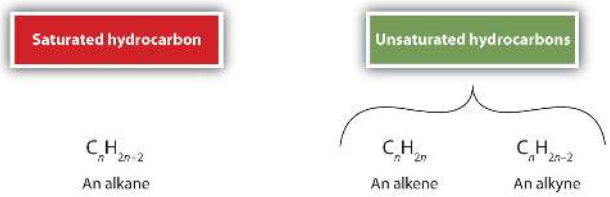
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2.2: Alkenes- Structures and Names

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:

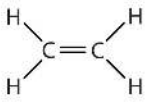


Some representative alkenes—their names, structures, and physical properties—are given in Table **2.2.1**.

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.

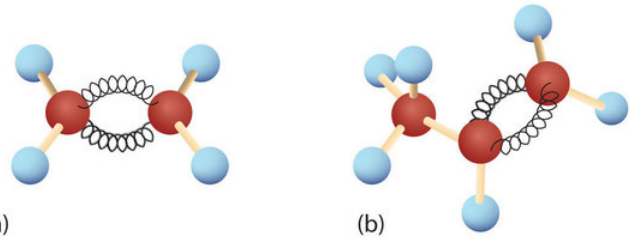
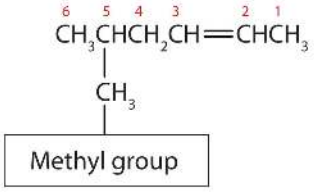


Figure **2.2.1**: Ethene and Propene. The ball-and-spring models of ethene/ethylene (a) and propene/propylene (b) show their respective shapes, especially bond angles.

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.

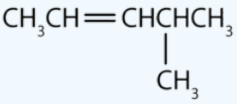
Here are some basic rules for naming alkenes from the International Union of Pure and Applied Chemistry (IUPAC):

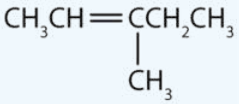
1. The longest chain of carbon atoms *containing the double bond* is considered the parent chain. It is named using the same stem as the alkane having the same number of carbon atoms but ends in *-ene* to identify it as an alkene. Thus the compound CH_2=$CHCH_3$ is *propene*.
2. If there are four or 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. 

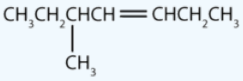
b. 

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.

1. $CH_3CH_2CH_2CH_2CH_2CH{=}CHCH_3$
2. 

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.

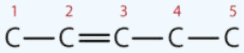
Example 2.2.2

Draw the structure for each compound.

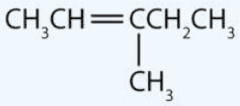
1. 3-methyl-2-pentene
2. cyclohexene

Solution

1. 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.

2. 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.

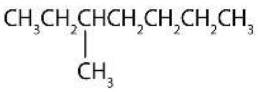
Exercise 2.2.2

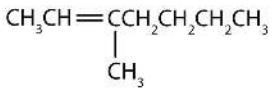
Draw the structure for each compound.

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

Concept Review Exercises

1. Briefly identify the important distinctions between a saturated hydrocarbon and an unsaturated hydrocarbon.
2. Briefly identify the important distinctions between an alkene and an alkane.
3. Classify each compound as saturated or unsaturated. Identify each as an alkane, an alkene, or an alkyne.

   a. 
   b. $CH_3CH_2C{\equiv}CCH_3$

c. 

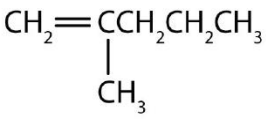
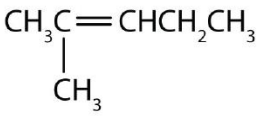
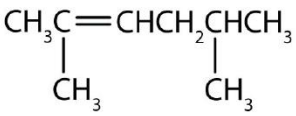
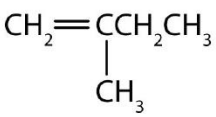
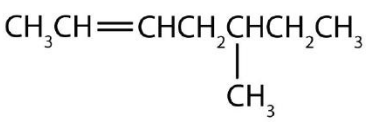
Answers

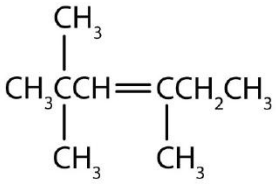
1. Unsaturated hydrocarbons have double or triple bonds and are quite reactive; saturated hydrocarbons have only single bonds and are rather unreactive.
2. An alkene has a double bond; an alkane has single bonds only.
3. a. saturated; alkane
   b. unsaturated; alkyne
   c. unsaturated; alkene

Key Takeaway

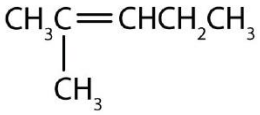
- Alkenes are hydrocarbons with a carbon-to-carbon double bond.

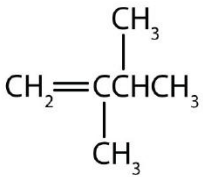
Exercises

1. Draw the structure for each compound.
   a. 2-methyl-2-pentene
   b. 2,3-dimethyl-1-butene
   c. cyclohexene
2. Draw the structure for each compound.
   a. 5-methyl-1-hexene
   b. 3-ethyl-2-pentene
   c. 4-methyl-2-hexene
3. Name each compound according to the IUPAC system.
   a. 
   b. 
   c. 
4. Name each compound according to the IUPAC system.
   a. 
   b. 

c. 

Answers

1. a. 

   b. 

   c. 

3. a. 2-methyl-1-pentene
   b. 2-methyl-2-pentene
   c. 2,5-dimethyl-2-hexene

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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**.

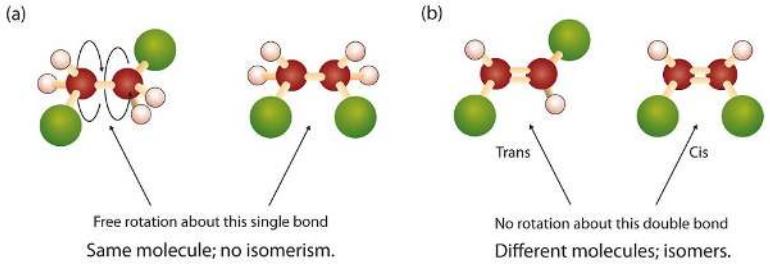


Figure* 2.3.1: Rotation about Bonds. In 1,2-dichloroethane (a), free rotation about the C–C bond allows the two structures to be interconverted by a twist of one end relative to the other. In 1,2-dichloroethene (b), restricted rotation about the double bond means that the relative positions of substituent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

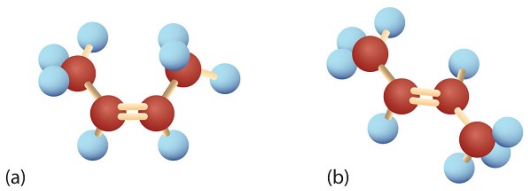


Figure **2.3.2**: Ball-and-Spring Models of (a) Cis-2-Butene and (b) Trans-2-Butene. Cis-trans isomers have different physical, chemical, and physiological properties.

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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 nomenclature 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=$CHCH_2CH_3$

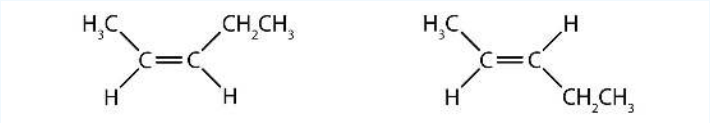
Solution

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:

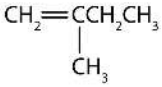


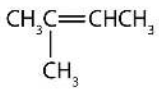
2. This compound has two hydrogen atoms on one of its doubly bonded carbon atoms; it fails rule 2 and does not exist as cis and trans isomers.
3. This compound has two methyl (CH_3) groups on one of its doubly bonded carbon atoms. It fails rule 2 and does not exist as cis and trans isomers.
4. This compound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



Exercise 2.3.1

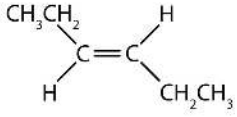
Which compounds can exist as cis-trans isomers? Draw them.

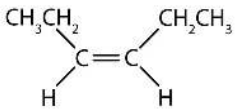
a. CH_2=$CHCH_2CH_2CH_3$
b. CH_3CH=$CHCH_2CH_3$
c. CH_3CH_2CH=$CHCH_2CH_3$
d. 

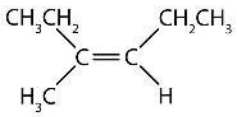
e. 

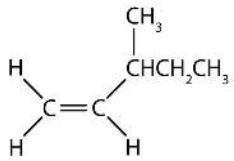
Concept Review Exercises

1. What are cis-trans (geometric) isomers? What two types of compounds can exhibit cis-trans isomerism?
2. Classify each compound as a cis isomer, a trans isomer, or neither.

a. 

b. 

c. 

d. 

Answers

1. Cis-trans isomers are compounds that have different configurations (groups permanently in different places in space) because of the presence of a rigid structure in their molecule. Alkenes and cyclic compounds can exhibit cis-trans isomerism.

2. a. trans (the two hydrogen atoms are on opposite sides)
   b. cis (the two hydrogen atoms are on the same side, as are the two ethyl groups)
   c. cis (the two ethyl groups are on the same side)
   d. neither (fliping the bond does not change the molecule. There are no isomers for this molecule)

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.

Exercises

1. Draw the structures of the cis-trans isomers for each compound. Label them cis and trans. If no cis-trans isomers exist, write none.

   a. 2-bromo-2-pentene
   b. 3-hexene
   c. 4-methyl-2-pentene
   d. 1,1-dibromo-1-butene

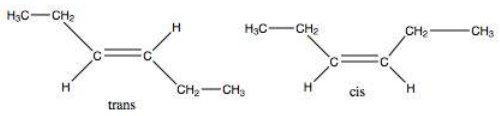
2. Draw the structures of the cis-trans isomers for each compound. Label them cis and trans. If no cis-trans isomers exist, write none.

   a. 2,3-dimethyl-2-pentene
   b. 5-methyl-2-hexene

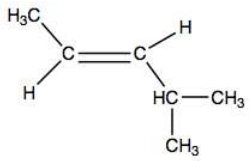
Answer

1. a: none. There are two distinct geometric isomers, but since there are four different groups off the double bond, these are both cis/trans isomers (they are technically E/Z isomers discussed elsewhere).

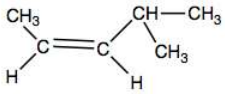
   b:

   c:



trans



cis

d: None

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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.

Concept Review Exercises

1. Briefly describe the physical properties of alkenes. How do these properties compare to those of the alkanes?
2. Without consulting tables, arrange the following alkenes in order of increasing boiling point: 1-butene, ethene, 1-hexene, and propene.

Answers

1. Alkenes have physical properties (low boiling points, insoluble in water) quite similar to those of their corresponding alkanes.
2. ethene < propene < 1-butene < 1-hexene

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

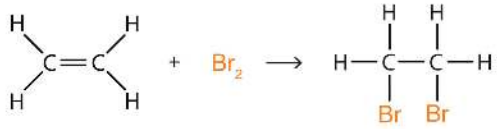
- To write equations for the addition reactions of alkenes with hydrogen, halogens, and water

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).

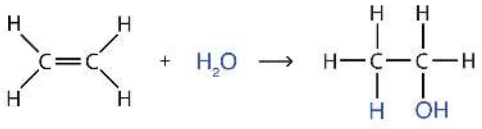


The product is an alkane having the same carbon skeleton as the alkene.

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.

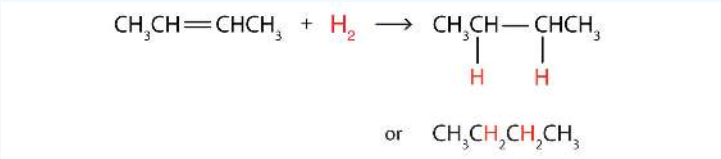
Example 2.5.1

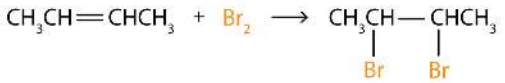
Write the equation for the reaction between $CH_3CH{=}CHCH_3$ and each substance.

a. H_2 (Ni catalyst)
b. Br_2
c. H_2O (H_2SO_4 an acid catalyst, H^+)

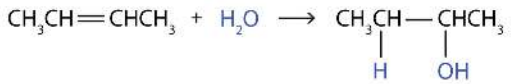
Solution

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

a. 

b. 

or $CH_3CHBrCHBrCH_3$

c. 

or $CH_3CH_2CHOHCH_3$

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)

Concept Review Exercises

1. What is the principal difference in properties between alkenes and alkanes? How are they alike?
2. If $C_{12}H_{24}$ reacts with Br_2 in an addition reaction, what is the molecular formula of the product?

Answers

1. Alkenes undergo addition reactions; alkanes do not. Both burn.
2. $C_{12}H_{24}Br_2$

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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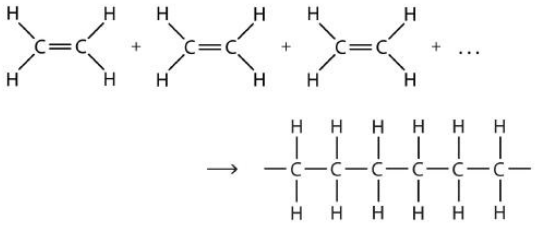
2.6: Polymers

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:



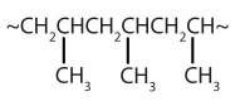
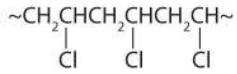
The bond lines extending at the ends in the formula of the product indicate that the structure extends for many units in each direction. Notice that all the atoms—two carbon atoms and four hydrogen atoms—of each monomer molecule are incorporated into the polymer structure. Because displays such as the 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 **2.6.1**. 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 **2.6.1***: 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.

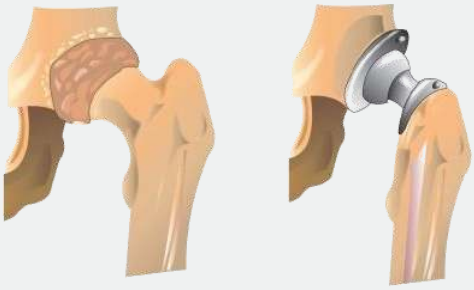


Figure **2.6.1**: Hip Joint Replacement. Synthetic polymers are an important part of a hip joint replacement. The hip is much like a ball-and-socket joint, and total hip replacements mimic this with a metal ball that fits in a plastic cup.

Concept Review Exercises

1. What is a monomer? What is a polymer? How do polymer molecules differ from the molecules we have discussed in earlier sections of this chapter?
2. What is addition polymerization? What structural feature usually characterizes molecules used as monomers in addition polymerization?

Answers

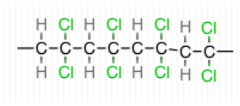
1. Monomers are small molecules that can be assembled into giant molecules referred to as polymers, which are much larger than the molecules we discussed earlier in this chapter.
2. In addition polymerization, the monomers add to one another in such a way that the polymer contains all the atoms of the starting monomers.

Key Takeaway

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

Exercises

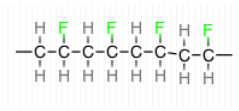
1. What is the name of the monomer from which Saran (a segment of the polymer of Saran is seen below) is formed?



2. Write the condensed structural formula for the section of a molecule formed from four units of the monomer CH_2=CHF.

Answers

1. $H_2C=CCl_2$, 1,1-dichloroethene, 

2. 

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2.7: 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 **2.7.1**). Its structure is H–C≡C–H.

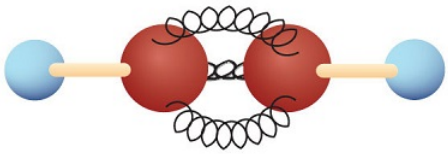


Figure **2.7.1**: Ball-and-Spring Model of Acetylene. Acetylene (ethyne) is the simplest member of the alkyne family.

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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2.8: Aromatic Compounds- Benzene

Learning Objectives

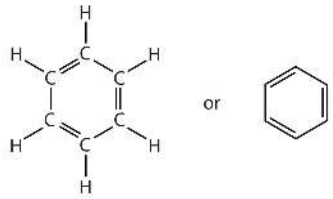
- To describe the bonding in benzene and the way typical reactions of benzene differ from those of the alkenes.

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.

Concept Review Exercises

1. Briefly describe the bonding in benzene.
2. What does the circle mean in the chemist's representation of benzene?

Answers

1. Valence electrons are shared equally by all six carbon atoms (that is, the electrons are delocalized).
2. The six electrons are shared equally by all six carbon atoms.

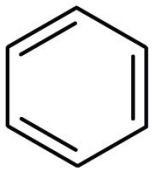
Key Takeaway

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

Exercises

1. Draw the structure of benzene as if it had alternate single and double bonds.
2. Draw the structure of benzene as chemists usually represent it today.

Answer

1. 

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2.9: 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.

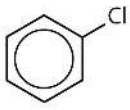
Historically, benzene-like substances were called aromatic hydrocarbons because they had distinctive aromas. Today, an aromatic compound is any compound that contains a benzene ring or has certain benzene-like properties (but not necessarily a strong aroma). You can recognize the aromatic compounds in 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 **2.9.1**, where the benzene ring is represented as C_6H_5.

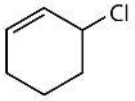
Table **2.9.1***: Some Representative Aromatic Compounds*

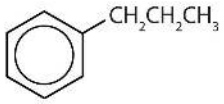
Name	Structure	Typical Uses
aniline	$C_6H_5–NH_2$	starting material for the synthesis of dyes, drugs, resins, varnishes, perfumes; solvent; vulcanizing rubber
benzoic acid	$C_6H_5–COOH$	food preservative; starting material for the synthesis of dyes and other organic compounds; curing of tobacco
bromobenzene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

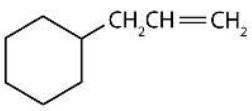
Example 2.9.1

Which compounds are aromatic?

1. 

2. 

3. 

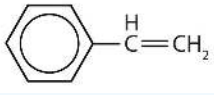
4. 

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 2.9.1

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 2.9.1 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.

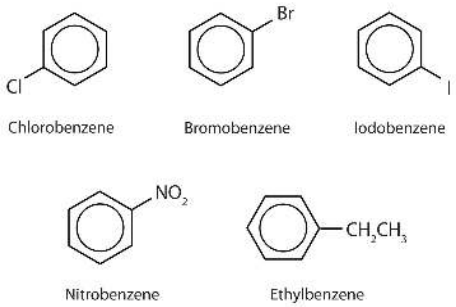


Figure 2.9.1: Some Benzene Derivatives. These compounds are named in the usual way with the group that replaces a hydrogen atom named as a substituent group: Cl as chloro, Br as bromo, I as iodo, NO_2 as nitro, and CH_3CH_2 as ethyl.

Although some compounds are referred to exclusively by IUPAC names, some are more frequently denoted by common names, as is indicated in Table 2.9.1.



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 2.9.2). 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.

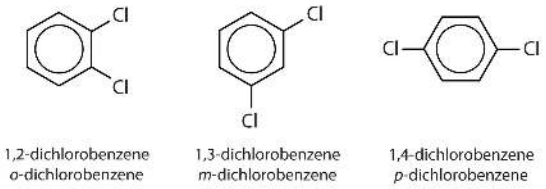
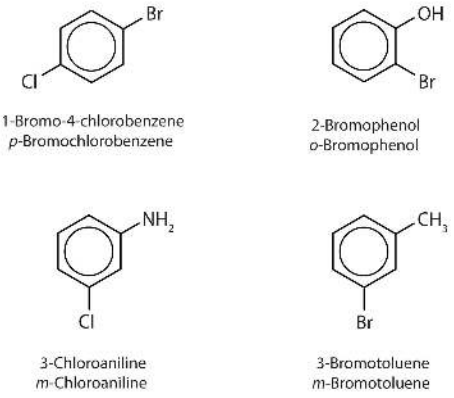


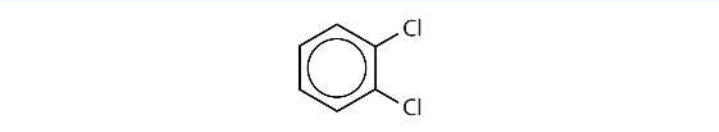
Figure **2.9.2**: The Three Isomeric Dichlorobenzenes

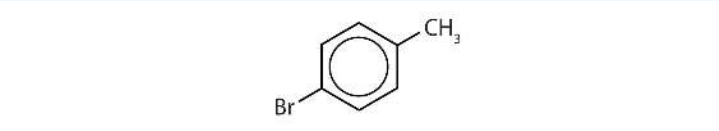
In Figure **2.9.2**, common names are also used: the prefix *ortho* (*o*-) for 1,2-disubstitution, *meta* (*m*-) for 1,3-disubstitution, and *para* (*p*-) for 1,4-disubstitution. The substituent names are listed in alphabetical order. The first substituent is given the lowest number. When a common name is used, the carbon atom that bears the group responsible for the name is given the number 1:



Example 2.9.2

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

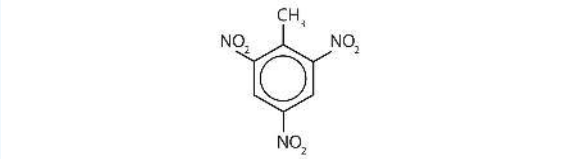
1. 

2. 

Solution

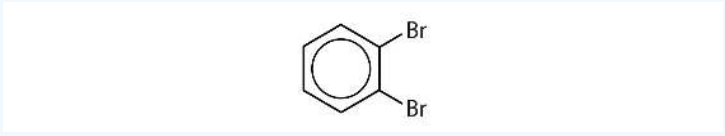
1. The benzene ring has two chlorine atoms (dichloro) in the first and second positions. The compound is *o*-dichlorobenzene or 1,2-dichlorobenzene.
2. The benzene ring has a methyl (CH_3) group. The compound is therefore named as a derivative of toluene. The bromine atom is on the fourth carbon atom,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

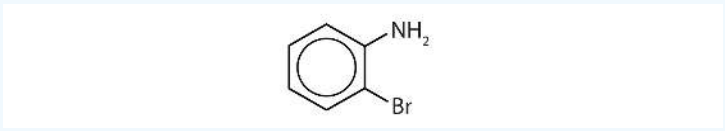
Note: The nitro (NO_2) group is a common substituent in aromatic compounds. Many nitro compounds are explosive, most notably 2,4,6-trinitrotoluene (TNT).

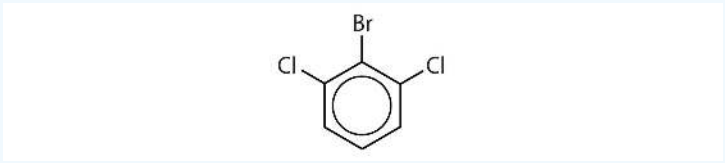


Exercise 2.9.2

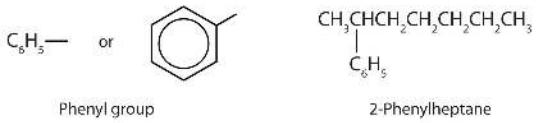
Name each compound using both the common name and the IUPAC name.

1. 

2. 

3. 

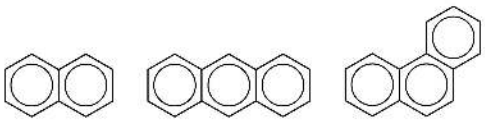
Sometimes an aromatic group is found as a substituent bonded to a nonaromatic entity or to another aromatic ring. The group of atoms remaining when a hydrogen atom is removed from an aromatic compound is called an aryl group. The most common aryl group is derived from benzene (C_6H_6) by removing one 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

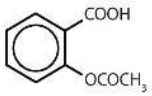
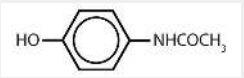
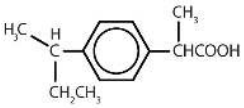
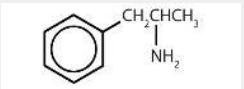
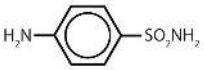
Substances containing the benzene ring are common in both animals and plants, although they are more abundant in the latter. Plants can synthesize the benzene ring from carbon dioxide, water, and inorganic materials. Animals cannot synthesize it, but they

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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 **2.9.2**, 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 **2.9.2**: Some Drugs That Contain a Benzene Ring

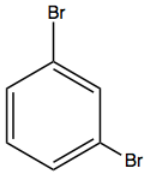
Name	Structure
aspirin	
acetaminophen	
ibuprofen	
amphetamine	
sulfanilamide	

Concept Review Exercises

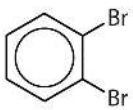
1. Briefly identify the important characteristics of an aromatic compound.
2. What is meant by the prefixes *meta*, *ortho*, or *para*? Give the name and draw the structure for a compound that illustrates each.
3. What is a phenyl group? Give the structure for 3-phenyloctane.

Answers

1. An aromatic compound is any compound that contains a benzene ring or has certain benzene-like properties.
2. meta = 1,3 disubstitution; (answers will vary)

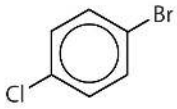


ortho = 1,2 disubstitution



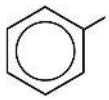
o-dibromobenzene or 1,2-dibromobenzene

para = 1,4 disubstitution or 1-bromo-4-chlorobenzene

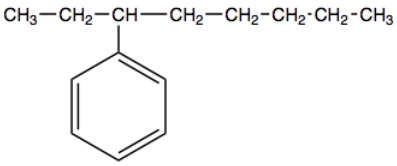


p-bromochlorobenzene or 1-bromo-2-chlorobenzene

3. phenyl group: C_6H_5 or



3-phenyloctane:

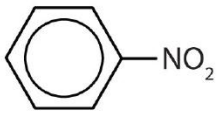


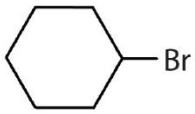
Key Takeaway

- 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.

Exercises

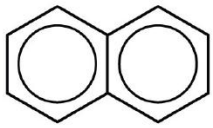
1. Is each compound aromatic?

a. 

b. 

2. Is each compound aromatic?

a. 

b. 

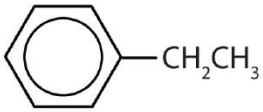
3. Draw the structure for each compound.

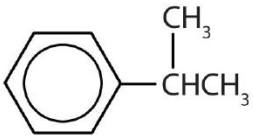
   a. toluene
   b. *m*-diethylbenzene

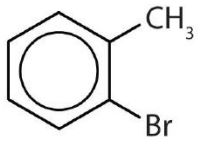
4. Draw the structure for each compound.

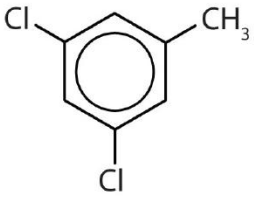
a. *p*-dichlorobenzene
b. 1,2,4-trimethylbenzene

5. Name each compound with its IUPAC name.

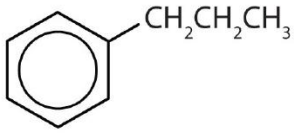
a. 

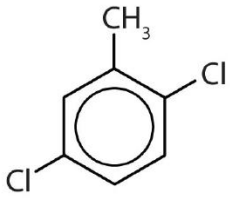
b. 

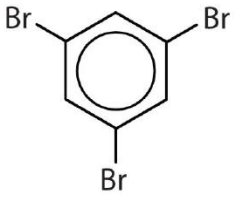
c. 

d. 

6. Name each compound with its IUPAC name.

a. 

b. 

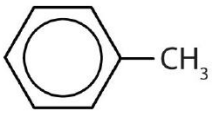
c. 

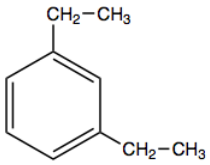
Answers

1. a. yes
   b. no

3. a.

b.





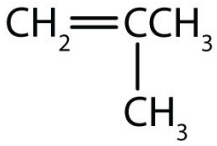
5. a. ethylbenzene
   b. isopropylbenzene
   c. 1-bromo-2-methylbenzene
   d. 1,3-dichloro-5-methylbenzene

2.9: Structure and Nomenclature of Aromatic Compounds is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

2.E: Unsaturated and Aromatic Hydrocarbons (Exercises)

Additional Exercises

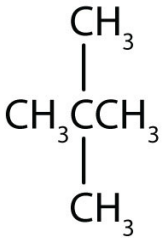
1. Classify each compound as saturated or unsaturated.



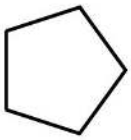
a.

b. $CH_3C{\equiv}CCH_3$

2. Classify each compound as saturated or unsaturated.

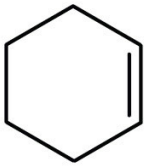


a.

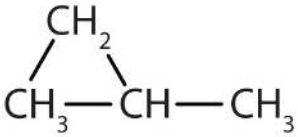


b.

3. Give the molecular formula for each compound.



a.



b.

4. When three isomeric pentenes—X, Y, and Z—are hydrogenated, all three form 2-methylbutane. The addition of Cl_2 to Y gives 1,2-dichloro-3-methylbutane, and the addition of Cl_2 to Z gives 1,2-dichloro-2-methylbutane. Draw the original structures for X, Y, and Z.

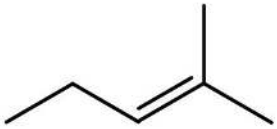
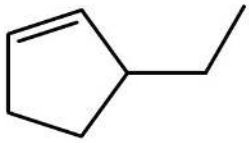
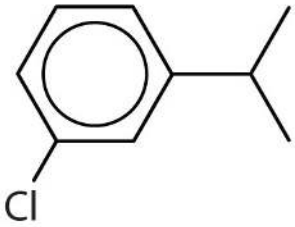
5. Pentane and 1-pentene are both colorless, low-boiling liquids. Describe a simple test that distinguishes the two compounds. Indicate what you would observe.

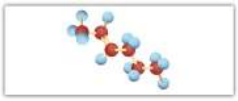
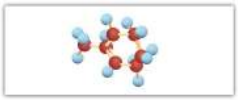
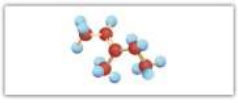
6. Draw and name all the alkene cis-trans isomers corresponding to the molecular formula C_5H_{10}. (Hint: there are only two.)

7. The complete combustion of benzene forms carbon dioxide and water:

   $C_6H_6 + O_2 \rightarrow CO_2 + H_2O$

   Balance the equation. What mass, in grams, of carbon dioxide is formed by the complete combustion of 39.0 g of benzene?

8. Describe a physiological effect of some PAHs.
9. What are some of the hazards associated with the use of benzene?
10. What is wrong with each name? Draw the structure and give the correct name for each compound.
    a. 2-methyl-4-heptene
    b. 2-ethyl-2-hexene
    c. 2,2-dimethyl-3-pentene
11. What is wrong with each name?
    a. 2-bromobenzene
    b. 3,3-dichlorotoluene
12. Following are line-angle formulas for three compounds. Draw the condensed structure and give the name for each.
    a. 
    b. 
    c. 

13. Following are ball-and-stick molecular models for three compounds (blue balls represent H atoms; red balls are C atoms). Write the condensed structural formula and give the name for each.
    a. 
    b. 
    c. 

Answers

1.
    a. unsaturated
    b. unsaturated

3.

a. C_6H_{10}
b. C_4H_8

5. Add bromine solution (reddish-brown) to each. Pentane will not react, and the reddish-brown color persists; 1-pentene will react, leaving a colorless solution.

7. $2C_6H_6 + 15O_2 \rightarrow 12CO_2 + 6H_2O$; 132 g

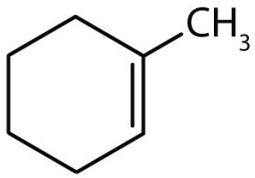
9. carcinogenic, flammable

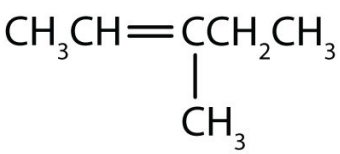
11.

a. number not needed
b. can’t have two groups on one carbon atom on a benzene ring

13.

a. $CH_3CH{=}CHCH_2CH_2CH_3$; 2-hexene

b. 

c. 

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2.S: Unsaturated and Aromatic Hydrocarbons (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.

Any hydrocarbon containing either a double or triple bond is an **unsaturated hydrocarbon**. **Alkenes** have a carbon-to-carbon double bond. The general formula for alkenes with one double bond is C_nH_{2n}. Alkenes can be straight chain, branched chain, or cyclic. Simple alkenes often have common names, but all alkenes can be named by the system of the International Union of Pure and Applied Chemistry.

Cis-trans isomers (or geometric isomers) are characterized by molecules that differ only in their configuration around a rigid part of the structure, such as a carbon–to-carbon double bond or a ring. The molecule having two identical (or closely related) atoms or groups on the same side is the **cis isomer**; the one having the two groups on opposite sides is the **trans isomer**.

The physical properties of alkenes are quite similar to those of alkanes. Like other hydrocarbons, alkenes are insoluble in water but soluble in organic solvents.

More reactive than alkanes, alkenes undergo **addition reactions** across the double bond:

- Addition of hydrogen (**hydrogenation**):

$$CH_2{=}CH_2 + H_2 \rightarrow CH_3CH_3$$

- Addition of halogen (**halogenation**):

$$CH_2{=}CH_2 + X_2 \rightarrow XCH_2CH_2X$$

  where X = F, Cl, Br, or I.

- Addition of water (**hydration**):

$$CH_2{=}CH_2 + HOH \rightarrow HCH_2CH_2OH$$

Alkenes also undergo **addition polymerization**, molecules joining together to form long-chain molecules.

$$\ldots CH_2{=}CH_2 + CH_2{=}CH_2 + CH_2{=}CH_2 + \ldots \rightarrow \ldots CH_2CH_2{-}CH_2CH_2{-}CH_2CH_2{-}\ldots$$

The reactant units are **monomers**, and the product is a **polymer**.

Alkynes have a carbon-to-carbon triple bond. The general formula for alkynes is $C_nH_{2n\,-\,2}$. The properties of alkynes are quite similar to those of alkenes. They are named much like alkenes but with the ending *-yne*.

The cyclic hydrocarbon *benzene* (C_6H_6) has a ring of carbon atoms. The molecule seems to be unsaturated, but it does not undergo the typical reactions expected of alkenes. The electrons that might be fixed in three double bonds are instead *delocalized* over all six carbon atoms.

A hydrocarbon containing one or more benzene rings (or other similarly stable electron arrangements) is an **aromatic hydrocarbon**, and any related substance is an **aromatic compound**. One or more of the hydrogen atoms on a benzene ring can be replaced by other atoms. When two hydrogen atoms are replaced, the product name is based on the relative position of the replacement atoms (or atom groups). A 1,2-disubstituted benzene is designated as an *ortho* (*o*-) isomer; 1,3-, a *meta* (*m*-) isomer; and 1,4-, a *para* (*p*-) isomer. A benzene ring as a substituent is called **phenyl**.

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CHAPTER OVERVIEW

3: Alcohols, Ethers and Thiols

Ethanol and resveratrol, a phenol, are representatives of two of the families of oxygen-containing compounds that we consider in this chapter. Two other classes, aldehydes and ketones, are formed by the oxidation of alcohols. Ethers, another class, are made by the dehydration of alcohols.

3.1: Prelude to Organic Compounds of Oxygen
3.2: Organic Compounds with Functional Groups
3.3: Alcohols - Nomenclature and Classification
3.4: Physical Properties of Alcohols
3.5: Redox Reactions in Organic Chemistry and Biochemistry
3.6: Reactions that Form Alcohols
3.7: Reactions of Alcohols
3.8: Glycols and Glycerol
3.9: Phenols
3.10: Ethers
3.11: Organic Sulfur Compounds
3.E: Organic Compounds of Oxygen (Exercises)

Template:HideTOC

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3.1: Prelude to Organic Compounds of Oxygen

One of the more familiar chemical compounds on Earth is ethyl alcohol (ethanol). As the intoxicant in alcoholic beverages, ethanol is often simply called alcohol. If ethanol is diluted, as it is in wine, beer, or mixed drinks with about 1 oz of liquor, and if it is consumed in small quantities, it is relatively safe. In excess—four or more drinks in a few hours—it causes intoxication, which is characterized by a loss of coordination, nausea and vomiting, and memory blackouts.

Excessive ingestion of ethanol over a long period of time leads to cirrhosis of the liver, alteration of brain cell function, nerve damage, and strong physiological addiction. Alcoholism—an addiction to ethanol—is the most serious drug problem in the United States. Heavy drinking shortens a person's life span by contributing to diseases of the liver, the cardiovascular system, and virtually every other organ of the body.

In small quantities—one or two drinks a day—ethanol might promote health. In addition to the possible benefits of modest amounts of ethanol, a chemical in red wines, resveratrol, is thought to lower the risk of heart disease. Resveratrol, found in red grapes, is an antioxidant. It inhibits the oxidation of cholesterol and subsequent clogging of the arteries. One need not drink wine to get the benefits of resveratrol, however. It can be obtained by eating the grapes or drinking red grape juice.

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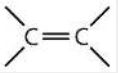
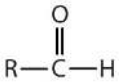
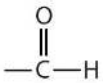
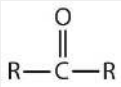
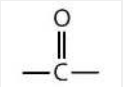
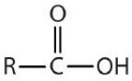
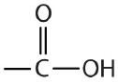
3.2: Organic Compounds with Functional Groups

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 **3.2.1**.

Table **3.2.1**: 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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3.3: Alcohols - Nomenclature and Classification

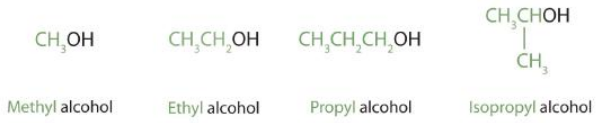
Learning Objectives

- 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*:



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 **3.3.1** shows some examples of the application of these rules.

Figure 3.3.1 shows some examples of the application of these rules.

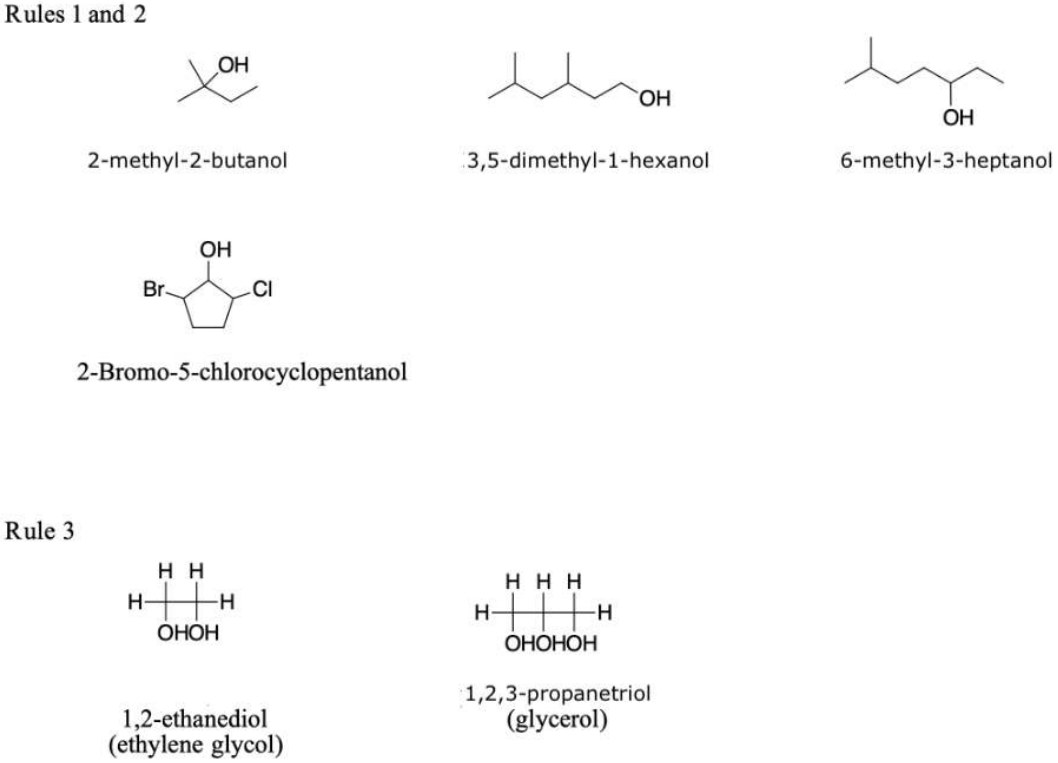
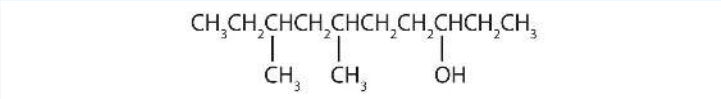


Figure 3.3.1: IUPAC Rules for Alcohols. The names and structures of some alcohols demonstrate the use of IUPAC rules.

Figure **3.3.1**: IUPAC Rules for Alcohols. The names and structures of some alcohols demonstrate the use of IUPAC rules.

Example 3.3.1

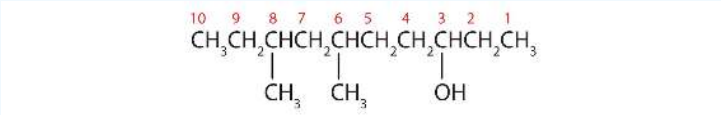
Give the IUPAC name for each compound.

a. 

b. $HOCH_2CH_2CH_2CH_2CH_2OH$

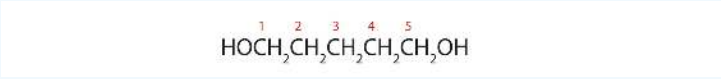
Solution

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).



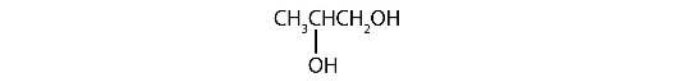
The carbon atoms are numbered from the end closest to the OH group. That fixes the two methyl (CH_3) groups at the sixth and eighth positions. The name is 6,8-dimethyl-3-decanol (not 3,5-dimethyl-8-decanol).

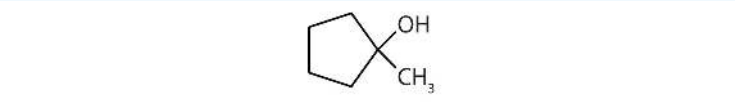
b. Five carbon atoms in the LCC make the compound a derivative of pentane. Two OH groups on the first and fifth carbon atoms make the compound a diol and give the name 1,5-pentanediol (rule 3).



Exercise 3.3.1

Give the IUPAC name for each compound.

a. 

b. 

Example 3.3.2

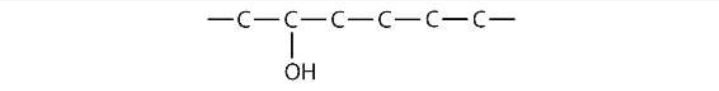
Draw the structure for each compound.

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

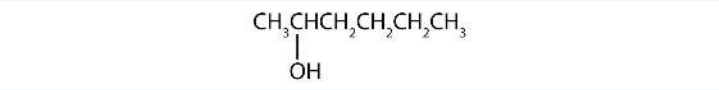
Solution

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–.

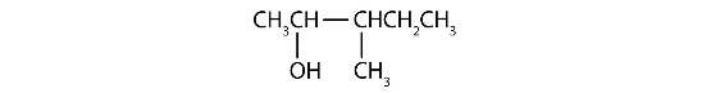
The 2 indicates that the OH group is attached to the second carbon atom.



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



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



Exercise 3.3.2

Draw the structure for each compound.

a. 3-heptanol

b. 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.

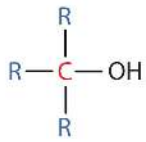
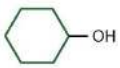


Table **3.3.1** names and classifies some of the simpler alcohols. Some of the common names reflect a compound's classification as secondary (*sec*-) or tertiary (*tert*-). These designations are not used in the IUPAC nomenclature system for alcohols. Note that there are four butyl alcohols in the table, corresponding to the four butyl groups: the butyl group ($CH_3CH_2CH_2CH_2$) discussed before, and three others:



Table **3.3.1**: Classification and Nomenclature of Some Alcohols

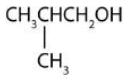
Condensed Structural Formula	Class of Alcohol	Common Name	IUPAC Name
CH_3OH	—	methyl alcohol	methanol
CH_3CH_2OH	primary	ethyl alcohol	ethanol
$CH_3CH_2CH_2OH$	primary	propyl alcohol	1-propanol
$(CH_3)_2CHOH$	secondary	isopropyl alcohol	2-propanol
$CH_3CH_2CH_2CH_2OH$	primary	butyl alcohol	1-butanol
$CH_3CH_2CHOHCH_3$	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.

Concept Review Exercises

1. Is isobutyl alcohol primary, secondary, or tertiary? Explain.



2. What is the LCC in 2-ethyl-1-hexanol? What is taken as the LCC in naming the compound? Explain.

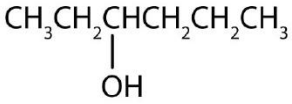
Answers

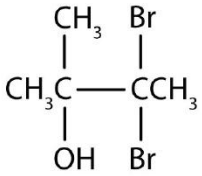
1. primary; the carbon atom bearing the OH group is attached to only one other carbon atom
2. 7 carbon atoms; the 6-atom chain includes the carbon atom bearing the OH group

Exercises

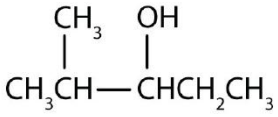
1. Name each alcohol and classify it as primary, secondary, or tertiary.

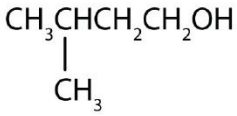
   a. $CH_3CH_2CH_2CH_2CH_2CH_2OH$

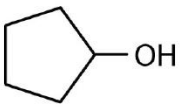
   b. 

   c. 

2. Name each alcohol and classify it as primary, secondary, or tertiary.

   a. 

   b. 

   c. 

3. Draw the structure for each alcohol.

   a. 3-hexanol
   b. 3,3-dimethyl-2-butanol
   c. cyclobutanol

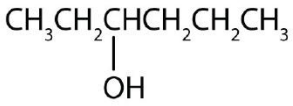
4. Draw the structure for each alcohol.

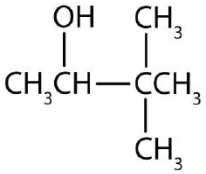
   a. cyclopentanol
   b. 4-methyl-2-hexanol
   c. 4,5-dimethyl-3-heptanol

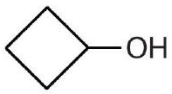
Answers

1. a. 1-hexanol; primary
   b. 3-hexanol; secondary

c. 3,3-dibromo-2-methyl-2-butanol; tertiary

3. a. 

b. 

c. 

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3.4: Physical Properties of Alcohols

Learning Objectives

- Explain why the boiling points of alcohols are higher than those of ethers and alkanes of similar molar masses.
- Explain why alcohols and ethers of four or fewer carbon atoms are soluble in water while comparable alkanes are not soluble.

Alcohols can be considered derivatives of water (H_2O; also written as HOH).



Like the H–O–H bond in water, the R–O–H bond is bent, and alcohol molecules are polar. This relationship is particularly apparent in small molecules and reflected in the physical and chemical properties of alcohols with low molar mass. Replacing a hydrogen atom from an alkane with an OH group allows the molecules to associate through hydrogen bonding (Figure **3.4.1**).

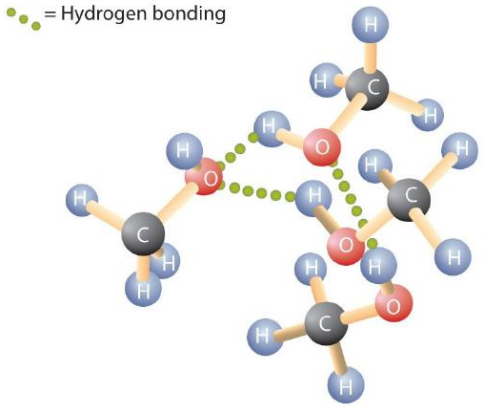


Figure **3.4.1**: Intermolecular Hydrogen Bonding in Methanol. The OH groups of alcohol molecules make hydrogen bonding possible.

Recall that physical properties are determined to a large extent by the type of intermolecular forces. Table **3.4.1** lists the molar masses and the boiling points of some common compounds. The table shows that substances with similar molar masses can have quite different boiling points.

Table **3.4.1**: Comparison of Boiling Points and Molar Masses

Formula	Name	Molar Mass	Boiling Point (°C)
CH_4	methane	16	–164
HOH	water	18	100
C_2H_6	ethane	30	–89
CH_3OH	methanol	32	65
C_3H_8	propane	44	–42
CH_3CH_2OH	ethanol	46	78
C_4H_{10}	butane	58	–1
$CH_3CH_2CH_2OH$	1-propanol	60	97

Alkanes are nonpolar and are thus associated only through relatively weak dispersion forces. Alkanes with one to four carbon atoms are gases at room temperature. In contrast, even methanol (with one carbon atom) is a liquid at room temperature. Hydrogen bonding greatly increases the boiling points of alcohols compared to hydrocarbons of comparable molar mass. The boiling point is a rough measure of the amount of energy necessary to separate a liquid molecule from its nearest neighbors. If the molecules interact through hydrogen bonding, a relatively large quantity of energy must be supplied to break those intermolecular attractions. Only then can the molecule escape from the liquid into the gaseous state.

Alcohols can also engage in hydrogen bonding with water molecules (Figure **3.4.2**). Thus, whereas the hydrocarbons are insoluble in water, alcohols with one to three carbon atoms are completely soluble. As the length of the chain increases, however, the solubility of alcohols in water decreases; the molecules become more like hydrocarbons and less like water. The alcohol 1-decanol ($CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2OH$) is essentially insoluble in water. We frequently find that the borderline of solubility in a family of organic compounds occurs at four or five carbon atoms.

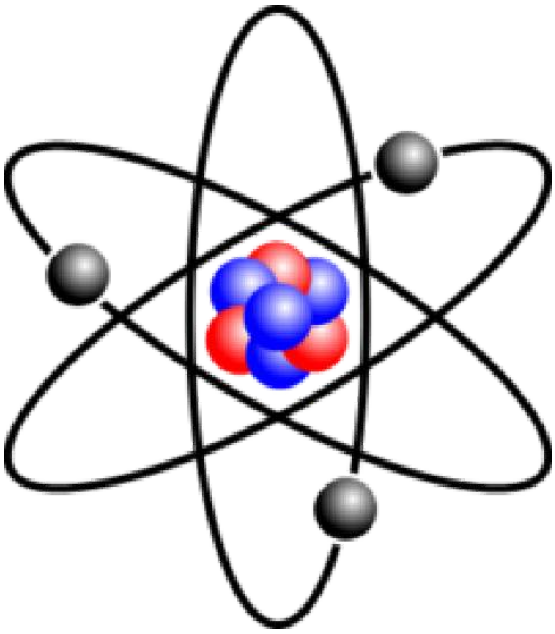


Figure **3.4.2**: Hydrogen Bonding between Methanol Molecules and Water Molecules. Hydrogen bonding between the OH of methanol and water molecules accounts for the solubility of methanol in water.

Summary

Alcohols have higher boiling points than do ethers and alkanes of similar molar masses because the OH group allows alcohol molecules to engage in hydrogen bonding. Alcohols of four or fewer carbon atoms are soluble in water because the alcohol molecules engage in hydrogen bonding with water molecules; comparable alkane molecules cannot engage in hydrogen bonding.

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3.5: Redox Reactions in Organic Chemistry and Biochemistry

Learning Objectives

- To identify oxidation-reduction reactions with organic compounds.

Oxidation-reduction reactions are of central importance in organic chemistry and biochemistry. The burning of fuels that provides the energy to maintain our civilization and the metabolism of foods that furnish the energy that keeps us alive both involve redox reactions.



Figure **3.5.1**: The Burning of Natural Gas. The burning of natural gas is not only a combustion reaction but also a redox reaction. Similar reactions include the burning of gasoline and coal. These are also redox reactions. from Wikipedia.

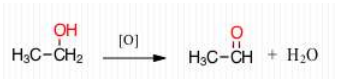
All combustion reactions are also redox reactions. A typical combustion reaction is the burning of methane, the principal component of natural gas (Figure **3.5.1**).

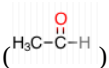
$$\mathbf{CH_4 + 2\,O_2 \rightarrow CO_2 + 2\,H_2O} \tag{3.5.1}$$

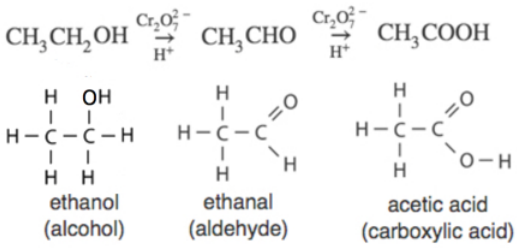
In respiration, the biochemical process by which the oxygen we inhale in air oxidizes foodstuffs to carbon dioxide and water, redox reactions provide energy to living cells. A typical respiratory reaction is the oxidation of glucose ($\mathbf{C_6H_{12}O_6}$), the simple sugar we encountered in the chapter-opening essay that makes up the diet of yeast:

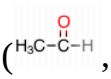
$$\mathbf{C_6H_{12}O_6 + 6\,O_2 \rightarrow 6\,CO_2 + 6\,H_2O} \tag{3.5.2}$$

Organic chemists use a variety of redox reactions. For example, potassium dichromate ($\mathbf{K_2Cr_2O_7}$) is a common oxidizing agent that can be used to oxidize alcohols (symbolized by the general formula ROH). The product of the reaction depends on the location of the OH functional group in the alcohol molecule, the relative proportions of alcohol and the dichromate ion, and reaction conditions such as temperature. If the OH group is attached to a terminal carbon atom and the product is distilled off as it forms, the product is an aldehyde, which has a terminal *carbonyl group* (C=O) and is often written as RCHO. One example is the reaction used by the Breathalyzer to detect ethyl alcohol ($\mathbf{CH_3CH_2OH}$) in a person's breath:

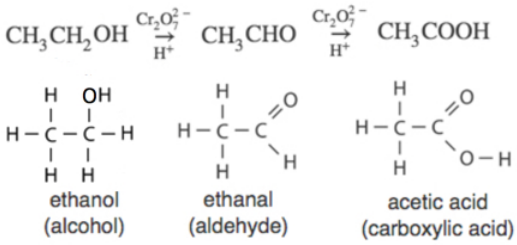


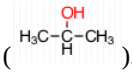
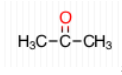
If the product acetaldehyde () is not removed as it forms, it is further oxidized to acetic acid ($\mathbf{CH_3COOH}$). In this case, the overall reaction is as follows:

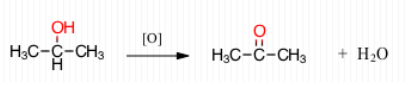


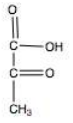
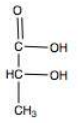
In this reaction, the chromium atom is reduced because it lost oxygen atoms from $Cr_2O_7^{2-}$ to Cr^{3+}. On the other hand, the carbon atom in ethanol is oxidized. In the **oxidation** of ethyl alcohol (CH_3-CH_2-OH, a.k.a. ethanol) to form acetaldehyde ( , a.k.a. ethanal), the **number of bonds to oxygen has increased and the number of hydrogen atoms has decreased** from six to four. Either or both of these indicate that an oxidation has occurred.

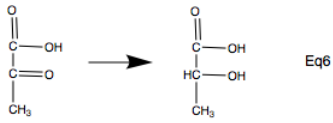
In the oxidation of acetaldehyde to acetic acid (a.k.a. ethanoic acid), the carbon atom that gained an additional oxygen is the element oxidized.



When the OH group of the alcohol is bonded to an interior carbon atom, the oxidation of an alcohol will produce a ketone (the formulas of ketones are often written as RCOR, and the carbon–oxygen bond is a double bond). The simplest ketone is derived from 2-propanol (). It is the common solvent acetone  , which is used in varnishes, lacquers, rubber cement, and nail polish remover. Acetone can be formed by the following redox reaction:



As we have just seen, aldehydes and ketones can be formed by the oxidation of alcohols. Conversely, aldehydes and ketones can be reduced to alcohols. Reduction of the carbonyl group is important in living organisms. For example, in anaerobic metabolism, in which biochemical processes take place in the absence of oxygen, pyruvic acid,  , is reduced to lactic acid,  , in the muscles.



(Pyruvic acid is both a carboxylic acid and a ketone; only the ketone group is reduced.) The buildup of lactic acid during vigorous exercise is responsible in large part for the fatigue that we experience.

In food chemistry, the substances known as antioxidants are reducing agents. Ascorbic acid (vitamin C; $C_6H_8O_6$) is thought to retard potentially damaging oxidation of living cells. In the process, it is oxidized to dehydroascorbic acid ($C_6H_6O_6$). In the stomach, ascorbic acid reduces the nitrite ion (NO_2^-) to nitric oxide (NO):

$$C_6H_8O_6 + 2H^+ + 2NO_2^- \rightarrow C_6H_6O_6 + 2H_2O + 2NO \tag{3.5.3}$$

https://chem.libretexts.org/@go/page/306604

> *If reaction in Equation 3.5.3 did not occur, nitrite ions from foods would oxidize the iron in hemoglobin, destroying its ability to carry oxygen.*

Tocopherol (vitamin E) is also an antioxidant. In the body, **vitamin E** is thought to act by scavenging harmful by-products of metabolism, such as the highly reactive molecular fragments called free radicals. In foods, vitamin E acts to prevent fats from being oxidized and thus becoming rancid. **Vitamin C** is also a good antioxidant (Figure 3.5.2).



Figure 3.5.2: Citrus Fruits. Citrus fruits, such as oranges, lemons, and limes, are good sources of vitamin C, which is an antioxidant. Wedges of pink grapefruit, lime, and lemon, and a half orange (clockwise from top). from Wikipedia.

Finally, and of greatest importance, green plants carry out the redox reaction that makes possible almost all life on Earth. They do this through a process called photosynthesis, in which carbon dioxide and water are converted to glucose ($C_6H_{12}O_6$). The synthesis of glucose requires a variety of proteins called enzymes and a green pigment called chlorophyll that converts sunlight into chemical energy (Figure 3.5.3). The overall change that occurs is as follows:

$$6\,CO_2 + 6\,H_2O \rightarrow C_6H_{12}O_6 + 6\,O_2 \tag{3.5.4}$$

In this reaction, carbon dioxide is reduced to glucose, and water is oxidized to oxygen gas. Other reactions convert the glucose to more complex carbohydrates, plant proteins, and oils.



Figure 3.5.3: Life on Earth. Photosynthesis is the fundamental process by which plants use sunlight to convert carbon dioxide and water into glucose and oxygen. Then plants make more complex carbohydrates. It is the ultimate source of all food on Earth, and it is a redox reaction. (Public Domain; Wikipedia).

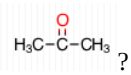
Summary

Redox reactions are common in organic and biological chemistry, including the combustion of organic chemicals, respiration, and photosynthesis.

Exercises

For the following questions, provide the answers by drawing the structures.

1. What would be the organic product if CH_3-CH_2-CH_2-OH were to be oxidized?
2. What would be the organic product if CH_3-CH_2-CH_2-CH_2-OH were to be oxidized?
3. What would be the organic product if 2-butanol were to be oxidized?
4. What would be the organic product if 3-pentanol were to be oxidized?

5. What alcohol (name and structure) is produced in the reduction of acetone  ?

6. What alcohol (name and structure) is produced in the reduction of propanal  ?

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3.6: Reactions that Form Alcohols

Learning Objectives

- To describe how to prepare alcohols from alkenes

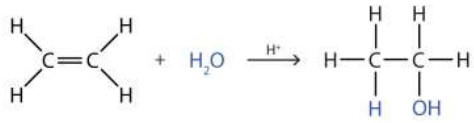
Methanol is prepared by combining hydrogen gas and carbon monoxide at high temperatures and pressures in the presence of a catalyst composed of zinc oxide (ZnO) and chromium oxide (Cr_2O_3) catalyst:

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

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.

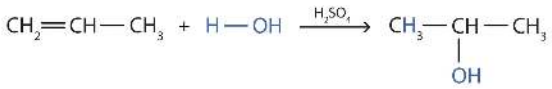
> *Nearly 2 billion gallons of methanol are produced each year in the United States by the catalytic reduction of carbon monoxide with hydrogen gas.*

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)

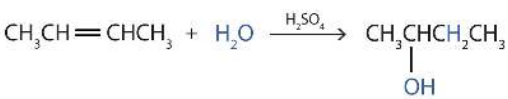
Additional Exercise **3.6.1** describes how to use a generalization called Markovnikov's rule to predict the results when the addition of water to an alcohol has two possible products.

Example 3.6.1

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 3.6.1

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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3.7: Reactions of Alcohols

Learning Objectives

1. Give two major types of reactions of alcohols.
2. Describe the result of the oxidation of a primary alcohol.
3. Describe the result of the oxidation of a secondary alcohol.

Chemical reactions in alcohols occur mainly at the functional group, but some involve hydrogen atoms attached to the OH-bearing carbon atom or to an adjacent carbon atom. Of the three major kinds of alcohol reactions, which are summarized in Figure **3.7.1**, two—dehydration and oxidation—are considered here. The third reaction type—esterification—is covered elsewhere.

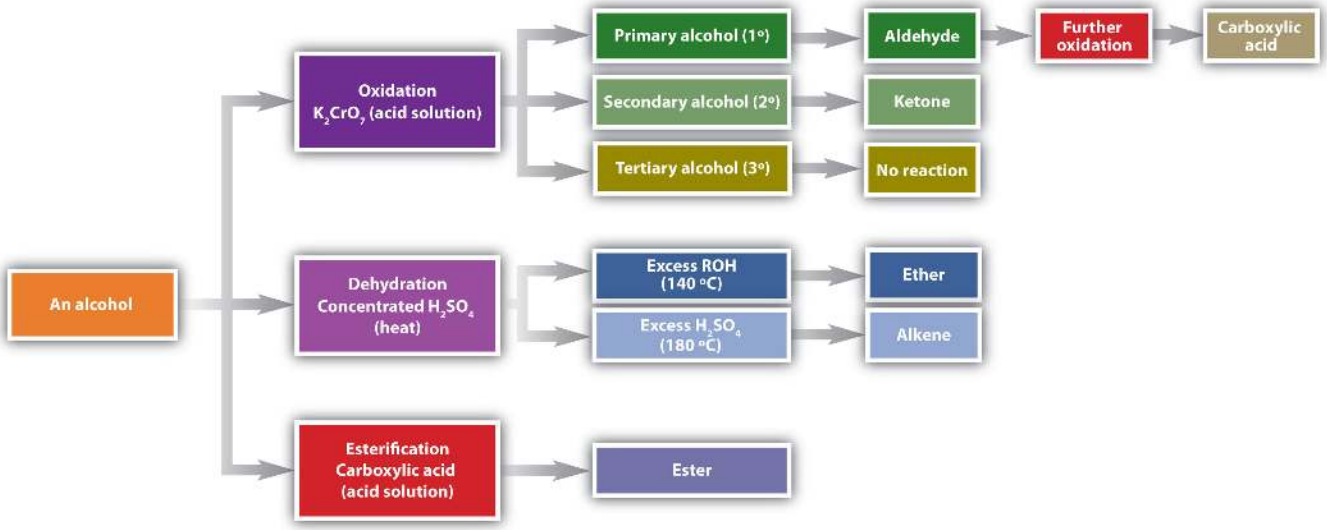
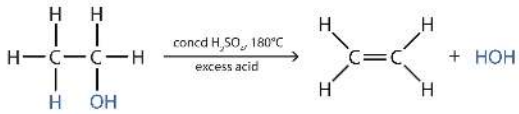


Figure **3.7.1**: Reactions of Alcohols. Oxidation and dehydration of alcohols are considered here.

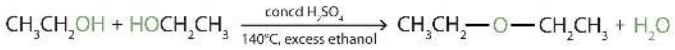
- ## Dehydration

  As noted in Figure **3.7.1**, an alcohol undergoes dehydration in the presence of a catalyst to form an alkene and water. The reaction removes the OH group from the alcohol carbon atom and a hydrogen atom from an adjacent carbon atom in the same molecule:



Ethanol Ethylene

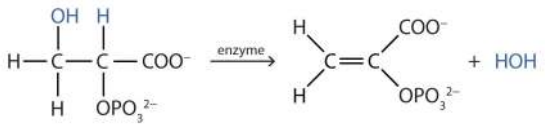
Under the proper conditions, it is possible for the dehydration to occur between *two* alcohol molecules. The entire OH group of one molecule and only the hydrogen atom of the OH group of the second molecule are removed. The two ethyl groups attached to an oxygen atom form an ether molecule.



Two molecules of ethanol Diethyl ether

(Ethers are discussed in elsewhere) Thus, depending on conditions, one can prepare either alkenes or ethers by the dehydration of alcohols.

> Both dehydration and hydration reactions occur continuously in cellular metabolism, with enzymes serving as catalysts and at a temperature of about 37°C. The following reaction occurs in the "Embden–Meyerhof" pathway

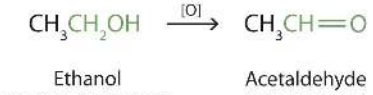


2-Phosphoglycerate Phosphoenolpyruvate

Although the participating compounds are complex, the reaction is the same: elimination of water from the starting material. The idea is that if you know the chemistry of a particular functional group, you know the chemistry of hundreds of different compounds.

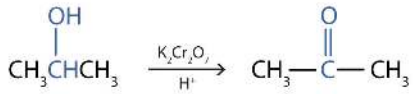
Oxidation

Primary and secondary alcohols are readily oxidized. We saw earlier how methanol and ethanol are oxidized by liver enzymes to form aldehydes. Because a variety of oxidizing agents can bring about oxidation, we can indicate an oxidizing agent without specifying a particular one by writing an equation with the symbol [O] above the arrow. For example, we write the oxidation of ethanol—a primary alcohol—to form acetaldehyde—an aldehyde—as follows:



Ethanol (a primary alcohol) Acetaldehyde (an aldehyde)

We shall see that aldehydes are even more easily oxidized than alcohols and yield carboxylic acids. Secondary alcohols are oxidized to *ketones*. The oxidation of isopropyl alcohol by potassium dichromate ($K_2Cr_2O_7$) gives acetone, the simplest ketone:



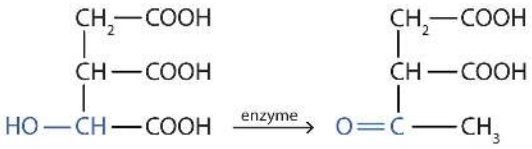
Isopropyl alcohol (a secondary alcohol) Acetone (a ketone)

Unlike aldehydes, ketones are relatively resistant to further oxidation, so no special precautions are required to isolate them as they form. Note that in oxidation of both primary (RCH_2OH) and secondary (R_2CHOH) alcohols, two hydrogen atoms are removed from the alcohol molecule, one from the OH group and other from the carbon atom that bears the OH group.

These reactions can also be carried out in the laboratory with chemical oxidizing agents. One such oxidizing agent is potassium dichromate. The balanced equation (showing only the species involved in the reaction) in this case is as follows:



Alcohol oxidation is important in living organisms. Enzyme-controlled oxidation reactions provide the energy cells need to do useful work. One step in the metabolism of carbohydrates involves the oxidation of the secondary alcohol group in isocitric acid to a ketone group:



Isocitrate Oxalosuccinate

The overall type of reaction is the same as that in the conversion of isopropyl alcohol to acetone.

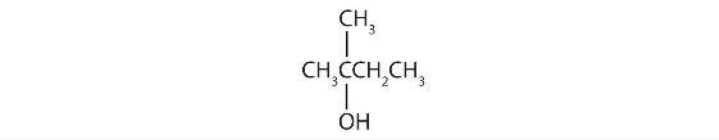
Tertiary alcohols (R_3COH) are resistant to oxidation because the carbon atom that carries the OH group does not have a hydrogen atom attached but is instead bonded to other carbon atoms. The oxidation reactions we have described involve the

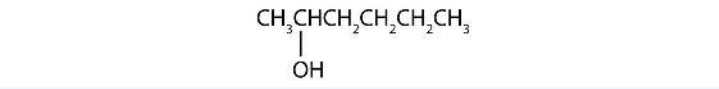
formation of a carbon-to-oxygen double bond. Thus, the carbon atom bearing the OH group must be able to release one of its attached atoms to form the double bond. The carbon-to-hydrogen bonding is easily broken under oxidative conditions, but carbon-to-carbon bonds are not. Therefore tertiary alcohols are not easily oxidized.

Example 3.7.1

Write an equation for the oxidation of each alcohol. Use [O] above the arrow to indicate an oxidizing agent. If no reaction occurs, write "no reaction" after the arrow.

a. $CH_3CH_2CH_2CH_2CH_2OH$

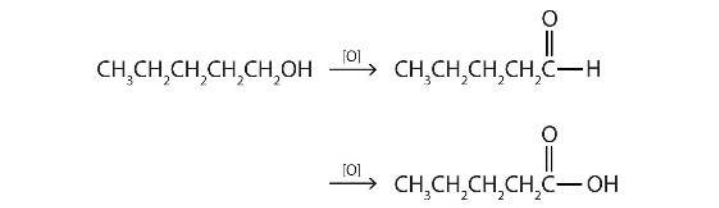
b. 

c. 

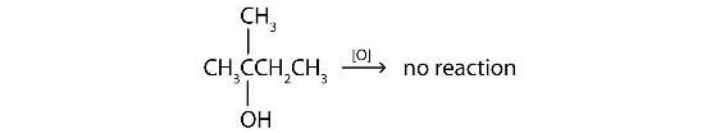
Solution

The first step is to recognize the class of each alcohol as primary, secondary, or tertiary.

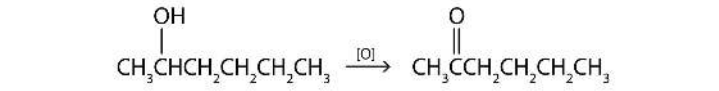
a. This alcohol has the OH group on a carbon atom that is attached to only *one* other carbon atom, so it is a primary alcohol. Oxidation forms first an aldehyde and further oxidation forms a carboxylic acid.



b. This alcohol has the OH group on a carbon atom that is attached to three other carbon atoms, so it is a tertiary alcohol. No reaction occurs.

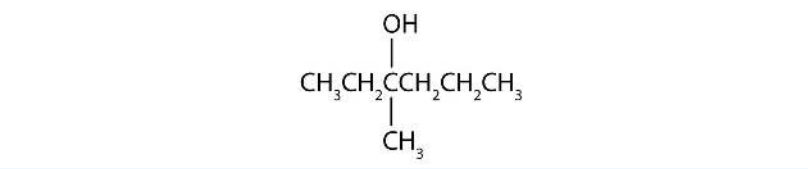


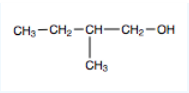
c. This alcohol has the OH group on a carbon atom that is attached to two other carbon atoms, so it is a secondary alcohol; oxidation gives a ketone.

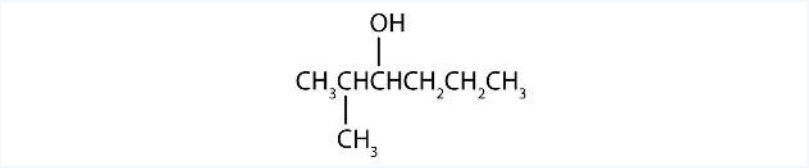


Exercise 3.7.1

Write an equation for the oxidation of each alcohol. Use [O] above the arrow to indicate an oxidizing agent. If no reaction occurs, write "no reaction" after the arrow.

1. 

2. 

3. 

Summary

Alcohols can be dehydrated to form either alkenes (higher temperature, excess acid) or ethers (lower temperature, excess alcohol). Primary alcohols are oxidized to form aldehydes. Secondary alcohols are oxidized to form ketones. Tertiary alcohols are not readily oxidized.

Concept Review Exercises

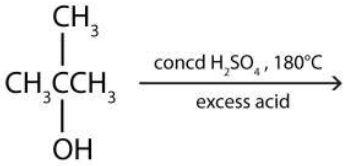
1. In a reaction, compound W with the molecular formula $C_4H_{10}O$ is converted to compound X with the formula C_4H_8O. Is W oxidized, reduced, dehydrated, or none of these? Explain.
2. In a reaction, 2 mol of compound Y with the molecular formula $C_4H_{10}O$ is converted to 1 mol of compound Z with the formula $C_8H_{18}O$. Is Y oxidized, reduced, or neither? Explain.

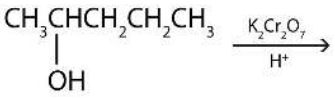
Answers

1. oxidized; H is removed
2. neither; water is removed

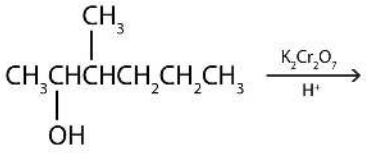
Exercises

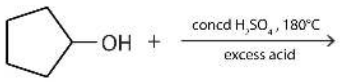
1. Name the three major types of chemical reactions of alcohols.
2. Why do tertiary alcohols not undergo oxidation? Can a tertiary alcohol undergo dehydration?
3. Draw the structure of the product for each reaction.

a. 

b. 

4. Draw the structure of the product for each reaction.

a. 

b. 

5. Draw an equation for the dehydration of 2-propanol to yield each compound type.

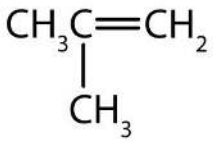
a. an alkene
b. an ether

6. Draw the structure of the alkene formed by the dehydration of cyclohexanol.

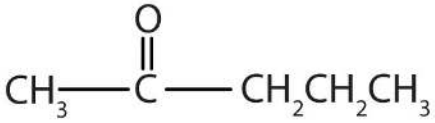
Answers

1. dehydration, oxidation, and esterification

3. a.

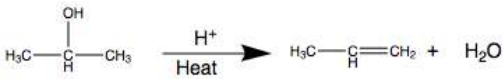


b.

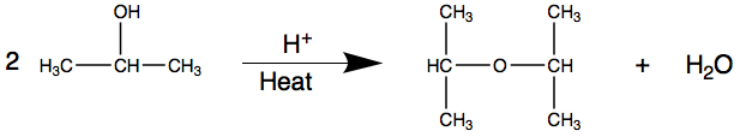


5.

a.



b.



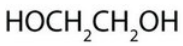
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3.8: Glycols and Glycerol

Learning Objectives

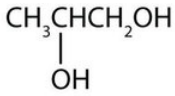
- To describe the structure and uses of some common polyhydric alcohols.

Alcohols with two OH groups on adjacent carbon atoms are commonly known as glycols. The most important of these is 1,2-ethanediol (the common name is ethylene glycol), a sweet, colorless, somewhat viscous liquid.



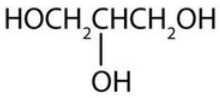
Ethylene glycol

Another common glycol, 1,2-propanediol, is commonly called propylene glycol. Its physical properties are quite similar to those of ethylene glycol.



Propylene glycol

Commonly called glycerol or glycerin, 1,2,3-propanetriol is the most important trihydroxy alcohol. Like the two glycols, it is a sweet, syrupy liquid. Glycerol is a product of the hydrolysis of fats and oils.

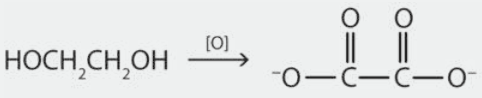


Glycerol

Ethylene glycol is the main ingredient in many antifreeze mixtures for automobile radiators. The two OH groups lead to extensive intermolecular hydrogen bonding. This results in a high boiling point—198°C; thus ethylene glycol does not boil away when it is used as an antifreeze. It is also completely miscible with water. A solution of 60% ethylene glycol in water freezes at −49°C (−56°F) and thus protects an automobile radiator down to that temperature. Ethylene glycol is also used in the manufacture of polyester fiber and magnetic film used in tapes for recorders and computers.

To Your Health: Glycols and Human Health

Ethylene glycol is quite toxic. Because it is sweet, pets often lap up spills of leaked antifreeze from a garage floor or driveway. Sometimes people, especially children, drink it. As with methanol, its toxicity is due to a metabolite. Liver enzymes oxidize ethylene glycol to oxalate ion.



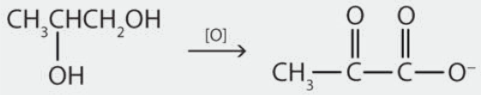
Ethylene glycol Oxalate ion

In the kidneys, the oxalate ion combines with the calcium (Ca^{2+}) ion, precipitating as calcium oxalate (CaC_2O_4).

$$Ca^{2+}(aq) + C_2O_4{}^{2-}(aq) \rightarrow CaC_2O_4(s)$$

These crystals cause renal damage and can lead to kidney failure and death.

Although propylene glycol has physical properties much like those of ethylene glycol, its physiological properties are quite different. Propylene glycol is essentially nontoxic, and it can be used as a solvent for drugs and as a moisturizing agent for foods. Like other alcohols, propylene glycol is oxidized by liver enzymes.



Propylene glycol Pyruvate ion

In this case, however, the product is pyruvate ion, a normal intermediate in carbohydrate metabolism. Glycerol, a product of fat metabolism, is essentially nontoxic.

Summary

Glycols are alcohols with two OH groups on adjacent carbon atoms. Glycerol is the most important trihydroxy alcohol.

Concept Review Exercises

1. In the oxidation of propylene glycol to pyruvic acid, what functional groups in the reactant are involved? What new functional groups appear in the product?
2. Oxalate ion is formed by the oxidation of ethylene glycol. In what kind of reaction is the oxalate ion involved?

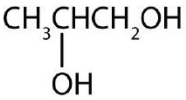
Answers

1. two OH groups; a ketone group and a carboxylic acid group
2. precipitation

Exercises

1. What is a glycol?
2. Why is ethylene glycol so much more toxic to humans than propylene glycol?
3. Draw the structure for each compound.
   a. 1,5-pentanediol
   b. propylene glycol
4. Draw the structure for each compound.
   a. 1,3-hexandiol
   b. glycerol

Answers

1. an alcohol with two OH groups on adjacent carbon atoms
3. a. $HOCH_2CH_2CH_2CH_2CH_2OH$
   b. 

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3.9: 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.

$$\mathrm{ArOH\,(aq) + NaOH\,(aq) \rightarrow ArONa\,(aq) + H_2O} \tag{3.9.1}$$

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.

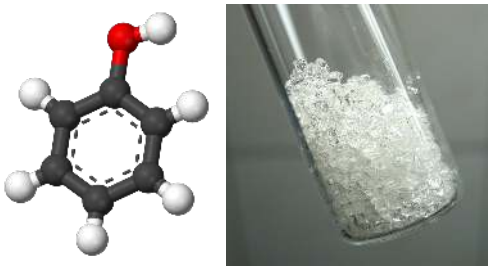


Figure 3.9.1: *(Left) Structure of Phenol (right) Approximately two grams of phenol in glass vial. Image used with permisison from Wikipedia*

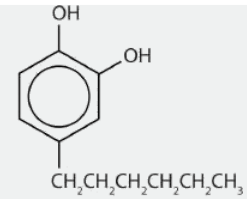
To Your Health: Phenols and Us

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.

Summary

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

Concept Review Exercises

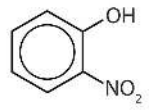
1. How do phenols differ from alcohols in terms of structure and properties?
2. How do phenols differ in properties from aromatic hydrocarbons?

Answers

1. Phenols have an OH group attached directly to an aromatic ring. Phenols are weakly acidic.
2. Phenols have an OH group and are somewhat soluble in water.

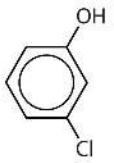
Exercises

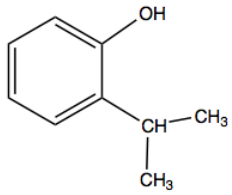
1. Name each compound.

a. 

b. 

2. Name each compound.

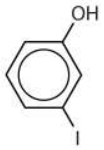
a. 

b. 

3. Draw the structure for each compound.
   a. *m*-iodophenol
   b. *p*-methylphenol (*p*-cresol)
4. Draw the structure for each compound.

a. 2,4,6-trinitrophenol (picric acid)
b. 3,5-diethylphenol

Answers

1. a. *o*-nitrophenol
   b. *p*-bromophenol
3. a. 

   b. 

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3.10: Ethers

Learning Objectives

- Describe the structural difference between an alcohol and an ether that affects physical characteristics and reactivity of each.
- Name simple ethers.
- Describe the structure and uses of some ethers.

With the general formula R-O-R′, an ether may be considered a derivative of water in which both hydrogen atoms are replaced by alkyl or aryl groups. It may also be considered a derivative of an alcohol (R-O-H) in which the hydrogen atom of the OH group is been replaced by a second alkyl or aryl group:

$$\mathrm{HOH} \xrightarrow[\text{H atoms}]{\text{replace both}} \mathrm{R-O-R'} \xleftarrow[\text{of OH group}]{\text{replace H atom}} \mathrm{R-O-H} \tag{3.10.1}$$

Simple ethers have simple common names, formed from the names of the groups attached to oxygen atom, followed by the generic name *ether*. For example, CH_3–O–CH_2-CH_2-CH_3 is methyl propyl ether. If both groups are the same, the group name should be preceded by the prefix *di-*, as in dimethyl ether (CH_3–O–CH_3) and diethyl ether CH_3-CH_2–O–CH_2-CH_3.

Ether molecules have no hydrogen atom on the oxygen atom (that is, no OH group). Therefore there is no intermolecular hydrogen bonding between ether molecules, and ethers therefore have quite low boiling points for a given molar mass. Indeed, ethers have boiling points about the same as those of alkanes of comparable molar mass and much lower than those of the corresponding alcohols (Table **3.10.1**).

Table **3.10.1**: 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_3-CH_2-CH_3	propane	44	–42	no
CH_3-O-CH_3	dimethyl ether or methoxymethane	46	–25	no
CH_3-CH_2-OH	ethyl alcohol or ethanol	46	78	yes
CH_3-CH_2-CH_2-CH_2-CH_3	pentane	72	36	no
CH_3-CH_2-O-CH_2-CH_3	diethyl ether or ethoxy ethane	74	35	no
CH_3-CH_2-CH_2-CH_2-OH	butyl alcohol or 1-butanol	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).

The IUPAC name for CH_3-O-CH_3 is methoxymethane and for CH_3–O–CH_2-CH_2-CH_3 is 1-methoxypropane. For CH_3–O–CH_2-CH_2-CH_3, the longer carbon chain on the right side of the oxygen is considered the base name and the shorter carbon chain on the left side of the oxygen is considered the substituent. However, since the methyl substituent is connected directly to an oxygen then the substituent name become methoxy.

Example 3.10.1

What is the IUPAC name for each ether?

a. CH_3-CH_2-CH_2-O-CH_2-CH_2-CH_3

b. 

Solution

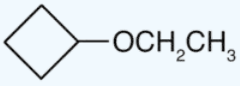
a. The carbon groups on either side of the oxygen atom are propyl ($CH_3CH_2CH_2$) groups, so the compound is propoxypropane.

b. The three-carbon group is attached by the middle carbon atom #2. The one-carbon group is a methyl group. The compound is 2-methoxypropane.

Exercise 3.10.1

What is the IUPAC name for each ether?

a. CH_3-CH_2-CH_2-CH_2-O-CH_2-CH_2-CH_2CH_3

b. 

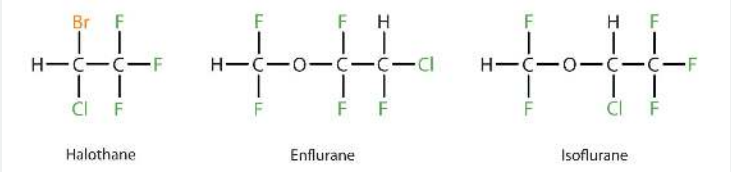
To Your Health: Ethers as General Anesthetics

A *general anesthetic* acts on the brain to produce unconsciousness and a general insensitivity to feeling or pain. Diethyl ether ($CH_3CH_2OCH_2CH_3$) was the first general anesthetic to be used.



William Morton, a Boston dentist, introduced diethyl ether into surgical practice in 1846. This painting shows an operation in Boston in 1846 in which diethyl ether was used as an anesthetic. Inhalation of ether vapor produces unconsciousness by depressing the activity of the central nervous system. Source: Painting of William Morton by Ernest Board.

Diethyl ether is relatively safe because there is a fairly wide gap between the dose that produces an effective level of anesthesia and the lethal dose. However, because it is highly flammable and has the added disadvantage of causing nausea, it has been replaced by newer inhalant anesthetics, including the fluorine-containing compounds halothane, enflurane, and isoflurane. Unfortunately, the safety of these compounds for operating room personnel has been questioned. For example, female operating room workers exposed to halothane suffer a higher rate of miscarriages than women in the general population.



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These three modern, inhalant, halogen-containing, anesthetic compounds are less flammable than diethyl ether.

Summary

To give ethers common names, simply name the groups attached to the oxygen atom, followed by the generic name *ether*. If both groups are the same, the group name should be preceded by the prefix *di-*. Ether molecules have no OH group and thus no intermolecular hydrogen bonding. Ethers therefore have quite low boiling points for a given molar mass. Ether molecules have an oxygen atom and can engage in hydrogen bonding with water molecules. An ether molecule has about the same solubility in water as the alcohol that is isomeric with it.

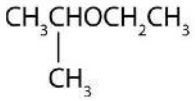
Concept Review Exercises

1. Why does ethoxyethane (CH_3-CH_2-O-CH_2-CH_3) have a much lower boiling point than 1-butanol (CH_3-CH_2-CH_2-CH_2-OH)?
2. Which is more soluble in water—methoxyethane (CH_3-CH_2-O-CH_3) or 1-butanol (CH_3-CH_2-CH_2-CH_2-OH)? Explain.

Answers

1. Diethyl ether has no intermolecular hydrogen bonding because there is no OH group; 1-butanol has an OH and engages in intermolecular hydrogen bonding.
2. Ethyl methyl ether (three carbon atoms, one oxygen atom) is more soluble in water than 1-butanol (four carbon atoms, one oxygen atom), even though both can engage in hydrogen bonding with water.

Exercises

1. How can ethanol give two different products when heated with an acid catalyst? Name these products.
2. Which of these ethers is isomeric with ethanol: CH_3-CH_2-O-CH_2-CH_3, CH_3-O-CH_2CH_3, or CH_3-O-CH_3?
3. Provide the IUPAC name each compound.
   a. CH_3-O-CH_2-CH_2-CH_3
   b. 

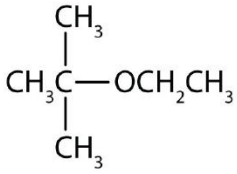
4. Provide the IUPAC name of each compound.
   a. CH_3-CH_2-CH_2-CH_2O-CH_3
   b. CH_3-CH_2-O-CH_2-CH_2CH_3
5. Draw the structure for each compound.
   a. methoxypropane
   b. 2-ethoxy-2-methyl propane
6. Draw the structure for each compound.
   a. 2-isopropoxypropane
   b. propoxycyclopropane

Answers

1. Intramolecular (both the H and the OH come from the same molecule) dehydration gives ethene; intermolecular (the H comes from one molecule and the OH comes from another molecule) dehydration gives ethoxyethane.

3. a. 1-methoxypropane
   b. 2-ethoxypropane

5. a. CH_3-O-CH_2-CH_3

b. 

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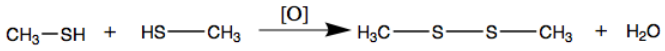
3.11: Organic Sulfur Compounds

Learning Objectives

- Identify thiols (mercaptans) by the presence of an SH group.
- The mild oxidation of thiols gives disulfides.

Because sulfur is in the same group (6A) of the periodic table as oxygen, the two elements have some similar properties. We might expect sulfur to form organic compounds related to those of oxygen, and indeed it does. Thiols (also called mercaptans), which are sulfur analogs of alcohols, have the general formula RSH. Methanethiol (also called methyl mercaptan), has the formula CH_3SH. Ethanethiol (ethyl mercaptan) is the most common odorant for liquid propane (LP) gas.

The mild oxidation of thiols gives compounds called disulfides.



The amino acids cysteine and methionine contain sulfur atoms, as do all proteins that contain these amino acids. Disulfide linkages (–S–S–) between protein chains are extremely important in protein structure.

Thioethers, which are sulfur analogs of ethers, have the form general formula RSR′. An example is dimethylsulfide (CH_3SCH_3), which is responsible for the sometimes unpleasant odor of cooking cabbage and related vegetables. Note that methionine has a thioether functional group.

Career Focus: Paramedic

Paramedics are highly trained experts at providing emergency medical treatment. Their critical duties often include rescue work and emergency medical procedures in a wide variety of settings, sometimes under extremely harsh and difficult conditions. Like other science-based professions, their work requires knowledge, ingenuity, and complex thinking, as well as a great deal of technical skill. The recommended courses for preparation in this field include anatomy, physiology, medical terminology, and—not surprisingly—chemistry. An understanding of basic principles of organic chemistry, for example, is useful when paramedics have to deal with such traumas as burns from fuel (hydrocarbons) or solvent (alcohols, ethers, esters, and so on) fires and alcohol and drug overdoses.

To become a paramedic requires 2–4 y of training and usually includes a stint as an emergency medical technician (EMT). An EMT provides basic care, can administer certain medications and treatments, such as oxygen for respiratory problems and epinephrine (adrenalin) for allergic reactions, and has some knowledge of common medical conditions. A paramedic, in contrast, must have extensive knowledge of common medical problems and be trained to administer a wide variety of emergency drugs.

Paramedics usually work under the direction of a medical doctor with a title such as “medical director.” Some paramedics are employed by fire departments and may work from a fire engine that carries medical equipment as well as fire-fighting gear. Some work from hospital-sponsored ambulances and continue to care for their patients after reaching the hospital emergency room. Still other paramedics work for a government department responsible for emergency health care in a specific geographical area. Finally, some work for private companies that contract to provide service for a government body.

An experienced paramedic has a broad range of employment options, including training for mountain or ocean rescue, working with police department special weapons and tactics (SWAT) teams, or working in isolated settings such as on oil rigs. With their expertise at treating and stabilizing patients before quickly moving them to a hospital, paramedics often provide the first critical steps in saving an endangered life. The following quotation, inscribed on the Arlington National Cemetery headstone of Army Lieutenant R. Adams Cowley, who is often called the “father” of shock trauma medicine, serves as the motto for many paramedic units: “Next to creating a life the finest thing a man can do is save one.” —Abraham Lincoln

Summary

Thiols, thioethers, and disulfides are common in biological compounds.

Concept Review Exercises

1. What is the functional group of a thiol? Write the condensed structural formula for ethanethiol (ethyl mercaptan).
2. What is the functional group of a disulfide? Write the condensed structural formula for dipropyl disulfide.

Answers

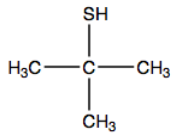
1. SH; CH_3CH_2SH
2. –S–S–; CH_3-CH_2-CH_2-S-S-CH_2-CH_2-CH_3

Exercises

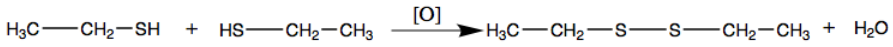
1. A common natural gas odorant is 2-methyl-2-propanethiol. What is its condensed structural formula?
2. Write the equation for the oxidation of ethanethiol to diethyl disulfide.

Answer

1.



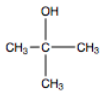
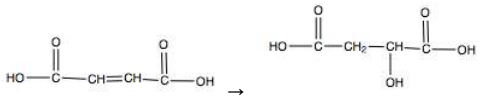
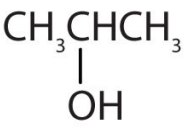
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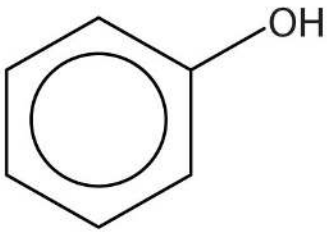


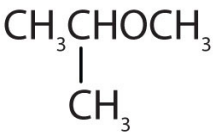
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3.E: Organic Compounds of Oxygen (Exercises)

Additional Exercises

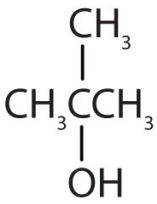
1. Describe two ways that ethanol can be prepared. Which method is used to produce alcoholic beverages?
2. Give the structure of the alkene that makes isopropyl alcohol when the alkene is reacted with water in an acidic solution.
3. Ethanol is used as a solvent for some drugs that are not soluble in water. Why is methanol not used in medicines?
4. Give the structure of the alkene that is made from *tert*-butyl alcohol () when *tert*-butyl alcohol is reacted with heat in an acidic solution.
5. Classify each conversion as oxidation, dehydration, or hydration (only the organic starting material and product are shown):
   a. $CH_3OH \rightarrow$ 
   b. 2-propanol $\rightarrow CH_3CH{=}CH_2$
   c. $CH_2{=}CHCH_2CH_3 \rightarrow$ 2-butanol
6. Classify each conversion as oxidation, dehydration, or hydration (only the organic starting material and product are shown.):
   a. 2-propanol → propanone (ketone)
   b. 
   c. $2\ CH_3OH \rightarrow CH_3OCH_3$
7. Why is methanol so much more toxic to humans than ethanol?
8. There are four isomers of four-carbon alcohols. Each alcohol isomer is treated with potassium dichromate ($K_2Cr_2O_7$, oxidizing agent) in acid. Give the product (if any) expected from each reaction.
9. Draw the structures and give IUPAC names for the four isomeric aldehydes having the formula $C_5H_{10}O$.
10. Write an equation for the reaction of phenol with aqueous NaOH.
11. Write an equation for the ionization of phenol in water.
12. Draw the structures and give the common and IUPAC names for the three isomeric ketones having the formula $C_5H_{10}O$.
13. As we shall see in the "Carbohydrates" chapter, 2,3-dihydroxypropanal and 1,3-dihydroxyacetone are important carbohydrates. Draw their structures.
14. Glutaraldehyde (pentanedial) is a germicide that is replacing formaldehyde as a sterilizing agent. It is less irritating to the eyes, the nose, and skin. Write the condensed structural formula of glutaraldehyde.
15. Why does the oxidation of isopropyl alcohol give a ketone, whereas the oxidation of isobutyl alcohol gives an aldehyde?
16. Identify each compound as an alcohol, a phenol, or an ether. Classify any alcohols as primary (1°), secondary (2°), or tertiary (3°).
   a. $CH_3CH_2CH_2OH$
   b. 

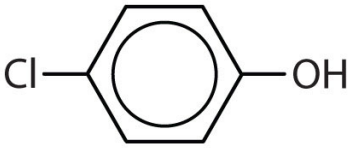
c. 

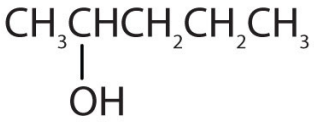
d. 

17. Identify each compound as an alcohol, a phenol, or an ether. Classify any alcohols as primary, secondary, or tertiary.

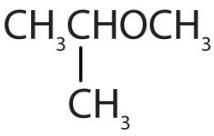
a. $CH_3CH_2OCH_2CH_3$

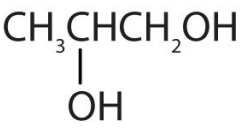
b. 

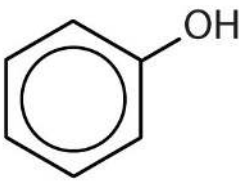
c. 

d. 

18. Tell whether each compound forms an acidic, a basic, or a neutral solution in water.

a. 

b. 

c. 

19. When water is added to ethylene in the presence of an acid catalyst, only one product—ethanol—is possible. However, when water is added to propylene, two products are possible—1-propanol and 2-propanol—but only 2-propanol is formed. In 1870, the Russian chemist Vladimir V. Markovnikov proposed a rule to predict the products of such reactions: Considering water to

be HOH, the hydrogen atom of water goes on the carbon atom (of the two involved in the double bond) that has the most hydrogen atoms already bonded to it. The OH group goes on the carbon atom with fewer hydrogen atoms. Use Markovnikov's rule to predict the product of the addition of water to each compound.

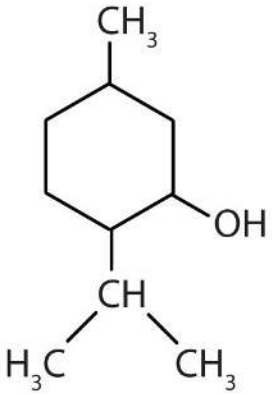
a. 2-methylpropene
b. 1-butene
c. 2-methyl-1-pentene
d. 2-methyl-2-pentene

20. Ethyl alcohol, like rubbing alcohol (isopropyl alcohol), is often used for sponge baths. What property of alcohols makes them useful for this purpose?

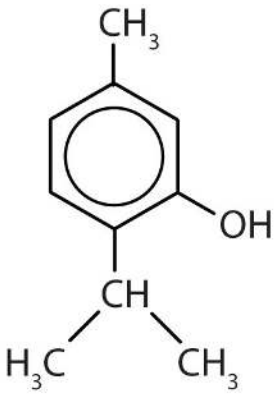
21. In addition to ethanol, the fermentation of grain produces other organic compounds collectively called fusel oils (FO). The four principal FO components are 1-propanol, isobutyl alcohol, 3-methyl-1-butanol, and 2-methyl-1-butanol. Draw a structure for each. (FO is quite toxic and accounts in part for hangovers.)

22. Draw and name the isomeric ethers that have the formula $C_5H_{12}O$.

23. Menthol is an ingredient in mentholated cough drops and nasal sprays. It produces a cooling, refreshing sensation when rubbed on the skin and so is used in shaving lotions and cosmetics. Thymol, the aromatic equivalent of menthol, is the flavoring constituent of thyme.



Menthol



Thymol

a. To what class of compounds does each belong?
b. Give an alternate name for thymol.

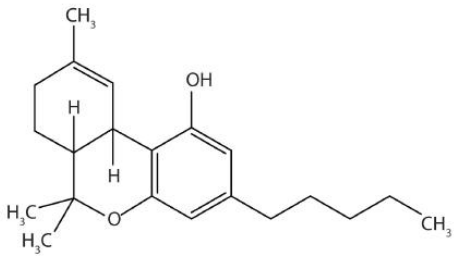
24. Write the equation for the production of ethanol by the addition of water to ethylene. How much ethanol can be made from 14.0 kg of ethylene?

25. Methanol is not particularly toxic to rats. If methanol were newly discovered and tested for toxicity in laboratory animals, what would you conclude about its safety for human consumption?

26. The amino acid cysteine has the formula $HSCH_2CH(NH_2)COOH$. What is the sulfur-containing functional group in the cysteine molecule?

27. The amino acid methionine has the formula $CH_3SCH_2CH_2CH(NH_2)COOH$. What functional groups are in methionine?

28. Tetrahydrocannabinol is the principal active ingredient in marijuana. What functional groups are present in this molecule?



Answers

1. addition of water to ethylene; fermentation (for beverages)

3. Methanol is too toxic.

5.

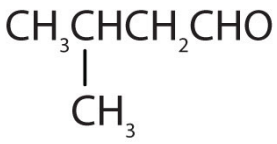
a. oxidation
b. dehydration
c. hydration

7. Methanol is oxidized in the body to toxic formaldehyde; ethanol is oxidized to the less toxic acetaldehyde.

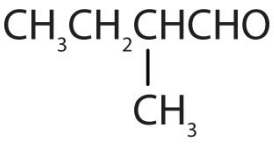
9.



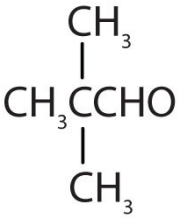
Pentanal



3-Methylbutanal



2-Methylbutanal



2,2-Dimethylpropanal

11. $C_6H_5OH + H_2O \rightarrow C_6H_5O^- + H_3O^+$

13.



15. Isopropyl alcohol is a secondary alcohol, whereas isobutyl alcohol is a primary alcohol.

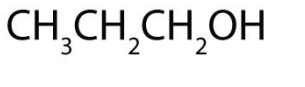
17.

a. ether
b. tertiary alcohol
c. phenol
d. secondary alcohol

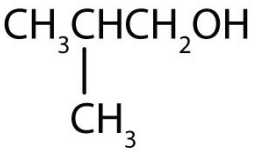
19.

a. *tert*-butyl alcohol
b. 2-butanol
c. 2-methyl-2-pentanol
d. 2-methyl-2-pentanol

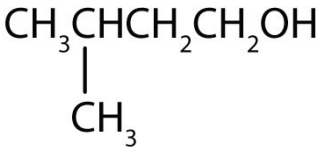
21.



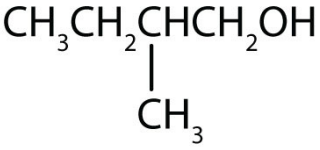
1-Propanol



Isobutyl alcohol



3-Methyl-1-butanol



2-Methyl-1-butanol

23.

a. menthol: alcohol; thymol: phenol
b. 2-isopropyl-5-methylphenol

25. It might be ruled safe until tested on humans.

27. sulfide, amino, and carboxylic acid

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CHAPTER OVERVIEW

4: Aldehydes and Ketones

4.1: Aldehydes and Ketones- Structure and Names

4.2: Properties of Aldehydes and Ketones

4.3: Addition Reactions for Aldehydes and Ketones

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4.1: Aldehydes and Ketones- Structure and Names

Learning Objectives

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

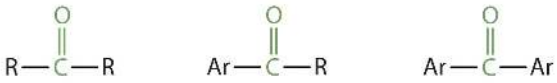
The next functional group we consider, the carbonyl group, has a carbon-to-oxygen double bond.



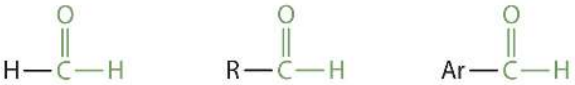
Carbonyl groups define two related families of organic compounds: the aldehydes and the ketones.

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

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

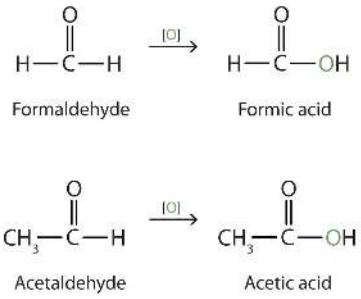


In an aldehyde, at least one of the attached groups must be a hydrogen atom. The following compounds are aldehydes:



- ## Naming Aldehydes and Ketones

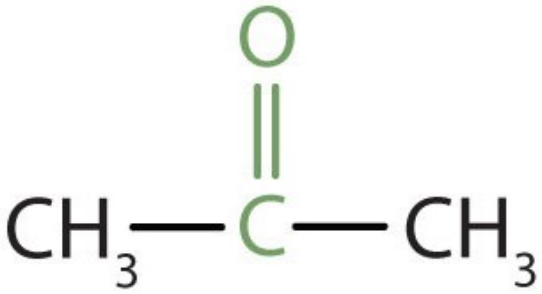
  Both common and International Union of Pure and Applied Chemistry (IUPAC) names are frequently used for aldehydes and ketones, with common names predominating for the lower homologs. The common names of aldehydes are taken from the names of the acids into which the aldehydes can be converted by *oxidation*.



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

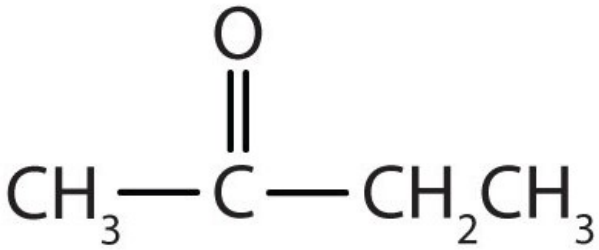
  - 1 carbon atom: *form-*
  - 2 carbon atoms: *acet-*
  - 3 carbon atoms: *propion-*
  - 4 carbon atoms: *butyr-*

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



Acetone

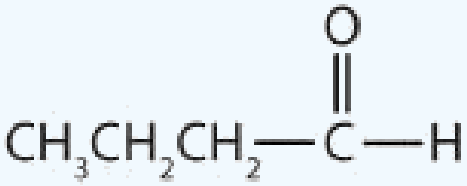
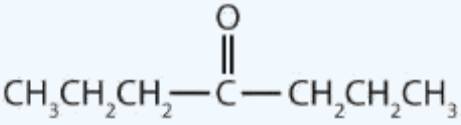
Generally, the common names of ketones consist of the names of the groups attached to the carbonyl group, followed by the word *ketone*. (Note the similarity to the naming of ethers.) Another name for acetone, then, is *dimethyl ketone*. The ketone with four carbon atoms is ethyl methyl ketone.



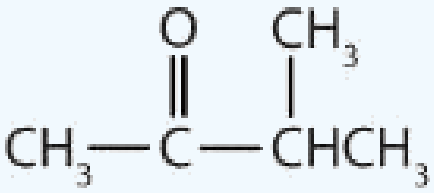
Ethyl methyl ketone

Example 4.1.1

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

1. 
2. 

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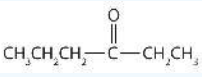
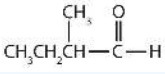
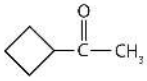
3. 

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 4.1.1

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

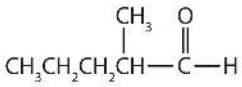
1. 
2. 
3. 

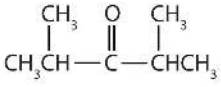
Here are some simple IUPAC rules for naming aldehydes and ketones:

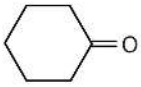
1. The stem names of aldehydes and ketones are derived from those of the parent alkanes, defined by the longest continuous chain (LCC) of carbon atoms that contains the functional group.
2. For an aldehyde, drop the *-e* from the alkane name and add the ending *-al*. Methanal is the IUPAC name for formaldehyde,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

Example 4.1.2

Give the IUPAC name for each compound.

a. 

b. 

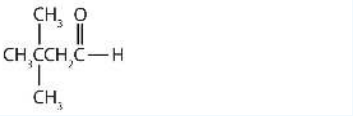
c. 

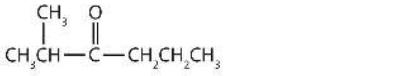
Solution

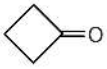
a. There are five carbon atoms in the LCC. The methyl group (CH_3) is a substituent on the second carbon atom of the chain; the aldehyde carbon atom is always C1. The name is derived from pentane. Dropping the *-e* and adding the ending *-al* gives pentanal. The methyl group on the second carbon atom 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 4.1.2

Give the IUPAC name for each compound.

a. 

b. 

c. 

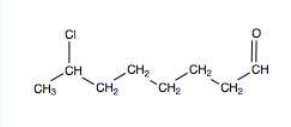
Example 4.1.3

Draw the structure for each compound.

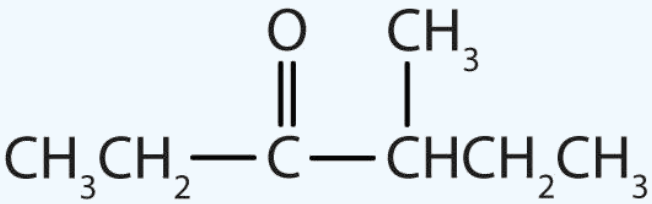
a. 7-chlorooctanal
b. 4-methyl–3-hexanone

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.



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



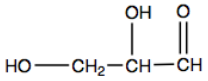
Exercise 4.1.3

Draw the structure for each compound.

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

Concept Review Exercises

1. Give the structure and IUPAC name for the compound that has the common name *m*-bromobenzaldehyde.



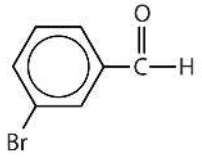
2. Give the IUPAC name for glyceraldehyde, . So here is where we have two functional groups on the same molecule. Aldehydes take priority over -OH groups. Thus, we keep the suffix -al, but use hydroxy to name the alcohol as the lower priority substituent.

   (Hint: as a substituent, the OH group is named *hydroxy*.)

Summary

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

Answers

1. 

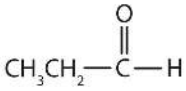
   3-Bromobenzaldehyde

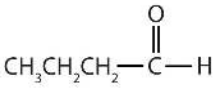
   3-bromobenzaldehyde

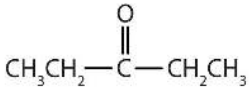
2. 2,3-dihydroxypropanal

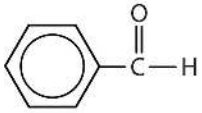
Exercises

1. Name each compound by IUPAC nomenclature.

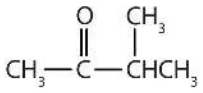
   a. 

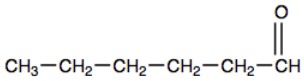
   b. 

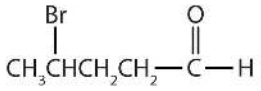
   c. 

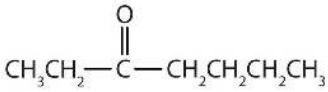
   d. 

2. Name each compound by IUPAC nomenclature.

a. 

b. 

c. 

d. 

3. Draw the structure for each compound.

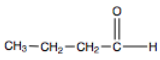
a. butanal
b. 2-hexanone
c. *p*-chlorobenzaldehyde

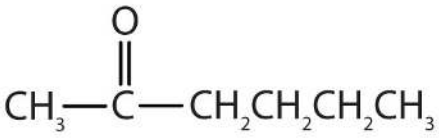
4. Draw the structure for each compound.

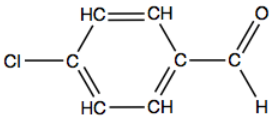
a. 5-ethyloctanal
b. 2-chloropropanal
c. 2-hydroxy-3-pentanone

Answers

1. a. propanal
   b. butanal
   c. 3-pentanone
   d. benzaldehyde

3. a. 

b. 

c. 

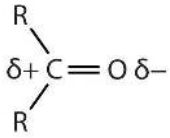
4.1: Aldehydes and Ketones- Structure and Names is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

4.2: 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.

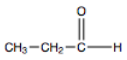
The carbon-to-oxygen double bond is quite polar, more polar than a carbon-to-oxygen single bond. The electronegative oxygen atom has a much greater attraction for the bonding electron pairs than does the carbon atom. The carbon atom has a partial positive charge, and the oxygen atom has a partial negative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



In aldehydes and ketones, this charge separation leads to dipole-dipole interactions that are great enough to significantly affect the boiling points. Table **4.2.1** shows that the polar single bonds in ethers have little such effect, whereas hydrogen bonding between alcohol molecules is even stronger.

Table **4.2.1**: Boiling Points of Compounds Having Similar Molar Masses but Different Types of Intermolecular Forces

Compound	Family	Type of Intermolecular Force
$CH_3CH_2CH_2CH_3$	alkane	dispersion only
$CH_3OCH_2CH_3$	ether	weak dipole

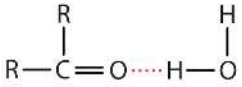
	aldehyde
$CH_3CH_2CH_2OH$	alcohol

strong polar hydrogen bonding

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.

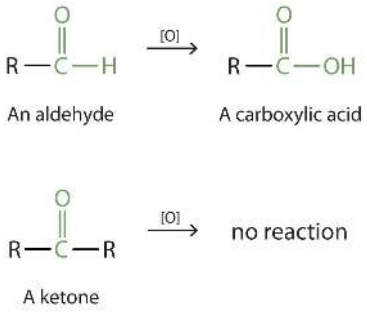
The oxygen atom of the carbonyl group engages in hydrogen bonding with a water molecule.



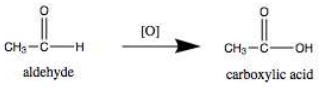
The solubility of aldehydes is therefore about the same as that of alcohols and ethers. Formaldehyde, acetaldehyde, and acetone are soluble in water. As the carbon chain increases in length, solubility in water decreases. The borderline of solubility occurs at about four carbon atoms per oxygen atom.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



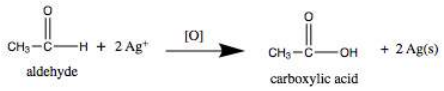
The aldehydes are, in fact, among the most easily oxidized of organic compounds. They are oxidized by oxygen (O_2) in air to carboxylic acids.



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.

$$H_3N—Ag^+—NH_3 \tag{4.2.1}$$

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

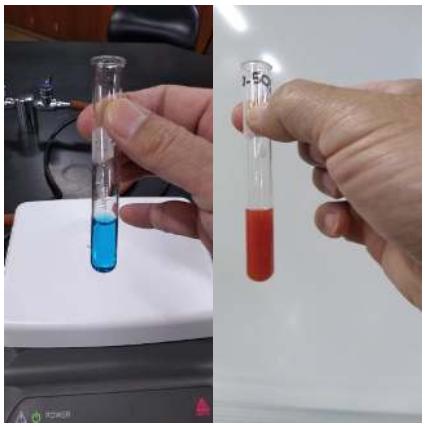


Deposited on a clean glass surface, the silver produces a mirror (Figure 4.2.1). Ordinary ketones do not react with Tollens' reagent.

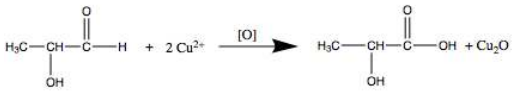


Figure 4.2.1: Aldehyde Reactions. A reaction related to the Tollens' reaction is often used to silver mirrors. These ornaments were silvered by such a reaction. Glucose, a simple sugar with an aldehyde functional group, is used as the reducing agent. Source: Photo courtesy of Krebs Glas Lauscha, commons.wikimedia.org/wiki/File:Silvering.jpg.

Another reagent named Benedict's reagent, also oxidizes aldehydes especially if there is an alcohol on the adjacent carbon next to the aldehyde functional group. Benedict's reagent contains Cu^{2+} ions (blue color in aqueous solutions) which upon oxidizing the aldehyde the Cu^{2+}will be reduced to a Cu^{1+} ion and form Cu_2O (reddish brown color).



Benedict's solution (blue) and Benedict's solution mixed with glucose (red).



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

- ## Reduction of Aldehydes and Ketones

Aldehydes and ketones can be reduced by adding hydrogen gas with a metal catalyst (i.e. Ni, Pt or Pd). Reduction of aldehydes produces primary alcohols and reduction of ketones produces secondary alcohols.

- ## Some Common Carbonyl Compounds

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

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

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

Acetaldehyde is an extremely volatile, colorless liquid. It is a starting material for the preparation of many other organic compounds. Acetaldehyde is formed as a metabolite in the fermentation of sugars and in the detoxification of alcohol in the liver. Aldehydes are the active components of many other familiar materials (Figure **4.2.2**).

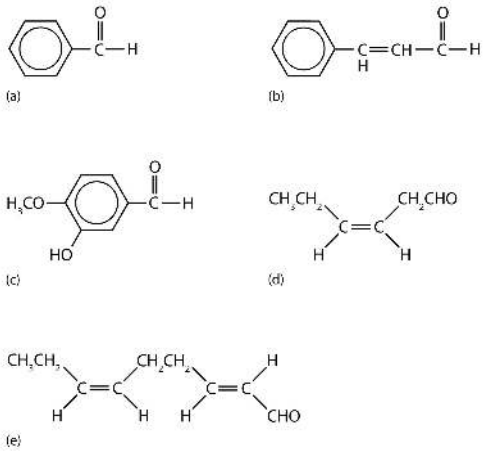


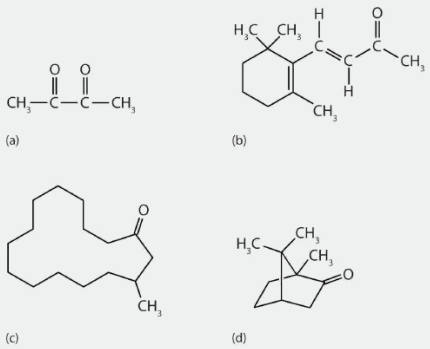
Figure **4.2.2** Some Interesting Aldehydes. (a) Benzaldehyde is an oil found in almonds; (b) cinnamaldehyde is oil of cinnamon; (c) vanillin gives vanilla its flavor; (d) *cis*-3-hexenal provides an herbal odor; and (e) *trans*-2-*cis*-6-nonadienal gives a cucumber odor.

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

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

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

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



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

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

Summary

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

Concept Review Exercises

1. What feature of their structure makes aldehydes easier to oxidize than ketones?
2. How does the carbon-to-oxygen bond of aldehydes and ketones differ from the carbon-to-carbon bond of alkenes?

Answers

1. the H on the carbonyl carbon atom
2. The carbon-to-oxygen double bond is polar; the carbon-to-carbon double bond is nonpolar.

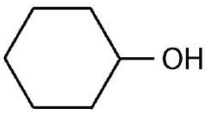
Exercises

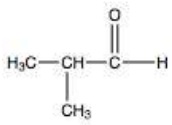
1. Which compound in each pair has the higher boiling point?
   a. propanone or 2-propanol
   b. methoxymethane or ethanal
2. Which compound in each pair has the higher boiling point?
   a. butanal or 1-butanol
   b. acetone (propanone) or 2-methylpropane
3. Draw the structure of the alcohol that could be oxidized to each compound.
   a. cyclohexanone
   b. 2-methylpropanal
4. Draw the structure of the alcohol that could be oxidized to each compound.
   a. 2-pentanone
   b. *o*-methylbenzaldehyde
5. Ethanal is treated with each substance.
   a. $Ag^+(aq)$—What organic product, if any, is formed?
   b. [O]—What organic product, if any, is formed?
6. Acetone (propanone) is treated with each substance.
   a. $Ag^+(aq)$ —What organic product, if any, is formed?
   b. [O] in an acid solution—What organic product, if any, is formed?

Answers

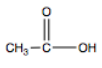
1. a. 2-propanol

   b. ethanal

3. a. 

   3. b. 

5. a. silver metal (Ag)

   b. ethanoic acid (

)

4.2: Properties of Aldehydes and Ketones is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

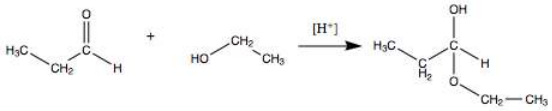
4.3: Addition Reactions for Aldehydes and Ketones

Learning Objectives

- To draw reactions consisting of alcohols with aldehyds or ketones.

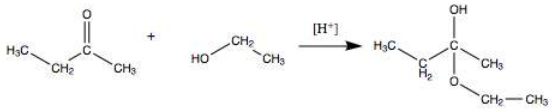
An alcohol can be added to an aldehyde with an acid catalyst to form an hemiacetal.

Reaction a:



If an alcohol is added to a ketone with an acid catalyst, a hemiketal will be produced.

Reaction b:

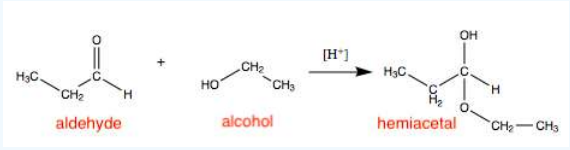


Exercise 4.3.1

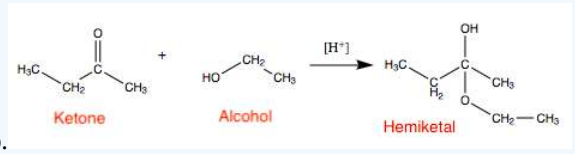
1. Redraw the above reactions and label the reactant aldehyde, ketone, and alcohol. Label the hemiacetal and hemiketal products.

Answer

1.a.

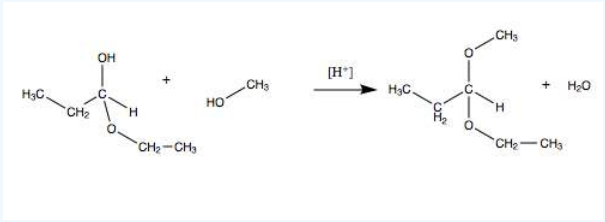


b.

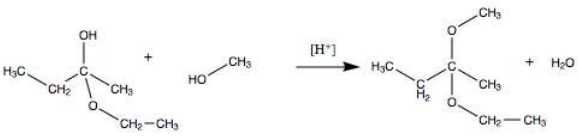


The addition of another alcohol to the hemiacetal or hemiketal will produce the acetal or ketal, respectively, along with the formation of water.

Reaction c:



Reaction d:

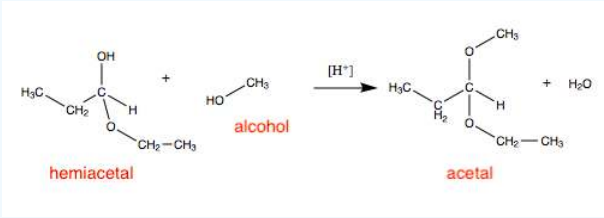


Exercise 4.3.2

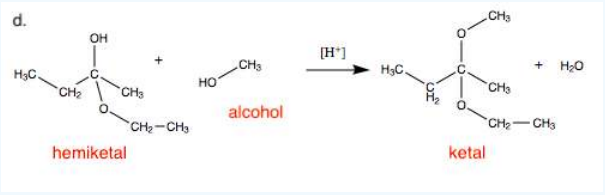
Redraw the above two reactions (c & d) and label the reactant hemiacetal, hemiketal, and alcohol. Label the acetal and ketal product.

Answer

c.



d.



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CHAPTER OVERVIEW

5: Organic Acids and Some of Their Derivatives

Organic acids have been known for ages. Prehistoric people likely made acetic acid when their fermentation reactions went awry and produced vinegar instead of wine. The Sumerians (2900–1800 BCE) used vinegar as a condiment, a preservative, an antibiotic, and a detergent. Citric acid was discovered by an Islamic alchemist, Jabir Ibn Hayyan (also known as Geber), in the 8th century, and crystalline citric acid was first isolated from lemon juice in 1784 by the Swedish chemist Carl Wilhelm Scheele. Medieval scholars in Europe were aware that the crisp, tart flavor of citrus fruits is caused by citric acid. Naturalists of the 17th century knew that the sting of a red ant's bite was due to an organic acid that the ant injected into the wound. The acetic acid of vinegar, the formic acid of red ants, and the citric acid of fruits all belong to the same family of compounds—carboxylic acids. Soaps are salts of long-chain carboxylic acids. Prehistoric people also knew about organic bases—by smell if not by name; amines are the organic bases produced when animal tissue decays. The organic compounds that we consider in this chapter are organic acids and bases. We will also consider two derivatives of carboxylic acids: esters and amides. An ester is derived from a carboxylic acid and an alcohol. Fats and oils are esters, as are many important fragrances and flavors. An amide is derived from a carboxylic acid and either ammonia or an amine. Proteins, often called "the stuff of life," are polyamides.

5.1: Prelude to Organic Acids and Bases and Some of Their Derivatives
5.2: Carboxylic Acids - Structures and Names
5.3: The Formation of Carboxylic Acids
5.4: Physical Properties of Carboxylic Acids
5.5: Chemical Properties of Carboxylic Acids- Ionization and Neutralization
5.6: Esters - Structures and Names
5.7: Physical Properties of Esters
5.8: Preparation of Esters
5.9: Hydrolysis of Esters
5.10: Esters of Phosphoric Acid

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5.1: Prelude to Organic Acids and Bases and Some of Their Derivatives

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Prehistoric people also knew about organic bases—by smell if not by name; amines are the organic bases produced when animal tissue decays.

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5.2: Carboxylic Acids - Structures and Names

Learning Objectives

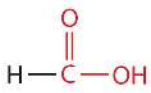
- Name carboxylic acids with common names.
- Name carboxylic acids according to IUPAC nomenclature.

Carboxylic acids occur widely in nature, often combined with alcohols or other functional groups, as in fats, oils, and waxes. They are components of many foods, medicines, and household products (Figure **5.2.1**). Not surprisingly, many of them are best known by common names based on Latin and Greek words that describe their source.



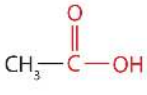
Figure **5.2.1**: Carboxylic Acids in the Home. Carboxylic acids occur in many common household items. (a) Vinegar contains acetic acid, (b) aspirin is acetylsalicylic acid, (c) vitamin C is ascorbic acid, (d) lemons contain citric acid, and (e) spinach contains oxalic acid. © Thinkstock

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



Formic acid

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



Acetic acid

Pure acetic acid solidifies at 16.6°C, only slightly below normal room temperature. In the poorly heated laboratories of the late 19th and early 20th centuries in northern North America and Europe, acetic acid often “froze” on the storage shelf. For that

reason, pure acetic acid (sometimes called concentrated acetic acid) came to be known as *glacial acetic acid*, a name that survives to this day.

The third homolog, propionic acid (CH_3CH_2COOH), is seldom encountered in everyday life. The fourth homolog, butyric acid ($CH_3CH_2CH_2COOH$), is one of the most foul-smelling substances imaginable. It is found in rancid butter and is one of the ingredients of body odor. By recognizing extremely small amounts of this and other chemicals, bloodhounds are able to track fugitives. Models of the first four carboxylic acids are shown in Figure **5.2.2**.

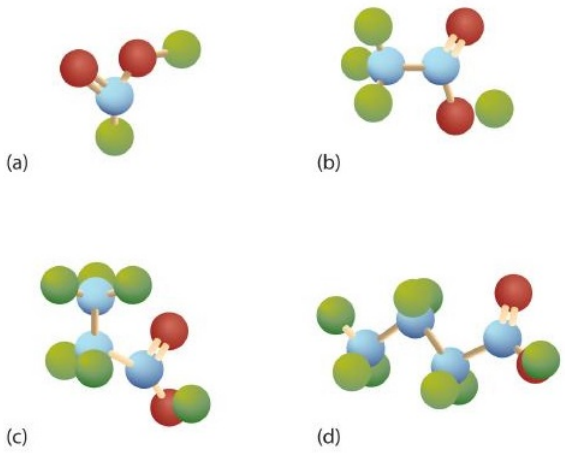
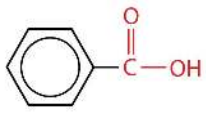


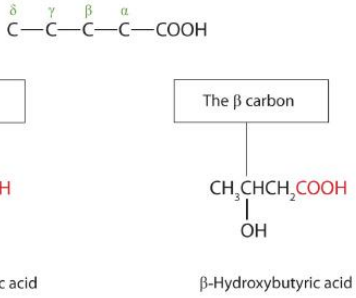
Figure **5.2.2**: Ball-and-Stick Models of Carboxylic Acids. Carboxylic acids feature a carbon atom doubly bonded to an oxygen atom and also joined to an OH group. The four acids illustrated here are formic acid (a), acetic acid (b), propionic acid (c), and butyric acid (d).

The acid with the carboxyl group attached directly to a benzene ring is called benzoic acid (C_6H_5COOH).



Benzoic acid

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



α-Methylpropionic acid

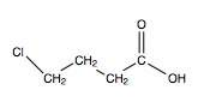
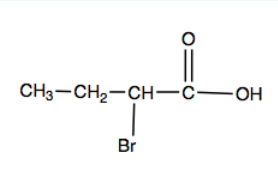
β-Hydroxybutyric acid

In the nomenclature system of the International Union of Pure and Applied Chemistry (IUPAC), the parent hydrocarbon is the one that corresponds to the longest continuous chain (LCC) containing the carboxyl group. The *-e* ending of the parent alkane is replaced by the suffix *-oic* and the word *acid*. For example, the carboxylic acid derived from pentane is pentanoic acid ($CH_3CH_2CH_2CH_2COOH$). As with aldehydes, the carboxyl carbon atom is counted first; numbers are used to indicate any substituted carbon atoms in the parent chain.

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

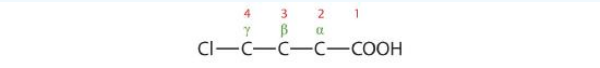
Example 5.2.1

Give the common and IUPAC names for each compound.

1. 
2. 

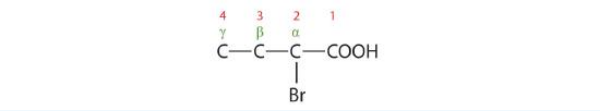
Solution

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



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

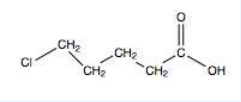
2. The LCC contains four carbon atoms; the compound is therefore named as a substituted butyric (or butanoic) acid.

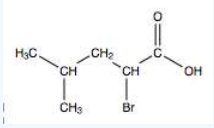


The bromine (Br) atom is at the α-carbon in the common system or C2 in the IUPAC system. The compound is α-bromobutyric acid or 2-bromobutanoic acid.

Exercise 5.2.1

Give the IUPAC name for each compound.

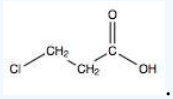
a. 

b. 

Example 5.2.2

Write the condensed structural formula for β-chloropropionic acid.

Solution

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

Exercise 5.2.2

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

Concept Review Exercises

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

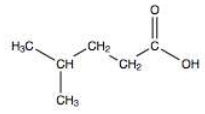
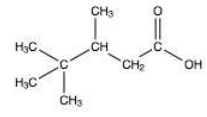
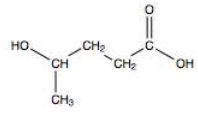
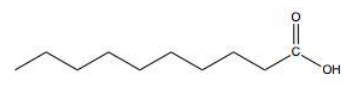
Answers

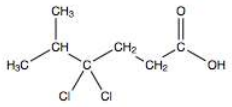
1. hexanoic acid
2. valeric acid

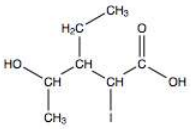
Key Takeaways

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

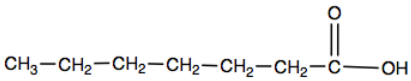
Exercises

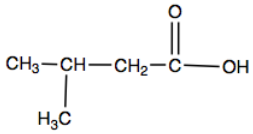
1. Draw the structure for each compound.
    a. heptanoic acid
    b. 3-methylbutanoic acid
    c. 2,3-dibromobenzoic acid
    d. β-hydroxybutyric acid
2. Draw the structure for each compound.
    a. *o*-aminobenzoic acid
    b. *p*-chlorobenzoic acid
    c. 3-chloropentanoic acid
    d. α-chloropropionic acid
3. Name each compound with the IUPAC name.
    a. 
    b. 
    c. 
4. Name each compound with its IUPAC name.
    a. 

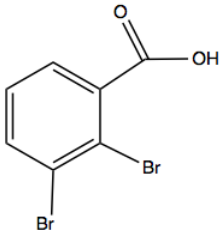
b. 

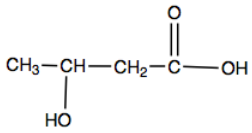
c. 

Answers

1. a. 

b. 

c. 

d. 

3. a. 3-methylbutanoic acid
   b. 3,4,4-trimethylpentanoic acid
   c. 4-hydroxybutanoic acid

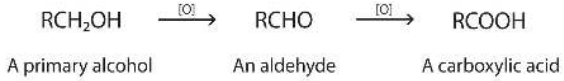
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5.3: The Formation of Carboxylic Acids

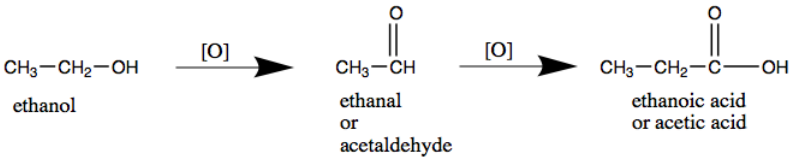
Learning Objectives

- To describe the preparation of carboxylic acids.

As we noted previously, the oxidation of aldehydes or primary alcohols forms carboxylic acids:



In the presence of an oxidizing agent, ethanol is oxidized to acetaldehyde, which is then oxidized to acetic acid.



This process also occurs in the liver, where enzymes catalyze the oxidation of ethanol to acetic acid.

$$\mathrm{CH_3CH_2OH} \xrightarrow[\text{oxidizing agent}]{\text{alcohol dehydrogenase}} \mathrm{CH_3CHO} \xrightarrow[\text{oxidizing agent}]{\text{alcohol dehydrogenase}} \mathrm{CH_3COOH} \tag{5.3.1}$$

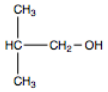
Acetic acid can be further oxidized to carbon dioxide and water.

Summary

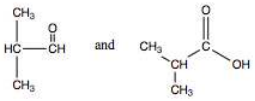
Whether in the laboratory or in the body, the oxidation of aldehydes or primary alcohols forms carboxylic acids.

Concept Review Exercises

1. Caproic acid (hexanoic acid) can be prepared in an oxidation reaction from
   a. what alcohol?
   b. what aldehyde?

1. Give the structures of the aldehyde and the carboxylic acid formed by the oxidation of isobutyl alcohol  .

Answers

1. a. CH_3-CH_2-CH_2-CH_2-CH_2-CH_2-OH b. 

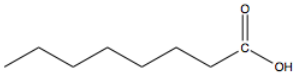
Exercises

1. Caprylic acid (octanoic acid) can be prepared in an oxidation reaction from
   a. what alcohol?
   b. what aldehyde?
2. Give the structures of the aldehyde and the carboxylic acid formed by the oxidation of

   1,4-butanediol (HO-CH_2-CH_2-CH_2-CH_2-OH).

Answer

1. a. CH_3-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-OH

   b. 

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5.4: Physical Properties of Carboxylic Acids

Learning Objectives

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

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

Carboxylic acids exhibit strong hydrogen bonding between molecules. They therefore have high boiling points compared to other substances of comparable molar mass.

The carboxyl group readily engages in hydrogen bonding with water molecules (Figure **5.4.1**). The acids with one to four carbon atoms are completely miscible with water. Solubility decreases as the carbon chain length increases because dipole forces become less important and dispersion forces become more predominant. Hexanoic acid [$CH_3(CH_2)_4COOH$] is barely soluble in water (about 1.0 g/100 g of water). Palmitic acid [$CH_3(CH_2)_{14}COOH$], with its large nonpolar hydrocarbon component, is essentially insoluble in water. The carboxylic acids generally are soluble in such organic solvents as ethanol, toluene, and diethyl ether.

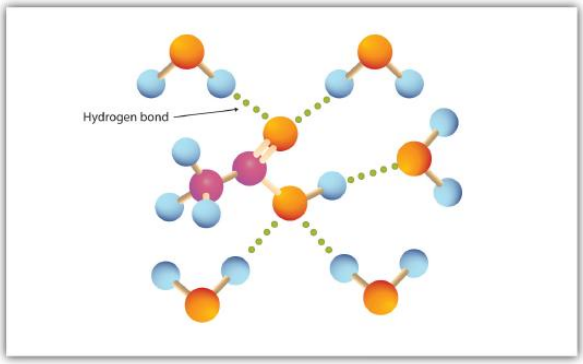


Figure **5.4.1**: Hydrogen Bonding between an Acetic Acid Molecule and Water Molecules. Carboxylic acids of low molar mass are quite soluble in water.

Table 15.4.1 lists some physical properties for selected carboxylic acids. The first six are homologs. Notice that the boiling points increase with increasing molar mass, but the melting points show no regular pattern.

Table **5.4.1**: Physical Constants of Carboxylic Acids

Condensed Structural Formula	Name of Acid	Melting Point (°C)	Boiling Point (°C)	Solubility (g/100 g of Water)
HCOOH	formic acid	8	100	miscible
CH_3COOH	acetic acid	17	118	miscible
CH_3CH_2COOH	propionic acid	–22	141	miscible
$CH_3(CH_2)_2COOH$	butyric acid	–5	163	miscible
$CH_3(CH_2)_3COOH$	valeric acid	–35	187	5
$CH_3(CH_2)_4COOH$	caproic acid	–3	205	1.1
C_6H_5COOH	benzoic acid	122	249	0.29

Concept Review Exercises

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

Answers

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

Key Takeaways

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

Exercises

1. Which compound has the higher boiling point—CH_3CH_2-O-CH_2CH_3 or $CH_3CH_2CH_2COOH$? Explain.
2. Which compound has the higher boiling point—$CH_3CH_2CH_2CH_2OH$ or $CH_3CH_2CH_2COOH$? Explain.
3. Which compound is more soluble in water—CH_3COOH or $CH_3CH_2CH_2CH_3$? Explain.
4. Which compound is more soluble in water—CH_3CH_2COOH or $CH_3CH_2CH_2CH_2CH_2COOH$? Explain.

Answers

1. $CH_3CH_2CH_2COOH$ because of hydrogen bonding (There is no intermolecular hydrogen bonding with CH_3CH_2-O-CH_2CH_3.)

3. CH_3COOH because it engages in hydrogen bonding with water (There is no intermolecular hydrogen bonding with $CH_3CH_2CH_2CH_3$.)

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5.5: Chemical Properties of Carboxylic Acids- Ionization and Neutralization

Learning Objectives

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

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

$$\mathbf{RCOOH + H_2O \rightleftharpoons RCOO^- + H_3O^+}$$

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

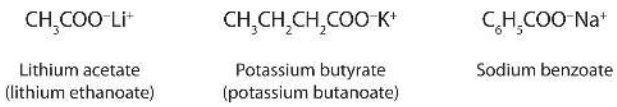
The anion formed when a carboxylic acid dissociates is called the *carboxylate* anion ($RCOO^-$).

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

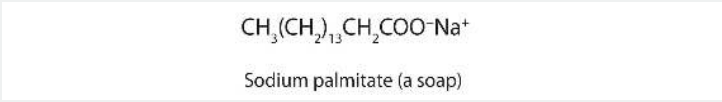
$$RCOOH + NaOH(aq) \rightarrow RCOO^-Na^+(aq) + H_2O$$

In these reactions, the carboxylic acids act like inorganic acids: they neutralize basic compounds.

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:



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



Example 5.5.1

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_3CH_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 5.5.1

Write an equation for each reaction.

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

Example 5.5.2

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

a. aqueous sodium hydoxide (NaOH)
b. aqueous potassium hydroxide (KOH)

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 KOH, the products are a salt and H_2O. $CH_3(CH_2)_8COOH + KOH(aq) \rightarrow CH_3(CH_2)_8COO^-K^+(aq) + H_2O(\ell)$

Exercise 5.5.3

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

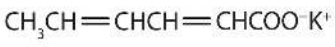
a. aqueous sodium hydroxide (NaOH)
b. aqueous potassium hydroxide (KOH)

To Your Health: Organic Salts as Preservatives

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



Calcium propionate



Potassium sorbate

Concept Review Exercises

1. What products are formed when a carboxylic acid is neutralized with a strong base? What additional product is formed when a carboxylic acid is neutralized with a carbonate or a bicarbonate?

Answers

1. A carboxylate salt and water.

Key Takeaways

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

Exercises

1. Write the equation for the ionization of $CH_3CH_2CH_2COOH$ in water.
2. Write the equation for the neutralization of $CH_3CH_2CH_2COOH$ with sodium hydroxide [NaOH(aq)].
3. Write the equation for the reaction of CH_3COOH with potassium hydroxide [KOH(aq)].
4. Write the equation for the reaction of CH_3CH_2COOH with sodium hydroxide [NaOH(aq)].
5. Write the equation for the ionization of propanoic acid in water.
6. Write the equation for the ionization of 4-chloropentanoic acid in water.
7. Write an equation for the reaction of benzoic acid with each compound.

   a. aqueous NaOH
   b. aqueous KOH

8. Write the condensed structural formula for each compound.

   a. potassium ethanoate
   b. lithium propanoate

9. Name each compound (IUPAC).

   a. $CH_3CH_2CH_2COO^-Li^+$
   b. $CH_3CH_2CH_2COO^-NH_4^+$

Answers

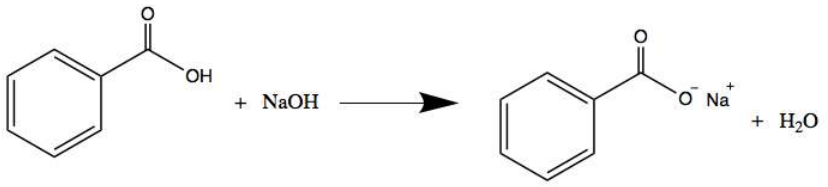
1. $CH_3CH_2CH_2COOH(aq) + H_2O(\ell) \rightarrow CH_3CH_2CH_2COO^-(aq) + H_3O^+(aq)$

3. $CH_3COOH + KOH(aq) \rightarrow 2CH_3COO^-K^+(aq) + H_2O(\ell)$

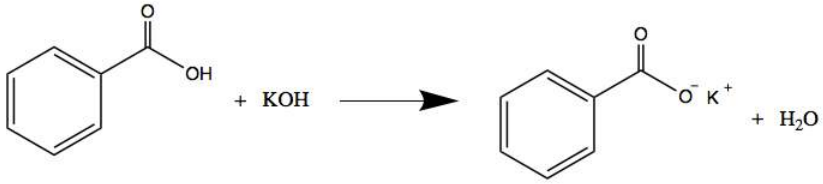
5. $CH_3CH_2COOH(aq) + H_2O(\ell) \rightarrow CH_3CH_2COO^-(aq) + H_3O^+(aq)$

7.

a.



b.



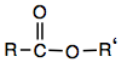
9. a. lithium butanoate b. ammonium butanoate

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5.6: Esters - Structures and Names

Learning Objectives

- Identify the general structure for an ester.
- Use common names to name esters.
- Name esters according to the IUPAC system.

Esters have the general formula,  , where R may be a hydrogen atom, an alkyl group, or an aryl group, and R′ may be an alkyl group or an aryl group but *not* a hydrogen atom. (If it were hydrogen atom, the compound would be a carboxylic acid.) Figure 5.6.1 shows models for two common esters.

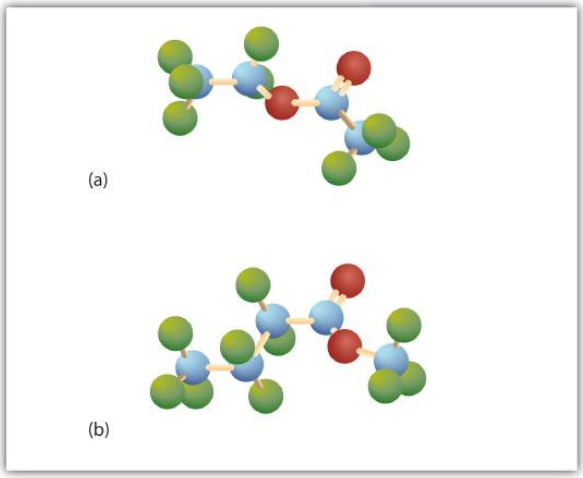


Figure 5.6.1: The Structure of Esters. Esters feature a carbon-to-oxygen double bond that is also singly bonded to a second oxygen atom, which is then joined to an alkyl or an aryl group. The esters shown here are ethyl acetate (a) and methyl butyrate (b).

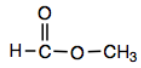
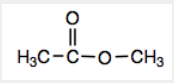
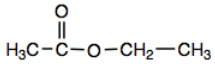
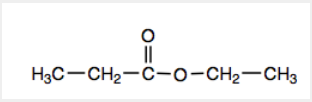
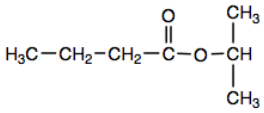
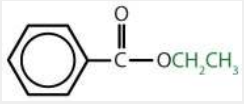
Esters occur widely in nature. Unlike carboxylic acids, esters generally have pleasant odors and are often responsible for the characteristic fragrances of fruits and flowers. Once a flower or fruit has been chemically analyzed, flavor chemists can attempt to duplicate the natural odor or taste. Both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

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

Names of Esters

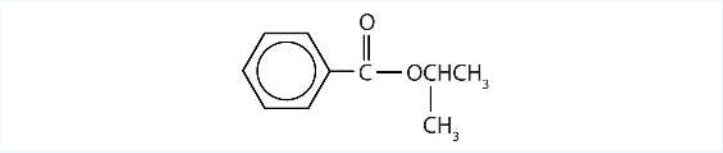
Although esters are covalent compounds and salts are ionic, esters are named in a manner similar to that used for naming salts. The group name of the alkyl or aryl portion is given first and is followed by the name of the acid portion. In both common and International Union of Pure and Applied Chemistry (IUPAC) nomenclature, the *-ic* ending of the parent acid is replaced by the suffix *-ate* (Table 5.6.1).

Table 5.6.1: Nomenclature of Esters

Condensed Structural Formula	Common Name	IUPAC Name
	methyl formate	methyl methanoate
	methyl acetate	methyl ethanoate
	ethyl acetate	ethyl ethanoate
	ethyl propionate	ethyl propanoate
	isopropyl butyrate	isopropyl butanoate
	ethyl benzoate	ethyl benzoate

Example 5.6.1

Give the common and IUPAC names for each compound.

1. 
2. 

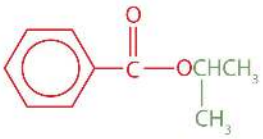
Solution

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



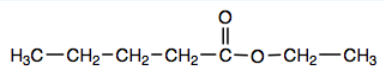
The part of the molecule derived from the carboxylic acid (in red) has three carbon atoms. It is called propionate (common) or propanoate (IUPAC). The ester is therefore butyl propionate or butyl propanoate.

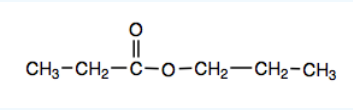
2. An alkyl group (in green) is attached directly to the oxygen atom by its middle carbon atom; it is an isopropyl group. The part derived from the acid (that is, the benzene ring and the carbonyl group, in red) is benzoate. The ester is therefore isopropyl benzoate (both the common name and the IUPAC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



Exercise 5.6.1

Give the IUPAC names for each compound.

a. 

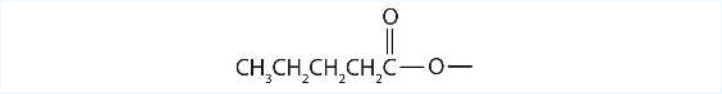
b. 

Example 5.6.2

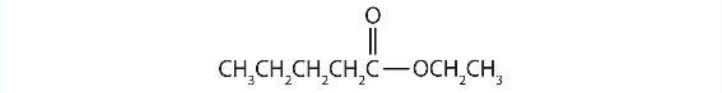
Draw the structure for ethyl pentanoate.

Solution

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



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



Exercise 5.6.2

Draw the structure for phenyl pentanoate.

Concept Review Exercises

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

Answers

1. hexanoic acid and 2-propanol
2. butanoic acid and cyclobutanol

Key Takeaway

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

Exercises

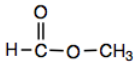
1. Draw the structure for each compound.
   a. methyl ethanoate
   b. ethyl pentanoate
   c. phenyl ethanoate

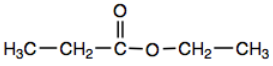
d. isopropyl propanoate

2. Draw the structure for each compound.

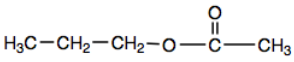
a. ethyl hexanoate
b. ethyl benzoate
c. phenyl benzoate
d. ethyl 3-methylhexanoate

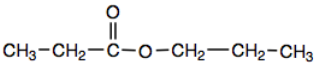
3. Name each compound with the IUPAC name.

a. 

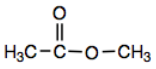
b. 

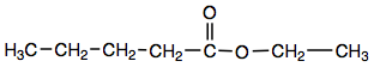
4. Name each compound with the IUPAC name.

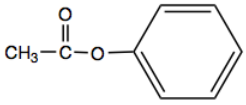
a. 

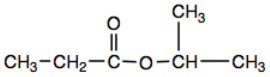
b. 

Answers

1. a. 

b. 

c. 

d. 

3. a. methyl methanoate
b. ethyl propanoate

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5.7: Physical Properties of Esters

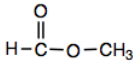
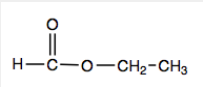
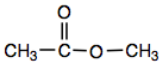
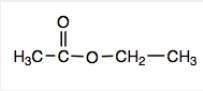
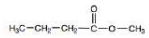
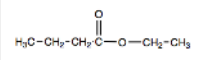
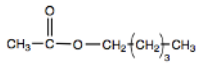
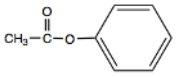
Learning Objectives

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

Ester molecules are polar but have no hydrogen atom attached directly to an oxygen atom. They are therefore incapable of engaging in intermolecular hydrogen bonding with one another and thus have considerably lower boiling points than their isomeric carboxylic acids counterparts. Because ester molecules can engage in hydrogen bonding with water molecules, however, esters of low molar mass are somewhat soluble in water. Borderline solubility occurs in those molecules that have three to five carbon atoms. Table 5.7.1 lists the physical properties of some common esters.

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

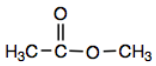
Table **5.7.1**: *Physical Properties of Some Esters*

Condensed Structural Formula	Name	Molar Mass	Melting Point (°C)	Boiling Point (°C)	Aroma
	methyl methanoate	60	−99	32	
	ethyl methanoate	74	−80	54	rum
	methyl ethanoate	74	−98	57	
	ethyl ethanoate	88	−84	77	
	methyl butanoate	102	−85	102	apple
	ethyl butanoate	116	−101	121	pineapple
	pentyl ethanoate	130	−71	148	pear
$CH_3COOCH_2CH_2CH(CH_3)_2$	isopentyl ethanoate	130	−79	142	banana
	phenyl ethanoate	150	−51	215	jasmine
$CH_3CH_2CH_2COO(CH_2)_4CH_3$	pentyl butanoate	158	−73	185	apricot
$CH_3COO(CH_2)_7CH_3$	octyl ethanoate	172	−39	210	orange

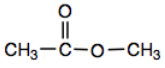
Summary

Esters have polar bonds but do not engage in hydrogen bonding and are therefore intermediate in boiling points between the nonpolar alkanes and the alcohols, which engage in hydrogen bonding. Ester molecules can engage in hydrogen bonding with water, so esters of low molar mass are therefore somewhat soluble in water.

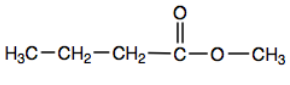
Concept Review Exercises

1. Which compound has the higher boiling point— CH_3-CH_2-CH_2-CH_2-OH or  ? Explain.

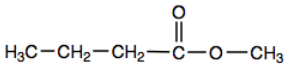
Answers

1. CH_3-CH_2-CH_2-CH_2-OH because there is intermolecular hydrogen bonding (There is no intermolecular hydrogen bonding in  .)

Exercises

1. Which compound has the higher boiling point— CH_3-CH_2-CH_2-COOH or  ? Explain.
2. Which compound is more soluble in water—methyl ethanoate or octyl ethanoate? Explain.

Answer

1. CH_3-CH_2-CH_2-COOH because there is intermolecular hydrogen bonding and forms a dimer (There is no intermolecular hydrogen bonding between ethers  .)

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5.8: Preparation of Esters

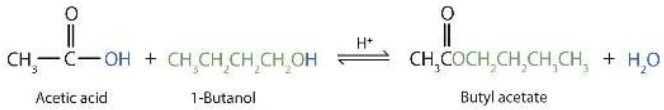
Learning Objectives

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

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



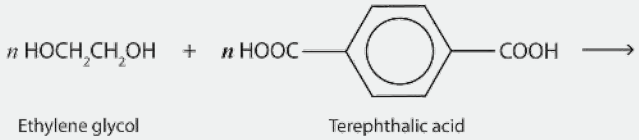
The reaction is reversible. As a specific example of an esterification reaction, butyl acetate can be made from acetic acid and 1-butanol.

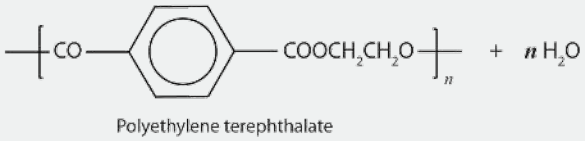


A Closer Look: Condensation Polymers

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

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





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

Summary

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

Concept Review Exercises

1. From what carboxylic acid and what alcohol can the ester isopropyl nonanoate be made?
2. From what carboxylic acid and what alcohol can the ester cyclobutyl butanoate be made?

Answers

1. nonanoic acid and 2-propanol
2. butanoic acid and cyclobutanol

Exercises

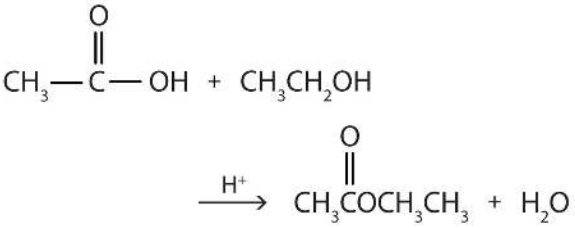
1. Write the equation for the reaction of ethanoic acid with each compound in the presence of a an acid catalyst.

    a. ethanol
    b. 1-butanol

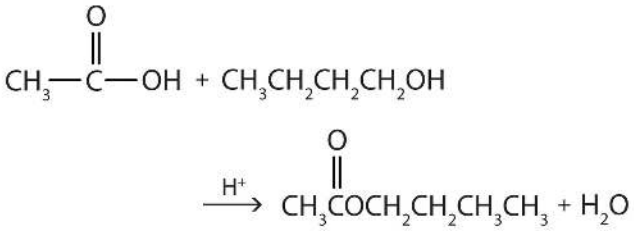
2. Write the equation for the reaction of benzoic acid with each compound in the presence of a an acid catalyst.

    a. methanol
    b. 1-propanol

Answer



1. a.



b.

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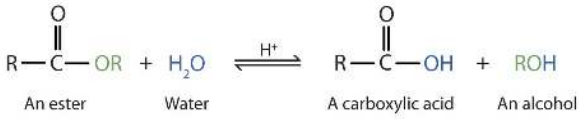
5.9: Hydrolysis of Esters

Learning Objectives

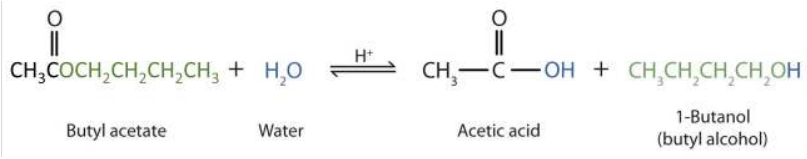
- Describe the typical reaction that takes place with esters.
- Identify the products of an acidic hydrolysis of an ester.
- Identify the products of a basic hydrolysis of an ester.

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

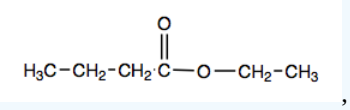
Acidic hydrolysis is simply the reverse of esterification. The ester is heated with a large excess of water containing a strong-acid catalyst. Like esterification, the reaction is reversible and does not go to completion.



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

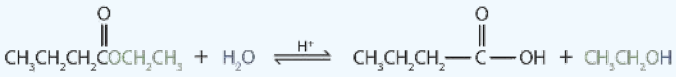


Example 5.9.1

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

Solution

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

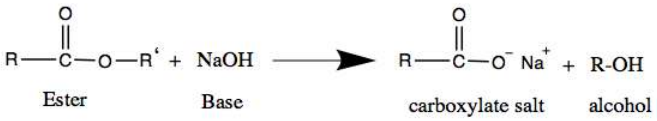


The products are butanoic acid and ethanol.

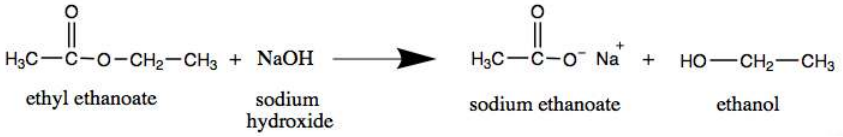
Exercise 5.9.1

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

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



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

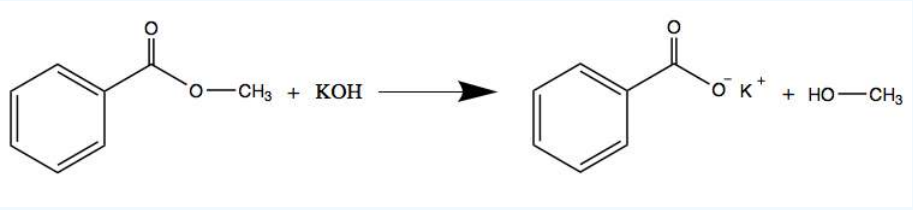


Example 5.9.2

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

Solution

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



Exercise 5.9.2

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

Summary

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

Concept Review Exercises

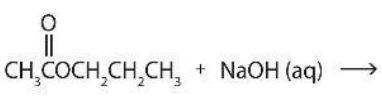
1. How do acidic hydrolysis and basic hydrolysis of an ester differ in terms of the products obtained?
2. What is saponification?

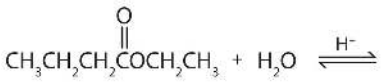
Answers

1. acidic hydrolysis: carboxylic acid + alcohol; basic hydrolysis: carboxylate salt + alcohol
2. the basic hydrolysis of an ester

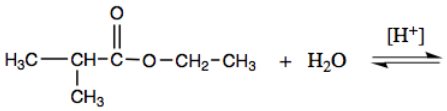
Exercises

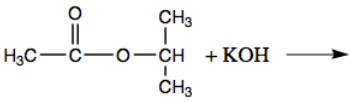
1. Write an equation for the acid-catalyzed hydrolysis of ethyl ethanoate.
2. Write an equation for the base-catalyzed hydrolysis of ethyl ethanoate.
3. Complete each equation.

a. 

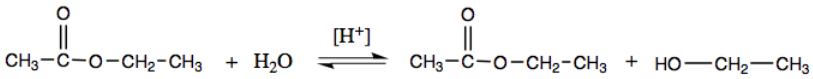
b. 

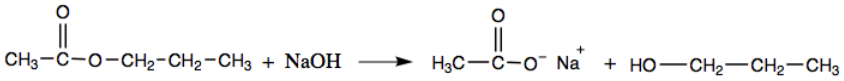
4. Complete each equation.

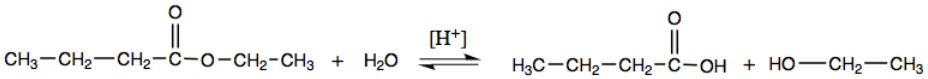
a. 

b. 

Answers

1. 

3. a. 

b. 

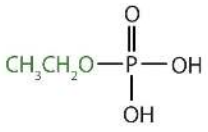
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5.10: Esters of Phosphoric Acid

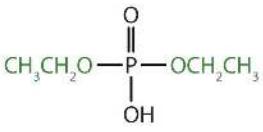
Learning Objectives

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

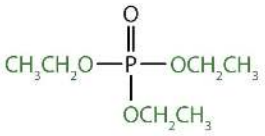
Just as carboxylic acids do, inorganic acids such as nitric acid (HNO_3), sulfuric acid (H_2SO_4), and phosphoric acid (H_3PO_4) also form esters. The esters of phosphoric acid are especially important in biochemistry. A phosphoric acid molecule can form a monoalkyl, a dialkyl, or a trialkyl ester by reaction with one, two, or three molecules of an alcohol.



Ethyl dihydrogen phosphate

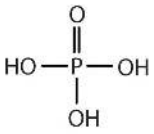


Diethyl hydrogen phosphate

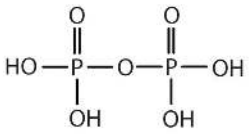


Triethyl phosphate

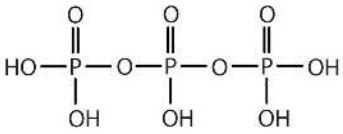
Esters of pyrophosphoric acid and triphosphoric acid are also important in biochemistry.



Phosphoric acid



Pyrophosphoric acid

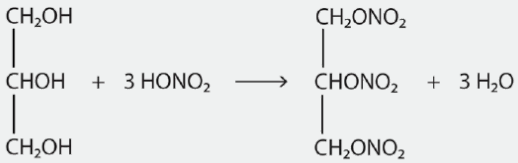


Triphosphoric acid

Esters of these acids are present in every plant and animal cell. They are biochemical intermediates in the transformation of food into usable energy. The bonds between phosphate units in adenosine triphosphate (ATP) are called **phosphoanhydride bonds**. These are high-energy bonds that store energy from the metabolism of foods. Hydrolysis of ATP releases energy as it is needed for biochemical processes (for instance, for muscle contraction). Phosphate esters are also important structural constituents of phospholipids and nucleic acids.

Nitroglycerin

The explosive nitroglycerin (glyceryl trinitrate) is an ester formed from glycerol and nitric acid. It is used in medicine to relieve chest pain in heart disease.



Glycerol

Glycerol trinitrate (nitroglycerin)

5.10.1 Exercise

What compounds combine to form phosphate esters?

Answer

phosphoric acids and alcohols

Summary

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

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6: Organic Bases and Some of Their Derivatives

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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**).

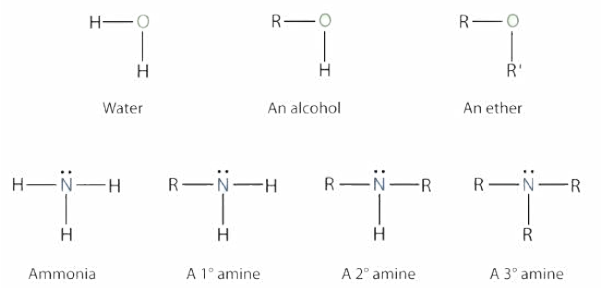
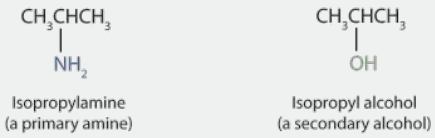


Figure **6.1.1**: The Structure of Amines Compared to Water, an Alcohol, and an Ether

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.

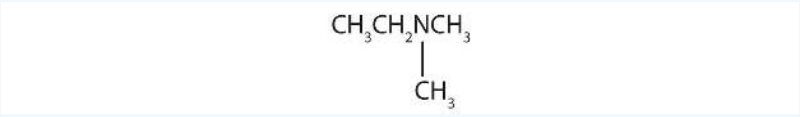


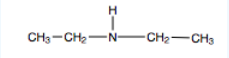
The common names for simple aliphatic amines consist of an alphabetic list of alkyl groups attached to the nitrogen atom, followed by the suffix *-amine*. (Systematic names are often used by some chemists.) The amino group (NH_2) is named as a substituent in more complicated amines, such as those that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

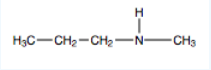
Example 6.1.1

Give the IUPAC name and classify each compound.

a. $CH_3CH_2CH_2NH_2$

b. 

c. 

d. 

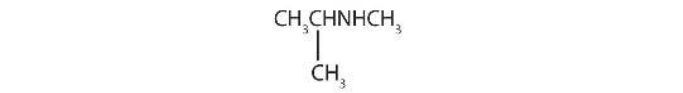
Solution

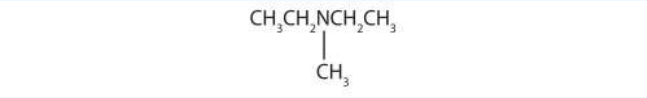
a. There is only one carbon grooup attached to the nitrogen atom, so the amine is primary. A group of three carbon atoms (propane) is attached to the NH_2 group through an end carbon atom, so the name is 1-propanamine.

b. There are two methyl groups and one ethyl group on the nitrogen atom. The compound is a tertiary amine. The IUPAC name would be N,N-dimethylethanamine
c. There are two ethyl groups attached to the nitrogen atom; the amine is secondary, its IUPAC name is N-ethylethanamine.
d. The nitrogen atom has a methyl group and a propyl group, so the IUPAC name is N-methyl-1-propanamine, a secondary amine.

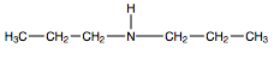
Exercise 6.1.1

Provide the IUPAC name and classify each compound.

a. 

b. 

c. $CH_3CH_2CH_2CH_2NH_2$

d. 

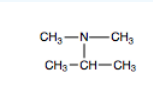
Example 6.1.2

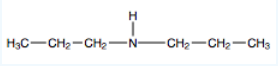
Draw the structure for each compound and classify.

a. N,N-dimethyl-2-propanamine
b. N-propyl-1-propanamine

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.



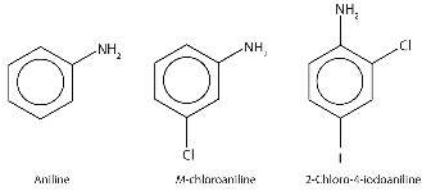
b. The name indicates that there are two propyl groups attached to the nitrogen atom; the amine is secondary. (The third bond on the nitrogen atom goes to a hydrogen atom.) 

Exercise 6.1.2

Draw the structure for each compound and classify.

a. N-ethyl-2-propanamine
b. N,N-diethy-1-propanamine

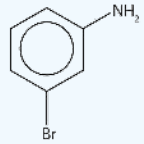
The primary amine in which the nitrogen atom is attached directly to a benzene ring has a special name—aniline. Aryl amines are named as derivatives of aniline.



Aniline M-chloroaniline 2-Chloro-4-iodoaniline

Example 6.1.3

Name this compound.

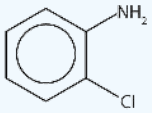


Solution

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 using both the IUPAC and common.

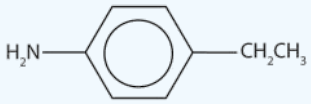


Example 6.1.4

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

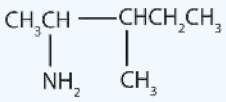
Draw the structure for *p*-isopropylaniline and classify.

Example 6.1.5

Draw the structure for 3-methyl-2-pentanamine.

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 3-ethyl-1-chloro-2-heptanamine.

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

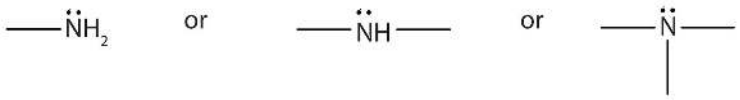
Exercise 6.1.6

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*.

Concept Review Exercises

1. To what inorganic compound are the amines related?
2. How are amines classified?

Answers

1. ammonia
2. by the number of hydrocarbon groups on the nitrogen atom: primary amine, one group; secondary amine, two groups; tertiary amine, three groups

Exercises

1. Draw the structure for each compound and classify the amine as primary, secondary, or tertiary.
   a. N-methylmethanamine
   b. N-ethyl-N-methylethanamine
   c. 2-aminoethanol
2. Draw the structure for each compound and classify the amine as primary, secondary, or tertiary.

a. 3-pentanamine
b. 1,6-hexanediamine
c. N-ethylaniline

3. Draw the structure for each compound.

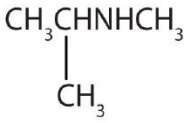
a. aniline
b. *m*-bromoaniline

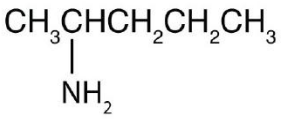
4. Draw the structure for each compound.

a. 2-chloroaniline
b. 3,5-dichloroaniline

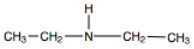
5. Name each compound using IUPAC form.

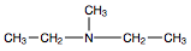
a. $CH_3CH_2CH_2NH_2$

b. 

c. 

6. Name each compound.

a. 

b. 

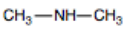
7. Draw the structure for each compound.

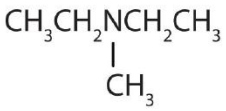
a. dimethylammonium chloride
b. anilinium chloride

8. Draw the structure for each compound.

a. ethylmethylammonium chloride

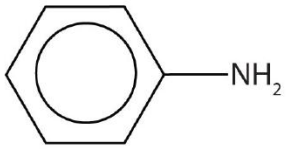
Answers

1. a.  ; secondary
   b. tertiary

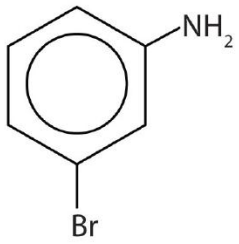


c.  ; primary

3. a.

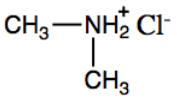


b.

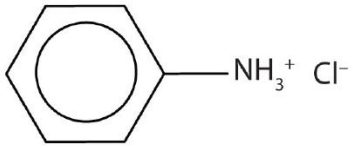


5. a. 1-propanamine
   b. N-ethyl-2-propanamine
   c. 2-pentanamine

7. a.



b.



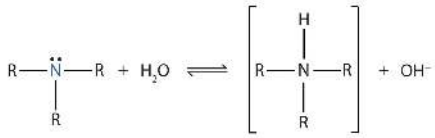
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6.2: Amines as Bases

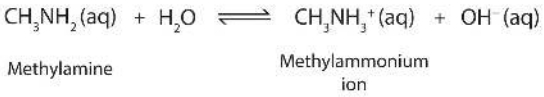
Learning Objectives

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

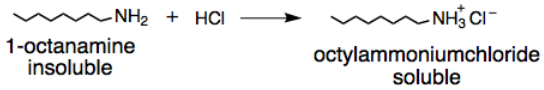
Recall that ammonia (NH_3) acts as a base because the nitrogen atom has a lone pair of electrons that can accept a proton. Amines also have a lone electron pair on their nitrogen atoms and can accept a proton from water to form substituted ammonium (NH_4^+) ions and hydroxide (OH^-) ions:



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

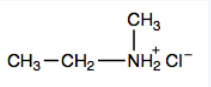


Nearly all amines, including those that are not very soluble in water, will react with strong acids to form salts soluble in water.

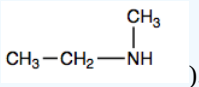


Amine salts are named like other salts: the name of the cation is followed by the name of the anion.

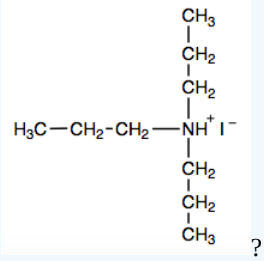
Example 6.2.1

What are the formulas of the acid and base that react to form  ?

Solution

The cation has two groups—methyl and ethyl—attached to the nitrogen atom. It comes from N-methylethanamine (). The anion is the chloride ion. It comes from hydrochoric acid (HCl).

Exercise 6.2.1

What are the formulas of the acid and base that react to form  ?

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.

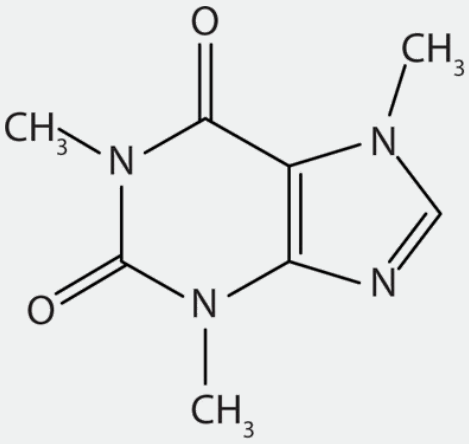
Heterocyclic Amines

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.

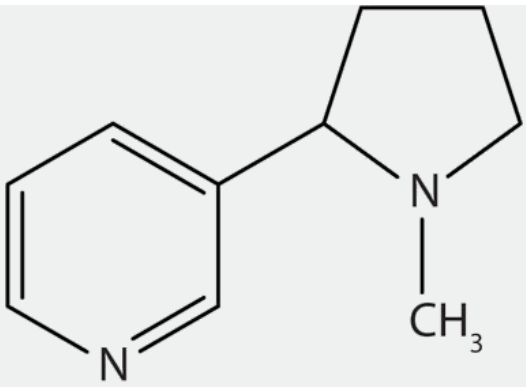
To Your Health: Three Well-Known Alkaloids

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.



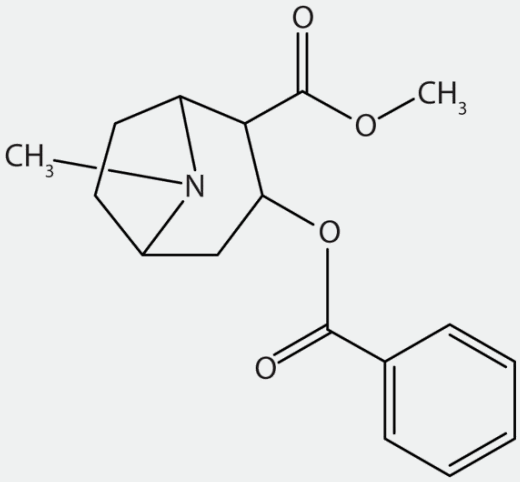
Caffeine

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.



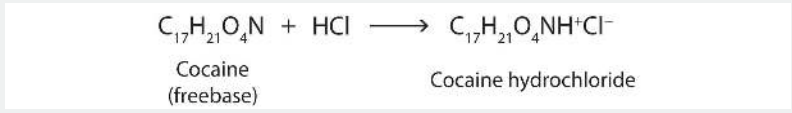
Nicotine

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*.



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.

Concept Review Exercises

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

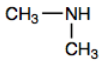
Answers

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

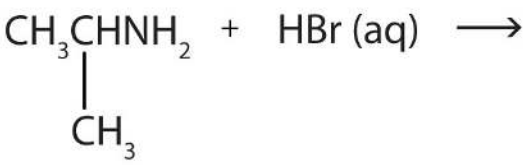
Exercises

1. What salt is formed in each reaction? Write its condensed structural formula.

   a. $CH_3NH_2(aq) + HBr(aq) \rightarrow$

   b.  (aq) + HCl(aq) →

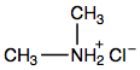
2. What salt is formed in each reaction? Draw its structure.

   a. 

   b. 

Answer

1. a. $CH_3NH_3^+Br^-(aq)$

   b.  (aq)

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6.3: 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 **6.3.1**), 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 **6.3.1**).

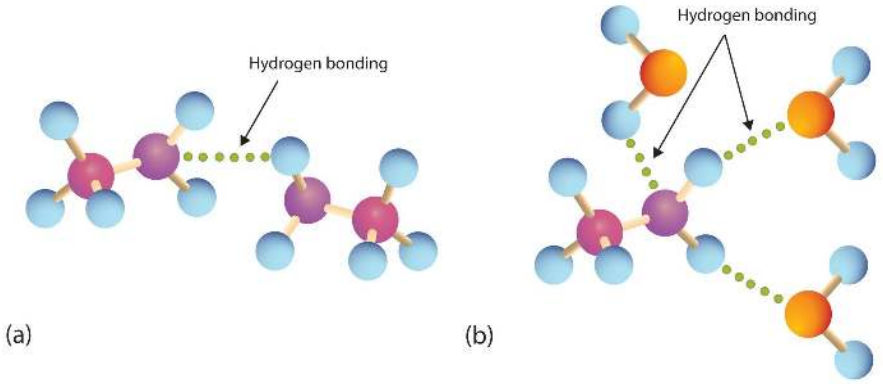
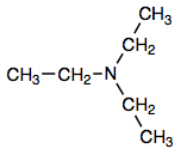


Figure **6.3.1**: Hydrogen Bonding. (a) Amine molecules are associated through hydrogen bonding. (b) An amine molecule can form a hydrogen bond with water molecules.

Table **6.3.1**: Physical Properties of Some Amines and Comparable Oxygen-Containing Compounds

Name	Condensed Structural Formula	Class	Solubility in Water (100 g/100 mL)
1-butamine	CH_3-CH_2-CH_2-CH_2-NH_2	1°	miscible
N-ethylethan	CH_3-CH_2-NH-CH_2CH_3	2°	[illegible] miscible

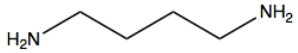
amine			
1-butanol	CH_3-CH_2-CH_2-CH_2OH	—	117.148
N-propyl-1-propanamine	CH_3-CH_2-CH_2-NH-CH_2-CH_2-CH_3	2°	101.191
N,N-diethylethana		3°	101.191

amine		
propoxy-1-propane	CH_3-CH_2-CH_2-O-CH_2-CH_2-CH_3	—

All three classes of amines can engage in hydrogen bonding with water (Figure 6.3.1b). Amines of low molar mass are quite soluble in water; the borderline of solubility in water is at five or six carbon atoms.

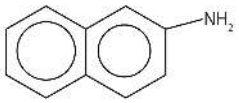
To Your Health: Amines in Death and Life

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.



Putrescine

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.

Concept Review Exercises

1. Which compound has the higher boiling point, CH_3-CH_2-CH_2-CH_2-CH_2-NH_2 or CH_3-CH_2-CH_2-CH_2-CH_2-CH_3? Explain.
2. Which compound is more soluble in water, CH_3-CH_2-CH_2-CH_2-CH_3 or CH_3-CH_2-NH-CH_2-CH_3? Explain.

Answers

1. CH_3-CH_2-CH_2-CH_2-CH_2-NH_2 because the nitrogen-to-hydrogen (N–H) bonds can engage in hydrogen bonding;

   CH_3-CH_2-CH_2-CH_2-CH_2-CH_3 cannot engage in hydrogen bonding
2. CH_3-CH_2-NH-CH_2-CH_3 because amines can engage in hydrogen bonding with water;

   alkanes cannot engage in hydrogen bonding

Exercises

1. Which compound of each pair has the higher boiling point? Explain.

   a. 1-butanamine or pentane
   b. CH_3-NH_2 or CH_3-CH_2-CH_2-CH_2-CH_2-NH_2
2. Which compound of each pair has the higher boiling point? Explain.

   a. 1-butanamine or 1-butanol
   b. trimethylamine (N,N-dimethylmethanamine) or 1-propanamine
3. Which compound is more soluble in water—CH_3-CH_2-CH_3 or CH_3-CH_2-NH_2? Explain.
4. Which compound is more soluble in water—CH_3-CH_2-CH_2-NH_2 or CH_3-CH_2-CH_2-CH_2-CH_2-CH_2-NH_2? Explain.

Answers

1. a. 1-butanamine because the N–H bonds can engage in hydrogen bonding; pentane cannot engage in hydrogen bonding
   b. CH_3-CH_2-CH_2-CH_2-CH_2-NH_2 because it has a longer carbon chain and therefore exhibit greater LDF than CH_3NH_2
3. CH_3-CH_2-NH_2? because amines can engage in hydrogen bonding with water; alkanes cannot engage in hydrogen bonding

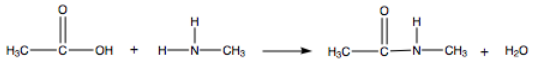
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6.4: Formation of Amides

Learning Objectives

- To describe the preparation procedure for amides.

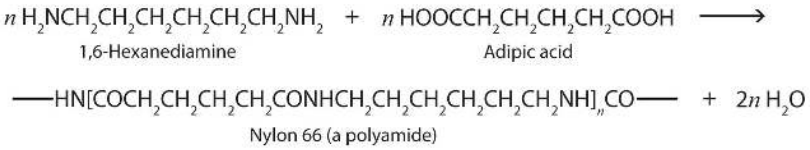
The addition of ammonia (NH_3) to a carboxylic acid forms an amide, but the reaction is very slow in the laboratory at room temperature. Water molecules are split out, and a bond is formed between the nitrogen atom and the carbonyl carbon atom.



In living cells, amide formation is catalyzed by enzymes. Proteins are polyamides; they are formed by joining amino acids into long chains. In proteins, the amide functional group is called a *peptide bond*.

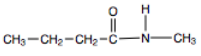
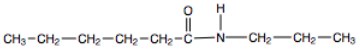
Polyamides

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.

Concept Review Exercises

1. Write the condensed structural formulas and give names of the two compounds from which N-methylbutanamide,  , is formed.
2. Write the condensed structural formulas and names of the two compounds from which  is formed.

Answers

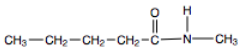
1. $CH_3CH_2CH_2COOH$ (butanoic acid) and CH_3-NH_2 (methanamine)
2. $CH_3CH_2CH_2CH_2CH_2COOH$ (hexanoic acid) and $CH_3CH_2CH_2NH_2$ (1-propanamine)

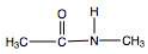
Key Takeaway

- Amides are prepared by the reaction of a carboxylic acid with ammonia or an amine.

Exercises

1. Write the condensed structural formulas and names of the two compounds from which N-methylpentanamide

() is formed.

2. Write the condensed structural formulas and names of the two compounds from which  is formed.

Answer

1. $CH_3CH_2CH_2CH_2COOH$ (pentanoic acid) and CH_3-NH_2 (methanamine)

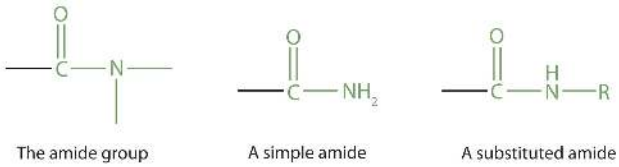
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6.5: Amides- Structures and Names

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*.



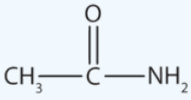
The carbonyl carbon-to-nitrogen bond is called an *amide linkage*. This bond is quite stable and is found in the repeating units of protein molecules, where it is called a *peptide linkage*.

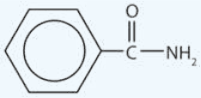
Simple amides are named as derivatives of carboxylic acids. The *-ic* ending of the common name or the *-oic* ending of the International Union of Pure and Applied Chemistry (IUPAC) name of the carboxylic acid is replaced with the suffix *-amide*.



Example 6.5.1

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

a. 

b. 

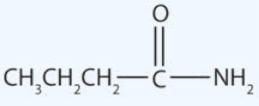
Solution

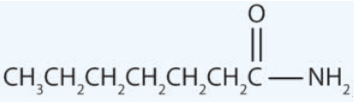
a. This amide has two carbon atoms and is thus derived from acetic acid. The OH of acetic acid is replaced by an NH_2 group. The *-ic* from *acetic* (or *-oic* from ethanoic) is dropped, and *-amide* is added to give *acetamide* (or ethanamide in the IUPAC system).

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

Exercise 6.5.1

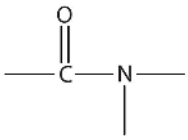
Name each compound with the IUPAC name.

a. 

b. 

Key Takeaways

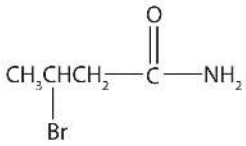
- Amides have a general structure in which a nitrogen atom is bonded to a carbonyl carbon atom.
- The functional group for an amide is as follows:



- 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*.

Concept Review Exercises

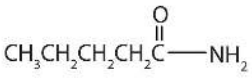
1. Name this compound with the common name and the IUPAC name.



2. Draw a the condensed structural formulae for pentanamide.

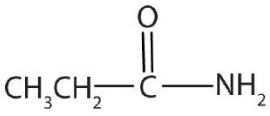
Answers

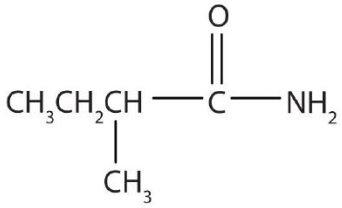
1. β-bromobutyramide (IUPAC: 3-bromobutanamide)

2. 

Exercises

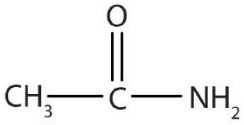
1. Draw the condensed structure for each compound.
    a. methanamide
    b. hexanamide
2. Draw the condensed structure for each compound.
    a. propanamide or propionamide (common name)
    b. butanamide
3. Name each compound with the IUPAC name.

a. 



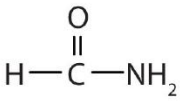
b.

4. Name the compound.



Answers

1. a.



b.



3. a. IUPAC: propanamide
   b. IUPAC: 2-methylbutanamide

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6.6: 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.

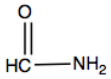
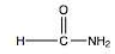
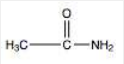
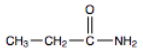
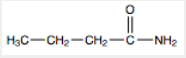
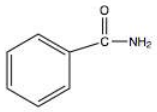
With the exception of methanamide (common name: formamide) (), which is a liquid, all simple amides are solids (Table **6.6.1**). The lower members of the series are soluble in water, with borderline solubility occurring in those that have five or six carbon atoms. Like the esters, solutions of amides in water usually are neutral—neither acidic nor basic.

Table **6.6.1**: *Physical Constants of Some Unsubstituted Amides*

Condensed Structural Formula	Name common or IUPAC	Melting Point (°C)	Boiling Point (°C)	Solubility in Water
	formamide or methanamide	2	193	soluble
	acetamide or ethanamide	82	222	soluble
	propionamide or propanamide	81	213	soluble
	butyramide or butanamide	115	216	soluble
	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 **6.6.1**). (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.

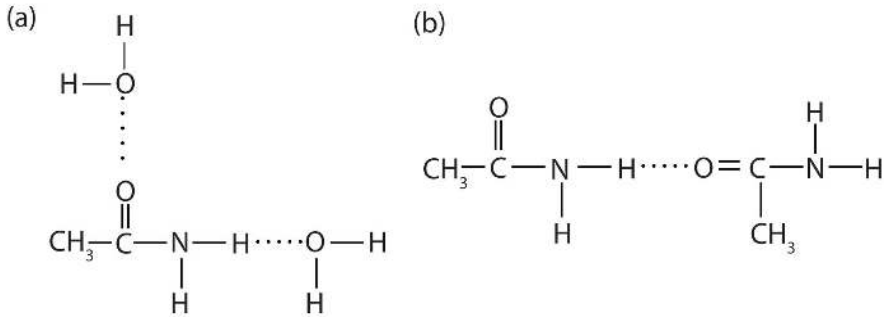
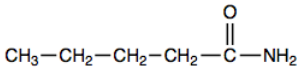
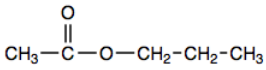
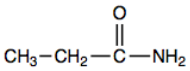


Figure **6.6.1**: Hydrogen Bonding in Amides. Amide molecules can engage in hydrogen bonding with water molecules (a). Those amides with a hydrogen atom on the nitrogen atom can also engage in hydrogen bonding (b). Both hydrogen bonding networks extend in all directions.

Concept Review Exercises

1. Which compound has the higher boiling point—pentanamide,  , or propyl ethanoate,  , ? Explain.
2. Which compound is more soluble in water—propanamide  or 1-pentene, CH_2=CH-CH_2-CH_2-CH_3, ? Explain.

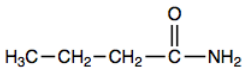
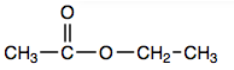
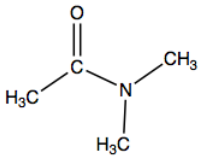
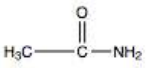
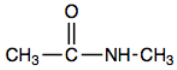
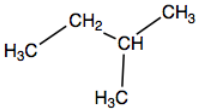
Answers

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

Key Takeaways

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

Exercises

1. Which compound has the higher boiling point—butanamide,  , or ethyl ethanoate,  , ? Explain.
2. Which compound has the higher boiling point—butanamide or N,N-dimethylethanamide  ? Explain.
3. Which compound is more soluble in water—ethanamide,  , or 1-butene, CH_2=CH-CH_2-CH_3, ? Explain.
4. Which compound is more soluble in water— N-methylethanamide,  , or 2-methylbutane,  , ? Explain.

Answers

1. Butanamide because the nitrogen-to-hydrogen (N–H) and the carbon-to-oxygen double (C=O) bonds can engage in hydrogen bonding; ethyl ethanoate cannot engage in hydrogen bonding

3. Ethanamide because the N–H and C=O bonds can engage in hydrogen bonding with water; 1-butene cannot engage in hydrogen bonding with water

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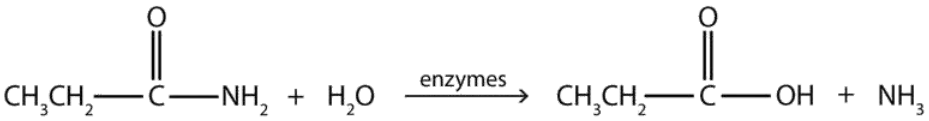
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6.7: Chemical Properties of Amides- Hydrolysis

Learning Objectives

- To identify the typical reaction that amides undergo.

Generally, amides resist hydrolysis in plain water, even after prolonged heating. In the presence of added acid or base, however, hydrolysis proceeds at a moderate rate. In living cells, amide hydrolysis is catalyzed by enzymes. Amide hydrolysis is illustrated in the following example:



> *Hydrolysis of an amide in acid solution actually gives a carboxylic acid and the salt of ammonia or an amine (the ammonia or amine initially formed is neutralized by the acid). Basic hydrolysis gives a salt of the carboxylic acid and ammonia or an amine.*

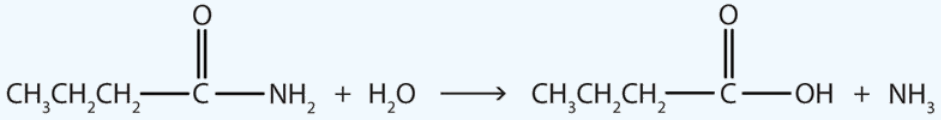
Example 6.7.1

Write the equation for the hydrolysis of each compound.

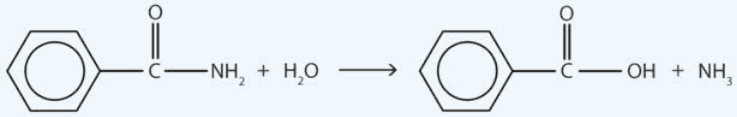
a. butanamide
b. benzamide

Solution

a. The hydrolysis of a simple amide produces an organic acid and ammonia. Butanamide thus yields butanoic acid and ammonia.



b. The hydrolysis of an amide produces an organic acid and ammonia. Benzamide thus yields benzoic acid and ammonia.



Exercise 6.7.1

Write the equation for the hydrolysis of each compound.

a. propanamide
b. hexanamide

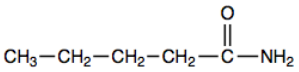
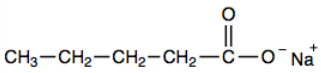
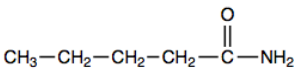
Career Focus: Athletic Trainer

Athletic training is an allied health-care profession recognized by the American Medical Association. The athletic trainer's role is to recognize, evaluate, and provide immediate care for athletic injuries; prevent athletic injuries by taping, bandaging, and bracing vulnerable body parts; make referrals to medical doctors when necessary; and rehabilitate injured athletes. Athletic trainers work in high schools, colleges, and other organizations where athletics programs are found. Athletic trainers usually have a degree from an accredited athletic training program whose curriculum includes such basic science courses as biology, chemistry, and physics. These studies provide the necessary background for more applied courses, such as anatomy and physiology, exercise physiology, kinesiology, and nutrition. Knowledge of chemistry is necessary for understanding

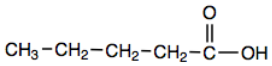
pharmacological and medical terminology. For example, athletic trainers must understand the action of numerous drugs, many of which are esters, amines, or amides like those mentioned in this chapter.

Athletic trainers may have administrative duties, such as the responsibility for ordering supplies. They also need to be able to evaluate nutritional supplements because providing the wrong one can get an athlete banned from competition and may bring sanctions against a school. In short, the athletic trainer is responsible for the overall health and well-being of the athletes in his or her charge.

Concept Review Exercises

1. What are the products of the acid hydrolysis of an amide?
2. When the amide  is hydrolyzed in an NaOH solution, the products are  and NH_3. What products are obtained when  is hydrolyzed in an hydrochloric acid solution?

Answers

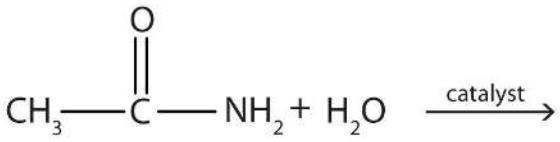
1. a carboxylic acid and ammonia or an amine
2. a  and NH_4Cl

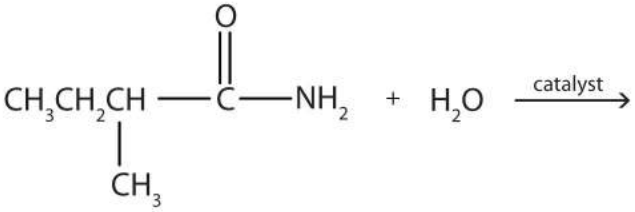
Key Takeaway

- The hydrolysis of an amide produces a carboxylic acid and ammonia or an amine.

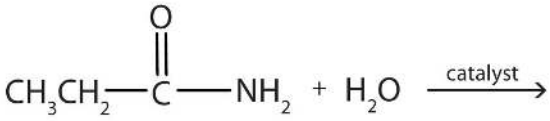
Exercises

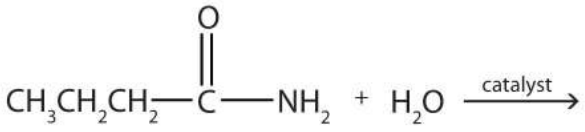
1. Complete the acid hydrolysis for the following reactions.

a. 

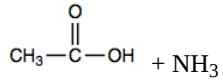
b. 

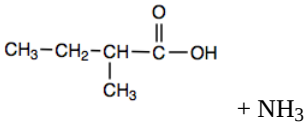
2. Complete acid hydrolyisis of the following reactions.

a. 

b. 

Answer

1. a. 

b. 

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6.S: Organic Acids and Bases and Some of Their Derivatives (Summary)

To ensure that you understand the material in this chapter, you should review the meanings of the following bold terms in the summary and ask yourself how they relate to the topics in the chapter.

A **carboxylic acid** (RCOOH) contains the functional group COOH, called the **carboxyl group**, which has an OH group attached to a carbonyl carbon atom. An **ester** (RCOOR′) has an OR′ group attached to a carbonyl carbon atom. An **amine** is derived from ammonia (NH_3), with one, two, or all three of the hydrogen atoms of NH_3 replaced by an alkyl (or an aryl) group. The **amide** functional group has a carbonyl group joined to a nitrogen atom from NH_3 or an amine.

There are many familiar carboxylic acids. The R group may be a hydrogen atom (as in formic acid, HCOOH), an alkyl group (as in acetic acid, CH_2COOH), or an aryl group (as in benzoic acid, C_6H_5COOH). The location of substituents along the carbon chain is indicated by a Greek letter (for common names) or a number (for names from the International Union of Pure and Applied Chemistry).

A carboxylic acid is formed by the oxidation of an aldehyde with the same number of carbon atoms. Because aldehydes are formed from primary alcohols, these alcohols are also a starting material for carboxylic acids.

Carboxylic acids have strong, often disagreeable, odors. They are highly polar molecules and readily engage in hydrogen bonding, so they have relatively high boiling points.

Carboxylic acids are weak acids. They react with bases to form salts and with carbonates and bicarbonates to form carbon dioxide gas and the salt of the acid.

Esters are pleasant-smelling compounds that are responsible for the fragrances of flowers and fruits. They have lower boiling points than comparable carboxylic acids because, even though ester molecules are somewhat polar, they cannot engage in hydrogen bonding. However, with water, esters can engage in hydrogen bonding; consequently, the low molar mass esters are soluble in water. Esters can be synthesized by **esterification**, in which a carboxylic acid and an alcohol are combined under acidic conditions. Esters are neutral compounds that undergo **hydrolysis**, a reaction with water. Under acidic conditions, hydrolysis is essentially the reverse of esterification. When carried out under basic conditions, the process is called **saponification**.

Inorganic acids also react with alcohols to form esters. Some of the most important esters in biochemistry are those formed from phosphoric acid.

Amines are nitrogen-containing organic molecules derived from ammonia (NH_3). A **primary (1°) amine** (RNH_2) has one organic group bonded to the nitrogen atom, a **secondary (2°) amine** (R_2NH) has two organic groups bonded to the nitrogen atom, and a **tertiary (3°) amine** (R_3N) has three organic groups bonded to the nitrogen atom. Amines are basic compounds that react with strong acids to produce ammonium (NH_4^+) salts. A cyclic compound in which the ring contains one or more noncarbon atoms is called a **heterocyclic compound**. There are many heterocyclic amines, including many physiologically important ones. **Alkaloids** are heterocyclic amines found in many plants. Caffeine, nicotine, and cocaine are familiar alkaloids.

Organic compounds containing a carbonyl group bonded to a nitrogen atom are amides, and the carbon-to-nitrogen bond is an amide linkage (or a peptide linkage). Most amides are colorless and odorless, and the lighter ones are soluble in water. Because they are polar molecules, amides have comparatively high boiling points and melting points. Amides are synthesized from carboxylic acids and NH_3 or amines. Amides are neutral compounds. They resist hydrolysis in water, but acids, bases, and enzymes catalyze the reaction.

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CHAPTER OVERVIEW

7: Conformations and Stereochemistry

Stereochemistry is the study of how bonds are oriented in three-dimensional space. It is difficult to overstate the importance of stereochemistry in nature, and in the fields of biology and medicine in particular. As Pasteur so convincingly demonstrated, life itself is chiral: living things recognize different stereoisomers of organic compounds and process them accordingly.

7.1: Chirality and stereoisomers

7.2: Fischer and Haworth projections

7.3: Exercises on Bond Line Structures, Drawing, and Isomers

7.4: Solutions to 7.3 Problems

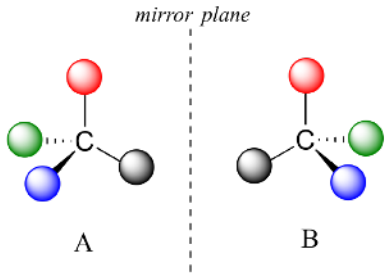
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7.1: Chirality and stereoisomers

We turn now to concept of chirality, the term **chiral**, from the Greek work for 'hand', refers to anything which cannot be superimposed on its own mirror image. Your hands, of course, are chiral - you cannot superimpose your left hand on your right, and you cannot fit your left hand into a right-handed glove (which is also a chiral object). Another way of saying this is that your hands do not have a **mirror plane of symmetry**: you cannot find any plane which bisects your hand in such a way that one side of the plane is a mirror image of the other side. *Chiral objects do not have a plane of symmetry*.

Your face, on the other hand is **achiral** - lacking chirality - because, some small deviations notwithstanding, you could superimpose your face onto its mirror image. If someone were to show you a mirror image photograph of your face, you could line the image up, point-for-point, with your actual face. Your face has a plane of symmetry, because the left side is the mirror image of the right side.

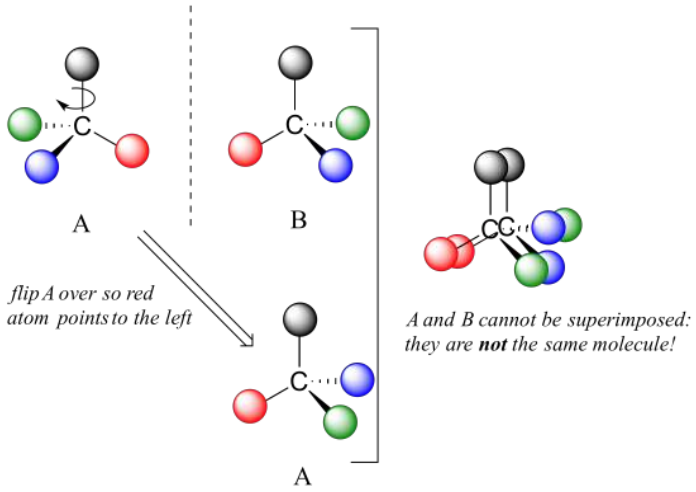
What Pasteur, Biot, and their contemporaries did not yet fully understand when Pasteur made his discovery of molecular chirality was the *source* of chirality at the molecular level. It stood to reason that a chiral molecule is one that does not contain a plane of symmetry, and thus cannot be superimposed on its mirror image. We now know that chiral molecules contain one or more **chiral centers**, which are almost always tetrahedral **carbons with four different substituents**. Consider the cartoon molecule A below: a tetrahedral carbon, with four different substituents denoted by balls of four different colors (for the time being, don't worry about exactly what these substituents could be - we will see real examples very soon).



Another image

The mirror image of A, which we will call B, is drawn on the right side of the figure, and an imaginary mirror is in the middle. Notice that every point on A lines up through the mirror with the same point on B: in other words, if A looked in the mirror, it would see B looking back.

Now, if we flip compound A over and try to superimpose it point for point on compound B, we find that we cannot do it: if we superimpose any two colored balls, then the other two are misaligned.

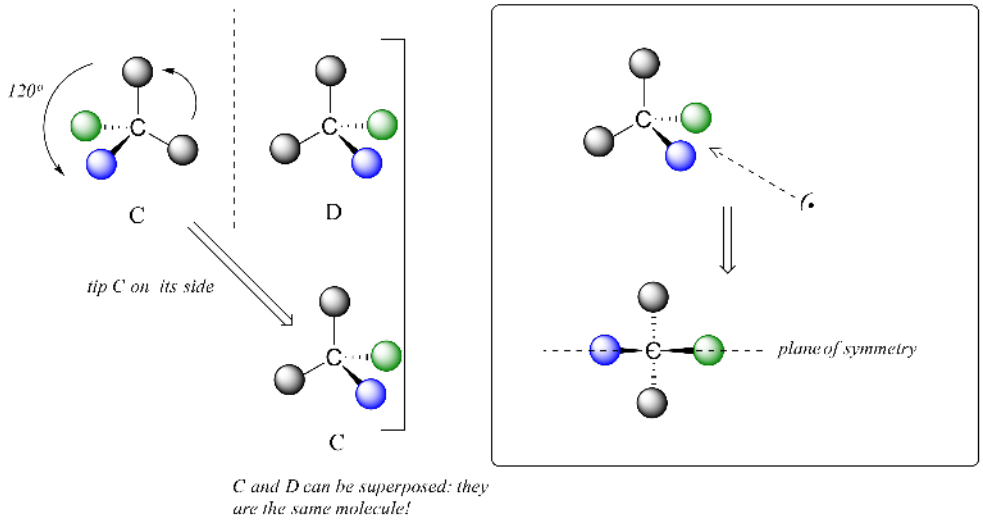


A is not superimposable on its mirror image (B), thus by definition A is a chiral molecule. It follows that B also is not superimposable on *its* mirror image (A), and thus it is also a chiral molecule. Also notice in the figure below (and convince yourself

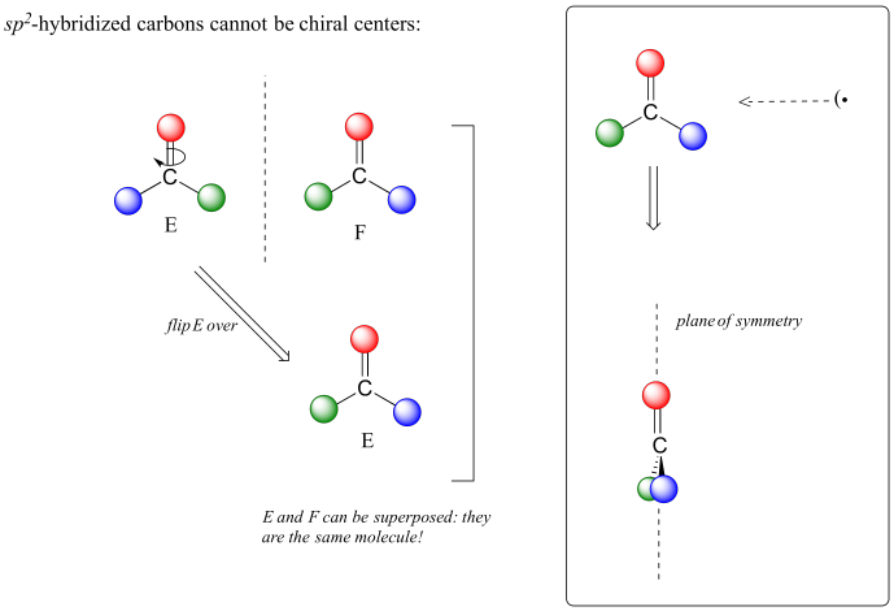
with models) that neither A nor B has an internal plane of symmetry.

A and B are **stereoisomers**: molecules with the same molecular formula and the same bonding arrangement, but *a different arrangement of atoms in space*. There are two types of stereoisomers: enantiomers and diastereomers. **Enantiomers** are pairs of stereoisomers which are mirror images of each other: thus, A and B are enantiomers. It should be self-evident that a chiral molecule will always have one (and *only* one) enantiomer: enantiomers come in pairs. Enantiomers have identical physical properties (melting point, boiling point, density, and so on). However, enantiomers do differ in how they interact with polarized light (we will learn more about this soon) and they may also interact in very different ways with other chiral molecules - proteins, for example. We will begin to explore this last idea in later in this chapter, and see many examples throughout the remainder of our study of biological organic chemistry.

We defined a chiral center as a tetrahedral carbon with four different substituents. If, instead, a tetrahedral carbon has two identical substituents (two black atoms in the cartoon figure below), then of course it still has a mirror image (*everything* has a mirror image). However, it is superimposable on its mirror image, and has a plane of symmetry.



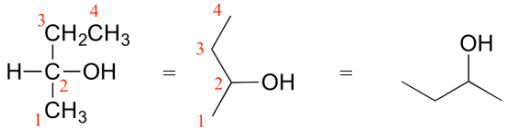
This molecule is **achiral** (lacking chirality). Using the same reasoning, we can see that a trigonal planar carbon is also not a chiral center.



Notice that structure E can be superimposed on F, its mirror image - all you have to do is pick E up, flip it over, and it is the same as F. This molecule has a plane of symmetry, and is achiral.

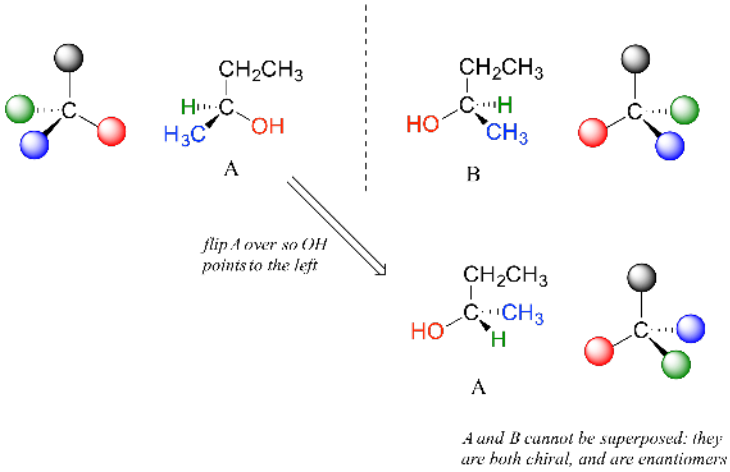
Let's apply our general discussion to real molecules. For now, we will limit our discussion to molecules with a single chiral center. It turns out that tartaric acid, the subject of our chapter introduction, has *two* chiral centers, so we will come back to it later.

Consider 2-butanol, drawn in two dimensions below.



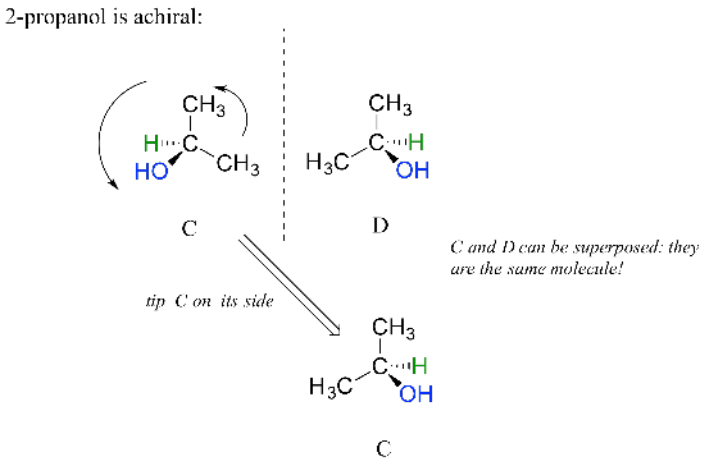
2-butanol
(drawn in 2D)

Carbon #2 is a chiral center: it is tetrahedral (even though it is not drawn that way above), and the four things attached to is are different: a hydrogen, a methyl ($-CH_3$) group, an ethyl ($-CH_2CH_3$) group, and a hydroxyl (OH) group. Let's draw the bonding at C_2 in three dimensions, and call this structure A. We will also draw the mirror image of A, and call this structure B.



When we try to superimpose A onto B, we find that we cannot do it. A and B are both chiral molecules, and they are enantiomers of each other.

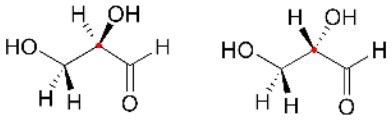
2-propanol, unlike 2-butanol, is *not* a chiral molecule. Carbon #2 is bonded to two identical substituents (methyl groups), and so it is not a chiral center.

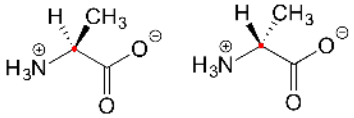


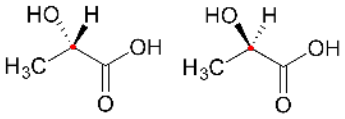
Notice that 2-propanol is superimposable on its own mirror image.

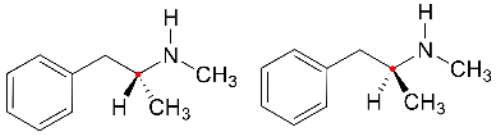
When we look at very simple molecules like 2-butanol, it is not difficult to draw out the mirror image and recognize that it is not superimposable. However, with larger, more complex molecules, this can be a daunting challenge in terms of drawing and three-dimensional visualization. The easy way to determine if a molecule is chiral is simply to look for the presence of one or more chiral centers: molecules with chiral centers will (almost always) be chiral. We insert the 'almost always' caveat here because it is possible to come up with the exception to this rule - we will have more to say on this later, but don't worry about it for now.

Here are four more examples of chiral biomolecules, each one shown as a pair of enantiomers, with chiral centers marked by red dots.

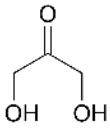

glyceraldehyde

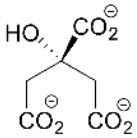

alanine

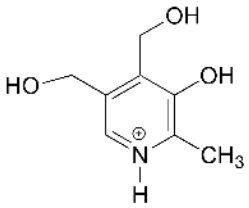

lactic acid

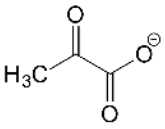

methamphetamine

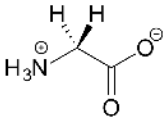
Here are some examples of ***achiral*** biomolecules - convince yourself that none of them contain a chiral center:

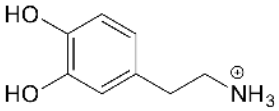

dihydroxyacetone


citrate


pyridoxine
(vitamin B_6)


pyruvate

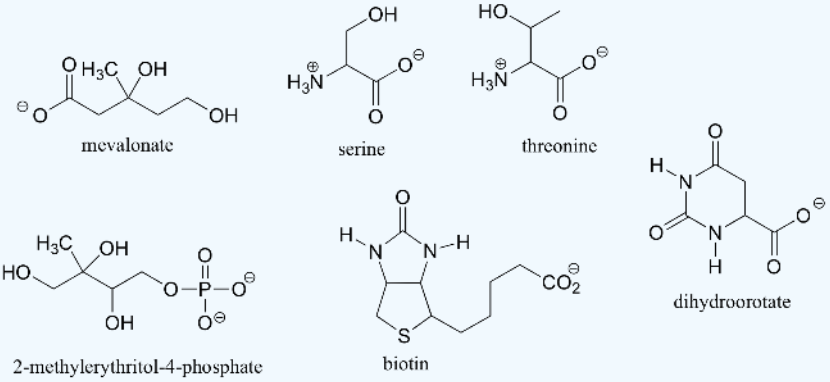

glycine
(amino acid)


dopamine
(neurotransmitter)

Exercise 7.1

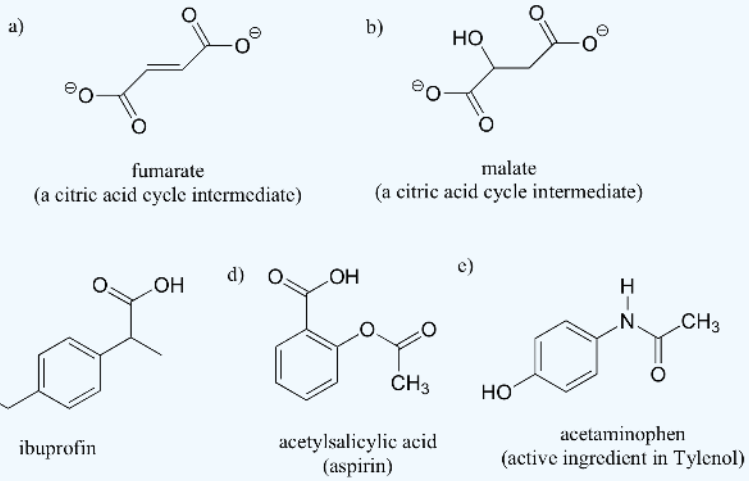
Locate all of the chiral centers (there may be more than one in a molecule). Remember, hydrogen atoms bonded to carbon usually are not drawn in the line structure convention - but they are still there!

https://chem.libretexts.org/@go/page/338707



Exercise 7.2

Label the molecules below as chiral or achiral, and locate all chiral centers.



Khan Academy video tutorials

Chirality

Enantiomers

Contributors and Attributions

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

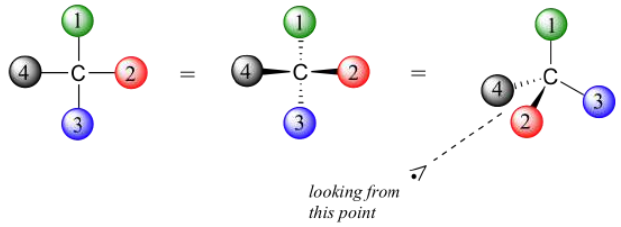
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7.2: Fischer and Haworth projections

When reading the chemical and biochemical literature, you are likely to encounter several different conventions for drawing molecules in three dimensions, depending on the context of the discussion. While organic chemists prefer to use the dashed/solid wedge convention to show stereochemistry, biochemists often use drawings called **Fischer projections** and **Haworth projections** to discuss and compare the structure of sugar molecules.

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



Notice that although a Haworth projection is a convenient way to show stereochemistry, it does not provide a realistic depiction of conformation. To show *both* conformation and stereochemistry, you must draw the ring in the chair form, as in structure C above.

Contributors and Attributions

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7.3: Exercises on Bond Line Structures, Drawing, and Isomers

1. Determine if the following sets of compounds are identical or isomers of one another.

a. 

b. 

c. 

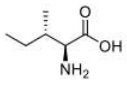
2. Determine if the following sets of molecules are identical, enantiomers, diastereomers, or constitutional isomers.

a. 

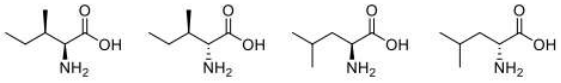
b. 

c. 

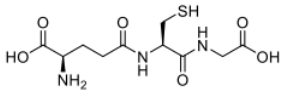
3. Determine if the following compounds are constitutional isomers, stereoisomers, or identical to isoleucine.



isoleucine



4. Glutathione is a tripeptide antioxidant. Identify the functional groups present in glutathione. What amino acids make up glutathione? How many stereoisomers are possible for glutathione?



glutathione

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7.4: Solutions to 7.3 Problems

Exercises on Bond Line Structures, Drawing, and Isomers

1.

a. Both compounds are 4-ethyl-2-methylhexane. Therefore, they are identical compounds.

b. The first compound is 2,3,5-trimethylheptane, and the second is 3-ethyl-2,5-dimethylhexane. Therefore, these are isomers of one another.

c. The first compound is 2,3,3-trimethylpentane, and the second is also 2,3,3-trimethylpentane. Therefore, these are identical.

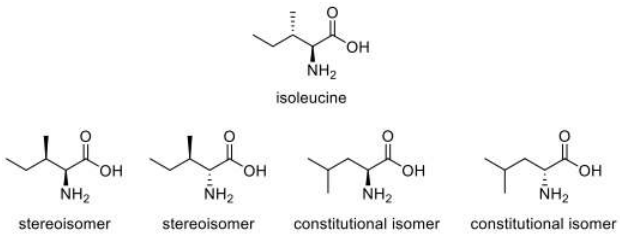
2.

a. Rotating the second structure yields the first structure. Therefore these are identical.

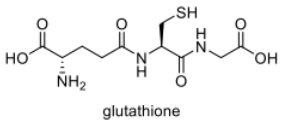
b. Non-mirror image and non-superimposable. Therefore, these are diastereomers.

c. Mirror images and non-superimposable on it's mirror image. These are enantiomers.

3.



4.



Functional groups: carboxylic acid, amine, amide, thiol

Amino acids: glutamate/glutamic acid, cysteine, glycine

Stereoisomers: two stereocenters, $2^2 = 4$ stereoisomers

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CHAPTER OVERVIEW

8: In The Beginning

8.1: Introduction - Basic Chemistry

8.2: Introduction - Water and Buffers

8.3: Prelude to Structure and Function

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8.1: Introduction - Basic Chemistry

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> *"Organic chemistry is the chemistry of carbon compounds. Biochemistry is the chemistry of carbon compounds that crawl" -Michael Adams.*

To understand biochemistry, one must possess at least a basic understanding of organic and general chemistry. In this brief section, we will provide a rapid review of the simple concepts necessary to understand cellular chemistry. Chemistry is chemistry, whether in a cell or outside it, but biological chemistry is a particular subset of organic chemistry that often involves enormous macromolecules, and that happens in the aqueous environment of the cell.



Figure 1.18 shows the various organic functional groups common in biochemistry. You will encounter these functional groups as you study the biosynthetic and breakdown pathways that build and recycle the chemical compounds of which cells are made. In addition to knowing the names and structures of these groups, students need a basic understanding of covalent and ionic bonds.

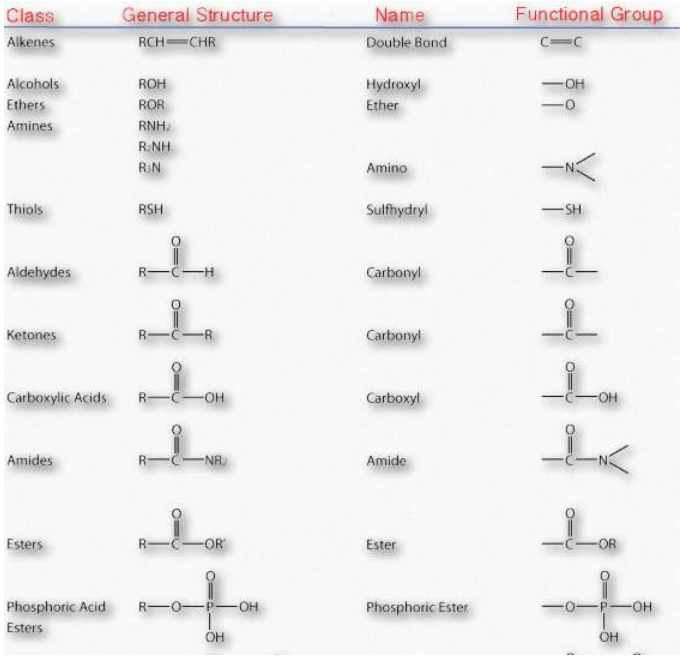


Figure 1.18 - Important functional groups in biochemistry Image by Aleia Kim

Covalent bonds, as you know, are the result of sharing of electrons between two atoms. Ionic bonds, by contrast, are formed when one atom donates an electron to another, such as in the formation of sodium chloride. Single covalent bonds can rotate freely, but double bonds cannot. Single bonds around a carbon atom are arranged in a tetrahedron with bond angles of 109.5° relative to each other, with the carbon at the center (Figure 1.19). Double bonded carbons create a planar structure with bond angles typically of about 120°.

Electronegativity

Electronegativity is a measure of the affinity a nucleus has for outer shell electrons (Table 1.2). High electronegativity corresponds to high affinity. Electrons in a covalent bond are held closer to the nucleus with a greater electronegativity compared to a nucleus with lower electronegativity.

Table 1.2
Electronegativities of Various Atoms

Atom	Electronegativity
Oxygen	3.5
Nitrogen	3.0
Sulfur	2.6
Carbon	2.5
Phosphorous	2.2
Hydrogen	2.1

Table 1.2 Image by Aleia Kim

For example, in a molecule of water, with hydrogen covalently bonded to oxygen, the electrons are “pulled” toward the oxygen, which is more electronegative. Because of this, there is a slightly greater negative charge near the oxygen atom of water, compared to the hydrogen (which, correspondingly has a slightly higher positive charge). This unequal charge distribution sets up a dipole, with one side being somewhat negative and the other somewhat positive. Because of this, the molecule is described as polar.

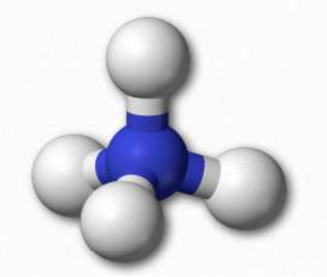


Figure 1.19 - Tetrahedral structure Wikipedia

Hydrogen bonds between water molecules are the result of the attraction of the partial positive and partial negative charges on different water molecules (Figure 1.20). Hydrogen bonds can also form between hydrogens with a partial positive charge and other strongly electronegative atoms, like nitrogen, with a partial negative charge. It is important to remember that hydrogen bonds are interactions between molecules (or parts of molecules) and are not bonds between atoms, like covalent or ionic bonds. Bonds between hydrogen and carbon do not form significant partial charges because the electronegativities of the two atoms are similar. Consequently, molecules containing many carbon-hydrogen bonds will not form hydrogen bonds and therefore, do not mix well with water. Such molecules are called hydrophobic. Other compounds with the ability to make hydrogen bonds are polar and can dissolve in water. They are called hydrophilic. Molecules possessing both characteristics are called amphiphilic.

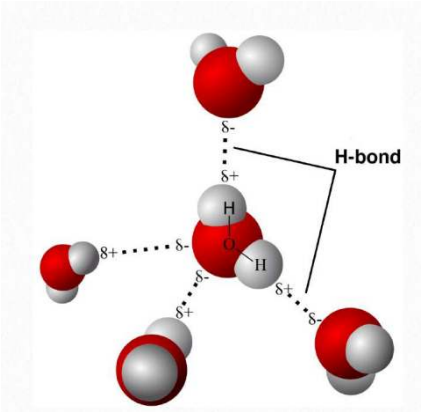


Figure 1.20 Hydrogen bonds (dotted lines) between water molecules Wikipedia

Weak interactions

Hydrogen bonds are one kind of electrostatic (i.e., based on charge) interaction between dipoles. Other forms of electrostatic interactions that are important in biochemistry include weak interactions between a polar molecule and a transient dipole, or between two temporary dipoles. These temporary dipoles result from the movement of electrons in a molecule. As electrons move around, the place where they are, at a given time, becomes temporarily more negatively charged and could now attract a temporary positive charge on another molecule. Since electrons don't stay put, these dipoles are very short-lived. Thus, the attraction that depends on these dipoles fluctuates and is very weak. Weak interactions like these are sometimes called van der Waals forces or dispersion forces. Many molecular interactions in cells depend on weak interactions. Although the individual hydrogen bonds or other dipole-dipole interactions are weak, because of their large numbers, they can result in quite strong interactions between molecules.

Oxidation/reduction

Oxidation involves loss of electrons and reduction results in gain of electrons. For every biological oxidation, there is a corresponding reduction - one molecule loses electrons to another molecule. Oxidation reactions tend to release energy and are a source of bioenergy for chemotrophic cells.

Ionization

Ionization of biomolecules, by contrast does not involve oxidation/reduction. In ionization, a hydrogen ion (H+) leaves behind its electron as it exits (leaving behind a negative charge) or joins a group (adding a positive charge). Biological ionizations typically involve carboxyl groups or amines, though phosphates or sulfates can also be ionized. A carboxyl group can have two ionization states - a charge of -1 corresponds to the carboxyl without its proton and a charge of zero corresponds to the charge of the carboxyl with its proton on. An amine also has two ionization states. A charge of zero corresponds to a nitrogen with three covalent bonds (usually in the form of C-NH2) and a charge of +1 corresponds to a nitrogen making four covalent bonds (usually X-NH3 +).

Stereochemistry

A carbon has the ability to make four single bonds (forming a tetrahedral structure) and if it bonds to four different chemical groups, their atoms can be arranged around the carbon in two different ways, giving rise to stereochemical "handedness" (Figure 1.21). Each carbon with such a property is referred to as an asymmetric center. The property of handedness only occurs when a carbon has four different groups bonded to it. Enzymes have very specific 3-D structures, so for biological molecules that can exist in different stereoisomeric forms, an enzyme that synthesizes it would make only one of the possible isomers. By contrast, the same molecules made chemically (not using enzymes) end up with equal amounts of both isomers, called a **racemic mix**.

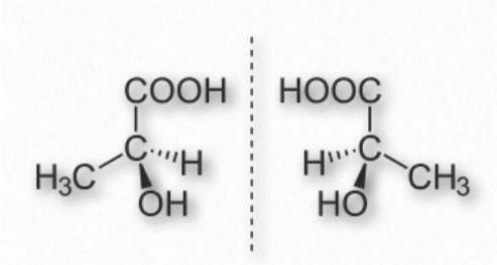


Figure 1.21 - Mirror images of lactic acid

Gibbs free energy

The Gibbs free energy calculation allows us to determine whether a reaction will be spontaneous, by taking into consideration two factors, change in enthalpy (ΔH) and change in entropy (ΔS). The free energy content of a system is given by the Gibbs free energy (G) and is equal to the enthalpy (H) for a process minus the absolute temperature (T) times the entropy (S)

$$G = H = TS \tag{8.1.1}$$

For a process, the change in the Gibbs free energy ΔG is given by

$$\Delta G = \Delta H - T\Delta S \tag{8.1.2}$$

A negative ΔG corresponds to release of free energy. Reactions that release energy are **exergonic**, whereas those that absorb energy are called **endergonic**.

The biological standard Gibbs free energy change (ΔG°') corresponds to the ΔG for a process under standard conditions of temperature, pressure, and at pH = 7. For a reaction

$$aA + bB \rightleftharpoons cC + dD, \tag{8.1.3}$$

the equilibrium constant, K_{eq} is equal to

$$K_{eq} = \frac{[C]_{eq}^{c}[D]_{eq}^{d}}{[A]_{eq}^{a}[B]_{eq}^{b}} \tag{8.1.4}$$

where a, b, c, and d are integers in the balanced equation. Large values of K_{eq} correspond to favorable reactions (more C and D produced than A and B) and small values of K_{eq} mean the opposite. At equilibrium,

$$\Delta G^{o'} = -RT \ln K_{eq} \tag{8.1.5}$$

If a process has a $\Delta G = Z$ and a second process has a $\Delta G = Y$, then if the two processes are linked, ΔG and $\Delta G^{o'}$ values for the overall reaction will be the sum of the individual ΔG and ΔG°' values.

$$\Delta G_{total} = \Delta G_1 + \Delta G_2 = Z + Y \tag{8.1.6}$$

$$\Delta G_{total}^{o'} = \Delta G_1^{o'} + \Delta G_2^{o'} \tag{8.1.7}$$

Catalysis

Catalysis is an increase in the rate of a reaction induced by a substance that is, itself, unchanged by the reaction. Because catalysts remain unchanged at the end of a reaction, a single catalyst molecule can be reused for many reaction cycles. Proteins that catalyze reactions in cells are called enzymes, while ribozymes are RNA molecules that act as catalysts.

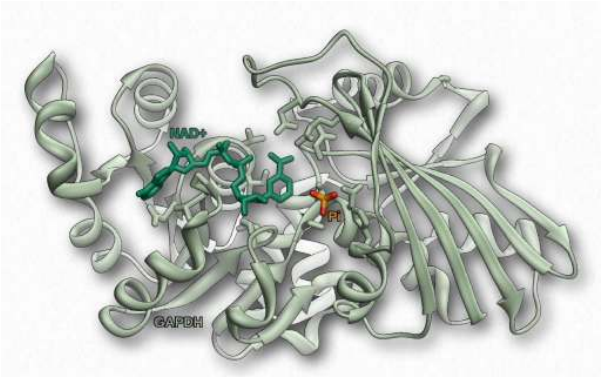


Figure 1.22 - Glyceraldehyde-3-phosphate dehydrogenase in the midst of catalysis Wikipedia

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8.2: Introduction - Water and Buffers

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When it comes to water, we're literally drowning in it, as water is by far the most abundant component of every cell. To understand life, we begin the discussion with the basics of water, because everything that happens in cells, even reactions buried deep inside enzymes, away from water, is influenced by water's chemistry.

The water molecule has wide 'V' shape (the HO-H angle is 104°) with uneven sharing of electrons between the oxygen and the hydrogen atoms (Figure 1.23). Oxygen, with its higher electronegativity, holds electrons closer to itself than the hydrogens do. The hydrogens, as a result, are described as having a partial positive charge (typically designated as δ+) and the oxygen has a partial negative charge (written as δ-). Thus, water is a polar molecule because charges are distributed around it unevenly, not symmetrically.

Water as a solvent

Water (Figure 1.23) is described as a solvent because of its ability to solvate (dissolve) many, but not all, molecules. Molecules that are ionic or polar dissolve readily in water, but non-polar substances dissolve poorly in water, if at all. Oil, for example, which is non-polar, separates from water when mixed with it. On the other hand, sodium chloride, which ionizes, and ethanol, which is polar, are able to form hydrogen bonds, so both dissolve in water. Ethanol's solubility in water is crucial for brewers, winemakers, and distillers – but for this property, there would be no wine, beer or spirits. As explained in an earlier section, we use the term hydrophilic to describe substances that interact well with water and dissolve in it and the term hydrophobic to refer to materials that are non-polar and do not dissolve in water. Table 1.3 illustrates some polar and non-polar substances. A third term, amphiphilic, refers to compounds that have both properties. Soaps, for example are amphiphilic, containing a long, non-polar aliphatic tail and a head that ionizes.

Hydrophilic vs Hydrophobic Compounds

Hydrophobic	Hydrophilic
Nonpolar hydrocarbons (hexane)	Ionic compounds (NaCl)
Lipids (fats and cholesterol)	Polar organic compounds (alcohols, ketones or carbonyls)
	Weak acids (phosphates, amino acids)
	Sugars/carbohydrates

Table 1.3 Image by Aleia Kim

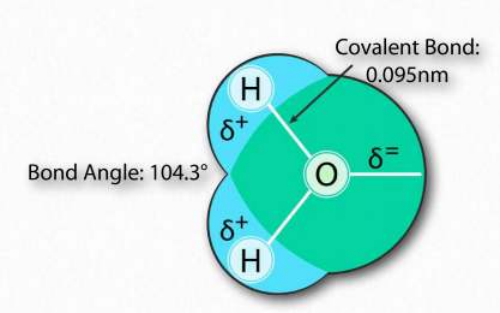


Figure 1.23 - Arrangement of atoms in water Image by Aleia Kim

The solubility of materials in water is based in free energy changes, as measured by ΔG. Remember, from chemistry, that H is the enthalpy (heat at constant pressure) and S is entropy. Given this,

$$\Delta G = \Delta H - T\Delta S \tag{8.2.1}$$

where T is the temperature in Kelvin. For a process to be favorable, the ΔG for it must be less than zero.

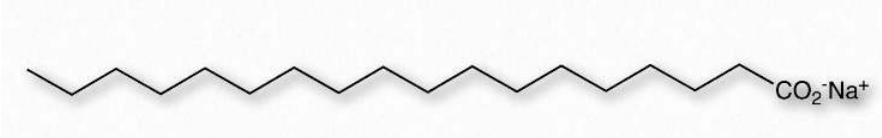


Figure 1.24 - Structure of a Soap

From the equation, lowered ΔG values will be favored with decreases in enthalpy and/or increases in entropy. Let us first consider why non-polar materials do not dissolve in water. We could imagine a situation where the process of dissolving involves the "surrounding" of each molecule of the nonpolar solute in water, just like each sodium and each chloride ion gets surrounded by water molecules as salt dissolves.

Water organization

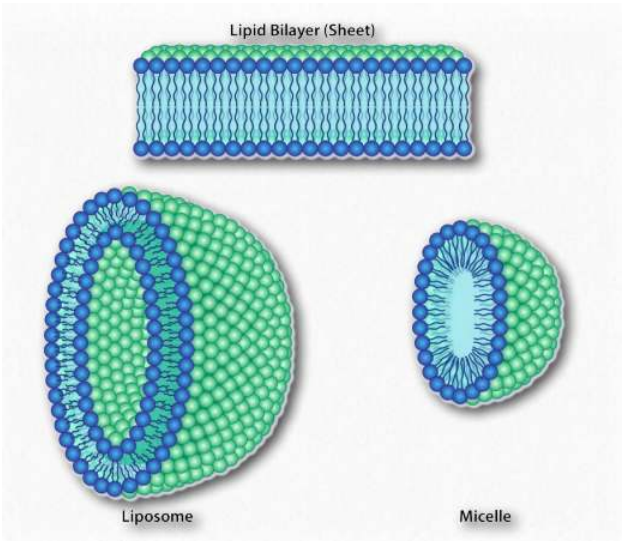


Figure 1.25 - Structures formed by amphiphilic substances in water. Image by Aleia Kim

There is a significant difference, though between surrounding a non-polar molecule with water molecules and surrounding ions (or polar compounds) with water molecules.

The difference is that since non-polar molecules don't really interact with water, the water behaves very differently than it does with ions or molecules that form hydrogen bonds. In fact, around each non-polar molecule, water gets very organized, aligning

itself regularly. As any freshman chemistry student probably remembers, entropy is a measure of disorder, so when something becomes ordered, entropy decreases, meaning the ΔS is negative, so the TΔS term in the equation is positive (negative of a negative).

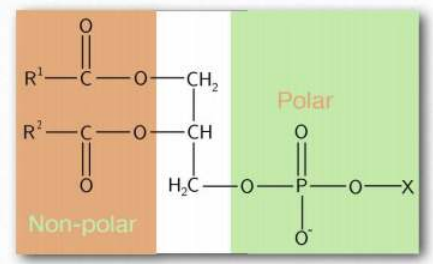


Figure 1.26 - A phospholipid - an amphiphilic substance

Since mixing a non-polar substance with water doesn't generally have any significant heat component, the ΔG is positive. This means, then, that dissolving a non-polar compound in water is not favorable and does not occur to any significant extent. Further, when the non-polar material associates with itself and not water, then the water molecules are free to mix, without being ordered, resulting in an increase of entropy. Entropy therefore drives the separation of non-polar substances from aqueous solutions.

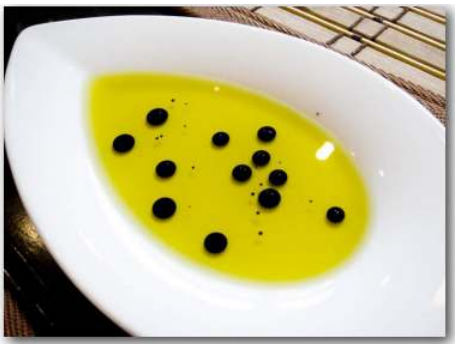


Figure 1.27 - Vinegar (black) and oil (yellow) A mix of polar and nonpolar compounds Wikipedia

Amphiphilic substances

Next, we consider mixing of an amphiphilic substance, such as a soap, with water (Figure 1.24). The sodium ions attached to the fatty acids in soap readily come off in aqueous solution, leaving behind a negatively charged molecule at one end and a non-polar region at the other end. The ionization of the soap causes in an increase in entropy - two particles instead of one. The non-polar portion of the negatively charged soap ion is problematic - if exposed to water, it will cause water to organize and result in a decrease of entropy and a positive ΔG.

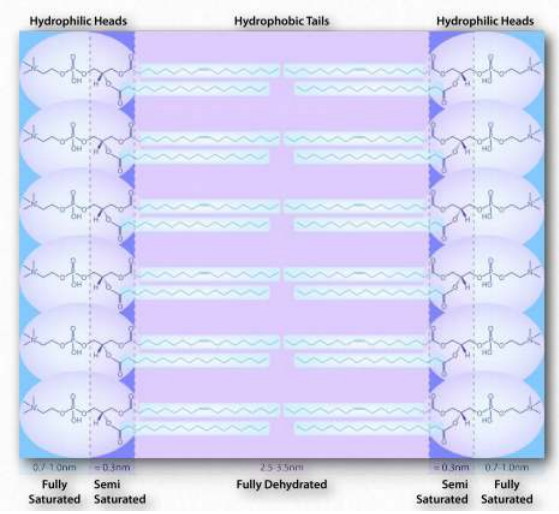


Figure 1.28 - Environment of a lipid bilayer. Water is concentrated away from the hydrophobic center, being saturated on the outside, semi-saturated near the head-tail junction and fully dehydrated in the middle. Image by Aleia Kim

Since we know fatty acids dissolve in water, there must be something else at play. There is. Just like the non-polar molecules in the first example associated with each other and not water, so too do the non-polar portions of the soap ions associate with each other and exclude water. The result is that the soap ions arrange themselves as micelles (Figure 1.25) with the non-polar portions on the interior of the structure away from water and the polar portions on the outside interacting with water.

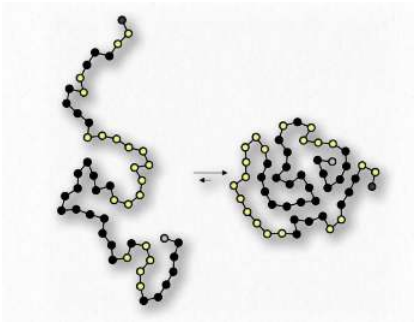


Figure 1.29 - Protein folding arranges hydrophobic amino acids (black dots) inside the protein

The interaction of the polar heads with water returns the water to its more disordered state. This increase in disorder, or entropy, drives the formation of micelles. As will be seen in the discussion of the lipid bilayer, the same forces drive glycerophospholipids and sphingolipids to spontaneously form bilayers where the non-polar portions of the molecules interact with each other to exclude water and the polar portions arrange themselves on the outsides of the bilayer (Figure 1.28).

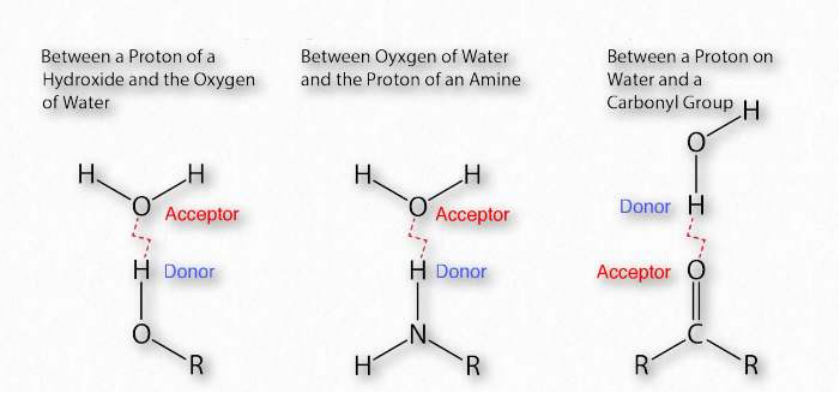


Figure 1.30 - Common hydrogen bonds in biochemistry Image by Aleia Kim

Yet another example is seen in the folding of globular proteins in the cytoplasm. Nonpolar amino acids are found in the interior portion of the protein (water excluded). Interaction of the non-polar amino acids turns out to be a driving force for the folding of

proteins as they are being made in an aqueous solution.

Hydrogen bonds

The importance of hydrogen bonds in biochemistry (Figure 1.30) is hard to overstate. Linus Pauling himself said,

" . . . . I believe that as the methods of structural chemistry are further applied to physiological problems it will be found that the significance of the hydrogen bond for physiology is greater than that of any other single structural feature."

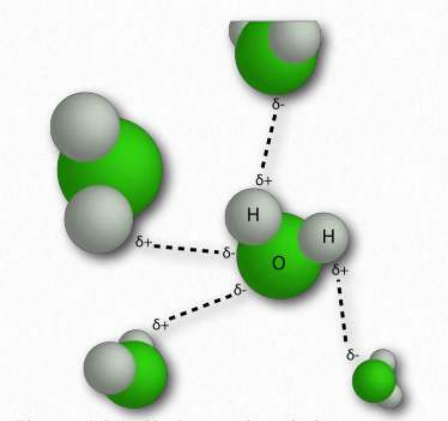


Figure 1.31 - Hydrogen bonds between water molecules Image by Pehr Jacobson

In 2011, an IUPAC task group gave an evidence-based definition of hydrogen bonding that states,

"The hydrogen bond is an attractive interaction between a hydrogen atom from a molecule or a molecular fragment X–H in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule, in which there is evidence of bond formation."

Partial Charges

The difference in electronegativity between hydrogen and the molecule to which it is covalently bound give rise to partial charges as described above. These tiny charges (δ+ and δ-) result in formation of hydrogen bonds, which occur when the partial positive charge of a hydrogen atom is attracted to the partial negative of another molecule. In water, that means the hydrogen of one water molecule is attracted to the oxygen of another (Figure 1.31). Since water is an asymmetrical molecule, it means also that the charges are asymmetrical. Such an uneven distribution is what makes a dipole. Dipolar molecules are important for interactions with other dipolar molecules and for dissolving ionic substances (Figure 1.32).

Hydrogen bonds are not exclusive to water. In fact, they are important forces holding together macromolecules that include proteins and nucleic acids. Hydrogen bonds occur within and between macromolecules.

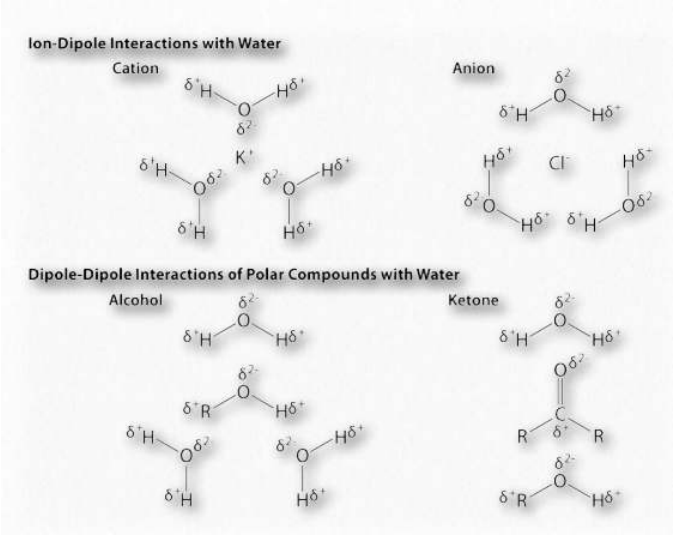


Figure 1.32 - Example dipole interactions in biochemistry Image by Aleia Kim

The complementary pairing that occurs between bases in opposite strands of DNA, for example, is based on hydrogen bonds. Each hydrogen bond is relatively weak (compared to a covalent bond, for example - Table 1.4), but collectively they can be quite strong.

Bond Energies

	Type of Bond	Bond Energy (kJ/mol)
Covalent Bonds	C—H	413
	O—H	460
Noncovalent Bonds	Hydrophobic Interaction	4-12
	Hydrogen Bond	20
	Ion-dipole Interaction	20

Table 1.4 Image by Aleia Kim

Benefits of weak interactions

Their weakness, however, is actually quite beneficial for cells, particularly as regards nucleic acids (Figure 1.33). The strands of DNA, for example, must be separated over short stretches in the processes of replication and the synthesis of RNA. Since only a few base pairs at a time need to be separated, the energy required to do this is small and the enzymes involved in the processes can readily take them apart, as needed. Hydrogen bonds also play roles in binding of substrates to enzymes, catalysis, and protein-protein interaction, as well as other kinds of binding, such as protein-DNA, or antibody-antigen.

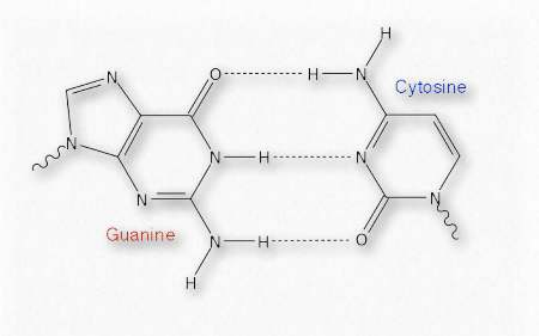


Figure 1.33 - Hydrogen bonds in a base pair of DNA Image by Aleia Kim

As noted, hydrogen bonds are weaker than covalent bonds (Table 1.4) and their strength varies form very weak (1-2 kJ/mol) to fairly strong (29 kJ/mol). Hydrogen bonds only occur over relatively short distances (2.2 to 4.0 Å). The farther apart the hydrogen bond distance is, the weaker the bond is.

The strength of the bond in kJ/mol represents the amount of heat that must be put into the system to break the bond - the larger the number, the greater the strength of the bond. Hydrogen bonds are readily broken using heat. The boiling of water, for example, requires breaking of H-bonds. When a biological structure, such as a protein or a DNA molecule, is stabilized by hydrogen bonds, breaking those bonds destabilizes the structure and can result in denaturation of the substance - loss of structure. It is partly for this reason that most proteins and all DNAs lose their native, or folded, structures when heated to boiling.

For DNA molecules, denaturation results in complete separation of the strands from each other. For most proteins, this means loss of their characteristic three-dimensional structure and with it, loss of the function they performed. Though a few proteins can readily reassume their original structure when the solution they are in is cooled, most can't. This is one of the reasons that we cook our food. Proteins are essential for life, so denaturation of bacterial proteins results in death of any microorganisms contaminating the food.

The importance of buffers

Water can ionize to a slight extent (10-7 M) to form H+ (proton) and OH- (hydroxide). We measure the proton concentration of a solution with pH, which is the negative log of the proton concentration.

$$pH = -Log[H+]$$

If the proton concentration, [H+]= 10-7 M, then the pH is 7. We could just as easily measure the hydroxide concentration with the pOH by the parallel equation,

$$pOH = -Log[OH^-]$$

In pure water, dissociation of a proton simultaneously creates a hydroxide, so the pOH of pure water is 7, as well. This also means that

$$pH + pOH = 14$$

Now, because protons and hydroxides can combine to form water, a large amount of one will cause there to be a small amount of the other. Why is this the case? In simple terms, if I dump 0.1 moles of H+ into a pure water solution, the high proton concentration will react with the relatively small amount of hydroxides to create water, thus reducing hydroxide concentration. Similarly, if I dump excess hydroxide (as NaOH, for example) into pure water, the proton concentration falls for the same reason.

Acids vs bases

Chemists use the term "acid" to refer to a substance which has protons that can dissociate (come off) when dissolved in water. They use the term "base" to refer to a substance that can absorb protons when dissolved in water. Both acids and bases come in strong and weak forms. (Examples of weak acids are shown in Table 1.5.) Strong acids, such as HCl, dissociate completely in water. If we add 0.1 moles ($6.02x10^{22}$ molecules) of HCl to a solution to make a liter, it will have 0.1 moles of H+ and 0.1 moles of Cl- or $6.02x10^{22}$ molecules of each . There will be no remaining HCl when this happens. A strong base like NaOH also dissociates completely into Na+ and OH- .

Clearing Confusion - Students are often puzzled and expect that

$$[H^+] = [A^-]$$

because the dissociation equation shows one of each from HA. This is, in fact, true ONLY when HA is allowed to dissociate in pure water. Usually the HA is placed into solution that has protons and hydroxides to affect things. Those protons and /or hydroxides change the H^+ and A^- concentration unequally, since A^- can absorb some of the protons and/or HA can release H^+ when influenced by the OH^- in the solution. Therefore, one must calculate the proton concentration from the pH using the Henderson Hasselbalch equation.

$$pH = pK_a + \log([Ac^-]/[HAc])$$

Weak Acids

Weak acids and bases differ from their strong counterparts. When you put one mole of acetic acid (HAc) into pure water, only a tiny percentage of the HAc molecules dissociate into H+ and Ac- . Clearly, weak acids are very different from strong acids. Weak bases behave similarly, except that they accept protons, rather than donate them. Since we can view everything as a form of a weak acid, we will not use the term weak base here.

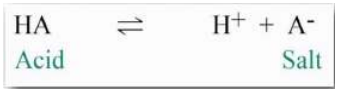


Figure 1.34 - Dissociation of a weak acid Image by Aleia Kim

Students are often puzzled and expect that $[H^+] = [A^-]$ because the dissociation equation shows one of each from HA. This is, in fact, true ONLY when HA is allowed to dissociate in pure water. Usually the HA is placed into solution that has protons and hydroxides to affect things. Those protons and/or hydroxides change the H+ and Aconcentration unequally, since A- can absorb some of the protons and/or HA can release H+ when influenced by the OH- in the solution. Therefore, one must calculate the proton concentration from the pH using the Henderson Hasselbalch equation: pH = pKa + log ($[Ac^-]$/[HAc]).

Salt/Acid Ratio as a Function of pK_as

pH	[Salt]/[Acid]
$pK_a + 3$	1000
$pK_a + 2$	100
$pK_a + 1$	10
pK_a	1
$pK_a - 1$	1/10
$pK_a - 2$	1/100
$pK_a - 3$	1/1000

Image by Aleia Kim Table 1.6

You may wonder why we care about weak acids. You may never have thought much of weak acids when you were in General Chemistry. Your instructor described them as buffers and you probably dutifully memorized the fact that “buffers are substances that resist change in pH” without really learning what Clearing Confusion - this meant. Buffers are much too important to be thought of in this way.

UPS

Weak acids are critical for life because their affinity for protons causes them to behave like a UPS. We’re not referring to the UPS that is the United Parcel Service, but instead, to the encased battery backup systems for computers called Uninterruptible Power Supplies that kick on to keep a computer running during a power failure. The battery in a laptop computer is a UPS, for example.

We can think of weak acids as Uninterruptible Proton Suppliers within certain pH ranges, providing (or absorbing) protons as needed. Weak acids thus help to keep the H+ concentration (and thus the pH) of the solution they are in relatively constant.

Consider the bicarbonate/carbonic acid system. Figure 1.35 shows what happens when H_2CO_3dissociates. Adding hydroxide ions (by adding a strong base like NaOH) to the solution causes the H+ ions to react with OH- ions to make water. Consequently, the concentration of H+ ions would go down and the pH would go up.

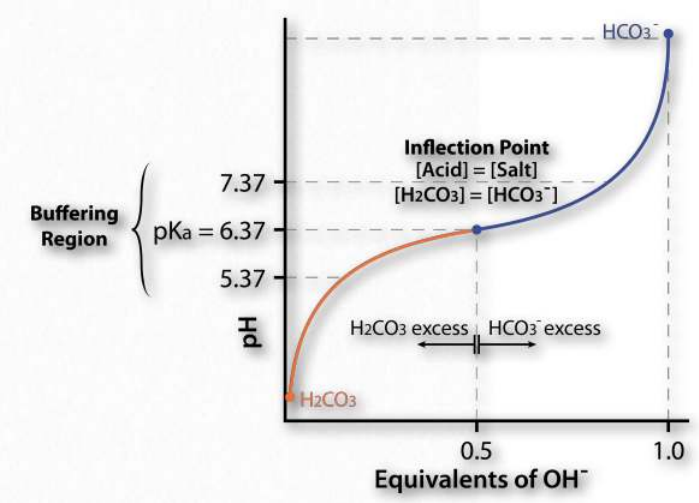


Figure 1.35 - Titration curve for carbonic acid Image by Aleia Kim

However, in contrast to the situation with a solution of pure water, there is a backup source of H+ available in the form of H_2CO_3. Here is where the UPS function kicks in. As protons are taken away by the added hydroxyl ions (making water), they are partly replaced by protons from the H_2CO_3. This is why a weak acid is a buffer. It resists changes in pH by releasing protons to compensate for those “used up” in reacting with the hydroxyl ions.

Why do we care about pH? Because biological molecules can, in some cases, be exquisitely sensitive to changes in it. As the pH of a solution changes, the charges of molecules in the solution can change, as you will see. Changing charges on biological molecules, especially proteins, can drastically affect how they work and even whether they work at all.

Henderson-Hasselbalch

It is useful to be able to predict the response of the H_2CO_3 system to changes in H+ concentration. The Henderson-Hasselbalch equation defines the relationship between pH and the ratio of HCO_3^- and H_2CO_3. It is

$$pH = pKa + \log ([HCO_3^-]/ [H_2CO_3])$$

This simple equation defines the relationship between the pH of a solution and the ratio of HCO_3^- and H_2CO_3 in it. The new term, called the pKa, is defined as

$$pKa = -\text{Log } K_a,$$

just as

$$pH = -\text{Log } [H^+].$$

The Ka is the acid dissociation constant and is a measure of the strength of an acid. For a general acid, HA, which dissociates as

$$HA \rightleftarrows H^+ + A^-,\ K_a = [H^+][A^-]/[HA]$$

Thus, the stronger the acid, the more protons that will dissociate from it when added to water and the larger the value its Ka will have. Large values of Ka translate to lower values of pKa. As a result, the lower the pKa value is for a given acid, the stronger the weak acid is.

Constant pKa

Please note that pKa is a constant for a given acid. The pKa for carbonic acid is 6.37. By comparison, the pKa for formic acid is 3.75. Formic acid is therefore a stronger acid than carbonic acid. A stronger acid will have more protons dissociated at a given pH than a weaker acid.

Now, how does this translate into stabilizing pH? Figure 1.35 shows a titration curve. In this curve, the titration begins with the conditions at the lower left (very low pH). At this pH, the H_2CO_3 form predominates, but as more and more OH- is added (moving to the 45 Why do we care about pH? Because biological molecules can, in some cases, be exquisitely sensitive to changes in it. As the pH of a solution changes, the charges of molecules in the solution can change, as you will see. Changing charges on biological molecules, especially proteins, can drastically affect how they work and even whether they work at all right), the pH goes up, the amount of HCO3- goes up and (correspondingly), the amount of H_2CO_3 goes down. Notice that the curve “flattens” near the pKa (6.37).

Buffering region

Flattening of the curve tells us is that the pH is not changing much (not going up as fast) as it did earlier when the same amount of hydroxide was added. The system is resisting a change in pH (not stopping the change, but slowing it) in the region of about one pH unit above and one pH unit below the pKa. Thus, the buffering region of the carbonic acid/ bicarbonate buffer is from about 5.37 to 7.37. It is maximally strong at a pH of 6.37.

Now it starts to become apparent how the buffer works. HA can donate protons when extras are needed (such as when OH- is added to the solution by the addition of NaOH). Similarly, A- can accept protons when extra H+ are added to the solution (adding HCl, for example). The maximum ability to donate or accept protons comes when

$$[A^-] = [HA]$$

This is consistent with the Henderson Hasselbalch equation and the titration curve. When $[A^-] = [HA]$, pH = 6.37 + Log(1). Since Log(1) = 0, pH = 6.37 = pKa for carbonic acid. Thus for any buffer, the buffer will have maximum strength and display flattening of its titration curve when $[A^-] = [HA]$ and when pH = pKa. If a buffer has more than one pKa (Figure 1.36), then each pKa region will display the behavior.

Buffered vs non-buffered

To understand how well a buffer protects against changes in pH, consider the effect of adding .01 moles of HCl to 1.0 liter of pure water (no volume change) at pH 7, compared to adding it to 1.0 liter of a 1M acetate buffer at pH 4.76. Since HCl completely dissociates, in 0.01M (10-2 M) HCl you will have 0.01M H+. For the pure water, the pH drops from 7.0 down to 2.0 (pH = -log(0.01M)).

By contrast, the acetate buffer’s pH after adding the same amount of HCl is 4.74. Thus, the pure water solution sees its pH fall from 7 to 2 (5 pH units), whereas the buffered solution saw its pH drop from 4.76 to 4.74 (0.02 pH units). Clearly, the buffer minimizes the impact of the added protons compared to the pure water.

Buffer capacity

It is important to note that buffers have capacities limited by their concentration. Let’s imagine that in the previous paragraph, we had added the 0.01 moles HCl to an acetate buffer that had a concentration of 0.01M and equal amounts of Ac- and HAc. When we try to do the math in parallel to the previous calculation, we see that there are 0.01M protons, but only 0.005M A- to absorb them. We could imagine that 0.005M of the protons would be absorbed, but that would still leave 0.005M of protons unbuffered. Thus, the pH of this solution would be approximately

$$pH = -\log(0.005M) = 2.30$$

Exceeding buffer capacity dropped the pH significantly compared to adding the same amount of protons to a 1M acetate buffer. Consequently, when considering buffers, it is important to recognize that their concentration sets their limits. Another limit is the

pH range in which one hopes to control proton concentration.

Multiple ionizable groups

Now, what happens if a molecule has two (or more) ionizable groups? It turns out, not surprisingly, that each group will have its own pKa and, as a consequence, will have multiple regions of buffering.

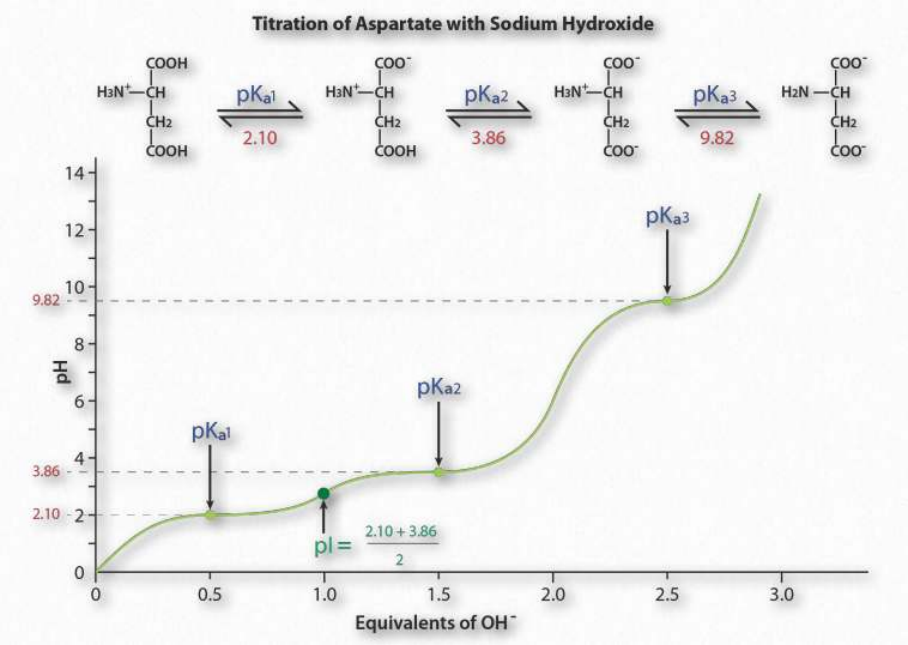


Figure 1.36 - Titration of an acidic amino acid Image by Aleia Kim

Figure 1.36 shows the titration curve for the amino acid aspartic acid. Note that in- stead of a single flattening of the curve, as was seen for acetic acid, aspartic acid's titration curve displays three such regions. These are individual buffering regions, each centered on the respective pKa values for the carboxyl group and the amine group.

Aspartic acid has four possible charges: +1 (α-carboxyl group, α-amino group, and R-group carboxyl each has a proton), 0 (α-carboxyl group missing proton, α- amino group has a proton, R-group carboxyl has a proton), -1 (α-carboxyl group and R-group carboxyl each lack a proton, α-amino group retains a proton), -2 (α-carboxyl, R-group carboxyl, and α-amino groups all lack extra proton).

Prediction

How does one predict the charge for an amino acid at a given pH? A good rule of thumb for estimating charge is that if the pH is more than one unit below the pKa for a group (carboxyl or amino), the proton is on. If the pH is more than one unit above the pKa for the group, the proton is off. If the pH is NOT more than one or less than one pH unit from the pKa, this simple assumption will not work.

Further, it is important to recognize that these rules of thumb are estimates only. The pI (pH at which the charge of a molecule is zero) is an exact value calculated as the average of the two pKa values on either side of the zero region. It is calculated at the average of the two pKa values around the point where the charge of the molecule is zero. For aspartic acid, this corresponds to $pK_{a1}$and pK_{a2}.

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8.3: Prelude to Structure and Function

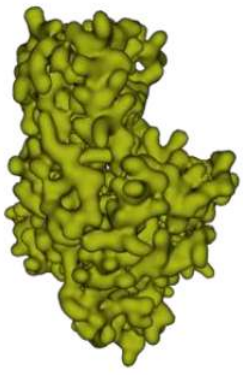
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"The man who does not read good books has no advantage over the man who cannot read them." Mark Twain



In this chapter, we will examine the structures of the major classes of biomolecules, with an eye to understanding how these structures relate to function.

As noted earlier, water is the most abundant molecule in cells, and provides the aqueous environment in which cellular chemistry happens. Dissolved in this water are inorganic ions like sodium, potassium and calcium. But the distinctiveness of biochemistry derives from the vast numbers of complex, large, carbon compounds, that are made by living cells. You have probably learned that the major classes of biological molecules are proteins, nucleic acids, carbohydrates and lipids. The first three of these major groups are macromolecules that are built as long polymers made up of smaller subunits or monomers, like strings of beads. The lipids, while not chains of monomers, also have smaller subunits that are assembled in various ways to make the lipid components of cells, including membranes. The chemical properties and three dimensional conformations of these molecules determine all the molecular interactions upon which life depends. Whether building structures within cells, transferring information, or catalyzing reactions, the activities of biomolecules are governed by their structures. The properties and shapes of macromolecules, in turn, depend on the subunits of which they are built.



Interactive 2.1: *The enzyme Hexokinase: as for all enzymes, the activity of hexokinase depends on its structure. Protein Database (PDB)*

We will next examine the major groups of biological macromolecules: proteins, polysaccharides, nucleic acids, and lipids. The building blocks of the first three, respectively, are amino acids, monosaccharides (sugars), and nucleotides. Acetyl-CoA is the most common building block of lipids.

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CHAPTER OVERVIEW

9: Acids and Bases

Acids and bases are important classes of chemical compounds. They are part of the foods and beverages we ingest, they are present in medicines and other consumer products, and they are prevalent in the world around us. In this chapter, we will focus on acids and bases and their chemistry.

9.1: Introduction
9.2: Arrhenius Acids and Bases
9.3: Brønsted-Lowry Acids and Bases
9.4: Strong and Weak Acids and Bases and their Salts
9.5: Autoionization of Water
9.6: The pH Scale
9.7: Acid-Base Titrations
9.8: Buffers
9.9: Acids, Bases, pH and Buffers- Questions

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9.1: Introduction

Formerly there were rather campy science-fiction television shows in which the hero was always being threatened with death by being plunged into a vat of boiling acid: "Mwa ha ha, Buck Rogers [or whatever the hero's name was], prepare to meet your doom by being dropped into a vat of boiling acid!" (The hero always escapes, of course.) This may have been interesting drama, but not very good chemistry. If the villain knew his/her/its science, the hero would have been dropped into a vat of boiling base.

Recall that the active component of a classic acid is the H^+ ion, while the active part of a classic base is the OH^- ion. Both ions are related to water in that all H^+ ion needs to become a water molecule is an OH^- ion, while all an OH^- ion needs to become water is an H^+ ion. Consider the relative masses involved: an ion of mass 1 needs an ion of mass 17 to make water, while an ion of mass 17 needs an ion of mass 1 to make water. Which process do you think will be easier?

In fact, bases are more potentially dangerous than acids because it is much easier for an OH^- ion to rip off an H^+ ion from surrounding matter than it is for an H^+ ion to rip off an OH^- ion. Certain household chemicals, such as some brands of cleaner, can be very concentrated bases, which makes them among the most potentially hazardous substances found around the home. If spilled on the skin, these strong caustic compounds can immediately remove H^+ ions from the flesh, resulting in chemical burns. Compare this to the fact that we occasionally purposefully ingest substances such as citrus fruits, vinegar, and wine—all of which contain acids. (Of course, some parts of the body, such as the eyes, are extremely sensitive to acids as well as bases.) It seems that our bodies are more capable of dealing with acids than with bases.



Figure **9.1.1** Household chemicals © Thinkstock. On the left is a common acid, and on the right is a common base. Which one is more potentially hazardous?

A note to all of the villains out there...get your chemistry right if you want to be successful!

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9.2: Arrhenius Acids and Bases

Learning Objective

- Identify an Arrhenius acid and an Arrhenius base.
- Write the chemical reaction between an Arrhenius acid and an Arrhenius base.

Historically, the first chemical definition of an acid and a base was put forward by Svante Arrhenius, a Swedish chemist, in 1884. An **Arrhenius acid** is a compound that increases the H^+ ion concentration in an aqueous solution. The H^+ ion is just a bare proton, and it is rather clear that bare protons are not floating around in an aqueous solution. Instead, chemistry has defined the **hydronium ion** (H_3O^+) as the actual chemical species that represents an H^+ ion. H^+ ions and H_3O^+ ions are often considered interchangeable when writing chemical equations (although a properly balanced chemical equation should also include the additional H_2O). Classic Arrhenius acids can be considered ionic compounds in which H^+ is the cation. Table **9.2.1** lists some Arrhenius acids and their names.

Table **9.2.1** Some Arrhenius Acids

Formula	Name
$HC_2H_3O_2$ (also written CH_3COOH)	acetic acid
$HClO_3$	chloric acid
HCl	hydrochloric acid
HBr	hydrobromic acid
HI	hydriodic acid
HF	hydrofluoric acid
HNO_3	nitric acid
$H_2C_2O_4$	oxalic acid
$HClO_4$	perchloric acid
H_3PO_4	phosphoric acid
H_2SO_4	sulfuric acid
H_2SO_3	sulfurous acid

An **Arrhenius base** is a compound that increases the OH^- ion concentration in aqueous solution. Ionic compounds of the OH^- ion are classic Arrhenius bases.

Example 9.2.1:

Identify each compound as an Arrhenius acid, an Arrhenius base, or neither.

a. HNO_3
b. CH_3OH
c. $Mg(OH)_2$

Solution

a. This compound is an ionic compound between H^+ ions and NO_3^- ions, so it is an Arrhenius acid.
b. Although this formula has an OH in it, we do not recognize the remaining part of the molecule as a cation. It is neither an acid nor a base. (In fact, it is the formula for methanol, an organic compound.)

c. This formula also has an OH in it, but this time we recognize that the magnesium is present as Mg^{2+} cations. As such, this is an ionic compound of the OH^- ion and is an Arrhenius base.

Exercise 9.2.1

Identify each compound as an Arrhenius acid, an Arrhenius base, or neither.

1. KOH
2. H_2SO_4
3. C_2H_6

Answer

1. Arrhenius base
2. Arrhenius acid
3. neither

Acids have some properties in common. They turn litmus, a plant extract, red. They react with some metals to give off H_2 gas. They react with carbonate and hydrogen carbonate salts to give off CO_2 gas. Acids that are ingested typically have a sour, sharp taste. (The name *acid* comes from the Latin word *acidus*, meaning "sour.") Bases also have some properties in common. They are slippery to the touch, turn litmus blue, and have a bitter flavor if ingested.

Acids and bases have another property: they react with each other to make water and an ionic compound called a salt. A **salt**, in chemistry, is any ionic compound made by combining an acid with a base. A reaction between an acid and a base is called a **neutralization reaction** and can be represented as:

$$\text{acid} + \text{base} \rightarrow H_2O + \text{salt}$$

The stoichiometry of the balanced chemical equation depends on the number of H^+ ions in the acid and the number of OH^- ions in the base.

Example 9.2.1:

Write the balanced chemical equation for the neutralization reaction between H_2SO_4 and KOH. What is the name of the salt that is formed?

Solution

The general reaction is as follows:

$$H_2SO_4 + KOH \rightarrow H_2O + \text{salt}$$

Because the acid has two H^+ ions in its formula, we need two OH^- ions to react with it, making two H_2O molecules as product. The remaining ions, K^+ and SO_4^{2-}, make the salt potassium sulfate (K_2SO_4). The balanced chemical reaction is as follows:

$$H_2SO_4 + 2KOH \rightarrow 2H_2O + K_2SO_4$$

Exercise 9.2.1

Write the balanced chemical equation for the neutralization reaction between HCl and $Mg(OH)_2$. What is the name of the salt that is formed?

Answer

$2HCl + Mg(OH)_2 \rightarrow 2H_2O + MgCl_2$; magnesium chloride

Key Takeaways

- An Arrhenius acid is a compound that increases the H^+ ion concentration in aqueous solution.
- An Arrhenius base is a compound that increases the OH^- ion concentration in aqueous solution.
- The reaction between an Arrhenius acid and an Arrhenius base is called neutralization and results in the formation of water and a salt.

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9.3: Brønsted-Lowry Acids and Bases

Learning Objectives

- Identify a Brønsted-Lowry acid and a Brønsted-Lowry base.
- Identify conjugate acid-base pairs in an acid-base reaction.

The Arrhenius definition of acid and base is limited to aqueous (that is, water) solutions. Although this is useful because water is a common solvent, it is limited to the relationship between the H^+ ion and the OH^- ion. What would be useful is a general definition more applicable to other chemical reactions and, importantly, independent of H_2O.

In 1923, Danish chemist Johannes Brønsted and English chemist Thomas Lowry independently proposed new definitions for acids and bases, ones that focus on proton transfer. A **Brønsted-Lowry acid** is any species that can donate a proton (H^+) to another molecule. A **Brønsted-Lowry base** is any species that can accept a proton from another molecule. In short, a Brønsted-Lowry acid is a proton donor (PD), while a Brønsted-Lowry base is a proton acceptor (PA).

It is easy to see that the Brønsted-Lowry definition covers the Arrhenius definition of acids and bases. Consider the prototypical Arrhenius acid-base reaction:

$$\underset{acid}{H^+(aq)} + \underset{base}{OH^-(aq)} \rightarrow H_2O\,(l)$$

Acid species and base species are marked. The proton, however, is (by definition) a proton donor (labeled PD), while the OH^- ion is acting as the proton acceptor (labeled PA):

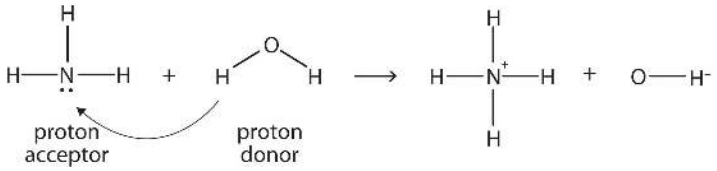
$$\underset{PD}{H^+(aq)} + \underset{PA}{OH^-(aq)} \rightarrow H_2O\,(l)$$

The proton donor is a Brønsted-Lowry acid, and the proton acceptor is the Brønsted-Lowry base:

$$\underset{BL\ acid}{H^+(aq)} + \underset{BL\ base}{OH^-(aq)} \rightarrow H_2O\,(l)$$

Thus H^+ is an acid by both definitions, and OH^- is a base by both definitions.

Ammonia (NH_3) is a base even though it does not contain OH^- ions in its formula. Instead, it generates OH^- ions as the product of a proton-transfer reaction with H_2O molecules; NH_3 acts like a Brønsted-Lowry base, and H_2O acts like a Brønsted-Lowry acid:



A reaction with water is called **hydrolysis**; we say that NH_3 hydrolyzes to make NH_4^+ ions and OH^- ions.

Even the dissolving of an Arrhenius acid in water can be considered a Brønsted-Lowry acid-base reaction. Consider the process of dissolving HCl(g) in water to make an aqueous solution of hydrochloric acid. The process can be written as follows:

$$HCl\,(g) + H_2O(\ell) \longrightarrow H_3O^+\,(aq) + Cl^-\,(aq)$$

HCl(g) is the proton donor and therefore a Brønsted-Lowry acid, while H_2O is the proton acceptor and a Brønsted-Lowry base. These two examples show that H_2O can act as both a proton donor and a proton acceptor, depending on what other substance is in the chemical reaction. A substance that can act as a proton donor or a proton acceptor is called **amphiprotic**. Water is probably the most common amphiprotic substance we will encounter, but other substances are also amphiprotic.

Example 9.3.1

Identify the Brønsted-Lowry acid and the Brønsted-Lowry base in this chemical equation.

$$\mathrm{C_6H_5OH + NH_2^- \longrightarrow C_6H_5O^- + NH_3}$$

Solution

The C_6H_5OH molecule is losing an H^+; it is the proton donor and the Brønsted-Lowry acid. The NH_2^- ion (called the amide ion) is accepting the H^+ ion to become NH_3, so it is the Brønsted-Lowry base.

Exercise 9.3.1: Aluminum Ions in Solution

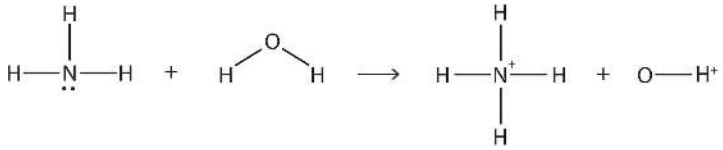
Identify the Brønsted-Lowry acid and the Brønsted-Lowry base in this chemical equation.

$$\mathrm{Al(H_2O)_6^{3+} + H_2O \longrightarrow Al(H_2O)_5(OH)^{2+} + H_3O^+}$$

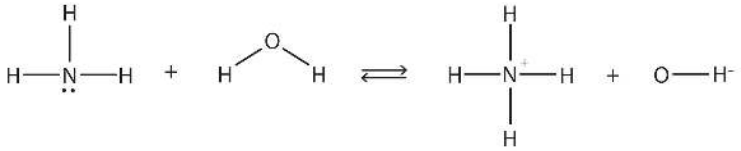
Answer

Brønsted-Lowry acid: $Al(H_2O)_6^{3+}$; Brønsted-Lowry base: H_2O

In the reaction between NH_3 and H_2O,



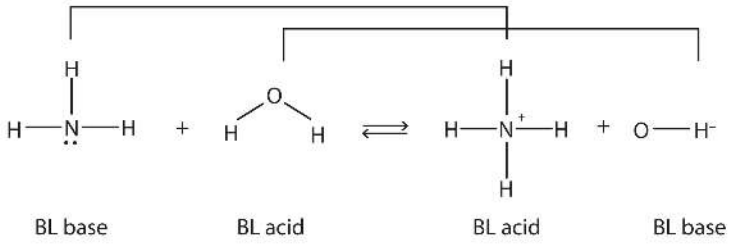
the chemical reaction does not go to completion; rather, the reverse process occurs as well, and eventually the two processes cancel out any additional change. At this point, we say the chemical reaction is at *equilibrium*. Both processes still occur, but any net change by one process is countered by the same net change of the other process; it is a *dynamic*, rather than a *static*, equilibrium. Because both reactions are occurring, it makes sense to use a double arrow instead of a single arrow:



What do you notice about the reverse reaction? The NH_4^+ ion is donating a proton to the OH^- ion, which is accepting it. This means that the NH_4^+ ion is acting as the proton donor, or Brønsted-Lowry acid, while the OH^- ion, the proton acceptor, is acting as a Brønsted-Lowry base. The reverse reaction is also a Brønsted-Lowry acid base reaction:

BL bases. NH4+ and H2O are the BL acids. lt-chem-64081" style="width: 750px; height: 173px;" width="750px" height="173px" src="/@api/deki/files/92035/3765cabac9591a0fb3dd5878f56075e2.jpg" data-quail-id="174">

This means that both reactions are acid-base reactions by the Brønsted-Lowry definition. If you consider the species in this chemical reaction, two sets of similar species exist on both sides. Within each set, the two species differ by a proton in their formulas, and one member of the set is a Brønsted-Lowry acid, while the other member is a Brønsted-Lowry base. These sets are marked here:



The two sets—NH_3/NH_4^+ and H_2O/OH^-—are called **conjugate acid-base pairs**. We say that NH_4^+ is the conjugate acid of NH_3, OH^- is the conjugate base of H_2O, and so forth. Every Brønsted-Lowry acid-base reaction can be labeled with two conjugate acid-base pairs.

✔ Example 9.3.2

Identify the conjugate acid-base pairs in this equilibrium.

$$(CH_3)_3N + H_2O \rightleftharpoons (CH_3)_3NH^+ + OH^-$$

Solution

One pair is H_2O and OH^-, where H_2O has one more H^+ and is the conjugate acid, while OH^- has one less H^+ and is the conjugate base. The other pair consists of $(CH_3)_3N$ and $(CH_3)_3NH^+$, where $(CH_3)_3NH^+$ is the conjugate acid (it has an additional proton) and $(CH_3)_3N$ is the conjugate base.

? Exercise 9.3.2

Identify the conjugate acid-base pairs in this equilibrium.

$$NH_2^- + H_2O \rightleftharpoons NH_3 + OH^-$$

Answer

H_2O (acid) and OH^- (base); NH_2^- (base) and NH_3 (acid)

✔ Chemistry is Everywhere: Household Acids and Bases

Many household products are acids or bases. For example, the owner of a swimming pool may use muriatic acid to clean the pool. Muriatic acid is another name for HCl(aq). In Section 4.6, vinegar was mentioned as a dilute solution of acetic acid [$HC_2H_3O_2$(aq)]. In a medicine chest, one may find a bottle of vitamin C tablets; the chemical name of vitamin C is ascorbic acid ($HC_6H_7O_6$).

One of the more familiar household bases is NH_3, which is found in numerous cleaning products. NH_3 is a base because it increases the OH^- ion concentration by reacting with H_2O:

$NH_3(aq) + H_2O(\ell) \rightarrow NH_4^+(aq) + OH^-(aq)$

Many soaps are also slightly basic because they contain compounds that act as Brønsted-Lowry bases, accepting protons from H_2O and forming excess OH^- ions. This is one explanation for why soap solutions are slippery.

Perhaps the most dangerous household chemical is the lye-based drain cleaner. Lye is a common name for NaOH, although it is also used as a synonym for KOH. Lye is an extremely caustic chemical that can react with grease, hair, food particles, and other substances that may build up and clog a water pipe. Unfortunately, lye can also attack body tissues and other substances in our bodies. Thus when we use lye-based drain cleaners, we must be very careful not to touch any of the solid drain cleaner or spill the water it was poured into. Safer, non-lye drain cleaners (like the one in the accompanying figure) use peroxide compounds to react on the materials in the clog and clear the drain.



Figure **9.3.1** Drain Cleaners. Drain cleaners can be made from a reactive material that is less caustic than a base. Source: Photo used by permission of Citrasolv, LLC.

Key Takeaways

- A Brønsted-Lowry acid is a proton donor; a Brønsted-Lowry base is a proton acceptor.
- Acid-base reactions include two sets of conjugate acid-base pairs.

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9.4: Strong and Weak Acids and Bases and their Salts

Learning Objectives

- Define a strong and a weak acid and base.
- Recognize an acid or a base as strong or weak.
- Determine if a salt produces an acidic or a basic solution.

Except for their names and formulas, so far we have treated all acids as equals, especially in a chemical reaction. However, acids can be very different in a very important way. Consider $\mathbf{HCl(aq)}$. When $\mathbf{HCl}$ is dissolved in $\mathbf{H_2O}$, it completely dissociates into $\mathbf{H^+(aq)}$ and $\mathbf{Cl^-(aq)}$ ions; all the $\mathbf{HCl}$ molecules become ions:

$$\mathbf{HCl \xrightarrow{100\%} H^+(aq) + Cl^-(aq)}$$

Any acid that dissociates 100% into ions is called a **strong acid**. If it does not dissociate 100%, it is a **weak acid**. Acetic acid ($\mathbf{HC_2H_3O_2}$) is an example of a weak acid:

$$\mathbf{HC_2H_3O_2 \xrightarrow{\sim 5\%} H^+(aq) + C_2H_3O_2^-(aq)}$$

Because this reaction does not go 100% to completion, it is more appropriate to write it as a reversible reaction:

$$\mathbf{HC_2H_3O_2 \rightleftharpoons H^+(aq) + C_2H_3O_2^-(aq)}$$

As it turns out, there are very few strong acids, which are given in Table **9.4.1**. If an acid is not listed here, it is a weak acid. It may be 1% ionized or 99% ionized, but it is still classified as a weak acid.

Table **9.4.1**: Strong Acids and Bases

Acids	Bases
HCl	LiOH
HBr	NaOH
HI	KOH
HNO_3	RbOH
H_2SO_4	CsOH
$HClO_3$	$Mg(OH)_2$
$HClO_4$	$Ca(OH)_2$
	$Sr(OH)_2$
	$Ba(OH)_2$

The issue is similar with bases: a **strong base** is a base that is 100% ionized in solution. If it is less than 100% ionized in solution, it is a **weak base**. There are very few strong bases (Table **9.4.1**); any base not listed is a weak base. All strong bases are OH^- compounds. So a base dependent on some other mechanism, such as NH_3 (which does not contain OH^- ions as part of its formula), will be a weak base.

Example 9.4.1

Identify each acid or base as strong or weak.

a. HCl
b. $Mg(OH)_2$
c. C_5H_5N

Solution

a. Because HCl is listed in Table **9.4.1**, it is a strong acid.
b. Because $Mg(OH)_2$ is listed in Table **9.4.1**, it is a strong base.
c. The nitrogen in C_5H_5N would act as a proton acceptor and therefore can be considered a base, but because it does not contain an OH compound, it cannot be considered a strong base; it is a weak base.

? Exercise 9.4.1

Identify each acid or base as strong or weak.

a. RbOH
b. HNO_2

Answer a

strong base

Answer b

weak acid

✓ Example 9.4.2

Write the balanced chemical equation for the dissociation of $Ca(OH)_2$ and indicate whether it proceeds 100% to products or not.

Solution

This is an ionic compound of Ca^{2+} ions and OH^- ions. When an ionic compound dissolves, it separates into its constituent ions:

$$Ca(OH)_2 \longrightarrow Ca^{2+}(aq) + 2\,OH^-(aq)$$

Because $Ca(OH)_2$ is listed in Table **9.4.1**, this reaction proceeds 100% to products.

? Exercise 9.4.2

Write the balanced chemical equation for the dissociation of hydrazoic acid (HN_3) and indicate whether it proceeds 100% to products or not.

Answer

The reaction is as follows:

$$HN_3 \longrightarrow H^+(aq) + N_3^-(aq)$$

It does not proceed 100% to products because hydrazoic acid is not a strong acid.

Certain salts will also affect the acidity or basicity of aqueous solutions because some of the ions will undergo hydrolysis, just like NH_3 does, to make a basic solution. The general rule is that salts with ions that are part of strong acids or bases will not hydrolyze, while salts with ions that are part of weak acids or bases will hydrolyze.

Consider NaCl. When it dissolves in an aqueous solution, it separates into Na^+ ions and Cl^- ions:

$$NaCl \longrightarrow Na^+(aq) + Cl^-(aq)$$

Will the $Na^+(aq)$ ion hydrolyze? If it does, it will interact with the OH^- ion to make NaOH:

$$Na^+(aq) + H_2O \longrightarrow NaOH + H^+(aq)$$

However, NaOH is a strong base, which means that it is 100% ionized in solution:

$$NaOH \longrightarrow Na^+(aq) + OH^-(aq)$$

The free $OH^-(aq)$ ion reacts with the $H^+(aq)$ ion to remake a water molecule:

$$H^+(aq) + OH^-(aq) \longrightarrow H_2O$$

The net result? There is no change, so there is no effect on the acidity or basicity of the solution from the $Na^+(aq)$ ion. What about the Cl^- ion? Will it hydrolyze? If it does, it will take an H^+ ion from a water molecule:

$$Cl^-(aq) + H_2O \longrightarrow HCl + OH^-$$

However, HCl is a strong acid, which means that it is 100% ionized in solution:

$$HCl \longrightarrow H^+(aq) + Cl^-(aq)$$

The free $H^+(aq)$ ion reacts with the $OH^-(aq)$ ion to remake a water molecule:

$$H^+(aq) + OH^-(aq) \longrightarrow H_2O$$

The net result? There is no change, so there is no effect on the acidity or basicity of the solution from the $Cl^-(aq)$ ion. Because neither ion in NaCl affects the acidity or basicity of the solution, NaCl is an example of a neutral salt. A neutral salt is any ionic compound that does not affect the acidity or basicity of its aqueous solution.

Things change, however, when we consider a salt like $NaC_2H_3O_2$. We already know that the Na^+ ion won't affect the acidity of the solution. What about the acetate ion? If it hydrolyzes, it will take an H^+ from a water molecule:

$$C_2H_3O_2^-(aq) + H_2O \rightleftharpoons HC_2H_3O_2 + OH^-(aq)$$

Does this happen? Yes, it does. Why? *Because $HC_2H_3O_2$ is a weak acid.* Any chance a weak acid has to form, it will (the same with a weak base). As some $C_2H_3O_2^-$ ions hydrolyze with H_2O to make the molecular weak acid, OH^- ions are produced. OH^- ions make solutions basic. Thus $NaC_2H_3O_2$ solutions are slightly basic, so such a salt is called a **basic salt**.

There are also salts whose aqueous solutions are slightly acidic. NH_4Cl is an example. When NH_4Cl is dissolved in H_2O, it separates into NH_4^+ ions and Cl^- ions. We have already seen that the Cl^- ion does not hydrolyze. However, the NH_4^+ ion will:

$$NH_4^+(aq) + H_2O \rightleftharpoons NH_3(aq) + H_3O^+(aq)$$

Recall from Section 12.2, that H_3O^+ ion is the hydronium ion, the more chemically proper way to represent the H^+ ion. This is the classic acid species in solution, so a solution of $NH_4^+(aq)$ ions is slightly acidic. NH_4Cl is an example of an **acid salt**. The molecule NH_3 is a weak base, and it will form when it can, just like a weak acid will form when it can.

So there are two general rules:

1. If an ion derives from a strong acid or base, it will not affect the acidity of the solution.
2. If an ion derives from a weak acid, it will make the solution basic; if an ion derives from a weak base, it will make the solution acidic.

✔ Example 9.4.3

Identify each salt as acidic, basic, or neutral.

a. KCl
b. KNO_2
c. NH_4Br

Solution

a. The ions from KCl derive from a strong acid (HCl) and a strong base (KOH). Therefore, neither ion will affect the acidity of the solution, so KCl is a neutral salt.
b. Although the K^+ ion derives from a strong base (KOH), the NO_2^- ion derives from a weak acid (HNO_2). Therefore the solution will be basic, and KNO_2 is a basic salt.

c. Although the Br^- ions derive from a strong acid (HBr), the NH_4^+ ion derives from a weak base (NH_3), so the solution will be acidic, and NH_4Br is an acidic salt.

? Exercise 9.4.3

Identify each salt as acidic, basic, or neutral.

A. $(C_5H_5NH)Cl$
B. Na_2SO_3

Answer a

acidic

Answer b

basic

Some salts are composed of ions that come from both weak acids and weak bases. The overall effect on an aqueous solution depends on which ion exerts more influence on the overall acidity. We will not consider such salts here.

Summary

- Strong acids and bases are 100% ionized in aqueous solution.
- Weak acids and bases are less than 100% ionized in aqueous solution.
- Salts of weak acids or bases can affect the acidity or basicity of their aqueous solutions.

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9.5: Autoionization of Water

Learning Objectives

- Describe the autoionization of water.
- Calculate the concentrations of H^+ and OH^- in solutions, knowing the other concentration.

We have already seen that H_2O can act as an acid or a base:

$$NH_3 + H_2O \rightarrow NH_4^+ + OH^- \text{ } (H_2O \text{ acts as an acid})$$

$$HCl + H_2O \rightarrow H_3O^+ + Cl^- \text{ } (H_2O \text{ acts as a base})$$

It may not be surprising to learn, then, that within any given sample of water, some H_2O molecules are acting as acids, and other H_2O molecules are acting as bases. The chemical equation is as follows:

$$H_2O + H_2O \rightarrow H_3O^+ + OH^-$$

This occurs only to a very small degree: only about 6 in 10^8 H_2O molecules are participating in this process, which is called the **autoionization of water**. At this level, the concentration of both $H^+(aq)$ and $OH^-(aq)$ in a sample of pure H_2O is about 1.0×10^{-7} M. If we use square brackets—[ ]—around a dissolved species to imply the molar concentration of that species, we have

$$[H^+] = [OH^-] = 1.0 \times 10^{-7} \text{ M}$$

for *any* sample of pure water because H_2O can act as both an acid and a base. The product of these two concentrations is 1.0×10^{-14}:

$$[H^+] \times [OH^-] = (1.0 \times 10^{-7})(1.0 \times 10^{-7}) = 1.0 \times 10^{-14}$$

In acids, the concentration of $H^+(aq)$—$[H^+]$—is greater than 1.0×10^{-7} M, while for bases the concentration of $OH^-(aq)$—$[OH^-]$—is greater than 1.0×10^{-7} M. However, the *product* of the two concentrations—$[H^+][OH^-]$—is *always* equal to 1.0×10^{-14}, no matter whether the aqueous solution is an acid, a base, or neutral:

$$[H^+][OH^-] = 1.0 \times 10^{-14}$$

This value of the product of concentrations is so important for aqueous solutions that it is called the **autoionization constant of water** and is denoted K_W:

$$K_W = [H^+][OH^-] = 1.0 \times 10^{-14}$$

This means that if you know $[H^+]$ for a solution, you can calculate what $[OH^-]$ has to be for the product to equal 1.0×10^{-14}, or if you know $[OH^-]$, you can calculate $[H^+]$. This also implies that as one concentration goes up, the other must go down to compensate so that their product always equals the value of K_W.

Example 9.5.1

What is $[OH^-]$ of an aqueous solution if $[H^+]$ is 1.0×10^{-4} M?

Solution

Using the expression and known value for K_W,

$$K_W = [H^+][OH^-] = 1.0 \times 10^{-14} = (1.0 \times 10^{-4})[OH^-]$$

We solve by dividing both sides of the equation by 1.0×10^{-4}:

$$[OH^-] = \frac{1.0 \times 10^{-14}}{1.0 \times 10^{-4}} = 1.0 \times 10^{-10} M$$

It is assumed that the concentration unit is molarity, so $[OH^-]$ is 1.0×10^{-10} M.

Exercise 9.5.1

What is $[H^+]$ of an aqueous solution if $[OH^-]$ is 1.0×10^{-9} M?

Answer

1.0×10^{-5} M

When you have a solution of a particular acid or base, you need to look at the formula of the acid or base to determine the number of H^+ or OH^- ions in the formula unit because $[H^+]$ or $[OH^-]$ may not be the same as the concentration of the acid or base itself.

Example 9.5.2

What is $[H^+]$ in a 0.0044 M solution of $Ca(OH)_2$?

Solution

We begin by determining $[OH^-]$. The concentration of the solute is 0.0044 M, but because $Ca(OH)_2$ is a strong base, there are two OH^- ions in solution for every formula unit dissolved, so the actual $[OH^-]$ is two times this, or 2×0.0044 M = 0.0088 M. Now we can use the K_W expression:

$$[H^+][OH^-] = 1.0 \times 10^{-14} = [H^+](0.0088\ M)$$

Divide both sides by 0.0088:

$$[H^+] = \frac{1.0 \times 10^{-14}}{(0.0088)} = 1.1 \times 10^{-12} M$$

$[H^+]$ has decreased significantly in this basic solution.

Exercise 9.5.2

What is $[OH^-]$ in a 0.00032 M solution of H_2SO_4? (Hint: assume both H^+ ions ionize.)

Answer

1.6×10^{-11} M

For strong acids and bases, $[H^+]$ and $[OH^-]$ can be determined directly from the concentration of the acid or base itself because these ions are 100% ionized by definition. However, for weak acids and bases, this is not so. The degree, or percentage, of ionization would need to be known before we can determine $[H^+]$ and $[OH^-]$.

Example 9.5.3

A 0.0788 M solution of $HC_2H_3O_2$ is 3.0% ionized into H^+ ions and $C_2H_3O_2^-$ ions. What are $[H^+]$ and $[OH^-]$ for this solution?

Solution

Because the acid is only 3.0% ionized, we can determine $[H^+]$ from the concentration of the acid. Recall that 3.0% is 0.030 in decimal form:

$[H^+] = 0.030 \times 0.0788 = 0.00236$ M

With this $[H^+]$, then $[OH^-]$ can be calculated as follows:

$$[OH^-] = \frac{1.0 \times 10^{-14}}{0.00236} = 4.2 \times 10^{-12} M$$

This is about 30 times higher than would be expected for a strong acid of the same concentration.

? Exercise 9.5.3

A 0.0222 M solution of pyridine (C_5H_5N) is 0.44% ionized into pyridinium ions ($C_5H_5NH^+$) and OH^- ions. What are $[OH^-]$ and $[H^+]$ for this solution?

Answer

$[OH^-] = 9.77 \times 10^{-5}$ M; $[H^+] = 1.02 \times 10^{-10}$ M

Summary

In any aqueous solution, the product of [H+] and [OH−] equals $\mathbf{1.0 \times 10^{-14}}$ (at room temperature).

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9.6: The pH Scale

Learning Objectives

- Define *pH*.
- Determine the pH of acidic and basic solutions.

As we have seen, $[H^+]$ and $[OH^-]$ values can be markedly different from one aqueous solution to another. So chemists defined a new scale that succinctly indicates the concentrations of either of these two ions.

pH is commonly defined as a logarithmic function of $[H^+]$:

$$\mathbf{pH = -\log[H^+]} \tag{9.6.1}$$

pH is usually (but not always) between 0 and 14. Knowing the dependence of pH on $[H^+]$, we can summarize as follows:

- If pH < 7, then the solution is acidic.
- If pH = 7, then the solution is neutral.
- If pH > 7, then the solution is basic.

This is known as the pH scale and is the range of values from 0 to 14 that describes the acidity or basicity of a solution. You can use pH to quickly determine whether a given aqueous solution is acidic, basic, or neutral.

Example 9.6.1

Label each solution as acidic, basic, or neutral based only on the stated pH.

a. milk of magnesia, pH = 10.5
b. pure water, pH = 7
c. wine, pH = 3.0

Solution

a. With a pH greater than 7, milk of magnesia is basic. (Milk of magnesia is largely $Mg(OH)_2$.)
b. Pure water, with a pH of 7, is neutral.
c. With a pH of less than 7, wine is acidic.

Exercise 9.6.1

Identify each substance as acidic, basic, or neutral based only on the stated pH.

1. human blood, pH = 7.4
2. household ammonia, pH = 11.0
3. cherries, pH = 3.6

Answers

1. basic
2. basic
3. acidic

Table **9.6.1** gives the typical pH values of some common substances. Note that several food items are on the list, and most of them are acidic.

Table **9.6.1** Typical pH Values of Various Substances*

Substance	pH
stomach acid	1.7
lemon juice	2.2
vinegar	2.9
soda	3.0
wine	3.5
coffee, black	5.0
milk	6.9
pure water	7.0
blood	7.4
seawater	8.5
milk of magnesia	10.5
ammonia solution	12.5
1.0 M NaOH	14.0
*Actual values may vary depending on conditions	

pH is a *logarithmic* scale. A solution that has a pH of 1.0 has 10 times the $[H^+]$ as a solution with a pH of 2.0, which in turn has 10 times the $[H^+]$ as a solution with a pH of 3.0 and so forth.

Using the definition of pH (Equation 9.6.1), it is also possible to calculate $[H^+]$ (and $[OH^-]$) from pH and vice versa. The general formula for determining $[H^+]$ from pH is as follows:

$$[H^+] = 10^{-pH}$$

Key Takeaways

- pH is a logarithmic function of $[H^+]$.
- $[H^+]$ can be calculated directly from pH.
- pOH is related to pH and can be easily calculated from pH.

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9.7: Acid-Base Titrations

Learning Objectives

- Describe a titration experiment.
- Explain what an indicator does.
- Perform a titration calculation correctly.

The reaction of an acid with a base to make a salt and water is a common reaction in the laboratory, partly because many compounds can act as acids or bases. Another reason that acid-base reactions are so prevalent is because they are often used to determine quantitative amounts of one or the other. Performing chemical reactions quantitatively to determine the exact amount of a reagent is called a **titration**. A titration can be performed with almost any chemical reaction for which the balanced chemical equation is known. Here, we will consider titrations that involve acid-base reactions.

In a titration, one reagent has a known concentration or amount, while the other reagent has an unknown concentration or amount. Typically, the known reagent (the **titrant**) is added to the unknown quantity and is dissolved in solution. The unknown amount of substance (the **analyte**) may or may not be dissolved in solution (but usually is). The titrant is added to the analyte using a precisely calibrated volumetric delivery tube called a burette (also spelled buret; see Figure 9.7.1). The burette has markings to determine how much volume of solution has been added to the analyte. When the reaction is complete, it is said to be at the **equivalence point**; the number of moles of titrant can be calculated from the concentration and the volume, and the balanced chemical equation can be used to determine the number of moles (and then concentration or mass) of the unknown reactant.



Figure 9.7.1 Equipment for Titrations. A burette is a type of liquid dispensing system that can accurately indicate the volume of liquid dispensed.

For example, suppose 25.66 mL (or 0.02566 L) of 0.1078 M HCl was used to titrate an unknown sample of NaOH. What mass of NaOH was in the sample? We can calculate the number of moles of HCl reacted:

$$\text{\# mol HCl} = (0.02566\ \text{L})(0.1078\ \text{M}) = 0.002766\ \text{mol HCl}$$

We also have the balanced chemical reaction between HCl and NaOH:

$$\text{HCl} + \text{NaOH} \rightarrow \text{NaCl} + \text{H}_2\text{O}$$

So we can construct a conversion factor to convert to number of moles of NaOH reacted:

$$0.002766\ \cancel{mol\ HCl} \times \frac{1\ mol\ NaOH}{1\ \cancel{mol\ HCl}} = 0.002766\ mol\ NaOH$$

Then we convert this amount to mass, using the molar mass of NaOH (40.00 g/mol):

$$0.002766\ \cancel{mol\ HCl} \times \frac{40.00\ g\ NaOH}{1\ \cancel{mol\ HCl}} = 0.1106\ g\ NaOH$$

This type of calculation is performed as part of a titration.

Example 9.7.1

What mass of $Ca(OH)_2$ is present in a sample if it is titrated to its equivalence point with 44.02 mL of 0.0885 M HNO_3? The balanced chemical equation is as follows:

$$2HNO_3 + Ca(OH)_2 \rightarrow Ca(NO_3)_2 + 2H_2O$$

Solution

In liters, the volume is 0.04402 L. We calculate the number of moles of titrant:

moles HNO_3 = (0.04402 L)(0.0885 M) = 0.00390 mol HNO_3

Using the balanced chemical equation, we can determine the number of moles of $Ca(OH)_2$ present in the analyte:

$$0.00390\ \cancel{mol\ HNO_3} \times \frac{1\ mol\ Ca(OH)_2}{2\ \cancel{mol\ HNO_3}} = 0.00195\ mol\ Ca(OH)_2$$

Then we convert this to a mass using the molar mass of $Ca(OH)_2$:

$$0.00195\ \cancel{mol\ Ca(OH)_2} \times \frac{74.1\ g\ Ca(OH)_2}{\cancel{mol\ Ca(OH)_2}} = 0.144\ g\ Ca(OH)_2$$

? Exercise 9.7.1

What mass of $H_2C_2O_4$ is present in a sample if it is titrated to its equivalence point with 18.09 mL of 0.2235 M NaOH? The balanced chemical reaction is as follows:

$$H_2C_2O_4 + 2\,NaOH \longrightarrow Na_2C_2O_4 + 2\,H_2O$$

Answer

0.182 g

How does one know if a reaction is at its equivalence point? Usually, the person performing the titration adds a small amount of an **indicator**, a substance that changes color depending on the acidity or basicity of the solution. Because different indicators change colors at different levels of acidity, choosing the correct one is important in performing an accurate titration.

Summary

A titration is the quantitative reaction of an acid and a base. Indicators are used to show that all of the analyte has reacted with the titrant.

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9.8: Buffers

Learning Objectives

- Define *buffer*.
- Correctly identify the two components of a buffer.

As indicated in Section 12.5, weak acids are relatively common, even in the foods we eat. But we occasionally encounter a strong acid or base, such as stomach acid, which has a strongly acidic pH of 1.7. By definition, strong acids and bases can produce a relatively large amount of H^+ or OH^- ions and consequently have marked chemical activities. In addition, very small amounts of strong acids and bases can change the pH of a solution very quickly. If 1 mL of stomach acid [approximated as 0.1 M HCl(aq)] were added to the bloodstream and no correcting mechanism were present, the pH of the blood would decrease from about 7.4 to about 4.7—a pH that is not conducive to continued living. Fortunately, the body has a mechanism for minimizing such dramatic pH changes.

This mechanism involves a **buffer**, a solution that resists dramatic changes in pH. Buffers do so by being composed of certain pairs of solutes: either a weak acid plus a salt derived from that weak acid, or a weak base plus a salt of that weak base. For example, a buffer can be composed of dissolved $HC_2H_3O_2$ (a weak acid) and $NaC_2H_3O_2$ (the salt derived from that weak acid). Another example of a buffer is a solution containing NH_3 (a weak base) and NH_4Cl (a salt derived from that weak base).

Let us use an $HC_2H_3O_2/NaC_2H_3O_2$ buffer to demonstrate how buffers work. If a strong base—a source of $OH^-(aq)$ ions—is added to the buffer solution, those OH^- ions will react with the $HC_2H_3O_2$ in an acid-base reaction:

$$\mathbf{HC_2H_3O_2\,(aq) + OH^-\,(aq) \rightarrow H_2O(\ell) + C_2H_3O_2^-\,(aq)} \tag{9.8.1}$$

Rather than changing the pH dramatically by making the solution basic, the added OH^- ions react to make H_2O, so the pH does not change much.

If a strong acid—a source of H^+ ions—is added to the buffer solution, the H^+ ions will react with the anion from the salt. Because $HC_2H_3O_2$ is a weak acid, it is not ionized much. This means that if lots of H^+ ions and $C_2H_3O_2^-$ ions are present in the same solution, they will come together to make $HC_2H_3O_2$:

$$\mathbf{H^+\,(aq) + C_2H_3O_2^-\,(aq) \rightarrow HC_2H_3O_2\,(aq)} \tag{9.8.2}$$

Rather than changing the pH dramatically and making the solution acidic, the added H^+ ions react to make molecules of a weak acid. Figure **9.8.1** illustrates both actions of a buffer.

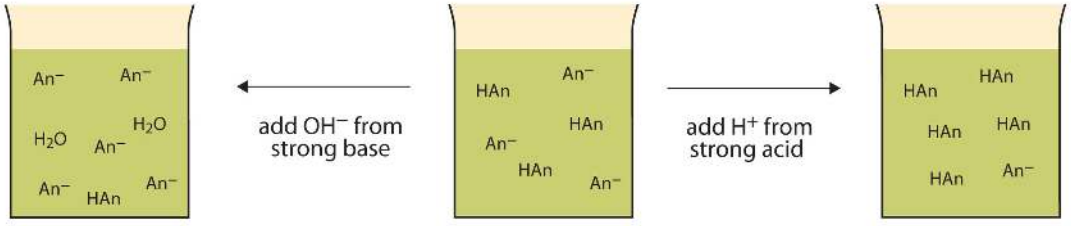


Figure **9.8.1** The Actions of Buffers. Buffers can react with both strong acids (top) and strong bases (side) to minimize large changes in pH.

Buffers made from weak bases and salts of weak bases act similarly. For example, in a buffer containing NH_3 and NH_4Cl, NH_3 molecules can react with any excess H^+ ions introduced by strong acids:

$$\mathbf{NH_3\,(aq) + H^+\,(aq) \rightarrow NH_4^+\,(aq)} \tag{9.8.3}$$

while the **ammonium ion** ($\mathbf{NH_4^+\,(aq)}$) can react with any hydroxide ions introduced by strong bases:

$$\mathbf{NH_4^+\,(aq) + OH^-\,(aq) \rightarrow NH_3\,(aq) + H_2O(\ell)} \tag{9.8.4}$$

Example 9.8.1:

Which combinations of compounds can make a buffer solution?

1. $HCHO_2$ and $NaCHO_2$
2. HCl and NaCl
3. CH_3NH_2 and CH_3NH_3Cl
4. NH_3 and NaOH

Solution

1. $HCHO_2$ is formic acid, a weak acid, while $NaCHO_2$ is the salt made from the anion of the weak acid (the formate ion [CHO_2^-]). The combination of these two solutes would make a buffer solution.
2. HCl is a strong acid, not a weak acid, so the combination of these two solutes would not make a buffer solution.
3. CH_3NH_2 is methylamine, which is like NH_3 with one of its H atoms substituted with a CH_3 group. Because it is not listed in Table **9.8.1**, we can assume that it is a weak base. The compound CH_3NH_3Cl is a salt made from that weak base, so the combination of these two solutes would make a buffer solution.
4. NH_3 is a weak base, but NaOH is a strong base. The combination of these two solutes would not make a buffer solution.

Exercise 9.8.1

Which combinations of compounds can make a buffer solution?

1. $NaHCO_3$ and NaCl
2. H_3PO_4 and NaH_2PO_4
3. NH_3 and $(NH_4)_3PO_4$
4. NaOH and NaCl

Answer a

No. Need a weak acid or base and a salt of its conjugate base or acid.

Answer b

Yes. Need a weak acid or base and a salt of its conjugate base or acid.

Answer c

Yes.

Answer d

No. Need a weak base and weak acid.

Buffers work well only for limited amounts of added strong acid or base. Once either solute is completely reacted, the solution is no longer a buffer, and rapid changes in pH may occur. We say that a buffer has a certain **capacity**. Buffers that have more initial solute dissolved within them have larger capacities, as might be expected.

Human blood has a buffering system to minimize extreme changes in pH. One buffer in blood is based on the presence of HCO_3^- and H_2CO_3 [the second compound is another way to write $CO_2(aq)$]. With this buffer present, even if some stomach acid were to find its way directly into the bloodstream, the change in the pH of blood would be minimal. Inside many of the body's cells, there is a buffering system based on phosphate ions.

Food and Drink Application: the Acid that Eases Pain

Although medicines are not exactly "food and drink," we do ingest them, so let's take a look at an acid that is probably the most common medicine: acetylsalicylic acid, also known as aspirin. Aspirin is well known as a pain reliever and antipyretic (fever reducer).

The structure of aspirin is shown in the accompanying figure. The acid part is circled; it is the H atom in that part that can be donated as aspirin acts as a Brønsted-Lowry acid. Because it is not given in Table **9.8.1**, acetylsalicylic acid is a weak acid. However, it is still an acid, and given that some people consume relatively large amounts of aspirin daily, its acidic nature can cause problems in the stomach lining, despite the stomach's defenses against its own stomach acid.

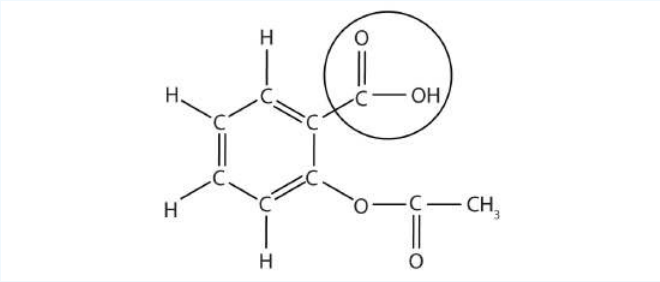


Figure **9.8.2**: The Molecular Structure of Aspirin. The circled atoms are the acid part of the molecule.

Because the acid properties of aspirin may be problematic, many aspirin brands offer a "buffered aspirin" form of the medicine. In these cases, the aspirin also contains a buffering agent—usually MgO—that regulates the acidity of the aspirin to minimize its acidic side effects.

As useful and common as aspirin is, it was formally marketed as a drug starting in 1899. The US Food and Drug Administration (FDA), the governmental agency charged with overseeing and approving drugs in the United States, wasn't formed until 1906. Some have argued that if the FDA had been formed before aspirin was introduced, aspirin may never have gotten approval due to its potential for side effects—gastrointestinal bleeding, ringing in the ears, Reye's syndrome (a liver problem), and some allergic reactions. However, recently aspirin has been touted for its effects in lessening heart attacks and strokes, so it is likely that aspirin will remain on the market.

Summary

A buffer is a solution that resists sudden changes in pH.

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9.9: Acids, Bases, pH and Buffers- Questions

Sacramento City College
CHEM 309: General, Organic and Biochemistry
Prof. Dianne Bennett

Template:HideTOC

ALL questions listed must be answered to earn credit for completing the text homework. Yes, even the Additional Exercises if applicable.

Properties of Acids and Bases

(01) According to the Arrhenius definition of acids, an acid gives off what in solution?

According to the Bronsted-Lowry, what is the definition of an acid? What is the definition of a base?

(02) For every given acid or base, write the equation of their reactions with water when they donate or accept one hydrogen ion.

a. Hydrocyanic acid
b. Carbonate ion
c. Ammonium ion
d. Sulfuric acid
e. Acetic acid

Conjugate Acids and Bases

(03) For each of the following acids, determine the form of their conjugate bases.

a. HSO_4^-
b. H_2CO_3
c. HF
d. HPO_4^{2-}
e. HCOOH

(04) For each of the following bases, determine the form of their conjugate acids.

a. Br^-
b. NO_3^-
c. S^{2-}
d. NH_3
e. HCO_3^-

Strengths of Acids and Bases

(05) Nitric acid, HNO_3, is a strong acid. Define 'strong' acid, and write the equation of nitric acid reacting with water. How does this equation differ from the reaction of a weak acid, such as hydrosulfuric acid (H_2S)? Sketch the reaction of hydrosulfuric acid with water to see the difference clearly.

(06) Lithium hydroxide, LiOH, is a strong base. Define 'strong base' and write the equation of lithium hydroxide reacting with water. Sketch an example of the reaction of a weak base with water and compare it to the strong base reaction. How do

they differ?

(07) Phosphoric acid is one of the few acids that has three acidic hydrogens, and is called 'triprotic'. Write a chemical equation for phosphoric acid reacting with water and losing one of its hydrogens. Using the products from the first equation, write another equation to show the second hydrogen being lost. Continue in this fashion to show the last hydrogen being lost.

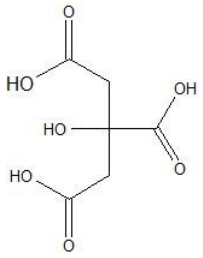
(08) For each chemical reaction, determine whether they are representative of the dissociation reaction of a strong acid, a weak acid, a strong base, or a weak base.

a. $Na(OH)_{(aq)} + H_2O_{(l)} \rightarrow Na^+_{(aq)} + OH^-_{(aq)}$
b. $HF_{(aq)} + H_2O_{(l)} \rightleftharpoons H_3O^+_{(aq)} + F^-_{(aq)}$
c. $H_2PO^-_{4\ (aq)} + H_2O_{(l)} \rightleftharpoons H_3PO_{4\ (aq)} + OH^-_{(aq)}$
d. $H_2PO^-_{4\ (aq)} + H_2O_{(l)} \rightleftharpoons HPO^{2-}_{4\ (aq)} + H_3O^+_{(aq)}$
e. $HCl_{(aq)} + H_2O_{(l)} \rightarrow Cl^-_{(aq)} + H_3O^+_{(aq)}$

(09) Perform the dissociation reactions for each of the given acids. Use the reaction arrow to tell whether they are strong acids or weak acids. For diprotic acids, show the loss of the first hydrogen ion. Hint: What are the six strong acids?

a. $HClO_4$
b. HSCN
c. HBr
d. H_2CO_3
e. CH_3COOH

(10) Study the following structure of citric acid. How many acidic groups are contained in this molecule? Circle the acidic hydrogens that can be removed by interactions with bases. Write the three consecutive dissociation reactions using bond-line structures, one reaction for each hydrogen being removed (one at a time).



Acid-Base Equilibria

(11) What is occurring when a reaction is said to be in equilibrium? Write an equation in which water **is in equilibrium with a proton and hydroxide. Are the concentrations changing when they are in equilibrium or do they remain constant? Why is using the double-arrows to separate products from reactants so important in equilibrium reactions?**

Le Chatelier's Principle

(12) Observe the following reaction and answer the questions beneath.

$$CH_3COOH_{(aq)} + H_2O_{(l)} \rightleftharpoons H_3O^+_{(aq)} + CH_3COO^-_{(aq)} \tag{9.9.1}$$

a. What will the effect on the equilibrium be if the concentration of hydronium ions is increased?
b. What will the effect on the equilibrium be if the concentration of acetate is decreased?
c. If you increase the concentration of water, will the equilibrium shift left or right?
d. If you decrease the concentration of acetic acid, will the equilibrium shift left or right?

(13) A generic example of an equilibrium reaction is shown below. Answer the following questions about what direction equilibrium shift according to Le Chatelier's principle.

$$A + B \rightleftharpoons C + D + \text{heat} \tag{9.9.2}$$

a. Removing some of compound A
b. Increasing the temperature
c. Adding more of compound D
d. Increasing concentration of compound B
e. Decreasing the temperature

(14) Some processes involve multiple equilibrium equations put together. For example, the carbonation effect that creates soda water involves more than one set of compounds separated by equilibrium arrows, as shown below.

$$CO_{2\,(g)} + H_2O_{(l)} \rightleftharpoons H_2CO_{3\,(aq)} \rightleftharpoons HCO^-_{3\,(aq)} + H^+_{(aq)} \tag{9.9.3}$$

a. During hypoventilation, what happens to the hydrogen ion concentration?

b. During hyperventilation, what happens to the hydrogen ion concentration?

Acid-Base Neutralization Reactions

(15) Write out the neutralization reactions for the following pairs. Make sure to balance the equations as necessary.

a. $Ba(OH)_2$ and HNO_3

b. $Ca(OH)_2$ and H_2SO_4

c. $RbOH$ and HI

d. KOH and $HClO_4$

e. $Mg(OH)_2$ and HBr

pH

(16) Examine the following pH measures and tell whether they are in the range to be considered acidic, basic or neutral.

a. 6.8
b. 13.5
c. 1.9
d. 4.2
e. 9.7

(17) Using the formula for converting concentration into pH, determine whether each of the following molarities are acidic, basic or neutral. Remember, -log[H^+]

a. 1.0×10^{-7} M H^+
b. 4.7×10^{-12} M H^+
c. 6.4×10^{-4} M H^+
d. 7.3×10^{-10} M H^+
e. 9.8×10^{-2} M H^+

(18) Fill in the blank portions of the table.

$[H_3O^+]$	$[OH^-]$	pH	Acidic, Basic or Neutral
1.0×10^{-1}			
	1.0×10^{-4}		
1.0×10^{-7}			
	1.0×10^{-9}		
1.0×10^{-13}			

(19) Given the following sets of information, calculate the requested quantities for each problem.

a. $[H_3O^+] = 4.1 \times 10^{-4}$ M. Find pH, and $[OH^-]$
b. $[OH^-] = 6.6 \times 10^{-9}$ M. Find pOH, and $[H_3O^+]$
c. pH = 9.0. Find $[H_3O^+]$, $[OH^-]$ and pOH
d. pOH = 12.5. Find $[OH^-]$, and $[H_3O^+]$
e. pOH = 7.0. Find $[H_3O^+]$, $[OH^-]$ and pH

Buffers

(20) What is the definition of a buffer solution? Determine whether or not each pair below can be used to prepare a buffer solution.

a. HI and H_2SO_4
b. CH_3COOH and CH_3COOK
c. $Ca(OH)_2$ and H_2O
d. acetic acid and methylamine
e. NH_3 and HNO_3

(21) Carbonic acid and bicarbonate ion are an conjugate aicd-base pairs. For each of the following compounds, would the carbonic acid or bicarbonate be more likely to react with them and serve as a buffer to prevent pH change?

a. HBr
b. LiOH
c. NH_4^+
d. $HCOO^-$
e. CH_3NH_2

(22) A person who spends a day swimming and diving underwater requires them to hold their breath for long stretches and to do this repeatedly. This is a contrast to the condition of hyperventilation where breaths are taken rapidly. If a person is holding in their inhaled breaths with few breaks in between, what effect does this have on the CO_2 levels in their body? Do they increase or decrease? What effect does this increase or decrease have on the pH of the bloodstream?

$$CO_{2\,(g)} + H_2O_{(l)} \rightleftharpoons H_2CO_{3\,(aq)} \rightleftharpoons HCO^-_{3\,(aq)} + H^+_{(aq)} \tag{9.9.4}$$

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CHAPTER OVERVIEW

10: 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.

10.1: Prelude to Amino Acids, Proteins, and Enzymes
10.2: Properties of Amino Acids
10.3: Reactions of Amino Acids
10.4: Structure and Function - Amino Acids
10.5: Peptides
10.6: Proteins
10.7: Proteins
10.8: Enzymes
10.9: Enzyme Activity
10.10: Enzyme Action
10.11: Enzyme Inhibition
10.12: Enzyme Cofactors and Vitamins
10.13: Basic Principles of Catalysis
10.14: Control of Enzymatic Activity
10.15: Mechanisms of Catalysis
10.E: Amino Acids, Proteins, and Enzymes (Exercises)
10.S: Amino Acids, Proteins, and Enzymes (Summary)

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10.1: 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 **10.1.1**: 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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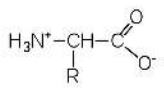
10.2: Properties of Amino Acids

Learning Objectives

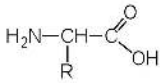
- To recognize amino acids and classify them based on the characteristics of their side chains.

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

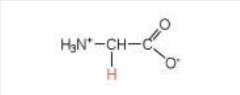
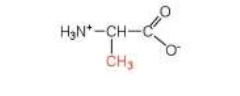
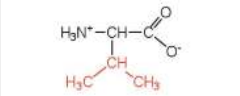
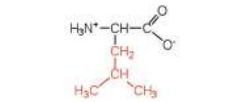
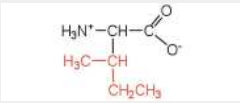
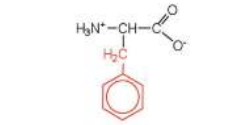
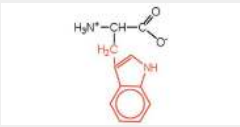
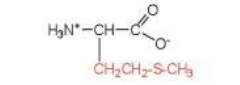
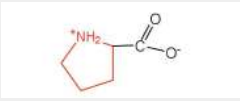
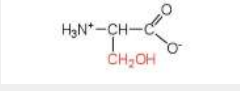
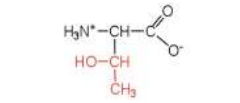
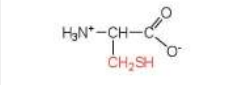


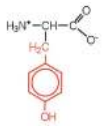
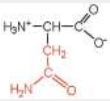
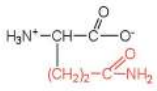
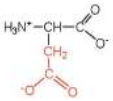
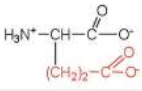
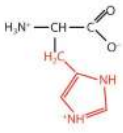
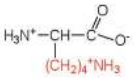
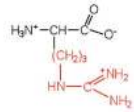
α-Amino acid drawn as an uncharged molecule; not an accurate respresentation of amino acid structure

Classification

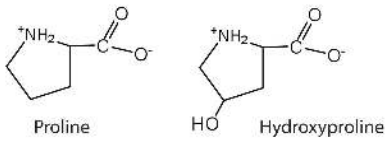
In addition to the amino and carboxyl groups, amino acids have a side chain or R group attached to the α-carbon. Each amino acid has unique characteristics arising from the size, shape, solubility, and ionization properties of its R group. As a result, the side chains of amino acids exert a profound 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 **10.2.1**.

Table **10.2.1**: Common Amino Acids Found in Proteins

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*

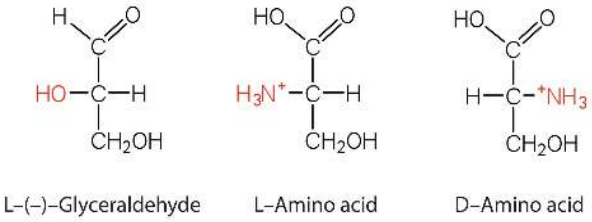
Common Name	Abbreviation	Structural Formula (at pH 6)	Molar Mass	Distinctive Feature
tyrosine	tyr (Y)		181	also classified as an aromatic amino acid
asparagine	asn (N)		132	the amide of aspartic acid
glutamine	gln (Q)		146	the amide of glutamic acid
Amino acids with a negatively charged R group				
aspartic 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 **10.2.1** 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.



L–(–)–Glyceraldehyde L–Amino acid D–Amino acid

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.

Exercises

1. What is the general structure of an α-amino acid?
2. Identify the amino acid that fits each description.

a. also known as aspartate

b. almost as strong a base as sodium hydroxide

c. does not have a chiral carbon

3. Write the side chain of each amino acid.

a. serine
b. arginine
c. phenylalanine

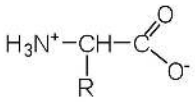
4. Draw the structure for each amino acid.

a. alanine
b. cysteine
c. histidine

5. Identify an amino acid whose side chain contains a(n)

a. amide functional group.
b. aromatic ring.
c. carboxyl group.

Answer to #1:



Answer to #2:

a) aspartic acid

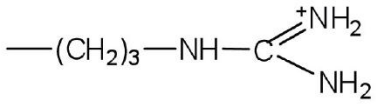
b) arginine

c) glycine

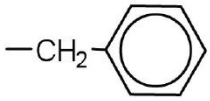
Answer to #3

a) $-CH_2-OH$

b)

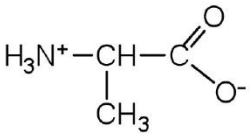


c)

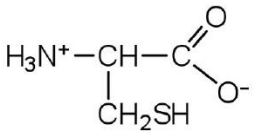


Answer to #4

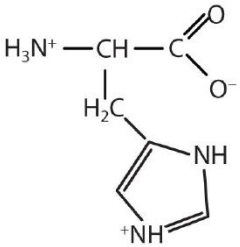
a)



b)



c)



Answer to # 5

a. asparagine or glutamine

b. phenylalanine, tyrosine, or tryptophan

c. aspartic acid or glutamic acid

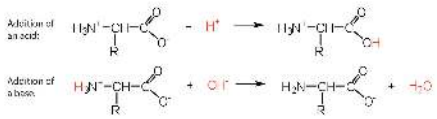
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10.3: Reactions of Amino Acids

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.

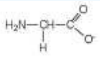


Example 10.3.1

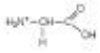
a. Draw the structure for the anion formed when glycine (at neutral pH) reacts with a base.
b. Draw the structure for the cation formed when glycine (at neutral pH) reacts with an acid.

Solution

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



b. The acid adds H^+ to the carboxylate group.



Exercise 10.3.1

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 **10.3.1**).

Table **10.3.1**: ExampIes of Some Representative Amino Acids

Amino Acid	Classification
alanine	nonpolar
valine	nonpolar
serine	polar, uncharged
threonine	polar, uncharged
arginine	positively charged (basic)
histidine	positively charged (basic)
lysine	positively charged (basic)
aspartic acid	negatively charged (acidic)
glutamic acid	negatively charged (acidic)

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.





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).

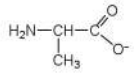
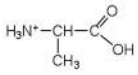
Concept Review Exercises

1. Define each term.
   a. zwitterion

b. isoelectric point

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

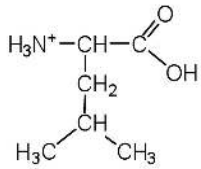
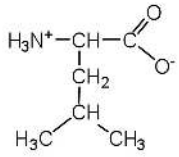
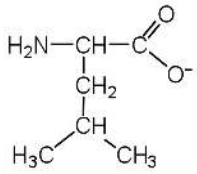
Answers

1. a. an electrically neutral compound that contains both negatively and positively charged groups
   b. the pH at which a given amino acid exists in solution as a zwitterion
2. 
3. 

Exercises

1. Draw the structure of leucine and determine the charge on the molecule in a(n)
   a. acidic solution (pH = 1).
   b. neutral solution (pH = 7).
   c. a basic solution (pH = 11)
2. Draw the structure of isoleucine and determine the charge on the molecule in a(n)
   a. acidic solution (pH = 1).
   b. neutral solution (pH = 7).
   c. basic solution (pH = 11).

Answer

1. a. 
   b. 
   c. 

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10.4: Structure and Function - Amino Acids

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All of the proteins on the face of the earth are made up of the same 20 amino acids. Linked together in long chains called polypeptides, amino acids are the building blocks for the vast assortment of proteins found in all living cells.



"It is one of the more striking generalizations of biochemistry ...that the twenty amino acids and the four bases, are, with minor reservations, the same throughout Nature." - Francis Crick

All amino acids have the same basic structure, which is shown in Figure 2.1. At the “center” of each amino acid is a carbon called the α carbon and attached to it are four groups - a hydrogen, an α- carboxyl group, an α-amine group, and an R-group, sometimes referred to as a side chain. The α carbon, carboxyl, and amino groups are common to all amino acids, so the R-group is the only unique feature in each amino acid. (A minor exception to this structure is that of proline, in which the end of the R-group is attached to the α-amine.) With the exception of glycine, which has an R-group consisting of a hydrogen atom, all of the amino acids in proteins have four different groups attached to them and consequently can exist in two mirror image forms, L and D. With only very minor exceptions, every amino acid found in cells and in proteins is in the L configuration.

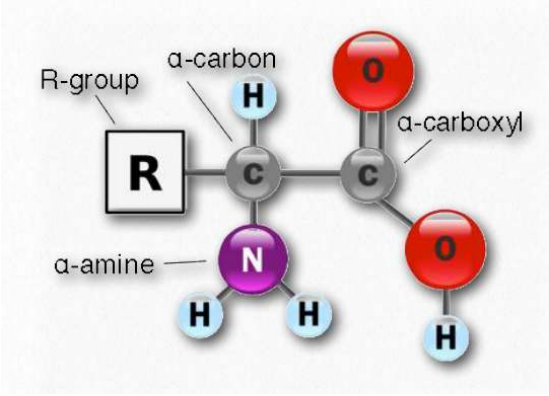


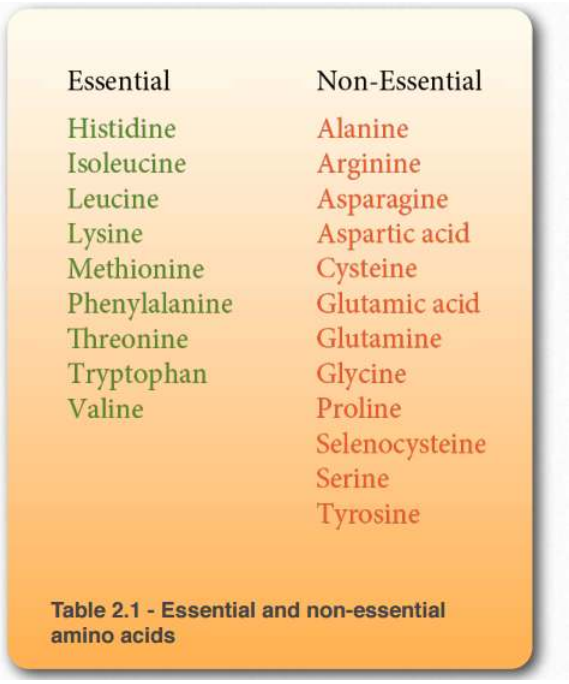
Figure 2.1 - General amino acid structure

Essential and non-essential

Nutritionists divide amino acids into two groups - essential amino acids (must be in the diet because cells can’t synthesize them) and non-essential amino acids (can be made by cells). This classification of amino acids has little to do with the structure of amino

acids. Essential amino acids vary considerable from one organism to another and even differ in humans, depending on whether they are adults or children. Table 2.1 shows essential and non-essential amino acids in humans.

Some amino acids that are normally nonessential, may need to be obtained from the diet in certain cases. Individuals who do not synthesize sufficient amounts of arginine, cysteine, glutamine, proline, selenocysteine, serine, and tyrosine, due to illness, for example, may need dietary supplements containing these amino acids.



Essential	Non-Essential
Histidine	Alanine
Isoleucine	Arginine
Leucine	Asparagine
Lysine	Aspartic acid
Methionine	Cysteine
Phenylalanine	Glutamic acid
Threonine	Glutamine
Tryptophan	Glycine
Valine	Proline
	Selenocysteine
	Serine
	Tyrosine

Table 2.1 - Essential and non-essential amino acids

Table 2.1 - Essential and non-essential amino acids

Table 2.2 - Amino acid categories (based on R-group properties)

We separate the amino acids into categories based on the chemistry of their R-groups. If you compare groupings of amino acids in different textbooks, you will see different names for the categories and (sometimes) the same amino acid being categorized differently by different authors. Indeed, we categorize tyrosine both as an aromatic amino acid and as a hydroxyl amino acid. It is useful to classify amino acids based on their R-groups, because it is these side chains that give each amino acid its characteristic properties. Thus, amino acids with (chemically) similar side groups can be expected to function in similar ways, for example, during protein folding.

Some Non-polar amino acids

- Alanine (Ala/A) is one of the most abundant amino acids found in proteins, ranking second only to leucine in occurrence. A D-form of the amino acid is also found in bacterial cell walls. Alanine is non-essential, being readily synthesized from pyruvate. It is coded for by GCU, GCC, GCA, and GCG.
- Glycine (Gly/G) is the amino acid with the shortest side chain, having an R-group consistent only of a single hydrogen. As a result, glycine is the only amino acid that is not chiral. Its small side chain allows it to readily fit into both hydrophobic and hydrophilic environments.

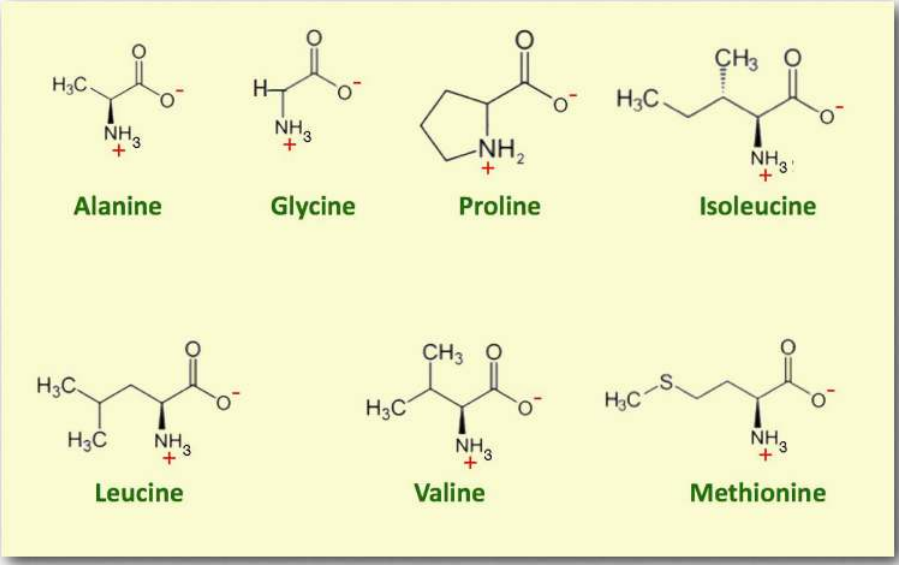


Figure 2.3 - Non-polar amino acids

Carboxyl Amino Acids

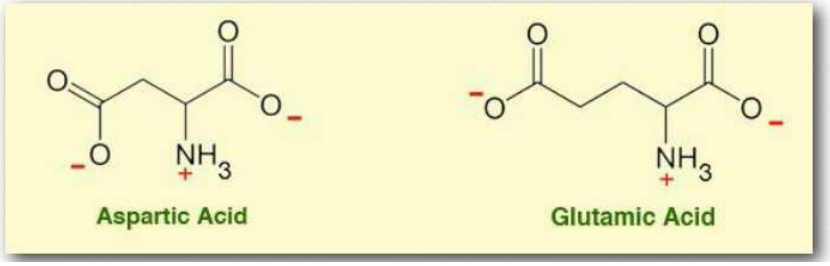


Figure 2.4 - Carboxyl amino acids

Amine amino acids



Figure 2.5 - Amine amino acids

Aromatic amino acids

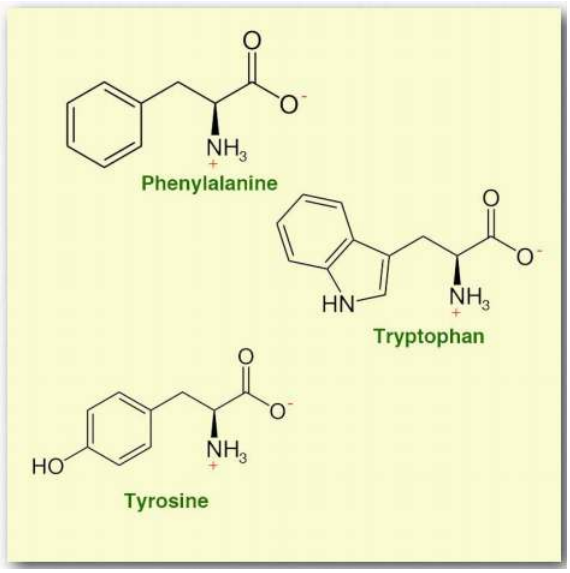


Figure 2.6 - Aromatic amino acids

Hydroxyl amino acids

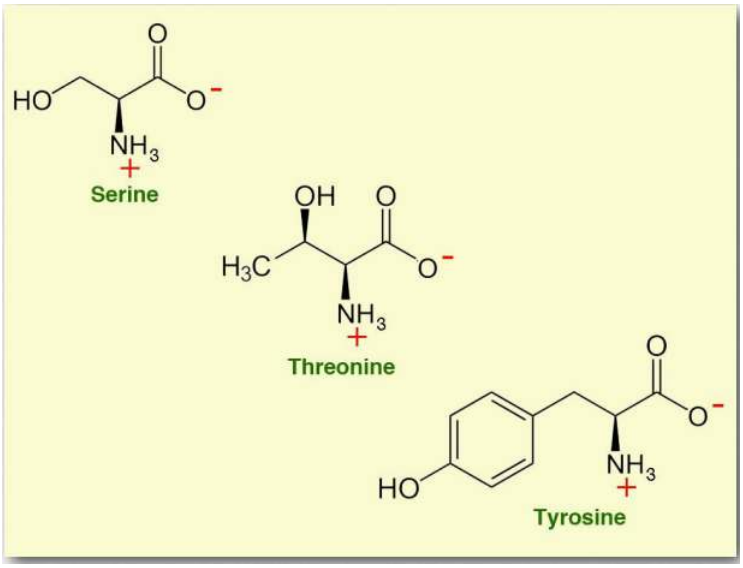
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Figure 2.7 - Hydroxyl amino acids

Figure 2.8 - Amino acid properties Wikipedia

Other amino acids

- Asparagine (Asn/N) is a non-essential amino acid coded by AAU and AAC. Its carboxyamide in the R-group gives it polarity. Asparagine is implicated in formation of acrylamide in foods cooked at high temperatures (deep frying) when it reacts with carbonyl groups. Asparagine can be made in the body from aspartate by an amidation reaction with an amine from glutamine. Breakdown of asparagine produces malate, which can be oxidized in the citric acid cycle.
- Cysteine (Cys/C) is the only amino acid with a sulfhydryl group in its side chain. It is nonessential for most humans, but may be essential in infants, the elderly and individuals who suffer from certain metabolic diseases. Cysteine's sulfhydryl group is readily oxidized to a disulfide when reacted with another one. In addition to being found in proteins, cysteine is also a component of the tripeptide, glutathione. Cysteine is specified by the codons UGU and UGC.

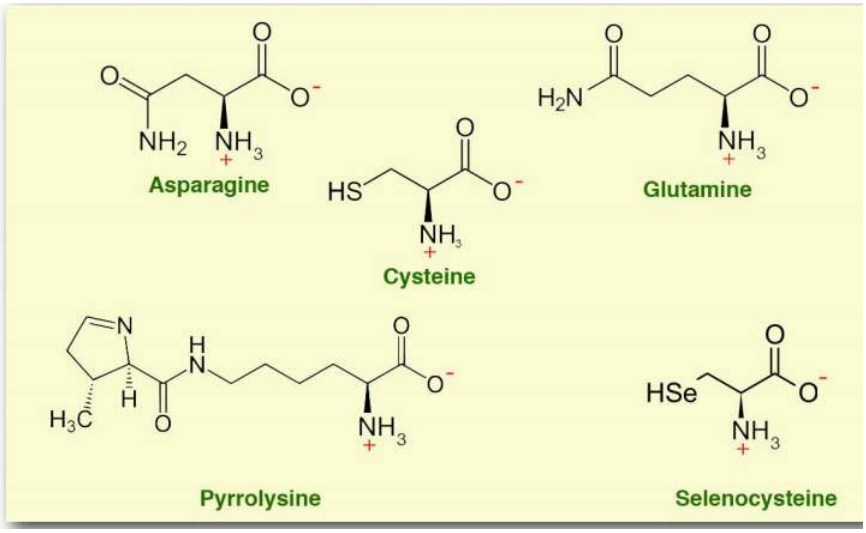


Figure 2.9 - Other amino acids

Ionizing groups

pKa values for amino acid side chains are very dependent upon the chemical environment in which they are present. For example, the R-group carboxyl found in aspartic acid has a pKa value of 3.9 when free in solution, but can be as high as 14 when in certain environments inside of proteins, though that is unusual and extreme. Each amino acid has at least one ionizable amine group (α-amine) and one ionizable carboxyl group (α- carboxyl). When these are bound in a peptide bond, they no longer ionize. Some, but not all amino acids have R-groups that can ionize. The charge of a protein then arises from the charges of the α-amine group, the α-carboxyl group. and the sum of the charges of the ionized R-groups. Titration/ionization of aspartic acid is depicted in Figure 2.10. Ionization (or deionization) within a protein's structure can have significant effect on the overall conformation of the protein and, since structure is related to function, a major impact on the activity of a protein.

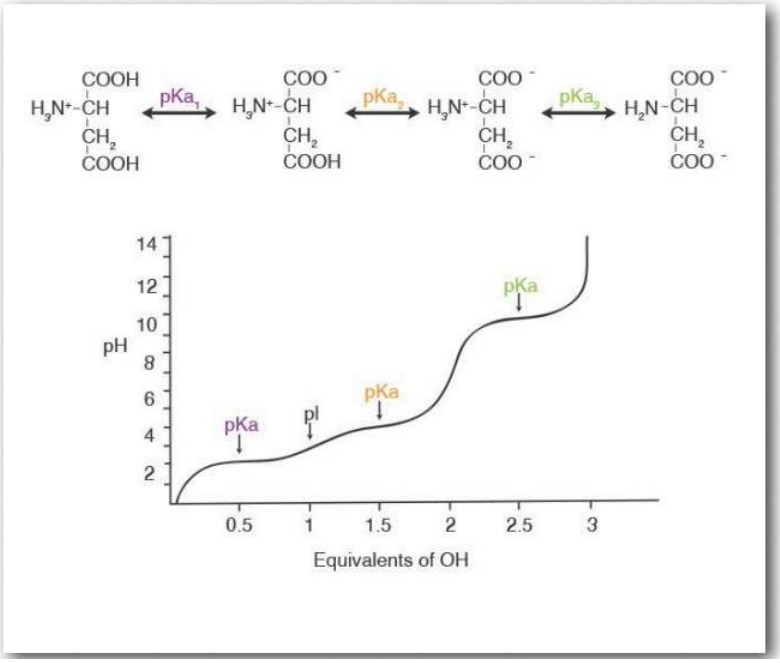


Figure 2.10 - Titration curve for aspartic acid Image by Penelope Irving

Most proteins have relatively narrow ranges of optimal activity that typically correspond to the environments in which they are found (Figure 2.11). It is worth noting that formation of peptide bonds between amino acids removes ionizable hydrogens from both the α- amine and α- carboxyl groups of amino acids. Thus, ionization/ deionization in a protein arises only from 1) the amino

terminus; 2) carboxyl terminus; 3) R-groups; or 4) other functional groups (such as sulfates or phosphates) added to amino acids post-translationally - see below.

Carnitine

Not all amino acids in a cell are found in proteins. The most common examples include ornithine (arginine metabolism), citrulline (urea cycle), and carnitine (Figure 2.12). When fatty acids destined for oxidation are moved into the mitochondrion for that purpose, they travel across the inner membrane attached to carnitine. Of the two stereoisomeric forms, the L form is the active one. The molecule is synthesized in the liver from lysine and methionine.

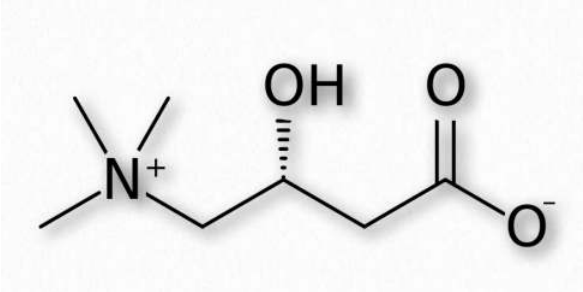


Figure 2.12 - L-Carnitine

From exogenous sources, fatty acids must be activated upon entry into the cytoplasm by being joined to coenzyme A. The CoA portion of the molecule is replaced by carnitine in the intermembrane space of the mitochondrion in a reaction catalyzed by carnitine acyltransferase I. The resulting acylcarnitine molecule is transferred across the inner mitochondrial membrane by the carnitineacylcarnitine translocase and then in the matrix of the mitochondrion, carnitine acyltransferase II replaces the carnitine with coenzyme A (Figure 6.88).

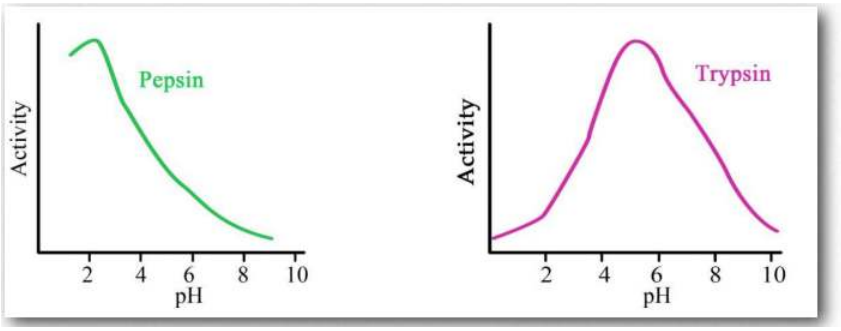


Figure 2.11 - Enzyme activity changes as pH changes Image by Aleia Kim

Building Polypeptides

Although amino acids serve other functions in cells, their most important role is as constituents of proteins. Proteins, as we noted earlier, are polymers of amino acids.

Amino acids are linked to each other by peptide bonds, in which the carboxyl group of one amino acid is joined to the amino group of the next, with the loss of a molecule of water. Additional amino acids are added in the same way, by formation of peptide bonds between the free carboxyl on the end of the growing chain and the amino group of the next amino acid in the sequence. A chain made up of just a few amino acids linked together is called an oligopeptide (oligo=few) while a typical protein, which is made up of many amino acids is called a polypeptide (poly=many). The end of the peptide that has a free amino group is called the N-terminus (for NH_2), while the end with the free carboxyl is termed the C-terminus (for carboxyl).

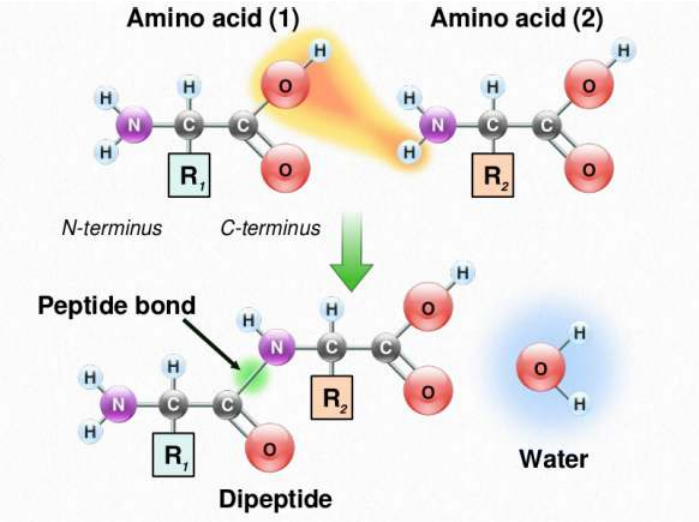


Figure 2.16 Formation of a peptide bond

As we've noted before, function is dependent on structure, and the string of amino acids must fold into a specific 3-D shape, or conformation, in order to make a functional protein. The folding of polypeptides into their functional forms is the topic of the next section.

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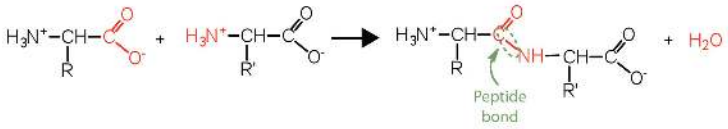
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10.5: Peptides

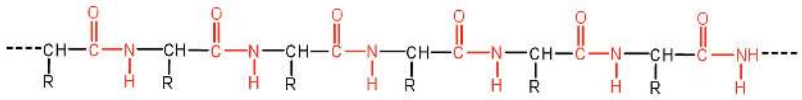
Learning Objectives

- Explain how a peptide is formed from individual amino acids.
- Explain why the sequence of amino acids in a protein is important.

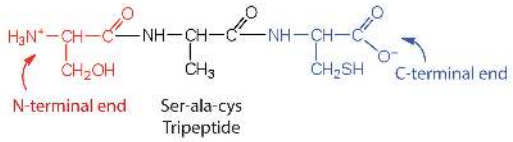
Two or more amino acids can join together into chains called peptides. Previously, we discussed the reaction between ammonia and a carboxylic acid to form an amide. In a similar reaction, the amino group on one amino acid molecule reacts with the carboxyl group on another, releasing a molecule of water 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.

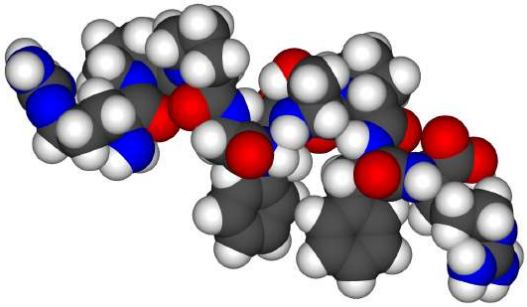


Figure **10.5.1**: Space-filling model of bradykinin. (Public Domain; Fvasconcellos)

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 **10.5.1**) 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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10.6: 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.

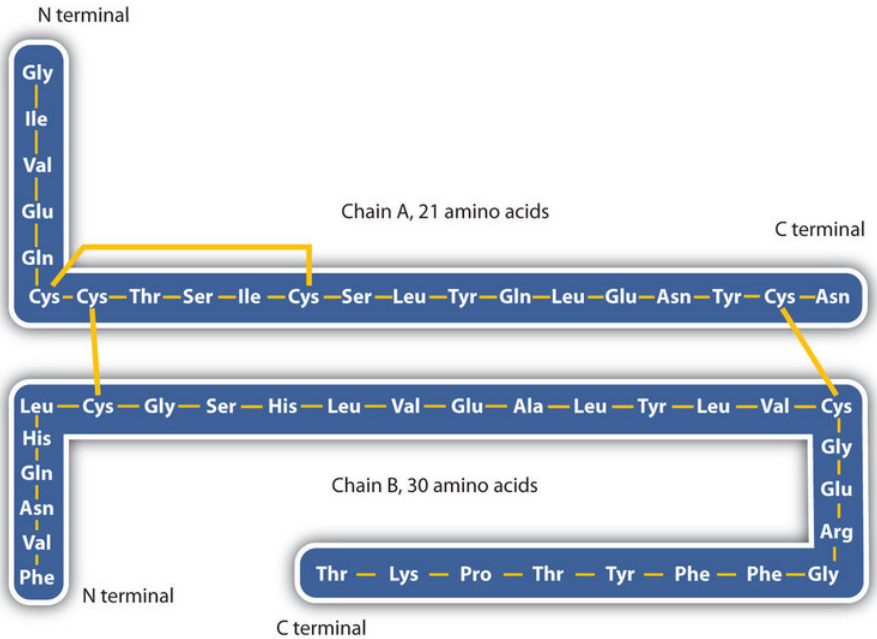


Figure **10.6.1**: Primary Structure of Human Insulin. Human insulin, whose amino acid sequence is shown here, is a hormone that is required for the proper metabolism of glucose.

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 **10.6.1**.

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 **10.6.2**). 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.

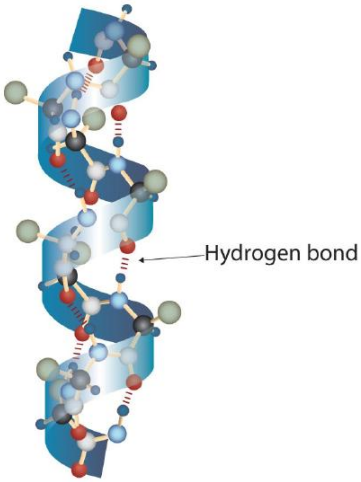


Figure **10.6.2** A Ball-and-Stick Model of an α-Helix. This ball-and-stick model shows the intrachain hydrogen bonding between carbonyl oxygen atoms and amide hydrogen atoms. Each turn of the helix spans 3.6 amino acids. Note that the side chains (represented as green spheres) point out from the helix.

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 **10.6.3**). 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.

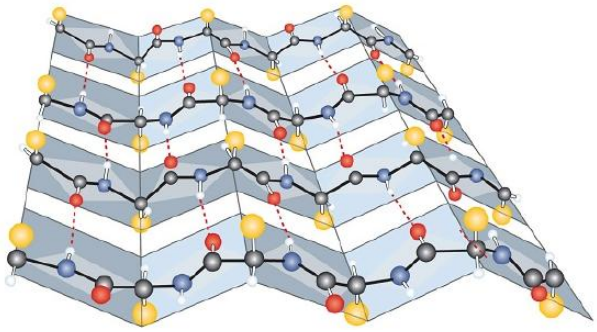


Figure **10.6.3**: A Ball-and-Stick Model of the β-Pleated Sheet Structure in Proteins. The side chains extend above or below the sheet and alternate along the chain. The protein chains are held together by interchain hydrogen bonding.

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 **10.6.4** shows a depiction of the three-dimensional structure of insulin.

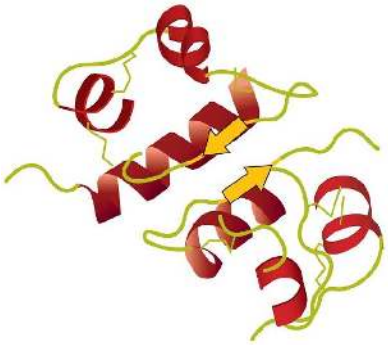
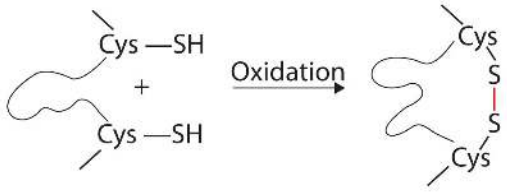


Figure **10.6.4**: A Ribbon Model of the Three-Dimensional Structure of Insulin. The spiral regions represent sections of the polypeptide chain that have an α-helical structure, while the broad arrows represent β-pleated sheet structures.

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 **10.6.5**).
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 **10.6.5**).
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 **10.6.5**). Intrachain disulfide linkages are found in many proteins, including insulin (yellow bars in Figure **10.6.1**) 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 **10.6.5**). 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.

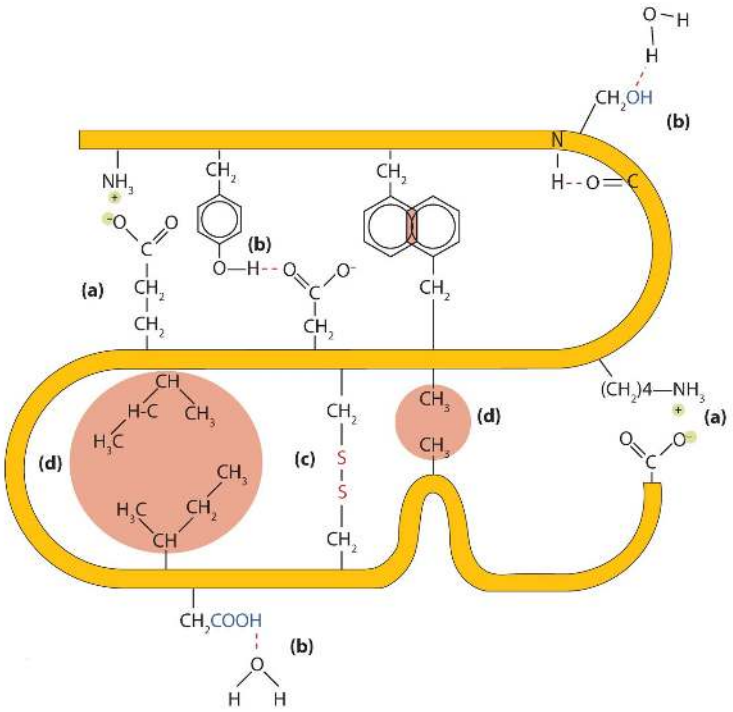


Figure **10.6.5**: Tertiary Protein Structure Interactions. Four interactions stabilize the tertiary structure of a protein: (a) ionic bonding, (b) hydrogen bonding, (c) disulfide linkages, and (d) dispersion forces.

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 **10.6.6**). 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 **10.6.7**.

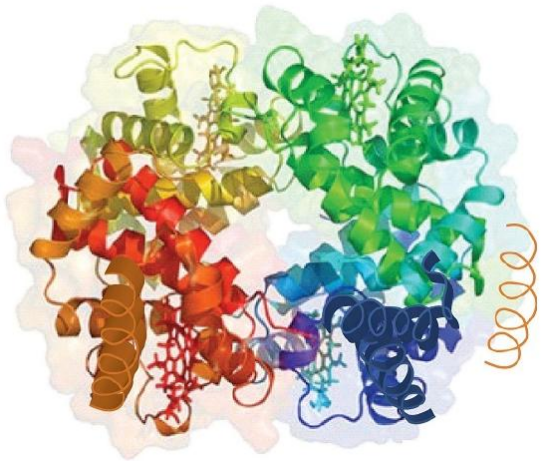


Figure **10.6.6** The Quaternary Structure of Hemoglobin. Hemoglobin is a protein that transports oxygen throughout the body.

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).

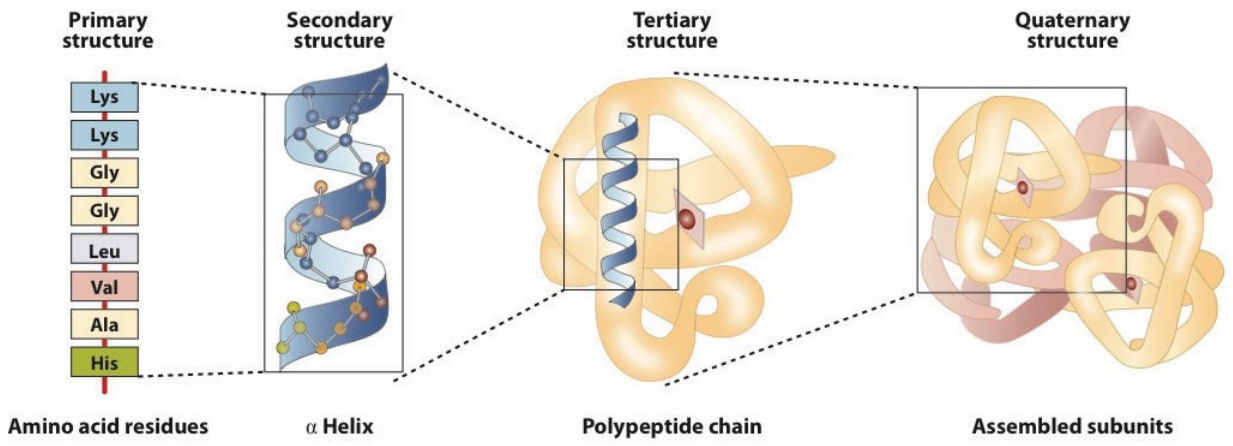


Figure **10.6.7**: Levels of Structure in Proteins

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 **10.6.1**).

Figure **10.6.1**: 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 **10.6.8**). 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.

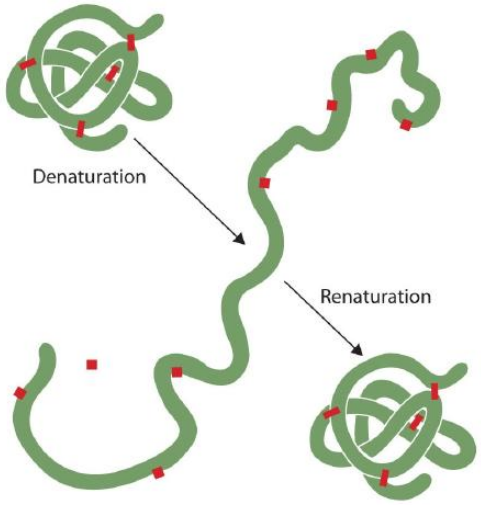


Figure **10.6.8**: Denaturation and Renaturation of a Protein. The denaturation (unfolding) and renaturation (refolding) of a protein is depicted. The red boxes represent stabilizing interactions, such as disulfide linkages, hydrogen bonding, and/or ionic bonds.

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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10.7: Proteins

Whereas nucleotides all are water soluble and have the same basic composition (sugar, base, phosphate) and the sugars also are water soluble and mostly contain 5 or 6 carbons (a few exceptions), the amino acids (general structure below) are structurally and chemically diverse.

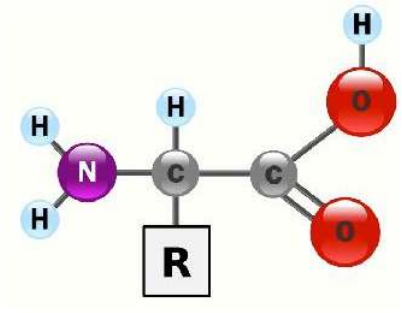


Figure 3.2.1: Amino Acid Schematic

Though all of the amino acids are, in fact, soluble in water, the interactions of their side chains with water differ significantly. This is important, because it is only in the side chains (R-groups) that amino acids differ from each other. Based on side chains, we can group the 20 amino acids found in proteins as follows:

- Aromatic (phenylalanine, tyrosine, tryptophan)
- Aliphatic (leucine, isoleucine, alanine, methionine, valine)
- Hydroxyl/Sulfhydryl (threonine, serine, tyrosine, cysteine)
- Carboxyamide (glutamine, asparagine)
- R-Acids (glutamic acid, aspartic acid)
- R-Amines (lysine, histidine, arginine)
- Odd (glycine, proline)

Note that tyrosine has a hydroxyl group and fits into two categories. Note also that biochemistry books vary in how they organize amino acids into categories. Amino acids are joined to each other by peptide bonds. This introduces a slight simplifying aspect to the structure of proteins – one need only consider the positioning of the R-groups around each peptide bond when determining protein structure schematically. Proteins that are in aqueous environments, such as the cytoplasm of the cell, have their amino acids arranged so that those with hydrophilic side chains (such as threonine or lysine) predominate on the exterior of the protein so as to interact with water. The hydrophobic amino acids in these proteins are found predominantly on the interior. When one examines the structure of proteins in non-aqueous environments, such as the interior of a lipid bilayer, the arrangement is flipped – hydrophobics predominate on the outside where they can interact with the hydrophobic side chains of membrane fatty acids and the hydrophilic amino acids are arranged anyplace where they can contact water. For a protein like porin, which provides an interior channel through which water can pass, this is where the hydrophilics are found. For transmembrane proteins, which project through both sides of the membrane, the hydrophilics are found at each point where the polypeptide chain emerges from the membrane.

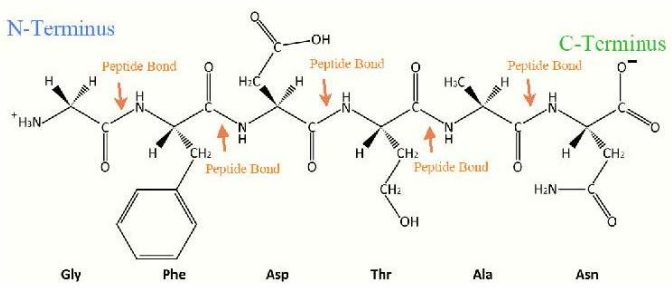


Figure 3.2.2: An image of the primary structure of a protein.

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Primary Structure

How do proteins obtain such arrangements of amino acids? As we shall see, the structures of all proteins ultimately arise from their amino acid sequences. The amino acid sequence is referred to as the primary structure and changes in it can affect every other level of structure as well as the properties of a protein. On a more immediate time scale, 3D protein structure arises as a result of a phenomenon called folding. Protein folding results from three different structural elements beyond primary structure. They are referred to as secondary, tertiary, and quaternary structures, each arising from interactions between progressively more distant amino acids in the primary structure.

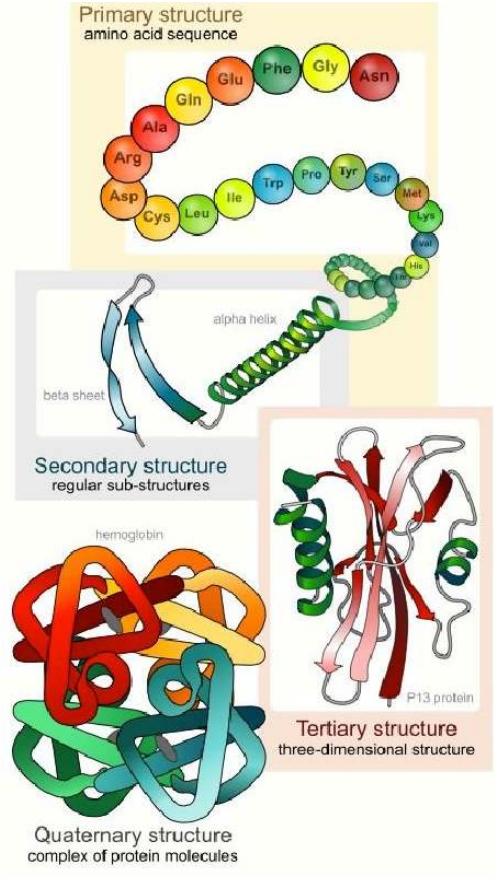


Figure 3.2.3: *Schematic of a protein.*

Secondary Structure

Interactions between amino acids within about ten units of each other give rise to regular repeating structures. These secondary structures include the well known alpha-helix and beta strands. Both were predicted by Linus Pauling, Robert Corey, and Herman Branson in 1951. Each structure has unique features. We use the terms rise, repeat, and pitch to describe the parameters of a helix. The repeat is the number of residues in a helix before it begins to repeat itself. The rise is the distance the helix elevates with addition of each residue. The pitch is the distance between the turns of the helix.

Alpha Helix

The alpha helix (Figure 3.1.3) forms as the result of interactions between amino acids separated by four residues. Interesting;y, the side chains of the amino acids in an alpha helix are all pointed outwards from the axis of the helix. Alpha helices have a repeat of 3.6 amino acid residues per turn of the helix, meaning that four turns of the helix have approximately 14 amino acid residues. Hydrogen bonds occur between the C=O of one amino acid and the N-H of another amino acid four residues distant and these help to stabilize the structure (note that the C=O and N-H involved are part of the polypeptide backbone, not the R-groups). Some amino acids have high helix forming tendencies. They include methionine, alanine, leucine, uncharged glutamate, and lysine. Others, such as proline, glycine, and negatively charged aspartate, disfavor its formation.

Beta Strands

Beta strands are the most fundamental helix, having essentially a 2D backbone of 'fold' like those of the pleats of a curtain. Indeed, beta strands can be arranged together to form what are called beta sheets. Other regular structures are also known. What determines whether a given stretch of a protein is in a helical or other structure? Here is where the shape and chemistry of the side chains play a role.

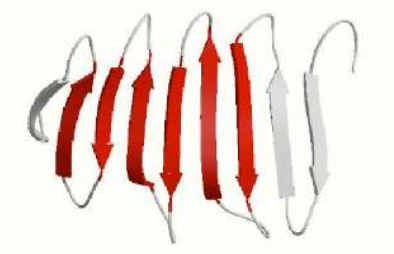


Figure 3.2.4: *A beta sheet.*

Fibrous Proteins

Not all proteins have significant amounts of tertiary or quaternary structure. (As we shall see, these last two levels of structure arise from 'bends' in polypeptide chains and interactions between separate polypeptide chains, respectively.)

Alpha keratin, for example, is what we refer to as a fibrous protein (also called scleroprotein). Alpha keratin has primary structure and secondary structure, but little tertiary or quaternary structure.

Consequently, alpha keratin exists mostly as long fibers, such as are found in hair. Beta-keratin is a harder fibrous protein found in nails, scales, and claws. It is made up mostly of beta sheets. Proline, which is the least flexible amino acid, due to attachment of the side chain to the alpha-amino grip, is less likely to be found in alpha helices, but curiously it is found abundantly in the fibrous protein known as collagen. Collagen is the most abundant protein in the human body and is the 'glue' that literally sticks us together. How does the inflexibility of proline permit it to be in a helix? The answer is probably the parallel abundance in collagen of glycine, which contains the smallest side group and therefore has the greatest flexibility.

As an interesting sidelight of the presence of proline in collagen is the chemical modification of prolines, by the addition of hydroxyl groups, after the protein is made. Such 'post-translational modifications' are not uncommon. Threonine, serine, and tyrosine frequently have their hydroxyl side-chains phosphorylated. Lysines in collagen too are hydroxylated post-translationally. The hydroxylated prolines and lysines play a role in the formation of interchain hydrogen bonds and crosslinking of triple helices during the assembly of collagen fibrils. These bonds provide structural integrity to the collagen. The enzymes that add hydroxyls to proline and lysine require vitamin C (ascorbic acid) for their activity. Lack of vitamin C leads to the production of weakened collagen fibrils, resulting in a condition called scurvy.

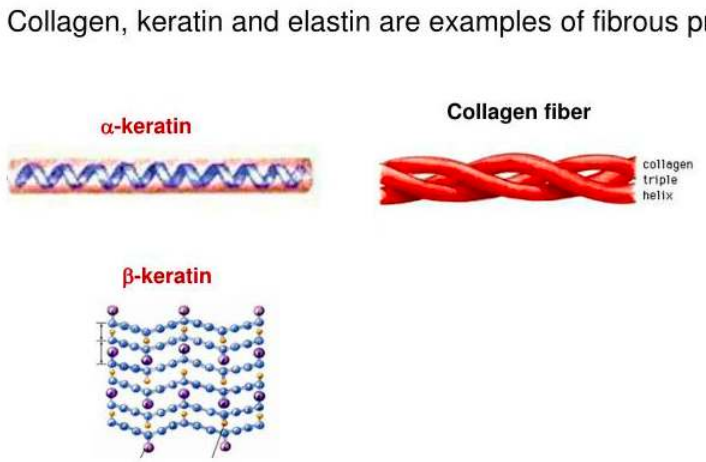


Figure 3.2.5: *Collagen.*

Tertiary Structure

In contrast to secondary structures, which arise from interactions between amino acids close in primary structure, tertiary structure arises from interactions between amino acids more distant in primary structure. Such interactions are not possible in an endlessly stretching fiber because each amino acid placed between two amino acids causes them to be moved farther away from each other in what is essentially the two dimensions of a secondary structure. For distant amino acids to interact, they must be brought into closer proximity and this requires bending and folding of the polypeptide chain. Proteins with such structures are referred to as ‘globular’ and they are, by far, the most abundant class of proteins. Indeed, it is in globular proteins that we have the most vivid images of the results of folding. “Folds" in polypeptides arise as a result of ‘bends’ between regions of secondary structure (such as alpha helix or beta strands). Such structures may be preferred due to incompatibility of a given amino acid side chain for a secondary structure formed by the amino acids preceding it. Bends occur commonly in proteins and proline is often implicated. Bends do not have the predictable geometry of alpha helices or beta strands and are often referred to as random coils. Thus, even though protein structure can be described easily as regions of secondary structure separated by bends, the variability of bend structures makes prediction of tertiary structure from amino acid sequence enormously more difficult than identifying/predicting regions of secondary structure.

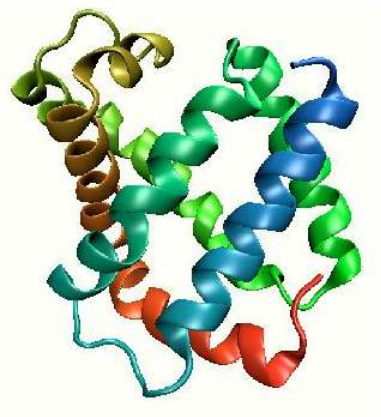


Figure 3.2.9: *The structure of Myoglobin*

Hydrophobic Effect

It is at the level of tertiary structure that the characteristic arrangement of hydrophobic and hydrophilic amino acids in a protein occurs. In an aqueous environment, for a protein to remain soluble, it must have favorable interactions with the water around it, hence, the positioning of hydrophilic amino acids externally. Another impetus for the folding phenomenon is a bit harder to understand. It is known as the hydrophobic effect. At a chemical level, it makes sense – hydrophobic amino acids will ‘prefer’ to interact with each other internally and away from water. The driving force for this phenomenon, though, is a bit more conceptually difficult. Consider a bottle containing oil and water. As everyone knows, the two liquids will not mix and instead will form separate layers. A reasonable question might be why they do this instead of one existing as tiny globules inside of the other. The answer to that question, as well as the positioning of hydrophobic amino acids in the interior of water soluble proteins, is the hydrophobic effect. To understand the hydrophobic effect, perform the following experiment – take the water-oil mixture and shake it vigorously. This will force the layers to mix and one will observe that tiny globules of both water and oil can, in fact, be found initially in the layer of each. Over time, though, the tiny globules break up and merge with the appropriate layer. This is due to the phenomenon of entropy and consideration of surface area. First, the sum of the surface area of the embedded tiny globs is far greater than the area of the region between the two layers after mixing is over. The smaller the globs, the more the surface area of interaction between the oil and the water. The minimum possible surface area of interaction occurs when there are no globs at all – just two layers and nothing else.



Figure 3.2.10: *A hydrophobic effect causes the water on this leaf to assume a spherical shape.*

How does this relate to entropy? Interactions between the water-hydrophobic layers causes the molecules at the interface to arrange themselves precisely/regularly so as to minimize their interactions. Ordering thus occurs at the layer interfaces. The maximum amount of ordering occurs when the maximum surface areas of oil and water interact. Small globules give rise to more exposed surface area between the water and hydrophobic layers and, as a consequence, more ordering. Since entropy in a closed system tends to increase, it will tend to reduce the amount of ordering, if left alone. Thus, one can increase the ordering on a nanoscopic scale (forming globules) by applying energy in the form of shaking. When left alone, however, the system will increase its disorder by reducing the interactions between hydrophobic groups and hydrophilic ones.

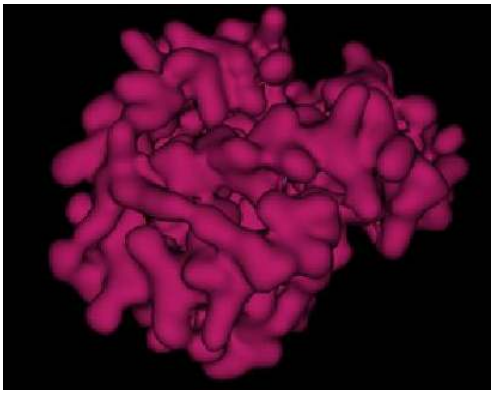


Figure 3.2.11: *Oxygenated Myoglobin.*

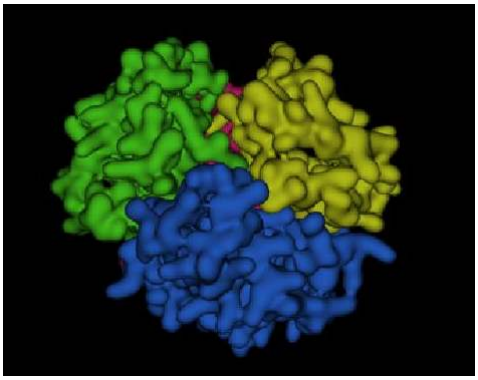


Figure 3.2.12: *Hemoglobin in the absence of oxygen.*

In the oil water mixture, this causes the tiny globs to break up and produce the two layers we are familiar with because this is the minimum surface area that can be made between the two layers and thus the least ordering. In proteins, hydrophobic amino acid side chains are ‘shielded’ from water by placement internal to the protein, thus also reducing interfaces between hydrophobic residues and water. In both cases, entropy is increased, due to the reduced organization of the layers. Once formed, the interactions between the hydrophobic amino acid side chains helps to stabilize the overall protein structure.

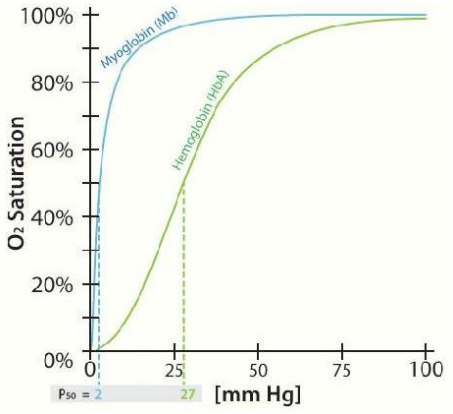


Figure 3.2.13

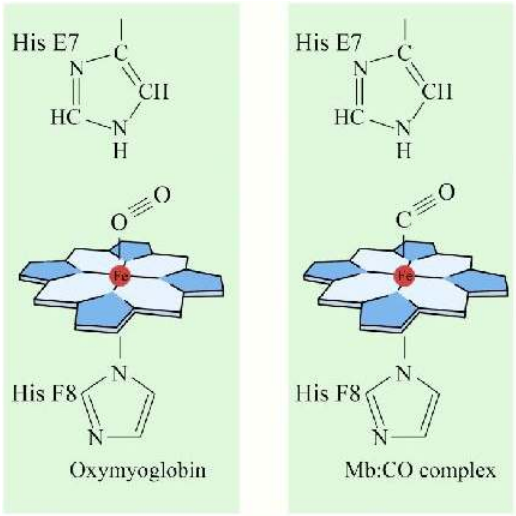


Figure 3.2.14: *Oxygen and Carbon Monoxide binding to heme.*

Quaternary Structure

The last level of protein structure we will consider is that of quaternary structure. In order to have quaternary structure, a protein must have multiple polypeptide subunits because the structure involves the arrangement of those subunits with respect to each other. Consider hemoglobin, the oxygen-carrying protein of our blood. It contains two identical subunits known as alpha and two other identical ones known as beta. These are arranged together in a fashion as shown on the previous page. By contrast, the related oxygen storage protein known as myoglobin only contains a single subunit. Hemoglobin has quaternary structure, but myoglobin does not. Multiple subunit proteins are common in cells and they give rise to very useful properties not found in single subunit proteins. In the case of hemoglobin, the multiple subunits confer the property of cooperativity – variable affinity for oxygen depending on the latter's concentration. In the case of enzymes, it can impart allosterism – the ability to have the activity of the enzyme altered by interaction with an effector molecule. We will discuss allosterism in detail in the next chapter.

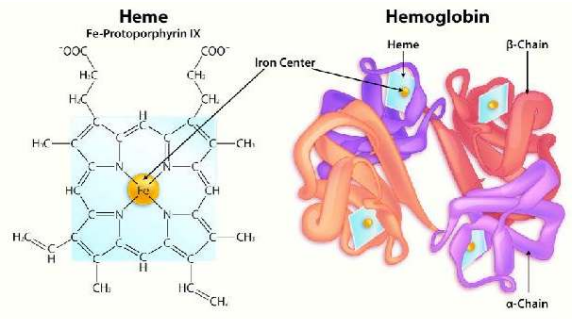


Figure 3.2.15: *Hemoglobin.*

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Other Protein Structural Features

Not everything found in a protein is an amino acid. Proteins frequently have other chemical groups, known as prosthetic groups, bound to them, that are necessary for the function of a protein. Examples include the porphyrin ring of heme in myoglobin and hemoglobin that carries an iron so that oxygen can be bound. Metals are frequently employed by enzymes in their catalysis. Several vitamins (referred to as coenzymes), such as thiamine (B1) and riboflavin(B2) are modified and chemically bound to enzymes to help them perform specific catalytic functions.

Cooperativity

An interesting and important aspect of some proteins is the phenomenon of cooperativity. Cooperativity refers to the fact that binding of one ligand molecule by a protein favors the binding of additional molecules of the same type. Hemoglobin, for example, exhibits cooperativity when the binding of an oxygen molecule by the iron of the heme group in one of the four subunits causes a slight conformation change in the subunit. This happens because the heme iron is attached to a histidine side chain and binding of oxygen 'lifts' the iron along with the histidine ring (also known as the imidazole ring).

Since each hemoglobin subunit interacts with and influences the other subunits, they too are induced to change shape slightly when the first subunit binds to oxygen (a transition described as going from the T-state to the R-state). These shape changes favor each of the remaining subunits binding oxygen, as well. This is very important in the lungs where oxygen is picked up by hemoglobin, because the binding of the first oxygen molecule facilitates the rapid uptake of more oxygen molecules. In the tissues, where the oxygen concentration is lower, the oxygen leaves hemoglobin and the proteins .ips from the R-state back to the T-state.

Cooperativity is only one of many fascinating structural aspects of hemoglobin that help the body to receive oxygen where it is needed and pick it up where it is abundant. Hemoglobin also assists in the transport of the product of cellular respiration (carbon dioxide) from the tissues producing it to the lungs where it is exhaled. Let us consider these individually.

Bohr Effect

The Bohr Effect was first described over 100 years ago by Christian Bohr. Shown graphically (above left), the observed effect is that hemoglobin's affinity for oxygen decreases as the pH decreases and/or as the concentration of carbon dioxide increases. Binding of the protons by histidine helps to facilitate structural changes in the protein and also with the uptake of carbon dioxide. Physiologically, this has great significance because actively respiring tissues (such as contracting muscles) require oxygen and release protons and carbon dioxide. The higher the concentration of protons and carbon dioxide, the more oxygen is released to feed the tissues that need it most.

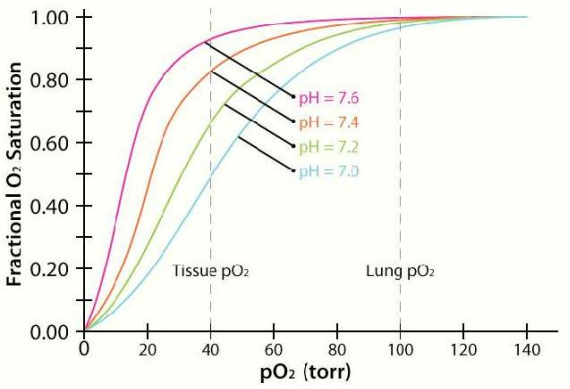


Figure 3.2.16: *The Bohr Effect.*

Smokers have a reason why their oxygen carrying capacity is lower than that of non-smokers. Cigarette smoke contains carbon monoxide and this molecule, which has almost identical dimensions to molecular oxygen, competes effectively with oxygen for binding to the iron atom of heme. Part of carbon monoxide's toxicity is due to its ability to bind hemoglobin and prevent oxygen from binding.

Denaturation

For proteins, function is dependent on precise structure. Loss of the precise, folded structure of a protein is known as denaturation and is usually accompanied by loss of function. Anyone who has ever worked to purify an enzyme knows how easy it is for one to lose its activity. A few enzymes, such as ribonuclease, are remarkably stable under even very harsh conditions. For most others, a small temperature or pH change can drastically affect activity. The reasons for these differences vary, but relate to 1) the strength of the forces holding the structure together and 2) the ability of a protein to refold itself after being denatured. Let us consider these separately below.

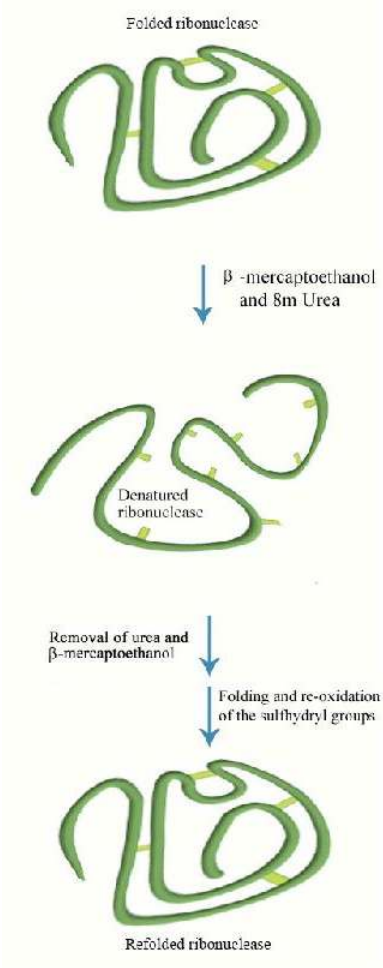


Figure 3.2.18: *Denaturation and renaturation of ribonuclease.*

Forces Stabilizing Structures

Amino acids are linked one to the other by peptide bonds. These covalent bonds are extraordinarily stable at neutral pHs, but can be broken by hydrolysis with heat under acidic conditions. Peptide bonds, however, only stabilize primary structure and, in fact, are the only relevant force responsible for it. Secondary structure, on the other hand, is generally stabilized by weaker forces, including hydrogen bonds. Hydrogen bonds are readily disrupted by heat, urea, or guanidinium chloride.

Forces stabilizing tertiary structure include ionic interactions, disulfide bonds, hydrophobic interactions, metallic bonds, and hydrogen
bonds. Of these, the ionic interactions are most sensitive to pH changes. Hydrophobic bonds are most sensitive to detergents. Thus, washing one's hands helps to kill bacteria by denaturing critical proteins they need to survive. Metallic bonds are sensitive to oxidation/reduction. Breaking disulfide bonds requires either a strong oxidizing agent, such as performic acid or a strong reducing agent
on another disulfide, such as mercaptoethanol or dithiothreitol.

Quaternary structures are stabilized by the same forces as tertiary structure and have the same sensitivities.

Refolding Denatured Proteins

All of the information for protein folding is contained in the primary structure of the protein. It may seem curious then that most proteins do not refold into their proper, fully active form after they have been denatured and the denaturant is removed. A few do, in fact, refold correctly under these circumstances. A good example is bovine ribonuclease (also called RNase). Its catalytic activity is very resistant to heat and urea. However, if one treats the enzyme with mercaptoethanol (which breaks disulfide bonds) prior to urea treatment and
heating, activity is lost, indicating that the covalent disulfide bonds help stabilize the overall enzyme structure. If one allows the enzyme
mixture to cool back down to room temperature, over time some enzyme activity reappears, indicating that ribonuclease can re-fold under the proper conditions.

Irreversible Denaturation

Most enzymes, however, do not behave like ribonuclease. Once denatured, their activity cannot be recovered to any significant extent. This may seem to contradict the idea that folding information is inherent to the sequence of amino acids in the protein. It does not. The reason most enzymes can’t refold properly is due to two phenomena. First, normal folding may occur as proteins are being made. Interactions among amino acids early in the synthesis are not “confused" by interactions with amino acids later in the synthesis because those amino acids aren’t present as protein synthesis starts. In many cases, the proper folding of newly made polypeptides is also assisted by special proteins called chaperones. Chaperones bind to newly made proteins, preventing interactions that might result in misfolding. Thus, early folding and the assistance of chaperones eliminate some potential “wrong-folding" interactions that can occur if the entire sequence was present when folding started.

Denatured full-length polypeptides have many more potential wrong folds that can occur. A second reason most proteins don’t refold properly after denaturation is probably that folding, like any other natural phenomenon, is driven by energy minimization. Though the folded structure may have a low energy, the path leading to it may not be all downhill. Like a chemical reaction that has energies of activation that must be overcome for the reaction to occur, folding likely has peaks and valleys of energy that do not automatically lead directly to the proper fold. Again, folding during synthesis leads the protein along a better-defined path through the energy maze of folding that denatured full-length proteins can’t navigate.

Prions and Misfolding

Folding and the stability of folded proteins is an important consideration for so-called “infectious" proteins known as prions. These mysterious proteins, which are implicated in diseases, such as mad cow disease and the related human condition known as Creutzfeldt-Jakob disease, result from the improper folding of a brain protein known as PrP. The misfolded protein has two important properties that lead to the disease. First, it tends to aggregrate into large complexes called amyloid plaques that damage/destroy nerve cells in the brain, leading ultimately to dementia and loss of brain function.

Second, and probably worse, the misfolded protein “induces" other copies of the same protein to misfold as well. Thus, a misfolded protein acts something like a catalytic center and the disease progresses rapidly. The question arises as to how the PrP protein misfolds to begin with, but the answer to this is not clear. There are suggestions that exposure in the diet to misfolded proteins may be a factor, but this is disputed. An outbreak of mad cow disease in Britain in the 1980s was followed by a rise in the incidence of a rare form of human Creutzfeld-Jakob disease called variant CJD (v-CJD), lending some credence to the hypothesis. It is possible that misfolding of many proteins occurs sporadically without consequence or observation, but if PrP misfolds, the results are readily apparent. Thus, Creutzfeld-Jakob disease may ultimately give insights into the folding process itself.

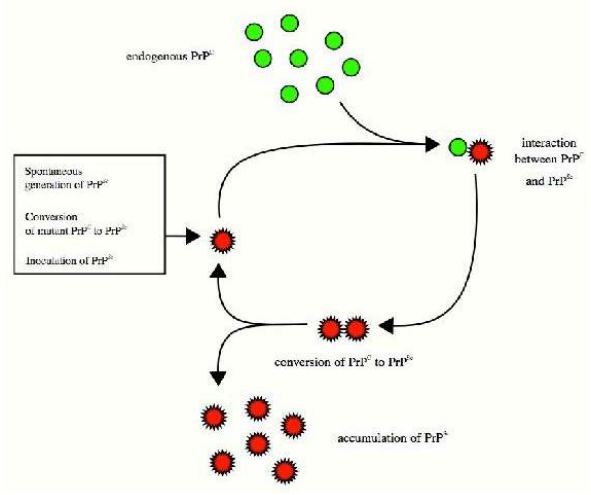


Figure 3.2.19: *Prion protein misfolding.*

Contributors

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10.8: 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 10.8.1: 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 10.8.1), with subgroups and secondary subgroups that specify the reaction more precisely.

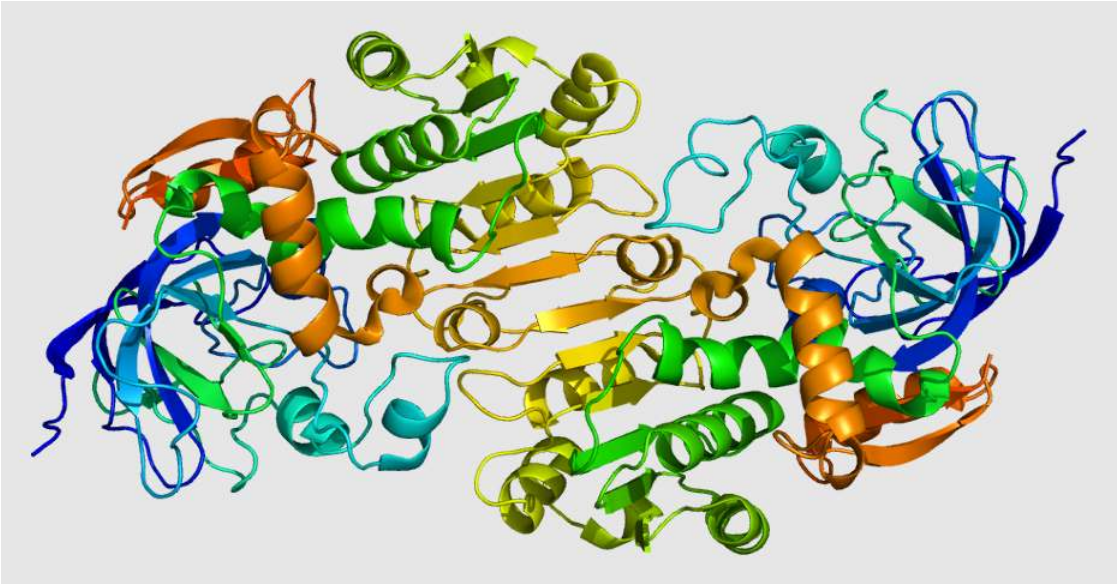
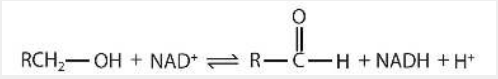


Figure* 10.8.1*: *Structure of the alcohol dehydrogenase protein.*

Each enzyme is 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 10.8.2: Assignment of an Enzyme Classification Number

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.

Concept Review Exercise

In the small intestine, sucrose is hydrolyzed to form glucose and fructose in a reaction catalyzed by sucrase.

1. Identify the substrate in this reaction.
2. Name the enzyme.

Answers

1. sucrose
2. sucrase

Exercises

1. Identify the substrate catalyzed by each enzyme.

a. lactase
b. cellulase
c. peptidase

2. Identify the substrate catalyzed by each enzyme.

a. lipase
b. amylase
c. maltase

3. Identify each type of enzyme.

a. decarboxylase
b. protease
c. transaminase

4. Identify each type of enzyme.

a. dehydrogenase
b. isomerase
c. lipase

Answers

1. a. lactose
   b. cellulose
   c. peptides

3. a. lyase
   b. hydrolase
   c. transferase

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10.9: 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 **10.9.1**). 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).

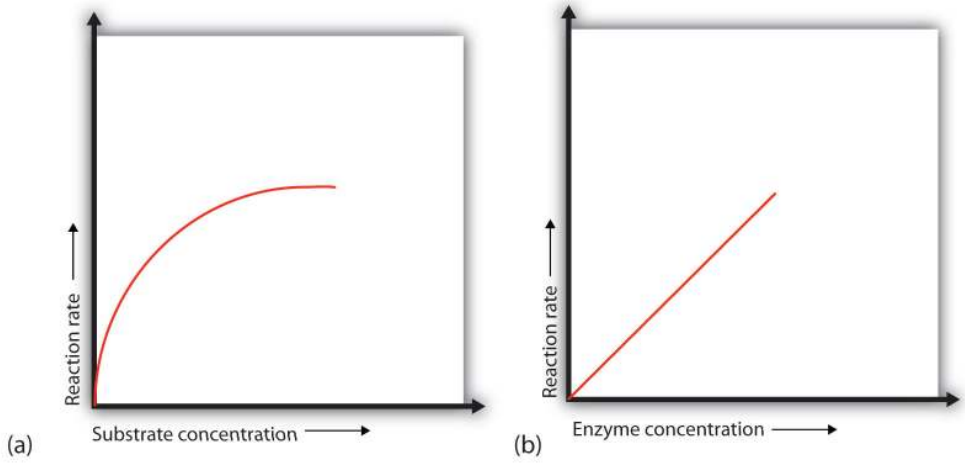


Figure **10.9.1**: Concentration versus Reaction Rate. (a) This graph shows the effect of substrate concentration on the rate of a reaction that is catalyzed by a fixed amount of enzyme. (b) This graph shows the effect of enzyme concentration on the reaction rate at a constant level of substrate.

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 **10.9.1**). 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 **10.9.2**). 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.

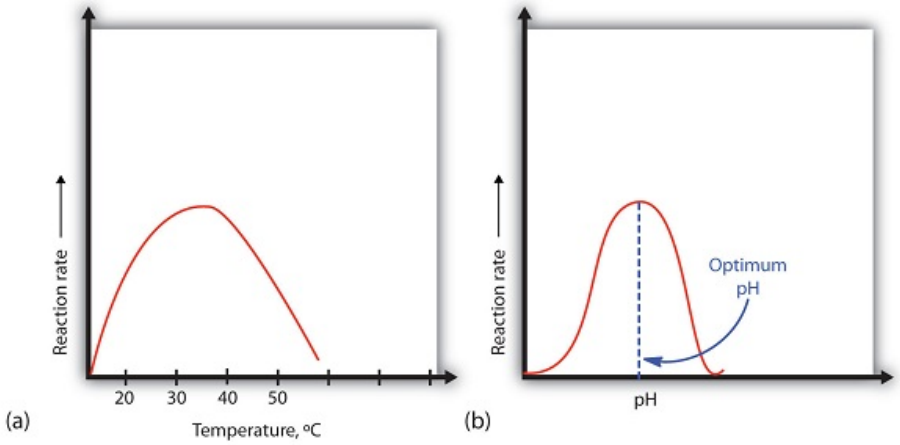


Figure **10.9.2**: Temperature and pH versus Concentration. (a) This graph depicts the effect of temperature on the rate of a reaction that is catalyzed by a fixed amount of enzyme. (b) This graph depicts the effect of pH on the rate of a reaction that is catalyzed by a fixed amount of enzyme.

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 **10.9.2**). 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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10.10: 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:

$$S + E \rightarrow E\text{–}S \tag{10.10.1}$$

$$E\text{–}S \rightarrow P + E \tag{10.10.2}$$

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 10.10.1).

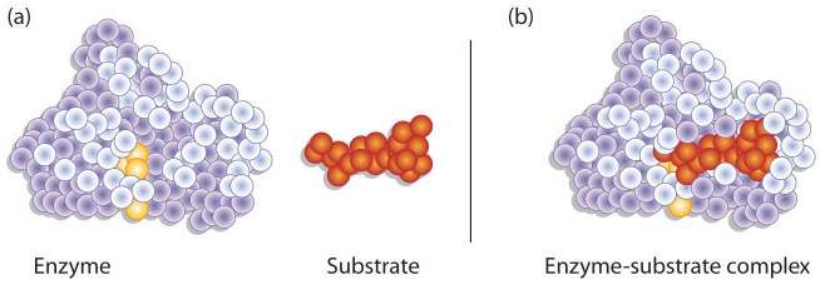


Figure 10.10.1: Substrate Binding to the Active Site of an Enzyme. The enzyme dihydrofolate reductase is shown with one of its substrates: $NADP^+$ (a) unbound and (b) bound. The $NADP^+$ (shown in red) binds to a pocket that is complementary to it in shape and ionic properties.

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 10.10.2). This model portrayed the enzyme as conformationally rigid and able to bond only to substrates that exactly fit the active site.

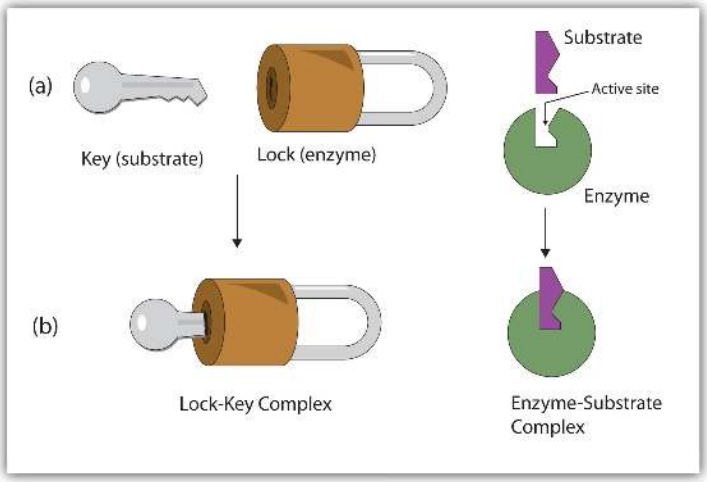


Figure 10.10.2: The Lock-and-Key Model of Enzyme Action. (a) Because the substrate and the active site of the enzyme have complementary structures and bonding groups, they fit together as a key fits a lock. (b) The catalytic reaction occurs while the two are bonded together in the enzyme-substrate complex.

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 **10.10.3**. After catalysis, the enzyme resumes its original structure.

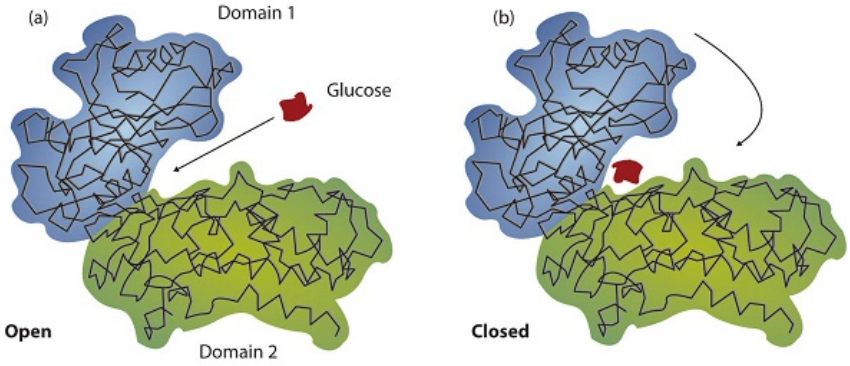


Figure 10.10.3: The Induced-Fit Model of Enzyme Action. (a) The enzyme hexokinase without its substrate (glucose, shown in red) is bound to the active site. (b) The enzyme conformation changes dramatically when the substrate binds to it, resulting in additional interactions between hexokinase and glucose.

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 10.10.1

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.

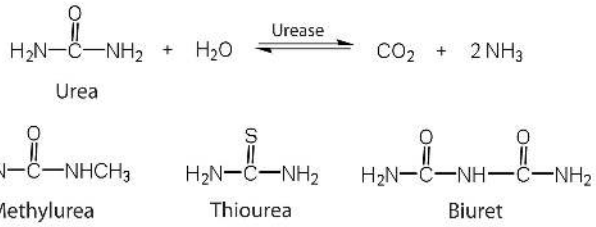
b. Several amino acid side chains would be able to engage in hydrogen bonding with an OH group. One example would be asparagine, which has an amide functional group.

? Exercise 10.10.1

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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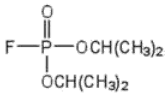
10.11: Enzyme Inhibition

Learning Objectives

- Explain what an enzyme inhibitor is.
- Distinguish between reversible and irreversible inhibitors.
- Distinguish between competitive and noncompetitive inhibitors.

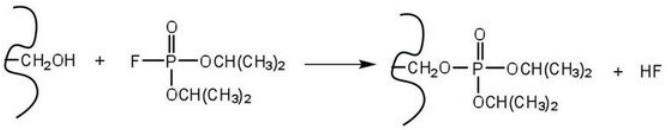
Previously, we noted that enzymes are inactivated at high temperatures and by changes in pH. These are nonspecific factors that would inactivate any enzyme. The activity of enzymes can also be regulated by more specific inhibitors. Many compounds are poisons because they bind covalently to particular enzymes or kinds of enzymes and inactivate them (Table **10.11.1**).

Table **10.11.1**: 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 10.11.1). 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.

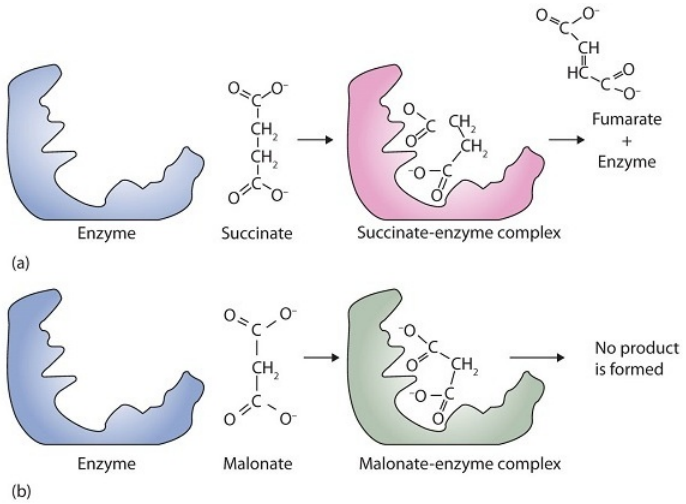


Figure 10.11.1: Competitive Inhibition. (a) Succinate binds to the enzyme succinate dehydrogenase. A dehydrogenation reaction occurs, and the product—fumarate—is released from the enzyme. (b) Malonate also binds to the active site of succinate dehydrogenase. In this case, however, no subsequent reaction 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.

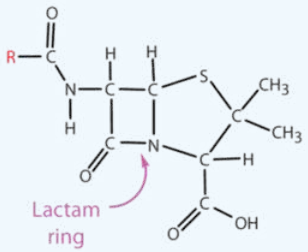
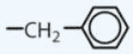
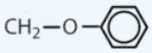
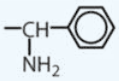
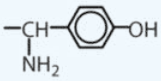
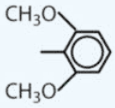
Penicillin, one of the most widely used antibiotics in the world, was fortuitously discovered by Alexander Fleming in 1928, when he noticed antibacterial properties in a mold growing on a bacterial culture plate. In 1938, Ernst Chain and Howard Florey began an intensive effort to isolate penicillin from 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.

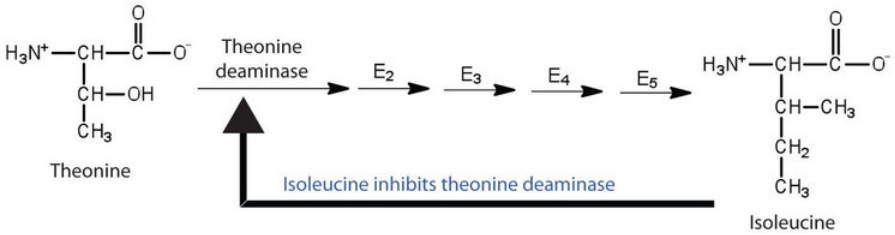


Figure 10.11.2: Feedback Inhibition of Threonine Deaminase by Isoleucine. Threonine deaminase is the first enzyme in the conversion of threonine to isoleucine. Isoleucine inhibits threonine deaminase through feedback inhibition.

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 10.11.2).

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.

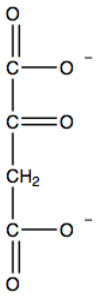
Concept Review Exercises

1. What are the characteristics of an irreversible inhibitor?
2. In what ways does a competitive inhibitor differ from a noncompetitive inhibitor?

Answers

1. It inactivates an enzyme by bonding covalently to a particular group at the active site.
2. A competitive inhibitor structurally resembles the substrate for a given enzyme and 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 and can bind to either the free enzyme or the enzyme-substrate complex.

Exercises

1. What amino acid is present in the active site of all enzymes that are irreversibly inhibited by nerve gases such as DIFP?
2. Oxaloacetate,  (-OOCCH2COCOO-), inhibits succinate dehydrogenase. Would you expect oxaloacetate to be a competitive or noncompetitive inhibitor? Explain.

Answer

1. serine

2. One would expect oxaloacetate to be a competitive inhibitor, since it is similar in structure to succinate and thus, may be able to fit in succinate dehydrogenase's active site.

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10.12: 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 **10.12.1**: 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 **10.12.1** and **10.12.2**.

Table **10.12.2**: 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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10.13: Basic Principles of Catalysis

A printable version of this section is here: BiochemFFA_4_1.pdf. The entire textbook is available for free from the authors at http://biochem.science.oregonstate.edu/content/biochemistry-free-and-easy

If there is a magical component to life, an argument can surely be made for it being catalysis. Thanks to catalysis, reactions that can take hundreds of years to complete in the uncatalyzed “real world,” occur in seconds in the presence of a catalyst. Chemical catalysts, such as platinum, can speed reactions, but enzymes (which are simply super-catalysts with a “twist,” as we shall see) put chemical catalysts to shame (Figure 4.1). To understand enzymatic catalysis, it is necessary first to understand energy. Chemical reactions follow the universal trend of moving towards lower energy, but they often have a barrier in place that must be overcome. The secret to catalytic action is reducing the magnitude of that barrier.

Enzyme	Nonenzymatic Half-Life	Uncatalyzed Rate (k_{un} s^{-1})	Catalyzed Rate (k_{cat} s^{-1})	Rate Enhancement (k_{cat} s^{-1}/k_{un} s^{-1})
OMP decarboxylase	78,000,000 years	28×10^{-16}	39	1.4×10^{17}
Staphylococcal nuclease	130,000 years	1.7×10^{-13}	95	5.6×10^{14}
Carboxypeptidase A	7.3 years	3.0×10^{-9}	578	1.9×10^{11}
Ketosteroid isomerase	7 weeks	1.7×10^{-7}	66,000	3.9×10^{11}
Triose phosphate isomerase	1.9 days	4.3×10^{-6}	4,300	1.0×10^{9}
Chorismate mutase	7.4 hours	2.6×10^{-5}	50	1.9×10^{6}
Carbonic anhydrase	5 seconds	1.3×10^{-1}	1×10^{6}	7.7×10^{6}

Abbreviations:
OMP - Orotine monophosphate
AMP - Adenosine monophosphate

Figure 4.1 - Rate enhancement for several enzymes Image by Aleia Kim

Before discussing enzymes, it is appropriate to pause and discuss an important concept relating to chemical/biochemical reactions. That concept is *equilibrium* and it is very often misunderstood. The “equi" part of the word relates to equal, as one might expect, but it does not relate to absolute concentrations. What happens when a biochemical reaction is at equilibrium is that the concentrations of reactants and products do not change over time. This does not mean that the reactions have stopped. Remember that reactions are reversible, so there is a forward reaction and a reverse reaction: if you had 8 molecules of A, and 4 of B at the beginning, and 2 molecules of A were converted to B, while 2 molecules of B were simultaneously converted back to A, the number of molecules of A and B remain unchanged, i.e., the reaction is at equilibrium. However, you will notice that this does not mean that there are equal numbers of A and B molecules.

Concentration Matters

So, contrary to the perceptions of many students, the concentrations of products and reactants are not equal at equilibrium, unless the ΔG°’ for a reaction is zero, because when this is the case,

$$\Delta G = \ln\left(\frac{[\text{Products}]}{[\text{Reactants}]}\right) \tag{10.13.1}$$

since the ΔG°’ is zero. Because ΔG itself is zero at equilibrium, then

$$[Products] = [Reactants]. \tag{10.13.2}$$

This is the only circumstance where

$$[Products] = [Reactants] \tag{10.13.3}$$

at equilibrium. Reiterating, at equilibrium, the concentrations of reactant and product do not change over time. That is, for a reaction $A \rightleftharpoons B[A]$ at time zero when equilibrium is reached, $[A]_{T_0}$, will be the same 5 minutes later (assuming A and B are chemically stable). Thus,

$$[A]_{T_0} = [A]_{T+5} \tag{10.13.4}$$

Similarly,

$$[B]_{T_0} = [B]_{T+5} \tag{10.13.5}$$

For that matter, at any amount of time X after equilibrium has been reached,

$$[A]T0 = [A]T + 5 = [A]TX \tag{10.13.6}$$

and

$$[B]T0 = [B]T + 5 = [B]TX \tag{10.13.7}$$

However, unless ΔG°' = 0, it is wrong to say [A]T0 = [B]T0 As we study biochemical reactions and reaction rates, it is important to remember that 1) reactions do not generally start at equilibrium; 2) all reactions move in the direction of equilibrium; and 3) reactions in cells behave just like those in test tubes - they do not begin at equilibrium, but they move towards it. Dynamic reactions The reactions occurring in cells, though, are very dynamic and complex. In a test tube, they can be studied one at a time. In cells, the product of one reaction is often the substrate for another one. Reactions in cells are interconnected in this way, giving rise to what are called metabolic pathways. There are, in fact, thousands of different interconnected reactions going on continuously in cells.

Attempts to study a single reaction in the chaos of a cell is daunting to say the least. For this reason, biochemists isolate enzymes from cells and study reactions individually. It is with this in mind that we begin our consideration of the phenomenon of catalysis by describing, first, the way in which enzymes work.

Activation energy

Figure 4.2 schematically depicts the energy changes that occur during the progression of a simple reaction. In order for the reaction to proceed, an activation energy must be overcome in order for the reaction to occur.

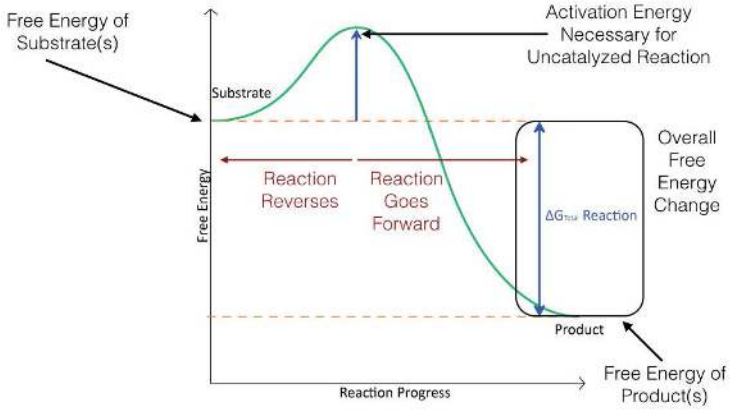


Figure 4.2 - Energy changes during the course of an uncatalyzed reaction. Image by Aleia Kim

In Figure 4.3, the activation energy for a catalyzed reaction is overlaid. As you can see, the reactants start at the same energy level for both catalyzed and uncatalyzed reactions and that the products end at the same energy for both as well. The catalyzed reaction, however, has a lower energy of activation (dotted line) than the uncatalyzed reaction. This is the secret to catalysis - overall ΔG for a reaction does NOT change with catalysis, but the activation energy is lowered.

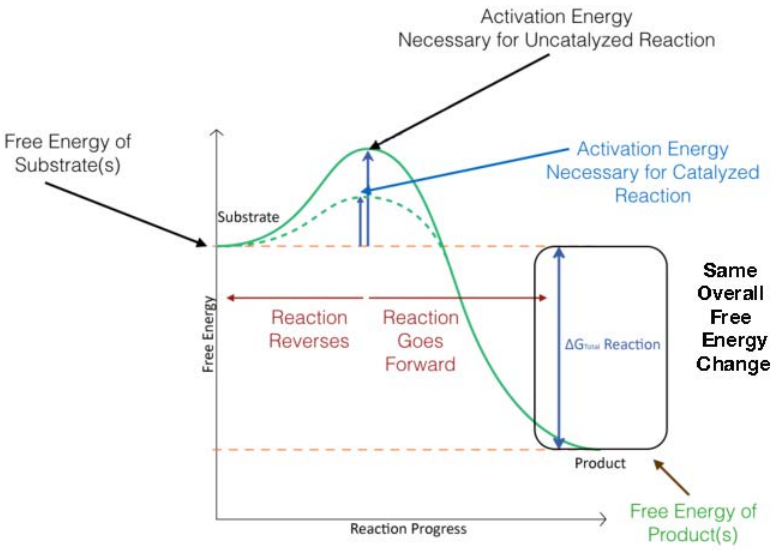


Figure 4.3 - Energy changes during the course of an uncatalyzed reaction (solid green line) and a catalyzed reaction (dotted green line). Image by Aleia Kim

Reversibility

The extent to which reactions will proceed forward is a function of the size of the energy difference between the product and reactant states. The lower the energy of the products compared to the reactants, the larger the percentage of molecules that will be present as products at equilibrium. It is worth noting that since an enzyme lowers the activation energy for a reaction that it can speed the reversal of a reaction just as it speeds a reaction in the forward direction. At equilibrium, of course, no change in concentration of reactants and products occurs. Thus, enzymes speed the time required to reach equilibrium, but do not affect the balance of products and reactants at equilibrium.

Exceptions

The reversibility of enzymatic reactions is an important consideration for equilibrium, the measurement of enzyme kinetics, for Gibbs free energy, for metabolic pathways, and for physiology. There are some minor exceptions to the reversibility of reactions, though. They are related to the disappearance of a substrate or product of a reaction. Consider the first reaction below which is catalyzed by the enzyme carbonic anhydrase:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons HCO_3^- + H^+ \tag{10.13.8}$$

In the forward direction, carbonic acid is produced from water and carbon dioxide. It can either remain intact in the solution or ionize to produce bicarbonate ion and a proton. In the reverse direction, water and carbon dioxide are produced. Carbon dioxide, of course, is a gas and can leave the solution and escape.

When reaction molecules are removed, as they would be if carbon dioxide escaped, the reaction is pulled in the direction of the molecule being lost and reversal cannot occur unless the missing molecule is replaced. In the second reaction occurring on the right, carbonic acid (H2CO3) is “removed” by ionization. This too would limit the reaction going back to carbon dioxide in water. This last type of “removal” is what occurs in metabolic pathways. In this case, the product of one reaction (carbonic acid) is the substrate for the next (formation of bicarbonate and a proton).

In the metabolic pathway of glycolysis, ten reactions are connected in this manner and reversing the process is much more complicated than if just one reaction was being considered.

General mechanisms of action

As noted above, enzymatically catalyzed reactions are orders of magnitude faster than uncatalyzed and chemical-catalyzed reactions. The secret of their success lies in a fundamental difference in their mechanisms of action.

Every chemistry student has been taught that a catalyst speeds a reaction without being consumed by it. In other words, the catalyst ends up after a reaction just the way it started so it can catalyze other reactions, as well. Enzymes share this property, but in the middle, during the catalytic action, an enzyme is transiently changed. In fact, it is the ability of an enzyme to change that leads to its incredible efficiency as a catalyst.

Changes

These changes may be subtle electronic ones, more significant covalent modifications, or structural changes arising from the flexibility inherent in enzymes, but not present in chemical catalysts. Flexibility allows movement and movement facilitates alteration of electronic environments necessary for catalysis. Enzymes are, thus, much more efficient than rigid chemical catalysts as a result of their abilities to facilitate the changes necessary to optimize the catalytic process.

Substrate binding

Another important difference between the mechanism of action of an enzyme and a chemical catalyst is that an enzyme has binding sites that not only ‘grab’ the substrate (molecule involved in the reaction being catalyzed), but also place it in a position to be electronically induced to react, either within itself or with another substrate.

The enzyme itself may play a role in the electronic induction or the induction may occur as a result of substrates being placed in very close proximity to each other. Chemical catalysts have no such ability to bind substrates and are dependent upon them colliding in the right orientation at or near their surfaces.

Active site

Reactions in an enzyme are catalyzed at a specific location within it known as the ‘active site’. Substrates bind at the active site and are oriented to provide access for the relevant portion of the molecule to the electronic environment of the enzyme where catalysis occurs.

Enzyme flexibility

As mentioned earlier, a difference between an enzyme and a chemical catalyst is that an enzyme is flexible. Its slight changes in shape (often arising from the binding of the substrate itself) help to optimally position substrates for reaction after they bind.

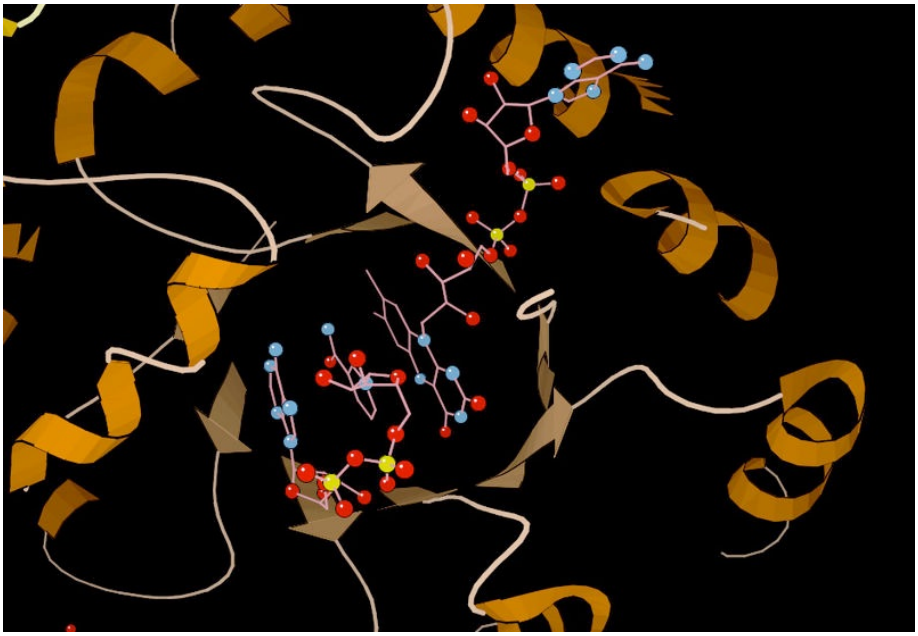


Figure 4.4 - Substrate binding by methylenetetrahydrofolate reductase

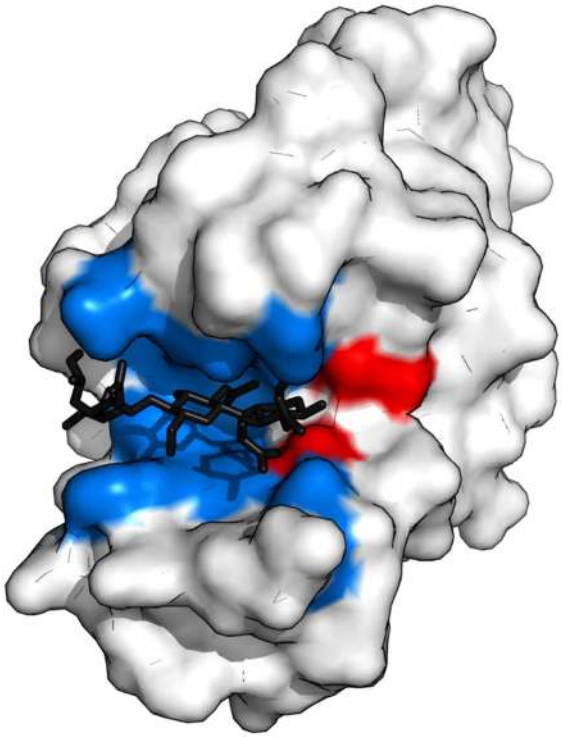


Figure 4.5 - Lysozyme with substrate binding site (blue), active site (red) and bound substrate (black). Wikipedia

Induced fit

These changes in shape are explained, in part, by Koshland's Induced Fit Model of Catalysis (Figure 4.6), which illustrates that not only do enzymes change substrates, but that substrates also transiently change enzyme structure. At the end of the catalysis, the enzyme is returned to its original state. Koshland's model is in contrast to the Fischer Lock and Key model, which says simply that an enzyme has a fixed shape that is perfectly matched for binding its substrate(s). Enzyme flexibility also is important for control of enzyme activity. Enzymes alternate between the T (tight) state, which is a lower activity state and the R (relaxed) state, which has greater activity.

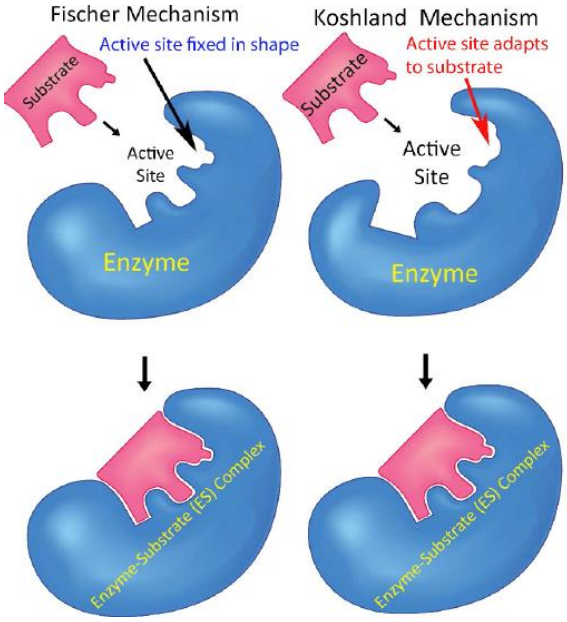


Figure 4.6 - Fischer's lock and key model (left) Vs. Koshland's induced fit model (right). Image by Aleia Kim

Induced Fit

The Koshland Induced Fit model of catalysis postulates that enzymes are flexible and change shape on binding substrate. Changes in shape help to 1) aid binding of additional substrates in reactions involving more than one substrate and/or 2) facilitate formation of an electronic environment in the enzyme that favors catalysis. This model is in contrast to the Fischer Lock and Key Model of catalysis which considers enzymes as having pre-formed substrate binding sites.

Ordered binding

The Koshland model is consistent with multi-substrate binding enzymes that exhibit ordered binding of substrates. For these systems, binding of the first substrate induces structural changes in the enzyme necessary for binding the second substrate.

There is considerable experimental evidence supporting the Koshland model. Hexokinase, for example, is one of many enzymes known to undergo significant structural alteration after binding of substrate. In this case, the two substrates are brought into very close proximity by the induced fit and catalysis is made possible as a result.

Enzyme kinetics

To understand how an enzyme enhances the rate of a reaction, we must understand enzyme kinetics. We present a model here proposed by Leonor Michaelis and Maud Menten. In order to understand the model, it is necessary to understand a few parameters.

First, we describe a reaction in simple terms proceeding as follows

E + S ⇄ ES -> E + P

where E is enzyme, S is substrate, and P is product. In this scheme, ES is the Enzyme-Substrate complex, which is simply the enzyme bound to its substrate.

We could define the ES state a bit further with

E + S ⇄ ES -> ES* -> EP -> E + P

where ES* is the activated state and EP is the enzyme-product complex before release of the product.

The first consideration we have is velocity. The velocity of a reaction is the rate of creation of product over time, measured as the concentration of product per time. The time is a critical consideration when measuring velocity. In a closed system (in which an enzyme operates), all reactions will advance towards equilibrium. Enzymatically catalyzed reactions are no different in the end result from non-enzymatic reactions, except that they get to equilibrium faster.

Equilibrium

At equilibrium, the ratio of product to reactant does not change. That is a property of equilibrium. Since the system is closed, the concentration of product over time will not change. The velocity will thus be zero under these conditions and we will have learned nothing about the reaction if we wait too long to study it.

Velocity

Enzyme	Turnover Number (per second)
Carbonic anhydrase	600,000
3-Ketoesteroid isomerase	280,000
Acetylcholinesterase	25,000
Penicillinase	2,000
Lactate dehydrogenase	1,000
Chymostrypsin	100
DNA Polymerase I	15
Tryptophan synthetase	2
Lysozyme	0.5

Figure 4.22 - Kcat/Km values for perfect enzymes. Image by Aleia Kim

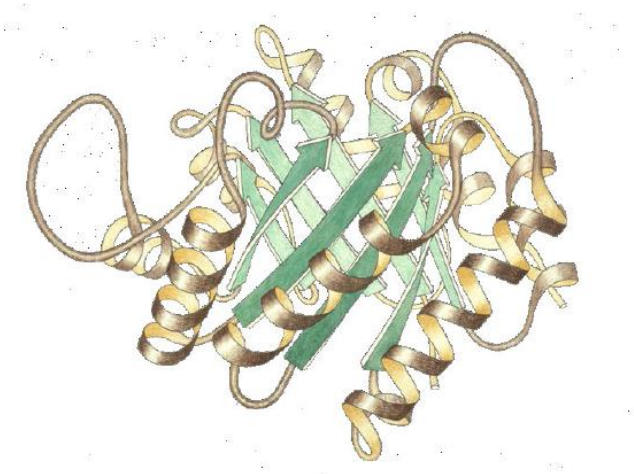


Figure 4.23 - Triose phosphate isomerase - A perfect enzyme. Wikipedia

Consequently, in Michaelis-Menten kinetics, velocity is measured as initial velocity (V_0). This is accomplished by measuring the rate of formation of product early in the reaction before equilibrium is established and under these conditions, there is very little if any of the reverse reaction occurring.

The other two assumptions are related. First, we use conditions where there is much more substrate than enzyme. This makes sense. If the substrate is not in great excess, then the enzyme's conversion of substrate to product will occur much faster than the enzyme can bind substrate.

Experimental considerations

Now we turn our attention to how studies of the kinetic properties of an enzyme are conducted. To perform an analysis, one would do the following experiment - 20 different tubes would be set up with enzyme buffer (to keep the enzyme stable), the same amount of enzyme, and then a different amount of substrate in each tube, ranging from tiny amounts in the first tubes to very large amounts in the last tubes. The reaction would be allowed to proceed for a fixed, short amount of time and then the reaction would be stopped and the amount of product contained in each tube would be determined.

The initial velocity (V_0) of the reaction then would be the concentration of product found in each tube divided by the time that the reaction was allowed to run. Data from the experiment would be plotted on a graph using initial velocity (V_0) on the Y-axis and the concentration of substrate on the X-axis, each tube, of course having a unique reaction velocity corresponding to a unique substrate concentration.

For an enzyme following Michaelis-Menten kinetics, a curve like that shown in Figure 4.18 or 4.19 would result. At low concentration of substrate, it is limiting and the enzyme converts it into product as soon as it can bind it. Consequently, at low

concentrations of substrate, the rate of increase of [P] is almost linear with [S] (Figure 4.19).

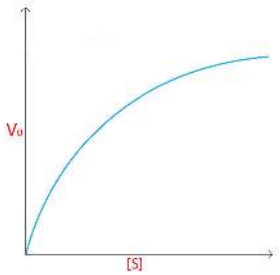


Figure 4.18 - Kinetics of an enzyme obeying Michaelis-Menten kinetics. Image by Aleia Kim

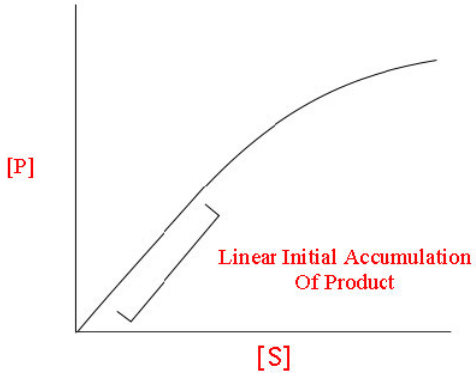


Figure 4.19 - Linear relationship between [P] and [S] at low [S]

Non-linear increase

As the substrate concentration increases, however, the velocity of the reaction in tubes with higher substrate concentration ceases to increase linearly and instead begins to flatten out, indicating that as the substrate concentration gets higher and higher, the enzyme has a harder time keeping up to convert the substrate to product.

Saturation

Not surprisingly, when the enzyme becomes completely saturated with substrate, it will not have to wait for substrate to diffuse to it and will therefore be operating at maximum velocity.

For an enzyme following Michaelis-Menten kinetics will have its velocity (v) at any given substrate concentration given by the following equation:

$$v = \frac{V_{\max}[S]}{K_m + [S]}$$

V_{max}

Two terms in the equation above require explanation. The first is V_{max}. It refers to the maximum velocity of an enzymatic reaction. Maximum velocity for a reaction occurs when an enzyme is saturated with substrate. Saturation is important because it means (per the assumption above) that none of the enzyme molecules are “waiting” for substrate after a product is released. Saturation ensures that another substrate is always instantly available. The unit of V_{max} is concentration of product per time = [P]/time.

On a plot of initial velocity versus substrate concentration (V0 vs. [S]), V_{max} is the value on the Y axis that the curve asymptotically approaches (dotted line in Figure 4.20). It should be noted that the value of V_{max} depends on the amount of enzyme used in a reaction. If you double the amount of enzyme used, you will double the V_{max}. If one wanted to compare the velocities of two different enzymes, it would be necessary to use the same amounts of enzyme in the reaction each one catalyzes.

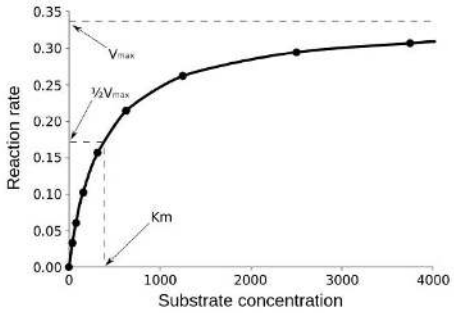


Figure 4.20 - V_{max}, $V_{max}/2$, and Km

Km

The second term is Km (also known as Ks). Referred to as the Michaelis constant, Km is the substrate concentration that causes the enzyme to work at half of maximum velocity (Vmax/2). What it measures, in simple terms, is the affinity an enzyme has for its substrate. The value of Km is inversely related to the affinity of the enzyme for its substrate. Enzymes with a high Km value will have a lower affinity for their substrate (will take more substrate to get to Vmax/2) whereas those with a low Km will have high affinity and take less substrate to get to Vmax/2. The unit of Km is concentration.

Affinities of enzymes for substrates vary considerably, so knowing Km helps us to understand how well an enzyme is suited to the substrate being used. Measurement of Km depends on the measurement of Vmax.

Common mistake

A common mistake students make in describing Vmax is saying that Km = Vmax /2. This is, of course, not true. Km is a substrate concentration and is the amount of substrate it takes for an enzyme to reach Vmax /2. On the other hand Vmax /2 is a velocity and a velocity certainly cannot equal a concentration.

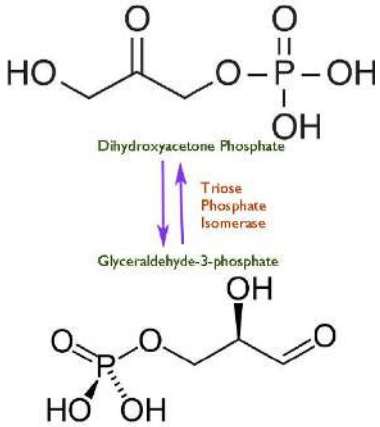


Figure 4.24 - Triose phosphate isomerase-catalyzed reaction

Lineweaver-Burk plots

The study of enzyme kinetics is typically the most math intensive component of biochemistry and one of the most daunting aspects of the subject for many students. Although attempts are made to simplify the mathematical considerations, sometimes they only serve to confuse or frustrate students. Such is the case with modified enzyme plots, such as Lineweaver-Burk (Figure 4.26).

Indeed, when presented by professors as simply another thing to memorize, who can blame students? In reality, both of these plots are aimed at simplifying the determination of parameters, such as K_m and V_{max}. In making either of these modified plots, it is

important to recognize that the same data is used as in making a V0 vs. [S] plot. The data are simply manipulated to make the plotting easier.

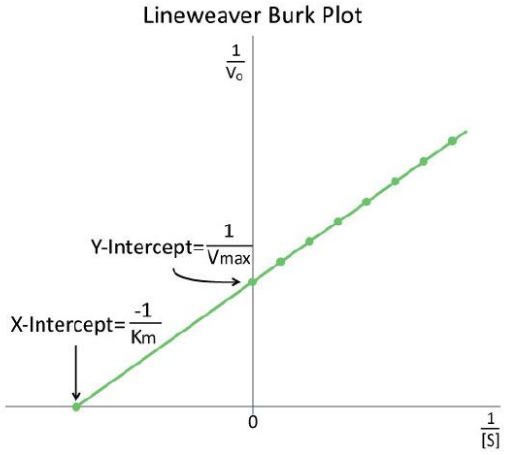


Figure 4.26 - A Lineweaver-Burk plot of $1/V_0$ *vs* $1/[S]$. *Image by Aleia Kim*

Double reciprocal

For a LineWeaver-Burk plot, the manipulation is using the reciprocal of the values of both the velocity and the substrate concentration. The inverted values are then plotted on a graph as $1/V_0$ vs. 1/[S]. Because of these inversions, Lineweaver-Burk plots are commonly referred to as 'double-reciprocal' plots. As can be seen in Figure 4.26, the value of Km on a Lineweaver Burk plot is easily determined as the negative reciprocal of the x-intercept , whereas the Vmax is the inverse of the y-intercept.

Coenzymes

Organic molecules that assist enzymes and facilitate catalysis are co-factors called coenzymes. The term co-factor is a broad category usually subdivided into inorganic ions and coenzymes. If the coenzyme is very tightly or covalently bound to the enzyme, it is referred to as a prosthetic group. Enzymes without their co-factors are inactive and referred to as apoenzymes. Enzymes containing all of their co-factors are called holoenzymes.

Cofactor	Enzyme
Coenzyme	
5′-Deoxyadenosyl cobalamin	Methylmalonyl mutase
Biotin	Pyruvate carboxylase
Coenzyme A (CoA)	Acetyl CoA carboxylase
Flavin adenine nucleotide	Monoamine oxidase
Nicotinamide adenine dinucleotide	Lactate dehydrogenase
Pyridoxal phosphate	Glycogen phosphorylase
Tetrahydrofolate	Thymidylate synthase
Thiamine pyrophosphate	Pyruvate dehydrogenase
Metal	
K^+	Propionyl CoA carboxylase
Mg^{2+}	Restriction Endonucleases; Hexokinase
Mn	Superoxide dismutase
Mo	Nitrate reductase
Ni^{2+}	Urease
Se	Glutathione peroxidase
Zn^{2+}	Carbonic anhydrase; Carboxypeptidase

Figure 4.27 - Enzyme cofactors. Image by Aleia Kim

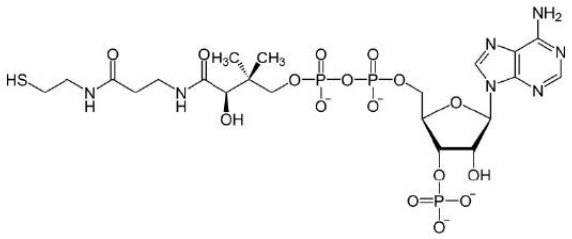


Figure 4.28 - Coenzyme A (CoA)

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10.14: Control of Enzymatic Activity

A printable version of this section is here: BiochemFFA_4_2.pdf. The entire textbook is available for free from the authors at http://biochem.science.oregonstate.edu/content/biochemistry-free-and-easy

Regulation of enzyme activity

Apart from their ability to greatly speed the rates of chemical reactions in cells, enzymes have another property that makes them valuable. This property is that their activity can be regulated, allowing them to be activated and inactivated, as necessary. This is tremendously important in maintaining homeostasis, permitting cells to respond in controlled ways to changes in both internal and external conditions.

Inhibition of specific enzymes by drugs can also be medically useful. Understanding the mechanisms that control enzyme activity is, therefore, of considerable importance.

Inhibition

We will first discuss four types of enzyme inhibition – competitive, non-competitive, uncompetitive, and suicide inhibition. Of these, the first three types are reversible. The last one, suicide inhibition, is not.

Competitive inhibition

Probably the easiest type of enzyme inhibition to understand is competitive inhibition and it is the one most commonly exploited pharmaceutically. Molecules that are competitive inhibitors of enzymes resemble one of the normal substrates of an enzyme. An example is methotrexate, which resembles the folate substrate of the enzyme dihydrofolate reductase (DHFR). This enzyme normally catalyzes the reduction of folate, an important reaction in the metabolism of nucleotides.

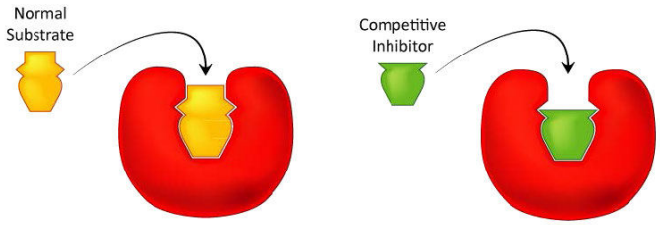


Figure 4.33 - Competitive inhibitors resemble the normal substrate and compete for binding at the active site. Image by Aleia Kim

Inhibitor binding

When the drug methotrexate is present, some of the DHFR enzyme binds to it, instead of to folate, and during the time methotrexate is bound, the enzyme is inactive and unable to bind folate. Thus, the enzyme is inhibited. Notably, the binding site on DHFR for methotrexate is the active site, the same place that folate would normally bind. As a result, methotrexate 'competes' with folate for binding to the enzyme. The more methotrexate there is, the more effectively it competes with folate for the enzyme's active site. Conversely, the more folate there is, the less of an effect methotrexate has on the enzyme because folate outcompetes it.

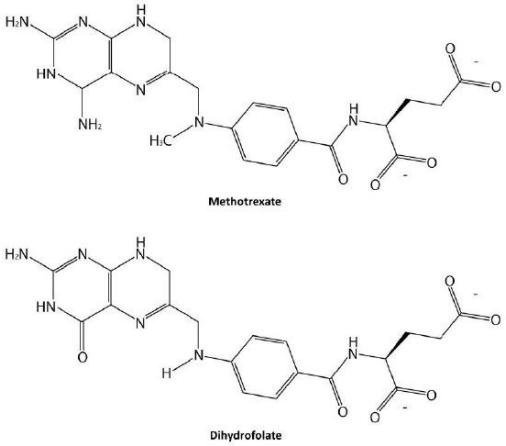


Figure 4.34 - Methotrexate and dihydrofolate. Image by Ben Carson

No effect on Vmax

How do we study competitive inhibition? It is typically done as follows. First, one performs a set of V0 vs. [S] reactions without inhibitor (20 or so tubes, with buffer and constant amounts of enzyme, varying amounts of substrate, equal reaction times). V0 vs. [S] is plotted (Figure 4.35 red line), as well as 1/V0 vs. 1/[S] (Figure 4.36 green line). Next, a second set of reactions is performed in the same manner as before, except that a fixed amount of the methotrexate inhibitor is added to each tube. At low concentrations of substrate, the methotrexate competes for the enzyme effectively, but at high concentrations of substrate, the inhibitor will have a much reduced effect, since the substrate outcompetes it, due to its higher concentration (remember that the inhibitor is at fixed concentration).

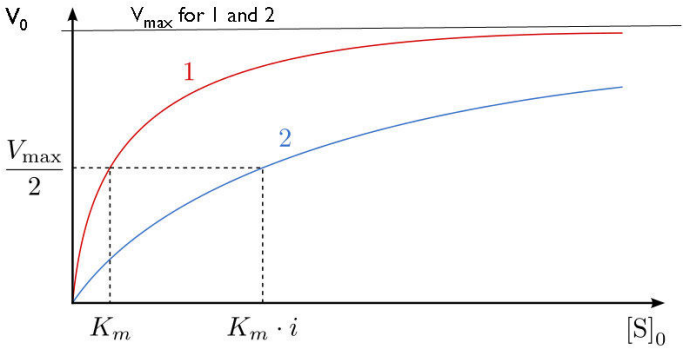


Figure 4.35 V0 vs [S] Plots for uninhibited reactions (red) and competitively inhibited reactions (blue). Both ultimately have same Vmax

Graphically, the results of these inhibitor experiments are shown in Figure 4.35 (blue line) and Figure 4.36 (orange line). Notice that at high substrate concentrations, the competitive inhibitor has essentially no effect, causing the V_{max} for the enzyme to remain unchanged. To reiterate, this is due to the fact that at high substrate concentrations, the inhibitor doesn't compete well. However, at lower substrate concentrations, it does.

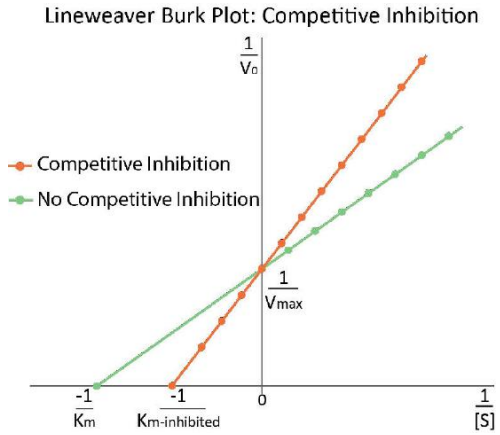


Figure 4.36 - Lineweaver-Burk plots - uninhibited reactions (green). Competitively inhibited reactions (orange). Lines cross on Y-axis at 1/Vmax Since Vmax is the same for both reactions. Image by Aleia Kim

Increased K_m

In competitively inhibited reactions, the apparent Km of the enzyme for the substrate increases ($-1/K_m$ gets closer to zero - red line in Figure 4.36) when the inhibitor is present compared to when the inhibitor is absent, thus illustrating the better competition of the inhibitor at lower substrate concentrations. It may not be obvious why we call the changed Km the apparent Km of the enzyme. The reason is that the inhibitor doesn't actually change the enzyme's affinity for the folate substrate. It only appears to do so. This is because of the way that competitive inhibition works. When the competitive inhibitor binds the enzyme, it is effectively 'taken out of action.' Inactive enzymes have NO affinity for substrate and no activity either. We can't measure Km for an inactive enzyme.

The enzyme molecules that are not bound by methotrexate can, in fact, bind folate and are active. Methotrexate has no effect on them and their Km values are unchanged. Why then, does Km appear higher in the presence of a competitive inhibitor? The reason is that the competitive inhibitor is having a greater effect of reducing the amount of active enzyme at lower concentrations of substrate than it does at higher concentrations of substrate. When the amount of enzyme is reduced, one must have more substrate to supply the reduced amount of enzyme sufficiently to get to Vmax/2.

It is worth noting that in competitive inhibition, the percentage of inactive enzyme changes drastically over the range of [S] values used. To start, at low [S] values, the greatest percentage of the enzyme is inhibited. At high [S], no significant percentage of enzyme is inhibited. This is not always the case, as we shall see in non-competitive inhibition.

Non-competitive inhibition

A second type of inhibition employs inhibitors that do not resemble the substrate and bind not to the active site, but rather to a separate site on the enzyme (Figure 4.37). The effect of binding a non-competitive inhibitor is significantly different from binding a competitive inhibitor because there is no competition. In the case of competitive inhibition, the effect of the inhibitor could be reduced and eventually overwhelmed with increasing amounts of substrate. This was because increasing substrate made increasing percentages of the enzyme active. With non-competitive inhibition, increasing the amount of substrate has no effect on the percentage of enzyme that is active. Indeed, in non-competitive inhibition, the percentage of enzyme inhibited remains the same through all ranges of [S].

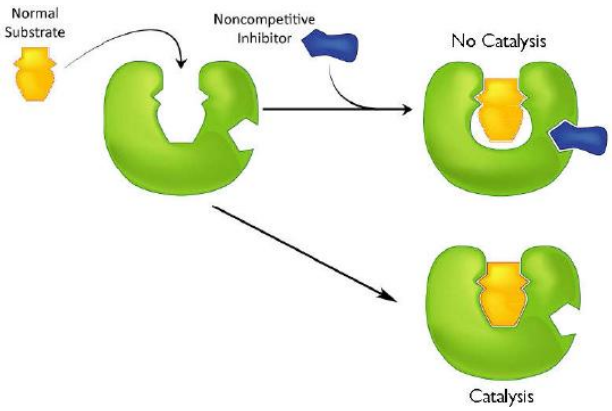


Figure 4.37 - Non-competitive inhibition - inhibitor does not resemble the substrate and binds to a site other than the active site. Image by Aleia Kim

This means, then, that non-competitive inhibition effectively reduces the amount of enzyme by the same fixed amount in a typical experiment at every substrate concentration used The effect of this inhibition is shown in Figure 4.38 & 4.39. As you can see, V_{max} is reduced in non-competitive inhibition compared to uninhibited reactions.

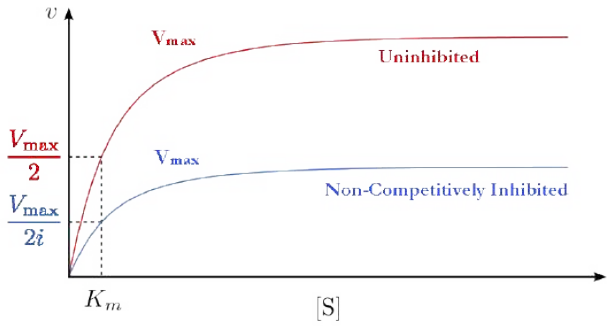


Figure 4.38 - V0 vs [S] plots of uninhibited reactions (red) and non-competitively inhibited reactions (blue). Vmax is reduced, but Km values are unchanged in non-competitively inhibited reactions

This makes sense if we remember that Vmax is dependent on the amount of enzyme present. Reducing the amount of enzyme present reduces V_{max}. In competitive inhibition, this doesn't occur detectably, because at high substrate concentrations, there is essentially 100% of the enzyme active and the V_{max} appears not to change. Additionally, Km for non-competitively inhibited reactions does not change from that of uninhibited reactions. This is because, as noted previously, one can only measure the K_m of active enzymes and K_m is a constant for a given enzyme.

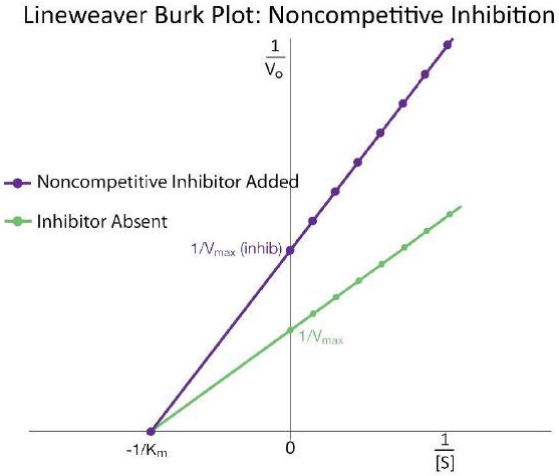


Figure 4.39 - Lineweaver Burk plots of uninhibited reactions (green) and non-competitively inhibited reactions (purple). Image by Aleia Kim

Control of enzymes

It is appropriate to talk at this point about mechanisms cells use to control enzymes. There are four general methods that are employed:

1. allosterism,
2. covalent modification,
3. access to substrate, and
4. control of enzyme synthesis/breakdown.

Some enzymes are controlled by more than one of these methods.

Allosterism

The term allosterism refers to the fact that the activity of certain enzymes can be affected by the binding of small molecules. Molecules causing allosteric effects come in two classifications. Ones that are substrates for the enzymes they affect are called **homotropic effectors** and those that are not substrates are called heterotropic effectors.

The homotropic effectors usually are activators of the enzymes they bind to and the results of their action can be seen in the conversion of the hyperbolic curve typical of a V_0 vs. [S] plot for an enzyme (Figure 4.18), being converted to a sigmoidal plot (Figure 4.44). This is due to the conversion of the enzyme from the T-state to the R-state on binding the substrate/homotropic effector.

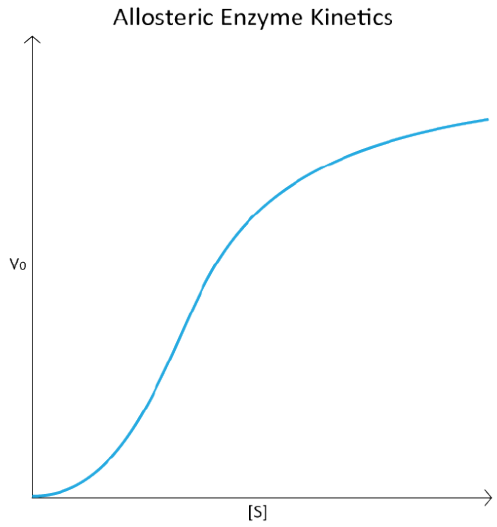


Figure 4.44 - Kinetic profile of an allosteric enzyme whose activity is controlled by a homotropic effector. Image by Aleia Kim

The V_0 vs. [S] plot of allosteric enzyme reactions resembles the oxygen binding curve of hemoglobin (see Figure 2.83). Even though hemoglobin is not an enzyme and is thus not catalyzing a reaction, the similarity of the plots is not coincidental. In both cases, the binding of an external molecule is being measured – directly, in the hemoglobin plot, and indirectly by the V0 vs. [S] plot, since substrate binding is a factor in enzyme reaction velocity.

Allosteric inhibition

Allosterically, regulation of these enzymes works by inducing different physical states (shapes, as it were) that affect their ability to bind to substrate. When an enzyme is inhibited by binding an effector, it is converted to the T-state (T=tight), it has a reduced affinity for substrate and it is through this means that the reaction is slowed.

Allosteric activation

On the other hand, when an enzyme is activated by effector binding, it converts to the R-state (R=relaxed) and binds substrate much more readily. When no effector is present, the enzyme may be in a mixture of T- and R-states.

Feedback inhibition

An interesting kind of allosteric control is exhibited by HMG-CoA reductase, which catalyzes an important reaction in the pathway leading to the synthesis of cholesterol. Binding of cholesterol to the enzyme reduces the enzyme's activity significantly. Cholesterol is not a substrate for the enzyme, so it is therefore a heterotropic effector.

Notably, though, cholesterol is the end-product of the pathway that HMG-CoA reductase catalyzes a reaction in. When enzymes are inhibited by an end-product of the pathway in which they participate, they are said to exhibit feedback inhibition.

Feedback inhibition always operates by allosterism and further, provides important and efficient control of an entire pathway. By inhibiting an early enzyme in a pathway, the flow of materials (and ATP hydrolysis required for their processing) for the entire pathway is stopped or reduced, assuming there are not alternate supply methods.

Pathway control

In the cholesterol biosynthesis pathway, stopping this one enzyme has the effect of shutting off (or at least slowing down) the entire pathway. This is significant because after catalysis by HMG-CoA reductase, there are over 20 further reactions necessary to make cholesterol, many of them requiring ATP energy. Shutting down one reactions stops all of them. Another excellent example of allosteric control and feedback inhibition is the enzyme ATCase, discussed below.

ATCase

Another interesting example of allosteric control and feedback inhibition is associated with the enzyme Aspartate Transcarbamoylase (ATCase). This enzyme, which catalyzes a step in the synthesis of pyrimidine nucleotides, has 12 subunits. These include six identical catalytic subunits and six identical regulatory subunits. The catalytic subunits bind to substrate and catalyze a reaction. The regulatory subunits bind to either ATP or CTP. If they bind to ATP, the enzyme subunits arrange themselves in the R-state.

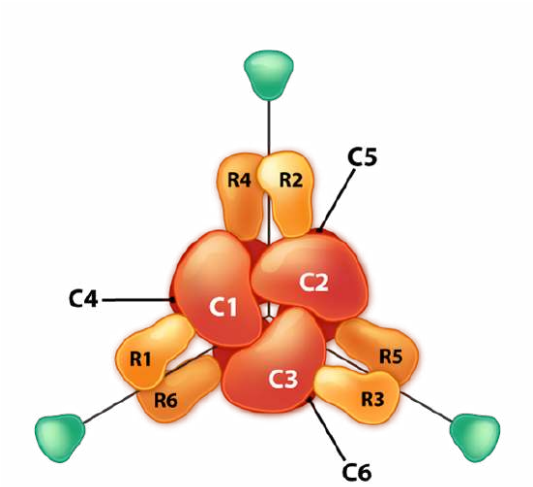


Figure 4.45 - Schematic structure of ATCase. Regulatory Units = R, Catalytic Units = C. Image by Aleia Kim

R-state

The R-state of ATCase allows the substrate to have easier access to the six active sites and the reaction occurs more rapidly. For the same amount of substrate, an enzyme in the R-state will have a higher velocity than the same enzyme that is not in the R-state. By contrast, if the enzyme binds to CTP on one of its regulatory subunits, the subunits will arrange in the T-state and in this form, the substrate will not have easy access to the active sites, resulting in a slower velocity for the same concentration of substrate compared to the R-state. ATCase is interesting in that it can also flip into the R-state when one of the substrates (aspartate) binds to an active site within one of the catalytic subunits.

Aspartate has the effect of activating the catalytic action of the enzyme by favoring the R-state. Thus, aspartate, which is a substrate of the enzyme is a homotropic effector and ATP and CTP, which are not substrates of the enzyme are heterotropic effectors of ATCase.

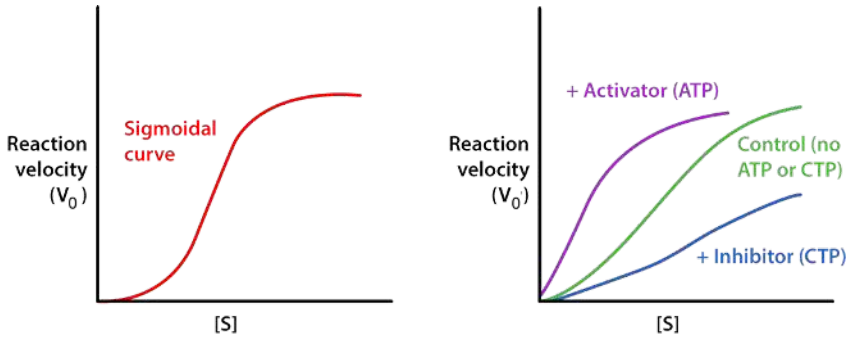


Figure 4.46 - Plots of V0 vs. [S] for ATCase. Left - Allosteric effect of aspartate. Right - Allosteric effects of ATP (activator) and CTP (inhibitor). Image by Pehr Jacobson

Allosteric models

There are three models commonly used to explain how allosterism regulates multi-subunit enzyme activity. They are known as

- the Monod-Wyman-Changeux (MWC) model (also known as the concerted model),
- the sequential model (also known as KNF),
- and the morpheein model.

All models describe a Tense (T) state that is less catalytically active and a Relaxed (R) state that is more catalytically active. The models differ in how the states change.

Sequential model

In the sequential model, binding of an allosteric effector by one subunit causes it to change from T to R state (or vice versa) and that change makes it easier for adjacent subunits to similarly change state. With this model , there is a cause/effect relationship between binding of an effector by one subunit and change of state by an adjacent subunit.

In hemoglobin, for example, binding of one oxygen by one unit of the complex may induce that unit to flip to the R-state and, through interactions with other subunits, cause them to favor adopting the R configuration before they bind to oxygen. In this way, binding of one subunit favors binding of others and cooperativity can be explained by the change in binding affinity as oxygen concentration changes.

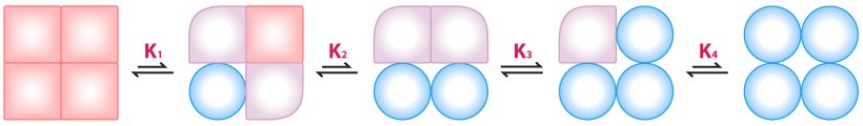


Figure 4.47 - Sequential model of allosteric regulation. Round = R-State. Square = T-state.. Image by Aleia Kim

MWC model

The MWC model is less intuitive. In it, the entire complex changes state from T to R (or vice versa) independently of the binding of effectors. Flipping between T-states and R-states is postulated to be in an equilibrium of states in the absence of effector (for example, a 50 to 1 ratio of T/R. This ratio is referred to as L, so L = T/R). Binding of effector by the enzyme complex has the tendency of “locking” the complex in a state. Binding of inhibitors will increase the ratio of T/R whereas binding of activators will increase R and thus decrease the ration of T/R.

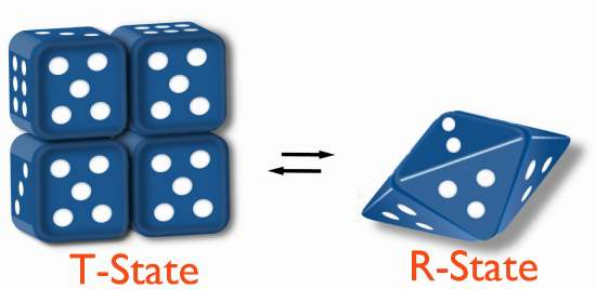


Figure 4.48 - The MWC Model - The multisubunit complex flips as a whole and is in equilibrium. Wikipedia

Morpheein model

The morpheein model is similar to the MWC model, but with an added step of dissociation of the subunits. The MWC model proposes that flipping between R and T states occurs by the complex as a whole and occurs on all units simultaneously. The morpheein model instead proposes that the multi-subunit enzyme breaks down to individual units which can then flip in structure and re-form the complex. In the morpheein model, only identically shaped units (all R, for example) can come together in the complex, thus explaining the “all-R-” or “all-T-” state found in the MWC model.

A large number of enzymes, including prominent ones like citrate synthase, acetyl-CoA carboxylase, glutamate dehydrogenase, ribonucleotide reductase and lactate dehydrogenase have behavior consistent with the morpheein model.



Figure 4.49 - Morpheein model of allosterism. States flip as monomers and aggregate only with same monomer. Wikipedia

Covalent control of enzymes

Some enzymes are synthesized in a completely inactive form and their activation requires covalent bonds in them to be cleaved. Such inactive forms of enzymes are called zymogens. Examples include the proteins involved in blood clotting and proteolytic enzymes of the digestive system, such as trypsin, chymotrypsin, pepsin, and others.

Synthesizing some enzymes in an inactive form makes very good sense when an enzyme’s activity might be harmful to the tissue where it is being made. For example, the painful condition known as pancreatitis arises when digestive enzymes made in the pancreas are activated too soon and end up attacking the pancreas.

Cascades

For both the blood clotting enzymes and the digestive enzymes, the zymogens are activated in a protease cascade. This occurs when activation of one enzyme activates others in a sort of chain reaction. In such a scheme the first enzyme activated proteolytically cleaves the second zymogen, causing it to be activated, which in turn activates a third and this may proceed through several levels of enzymatic action (Figure 4.50).

The advantage of cascades is that they allow a large amount of zymogens to become activated fairly quickly, since there is an amplification of the signal at each level of catalysis.

Zymogens are also abundant in blood. Blood clotting involves polymerization of a protein known as fibrin. Since random formation of fibrin is extremely hazardous because it can block the flow of blood, potentially causing heart attack/stroke, the body synthesizes fibrin as a zymogen (fibrinogen) and its activation results from a “cascade” of activations of proteases that arise when a signal is received from a wound. Similarly, the enzyme catalyzing removal of fibrin clots (plasmin) is also synthesized as a zymogen (plasminogen), since random clot removal would also be hazardous (see below also).

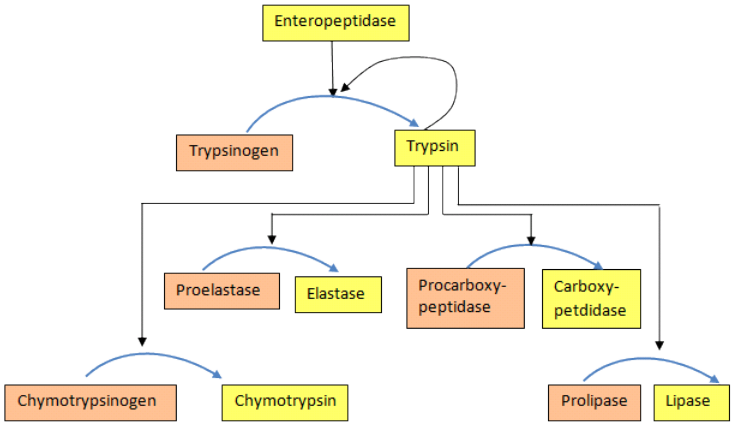


Figure 4.50 - Protease activation scheme. Wikipedia

Phosphorylation/dephosphorylation

Another common mechanism for control of enzyme activity by covalent modification is phosphorylation. The phosphorylation of enzymes (on the side chains of serine, threonine or tyrosine residues) is carried out by protein kinases. Enzymes activated by phosphorylation can be regulated by the addition of phosphate groups by kinases or their removal by phosphatases. Thus, this type of covalent modification is readily reversible, in contrast to proteolytic cleavage.

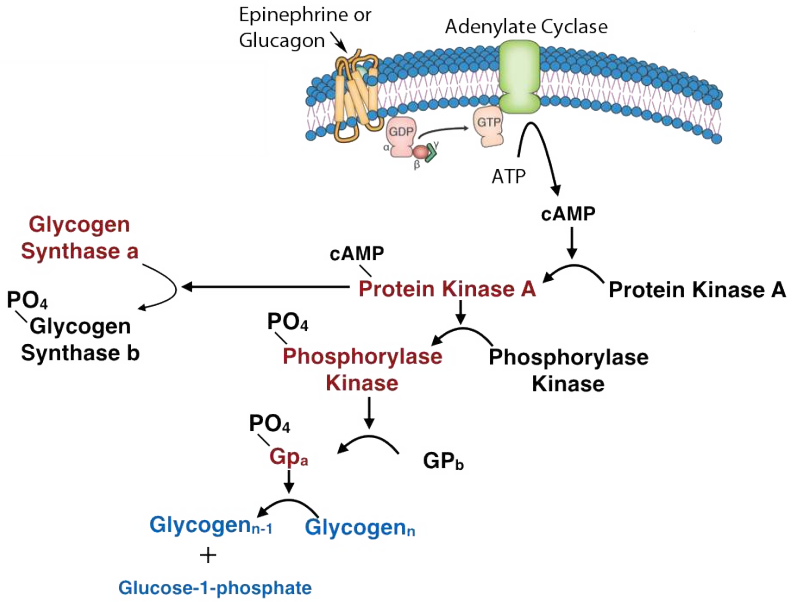


Figure 4.51 - Regulation by covalent modification of glycogen catabolism enzymes

Reduction/oxidation

An interesting covalent control of enzymes using reduction/oxidation is exhibited in photosynthetic plants. In the light phase of photosynthesis, electrons are excited by light and flow through carriers to NADP+, forming NADPH. Thus, in the light, the NADPH concentration is high. When NADPH concentration is high, the concentration of reduced ferredoxin (a molecule donating electrons to NADP+) is also high.

Reduced ferredoxin can transfer electrons to thioredoxin, reducing it. Reduced thioredoxin can, in turn, transfer electrons to proteins to reduce their disulfide bonds. Four enzymes related to the Calvin cycle can receive electrons from thioredoxin and become activated, as a result.

These include sedoheptulose 1,7-bisphosphatase, ribulose-5-phosphate kinase, fructose 1,6-bisphosphatase, and glyceraldehyde 3-phosphate dehydrogenase. Thus, in the light, electrons flow, causing NADPH to accumulate and ferredoxin to push electrons in the

direction of these enzymes above, activating them and favoring the Calvin cycle. In the dark, the concentration of reduced NADPH, reduced ferredoxin, and reduced thioredoxin fall, resulting in loss of electrons by the Calvin cycle enzymes (oxidations that re-form disulfide bonds) and the Calvin cycle inactivates.

Other enzyme control mechanisms

Other means of controlling enzymes relate to access to substrate (substrate-level control) and control of enzyme synthesis. Hexokinase is an enzyme that is largely regulated by availability of its substrate, glucose. When glucose concentration is low, the product of the enzyme's catalysis, glucose-6-phosphate, inhibits the enzyme's function.

Regulation of enzymes by controlling their synthesis is covered later in the book in the discussion relating to control of gene expression.

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10.15: Mechanisms of Catalysis

A printable version of this section is here: BiochemFFA_4_3.pdf. The entire textbook is available for free from the authors at http://biochem.science.oregonstate.edu/content/biochemistry-free-and-easy

The magic of enzymes, as noted, is in their ability to create electronic environments conducive to initiation of a reaction. There are more mechanisms of reaction than we could ever hope to cover in a book like this, and comprehensive discussion of these is not our aim. Instead, we will cite some examples and go into detail on one of them - the mechanism of action of serine proteases.

Chymotrypsin

We will begin with mechanism of action of one enzyme - chymotrypsin. Found in our digestive system, chymotrypsin's catalytic activity is cleaving peptide bonds in proteins and it uses the side chain of a serine in its mechanism of catalysis. Many other protein-cutting enzymes employ a very similar mechanism and they are known collectively as serine proteases (Figure 4.52).

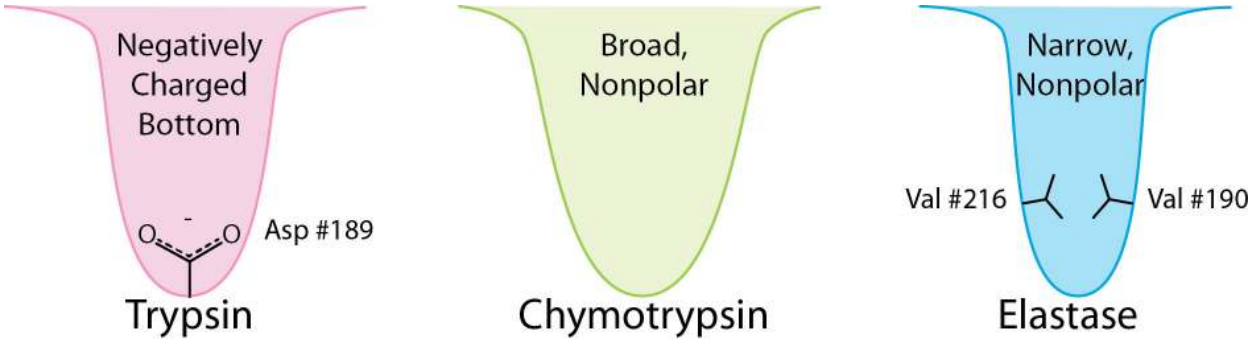


Figure 4.52 - Substrate binding sites (S1 pockets) of three serine proteases. Image by Aleia Kim

These enzymes are found in prokaryotic and eukaryotic cells and all use a common set of three amino acids in the active site called a catalytic triad (Figure 4.53). It consists of aspartic acid, histidine, and serine. The serine is activated in the reaction mechanism to form a nucleophile in these enzymes and gives the class their name. With the exception of the recognition that occurs at the substrate binding site, the mechanism shown here for chymotrypsin would be applicable to any of the serine proteases.

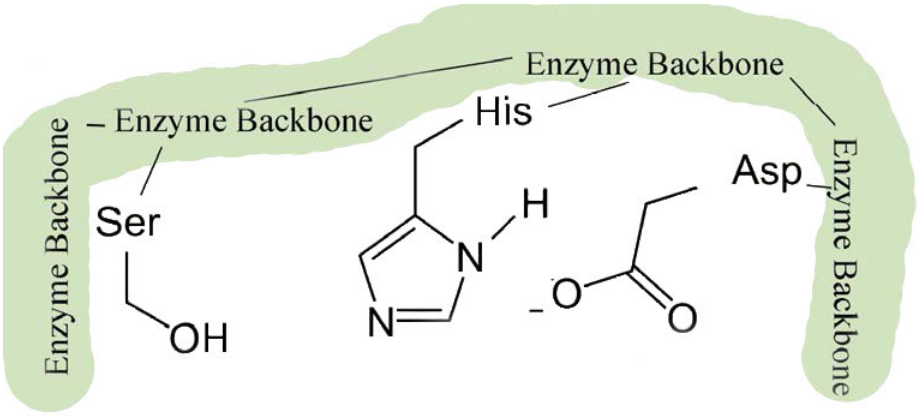


Figure 4.53 - 1. Active site of chymotrypsin showing the catalytic triad of serine - histidine-aspartic acid

Specificity

As a protease, chymotrypsin acts fairly specifically, cutting not all peptide bonds, but only those that are adjacent to relatively non-polar amino acids in the protein. One of the amino acids it cuts adjacent to is phenylalanine. The enzyme's action occurs in two phases – a fast phase that occurs first and a slower phase that follows. The enzyme has a substrate binding site that includes a region of the enzyme known as the S1 pocket. Let us step through the mechanism by which chymotrypsin cuts adjacent to phenylalanine.

Substrate binding

The process starts with the binding of the substrate in the S1 pocket (Figure 4.54). The S1 pocket in chymotrypsin has a hydrophobic hole in which the substrate is bound. Preferred substrates will include amino acid side chains that are bulky and hydrophobic, like phenylalanine. If an ionized side chain, like that of glutamic acid binds in the S1 pocket, it will quickly exit, much like water would avoid an oily interior.

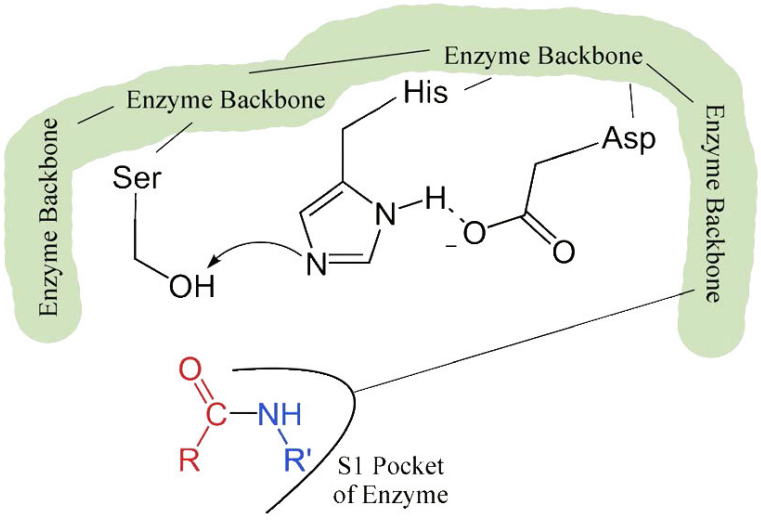


Figure 4.54 - 2. Binding of substrate to S1 pocket in the active site

Shape change on binding

When the proper substrate binds in the S1 pocket, its presence induces an ever so slight change in the shape of the enzyme. This subtle shape change on the binding of the proper substrate starts the steps of the catalysis. Since the catalytic process only starts when the proper substrate binds, this is the reason that the enzyme shows specificity for cutting at specific amino acids in the target protein. Only amino acids with the side chains that interact well with the S1 pocket start the catalytic wheels turning.

The slight changes in shape involve changes in the positioning of three amino acids (aspartic acid, histidine, and serine) in the active site known as the *catalytic triad*.

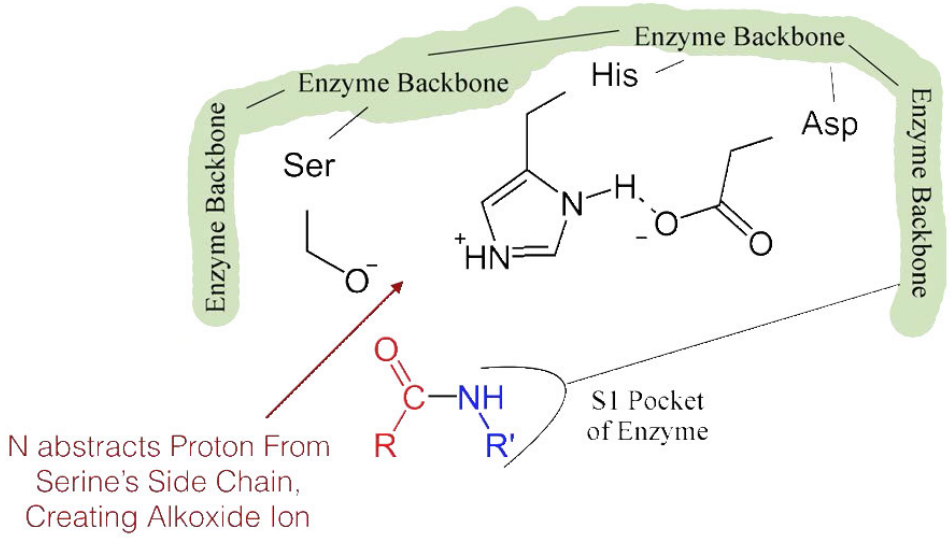


Figure 4.55 - 3. Formation of alkoxide ion

The shift of the negatively charged aspartic acid towards the electron rich histidine ring favors the abstraction of a proton by the histidine from the hydroxyl group on the side chain of serine, resulting in production of a very reactive alkoxide ion in the active

site (Figure 4.55).

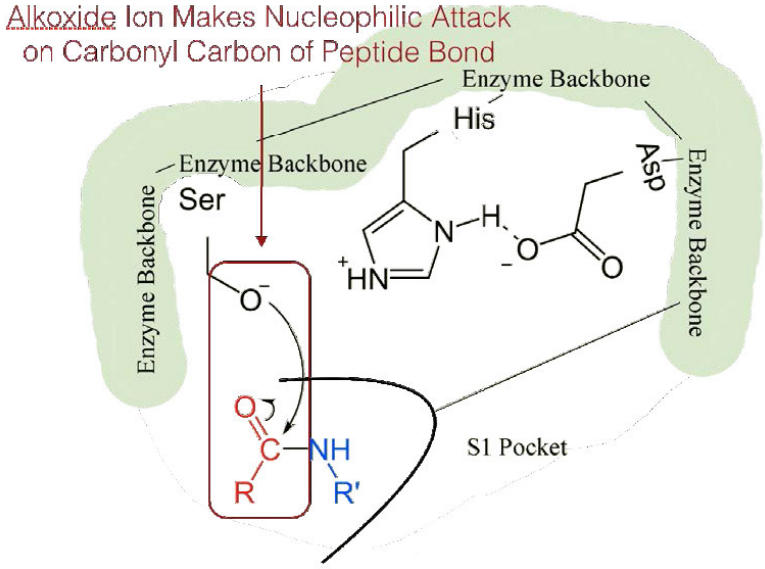


Figure 4.56 - 4. Nucleophilic attack

Since the active site at this point also contains the polypeptide chain positioned with the phenylalanine side chain embedded in the S1 pocket, the alkoxide ion performs a nucleophilic attack on the peptide bond on the carboxyl side of phenylalanine sitting in the S1 pocket (Figure 4.56). This reaction breaks the peptide bond (Figure 4.57) and causes two things to happen.

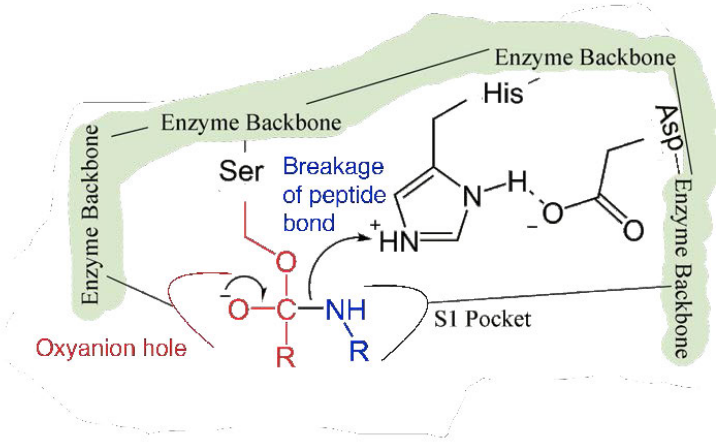


Figure 4.57 - 5. Stabilization by oxyanion hole. Breakage of peptide bond.

First, one end of the original polypeptide is freed and exits the active site (Figure 4.58). The second is that the end containing the phenylalanine is covalently linked to the oxygen of the serine side chain. At this point we have completed the first (fast) phase of the catalysis.

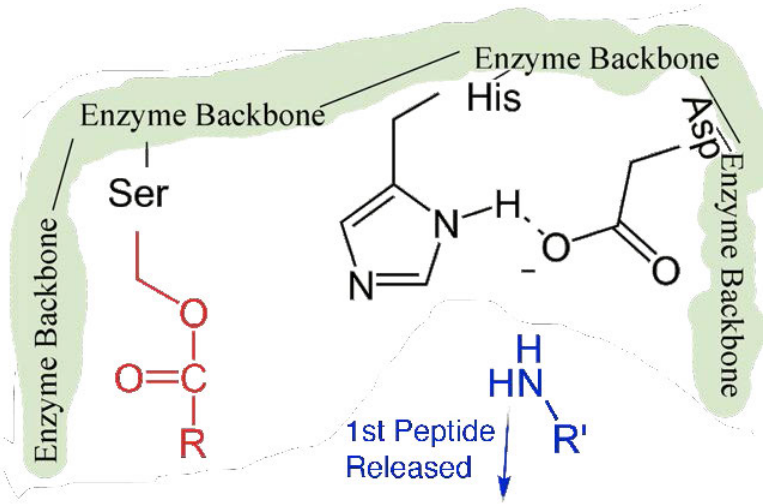


Figure 4.58 - 6. First peptide released. Other half bonded to serine.

Slower second phase

The second phase of the catalysis by chymotrypsin is slower. It requires that the covalent bond between phenylalanine and serine's oxygen be broken so the peptide can be released and the enzyme can return to its original state. The process starts with entry of water into the active site. Water is attacked in a fashion similar to that of the serine side chain in the first phase, creating a reactive hydroxyl group (Figure 4.59) that performs a nucleophilic attack on the phenylalanine-serine bond (Figure 4.60), releasing it and replacing the proton on serine. The second peptide is released in the process and the reaction is complete with the enzyme back in its original state (Figure 4.61).

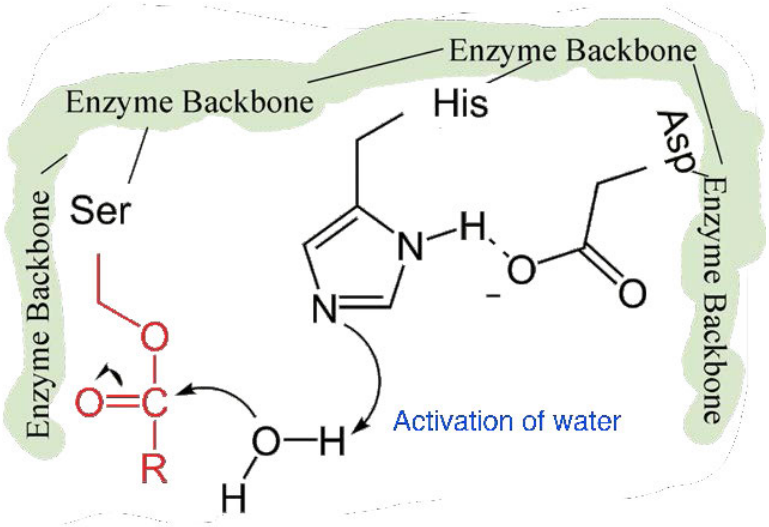


Figure 4.59 - 7. Activation of water by histidine

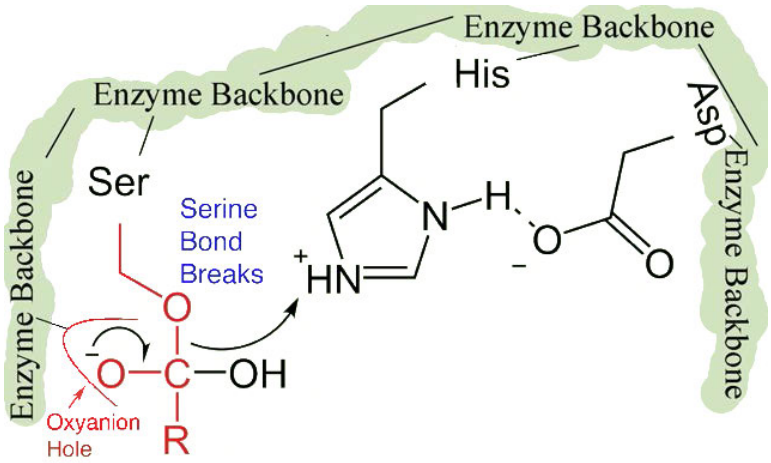


Figure 4.60 - 8. Nucleophile attack by hydroxyl creates tetrahydryl intermediate stabilized by oxyanion hole. Bond to serine breaks.

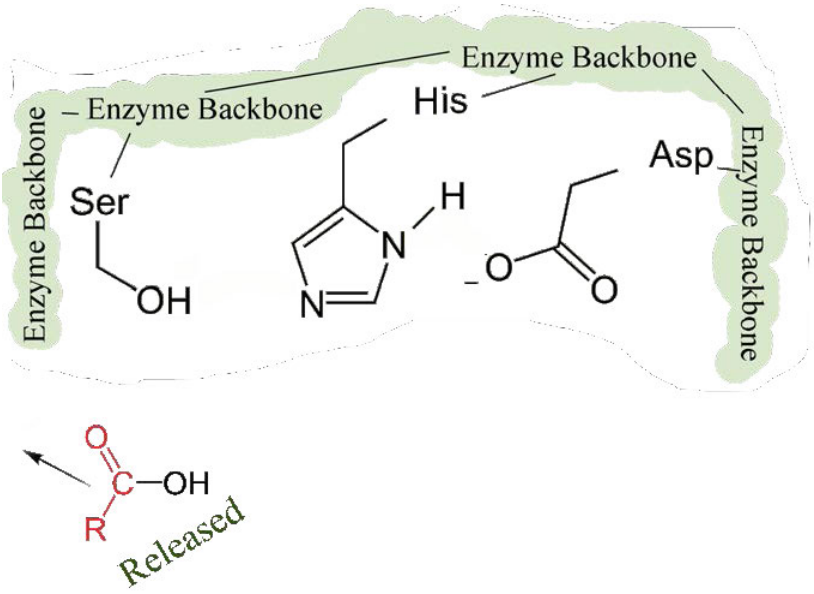


Figure 4.61 - 9. Second half of peptide released. Enzyme active site restored.

Protease inhibitors

Molecules which inhibit the catalytic action of proteases are known as protease inhibitors. These come in a variety of forms and have biological and medicinal uses. Many biological inhibitors are proteins themselves.

Anti-viral Agents

Protease inhibitors are used as anti-viral agents to prohibit maturation of viral proteins - commonly viral coat proteins.

They are part of drug “cocktails” used to inhibit the spread of HIV in the body and are also used to treat other viral infections, including hepatitis C. They have also been investigated for use in treatment of malaria and may have some application in anti-cancer therapies as well.

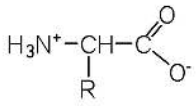
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10.E: Amino Acids, Proteins, and Enzymes (Exercises)

18.1: Properties of Amino Acids

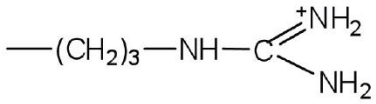
Concept Review Exercises

1. What is the general structure of an α-amino acid?
2. Identify the amino acid that fits each description.
   a. also known as aspartate
   b. almost as strong a base as sodium hydroxide
   c. does not have a chiral carbon
3. 

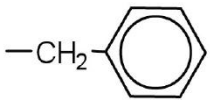
4. a. aspartic acid
   b. arginine
   c. glycine
5. Write the side chain of each amino acid.
   a. serine
   b. arginine
   c. phenylalanine
6. Write the side chain of each amino acid.
   a. aspartic acid
   b. methionine
   c. valine
7. Draw the structure for each amino acid.
   a. alanine
   b. cysteine
   c. histidine
8. Draw the structure for each amino acid.
   a. threonine
   b. glutamic acid
   c. leucine
9. Identify an amino acid whose side chain contains a(n)
   a. amide functional group.
   b. aromatic ring.
   c. carboxyl group.
10. Identify an amino acid whose side chain contains a(n)
    a. OH group
    b. branched chain
    c. amino group

1. a. CH_2OH^-

b.

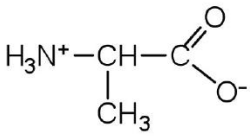


c.

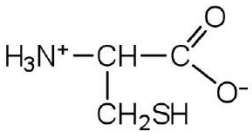


2.

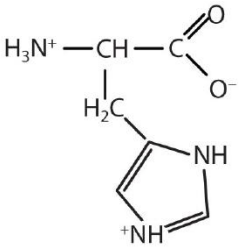
3. a.



b.



c.



4.

5. a. asparagine or glutamine
   b. phenylalanine, tyrosine, or tryptophan
   c. aspartic acid or glutamic acid

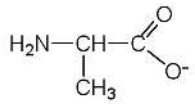
18.2: Reactions of Amino Acids

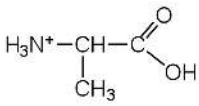
Concept Review Exercises

1. Define each term.
   a. zwitterion
   b. isoelectric point
2. Draw the structure for the anion formed when alanine (at neutral pH) reacts with a base.
3. Draw the structure for the cation formed when alanine (at neutral pH) reacts with an acid.

Answers

1. a. an electrically neutral compound that contains both negatively and positively charged groups
   b. the pH at which a given amino acid exists in solution as a zwitterion

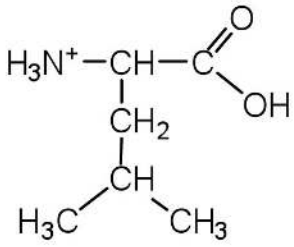
2. 

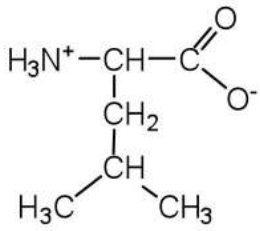
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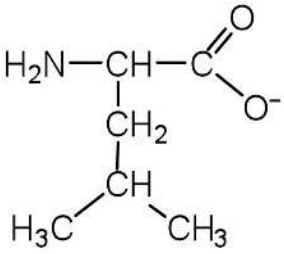
Exercises

1. Draw the structure of leucine and determine the charge on the molecule in a(n)
   a. acidic solution (pH = 1).
   b. neutral solution (pH = 7).
   c. a basic solution (pH = 11)
2. Draw the structure of isoleucine and determine the charge on the molecule in a(n)
   a. acidic solution (pH = 1).
   b. neutral solution (pH = 7).
   c. basic solution (pH = 11).

Answer

1. a. 

   b. 

   c. 

18.3: Peptides

Concept Review Exercises

1. Distinguish between the N-terminal amino acid and the C-terminal amino acid of a peptide or protein.
2. Describe the difference between an amino acid and a peptide.
3. Amino acid units in a protein are connected by peptide bonds. What is another name for the functional group linking the amino acids?

Answers

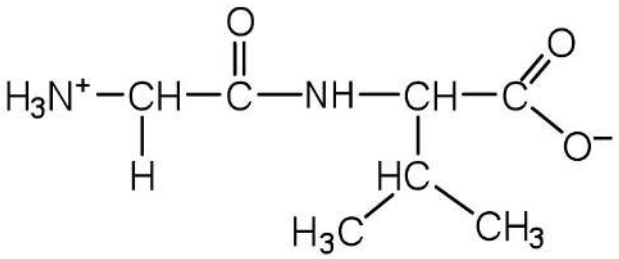
1. The N-terminal end is the end of a peptide or protein whose amino group is free (not involved in the formation of a peptide bond), while the C-terminal end has a free carboxyl group.
2. A peptide is composed of two or more amino acids. Amino acids are the building blocks of peptides.
3. amide bond

Exercises

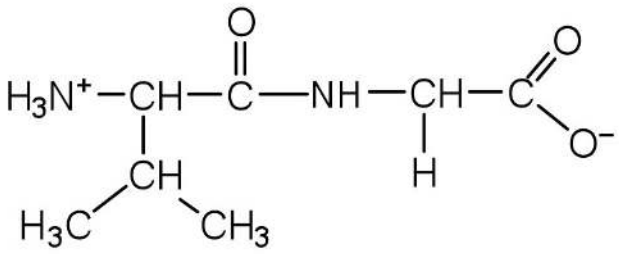
1. Draw the structure for each peptide.
   a. gly-val
   b. val-gly
2. Draw the structure for cys-val-ala.
3. Identify the C- and N-terminal amino acids for the peptide lys-val-phe-gly-arg-cys.
4. Identify the C- and N-terminal amino acids for the peptide asp-arg-val-tyr-ile-his-pro-phe.

Answers

1. a.



   b.



3. C-terminal amino acid: cys; N-terminal amino acid: lys

18.4: Proteins

Concept Review Exercises

1. What is the predominant attractive force that stabilizes the formation of secondary structure in proteins?
2. Distinguish between the tertiary and quaternary levels of protein structure.
3. Briefly describe four ways in which a protein could be denatured.

Answers

1. hydrogen bonding
2. Tertiary structure refers to the unique three-dimensional shape of a single polypeptide chain, while quaternary structure describes the interaction between multiple polypeptide chains for proteins that have more than one polypeptide chain.
3. (1) heat a protein above 50°C or expose it to UV radiation; (2) add organic solvents, such as ethyl alcohol, to a protein solution; (3) add salts of heavy metal ions, such as mercury, silver, or lead; and (4) add alkaloid reagents such as tannic acid

Exercises

1. Classify each protein as fibrous or globular.
   a. albumin
   b. myosin
   c. fibroin
2. Classify each protein as fibrous or globular.
   a. hemoglobin
   b. keratin
   c. myoglobin
3. What name is given to the predominant secondary structure found in silk?
4. What name is given to the predominant secondary structure found in wool protein?
5. A protein has a tertiary structure formed by interactions between the side chains of the following pairs of amino acids. For each pair, identify the strongest type of interaction between these amino acids.
   a. aspartic acid and lysine
   b. phenylalanine and alanine
   c. serine and lysine
   d. two cysteines
6. A protein has a tertiary structure formed by interactions between the side chains of the following pairs of amino acids. For each pair, identify the strongest type of interaction between these amino acids.
   a. valine and isoleucine
   b. asparagine and serine
   c. glutamic acid and arginine
   d. tryptophan and methionine
7. What level(s) of protein structure is(are) ordinarily disrupted in denaturation? What level(s) is(are) not?
8. Which class of proteins is more easily denatured—fibrous or globular?

Answers

1. a. globular
   b. fibrous
   c. fibrous
3. β-pleated sheet
5. a. ionic bonding
   b. dispersion forces
   c. dispersion forces
   d. disulfide linkage
7. Protein denaturation disrupts the secondary, tertiary, and quaternary levels of structure. Only primary structure is unaffected by denaturation.

18.5: Enzymes

Concept Review Exercise

In the small intestine, sucrose is hydrolyzed to form glucose and fructose in a reaction catalyzed by sucrase.

1. Identify the substrate in this reaction.
2. Name the enzyme.

Answers

1. sucrose
2. sucrase

Exercises

1. Identify the substrate catalyzed by each enzyme.
    a. lactase
    b. cellulase
    c. peptidase
2. Identify the substrate catalyzed by each enzyme.
    a. lipase
    b. amylase
    c. maltase
3. Identify each type of enzyme.
    a. decarboxylase
    b. protease
    c. transaminase
4. Identify each type of enzyme.
    a. dehydrogenase
    b. isomerase
    c. lipase

Answers

1. a. lactose
    b. cellulose
    c. peptides
3. a. lyase
    b. hydrolase
    c. transferase

18.6: Enzyme Action

Concept Review Exercises

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

Answers

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

Exercises

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

Answers

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

18.7: Enzyme Activity

Concept Review Exercises

1. The concentration of substrate X is low. What happens to the rate of the enzyme-catalyzed reaction if the concentration of X is doubled?
2. What effect does an increase in the enzyme concentration have on the rate of an enzyme-catalyzed reaction?

Answers

1. If the concentration of the substrate is low, increasing its concentration will increase the rate of the reaction.
2. An increase in the amount of enzyme will increase the rate of the reaction (provided sufficient substrate is present).

Exercises

1. In non-enzyme-catalyzed reactions, the reaction rate increases as the concentration of reactant is increased. In an enzyme-catalyzed reaction, the reaction rate initially increases as the substrate concentration is increased but then begins to level off, so that the increase in reaction rate becomes less and less as the substrate concentration increases. Explain this difference.
2. Why do enzymes become inactive at very high temperatures?
3. An enzyme has an optimum pH of 7.4. What is most likely to happen to the activity of the enzyme if the pH drops to 6.3? Explain.
4. An enzyme has an optimum pH of 7.2. What is most likely to happen to the activity of the enzyme if the pH increases to 8.5? Explain.

Answers

1. In an enzyme-catalyzed reaction, the substrate binds to the enzyme to form an enzyme-substrate complex. If more substrate is present than enzyme, all of the enzyme binding sites will have substrate bound, and further increases in substrate concentration cannot increase the rate.
3. The activity will decrease; a pH of 6.3 is more acidic than 7.4, and one or more key groups in the active site may bind a hydrogen ion, changing the charge on that group.

18.8: Enzyme Inhibition

Concept Review Exercises

1. What is the difference between a cofactor and a coenzyme?
2. How are vitamins related to coenzymes?

Answers

1. A coenzyme is one type of cofactor. Coenzymes are organic molecules required by some enzymes for activity. A cofactor can be either a coenzyme or an inorganic ion.
2. Coenzymes are synthesized from vitamins.

Exercises

1. Identify each vitamin as water soluble or fat soluble.
    a. vitamin D
    b. vitamin C
    c. vitamin B_{12}
2. Identify each vitamin as water soluble or fat soluble.
    a. niacin
    b. cholecalciferol
    c. biotin
3. What vitamin is needed to form each coenzyme?
    a. pyridoxal phosphate
    b. flavin adenine dinucleotide
    c. coenzyme A
    d. nicotinamide adenine dinucleotide
4. What coenzyme is formed from each vitamin?
    a. niacin
    b. thiamine
    c. cyanocobalamin
    d. pantothenic acid

5. What is the function of each vitamin or coenzyme?
   a. flavin adenine dinucleotide
   b. vitamin A
   c. biotin
6. What is the function of each vitamin or coenzyme?
   a. vitamin K
   b. pyridoxal phosphate
   c. tetrahydrofolate

Answers

1. a. fat soluble
   b. water soluble
   c. water soluble
3. a. vitamin B_6 or pyridoxine
   b. vitamin B_2 or riboflavin
   c. pantothenic acid
   d. vitamin B_3 or niacin
5. a. needed by enzymes that catalyze oxidation-reduction reactions in which two hydrogen atoms are transferred
   b. needed for the formation of vision pigments
   c. needed by enzymes that catalyze carboxylation reactions

18.9: Enzyme Cofactors and Vitamins

Concept Review Exercises

1. What are the characteristics of an irreversible inhibitor?
2. In what ways does a competitive inhibitor differ from a noncompetitive inhibitor?

Answers

1. It inactivates an enzyme by bonding covalently to a particular group at the active site.
2. A competitive inhibitor structurally resembles the substrate for a given enzyme and 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 and can bind to either the free enzyme or the enzyme-substrate complex.

Exercises

1. What amino acid is present in the active site of all enzymes that are irreversibly inhibited by nerve gases such as DIFP?
2. Oxaloacetate (OOCCH2COCOO) inhibits succinate dehydrogenase. Would you expect oxaloacetate to be a competitive or noncompetitive inhibitor? Explain.

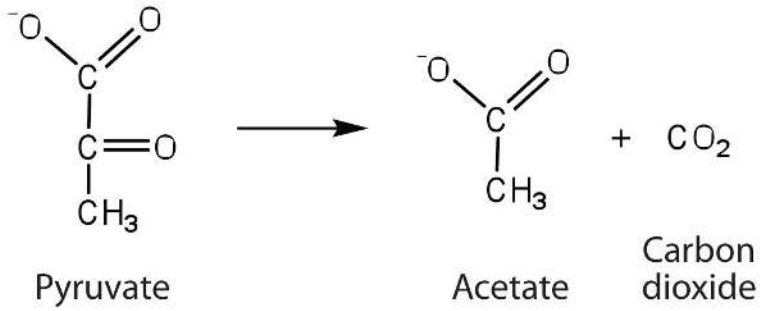
Answer

1. serine

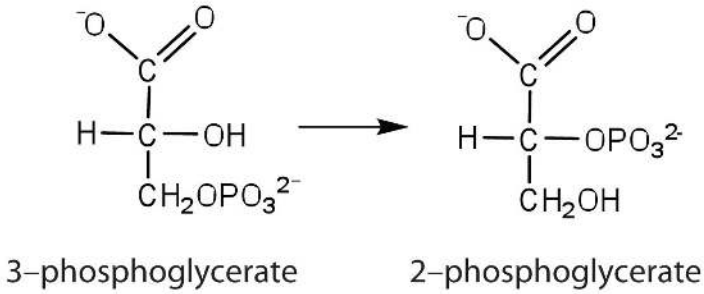
Additional Exercises

1. Draw the structure of the amino acid γ-aminobutyric acid (GABA). Would you expect to find GABA in the amino acid sequence of a protein? Explain.
2. Draw the structure of the amino acid homocysteine (R group = CH_2CH_2SH). Would you expect to find homocysteine in the amino acid sequence of a protein? Justify your answer.
3. Write equations to show how leucine can act as a buffer (that is, how it can neutralize added acid or base).

4. Write equations to show how isoleucine can act as a buffer (that is, how it can neutralize added acid or base).
5. Glutathione (γ-glutamylcysteinylglycine) is a tripeptide found in all cells of higher animals. It contains glutamic acid joined in an unusual peptide linkage involving the carboxyl group of the R group (known as γ-carboxyl group), rather than the usual carboxyl group (the α-carboxyl group). Draw the structure of glutathione.
6. Draw the structure of the pentapeptide whose sequence is arg-his-gly-leu-asp. Identify which of the amino acids have R groups that can donate or gain hydrogen ions.
7. Bradykinin is a peptide hormone composed of nine amino acids that lowers blood pressure. Its primary structure is arg-pro-pro-gly-phe-ser-pro-phe-arg. Would you expect bradykinin to be positively charged, negatively charged, or neutral at a pH of 6.0? Justify your answer.
8. One of the neurotransmitters involved in pain sensation is a peptide called substance P, which is composed of 11 amino acids and is released by nerve-cell terminals in response to pain. Its primary structure is arg-pro-lys-pro-gln-gln-phe-phe-gly-leu-met. Would you expect this peptide to be positively charged, negatively charged, or neutral at a pH of 6.0? Justify your answer.
9. Carbohydrates are incorporated into *glycoproteins*. Would you expect the incorporation of sugar units to increase or decrease the solubility of a protein? Justify your answer.
10. Some proteins have phosphate groups attached through an ester linkage to the OH groups of serine, threonine, or tyrosine residues to form *phosphoproteins*. Would you expect the incorporation of a phosphate group to increase or decrease the solubility of a protein? Justify your answer.
11. Refer to Table 18.5 and determine how each enzyme would be classified.
    a. the enzyme that catalyzes the conversion of ethanol to acetaldehyde
    b. the enzyme that catalyzes the breakdown of glucose 6-phosphate to glucose and inorganic phosphate ion (water is also a reactant in this reaction)
12. Refer to Table 18.5 and determine how each enzyme would be classified.
    a. the enzyme that catalyzes the removal of a carboxyl group from pyruvate to form acetate

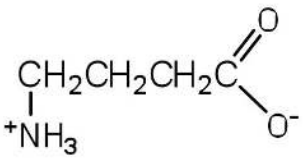


    b. the enzyme that catalyzes the rearrangement of 3-phosphoglycerate to form 2-phosphoglycerate



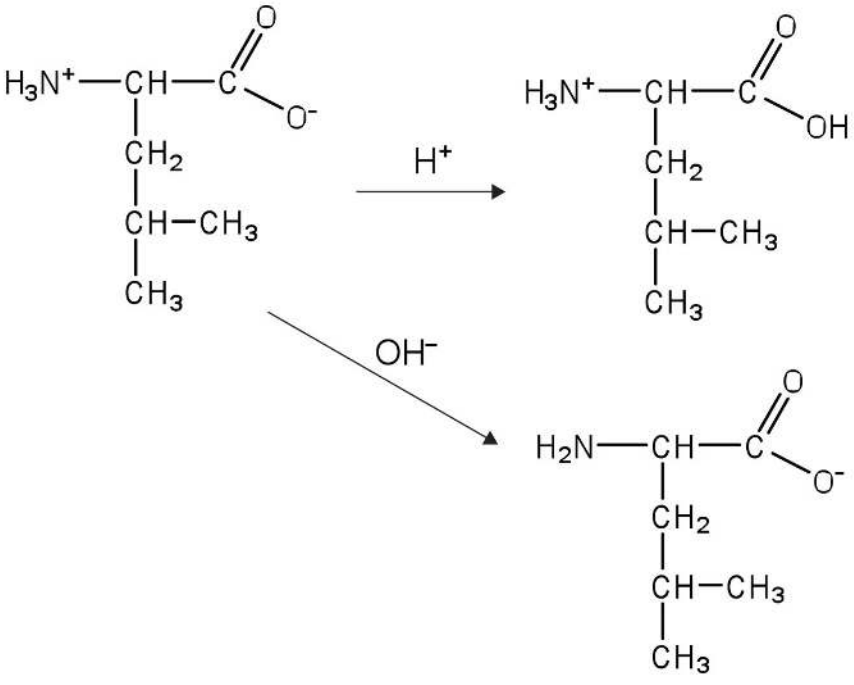
13. The enzyme lysozyme has an aspartic acid residue in the active site. In acidic solution, the enzyme is inactive, but activity increases as the pH rises to around 6. Explain why.
14. The enzyme lysozyme has a glutamic acid residue in the active site. At neutral pH (6–7), the enzyme is active, but activity decreases as the pH rises. Explain why.
15. The activity of a purified enzyme is measured at a substrate concentration of 1.0 μM and found to convert 49 μmol of substrate to product in 1 min. The activity is measured at 2.0 μM substrate and found to convert 98 μmol of substrate to product/minute.
    a. When the substrate concentration is 100 μM, how much substrate would you predict is converted to product in 1 min? What if the substrate concentration were increased to 1,000 μM (1.0 mM)?
    b. The activities actually measured are 676 μmol product formed/minute at a substrate concentration of 100 μM and 698 μmol product formed/minute at 1,000 μM (1.0 mM) substrate. Is there any discrepancy between these values and those you predicted in Exercise 15a? Explain.
16. A patient has a fever of 39°C. Would you expect the activity of enzymes in the body to increase or decrease relative to their activity at normal body temperature (37°C)?
17. Using your knowledge of factors that influence enzyme activity, describe what happens when milk is pasteurized.

Answers



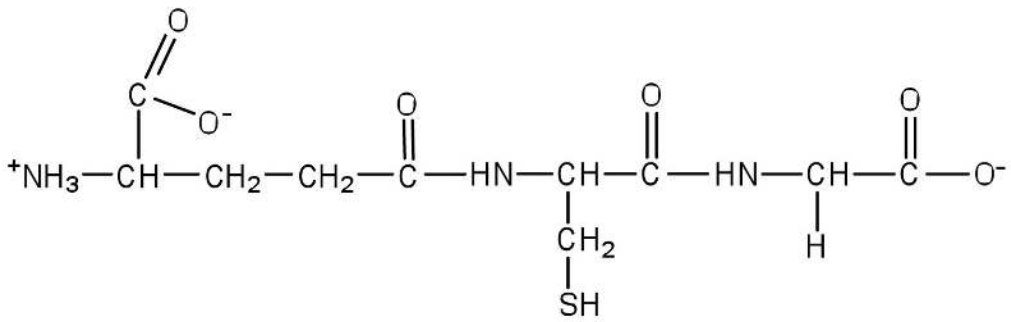
1.

This amino acid would not be found in proteins because it is not an α-amino acid.



3.

https://chem.libretexts.org/@go/page/306659

5. 

7. Bradykinin would be positively charged; all of the amino acids, except for arginine, have R groups that do not become either positively or negatively charged. The two arginines are R groups that are positively charged at neutral pH, so the peptide would have an overall positive charge.

9. Carbohydrates have many OH groups attached, which can engage in hydrogen bonding with water, which increases the solubility of the proteins.

11.

a. oxidoreductase
b. hydrolase

13. The enzyme is active when the carboxyl group in the R group of aspartic acid does not have the hydrogen attached (forming COO^-); the hydrogen is removed when the pH of the solution is around pH 6 or higher.

15.

a. at 100 µM, you would predict that the rate would increase 100 times to 4,900 µmol of substrate to product in 1 min; at 1.0 mM, you would predict an increase to 49,000 µmol of substrate to product in 1 min.
b. There is a great discrepancy between the predicted rates and actual rates; this occurs because the enzyme becomes saturated with substrate, preventing a further increase in the rate of the reaction (the reaction is no longer linear with respect to substrate concentration because it is at very low concentrations).

17. When milk is pasteurized, it is heated to high temperatures. These high temperatures denature the proteins in bacteria, so they cannot carry out needed functions to grow and multiply.

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10.S: Amino Acids, Proteins, and Enzymes (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 **protein** is a large biological polymer synthesized from **amino acids**, which are carboxylic acids containing an α-amino group. Proteins have a variety of important roles in living organisms, yet they are made from the same 20 L-amino acids. About half of these amino acids, the **essential amino acids**, cannot be synthesized by the human body and must be obtained from the diet. In the solid state and in neutral solutions, amino acids exist as **zwitterions**, species that are charged but electrically neutral. In this form, they behave much like inorganic salts. Each amino acid belongs to one of four classes depending on the characteristics of its R group or amino acid side chain: nonpolar, polar but neutral, positively charged, and negatively charged. Depending on the conditions, amino acids can act as either acids or bases, which means that proteins act as buffers. The pH at which an amino acid exists as the zwitterion is called the **isoelectric point (pI)**.

The amino acids in a protein are linked together by **peptide bonds**. Protein chains containing 10 or fewer amino acids are usually referred to as **peptides**, with a prefix such as di- or tri- indicating the number of amino acids. Chains containing more than 50 amino acid units are referred to as *proteins* or **polypeptides**. Proteins are classified globular or fibrous, depending on their structure and resulting solubility in water. **Globular proteins** are nearly spherical and are soluble in water; **fibrous proteins** have elongated or fibrous structures and are not soluble in water.

Protein molecules can have as many as four levels of structure. The **primary structure** is the sequence of amino acids in the chain. The **secondary structure** is the arrangement of adjacent atoms in the peptide chain; the most common arrangements are α-helices or β-pleated sheets. The **tertiary structure** is the overall three-dimensional shape of the molecule that results from the way the chain bends and folds in on itself. Proteins that consist of more than one chain have **quaternary structure**, which is the way the multiple chains are packed together.

Four types of intramolecular and intermolecular forces contribute to secondary, tertiary, and quaternary structure: (1) **hydrogen bonding** between an oxygen or a nitrogen atom and a hydrogen atom bound to an oxygen atom or a nitrogen atom, either on the same chain or on a neighboring chain; (2) **ionic bonding** between one positively charged side chain and one negatively charged side chain; (3) **disulfide linkages** between cysteine units; and (4) **dispersion forces** between nonpolar side chains.

Because of their complexity, protein molecules are delicate and easy to disrupt. A *denatured* protein is one whose conformation has been changed, in a process called **denaturation**, so that it can no longer do its physiological job. A variety of conditions, such as heat, ultraviolet radiation, the addition of organic compounds, or changes in pH can denature a protein.

An **enzyme** is an organic catalyst produced by a living cell. Enzymes are such powerful catalysts that the reactions they promote occur rapidly at body temperature. Without the help of enzymes, these reactions would require high temperatures and long reaction times.

The molecule or molecules on which an enzyme acts are called its **substrates**. An enzyme has an **active site** where its substrate or substrates bind to form an enzyme-substrate complex. The reaction occurs, and product is released:

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

The original **lock-and-key model** of enzyme and substrate binding pictured a rigid enzyme of unchanging configuration binding to the appropriate substrate. The newer **induced-fit model** describes the enzyme active site as changing its conformation after binding to the substrate.

Most enzymes have maximal activity in a narrow pH range centered on an **optimum pH**. In this pH range, the enzyme is correctly folded, and catalytic groups in the active site have the correct charge (positive, negative, or neutral). For most enzymes, the optimum pH is between 6 and 8.

Substances that interfere with enzyme function are called inhibitors. An **irreversible inhibitor** inactivates enzymes by forming covalent bonds to the enzyme, while a **reversible inhibitor** inactivates an enzyme by a weaker, noncovalent interaction that is easier to disrupt. A **competitive inhibitor** is a reversible inhibitor that is structurally similar to the substrate and binds to the active site. When the inhibitor is bound, the substrate is blocked from the active site and no reaction occurs. Because the binding of such

an inhibitor is reversible, a high substrate concentration will overcome the inhibition because it increases the likelihood of the substrate binding. A **noncompetitive inhibitor** binds reversibly at a site distinct from the active site. Thus, it can bind to either the enzyme or the enzyme-substrate complex. The inhibitor changes the conformation of the active site so that the enzyme cannot function properly. Noncompetitive inhibitors are important in **feedback inhibition**, in which the amount of product produced by a series of reactions is carefully controlled. The final product in a series of reactions acts as a noncompetitive inhibitor of the initial enzyme.

Simple enzymes consist entirely of one or more amino acid chains. Complex enzymes are composed of one or more amino acid chains joined to **cofactors**—inorganic ions or organic **coenzymes**. **Vitamins** are organic compounds that are essential in very small amounts for the maintenance of normal metabolism and generally cannot be synthesized at adequate levels by the body. Vitamins are divided into two broad categories: *fat-soluble* vitamins and *water-soluble* vitamins. Many of the water-soluble vitamins are used for the synthesis of coenzymes.

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CHAPTER OVERVIEW

11:9 Solutions

Solutions are all around us. Air, for example, is a solution. If you live near a lake, a river, or an ocean, that body of water is not pure H_2O but most probably a solution. Much of what we drink—for example, soda, coffee, tea, and milk—is at least in part a solution. Solutions are a large part of everyday life. A lot of the chemistry occurring around us happens in solution. In fact, much of the chemistry that occurs in our own bodies takes place in solution, and many solutions—such as the Ringer's lactate IV solution—are important for our health. In our understanding of chemistry, we need to understand a little bit about solutions. In this chapter, you will learn about the special characteristics of solutions, how solutions are characterized, and some of their properties.

11.1: Prelude to Solutions
11.2: Solutions
11.3: Concentration
11.4: The Dissolution Process
11.5: Solubility Rules
11.6: Molecular and Ionic Equations
11.7: Net Ionic Equations
11.8: Osmosis and Diffusion
11.9: Solutions, Colloids and Membranes- Questions
11.9: Homework Solutions
11.S: Solutions (Summary)

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11.1: Prelude to Solutions

If you watch any of the medical dramas on television, you may have heard a doctor (actually an actor) call for an intravenous solution of “Ringer’s lactate” (or “lactated Ringer’s” or "Ri-Lac"). So what is Ringer’s lactate?

Intravenous (IV) solutions are administered for two main reasons:

1. to introduce necessary substances into the bloodstream, such as ions for proper body function, sugar and other food substances for energy, or drugs to treat a medical condition, and
2. to increase the volume of the bloodstream.

Many people with acute or long-term medical conditions have received some type of an IV solution.

One basic IV solution, called a *normal saline solution*, is simply a dilute solution of NaCl dissolved in water. Normal saline is 9.0 g of NaCl dissolved in each liter of solution. *Ringer’s lactate* is a normal saline solution that also has small amounts of potassium and calcium ions mixed in. In addition, it contains about 2.5 g of lactate ions ($C_3H_5O_3^-$) per liter of solution. The liver metabolizes lactate ions into bicarbonate (HCO_3^-) ions, which help maintain the acid-base balance of blood. Many medical problems, such as heart attacks and shock, affect the acid-base balance of blood, and the presence of lactate in the IV solution eases problems caused by this imbalance.

Physicians can select from a range of premade IV solutions, in accordance with a patient’s particular needs. Ringer’s lactate is commonly used when a patient’s blood volume must be increased quickly. Another frequently used IV solution, called D5W, is a 5% solution of dextrose (a form of sugar) in water.

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11.2: Solutions

Learning Objectives

- To understand what causes solutions to form.

A solution is another name for a homogeneous mixture. A *mixture* as a material composed of two or more substances. In a solution, the combination is so intimate that the different substances cannot be differentiated by sight, even with a microscope. Compare, for example, a mixture of salt and pepper and another mixture consisting of salt and water. In the first mixture, we can readily see individual grains of salt and the flecks of pepper. A mixture of salt and pepper is not a solution. However, in the second mixture, no matter how carefully we look, we cannot see two different substances. Salt dissolved in water is a solution.

The major component of a solution, called the **solvent**, is typically the same phase as the solution itself. Each minor component of a solution (and there may be more than one) is called the **solute**. In most of the solutions we will describe in this textbook, there will be no ambiguity about whether a component is the solvent or the solute. For example, in a solution of salt in water, the solute is salt, and solvent is water.

Solutions come in all phases, and the solvent and the solute do not have to be in the same phase to form a solution (such as salt and water). For example, air is a gaseous solution of about 80% nitrogen and about 20% oxygen, with some other gases present in much smaller amounts. An alloy is a solid solution consisting of a metal (like iron) with some other metals or nonmetals dissolved in it. Steel, an alloy of iron and carbon and small amounts of other metals, is an example of a solid solution. Table **11.2.1** lists some common types of solutions, with examples of each.

Table **11.2.1**: Types of Solutions

Solvent Phase	Solute Phase	Example
gas	gas	air
liquid	gas	carbonated beverages
liquid	liquid	ethanol (C_2H_5OH) in H_2O (alcoholic beverages)
liquid	solid	saltwater
solid	gas	H_2 gas absorbed by Pd metal
solid	liquid	Hg(ℓ) in dental fillings
solid	solid	steel alloys

What causes a solution to form? The simple answer is that the solvent and the solute must have similar intermolecular interactions. When this is the case, the individual particles of solvent and solute can easily mix so intimately that each particle of solute is surrounded by particles of solvent, forming a solution. However, if two substances have very different intermolecular interactions, large amounts of energy are required to force their individual particles to mix intimately, so a solution does not form. Thus two alkanes like *n*-heptane, C_7H_{16}, and *n*-hexane, C_6H_{14}, are completely miscible in all proportions. The C_7H_{16} and C_6H_{14} molecules are so similar (recall Section 4.6) that there are only negligible differences in intermolecular forces.

For a similar reason, methanol, CH_3OH, is completely miscible with water. In this case both molecules are polar and can form hydrogen bonds among themselves, and so there are strong intermolecular attractions within each liquid. However, CH_3OH dipoles can align with H_2O dipoles, and CH_3OH molecules can hydrogen bond to H_2O molecules, and so the attractions among unlike molecules in the solution are similar to those among like molecules in each pure liquid.

This process leads to a simple rule of thumb: *like dissolves like*. Solvents that are very polar will dissolve solutes that are very polar or even ionic. Solvents that are nonpolar will dissolve nonpolar solutes. Thus water, being polar, is a good solvent for ionic

compounds and polar solutes like ethanol (C_2H_5OH). However, water does not dissolve nonpolar solutes, such as many oils and greases (Figure **11.2.1**).



Figure **11.2.1**: A beaker holds water with blue food dye (upper liquid layer) and a much more dense perfluoroheptane (a fluorocarbon) lower liquid layer. The two fluids cannot mix and the dye cannot dissolve in fluorocarbon. A goldfish and a crab have been introduced into the water. The goldfish cannot penetrate the dense fluorocarbon. The crab floats at the liquid boundary with only parts of his legs penetrating the fluorocarbon fluid, unable to sink to the bottom of the beaker. Quarter coins rest on the bottom of the beaker. Animals were rescued from their predicament after the photo was taken. Figure used with permission from Wikipedia (Sbharris (Steven B. Harris)).

We use the word soluble to describe a solute that dissolves in a particular solvent, and the word insoluble for a solute that does not dissolve in a solvent. Thus, we say that sodium chloride is soluble in water but insoluble in hexane (C_6H_{14}). If the solute and the solvent are both liquids and soluble in any proportion, we use the word miscible, and the word immiscible if they are not.

✔ Example 11.2.1

Water is considered a polar solvent. Which substances should dissolve in water?

1. methanol (CH_3OH)
2. sodium sulfate (Na_2SO_4)
3. octane (C_8H_{18})

Solution

Because water is polar, substances that are polar or ionic will dissolve in it.

1. Because of the OH group in methanol, we expect its molecules to be polar. Thus, we expect it to be soluble in water. As both water and methanol are liquids, the word *miscible* can be used in place of *soluble*.
2. Sodium sulfate is an ionic compound, so we expect it to be soluble in water.
3. Like other hydrocarbons, octane is nonpolar, so we expect that it would not be soluble in water.

? Exercise 11.2.1

Toluene ($C_6H_5CH_3$) is widely used in industry as a nonpolar solvent. Which substances should dissolve in toluene?

a. water (H_2O)
b. sodium sulfate (Na_2SO_4)
c. octane (C_8H_{18})

Answer

Octane only.

Example 11.2.2

Predict which of the following compounds will be most soluble in water:

a. $\underset{\text{Ethanol}}{CH_3CH_2OH}$

b. $\underset{\text{Hexanol}}{CH_3CH_2CH_2CH_2CH_2CH_2OH}$

Solution

Since ethanol contains an **OH** group, it can hydrogen bond to water. Although the same is true of hexanol, the OH group is found only at one end of a fairly large molecule. The rest of the molecule can be expected to behave much as though it were a nonpolar alkane. This substance should thus be much less soluble than the first. Experimentally we find that ethanol is completely miscible with water, while only 0.6 g hexanol dissolves in 100 g water.

11.2.2 Exercise

Would I_2 be more soluble in CCl_4 or H_2O?

Answer

I_2 is nonpolar. Of the two solvents, CCl_4 is nonpolar and H_2O is polar, so I_2 would be expected to be more soluble in CCl_4.

Key Takeaway

- Solutions form because a solute and a solvent experience similar intermolecular interactions.

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11.3: Concentration

Learning Objectives

- Calculate percentage concentration (m/m, v/v, m/v), ppm and ppb.
- Calculate the molarity of a solution.
- Use concentration units to calculate the amount of solute in a solution.
- Use molarity to determine quantities in chemical reactions.
- Determine the resulting concentration of a diluted solution.

To define a solution precisely, we need to state its concentration: how much solute is dissolved in a certain amount of solvent. Words such as *dilute* or *concentrated* are used to describe solutions that have a little or a lot of dissolved solute, respectively, but these are relative terms whose meanings depend on various factors.

Solubility

There is usually a limit to how much solute will dissolve in a given amount of solvent. This limit is called the **solubility** of the solute. Some solutes have a very small solubility, while other solutes are soluble in all proportions. Table **11.3.1** lists the solubilities of various solutes in water. Solubilities vary with temperature, so Table **11.3.1** includes the temperature at which the solubility was determined.

Table **11.3.1**: Solubilities of Various Solutes in Water at 25°C (Except as Noted)

Substance	Solubility (g in 100 mL of H2O)
AgCl(s)	0.019
$C_6H_6(\ell)$ (benzene)	0.178
$CH_4(g)$	0.0023
$CO_2(g)$	0.150
$CaCO_3(s)$	0.058
$CaF_2(s)$	0.0016
$Ca(NO_3)_2(s)$	143.9
$C_6H_{12}O_6$ (glucose)	120.3 (at 30°C)
KBr(s)	67.8
$MgCO_3(s)$	2.20
NaCl(s)	36.0
$NaHCO_3(s)$	8.41
$C_{12}H_{22}O_{11}$ (sucrose)	204.0 (at 20°C)

If a solution contains so much solute that its solubility limit is reached, the solution is said to be **saturated**, and its concentration is known from information contained in Table **11.3.1**. If a solution contains less solute than the solubility limit, it is **unsaturated**. Under special circumstances, more solute can be dissolved even after the normal solubility limit is reached; such solutions are called ***supersaturated*** and are not stable. If the solute is solid, excess solute can easily recrystallize. If the solute is a gas, it can bubble out of solution uncontrollably, like what happens when you shake a soda can and then immediately open it.

Precipitation from Supersaturated Solutions

Recrystallization of excess solute from a supersaturated solution usually gives off energy as heat. Commercial heat packs containing supersaturated sodium acetate ($NaC_2H_3O_2$) take advantage of this phenomenon. You can probably find them at your local drugstore.



Video* 11.3.1*: Watered-down sodium acetate trihydrate. Needle crystal is truly wonderful structures

Most solutions we encounter are unsaturated, so knowing the solubility of the solute does not accurately express the amount of solute in these solutions. There are several common ways of specifying the concentration of a solution.

Percent Composition

There are several ways of expressing the concentration of a solution by using a percentage. The **mass/mass percent** (% m/m) is defined as the mass of a solute divided by the mass of a solution times 100:

$$\%\,\mathrm{m/m} = \frac{\text{mass of solute}}{\text{mass of solution}} \times 100\% \tag{11.3.1}$$

If you can measure the masses of the solute and the solution, determining the mass/mass percent is easy. Each mass must be expressed in the same units to determine the proper concentration.

Example 11.3.1

A saline solution with a mass of 355 g has 36.5 g of NaCl dissolved in it. What is the mass/mass percent concentration of the solution?

Solution

We can substitute the quantities given in the equation for mass/mass percent:

$$\%\,\mathrm{m/m} = \frac{36.5\ \mathrm{g}}{355\ \mathrm{g}} \times 100\% = 10.3\%$$

Exercise 11.3.1

A dextrose (also called D-glucose, $C_6H_{12}O_6$) solution with a mass of 2.00×10^2 g has 15.8 g of dextrose dissolved in it. What is the mass/mass percent concentration of the solution?

Answer

7.90%

For gases and liquids, volumes are relatively easy to measure, so the concentration of a liquid or a gas solution can be expressed as a **volume/volume percent** (% v/v): the volume of a solute divided by the volume of a solution times 100:

$$\%\ \text{v/v} = \frac{\text{volume of solute}}{\text{volume of solution}} \times 100\% \tag{11.3.2}$$

Again, the units of the solute and the solution must be the same. A hybrid concentration unit, **mass/volume percent** (% m/v), is commonly used for intravenous (IV) fluids (Figure 11.3.1). It is defined as the mass in grams of a solute, divided by volume in milliliters of solution times 100:

$$\%\ \text{m/v} = \frac{\text{mass of solute (g)}}{\text{volume of solution (mL)}} \times 100\% \tag{11.3.3}$$



Figure 11.3.1: Mass/Volume Percent.The 0.9% NaCl concentration on this IV bag is mass/volume percent (left). Such solution is used for other purposes and available in bottles (right). Figures used with permission from Wikipedia

Using Percent Composition in Calculations

The **percent concentration** can be used to produce a **conversion factor** between the **amount of solute** and the **amount of solution**. As such, concentrations can be useful in a variety of stoichiometry problems as discussed in Chapter 6. In many cases, it is best to use the original definition of the concentration unit; it is that definition that provides the conversion factor.

As an example, if the given concentration is **5% v/v solution of alcohol**, this means that there are 5 mL of alcohol dissolved in every 100 mL solution.

5 mL alcohol = 100 mL solution

The two possible conversion factors are written as follows:

$$\frac{\text{5 mL alcohol}}{\text{100 mL solution}} \text{ or } \frac{\text{100 mL solution}}{\text{5 mL alcohol}}$$

Use the first conversion factor to convert from a given amount of solution to amount of solute. The second conversion factor is used to convert from a given amount of solute to amount of solution. Given any two quantities in any percent composition, the third quantity can be calculated, as the following example illustrates.

Example 11.3.2

A sample of 45.0% v/v solution of ethanol (C_2H_5OH) in water has a volume of 115 mL. What volume of ethanol solute does the sample contain?

Solution

A percentage concentration is simply the number of parts of solute per 100 parts of solution. Thus, the percent concentration of 45.0% v/v implies the following:

$$45.0\%\ \text{v/v} \rightarrow \frac{45\ \text{mL}\ C_2H_5OH}{100\ \text{mL solution}}$$

That is, there are 45 mL of C_2H_5OH for every 100 mL of solution. We can use this fraction as a **conversion factor** to determine the amount of C_2H_5OH in 115 mL of solution:

$$115\ \text{mL solution} \times \frac{45\ \text{mL}\ C_2H_5OH}{100\ \text{mL solution}} = 51.8\ \text{mL}\ C_2H_5OH$$

Exercise 11.3.2

What volume of a 12.75% m/v solution of glucose ($C_6H_{12}O_6$) in water is needed to obtain 50.0 g of $C_6H_{12}O_6$?

Answer

$$50.0\ \text{g}\ C_6H_12O_6 \times \frac{100\ \text{mL solution}}{12.75\ \text{g}\ C_6H_12O_6} = 392\ \text{mL solution}$$

Example 11.3.3

A normal saline IV solution contains 9.0 g of NaCl in every liter of solution. What is the mass/volume percent of normal saline?

Solution

We can use the definition of mass/volume percent, but first we have to express the volume in milliliter units:

1 L = 1,000 mL

Because this is an exact relationship, it does not affect the significant figures of our result.

$$\%\ \text{m/v} = \frac{9.0\ \text{g NaCl}}{1,000\ \text{mL solution}} \times 100\% = 0.90\%\ \text{m/v}$$

Exercise 11.3.3

The chlorine bleach that you might find in your laundry room is typically composed of 27.0 g of sodium hypochlorite (NaOCl), dissolved to make 500.0 mL of solution. What is the mass/volume percent of the bleach?

Answer

$$\%\ \text{m/v} = \frac{27.0\ \text{g NaOCl}}{500.0\ \text{mL solution}} \times 100\% = 5.40\%\ \text{m/v}$$

In addition to percentage units, the units for expressing the concentration of extremely dilute solutions are parts per million (ppm) and parts per billion (ppb). Both of these units are mass based and are defined as follows:

$$\text{ppm} = \frac{\text{mass of solute}}{\text{mass of solution}} \times 1,000,000 \tag{11.3.4}$$

$$\text{ppb} = \frac{\text{mass of solute}}{\text{mass of solution}} \times 1,000,000,000 \tag{11.3.5}$$

> *Similar to parts per million and parts per billion, related units include parts per thousand (ppth) and parts per trillion (ppt).*

Concentrations of *trace elements* in the body—elements that are present in extremely low concentrations but are nonetheless necessary for life—are commonly expressed in parts per million or parts per billion. Concentrations of poisons and pollutants are also described in these units. For example, cobalt is present in the body at a concentration of 21 ppb, while the State of Oregon's Department of Agriculture limits the concentration of arsenic in fertilizers to 9 ppm.

> *In aqueous solutions, 1 ppm is essentially equal to 1 mg/L, and 1 ppb is equivalent to 1 μg/L.*

Example 11.3.4

If the concentration of cobalt in a human body is 21 ppb, what mass in grams of Co is present in a body having a mass of 70.0 kg?

Solution

A concentration of 21 ppb means "21 g of solute per 1,000,000,000 g of solution." Written as a **conversion factor,** this concentration of Co is as follows:

$$21 \text{ ppb Co} \rightarrow \frac{21 \text{ g Co}}{1,000,000,000 \text{ g solution}}$$

We can use this as a conversion factor, but first we must convert 70.0 kg to gram units:

$$70.0 \text{ kg} \times \frac{1,000 \text{ g}}{1 \text{ kg}} = 7.00 \times 10^4 \text{ g}$$

Now we determine the amount of Co:

$$7.00 \times 10^4 \text{ g solution} \times \frac{21 \text{ g Co}}{1,000,000,000 \text{ g solution}} = 0.0015 \text{ g Co}$$

This is only 1.5 mg.

Exercise 11.3.4

An 85 kg body contains 0.012 g of Ni. What is the concentration of Ni in parts per million?

Answer

0.14 ppm

Molarity

Another way of expressing concentration is to give the number of moles of solute per unit volume of solution. Such concentration units are useful for discussing chemical reactions in which a solute is a product or a reactant. Molar mass can then be used as a conversion factor to convert amounts in moles to amounts in grams.

Molarity is defined as the number of moles of a solute dissolved per liter of solution:

$$\text{molarity} = \frac{\text{number of moles of solute}}{\text{number of liters of solution}} \tag{11.3.6}$$

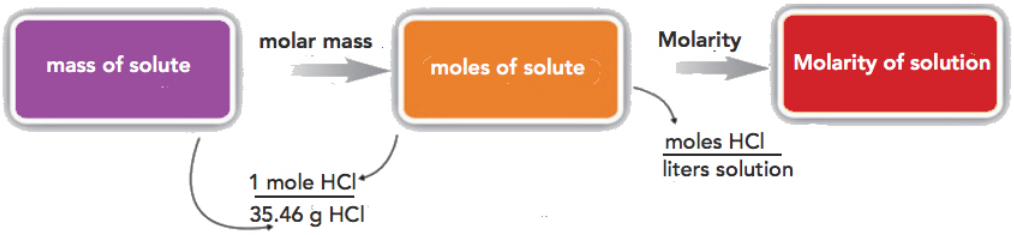
Molarity is abbreviated M (often referred to as "molar"), and the units are often abbreviated as mol/L. It is important to remember that "mol" in this expression refers to moles of solute and that "L" refers to liters of solution. For example, if you have 1.5 mol of NaCl dissolved in 0.500 L of solution, its molarity is therefore

$$\frac{1.5 \text{ mol NaCl}}{0.500 \text{ L solution}} = 3.0 \text{ M NaCl} \tag{11.3.7}$$

which is read as "three point oh **molar** sodium chloride." Sometimes (aq) is added when the solvent is water, as in "3.0 M NaCl(aq)."

Before a molarity concentration can be calculated, the amount of the **solute must be expressed in moles**, and the **volume of the solution** must be expressed in **liters**.

If the quantity of the solute is given in mass units, you must convert mass units to mole units before using the definition of molarity to calculate concentration. For example, what is the molar concentration of a solution of 22.4 g of HCl dissolved in 1.56 L?



Step 1: convert the **mass of solute** to **moles** using the **molar mass of HCl (36.46 g/mol):**

$$22.4\ \cancel{g HCl} \times \frac{1\ mol\ HCl}{36.46\ \cancel{g HCl}} = 0.614\ mol\ HCl \tag{11.3.8}$$

Step 2: use the **definition of molarity** to determine the concentration:

$$M = \frac{0.614\ mol\ HCl}{1.56 L\ solution} = 0.394\ MHCl \tag{11.3.9}$$

Example 11.3.5

What is the molarity of an aqueous solution of 25.0 g of NaOH in 750 mL?

Solution

Before we substitute these quantities into the definition of molarity, we must convert them to the proper units. The mass of NaOH must be converted to moles of NaOH. The molar mass of NaOH is 40.00 g/mol:

$$25.0\ \text{g NaOH} \times \frac{1\ \text{mol NaOH}}{40.00\ \text{g NaOH}} = 0.625\ \text{mol NaOH}$$

Next, we convert the volume units from milliliters to liters:

$$750\ \text{mL} \times \frac{1\ \text{L}}{1,000\ \text{mL}} = 0.750\ \text{L}$$

Now that the quantities are expressed in the proper units, we can substitute them into the definition of molarity:

$$\text{M} = \frac{0.625\ \text{mol NaOH}}{0.750\ \text{L}} = 0.833\ \text{M NaOH}$$

Exercise 11.3.5

If a 350 mL cup of coffee contains 0.150 g of caffeine ($C_8H_{10}N_4O_2$), what is the molarity of this caffeine solution?

Answer

0.00221 M

Using Molarity in Calculations

The definition of molarity can also be used to calculate a needed volume of solution, given its concentration and the number of moles desired, or the number of moles of solute (and subsequently, the mass of the solute), given its concentration and volume. As in the percent concentration, molarity can also be expressed as a **conversion factor**.

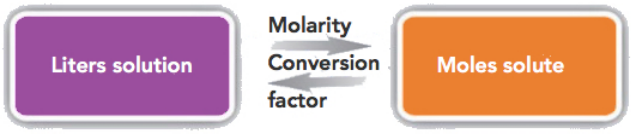
Molarity is defined as moles solute per liter solution. There is an understood 1 in the denominator of the conversion factor. For example, a **3.0 M solution of sucrose** means that there are three moles of sucrose dissolved in every **liter of solution**. Mathematically, this is stated as follows:

3.0 moles sucrose = 1 L solution

Dividing both sides of this expression by either side, we generate two possible conversion factors:

$$\frac{3.0\ \text{mol sucrose}}{1\ \text{L solution}} \text{ or } \frac{1\ \text{L solution}}{3.0\ \text{mol sucrose}}$$

The first conversion factor can be used to convert from *volume (L) of solution to moles solute*, and the *second converts from moles of solute to volume (L) of solution*.



For example, suppose we are asked how many moles of sucrose are present in 0.108 L of a 3.0 M sucrose solution. The given volume (0.108 L) is multiplied by the first conversion factor to cancel the L units, and find that 0.32 moles of sucrose are present.

$$0.108\ \cancel{L\ solution} \times \frac{3.0\ mol\ sucrose}{\cancel{1\ L\ solution}} = 0.32\ mol\ sucrose \tag{11.3.10}$$

How many liters of 3.0 M sucrose solution are needed to obtain 4.88 mol of sucrose? In such a conversion, we multiply the given (4.88 moles sucrose) with the second conversion factor. This cancels the moles units and converts it to liters of solution.

$$4.88\ \cancel{mol\ sucrose} \times \frac{1\ L\ solution}{\cancel{3.0\ mol\ sucrose}} = 1.63\ L\ solution \tag{11.3.11}$$

Example 11.3.6

1. What volume of a 0.0753 M solution of dimethylamine [$(CH_3)_2NH$] is needed to obtain 0.450 mol of the compound?
2. Ethylene glycol ($C_2H_6O_2$) is mixed with water to make auto engine coolants. How many grams of $C_2H_6O_2$ are in 5.00 L of a 6.00 M aqueous solution?

Solution

1. To solve for the volume, multiply the "given" (0.450 mol of dimethylamine) with the molarity conversion factor (0.0753 M). Use the proper conversion factor to cancel the unit "mol" and get the unit volume (L) of solution:

$$0.450\ \text{mol dimethylamine} \times \frac{1\ \text{L solution}}{0.0753\ \text{mol dimethylamine}} = 5.98\ \text{L solution}$$

2. The strategy in solving this problem is to convert the given volume (5.00 L) using the 6.00 M (conversion factor) to solve for moles of ethylene glycol, which can then be converted to grams.

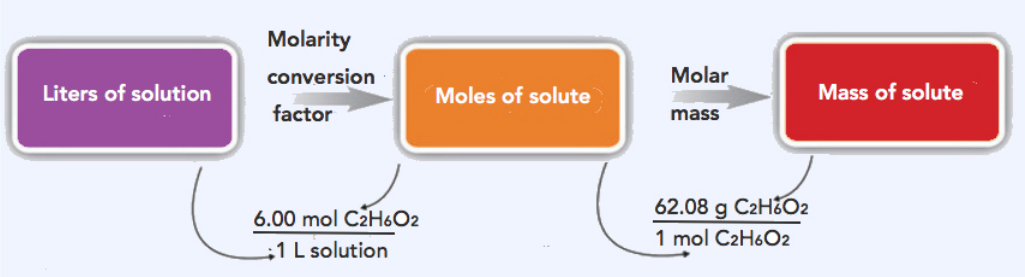
Step 1: Convert the given volume (5.00 L) to moles ethylene glycol.

$$5.00\ \text{L solution} \times \frac{6.00\ \text{mol}\ C_2H_6O_2}{1\ \text{L solution}} = 30.0\ \text{mol}\ C_2H_6O_2$$

Step 2: Convert 30.0 mols $C_2H_6O_2$ to grams $C_2H_6O_2$. Molar mass of $C_2H_6O_2$= 62.08 g/mol

$$30.0\ \text{mol}\ C_2H_6O_2 \times \frac{62.08\ \text{g}\ C_2H_6O_2}{1\ \text{mol}\ C_2H_6O_2} = 1,860\ \text{g}\ C_2H_6O_2$$

The same two-step problem can also be worked out in a single line, rather than as two separate steps, as follows:



$$5.00\ \text{L solution} \times \frac{6.00\ \text{mol}\ C_2H_6O_2}{1\ \text{L solution}} \times \frac{62.08\ \text{g}\ C_2H_6O_2}{1\ \text{mol}\ C_2H_6O_2} = 1,860\ \text{g}\ C_2H_6O_2$$

The final answer is rounded off to 3 significant figures. Thus, there are 1,860 g of $C_2H_6O_2$ in the specified amount of engine coolant.

Note: Dimethylamine has a “fishy” odor. In fact, organic compounds called amines cause the odor of decaying fish.

Example 11.3.6A

1. What volume of a 0.0753 M solution of dimethylamine [$(CH_3)_2NH$] is needed to obtain 0.450 mol of the compound?
2. Ethylene glycol ($C_2H_6O_2$) is mixed with water to make auto engine coolants. How many grams of $C_2H_6O_2$ are in 5.00 L of a 6.00 M aqueous solution?

Solution

This is an alternative method in case you don't want to use the conversion factor for molarity. In both parts, we will use the definition of molarity to solve for the desired quantity.

1. $$0.0753\ \text{M} = \frac{0.450\ \text{mol}\ (CH_3)_2NH}{\text{volume of solution}}$$

   To solve for the volume of solution, we multiply both sides by volume of solution and divide both sides by the molarity value to isolate the volume of solution on one side of the equation:

   $$\text{volume of solution} = \frac{0.450\ \text{mol}\ (CH_3)_2NH}{0.0753\ \text{M}} = 5.98\ \text{L}$$

   Note that because the definition of molarity is mol/L, the division of mol by M yields L, a unit of volume.

2. The molar mass of $C_2H_6O_2$ is 62.08 g/mol., so

   $$6.00\ \text{M} = \frac{\text{moles of solute}}{5.00\ \text{L}}$$

   To solve for the number of moles of solute, we multiply both sides by the volume:

   $$\text{moles of solute} = (6.00\ \text{M})(5.00\ \text{L}) = 30.0\ \text{mol}$$

   Note that because the definition of molarity is mol/L, the product M × L gives mol, a unit of amount. Now, using the molar mass of $C_3H_8O_3$, we convert mol to g:

   $$30.0\ \text{mol} \times \frac{62.08\ \text{g}}{\text{mol}} = 1,860\ \text{g}$$

   Thus, there are 1,860 g of $C_2H_6O_2$ in the specified amount of engine coolant.

Exercise 11.3.6

a. What volume of a 0.0902 M solution of formic acid (HCOOH) is needed to obtain 0.888 mol of HCOOH?
b. Acetic acid ($HC_2H_3O_2$) is the acid in vinegar. How many grams of $HC_2H_3O_2$ are in 0.565 L of a 0.955 M solution?

Answer

a. 9.84 L

b. 32.4 g

Using Molarity in Stoichiometry Problems

Of all the ways of expressing concentration, molarity is the one most commonly used in stoichiometry problems because it is directly related to the mole unit. Consider the following chemical equation:

$$HCl(aq) + NaOH(s) \rightarrow H_2O(\ell) + NaCl(aq)$$

Suppose we want to know how many liters of aqueous HCl solution will react with a given mass of NaOH. A typical approach to answering this question is as follows:

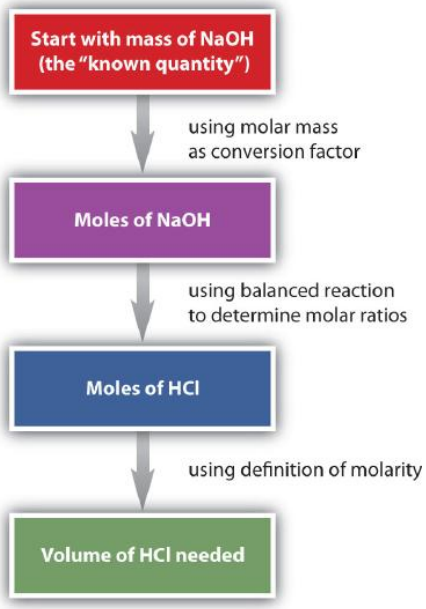


***Figure* 11.3.2**: *Typical approach to solving Molarity problems*

In itself, each step is a straightforward conversion. It is the combination of the steps that is a powerful quantitative tool for problem solving.

Example 11.3.7

How many milliliters of a 2.75 M HCl solution are needed to react with 185 g of NaOH? The balanced chemical equation for this reaction is as follows:

$$HCl(aq) + NaOH(s) \rightarrow H_2O(\ell) + NaCl(aq)$$

Solution

We will follow the flowchart to answer this question. First, we convert the mass of NaOH to moles of NaOH using its molar mass, 40.00 g/mol:

$$185\ \text{g NaOH} \times \frac{1\ \text{mol NaOH}}{40.00\ \text{g NaOH}} = 4.63\ \text{mol NaOH}$$

Using the balanced chemical equation, we see that there is a one-to-one ratio of moles of HCl to moles of NaOH. We use this to determine the number of moles of HCl needed to react with the given amount of NaOH:

$$4.63\ \text{mol NaOH} \times \frac{1\ \text{mol HCl}}{1\ \text{mol NaOH}} = 4.63\ \text{mol HCl}$$

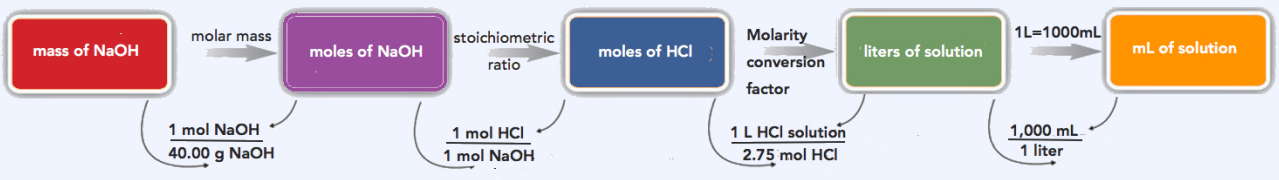
Finally, we use the definition of molarity to determine the volume of 2.75 M HCl needed:

$$2.75\ \text{M HCl} = \frac{4.63\ \text{mol HCl}}{\text{volume of HCl solution}}$$

$$\text{volume of HCl} = \frac{4.63\ \text{mol HCl}}{2.75\ \text{M HCl}} = 1.68\ \text{L} \times \frac{1,000\ \text{mL}}{1\ \text{L}} = 1,680\ \text{mL}$$

We need 1,680 mL of 2.75 M HCl to react with the NaOH.

The same multi-step problem can also be worked out in a single line, rather than as separate steps, as follows:



https://chem.libretexts.org/@go/page/306664

$$185\ \text{g NaOH} \times \frac{1\ \text{mol NaOH}}{40.00\ \text{g NaOH}} \times \frac{1\ \text{mol HCl}}{1\ \text{mol NaOH}} \times \frac{1\ \text{L HCl solution}}{2.75\ \text{mol HCl}} \times \frac{1000\ \text{mL HCl solution}}{1\ \text{L HCl solution}} = 1,680\ \text{mL HCl solution}$$

Our final answer (rounded off to three significant figures) is 1,680 mL HCl solution.

Exercise 11.3.7

How many milliliters of a 1.04 M H_2SO_4 solution are needed to react with 98.5 g of $Ca(OH)_2$? The balanced chemical equation for the reaction is as follows:

$$H_2SO_{4(aq)} + Ca(OH)_{2(s)} \rightarrow 2H_2O_{(\ell)} + CaSO_{4(aq)}$$

Answer

1,280 mL

The general steps for performing stoichiometry problems such as this are shown in Figure **11.3.3**. You may want to consult this figure when working with solutions in chemical reactions. The double arrows in Figure **11.3.3** indicate that you can start at either end of the chart and, after a series of simple conversions, determine the quantity at the other end.

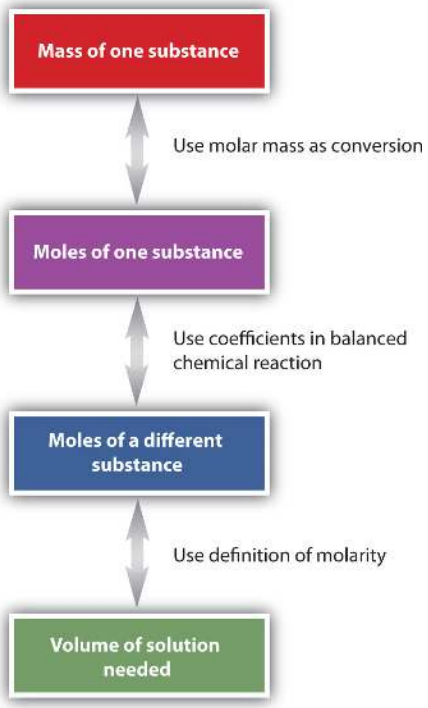


Figure **11.3.3**: Diagram of Steps for Using Molarity in Stoichiometry Calculations. When using molarity in stoichiometry calculations, a specific sequence of steps usually leads you to the correct answer.

Many of the fluids found in our bodies are solutions. The solutes range from simple ionic compounds to complex proteins. Table **11.3.2** lists the typical concentrations of some of these solutes.

Table **11.3.2**: Approximate Concentrations of Various Solutes in Some Solutions in the Body*

Solution	Solute	Concentration (M)
blood plasma	Na^+	0.138
	K^+	0.005
	Ca^{2+}	0.004
	Mg^{2+}	0.003
	Cl^-	0.110
	HCO_3^-	0.030
stomach acid	HCl	0.10
urine	NaCl	0.15
	PO_4^{3-}	0.05
	NH_2CONH_2 (urea)	0.30

*Note: Concentrations are approximate and can vary widely.

Looking Closer: The Dose Makes the Poison

Why is it that we can drink 1 qt of water when we are thirsty and not be harmed, but if we ingest 0.5 g of arsenic, we might die? There is an old saying: *the dose makes the poison*. This means that what may be dangerous in some amounts may not be dangerous in other amounts.

Take arsenic, for example. Some studies show that arsenic deprivation limits the growth of animals such as chickens, goats, and pigs, suggesting that arsenic is actually an essential trace element in the diet. Humans are constantly exposed to tiny amounts of arsenic from the environment, so studies of completely arsenic-free humans are not available; if arsenic is an essential trace mineral in human diets, it is probably required on the order of 50 ppb or less. A toxic dose of arsenic corresponds to about 7,000 ppb and higher, which is over 140 times the trace amount that may be required by the body. Thus, arsenic is not poisonous in and of itself. Rather, it is the amount that is dangerous: the dose makes the poison.

Similarly, as much as water is needed to keep us alive, too much of it is also risky to our health. Drinking too much water too fast can lead to a condition called water intoxication, which may be fatal. The danger in water intoxication is not that water itself becomes toxic. It is that the ingestion of too much water too fast dilutes sodium ions, potassium ions, and other salts in the bloodstream to concentrations that are not high enough to support brain, muscle, and heart functions. Military personnel, endurance athletes, and even desert hikers are susceptible to water intoxication if they drink water but do not replenish the salts lost in sweat. As this example shows, even the right substances in the wrong amounts can be dangerous!

Equivalents

Concentrations of ionic solutes are occasionally expressed in units called equivalents (Eq). One equivalent equals 1 mol of positive or negative charge. Thus, 1 mol/L of $Na^+(aq)$ is also 1 Eq/L because sodium has a 1+ charge. A 1 mol/L solution of $Ca^{2+}(aq)$ ions has a concentration of 2 Eq/L because calcium has a 2+ charge. Dilute solutions may be expressed in milliequivalents (mEq)—for example, human blood plasma has a total concentration of about 150 mEq/L. (For more information about the ions present in blood plasma, see Chapter 3 "Ionic Bonding and Simple Ionic Compounds", Section 3.3 "Formulas for Ionic Compounds".)

Exercise 11.3.8*a*

a) How many equivalents (Eq) would 1 mole of Al^{3+} equal?

b) How many equivalents (Eq) would 2 mole of Cl^- equal?

c) How many equivalents (Eq) would 3.5 mole of CO_3^{2-} equal?

Answer

a. 3 Eq

b. 2 Eq

c. 7 Eq

Dilutions

When additional water is added to an aqueous solution, the concentration of that solution decreases. This is because the number of **moles of the solute does not change**, while the **volume of the solution increases**. We can set up an equality between the moles of the solute before the dilution (1) and the moles of the solute after the dilution (2).

$$\text{mol}_1 = \text{mol}_2 \tag{11.3.12}$$

Since the moles of solute in a solution is equal to the molarity multiplied by the liters, we can set those equal.

$$M_1 \times L_1 = M_2 \times L_2 \tag{11.3.13}$$

Finally, because the two sides of the equation are set equal to one another, the volume can be in any units we choose, as long as that unit is the same on both sides. Our equation for calculating the molarity of a diluted solution becomes:

$$M_1 \times V_1 = M_2 \times V_2 \tag{11.3.14}$$

Suppose that you have $100.\ \text{mL}$ of a $2.0\ \text{M}$ solution of HCl. You dilute the solution by adding enough water to make the solution volume $500.\ \text{mL}$. The new molarity can easily be calculated by using the above equation and solving for M_2.

$$M_2 = \frac{M_1 \times V_1}{V_2} = \frac{2.0\ \text{M} \times 100.\ \text{mL}}{500.\ \text{mL}} = 0.40\ \text{M HCl} \tag{11.3.15}$$

The solution has been diluted by one-fifth since the new volume is five times as great as the original volume. Consequently, the molarity is one-fifth of its original value.

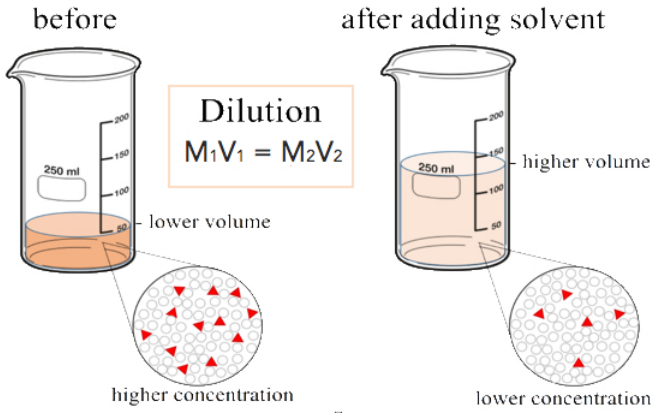


Figure 11.3.1: Figure 11.3.4: Diluting a solution by adding more solvent. Through the dilution process, the volume increases and the concentrations of the solutes decrease. As a consequence, there is more solution in the beaker after dilution, and the color of the solution becomes fainter. The inset shows that at the particular level (picometer to nanometer scale), there are less solute particles (red triangles) per volume. The content in the central box shows the dilution law, i.e. that the product of concentration and volume stays constant upon dilution. CC BY-SA 4.0.

Dilution Equations

Any units of concentration and volume can be used, as long as both concentrations and both volumes have the same unit. For example, if we are using M (molarity), then we can express the equation as follows:

$$\text{Molarity}_{\text{initial}} \times \text{volume}_{\text{initial}} = \text{Molarity}_{\text{final}} \times \text{volume}_{\text{final}} \text{ or}$$

$$M_1V_1 = M_2V_2$$

If we are using percent, the dilution equation is as follows:

$$\%_{initial} \times volume_{initial} = \%_{final} \times volume_{final} \text{ or}$$

$$\%_1V_1 = \%_2V_2$$

Example 11.3.8

A 125 mL sample of 0.900 M NaCl is diluted to 1,125 mL. What is the final concentration of the diluted solution?

Solution

Because the volume units are the same, and we are looking for the molarity of the final solution, we can use (concentration × volume)$_{initial}$ = (concentration × volume)$_{final}$:

$$(0.900\ M \times 125\ mL) = (\text{concentration} \times 1{,}125\ mL)$$

We solve by isolating the unknown concentration by itself on one side of the equation. Dividing by 1,125 mL gives

$$\text{concentration} = \frac{0.900\ M \times 125\ mL}{1{,}125\ mL} = 0.100\ M$$

as the final concentration.

Exercise 11.3.8

a. A nurse uses a syringe to inject 5.00 mL of 0.550 M heparin solution (heparin is an anticoagulant drug) into a 250 mL IV bag, for a final volume of 255 mL. What is the concentration of the resulting heparin solution?

b. A 0.885 M solution of KBr whose initial volume is 76.5 mL has more water added until its concentration is 0.500 M. What is the new volume of the solution?

Answer

a. 0.0108 M

b. 135.4 mL

Preparing IV Solutions

In a hospital emergency room, a physician orders an intravenous (IV) delivery of 100 mL of 0.5% KCl for a patient suffering from hypokalemia (low potassium levels). Does an aide run to a supply cabinet and take out an IV bag containing this concentration of KCl?

Not likely. It is more probable that the aide must make the proper solution from an IV bag of sterile solution and a more concentrated, sterile solution, called a *stock solution*, of KCl. The aide is expected to use a syringe to draw up some stock solution and inject it into the waiting IV bag and dilute it to the proper concentration. Thus the aide must perform a dilution calculation.



Figure 11.3.5:*Preparing IV Solution © Thinkstock. Medical personnel commonly must perform dilutions for IV solutions.*

If the stock solution is 10.0% KCl and the final volume and concentration need to be 100 mL and 0.50%, respectively, then it is an easy calculation to determine how much stock solution to use:

$$(10\%)V_1 = (0.50\%)(100\text{ mL})$$

$$V_1 = 5\text{ mL}$$

Of course, the addition of the stock solution affects the total volume of the diluted solution, but the final concentration is likely close enough even for medical purposes.

Medical and pharmaceutical personnel are constantly dealing with dosages that require concentration measurements and dilutions. It is an important responsibility: calculating the *wrong* dose can be useless, harmful, or even fatal!

Key Takeaways

- Various concentration units are used to express the amounts of solute in a solution.
- Concentration units can be used as conversion factors in stoichiometry problems.
- New concentrations can be easily calculated if a solution is diluted.

Concept Review Exercises

1. What are some of the units used to express concentration?
2. Distinguish between the terms *solubility* and *concentration*.

Answers

1. % m/m, % m/v, ppm, ppb, molarity, and Eq/L (answers will vary)
2. Solubility is typically a limit to how much solute can dissolve in a given amount of solvent. Concentration is the quantitative amount of solute dissolved at any concentration in a solvent.

Exercises

1. Define *solubility*. Do all solutes have the same solubility?
2. Explain why the terms *dilute* or *concentrated* are of limited usefulness in describing the concentration of solutions.
3. If the solubility of sodium chloride (NaCl) is 30.6 g/100 mL of H_2O at a given temperature, how many grams of NaCl can be dissolved in 250.0 mL of H_2O?
4. If the solubility of glucose ($C_6H_{12}O_6$) is 120.3 g/100 mL of H_2O at a given temperature, how many grams of $C_6H_{12}O_6$ can be dissolved in 75.0 mL of H_2O?
5. How many grams of sodium bicarbonate ($NaHCO_3$) can a 25.0°C saturated solution have if 150.0 mL of H_2O is used as the solvent?
6. If 75.0 g of potassium bromide (KBr) are dissolved in 125 mL of H_2O, is the solution saturated, unsaturated, or supersaturated?
7. Calculate the mass/mass percent of a saturated solution of NaCl. Use the data from Table **11.3.1** "Solubilities of Various Solutes in Water at 25°C (Except as Noted)", assume that masses of the solute and the solvent are additive, and use the density of H_2O (1.00 g/mL) as a conversion factor.
8. Calculate the mass/mass percent of a saturated solution of $MgCO_3$ Use the data from Table **11.3.1** "Solubilities of Various Solutes in Water at 25°C (Except as Noted)", assume that masses of the solute and the solvent are additive, and use the density of H_2O (1.00 g/mL) as a conversion factor.
9. Only 0.203 mL of C_6H_6 will dissolve in 100.000 mL of H_2O. Assuming that the volumes are additive, find the volume/volume percent of a saturated solution of benzene in water.
10. Only 35 mL of aniline ($C_6H_5NH_2$) will dissolve in 1,000 mL of H_2O. Assuming that the volumes are additive, find the volume/volume percent of a saturated solution of aniline in water.
11. A solution of ethyl alcohol (C_2H_5OH) in water has a concentration of 20.56% v/v. What volume of C_2H_5OH is present in 255 mL of solution?
12. What mass of KCl is present in 475 mL of a 1.09% m/v aqueous solution?
13. The average human body contains 5,830 g of blood. What mass of arsenic is present in the body if the amount in blood is 0.55 ppm?
14. The Occupational Safety and Health Administration has set a limit of 200 ppm as the maximum safe exposure level for carbon monoxide (CO). If an average breath has a mass of 1.286 g, what is the maximum mass of CO that can be inhaled at that maximum safe exposure level?
15. Which concentration is greater—15 ppm or 1,500 ppb?
16. Express the concentration 7,580 ppm in parts per billion.
17. What is the molarity of 0.500 L of a potassium chromate solution containing 0.0650 mol of K_2CrO_4?
18. What is the molarity of 4.50 L of a solution containing 0.206 mol of urea [$(NH_2)_2CO$]?
19. What is the molarity of a 2.66 L aqueous solution containing 56.9 g of NaBr?
20. If 3.08 g of $Ca(OH)_2$ is dissolved in enough water to make 0.875 L of solution, what is the molarity of the $Ca(OH)_2$?
21. What mass of HCl is present in 825 mL of a 1.25 M solution?
22. What mass of isopropyl alcohol (C_3H_8O) is dissolved in 2.050 L of a 4.45 M aqueous C_3H_8O solution?
23. What volume of 0.345 M NaCl solution is needed to obtain 10.0 g of NaCl?
24. How many milliliters of a 0.0015 M cocaine hydrochloride ($C_{17}H_{22}ClNO_4$) solution is needed to obtain 0.010 g of the solute?
25. Aqueous calcium chloride reacts with aqueous silver nitrate according to the following balanced chemical equation:

$$CaCl_2(aq) + 2AgNO_3(aq) \rightarrow 2AgCl(s) + Ca(NO_3)_2(aq)$$

How many moles of AgCl(s) are made if 0.557 L of 0.235 M $CaCl_2$ react with excess $AgNO_3$? How many grams of AgCl are made?

26. Sodium bicarbonate ($NaHCO_3$) is used to react with acid spills. The reaction with sulfuric acid (H_2SO_4) is as follows:

$$2NaHCO_3(s) + H_2SO_4(aq) \rightarrow Na_2SO_4(aq) + 2H_2O(\ell) + 2CO_2(g)$$

If 27.6 mL of a 6.25 M H_2SO_4 solution were spilled, how many moles of $NaHCO_3$ would be needed to react with the acid? How many grams of $NaHCO_3$ is this?

27. The fermentation of glucose to make ethanol and carbon dioxide has the following overall chemical equation:

$$C_6H_{12}O_6(aq) \rightarrow 2C_2H_5OH(aq) + 2CO_2(g)$$

If 1.00 L of a 0.567 M solution of $C_6H_{12}O_6$ were completely fermented, what would be the resulting concentration of the C_2H_5OH solution? How many moles of CO_2 would be formed? How many grams is this? If each mole of CO_2 had a volume of 24.5 L, what volume of CO_2 is produced?

28. Aqueous sodium bisulfite gives off sulfur dioxide gas when heated:

$$2NaHSO_3(aq) \rightarrow Na_2SO_3(aq) + H_2O(\ell) + SO_2(g)$$

If 567 mL of a 1.005 M $NaHSO_3$ solution were heated until all the $NaHSO_3$ had reacted, what would be the resulting concentration of the Na_2SO_3 solution? How many moles of SO_2 would be formed? How many grams of SO_2 would be formed? If each mole of SO_2 had a volume of 25.78 L, what volume of SO_2 would be produced?

29. What is the concentration of a 1.0 M solution of $K^+(aq)$ ions in equivalents/liter?

30. What is the concentration of a 1.0 M solution of $SO_4^{2-}(aq)$ ions in equivalents/liter?

31. A solution having initial concentration of 0.445 M and initial volume of 45.0 mL is diluted to 100.0 mL. What is its final concentration?

32. A 50.0 mL sample of saltwater that is 3.0% m/v is diluted to 950 mL. What is its final mass/volume percent?

Answers

1. Solubility is the amount of a solute that can dissolve in a given amount of solute, typically 100 mL. The solubility of solutes varies widely.

2. The term *dilute* means relatively less solute and the term *concentrated* implies relatively more solute. Both are of limited usefulness because these are not accurate.

3. 76.5 g

4. 90.2 g

5. 12.6 g

6. unsaturated

7. 26.5%

8. 2.15%

9. 0.203%

10. 3.4%

11. 52.4 mL

12. 5.18 g

13. 0.00321 g

14. 2.57×10^{-4} g

15. 15 ppm

16. 7,580,000 ppb

17. 0.130 M

18. 0.0458 M

19. 0.208 M

20. 0.0475 M

21. 37.6 g

22. 548 g

23. 0.496 L

24. 20 mL

25. 0.262 mol; 37.5 g

26. 0.345 mol; 29.0 g

27. 1.13 M C_2H_5OH; 1.13 mol of CO_2; 49.7 g of CO_2; 27.7 L of CO_2

28. 0.503 M Na_2SO_3; 0.285 mol SO_2; 18.3 g SO_2; 471 L SO_2

29. 1.0 Eq/L

30. 2.0 Eq/L

31. 0.200 M

32. 0.16 % m/v

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11.4: The Dissolution Process

Learning Objectives

- To describe the dissolution process at the molecular level

The Dissolution Process

What occurs at the molecular level to cause a solute to dissolve in a solvent? The answer depends in part on the solute, but there are some similarities common to all solutes.

Recall the rule that *like dissolves like*. This means that substances must have similar intermolecular forces to form solutions. When a soluble solute is introduced into a solvent, the particles of solute can interact with the particles of solvent. In the case of a solid or liquid solute, the interactions between the solute particles and the solvent particles are so strong that the individual solute particles separate from each other and, surrounded by solvent molecules, enter the solution. (Gaseous solutes already have their constituent particles separated, but the concept of being surrounded by solvent particles still applies.) This process is called **solvation** and is illustrated in Figure 11.4.1. When the solvent is water, the word **hydration**, rather than solvation, is used.

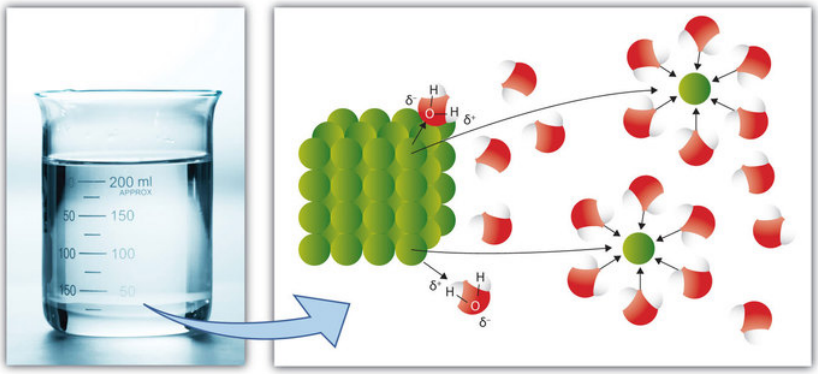


Figure 11.4.1: Solvation. When a solute dissolves, the individual particles of solute become surrounded by solvent particles. Eventually the particle detaches from the remaining solute, surrounded by solvent molecules in solution. Source: Photo © Thinkstock

Ionic Compounds and Covalent Compounds as Solutes

In the case of molecular solutes like glucose, the solute particles are individual molecules. However, if the solute is ionic, the individual ions separate from each other and become surrounded by solvent particles. That is, the cations and anions of an ionic solute separate when the solute dissolves. This process is referred to as **dissociation** (Figure 11.4.1).

The dissociation of soluble ionic compounds gives solutions of these compounds an interesting property: they conduct electricity. Because of this property, soluble ionic compounds are referred to as electrolytes. Many ionic compounds dissociate completely and are therefore called **strong electrolytes**. Sodium chloride is an example of a strong electrolyte. Some compounds dissolve but dissociate only partially, and solutions of such solutes may conduct electricity only weakly. These solutes are called **weak electrolytes**. Acetic acid (CH_3COOH), the compound in vinegar, is a weak electrolyte. Solutes that dissolve into individual neutral molecules without dissociation do not impart additional electrical conductivity to their solutions and are called nonelectrolytes. Table sugar ($C_{12}H_{22}O_{11}$) is an example of a nonelectrolyte.

> *The term electrolyte is used in medicine to mean any of the important ions that are dissolved in aqueous solution in the body. Important physiological electrolytes include Na^+, K^+, Ca^{2+}, Mg^{2+}, and Cl^-.*

Example 11.4.1

The following substances all dissolve to some extent in water. Classify each as an electrolyte or a nonelectrolyte.

1. potassium chloride (KCl)
2. fructose ($C_6H_{12}O_6$)
3. isopropyl alcohol [$CH_3CH(OH)CH_3$]
4. magnesium hydroxide [$Mg(OH)_2$]

Solution

Each substance can be classified as an ionic solute or a nonionic solute. Ionic solutes are electrolytes, and nonionic solutes are nonelectrolytes.

1. Potassium chloride is an ionic compound; therefore, when it dissolves, its ions separate, making it an electrolyte.
2. Fructose is a sugar similar to glucose. (In fact, it has the same molecular formula as glucose.) Because it is a molecular compound, we expect it to be a nonelectrolyte.
3. Isopropyl alcohol is an organic molecule containing the alcohol functional group. The bonding in the compound is all covalent, so when isopropyl alcohol dissolves, it separates into individual molecules but not ions. Thus, it is a nonelectrolyte
4. Magnesium hydroxide is an ionic compound, so when it dissolves it dissociates. Thus, magnesium hydroxide is an electrolyte.

Exercise 11.4.1

The following substances all dissolve to some extent in water. Classify each as an electrolyte or a nonelectrolyte.

a. acetone (CH_3COCH_3)
b. iron(III) nitrate [$Fe(NO_3)_3$]
c. elemental bromine (Br_2)
d. sodium hydroxide (NaOH)

Answer

a. nonelectrolyte

b. electrolyte

c. nonelectrolyte

d. electrolyte

Electrolytes in Body Fluids

Our body fluids are solutions of electrolytes and many other things. The combination of blood and the circulatory system is the *river of life*, because it coordinates all the life functions. When the heart stops pumping in a heart attack, the life ends quickly. Getting the heart restarted as soon as one can is crucial in order to maintain life.

The primary electrolytes required in the body fluid are cations (of calcium, potassium, sodium, and magnesium) and anions (of chloride, carbonates, aminoacetates, phosphates, and iodide). These are nutritionally called **macrominerals**.

Electrolyte balance is crucial to many body functions. Here's some extreme examples of what can happen with an imbalance of electrolytes: elevated potassium levels may result in cardiac arrhythmias; decreased extracellular potassium produces paralysis; excessive extracellular sodium causes fluid retention; and decreased plasma calcium and magnesium can produce muscle spasms of the extremities.

When a patient is dehydrated, a carefully prepared (commercially available) electrolyte solution is required to maintain health and well being. In terms of child health, oral electrolyte is given when a child is dehydrated due to diarrhea. The use of oral electrolyte maintenance solutions, which is responsible for saving millions of lives worldwide over the last 25 years, is one of the most

important medical advances in protecting the health of children in the century, explains Juilus G.K. Goepp, MD, assistant director of the Pediatric Emergency Department of the Children's Center at Johns Hopkins Hospital. If a parent provides an oral electrolyte maintenance solution at the very start of the illness, dehydration can be prevented. The functionality of electrolyte solutions is related to their properties, and interest in electrolyte solutions goes far beyond chemistry.

Sports drinks are designed to rehydrate the body after excessive fluid depletion. Electrolytes in particular promote normal rehydration to prevent fatigue during physical exertion. Are they a good choice for achieving the recommended fluid intake? Are they performance and endurance enhancers like they claim? Who should drink them?

Typically, eight ounces of a sports drink provides between fifty and eighty calories and 14 to 17 grams of carbohydrate, mostly in the form of simple sugars. Sodium and potassium are the most commonly included electrolytes in sports drinks, with the levels of these in sports drinks being highly variable. The American College of Sports Medicine says a sports drink should contain 125 milligrams of sodium per 8 ounces as it is helpful in replenishing some of the sodium lost in sweat and promotes fluid uptake in the small intestine, improving hydration.

Gatorade

In the summer of 1965, the assistant football coach of the University of Florida Gators requested scientists affiliated with the university study why the withering heat of Florida caused so many heat-related illnesses in football players and provide a solution to increase athletic performance and recovery post-training or game. The discovery was that inadequate replenishment of fluids, carbohydrates, and electrolytes was the reason for the “wilting” of their football players. Based on their research, the scientists concocted a drink for the football players containing water, carbohydrates, and electrolytes and called it “Gatorade.” In the next football season the Gators were nine and two and won the Orange Bowl. The Gators’ success launched the sports-drink industry, which is now a multibillion-dollar industry that is still dominated by Gatorade.



University of Florida football player Chip Hinton testing Gatorade in 1965, pictured next to the leader of its team of inventors, Robert Cade.

Key Takeaway

- When a solute dissolves, its individual particles are surrounded by solvent molecules and are separated from each other.

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11.5: Solubility Rules

To determine if a salt is soluble or to judge whether double-replacement reactions will occur, we need to know what kinds of ionic compounds will be insoluble in aqueous solutions. For this, we use **solubility rules**, which are general statements that predict which ionic compounds dissolve (are soluble) and which do not (are not soluble, or insoluble). Table **11.5.1** lists some general solubility rules. We need to consider each ionic compound (both the reactants and the possible products) in light of the solubility rules. If a compound is soluble, we use the (aq) label with it, indicating that it dissolves. If a compound is not soluble, we use the (s) label with it and assume that it will precipitate out of solution. If everything is soluble, then no reaction will be expected.

Table **11.5.1**: Some Useful Solubility Rules (soluble)

These compounds generally dissolve in water (are soluble):	Exceptions:
All compounds of Li^+, Na^+, K^+, Rb^+, Cs^+, and NH_4^+	None
All compounds of NO_3^- and $C_2H_3O_2^-$	None
Compounds of Cl^-, Br^-, I^-	Ag^+, Hg_2^{2+}, Pb^{2+}
Compounds of SO_4^{2}	Hg_2^{2+}, Pb^{2+}, Sr^{2+}, Ba^{2+}

Table **11.5.2**: Some Useful Solubility Rules (insoluble)

These compounds generally do not dissolve in water (are insoluble):	Exceptions:
Compounds of CO_3^{2-} and PO_4^{3-}	Compounds of Li^+, Na^+, K^+, Rb^+, Cs^+, and NH_4^+
Compounds of OH^-	Compounds of Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, Sr^{2+}, and Ba^{2+}

For example, consider the possible double-replacement reaction between Na_2SO_4 and $SrCl_2$. The solubility rules say that all ionic sodium compounds are soluble and all ionic chloride compounds are soluble, except for Ag^+, Hg_2^{2+}, and Pb^{2+}, which are not being considered here. Therefore, Na_2SO_4 and $SrCl_2$ are both soluble. The possible double-replacement reaction products are NaCl and $SrSO_4$. Are these soluble? NaCl is (by the same rule we just quoted), but what about $SrSO_4$? Compounds of the sulfate ion are generally soluble, but Sr^{2+} is an exception: we expect it to be insoluble—a precipitate. Therefore, we expect a reaction to occur, and the balanced chemical equation would be:

$$\mathrm{Na_2SO_4\,(aq) + SrCl_2\,(aq) \longrightarrow 2\,NaCl\,(aq) + SrSO_4\,(s)}$$

You would expect to see a visual change corresponding to $SrSO_4$ precipitating out of solution (Figure **11.5.2**).



Figure **11.5.2**: Double-Replacement Reactions. Some double-replacement reactions are obvious because you can see a solid precipitate coming out of solution. Source: Photo courtesy of Choij, http://commons.wikimedia.org/wiki/File:Copper_solution.jpg.

Example 11.5.4:

Will a double-replacement reaction occur? If so, identify the products.

1. $Ca(NO_3)_2$ + KBr → ?
2. NaOH + $FeCl_2$ → ?

Solution

1. According to the solubility rules, both $Ca(NO_3)_2$ and KBr are soluble. Now we consider what the double-replacement products would be by switching the cations (or the anions)—namely, $CaBr_2$ and KNO_3. However, the solubility rules predict that these two substances would also be soluble, so no precipitate would form. Thus, we predict no reaction in this case.
2. According to the solubility rules, both NaOH and $FeCl_2$ are expected to be soluble. If we assume that a double-replacement reaction may occur, we need to consider the possible products, which would be NaCl and $Fe(OH)_2$. NaCl is soluble, but, according to the solubility rules, $Fe(OH)_2$ is not. Therefore, a reaction would occur, and $Fe(OH)_2$(s) would precipitate out of solution. The balanced chemical equation is

$$\mathrm{2\,NaOH\,(aq) + FeCl_2\,(aq) \longrightarrow 2\,NaCl\,(aq) + Fe(OH)_2\,(s)}$$

Exercise 11.5.4

$$\mathrm{Sr(NO_3)_2 + KCl \longrightarrow}$$

Answer

No reaction; all possible products are soluble.

Key Takeaways

- Solubility rules are used to predict whether some double-replacement reactions will occur.

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11.6: Molecular and Ionic Equations

One of the unfortunate byproducts of industrialized society is acid rain. Sulfur dioxide from burning coal and nitrogen oxides from vehicle emissions both form acids. When these acids react with limestone (calcium carbonate), reactions occur that dissolve the limestone and release water and carbon dioxide. Over a period of time, serious damage is caused to the limestone structure.

Molecular and Ionic Equations

When ionic compounds are dissolved into water, the polar water molecules break apart the solid crystal lattice, resulting in the hydrated ions being evenly distributed through the water. This process is called dissociation and is the reason that all ionic compounds are strong electrolytes. When two different ionic compounds that have been dissolved in water are mixed, a chemical reaction may occur between certain pairs of the hydrated ions. Consider the double-replacement reaction that occurs when a solution of sodium chloride is mixed with a solution of silver nitrate:

$$\mathrm{NaCl}\,(aq) + \mathrm{AgNO_3}\,(aq) \rightarrow \mathrm{NaNO_3}\,(aq) + \mathrm{AgCl}\,(s)$$

The driving force behind this reaction is the formation of the silver chloride precipitate (see figure below).

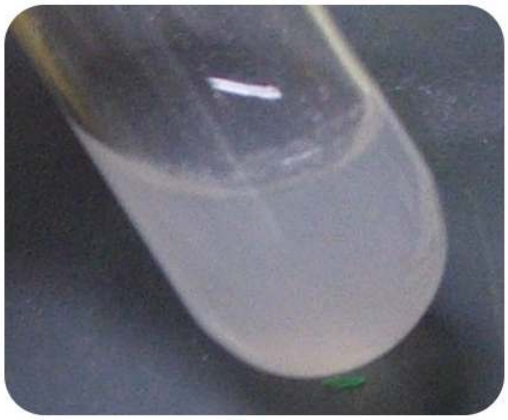


Figure **11.6.1**: The white silver chloride precipitate instantly forms when a solution of silver nitrate is added to a solution of sodium chloride.

This is called a molecular equation. A **molecular equation** is an equation in which the formulas of the compounds are written as though all substances exist as molecules. However, there is a better way to show what is happening in this reaction. All of the aqueous compounds should be written as ions, because they are present in the water as separated ions—a result of their dissociation.

$$\mathrm{Na^+}\,(aq) + \mathrm{Cl^-}\,(aq) + \mathrm{Ag^+}\,(aq) + \mathrm{NO_3^-}\,(aq) \rightarrow \mathrm{Na^+}\,(aq) + \mathrm{NO_3^-}\,(aq) + \mathrm{AgCl}\,(s)$$

This equation is called an **ionic equation**, an equation in which dissolved ionic compounds are shown as free ions.

Some other double-replacement reactions do not produce a precipitate as one of the products. The production of a gas and/or a molecular compound such as water may also drive the reaction. For example, consider the reaction of a solution of sodium carbonate with a solution of hydrochloric acid (HCl). The products of the reaction are aqueous sodium chloride, carbon dioxide, and water. The balanced molecular equation is:

$$\mathrm{Na_2CO_3}\,(aq) + 2\mathrm{HCl}\,(aq) \rightarrow 2\mathrm{NaCl}\,(aq) + \mathrm{CO_2}\,(g) + \mathrm{H_2O}\,(l)$$

The ionic equation is:

$$2\mathrm{Na^+}\,(aq) + \mathrm{CO_3^{2-}}\,(aq) + 2\mathrm{H^+}\,(aq) + 2\mathrm{Cl^-}\,(aq) \rightarrow 2\mathrm{Na^+}\,(aq) + 2\mathrm{Cl^-}\,(aq) + \mathrm{CO_2}\,(g) + \mathrm{H_2O}\,(l)$$

A single-replacement reaction is one in which an element replaces another element in a compound. An element is in either the solid, liquid, or gas state and is not an ion. The example below shows the reaction of solid magnesium metal with aqueous silver nitrate to form aqueous magnesium nitrate and silver metal.

Balanced molecular equation:

$$Mg\,(s) + 2AgNO_3\,(aq) \rightarrow Mg(NO_3)_2\,(aq) + 2Ag\,(s)$$

Ionic equation:

$$Mg\,(s) + 2Ag^+\,(aq) + 2NO_3{}^-\,(aq) \rightarrow Mg^{2+}\,(aq) + 2NO_3{}^-\,(aq) + Ag\,(s)$$

This type of single-replacement reaction is called a metal replacement. Other common categories of single-replacement reactions are: hydrogen replacement and halogen replacement.

Summary

- A molecular equation is an equation in which the formulas of the compounds are written as though all substances exist as molecules.
- An ionic equation is one in which dissolved ionic compounds are shown as free ions.
- Examples of molecular and ionic equations are shown.

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11.7: Net Ionic Equations

At sports events around the world, a small number of athletes fiercely compete on fields and in stadiums. They get tired, dirty, and sometimes hurt as they try to win the game. Surrounding them are thousands of spectators watching and cheering. Would the game be different without the spectators? Definitely! Spectators provide encouragement to the team and generate enthusiasm. Although the spectators are not playing the game, they are certainly a part of the process.

Net Ionic Equations

We can write a molecular equation for the formation of silver chloride precipitate:

$$\mathrm{NaCl} + \mathrm{AgNO_3} \rightarrow \mathrm{NaNO_3} + \mathrm{AgCl}$$

The corresponding ionic equation is:

$$\mathrm{Na^+}\,(aq) + \mathrm{Cl^-}\,(aq) + \mathrm{Ag^+}\,(aq) + \mathrm{NO_3^-}\,(aq) \rightarrow \mathrm{Na^+}\,(aq) + \mathrm{NO_3^-}\,(aq) + \mathrm{AgCl}\,(s)$$

If you look carefully at the ionic equation, you will notice that the sodium ion and the nitrate ion appear unchanged on both sides of the equation. When the two solutions are mixed, neither the $\mathrm{Na^+}$ nor the $\mathrm{NO_3^-}$ ions participate in the reaction. They can be eliminated from the reaction.

$$\cancel{\mathrm{Na^+}\,(aq)} + \mathrm{Cl^-}\,(aq) + \mathrm{Ag^+}\,(aq) + \cancel{\mathrm{NO_3^-}\,(aq)} \rightarrow \cancel{\mathrm{Na^+}\,(aq)} + \cancel{\mathrm{NO_3^-}\,(aq)} + \mathrm{AgCl}\,(s)$$

A **spectator ion** is an ion that does not take part in the chemical reaction and is found in solution both before and after the reaction. In the above reaction, the sodium ion and the nitrate ion are both spectator ions. The equation can now be written without the spectator ions:

$$\mathrm{Ag^+}\,(aq) + \mathrm{Cl^-}\,(aq) \rightarrow \mathrm{AgCl}\,(s)$$

The **net ionic equation** is the chemical equation that shows only those elements, compounds, and ions that are directly involved in the chemical reaction. Notice that in writing the net ionic equation, the positively-charged silver cation was written first on the reactant side, followed by the negatively-charged chloride anion. This is somewhat customary because that is the order in which the ions must be written in the silver chloride product. However, it is not absolutely necessary to order the reactants in this way.

Net ionic equations must be balanced by both mass and charge. Balancing by mass means ensuring that there are equal masses of each element on the product and reactant sides. Balancing by charge means making sure that the overall charge is the same on both sides of the equation. In the above equation, the overall charge is zero, or neutral, on both sides of the equation. As a general rule, if you balance the molecular equation properly, the net ionic equation will end up being balanced by both mass and charge.

Example 11.7.1

When aqueous solutions of copper (II) chloride and potassium phosphate are mixed, a precipitate of copper (II) phosphate is formed. Write a balanced net ionic equation for this reaction.

Solution

Step 1: Plan the problem.

Write and balance the molecular equation first, making sure that all formulas are correct. Then write the ionic equation, showing all aqueous substances as ions. Carry through any coefficients. Finally, eliminate spectator ions and write the net ionic equation.

Step 2: Solve.

Molecular equation:

$$3\mathrm{CuCl_2}\,(aq) + 2\mathrm{K_3PO_4}\,(aq) \rightarrow 6\mathrm{KCl}\,(aq) + \mathrm{Cu_3(PO_4)_2}\,(s)$$

Ionic equation:

$$3\mathrm{Cu^{2+}}\,(aq) + 6\mathrm{Cl^-}\,(aq) + 6\mathrm{K^+}\,(aq) + 2\mathrm{PO_4^{3-}}\,(aq) \rightarrow 6\mathrm{K^+}\,(aq) + 6\mathrm{Cl^-}\,(aq) + \mathrm{Cu_3(PO_4)_2}\,(s)$$

Notice that the balance of the equation is carried through when writing the dissociated ions. For example, there are six chloride ions on the reactant side because the coefficient of 3 is multiplied by the subscript of 2 on the copper (II) chloride formula. The spectator ions, $\mathrm{K^+}$ and $\mathrm{Cl^-}$, can be eliminated.

Net ionic equation:

$$\mathrm{3Cu^{2+}}\,(aq) + \mathrm{2PO_4^{3-}}\,(aq) \rightarrow \mathrm{Cu_3(PO_4)_2}\,(s)$$

Step 3: Think about your result.

For a precipitation reaction, the net ionic equation always shows the two ions that come together to form the precipitate. The equation is balanced by mass and charge.

Summary

- A spectator ion is an ion that does not take part in the chemical reaction and is found in solution both before and after the reaction.
- The net ionic equation is the chemical equation that shows only those elements, compounds, and ions that are directly involved in the chemical reaction.
- An example of writing a net ionic equation is outlined.

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11.8: Osmosis and Diffusion

Learning Outcomes

- Define osmosis and diffusion.
- Distinguish among hypotonic, hypertonic, and isotonic solutions.
- Describe a semipermeable membrane.
- Predict behavior of blood cells in different solution types.
- Describe flow of solvent molecules across a membrane.
- Identify the polar and nonpolar regions of a cell membrane.
- Explain the components present in a phospholipid.

Fish cells, like all cells, have semipermeable membranes. Eventually, the concentration of "stuff" on either side of them will even out. A fish that lives in salt water will have somewhat salty water inside itself. Put it in freshwater, and the freshwater will, through osmosis, enter the fish, causing its cells to swell, and the fish will die. What will happen to a freshwater fish in the ocean?

Osmosis

Imagine you have a cup that has $100\ \text{mL}$ water, and you add $15\ \text{g}$ of table sugar to the water. The sugar dissolves and the mixture that is now in the cup is made up of a **solute** (the sugar) that is dissolved in the **solvent** (the water). The mixture of a solute in a solvent is called a **solution**.

Imagine now that you have a second cup with $100\ \text{mL}$ of water, and you add $45\ \text{g}$ of table sugar to the water. Just like the first cup, the sugar is the solute, and the water is the solvent. But now you have two mixtures of different solute concentrations. In comparing two solutions of unequal solute concentration, the solution with the higher solute concentration is **hypertonic**, and the solution with the lower solute concentration is **hypotonic**. Solutions of equal solute concentration are **isotonic**. The first sugar solution is hypotonic to the second solution. The second sugar solution is hypertonic to the first.

You now add the two solutions to a beaker that has been divided by a semipermeable membrane, with pores that are too small for the sugar molecules to pass through, but are big enough for the water molecules to pass through. The hypertonic solution is one side of the membrane and the hypotonic solution on the other. The hypertonic solution has a lower water concentration than the hypotonic solution, so a concentration gradient of water now exists across the membrane. Water molecules will move from the side of higher water concentration to the side of lower concentration until both solutions are isotonic. At this point, **equilibrium** is reached.

Red blood cells behave the same way (see figure below). When red blood cells are in a hypertonic (higher concentration) solution, water flows out of the cell faster than it comes in. This results in *crenation* (shriveling) of the blood cell. On the other extreme, a red blood cell that is hypotonic (lower concentration outside the cell) will result in more water flowing into the cell than out. This results in swelling of the cell and potential *hemolysis* (bursting) of the cell. In an isotonic solution, the flow of water in and out of the cell is happening at the same rate.

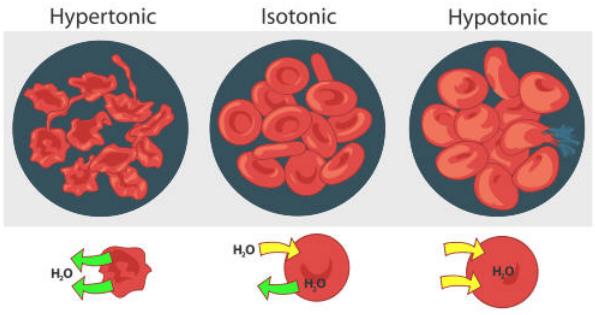


Figure 9.7.1: Red blood cells in hypertonic, isotonic, and hypotonic solutions.

Osmosis is the diffusion of water molecules across a semipermeable membrane from an area of lower concentration solution (i.e., higher concentration of water) to an area of higher concentration solution (i.e., lower concentration of water). Water moves into and

out of cells by osmosis.

- If a cell is in a hypertonic solution, the solution has a lower water concentration than the cell cytosol, and water moves out of the cell until both solutions are isotonic.
- Cells placed in a hypotonic solution will take in water across their membranes until both the external solution and the cytosol are isotonic.

A red blood cell will swell and undergo hemolysis (burst) when placed in a hypotonic solution. When placed in a hypertonic solution, a red blood cell will lose water and undergo *crenation* (shrivel). Animal cells tend to do best in an isotonic environment, where the flow of water in and out of the cell is occurring at equal rates.

Diffusion

Passive transport is a way that small molecules or ions move across the cell membrane without input of energy by the cell. The three main kinds of passive transport are diffusion (or simple diffusion), osmosis, and facilitated diffusion. Simple diffusion and osmosis do not involve transport proteins. Facilitated diffusion requires the assistance of proteins.

Diffusion is the movement of molecules from an area of high concentration of the molecules to an area with a lower concentration. For cell transport, diffusion is the movement of small molecules across the cell membrane. The difference in the concentrations of the molecules in the two areas is called the **concentration gradient**. The kinetic energy of the molecules results in random motion, causing diffusion. In simple diffusion, this process proceeds without the aid of a transport protein. It is the random motion of the molecules that causes them to move from an area of high concentration to an area with a lower concentration.

Diffusion will continue until the concentration gradient has been eliminated. Since diffusion moves materials from an area of higher concentration to the lower, it is described as moving solutes "down the concentration gradient". The end result is an equal concentration, or **equilibrium**, of molecules on both sides of the membrane. At equilibrium, movement of molecules does not stop. At equilibrium, there is equal movement of materials in both directions.

Not everything can make it into your cells. Your cells have a plasma membrane that helps to guard your cells from unwanted intruders.

The Plasma Membrane and Cytosol

If the outside environment of a cell is water-based, and the inside of the cell is also mostly water, something has to make sure the cell stays intact in this environment. What would happen if a cell dissolved in water, like sugar does? Obviously, the cell could not survive in such an environment. So something must protect the cell and allow it to survive in its water-based environment. All cells have a barrier around them that separates them from the environment and from other cells. This barrier is called the **plasma membrane**, or cell membrane.

The Plasma Membrane

The plasma membrane (see figure below) is made of a double layer of special lipids, known as **phospholipids**. The phospholipid is a lipid molecule with a hydrophilic ("water-loving") head and two hydrophobic ("water-hating") tails. Because of the hydrophilic and hydrophobic nature of the phospholipid, the molecule must be arranged in a specific pattern as only certain parts of the molecule can physically be in contact with water. Remember that there is water outside the cell, and the **cytoplasm** inside the cell is mostly water as well. So the phospholipids are arranged in a double layer (a bilayer) to keep the cell separate from its environment. Lipids do not mix with water (recall that oil is a lipid), so the phospholipid bilayer of the cell membrane acts as a barrier, keeping water out of the cell, and keeping the cytoplasm inside the cell. The cell membrane allows the cell to stay structurally intact in its water-based environment.

The function of the plasma membrane is to control what goes in and out of the cell. Some molecules can go through the cell membrane to enter and leave the cell, but some cannot. The cell is therefore not completely permeable. "Permeable" means that anything can cross a barrier. An open door is completely permeable to anything that wants to enter or exit through the door. The plasma membrane is **semipermeable**, meaning that some things can enter the cell, and some things cannot.

Molecules that cannot easily pass through the bilayer include ions and small hydrophilic molecules, such as glucose, and macromolecules, including proteins and RNA. Examples of molecules that can easily diffuse across the plasma membrane include

carbon dioxide and oxygen gas. These molecules diffuse freely in and out of the cell, along their concentration gradient. Though water is a polar molecule, it can also diffuse through the plasma membrane.

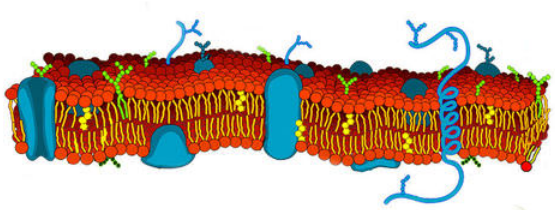


Figure 9.7.2: Plasma membranes are primarily made up of phospholipids (orange). The hydrophilic ("water-loving") head and two hydrophobic ("water-hating") tails are shown. The phospholipids form a bilayer (two layers). The middle of the bilayer is an area without water. There can be water on either side of the bilayer. There are many proteins throughout the membrane.

Cytosol

The inside of all cells also contain a jelly-like substance called **cytosol**. Cytosol is composed of water and other molecules, including **enzymes**, which are proteins that speed up the cell's chemical reactions. Everything in the cell sits in the cytosol, like fruit in a Jell-o mold. The term cytoplasm refers to the cytosol and all of the organelles, the specialized compartments of the cell. The cytoplasm does not include the nucleus. As a prokaryotic cell does not have a nucleus, the DNA is in the cytoplasm.

Supplemental Resources

- The Plasma Membrane: www.youtube.com/watch?v=moPJkCbKjBs

Concept Review Exercises

1. What are some of the features of a semipermeable membrane?

2. What do the prefixes hyper, hypo, and iso mean?

Answers

1. A semipermeable membrane allows some substances to pass through but not others.

2. hyper – higher; hypo – lower; iso - same

Key Takeaways

- Water moves into and out of cells by osmosis.
- Water (solvent) moves from an area of lower concentration solution (i.e., higher concentration of water) to an area of higher concentration solution (i.e., lower concentration of water).

EXERCISES

1. Two solutions are separated by a semipermeable membrane. Solution A contains 25.0 g of NaCl in 100.0 mL of water and solution B contains 35.0 g of NaCl in 100.0 mL of water.

   a. Which one has a higher concentration?
   b. Which way will water molecules flow?
   c. Which volume will increase?
   d. Which volume will decrease?
   e. What will happen to the concentration of solution A?
   f. What will happen to the concentration of solution B?

4. Cells are placed in a solution and the cells then undergo hemolysis. What can be said about the relative concentrations of solute in the cell and the solution?

5. Describe the relative concentrations inside and outside a red blood cell when crenation occurs.

6. A saltwater fish is placed in a freshwater tank. What will happen to the fish? Describe the flow of water molecules to explain the outcome.

Answers

1. Two solutions are separated by a semipermeable membrane. Solution A contains 25.0 g of NaCl in 100.0 mL of water and solution B contains 35.0 g of NaCl in 100.0 mL of water.

a. Solution B
b. A → → B
c. B
d. A
e. increase
f. decrease

4. Cells contain fluid with higher concentration than solution outside the cell.

5. Cells contain fluid with a lower concentration than the solution outside the cell.

6. Water molecules will flow from the tank water into the fish because the fish has a higher concentration of salt. If the fish absorbs too much water, it will die.

Contributors

-
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11.9: Solutions, Colloids and Membranes- Questions

Sacramento City College
CHEM 309: General, Organic and Biochemistry
Prof. Dianne Bennett

Agenda (Fall) • Agenda (Spring) • Homework Problems • Homework Solutions
Chapters • Video Tutorials • Basic Knowledge Practice Quizzes

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ALL questions listed must be answered to earn credit for completing the text homework. Yes, even the Additional Exercises if applicable.

Mixtures and Solutions

(01) Answer the following True or False statements.

a. In a solution, the solvent is the substance being dissolved
b. An electrolyte is another word for molecule
c. A solution is a pure substance
d. Homogenous is the best way to describe a solution
e. A solute is all that is needed to make a solution

(02) Of the following examples of solutions, determine whether the solute is an electrolyte or a molecule.

a. Plain soda (carbonated) water
b. Apple juice from concentrate
c. A bottle of rubbing alcohol (2-propanol)
d. A saline solution of KCl
e. A sodium bicarbonate buffer for use in acid-base experiments

(03) It is important to distinguish between the solute and the solvent. For each example that is a solution, identify which substance is the solute and which is the solvent.

a. carbonated water
b. a saline solution of sodium chloride
c. sugar water for a bird feeder
d. a sodium bicarbonate buffer solution
e. oxygen in air

Solution Concentrations

(04) Many different biological molecules must be monitored to maintain a healthy body. Perform the following operations to convert one unit of measurement to another.

a. Blood sugar (glucose) level of 60 mg/dL to g/L
b. Blood cholesterol level of 185 mg/dL to mcg/mL
c. Iron level of 142 mcg/dL to mg/L
d. Blood alcohol level of 10 mg/dL to g/L
e. Sodium level of 150 mg/dL to mcg/mL

(05) What mass in grams of glucose will you need if you wish to make a solution of 5.00% (m/v) of 250 mL?

(06) You have 23.0 g of potassium phosphate with which to make a 20.0% (m/v) solution. What volume of solvent will you need to get this concentration?

(07) Convert the following quantities to the desired units.

a. 860 mmol/L to mol/L
b. 70 mol/dL to mol/L
c. 8 mol/L to mmol/mL
d. 900 mmol/mL to mol/L
e. 17 mol/L to mmol/dL

(08) How many moles of hydroxide are there in a 300. mL solution of 0.50 M aluminum hydroxide? How many moles of aluminum are there?

(09) A blood test reveals different concentrations of various essential minerals. A concentration of 0.65 mmol/L of copper (II), 0.09 mmol/L of manganese (IV), and 0.80 mmol/L of zinc. For each concentration, convert them to milliequivalents/L.

(10) A solution of calcium sulfate has a concentration of 0.20 M. How many equivalents/L of calcium ions are there? How many equivalents/L of sulfate ions?

(11) A doctor prescribes a dosage of 150,000 units of medication. 75 mg of the medication is equivalent to 1.0 x 10^5 units. The method of delivery provides only 50. mg of the active ingredient per mL. How many milliliters of the medication will be administered in each dose?

(12) A prescription calls for 20. g of medication for a patient. Two possible suspensions are available, one with a dosage of 7.0g/10. mL and 10.g/25 mL. How many milliliters of each suspension will be needed to meet the dosage the prescription calls for?

(13) The dosage is 4.0 mg and must be equally distributed throughout a ten-minute period. If the solution is only available in 3.0 mg/10 mL, what will the flow rate be in mL/min?

(14) A doctor calls for a dosage to be increased. Currently the patient is receiving a flow of 50. mL/hr, with the concentration of 30. mg/200. mL. The doctor calls for the dosage, in mg/min, to be increased by 50.%. What will the new flow rate, in mg/min, be?

(15) An infant weighing 20. lbs. is prescribed a dose of 100. mg three times a day. A report emerges that the safe dosage of that medication is between 25 and 45 mg/kg of body weight per day. Is the prescribed dosage within the safe limit for the infant?

Converting Between Different Concentration Units

(16) Convert a 0.65 % (m/v) calcium chloride concentration to molarity. How many Eq/L of calcium ions are present? How many Eq/L of chloride ions are present?

Colloids and Suspensions

(17) Differentiate between the following pairs, which is the colloid and which the solution.

a. Chocolate milk and rice pudding
b. Tuna salad and vinegar-based dressing
c. Light syrup and pureed fruit
d. Rocky road ice cream and fruit juice
e. Mashed potatoes and vegetable oil

Membranes, Osmosis and Dialysis

(18) Given the following situations, wherein two tanks of different solutions are separated by a semipermeable membrane, determine the direction of the flow of solvent (water).

a. Solution A contains a 0.40 M concentration of $CaCl_2$, while Solution B contains a 0.45 M concentration of KI

b. Solution A contains a 1.00 M concentration of NH_4Cl, while Solution B contains a 1.00 M concentration of CH_2O
c. Solution A contains 0.20 M NaCl and Solution B contains 0.30 M KCl

(19) Define 'isotonic'. If two solutions are isotonic, based on your definition, will there be any osmosis occurring?

(20) Given the following pairs, tell which direction (if applicable) the flow of solvent travels.

a. Hypotonic with Hypertonic
b. Hypertonic with Hypotonic
c. Isotonic with Isotonic

(21) Two solutions with different concentrations and compositions are separated by a semipermeable membrane. The left-hand solution is a .50 M solution of $MgSO_4$, while the right-hand solution contains $CaCl_2$ at a concentration of .40 M. Determine the direction of the flow of solvent, left or right.

Chemistry in Medicine

(22) If we have a solution of aluminum chloride with an aluminum ion concentration of 7.0 Eq/300. mL, what is the molarity of aluminum ions?

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11.9: Homework Solutions

Sacramento City College
CHEM 309: General, Organic and Biochemistry
Prof. Dianne Bennett

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Mixtures and Solutions

(01)

a. F
b. F
c. F
d. T
e. F

(02) Of the following examples of solutions, determine whether the solute is an electrolyte or a molecule.

a. molecule
b. molecule
c. molecule
d. electrolyte
e. electrolyte

(03)

a. solute is CO_2 & solvent is H_2O
b. solute is NaCl & solvent is H_2O
c. solute is sugar & solvent is H_2O
d. solute is sodium bicarbonate & solvent is H_2O
e. solute is O_2 & solvent is air (mostly N_2)

Solution Concentrations

(04)

a. 0.6 g/L glucose
b. 1850 mcg/mL cholesterol
c. 1.42 mg/L iron
d. 0.1 g/L blood alcohol
e. 1.50 x 10^3 mcg/mL sodium ions

(05) 12.5 g glucose

(06) 115 mL

(07)

a. 0.86 mol/L
b. 7.0 x 10^2 mol/L
c. 8 mmol/mL

d. 900 mol/L
e. 1700 mmol/dL

(08) 0.45 mol hydroxide & 0.15 mol aluminum ions

(09) 1.3 mEq/L Cu^{2+}; 0.36 mEq/L Mn^{4+}; 1.6 mEq/L Zn^{2+}

(10) 0.40 Eq Ca^{2+}; 0.40 Eq SO_4^{2-}

(11) 2.3 mL

(12) 29 mL of 7.0g/10mL or 50. mL of 10g/25 mL

(13) 1.3 mL/min

(14) 0.19 mg/min

(15) 33 mg/kg; yes the levels are within safe limits.

Converting Between Different Concentration Units

(16) 0.12 Eq/L of Ca^{2+}; 0.12 Eq/L Cl^-

Colloids and Suspensions

(17)

a. Chocolate milk - solution and rice pudding - colloid
b. Tuna salad - colloid and vinegar-based dressing - solution
c. Light syrup - solution and pureed fruit - colloid
d. Rocky road ice cream- colloid and fruit juice - solution
e. Mashed potatoes - colloid and vegetable oil - solution

Membranes, Osmosis and Dialysis

(18)

a. Water moves from B to A
b. Water moves from B to A
c. Water moves from A to B

(19) isotonic: soluitons with equal total solute concentrations, therefore, NO osmosis

(20)

a. Hypotonic into Hypertonic
b. Hypotonic into Hypertonic
c. no flow

(21) Water flows from the magnesium sulfate solution into the calcium chloride solution.

(22) 7.8 M Al^{3+}

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11.S: Solutions (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 **solution** is a homogeneous mixture. The major component is the **solvent**, while the minor component is the **solute**. Solutions can have any phase; for example, an **alloy** is a solid solution. Solutes are **soluble** or **insoluble**, meaning they dissolve or do not dissolve in a particular solvent. The terms **miscible** and **immiscible**, instead of soluble and insoluble, are used for liquid solutes and solvents. The statement *like dissolves like* is a useful guide to predicting whether a solute will dissolve in a given solvent.

The amount of solute in a solution is represented by the **concentration** of the solution. The maximum amount of solute that will dissolve in a given amount of solvent is called the **solubility** of the solute. Such solutions are **saturated**. Solutions that have less than the maximum amount are **unsaturated**. Most solutions are unsaturated, and there are various ways of stating their concentrations. **Mass/mass percent**, **volume/volume percent**, and **mass/volume percent** indicate the percentage of the overall solution that is solute. **Parts per million (ppm)** and **parts per billion (ppb)** are used to describe very small concentrations of a solute. **Molarity**, defined as the number of moles of solute per liter of solution, is a common concentration unit in the chemistry laboratory. **Equivalents** express concentrations in terms of moles of charge on ions. When a solution is diluted, we use the fact that the amount of solute remains constant to be able to determine the volume or concentration of the final diluted solution.

Dissolving occurs by **solvation**, the process in which particles of a solvent surround the individual particles of a solute, separating them to make a solution. For water solutions, the word **hydration** is used. If the solute is molecular, it dissolves into individual molecules. If the solute is ionic, the individual ions separate from each other, forming a solution that conducts electricity. Such solutions are called **electrolytes**. If the dissociation of ions is complete, the solution is a **strong electrolyte**. If the dissociation is only partial, the solution is a **weak electrolyte**. Solutions of molecules do not conduct electricity and are called **nonelectrolytes**.

Solutions have properties that differ from those of the pure solvent. Some of these are **colligative** properties, which are due to the number of solute particles dissolved, not the chemical identity of the solute. Colligative properties include **vapor pressure depression**, **boiling point elevation**, **freezing point depression**, and **osmotic pressure**. Osmotic pressure is particularly important in biological systems. It is caused by **osmosis**, the passage of solvents through certain membranes like cell walls. The **osmolarity** of a solution is the product of a solution's molarity and the number of particles a solute separates into when it dissolves. Osmosis can be reversed by the application of pressure; this reverse osmosis is used to make fresh water from saltwater in some parts of the world. Because of osmosis, red blood cells placed in hypotonic or hypertonic solutions lose function through either hemolysis or crenation. If they are placed in isotonic solutions, however, the cells are unaffected because osmotic pressure is equal on either side of the cell membrane.

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CHAPTER OVERVIEW

12: Carbohydrates

Glucose is one of the carbohydrates you will learn about in this chapter as we begin the study of biochemistry—the chemistry of molecules found in living organisms. Later we will study the other three major types of macromolecules found in living organisms: lipids, proteins, and nucleic acids.

- 12.1: Prelude to Carbohydrates
- 12.2: Carbohydrates
- 12.3: Classes of Monosaccharides
- 12.4: Important Hexoses
  - 12.4.1: Fructose
  - 12.4.2: Galactose
- 12.5: Properties of Monosaccharides
- 12.6: Cyclic Structures of Monosaccharides
- 12.7: Disaccharides
  - 12.7.1: Lactose
  - 12.7.2: Sucrose
- 12.8: Polysaccharides
  - 12.8.1: Starch
  - 12.8.2: Glycogen
  - 12.8.3: Cellulose
  - 12.8.4: Glycation and Heteropolysaccharides
- 12.9: Carbohydrates (Structure and Function)- Questions
- 12.10: Homework Solutions
- 12.11: Carbohydrates Summary
- 12.S: Carbohydrates (Short Summary)

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12.1: Prelude to Carbohydrates

In the United States, 17.9 million people have been diagnosed with diabetes, and experts estimate that at least another 5.7 million people have the disease but have not been diagnosed. In 2006, diabetes was the seventh leading cause of death, listed on 72,507 death certificates. Moreover, it was a contributing factor in over 200,000 deaths in which the cause was listed as something else, such as heart or kidney disease.

People with diabetes are impaired in their ability to metabolize glucose, a sugar needed by the body for energy; as a result, excessive quantities of glucose accumulate in the blood and the urine. The characteristic symptoms of diabetes are weight loss, constant hunger, extreme thirst, and frequent urination (the kidneys excrete large amounts of water in an attempt to remove the excess sugar from the blood).

An important diagnostic test for diabetes is the oral glucose tolerance test, which measures the level of glucose in blood plasma. A first measurement is made after a fast of at least 8 h, followed by another measurement 2 h after the person drinks a flavored solution of 75 g of glucose dissolved in water. At the second measurement, the glucose plasma level should be no higher than 139 mg/dL. Individuals with a value between 140 and 199 mg/dL are diagnosed with prediabetes, while those with a value of 200 mg/dL or above are diagnosed with diabetes. Following a diagnosis of diabetes a person will need to monitor his or her blood glucose levels daily (or more often) using a glucose meter.



Figure **12.1.1**: Using a Glucose Meter to Test Blood Glucose Level. (Public Domain; Centers for Disease Control and Prevention).

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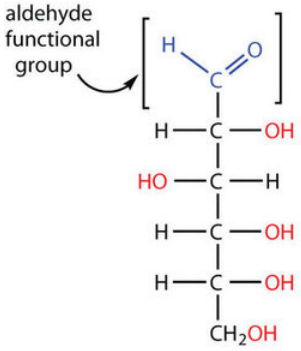
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12.2: Carbohydrates

Learning Objectives

- To recognize carbohydrates and classify them as mono-, di-, or polysaccharides.

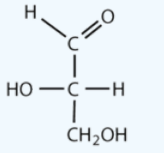
All carbohydrates consist of carbon, hydrogen, and oxygen atoms and are polyhydroxy aldehydes or ketones or are compounds that can be broken down to form such compounds. Examples of carbohydrates include starch, fiber, the sweet-tasting compounds called sugars, and structural materials such as cellulose.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

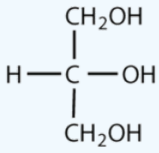


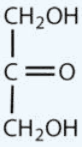
Because glucose has an aldehyde functional group and several –OH (hydroxyl) groups, it is described as a polyhydroxy aldehyde.

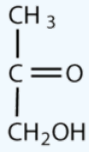
Example 12.2.1

Which compounds would be classified as carbohydrates?

a. 

b. 

c. 

d. 

Solution

a. This is a carbohydrate because the molecule contains an aldehyde functional group with OH groups on the other two carbon atoms.

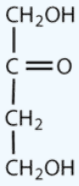
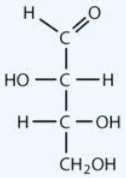
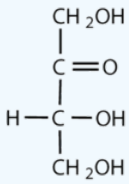
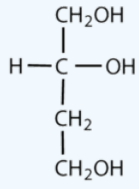
b. This is not a carbohydrate because the molecule does not contain an aldehyde or a ketone functional group.

c. This is a carbohydrate because the molecule contains a ketone functional group with OH groups on the other two carbon atoms.

d. This is not a carbohydrate; although it has a ketone functional group, one of the other carbons atoms does not have an OH group attached.

? Exercise 12.2.1

Which compounds would be classified as carbohydrates?

1. 
2. 
3. 
4. 

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

$$6\,CO_2 + 6\,H_2O + 686\text{ kcal} \rightarrow C_6H_{12}O_6 + 6\,O_2 \tag{12.2.1}$$

(The 686 kcal come from solar energy.) Plants can use the glucose for energy or convert it to larger carbohydrates, such as starch or cellulose. Starch provides energy for later use, perhaps as nourishment for a plant's seeds, while cellulose is the structural material of plants. We can gather and eat the parts of a plant that store energy—seeds, roots, tubers, and fruits—and use some of that energy ourselves. Carbohydrates are also needed for the synthesis of nucleic acids and many proteins and lipids.

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

The simplest carbohydrates—those that cannot be hydrolyzed to produce even smaller carbohydrates—are called monosaccharides. Two or more monosaccharides can link together to form chains that contain from two to several hundred or thousand monosaccharide units. Prefixes are used to indicate the number of such units in the chains. Disaccharide molecules have two monosaccharide units, *trisaccharide* molecules have three units, and so on. Chains with many monosaccharide units joined together are called polysaccharides. All these so-called higher saccharides can be hydrolyzed back to their constituent monosaccharides.

> *Compounds that cannot be hydrolyzed will not react with water to form two or more smaller compounds.*

Summary

Carbohydrates are an important group of biological molecules that includes sugars and starches. Photosynthesis is the process by which plants use energy from sunlight to synthesize carbohydrates. A monosaccharide is the simplest carbohydrate and cannot be hydrolyzed to produce a smaller carbohydrate molecule. Disaccharides contain two monosaccharide units, and polysaccharides contain many monosaccharide units.

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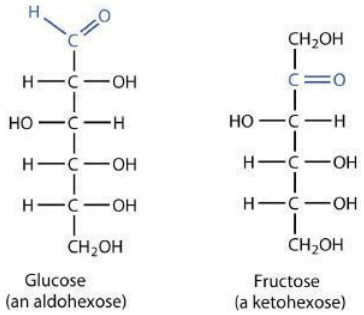
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12.3: Classes of Monosaccharides

Learning Objectives

- Classify monosaccharides as aldoses or ketoses and as trioses, tetroses, pentoses, or hexoses.
- Distinguish between a D sugar and an L sugar.

The naturally occurring monosaccharides contain three to seven carbon atoms per molecule. Monosaccharides of specific sizes may be indicated by names composed of a stem denoting the number of carbon atoms and the suffix *-ose*. For example, the terms *triose*, *tetrose*, *pentose*, and *hexose* signify monosaccharides with, respectively, three, four, five, and six carbon atoms. Monosaccharides are also classified as aldoses or ketoses. Those monosaccharides that contain an aldehyde functional group are called aldoses; those containing a ketone functional group on the second carbon atom are ketoses. Combining these classification systems gives general names that indicate both the type of carbonyl group *and* the number of carbon atoms in a molecule. Thus, monosaccharides are described as aldotetroses, aldopentoses, ketopentoses, ketoheptoses, and so forth. Glucose and fructose are specific examples of an aldohexose and a ketohexose, respectively.



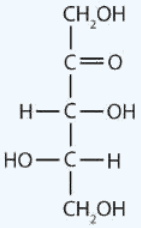
Example 12.3.1

Draw an example of each type of compound.

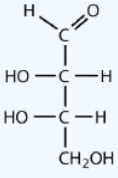
a. a ketopentose
b. an aldotetrose

Solution

a. The structure must have five carbon atoms with the second carbon atom being a carbonyl group and the other four carbon atoms each having an OH group attached. Several structures are possible, but one example is shown.



- The structure must have four carbon atoms with the first carbon atom part of the aldehyde functional group. The other three carbon atoms each have an OH group attached. Several structures are possible, but one example is shown.



? Exercise 12.3.1

Draw an example of each type of compound.

a. an aldohexose
b. a ketotetrose

The simplest sugars are the trioses. The possible trioses are shown in part (a) of Figure **12.3.1**; glyceraldehyde is an aldotriose, while dihydroxyacetone is a ketotriose. Notice that two structures are shown for glyceraldehyde. These structures are stereoisomers, and hence are isomers having the same structural formula but differing in the arrangement of atoms or groups of atoms in three-dimensional space. If you make models of the two stereoisomers of glyceraldehyde, you will find that you cannot place one model on top of the other and have each functional group point in the same direction. However, if you place one of the models in front of a mirror, the image in the mirror will be identical to the second stereoisomer in part (b) of Figure **12.3.1**. Molecules that are nonsuperimposable (nonidentical) mirror images of each other are a type of stereoisomer called enantiomers (Greek *enantios*, meaning "opposite").

Note

These are another type of stereoisomers than the *cis-trans* (geometric) isomers previously discussed.

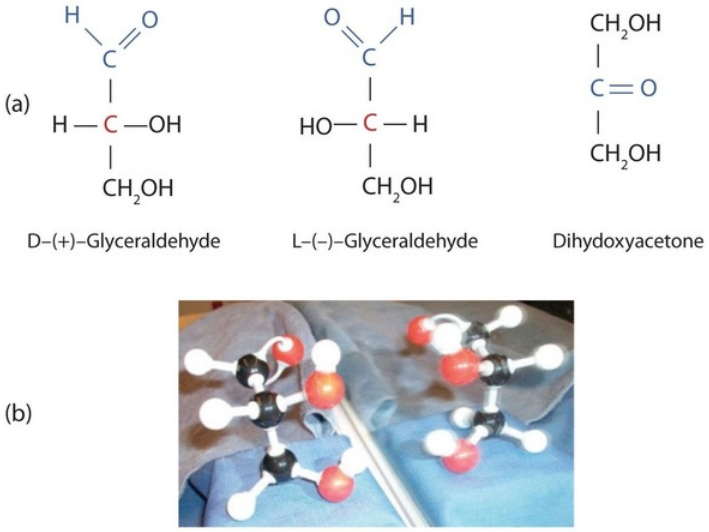


Figure **12.3.1**: Structures of the Trioses. (a) D- and L-glyceraldehyde are mirror images of each other and represent a pair of enantiomers. (b) A ball-and-stick model of D-glyceraldehyde is reflected in a mirror. Note that the reflection has the same structure as L-glyceraldehyde.

A key characteristic of enantiomers is that they have a carbon atom to which four different groups are attached. Note, for example, the four different groups attached to the central carbon atom of glyceraldehyde (part (a) of Figure **12.3.1**). A carbon atom that has four different groups attached is a chiral carbon. If a molecule contains one or more chiral carbons, it is likely to exist as two or more stereoisomers. Dihydroxyacetone does not contain a chiral carbon and thus does not exist as a pair of stereoisomers. Glyceraldehyde, however, has a chiral carbon and exists as a pair of enantiomers. Except for the direction in which each enantiomer rotates plane-polarized light, these two molecules have identical physical properties. One enantiomer has a specific rotation of +8.7°, while the other has a specific rotation of −8.7°.

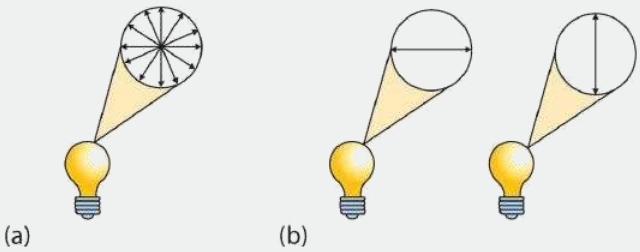
H. Emil Fischer, a German chemist, developed the convention commonly used for writing two-dimensional representations of the monosaccharides, such as those in part (a) of Figure **12.3.1**. In these structural formulas, the aldehyde group is written at the top, and the hydrogen atoms and OH groups that are attached to each chiral carbon are written to the right or left. (If the monosaccharide is a ketose, the ketone functional group is the second carbon atom.) Vertical lines represent bonds pointing away from you, while horizontal lines represent bonds coming toward you. The formulas of chiral molecules represented in this manner are referred to as **Fischer projections**.

The two enantiomers of glyceraldehyde are especially important because monosaccharides with more than three carbon atoms can be considered as being derived from them. Thus, D- and L-glyceraldehyde provide reference points for designating and drawing all other monosaccharides. Sugars whose Fischer projections terminate in the same configuration as D-glyceraldehyde are designated as D sugars; those derived from L-glyceraldehyde are designated as L sugars.

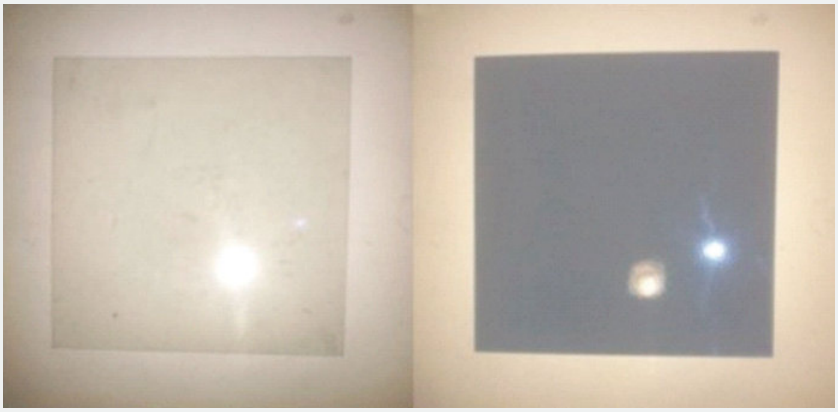
> *By convention, the penultimate (next-to-last) carbon atom has been chosen as the carbon atom that determines if a sugar is D or L. It is the chiral carbon farthest from the aldehyde or ketone functional group.*

Looking Closer: Polarized Light

A beam of ordinary light can be pictured as a bundle of waves; some move up and down, some sideways, and others at all other conceivable angles. When a beam of light has been polarized, however, the waves in the bundle all vibrate in a single plane. Light altered in this way is called *plane-polarized light*. Much of what chemists know about stereoisomers comes from studying the effects they have on plane-polarized light. In this illustration, the light on the left is not polarized, while that on the right is polarized.



Sunlight, in general, is not polarized; light from an ordinary light bulb or an ordinary flashlight is not polarized. One way to polarize ordinary light is to pass it through Polaroid sheets, special plastic sheets containing carefully oriented organic compounds that permit only light vibrating in a single plane to pass through. To the eye, polarized light doesn't "look" any different from nonpolarized light. We can detect polarized light, however, by using a second sheet of polarizing material, as shown here.



In the photo on the left, two Polaroid sheets are aligned in the same direction; plane-polarized light from the first Polaroid sheet can pass through the second sheet. In the photo on the right, the top Polaroid sheet has been rotated 90° and now blocks the plane-polarized light that comes through the first Polaroid sheet.

Certain substances act on polarized light by rotating the plane of vibration. Such substances are said to be optically active. The extent of optical activity is measured by a polarimeter, an instrument that contains two polarizing lenses separated by a sample tube, as shown in the accompanying figure. With the sample tube empty, maximum light reaches the observer's eye when the two lenses are aligned so that both pass light vibrating in the same plane. When an optically active substance is placed in the sample tube, that substance rotates the plane of polarization of the light passing through it, so that the polarized light emerging from the

sample tube is vibrating in a different direction than when it entered the tube. To see the maximum amount of light when the sample is in place, the observer must rotate one lens to accommodate the change in the plane of polarization.

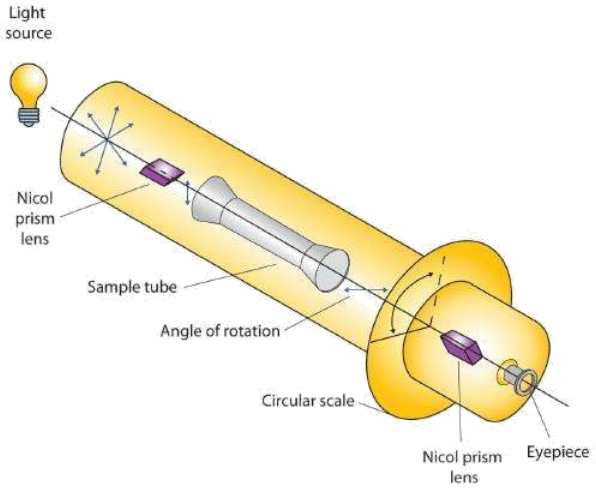


Figure **12.3.2**: Diagram of a Polarimeter

Some optically active substances rotate the plane of polarized light to the right (clockwise) from the observer's point of view. These compounds are said to be dextrorotatory; substances that rotate light to the left (counterclockwise) are levorotatory. To denote the direction of rotation, a positive sign (+) is given to dextrorotatory substances, and a negative sign (−) is given to levorotatory substances.

Summary

Monosaccharides can be classified by the number of carbon atoms in the structure and/or the type of carbonyl group they contain (aldose or ketose). Most monosaccharides contain at least one chiral carbon and can form stereoisomers. Enantiomers are a specific type of stereoisomers that are mirror images of each other.

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12.4: Important Hexoses

Learning Objectives

- To identify the structures of D-glucose, D-galactose, and D-fructose and describe how they differ from each other.

Although a variety of monosaccharides are found in living organisms, three hexoses are particularly abundant: D-glucose, D-galactose, and D-fructose (Figure 12.4.1). Glucose and galactose are both aldohexoses, while fructose is a ketohexose.

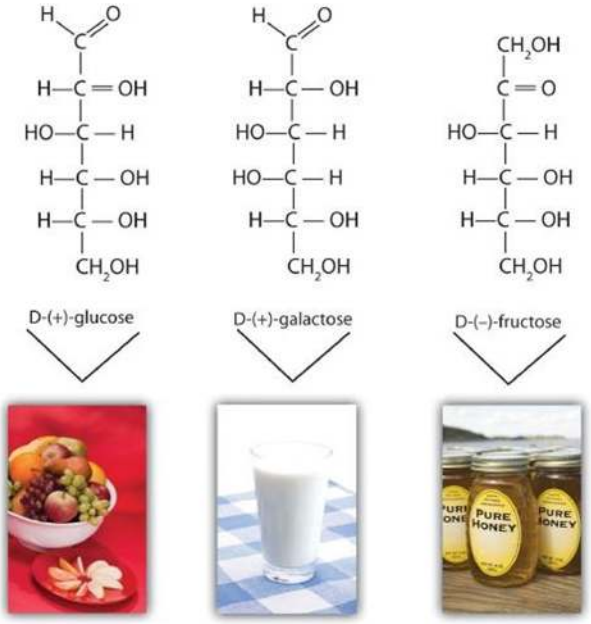


Figure 12.4.1: Structures of Three Important Hexoses. Each hexose is pictured with a food source in which it is commonly found. Source: Photos © Thinkstock.

Glucose

D-Glucose, generally referred to as simply glucose, is the most abundant sugar found in nature; most of the carbohydrates we eat are eventually converted to it in a series of biochemical reactions that produce energy for our cells. It is also known by three other names: *dextrose*, from the fact that it rotates plane-polarized light in a clockwise (dextrorotatory) direction; *corn sugar* because in the United States cornstarch is used in the commercial process that produces glucose from the hydrolysis of starch; and *blood sugar* because it is the carbohydrate found in the circulatory system of animals. Normal blood sugar values range from 70 to 105 mg glucose/dL plasma, and normal urine may contain anywhere from a trace to 20 mg glucose/dL urine.

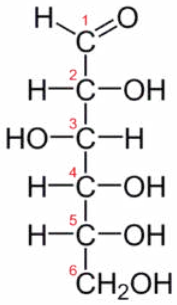


Figure 12.4.2: Fischer projection of D-glucose

The Fischer projection of D-glucose is given in Figure 12.4.2. Glucose is a D sugar because the OH group on the fifth carbon atom (the chiral center farthest from the carbonyl group) is on the right. In fact, all the OH groups except the one on the third carbon atom are to the right.

Galactose

D-Galactose does not occur in nature in the uncombined state. It is released when lactose, a disaccharide found in milk, is hydrolyzed. The galactose needed by the human body for the synthesis of lactose is obtained by the metabolic conversion of D-glucose to D-galactose. Galactose is also an important constituent of the glycolipids that occur in the brain and the myelin sheath of nerve cells. For this reason it is also known as *brain sugar*. The structure of D-galactose is shown in Figure 12.4.1. Notice that the configuration differs from that of glucose only at the fourth carbon atom.

Fructose

D-Fructose, also shown in Figure 12.4.1, is the most abundant ketohexose. Note that from the third through the sixth carbon atoms, its structure is the same as that of glucose. It occurs, along with glucose and sucrose, in honey (which is 40% fructose) and sweet fruits. Fructose (from the Latin *fructus*, meaning "fruit") is also referred to as *levulose* because it has a specific rotation that is strongly levorotatory (−92.4°). It is the sweetest sugar, being 1.7 times sweeter than sucrose, although many nonsugars are several hundred or several thousand times as sweet (Table 12.4.1).

Table 12.4.1: The Relative Sweetness of Some Compounds (Sucrose = 100)

Compound	Relative Sweetness
lactose	16
maltose	32
glucose	74
sucrose	100
fructose	173
aspartame	18,000
acesulfame K	20,000
saccharin	30,000
sucralose	60,000

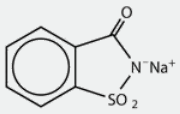
Looking Closer: Artificial Sweeteners

Although sweetness is commonly associated with mono- and disaccharides, it is not a property found only in sugars. Several other kinds of organic compounds have been synthesized that are far superior as sweetening agents. These so-called high-intensity or artificial sweeteners are useful for people with diabetes or other medical conditions that require them to control their carbohydrate intake. The synthetic compounds are noncaloric or used in such small quantities that they do not add significantly to the caloric value of food.

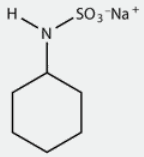
The first artificial sweetener—saccharin—was discovered by accident in 1879. It is 300 times sweeter than sucrose, but it passes through the body unchanged and thus adds no calories to the diet. After its discovery, saccharin was used until it was banned in the early 1900s. However, during the sugar-short years of World War I, the ban was lifted and was not reinstated at the war's end. One drawback to the use of saccharin is its bitter, metallic aftertaste. The initial solution to this problem was to combine saccharin with cyclamate, a second artificial sweetener discovered in 1937.

In the 1960s and 1970s, several clinical tests with laboratory animals implicated both cyclamate and saccharin as carcinogenic (cancer-causing) substances. The results from the cyclamate tests were completed first, and cyclamate was banned in the United States in 1969. Then a major study was released in Canada in 1977 indicating that saccharin increased the incidence of

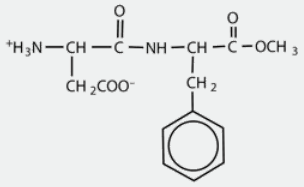
bladder cancer in rats. The US Food and Drug Administration (FDA) proposed a ban on saccharin that raised immediate public opposition because saccharin was the only artificial sweetener still available. In response, Congress passed the Saccharin Study and Labeling Act in 1977, permitting the use of saccharin as long as any product containing it was labeled with a consumer warning regarding the possible elevation of the risk of bladder cancer. Today this warning is no longer required; moreover, the FDA is currently reviewing the ban on cyclamate, as 75 additional studies and years of usage in other countries, such as Canada, have failed to show that it has any carcinogenic effect.



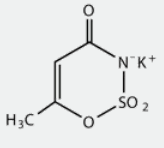
Saccharin



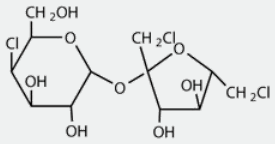
Cyclamate



Aspartame



Acesulfame K



Sucralose

A third artificial sweetener, aspartame, was discovered in 1965. This white crystalline compound is about 180 times sweeter than sucrose and has no aftertaste. It was approved for use in 1981 and is used to sweeten a wide variety of foods because it blends well with other food flavors. Aspartame is not used in baked goods, however, because it is not heat stable.

In the body (or when heated), aspartame is initially hydrolyzed to three molecules: the amino acids aspartic acid and phenylalanine and an alcohol methanol. Repeated controversy regarding the safety of aspartame arises partly from the fact that the body metabolizes the released methanol to formaldehyde. It should be noted, though, that a glass of tomato juice has six times as much methanol as a similar amount of a diet soda containing aspartame. The only documented risk connected to aspartame use is for individuals with the genetic disease *phenylketonuria* (PKU); these individuals lack the enzyme needed to metabolize the phenylalanine released when aspartame is broken down by the body. Because of the danger to people with PKU, all products containing aspartame must carry a warning label.

Acesulfame K, discovered just two years after aspartame (1967), was approved for use in the United States in 1988. It is 200 times sweeter than sugar and, unlike aspartame, is heat stable. It has no lingering aftertaste.

One of the newest artificial sweeteners to gain FDA approval (April 1998) for use in the United States is sucralose, a white crystalline solid approximately 600 times sweeter than sucrose. Sucralose is synthesized from sucrose and has three chlorine atoms substituted for three OH groups. It is noncaloric because it passes through the body unchanged. It can be used in baking because it is heat stable.

All of the extensive clinical studies completed to date have indicated that these artificial sweeteners approved for use in the United States are safe for consumption by healthy individuals in moderate amounts.

Summary

Three abundant hexoses in living organisms are the aldohexoses D-glucose and D-galactose and the ketohexose D-fructose.

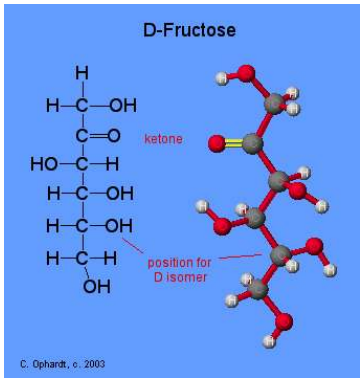
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12.4.1: Fructose

Fructose is more commonly found together with glucose and sucrose in honey and fruit juices. Fructose, along with glucose are the monosaccharides found in disaccharide, sucrose. Fructose is classified as a monosaccharide, the most important **ketose sugar**, a hexose, and is a reducing sugar.

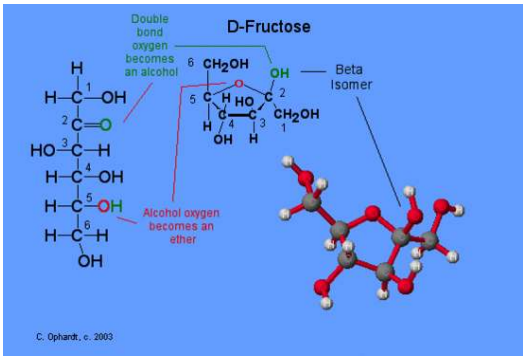
Introduction

An older common name for fructose is levulose, after its levorotatory property of rotating plane polarized light to the left (in contrast to glucose which is dextrorotatory). Bees gather nectar from flowers which contains sucrose. They then use an enzyme to hydrolyze or break apart the sucrose into its component parts of glucose and fructose. High Fructose Corn Syrup



Ring Structure for Fructose

The chair form of fructose follows a similar pattern as that for glucose with a few exceptions. Since fructose has a ketone functional group, the ring closure occurs at carbon # 2. In the case of fructose a five membered ring is formed. The -OH on carbon #5 is converted into the ether linkage to close the ring with carbon #2. This makes a 5 member ring - four carbons and one oxygen.



Steps in the ring closure (hemiketal synthesis)

1. The electrons on the alcohol oxygen are used to bond the carbon #2 to make an ether (red oxygen atom).
2. The hydrogen (green) is transferred to the carbonyl oxygen (green) to make a new alcohol group (green).

The ring structure is written with the orientation depicted on the left for the monosaccharide and is consistent with the way the glucose is depicted.

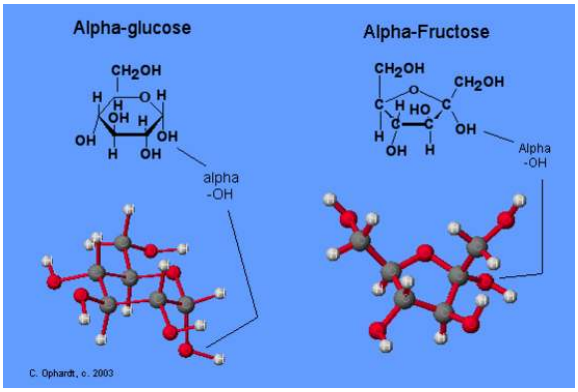
Hemiketal Functional Group

The **anomeric carbon** is the center of a hemiketal functional group. A carbon that has both an ether oxygen and an alcohol group (and is attached to two other carbons is a hemiketal.

Compare Alpha and Beta Fructose

The **Beta position** is defined as the -OH being on the same side of the ring as the C # 6. In the ring structure this results in a **upwards projection** for the -OH on carbon # 2. The **Alpha position** is defined as the -OH being on the opposite side of the ring as the C # 6. In the ring structure this results in a **downward projection** for the -OH on carbon # 2. The alpha and beta label is not applied to any other carbon - only the anomeric carbon, in this case # 2.

Figure: Compare Alpha and Beta Fructose



Compare Glucose and Fructose in the Chair Structures

The six member ring and the position of the -OH group on the **carbon (#4) identifies glucose** from the -OH on C # 4 in a down projection in the Haworth structure). **Fructose** is recognized by having a five member ring and having six carbons, a hexose. Both glucose and fructose may be either alpha or beta on the anomeric carbon, so this is not distinctive between them.

Problems

Which carbon in the structure on the in Figure 2 is the anomeric carbon?

Contributors

- Charles Ophardt, Professor Emeritus, Elmhurst College; Virtual Chembook

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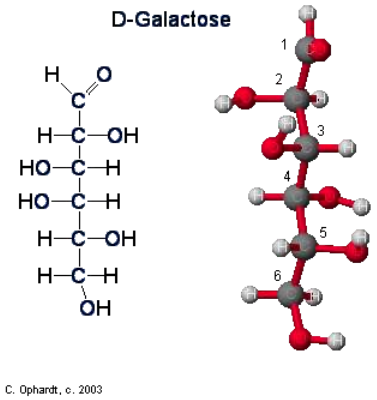
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12.4.2: Galactose

Galactose is more commonly found in the disaccharide, lactose or milk sugar. It is found as the monosaccharide in peas. Galactose is classified as a monosaccharide, an aldose, a hexose, and is a reducing sugar.

Galactosemia - Genetic Enzyme Deficiency

One baby out of every 18,000 is born with a genetic defect of not being able to utilize galactose. Since galactose is in milk as part of lactose, it will build up in the blood and urine. Undiagnosed it may lead to mental retardation, failure to grow, formation of cataracts, and in sever cases death by liver damage. The disorder is caused by a deficiency in one or more enzymes required to metabolize galactose. The treatment for the disorder is to use a formula based upon the sugar sucrose rather than milk with lactose. The galactose free diet is critical only in infancy, since with maturation another enzyme is developed that can metabolize galactose.



Ring Structure for Galactose

The chair form of galactose follows the same pattern as that for glucose. The **anomeric carbon** is the center of a hemiacetal functional group. A carbon that has both an ether oxygen and an alcohol group is a hemiacetal.

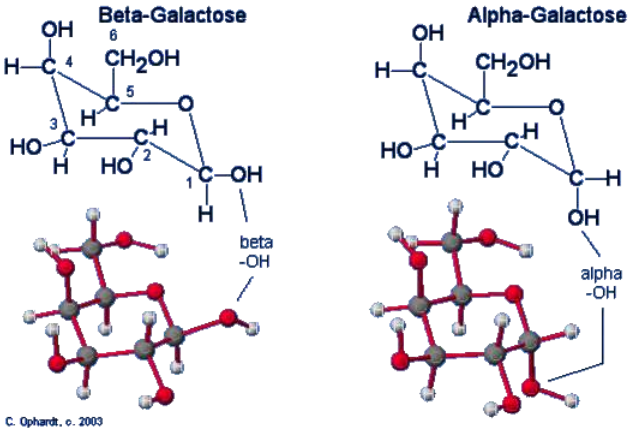


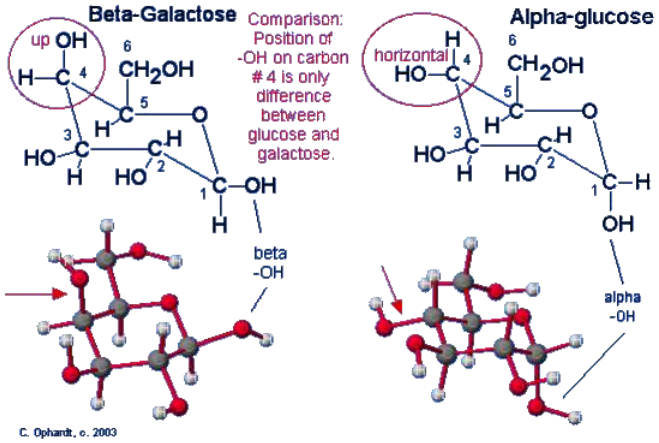
Figure* 12.4.2.1*: *Compare Alpha and Beta Galactose in the Chair form below.*

he **Beta position** is defined as the -OH being on the same side of the ring as the C # 6. In the chair structure this results in a **horizontal projection** (Haworth - an upwards projection). The **Alpha position** is defined as the -OH being on the opposite side of the ring as the C # 6. In the chair and Haworth structure this results in a **downward projection**.

Compare Glucose and Galactose in the Chair Structures

The position of the -OH group on the **carbon (#4) is the only** distinction between glucose and galactose. **Glucose** is defined as the -OH on C # 4 in a **horizontal projection** in the chair form, (down in the Haworth structure). **Galactose** is defined as the -OH on C

4 in a **upward projection** in the chair form,(also upward in the Haworth structure). Both glucose and galactose may be either alpha or beta on the anomeric carbon, so this is not distinctive between them.



? Exercise 12.4.2.1

Which carbon in the structure on the left is the anomeric carbon on galactose?

Contributors

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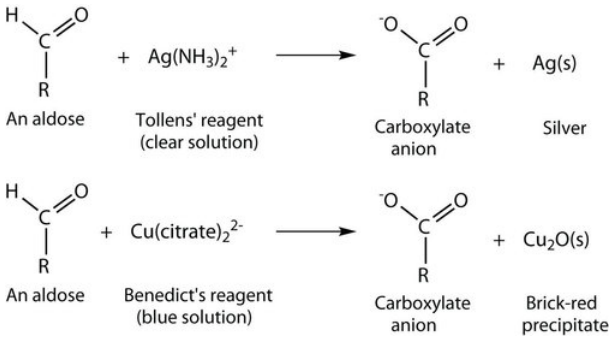
12.5: Properties of Monosaccharides

Learning Objectives

- To identify the physical and chemical properties of monosaccharides.

Monosaccharides such as glucose and fructose are crystalline solids at room temperature, but they are quite soluble in water, each molecule having several OH groups that readily engage in hydrogen bonding. The chemical behavior of these monosaccharides is likewise determined by their functional groups.

An important reaction of monosaccharides is the oxidation of the aldehyde group, one of the most easily oxidized organic functional groups. Aldehyde oxidation can be accomplished with any mild oxidizing agent, such as Tollens' reagent or Benedict's reagent. With the latter, complexed copper(II) ions are reduced to copper(I) ions that form a brick-red precipitate [copper(I) oxide; Figure 12.5.1].



Any carbohydrate capable of reducing either Tollens' or Benedict's reagents without first undergoing hydrolysis is said to be a reducing sugar. Because both the Tollens' and Benedict's reagents are basic solutions, ketoses (such as fructose) also give positive tests due to an equilibrium that exists between ketoses and aldoses in a reaction known as *tautomerism*.

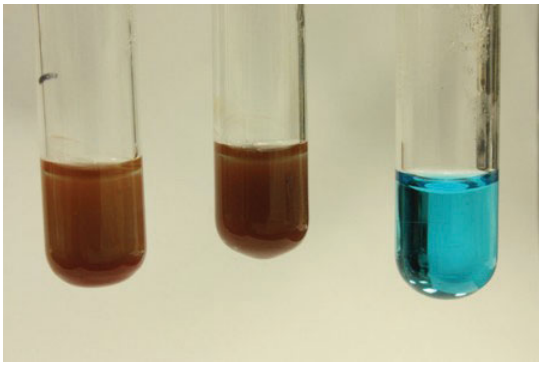


Figure 12.5.1: Benedict's Test. Benedict's test was performed on three carbohydrates, depicted from left to right: fructose, glucose, and sucrose. The solution containing sucrose remains blue because sucrose is a nonreducing sugar.

These reactions have been used as simple and rapid diagnostic tests for the presence of glucose in blood or urine. For example, Clinitest tablets, which are used to test for sugar in the urine, contain copper(II) ions and are based on Benedict's test. A green color indicates very little sugar, whereas a brick-red color indicates sugar in excess of 2 g/100 mL of urine.

Summary

Monosaccharides are crystalline solids at room temperature and quite soluble in water. Monosaccharides are reducing sugars; they reduce mild oxidizing agents, such as Tollens' or Benedict's reagents.

Concept Review Exercises

1. Why are monosaccharides soluble in water?

2. What is a reducing sugar?

Answers

1. Monosaccharides are quite soluble in water because of the numerous OH groups that readily engage in hydrogen bonding with water.
2. any carbohydrate capable of reducing a mild oxidizing agent, such as Tollens' or Benedict's reagents, without first undergoing hydrolysis

Exercises

1. Which gives a positive Benedict's test—L-galactose, levulose, or D-glucose?'

Answers

1. All three will give a positive Benedict's test because they are all monosaccharides.

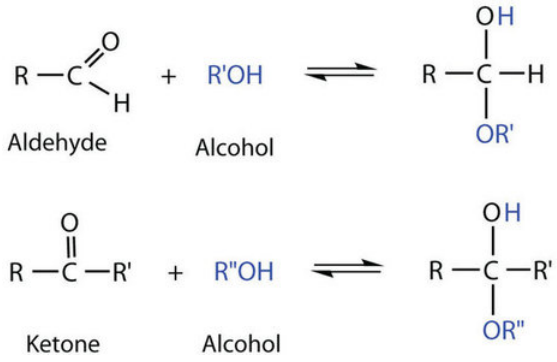
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12.6: Cyclic Structures of Monosaccharides

Learning Objectives

- Define what is meant by anomers and describe how they are formed.
- Explain what is meant by mutarotation.

So far we have represented monosaccharides as linear molecules, but many of them also adopt cyclic structures. This conversion occurs because of the ability of aldehydes and ketones to react with alcohols:



You might wonder why the aldehyde reacts with the OH group on the fifth carbon atom rather than the OH group on the second carbon atom next to it. Recall that cyclic alkanes containing five or six carbon atoms in the ring are the most stable. The same is true for monosaccharides that form cyclic structures: rings consisting of five or six carbon atoms are the most stable.

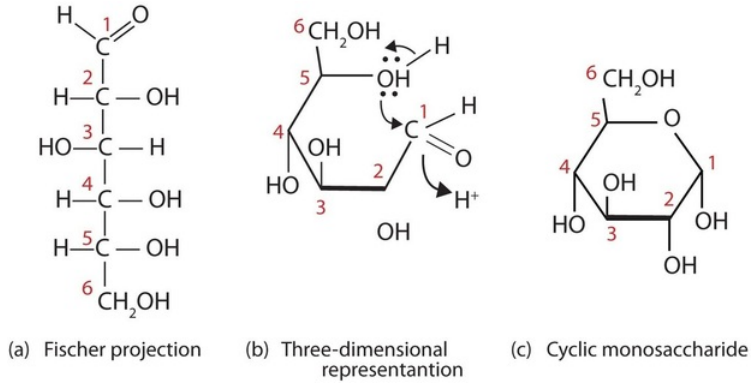


Figure 12.6.1: Cyclization of D-Glucose. D-Glucose can be represented with a Fischer projection (a) or three dimensionally (b). By reacting the OH group on the fifth carbon atom with the aldehyde group, the cyclic monosaccharide (c) is produced.

When a straight-chain monosaccharide, such as any of the structures shown in Figure 12.6.1, forms a cyclic structure, the carbonyl oxygen atom may be pushed either up or down, giving rise to two stereoisomers, as shown in Figure 12.6.2. The structure shown on the left side of Figure 12.6.2, with the OH group on the first carbon atom projected downward, represent what is called the *alpha (α) form*. The structures on the right side, with the OH group on the first carbon atom pointed upward, is the *beta (β) form*. These two stereoisomers of a cyclic monosaccharide are known as anomers; they differ in structure around the anomeric carbon—that is, the carbon atom that was the carbonyl carbon atom in the straight-chain form.

It is possible to obtain a sample of crystalline glucose in which all the molecules have the α structure or all have the β structure. The α form melts at 146°C and has a specific rotation of +112°, while the β form melts at 150°C and has a specific rotation of +18.7°. When the sample is dissolved in water, however, a mixture is soon produced containing both anomers as well as the straight-chain form, in dynamic equilibrium (part (a) of Figure 12.6.2). You can start with a pure crystalline sample of glucose consisting entirely of either anomer, but as soon as the molecules dissolve in water, they open to form the carbonyl group and then reclose to form either the α or the β anomer. The opening and closing repeats continuously in an ongoing interconversion between anomeric forms and is referred to as mutarotation (Latin *mutare*, meaning “to change”). At equilibrium, the mixture consists of

about 36% α-D-glucose, 64% β-D-glucose, and less than 0.02% of the open-chain aldehyde form. The observed rotation of this solution is +52.7°.

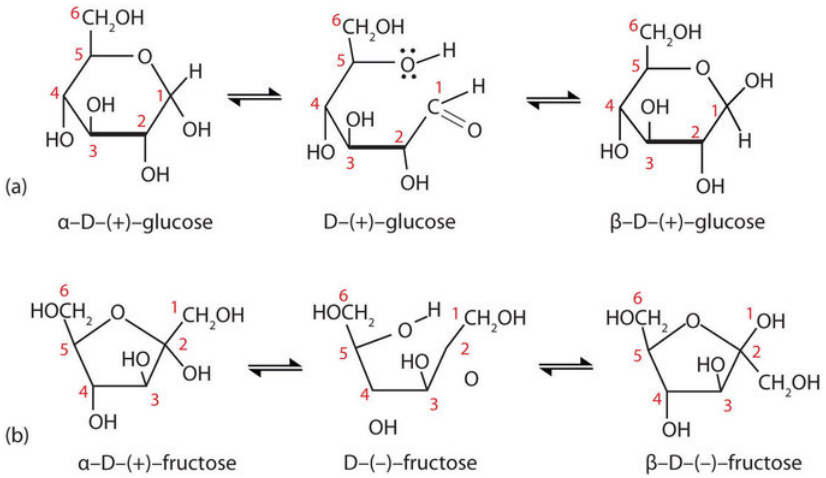


Figure **12.6.2**: Monosaccharides. In an aqueous solution, monosaccharides exist as an equilibrium mixture of three forms. The interconversion between the forms is known as *mutarotation*, which is shown for D-glucose (a) and D-fructose (b).

Even though only a small percentage of the molecules are in the open-chain aldehyde form at any time, the solution will nevertheless exhibit the characteristic reactions of an aldehyde. As the small amount of free aldehyde is used up in a reaction, there is a shift in the equilibrium to yield more aldehyde. Thus, *all* the molecules may eventually react, even though very little free aldehyde is present at a time.

Commonly, (e.g., in Figures **12.6.1** and **12.6.2**) the cyclic forms of sugars are depicted using a convention first suggested by Walter N. Haworth, an English chemist. The molecules are drawn as planar hexagons with a darkened edge representing the side facing toward the viewer. The structure is simplified to show only the functional groups attached to the carbon atoms. Any group written to the right in a Fischer projection appears below the plane of the ring in a Haworth projection, and any group written to the left in a Fischer projection appears above the plane in a Haworth projection.

The difference between the α and the β forms of sugars may seem trivial, but such structural differences are often crucial in biochemical reactions. This explains why we can get energy from the starch in potatoes and other plants but not from cellulose, even though both starch and cellulose are polysaccharides composed of glucose molecules linked together.

Summary

Monosaccharides that contain five or more carbons atoms form cyclic structures in aqueous solution. Two cyclic stereoisomers can form from each straight-chain monosaccharide; these are known as anomers. In an aqueous solution, an equilibrium mixture forms between the two anomers and the straight-chain structure of a monosaccharide in a process known as mutarotation.

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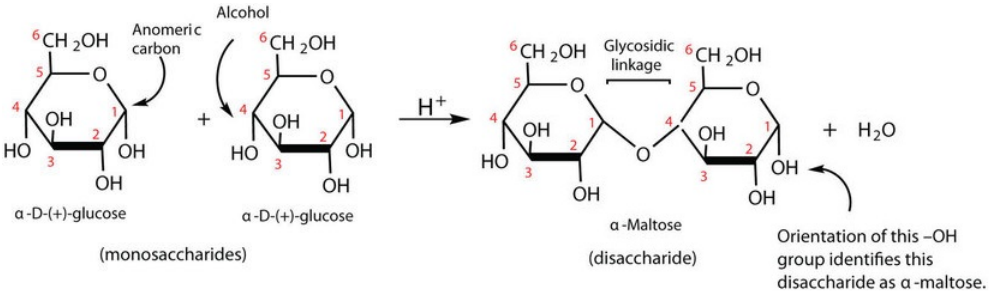
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12.7: Disaccharides

Learning Objectives

- Identify the structures of sucrose, lactose, and maltose.
- Identify the monosaccharides that are needed to form sucrose, lactose, and maltose

Previously, you learned that monosaccharides can form cyclic structures by the reaction of the carbonyl group with an OH group. These cyclic molecules can in turn react with another alcohol. Disaccharides ($C_{12}H_{22}O_{11}$) are sugars composed of two monosaccharide units that are joined by a carbon–oxygen-carbon linkage known as a glycosidic linkage. This linkage is formed from the reaction of the anomeric carbon of one cyclic monosaccharide with the OH group of a second monosaccharide.



The disaccharides differ from one another in their monosaccharide constituents and in the specific type of glycosidic linkage connecting them. There are three common disaccharides: maltose, lactose, and sucrose. All three are white crystalline solids at room temperature and are soluble in water. We'll consider each sugar in more detail.

Maltose

Maltose occurs to a limited extent in sprouting grain. It is formed most often by the partial hydrolysis of starch and glycogen. In the manufacture of beer, maltose is liberated by the action of malt (germinating barley) on starch; for this reason, it is often referred to as *malt sugar*. Maltose is about 30% as sweet as sucrose. The human body is unable to metabolize maltose or any other disaccharide directly from the diet because the molecules are too large to pass through the cell membranes of the intestinal wall. Therefore, an ingested disaccharide must first be broken down by hydrolysis into its two constituent monosaccharide units.

In the body, such hydrolysis reactions are catalyzed by enzymes such as *maltase*. The same reactions can be carried out in the laboratory with dilute acid as a catalyst, although in that case the rate is much slower, and high temperatures are required. Whether it occurs in the body or a glass beaker, the hydrolysis of maltose produces two molecules of D-glucose.

$$\text{maltose} \xrightarrow{\text{H}^+ \text{ or maltase}} 2\ \text{D-glucose}$$

Maltose is a reducing sugar. Thus, its two glucose molecules must be linked in such a way as to leave one anomeric carbon that can open to form an aldehyde group. The glucose units in maltose are joined in a *head-to-tail* fashion through an α-linkage from the first carbon atom of one glucose molecule to the fourth carbon atom of the second glucose molecule (that is, an α-1,4-glycosidic linkage; see Figure **12.7.1**). The bond from the anomeric carbon of the first monosaccharide unit is directed downward, which is why this is known as an α-glycosidic linkage. The OH group on the anomeric carbon of the second glucose can be in either the α or the β position, as shown in Figure **12.7.1**.

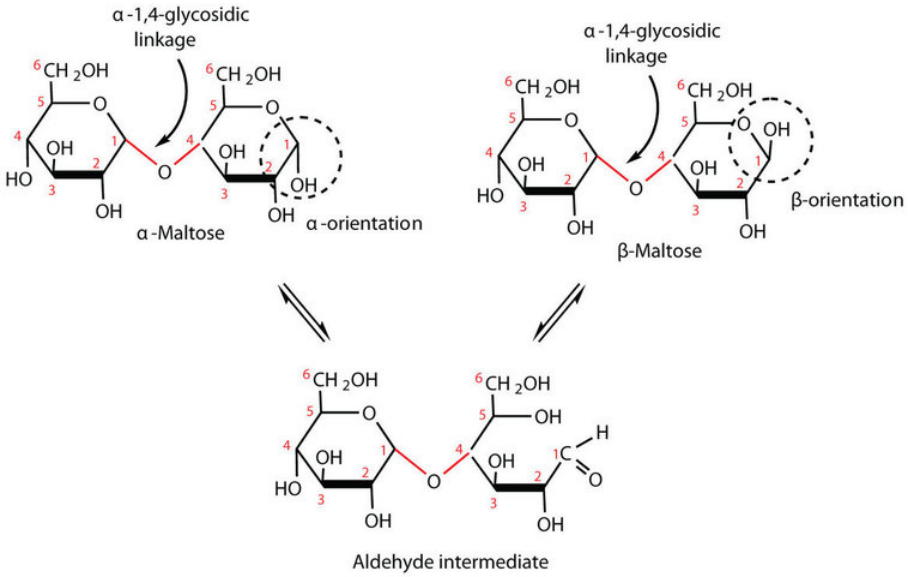
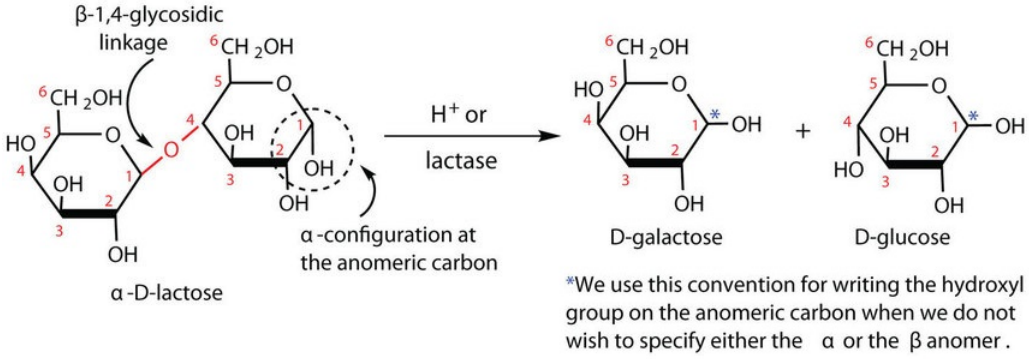


Figure **12.7.1**: An Equilibrium Mixture of Maltose Isomers

Lactose

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

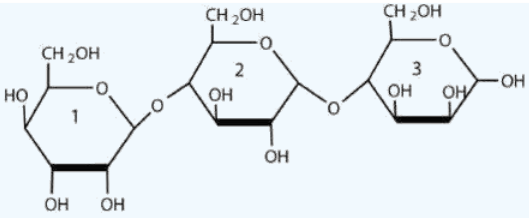
Lactose is a reducing sugar composed of one molecule of D-galactose and one molecule of D-glucose joined by a β-1,4-glycosidic bond (the bond from the anomeric carbon of the first monosaccharide unit being directed upward). The two monosaccharides are obtained from lactose by acid hydrolysis or the catalytic action of the enzyme *lactase*:



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

Example 12.7.1

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

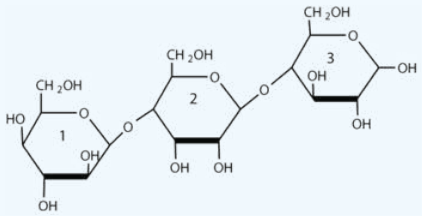


Solution

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

? Exercise 12.7.1

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



To Your Health: Lactose Intolerance and Galactosemia

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

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

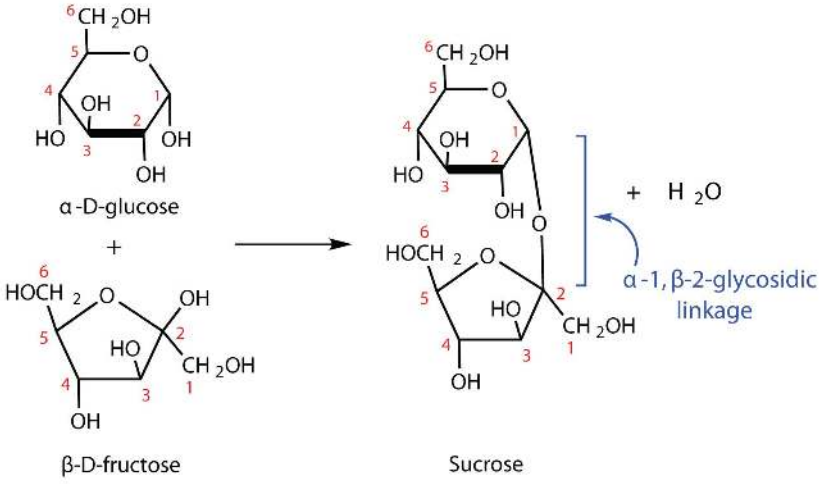
The symptoms disappear if milk or other sources of lactose are excluded from the diet or consumed only sparingly. Alternatively, many food stores now carry special brands of milk that have been pretreated with lactase to hydrolyze the lactose. Cooking or fermenting milk causes at least partial hydrolysis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

Galactosemia is a condition in which one of the enzymes needed to convert galactose to glucose is missing. Consequently, the blood galactose level is markedly elevated, and galactose is found in the urine. An infant with galactosemia experiences a lack of appetite, weight loss, diarrhea, and jaundice. The disease may result in impaired liver function, cataracts, mental retardation, and even death. If galactosemia is recognized in early infancy, its effects can be prevented by the exclusion of milk and all other sources of galactose from the diet. As a child with galactosemia grows older, he or she usually develops an alternate pathway for metabolizing galactose, so the need to restrict milk is not permanent. The incidence of galactosemia in the United States is 1 in every 65,000 newborn babies.

Sucrose

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

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



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

The hydrolysis of sucrose in dilute acid or through the action of the enzyme *sucrase* (also known as invertase) gives an equimolar mixture of glucose and fructose. This 1:1 mixture is referred to as *invert sugar* because it rotates plane-polarized light in the opposite direction than sucrose. The hydrolysis reaction has several practical applications. Sucrose readily recrystallizes from a solution, but invert sugar has a much greater tendency to remain in solution. In the manufacture of jelly and candy and in the canning of fruit, the recrystallization of sugar is undesirable. Therefore, conditions leading to the hydrolysis of sucrose are employed in these processes. Moreover, because fructose is sweeter than sucrose, the hydrolysis adds to the sweetening effect. Bees carry out this reaction when they make honey.

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

Summary

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

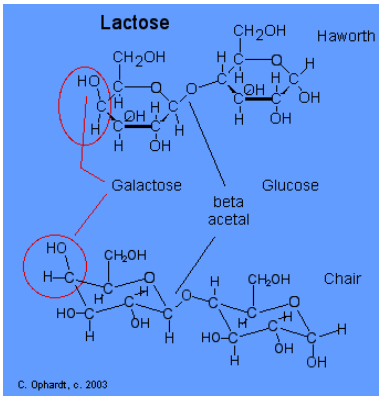
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12.7.1: Lactose

Lactose or milk sugar occurs in the milk of mammals - 4-6% in cow's milk and 5-8% in human milk. It is also a by product in the the manufacture of cheese. Lactose is made from galactose and glucose units. The galactose and glucose units are joined by an acetal oxygen bridge in the beta orientation. To recognize galactose look for the upward projection of the -OH on carbon # 4. See details on the galactose page towards the bottom.

Lactose intolerance

Lactose intolerance is the inability to digest significant amounts of lactose, the predominant sugar of milk. This inability results from a shortage of the enzyme lactase, which is normally produced by the cells that line the small intestine. Lactase breaks down the lactose, milk sugar, into glucose and galactose that can then be absorbed into the bloodstream. When there is not enough lactase to digest the amount of lactose consumed, produce some uncomfortable symptoms. Some adults have low levels of lactase. This leads to lactose intolerance. The ingested lactose is not absorbed in the small intestine, but instead is fermented by bacteria in the large intestine, producing uncomfortable volumes of carbon dioxide gas. While not all persons deficient in lactase have symptoms, those who do are considered to be lactose intolerant.

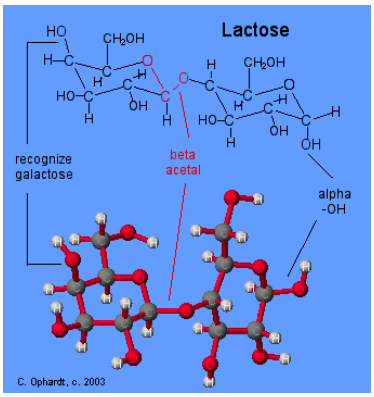


Common symptoms include nausea, cramps, bloating, gas, and diarrhea, which begin about 30 minutes to 2 hours after eating or drinking foods containing lactose. The severity of symptoms varies depending on the amount of lactose each individual can tolerate.

Fortunately, lactose intolerance is relatively easy to treat by controlling the diet. No cure or treatment exists to improve the body's ability to produce lactase. Young children with lactase deficiency should not eat any foods containing lactose. Most older children and adults need not avoid lactose completely, but individuals differ in the amounts and types of foods they can handle. Dietary control of lactose intolerance depends on each person's learning through trial and error how much lactose he or she can handle.

Acetal Functional Group

Carbon # 1 (red on left) is called the **anomeric carbon** and is the center of an acetal functional group. A carbon that has two ether oxygens attached is an acetal. The **Beta position** is defined as the ether oxygen being on the same side of the ring as the C # 6. In the chair structure this results in a **horizontal or up projection**. This is the same definition as the -OH in a hemiacetal.

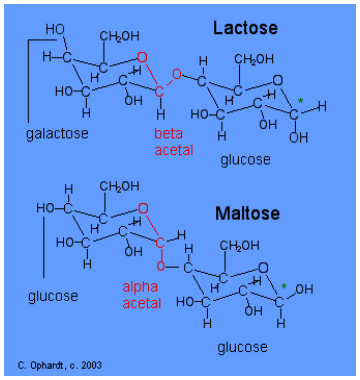


Compare Lactose and Maltose Acetals

The position of the oxygen in the acetal on the anomeric carbon (#1) is an important distinction for disaccharide chemistry. **Lactose has a beta acetal.** The **Beta position** is defined as the oxygen in the acetal being on the same side of the ring as the C # 6. In the chair structure this results in a **horizontal projection**. **Maltose has an alpha acetal.** The **Alpha position** is defined as the oxygen in the acetal being on the opposite side of the ring as the C # 6. In the chair structure this results in a **downward projection**. The alpha and beta acetal label is not applied to any other carbon - only the anomeric carbon of the left monosaccharide, in this case # 1 (red).

Recognize galactose and glucose

To further identify lactose and maltose, identify the presence of **galactose in lactose** in the left most structure by the upward -OH on the carbon # 4. Identify **glucose in maltose** in the left most structure by the horizontal -OH on the carbon # 4.



Contributors

- Charles Ophardt, Professor Emeritus, Elmhurst College; Virtual Chembook

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12.7.2: Sucrose

Sucrose or table sugar is obtained from sugar cane or sugar beets. Sucrose is made from glucose and fructose units. The glucose and fructose units are joined by an acetal oxygen bridge in the alpha orientation. The structure is easy to recognize because it contains the six member ring of glucose and the five member ring of fructose.

Introduction

To recognize glucose look for the horizontal projection of the -OH on carbon #4. The alpha acetal is is really part of a double acetal, since the two monosaccharides are joined at the hemiacetal of glucose and the hemiketal of the fructose. There are no hemiacetals remaining in the sucrose and therefore sucrose is a *non-reducing sugar*.

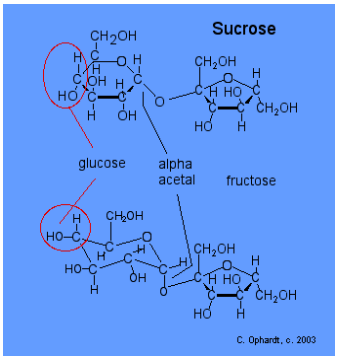


Figure* 12.7.2.1*: *Sucrose*

Sugar Processing

Sugar or more specifically sucrose is a carbohydrate that occurs naturally in every fruit and vegetable. It is the major product of photosynthesis, the process by which plants transform the sun's energy into food. Sugar occurs in greatest quantities in sugar cane and sugar beets from which it is separated for commercial use.

In the first stage of processing the natural sugar stored in the cane stalk or beet root is separated from the rest of the plant material by physical methods. For sugar cane, this is accomplished by:

1. pressing the cane to extract the juice containing the sugar
2. boiling the juice until it begins to thicken and sugar begins to crystallize
3. spinning the sugar crystals in a centrifuge to remove the syrup, producing raw sugar; the raw sugar still contains many impurities
4. shipping the raw sugar to a refinery where it is washed and filtered to remove remaining non-sugar ingredients and color
5. crystallizing, drying and packaging the refined sugar.

Beet sugar processing is similar, but it is done in one continuous process without the raw sugar stage. The sugar beets are washed, sliced and soaked in hot water to separate the sugar-containing juice from the beet fiber. The sugar-laden juice is purified, filtered, concentrated and dried in a series of steps similar to cane sugar processing.

Acetal Functional Group

Carbon # 1 (red on left) is called the **anomeric carbon** and is the center of an acetal functional group. A carbon that has two ether oxygens attached is an acetal. The **Alpha position** is defined as the ether oxygen being on the opposite side of the ring as the C # 6. In the chair structure this results in a **down projection**. This is the same definition as the -OH in a hemiacetal.

A second acetal grouping is defined by the green atoms. This result because the the formation reaction of the disaccharide is between the hemiacetal of glucose and the hemiketal of the fructose.

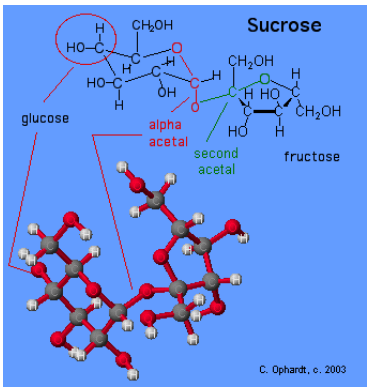


Figure* 12.7.2.2*: *Sucrose*

Invert Sugar

When sucrose is hydrolyzed it forms a 1:1 mixture of glucose and fructose. This mixture is the main ingredient in honey. It is called invert sugar because the angle of the specific rotation of the plain polarized light changes from a positive to a negative value due to the presence of the optical isomers of the mixture of glucose and fructose sugars.

Hydrolysis of Sucrose

In the hydrolysis of any di- or poly saccharide, a water molecule helps to break the acetal bond as shown in red. The acetal bond is broken, the H from the water is added to the oxygen on the glucose. The -OH is then added to the carbon on the fructose.

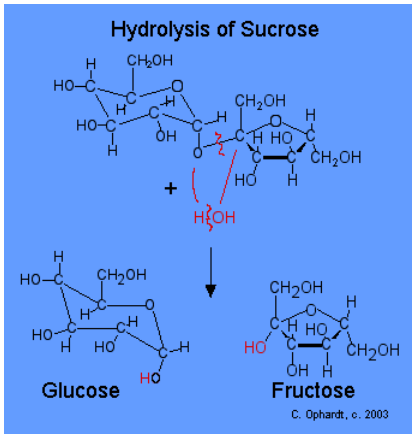


Figure* 12.7.2.1*: *Hydrolosis of Sucrose*

? Exercise 12.7.2.1

Is glucose - alpha or beta?

Answer

The -OH on carbon # 1 is projected down therefore, alpha.

? Exercise 12.7.2.2

Is fructose - alpha or beta?

Answer

The -OH on carbon # 1 is projected downand is on the same side of the ring as C#6, extreme right on fructose therefore, beta.

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12.8: Polysaccharides

Learning Objectives

- To compare and contrast the structures and uses of starch, glycogen, and cellulose.

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

Starch

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

Starch is a mixture of two polymers: amylose and amylopectin. Natural starches consist of about 10%–30% amylose and 70%–90% amylopectin. Amylose is a linear polysaccharide composed entirely of D-glucose units joined by the α-1,4-glycosidic linkages we saw in maltose (part (a) of Figure **12.8.1**). Experimental evidence indicates that amylose is not a straight chain of glucose units but instead is coiled like a spring, with six glucose monomers per turn (part (b) of Figure **12.8.1**). When coiled in this fashion, amylose has just enough room in its core to accommodate an iodine molecule. The characteristic blue-violet color that appears when starch is treated with iodine is due to the formation of the amylose-iodine complex. This color test is sensitive enough to detect even minute amounts of starch in solution.

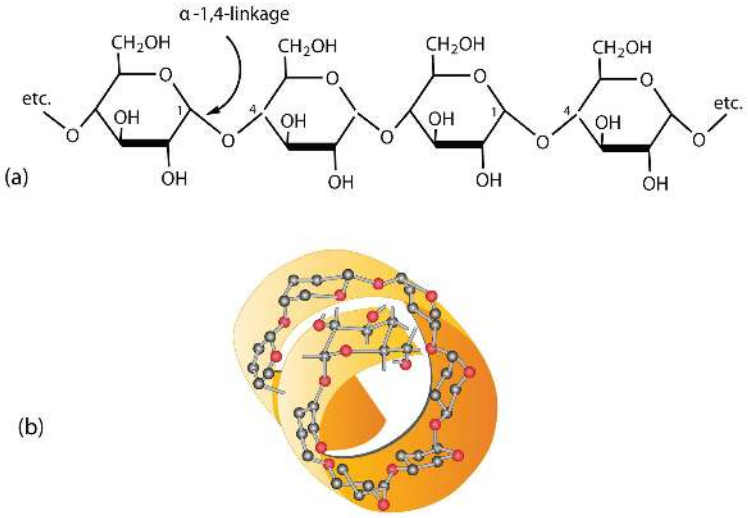


Figure **12.8.1**: Amylose. (a) Amylose is a linear chain of α-D-glucose units joined together by α-1,4-glycosidic bonds. (b) Because of hydrogen bonding, amylose acquires a spiral structure that contains six glucose units per turn.

Amylopectin is a branched-chain polysaccharide composed of glucose units linked primarily by α-1,4-glycosidic bonds but with occasional α-1,6-glycosidic bonds, which are responsible for the branching. A molecule of amylopectin may contain many thousands of glucose units with branch points occurring about every 25–30 units (Figure **12.8.2**). The helical structure of amylopectin is disrupted by the branching of the chain, so instead of the deep blue-violet color amylose gives with iodine, amylopectin produces a less intense reddish brown.

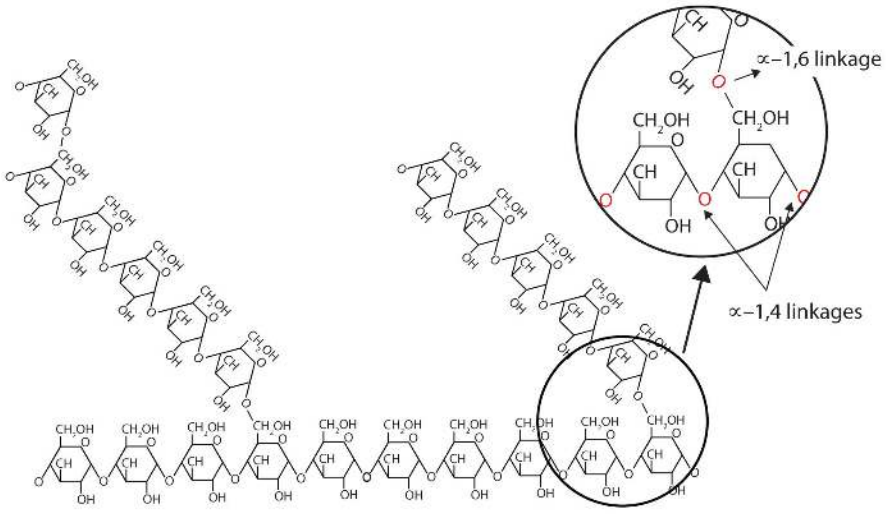


Figure **12.8.2**: Representation of the Branching in Amylopectin and Glycogen. Both amylopectin and glycogen contain branch points that are linked through α-1,6-linkages. These branch points occur more often in glycogen.

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

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

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

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

Glycogen

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

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

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

Cellulose

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

Like amylose, cellulose is a linear polymer of glucose. It differs, however, in that the glucose units are joined by β-1,4-glycosidic linkages, producing a more extended structure than amylose (part (a) of Figure **12.8.3**). This extreme linearity allows a great deal of hydrogen bonding between OH groups on adjacent chains, causing them to pack closely into fibers (part (b) of Figure **12.8.3**). As a result, cellulose exhibits little interaction with water or any other solvent. Cotton and wood, for example, are completely insoluble in water and have considerable mechanical strength. Because cellulose does not have a helical structure, it does not bind to iodine to form a colored product.

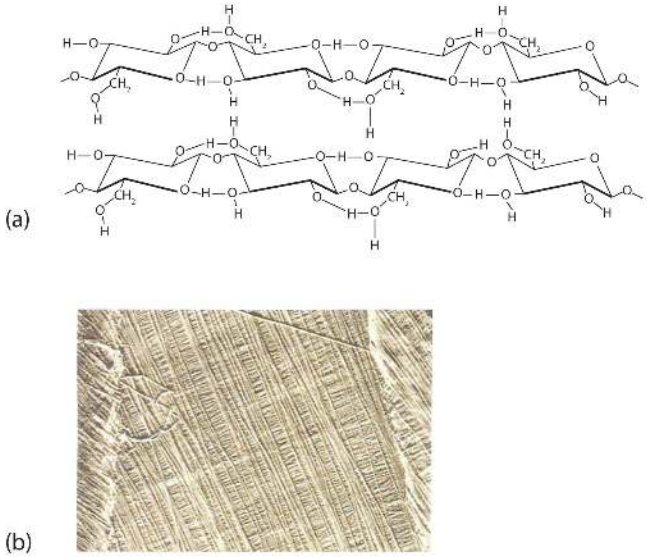


Figure **12.8.3**: Cellulose. (a) There is extensive hydrogen bonding in the structure of cellulose. (b) In this electron micrograph of the cell wall of an alga, the wall consists of successive layers of cellulose fibers in parallel arrangement.

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

Career Focus: Certified Diabetes Educator

Certified diabetes educators come from a variety of health professions, such as nursing and dietetics, and specialize in the education and treatment of patients with diabetes. A diabetes educator will work with patients to manage their diabetes. This involves teaching the patient to monitor blood sugar levels, make good food choices, develop and maintain an exercise program, and take medication, if required.



A certified diabetes educator at Naval Medical Center Portsmouth (left) and a registered dietician at the medical center (center), provide nutritional information to a diabetes patient and her mother at the Diabetes Boot Camp.

> Diabetes educators also work with hospital or nursing home staff to improve the care of diabetic patients. Educators must be willing to spend time attending meetings and reading the current literature to maintain their knowledge of diabetes medications, nutrition, and blood monitoring devices so that they can pass this information to their patients.

Summary

Starch is a storage form of energy in plants. It contains two polymers composed of glucose units: amylose (linear) and amylopectin (branched). Glycogen is a storage form of energy in animals. It is a branched polymer composed of glucose units. It is more highly branched than amylopectin. Cellulose is a structural polymer of glucose units found in plants. It is a linear polymer with the glucose units linked through β-1,4-glycosidic bonds.

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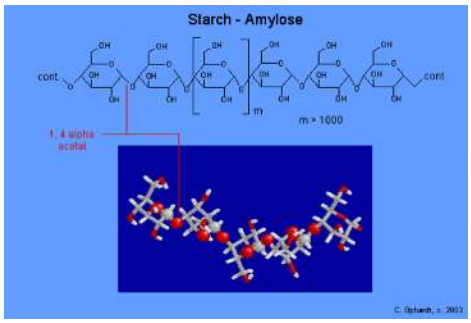
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12.8.1: Starch

Polysaccharides are carbohydrate polymers consisting of tens to hundreds to several thousand monosaccharide units. All of the common polysaccharides contain glucose as the monosaccharide unit. Polysaccharides are synthesized by plants, animals, and humans to be stored for food, structural support, or metabolized for energy.

Introduction

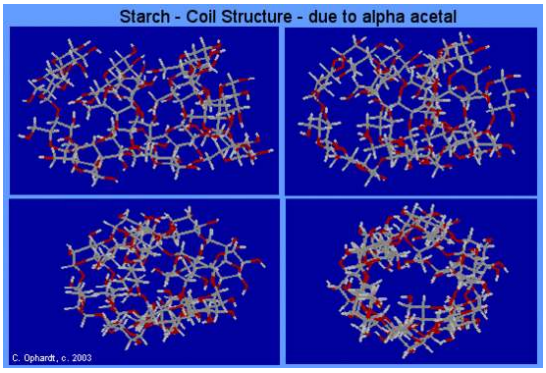
Plants store glucose as the polysaccharide starch. The cereal grains (wheat, rice, corn, oats, barley) as well as tubers such as potatoes are rich in starch. Starch can be separated into two fractions--**amylose and amylopectin**. Natural starches are mixtures of amylose (10-20%) and amylopectin (80-90%).



Amylose forms a colloidal dispersion in hot water, while amylopectin is soluble it is demanding of more extensive heating than amylose. The structure of amylose consists of long polymer chains of glucose units connected by an **alpha acetal** linkage. The graphic on the left shows a very small portion of an amylose chain. All of the monomer units are alpha -D-glucose, and all the alpha acetal links connect C #1 of one glucose and C #4 of the next glucose.

Acetal Functional Group

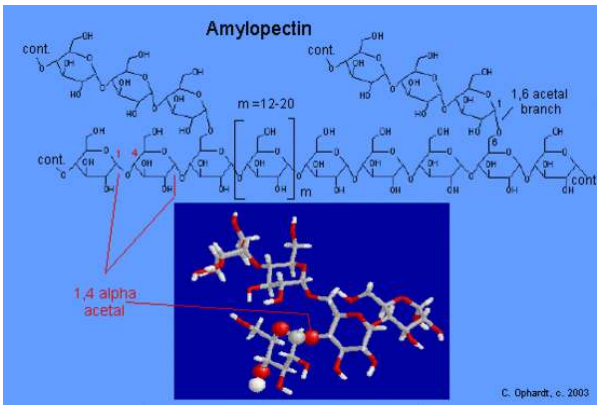
Carbon # 1 is called the **anomeric carbon** and is the center of an acetal functional group. A carbon that has two ether oxygens attached is an acetal. The **Alpha position** is defined as the ether oxygen being on the opposite side of the ring as the C # 6. In the chair structure this results in a **downward projection**. This is the same definition as the -OH in a hemiacetal.



As a result of the bond angles in the alpha acetal linkage, amylose actually forms a spiral much like a coiled spring. Amylose is responsible for the formation of a deep blue color in the presence of iodine, which slips inside of the amylose coil.

Amylopectin

The graphic on the left shows very small portion of an amylopectin-type structure showing two branch points [drawn closer together than they should be]. The acetal linkages are alpha connecting C #1 of one glucose to C #4 of the next glucose.



The branches are formed by linking C #1 to a C #6 through an acetal linkages. Amylopectin has 12-20 glucose units between the branches. Natural starches are mixtures of amylose and amylopectin. In glycogen, the branches occur at intervals of 8-10 glucose units, while in amylopectin the branches are separated by 10-12 glucose units.

Contributors

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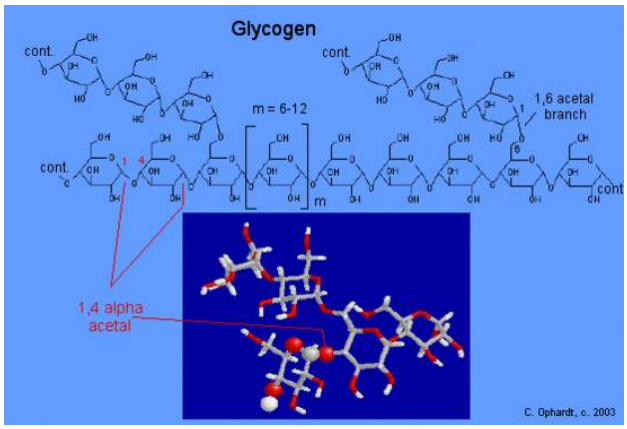
12.8.2: Glycogen

Polysaccharides are carbohydrate polymers consisting of tens to hundreds to several thousand monosaccharide units. All of the common polysaccharides contain glucose as the monosaccharide unit. Polysaccharides are synthesized by plants, animals, and humans to be stored for food, structural support, or metabolized for energy.

Introduction

Glycogen is the storage form of glucose in animals and humans which is analogous to the starch in plants. Glycogen is synthesized and stored mainly in the liver and the muscles. Structurally, glycogen is very similar to amylopectin with alpha acetal linkages, however, it has even more branching and more glucose units are present than in amylopectin. Various samples of glycogen have been measured at 1,700-600,000 units of glucose.

The structure of glycogen consists of long polymer chains of glucose units connected by an **alpha acetal** linkage. The graphic on the left shows a very small portion of a glycogen chain. All of the monomer units are alpha-D-glucose, and all the alpha acetal links connect C # 1 of one glucose to C # 4 of the next glucose.



The branches are formed by linking C #1 to a C #6 through an acetal linkages. In glycogen, the branches occur at intervals of 8-10 glucose units, while in amylopectin the branches are separated by 12-20 glucose units.

Acetal Functional Group

Carbon # 1 is called the **anomeric carbon** and is the center of an acetal functional group. A carbon that has two ether oxygens attached is an acetal. The **Alpha position** is defined as the ether oxygen being on the opposite side of the ring as the C # 6. In the chair structure this results in a **downward projection**. This is the same definition as the -OH in a hemiacetal.

Starch vs. Glycogen

Plants make starch and cellulose through the photosynthesis processes. Animals and human in turn eat plant materials and products. Digestion is a process of hydrolysis where the starch is broken ultimately into the various monosaccharides. A major product is of course glucose which can be used immediately for metabolism to make energy. The glucose that is not used immediately is converted in the liver and muscles into glycogen for storage by the process of glycogenesis. Any glucose in excess of the needs for energy and storage as glycogen is converted to fat.

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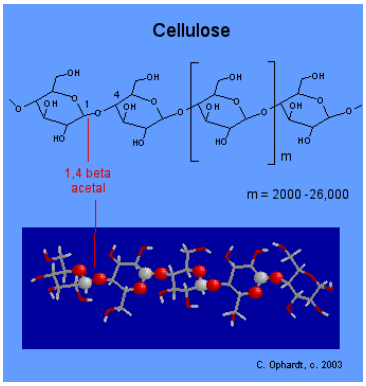
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12.8.3: Cellulose

Polysaccharides are carbohydrate polymers consisting of tens to hundreds to several thousand monosaccharide units. All of the common polysaccharides contain glucose as the monosaccharide unit. Polysaccharides are synthesized by plants, animals, and humans to be stored for food, structural support, or metabolized for energy.

The major component in the rigid cell walls in plants is cellulose. Cellulose is a linear polysaccharide polymer with many glucose monosaccharide units. The acetal linkage is beta which makes it different from starch. This peculiar difference in acetal linkages results in a major difference in digestibility in humans. Humans are unable to digest cellulose because the appropriate enzymes to breakdown the beta acetal linkages are lacking. Indigestible cellulose is the fiber which aids in the smooth working of the intestinal tract.



Animals such as cows, horses, sheep, goats, and termites have symbiotic bacteria in the intestinal tract. These symbiotic bacteria possess the necessary enzymes to digest cellulose in the GI tract. They have the required enzymes for the breakdown or hydrolysis of the cellulose; the animals do not, not even termites, have the correct enzymes. No vertebrate can digest cellulose directly.

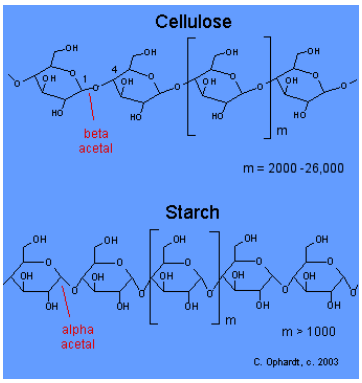
Even though we cannot digest cellulose, we find many uses for it including: Wood for building; paper products; cotton, linen, and rayon for clothes; nitrocellulose for explosives; cellulose acetate for films. The structure of cellulose consists of long polymer chains of glucose units connected by a beta acetal linkage. The graphic on the left shows a very small portion of a cellulose chain. All of the monomer units are beta-D-glucose, and all the beta acetal links connect C # 1 of one glucose to C # 4 of the next glucose.

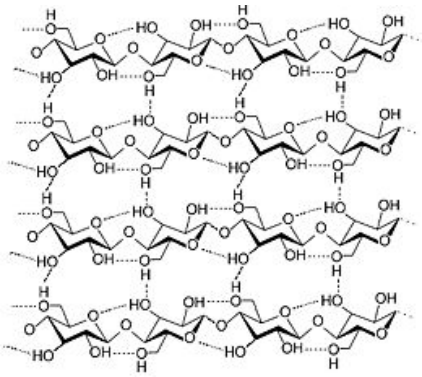
Acetal Functional Group

Carbon # 1 is called the anomeric carbon and is the center of an acetal functional group. A carbon that has two ether oxygens attached is an acetal. The Beta position is defined as the ether oxygen being on the same side of the ring as the C # 6. In the chair structure this results in a horizontal or up projection. This is the same definition as the -OH in a hemiacetal.

Compare Cellulose and Starch Structures

Cellulose: Beta glucose is the monomer unit in cellulose. As a result of the bond angles in the beta acetal linkage, cellulose is mostly a linear chain. Starch: Alpha glucose is the monomer unit in starch. As a result of the bond angles in the alpha acetal linkage, starch-amylose actually forms a spiral much like a coiled spring.





Fiber in the Diet

Dietary fiber is the component in food not broken down by digestive enzymes and secretions of the gastrointestinal tract. This fiber includes hemicelluloses, pectins, gums, mucilages, cellulose, (all carbohydrates) and lignin, the only non-carbohydrate component of dietary fiber. High fiber diets cause increased stool size and may help prevent or cure constipation. Cereal fiber, especially bran, is most effective at increasing stool size while pectin has little effect. Lignin can be constipating.

Fiber may protect against the development of colon cancer, for populations consuming high fiber diets have a low incidence of this disease. The slow transit time (between eating and elimination) associated with a low fiber intake would allow more time for carcinogens present in the colon to initiate cancer. But constipated people do not have a higher incidence of colon cancer than fast eliminators, so fiber's role in colon cancer remains unclear.

Dietary fiber may limit cholesterol absorption by binding bile acids. High fiber diets lower serum cholesterol and may prevent cardiovascular disease. Some fibers, such as pectin and rolled oats, are more effective than others, such as wheat, at lowering serum cholesterol. Dietary fiber is found only in plant foods such as fruits, vegetables, nuts, and grains. Whole wheat bread contains more fiber than white bread and apples contain more fiber than apple juice, which shows that processing food generally removes fiber.

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12.8.4: Glycation and Heteropolysaccharides



Figure 2.171 - Repeating unit of amylose

Endogenous glycation, on the other hand, arises with a frequency that is proportional to the concentration of free sugar in the body. These occur most frequently with fructose, galactose, and glucose in that decreasing order and are detected in the bloodstream. Both proteins and lipids can be glycated and the accumulation of endogenous advanced glycation endproducts (AGEs) is associated with Type 2 diabetes, as well as in increases in cardiovascular disease (damage to endothelium, cartilage, and fibrinogen), peripheral neuropathy (attack of myelin sheath), and deafness (loss of myelin sheath).

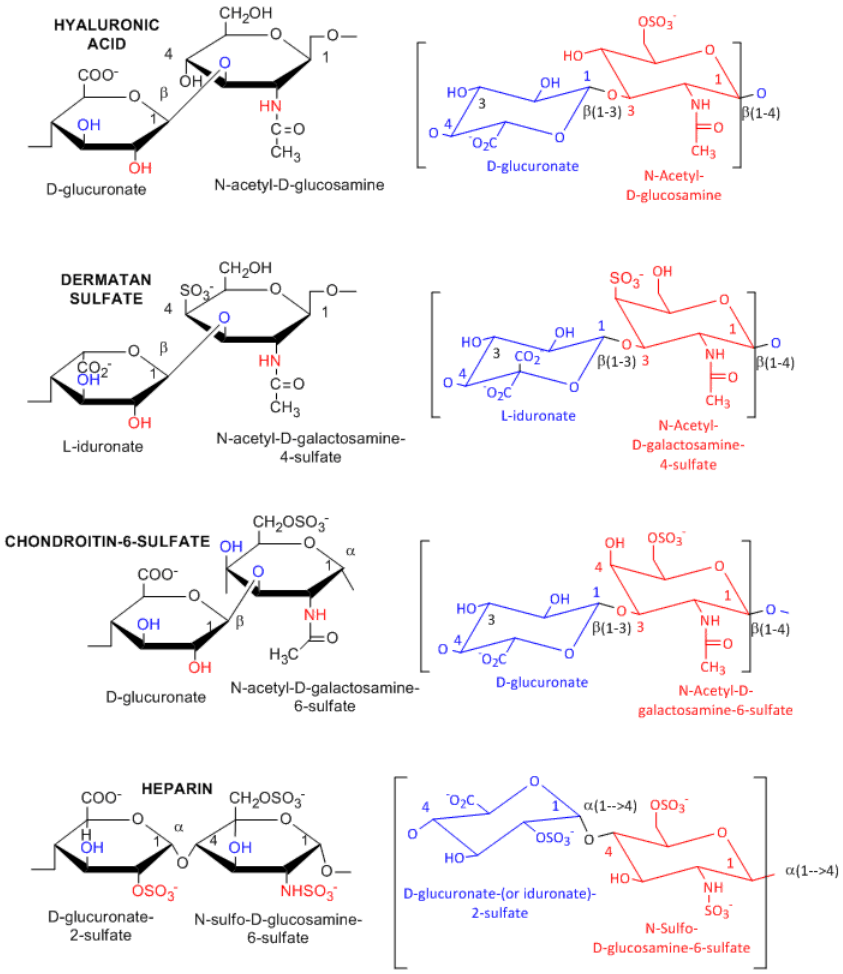
The formation of AGEs increases oxidative stress, but is also thought to be exacerbated by it. Increased oxidative stress, in turn causes additional harm. Damage to collagen in blood cells causes them to stiffen and weaken and is a factor in hardening of the arteries and formation of aneurysms, respectively. One indicator of diabetes is increased glycation of hemoglobin in red blood cells, since circulating sugar concentration are high in the blood of diabetics. Hemoglobin glycation is measured in testing for blood glucose control in diabetic patients.

Heteropolysaccharides

Many polysaccharides consist of repeating dissacharides units. Agarose, a polymer of a disaccharide repeat of (1-->3)-β-D-galactopyranose-(1 --> 4)-3,6-anhydro-α-L-galactopyranose, is often used for a gelable solid phase for electrophoresis of nucleic acid and as a component of chromatography beads. A major class of polysaccharides with dissacharide repeats include the following glycosaminoglycans (GAGs), all which contain one amino sugar in the repeat and in which one or both of the sugars contain negatively charged sulfate or carboxyl groups. The extent and position of sulfation varies widely between and within GAGs.

GAGs are found in the vitreous humor of the eye and synovial fluid of joints, and in connective tissue like tendons, cartilage, etc, as well as skin. They are found in the extracellular matrix and are often covalently attached to proteins to form proteoglycans.

Figure: Glycosaminoglycans



Function in skin

Hyaluronic acid is a major component of skin and has functions in tissue repair. With exposure to excess UVB radiation, cells in the dermis produce less hyaluronan and increase its degradation.

For some cancers the plasma level of hyaluronic acid correlates with malignancy. Hyaluronic acid levels have been used as a marker for prostate and breast cancer and to follow disease progression. The compound can to used to induce healing after cataract surgery. Hyaluronic acid is also abundant in the granulation tissue matrix that replaces a fibrin clot during the healing of wounds. In wound healing, it is thought that large polymers of hyaluronic acid appear early and they physically make room for white blood cells to mediate an immune response.

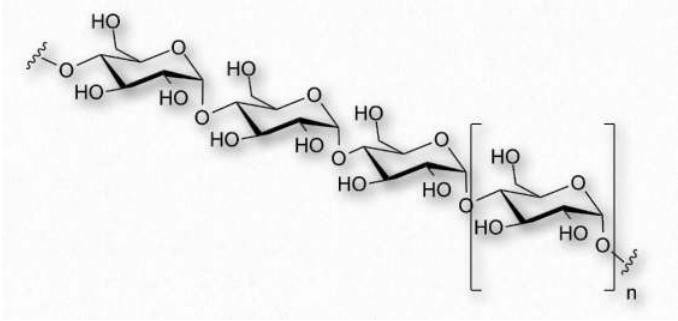


Figure 2.189). Along with the proteoglycan called lubricin, hyaluronic acid turns water into lubricating material. Hyaluronic acid is present as a coat around each cell of articular cartilage and forms complexes with proteoglycans that absorb water, giving resilience (resistance to compression) to cartilage. Aging causes a decrease in size of hyaluronans, but an increase in concentration.

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12.9: Carbohydrates (Structure and Function)- Questions

Sacramento City College
CHEM 309: General, Organic and Biochemistry
Prof. Dianne Bennett

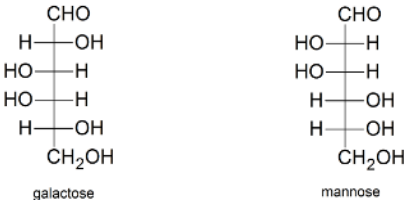
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ALL questions listed must be answered to earn credit for completing the text homework. Yes, even the Additional Exercises if applicable.

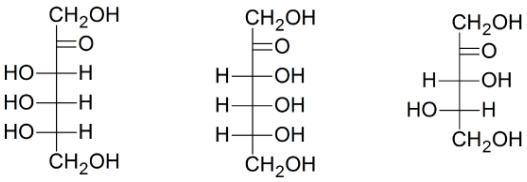
Carbohydrate Structure

(01) Study the following Fischer projections to answer the questions below.



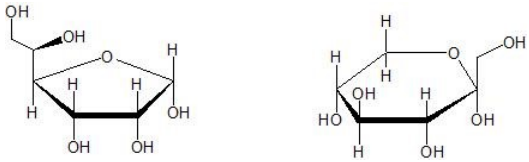
a. Is galactose a D-sugar or an L-sugar?
b. Is mannose a D-sugar or an L-sugar?
c. Choose either one, and sketch it as it would appear if it was an L-sugar.
d. Are these two carbohydrates enantiomers? If not, in how many places do they differ?
e. What is the term to describe the relationship between galactose and mannose?

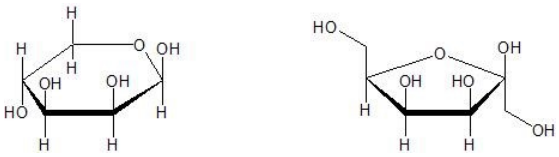
(02) Are any of the following carbohydrates L-sugars? What makes something an L-sugar as opposed to a D-sugar? Rewrite each structure into an L-sugar if they are not already in that conformation.



(03) Which carbon is considered the anomeric carbon? How do you distinguish between the alpha and beta types of anomers?

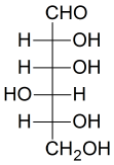
(04) Study these Haworth projections to answer the following for each of them.





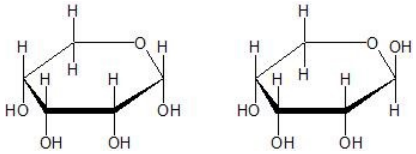
a. Is it a furanose or a pyranose?
b. Is it an alpha or beta anomer?
c. Circle the anomeric carbon.

(05) Examine the structure of this Fischer projection of D-gulose.



a. Number each carbon from 1 to 6. What number is the anomeric carbon?
b. Circle the –OH group that determines whether it is a D- or L-sugar.
c. Sketch the structure of L-gulose for comparison. Are the two versions of gulose enantiomers of one another or diastereomers?
d. Now sketch the structure of D-glucose for comparison. Are D-gulose and D-glucose enantiomers or diastereomers?

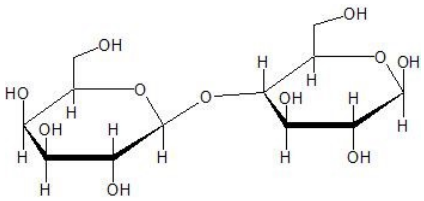
(06) Examine the following Haworth projections to answer the questions below.



a. Circle each anomeric carbon
b. Which of the two is the alpha anomer and which is the beta anomer?
c. Are these structures considered enantiomers or diastereomers?
d. Are these monosaccharides reducing sugars? Explain.
e. Can you convert the alpha anomer to a beta anomer? Explain.

(07) Consult your text and notes for the structure of lactose. Lactose utilizes a beta-1,4 linkage to form a disaccharide. Sketch a hypothetical disaccharide where it instead links the two monosaccharides that form lactose via an alpha-1,6 formation.

(08) Some people cannot digest the disaccharide lactose. The term for this is known as lactose intolerance. Lactose is shown below. Answer the following questions.



a. What is the name of the enzyme that would be required for someone to be able to digest lactose?
b. Classify lactose as a mono-, di-, oligo-, or polysaccharide.

c. Label anomeric carbons by circling them. Is lactose a reducing sugar?
d. Draw an arrow pointing to the glycosidic bond. Is the glycosidic bond connected to both anomeric carbons?
e. Classify the glycosidic bonds using the alpha or beta-(#,#) format.
f. If the glycosidic bond is hydrolyzed, what are the names of the monosaccharides produced. Remember to include the alpha or beta classification for the anomeric carbon.

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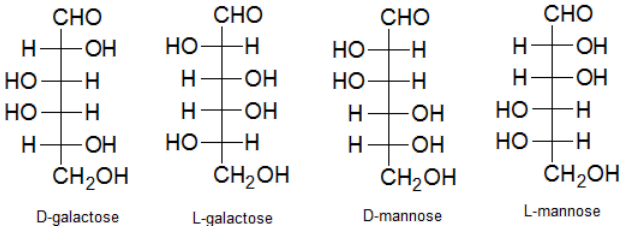
12.10: Homework Solutions

Sacramento City College
CHEM 309: General, Organic and Biochemistry
Prof. Dianne Bennett

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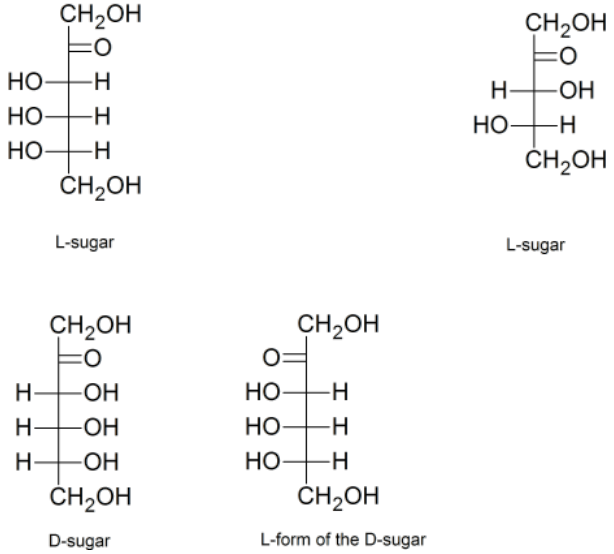
Carbohydrate Structure

(01)



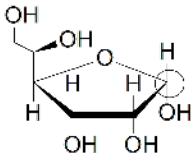
a. D-sugar
b. D-sugar
c. See strucutres above
d. No, they differ at C-2 and C-4.
e. Diastereomers

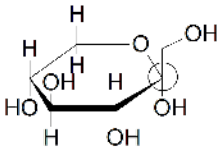
(02) The D- or L- classification is determined by the orientation of the hydroxyl group on the chiral carbon furthest from the carbonyl carbon. If this hydroxyl group is positioned on the right, then the sugar is a D-sugar. If this hydroxyl group is positioned on the left, then the sugar is an L-sugar.

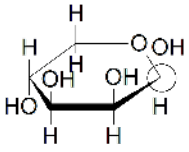


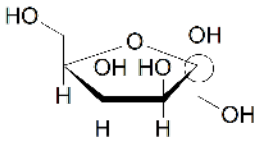
(03) The anomeric carbon is the carbon with two single bonds to two different oxygen atoms. For the alpha anomer, the hydroxyl group on the anomeric carbon points down. For the beta anomer, the hydroxyl group on the anomeric carbon points up.

(04)

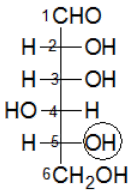

alpha-furanose

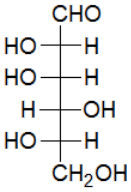

alpha-pyranose

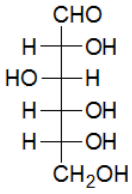

beta-pyranose


beta-furanose

(05)

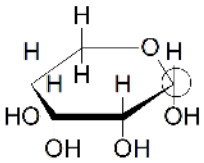

D-gulose

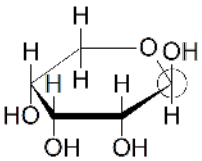

L-gulose


D-glucose

a. See above
b. See above
c. See above; enantiomers
d. See above; diastereomers

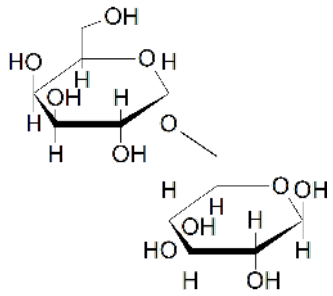
(06)


alpha

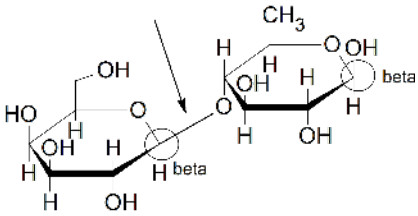

beta

a. See above
b. See above
c. diastereomers - only one chiral carbon is the mirror image
d. Yes, because the ring can open for the sugar to oxidize.
e. Yes, because the ring of the sugar is constantly opening and closing and the trigonal planar molecular shape of the carbonyl carbon allows both anomers to form.

(07)



(08)



a. lactase
b. disaccharide.
c. see above; yes lactose is a reducing sugar
d. See above; No, the glycosidic bond is connected to the anomeric carbon of the sugar on the left (galactose), but it is bonded to a hydroxyl group on C-4 of the sugar on the right (glucose).
e. beta-(1,4)
f. beta-D-galactose and beta-D-glucose

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12.11: Carbohydrates Summary

The last class of macromolecules we will consider structurally here is the carbohydrates. Built of sugars or modified sugars, carbohydrates have several important functions, including structural integrity, cellular identification, and energy storage.

Monosaccharides

Simple sugars, also known as monosaccharides, can generally be written in the form $C_x(H_2O)_x$. It is for this reason they are referred to as carbo-hydrates. By convention, the letters 'ose' at the end of a biochemical name flags a molecule as a sugar. Thus, there are glucose, galactose, sucrose, and many other '-oses'. Other descriptive nomenclature involves use of a prefix that tells how many carbons the sugar contains. For example, glucose, which contains six carbons, is described as a hexose. The following list shows the prefixes for numbers of carbons in a sugar:

- Tri- = 3
- Tetr- = 4
- Pent- = 5
- Hex- =6
- Hept- = 7
- Oct- = 8

Other prefixes identify whether the sugar contains an aldehyde group (aldo-) or a ketone (keto) group. Prefixes may be combined. Glucose, which contains an aldehyde group, can be described as an aldo-hexose. The list that follows gives some common sugars and some descriptors.

- Ribose = aldo-pentose
- Glucose = aldo-hexose
- Galactose = aldo-hexose
- Mannose = aldo-hexose
- Glyceraldehyde = aldo-triose
- Erythrose – aldo-tetrose
- Fructose = keto-hexose
- Ribulose = keto-pentose
- Sedoheptulose = keto-heptose
- Dihydroxyacetone = keto-triose

Stereoisomer Nomenclature

Sugars of a given category (hexoses, for example) differ from each other in the stereoisomeric configuration of their carbons. Two sugars having the same number of carbons (hexoses, for example) and the same chemical form (aldoses, for example), but differing in the stereoisomeric configuration of their carbons are called diastereomers. Biochemists use D and L nomenclature to describe sugars, as explained below.

D-sugars predominate in nature, though L-forms of some sugars, such as fucose, do exist. The D and L designation is a bit more complicated than it would appear on the surface. To determine if a sugar is a D-sugar or an L-sugar, one simply examines the configuration of the highest numbered asymmetric carbon. If the hydroxyl is written to the right, it is a D-sugar. If the hydroxyl is on the left, it is an L-sugar. That part is simple. The confusion about D and L arises because L sugars of a given name (glucose, for example) are mirror images of D sugars of the same name. The figure on the previous page shows the structure of D- and L-glucose. Notice that D-glucose is not converted into L-glucose simply by .ipping the configuration of the fifth carbon in the molecule. There is another name for sugars that are mirror images of each other. They are called enantiomers. Thus, L-glucose and D-glucose are enantiomers, but D-Erythrose and D-Threose are diastereomers.

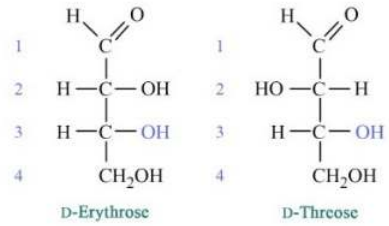


Figure 12.11.1: *Diastereomers.*

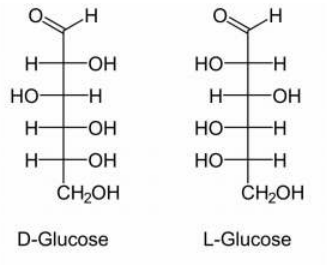


Figure 12.11.2: *Enantiomers.*

Sugars of 5-7 carbons can fairly easily form ring structures (called Haworth structures). For aldoses like glucose, this involves formation of a hemi-acetal. For ketoses like fructose, it involves formation of a hemi-ketal. The bottom line for both is that the oxygen that was part of the aldehyde or the ketone group is the one that becomes a part of the ring. More important than the oxygen, though, is the fact that the carbon attached to it (carbon #1 in aldoses or #2 in ketoses) becomes asymmetric as a byproduct of the cyclization. This new asymmetric carbon is called the anomeric carbon and it has two possible configurations, called alpha and beta.

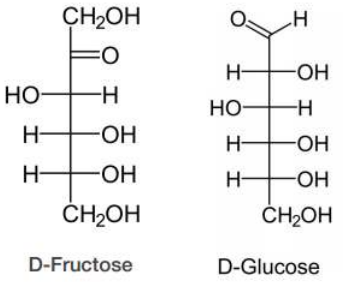


Figure 12.11.3: *Ketose and Aldose.*

A solution of glucose will contain a mixture of alpha and beta forms. Whether the alpha or the beta arises upon cyclization is partly determined by geometry and partly random. Thus, one can find a bias for one form, but usually not that form exclusively. A given molecule of sugar will flip between alpha and beta over time. A requirement for this is that the hydroxyl on the anomeric carbon is unaltered, thus facilitating flipping back to the straight chain form followed by recyclization. If the hydroxyl becomes chemically altered in any way (for example, replacement of its hydrogen by a methyl group), a glycoside is formed. Glycosides are locked in the same alpha or beta configuration they were in when the modification was made. Glycosides are commonly found in nature. Sucrose, for example , is a di-glycoside – both the glucose and the fructose have had their anomeric hydroxyls altered by being joined together.

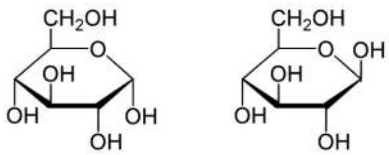


Figure 12.11.4: *alpha-D Glucose (left) and beta-D Glucose (right)*

The last considerations for sugars relative to their structure are their chemical reactivity and modification. The aldehyde group of aldoses is susceptible to oxidation, whereas ketoses are less so. Sugars that are readily oxidized are called ‘ reducing sugars ’ because their oxidation causes other reacting molecules to be reduced. Reducing sugars can easily be identified in a chemical test. Chemical modification of sugars occurs readily in cells. As we will see, phosphorylation of sugars occurs routinely during metabolism. Oxidation of sugars to create carboxyl groups also can occur. Reduction of aldehyde/ketone groups of sugars creates what are called sugar alcohols, and other modifications, such as addition of sulfates and amines also readily occur.

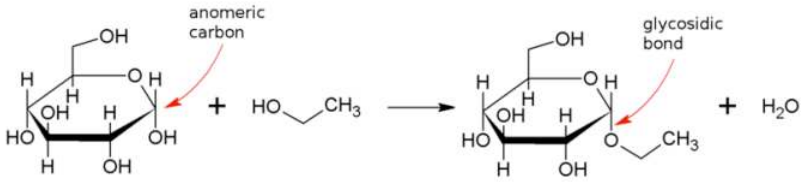


Figure **12.11.5**: *Glycoside formation*

Disaccharides

Sugars are readily joined together (and broken apart) in cells. Sucrose (Figure **12.11.7**), which is common table sugar, is made by joining the anomeric hydroxyl of alpha-D-glucose to the anomeric hydroxyl of beta-D-fructose. Not all disaccharides join the anomeric hydroxyls of both sugars. For example, lactose (milk sugar) is made by linking the anomeric hydroxyl of galactose in the beta configuration to the hydroxyl of carbon #4 of glucose.

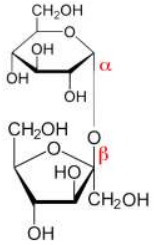


Figure **12.11.7**: *Sucrose*

Polysaccharides

Polysaccharides, as their name implies, are made by joining together many sugars. The functions for polysaccharides are varied. They include energy storage, structural strength, and lubrication. Polysaccharides involved in energy storage include the plant polysaccharides, amylose and amylopectin. The polysaccharide involved in energy storage in animals is called glycogen and it is mostly found in the muscles and liver.

Amylose/Amylopectin

Amylose is the simplest of the polysaccharides, being comprised solely of glucose units joined in an alpha 1-4 linkage. Amylose is broken down by the enzyme alpha-amylase, found in saliva. Amylopectin is related to amylose in being composed only of glucose, but it differs in how the glucose units are joined together. Alpha 1-4 linkages predominate, but every 30-50 residues, a ‘branch’ arises from an alpha 1-6 linkage. Branches make the structure of amylopectin more complex than that of amylose.

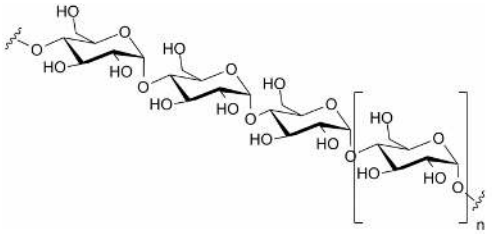


Figure **12.11.9**: Amylose.

Glycogen

Glycogen is a polysaccharide that is physically related to amylopectin in being built only of glucose and in having a mix of alpha 1-4 and alpha 1-6 bonds. Glycogen, however, has many more alpha 1-6 branches than amylopectin, with such bonds occurring about every 10 residues. One might wonder why such branching occurs more abundantly in animals than in plants. A plausible explanation is based on the method by which these molecules are broken down. The breakdown of these polysaccharides is catalyzed by enzymes, known as phosphorylases, that clip glucose residues from the ends of glycogen chains and attach a phosphate to them in the process, producing glucose-1-phosphate. More highly branched polysaccharides have more ends to clip, and this translates to more glucose-1-phosphates that can be removed simultaneously by numerous phosphorylases. Since glucose is used for energy by muscles, glucose concentrations can be increased faster the more branched the glycogen is. Plants, which are immobile do not have needs for such immediate release of glucose and thus have less need for highly branched polysaccharides.

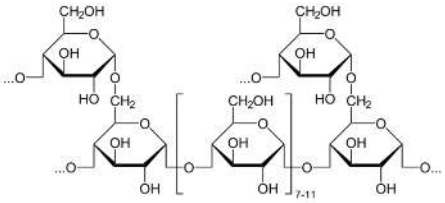


Figure **12.11.10**: *Glycogen Structure*

Cellulose

Another important polysaccharide containing only glucose is cellulose. It is a polymer of glucose used to give plant cell walls structural integrity and has the individual units joined solely in a beta 1-4 configuration. That simple structural change makes a radical diff erence in its digestibility. Humans are unable to break down cellulose and it passes through the digestive system as roughage. Ruminant animals, such as cattle, however have bacteria in their rumens that contain the enzyme cellulase. It breaks the beta 1-4 links of the glucoses in cellulose to release the sugars for energy.

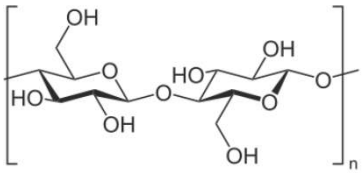


Figure **12.11.11**: *The repeating structure of cellulose.*

Another polysaccharide used for structural integrity is known as chitin. Chitin makes up the exoskeleton of insects and is a polymer of a modified form of glucose known as N-acetyl-glucosamine.

Glycosaminoglycans

Yet another category of polysaccharides are the glycosaminoglycans (also called mucopolysaccharides), some examples of which include keratan sulfate, heparin, hyaluronic acid (right), and chondroitin sulfate. The polysaccharide compounds are linked to proteins, but differ from glycoproteins in having a much larger contingent of sugar residues and, further, the sugars are considerably more chemically modified. Each of them contains a repeating unit of a disaccharide that contains at least one negatively charged residue. The result is a polyanionic substance that, in its interactions with water, makes for a “slimy" feel. Glycosaminoglycans are found in snot, and in synovial fluid, which lubricates joints. Heparin is a glycosaminoglycan that helps to prevent blood from clotting.

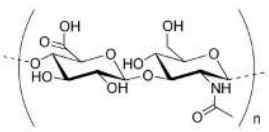


Figure **12.11.12**: *The repeating unit of a glycosaminoglycan structure.*

Contributors

- Template:ContribAhern

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12.S: Carbohydrates (Short 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.

Carbohydrates, a large group of biological compounds containing carbon, hydrogen, and oxygen atoms, include sugars, starch, glycogen, and cellulose. All carbohydrates contain alcohol functional groups, and either an aldehyde or a ketone group (or a functional group that can be converted to an aldehyde or ketone). The simplest carbohydrates are **monosaccharides**. Those with two monosaccharide units are **disaccharides**, and those with many monosaccharide units are **polysaccharides**. Most sugars are either monosaccharides or disaccharides. Cellulose, glycogen, and starch are polysaccharides.

Many carbohydrates exist as **stereoisomers**, in which the three-dimensional spatial arrangement of the atoms in space is the only difference between the isomers. These particular stereoisomers contain at least one **chiral carbon**, a carbon atom that has four different groups bonded to it. A molecule containing a chiral carbon is nonsuperimposable on its mirror image, and two molecules that are nonsuperimposable mirror images of each other are a special type of stereoisomer called **enantiomers**. Enantiomers have the same physical properties, such as melting point, but differ in the direction they rotate polarized light.

A sugar is designated as being a D sugar or an L sugar according to how, in a Fischer projection of the molecule, the hydrogen atom and OH group are attached to the *penultimate* carbon atom, which is the carbon atom immediately before the terminal alcohol carbon atom. If the structure at this carbon atom is the same as that of D-glyceraldehyde (OH to the right), the sugar is a **D sugar**; if the configuration is the same as that of L-glyceraldehyde (OH to the left), the sugar is an **L sugar**.

Monosaccharides of five or more carbons atoms readily form cyclic structures when the carbonyl carbon atom reacts with an OH group on a carbon atom three or four carbon atoms distant. Consequently, glucose in solution exists as an equilibrium mixture of three forms, two of them cyclic (α- and β-) and one open chain. In Haworth projections, the *alpha* form is drawn with the OH group on the "former" carbonyl carbon atom (**anomeric carbon**) pointing downward; the *beta* form, with the OH group pointing upward; these two compounds are stereoisomers and are given the more specific term of **anomers**. Any solid sugar can be all alpha or all beta. Once the sample is dissolved in water, however, the ring opens up into the open-chain structure and then closes to form either the α- or the β-anomer. These interconversions occur back and forth until a dynamic equilibrium mixture is achieved in a process called **mutarotation**.

The carbonyl group present in monosaccharides is easily oxidized by Tollens' or Benedict's reagents (as well as others). Any mono- or disaccharide containing a free anomeric carbon is a **reducing sugar**. The disaccharide *maltose* contains two glucose units joined in an α-1,4-glycosidic linkage. The disaccharide *lactose* contains a galactose unit and a glucose unit joined by a β-1,4-glycosidic linkage. Both maltose and lactose contain a free anomeric carbon that can convert to an aldehyde functional group, so they are reducing sugars; they also undergo mutarotation. Many adults, and some children, have a deficiency of the enzyme lactase (which is needed to break down lactose) and are said to be **lactose intolerant**. A more serious problem is the genetic disease **galactosemia**, which results from the absence of an enzyme needed to convert galactose to glucose.

The disaccharide *sucrose* (table sugar) consists of a glucose unit and a fructose unit joined by a glycosidic linkage. The linkage is designated as an α-1,β-2-glycosidic linkage because it involves the OH group on the first carbon atom of glucose and the OH group on the second carbon atom of fructose. Sucrose is not a reducing sugar because it has no anomeric carbon that can reform a carbonyl group, and it cannot undergo mutarotation because of the restrictions imposed by this linkage.

Starch, the principal carbohydrate of plants, is composed of the polysaccharides **amylose** (10%–30%) and **amylopectin** (70%–90%). When ingested by humans and other animals, starch is hydrolyzed to glucose and becomes the body's energy source. *Glycogen* is the polysaccharide animals use to store excess carbohydrates from their diets. Similar in structure to amylopectin, glycogen is hydrolyzed to glucose whenever an animal needs energy for a metabolic process. The polysaccharide *cellulose* provides structure for plant cells. It is a linear polymer of glucose units joined by β-1,4-glycosidic linkages. It is indigestible in the human body but digestible by many microorganisms, including microorganisms found in the digestive tracts of many herbivores.

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CHAPTER OVERVIEW

13: Energy

13.1: Basics of Energy

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13.1: Basics of Energy

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Living organisms are made up of cells, and cells contain a horde of biochemical components. Living cells, though, are not random collections of these molecules. They are extraordinarily organized or "ordered". By contrast, in the nonliving world, there is a universal tendency to increasing disorder. Maintaining and creating order in cells takes the input of energy. Without energy, life is not possible.

Oxidative Energy

The primary mechanism used by non-photosynthetic organisms to obtain energy is oxidation and carbon is the most commonly oxidized energy source. The energy released during the oxidative steps is “captured” in ATP and can be used later for energy coupling. The more reduced a carbon atom is, the more energy can be realized from its oxidation. Fatty acids are highly reduced, whereas carbohydrates are moderately so. Complete oxidation of both leads to carbon dioxide, which has the lowest energy state. Conversely, the more oxidized a carbon atom is, the more energy it takes to reduce it.

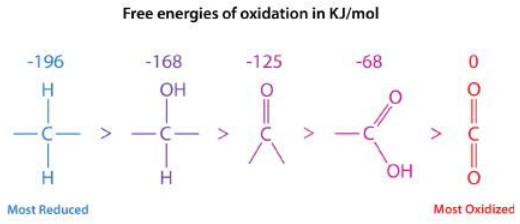


Figure 13.1.1: Five oxidation states of carbon. Image by Pehr Jacobson

In the series shown in Figure 13.1.1, the most reduced form of carbon is on the left. The energy of oxidation of each form is shown above it. The reduction states of fatty acids and carbohydrates can be seen by their formulas.

- Palmitic acid: $C_{16}H_{34}O_2$
- Glucose: $C_6H_{12}O_6$

Palmitic acid only contains two oxygens per sixteen carbons, whereas glucose has six oxygen atoms per six carbons. Consequently, when palmitic acid is fully oxidized, it generates more ATP per carbon (128/16) than glucose (38/6). It is because of this that we use fat (contains fatty acids) as our primary energy storage material.

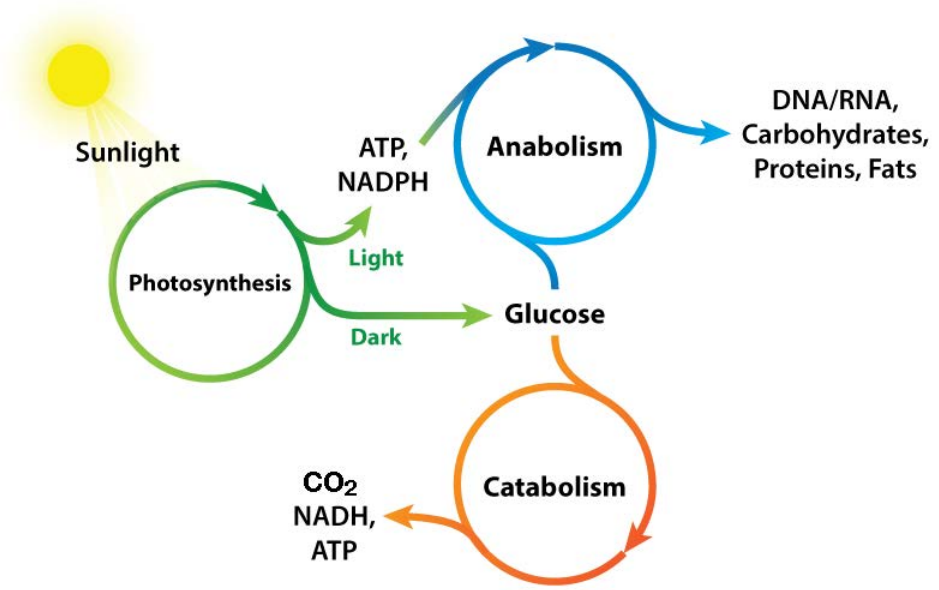


Figure* 13.1.2: Photosynthesis: The primary source of biological energy. Image by Aleia Kim*

Oxidation vs. Reduction in Metabolism

Biochemical processes that break things down from larger to smaller are called *catabolic processes*. Catabolic processes are often oxidative in nature and energy releasing. Some, but not all, of that energy is captured as ATP. If not all of the energy is captured as ATP, what happens to the rest of it? The answer is simple. It is released as heat and it is for this reason we get hot when we exercise.

By contrast, synthesizing large molecules from smaller ones (for example, making proteins from amino acids) is referred to as anabolism. Anabolic processes are often reductive in nature (Figures 5.3 & 5.4) and require energy input. By themselves, they would not occur, as they are reversing oxidation and decreasing entropy (making many small things into a larger one). To overcome this energy barrier, cells must expend energy. For example, if one wishes to reduce CO_2 to carbohydrate, energy must be used to do so. Plants do this during the dark reactions of photosynthesis (Figure **13.1.3**). The energy source for the reduction is ultimately the sun. The electrons for the reduction come from water, and the CO_2 is removed from the atmosphere and gets incorporated into a sugar.

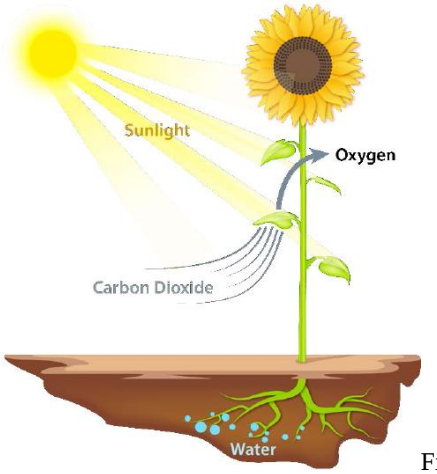
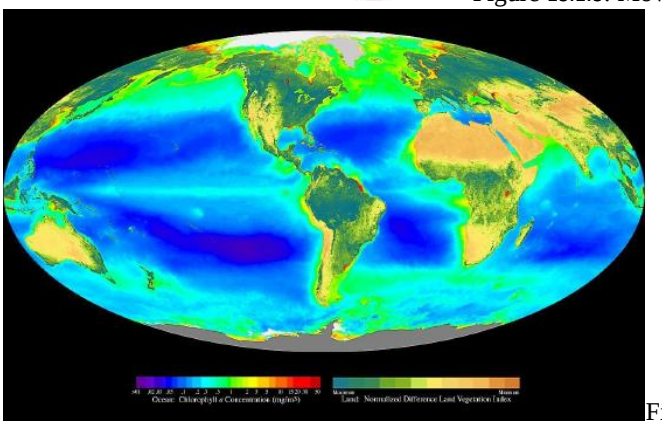


Figure 13.1.3: Movement of biological energy. Image by Aleia Kim


Figure 13.1.4: Photosynthesis as measured by chlorophyll concentration

Energy Coupling

The synthesis of the many molecules needed by cells needs the input of energy to occur. Cells overcome this energy obstacle by using ATP to “drive” the reaction (Figure 13.1.6). The energy needed to drive reactions is harvested in very controlled conditions in enzymes. This involves a process called ‘coupling’. Coupled reactions rely on linking an energetically favorable reaction (i.e., one with a negative ΔG°’) with the reaction requiring an energy input, which has a positive ΔG°’. As long as the overall ΔG°’ of the two reactions together is negative, the reaction can proceed. Hydrolysis of ATP is a very energetically favorable reaction that is commonly linked to many energy requiring reactions in cells. Without the hydrolysis of ATP (or GTP, in some cases), the reaction would not be feasible.

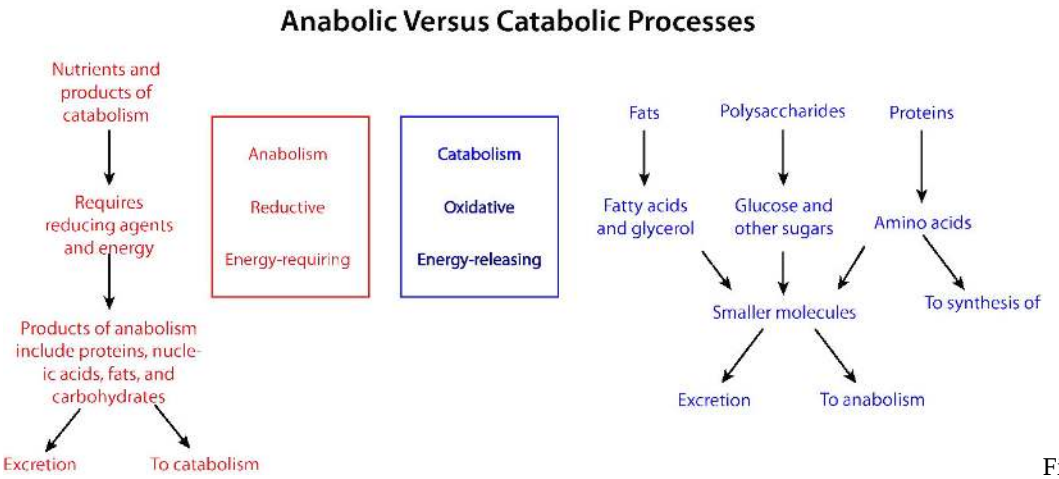


Figure 13.1.5: Synthesis and breakdown pathways in metabolism. Image by Pehr Jacobson

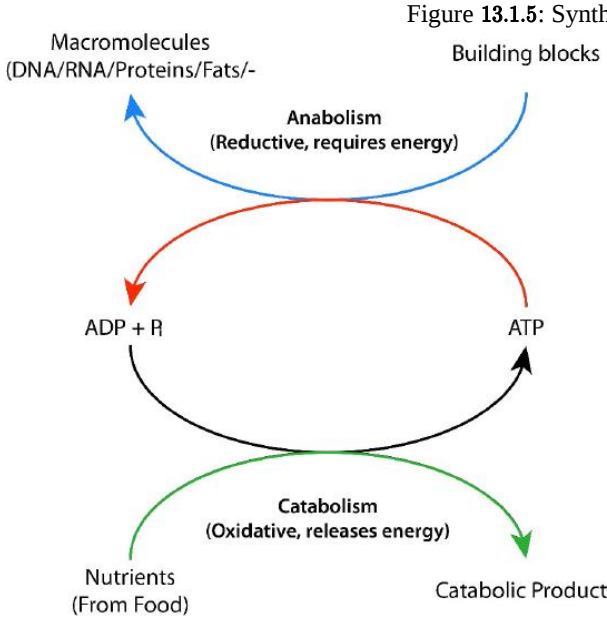


Figure 13.1.6: Cycling of biological energy via ADP and ATP. Image by Pehr Jacobson

Entropy and energy

Most students who have had some chemistry know about the Second Law of Thermodynamics with respect to increasing disorder of a system. Cells are very organized or ordered structures, leading some to mistakenly conclude that life somehow violates the second law. In fact, that notion is incorrect. The second law doesn't say that entropy always increases, just that, left alone, it tends to do so, in an isolated system. Cells are not isolated systems, though, in that they obtain energy, either from the sun, if they are autotrophic, or food, if they are heterotrophic.

To counter the universal tendency towards disorder on a local scale requires energy. As an example, take a fresh deck of cards which is neatly aligned with Ace-King-Queen . . . . 4,3,2 for each suit. Throw the deck into the air, letting the cards scatter. When you pick them up, they will be more disordered than when they started. However, if you spend a few minutes (and expend a bit of energy), you can reorganize the same deck back to its previous, organized state. If entropy always increased everywhere, you could not do this. However, with the input of energy, you overcame the disorder. This illustrates an important concept: the cost of fighting disorder is energy.

Biological energy

There are, of course, other reasons that organisms need energy. Muscular contraction, synthesis of molecules, neurotransmission, signaling, thermoregulation, and subcellular movements are examples. Where does this energy come from? The currencies of energy are generally high-energy phosphate-containing molecules. ATP is the best known and most abundant, but GTP is also an

important energy source (energy source for protein synthesis). CTP is involved in synthesis of glycerophospholipids and UTP is used for synthesis of glycogen and other sugar compounds. In each of these cases, the energy is in the form of potential chemical energy stored in the multi-phosphate bonds. Hydrolyzing those bonds releases the energy in them.

Of the triphosphates, ATP is the primary energy source, acting to facilitate the synthesis of the others by action of the enzyme NDPK. ATP is made by three distinct types of phosphorylation – oxidative phosphorylation (in mitochondria), photophosphorylation (in chloroplasts of plants), and substrate level phosphorylation (in enzymatically catalyzed reactions).

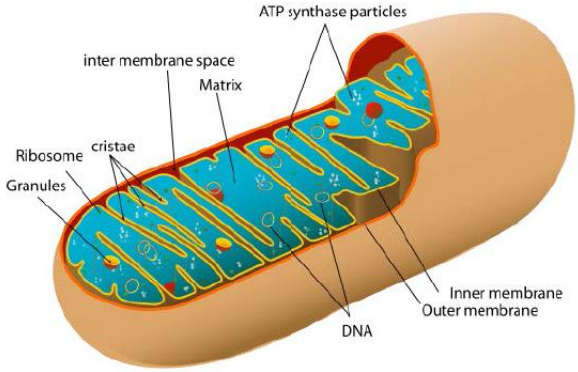


Figure 13.1.7: Mitochondrion

Gibbs free energy in Biology

ATP is generally considered the “storage battery” of cells (See also ‘Molecular Battery Backups for Muscles HERE). In order to understand how energy is captured, we must first understand Gibbs free energy and in doing so, we begin to see the role of energy in determining the directions chemical reactions take.

Gibbs free energy may be thought of as the energy available to do work in a thermodynamic system at constant temperature and pressure. Mathematically, the Gibbs free energy is given as:

$$G = H – TS \tag{13.1.1}$$

where H is the enthalpy, T is the temperature in Kelvin, and S is the entropy. At standard temperature and pressure, every system seeks to achieve a minimum of free energy. Thus, increasing entropy, S, will reduce Gibbs free energy. Similarly, if excess heat is available (reducing the enthalpy, H), the free energy can also be reduced.

Cells must work within the laws of thermodynamics, as noted, so all of their biochemical reactions, too, are ruled by these laws. Now we shall consider energy in the cell. The change in Gibbs free energy (ΔG) for a reaction is crucial, for it, and it alone, determines whether or not a reaction goes forward.

$$\Delta G = \Delta H – T\Delta S. \tag{13.1.2}$$

There are three cases

- ΔG < 0: the reaction proceeds as written
- ΔG = 0: the reaction is at equilibrium
- ΔG > 0: the reaction runs in reverse

For a reaction

$$a\,\mathrm{A} \rightleftharpoons b\,\mathrm{B} \tag{13.1.3}$$

(where ‘a’ and ‘b’ are integers and A and B are molecules) at pH 7, ΔG can be determined by the following equation,

$$\Delta G = \Delta G^{\circ\prime} + RT\ln\left(\frac{[B]^b}{[A]^a}\right) \tag{13.1.4}$$

For multiple substrate reactions, such as

$$a\,\mathrm{A} + c\,\mathrm{C} \rightleftharpoons b\,\mathrm{B} + d\,\mathrm{D} \tag{13.1.5}$$

$$\Delta G = \Delta G^{\circ\prime} + RT \ln\left(\frac{[B]^b[D]^d}{[A]^a[C]^c}\right) \tag{13.1.6}$$

The ΔG°' term is called the change in Standard Gibbs Free energy, which is the change in energy that occurs when all of the products and reactants are at standard conditions and the pH is 7.0. It is a constant for a given reaction.

In simple terms, we can collect all of the terms of the numerator together and call them {Products} and all of the terms of the denominator together and call them {Reactants},

$$\Delta G = \Delta G^{\circ\prime} + RT \ln\left(\frac{\{\text{Products}\}}{\{\text{Reactants}\}}\right) \tag{13.1.7}$$

For most biological systems, the temperature, T, is a constant for a given reaction. Since ΔG°' is also a constant for a given reaction, the ΔG is changed almost exclusively as the ratio of {Products}/{Reactants} changes.

Importance of ΔG°'

If one starts out at standard conditions, where everything except protons is at 1M, the RTln({Products}/{Reactants}) term is zero, so the ΔG°' term equals the ΔG, and the ΔG°' determines the direction the reaction will take (only under those conditions). This is why people say that a negative ΔG°' indicates an energetically favorable reaction, whereas a positive ΔG°' corresponds to an unfavorable one.

Increasing the ratio of {Products}/{Reactants} causes the value of the natural log (ln) term to become more positive (less negative), thus making the value of ΔG more positive. Conversely, as the ratio of {Products}/{Reactants} decreases, the value of the natural log term becomes less positive (more negative), thus making the value of ΔG more negative.

System response to stress

Intuitively, this makes sense and is consistent with Le Chatelier's Principle – a system responds to stress by acting to alleviate the stress. If we examine the ΔG for a reaction in a closed system, we see that it will always move to a value of zero (equilibrium), no matter whether it starts with a positive or negative value.

Another type of free energy available to cells is that generated by electrical potential. For example, mitochondria and chloroplasts partly use Coulombic energy (based on charge) from a proton gradient across their membranes to provide the necessary energy for the synthesis of ATP. Similar energies drive the transmission of nerve signals (sodium and potassium gradients) and the movement of some molecules in secondary active transport processes across membranes (e.g., H+ differential driving the movement of lactose). From the Gibbs free energy change equation,

$$\Delta G = \Delta H – T\Delta S \tag{13.1.8}$$

it should be noted that an increase in entropy will help contribute to a decrease in ΔG. This happens, for example when a large molecule is being broken into smaller pieces or when the rearrangement of a molecule increases the disorder of molecules around it. The latter situation arises in the hydrophobic effect, which helps drive the folding of proteins.

Chemical and electrical potential

It is said that absence makes the heart grow fonder. We won't tackle that philosophical issue here, but we will say that separation provides potential energy that cells can and do harvest. The lipid bilayer of cell and (in eukaryotic cells) organelle membranes provide the necessary barrier for separation.

Impermeable to most ions and polar compounds, biological membranes are essential for processes that generate cellular energy. Consider Figure 5.8. A lipid bilayer separates two solutions with different concentrations of a solute. There is a greater concentration of negative ions in the bottom and a greater concentration of positive ions on the top.

Whenever there is a difference in concentration of molecules across a membrane, there is said to be a concentration gradient across it. A difference in concentration of ions across a membrane also creates a charge (or electrical) gradient. Because there is a difference in both the chemical concentration of the ions and in the charge on the two sides of the membrane, this is described as an electrochemical gradient (Figures 5.8 -5.10).

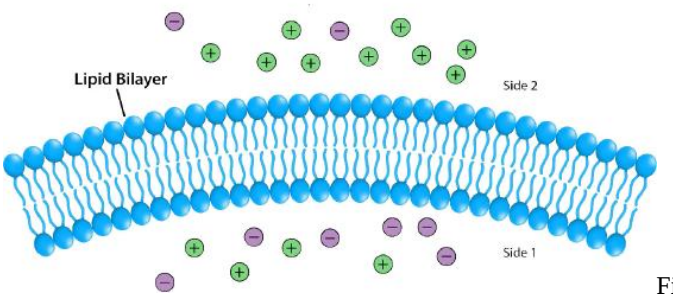


Figure 5.8: Differences in ion concentration across a membrane give rise to chemical and electrical gradients. Image by Pehr Jacobson

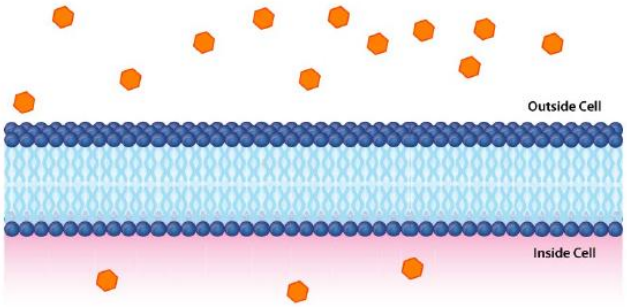


Figure **13.1.9**: A chemical gradient. Image by Aleia Kim

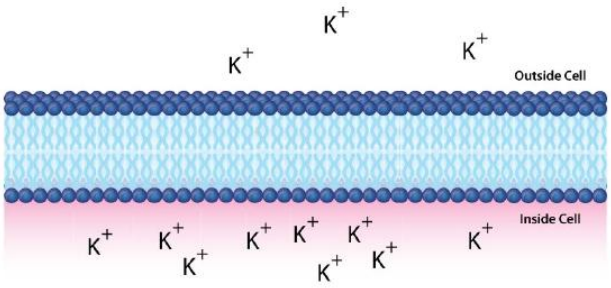


Figure **13.1.10**: An electrochemical gradient of potassium ions. Image by Aleia Kim

Potential energy

Such gradients function like batteries and contain potential energy. When the potential energy is harvested by cells, they can create ATP, transmit nerve signals, pump molecules across membranes, and more. It is important, therefore, to understand how to calculate the potential energy of electrochemical gradients.

First, we consider chemical (solute) gradients. In Figure 5.9, two concentrations of glucose are separated by a lipid bilayer. Let's assume C2 be the concentration of glucose inside the cell (bottom) and C1 be the glucose concentration outside (top). The Gibbs free energy associated with moving glucose in the direction of C2 (into the cell) is given by

ΔG = RTln[C2/C1]

To move it in the direction of C1 (to the outside of the cell) the expression would be

$$\Delta G = RT \ln[C_1/C_2] \tag{13.1.9}$$

Since C2 is smaller than C1 (i.e., there are fewer glucose molecules inside the cell) then the ΔG is negative and diffusion would be favored into the cell, if the glucose could traverse the bilayer.

Conversely, if C2 was greater than C1 (more glucose was in the cell than outside) the ΔG would be positive, so movement in the direction of C2 would not be favored and instead the glucose would tend to move towards C1 , that is, out of the cell.

If C2 = C1, with the same concentration of glucose inside and outside, then the ΔG would be zero and there would be no net movement, as the system would be at equilibrium.

In the example above, we considered glucose, which is an uncharged molecule. When ions are involved, their charges must also be taken into consideration. Figure 13.1.10 depicts a similar situation across a lipid bilayer. In this case, a difference of concentration and charge exists. There are more positive charges inside the cell than outside.

Using C2 to indicate the concentration of materials inside the cell and C1 for the concentration outside the cell (as before), then the free energy for movement of an ion from top to bottom is given by the following equation

$$\Delta G = RT \ln[C_2/C_1] + ZF\Delta\psi \tag{13.1.10}$$

Note here that this equation must take into consideration both the concentration differences and the charge differences. Z refers to the charge of the transported species, F is the Faraday constant (96,485 Coulombs/mol), and Δψ is the electrical potential difference (voltage difference) across the membrane.

If we were to calculate the ΔG for movement of the potassium ion from top to bottom, it would be positive, since [C2/C1] is greater than 1 (making for a positive ln term), and the ZFΔψ is positive because positively charged ions (Z) are moving against a positive charge gradient given by Δψ (greater concentration at the target (bottom) than the starting point (top)). If we were to calculate the concentration of ions moving from bottom to top, then the ln term would be negative (C2<C1) and the ZFΔψ would be negative as well (Z=positive, but Δψ negative).

Reduction Potential

In discussing chemical potential, we must also consider reduction potential. Reduction potential measures the tendency of a chemical to be reduced by electrons. It is also designated by several other names/variables. These include redox potential, oxidation/reduction potential, ORP, pE, ε, E, and Eh.

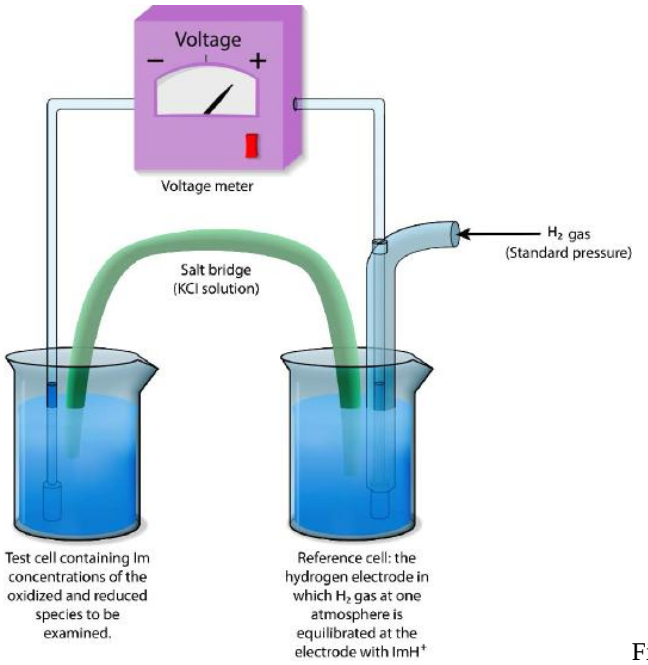


Figure 13.1.11: Reference electrode for measuring reduction potentials. Image by Pehr Jacobson

Reduction potential is measured in volts, or millivolts. A substance with a higher reduction potential will have a greater tendency to accept electrons and be reduced. If two substances are mixed in an aqueous solution, the one with the greater (more positive) reduction potential will tend to take electrons away, thus being reduced, from the one with the lower reduction potential, which becomes oxidized.

Relative measures

Absolute reduction potentials are difficult to measure, so reduction potentials are typically defined relative to a reference electrode. In aqueous solutions, reduction potentials are measured as the potential difference between an inert sensing electrode (typically

platinum) in contact with the test solution and a stable reference electrode (measured as a Standard Hydrogen Electrode: SHE) as shown in Figure **13.1.1**1. The standard of reference for measurement is the half-reaction

$$H^+ + e^- \rightarrow \frac{1}{2} H_2$$

The electrode where this reaction occurs (referred to as a half-cell) is given the value of E° (Standard Reduction Potential) of 0.00 volts. The hydrogen electrode is connected via an external circuit to another half cell containing a mixture of the reduced and oxidized species of another molecule (for example, Fe^{++} and Fe^{+++}) at 1M each and standard conditions of temperature (25°C) and pressure (1 atmosphere).

Direction and voltage measured

The direction and magnitude of electron movement is then measured. If the test mixture takes electrons from the hydrogen electrode, the sign of the voltage is positive and if the direction is reversed, the voltage is negative.

Thus, compounds which have greater affinity for electrons than hydrogen will register a positive voltage and negative voltages correspond to compounds with lesser affinity for electrons than hydrogen.

Movement of electrons

Under standard conditions, electrons will move from compounds generating lower voltages to ones generating higher (more positive) voltages. Just as the standard Gibbs free energy change is the Gibbs free energy change under standard conditions, so, too, is the standard reduction potential E° the reduction potential E under standard conditions.

The actual reduction potential of a half cell will vary with the concentration of each chemical species in the cell. The relationship between the reduction potential E and the standard reduction potential E° is given by the following equation (also called the Nernst equation)

$$E = E^\circ + (RT/nF)*\ln\left(\frac{[\text{reduced molecule}]}{[\text{oxidized molecule}]}\right)$$

where F is the Faraday constant (96,480 J/(Volts*moles), R is the gas constant (8.315 J/(moles*K), n is the number of moles of electrons being transferred, and T is the absolute temperature in Kelvin.

At 25°C, this equation becomes

$$E = E^\circ + (0.026V/n)*\ln\left(\frac{[\text{reduced molecule}]}{[\text{oxidized molecule}]}\right)$$

As for Gibbs free energy, it is useful to measure values at conditions found in cells. This means doing measurements at pH = 7, which differs from having all species at 1M.

Adjustment

Because of this adjustment, a slightly different standard reduction potential is defined and we designate it by E°', just as we defined a special standard Gibbs free energy change at pH 7 as ΔG°'.

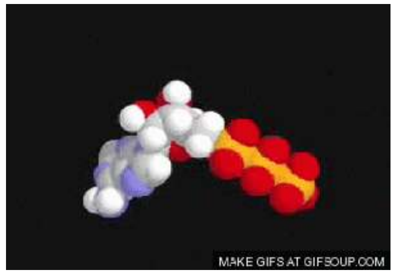
There is a relationship between the change in Gibbs free energy ΔG and the change in reduction potential (ΔE). It is

$$\Delta G = -nF\Delta E \tag{13.1.11}$$

Similarly, the relation between the change in standard Gibbs free energy and the change in standard reduction potential is

\]ΔG°' = -nFΔE°'\]

Energy Storage in Triphosphates



Movie 5.1: ATP: The fuel of the cell

Formation of triphosphates, like ATP, is essential to meeting the cell's energy needs for synthesis, motion, and signaling. In a given day, an average human body makes and breaks down more than its weight in triphosphates. This is especially remarkable considering that there is only about 250 g of the molecule present in the body at any given time. Energy in ATP is released by hydrolysis of a phosphate from the molecule.

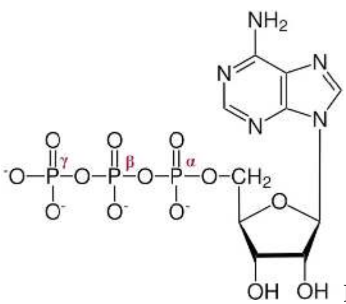


Figure 13.1.12 ATP showing α, β and γ phosphates

The three phosphates, starting with the one closest to the sugar are referred to as α, β, and γ (Figure 13.1.12). It is the γ phosphate that is cleaved in hydrolysis and the product is ADP. In a few reactions, the bond between the α and β is cleaved. When this happens, a pyrophosphate (β linked to γ) is released and AMP is produced. This latter reaction to produce AMP releases more energy ($\Delta G°'$ = -45.6 kJ/mol) than the first reaction which produces ADP ($\Delta G°'$ = -30.5 kJ/mol).

Since triphosphates are the "currency" that meet immediate needs of the cell, it is important to understand how triphosphates are made. There are three phosphorylation mechanisms – 1) substrate level; 2) oxidative; and 3) photophosphorylation. We consider them here individually.

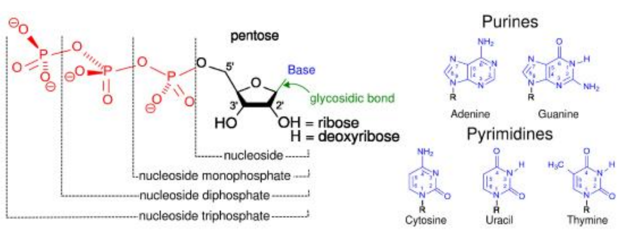


Figure 13.1.13: Nucleotides, nucleosides, and bases

Substrate level phosphorylation

The easiest type of phosphorylation to understand is that which occurs at the substrate level. This type of phosphorylation involves the direct synthesis of ATP from ADP and a high energy intermediate, typically a phosphate-containing molecule. Substrate level phosphorylation is a relatively minor contributor to the total synthesis of triphosphates by cells. An example substrate phosphorylation comes from glycolysis.

$$\text{Phosphoenolpyruvate (PEP)} + \text{ADP} \rightleftharpoons \text{Pyruvate} + \text{ATP}$$

This reaction has a very negative $\Delta G°'$ (-31.4 kJ/mol), indicating that the PEP contains more energy than ATP, thus tending to energetically favor ATP's synthesis. Other triphosphates can be made by substrate level phosphorylation, as well. For example, GTP can be synthesized by the following citric acid cycle reaction.

$$\text{Succinyl-CoA + GDP + Pi } \rightleftharpoons \text{ Succinate + GTP + CoA-SH}$$

Triphosphates can be interchanged readily in substrate level phosphorylations catalyzed by the enzyme Nucleoside Diphosphate Kinase (NDPK). A generalized form of the reactions catalyzed by this enzyme is as follows:

$$\text{XTP + YDP} \rightleftharpoons \text{XDP + YTP}$$

where X = adenosine, cytidine, uridine, thymidine, or guanosine and Y can be any of these as well. Further, XTP and YDP can be any of the deoxynucleotides as well.

Last, an unusual way of synthesizing ATP by substrate level phosphorylation is via the reaction catalyzed by adenylate kinase

$$\text{2 ADP} \rightleftharpoons \text{ATP + AMP}$$

ATP source

This reaction is an important means of generating ATP when the cell doesn't have other sources of energy. Accumulation of AMP resulting from this reaction activates enzymes, such as phosphofructokinase, of glycolysis, which will catalyze reactions to give the cell additional, needed energy.

It is important to note that enzymes cannot make reactions happen that are energetically unfavorable. Enzymes speed reactions, but do not change their direction. Cells are thus bound by the rules of Gibbs free energy. So, how do energetically unfavorable reactions happen in a cell?

Reaction coupling

Reactions that are energetically unfavorable, can be made favorable by coupling them with the hydrolysis of ATP, a very energetically favorable reaction. There are numerous parallels in the "real world." Movement of automobiles is energetically unfavorable, but coupling movement of the automobile to oxidation of gasoline makes an unfavorable process favorable. Another approach to making an unfavorable reaction favorable is to manipulate the concentration of reactants and products. Consider the reaction below, which occurs in pyrimidine nucleotide metabolism:

$$\text{orotate + PRPP} \rightleftharpoons \text{OMP + PP}_\text{i}$$

The ΔG°' for this reaction is -0.8 kJ/mol, meaning that if one starts with equal concentrations of reactants and products, at equilibrium, there will be a small excess of products. In the cell, however, this reaction moves strongly to the right (ΔG = very negative). Given that the ΔG°' is very close to zero, a very negative ΔG can only occur if the concentrations of reactants and products are altered, since

$$\Delta G = \Delta G^{\circ\prime} + RT \ln\left(\frac{[\text{OMP}][\text{PP}_\text{i}]}{[\text{Orotate}][\text{PRPP}]}\right) \tag{13.1.12}$$

Manipulation is exactly what happens here. The key item whose concentration is adjusted in this reaction is the pyrophosphate (PPi). This is possible because cells contain an enzyme called pyrophosphorylase that catalyzes the following reaction

$$\text{PP}_\text{i} + \text{H}_2\text{O} \rightleftharpoons \text{2 P}_\text{i}$$

Hydrolysis of pyrophosphate is very energetically favored, causing the PPi produced in the reaction to be quickly hydrolyzed. As a result, the concentration of PPi in the cell is kept very low. A low concentration of a product (PPi) causes the natural log (ln) term of the orotate equation to become more negative, driving the ΔG term for the overall reaction to become much more negative.

Pushing and pulling

Reactions that yield pyrophosphate as a product are produced in the synthesis of DNA and RNA, as well as many other molecules. As shown in the previous example, this pyrophosphate is rapidly hydrolyzed, causing the overall reaction to move in the direction of pyrophosphate production. When reactants are removed/reduced in a metabolic reaction to decrease the concentration of a product, we say that the reaction is "pulled", to represent the increase in the forward reaction as a result of product depletion.

Pushing happens when reactants in a reaction are added/increased. This too has the effect of reducing the ΔG of a reaction and making it more favorable because the ratio of [Products]/[Reactants] is decreased with increasing [Reactants]. Pushing and pulling

of reactions are additional tools for cells to overcome energy barriers, just like coupling energetically favorable processes to energetically unfavorable ones.

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SECTION OVERVIEW

14.1: 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.

14.1.1: Perspectives

14.1.2: Prelude to Energy Metabolism

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14.1.14: Molecular Backups for Muscles

14.1.E: Energy Metabolism (Exercises)

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14.1.1: Perspectives

We can view metabolism at several levels. At the highest level, we have nutrients, such as sugars, fatty acids and amino acids entering cells and carbon dioxide and other waste products (such as urea) exiting. Cells use the incoming materials for energy and substance to synthesize sugars, nucleotides, and other amino acids as building blocks for the carbohydrates, nucleic acids, fatty compounds, and proteins necessary for life. As we zoom in, we can imagine pathways made up of reactions for breakdown and synthesis of each of these compounds. The figure at left shows such a simple schematic and how the pathways are not isolated from each other – molecular products of one are substrates for another. At a deeper level, we can study individual reactions and discover the enormous complexity and commonality of metabolic reactions.

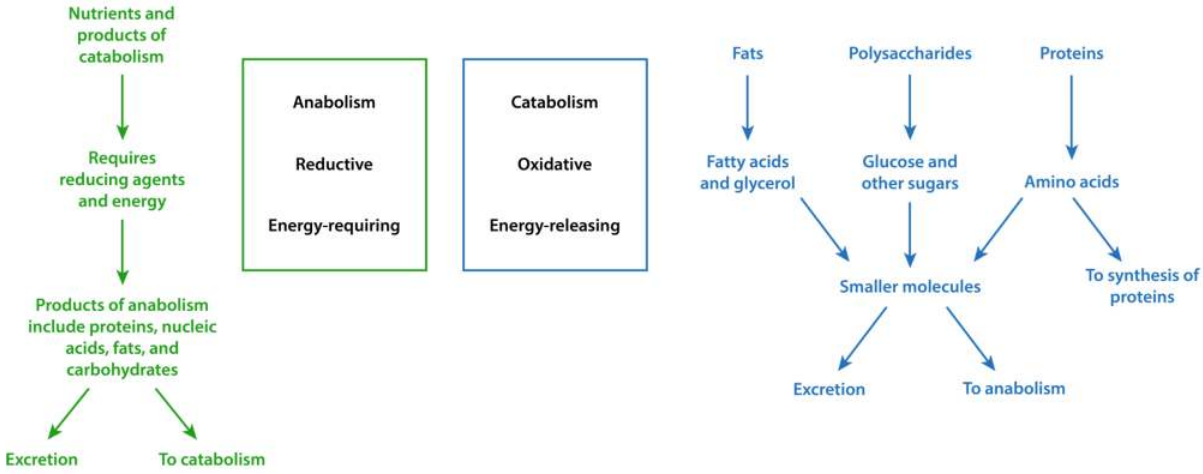


Figure 6.2.1: *Anabolic vs Catabolic Processes*

In studying metabolism, we recognize that metabolic pathways are manmade concepts with artificial boundaries. Students commonly think of the molecules in the pathways being tied exclusively to those individual pathways, but with the exception of reactions that have physical barriers (such as those occurring within an organelle), metabolic pathways have many common intermediates used in multiple reactions occurring in the same location at the same time and thus cannot be ascribed to any one pathway. The best we can do is understand general directions of pathways in cells.

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14.1.2: 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 **14.1.2.1**: 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.

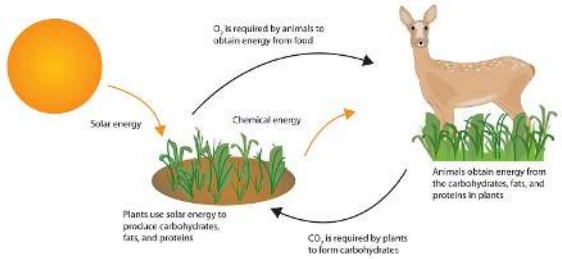


Figure **14.1.2.2**: Some Energy Transformations in Living Systems. Plants and animals exist in a cycle; each requires products of the other.

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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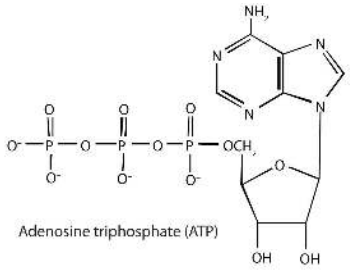
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14.1.3: ATP- the Universal Energy Currency

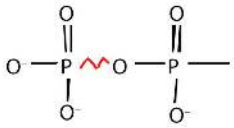
Learning Objectives

- 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).

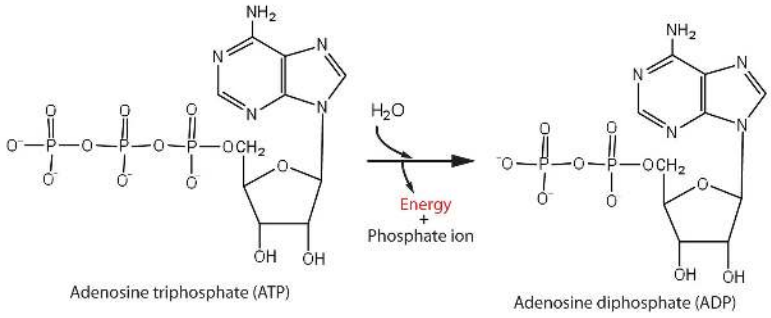


Figure **14.1.3.1**: Hydrolysis of ATP to Form ADP

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:

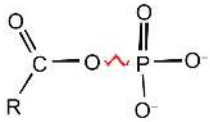
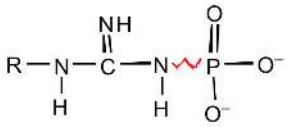
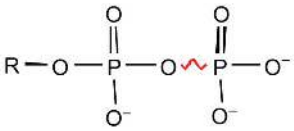
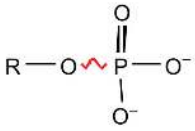
$$ATP + H_2O \rightarrow ADP + P_i + 7.4\ kcal/mol$$

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 **14.1.3.1**. 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 **14.1.3.1**: 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 → 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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14.1.4: 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 **14.1.4.1**). 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.

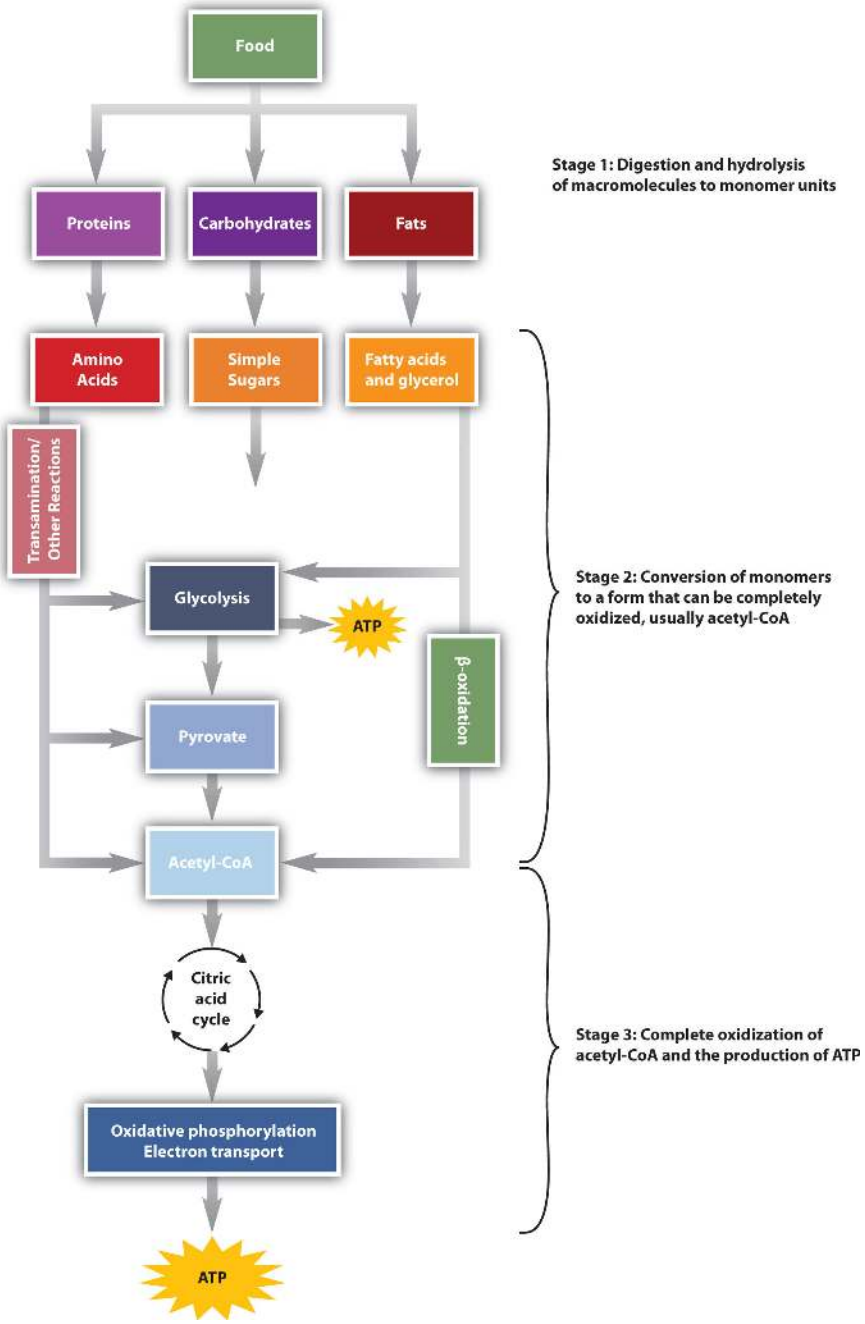


Figure **14.1.4.1**: Energy Conversions

The conversion of food into cellular energy (as ATP) occurs in three stages.

Digestion of Carbohydrates

Carbohydrate digestion begins in the mouth (Figure **14.1.4.2**) 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.

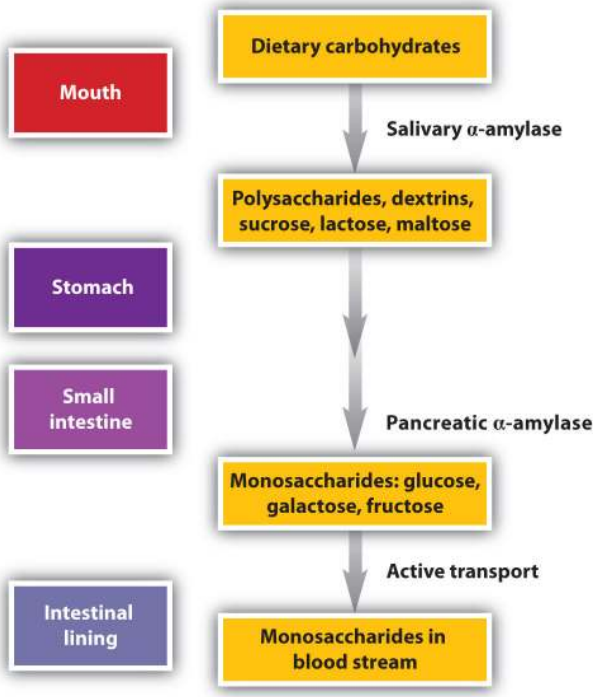


Figure **14.1.4.2**: The Principal Events and Sites of Carbohydrate Digestion

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 **14.1.4.3**), 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.

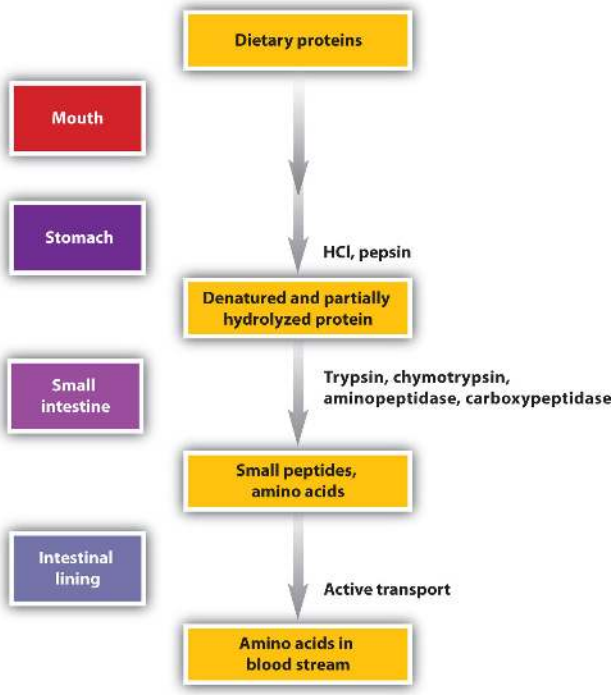


Figure **14.1.4.3**: The Principal Events and Sites of Protein Digestion

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 **14.1.4.4**): 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.

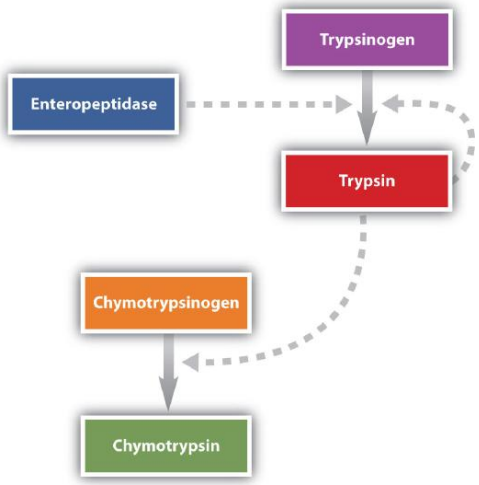


Figure **14.1.4.4**: Activation of Some Pancreatic Enzymes in the Small Intestine

Aminopeptidases in the intestinal juice remove amino acids from the N-terminal end of peptides and proteins possessing a free amino group. Figure **14.1.4.5** 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.

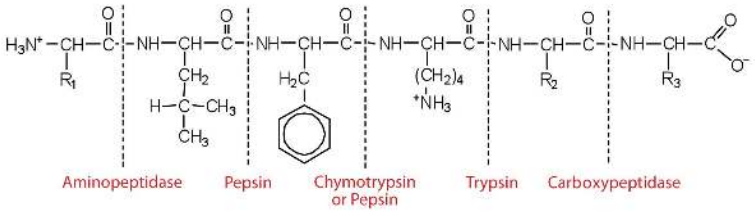


Figure **14.1.4.5**: Hydrolysis of a Peptide by Several Peptidases

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 **14.1.4.6**). 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.

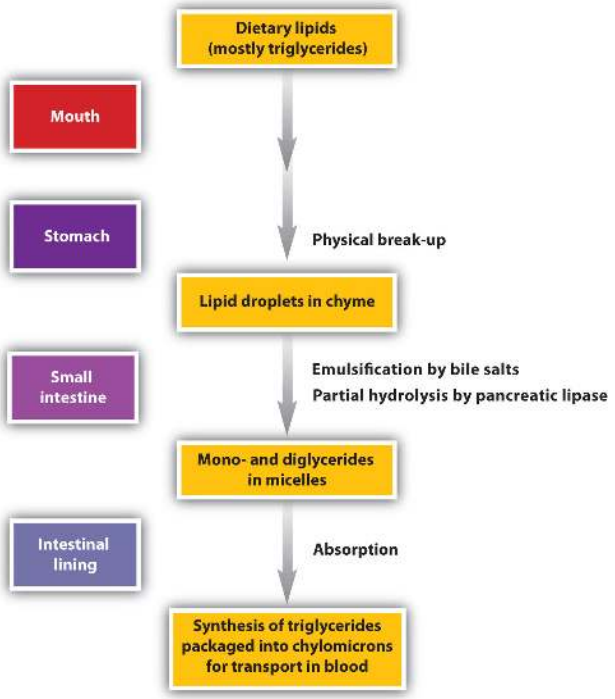
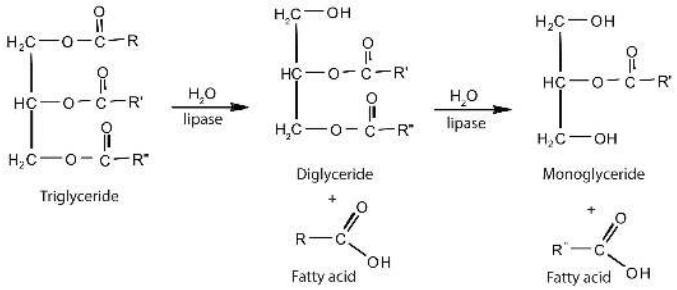


Figure **14.1.4.6**: The Principal Events and Sites of Lipid (Primarily Triglyceride) Digestion

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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14.1.5: 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 **14.1.5.1** and **14.1.5.2**, 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.

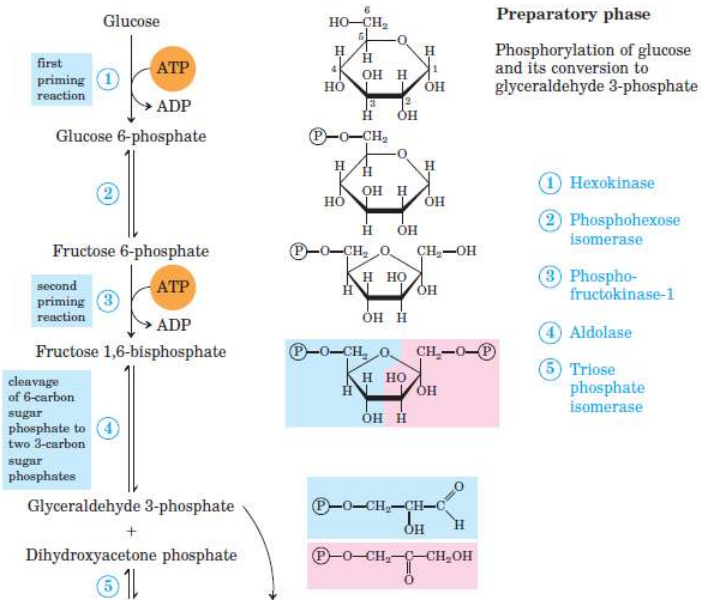


Figure **14.1.5.1**: Phase 1 (preparatory phase) of Glycolysis

- 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.

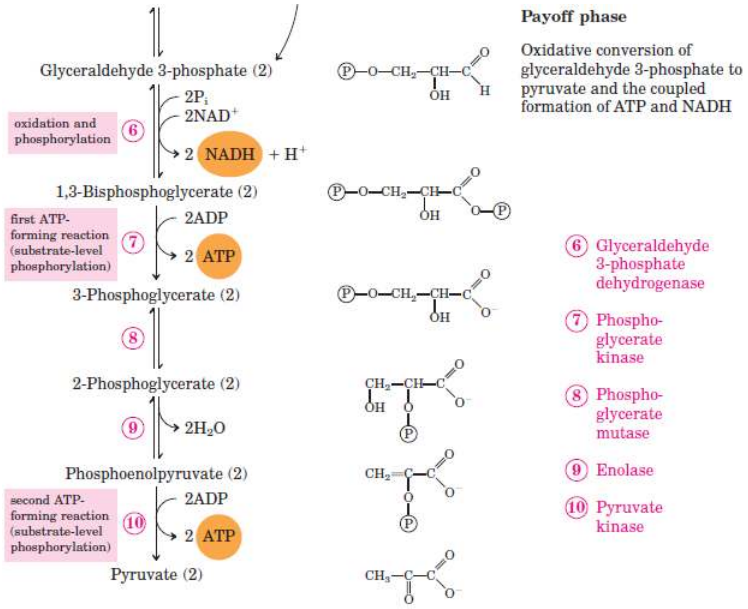


Figure **14.1.5.2**: Phase 2 (payoff phase) of Glycolysis

In the initial step of phase II (Figure **14.1.5.2**), 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 **14.1.5.1**) 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 **14.1.5.1**: 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.

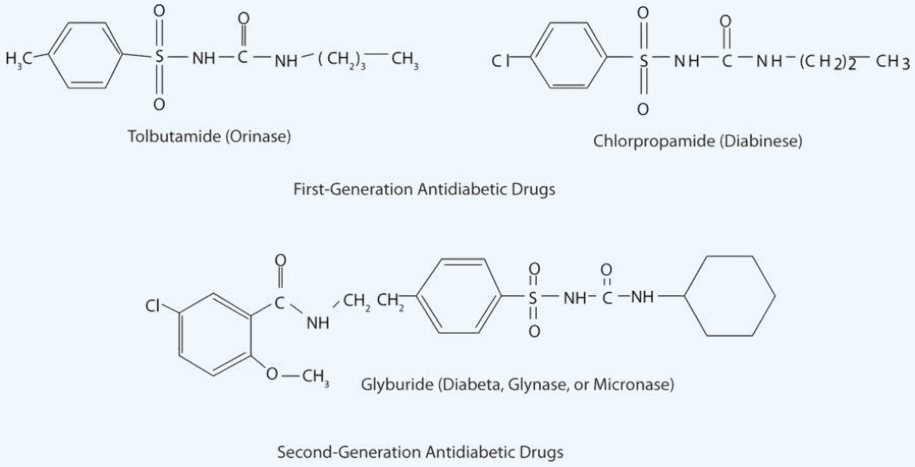
Because a person with diabetes is unable to use glucose properly, excessive quantities accumulate in the blood and the urine. Other characteristic symptoms are constant hunger, weight loss, extreme thirst, and frequent urination because the kidneys excrete large amounts of water in an attempt to remove 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 **14.1.5.2**. The conversion to lactate or ethanol under anaerobic conditions allows for the reoxidation of NADH to NAD^+ in the absence of oxygen.

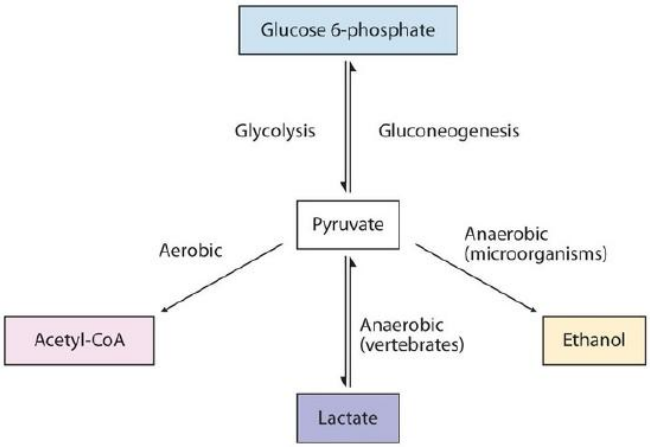


Figure 14.1.5.2: Metabolic Fates of Pyruvate

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 14.1.5.1. 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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14.1.6: Glycolysis

Glycolysis, which literally means “breakdown of sugar," is a catabolic process in which six-carbon sugars (hexoses) are oxidized and broken down into pyruvate molecules. The corresponding anabolic pathway by which glucose is synthesized is termed gluconeogenesis. Both glycolysis and gluconeogenesis are not major oxidative/reductive processes by themselves, with one step in each one involving loss/gain of electrons, but the product of glycolysis, pyruvate, can be completely oxidized to carbon dioxide. Indeed, without production of pyruvate from glucose in glycolysis, a major energy source for the cell is not available. By contrast, gluconeogenesis can synthesize glucose reductively from very simple materials, such as pyruvate and acetyl-CoA/ glyoxylate (at least in plants). For these reasons we include these pathways in the red/ox collection.

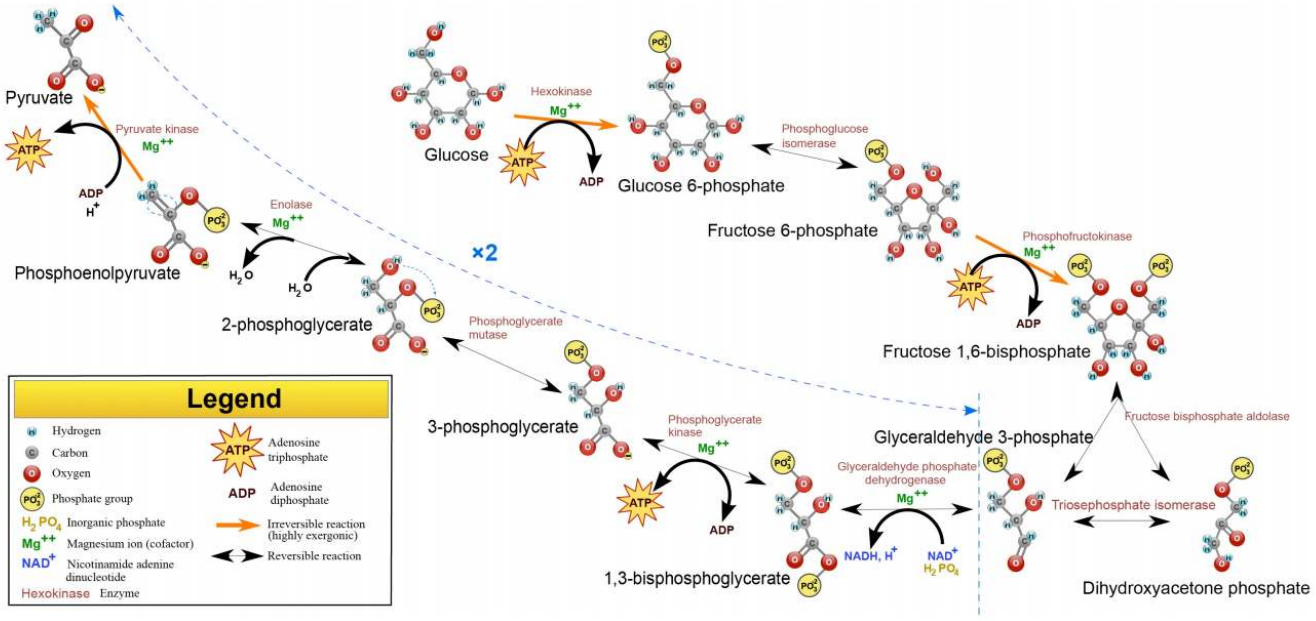


Figure 6.3.1: *The Reactions of Glycolysis*

Glucose is the most abundant hexose in nature and is the one people typically associate with glycolysis, but fructose (in the form of fructose-6-phosphate) is metabolized in the cell and galactose can easily be converted into glucose for catabolism in the pathway as well. The end metabolic products of the pathway are two molecules of ATP, two molecules of NADH and two molecules of pyruvate, which, in turn, can be oxidized further in citric acid cycle.

Intermediates

Glucose and fructose are the sugar ‘funnels’ serving as entry points to the glycolytic pathway. Other sugars must be converted to either of these forms to be directly metabolized. Some pathways, including the Calvin Cycle and the Pentose Phosphate Pathway (PPP, see below) contain intermediates in common with glycolysis, so in that sense, almost any cellular sugar can be metabolized here. Intermediates of glycolysis that are common to other pathways include glucose-6-phosphate (PPP, glycogen metabolism), F6P (PPP), G3P (Calvin, PPP), DHAP (PPP, glycerol metabolism, Calvin), 3PG (Calvin, PPP), PEP (C4 plant metabolism, Calvin), and pyruvate (fermentation, acetyl-CoA genesis, amino acid metabolism).

Reactions

The pathway of glycolysis begins with two inputs of energy. First, glucose gets a phosphate from ATP to make glucose-6-phosphate (G6P) and later fructose-6-phosphate (F6P) gets another phosphate from ATP to make fructose-1,6-bisphosphate (F1,6BP). With the pump thus primed, the pathway proceeds first to split the F1,6BP into two 3-carbon intermediates. Later the only oxidation step in the entire pathway occurs. In that reaction, glyceraldehyde-3-phosphate (G3P) is oxidized and a phosphate is added, creating 1,3-bisphosphoglycerate (1,3 BPG).

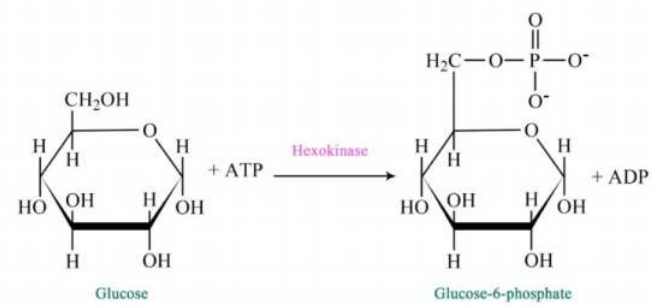


Figure 6.3.2: *Step 1 of Glycolysis*

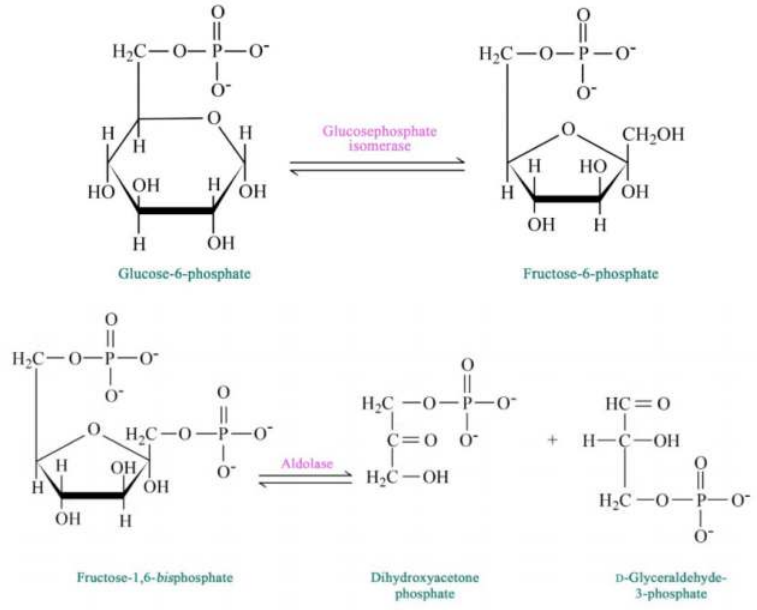


Figure 6.3.3: *Step 2 and 4 of Glycolysis*

The addition of the phosphate sometimes conceals the oxidation that occurred. G3P was an aldehyde. 1,3 BGP is an acid esterified to a phosphate. The two phosphates in the tiny 1,3BPG molecule repel each other and give the molecule high energy. It uses this energy to phosphorylate ADP to make ATP.

Since there are two 1,3 BPGs produced for every glucose, the two ATP produced replenish the two ATPs used to start the cycle.

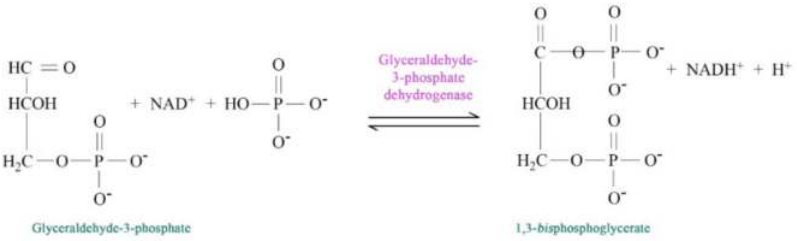


Figure 6.3.4: *Step 5 of Glycolysis*

The synthesis of ATP directly from a metabolic reaction is known as substrate level phosphorylation, though it is not a significant source of ATP. Glycolysis has two reactions during which substrate-level phosphorylation occurs.

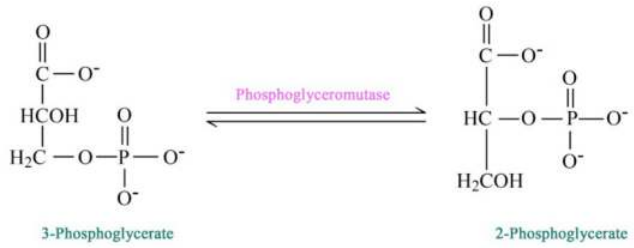


Figure 6.3.5: *Step 8 of Glycolysis*

The transfer of phosphate from 1,3BPG to ATP creates 3-phosphoglycerate (3-PG). Conversion of 3-PG to 2-PG occurs by an important mechanism. An intermediate in the reaction (catalyzed by phosphogly cerate mutase) is 2,3 BPG. This intermediate, which is stable, is released with low frequency by the enzyme instead of being converted to 2-PG. 2,3BPG is important because it binds to hemoglobin and stimulates release of oxygen. Thus, cells which are metabolizing glucose rapidly release more 2,3BPG and, as a result, stimulate release of more oxygen, supporting their needs.

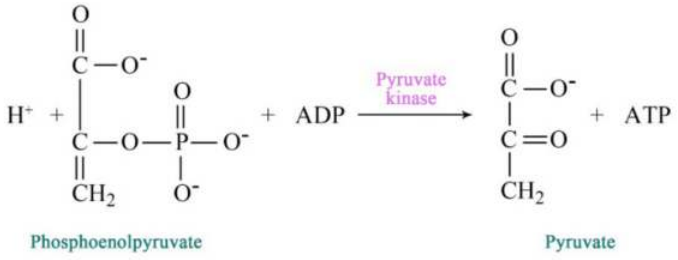


Figure 6.3.6: *Step 10 of Glycolysis*

2-PG is converted to phosphoenolpyyruvate (PEP) by removal of water, creating a very high energy intermediate. Conversion of PEP to pyruvate is the second substrate level phosphorylation of glycolysis, creating ATP. There is almost enough energy in PEP to stimulate production of a second ATP, but it is not used. Consequently, the energy is lost as heat. If you wonder why you get hot when you exercise, the reaction that converts PEP to pyruvate is a prime culprit.

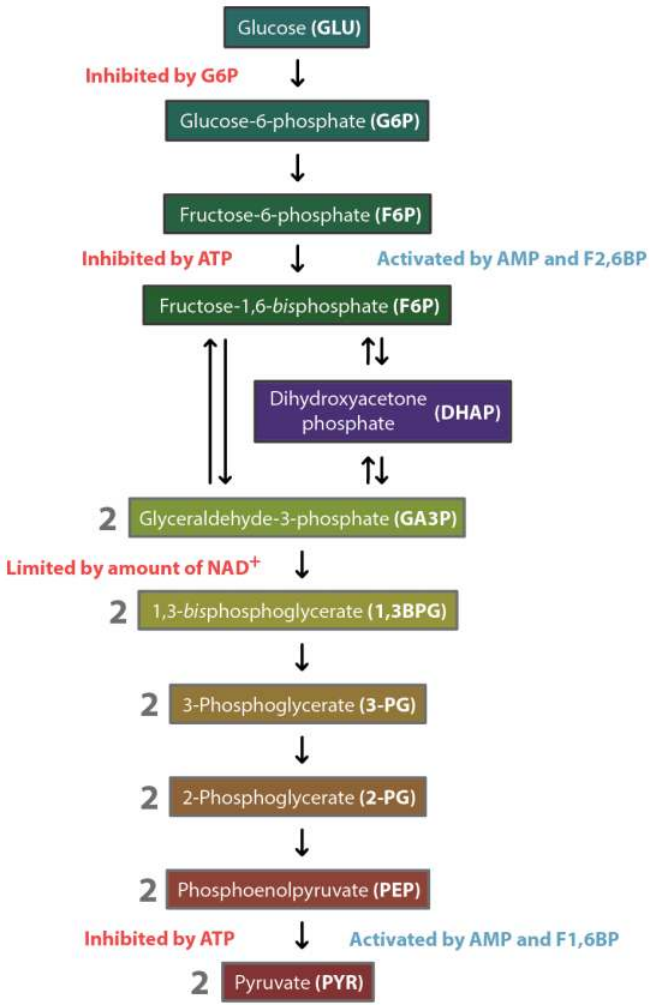


Figure 6.3.7: *Glycolysis Regulation*

Enzymes/Control

Control of glycolysis is unusual for a metabolic pathway, in that regulation occurs at three enzymatic points:

$$\underbrace{\text{Glucose} \rightleftharpoons \text{G}_6\text{P}}_{\text{hexokinase}} \tag{14.1.6.1}$$

$$\underbrace{\text{F}_6\text{P} \rightleftharpoons \text{F}_1,6\,\text{BP}}_{\text{phosphofructokinase (PFK)}} \tag{14.1.6.2}$$

and

$$\underbrace{\text{PEP} \rightleftharpoons \text{pyruvate}}_{\text{pyruvate kinase}}. \tag{14.1.6.3}$$

Glycolysis is regulated in a reciprocal fashion compared to its corresponding anabolic pathway, gluconeogenesis. Reciprocal regulation occurs when the same molecule or treatment (phosphorylation, for example) has opposite effects on catabolic and anabolic pathways. Reciprocal regulation is important when anabolic and corresponding catabolic pathways are occurring in the same cellular location.

As an example, consider regulation of PFK. It is activated by several molecules, most importantly fructose-2,6- bisphosphate (F2,6BP). This molecule has an inhibitory effect on the corresponding gluconeogenesis enzyme, fructose-1,6-bisphosphatase (F1,6BPase).

You might wonder why pyruvate kinase, the last enzyme in the pathway, is regulated. The answer is simple. Pyruvate kinase catalyzes the most energetically rich reaction of glycolysis. The reaction is favored so strongly in the forward direction that cells

must do a ‘two-step’ around it in the reverse direction when making glucose. In other words, it takes two enzymes, two reactions, and two triphosphates to go from pyruvate back to PEP in gluconeogenesis. When cells are needing to make glucose, they can’t be sidetracked by having the PEP they have made in gluconeogenesis be converted directly back to pyruvate by pyruvate kinase. Consequently, pyruvate kinase is inhibited during gluconeogenesis, lest a “futile cycle" occur.

Another interesting control mechanism called feedforward activation involves pyruvate kinase. Pyruvate kinase is activated allosterically by F1,6BP. This molecule is a product of the PFK reaction and a substrate for the aldolase reaction. It should be noted that the aldolase reaction is energetically unfavorable (high +ΔG°’), thus allowing F1,6BP to accumulate. When this happens, some of the excess F1,6BP activates pyruvate kinase, which jump-starts the conversion of PEP to pyruvate. The resulting drop in PEP levels has the effect of “pulling" on the reactions preceding pyruvate kinase. As a consequence, the concentrations of G3P and DHAP fall, helping to move the aldolase reaction forward.

Pyruvate Metabolism

As noted, pyruvate produced in glycolysis can be oxidized to acetyl-CoA, which is itself oxidized in the citric acid cycle to carbon dioxide. That is not the only metabolic fate of pyruvate, though.

Pyruvate is a “starting" point for gluconeogenesis, being converted to oxaloacetate in the mitochondrion in the first step. Pyruvate in animals can also be reduced to lactate when oxygen is limiting. This reaction, which requires NADH produces $\mathbf{NAD^+}$ and is critical for generating the latter molecule to keep the glyceraldehyde-3-phosphate dehydrogenase reaction of glycolysis going when there is no oxygen.

Oxygen is necessary for the electron transport system to operate and this, in turn, is what oxidizes NADH to $\mathbf{NAD^+}$. In the absence of oxygen, thus, an alternative means of making $\mathbf{NAD^+}$ is necessary, or else glycolysis will halt. Bacteria and yeast have NADH requiring reactions that regenerate $\mathbf{NAD^+}$ while producing ethanol from pyruvate under anaerobic conditions, instead of lactic acid. Thus, fermentation of pyruvate is necessary to keep glycolysis operating when oxygen is limiting. It is also for these reasons that brewing of beer (using yeast) involves depletion of oxygen and muscles low in oxygen produce lactic acid (animals).

Pyruvate is a precursor of alanine which can be easily synthesized by transfer of a nitrogen from an amine donor, such as glutamic acid. Pyruvate can also be converted into oxaloacetate by carboxylation in the process of gluconeogenesis (see Figure 6.3.8).

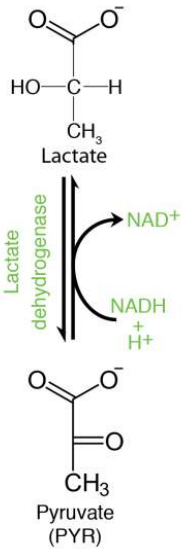


Figure 6.3.8: *Pyruvate Reduction*

The enzymes involved in pyruvate metabolism include pyruvate dehydrogenase (makes acetyl-CoA), lactate dehydrogenase (makes lactate), transaminases (make alanine), an
pyruvate carboxylase (makes oxaloacetate).

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14.1.7: Gluconeogenesis

The anabolic counterpart to glycolysis is gluconeogenesis, which occurs mostly in the cells of the liver and kidney. In seven of the eleven reactions of gluconeogenesis (starting from pyruvate), the same enzymes are used as in glycolysis, but the reaction directions are reversed. Notably, the ΔG values of these reactions in the cell are typically near zero, meaning their direction can be readily controlled by changing substrate and product concentrations.

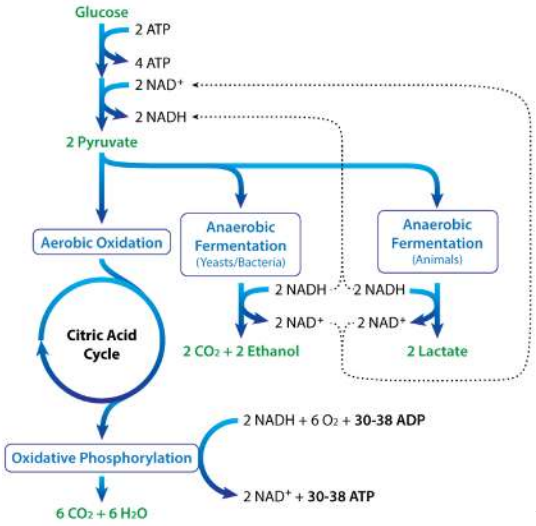


Figure 6.4.1: *Metabolic Redox*

The three regulated enzymes of glycolysis all catalyze reactions whose ΔG values are not close to zero, making manipulation of reaction direction non-trivial. Consequently, cells employ “work-around" reactions catalyzed by four different enzymes to favor gluconeogenesis, when appropriate.

Two of the enzymes (pyruvate carboxylase and PEP carboxykinase -PEPCK) catalyze reactions that bypass pyruvate kinase. F1,6BPase bypasses PFK and G6Pase bypasses hexokinase. Notably, pyruvate carboxylase and G6Pase are found in the mitochondria and endoplasmic reticulum, respectively, whereas the other two are found in the cytoplasm along with all of the enzymes of glycolysis. As a result, all of glycolysis and most of gluconeogenesis occurs in the cytoplasm. Controlling these pathways then becomes of critical importance because cells generally need to minimize the extent to which paired anabolic and catabolic pathways are occurring simultaneously, lest they waste energy and make no tangible product except heat. The mechanisms of controlling these pathways work, in some ways, in opposite fashions, called reciprocal regulation (see above).

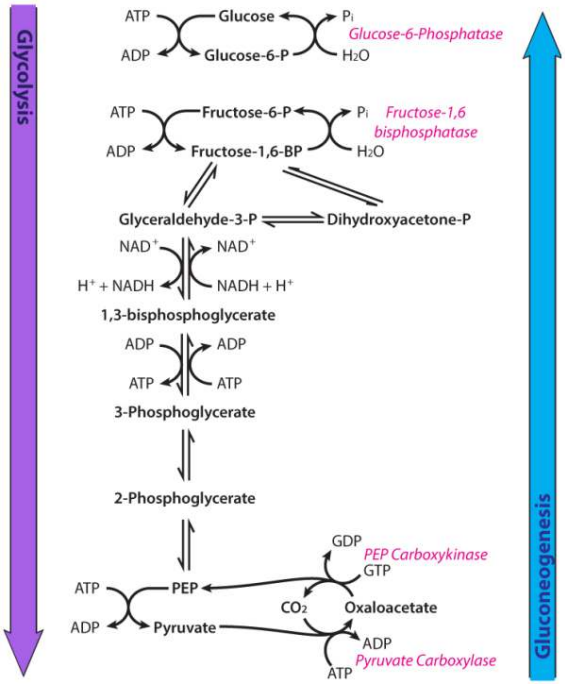


Figure 6.4.2: *Gluconeogensis and Glycolysis*

Besides reciprocal regulation, other mechanisms help control gluconeogenesis. First, PEPCK is controlled largely at the level of synthesis. Overexpression of PEPCK (stimulated by glucagon, glucocorticoids, and cAMP and inhibited by insulin) causes symptoms of diabetes. Pyruvate carboxylase is sequestered in the mitochondrion and is sensitive to acetyl-CoA, which is an allosteric activator. Acetyl-CoA concentrations increase as the citric acid cycle activity decreases. Glucose-6-phosphatase is present in low concentrations in many tissues, but is found most abundantly and importantly in the major gluconeogenic organs – the liver and kidney cortex.

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14.1.8: Pentose Phospate Pathway

The Pentose Phosphate Pathway (PPP) is one that many students are confused by. Perhaps the reason for this is that it does not really have a single direction in which it proceeds, as will be apparent below.

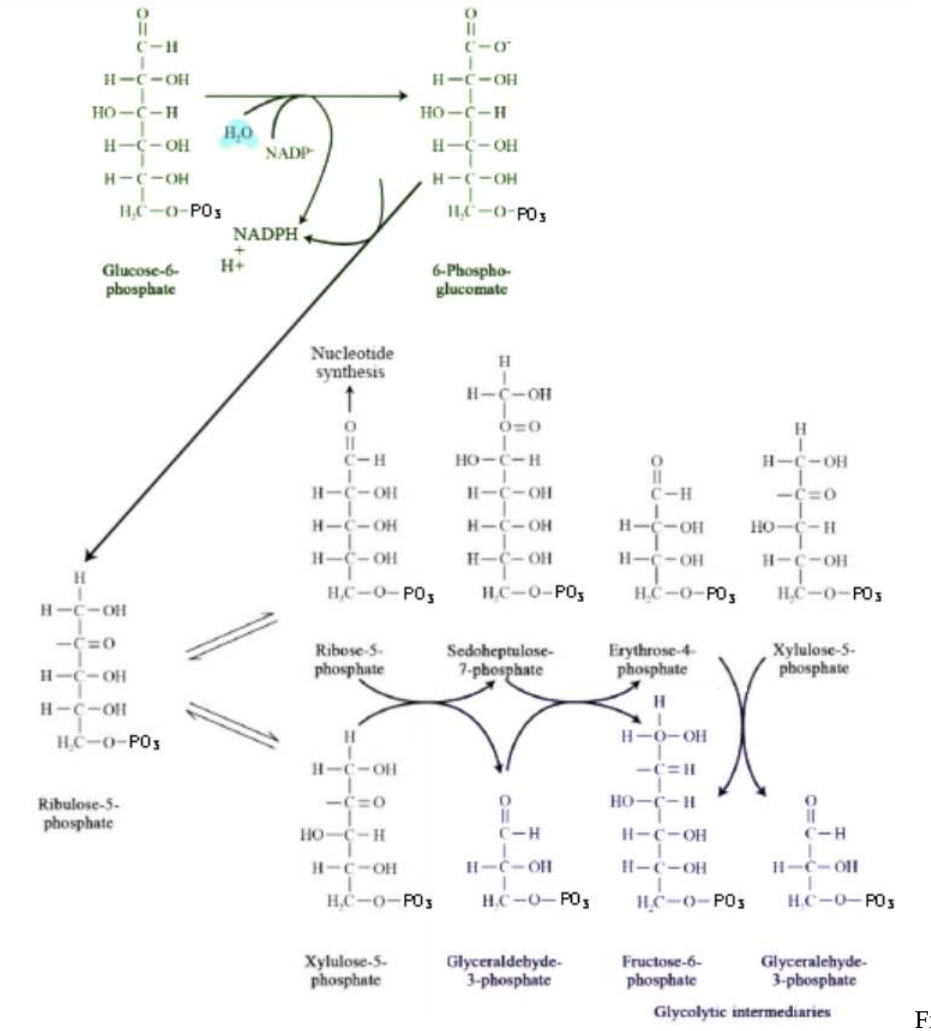


Figure 7.2.1: *Pentose Phosphate Pathway*

Portions of the PPP are similar to the Calvin Cycle of plants, also known as the dark reactions of photosynthesis. We discuss these reactions separately in the next section. The primary functions of the PPP are to produce NADPH (for use in anabolic reductions), ribose-5-phosphate (for making nucleotides), and erythrose-4-phosphate (for making aromatic amino acids). Three molecular intermediates of glycolysis can funnel into PPP (or be used as usual in glycolysis). They include G6P, fructose-6-phosphate (in two places), and glyceraldehyde-3-phosphate (also in two places).

A starting point for the pathway (though there are other entry points) is the oxidative phase. It includes two reactions generating NADPH. In the first of these, oxidation of glucose-6-phosphate (catalyzed by glucose-6-phosphate dehydrogenase), produces NADPH and 6-phosphogluconolactone. 6-phosphogluconolactone spontaneously gains water and loses a proton to become 6-phosphogluconate. Oxidation of this produces ribulose-5-phosphate and another NADPH and releases $\mathbf{CO_2}$. The remaining steps of the pathway are known as the non-oxidative phase and involve interconversion of sugar phosphates.

For example, ribulose-5-phosphate is converted to ribose-5-phosphate (R5P) by the enzyme ribulose-5-phosphate isomerase. Alternatively, ribulose-5-phosphate can be converted to xylulose-5-phosphate (Xu5P). R5P and Xu5P (10 carbons total) can be combined and rearranged by transketolase to produce intermediates with 3 and 7 carbons (glyceraldehyde-3-phosphate and sedoheptulose-7-phosphate, respectively). These last two molecules can, in turn be rearranged by transaldolase into 6 and 4 carbon

sugars (fructose-6-phosphate and erythrose-4-phosphate, respectively). Further, the erythrose-4-phosphate can swap parts with Xu5P to create glyceraldehyde-3-phosphate and fructose-6-phosphate.

It is important to recognize that the PPP pathway is not a “top-down" pathway, with all the intermediates derived from a starting G6P. All of the reactions are reversible, so that, for example, fructose-6-phosphate and glyceraldehyde-3-phosphate from glycolysis can reverse the last reaction of the previous paragraph to provide a means of synthesizing ribose-5-phosphate non-oxidatively. The pathway also provides a mechanism to cells for metabolizing sugars, such as Xu5P and ribulose-5-phosphate. In the bottom line of the pathway, the direction the pathway goes and the intermediates it produces are determined by the needs of, and intermediates available to, the cell.

As noted above, the pathway connects in three places with glycolysis. In non- plant cells, the PPP pathway occurs in the cytoplasm (along with glycolysis), so considerable “intermingling" of intermediates can and does occur. Erythrose-4-phosphate is an important precursor of aromatic amino acids and ribose-5-phosphate is an essential precursor for making nucleotides.

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14.1.9: Cori Cycle and Citric Acid Cycle

Cori Cycle

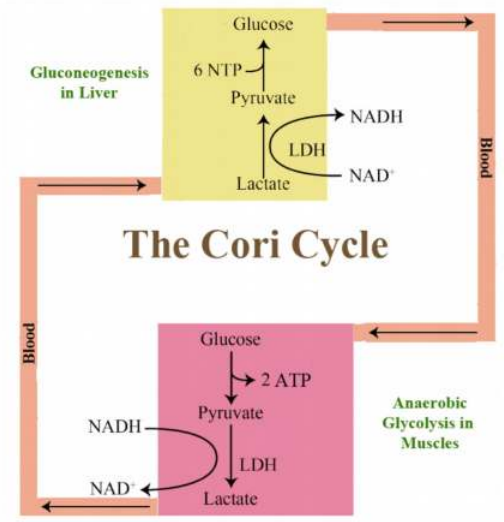


Figure 6.5.2: *The Citric Acid Cycle Reactions*

Focusing on the pathway itself, the traditional point to start discussion is addition of acetyl-CoA to oxaloacetate (OAA) to form citrate. Acetyl-CoA for the pathway can come from a variety of sources. They include pyruvate oxidation (from glycolysis and amino acid metabolism), fatty acid oxidation, and amino acid metabolism. The reaction joining it to OAA is catalyzed by citrate synthase and the $\Delta G°'$ is fairly negative. This, in turn, helps to “pull" the reaction preceding it in the cycle (catalyzed by malate dehydrogenase).

In the next reaction, citrate is isomerized to isocitrate by action of the enzyme called aconitase. Isocitrate is a branch point in plants and bacteria for the glyoxylate cycle. Oxidative decarboxylation of isocitrate by isocitrate dehydrogenase produces the first NADH and yields alpha-ketoglutarate. This five carbon intermediate is a branch point for synthesis of glutamate. In addition, glutamate can also be made easily into this citric acid cycle intermediate. Decarboxylation of alpha-ketoglutarate yields succinyl-CoA and is catalyzed by alpha- ketoglutarate dehydrogenase. This enzyme is structurally very similar to pyruvate dehydrogenase and employs the same five coenzymes – NAD, FAD, CoASH, TPP, and lipoic acid.

The remainder of the citric acid cycle involves conversion of the four carbon succinyl-CoA into oxaloacetate. Succinyl-CoA is a branch point for the synthesis of heme. Succinyl-CoA is converted to succinate in a reaction catalyzed by succinyl-CoA synthetase (named for the reverse reaction) and a GTP is produced, as well – the only substrate level phosphorylation in the cycle. The energy for the synthesis of the GTP comes from hydrolysis of the high energy thioester bond between succinate and the CoA. Evidence for the high energy of a thioester bond is also evident in the citrate synthase reaction, which is also very energetically favorable. Succinate is also produced by metabolism of odd-chain fatty acids (see below).

Oxidation of succinate occurs in the next step, catalyzed by succinate dehydrogenase. This interesting enzyme both catalyzes this reaction and participates in the electron transport system, funneling electrons from the $\mathbf{FADH_2}$ it gains in the reaction to coenzyme Q. The product of the reaction, fumarate gains a water across its trans double bond in the next reaction, catalyzed by fumarase to form malate . Fumarate is also a byproduct of nucleotide metabolism and of the urea cycle . Malate is important also for transporting electrons across membranes in the malate aspartate shuttle and in ferrying carbon dioxide in C4 plants.

Conversion of malate to OAA is a rare biological oxidation that has a $\Delta G°'$ with a positive value. The reaction product includes NADH and the reaction is ‘pulled’ by the energetically favorable conversion of OAA to citrate in what was described above as the first reaction of the cycle. OAA intersects other important pathways, including amino acid metabolism (readily converted to aspartic acid), transamination (nitrogen movement) and gluconeogenesis.

Contributors

- Template:ContribAhern

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14.1.10: 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 **14.1.10.1**). 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 **14.1.10.1**, 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.

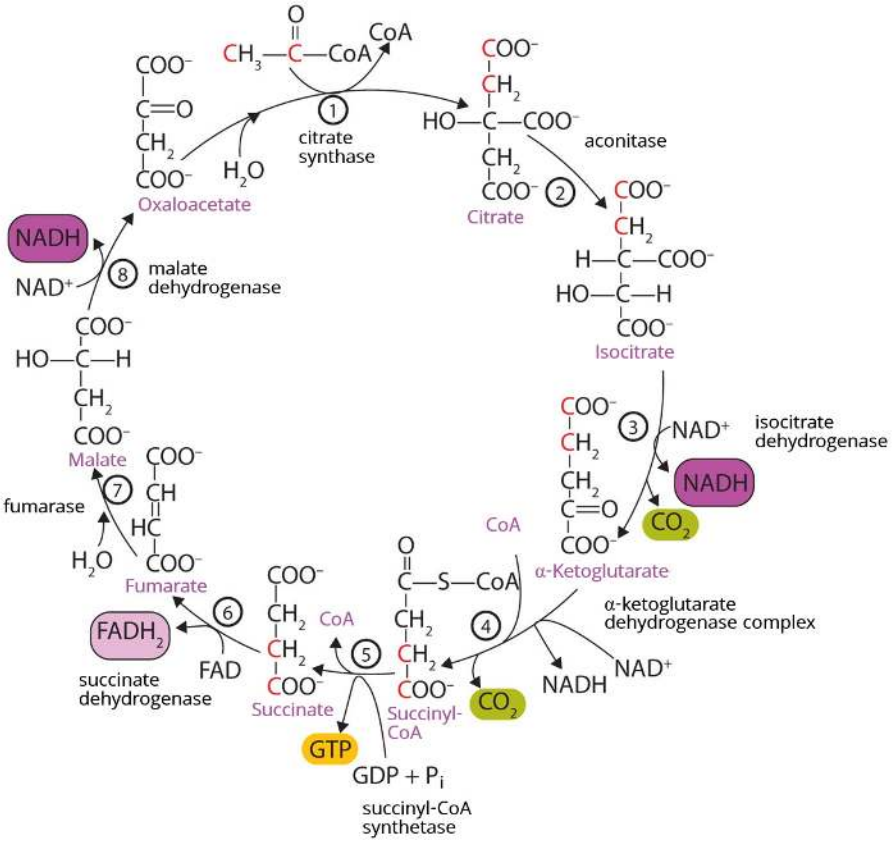


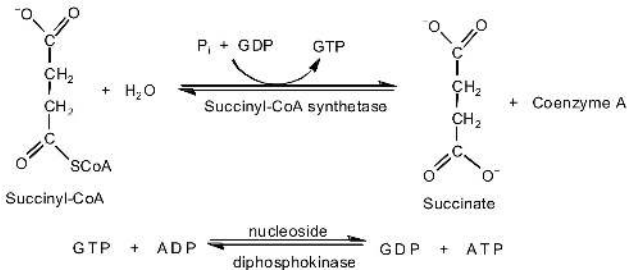
Figure **14.1.10.1**: Reactions of the Citric Acid Cycle

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 **14.1.10.2**). 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.

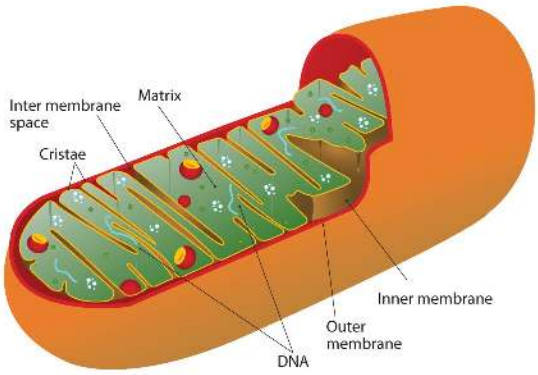


Figure **14.1.10.2**: Respiration

Cellular respiration occurs in the mitochondria

Figure **14.1.10.2** 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 **14.1.10.3** 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.

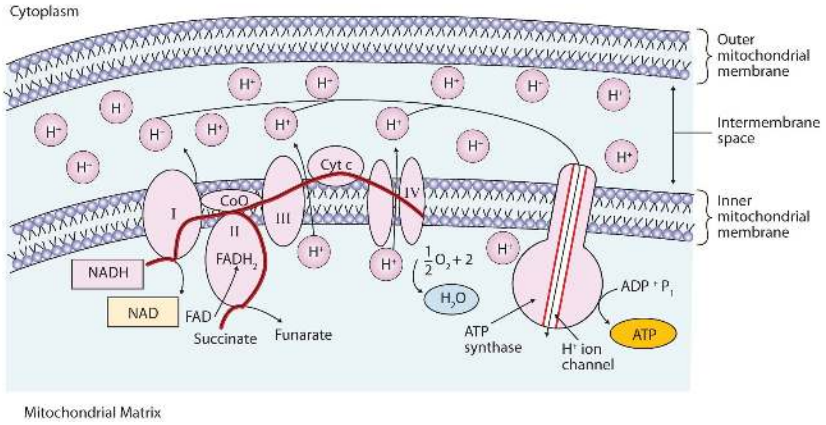
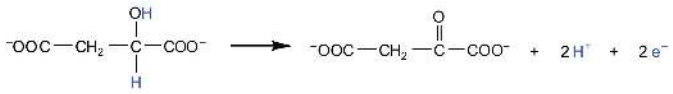


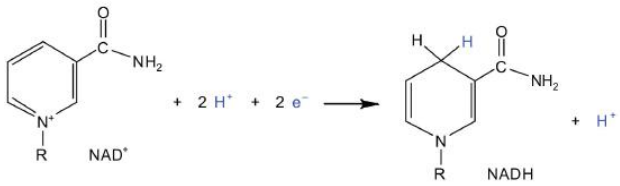
Figure **14.1.10.3**: The Mitochondrial Electron Transport Chain and ATP Synthase. The red line shows the path of electrons.

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*:

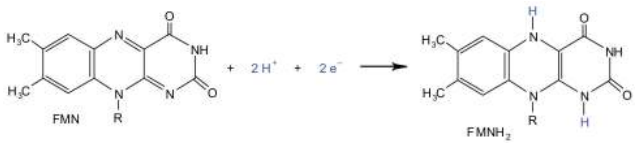


In the oxidation half-reaction, two hydrogen (H^+) ions and two electrons are removed from the substrate. In the reduction half-reaction, the NAD^+ molecule accepts both of those electrons and one of the H^+ ions. The other H^+ ion is transported from the matrix, across the inner mitochondrial membrane, 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*:

$$\mathbf{2\,Fe(III)\cdot S + 2e^- \longrightarrow 2\,Fe(II)\cdot S}$$

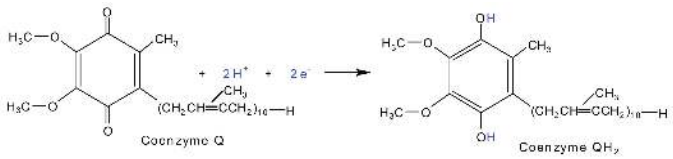
Electrons from complexes I and II are then transferred from the $\mathbf{Fe\cdot S}$ protein to coenzyme Q (CoQ), a mobile electron carrier that acts as the electron shuttle between complexes I or II and complex III.

> *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 **14.1.10.4**). 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*:

$$O_2 + 4\,H^+ + 4\,e^- \longrightarrow 2\,H_2O$$

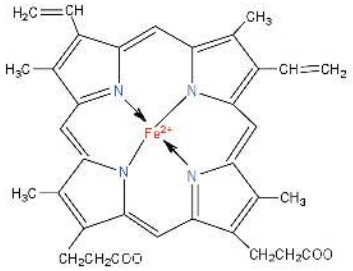


Figure **14.1.10.4**: An Iron Porphyrin. Iron porphyrins are present in cytochromes as well as in myoglobin and hemoglobin.



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 **14.1.10.3**, 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 **14.1.10.1** 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 **14.1.10.1**: 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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14.1.11: Cellular Phosphorylations

Formation of triphosphates is essential to meet the cell's immediate energy needs for synthesis, motion, and signaling. In a given day, an average human being uses more than their body weight in triphosphates. Since triphosphates are the "currency" that meet immediate needs of the cell, it is important to understand how triphosphates are made. There are three phosphorylation mechanisms – 1) substrate level; 2) oxidative; and 3) photophosphorylation. We consider them here individually.

Substrate Level Phosphorylation

The easiest type of phosphorylation to understand is that which occurs at the substrate level. This type of phosphorylation involves the direct synthesis of ATP from ADP and a reactive intermediate, typically a high energy phosphate-containing molecule. Substrate level phosphorylation is a relatively minor contributor to the total synthesis of triphosphates by cells. An example substrate phosphorylation comes from glycolysis.

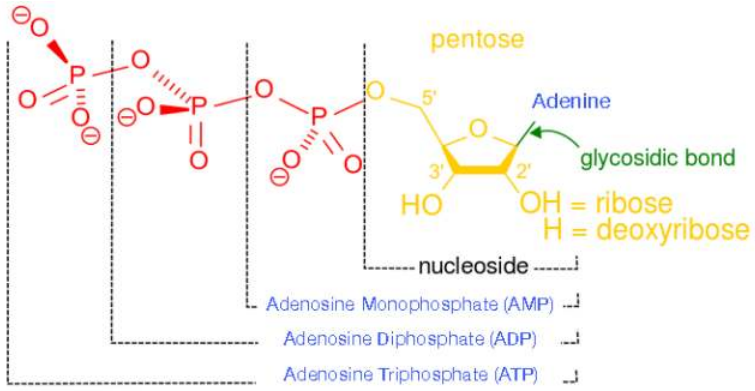


Figure 14.1.11.1: *Adenine nucleotides.*

$$\text{Phosphoenolpyruvate (PEP)} + \text{ADP} \rightleftharpoons \text{Pyuvate} + \text{ATP} \tag{14.1.11.1}$$

This reaction has a very negative $\Delta G^{o'}$ (-31.4 kJ/mol), indicating that the PEP contains more energy than ATP, thus energetically favoring ATP's synthesis. Other triphosphates can be made by substrate level phosphorylation, as well. For example, GTP can be synthesized by the following citric acid cycle reaction

$$\text{Succinyl}-\text{CoA} + \text{GDP} + \text{P}_\text{i} \rightleftharpoons \text{Succinate} + \text{GTP} + \text{CoA}-\text{SH} \tag{14.1.11.2}$$

Triphosphates can be interchanged readily in substrate level phosphorylations catalyzed by the enzyme Nucleoside Diphosphate Kinase (NDPK). A generalized form of the reactions catalyzed by this enzyme is as follows:

$$\text{XTP} + \text{YDP} \rightleftharpoons \text{XDP} + \text{YTP} \tag{14.1.11.3}$$

where **X** can be adenosine, cytidine, uridine, thymidine, or guanosine and **Y** can be any of these as well. Last, an unusual way of synthesizing ATP by substrate level phosphorylation is that catalyzed by adenylate kinase

$$2\,\text{ADP} \rightleftharpoons \text{ATP} + \text{AMP} \tag{14.1.11.4}$$

This reaction is an important means of generating ATP when the cell doesn't have other sources of energy. The accumulation of AMP resulting from this reaction activates enzymes, such as phosphofructokinase, of glycolysis, that will catalyze reactions to give the cell additional, needed energy.

Electron Transport/Oxidative Phosphorylation

Mitocohondria are called the power plants of the cell because most of a cell's ATP is produced there, in a process referred to as oxidative phosphorylation. The mechanism by which ATP is made in oxidative phosphorylation is one of the most interesting processes in all of biology. It has three primary considerations. The first is electrical – electrons from reduced energy carriers, such as NADH and FADH2, enter an electron transport system via protein complexes containing iron. As seen in the figure on the following page,electrons move from one complex to the next, not unlike the way they might move through an electrical circuit.

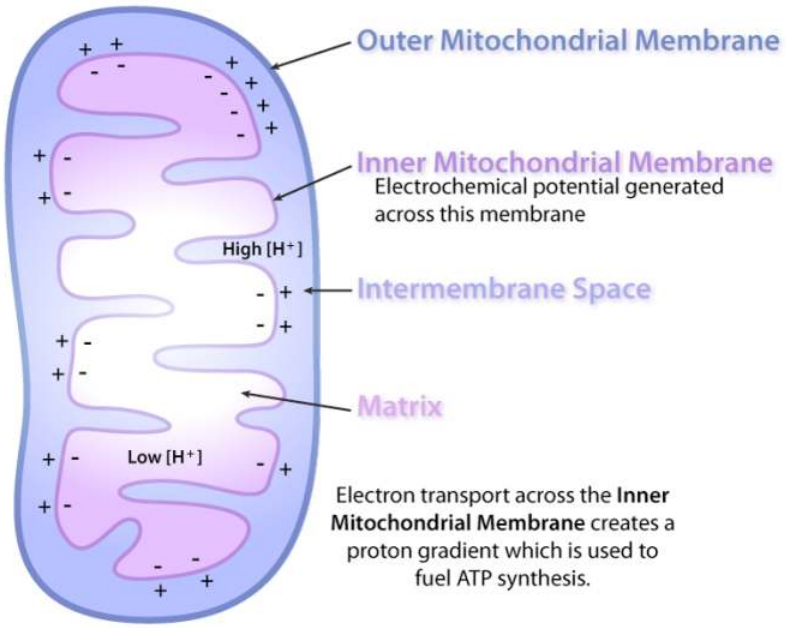


Figure 14.1.11.2: Mitochondria.

The next consideration arises as a secondary phenomenon. When electrons pass through complexes I, III, and IV, protons are moved from the mitochondrial matrix (inside of mitochondrion) and deposited in the intermembrane space (between the inner and outer membranes of the mitochondrion). The effect of this redistribution is to increase the electrical and chemical potential across the membrane. Students may think of the process as "charging the battery."

Just like a charged battery, the potential arising from the proton differential across the membrane can be used to do things. This is the third consideration. In the mitochondrion, the "thing" that the proton gradient does is create ATP from ADP and Pi (inorganic phosphate). This process requires energy and is accomplished by movement of protons through a protein complex in the inner mitochondrial membrane. The protein complex is an enzyme that has several names, including Complex V, PTAS (Proton Translocating ATP Synthase), and ATP Synthase. Central to its function is the movement of protons through it (from outside back into the matrix). Protons will only move through ATP Synthase if their concentration is greater outside the inner membrane than in the matrix.

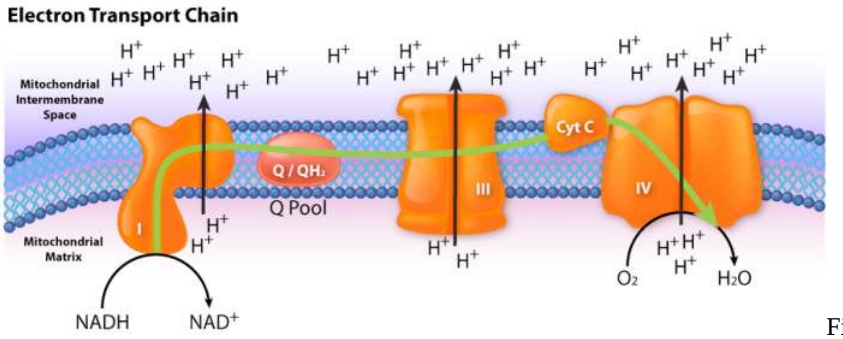


Figure 14.1.11.3: *Electron transport starting with complex I.*

In summary, the electron transport system charges the battery for oxidative phosphorylation by pumping protons out of the mitochondrion. The intact inner membrane of the mitochondrion keeps the protons out, except for those that re-enter through ATP Synthase. The ATP Synthase allows protons to re-enter the mitochondrial matrix and harvests their energy to make ATP.

ATP Synthase

The ATP Synthase itself is an amazing nanomachine that makes ATP using a gradient of protons flowing through it from the intermembrane space back into the matrix. It is not easy to depict in a single image what the synthase does. The figure at the right illustrates the multi-subunit nature of this membrane protein, which acts like a turbine at a hydroelectric dam. The movement of protons through the ATP Synthase causes it to spin like a turbine, and the spinning is necessary for making ATP.

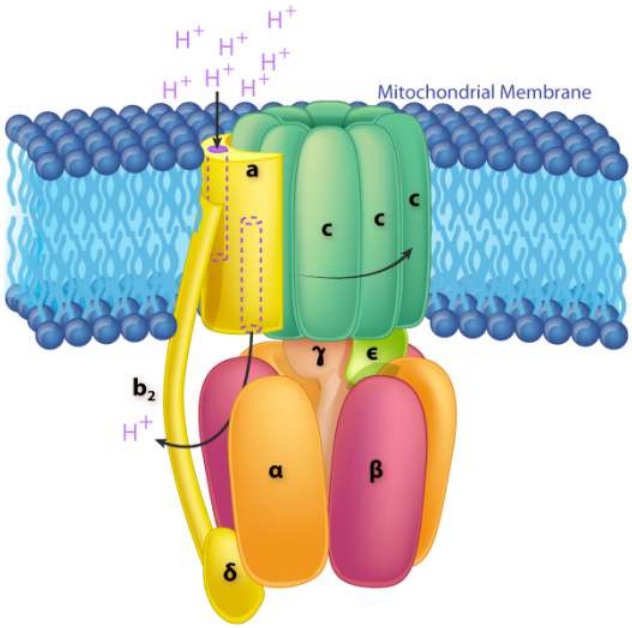


Figure 14.1.11.4: *ATP Synthase (complex V).*

In ATP Synthase, the spinning component is the membrane portion (c ring) of the F0 stalk. The c ring proteins are linked to the gamma-epsilon stalk, which projects into the F1 head of the mushroom structure. The F1 head contains the catalytic ability to make ATP. The F1 head is hexameric in structure with paired alpha and beta proteins arranged in a trimer of dimers. Movement of the gamma protein inside the alpha-beta trimer causes each set of beta proteins to change structure slightly into three different forms called Loose, Tight, and Open (L,T,O). Each of these forms has a function. The Loose form binds **ADP** and $\mathbf{P_i}$. The tight form "squeezes" them together to form the ATP. The open form releases the ATP into the mitochondrial matrix. Thus,as a result of the proton excess in the intermembrane space, ATP is made.

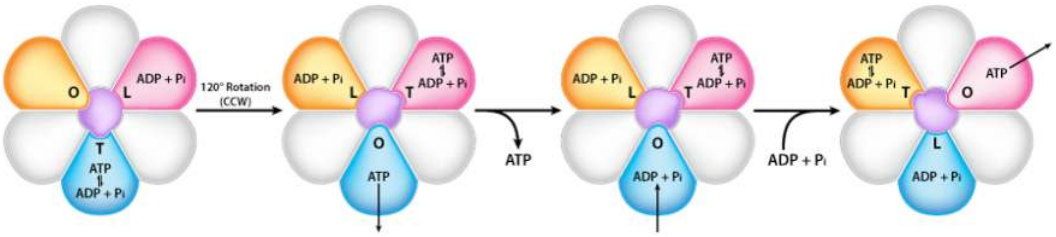


Figure 14.1.11.5: *Three states of ATP Synthase.*

Photophosphorylation

The third type of phosphorylation to make ATP is found only in cells that carry out photosynthesis. This process is similar to oxidative phosphorylation in several ways. A primary difference is the ultimate source of the energy for ATP synthesis. In oxidative phosphorylation, the energy comes from electrons produced by oxidation of biological molecules. In the case of photosynthesis, the energy comes from the light of the sun.

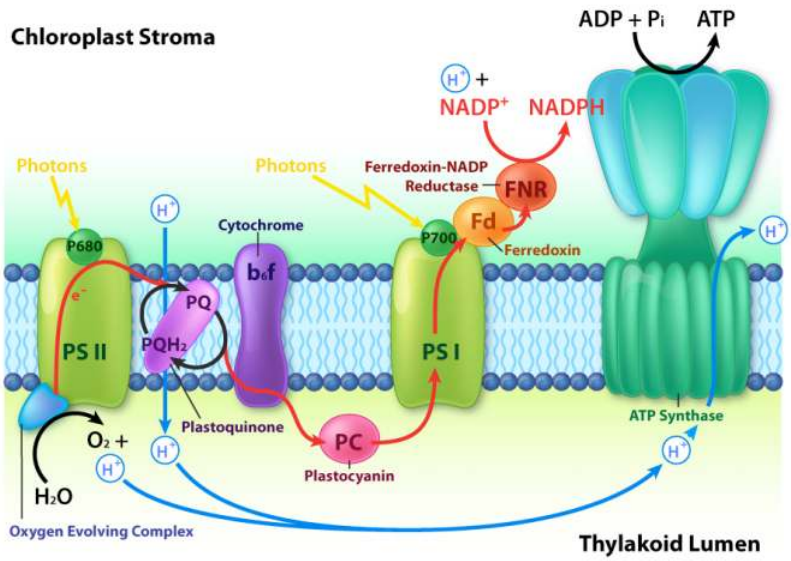


Figure **14.1.11.6**: Photophosphorylation.

Photons from the sun interact with chlorophyll molecules in reaction centers in the chloroplasts of plants or membranes of photosynthetic bacteria. A schematic of the process is shown above. The similarities of photophosphorylation to oxidative phosphorylation include:

- an electron transport chain
- creation of a proton gradient
- harvesting energy of the proton gradient by making ATP

with the help of an ATP synthase. Some of the differences include:

- the source of the electrons – $\mathbf{H_2O}$ for photosynthesis versus $\mathbf{NADH/FADH_2}$ for oxidative phosphorylation
- direction of proton pumping – into the thylakoid space of the chloroplasts versus outside the matrix of the mitochondrion
- movement of protons during ATP synthesis – out of the thylakoid space in photosynthesis versus into the mitochondrial matrix
- nature of the terminal electron acceptor – $\mathbf{NADP^+}$ in photosynthesis versus $\mathbf{O_2}$ in oxidative phosphorylation.

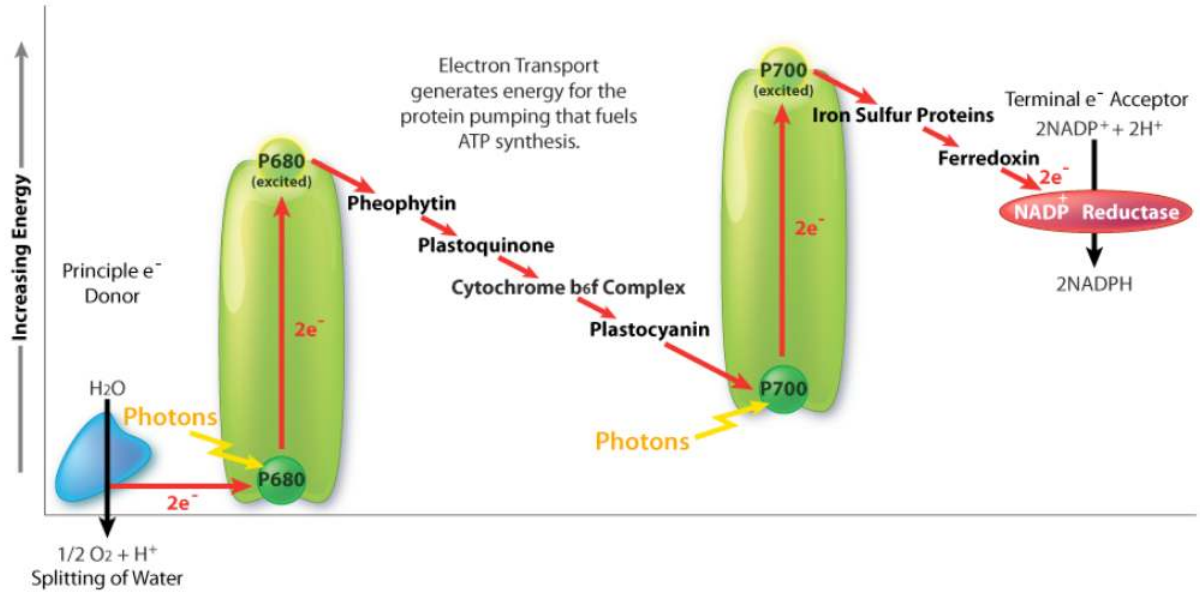


Figure **14.1.11.7**: Electron movement in photosynthesis.

https://chem.libretexts.org/@go/page/338393

Electron Transport in Chloroplasts vs. Mitochondria

In some ways, the movement of electrons in chloroplasts during photosynthesis is opposite that of electron transport in mitochondria. In photosynthesis, water is the source of electrons and their final destination is NADPH. In mitochondria, NADH/ $\mathrm{FADH_2}$ are electron sources and $\mathrm{H_2O}$ is their final destination.

How do biological systems get electrons to go both ways? It would seem to be the equivalent of going to and from a particular place while always going downhill, since electrons will move according to potential. The answer is the captured energy of the photons, which elevates electrons in photosynthesis to an energy where they move "downhill" to their NADPH destination in a Z-shaped scheme. The movement of electrons through this scheme in plants requires energy from photons in two places to "lift" the energy of the electrons sufficiently. Last, it should be noted that photosynthesis actually has two phases, referred to as the *light cycle* (described above) and the *dark cycle*, which is a set of chemical reactions that captures $\mathrm{CO_2}$ from the atmosphere and "fixes" it, ultimately into glucose. The dark cycle is also referred to as the Calvin Cycle.

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14.1.12: Energy Efficiency

Cells are not 100% efficient in energy use; nothing that we know of is. Consequently, cells do not get as much energy out of catabolic processes as they put into anabolic processes. A good example is the synthesis and breakdown of glucose, something liver cells are frequently doing. The complete conversion of glucose to pyruvate in glycolysis (catabolism) yields two pyruvates plus 2 NADH plus 2 ATPs.

Conversely, the complete conversion of two pyruvates into glucose by gluconeogenesis (anabolism) requires 4 ATPs, 2 NADH, and 2 GTPs. Since the energy of GTP is essentially equal to that of ATP, gluconeogenesis requires a net of 4 ATPs more than glycolysis yields. This difference must be made up in order for the organism to balance everything. It is for this reason that we eat. In addition, the inefficiency of our capture of energy in reactions results in the production of heat and helps to keep us warm.

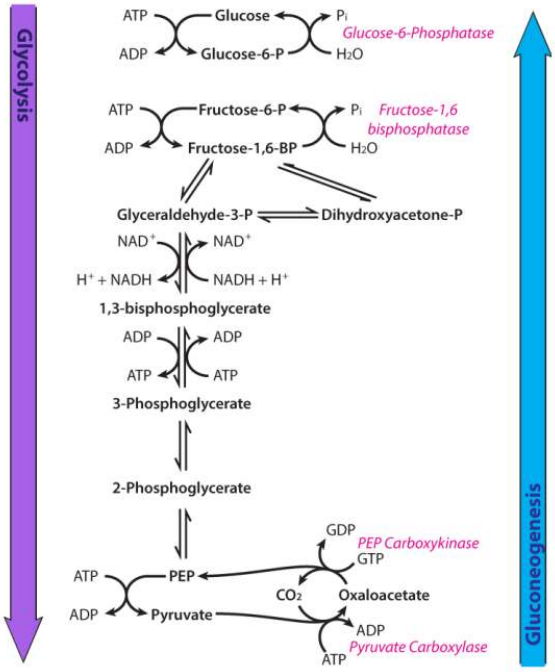


Figure 2.8.1: *Glycolysis and gluconeogenesis.*

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14.1.13: Metabolic Controls of Energy

It is also noteworthy that cells do not usually have both catabolic and anabolic processes for the same molecules (for example, breakdown of glucose and synthesis of glucose, shown on the previous page) occurring simultaneously inside of them because the cell would see no net production of anything but heat and a loss of ATPs with each turn of the cycle. Such cycles are called futile cycles and cells have controls in place to limit the extent to which they occur. Since futile cycles can, in fact, yield heat, they are sources of heat in some types of tissue.

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14.1.14: Molecular Backups for Muscles

For plants, the needs for energy are different than for animals. Plants do not need to access energy sources as rapidly as animals do, nor do they have to maintain a constant internal temperature. Plants can neither flee predators, nor chase prey. These needs of animals are much more immediate and require that energy stores be accessible on demand. Muscles, of course, enable the motion of animals and the energy required for muscle contraction is ATP. To have stores of energy readily available, muscles have, in addition to ATP, creatine phosphate and glycogen for quick release of glucose from glycogen. The synthesis of creatine phosphate is a prime example of the effects of concentration on the synthesis of high energy molecules. For example, creatine phosphate has an energy of hydrolysis of -43.1 kJ/mol whereas ATP has an energy of hydrolysis of -30.5 kJ/mol Creatine phosphate, however, is made from creatine and ATP in the reaction shown below. How is this possible?

Creatine + ATP <=> Creatine phosphate + ADP

The ΔG°' of this reaction is +12.6 kJ/mol, reflecting the energies noted above. In a resting muscle cell, ATP is abundant and ADP is low, driving the reaction to the right, creating creatine phosphate. When muscular contraction commences, ATP levels fall and ADP levels climb. The above reaction then reverses and proceeds to synthesize ATP immediately. Thus creatine phosphate acts like a battery, storing energy when ATP levels are high and releasing it almost instantaneously to create ATP when its levels fall.

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14.1.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^+.

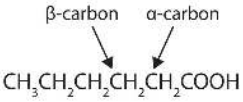
   b. Pyruvate is converted to ethanol and carbon dioxide, and NADH is reoxidized to NAD^+.

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

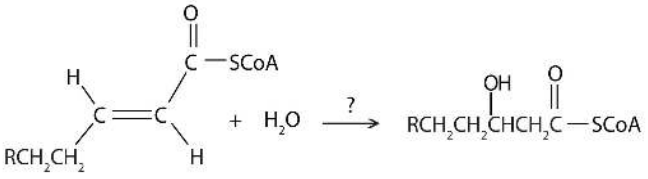
1. They react with CoA to form fatty acyl-CoA molecules.
2. 

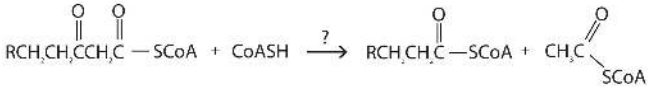
Key Takeaways

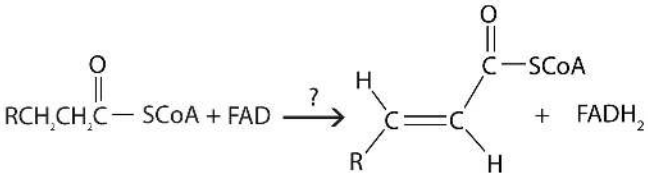
- Fatty acids, obtained from the breakdown of triglycerides and other lipids, are oxidized through a series of reactions known as β-oxidation.
- In each round of β-oxidation, 1 molecule of acetyl-CoA, 1 molecule of NADH, and 1 molecule of $FADH_2$ are produced.
- The acetyl-CoA, NADH, and $FADH_2$ are 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

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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

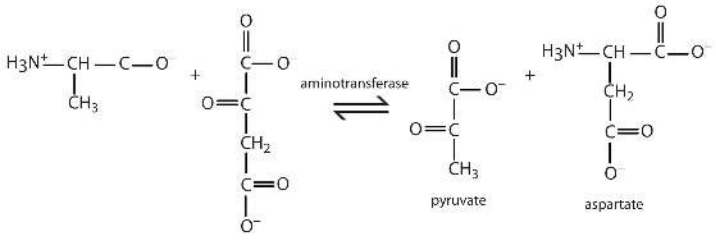
1. a. Write the equation for the transamination reaction between alanine and oxaloacetate.

   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.

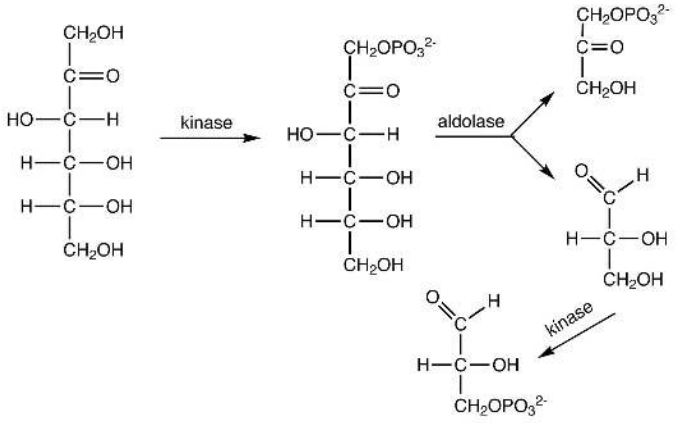
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3.

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.

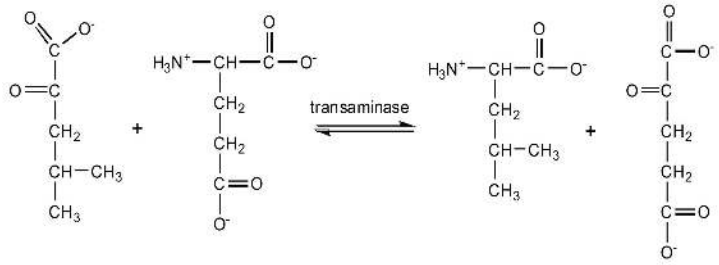
7.



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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14.1.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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SECTION OVERVIEW

14.2: Carbohydrate Metabolism Details

14.2.1: Metabolism - Sugars

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14.2.1: Metabolism - Sugars

Glycolysis

Carbohydrates, whether synthesized by photosynthetic organisms, stored in cells as glycogen, or ingested by heterotrophs, must be broken down to obtain energy for the cell's activities as well as to synthesize other molecules required by the cell. Starch and glycogen, polymers of glucose, are the main energy storage forms of carbohydrates in plants and animals, respectively. To use these sources of energy, cells must first break down the polymers to yield glucose. The glucose is then taken up by cells through transporters in cell membranes. The metabolism of glucose, as well as other six carbon sugars (hexoses) begins with the catabolic pathway called glycolysis. In this pathway, sugars are oxidized and broken down into pyruvate molecules. The corresponding anabolic pathway by which glucose is synthesized is termed gluconeogenesis. Neither glycolysis nor gluconeogenesis is a major oxidative/reductive process, with one step in each one involving loss/gain of electrons, but the product of glycolysis, pyruvate, can be completely oxidized to carbon dioxide (TCA cycle). Indeed, without production of pyruvate from glucose in glycolysis, a major energy source for the cell would not be available.

Glucose is the most abundant hexose in nature and is traditionally used to illustrate the reactions of glycolysis, but fructose (in the form of fructose-6- phosphate) is also readily metabolized, while galactose can easily be converted into glucose for catabolism in the pathway as well. The end metabolic products of glycolysis are two molecules of ATP, two molecules of NADH and two molecules of pyruvate (Figure 1), which, in turn, can be oxidized further in the citric acid cycle.

Other pathways

Intermediates of glycolysis and gluconeogenesis that are common to other pathways include glucose-6-phosphate (PPP, glycogen metabolism), Fructose-6-phosphate (PPP), Glyceraldehyde-3- phosphate (PPP), dihydroxyacetone phosphate (PPP, glycerol metabolism), 3- phosphoglycerate (PPP), and pyruvate (amino acid metabolism). It is worth noting that glycerol from the breakdown of fat can readily be metabolized to dihydroxyacetone phosphate (DHAP) and thus enter the glycolysis pathway. It is the only part of a fat that is used in these pathways.

Reaction 1

Glucose gets a phosphate from ATP to make glucose-6-phosphate (G6P) in a reaction catalyzed by the enzyme hexokinase, a transferase enzyme.

Glucose + ATP ⇄ G6P + ADP

Hexokinase is one of three regulated enzymes in glycolysis and is inhibited by one of the products of its action - G6P. Hexokinase has flexibility in its substrate binding and is able to phosphorylate a variety of hexoses, including fructose, mannose, and galactose.

Why phosphorylate glucose?

Phosphorylation of glucose serves two important purposes. First, the addition of a phosphate group to glucose effectively traps it in the cell, as G6P cannot diffuse across the lipid bilayer. Second, the reaction decreases the concentration of free glucose, favoring additional import of the molecule. G6P is a substrate for the pentose phosphate pathway and can also be converted to glucose-1-phosphate (G1P) for use in glycogen synthesis and galactose metabolism.

It is worth noting that the liver has an enzyme like hexokinase called glucokinase, which Reaction #1 - Phosphorylation of glucose - catalyzed by hexokinase has a much higher Km (lower affinity) for glucose. This is important, because the liver is a site of glucose synthesis (gluconeogenesis) where cellular concentrations of glucose can be relatively high. With a lower affinity glucose phosphorylating enzyme, glucose is not converted to G6P unless glucose concentrations get high, so the liver is able to release the glucose it makes into the bloodstream for the rest of the body to use.

Reaction 2

Next, G6P is converted to fructose-6-phosphate (F6P), in a reaction catalyzed by the enzyme phosphoglucose isomerase.

G6P⇄F6P

The reaction has a low ΔG°', so it is readily favorable in either direction.

Reaction 3

F6P+ATP⇄F1,6BP+ADP

The second input of energy occurs when F6P gets another phosphate from ATP in a reaction catalyzed by the enzyme phosphofructokinase (PFK) to make fructose-1,6- bisphosphate (F1,6BP). PFK is a very important enzyme regulating glycolysis, with several allosteric activators and inhibitors.

Like the hexokinase reaction the energy from ATP is needed to make the reaction energetically favorable. PFK is the most important regulatory enzyme in the pathway and this reaction is the rate limiting step. It is also one of three essentially irreversible reactions in glycolysis.

Reaction 4

F1,6BP⇄Ga-3P+DHAP

With the glycolysis pump thus primed, the pathway proceeds to split the F1,6BP into two 3-carbon intermediates. This reaction catalyzed by the lyase known as aldolase is energetically a "hump" to overcome in the glycolysis direction (ΔG°' = +24 kJ/mol) so to get over the energy hump, cells must increase the concentration the reactant (F1,6BP) and decrease the concentration of the products, which are glyceraldehyde- 3-phosphate (Ga-3P) and dihydroxyacetone phosphate (DHAP).

Reaction 5

DHAP⇄Ga-3P

In the next step, DHAP is converted to Ga-3P in a reaction catalyzed by the enzyme triosephosphate isomerase. At this point, the six carbon glucose molecule has been broken down to two units of three carbons each - Ga-3P. From this point forward each reaction of glycolysis contains two of each molecule. Reaction #5 is fairly readily reversible in cells.

Reaction 6

Ga-3P+NAD++Pi ⇄ 1,3BPG+NADH+H+

In this reaction, Ga-3P is oxidized in the only oxidation step of glycolysis catalyzed by the enzyme glyceraldehyde-3- phosphate dehydrogenase, an oxidoreductase. The aldehyde in this reaction is oxidized, then linked to a phosphate to make an ester - 1,3-bisphospho-glycerate (1,3BPG). Electrons from the oxidation are donated to NAD+, creating NADH.

NAD+ is a critical constituent in this reaction and can be regenerated anaerobically at the end of the pathway .

Note here that ATP energy was not required to put the phosphate onto the oxidized Ga-3P. The reason for this is because the energy provided by the oxidation reaction is sufficient for adding the phosphate.

Reaction 7

1,3-BPG + ADP ⇄ 3-PGA + ATP

The two phosphates in the tiny 1,3-BPG molecule repel each other and give the molecule high potential energy. This energy is utilized by the enzyme phosphoglycerate kinase (another transferase) to phosphorylate ADP and make ATP, as well as the product, 3-phosphoglycerate (3-PGA). This is an example of a substrate-level phosphorylation. Such mechanisms for making ATP require an intermediate with a high enough energy to phosphorylate ADP to make ATP.

Though there are a few substrate level phosphorylations in cells (including another one at the end of glycolysis), the vast major of ATP is made by oxidative phosphorylation in the mitochondria (in animals). Since there are two 1-3 BPGs produced for every glucose, the two ATPs produced in this reaction replenish the two ATPs used to start the cycle and the net ATP count at this point of the pathway is zero.

Reaction 8

3−PGA ⇄ 2−PGA

Conversion of the 3-PGA intermediate to 2-PGA (2- phosphoglycerate).

Reaction 9

2−PGA ⇄ PEP + H2O

2-PGA is converted by enolase (a lyase) to phosphoenolpyruvate (PEP) by removal of water, creating a very high energy intermediate. The reaction is readily reversible, but with PEP, the cell has one of its highest energy molecules and that is important for the next reaction.

Reaction 10

PEP + ADP ⇄ PYR + ATP

Conversion of PEP to pyruvate by pyruvate kinase is the second substrate level phosphorylation of glycolysis, creating ATP. This reaction is what some refer to as the "Big Bang" of glycolysis because there is almost enough energy in PEP to stimulate production of a second ATP ($\Delta G°' = 31.6$ kJ/ mol), but it is not used. Consequently, this energy is lost as heat. If you wonder why you get hot when you exercise, the heat produced in the breakdown of glucose is a prime contributor and the pyruvate kinase reaction is a major source.

Pyruvate kinase is the third and last enzyme of glycolysis that is regulated (Figure 3). The primary reason this is the case is to be able to prevent this reaction from occurring when cells are making PEP while going through gluconeogenesis (Figure 3).

Catabolism of other sugars

Though glycolysis is a pathway focused on the metabolism of glucose and fructose, the fact that other sugars can be readily metabolized into glucose means that glycolysis can be used for extracting energy from them as well. Galactose is a good example. It is commonly produced in the produced in the body as a result of hydrolysis of lactose, catalyzed by the enzyme known as lactase. Deficiency of lactase is the cause of lactose intolerance.

Galactose begins preparation for entry into glycolysis by being converted to galactose-1- phosphate. Each turn of the cycle takes in one galactose-1-phosphate and releases one glucose-1-phosphate.

Deficiency of galactose conversion enzymes results in accumulation of galactose (from breakdown of lactose). Excess galactose is converted to galactitol, a sugar alcohol. Galactitol in the human eye lens causes it to absorb water and this may be a factor in formation of cataracts.

Free fructose can also enter glycolysis by two mechanisms. First, it can be phosphorylated to fructose-6-phosphate by hexokinase. Or, phosphorylation of fructose by fructokinase produces fructose-1-phosphate and cleavage of that by fructose-1-phosphate aldolase yields DHAP and glyceraldehyde.

Phosphorylation of glyceraldehyde by triose kinase yields Ga-3P. This alternative entry means for fructose may have important implications because DHAP and Ga-3P are introduced into the glycolysis pathway while bypassing PFK regulation. Some have proposed this may be important when considering metabolism of high fructose corn syrup, since it forces production of pyruvate, a precursor of acetyl-CoA, which is itself a precursor of fatty acids when ATP levels are high.

Glycerol metabolism

Glycerol is an important molecule for the synthesis of fats, glycerophospholipids, and other membrane lipids.

All of the intermediates of the citric acid cycle can be converted ultimately to oxaloacetate, which is a gluconeogenesis intermediate, as well.

It is worth noting that animals are unable to use fatty acids as materials for gluconeogenesis in net amounts, but they can, in fact, use glycerol in both glycolysis and gluconeogenesis. It is the only part of the fat molecule that can be so used.

Pyruvate metabolism

As noted, pyruvate produced in glycolysis can be oxidized to acetyl-CoA, which is itself oxidized in the citric acid cycle to carbon dioxide. That is not the only metabolic fate of pyruvate, though.

Pyruvate is a "starting" point for gluconeogenesis, being converted to oxaloacetate in the mitochondrion in the first step. Pyruvate in animals can also be reduced to lactate by adding electrons from NADH. This reaction produces NAD^+ and is critical for

generating the latter molecule to keep the glyceraldehyde-3-phosphate dehydrogenase reaction of glycolysis (reaction #6) going under conditions when there is no oxygen.

This is because oxygen is necessary for the electron transport system (ETS) to operate and it performs the important function of converting NADH back to NAD^+. When the ETS is running, NADH donates electrons to Complex I and is oxidized to NAD^+ in the process, generating the intermediate needed for oxidizing Ga-3P. In the absence of oxygen, however, NADH cannot be converted to NAD^+ by the ETS, so an alternative means of making NAD^+ is necessary for keeping glycolysis running under low oxygen conditions (fermentation).

Bacteria and yeast generate NAD^+ under oxygen deprived conditions by doing fermentation in a different way. They use NADH-requiring reactions that regenerate NAD^+ while producing ethanol from pyruvate instead of making lactate. Thus, fermentation of pyruvate is essential to keep glycolysis operating when oxygen is limiting. It is also for these reasons that brewing of beer (using yeast) involves depletion of oxygen and muscles low in oxygen produce lactic acid (animals).

Pyruvate is a precursor of alanine which can be easily synthesized by transfer of a nitrogen from an amine donor, such as glutamic acid. Pyruvate can also be converted into oxaloacetate by carboxylation in the process of gluconeogenesis.

The enzymes involved in pyruvate metabolism include pyruvate dehydrogenase (makes acetyl-CoA), lactate dehydrogenase (makes lactate), transaminases (makes alanine), pyruvate carboxylase (makes OAA). When oxygen is absent, pyruvate is converted to lactate (animals) or ethanol (bacteria and yeast). When oxygen is present, pyruvate is converted to acetyl-CoA.

Gluconeogenesis

The anabolic counterpart to glycolysis is gluconeogenesis, which occurs mostly in the cells of the liver and kidney and virtually no other cells in the body. In seven of the eleven reactions of gluconeogenesis (starting from pyruvate), the same enzymes are used as in glycolysis, but the reaction directions are reversed. Notably, the ΔG values of these reactions in the cell are typically near zero, meaning their direction can be readily controlled by changing substrate and product concentrations by small amounts.

The three regulated enzymes of glycolysis all catalyze reactions whose cellular ΔG values are not close to zero, making manipulation of reaction direction for their reactions non-trivial. Consequently, cells employ “work-around” reactions catalyzed by four different enzymes to favor gluconeogenesis, when appropriate.

Bypassing pyruvate kinase

Two of the enzymes (pyruvate carboxylase and PEP carboxykinase - PEPCK) catalyze reactions that bypass pyruvate kinase. F1,6BPase bypasses PFK and G6Pase bypasses hexokinase. Notably, pyruvate carboxylase and G6Pase are found in the mitochondria and endoplasmic reticulum, respectively, whereas the other two are found in the cytoplasm along with all of the enzymes of glycolysis.

Biotin An important coenzyme used by pyruvate carboxylase is biotin. Biotin is commonly used by carboxylases to carry CO_2 to incorporate into the substrate.

Also known as vitamin H, biotin is a water soluble B vitamin (B7) needed for many metabolic processes, including fatty acid synthesis, gluconeogenesis, and amino acid metabolism. Deficiency of the vitamin is rare, since it is readily produced by gut bacteria.

Reciprocal regulation

All of the enzymes of glycolysis and nine of the eleven enzymes of gluconeogenesis are all in the cytoplasm, necessitating a coordinated means of controlling them. Cells generally need to minimize the extent to which paired anabolic and catabolic pathways are occurring simultaneously, lest they produce a futile cycle, resulting in wasted energy with no tangible product except heat. The mechanisms of controlling these pathways have opposite effects on catabolic and anabolic processes. This method of control is called reciprocal regulation.

Allosteric Regulation of Glycolysis & Gluconeogenesis

Reciprocal Regulation

AMP - Activates PFK, Inhibits F1,6BPase

Citrate - Activates PFK, Inhibits F1,6BPase

Glycolysis Only

ATP - Inhibits PFK and Pyruvate Kinase

Alanine - Inhibits Pyruvate Kinase

Reciprocal allosteric effects For example, in glycolysis, the enzyme known as phosphofructokinase (PFK) is allosterically activated by AMP . The corresponding enzyme from gluconeogenesis catalyzing a reversal of the glycolysis reaction is known as F1,6BPase. F1,6BPase is inhibited by AMP.

Reciprocal covalent effects

In glycogen metabolism, the enzymes phosphorylase kinase and glycogen phosphorylase catalyze reactions important for the breakdown of glycogen. The enzyme glycogen synthase catalyzes the synthesis of glycogen.

Phosphorylation of glycogen phosphorylase has the effect of activation, whereas phosphorylation of glycogen synthase makes it less active. Conversely, dephosphorylation has the reverse effects on these enzymes - glycogen phosphorylase become less active and glycogen synthase becomes more active.

Simple and efficient

The advantage of reciprocal regulation schemes is that they are very efficient. It doesn't take separate molecules or separate treatments to control two pathways simultaneously. Further, its simplicity ensures that when one pathway is turned on, the other is turned off.

This is especially important with catabolic/ anabolic regulation, because having both pathways going on simultaneously in a cell is not very productive, leading only to production of heat in a futile cycle.

Specific gluconeogenesis controls

Besides reciprocal regulation, other mechanisms help control gluconeogenesis. First, PEP carboxykinase (PEPCK) is controlled largely at the level of synthesis.

Pyruvate carboxylase is sequestered in the mitochondrion (one means of regulation) and is sensitive to acetyl-CoA, which is an allosteric activator. Acetyl-CoA concentrations increase as the citric acid cycle activity decreases. Glucose-6-phosphatase is present in low concentrations in many tissues, but is found most abundantly and importantly in the major gluconeogenic organs – the liver and kidney cortex.

Specific glycolysis controls

Control of glycolysis and gluconeogenesis is unusual for metabolic pathways, in that regulation occurs at multiple points. For glycolysis, this involves three enzymes:

1. Hexokinase (Glucose ⇄ G6P)

2. Phosphofructokinase-1 (F6P ⇄ F1,6BP)

3. Pyruvate kinase (PEP ⇄ Pyruvate).

Regulation of hexokinase is the simplest of these. The enzyme is unusual in being inhibited by its product, glucose-6-phosphate. This ensures when glycolysis is slowing down hexokinase is also slowing down to reduce feeding the pathway.

Pyruvate kinase

It might also seem odd that pyruvate kinase, the last enzyme in the pathway, is regulated, but the reason is simple. Pyruvate kinase catalyzes the most energetically rich reaction of glycolysis. The reaction is favored so strongly in the forward direction that cells must do a 'two-step' around it in the reverse direction when making glucose in the gluconeogenesis pathway. In other words, it takes two enzymes, two reactions, and two triphosphates (ATP and GTP) to go from one pyruvate back to one PEP in gluconeogenesis. When cells are needing to make glucose, they can't be sidetracked by having the PEP they have made in gluconeogenesis be converted directly back to pyruvate by pyruvate kinase. Consequently, pyruvate kinase must be inhibited during gluconeogenesis or a futile cycle will occur and no glucose will be made.

Reactions pulled

As noted above, the aldolase reaction is energetically unfavorable (high positive ΔG°'), thus allowing F1,6BP to accumulate. When this happens, some of the excess F1,6BP binds to pyruvate kinase, which activates and jump starts the conversion of PEP to pyruvate. The resulting drop in PEP levels has the effect of "pulling" on the reactions preceding pyruvate kinase. As a consequence, the concentrations of Ga-3P and DHAP fall, helping to pull the aldolase reaction forward.

PFK regulation

PFK has a complex regulation scheme. PFK is allosterically activated by AMP.

Citrate inhibits PFK. PFK is also inhibited by ATP. PFK's inhibition by ATP is noteworthy and odd at first glance because ATP is also a substrate whose increasing concentration should favor the reaction instead of inhibit it. The root of this conundrum is that PFK has two ATP binding sites - one at an allosteric site that binds ATP relatively inefficiently and one that the active site that binds ATP with high affinity. Thus, only when ATP concentration is high is binding at the allosteric site favored and only then can ATP turn off the enzyme.

Cori cycle

With respect to energy, the liver and muscles act complementarily. The liver is the major organ in the body for the synthesis of glucose. Muscles are major users of glucose to make ATP. Actively exercising muscles use oxygen faster than the blood can deliver it. As a consequence, the muscles go anaerobic and produce lactate. This lactate is of no use to muscle cells, so they dump it into the blood. Lactate travels in the blood to the liver, which takes it up and reoxidizes it back to pyruvate, catalyzed by the enzyme lactate dehydrogenase.

Pyruvate in the liver is then converted to glucose by gluconeogenesis. The glucose thus made by the liver is dumped into the bloodstream where it is taken up by muscles and used for energy, completing the important intercellular pathway known as the Cori cycle.

Polysaccharide metabolism

Sugars are metabolized rapidly in the body and that is one of the primary reasons they are used. Managing levels of glucose in the body is very important - too much leads to complications related to diabetes and too little gives rise to hypoglycemia (low blood sugar). Sugars in the body are maintained by three processes - 1) diet; 2) synthesis (gluconeogenesis); and 3) storage. The storage forms of sugars are, of course, the polysaccharides and their metabolism is our next topic of discussion.

Glycogen

Animals store glucose primarily in liver and muscle in the form of a compound related to amylopectin known as glycogen. The structural differences between glycogen and amylopectin are solely due to the frequency of the α-1,6 branches of glucoses. In glycogen they occur about every 10 residues instead of every 30-50, as in amylopectin.

Glycogen provides an additional source of glucose besides that produced via gluconeogenesis. Because glycogen contains so many glucoses, it acts like a battery backup for the body, providing a quick source of glucose when needed and providing a place to store excess glucose when glucose concentrations in the blood rise.

The branching of glycogen is an important feature of the molecule metabolically as well. Since glycogen is broken down from the "ends" of the molecule, more branches translate to more ends, and more glucose that can be released at once.

Just as in gluconeogenesis, the cell has a separate mechanism for glycogen synthesis that is distinct from glycogen breakdown. As noted previously, this allows the cell to separately control the reactions, avoiding futile cycles, and enabling a process to occur efficiently (synthesis of glycogen) that would not occur if it were simply the reversal of glycogen breakdown.

Glycogen breakdown

Breakdown of glycogen involves 1) release of glucose-1-phosphate (G1P), 2) rearranging the remaining glycogen (as necessary) to permit continued breakdown, and 3) conversion of G1P to G6P for further metabolism. G6P can be 1) used in glycolysis, 2) converted to glucose by gluconeogenesis, or 3) oxidized in the pentose phosphate pathway.

Glycogen phosphorylase (sometimes simply called phosphorylase) catalyzes breakdown of glycogen into glucose-1- Phosphate (G1P). The reaction that produces G1P from glycogen is a phosphorolysis, not a hydrolysis reaction. The distinction is that

hydrolysis reactions use water to cleave bigger molecules into smaller ones, but phosphorolysis reactions use phosphate instead for the same purpose. Note that the phosphate is just that - it does NOT come from ATP. Since ATP is not used to put phosphate on G1P, the reaction saves the cell energy.

G1P can be converted to G6P by action of an enzyme called phosphoglucomutase. This reaction is readily reversible, allowing G6P and G1P to be interconverted as the concentration of one or the other increases. This is important, because phosphoglucomutase is needed to form G1P for glycogen synthesis.

Regulation of glycogen metabolism

Regulation of glycogen metabolism is complex, occurring both allosterically and via hormone-receptor controlled events that result in protein phosphorylation or dephosphorylation. In order to avoid a futile cycle of glycogen synthesis and breakdown simultaneously, cells have evolved an elaborate set of controls that ensure only one pathway is primarily active at a time.

Regulation of glycogen metabolism is managed by the enzymes glycogen phosphorylase and glycogen synthase. Glycogen phosphorylase is regulated by covalent modification (phosphorylation / dephosphorylation). Its regulation is consistent with the energy needs of the cell.

PKA and cAMP

PKA is activated by cAMP, which is, in turn, produced by adenylate cyclase after activation by a G-protein. Epinephrine exerts its greatest effects on muscle and glucagon works preferentially on the liver. Thus, epinephrine and glucagon can activate glycogen breakdown by stimulating synthesis of cAMP followed by the cascade of events.

Glycogen synthesis

The anabolic pathway opposing glycogen breakdown is that of glycogen synthesis. Synthesis of glycogen starts with G1P, which is converted to an 'activated' intermediate, UDPglucose. This activated intermediate is what 'adds' the glucose to the growing glycogen chain in a reaction catalyzed by the enzyme known as glycogen synthase.

Steps

Let us first consider the steps in glycogen synthesis. 1) Glycogen synthesis from glucose involves phosphorylation to form G6P, and isomerization to form G1P (using phospho-glucomutase, common to glycogen breakdown). G1P is reacted with UTP to form UDP-glucose in a reaction catalyzed by UDP-glucose pyrophosphorylase. Glycogen synthase catalyzes synthesis of glycogen by joining carbon #1 of the UDP-derived glucose onto the carbon #4 of the non-reducing end of a glycogen chain, to form the familiar α(1,4) glycogen links. Another product of the reaction is UDP.

Effect of phosphorylation

In glycogen synthesis, protein kinase A phosphorylates the active form of glycogen synthase, and converts it into the usually inactive b form.

Glycogen synthase, glycogen phosphorylase can all be dephosphorylated by the same enzyme and it is activated when insulin binds to its receptor in the cell membrane.

Big picture

In the big picture, binding of epinephrine or glucagon to appropriate cell receptors stimulates a phosphorylation cascade which simultaneously activates breakdown of glycogen by glycogen phosphorylase and inhibits synthesis of glycogen by glycogen synthase. Epinephrine, is also known as adrenalin, and the properties that adrenalin gives arise from a large temporary increase of blood glucose, which powers muscles.

On the other hand, insulin stimulates dephosphorylation by activating phosphoprotein phosphatase. Dephosphorylation reduces action of glycogen phosphorylase (less glycogen breakdown) and activates glycogen synthase (starts glycogen synthesis). Our bodies make glycogen when blood glucose levels rise. Since high blood glucose levels are harmful, insulin stimulates cells to take up glucose. In the liver and in muscle cells, the uptaken glucose is made into glycogen.

Pentose phosphate pathway

The pentose phosphate pathway (PPP) is an oxidative pathway involving sugars that is sometimes described as a parallel pathway to glycolysis. It is, in fact, a pathway with multiple inputs and outputs. PPP is also a major source of NADPH for biosynthetic reactions and can provide ribose-5-phosphate for nucleotide synthesis.

Oxidation

Beginning with G6P, PPP proceeds through its oxidative phase as follows:

The enzyme catalyzing the reaction is G6P dehydrogenase. It is the rate limiting step of the pathway and the enzyme is inhibited both by NADPH and acetyl-CoA. NADPH is important for anabolic pathways, such as fatty acid synthesis and also for protection against damage from reactive oxygen species.

In the reversible reactions of the pentose phosphate pathway, one can see how glycolysis intermediates can easily be rearranged and made into other sugars. Thus, Ga-3-P and F6P can be readily made into Ribose-5- phosphate for nucleotide synthesis.

Involvement of F6P in the pathway permits cells to continue making nucleotides (by making R-5-P).

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CHAPTER OVERVIEW

15: Lipids

The lipids are a large and diverse group of naturally occurring organic compounds that are related by their solubility in nonpolar organic solvents (e.g., ether, chloroform, acetone and benzene) and general insolubility in water. There is great structural variety among the lipids, as will be demonstrated in the following sections.

15.1: Prelude to Lipids
15.2: Fatty Acids
15.3: Fats and Oils
15.4: Membranes and Membrane Lipids
15.5: Membranes
15.5.1: Basic Concepts in Membranes
15.5.2: Transport in Membranes
15.6: Structure and Function - Lipids and Membranes
15.7: Steroids
15.8: 15.8-Lipid Catabolism
15.9: Overview of Lipid Catabolism
15.10: Lipid Details
15.10.1: Fatty Acid Oxidation
15.10.2: Acetyl-CoA Metabolism
15.10.3: Fatty Acid Synthesis
15.10.4: Cholesterol Metabolism
15.10.5: Ketone Body Synthesis
15.10.6: Prostaglandin Synthesis
15.E: Exercises
15.S: Lipids (Summary)

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15.1: Prelude to Lipids

On July 11, 2003, the Food and Drug Administration amended its food labeling regulations to require that manufacturers list the amount of *trans* fatty acids on Nutrition Facts labels of foods and dietary supplements, effective January 1, 2006. This amendment was a response to published studies demonstrating a link between the consumption of *trans* fatty acids and an increased risk of heart disease. *Trans* fatty acids are produced in the conversion of liquid oils to solid fats, as in the creation of many commercial margarines and shortenings. They have been shown to increase the levels of low-density lipoproteins (LDLs)—complexes that are often referred to as bad cholesterol—in the blood. In this chapter, you will learn about fatty acids and what is meant by a *trans* fatty acid, as well as the difference between fats and oils. You will also learn what cholesterol is and why it is an important molecule in the human body.

Fats and oils, found in many of the foods we eat, belong to a class of biomolecules known as lipids. Gram for gram, they pack more than twice the caloric content of carbohydrates: the oxidation of fats and oils supplies about 9 kcal of energy for every gram oxidized, whereas the oxidation of carbohydrates supplies only 4 kcal/g. Although the high caloric content of fats may be bad news for the dieter, it says something about the efficiency of nature's designs. Our bodies use carbohydrates, primarily in the form of glucose, for our *immediate* energy needs. Our capacity for storing carbohydrates for later use is limited to tucking away a bit of glycogen in the liver or in muscle tissue. We store our *reserve* energy in lipid form, which requires far less space than the same amount of energy stored in carbohydrate form. Lipids have other biological functions besides energy storage. They are a major component of the membranes of the 10 trillion cells in our bodies. They serve as protective padding and insulation for vital organs. Furthermore, without lipids in our diets, we would be deficient in the fat-soluble vitamins A, D, E, and K.

Lipids are not defined by the presence of specific functional groups, as carbohydrates are, but by a physical property—solubility. Compounds isolated from body tissues are classified as lipids if they are more soluble in organic solvents, such as dichloromethane, than in water. By this criterion, the lipid category includes not only fats and oils, which are esters of the trihydroxy alcohol glycerol and fatty acids, but also compounds that incorporate functional groups derived from phosphoric acid, carbohydrates, or amino alcohols, as well as steroid compounds such as cholesterol (Figure 15.1.1 presents one scheme for classifying the various kinds of lipids). We will discuss the various kinds of lipids by considering one subclass at a time and pointing out structural similarities and differences as we go.

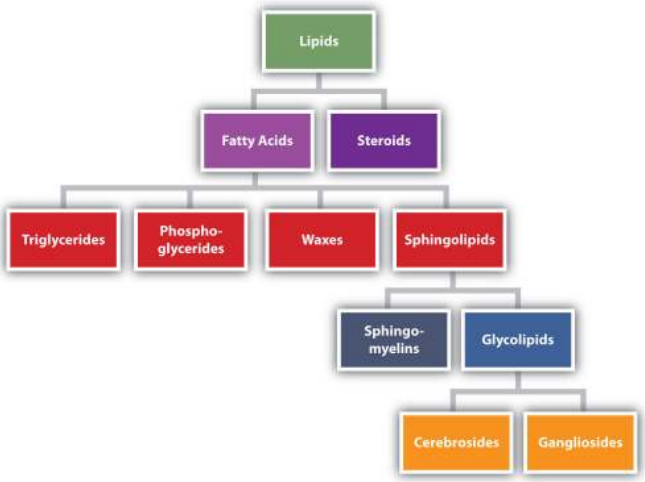


Figure 15.1.1: Lipid Organization Based on Structural Relationships

Lipid categorized into fatty acids and steroids. Fatty acids are further separated into triglycerides, phospho-glycerides, waxes, and sphingolipids. Sphingolipids are separated into sphingo-myelins and glycolipids. Glycolipids are separated into cerebrosides and gangliosides.

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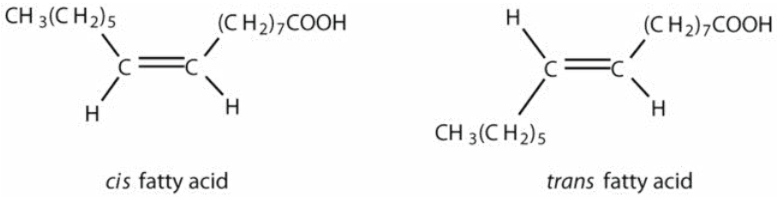
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15.2: Fatty Acids

Learning Objectives

- To recognize the structures of common fatty acids and classify them as saturated, monounsaturated, or polyunsaturated.

Fatty acids are carboxylic acids that are structural components of fats, oils, and all other categories of lipids, except steroids. More than 70 have been identified in nature. They usually contain an even number of carbon atoms (typically 12–20), are generally unbranched, and can be classified by the presence and number of carbon-to-carbon double bonds. Thus, saturated fatty acids contain no carbon-to-carbon double bonds, monounsaturated fatty acids contain one carbon-to-carbon double bond, and polyunsaturated fatty acids contain two or more carbon-to-carbon double bonds.



Cis fatty acids have two H atoms on the same side of the plane of the fatty acid while trans has the two H atoms on opposite sides.

Table **15.2.1** lists some common fatty acids and one important source for each. The atoms or groups around the double bonds in unsaturated fatty acids can be arranged in either the cis or trans isomeric form. Naturally occurring fatty acids are generally in the cis configuration.

Table **15.2.1**: Some Common Fatty Acids Found in Natural Fats

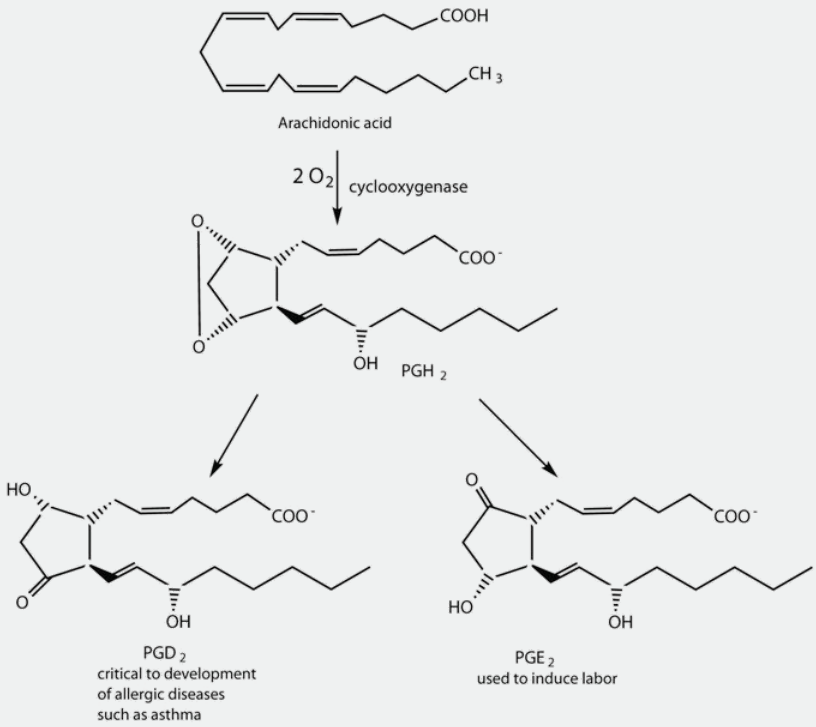
Name	Abbreviated Structural Formula	Condensed Structural Formula	Melting Point (°C)	Source
lauric acid	$C_{11}H_{23}COOH$	$CH_3(CH_2)_{10}COOH$	44	palm kernel oil
myristic acid	$C_{13}H_{27}COOH$	$CH_3(CH_2)_{12}COOH$	58	oil of nutmeg
palmitic acid	$C_{15}H_{31}COOH$	$CH_3(CH_2)_{14}COOH$	63	palm oil
palmitoleic acid	$C_{15}H_{29}COOH$	$CH_3(CH_2)_5CH=CH(CH_2)_7COOH$	0.5	macadamia oil
stearic acid	$C_{17}H_{35}COOH$	$CH_3(CH_2)_{16}COOH$	70	cocoa butter
oleic acid	$C_{17}H_{33}COOH$	$CH_3(CH_2)_7CH=CH(CH_2)_7COOH$	16	olive oil
linoleic acid	$C_{17}H_{31}COOH$	$CH_3(CH_2)_3(CH_2CH=CH)_2(CH_2)_7COOH$	−5	canola oil
α-linolenic acid	$C_{17}H_{29}COOH$	$CH_3(CH_2CH=CH)_3(CH_2)_7COOH$	−11	flaxseed
arachidonic acid	$C_{19}H_{31}COOH$	$CH_3(CH_2)_4(CH_2CH=CH)_4(CH_2)_2COOH$	−50	liver

Two polyunsaturated fatty acids—linoleic and α-linolenic acids—are termed essential fatty acids because humans must obtain them from their diets. Both substances are required for normal growth and development, but the human body does not synthesize them. The body uses linoleic acid to synthesize many of the other unsaturated fatty acids, such as arachidonic acid, a precursor for the synthesis of prostaglandins. In addition, the essential fatty acids are necessary for the efficient transport and metabolism of cholesterol. The average daily diet should contain about 4–6 g of the essential fatty acids.

To Your Health: Prostaglandins

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

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



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

Although we often draw the carbon atoms in a straight line, they actually have more of a zigzag configuration (Figure **15.2.2*a***). Viewed as a whole, however, the saturated fatty acid molecule is relatively straight (Figure **15.2.2*b***). Such molecules pack closely together into a crystal lattice, maximizing the strength of dispersion forces and causing fatty acids and the fats derived from them to have relatively high melting points. In contrast, each *cis* carbon-to-carbon double bond in an unsaturated fatty acid produces a pronounced bend in the molecule, so that these molecules do not stack neatly. As a result, the intermolecular attractions of unsaturated fatty acids (and unsaturated fats) are weaker, causing these substances to have lower melting points. Most are liquids at room temperature.

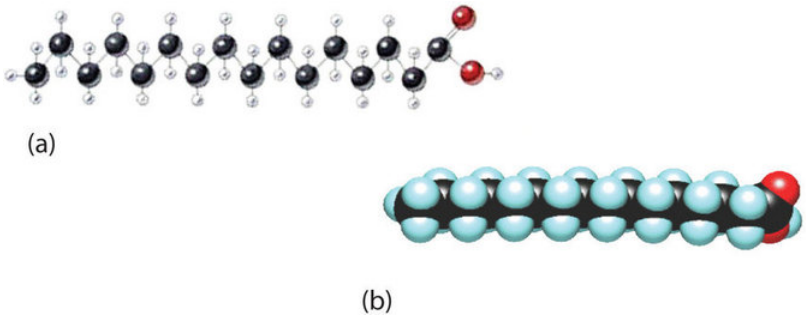
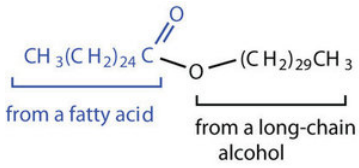


Figure **15.2.2**: The Structure of Saturated Fatty Acids. (a) There is a zigzag pattern formed by the carbon-to-carbon single bonds in the ball-and-stick model of a palmitic acid molecule. (b) A space-filling model of palmitic acid shows the overall straightness of a saturated fatty acid molecule.

Waxes are esters formed from long-chain fatty acids and long-chain alcohols. Most natural waxes are mixtures of such esters. Plant waxes on the surfaces of leaves, stems, flowers, and fruits protect the plant from dehydration and invasion by harmful microorganisms. Carnauba wax, used extensively in floor waxes, automobile waxes, and furniture polish, is largely myricyl cerotate, obtained from the leaves of certain Brazilian palm trees. Animals also produce waxes that serve as protective coatings, keeping the surfaces of feathers, skin, and hair pliable and water repellent. In fact, if the waxy coating on the feathers of a water bird is dissolved as a result of the bird swimming in an oil slick, the feathers become wet and heavy, and the bird, unable to maintain its buoyancy, drowns.



Myricyl cerotate
(found in carnauba wax)

Summary

Fatty acids are carboxylic acids that are the structural components of many lipids. They may be saturated or unsaturated. Most fatty acids are unbranched and contain an even number of carbon atoms. Unsaturated fatty acids have lower melting points than saturated fatty acids containing the same number of carbon atoms.

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15.3: Fats and Oils

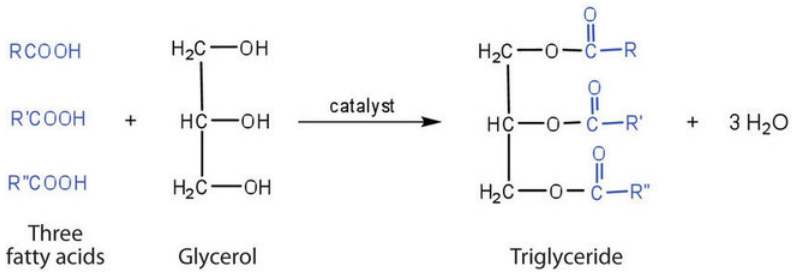
Learning Objectives

- Explain why fats and oils are referred to as triglycerides.
- Explain how the fatty acid composition of the triglycerides determines whether a substance is a fat or oil.
- Describe the importance of key reactions of triglycerides, such as hydrolysis, hydrogenation, and oxidation.

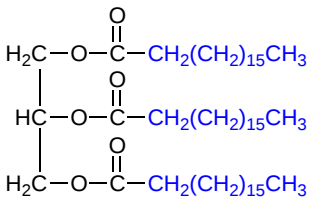
Fats and oils are the most abundant lipids in nature. They provide energy for living organisms, insulate body organs, and transport fat-soluble vitamins through the blood.

Structures of Fats and Oils

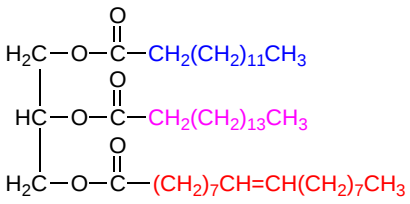
Fats and oils are called triglycerides (or *triacylcylgerols*) because they are esters composed of three fatty acid units joined to *glycerol*, a trihydroxy alcohol:



If all three OH groups on the glycerol molecule are esterified with the same fatty acid, the resulting ester is called a *simple triglyceride*. Although simple triglycerides have been synthesized in the laboratory, they rarely occur in nature. Instead, a typical triglyceride obtained from naturally occurring fats and oils contains two or three different fatty acid components and is thus termed a *mixed triglyceride*.



Tristearin
a simple triglyceride



a mixed triglyceride

A triglyceride is called a fat if it is a solid at 25°C; it is called an oil if it is a liquid at that temperature. These differences in melting points reflect differences in the degree of unsaturation and number of carbon atoms in the constituent fatty acids. Triglycerides obtained from animal sources are usually solids, while those of plant origin are generally oils. Therefore, we commonly speak of animal fats and vegetable oils.

No single formula can be written to represent the naturally occurring fats and oils because they are highly complex mixtures of triglycerides in which many different fatty acids are represented. Table 15.3.1 shows the fatty acid compositions of some common

fats and oils. The composition of any given fat or oil can vary depending on the plant or animal species it comes from as well as on dietetic and climatic factors. To cite just one example, lard from corn-fed hogs is more highly saturated than lard from peanut-fed hogs. Palmitic acid is the most abundant of the saturated fatty acids, while oleic acid is the most abundant unsaturated fatty acid.

Table **15.3.1**: Average Fatty Acid Composition of Some Common Fats and Oils (%)*

	Lauric	Myristic	Palmitic	Stearic	Oleic	Linoleic	Linolenic
Fats							
butter (cow)	3	11	27	12	29	2	1
tallow		3	24	19	43	3	1
lard		2	26	14	44	10	
Oils							
canola oil			4	2	62	22	10
coconut oil†	47	18	9	3	6	2	
corn oil			11	2	28	58	1
olive oil			13	3	71	10	1
peanut oil			11	2	48	32	
soybean oil			11	4	24	54	7

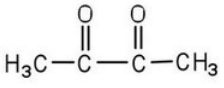
*Totals less than 100% indicate the presence of fatty acids with fewer than 12 carbon atoms or more than 18 carbon atoms.

†Coconut oil is highly saturated. It contains an unusually high percentage of the low-melting C_8, C_{10}, and C_{12} saturated fatty acids.

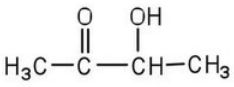
Terms such as *saturated fat* or *unsaturated oil* are often used to describe the fats or oils obtained from foods. Saturated fats contain a high proportion of saturated fatty acids, while unsaturated oils contain a high proportion of unsaturated fatty acids. The high consumption of saturated fats is a factor, along with the high consumption of cholesterol, in increased risks of heart disease.

Physical Properties of Fats and Oils

Contrary to what you might expect, *pure* fats and oils are colorless, odorless, and tasteless. The characteristic colors, odors, and flavors that we associate with some of them are imparted by foreign substances that are lipid soluble and have been absorbed by these lipids. For example, the yellow color of butter is due to the presence of the pigment carotene; the taste of butter comes from two compounds—diacetyl and 3-hydroxy-2-butanone—produced by bacteria in the ripening cream from which the butter is made.



Diacetyl

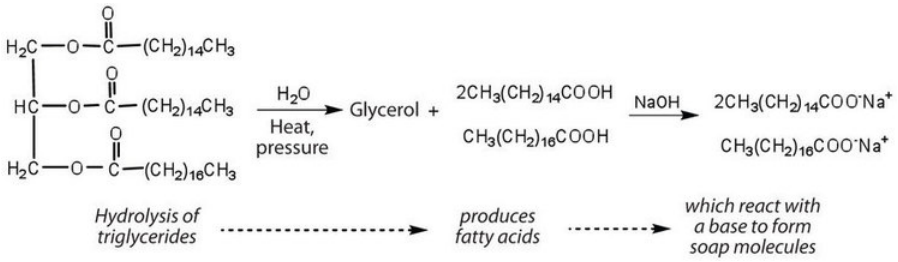


3-hydroxy-2-butanone

Fats and oils are lighter than water, having densities of about 0.8 g/cm^3. They are poor conductors of heat and electricity and therefore serve as excellent insulators for the body, slowing the loss of heat through the skin.

Chemical Reactions of Fats and Oils

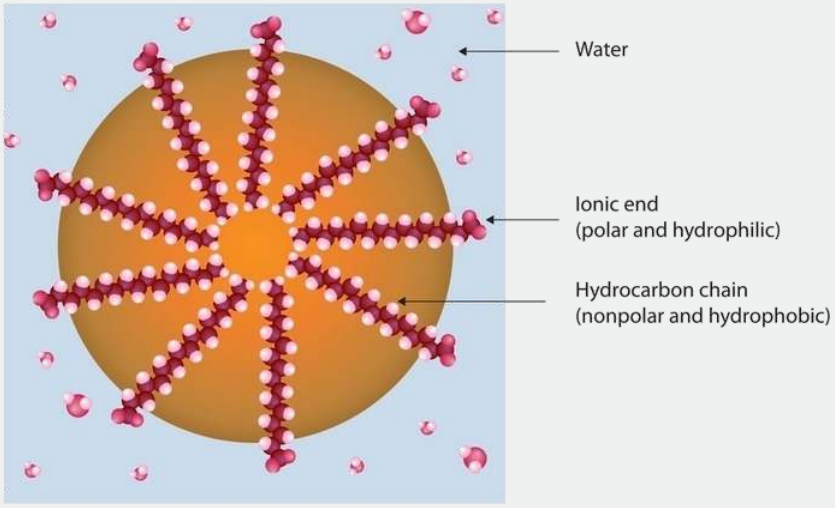
Fats and oils can participate in a variety of chemical reactions—for example, because triglycerides are esters, they can be hydrolyzed in the presence of an acid, a base, or specific enzymes known as lipases. The hydrolysis of fats and oils in the presence of a base is used to make soap and is called saponification. Today most soaps are prepared through the hydrolysis of triglycerides (often from tallow, coconut oil, or both) using water under high pressure and temperature [700 lb/in^2 (~50 atm or 5,000 kPa) and 200°C]. Sodium carbonate or sodium hydroxide is then used to convert the fatty acids to their sodium salts (soap molecules):



Looking Closer: Soaps

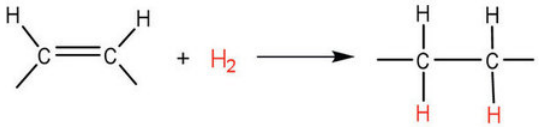
Ordinary soap is a mixture of the sodium salts of various fatty acids, produced in one of the oldest organic syntheses practiced by humans (second only to the fermentation of sugars to produce ethyl alcohol). Both the Phoenicians (600 BCE) and the Romans made soap from animal fat and wood ash. Even so, the widespread production of soap did not begin until the 1700s. Soap was traditionally made by treating molten lard or tallow with a slight excess of alkali in large open vats. The mixture was heated, and steam was bubbled through it. After saponification was completed, the soap was precipitated from the mixture by the addition of sodium chloride (NaCl), removed by filtration, and washed several times with water. It was then dissolved in water and reprecipitated by the addition of more NaCl. The glycerol produced in the reaction was also recovered from the aqueous wash solutions.

Pumice or sand is added to produce scouring soap, while ingredients such as perfumes or dyes are added to produce fragrant, colored soaps. Blowing air through molten soap produces a floating soap. Soft soaps, made with potassium salts, are more expensive but produce a finer lather and are more soluble. They are used in liquid soaps, shampoos, and shaving creams.



Dirt and grime usually adhere to skin, clothing, and other surfaces by combining with body oils, cooking fats, lubricating greases, and similar substances that act like glues. Because these substances are not miscible in water, washing with water alone does little to remove them. Soap removes them, however, because soap molecules have a dual nature. One end, called the *head*, carries an ionic charge (a carboxylate anion) and therefore dissolves in water; the other end, the *tail*, has a hydrocarbon structure and dissolves in oils. The hydrocarbon tails dissolve in the soil; the ionic heads remain in the aqueous phase, and the soap breaks the oil into tiny soap-enclosed droplets called *micelles*, which disperse throughout the solution. The droplets repel each other because of their charged surfaces and do not coalesce. With the oil no longer “gluing” the dirt to the soiled surface (skin, cloth, dish), the soap-enclosed dirt can easily be rinsed away.

The double bonds in fats and oils can undergo hydrogenation and also oxidation. The hydrogenation of vegetable oils to produce semisolid fats is an important process in the food industry. Chemically, it is essentially identical to the catalytic hydrogenation reaction described for alkenes.



In commercial processes, the number of double bonds that are hydrogenated is carefully controlled to produce fats with the desired consistency (soft and pliable). Inexpensive and abundant vegetable oils (canola, corn, soybean) are thus transformed into margarine and cooking fats. In the preparation of margarine, for example, partially hydrogenated oils are mixed with water, salt, and nonfat dry milk, along with flavoring agents, coloring agents, and vitamins A and D, which are added to approximate the look, taste, and nutrition of butter. (Preservatives and antioxidants are also added.) In most commercial peanut butter, the peanut oil has been partially hydrogenated to prevent it from separating out. Consumers could decrease the amount of saturated fat in their diet by using the original unprocessed oils on their foods, but most people would rather spread margarine on their toast than pour oil on it.

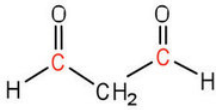
Many people have switched from butter to margarine or vegetable shortening because of concerns that saturated animal fats can raise blood cholesterol levels and result in clogged arteries. However, during the hydrogenation of vegetable oils, an isomerization reaction occurs that produces the *trans* fatty acids mentioned in the opening essay. However, studies have shown that *trans* fatty acids also raise cholesterol levels and increase the incidence of heart disease. *Trans* fatty acids do not have the bend in their structures, which occurs in *cis* fatty acids and thus pack closely together in the same way that the saturated fatty acids do. Consumers are now being advised to use polyunsaturated oils and soft or liquid margarine and reduce their total fat consumption to less than 30% of their total calorie intake each day.

Fats and oils that are in contact with moist air at room temperature eventually undergo oxidation and hydrolysis reactions that cause them to turn rancid, acquiring a characteristic disagreeable odor. One cause of the odor is the release of volatile fatty acids by hydrolysis of the ester bonds. Butter, for example, releases foul-smelling butyric, caprylic, and capric acids. Microorganisms present in the air furnish lipases that catalyze this process. Hydrolytic rancidity can easily be prevented by covering the fat or oil and keeping it in a refrigerator.

Another cause of volatile, odorous compounds is the oxidation of the unsaturated fatty acid components, particularly the readily oxidized structural unit



in polyunsaturated fatty acids, such as linoleic and linolenic acids. One particularly offensive product, formed by the oxidative cleavage of both double bonds in this unit, is a compound called *malonaldehyde*.



Malonaldehyde

Rancidity is a major concern of the food industry, which is why food chemists are always seeking new and better antioxidants, substances added in very small amounts (0.001%–0.01%) to prevent oxidation and thus suppress rancidity. Antioxidants are compounds whose affinity for oxygen is greater than that of the lipids in the food; thus they function by preferentially depleting the supply of oxygen absorbed into the product. Because vitamin E has antioxidant properties, it helps reduce damage to lipids in the body, particularly to unsaturated fatty acids found in cell membrane lipids.

Summary

Fats and oils are composed of molecules known as triglycerides, which are esters composed of three fatty acid units linked to glycerol. An increase in the percentage of shorter-chain fatty acids and/or unsaturated fatty acids lowers the melting point of a fat or oil. The hydrolysis of fats and oils in the presence of a base makes soap and is known as saponification. Double bonds present in unsaturated triglycerides can be hydrogenated to convert oils (liquid) into margarine (solid). The oxidation of fatty acids can form compounds with disagreeable odors. This oxidation can be minimized by the addition of antioxidants.

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15.4: Membranes and Membrane Lipids

Learning Objectives

- Identify the distinguishing characteristics of membrane lipids.
- Describe membrane components and how they are arranged.

All living cells are surrounded by a cell membrane. Plant cells (Figure 15.4.1*A*) and animal cells (Figure 15.4.1*B*) contain a cell nucleus that is also surrounded by a membrane and holds the genetic information for the cell. Everything between the cell membrane and the nuclear membrane—including intracellular fluids and various subcellular components such as the mitochondria and ribosomes—is called the cytoplasm. The membranes of all cells have a fundamentally similar structure, but membrane function varies tremendously from one organism to another and even from one cell to another within a single organism. This diversity arises mainly from the presence of different proteins and lipids in the membrane.

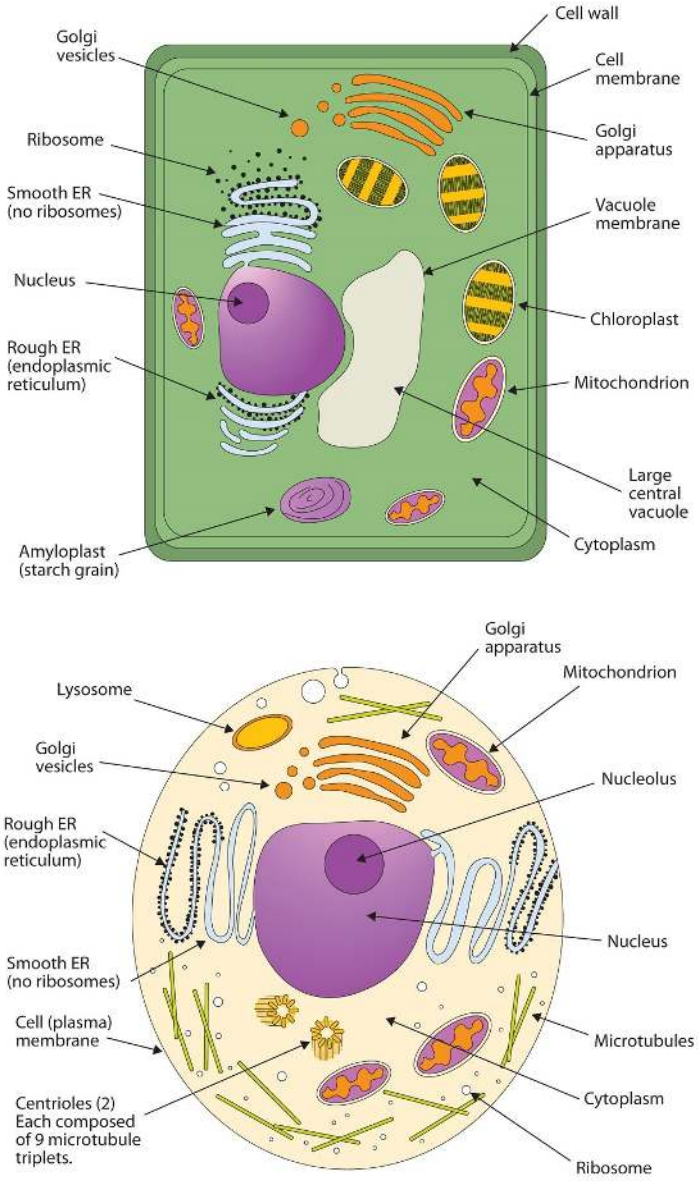


Figure 15.4.1: (A) An Idealized Plant Cell. Not all the structures shown here occur in every type of plant cell. (B) An Idealized Animal Cell. The structures shown here will seldom all be found in a single animal cell.

The lipids in cell membranes are highly polar but have dual characteristics: part of the lipid is ionic and therefore dissolves in water, whereas the rest has a hydrocarbon structure and therefore dissolves in nonpolar substances. Often, the ionic part is referred to as hydrophilic, meaning “water loving,” and the nonpolar part as hydrophobic, meaning “water fearing” (repelled by water). When allowed to float freely in water, polar lipids spontaneously cluster together in any one of three arrangements: micelles, monolayers, and bilayers (Figure **15.4.2**).

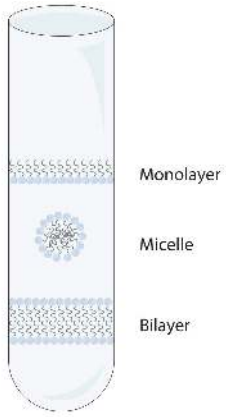


Figure **15.4.2**: Spontaneously Formed Polar Lipid Structures in Water: Monolayer, Micelle, and Bilayer

Micelles are aggregations in which the lipids’ hydrocarbon tails—being hydrophobic—are directed toward the center of the assemblage and away from the surrounding water while the hydrophilic heads are directed outward, in contact with the water. Each micelle may contain thousands of lipid molecules. Polar lipids may also form a monolayer, a layer one molecule thick on the surface of the water. The polar heads face into water, and the nonpolar tails stick up into the air. Bilayers are double layers of lipids arranged so that the hydrophobic tails are sandwiched between an inner surface and an outer surface consisting of hydrophilic heads. The hydrophilic heads are in contact with water on either side of the bilayer, whereas the tails, sequestered inside the bilayer, are prevented from having contact with the water. Bilayers like this make up every cell membrane (Figure **15.4.3**).

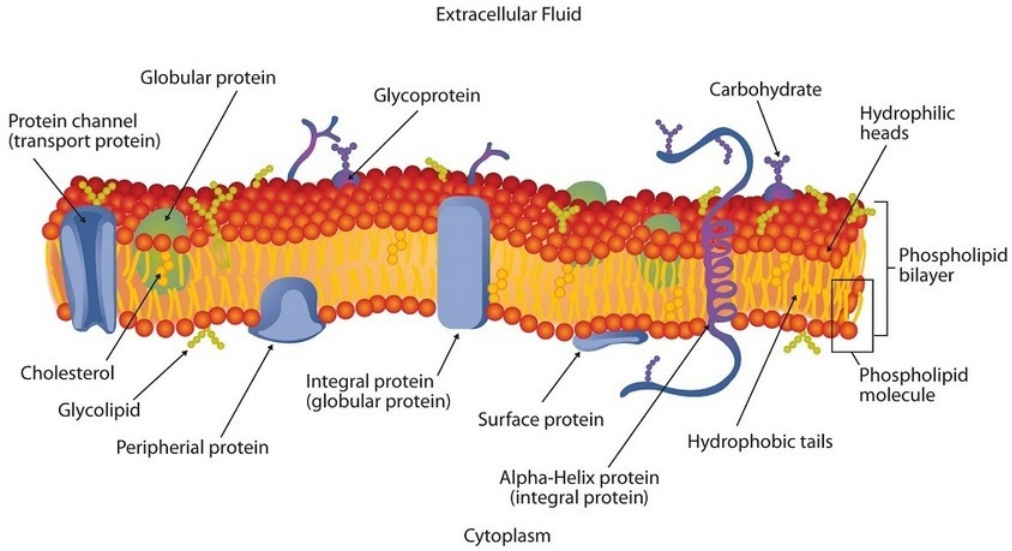


Figure **15.4.3**: Schematic Diagram of a Cell Membrane. The membrane enclosing a typical animal cell is a phospholipid bilayer with embedded cholesterol and protein molecules. Short oligosaccharide chains are attached to the outer surface.

In the bilayer interior, the hydrophobic tails (that is, the fatty acid portions of lipid molecules) interact by means of dispersion forces. The interactions are weakened by the presence of unsaturated fatty acids. As a result, the membrane components are free to mill about to some extent, and the membrane is described as fluid.

The lipids found in cell membranes can be categorized in various ways. Phospholipids are lipids containing phosphorus. Glycolipids are sugar-containing lipids. The latter are found exclusively on the outer surface of the cell membrane, acting as distinguishing surface markers for the cell and thus serving in cellular recognition and cell-to-cell communication. Sphingolipids

are phospholipids or glycolipids that contain the unsaturated amino alcohol sphingosine rather than glycerol. Diagrammatic structures of representative membrane lipids are presented in Figure **15.4.4**.

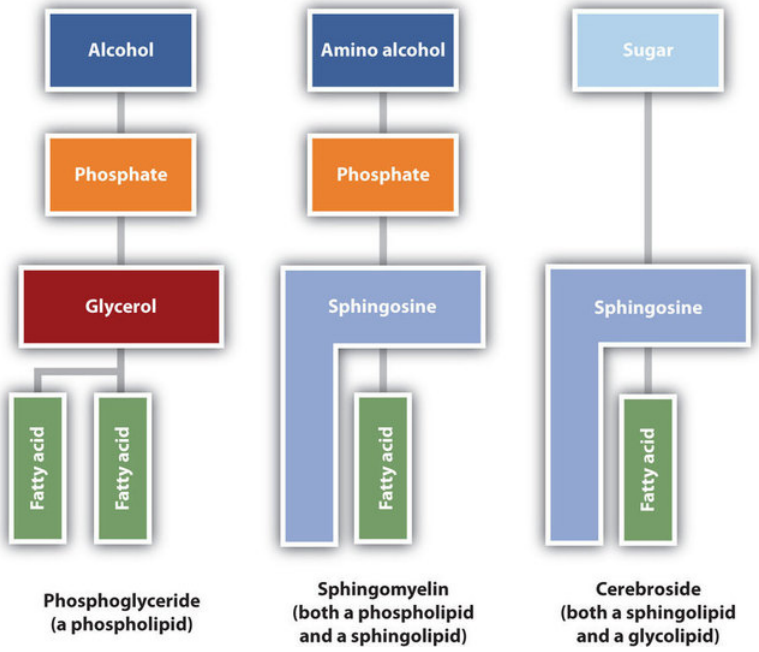


Figure **15.4.4**: Component Structures of Some Important Membrane Lipids

Phosphoglyceride are composed of alcohol, phosphate, glycerol and 2 fatty acids. A sphingomyelin contains phosphate, sphingosine, and a fatty acid. A cerbroside contains sugar, sphingosine and a fatty acid.

Phosphoglycerides (also known as glycerophospholipids) are the most abundant phospholipids in cell membranes. They consist of a glycerol unit with fatty acids attached to the first two carbon atoms, while a phosphoric acid unit, esterified with an alcohol molecule (usually an amino alcohol, as in part (a) of Figure **15.4.5**) is attached to the third carbon atom of glycerol (part (b) of Figure **15.4.5**). Notice that the phosphoglyceride molecule is identical to a triglyceride up to the phosphoric acid unit (part (b) of Figure **15.4.5**).

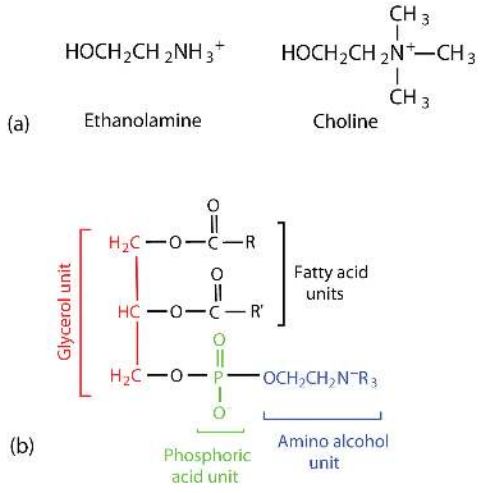
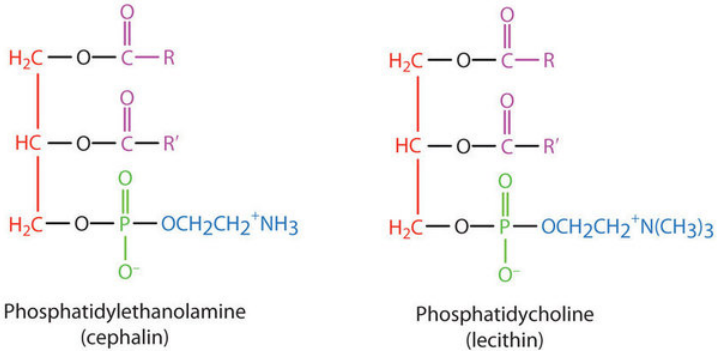


Figure **15.4.5**: Phosphoglycerides. (a) Amino alcohols are commonly found in phosphoglycerides, which are evident in its structural formula (b).

Structural formula of ethanolamine and choline are shown. The structural formula of a phosphoglyceride is shown with the glycerol unit, phosphoric unit, and amino alcohol unit highlighted in different colors.

There are two common types of phosphoglycerides. Phosphoglycerides containing ethanolamine as the amino alcohol are called *phosphatidylethanolamines* or *cephalins*. Cephalins are found in brain tissue and nerves and also have a role in blood clotting. Phosphoglycerides containing choline as the amino alcohol unit are called *phosphatidylcholines* or *lecithins*. Lecithins occur in all

living organisms. Like cephalins, they are important constituents of nerve and brain tissue. Egg yolks are especially rich in lecithins. Commercial-grade lecithins isolated from soybeans are widely used in foods as emulsifying agents. An emulsifying agent is used to stabilize an emulsion—a dispersion of two liquids that do not normally mix, such as oil and water. Many foods are emulsions. Milk is an emulsion of butterfat in water. The emulsifying agent in milk is a protein called *casein*. Mayonnaise is an emulsion of salad oil in water, stabilized by lecithins present in egg yolk.



Sphingomyelins, the simplest sphingolipids, each contain a fatty acid, a phosphoric acid, sphingosine, and choline (Figure **15.4.6**). Because they contain phosphoric acid, they are also classified as phospholipids. Sphingomyelins are important constituents of the myelin sheath surrounding the axon of a nerve cell. Multiple sclerosis is one of several diseases resulting from damage to the myelin sheath.

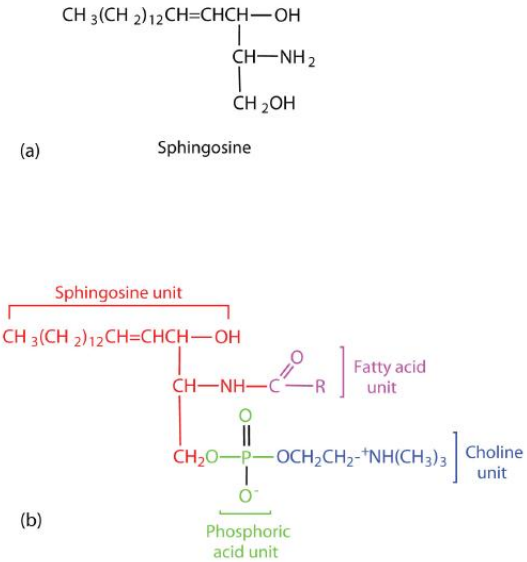


Figure **15.4.6**: Sphingolipids. (a) Sphingosine, an amino alcohol, is found in all sphingolipids. (b) A sphingomyelin is also known as a phospholipid, as evidenced by the phosphoric acid unit in its structure.

Structural formula of sphingosine is shown. The general structure of a sphingolipid is shown with the sphingosine unit, fatty acid unit, phosphoric acid unit, and choline unit highlighted in different colors.

Most animal cells contain sphingolipids called cerebrosides (Figure **15.4.7**). Cerebrosides are composed of sphingosine, a fatty acid, and galactose or glucose. They therefore resemble sphingomyelins but have a sugar unit in place of the choline phosphate group. Cerebrosides are important constituents of the membranes of nerve and brain cells.

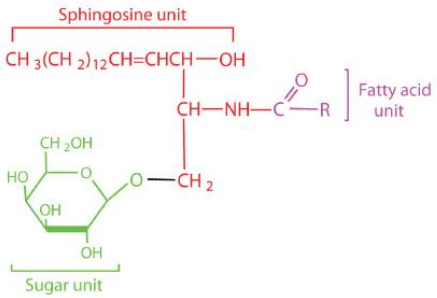


Figure 15.4.7: Cerebrosides. Cerebrosides are sphingolipids that contain a sugar unit.

General structure of a cerebroside with its sugar unit, sphingosine unit, and fatty acid unit highlighted in different colors.

The sphingolipids called gangliosides are more complex, usually containing a branched chain of three to eight monosaccharides and/or substituted sugars. Because of considerable variation in their sugar components, about 130 varieties of gangliosides have been identified. Most cell-to-cell recognition and communication processes (e.g., blood group antigens) depend on differences in the sequences of sugars in these compounds. Gangliosides are most prevalent in the outer membranes of nerve cells, although they also occur in smaller quantities in the outer membranes of most other cells. Because cerebrosides and gangliosides contain sugar groups, they are also classified as glycolipids.

Membrane Proteins

If membranes were composed only of lipids, very few ions or polar molecules could pass through their hydrophobic "sandwich filling" to enter or leave any cell. However, certain charged and polar species do cross the membrane, aided by proteins that move about in the lipid bilayer. The two major classes of proteins in the cell membrane are integral proteins, which span the hydrophobic interior of the bilayer, and peripheral proteins, which are more loosely associated with the surface of the lipid bilayer (Figure 15.4.3). Peripheral proteins may be attached to integral proteins, to the polar head groups of phospholipids, or to both by hydrogen bonding and electrostatic forces.

Small ions and molecules soluble in water enter and leave the cell by way of channels through the integral proteins. Some proteins, called *carrier proteins*, facilitate the passage of certain molecules, such as hormones and neurotransmitters, by specific interactions between the protein and the molecule being transported.

Summary

Lipids are important components of biological membranes. These lipids have dual characteristics: part of the molecule is hydrophilic, and part of the molecule is hydrophobic. Membrane lipids may be classified as phospholipids, glycolipids, and/or sphingolipids. Proteins are another important component of biological membranes. Integral proteins span the lipid bilayer, while peripheral proteins are more loosely associated with the surface of the membrane.

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SECTION OVERVIEW

15.5: Membranes

15.5.1: Basic Concepts in Membranes

15.5.2: Transport in Membranes

Thumbnail: The cell membrane, also called the plasma membrane or plasmalemma, is a semipermeable lipid bilayer common to all living cells. It contains a variety of biological molecules, primarily proteins and lipids, which are involved in a vast array of cellular processes. It also serves as the attachment point for both the intracellular cytoskeleton and, if present, the cell wall. Image used with permission (CC BU-SA 3.0; Dhatfield and LadyofHats).

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15.5.1: Basic Concepts in Membranes

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Lipid bilayers

The protective membrane around cells contains many components, including cholesterol, proteins, glycolipids, glycerophospholipids, and sphingolipids. The last two of these will, when mixed vigorously with water, spontaneously form what is called a lipid bilayer (Figure 3.1), which serves as a protective boundary for the cell that is largely impermeable to the movement of most materials across it. With the notable exceptions of water, carbon dioxide, carbon monoxide, and oxygen, most polar/ionic require transport proteins to help them to efficiently navigate across the bilayer. The orderly movement of these compounds is critical for the cell to be able to 1) get food for energy; 2) export materials; 3) maintain osmotic balance; 4) create gradients for secondary transport; 5) provide electromotive force for nerve signaling; and 6) store energy in electrochemical gradients for ATP production (oxidative phosphorylation or photosynthesis). In some cases, energy is required to move the substances (active transport).

Facilitated Diffusion

In other cases, no external energy is required and they move by diffusion through specific cellular channels. This is referred to as facilitated diffusion. Before we discuss movement of materials across membranes, it is appropriate we discuss the composition of cellular membranes. Plasma membranes differ from cell walls both in the materials comprising them and in their flexibility. Cell walls will be covered near the end of this chapter.

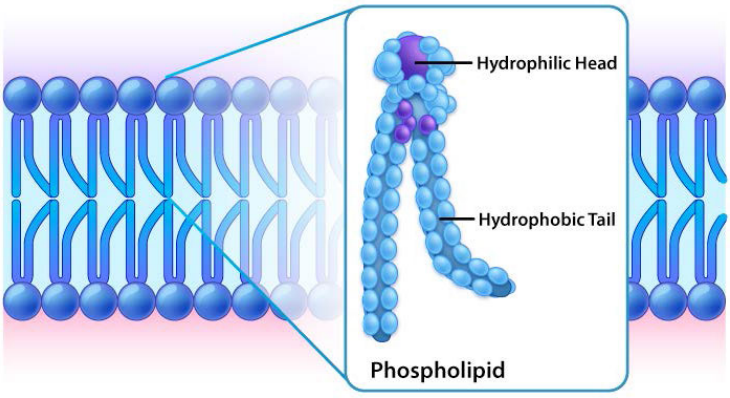


Figure 3.1: Lipid bilayer closeup Image by Aleia Kim

Though some cells do not have cell walls (animal cells) and others do (bacteria, fungi, and plants), there is commonality among cells in that they all possess plasma membranes. There is also commonality in the components of the membranes, though the relative amount of constituents varies. Figures 3.1 and 3.2 illustrate the structure and environments of plasma membranes. All plasma membranes contain a significant amount of amphiphilic substances linked to fatty acids. These include the glycerophospholipids and the sphingolipids. The fatty acid(s) are labeled as hydrophobic tails in the figures.

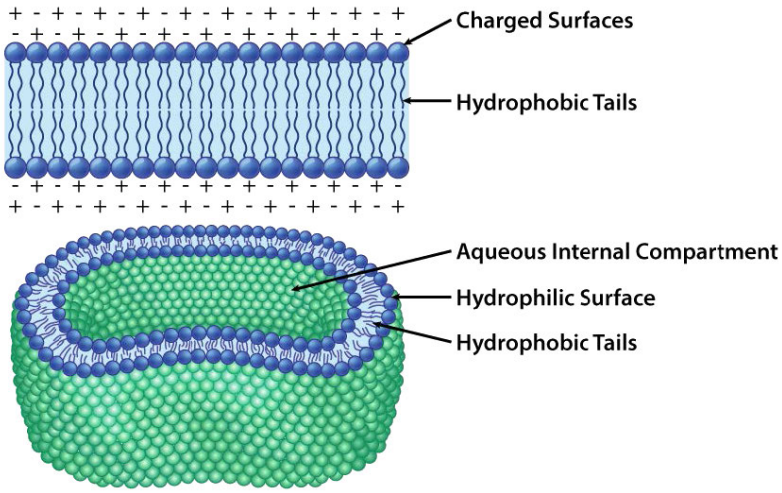


Figure 3.2: Organization of the lipid bilayer Image by Aleia Kim

Hydrophilic heads

The composition of the hydrophilic heads varies considerably. In glycerophospholipids, a phosphate is always present, of course, and it is often esterified to another substance to make a phosphatide (Figure 3.3). Common compounds linked to the phosphate (at the X position) include serine, ethanolamine, and choline. These vary in the their charges so in this way, the charge on the external or internal surface can be controlled. Cells tend to have more negative charges on the exterior half of the lipid bilayer (called the outer leaflet) and more positive charges on the interior half (inner leaflet).

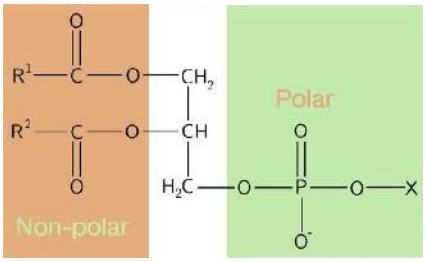


Figure 3.3 - Schematic diagram of a phosphatide

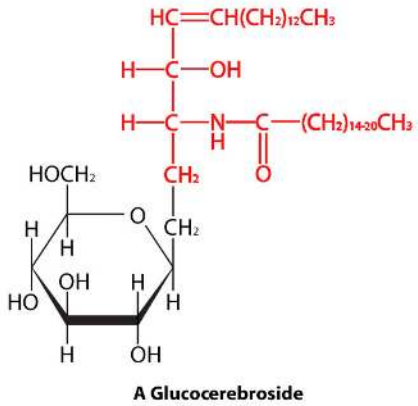


Figure 3.4: A sphingolipid. Polar head in black. Nonpolar tail in red Image by Aleia Kim

Sphingolipids

In sphingolipids (Figure 3.4), the hydrophilic head can contain a phosphate linked to ethanolamine or choline and this describes the structure of sphingomyelin, an important component of neural membranes. Most sphingolipids lack the phosphate and have instead a hydrophilic head of a single sugar (cerebrosides) or a complex oligosaccharide (gangliosides).

Water exclusion

In each case, the glycerophospholipid or sphingolipid has one end that is polar and one end that is non-polar. As we saw in the organization of amino acids with hydrophobic side chains occurring preferentially on the inside of a folded protein to exclude water, so too do the non-polar portions of these amphiphilic molecules arrange themselves so as to exclude water. Remember that the cytoplasm of a cell is mostly water and the exterior of the cell is usually bathed in an aqueous layer. It therefore makes perfect sense that the polar portions of the membrane molecules arrange themselves as they do - polar parts outside interacting with water and non-polar parts in the middle of the bilayer avoiding/excluding water.

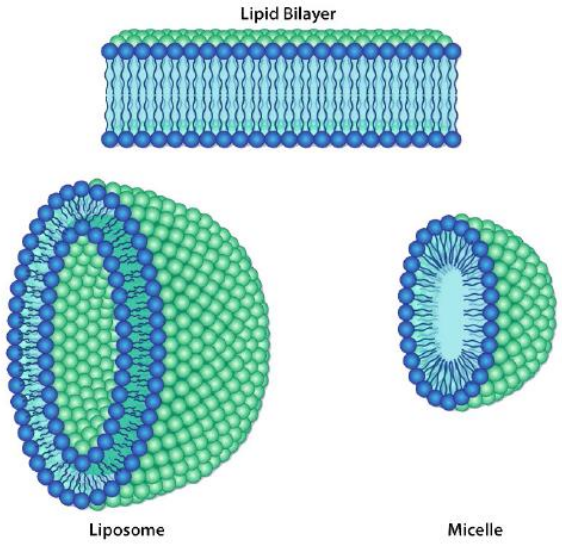


Figure 3.6 - Different lipid bilayer structures Image by Aleia Kim

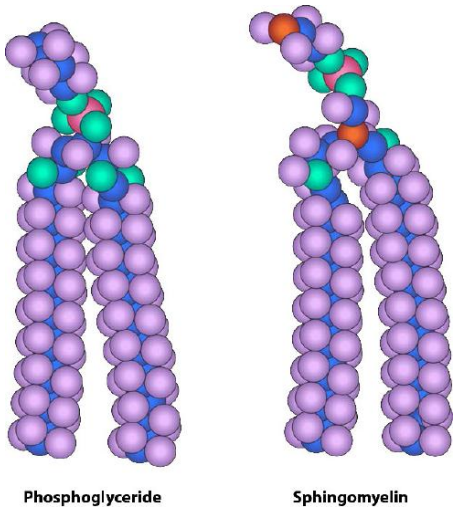


Figure 3.5 - Similarity of form between a phosphoglyceride and sphingomyelin Image by Aleia Kim

Figure 3.7: Differential distribution of membrane lipids by inner and outer leaflet Image by Pehr Jacobson

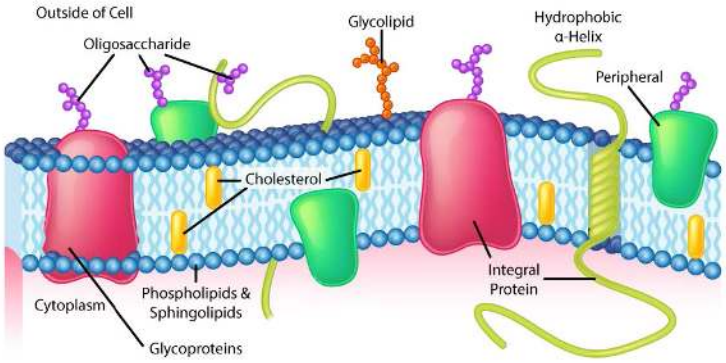


Figure 3.8 - Molecular organization of the lipid bilayer Image by Aleia Kim

Other components of lipid bilayer

Besides glycerophospholipids and sphingolipids, there are other materials commonly found in lipid bilayers of cellular membranes. Two important prominent ones are cholesterol (Figure 3.13) and proteins. Besides serving as a metabolic precursor of steroid hormones and the bile acids, cholesterol's main role in cells is in the membranes. The flatness and hydrophobicity of the sterol rings allow cholesterol to interact with the nonpolar portions of the lipid bilayer while the hydroxyl group on the end can interact with the hydrophilic part.

Membrane fluidity

Cholesterol's function in the lipid bilayer is complex (Figure 3.13). It influences membrane fluidity. Figure 3.14 shows the phase transition for a membrane as it is heated, moving from a more "frozen" character to that of a more "fluid" one as the temperature rises. The mid-point of this transition, referred to as the Tm, is influenced by the fatty acid composition of the lipid bilayer compounds. Longer and more saturated fatty acids will favor higher Tm values, whereas unsaturation and short fatty acids will favor lower Tm values. It is for this reason that fish, which live in cool environments, have a higher level of unsaturated fatty acids in them - to use to make membrane lipids that will remain fluid at ocean temperatures. Interestingly, cholesterol does not change the Tm value, but instead widens the transition range between frozen and fluid forms of the membrane, allowing it to have a wider range of fluidity.

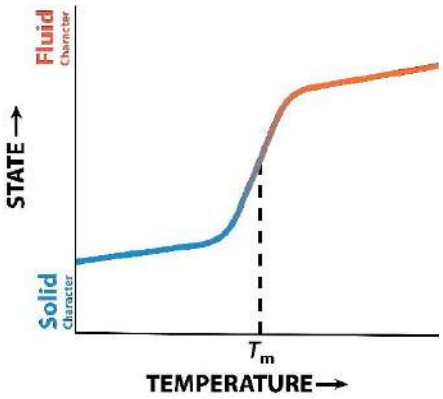


Figure 3.14 - Membrane transition temperature Image by Aleia Kim

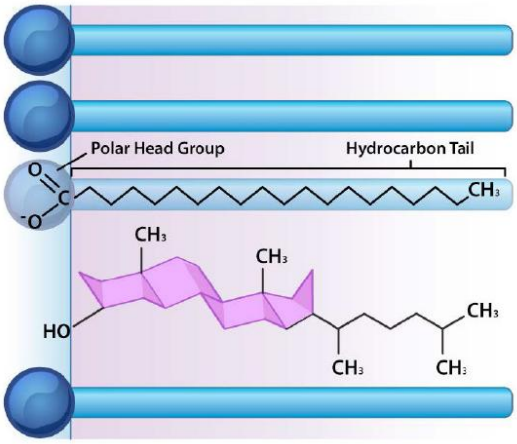


Figure 3.13 - Cholesterol in the lipid bilayer Image by Aleia Kim

Barrier

Transport of materials across membranes is essential for a cell to exist. The lipid bilayer is an effective barrier to the entry of most molecules and without a means of allowing food molecules to enter a cell, it would die. The primary molecules that move freely across the lipid bilayer are small, uncharged ones, such as H2O, CO2, CO, and O2, so larger molecules, like glucose, that the cell needs for energy, would be effectively excluded if there were not proteins to facilitate its movement across the membrane.

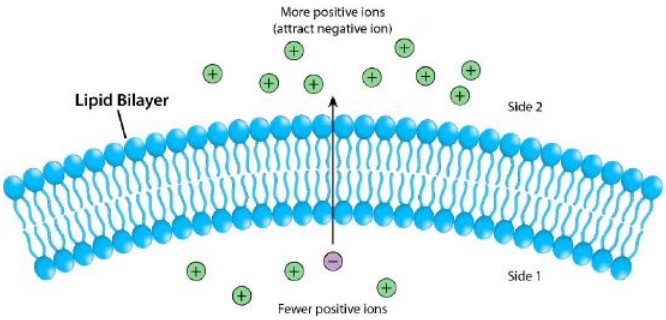


Figure 3.17 - The lipid bilayer as a barrier Image by Pehr Jacobson

Figure 3.17 depicts the barrier that the lipid bilayer provides to movement across it and the pressures (ionic attraction, in this case) that can affect movement. Potential energy from charge and concentration differences are harvested by cells for purposes that include synthesis of ATP, and moving materials against a concentration gradient in a process called active transport.

Membrane proteins

Proteins in a lipid bilayer can vary in quantity enormously, depending on the membrane. Protein content by weight of various membranes typically ranges between 30 and 75% by weight. Some mitochondrial membranes can have up to 90% protein. Proteins linked to and associated with membranes come in several types.

Transmembrane proteins

Transmembrane proteins are integral membrane proteins that completely span from one side of a biological membrane to the other and are firmly embedded in the membrane (Figure 3.18). Transmembrane proteins can function as docking sites for attachment (to the extracellular matrix, for example), as receptors in the cellular signaling system, or facilitate the specific transport of molecules into or out of the cell.

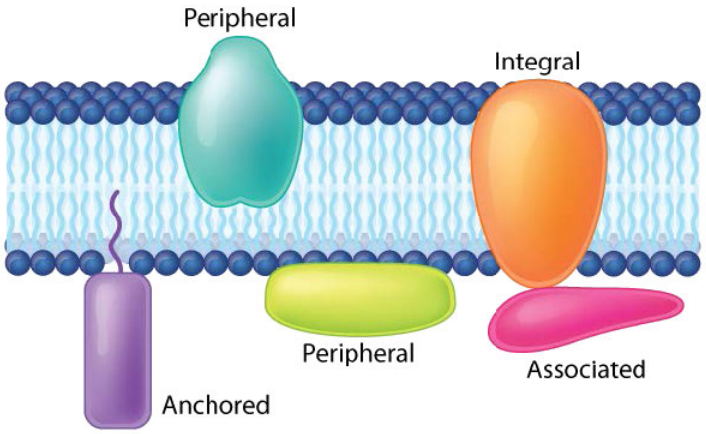


Figure 3.18 - Membrane protein types Image by Aleia Kim

Example of integrated/ transmembrane proteins include those involved in transport (e.g., Na+/K+ ATPase), ion channels (e.g., potassium channel of nerve cells) and signal transduction across the lipid bilayer (e.g., GProtein Coupled Receptors).

Peripheral membrane proteins interact with part of the bilayer (usually does not involve hydrophobic interactions), but do not project through it. A good example is phospholipase A2, which cleaves fatty acids from glycerophospholipids in membranes. Associated membrane proteins typically do not have external hydrophobic regions, so they cannot embed in a portion of the lipid bilayer, but are found near them. Such association may arise as a result of interaction with other proteins or molecules in the lipid bilayer. A good example is ribonuclease.

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15.5.2: Transport in Membranes

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Movement of materials across membranes

As noted earlier, it is essential for cells to be able to uptake nutrients. This function along with movement of ions and other substances is provided by proteins/protein complexes that are highly specific for the compounds they move.

Selective movement of ions by membrane proteins and the ions' extremely low permeability across the lipid bilayer are important for helping to maintain the osmotic balance of the cell and also for providing for the most important mechanism for it to make ATP - the process of oxidative phosphorylation.

Channels and transporters

With respect to movement of materials through membrane proteins, there is a difference between channels (sometimes called pores) and transporters. Channels largely provide openings with some specificity and molecules pass through them at close to the rate of diffusion. They usually involve movement of water or ions. Examples would be the sodium or potassium channels of nerve cells. Transporters have high specificity and transfer rates that are orders of magnitude slower. Transport proteins include the sodium-potassium pump, the sodium-calcium exchanger, and lactose permease, amongst many others).

Facilitated diffusion

As noted, the driving force for facilitated diffusion is concentration, meaning that in facilitated diffusion, materials will only move from a higher concentration to a lower concentration and that at the end of the process, the concentration of materials on each side of a bilayer will be equal (Figure 3.28). This may work well in many cases.

For example, the blood concentration of glucose is sufficiently high that red blood cells can use facilitated diffusion as a means of acquiring glucose. Other cells, further removed from the blood supply where the glucose concentration is lower, must use active transport mechanisms because there is not a sufficient concentration of glucose to provide cells with the glucose they need.

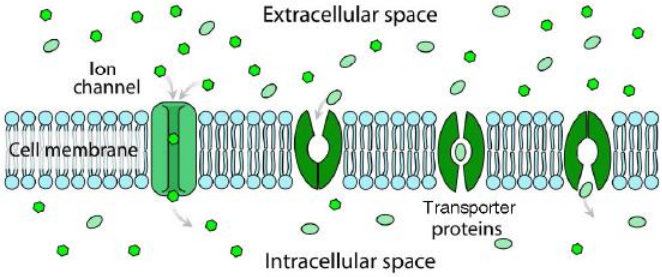


Figure 3.27 - Ion channel and transporter proteins

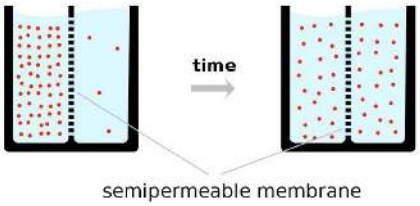


Figure 3.28 - In diffusion, solutes move from high concentration to lower concentration and eventually equalize

Ion channels

Ion channels are pore-forming membrane proteins in the membranes of all cells that regulate movement of selected ions across a membrane (Figures 3.29 & 3.30). They help to establish the resting membrane potential and to affect action potentials and other electrical signals. They are very important in the process of nerve transmission. Ion channels control the flow of ions across secretory and epithelial cells, and consequently help to regulate cell volume by affecting osmotic pressure.

Ion channels are essential features of almost all cells, functioning as selective “tunnels” that restrict movement through them to ions with specific characteristics (typically size). The size of the opening is very narrow (usually one or two atoms wide) and is able to select even against ions that are too small.

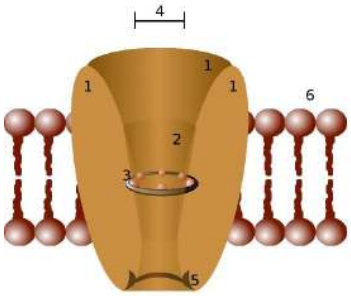


Figure 3.29 - Schematic structure of an ion channel protein - 1 = General structure / 2 = Entrance / 3 = Selectivity filter / 4 = Effective diameter / 5 = Controllable opening

Transporter proteins

Not all facilitated transport occurs through ion channel proteins. Transporter proteins, as noted earlier (HERE and Figure 3.27) facilitate movement of materials across a lipid bilayer, but are slower than ion channels. Figure 3.36 illustrates a transporter protein in action. As can be seen, transporter proteins rely on a specific receptor site for proper recognition of the molecule to be moved.

Binding of the proper molecule causes a conformational change in the shape of the protein (an eversion) which results in a flipping of the open side of the protein to the other side of the lipid bilayer. In this way, the molecule is moved. Like ion channels, transporter proteins facilitate movement of materials in either direction, driven only by the concentration difference between one side and the other.

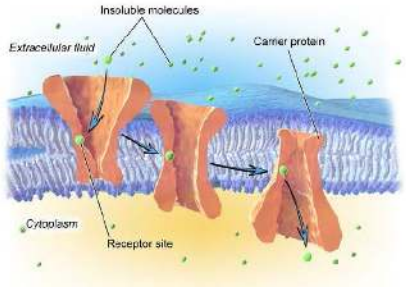


Figure 3.36 - Facilitated diffusion with a transporter protein - Wikipedia

Active transport

All of the transport mechanisms described so far are driven solely by a concentration gradient - moving from higher concentrations in the direction of lower concentrations. These movements can occur in either direction and, as noted, result in equal concentrations on either side of the bilayer, if allowed to go to completion. Many times, however, cells must move materials against a concentration gradient and when this occurs, another source of energy is required. This process is known as active transport.

A good definition of active transport is that in active transport, at least one molecule is being moved against a concentration gradient. A common, but not exclusive, energy source is ATP.

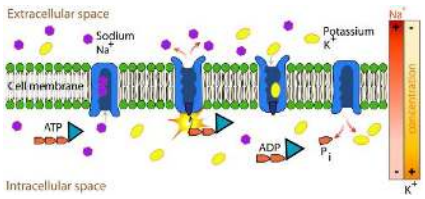


Figure 3.37 - An overview of active transport by the Na+K+ ATPase

Nerve transmission

Now that you have seen how the Na+/K+ ATPase functions, it is appropriate to discuss how nerve cells use ion gradients created with it to generate and transmit nerve signals. Neurons are cells of the nervous system that use chemical and electrical signals to rapidly transmit information across the body (Figure 3.40). The sensory nerve system links receptors for vision, hearing, touch, taste, and smell to the brain for perception. Motor neurons run from the spinal cord to muscle cells. These neurons have a cell body and a very long, thin extension called an axon, that stretches from the cell body in the spinal cord all the way to the muscles they control. Nerve impulses travel down the axon to stimulate muscle contraction.

Signals travel through neurons, ultimately arriving at junctions with other nerve cells or target cells such as muscle cells. Note that neurons do not make physical contact with each other or with muscle cells. The tiny space between two neurons or between a neuron and a muscle cell is called the synaptic cleft. At the synaptic cleft, the neuron releases neurotransmitters that exit the nerve cell and travel across the junction to a recipient cell where a response is generated. That response may be creating another nerve signal, if the adjacent cell is a nerve cell or it may be a muscular contraction if the recipient is a muscle cell (Figure 3.41).

In considering information movement via nerve cells, then, we will discuss two steps - 1) creation and propagation of a signal in a nerve cell and 2) action of neurotransmitters exiting a nerve cell and transiting a synaptic junction.

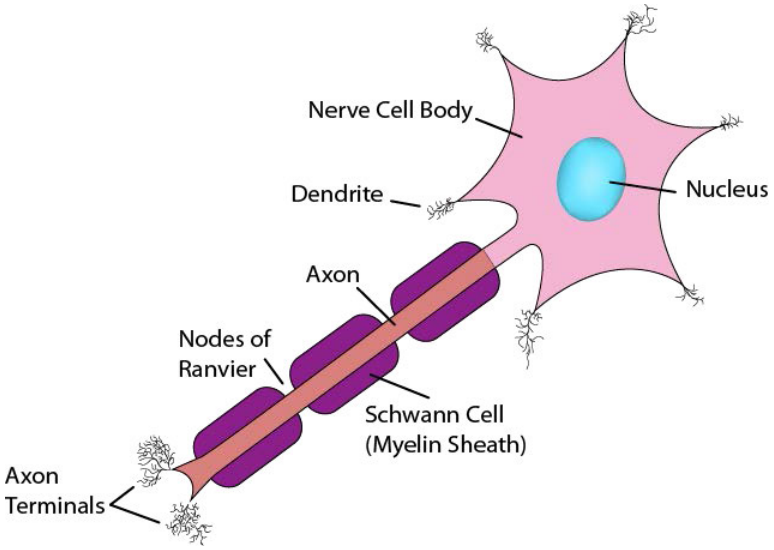


Figure 3.40 - Anatomy of a nerve cell - Image by Pehr Jacobson

Signal source

Creation of a nerve signal begins with a stimulus to the nerve cell. In the case of muscle contraction, the motor cortex of the brain sends signals to the appropriate motor neurons, stimulating them to generate a nerve impulse. How is such an impulse generated?

Resting potential

In the unstimulated state, all cells, including nerve cells, have a small voltage difference (called the resting potential) across the plasma membrane, arising from unequal pumping of ions across the membrane. The Na+/K+ ATPase, for example, pumps sodium ions out of the cell and potassium ions into cells. Since three sodium ions get pumped out for every two potassium ions pumped in, a charge and chemical gradient is created. It is the charge gradient that gives rise to the resting potential.

Altering the gradients of ions across membranes provide the driving force for nerve signals. This happens as a result of opening and closing of gated ion channels. Opening of gates to allow ions to pass through the membrane swiftly changes the ionic balance across the membrane resulting in a new voltage difference called the action potential. It is the action potential that is the impetus of nerve transmission.

Initiation of signal

The signal generated by a motor neuron begins with opening of sodium channels in the membrane of the nerve cell body causing a rapid influx of sodium ions into the nerve cell. This step, called depolarization (Figure 3.42), triggers an electrochemical signal - the action potential. Remember that the Na+/K+ ATPase has created a large sodium gradient, so sodium ions rush into the cell

when sodium channels open. After the initial depolarization, potassium channel gates, responding to the depolarization, open, allowing potassium ions to rapidly diffuse out of the cell (remember K+ ions are more abundant inside of the cell). This phase is called the repolarization phase and during it, the sodium gates close.

The rapid exit of potassium ions causes the voltage difference to “overshoot” the resting potential and potassium gates close. This followed by the so-called refractory period, when the Na+/K+ ATPase begins its work to re-establish the original conditions by pumping sodium ions out and potassium ions into the nerve cell. Eventually, the system recovers and the resting potential is re-established. The initiating end of the nerve cell is then ready for another signal.

Propagation of action potential

What we have described here is only the initiation of the nerve signal in one part of the nerve cell. For the signal to be received, the action potential must travel the entirety of the length of the nerve cell (the axon) and cause a chemical signal to be released into the synaptic cleft to get to its target. Propagating the nerve signal (action potential) in the original nerve cell is the function of all of the rest of the gated ion channels (Figure 3.43) positioned on the sides of the nerve cell. The sodium and potassium gates involved in propagation of the signal all act in response to voltage changes created by the electrochemical gradient moving down the nerve cell (Figure 3.44). Remember that opening of the initial gates at initiation of the signal created an influx of sodium ions and an efflux of potassium ions.

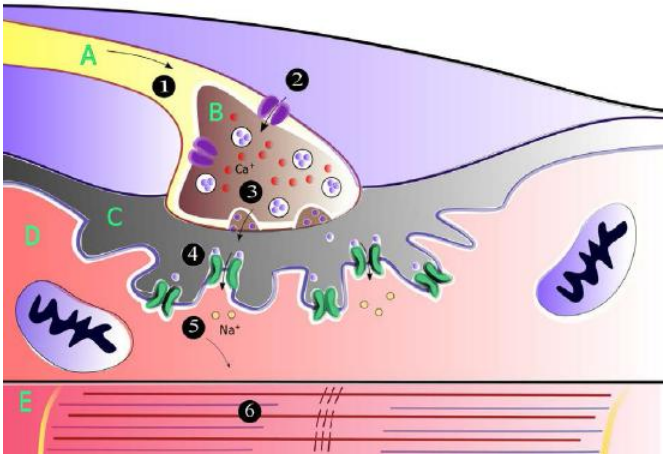


Figure 3.41 - (1) The action potential reaches the axon terminal; (2) voltage-dependent calcium gates open - calcium enters the axon terminal; (3) neurotransmitter vesicles fuse with the presynaptic membrane and release acetylcholine (ACh); (4) ACh binds to postsynaptic receptors on the sarcolemma; (5) ion channels open in response and allow sodium ions to flow into the muscle cell; (6) The flow of sodium ions into the muscle cell generates an action potential which travels to the myofibril and results in muscle contraction. - Wikipedia

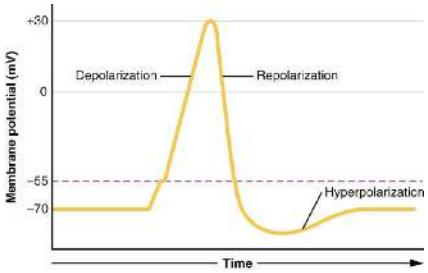


Figure 3.42 - Depolarization and repolarization of a nerve cell - Wikipedia

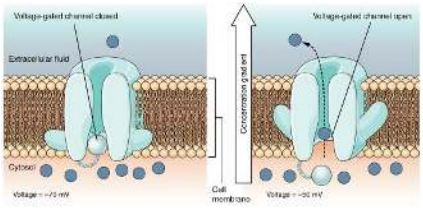


Figure 3.43 - Voltage gated ion channels - Wikipedia

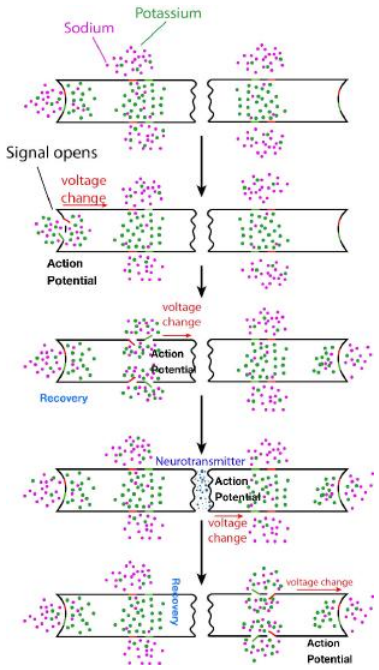


Figure 3.44 - Action potential moving across a synaptic junction of two nerve cells - Image by Pehr Jacobson

Moving signal

This chemical and electrical change that creates the action potential leaves the end of the nerve cell where it started and travels down the axon towards the other end of the nerve cell. Along the way, it encounters more sodium and potassium gated channels. In each case, these respond simply to the voltage change of the action potential and open and close, exactly in the same way the gates opened to start the signal. Thus, a rapid wave of increasing sodium ions and decreasing potassium ions moves along the nerve cell, propagated (and amplified) by gates opening and closing as the ions and charges move down the nerve cell. Eventually, the ionic tidal wave reaches the end of the nerve cell (axon terminal) facing the synaptic cleft.

Crossing the synaptic cleft

For the signal to be received by the intended target (postsynaptic cell) from the originating neuron (presynaptic neuron), it must cross the synaptic cleft and stimulate the neighboring cell (Figure 3.45). Communicating information across a synaptic cleft is the job of neurotransmitters. These are small molecules synthesized in nerve cells that are packaged in membrane vesicles called synaptic vesicles in the nerve cell. Neurotransmitters come in all shapes and chemical forms, from small chemicals like acetylcholine to peptides like neuropeptide Y. The most abundant neurotransmitter is glutamate, which acts at over 90% of the synapses in the human brain.

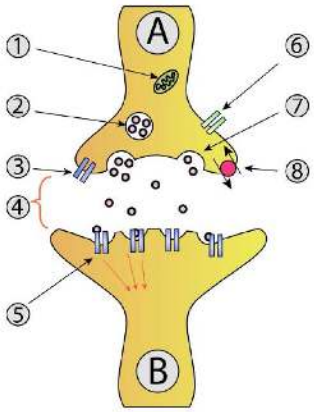


Figure 3.45 - A) Pre-synaptic neuron; B) post-synaptic neuron; 1) Mitochondria; 2) synaptic vesicle with neurotransmitters; 3) autoreceptor; 4) synapse with neurotransmitter released (serotonin); 5) postsynaptic receptors activated by neurotransmitter; 6) calcium channel; 7) exocytosis of a vesicle; 8) recaptured neurotransmitter. Wikipedia

Movie 3.2 - Movement of an action potential down a nerve cell - Wikipedia

Into the cleft

As the action potential in the presynaptic neuron approaches the axon terminus, synaptic vesicles begin to fuse with the membrane and their neurotransmitter contents spill into the synaptic cleft. Once in the cleft, the neurotransmitters diffuse, some of them reaching receptors on the postsynaptic cell. Binding of the neurotransmitter to the receptors on the membrane of the postsynaptic cell stimulates a response.

For motor neurons, the postsynaptic cell will be a muscle cell, and the response will be muscle contraction/relaxation. At this point, the originating nerve cell has done its job and communicated its information to its immediate target. If the postsynaptic cell is a nerve cell, the process repeats in that cell until it gets to its destination.

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15.6: Structure and Function - Lipids and Membranes

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Lipids are a diverse group of molecules that all share the characteristic that at least a portion of them is hydrophobic. Lipids play many roles in cells, including serving as energy storage (fats/oils), constituents of membranes (glycerophospholipids, sphingolipids, cholesterol), hormones (steroids), vitamins (fat soluble), oxygen/ electron carriers (heme), among others. For lipids that are very hydrophobic, such as fats/ oils, movement and storage in the aqueous environment of the body requires special structures. Other, amphipathic lipids, such as glycerophospholipids and sphingolipids spontaneously organize themselves into lipid bilayers when placed in water. Interestingly, major parts of many lipids can be derived from acetyl-CoA.

Fatty acids

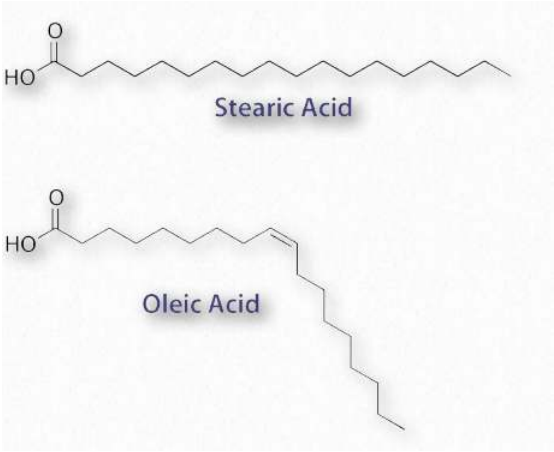


Figure 2.190 - Saturated fatty acid (stearic acid) and unsaturated fatty acid (oleic acid)

The most ubiquitous lipids in cells are the fatty acids. Found in fats, glycerophospholipids, sphingolipids and serving as as membrane anchors for proteins and other biomolecules, fatty acids are important for energy storage, membrane structure, and as precursors of most classes of lipids. Fatty acids, as can be seen from Figure 2.190 are characterized by a polar head group and a long hydrocarbon tail. Fatty acids with hydrocarbon tails that lack any double bonds are described as saturated, while those with one or more double bonds in their tails are known as unsaturated fatty acids. The effect of double bonds on the fatty acid tail is to introduce a kink, or bend, in the tail, as shown for oleic acid.

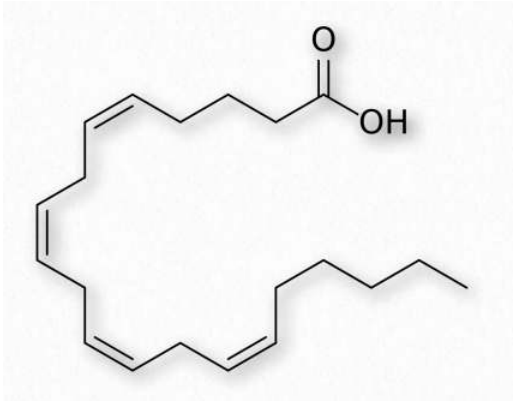


Figure 2.191 - Arachidonic acid - A polyunsaturated fatty acid Wikipedia

Stearic acid, a saturated fatty acid, by contrast has a straight hydrocarbon tail. Figures 2.190-2.194 show the most common saturated and unsaturated fatty acids. Fatty acids with unsaturated tails have a lower melting temperature than those with saturated tails of the same length. Shorter tails also decrease melting temperature. These properties carry over to the fats/oils containing them.

Common name	Chemical structure	
Caprylic acid	$CH_3(CH_2)_6COOH$	8
Capric acid	$CH_3(CH_2)_8COOH$	10
Lauric acid	$CH_3(CH_2)_{10}COOH$	12
Myristic acid	$CH_3(CH_2)_{12}COOH$	14
Palmitic acid	$CH_3(CH_2)_{14}COOH$	16
Stearic acid	$CH_3(CH_2)_{16}COOH$	18
Arachidic acid	$CH_3(CH_2)_{18}COOH$	20
Behenic acid	$CH_3(CH_2)_{20}COOH$	22
Lignoceric acid	$CH_3(CH_2)_{22}COOH$	24
Cerotic acid	$CH_3(CH_2)_{24}COOH$	26

Figure 2.192 - Saturated fatty acids. Number of carbons in right column Wikipedia

Fatty acids with more than one double bond are called polyunsaturated. Plants are excellent sources of unsaturated and polyunsaturated fatty acids. The position of the double bond(s) in fatty acids has important considerations both for their synthesis and for their actions in the body. Biochemically, the double bonds found in fatty acids are predominantly in the cis configuration. So-called trans fats arise as a chemical by-product of partial hydrogenation of vegetable oil.

Name	Double Bond Info	
Myristoleic acid	*cis*-Δ^9	14:1
Palmitoleic acid	*cis*-Δ^9	16:1
Sapienic acid	*cis*-Δ^6	16:1
Oleic acid	*cis*-Δ^9	18:1
Elaidic acid	*trans*-Δ^9	18:1
Vaccenic acid	*trans*-Δ^{11}	18:1
Linoleic acid	*cis,cis*-Δ^9,Δ^{12}	18:2
Linoelaidic acid	*trans,trans*-Δ^9,Δ^{12}	18:2
α-Linolenic acid	*cis,cis,cis*-$\Delta^9,\Delta^{12},\Delta^{15}$	18:3
Arachidonic acid	*cis,cis,cis,cis*-$\Delta^5\Delta^8,\Delta^{11},\Delta^{14}$	20:4
Eicosapentaenoic acid	*cis,cis,cis,cis,cis*-$\Delta^5,\Delta^8,\Delta^{11},\Delta^{14},\Delta^{17}$	20:5
Erucic acid	*cis*-Δ^{13}	22:1
Docosahexaenoic acid	*cis,cis,cis,cis,cis,cis*-$\Delta^4,\Delta^7,\Delta^{10},\Delta^{13},\Delta^{16},\Delta^{19}$	22:6

Figure 2.193 - Unsaturated fatty acids. Right column Indicates number of carbons and double bonds Wikipedia

In humans, consumption of trans fat raises low density lipoprotein (LDL) levels and lowers high density lipoprotein (HDL) levels. Each is thought to contribute to the risk of developing coronary artery disease. The most Figure 2.194 - Fatty acid models. Carboxyl end labeled in red Wikipedia common fatty acids in our body include palmitate, stearate, oleate, linolenate, linoleate, and arachidonate. Two notable shorter fatty acids are nonanoic (9 carbons) and decanoic acid (10 carbons), both of which appear to have anti-seizure effects. Decanoic acid directly inhibits excitatory neurotransmission in the brain and may contribute to the anticonvulsant effect of the ketogenic diet.

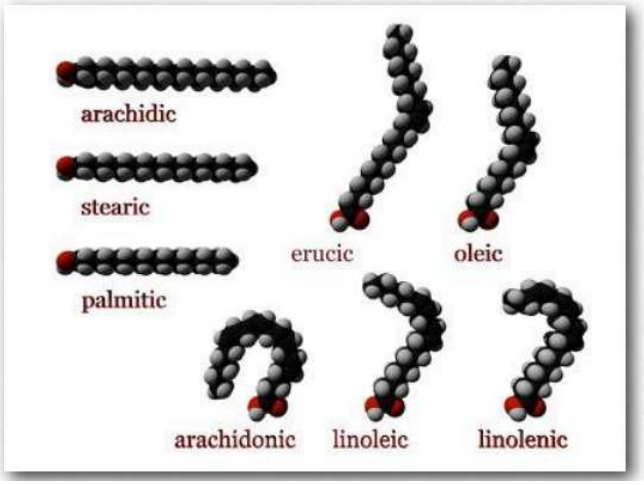


Figure 2.194 - Fatty acid models. Carboxyl end labeled in red Wikipedia

Numbering

Figure 2.195 shows two different systems for locating double bonds in a fatty acid. The ω system counts carbons starting with the methyl end (shown in red) while the Δ system counts from the carboxyl end (shown in blue). For example, an ω-3 (omega 3) fatty acid would have a double bond at the third carbon from the methyl end. In the Δ system, a fatty acid that has a cis double bond at carbon 6, counting from the carboxyl end, would be written as cis-Δ6.

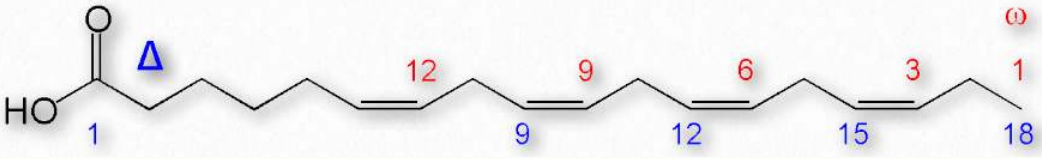


Figure 2.195 - Δ and ω numbering systems for fatty acids Image by Pehr Jacobson

Fatty acids are described as essential fatty acids if they must be in the diet (can't be synthesized by the organism) and nonessential fatty acids if the organism can synthesize them. Humans and other animals lack the desaturase enzymes necessary to make double bonds at positions greater than Δ-9, so fatty acids with double bonds beyond this position must be obtained in the diet. Linoleic acid and linolenic acid, both fall in this category. Related unsaturated fatty acids can be made from these fatty acids, so the presence of linoleic and linolenic acids in the diet eliminates the need to have all unsaturated fatty acids in the diet. Both linoleic and linolenic acid contain 18 carbons, but linoleic acid is an ω-6 fatty acid, whereas linolenic acid is an ω-3 fatty acid. Notably, ω-6 fatty acids tend to be proinflammatory, whereas ω-3 fatty acids are lesser so.

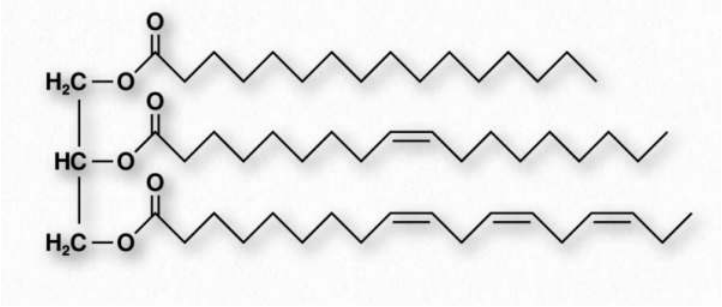


Figure 2.196 - Structure of a fat/oil

Fats/oils

Fats and oils are the primary energy storage forms of animals and are also known as triacylglycerols and triglycerides, since they consist of a glycerol molecule linked via ester bonds to three fatty acids (Figure 2.196). Fats and oils have the same basic structure. We give the name fat to those compounds that are solid at room temperature and the name oil to those that are liquid at room temperature. Note that biological oils are not the same as petroleum oils.

Increasing the number of unsaturated fatty acids (and the amount of unsaturation in a given fatty acid) in a fat decreases the melting temperature of it. Organisms like fish, which live in cool environments, have fats with more unsaturation and this is why fish oil contains polyunsaturated fatty acids.

Adipocytes

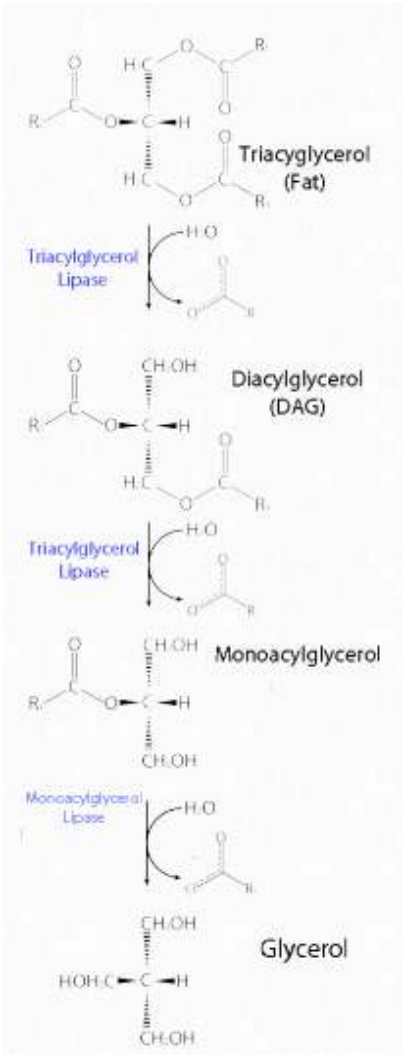


Figure 2.197 - Lipase action on a fat Image by Aleia Kim

Fats are stored in the body in specialized cells known as adipocytes. Enzymes known as lipases release fatty acids from fats by hydrolysis reactions (Figure 2.197). Triacylglycercol lipase (pancreatic - Figure 2.198) is able to cleave the first two fatty acids from the fat. A second enzyme, monoacylglycerol lipase, cleaves the last fatty acid. Fats can be synthesized by replacing the phosphate on phosphatidic acid with a fatty acid.

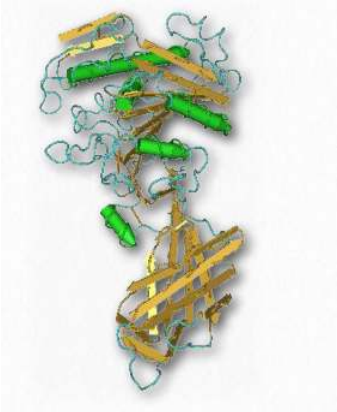


Figure 2.198 - Pancreatic lipase

Glycerophospholipids

Glycerophospholipids (phosphoglycerides) are important components of the lipid bilayer of cellular membranes. Phosphoglycerides are structurally related to fats, as both are derived from phosphatidic acid (Figure 2.199). Phosphatidic acid is a simple glycerophospholipid that is usually converted into phosphatidyl compounds. These are made by esterifying various groups, such as ethanolamine, serine, choline, inositol, and others (Figure 2.200) to the phosphate of phosphatidic acid. All of these compounds form lipid bilayers in aqueous solution , due to their amphiphilic nature.

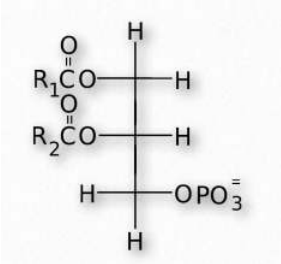


Figure 2.199 - Structure of phosphatidic acid. R1 and R2 are alkyl groups of fatty acids.

Phosphatidylethanolamines

Since all glycerolipids can have a variety of fatty acids at positions 1 and 2 on the glycerol, they all are families of compounds. The phosphatidylethanolamines are found in all living cells and are one of the most common phosphatides, making up about 25% of them. They are common constituents of brain tissue and in the spinal cord, making up as much as 45% of the total phospholipids. Phosphatidylethanolamines are asymmetrically distributed across membranes, being preferentially located on the inner leaflet (closest to the cytoplasm) of the plasma membrane. Metabolically, phosphatidylethanloamines are precursors of phosphatidylcholines. Phosphatidylserines Phosphatidylserines are another group of phosphatidyl compounds that are preferentially distributed across the lipid bilayer of the plasma membrane. Like the phosphatidylethanolamines, phosphatidylserines are preferentially located on the inner leaflet of the plasma membrane. When apoptosis (cell suicide) occurs, the preferential distribution is lost and the phosphatidylserines appear on the outer leaflet where they serve as a signal to macrophages to bind and destroy the cell.

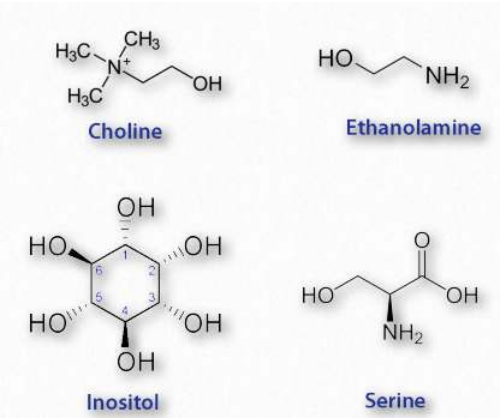


Figure 2.200 - Four common components of phosphatides Wikipedia

Phosphatidylcholines

Phosphatidylcholines (Figure 2.201) are another group of important membrane components. They tend to be found more commonly on the outer leaflet of the plasma membrane. Nutritionally, the compounds are readily obtained from eggs and soybeans. Phosphatidylcholines are moved across membranes by Phosphatidylcholine transfer protein (PCTP). This protein, which is sensitive to the levels of phosphatidylcholines, acts to stimulate the activity of a thioesterase (breaks thioester bonds, such as acyl-CoAs) and activates PAX3 transcription factors.

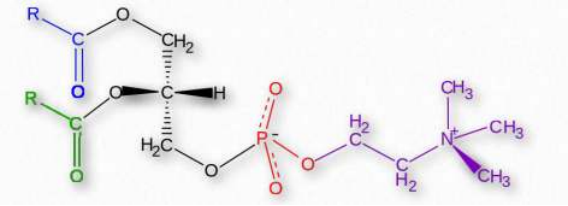


Figure 2.201 - Phosphatidylcholine

Diacylglycerol

Diacylglycerol (also called diglyceride and DAG - Figure 2.204) is an important intermediate in metabolic pathways. It is produced, for example, in the first step of the hydrolysis of fat.

Lecithin

Lecithin is a generic term for a combination of lipid substances that includes phosphoric acid, glycerol, glycolipids, triglycerides, and phospholipids. Lecithin is a wetting agent helpful with emulsification and encapsulation and is even used as an anti-sludge additive in motor lubricants. Lecithin is used in candy bars to keep cocoa and cocoa butter from separating. Though considered safe as a food ingredient, lecithin can be converted by gut bacteria to trimethylamine-N-oxide which may contribute to cholesterol deposition and atherosclerosis.

Sphingolipids

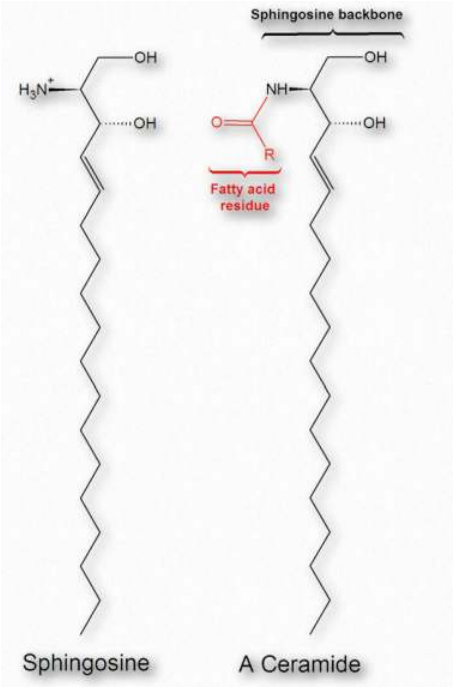


Figure 2.210 - Sphingosine and a ceramide made from it Wikipedia

Fatty acids are also components of a broad class of molecules called sphingolipids. Sphingolipids are structurally similar to glycerophospholipids, though they are synthesized completely independently of them starting with palmitic acid and the amino acid serine. Sphingolipids are named for the amino alcohol known as sphingosine (Figure 2.210), though they are not directly synthesized from it. Figure 2.211 shows the generalized structure of sphingolipids.

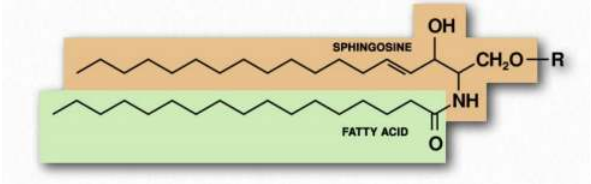


Figure 2.211 Schematic structure of a sphingolipid

If the R-group is a hydrogen, the molecule is called a ceramide. When the R-group is phosphoethanolamine the resulting molecule is sphingomyelin, an important component of the myelin sheath and lipid membranes. If a single, simple sugar is instead added, a cerebroside is created (Figure 2.212). Addition of a complex oligosaccharide creates a ganglioside.

Complex sphingolipids may play roles in cellular recognition and signaling. Sphingolipids are found most abundantly in plasma membrane and are almost completely absent from mitochondrial and endoplasmic reticulum membranes. In animals, dietary sphingolipids have been linked to reduced colon cancer, reductions in LDLs, and increases in HDLs. Like the glycerophospholipids, sphingolipids are amphiphilic. Most sphingolipids except sphingomyelin do not contain phosphate.

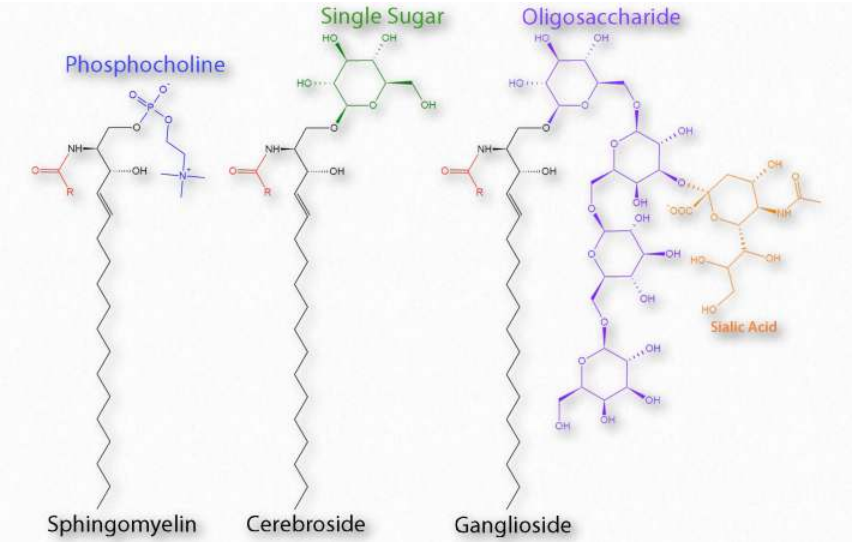


Figure 2.212 - Categories of Sphingolipid Wikipedia

Eicosanoids

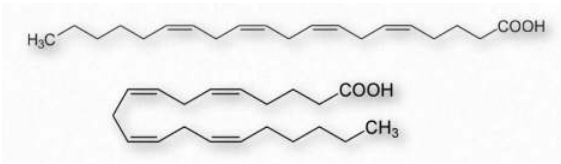


Figure 2.213 - Arachidonic acid drawn as straight (top) and bent (bottom)

Fatty acids made from omega-6 and omega-3 fatty acids include three important fatty acids containing 20 carbons. They include arachidonic acid (an ω-6 fatty acid with four double bonds (Δ-5,8,11,14) - Figure 2.213). The class of compounds known as eicosanoids is made by oxidation of arachidonic acid. Subclasses include include prostaglandins, thromboxanes, and leukotrienes (Figures 2.214-2.219). Eicosanoids play important roles affecting inflammation, immunity, mood, and behavior.

Prostaglandins

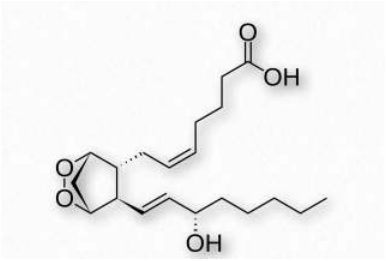


Figure 2.214 - Prostaglandin PGH_2

A collection of molecules acting like hormones, prostaglandins are derived from arachidonic acid and have many differing (even conflicting) physiological effects. These include constriction or dilation of vascular smooth muscle cells, induction of labor, regulation of inflammation, and action on the thermoregulatory center of the hypothalamus to induce fever, among others.

Prostaglandins are grouped with the thromboxanes (below) and prostacyclins (below), as prostanoids. The prostanoids, which all contain 20 carbons are a subclass of the eicosanoids. Prostaglandins are found in most tissues of higher organisms. The primary precursor of the prostaglandins is the fatty acid known as arachidonic acid and the prostaglandin made from it is known as PGH2 (Figure 2.214), which, in turn is a precursor of other prostaglandins, as well as the prostacyclins and thromboxanes.

Thromboxanes

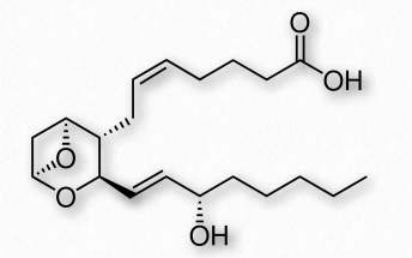


Figure 2.217 Thromboxane A2 $_2$

Thromboxanes play roles in clot formation and named for their role in thrombosis. They are potent vasoconstrictors and facilitate platelet aggregation. They are synthesized in platelets, as well. The anti-clotting effects of aspirin have their roots in the inhibition of synthesis of PGH2, which is the precursor of the thromboxanes. The most common thromboxanes are A2 (Figure 2.217) and B2.

Leukotrienes

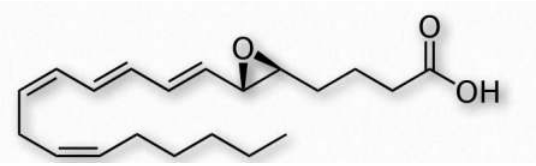


Figure 2.219 - Leukotriene A_4 (LTA_4)

Another group of eicosanoid compounds are the leukotrienes (Figure 2.219). Like prostaglandins, leukotrienes are made from arachidonic acid. The enzyme catalyzing their formation is a dioxygenase known as arachidonate 5-lipoxygenase. Leukotrienes are involved in regulating immune responses. They are found in leukocytes and other immunocompetent cells, such as neutrophils, monocytes, mast cells, eosinophils, and basophils. Leukotrienes are associated with production of histamines and prostaglandins, which act as mediators of inflammation. Leukotrienes also trigger contractions in the smooth muscles of the bronchioles. When overproduced, they may pay a role in asthma and allergic reactions. Some treatments for asthma aim at inhibiting production or action of leukotrienes.

Cholesterol

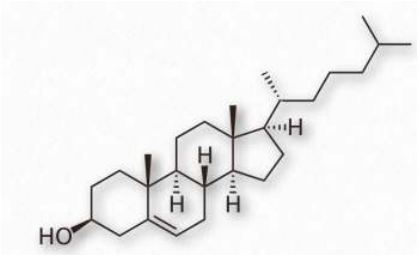


Figure 2.220 - Structure of cholesterol

Arguably, no single biomolecule has generated as much discussion and interest as has cholesterol (Figure 2.220). Certainly, from the perspective of the Nobel Prize committee, no small molecule even comes close, with 13 people having been awarded prizes for work on it. Evidence for cholesterol's importance comes from the study of brain tissue where it comprises 10-15% of the dry mass.

Membrane flexibility

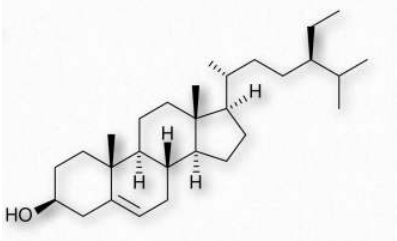


Figure 2.221 - Sitosterol - A phytosterol

In animal cells, cholesterol provides for membrane flexibility that allows for cellular movement that is in contrast to plant and bacterial cells with fixed structures. Cholesterol is made in many cells of the body, with the liver making the greatest amount. The anabolic pathway leading to synthesis of cholesterol is known as the isoprenoid pathway and branches of it lead to other molecules including other fat-soluble vitamins.



Figure 2.222 - Margarine - A common source of trans fat Wikipedia

Cholesterol is only rarely found in prokaryotes (Mycoplasma, which requires it for growth, is an exception) and is found in only trace amounts in plants. Instead, plants synthesize similar compounds called phytosterols (Figure 2.221). On average, the body of a 150 pound adult male makes about 1 gram of cholesterol per day, with a total content of about 35 grams.

Packaging

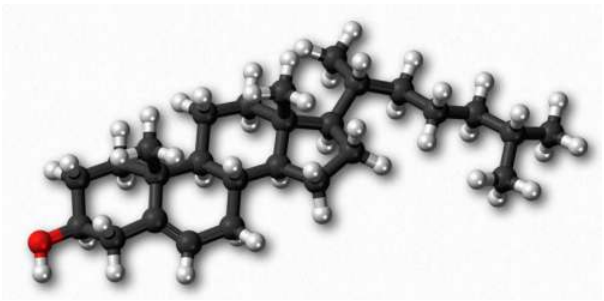


Figure 2.223 - Cholesterol - Ball and stick model

Cholesterol's (and other lipids') hydrophobicity requires special packaging into lipoprotein complexes (called chylomicrons, VLDLs, LDLs, and HDLs) for movement in the lymph system and bloodstream. Though cholesterol can be made by cells, they also take it up from the blood supply by absorbing cholesterol-containing LDLs directly in a process called receptor-mediated endocytosis.

Oxidative damage to LDLs can lead to formation of atherosclerotic plaques and this is why cholesterol has gotten such a negative image in the public eye. The liver excretes cholesterol through the bile for elimination into the digestive system, but the compound is recycled there.

Reducing cholesterol levels

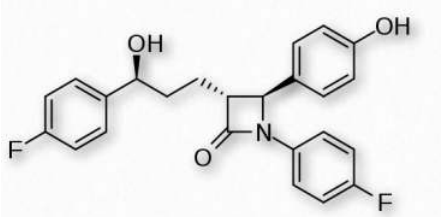


Figure 2.224 - Ezetimibe - An inhibitor of cholesterol absorption

Strategies for reducing cholesterol in the body focus primarily on three areas - reducing consumption, reducing endogenous synthesis, and reducing the recycling. Dietary considerations, such as saturated fat versus unsaturated fat consumption are currently debated. Dietary trans fats, though, correlate with incidence of coronary heart disease. Consumption of vegetables may provide some assistance with reducing levels of cholesterol recycled in the digestive system, because plant phytosterols compete with cholesterol for reabsorption and when this happens, a greater percentage of cholesterol exits the body in the feces. Drugs related to penicillin are also used to inhibit cholesterol recycling. One of these is ezetimibe, shown in Figure 2.224.

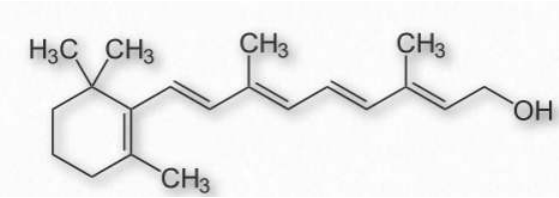


Figure 2.225 - All-trans retinol

Genetic defects in the cholesterol movement system are a cause of the rare disease known as familial hypercholesterolemia in which the blood of afflicted individuals contains dangerously high levels of LDLs. Left untreated, the disease is often fatal in the first 10-20 years of life. While LDLs have received (and deserve) a bad rap, another group of lipoprotein complexes known as the HDLs (high density lipoprotein complexes) are known as “good cholesterol” because their levels correlate with removal of debris (including cholesterol) from arteries and reduce inflammation.

Membrane function

In membranes, cholesterol is important as an insulator for the transmission of signals in nerve tissue and it helps to manage fluidity of membranes over a wide range of temperatures. Stacked in the lipid bilayer, cholesterol decreases a membrane’s fluidity and its permeability to neutral compounds, as well as protons and sodium ions. Cholesterol may play a role in signaling by helping with construction of lipid rafts within the cell membrane.

Vitamin A

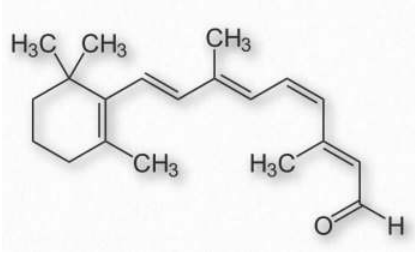


Figure 2.226 - 11-cis retinal

Vitamin A comes in three primary chemical forms, retinol (storage in liver - Figure 2.225), retinal (role in vision - Figure 2.226), and retinoic acid (roles in growth and development). All vitamin A forms are diterpenoids and differ only in the chemical form of the terminal group. Retinol is mostly used as the storage form of the vitamin.

Retinol is commonly esterified to a fatty acid and kept in the liver. In high levels, the compound is toxic. Retinol is obtained in the body by hydrolysis of the ester or by reduction of retinal. Importantly, neither retinal nor retinol can be made from retinoic acid. Retinoic acid is important for healthy skin and teeth, as well as bone growth. It acts in differentiation of stem cells through a specific cellular retinoic acid receptor.

Sources

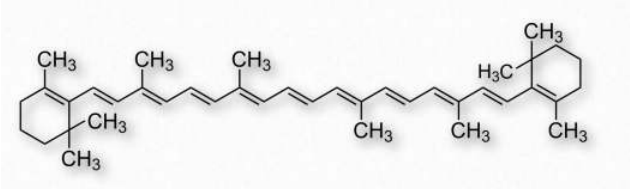


Figure 2.227 - β-Carotene

Good sources of vitamin A are liver and eggs, as well as many plants, including carrots, which have a precursor, β-carotene (Figure 2.227) from which retinol may be made by action of a dioxygenase.

Light sensitivity The conjugated double bond system in the side chain of vitamin A is sensitive to light and can flip between cis and trans forms on exposure to it. It is this response to light that makes it possible for retinal to have a role in vision in the rods and cones of the eyes. Here, the aldehyde form (retinal) is bound to the protein rhodopsin in the membranes of rod and cone cells.

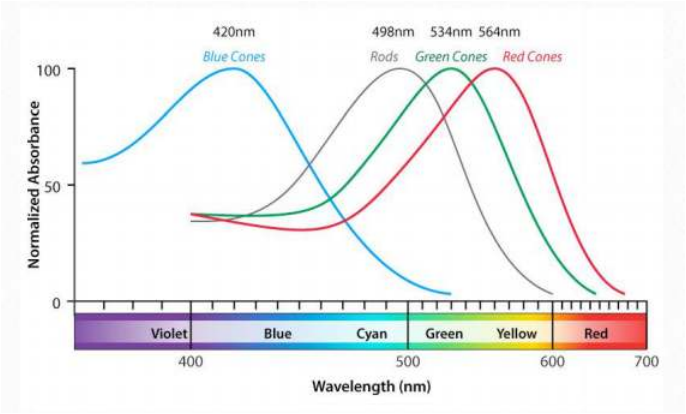


Figure 2.228 - Color sensitivity for cones and rods Image by Aleia Kim

When exposed to light of a particular wavelength, the “tail” of the retinal molecule will flip back and forth from cis to trans at the double bond at position 11 of the molecule. When this happens, a nerve signal is generated that signals the brain of exposure to light. Slightly different forms of rhodopsin have different maximum absorption maxima allowing the brain to perceive red, green and blue specifically and to assemble those into the images we see (Figure 2.228). Cones are the cells responsible for color vision, whereas rods are mostly involved in light detection in low light circumstances.

Deficiency and surplus

Deficiency of vitamin A is common in developing countries and was inspiration for the design and synthesis of the genetically modified golden rice, which is used as a source of vitamin A to help prevent blindness in children. Overdose of vitamin A, called hypervitaminosis A is dangerous and can be fatal. Excess vitamin A is also suspected to be linked to osteoporosis. In smokers, excess vitamin A is linked to an increased rate of lung cancer, but non-smokers have a reduced rate.

Vitamin D

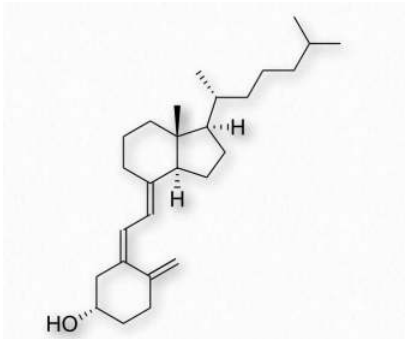


Figure 2.229 - Cholecalciferol - Vitamin D3

The active form of vitamin D plays important roles in the intestinal absorption of calcium and phosphate and thus in healthy bones. Technically, vitamin D isn't even a vitamin, as it is a compound made by the body. Rather, it behaves more like a hormone.

Derived from ultimately from cholesterol, vitamin D can be made in a reaction catalyzed by ultraviolet light. In the reaction, the intermediate 7-dehydrocholesterol is converted to cholecalciferol (vitamin D3) by the uv light (Figure 2.229). The reaction occurs most readily in the bottom two layers of the skin shown in Figure 2.230.

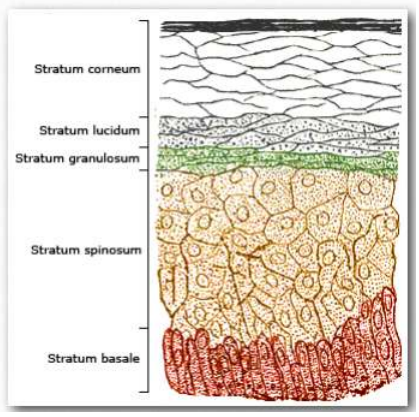


Figure 2.230 - Layers of the skin. Outside is at top.

Deficiency/excess

Deficiency of vitamin D is a cause of the disease known as rickets, which is characterized by soft, weak bones and most commonly is found in children. It is not common in the developed world, but elsewhere is of increasing concern.

Excess of vitamin D is rare, but has toxic effects, including hypercalcemia, which results in painful calcium deposits in major organs. Indications of vitamin D toxicity are increased urination and thirst. Vitamin D toxicity can lead to mental retardation and many other serious health problems.

Vitamin E

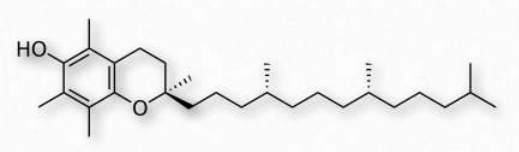


Figure 2.232 α-tocopherol - The most biologically active form of vitamin E Figure

Vitamin E comprises a group of two compounds (tocopherols and tocotrienols - Figure 2.232) and stereoisomers of each. It is commonly found in plant oils. The compounds act in cells as fat-soluble antioxidants. α-tocopherol (Figure 2.233), the most active form of the vitamin, works 1) through the glutathione peroxidase protective system and 2) in membranes to interrupt lipid peroxidation chain reactions. In both actions, vitamin E reduces levels of reactive oxygen species in cells.

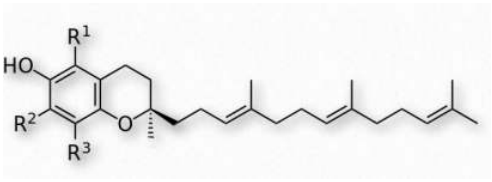


Figure 2.233 - Structure of tocotrienols

Action

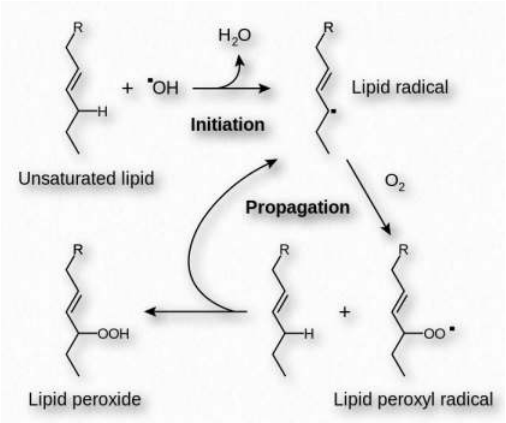


Figure 2.234 - Lipid peroxidation reactions

Vitamin E scavenges oxygen radicals (possessing unpaired electrons) by reacting with them to produce a tocopheryl radical. This vitamin E radical can be converted back to its original form by a hydrogen donor. Vitamin C is one such donor. Acting in this way, Vitamin E helps reduce oxidation of easily oxidized compounds in the lipid peroxidation reactions (Figure 2.234).

Vitamin E also can affect enzyme activity. The compound can inhibit action of protein kinase C in smooth muscle and simultaneously activate catalysis of protein phosphatase 2A to remove phosphates, stopping smooth muscle growth.

Deficiency/excess

Deficiency of vitamin E can lead to poor conduction of nerve signals and other issues arising from nerve problems. Low levels of the vitamin may be a factor in low birth weights and premature deliveries. Deficiency, however, is rare, and not usually associated with diet.

Excess Vitamin E reduces vitamin K levels, thus reducing the ability to clot blood. Hypervitaminosis of vitamin E in conjunction with aspirin can be life threatening. At lower levels, vitamin E may serve a preventative role with respect to atherosclerosis by reducing oxidation of LDLs, a step in plaque formation.

Vitamin K

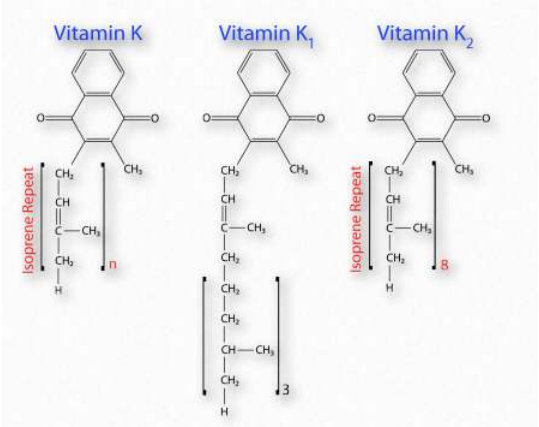


Figure 2.235 - Forms of vitamin K Image by Pehr Jacobson

Like the other fat-soluble vitamins, Vitamin K comes in multiple forms (Figure 2.235) and is stored in fat tissue in the body.

Action

Modification of prothrombin is an important step in the process of blood clotting. Reduced levels of vitamin K result in less blood clotting, a phenomenon sometimes referred to as blood thinning. Drugs that block recycling of vitamin K (Figure 2.236) by inhibiting the vitamin K epoxide reductase, produce lower levels of the vitamin and are employed in treatments for people prone to excessive clotting. Warfarin (coumadin) is one such compound that acts in this way and is used therapeutically. Individuals respond

to the drug differentially, requiring them to periodically be tested for levels of clotting they possess, lest too much or too little occur.

Sources

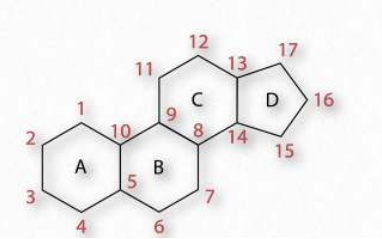


Figure 2.237 - Steroid numbering scheme Image by Pehr Jacobson

Steroids

Steroids, such as cholesterol are found in membranes and act as signaling hormones in traveling through the body.

Steroid hormones are all made from cholesterol and are grouped into five categories - mineralocorticoids (21 carbons), glucocorticoids (21 carbons), progestagens (21 carbons), androgens (19 carbons), and estrogens (18 carbons).

Mineralocorticoids

Mineralocorticoids are steroid hormones that influence water and electrolyte balances. Aldosterone (Figure 2.238) is the primary mineralocorticoid hormone, though other steroid hormones (including progesterone) have some functions like it. Aldosterone stimulates kidneys to reabsorb sodium, secrete potassium, and passively reabsorb water. These actions have the effect of increasing blood pressure and blood volume. Mineralocorticoids are produced by the zona glomerulosa of the cortex of the adrenal gland.

Glucocorticoids

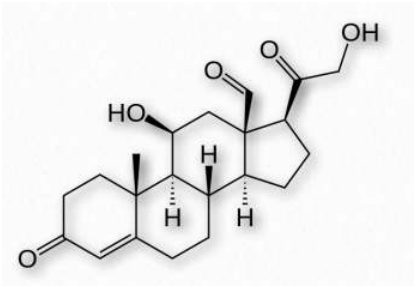


Figure 2.238 - Aldosterone - A mineralocorticoid

Glucocorticoids (GCs) bind to glucocorticoid receptors found in almost every vertebrate animal cell and act in a feedback mechanism in the immune system to reduce its activity. GCs are used to treat diseases associated with overactive immune systems. These include allergies, asthma, and autoimmune dis- Figure 2.237 - Steroid numbering scheme Image by Pehr Jacobson eases. Cortisol (Figure 2.239) is an important glucocorticoid with cardiovascular, metabolic, and immunologic functions. The synthetic glucocorticoid known as dexamethasone has medical applications for treating rheumatoid arthritis, bronchospasms (in asthma), and inflammation due to its increased potency (25-fold) compared to cortisol. Glucocorticoids are produced primarily in the zona fasciculata of the adrenal cortex.

Progestagens

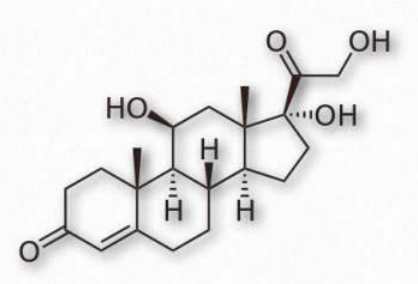


Figure 2.239 - Cortisol - A glucocorticoid

Progesterone (also called P4 - Figure 2.240) has functions in maintaining pregnancy. Progesterone is produced primarily in the diestrus phase of the estrous cycle by the corpus luteum of mammalian ovaries. In pregnancy, the placenta takes over most progesterone production.

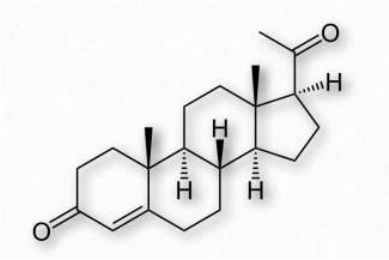


Figure 2.240 Progesterone - A progestagen

Estrogens

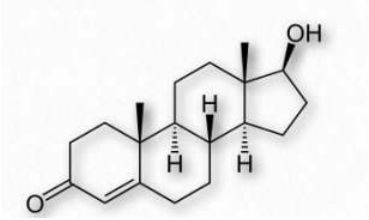


Figure 2.241 - Testosterone - An androgen

The estrogen steroid hormones are a class of compounds with important roles in menstrual and estrous cycles. They are the most important female sex hormones. Estrogens act by activating estrogen receptors inside of cells. These receptors, in turn, affect expression of many genes. The major estrogens in women include estrone (E1), estradiol (E2 - Figure 2.242), and estriol (E3). In the reproductive years, estradiol predominates. During pregnancy, estriol predominates and during menopause, estrone is the major estrogen.

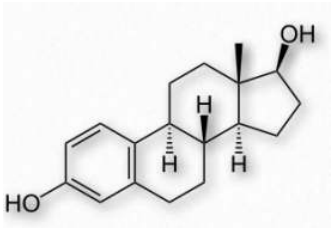


Figure 2.242 - Estradiol - An estrogen

Estrogens are made from the androgen hormones testosterone and androstenedione in a reaction catalyzed by the enzyme known as aromatase. Inhibition of this enzyme with aromatase inhibitors, such as exemestane, is a strategy for stopping estrogen production. This may be part of a chemotherapeutic treatment when estrogenresponsive tumors are present.

Lipoprotein complexes and lipid movement in the body

Lipoprotein complexes are combinations of apolipoproteins and lipids bound to them that solubilize fats and other non-polar molecules, such as cholesterol, so they can travel in the bloodstream between various tissues of the body. The apolipoproteins

provide the emulsification necessary for this. Lipoprotein complexes are formed in tiny “balls” with the water soluble apolipoproteins on the outside and non-polar lipids, such as fats, cholesteryl esters, and fat soluble vitamins on the inside.

They are categorized by their densities. These include (from highest density to the lowest) high density lipoproteins (HDLs), Low Density Lipoproteins (LDLs), Very Low Density Lipoproteins (VLDLs) and the chylomicrons. These particles are synthesized in the liver and small intestines.

Lipoprotein lipase is a cellular enzyme that catalyzes the breakdown of fat from the complexes.

Movement

The movement of fats in the body is important because they are not stored in all cells. Only specialized cells called adipocytes store fat. There are three relevant pathways in the body for moving lipids. As described below, they are 1) the exogenous pathway; 2) the endogenous pathway, and 3) the reverse transport pathway.

Exogenous pathway

Dietary fat entering the body from the intestinal system must be transported, as appropriate, to places needing it or storing it. This is the function of the exogenous pathway of lipid movement in the body. All dietary lipids (fats, cholesterol, fat soluble vitamins, and other lipids) are moved by it. In the case of dietary fat, it begins its journey after ingestion first by being solubilized by bile acids in the intestinal tract. After passing through the stomach, pancreatic lipases clip two fatty acids from the fat, leaving a monoacyl glycerol. The fatty acids and monoacyl glycerol are absorbed by intestinal cells and reassembled back into a fat, and then this is mixed with phospholipids, cholesterol esters, and apolipoprotein and processed to form chylomicrons (Figures 2.259).

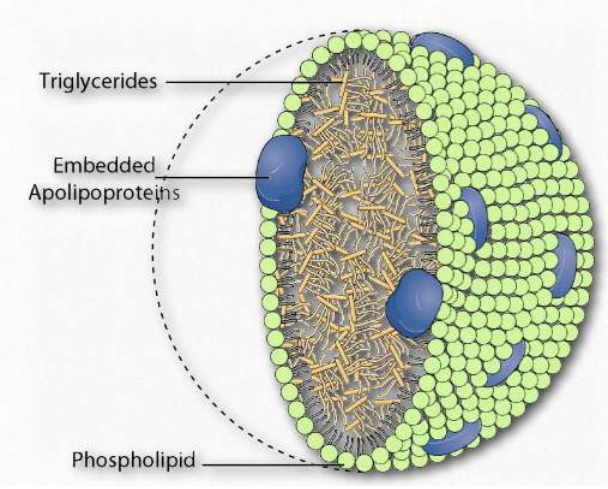


Figure 2.259 - Another perspective of a chylomicron WIkipedia

The chylomicrons enter the bloodstream and travel to the liver or adipose cells where they are absorbed (Figure 2.260) and broken down by lipoprotein lipase.

Endogenous pathway

The liver plays a central role in managing the body’s needs for lipids. When lipids are needed by the body or when the capacity of the liver to contain more lipids than is supplied by the diet, the liver packages up fats and cholesteryl esters into Very Low Density Lipoprotein (VLDL) complexes and exports them via the endogenous pathway. VLDLs enter the blood and travel to muscles and adipose tissue where lipoprotein lipase is activated. In the muscle cells, the released fatty acids are taken up and oxidized. By contrast, in the adipoctyes, the fatty acids are taken up and reassembled back into triacylglycerides (fats) and stored in fat droplets.

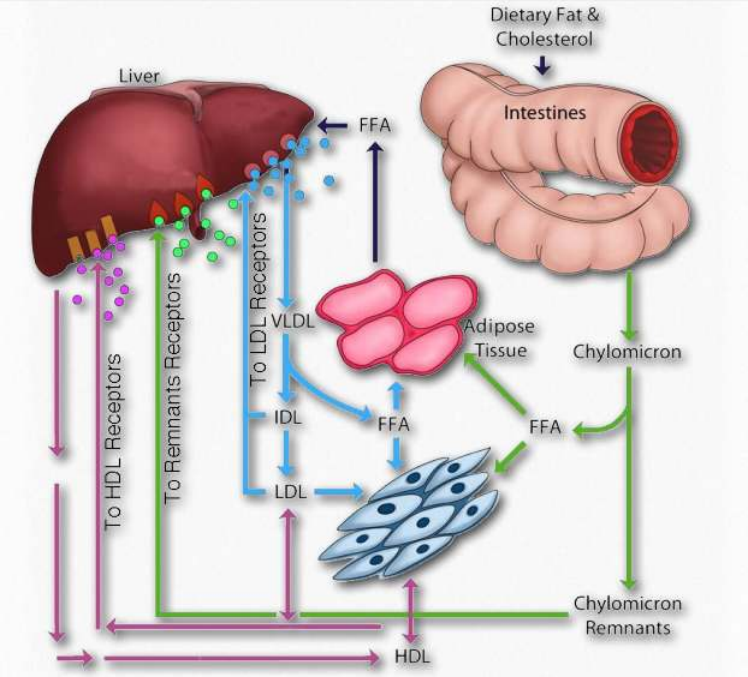


Figure 2.260 - Movement of lipids in the body - Green = exogenous pathway; Blue = endogenous pathway; Purple = reverse transport pathway Image by Aleia Kim

Reverse transport pathway

Another important consideration of the movement of lipids in the body is the reverse transport pathway (Figure 2.260). It is also called the reverse cholesterol transport pathway, since cholesterol is the primary molecule involved. This pathway involves the last class of lipoprotein complexes known as the High Density Lipoproteins (HDLs). In contrast to the LDLs, which are commonly referred to as “bad cholesterol” (see below also), the HDLs are known as “good cholesterol.”

HDLs are synthesized in the liver and small intestine. They contain little or no lipid when made (called depleted HDLs), but serve the role of “scavenger” for cholesterol in the blood and from remnants of other (damaged) lipoprotein complexes in the blood. To perform its task, HDLs carry the enzyme known as lecithincholesterol acyl transferase (LCAT), which they use to form cholesteryl esters using fatty acids from lecithin (phosphatidylcholine) and then they internalize them.

The cholesterol used for this purpose comes from the bloodstream, from macrophages, and from foam cells (macrophage-LDL complexes - Figure 2.262). Addition of cholesteryl esters causes the HDL to swell and Figure 2.261 - The process of receptor-mediated endocytosis Image by Aleia Kim when it is mature, it returns its load of cholesterol back to the liver or, alternatively, to LDL molecules for endocytosis. HDLs have the effect of lowering levels of cholesterol and it is for that reason they are described as “good cholesterol.”

Regulation of lipid transfer

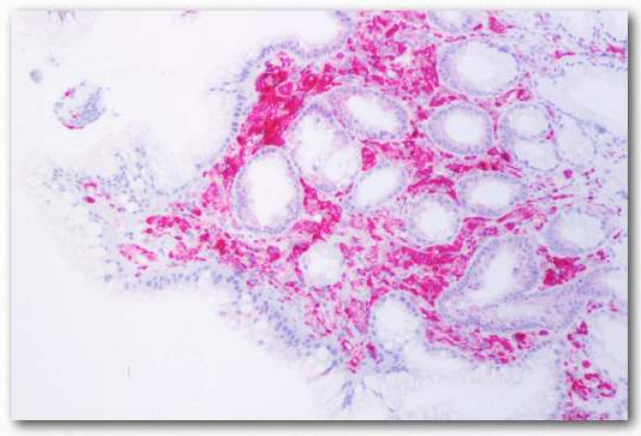


Figure 2.262 - Foam cell aggregate Wikipedia

It is important that cells get food when they need it so some control of the movement of nutrients is critical. The liver, which plays the central role in modulating blood glucose levels, is also important for performing the same role for lipids. It accomplishes this task the use of specialized LDL receptors on its surface. Liver LDL receptors bind LDLs that were not taken up by other cells in their path through the bloodstream. High levels of LDLs are a signal to the liver to reduce the creation of VLDLs for release.

People with the genetic disease known as familial hypercholesterolemia, which manifests with dangerously high levels of LDLs, lack properly functioning LDL receptors on their liver cells.Figure 2.263 - Progression of atherosclerosis Wikipedia Figure 2.263 - Progression of atherosclerosis Wikipedia Figure 2.263 - Progression of atherosclerosis Wikipedia

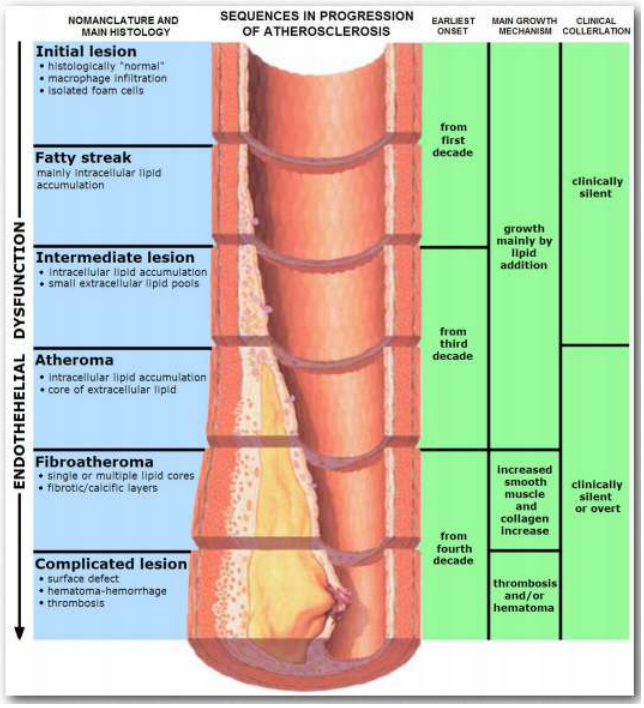


Figure 2.263 - Progression of atherosclerosis Wikipedia

In sufferers of this disease, the liver never gets the signal that the LDL levels are high. In fact, to the liver, it appears that all VLDLs and LDLs are being taken up by peripheral tissues, so it creates more VLDLs to attempt to boost levels. Untreated, the disease used to be fatal early, but newer drugs like the statins have significantly increased life spans of patients. Cellular needs for the contents of LDLs are directly linked to the levels of synthesis of LDL receptors on their membranes. As cells are needing more cholesterol, their synthesis of components for receptors goes up and it decreases as need diminishes.

Good cholesterol / bad cholesterol

It is commonly accepted that “high cholesterol” levels are not healthy. This is due, at least indirectly, to the primary carriers of cholesterol, the LDLs. A primary function of the LDLs is to deliver cholesterol and other lipids directly into cells by receptor mediated endocytosis (Figure 2.237). High levels of LDLs, though, are correlated with formation of atherosclerotic plaques (Figure 2.263 & 2.264) and incidence of atherosclerosis, leading to the description of them as “bad cholesterol.” This is because when LDL levels are very high, plaque formation begins. It is thought that reactive oxygen species (higher in the blood of smokers) causes partial oxidation of fatty acid groups in the LDLs. When levels are high, they tend to accumulate in the extracellular matrix of the epithelial cells on the inside of the arteries. Macrophages of the immune system take up the damaged LDLs (including the cholesterol).

Since macrophages can’t control the amount of cholesterol they take up, cholesterol begins to accumulate in them and they take on appearance that leads to their being described as “foam cells.” With too much cholesterol, the foam cells, however, are doomed to die by the process of programmed cell death (apoptosis). Accumulation of these, along with scar tissue from inflammation result in formation of a plaque. Plaques can grow and block the flow of blood or pieces of them can break loose and plug smaller openings in the blood supply, ultimately leading to heart attack or stroke.

Good cholesterol

On the other hand, high levels of HDL are inversely correlated with atherosclerosis and arterial disease. Depleted HDLs are able to remove cholesterol from foam cells.



Figure 2.264 - Actual carotid artery plaque Wikipedia

Deficiency of the ABCA-1 gene leads to Tangier disease. In this condition, HDLs are almost totally absent because they remain empty as a result of not being able to take up cholesterol from foam cells, so they are destroyed by the body.

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15.7: Steroids

Learning Objectives

- To identify the functions of steroids produced in mammals.

All the lipids discussed so far are *saponifiable*, reacting with aqueous alkali to yield simpler components, such as glycerol, fatty acids, amino alcohols, and sugars. Lipid samples extracted from cellular material, however, also contain a small but important fraction that does not react with alkali. The most important nonsaponifiable lipids are the steroids. These compounds include the *bile salts*, *cholesterol* and related compounds, and certain *hormones* (such as cortisone and the sex hormones).

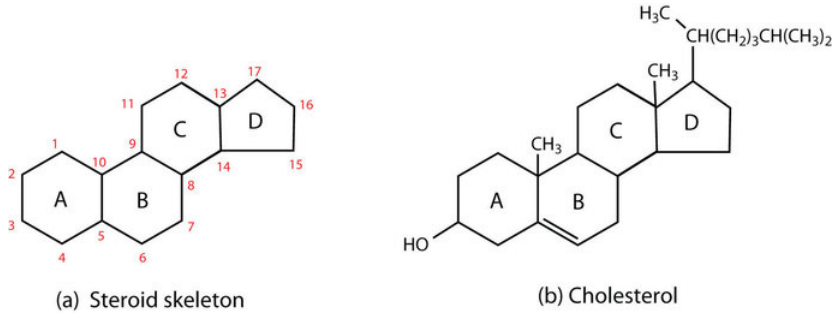


Figure 15.7.1 Steroids. (a) The four-fused-ring steroid skeleton uses letter designations for each ring and the numbering of the carbon atoms. (b) The cholesterol molecule follows this pattern.

Steroids occur in plants, animals, yeasts, and molds but not in bacteria. They may exist in free form or combined with fatty acids or carbohydrates. All steroids have a characteristic structural component consisting of four fused rings. Chemists identify the rings by capital letters and number the carbon atoms as shown in Figure 15.7.1*a*. Slight variations in this structure or in the atoms or groups attached to it produce profound differences in biological activity.

Cholesterol

Cholesterol (Figure 15.7.1*b*) does not occur in plants, but it is the most abundant steroid in the human body (240 g is a typical amount). Excess cholesterol is believed to be a primary factor in the development of atherosclerosis and heart disease, which are major health problems in the United States today. About half of the body's cholesterol is interspersed in the lipid bilayer of cell membranes. Much of the rest is converted to cholic acid, which is used in the formation of bile salts. Cholesterol is also a precursor in the synthesis of sex hormones, adrenal hormones, and vitamin D.

Excess cholesterol not metabolized by the body is released from the liver and transported by the blood to the gallbladder. Normally, it stays in solution there until being secreted into the intestine (as a component of bile) to be eliminated. Sometimes, however, cholesterol in the gallbladder precipitates in the form of gallstones (Figure 15.7.2). Indeed, the name *cholesterol* is derived from the Greek *chole*, meaning "bile," and *stereos*, meaning "solid."



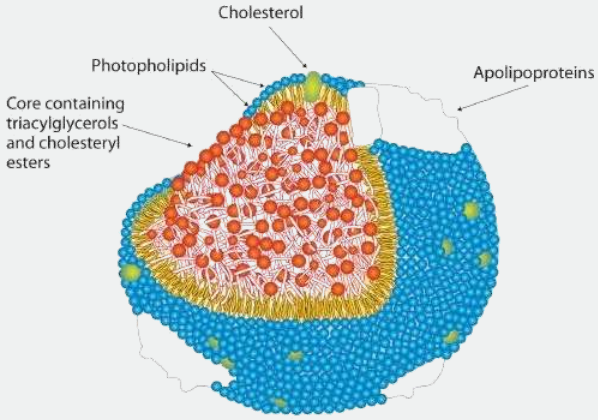
Figure 15.7.2: Numerous small gallstones made up largely of cholesterol, all removed in one patient. Grid scale 1 mm

To Your Health: Cholesterol and Heart Disease

Heart disease is the leading cause of death in the United States for both men and women. The Centers for Disease Control and Prevention reported that heart disease claimed 631,636 lives in the United States (26% of all reported deaths) in 2006.

Scientists agree that elevated cholesterol levels in the blood, as well as high blood pressure, obesity, diabetes, and cigarette smoking, are associated with an increased risk of heart disease. A long-term investigation by the National Institutes of Health showed that among men ages 30 to 49, the incidence of heart disease was five times greater for those whose cholesterol levels were above 260 mg/100 mL of serum than for those with cholesterol levels of 200 mg/100 mL or less. The cholesterol content of blood varies considerably with age, diet, and sex. Young adults average about 170 mg of cholesterol per 100 mL of blood, whereas males at age 55 may have cholesterol levels at 250 mg/100 mL or higher because the rate of cholesterol breakdown decreases with age. Females tend to have lower blood cholesterol levels than males.

To understand the link between heart disease and cholesterol levels, it is important to understand how cholesterol and other lipids are transported in the body. Lipids, such as cholesterol, are not soluble in water and therefore cannot be transported in the blood (an aqueous medium) unless they are complexed with proteins that are soluble in water, forming assemblages called *lipoproteins*. Lipoproteins are classified according to their density, which is dependent on the relative amounts of protein and lipid they contain. Lipids are less dense than proteins, so lipoproteins containing a greater proportion of lipid are less dense than those containing a greater proportion of protein.



Research on cholesterol and its role in heart disease has focused on serum levels of low-density lipoproteins (LDLs) and high-density lipoproteins (HDLs). One of the most fascinating discoveries is that high levels of HDLs reduce a person's risk of developing heart disease, whereas high levels of LDLs increase that risk. Thus the serum LDL:HDL ratio is a better predictor of heart disease risk than the overall level of serum cholesterol. Persons who, because of hereditary or dietary factors, have high LDL:HDL ratios in their blood have a higher incidence of heart disease.

How do HDLs reduce the risk of developing heart disease? No one knows for sure, but one role of HDLs appears to be the transport of excess cholesterol to the liver, where it can be metabolized. Therefore, HDLs aid in removing cholesterol from blood and from the smooth muscle cells of the arterial wall.

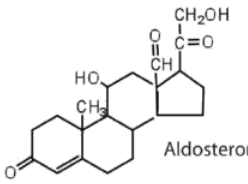
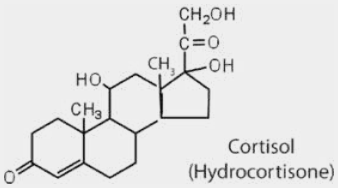
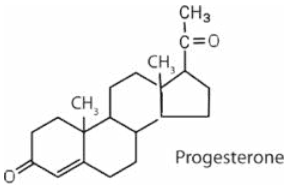
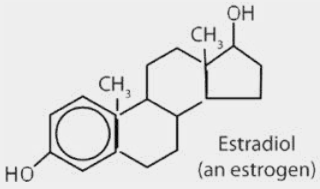
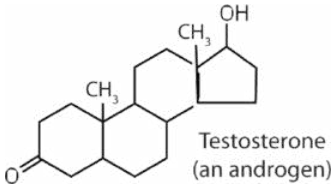
Dietary modifications and increased physical activity can help lower total cholesterol and improve the LDL:HDL ratio. The average American consumes about 600 mg of cholesterol from animal products each day and also synthesizes approximately 1 g of cholesterol each day, mostly in the liver. The amount of cholesterol synthesized is controlled by the cholesterol level in the blood; when the blood cholesterol level exceeds 150 mg/100 mL, the rate of cholesterol biosynthesis is halved. Hence, if cholesterol is present in the diet, a feedback mechanism suppresses its synthesis in the liver. However, the ratio of suppression is not a 1:1 ratio; the reduction in biosynthesis does not equal the amount of cholesterol ingested. Thus, dietary substitutions of unsaturated fat for saturated fat, as well as a reduction in consumption of *trans* fatty acids, is recommended to help lower serum cholesterol and the risk of heart disease.

Steroid Hormones

Hormones are chemical messengers that are released in one tissue and transported through the circulatory system to one or more other tissues. One group of hormones is known as steroid hormones because these hormones are synthesized from cholesterol, which is also a steroid. There are two main groups of steroid hormones: adrenocortical hormones and sex hormones.

The adrenocortical hormones, such as aldosterone and cortisol (Table **15.7.1**), are produced by the adrenal gland, which is located adjacent to each kidney. Aldosterone acts on most cells in the body, but it is particularly effective at enhancing the rate of reabsorption of sodium ions in the kidney tubules and increasing the secretion of potassium ions and/or hydrogen ions by the tubules. Because the concentration of sodium ions is the major factor influencing water retention in tissues, aldosterone promotes water retention and reduces urine output. Cortisol regulates several key metabolic reactions (for example, increasing glucose production and mobilizing fatty acids and amino acids). It also inhibits the inflammatory response of tissue to injury or stress. Cortisol and its analogs are therefore used pharmacologically as immunosuppressants after transplant operations and in the treatment of severe skin allergies and autoimmune diseases, such as rheumatoid arthritis.

Table **15.7.1**: Representative Steroid Hormones and Their Physiological Effects

Hormone	Effect
 Aldosterone	regulates salt metabolism; stimulates kidneys to retain sodium and excrete potassium
 Cortisol (Hydrocortisone)	stimulates the conversion of proteins to carbohydrates
 Progesterone	regulates the menstrual cycle; maintains pregnancy
 Estradiol (an estrogen)	stimulates female sex characteristics; regulates changes during the menstrual cycle
 Testosterone (an androgen)	stimulates and maintains male sex characteristics

The sex hormones are a class of steroid hormones secreted by the gonads (ovaries or testes), the placenta, and the adrenal glands. Testosterone and androstenedione are the primary male sex hormones, or *androgens*, controlling the primary sexual characteristics of males, or the development of the male genital organs and the continuous production of sperm. Androgens are also responsible for the development of secondary male characteristics, such as facial hair, deep voice, and muscle strength. Two kinds of sex

hormones are of particular importance in females: progesterone, which prepares the uterus for pregnancy and prevents the further release of eggs from the ovaries during pregnancy, and the estrogens, which are mainly responsible for the development of female secondary sexual characteristics, such as breast development and increased deposition of fat tissue in the breasts, the buttocks, and the thighs. Both males and females produce androgens and estrogens, differing in the amounts of secreted hormones rather than in the presence or absence of one or the other.

Sex hormones, both natural and synthetic, are sometimes used therapeutically. For example, a woman who has had her ovaries removed may be given female hormones to compensate. Some of the earliest chemical compounds employed in cancer chemotherapy were sex hormones. For example, estrogens are one treatment option for prostate cancer because they block the release and activity of testosterone. Testosterone enhances prostate cancer growth. Sex hormones are also administered in preparation for sex-change operations, to promote the development of the proper secondary sexual characteristics. Oral contraceptives are synthetic derivatives of the female sex hormones; they work by preventing ovulation.

Bile Salts

Bile is a yellowish green liquid (pH 7.8–8.6) produced in the liver. The most important constituents of bile are bile salts, which are sodium salts of amidelike combinations of bile acids, such as cholic acid (part (a) of Figure **15.7.3**) and an amine such as the amino acid glycine (part (b) of Figure **15.7.3**). They are synthesized from cholesterol in the liver, stored in the gallbladder, and then secreted in bile into the small intestine. In the gallbladder, the composition of bile gradually changes as water is absorbed and the other components become more concentrated.

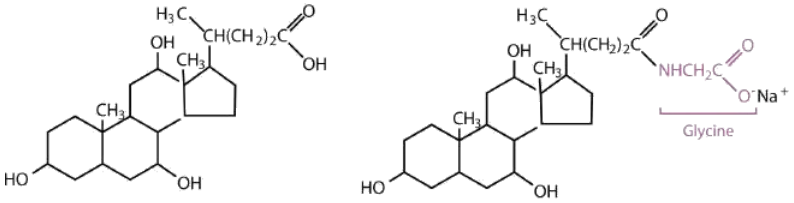


Figure **15.7.3** Bile Acids. (a) Cholic acid is an example of a bile acid. (b) Sodium glycocholate is a bile salt synthesized from cholic acid and glycine.

Because they contain both hydrophobic and hydrophilic groups, bile salts are highly effective detergents and emulsifying agents; they break down large fat globules into smaller ones and keep those smaller globules suspended in the aqueous digestive environment. Enzymes can then hydrolyze fat molecules more efficiently. Thus, the major function of bile salts is to aid in the digestion of dietary lipids.

> Surgical removal is often advised for a gallbladder that becomes infected, inflamed, or perforated. This surgery does not seriously affect digestion because bile is still produced by the liver, but the liver's bile is more dilute and its secretion into the small intestine is not as closely tied to the arrival of food.

Summary

Steroids have a four-fused-ring structure and have a variety of functions. Cholesterol is a steroid found in mammals that is needed for the formation of cell membranes, bile acids, and several hormones. Bile salts are secreted into the small intestine to aid in the digestion of fats.

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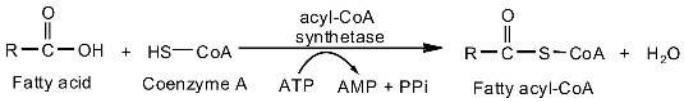
15.8: 15.8-Lipid Catabolism

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 **15.8.1**).

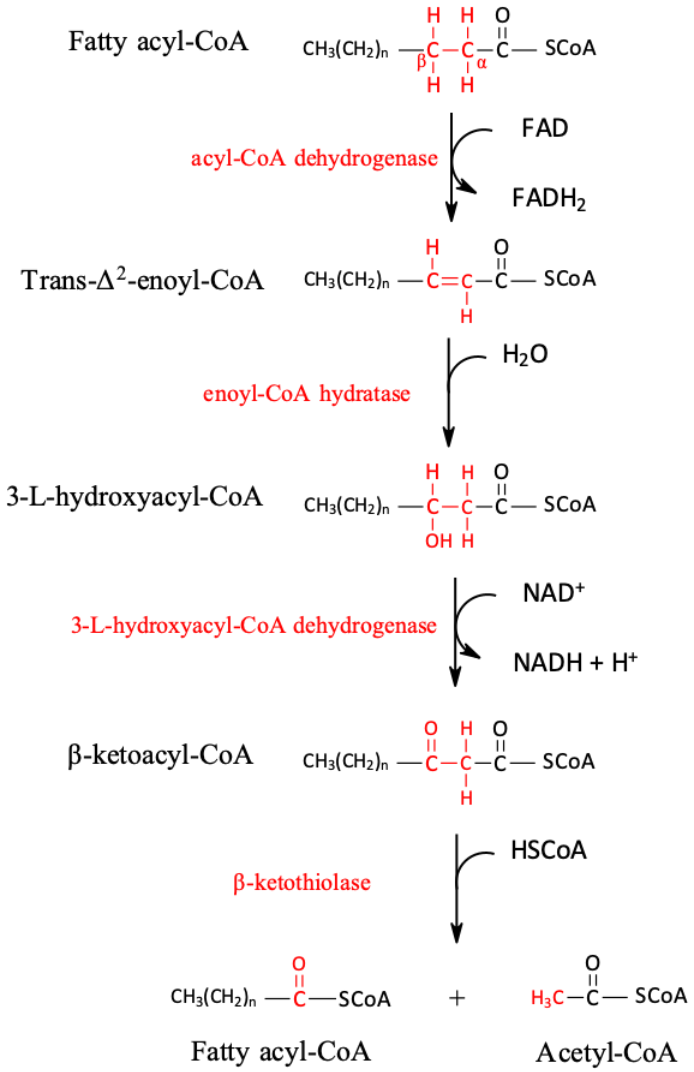


Figure 15.8.1: Fatty Acid Oxidation. The fatty acyl-CoA formed in the final step becomes the substrate for the first step in the next round of β-oxidation. β-oxidation continues until two acetyl-CoA molecules are produced in the final step.

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 ($FADH_2$).

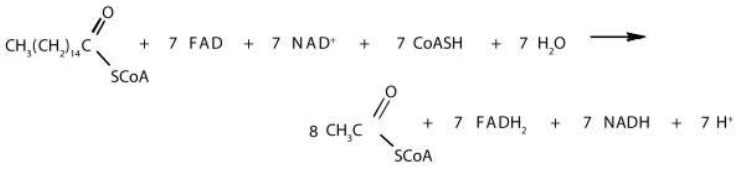
> The $FADH_2$ is reoxidized back to FAD via the electron transport chain that supplies energy to form 1.5–2 molecules of ATP.

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:

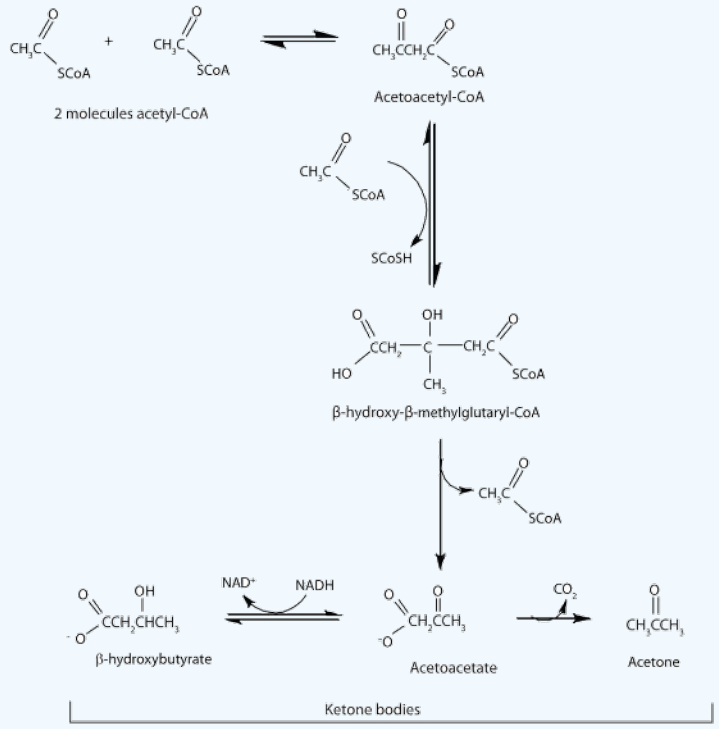


> *Because each shortened fatty acyl-CoA cycles back to the beginning of the pathway, β-oxidation is sometimes referred to as the fatty acid spiral.*

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:

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:

$$C_{16}H_{32}O_2 + 23O_2 \rightarrow 16CO_2 + 16H_2O + 2,340\ kcal \tag{15.8.1}$$

The percentage of this energy that is conserved by the cell in the form of ATP is as follows:

$$\frac{\text{energy conserved}}{\text{total energy available}} \times 100 = \frac{(129\ \text{ATP})(7.4\ \text{kcal/ATP})}{2,340\ \text{kcal}} \times 100 = 41\% \tag{15.8.2}$$

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 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

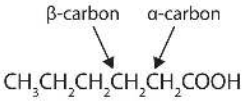
- Fatty acids, obtained from the breakdown of triglycerides and other lipids, are oxidized through a series of reactions known as β-oxidation.

- 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.

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

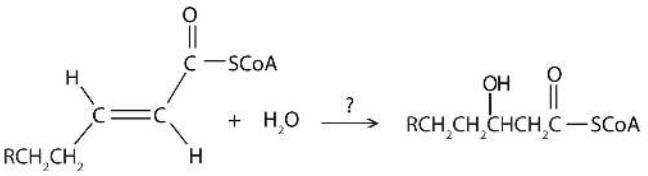
1. They react with CoA to form fatty acyl-CoA molecules.
2. 

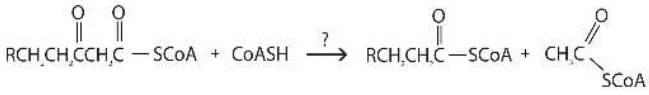
Key Takeaways

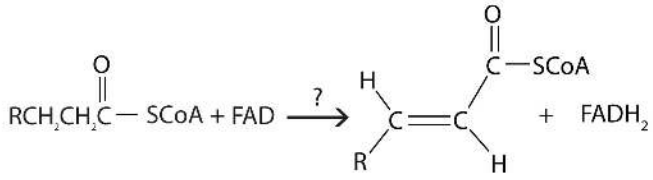
- Fatty acids, obtained from the breakdown of triglycerides and other lipids, are oxidized through a series of reactions known as β-oxidation.
- In each round of β-oxidation, 1 molecule of acetyl-CoA, 1 molecule of NADH, and 1 molecule of $FADH_2$ are produced.
- The acetyl-CoA, NADH, and $FADH_2$ are 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

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15.9: Overview of Lipid 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.

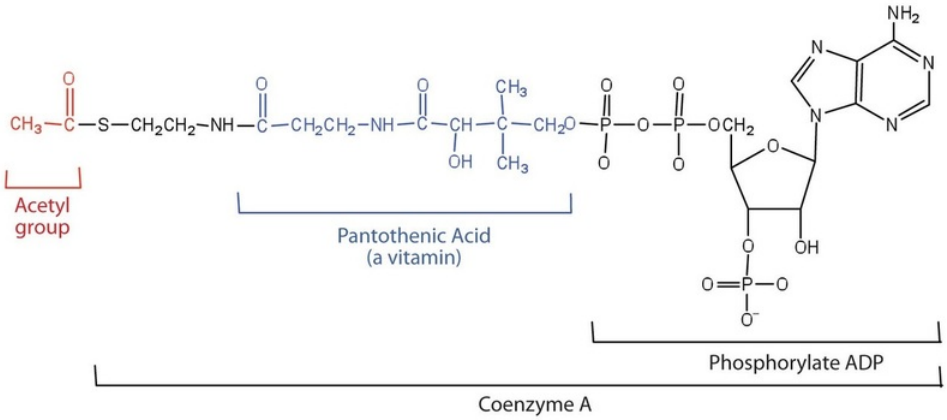


Figure **15.9.1**: The Structure of Acetyl-Coenzyme A (Acetyl-CoA)

Acetyl-CoA is shown in Figure **15.9.1**. 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 **15.9.1**.

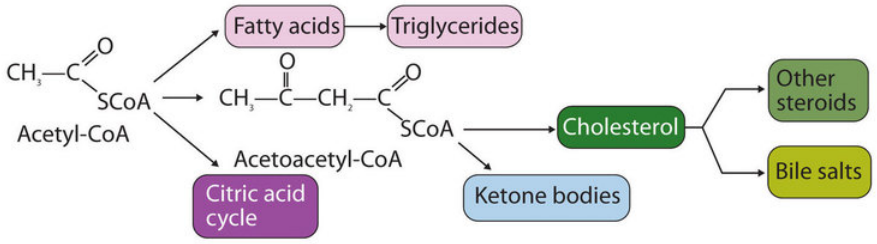


Figure **15.9.2**: Cell Chemistry. Acetyl-CoA plays a variety of roles in cell chemistry.

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 **15.9.1**: 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 http://vcell.ndsu.edu/animations.

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 **15.9.3**.

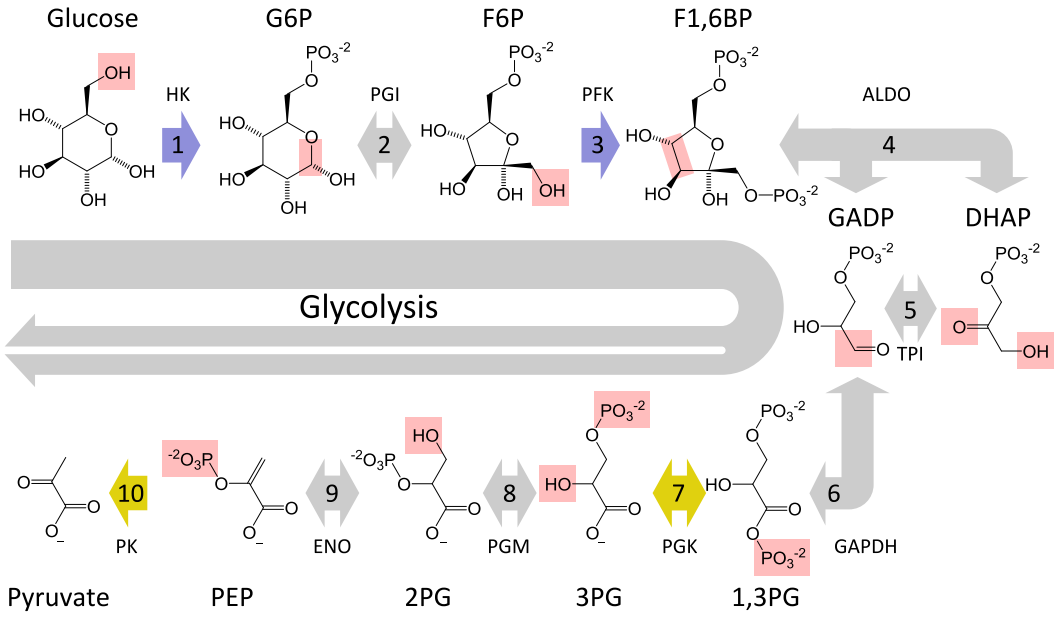


Figure **15.9.3**: Glycolysis pathway. (CC BY-SA 4.0; International; Thomas Shafee via Wikipedia)

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 **15.9.2**: 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.

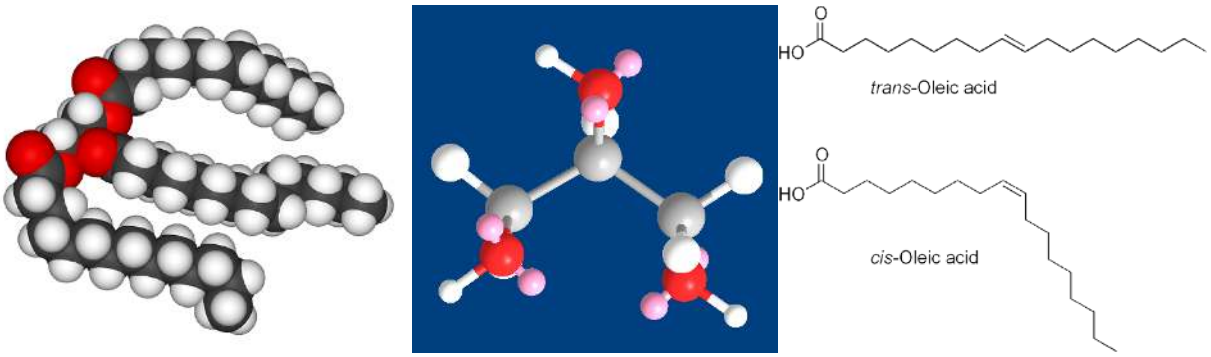


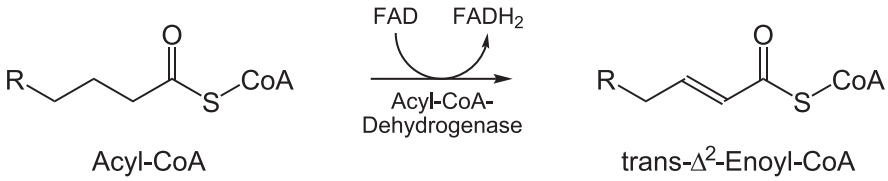
Figure 15.9.4: Key molecules in beta-oxidation: (left) A triglyceride molecule, (middle) Glycerol, (right) Fatty Acids (unsaturated)

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.

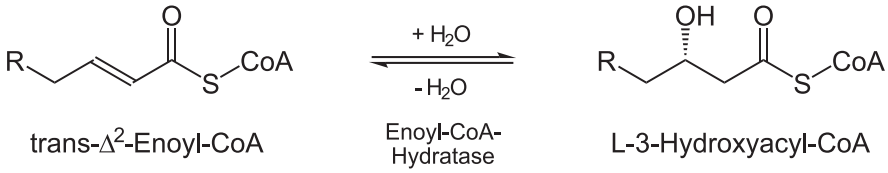
Oxidation Step

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.



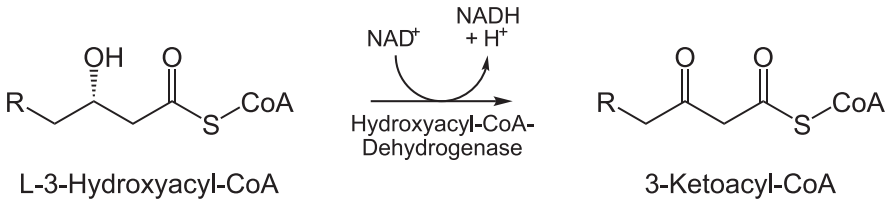
Hydration Step

The trans alkene is then hydrated with the help of Enoyl-CoA hydratase



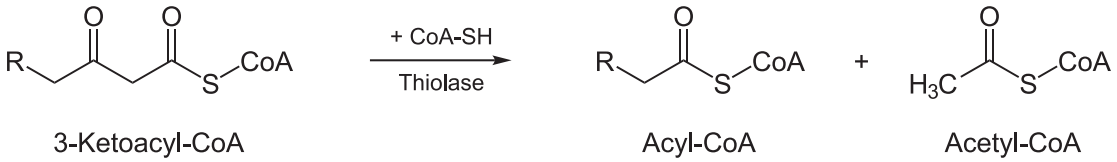
Oxidation Step

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.

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

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SECTION OVERVIEW

15.10: Lipid Details

15.10.1: Fatty Acid Oxidation

15.10.2: Acetyl-CoA Metabolism

15.10.3: Fatty Acid Synthesis

15.10.4: Cholesterol Metabolism

15.10.5: Ketone Body Synthesis

15.10.6: Prostaglandin Synthesis

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15.10.1: Fatty Acid Oxidation

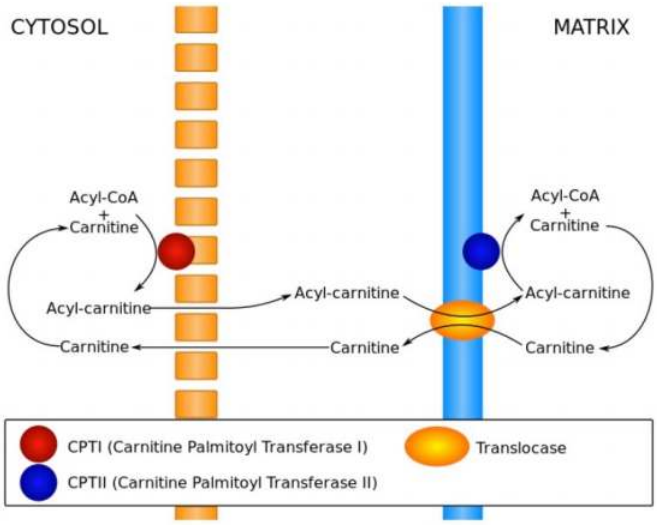


Figure 6.11.1: *Movement of Acyl-CoAs into the Mitochondrial Matrix*

The process of fatty acid oxidation, called beta oxidation, is fairly simple. The reactions all occur between carbons 2 and 3 (with #1 being the one linked to the CoA) and sequentially include the following:

1. dehydrogenation to create $\mathbf{FADH_2}$ and a fatty acyl group with a double bond in the trans configuration;
2. hydration across the double bond to put a hydroxyl group on carbon 3 in the L configuration;
3. oxidation of the hydroxyl group to make a ketone; and
4. thiolytic cleavage to release acetyl-CoA and a fatty acid two carbons shorter than the starting one.

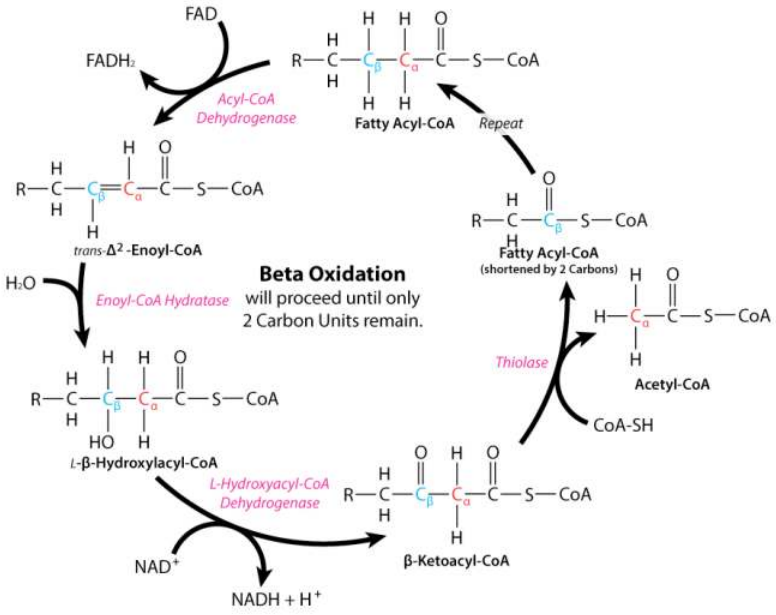


Figure 6.11.2: *Beta Oxidation of Fatty Acids*

Reactions two and three in beta oxidation are catalyzed by enoyl-CoA hydratase and 3-hydroxyacyl-CoA dehydrogenase, respectively. The latter reaction yields an NADH. The final enzyme of beta oxidation is thiolase and this enzyme is notable in not only catalyzing the formation of acetyl-CoAs in beta oxidation, but also catalyzing the joining of two acetyl-CoAs (essentially the reversal of the last step of beta oxidation) to form acetoacetyl-CoA– essential for the pathways of ketone body synthesis and cholesterol biosynthesis.

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15.10.2: Acetyl-CoA Metabolism

Acetyl-CoA is one of the most “connected" metabolites in biochemistry, appearing in fatty acid oxidation/reduction, pyruvate oxidation, the citric acid cycle, amino acid anabolism/catabolism, ketone body metabolism, steroid/bile acid synthesis, and (by extension from fatty acid metabolism) prostaglandin synthesis. Most of these pathways will be dealt with separately. Here we will cover the last three.

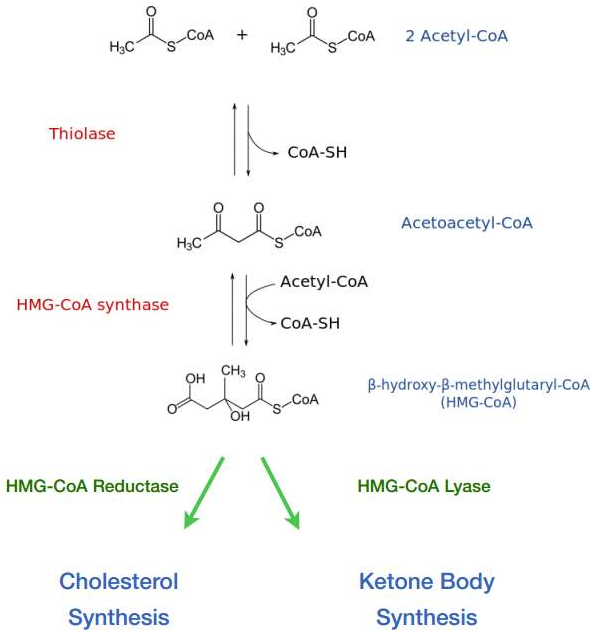


Figure 6.7.1: *Pathways for Cholestrol and Ketone Body Synthesis*

The pathways for ketone body synthesis and cholesterol biosynthesis overlap at the beginning. Each of these starts by combining two acetyl-CoAs together to make acetoacetyl-CoA. Not coincidentally, that is the next to last product of oxidation of fatty acids with even numbers of carbons. In fact, the enzyme that catalyzes the joining is the same as the one that catalyzes its breakage in fatty acid oxidation – thiolase. Thus, these pathways start by reversing the last step of the last round of fatty acid oxidation. Both pathways also include addition of two more carbons from a third acetyl-CoA to form Hydroxy-Methyl-Glutaryl-CoA, or HMG-CoA, as it is more commonly known. It is at this point that the two pathways diverge.

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15.10.3: Fatty Acid Synthesis

Synthesis of fatty acids occurs in the cytoplasm and endoplasmic reticulum of the cell and is chemically similar to the beta-oxidation process, but with a couple of key differences. The first of these occur in preparing substrates for the reactions that grow the fatty acid. Transport of acetyl-CoA from the mitochondria occurs when it begins to build up. Two molecules can play roles in moving it to the cytoplasm – citrate and acetylcarnitine. Joining of oxaloacetate with acetyl-CoA in the mitochondrion creates citrate which moves across the membrane, followed by action of citrate lyase in the cytoplasm of the cell to release acetyl-CoA and oxaloacetate. Additionally, when free acetyl-CoA accumulates in the mitochondrion, it may combine with carnitine and be transported out to the cytoplasm.

Starting with two acetyl-CoA, one is converted to malonyl-CoA by carboxylation catalyzed by the enzyme acetyl-CoA carboxylase (ACC), the only regulatory enzyme of fatty acid synthesis (Figure **15.10.3.1**). Next, both molecules have their CoA portions replaced by a carrier protein known as ACP (acyl-carrier protein) to form acetyl-ACP and malonyl-ACP. Joining of a fatty acyl-ACP (in this case, acetyl-ACP) with malonyl-ACP splits out the carboxyl that was added and creates the intermediate at the upper right in the figure at left.

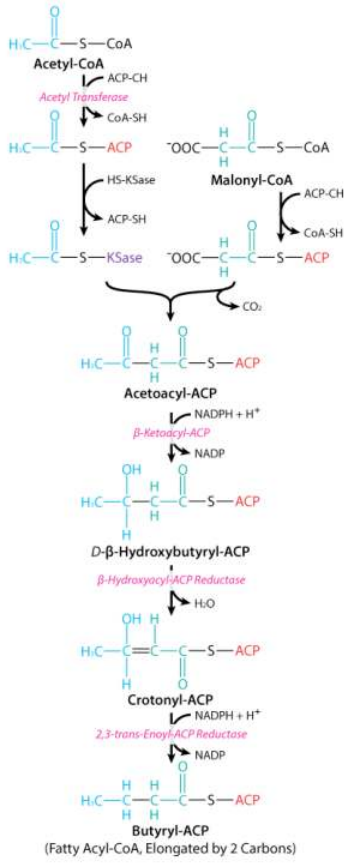


Figure* 15.10.3.1*:*Fatty Acid Synthesis***

From this point forward, the chemical reactions resemble those of beta oxidation reversed. First, the ketone is reduced to a hydroxyl using NADPH. In contrast to the hydroxylated intermediate of beta oxidation, the beta intermediate here is in the D-configuration. Next, water is removed from carbons 2 and 3 of the hydroxyl intermediate to produce a trans doubled bonded molecule. Last, the double bond is hydrogenated to yield a saturated intermediate. The process cycles with the addition of another malonyl-ACP to the growing chain until ultimately an intermediate with 16 carbons is produced (palmitoyl-CoA). At this point, the cytoplasmic synthesis ceases.

Enzymes of Fatty Acid Synthesis

Acetyl-CoA carboxylase, which catalyzes synthesis of malonyl-CoA, is the only regulated enzyme in fatty acid synthesis. Its regulation involves both allosteric control and covalent modification. The enzyme is known to be phosphorylated by both AMP Kinase and Protein Kinase A. Dephosphorylation is stimulated by phosphatases activated by insulin binding. Dephosphorylation activates the enzyme and favors its assembly into a long polymer, while phosphorylation reverses the process.Citrate acts as an allosteric activator and may also favor polymerization. Palmitoyl-CoA allosterically inactivates it.

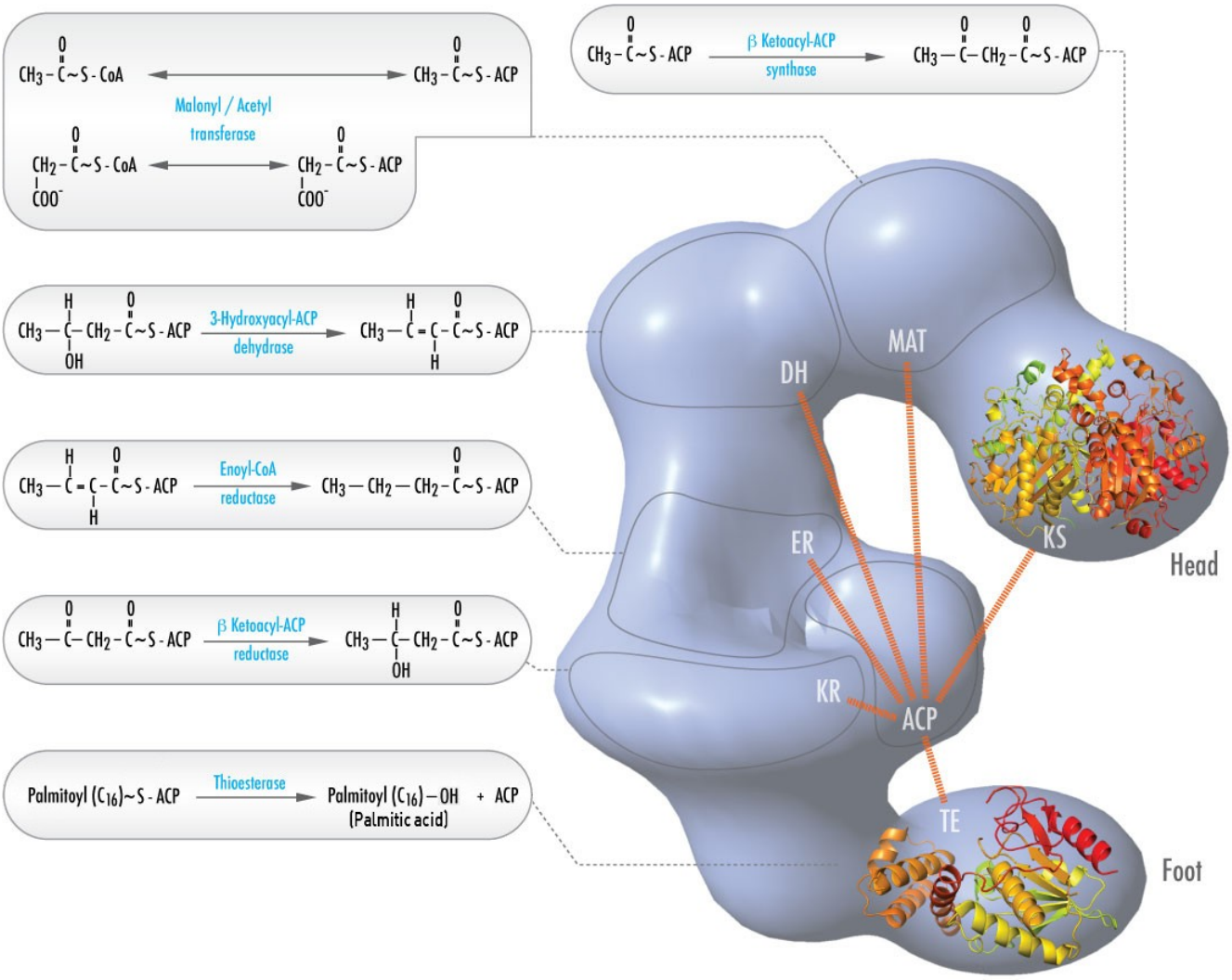


Figure **15.10.3.2**: Fatty Acid Synthase (FAS) revised model with positions of polypeptides, three catalytic domains and their corresponding reactions, visualization by Kosi Gramatikoff. Note that FAS is only active as a homodimer rather than the monomer pictured. (Public Domain; Kosigrim)

In animals, six different catalytic activities necessary for the remaining catalytic actions to fully make palmitoyl-CoA are contained in a single complex called Fatty Acid Synthase (Figure **15.10.3.2**). These include transacylases for swapping CoA with ACP on acetyl-CoA and malonyl-CoA; a synthase to catalyze addition of the two carbon unit from the three carbon malonyl-ACP in the first step of the elongation process; a reductase to reduce the ketone; a dehydrase to catalyze removal of water, and a reductase to reduce the trans double bond. In bacteria, these activities are found on separate enzymes and are not part of a complex.

Elongation of Fatty Acids

Elongation to make fatty acids longer than 16 carbons occurs in the endoplasmic reticulum and is catalyzed by enzymes described as elongases. Mitochondria also can elongate fatty acids, but their starting materials are generally shorter than 16 carbons long. The mechanisms in both environments are similar to those in the cytoplasm (a malonyl group is used to add two carbons, for example),

but CoA is attached to the intermediates, not ACP. Further, whereas cytoplasmic synthesis employs the fatty acid synthase complex (Figure **15.10.3.2**), the enzymes in these organelles are separable and not part of a complex.

Desaturation of Fatty Acids

Fatty acids are synthesized in the saturated form and desaturation occurs later. Enzymes called desaturases catalyze the formation of cis double bonds in mature fatty acids. These enzymes are found in the endoplasmic reticulum. Animals are limited in the desaturated fatty acids they can make, due to an inability to catalyze reactions beyond carbons 9 and 10. Thus, humans can make oleic acid, but cannot synthesis linoleic acid or linolenic acid. Consequently, these two must be provided in the diet and are referred to as essential fatty acids.

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15.10.4: Cholesterol Metabolism

The cholesterol biosynthesis pathway is a long one and it requires significant amounts of reductive and ATP energy, which is why it is included here. Cholesterol has important roles in the body in membranes. It as also a precursor of steroid hormones and bile acids and its immediate metabolic precursor, 7-dehydrocholesterol, is a precursor of Vitamin D. The pathway leading to cholesterol is known as the isoprenoid pathway and branches of it lead to other molecules including other fat-soluble vitamins.

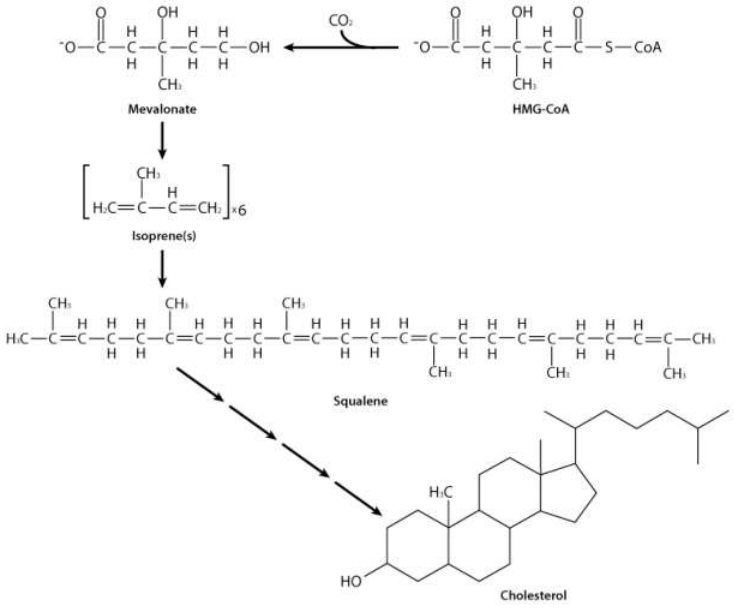


Figure 6.8.1: *The pathway to cholesterol*

From HMG-CoA, the enzyme HMG-CoA reductase catalyzes the formation of mevalonate. The reaction requires NADPH and results in release of coenzyme A and appears to be one of the most important regulatory steps in the synthesis pathway. The enzyme is regulated both by feedback inhibition (cholesterol inhibits it) and by covalent modification (phosphorylation inhibits it). The enzyme's synthesis is also regulated transcriptionally. When cholesterol levels fall, transcription of the gene increases.

Mevalonate gets phosphorylated twice and then decarboxylated to yield the five carbon intermediate known as isopentenyl-pyrophosphate (IPP). IPP is readily converted to dimethylallylpyrophosphate (DMAPP). These two five carbon compounds, also called isoprenes, are the building blocks for the synthesis of cholesterol and related compounds. This pathway is known as the isoprenoid pathway. It proceeds in the direction of cholesterol starting with the joining of IPP and DMAPP to form geranyl-pyrophosphate. Geranyl-pyrophosphate combines with another IPP to make farnesyl-pyrophosphate, a 15-carbon compound. Two farnesyl-pyrophosphates join to create the 30-carbon compound known as squalene. Squalene, in a complicated rearrangement involving reduction and molecular oxygen forms a cyclic intermediate known as lanosterol that resembles cholesterol. Conversion of lanosterol to cholesterol is a lengthy process involving 19 steps that occur in the endoplasmic reticulum.

Branching from cholesterol, one can form *Vitamin D* or the steroid hormones, which include the progestagens, androgens, estrogens, mineralocorticoids, and the glucocorticoids. The branch molecule for all of these is the cholesterol metabolite (and progestagen) known as *pregnenalone*. The progestagens are precursors of all of the other classes.

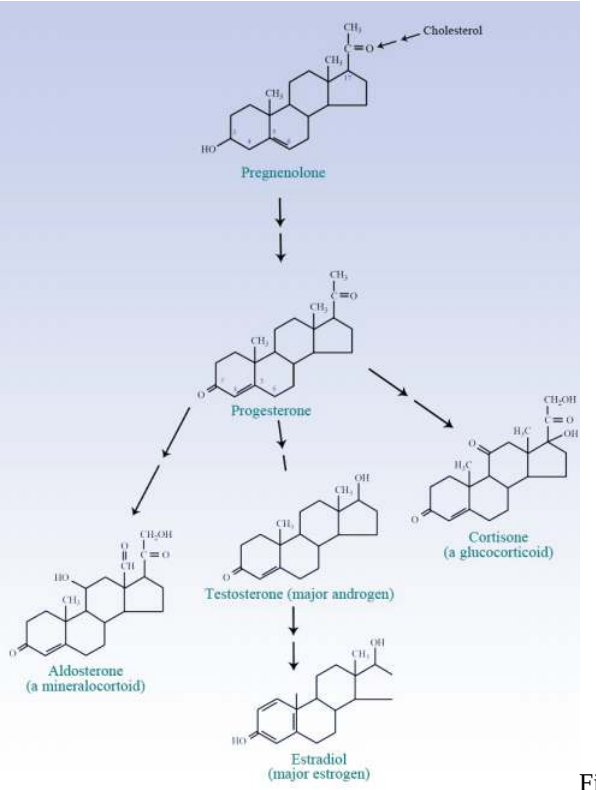


Figure 6.8.2: *Steroid Hormone Synthesis*

The estrogens are derived from the androgens in an interesting reaction that required formation of an aromatic ring. The enzyme catalyzing this reaction is known as an *aromatase* and it is of medical significance. The growth of some tumors is stimulated by estrogens, so aromatase inhibitors are prescribed to prevent the formation of estrogens and slow tumor growth. It is worth noting that synthesis of other fat soluble vitamins and chlorophyll also branches from the isoprenoid synthesis pathway at geranylpyrophosphate. Joining of two geranylgeranylpyrophosphates occurs in plants and bacteria and leads to synthesis of lycopene, which, in turn is a precursor of beta-carotene, the final precursor of Vitamin A. Vitamins E and K, as well as chlorophyll are all also synthesized from geranylgeranylpyrophosphate.

Bile Acid Metabolism

Another pathway from cholesterol leads to the polar bile acids, which are important for the solubilization of fat during digestion. Converting the very non-polar cholesterol to a bile acid involves oxidation of the terminal carbon on the side chain off the rings. Other alterations to increase the polarity of these compounds include hydroxylation of the rings and linkage to other polar compounds.

Common bile acids include cholic acid, chenodeoxycholic acid, glycocholic acid, taurocholic acid, and deoxycholic acid. Another important fact about bile acids is that their synthesis reduces the amount of cholesterol available and promotes uptake of LDLs by the liver. Normally bile acids are recycled efficiently resulting in limited reduction of cholesterol levels. However, inhibitors of the recycling promote reduction of cholesterol levels.

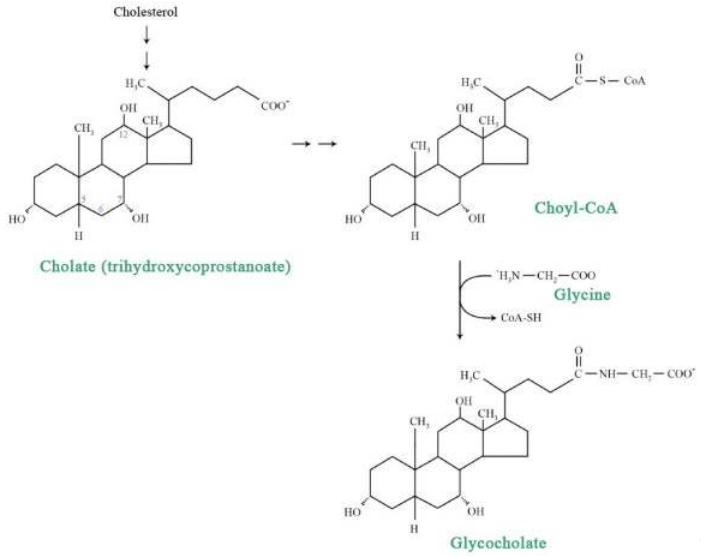


Figure 6.8.3: *Bile Salts*

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15.10.5: Ketone Body Synthesis

In ketone body synthesis, an acetyl-CoA is split off from HMG-CoA, yielding acetoacetate, a four carbon ketone body that is somewhat unstable, chemically. It will decarboxylate spontaneously to some extent to yield acetone. Ketone bodies are made when the blood levels of glucose fall very low. Ketone bodies can be converted to acetyl-CoA, which can be used for ATP synthesis via the citric acid cycle. People who are very hypoglycemic (including some diabetics) will produce ketone bodies and these are often first detected by the smell of acetone on their breath.

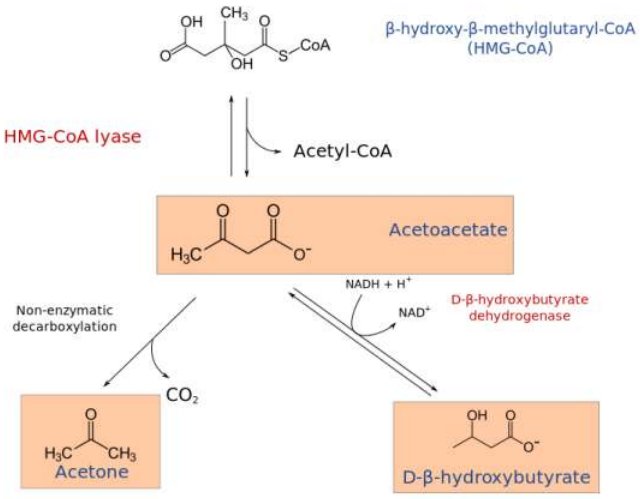


Figure 6.9.1: *Ketone Body Reactions*

Acetone is of virtually no use for energy production since it is not readily converted to acetyl-CoA. Consequently, cells convert acetoacetate into beta-hydroxybutyrate, which is more chemically stable. Though technically not a ketone, beta-hydroxybutyrate is frequently referred to as a ketone body. Upon arrival at a target cell, it can be oxidized back to acetoacetate with conversion to acetyl-CoA. Both acetoacetate and beta-hydroxybutyrate can cross the blood-brain barrier and provide important energy for the brain when glucose is limiting.

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15.10.6: Prostaglandin Synthesis

The pathway for making prostaglandins is an extension of the fatty acid synthesis pathway (Figure 6.10.1). Prostaglandins, molecules associated with localized pain, are synthesized in cells from arachidonic acid (see previous page) which has been cleaved from membrane lipids. The enzyme catalyzing their synthesis is known as prostaglandin synthase, but is more commonly referred to as a cyclooxygenase (or COX) enzyme. Inhibition of the action of this enzyme is a strategy of non- steroidal pain relievers (also called NSAIDs), such as aspirin or ibuprofen. Inhibition of the release of arachidonic acid from membranes is the mechanism of action of steroidal anti-inffammatories, which inhibit the phospholipase $\mathbf{A_2}$($\mathbf{PLA_2}$) that catalyzes the cleavage reaction.

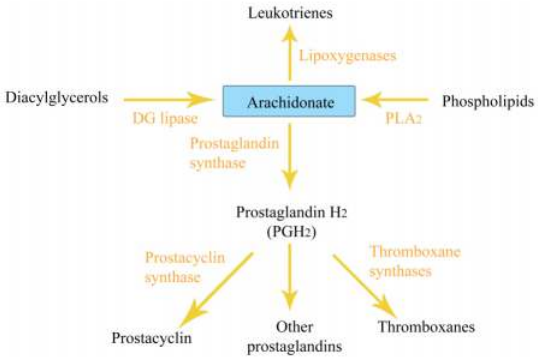


Figure 6.10.1: *Prostaglandin Metabolism*

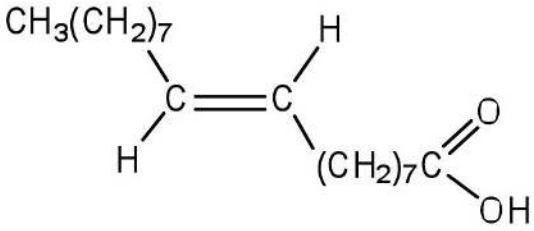
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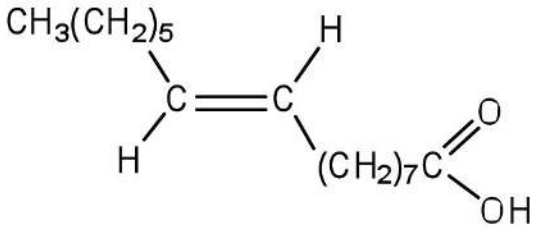
15.E: Exercises

Additional Exercises

1. The melting point of elaidic acid is 52°C.
   a. What trend is observed when comparing the melting points of elaidic acid, oleic acid, and stearic acid? Explain.
   b. Would you expect the melting point of palmitelaidic acid to be lower or higher than that of elaidic acid? Explain.

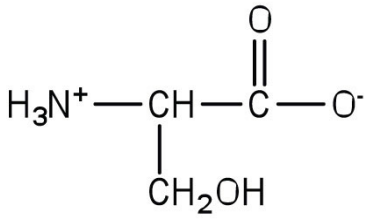


Elaidic acid



Palmitelaidic acid

2. Examine the labels on two brands of margarine and two brands of shortening and list the oils used in the various brands.
3. Draw a typical lecithin molecule that incorporates glycerol, palmitic acid, oleic acid, phosphoric acid, and choline. Circle all the ester bonds.
4. In cerebrosides, is the linkage between the fatty acid and sphingosine an amide bond or an ester bond? Justify your answer.
5. Serine is an amino acid that has the following structure. Draw the structure for a phosphatidylserine that contains a palmitic acid and a palmitoleic acid unit.

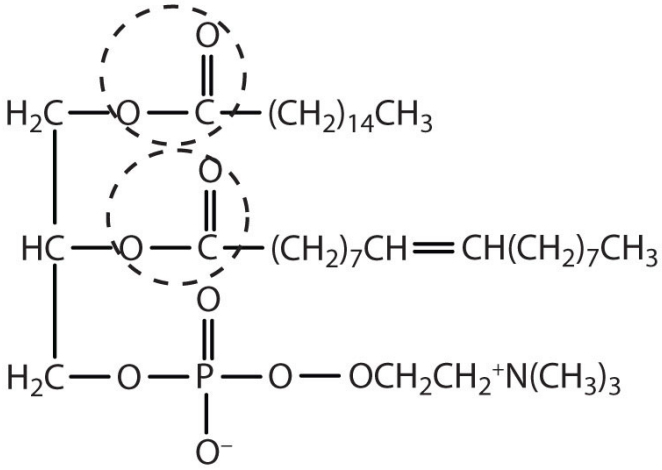


6. Explain whether each compound would be expected to diffuse through the lipid bilayer of a cell membrane.
   a. potassium chloride
   b. $CH_3CH_2CH_2CH_2CH_2CH_3$
   c. fructose
7. Identify the role of each steroid hormone in the body.
   a. progesterone
   b. aldosterone
   c. testosterone
   d. cortisol
8. How does the structure of cholic acid differ from that of cholesterol? Which compound would you expect to be more polar? Why?
9. a. What fatty acid is the precursor for the prostaglandins?
   b. Identify three biological effects of prostaglandins.
10. Why is it important to determine the ratio of LDLs to HDLs, rather than just the concentration of serum cholesterol?

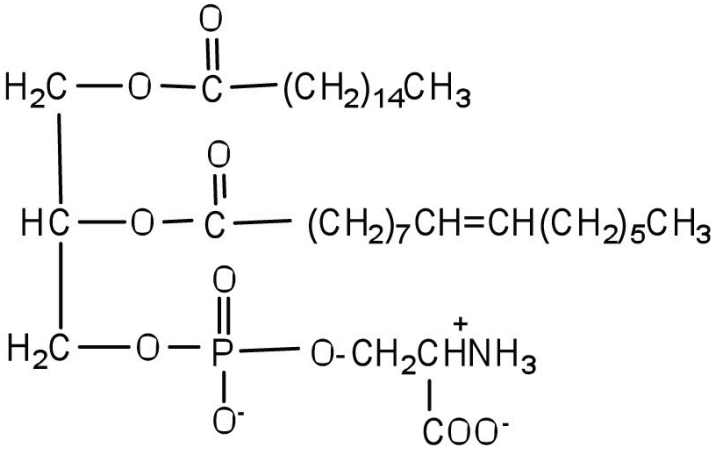
Answers

1. a. Stearic acid has the highest melting point, followed by elaidic acid, and then oleic acid with the lowest melting point. Elaidic acid is a *trans* fatty acid, and the carbon chains can pack together almost as tightly as those of the saturated stearic acid. Oleic acid is a *cis* fatty acid, and the bend in the hydrocarbon chain keeps these carbon chains from packing as closely together; fewer interactions lead to a much lower melting point.
   b. The melting point of palmitelaidic acid should be lower than that of elaidic acid because it has a shorter carbon chain (16, as compared to 18 for elaidic acid). The shorter the carbon chain, the lower the melting point due to a decrease in intermolecular interactions.

3.



5.



7. a. regulates the menstrual cycle and maintains pregnancy
   b. regulates salt metabolism by stimulating the kidneys to retain sodium and excrete potassium
   c. stimulates and maintains male sex characteristics
   d. stimulates the conversion of proteins to carbohydrates

9. a. arachidonic acid
   b. induce smooth muscle contraction, lower blood pressure, and contribute to the inflammatory response

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15.S: Lipids (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.

Lipids, found in the body tissues of all organisms, are compounds that are more soluble in organic solvents than in water. Many of them contain **fatty acids**, which are carboxylic acids that generally contain an even number of 4–20 carbon atoms in an unbranched chain. **Saturated fatty acids** have no carbon-to-carbon double bonds. **Monounsaturated fatty acids** have a single carbon-to-carbon double bond, while **polyunsaturated fatty acids** have more than one carbon-to-carbon double bond. Linoleic and linolenic acid are known as **essential fatty acids** because the human body cannot synthesize these polyunsaturated fatty acids. The lipids known as **fats** and **oils** are triacylglycerols, more commonly called **triglycerides**—esters composed of three fatty acids joined to the trihydroxy alcohol glycerol. Fats are triglycerides that are solid at room temperature, and oils are triglycerides that are liquid at room temperature. Fats are found mainly in animals, and oils found mainly in plants. *Saturated triglycerides* are those containing a higher proportion of saturated fatty acid chains (fewer carbon-to-carbon double bonds); *unsaturated triglycerides* contain a higher proportion of unsaturated fatty acid chains.

Saponification is the hydrolysis of a triglyceride in a basic solution to form glycerol and three carboxylate anions or soap molecules. Other important reactions are the hydrogenation and oxidation of double bonds in unsaturated fats and oils.

Phospholipids are lipids containing phosphorus. In **phosphoglycerides**, the phosphorus is joined to an amino alcohol unit. Some phosphoglycerides, like lecithins, are used to stabilize an **emulsion**—a dispersion of two liquids that do not normally mix, such as oil and water. **Sphingolipids** are lipids for which the precursor is the amino alcohol sphingosine, rather than glycerol. A **glycolipid** has a sugar substituted at one of the OH groups of either glycerol or sphingosine. All are highly polar lipids found in cell membranes.

Polar lipids have dual characteristics: one part of the molecule is ionic and dissolves in water; the rest has a hydrocarbon structure and dissolves in nonpolar substances. Often, the ionic part is referred to as **hydrophilic** (literally, “water loving”) and the nonpolar part as **hydrophobic** (“water fearing”). When placed in water, polar lipids disperse into any one of three arrangements: *micelles*, *monolayers*, and *bilayers*. **Micelles** are aggregations of molecules in which the hydrocarbon tails of the lipids, being hydrophobic, are directed inward (away from the surrounding water), and the hydrophilic heads that are directed outward into the water. **Bilayers** are double layers arranged so that the hydrophobic tails are sandwiched between the two layers of hydrophilic heads, which remain in contact with the water.

Every living cell is enclosed by a *cell membrane* composed of a lipid bilayer. In animal cells, the bilayer consists mainly of phospholipids, glycolipids, and the steroid cholesterol. Embedded in the bilayer are **integral proteins**, and **peripheral proteins** are loosely associated with the surface of the bilayer. Everything between the cell membrane and the membrane of the cell nucleus is called the **cytoplasm**.

Most lipids can be saponified, but some, such as **steroids**, cannot be saponified. The steroid **cholesterol** is found in animal cells but never in plant cells. It is a main component of all cell membranes and a precursor for hormones, vitamin D, and bile salts. Bile salts are the most important constituents of **bile**, which is a yellowish-green liquid secreted by the gallbladder into the small intestine and is needed for the proper digestion of lipids.

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CHAPTER OVERVIEW

16: Amino Acid Metabolism

16.1: Amino Acid Metabolism

16.2: Amino Acid Catabolism

16.3: Amino Acids and the Urea Cycle

16.4: Stage II of Protein Catabolism

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16.1: Amino Acid Metabolism

The pathways for the synthesis and degradation of amino acids used in proteins are the most varied among the reactions synthesizing biological building blocks. We start with some terms. First, not all organisms can synthesize all the amino acids they need. Amino acids that an organism cannot synthesize (and therefore must have in their diets) are called *essential amino acids*. The remaining amino acids that the body can synthesize are called non-essential.

Glucogenic and Ketogenic Amino Acids

Glucogenic	Both Glucogenic and Ketogenic	Ketogenic
Aspartate	Isoleucine	Leucine
Asparagine	Phenylalanine	Lysine
Alanine	Tryptophan	
Glycine	Tyrosine	
Serine		
Threonine		
Cysteine		
Glutamate		
Glutamine		
Arginine		
Proline		
Histidine		
Valine		
Methionine		

Figure 7.7.1: *Glucogenic and Ketogenic Amino Acids*

Amino acids are also divided according to the pathways involved in their degradation; there are three general categories. Ones that yield intermediates in the glycolysis pathway are called *glucogenic* and those that yield intermediates of acetyl-CoA or acetoacetate are called *ketogenic*. Those that involve both are called glucogenic and ketogenic.

An important general consideration in amino acid metabolism is that of transamination. In this process, an exchange of amine and oxygen between an amino acid and an alpha-ketoacid occurs (see below)

$$\text{Alpha-ketoacid} + \text{amino acid} \leftrightarrow \text{amino acid} + \text{alpha-ketoacid} \tag{16.1.1}$$

An example reaction follows

$$\text{Pyruvate} + \text{Aspartic acid} \leftrightarrow \text{Alanine} + \text{Oxaloacetate} \tag{16.1.2}$$

This reaction is catalyzed by an enzyme known as a transaminase. Amino acids, such as glutamate, can also gain nitrogen directly from ammonium ion, as shown below

$$\text{Alpha-ketoglutarate} + NH_4^+ \leftrightarrow \text{Glutamate} \tag{16.1.3}$$

This reaction can occur, for example, in nitrifying bacteria, and in places where ammonia waste is produced. Many amino acids can be synthesized from citric acid cycle intermediates. For example, synthesis of the non-essential amino acids occurs as follows: aspartic acid can be made by transamination of oxaloacetate. Glutamate comes from transamination of alpha-ketoglutarate. Pyruvate, as noted, is a precursor of alanine (via transamination). Amino acids that can be made from glutamate include glutamine (by addition of an additional ammonium ion), proline, and arginine, Asparagine is made from aspartate by addition of ammonium ion also. Serine is formed from 3-phosphoglycerate and is itself the precursor of both glycine and cysteine. Cysteine and serine are also made from methionine. Tyrosine is made by hydroxylation of phenylalanine.

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16.2: Amino Acid Catabolism

Breakdown of glutamine by glutaminase is a source of ammonium ion in the cell. The other product is glutamate. Glutamate, of course, can be converted by a transamination reaction to alpha-ketoglutarate, which can be oxidized in the citric acid cycle.

- Asparagine can similarly be broken to ammonium and aspartate by asparaginase and aspartate can be converted by transamination to oxaloacetate for oxidation in the citric acid cycle.
- Alanine is converted to pyruvate in a transamination reaction, making it glucogenic.
- Arginine is hydrolzyed in the urea cycle to yield urea and ornithine.
- Proline is catabolized to glutamate in a reversal of its synthesis pathway.
- Serine donates a carbon to form a folate and the other product of the reaction is glycine, which is itself oxidized to carbon dioxide and ammonia. Glycine can also be converted back to serine, which can also be converted back to 3-phosphoglycerate or pyruvate.
- Threonine can be broken down in three pathways, though only two are relevant for humans. One pathway leads to acetyl-CoA and glycine. The other leads to pyruvate.
- Cysteine can be broken down in several ways. The simplest occurs in the liver, where a desulfurase can act on it to yield hydrogen sulfide and pyruvate.
- Methionine can be converted to cysteine for further metabolism. It can be converted to succinyl-CoA for oxidation in the citric acid cycle. It can also be converted to S-Adenosyl-Methionine (SAM), a carbon donor.
- Isoleucine and valine can also be converted to succinyl-CoA after conversion first to propionyl-CoA. Since conversion of propionyl-CoA to succinyl-CoA requires vitamin $\mathbf{B_{12}}$, catabolism of these amino acids also requires the vitamin.
- Phenylalanine is converted during catabolism to tyrosine, which is degraded ultimately to fumarate and acetoacetate. Thus, both of these amino acids are glucogenic and ketogenic. Tyrosine can also be converted to dopamine, norepinephrine, and epinephrine.
- Leucine and lysine can be catabolized to acetoacetate and acetyl-CoA. Lysine is also an important precursor of carnitine.
- Histidine can be catabolized by bacteria in intestines to histamine, which causes construction or dilation of various blood vessels when in excess.
- Tryptophan's catabolism is complex, but can proceed through alanine, acetoacetate and acetyl-CoA

In summary, the following are metabolized to pyruvate – alanine, cysteine, glycine, serine, and threonine

- Oxaloacetate is produced from aspartate and asparagine
- Succinyl-CoA is produced from isoleucine, valine, and methionine
- Alpha-ketoglutarate is produced from arginine, glutamate, glutamine, histidine and proline.
- Phenylalanine and tyrosine are broken down to fumarate and acetoacetate
- Leucine and lysine yield acetoacetate and acetyl-CoA.
- Tryptophan leads to alanine, acetoacetate and acetyl-CoA.

Last, amino acids, besides being incorporated into proteins, serve as precursors of important compounds, including serotonin (from tryptophan), porphyrin heme (from glycine), nitric oxide (from arginine), and nucleotides (from aspartate, glycine, and glutamine).

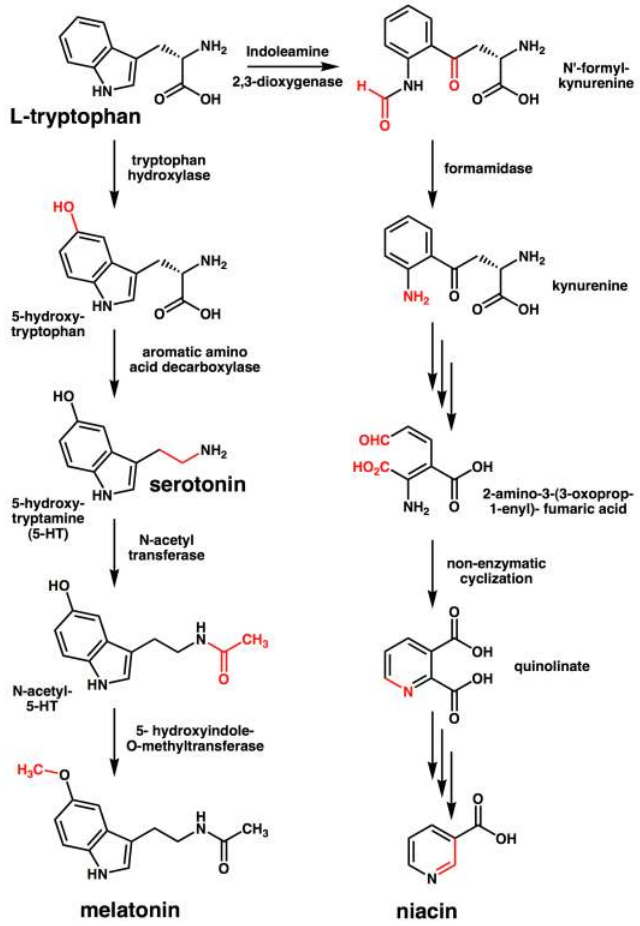


Figure 7.8.1: *Conversion of L-Tryptophan into Serotonin, Melatonin, and Niacin*

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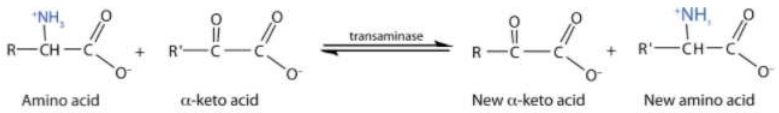
16.3: Amino Acids and the Urea Cycle

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In contrast to some of the metabolic pathways described to this point, amino acid metabolism is not a single pathway. The 20 amino acids have some parts of their metabolism that overlap with each other, but others are very different from the rest. In discussing amino acid metabolism, we will group metabolic pathways according to common metabolic features they possess (where possible). First, we shall consider the anabolic pathways.

Transamination

Before beginning discussion of the pathways, it is worthwhile to discuss a reaction common to the metabolism of most of the amino acids and other nitrogen-containing compounds and that is transamination. In cells, nitrogen is a nutrient that moves from one molecule to another in a sort of hand-off process. A general transamination reaction is shown below.



Glutamate and glutamine play central roles in transamination, each containing one more amine group than α-ketoglutarate and glutamate, respectively. Transamination reactions, as noted earlier, occur by a ping-pong mechanism and involve swaps of amines and oxygens.

Synthesis varies

It is also important to recognize that organisms differ considerably in the amino acids that they can synthesize. Humans, for example, cannot make 9 of the 20 amino acids needed to make proteins, and the number of these that can be synthesized in needed amounts varies between adults and children.

Amino acids that cannot be made by an organism must be in the diet and are called essential amino acids. Non-essential amino acids are those an organism can make in sufficient quantities (Figure 6.135). Though amino acids do not have a common pathway of metabolism, they are often organized in “families” of amino acids with overlapping metabolic reactions common to members of each group. To designate amino acid families in the text we will use a blue font for headings to distinguish them.

α-ketoglutarate family

This family of amino acids arises from α-ketoglutarate of the citric acid cycle. It includes the amino acids glutamic acid, glutamine, proline, and arginine. It is also called the glutamate family, since all the amino acids in it derive from glutamate.

Glutamate

α-ketoglutarate is readily converted to glutamate in transamination reactions, as noted above. It can also be produced by the enzyme glutamate dehydrogenase, which catalyzes the reaction below (in reverse) to make glutamate.

In the forward direction, the reaction is a source of ammonium ion, which is important both for the urea cycle and for glutamine metabolism. Because it is a byproduct of a citric acid cycle intermediate, glutamate can therefore trace its roots to any of the intermediates of the cycle. Citrate and isocitrate, for example, can be thought of as precursors of glutamate. In addition, glutamate can be made by transamination from α-ketoglutarate in numerous transamination reactions involving other amino acids.

Aspartate family

Metabolism of aspartic acid is similar to that of glutamate. Aspartic acid can arise from transamination of a citric acid cycle intermediate (oxaloacetate).

Aspartate is also a precursor to four amino acids that are essential in humans. They are methionine, isoleucine, threonine, and lysine. Because oxaloacetate can be produced from aspartate, aspartate is an important intermediate for gluconeogenesis when

proteins are the energy source

Aromatic amino acids

The aromatic amino acids, tryptophan, phenylalanine, and tyrosine can all be made starting with two simple molecules - PEP and erythrose-4-phosphate (Figure 6.145). All three aromatic amino acids are also important sources of hormones, neurotransmitters, and even the skin pigment melanin.

Tryptophan synthesis

Tryptophan is an essential amino acid.

Regulation

Tryptophan is an important precursor of serotonin (neurotransmitter) and melatonin (hormone).

Melatonin

Melatonin is a compound made from tryptophan that is found in a wide spectrum of biological systems, including plants, animals, fungi, and bacteria. In animals, it acts as a hormone for circadian rhythm synchronization, signaling the onset of darkness each day. It has effects on the timing of sleep, seasonal effects, and can affect blood pressure, among other physiological phenomena. It can cross cell membranes, as well as the blood-brain barrier. Melatonin is a potent anti-oxidant and provides protective functions for nucleic acids. It is used sometimes to help in treatment of sleep disorders. Some reports have indicated that children with autism have abnormal melatonin pathways with low levels of the hormone.

Blue light

Melatonin production is affected by blue light and may be linked to sleep abnormalities for people using computer monitors after dark. To protect against this, some computer programs are available that reduce the screen's blue light output in the evenings. Special eyeglasses that block blue light are also available. Though melatonin is linked to sleep in some animals (including humans), nocturnal animals are activated by increasing melatonin levels. Varying day/night lengths during the year alter melatonin production and provide biological signals of the seasons. These are especially important in the seasonal coloring and breeding habits of some animals. Melatonin is present in cherries, bananas, grapes, rice, cereals, olive oil, wine, and beer.

Serotonin

Serotonin, or 5-hydroxytryptamine, is a monoamine neurotransmitter derived from tryptophan. Blood platelets store serotonin and release it when they bind to a clot, causing vasoconstriction. Serotonin plays a role in cognitive functions and enhances memory and learning. Serotonin is widely thought to be a contributor to feelings of happiness and well-being. Some common anti-depressant drugs, including Prozac, Paxil and Zoloft, act to modulate action of serotonin at synapses.

Phenylalanine

Phenylalanine is an essential, hydrophobic amino acid in humans that is a precursor of tyrosine and since tyrosine is a precursor of several important catecholamines, phenylalanine is, thus, a precursor of them as well.

PKU

Phenylalanine is linked to the genetic disease phenylketonuria (PKU) which arises from an inability to metabolize the amino acid in people lacking (or deficient in) the enzyme phenylalanine hydroxylase. If left untreated, the disease can cause brain damage and even death, but if detected early, it can be easily managed by carefully monitoring dietary intake of the amino acid. Because of this, newborns are routinely tested for PKU. Phenylalanine is a component of the artificial sweetener known as aspartame (Nutrasweet - Figure 6.154) and is consequently dangerous for people suffering from this disorder.

Transamination of phenylpyruvate yields phenylalanine.

Hydroxylation of phenylalanine by aromatic amino acid hydroxylase (phenylalanine hydroxylase) yields tyrosine.

Tyrosine

Because tyrosine is made from phenylalanine and the latter is an essential amino acid in humans, it is not clear whether to classify tyrosine as essential or non-essential. Some define it as a conditionally essential amino acid. Others simply categorize it as non-

essential.

As noted above, tyrosine can arise as a result of hydroxylation of phenylalanine.

The hydroxyl group on tyrosine is a target for phosphorylation by protein kinase enzymes involved in signal transduction pathways. When located in membranes, these enzymes are referred to as receptor tyrosine kinases and they play important roles in controlling cellular behavior/response.

Tyrosine metabolites

Tyrosine is a precursor of catecholamines, such as L-dopa, dopamine, norepinephrine, and epinephrine.

Dopamine

Dopamine plays several important roles in the brain and body. A member of the catecholamine and phenethylamine families, its name comes from the fact that it is an amine made by removing a carboxyl group from L-DOPA. Dopamine is synthesized in the brain and kidneys. Dopamine is a neurotransmitter, being released by one nerve cell and then traveling across a synapse to signal an adjacent nerve cell. Dopamine plays a major role in the brain's reward-mediated behavior. Rewards, such as food or social interaction, increase dopamine levels in the brain, as do addictive drugs. Other brain dopamine pathways are involved in motor control and in managing the release of various hormones.

Chemical messenger

Outside the nervous system, dopamine is a local chemical messenger. In blood vessels, it inhibits norepinephrine release and causes vasodilation. In the kidneys, it increases sodium excretion and urine output. It reduces gastrointestinal motility and protects intestinal mucosa in the digestive system and in the immune system, it reduces lymphocyte activity. The effect dopamine has on the pancreas is to reduce insulin production. With the exception of the blood vessels, dopamine is synthesized locally and exerts its effects near the cells that release it.

Epinephrine

Epinephrine (also called adrenalin) is a catecholamine chemically related to norepinephrine that is a hormone with medical applications. It is used to treat anaphylaxis, cardiac arrest, croup, and, in some cases, asthma, when other treatments are not working, due to its ability to favor bronchodilation.

Epinephrine is the drug of choice for treating anaphylaxis. The compound may be given through inhalation, by intravenous injection, or subcutaneous injection and exerts effects through the α- and β-adrenergic receptors. In the body, it is produced and released by adrenal glands and some neurons.

Effects

Physiological effects of epinephrine may include rapid heart beat, increased blood pressure, heart output, pupil dilation, blood sugar concentration and increased sweating. Other physical effects may include shakiness, increased anxiety, and an abnormal heart rhythm.

Norepinephrine

Norepinephrine (also called noradrenalin) is a catecholamine molecule that acts as a hormone and neurotransmitter. It is chemically similar to epinephrine, differing only in the absence of a methyl group on its amine. Norepinephrine is made and released by the central nervous system (locus coeruleus of the brain) and the sympathetic nervous system. The compound is released into the blood stream from adrenal glands and affects α- and β-adrenergic receptors.

Norepinephrine is at its lowest levels during sleep and at its highest levels during stress (fight or flight response). The primary function of norepinephrine is to prepare the body for action. It increases alertness, enhances memory functions, and helps to focus attention. Norepinephrine increases heart rate and blood pressure, increases blood glucose and blood flow to skeletal muscle and decreases flow of blood to the gastrointestinal system.

Medical considerations

Norepinephrine may be injected to overcome critically low blood pressure and drugs countering its effects are used to treat heart conditions. α-blockers, for example, are used to battle cardiovascular and psychiatric disorders. β-blockers counter a different set of

norepinephrine’s effects than α-blockers and are used to treat glaucoma, migraine headaches and other cardiovascular problems.

Pyruvate family

Alanine

Alanine is the amino acid that is most easily produced from pyruvate. The simple transamination catalyzed by alanine transaminase produces alanine from pyruvate.

Leucine

Like valine and isoleucine, leucine is an essential amino acid in humans.

Urea cycle

The urea cycle holds the distinction of being the first metabolic cycle discovered - in 1932, five years before the citric acid cycle. It is an important metabolic pathway for balancing nitrogen in the bodies of animals and it takes place primarily in the liver and kidney.

Ammonia, of course, is generated by metabolism of amines and is toxic, so managing levels of it is critical for any organism. Excretion of ammonia by fish is one reason that an aquarium periodically requires cleaning and replacement of water.

Liver failure can lead to accumulation of nitrogenous waste and exacerbates the problem.

Urea is less toxic than ammonia and is released in the urine.

Complete deficiency of any urea cycle enzyme is fatal at birth.

Energy generation

Amino acid catabolism

Amino acids are divided according to the pathways involved in their degradation. There are three general categories. Ones that yield intermediates in the glycolysis pathway are called glucogenic and those that yield intermediates of acetyl-CoA or acetoacetate are called ketogenic. Those that involve both are called glucogenic and ketogenic.

As seen in the two figures, amino acids largely produce breakdown products related to intermediates of the citric acid cycle or glycolysis, but this isn’t the complete picture. Some amino acids, like tryptophan, phenylalanine, and tyrosine yield hormones or neurotransmitters on further metabolism (as noted earlier). Others like cysteine and methionine must dispose of their sulfur and all of the amino acids must rid themselves of nitrogen, which can happen via the urea cycle, transamination, or both.

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16.4: 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.

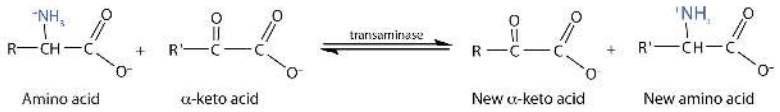


Figure **16.4.1**).

> *In an α-keto acid, the carbonyl or keto group is located on the carbon atom adjacent to the carboxyl group of the acid.*

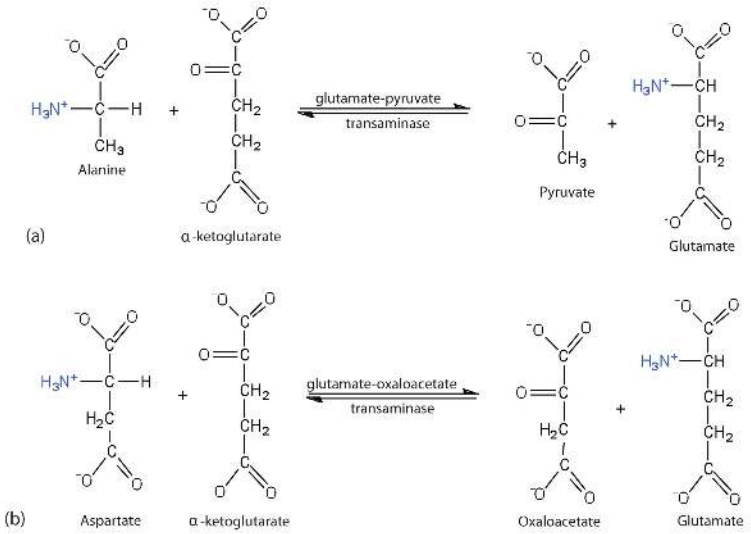
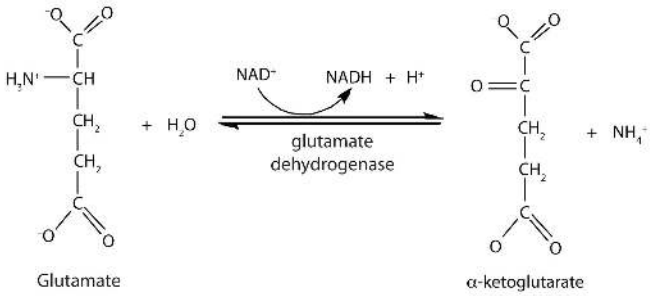


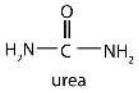
Figure **16.4.1**: Two Transamination Reactions. In both reactions, the final acceptor of the amino group is α-ketoglutarate, and the final product is glutamate.

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.

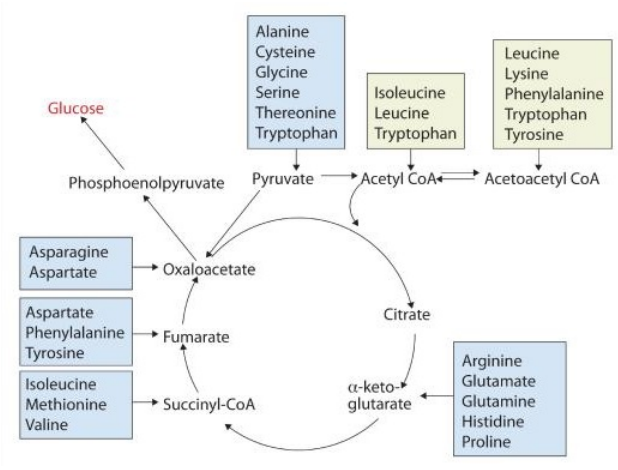


Figure **16.4.2**: Fates of the Carbon Skeletons of Amino Acids

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 **16.4.2** 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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CHAPTER OVERVIEW

17: 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.

- 17.1: Prelude to Nucleic Acids
- 17.2: Nucleotides
- 17.3: Nucleic Acid Structure
- 17.4: Replication and Expression of Genetic Information
- 17.5: Protein Synthesis and the Genetic Code
- 17.6: Mutations and Genetic Diseases
- 17.7: Viruses
- 17.8: Flow of Genetic Information
  - 17.8.1: DNA Replication
  - 17.8.2: DNA Repair
  - 17.8.3: Transcription
  - 17.8.4: Regulation of Transcription
  - 17.8.5: RNA Processing
  - 17.8.6: Translation
- 17.E: Nucleic Acids (Exercises)
- 17.S: Nucleic Acids (Summary)

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17.1: 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 **17.1.1**: A vial of insulin. It has been given a trade name, Actrapid, by the manufacturer. (Public Domain; Mr Hyde).

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17.2: Nucleotides

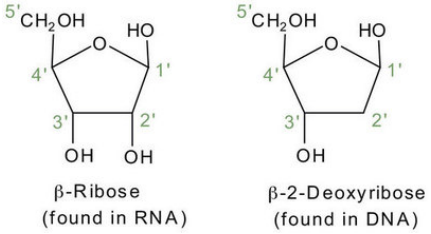
Learning Objectives

- 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 **17.2.1**).

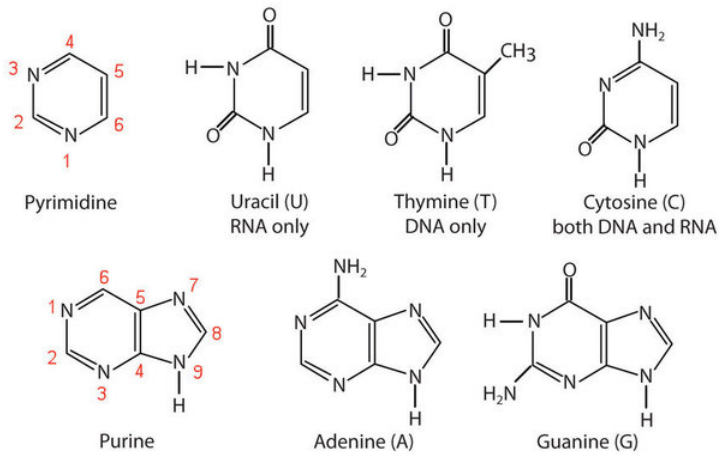


Figure **17.2.1**: The Nitrogenous Bases Found in DNA and RNA

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 **17.2.1** 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 **17.2.1**: 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 **17.2.2**.

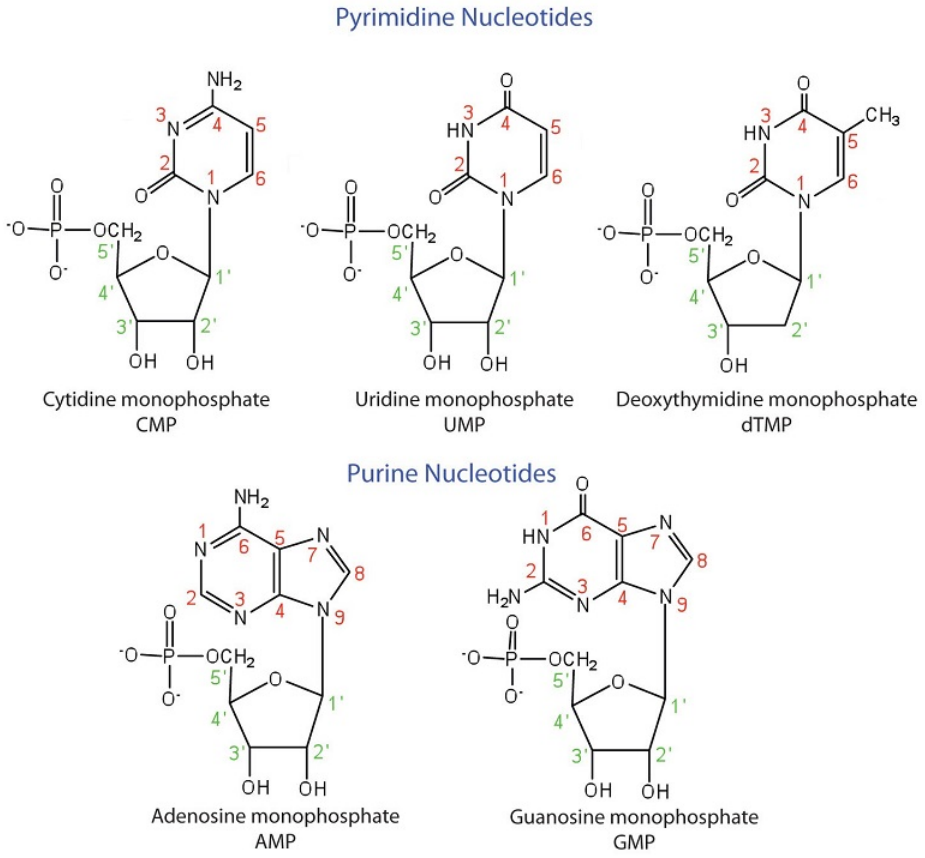


Figure **17.2.2**: The Pyrimidine and Purine Nucleotides

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 **17.2.3**, 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.

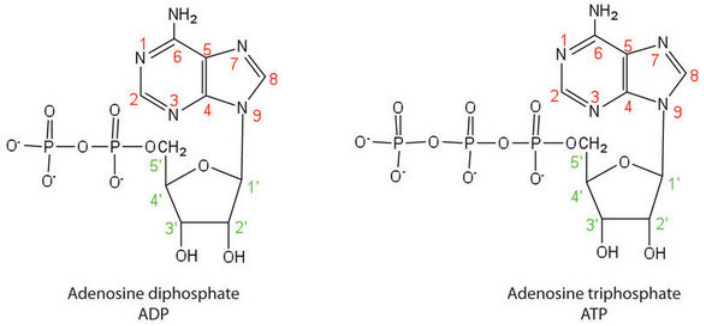


Figure **17.2.3**: Structures of Two Important Adenine-Containing Nucleotides

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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17.3: 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 **17.3.1**). 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.*

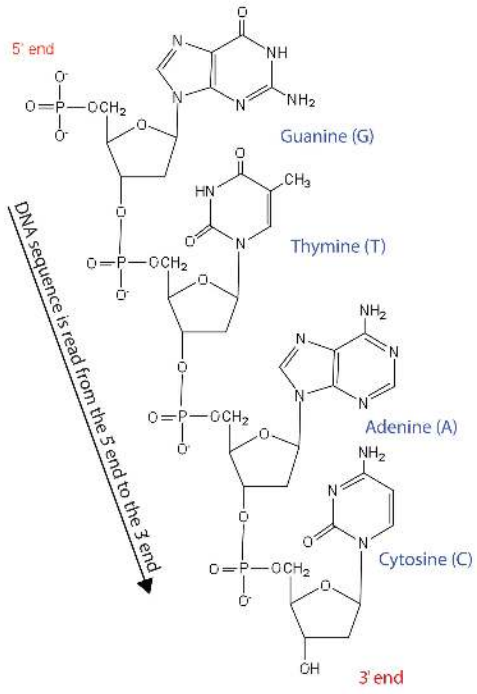


***Figure* 17.3.1** *Structure of a Segment of DNA. A similar segment of RNA would have OH groups on each C2', and uracil would replace thymine.*

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 **17.3.1**) 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 **17.3.1** 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 **17.3.2**).

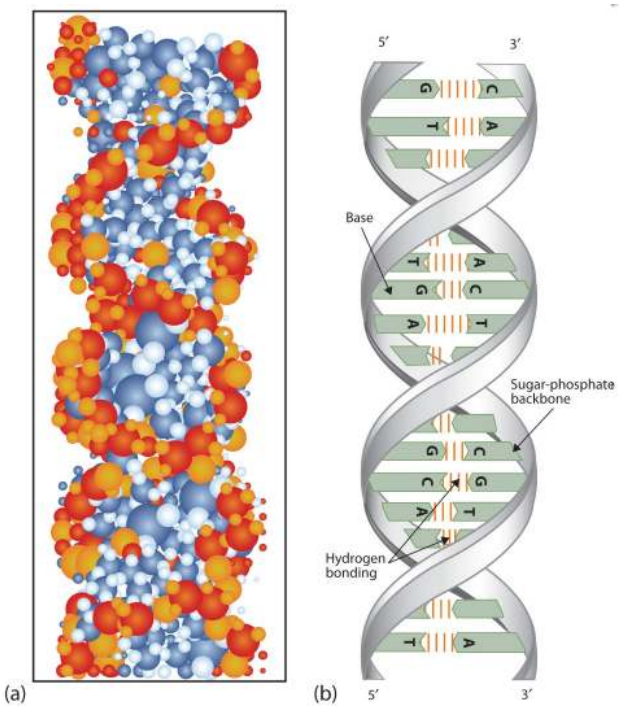


***Figure* 17.3.2** *DNA Double Helix. (a) This represents a computer-generated model of the DNA double helix. (b) This represents a schematic representation of the double helix, showing the complementary bases.*

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 **17.3.3** 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).

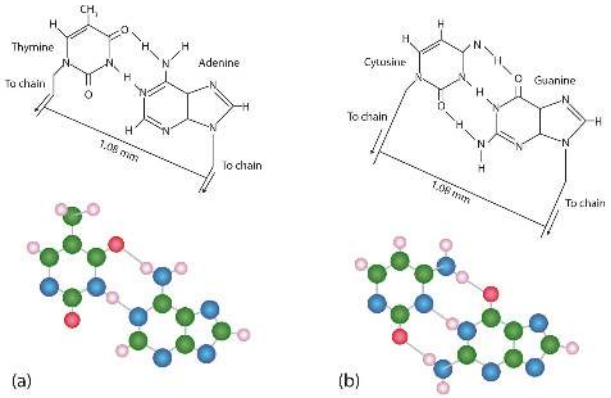


***Figure* 17.3.3** *Complementary Base Pairing. Complementary bases engage in hydrogen bonding with one another: (a) thymine and adenine; (b) cytosine and guanine.*

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 **17.3.4**. 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 **17.3.3** 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.

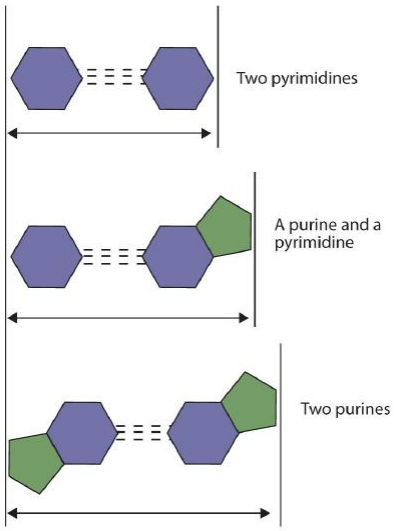


***Figure* 17.3.4** *Difference in Widths of Possible Base Pairs*

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

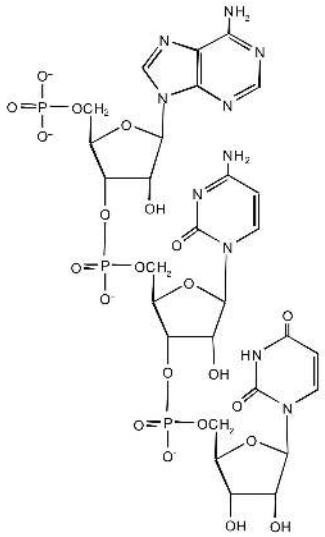
1.
   a. Name the two kinds of nucleic acids.
   b. Which type of nucleic acid stores genetic information in the cell?
2. What are complementary bases?
3. Why is it structurally important that a purine base always pair with a pyrimidine base in the DNA double helix?

Answers

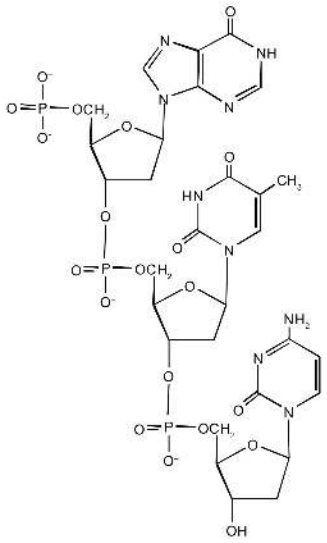
1.
   a. deoxyribonucleic acid (DNA) and ribonucleic acid (RNA)
   b. DNA
2. the specific base pairings in the DNA double helix in which guanine is paired with cytosine and adenine is paired with thymine
3. The width of the DNA double helix is kept at a constant width, rather than narrowing (if two pyrimidines 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?

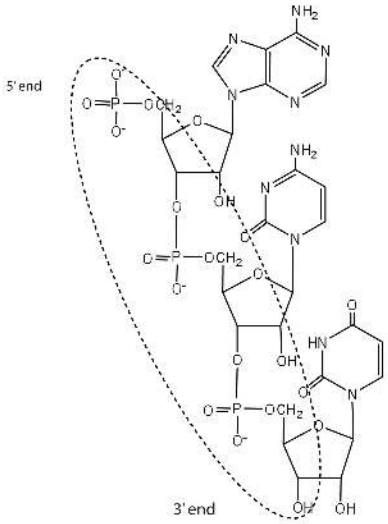
   5′ ATGCGACTA 3′ 3′ TACGCTGAT 5′

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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17.4: 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 **17.4.1**). 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.

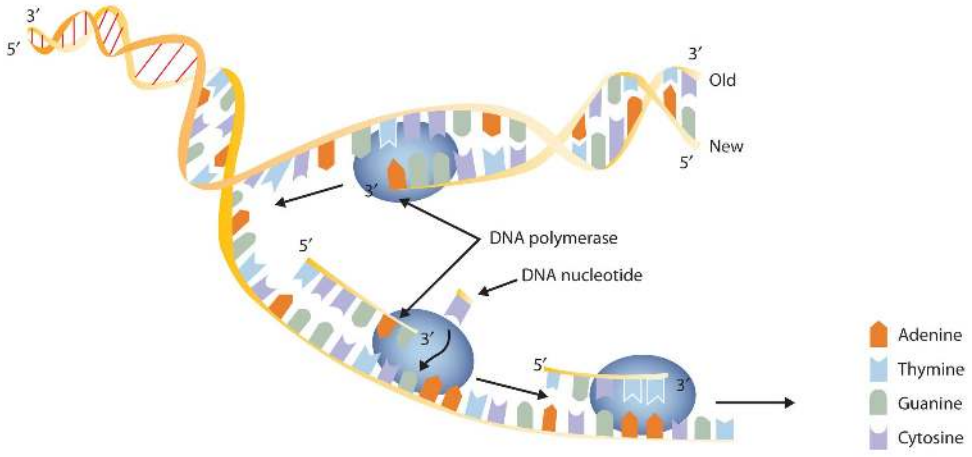


Figure **17.4.1**: A Schematic Diagram of DNA Replication. DNA replication occurs by the sequential unzipping of segments of the double helix. Each new nucleotide is brought into position by DNA polymerase and is added to the growing strand by the formation of a phosphate ester bond. Thus, two double 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 17.4.1

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 17.4.1

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 17.4.2). 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.

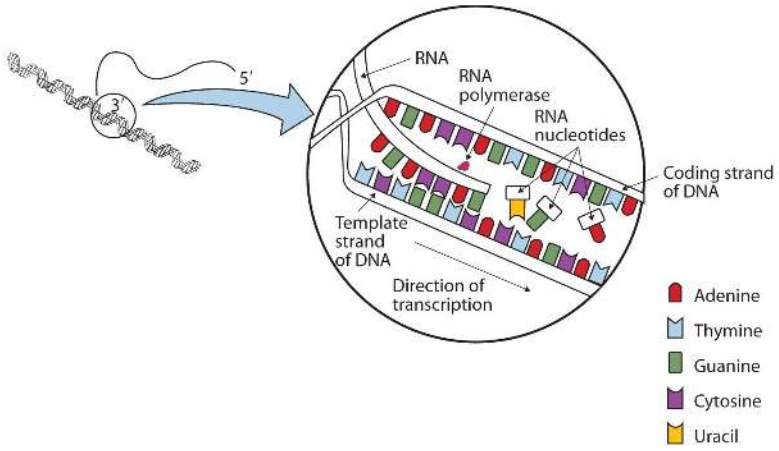


Figure 17.4.2: A Schematic Diagram of RNA Transcription from a DNA Template. The representation of RNA polymerase is proportionately much smaller than the actual molecule, which encompasses about 50 nucleotides at a time.

Example 17.4.2

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 17.4.2

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 17.4.1). 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 17.4.1: 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.

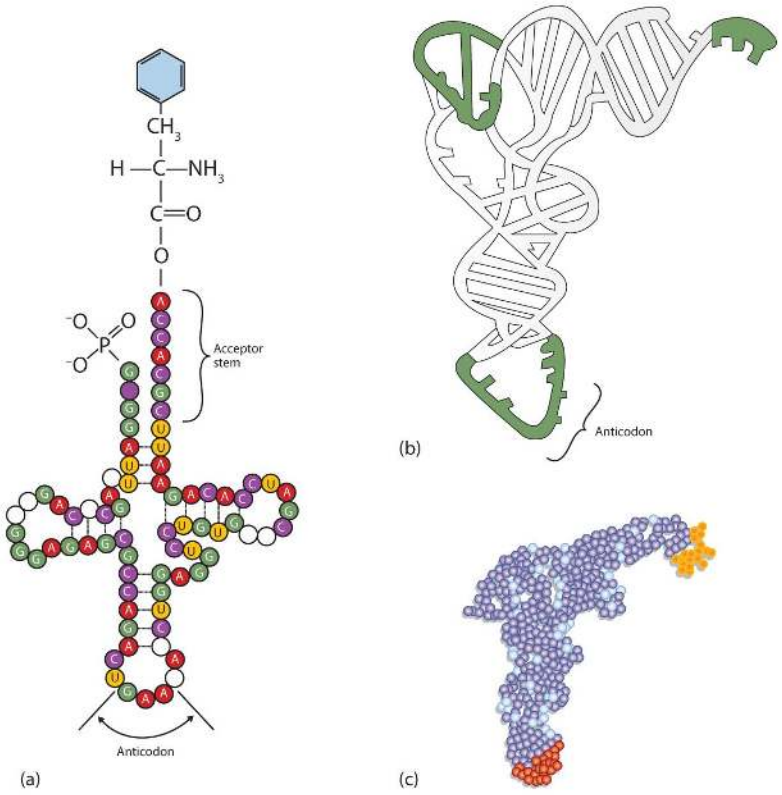


Figure 17.4.3: Transfer RNA. (a) In the two-dimensional structure of a yeast tRNA molecule for phenylalanine, the amino acid binds to the acceptor stem located at the 3′ end of the tRNA primary sequence. (The nucleotides that are not specifically identified here are slightly altered analogs of the four 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 17.4.3). 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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17.5: 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.

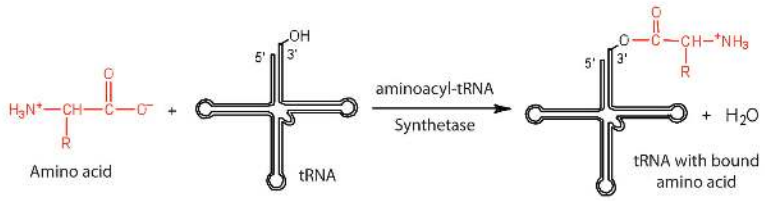


Figure 17.5.1: Binding of an Amino Acid to Its tRNA

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 17.5.1). 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 17.5.2 depicts a schematic stepwise representation of this all-important process.

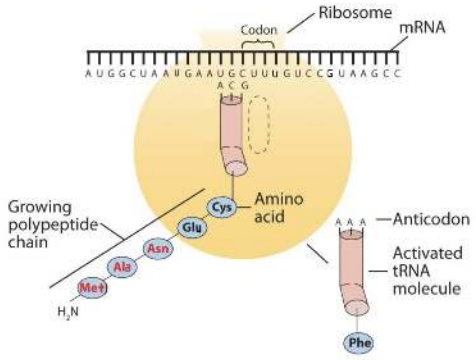


Figure 17.5.2a: The Elongation Steps in Protein Synthesis - Protein synthesis is already in progress at the ribosome. The growing polypeptide chain is attached to the tRNA that brought in the previous amino acid (in this illustration, cys.)

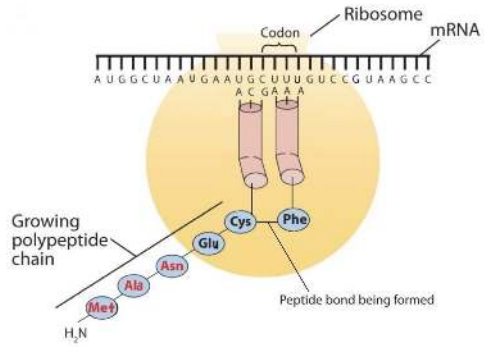


Figure 17.5.2b: The Elongation Steps in Protein Synthesis - An activated tRNA, which has the anticodon AAA, binds to the ribosome next to the previous bound tRNA and interacts with the mRNA molecule though basepairing of the codon and anticodon. The amino acid Phe is being incorporated into the polypeptide 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.

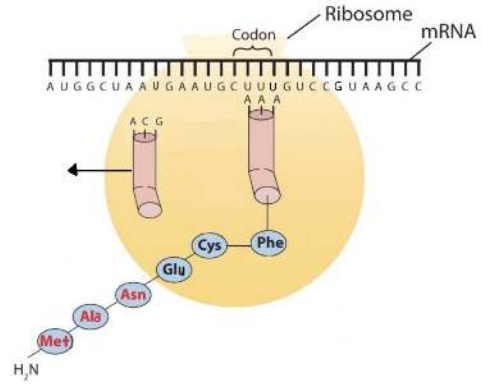


Figure **17.5.2*c***: The Elongation Steps in Protein Synthesis - The Cys-Phe linkage is now complete, and the growing polypeptide chain remains attached to the tRNA for Phe.

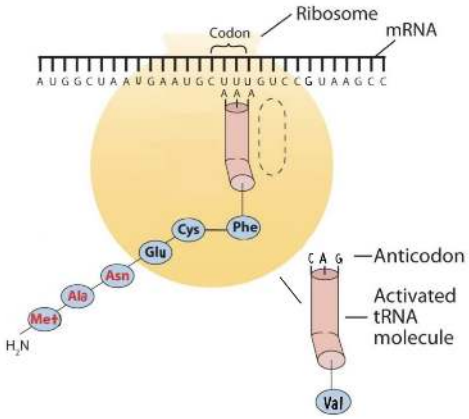


Figure **17.5.2*d***: The Elongation Steps in Protein Synthesis - The ribosome moves to the right along the mRNA strand. This shift brings the next codon, GUC, into its correct position on the surface of the ribosome. Note that an activated tRNA molecule, containing the next amino acid to be attached 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 **17.5.3**, 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.

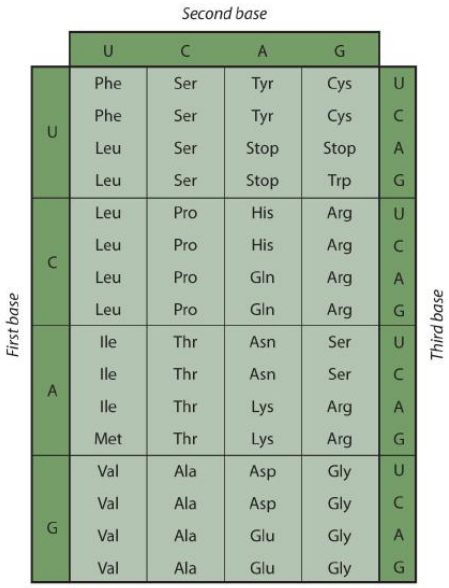


Figure **17.5.3**: The Genetic Code

Example 17.5.1: 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 **17.5.3** 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 17.5.4

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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17.6: 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 **17.6.1**). 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.

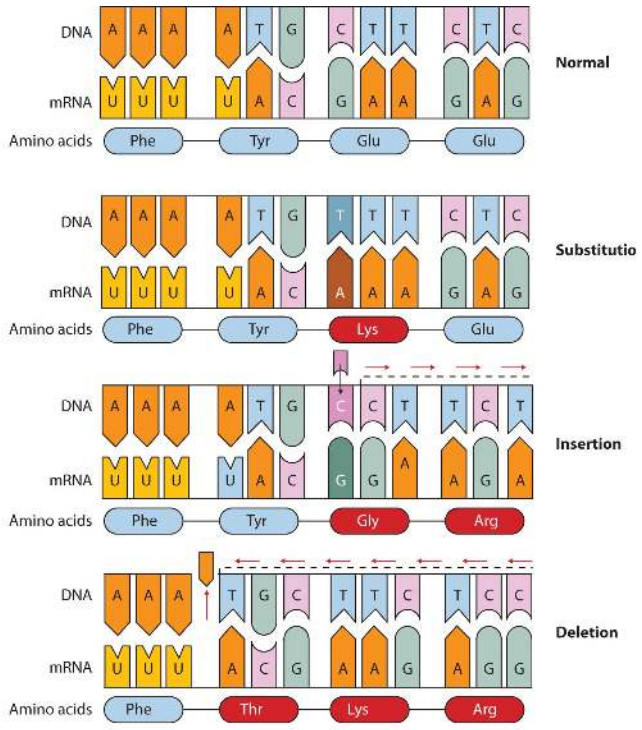


Figure **17.6.1**: Three Types of Point Mutations

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 **17.6.2**). 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.

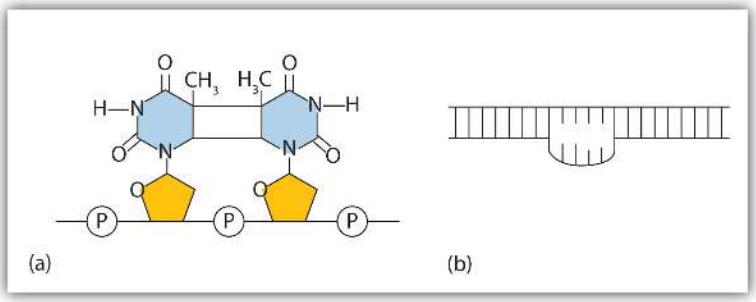


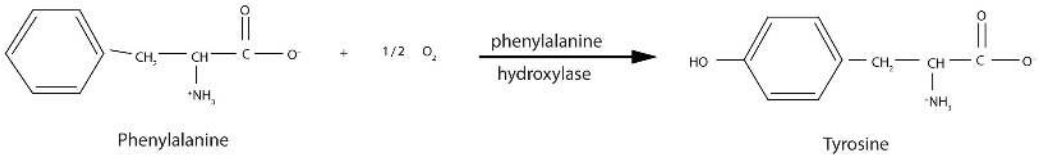
Figure **17.6.2**: An Example of Radiation Damage to DNA. (a) The thymine dimer is formed by the action of UV light. (b) When a defect in the double strand is produced by the thymine dimer, this defect temporarily stops DNA replication, but the dimer can be removed, and the region can be repaired by 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 **17.6.1**, 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.

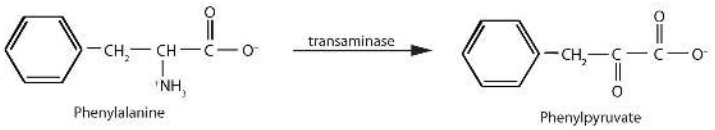
Figure **17.6.1**: Some Representative Genetic Diseases in Humans and the Protein or Enzyme Responsible

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.

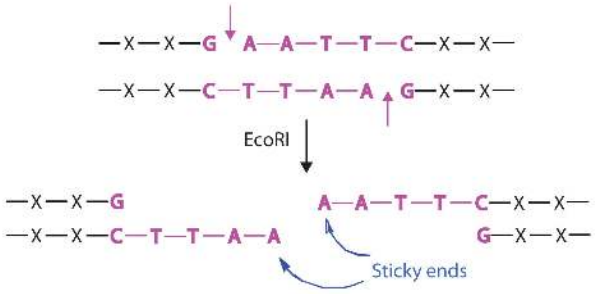
> *Every state in the United States has mandated that screening for PKU be provided to all newborns.*

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.

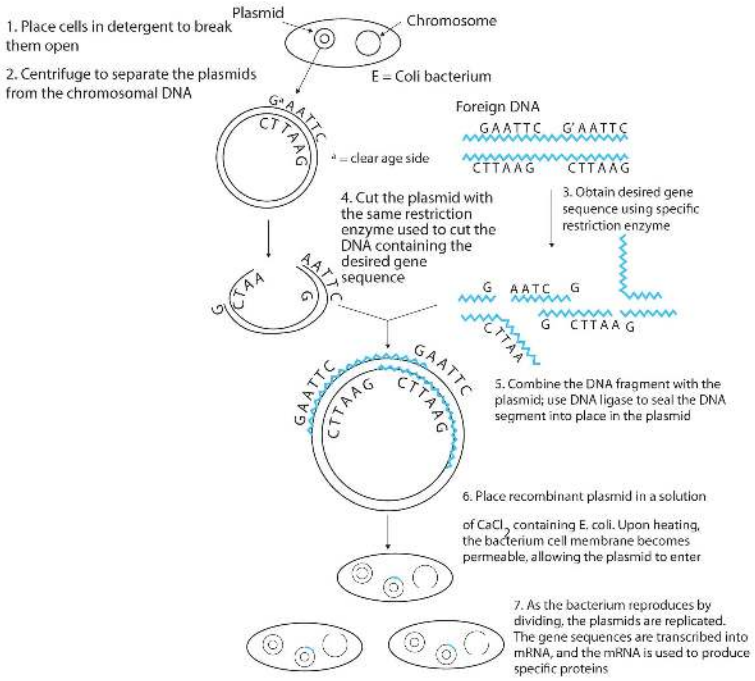
Isolating the specific gene or genes that cause a particular genetic disease is a monumental task. One reason for the difficulty is the enormous amount of a cell's DNA, only a minute portion of which contains the gene sequence. Thus, the first task is to obtain smaller pieces of DNA that can be more 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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17.7: 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 **17.7.1**).

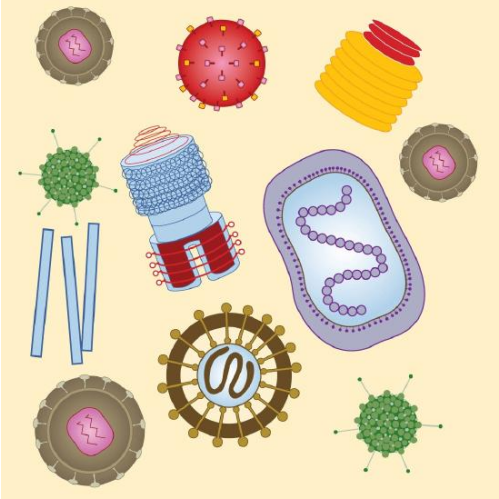


Figure **17.7.1**: Viruses. Viruses come in a variety of shapes that are determined by their protein coats.

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 **17.7.2**), 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.

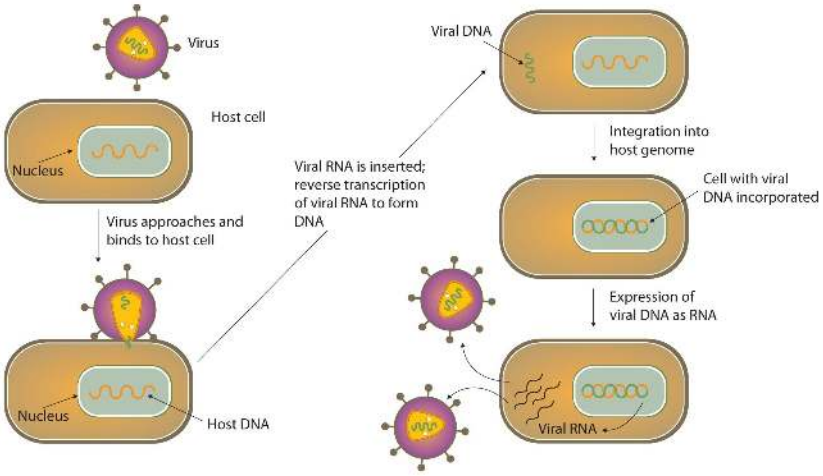
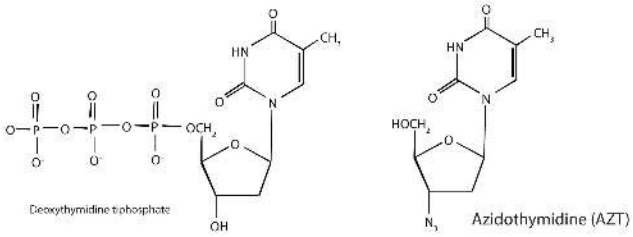
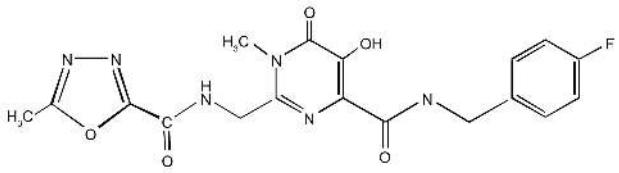


Figure **17.7.2**: Life Cycle of a Retrovirus

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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SECTION OVERVIEW

17.8: Flow of Genetic Information

As the cell's so-called blueprint, DNA must be copied to pass on to new cells and its integrity safeguarded. The information in the DNA must also be accessed and transcribed to make the RNA instructions that direct the synthesis of proteins.

17.8.1: DNA Replication

17.8.2: DNA Repair

17.8.3: Transcription

17.8.4: Regulation of Transcription

17.8.5: RNA Processing

17.8.6: Translation

Contributors

- Template:ContribAhern

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17.8.1: DNA Replication

The only way to make new cells is by the division of pre-existing cells. This means that all organisms depend on cell division for their continued existence. DNA, as you know, carries the genetic information that each cell needs. Each time a cell divides, all of its DNA must be copied faithfully so that a copy of this information can be passed on to the daughter cell. This process is called DNA replication. Before examining the actual process of DNA replication, it is useful to think about what it takes to accomplish this task successfully. Consider the challenges facing a cell in this process:

- The sheer number of nucleotides to be copied is enormous: e.g., in human cells, on the order of several billion.
- A double-helical parental DNA molecule must be unwound to expose single strands of DNA that can serve as templates for the synthesis of new DNA strands.
- This unwinding must be accomplished without introducing significant topological distortion into the molecule.
- The unwound single strands of DNA must be kept from coming back together long enough for the new strands to be synthesized.
- DNA polymerases cannot begin synthesis of a new DNA strand de novo and require a free 3' OH to which they can add DNA nucleotides.
- DNA polymerases can only extend a strand in the 5' to 3' direction. The 5' to 3' extension of both new strands at a single replication fork means that one of the strands is made in pieces.
- The use of RNA primers requires that the RNA nucleotides must be removed and replaced with DNA nucleotides and the resulting DNA fragments must be joined.
- Ensuring accuracy in the copying of so much information.

With this in mind, we can begin to examine how cells deal with each of these challenges. Our understanding of the process of DNA replication is derived from studies using bacteria, yeast, and other systems, such as Xenopus eggs. These investigations have revealed that DNA replication is carried out by the action of a large number of proteins that act together as a complex protein machine called the replisome. Numerous proteins involved in replication have been identified and characterized, including multiple different DNA polymerases in both prokaryotes and eukaryotes. Although the specific proteins involved are different in bacteria and eukaryotes, it is useful to understand the basic considerations that are relevant in all cells, before attempting to address the details of each system.

A generalized account of the steps in DNA replication is presented below, focused on the challenges mentioned above.

- The sheer number of nucleotides to be copied is enormous.

For example, in human cells, the number of nucleotides to be copied is on the order of several billion. Even in bacteria, the number is in the millions. Cells, whether bacterial or eukaryotic, have to replicate all of their DNA before they can divide. In cells like our own, the vast amount of DNA is broken up into many chromosomes, each of which is composed of a linear strand of DNA. In cells like those of E. coli, there is a single circular chromosome.

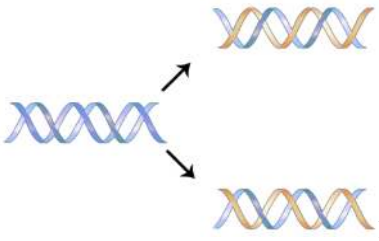


Figure 5.1.1: *Semi-conservative DNA replication*

In either situation, DNA replication is initiated at sites called origins of replication. These are regions of the DNA molecule that are recognized by special origin recognition proteins that bind the DNA. The binding of these proteins helps open up a region of single-stranded DNA where the synthesis of new DNA can begin. In the case of E. coli, there is a single origin of replication on its circular chromosome. In eukaryotic cells, there may be many thousands of origins of replication, with each chromosome having hundreds. DNA replication is thus initiated at multiple points along each chromosome in eukaryotes as shown in Figure 5.1.3. Electron micrographs of replicating DNA from eukaryotic cells show many replication “bubbles" on a single chromosome.

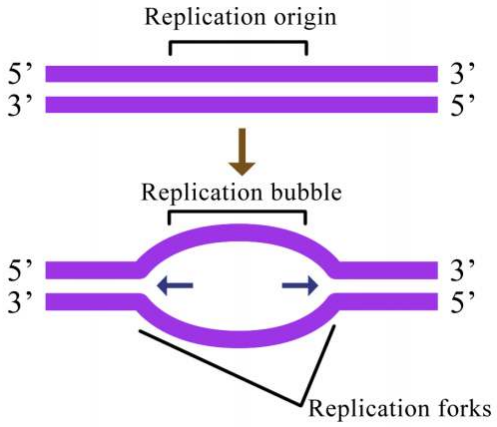


Figure 5.1.2: *Image of a replication bubble*

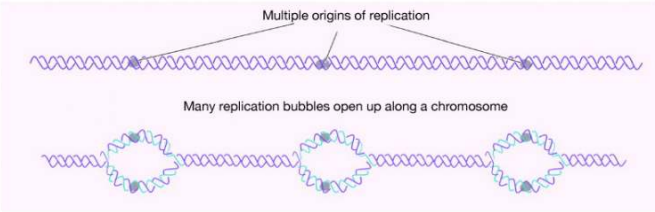


Figure 5.1.3: *Multiple replication bubbles*

This makes sense in light of the large amount of DNA that there is to be copied in cells like our own, where beginning at one end of each chromosome and replicating all the way through to the other end from a single origin would simply take too long. This is despite the fact that the DNA polymerases in human cells are capable of building new DNA strands at the very respectable rate of about 50 nucleotides per second!

- A double-helical parental molecule must be unwound to expose single strands of DNA that can serve as templates for the synthesis of new DNA strands.

Once a small region of the DNA is opened up at each origin of replication, the DNA helix must be unwound to allow replication to proceed. How are the strands of the parental DNA double helix separated? The unwinding of the DNA helix requires the action of an enzyme called helicase. Helicase uses the energy released when ATP is hydrolyzed to unwind the DNA helix. Note that each replication bubble is made up of two replication forks that "move" or open up, in opposite directions. At each replication fork, the parental DNA strands must be unwound to expose new sections of single-stranded template.

- This unwinding must be accomplished without introducing topological distortion into the molecule.

What is the effect of unwinding one region of the double helix? Unwinding the helix locally causes over-winding or topological distortion of the DNA ahead of the unwound region. The DNA ahead of the unwound helix has to rotate, or it will get twisted on itself. How is this problem solved? Enzymes called topoisomerases can relieve the topological stress caused by local unwinding of the double helix. They do this by cutting the DNA and allowing the strands to swivel around each other to release the tension before rejoining the ends. In E. coli, the topoisomerase that performs this function is called gyrase.

- The unwound single strands of DNA must be kept from coming back together long enough for the new strands to be synthesized.

Once the two strands of the parental DNA molecule are separated, they must be prevented from going back together to form double-stranded DNA. To ensure that unwound regions of the parental DNA remain single-stranded and available for copying, the separated strands of the parental DNA are bound by many molecules of a protein called single-strand DNA binding protein (SSB).

- DNA polymerases cannot begin synthesis of a new DNA strand de novo and require a free 3' OH to which they can add DNA nucleotides.

Although single-stranded parental DNA is now available for copying, DNA polymerases cannot begin synthesis of a complementary strand de novo. This is because all DNA polymerases can only add new nucleotides to the 3' end of a pre- existing chain. This means that some enzyme other than a DNA polymerase must first make a small region of nucleic acid, complementary to the parental strand, that can provide a free 3' OH to which DNA polymerase can add a deoxyribonucleotide.

This task is accomplished by an enzyme called a *primase*, which assembles a short stretch of RNA, called the primer, across from the parental DNA template. This provides a short base-paired region with a free 3'OH group to which DNA polymerase can add the first new DNA nucleotide (see figure on previous page). Once a primer provides a free 3'OH for extension, other proteins get into the act. These proteins are involved in loading the DNA polymerase onto the primed template and help to keep it attached to the DNA once it's on.

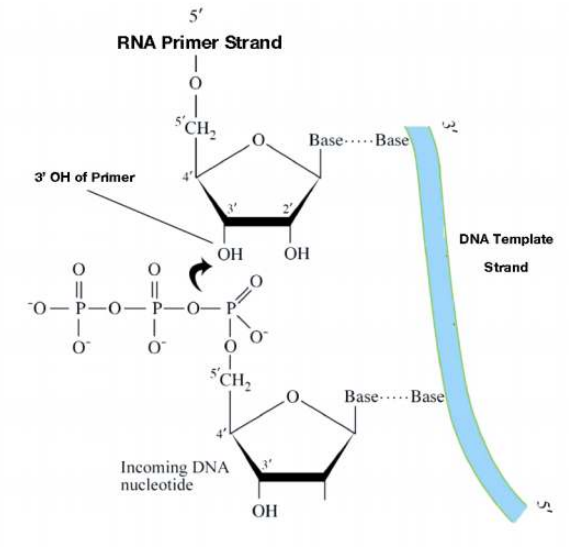


Figure 5.1.4: *Addition of a nucleotide to a growing strand*

The first of these is the clamp loader. As its name suggests, the clamp loader helps to load a protein complex called the sliding clamp onto the DNA at the replication fork. The sliding clamp is then joined by the DNA Polymerase. The function of the sliding clamp is to increase the processivity of the DNA polymerase. This is a fancy way of saying that it keeps the polymerase associated with the replication fork by preventing it from falling off - in fact, the sliding clamp has been described as a seat-belt for the DNA polymerase.

The DNA polymerase is now poised to start synthesis of the new DNA strand (in E. coli, the primary replicative polymerase is called DNA polymerase III). As you already know, the synthesis of new DNA is accomplished by the addition of new nucleotides complementary to those on the parental strand. DNA polymerase catalyzes the reaction by which an incoming deoxyribonucleotide is added onto the 3' end of the previous nucleotide, starting with the 3'OH on the end of the RNA primer.

The 5' phosphate on each incoming nucleotide is joined by the DNA polymerase to the 3' OH on the end of the growing nucleic acid chain. As we already noted, the new DNA strands are synthesized by the addition of DNA nucleotides to the end of an RNA primer. The new DNA molecule thus has a short piece of RNA at the beginning.

- DNA polymerases can only extend a strand in the 5' to 3' direction. The 5' to 3' growth of both new strands means that one of the strands is made in pieces.

We have noted that DNA polymerase can only build a new DNA strand in the 5' to 3' direction. We also know that the two parental strands of DNA are antiparallel. This means that at each replication fork, one new strand, called the leading strand can be synthesized continuously in the 5' to 3' direction because it is being made in the same direction that the replication fork is opening up.

The synthesis of the other new strand, called the lagging strand, requires that multiple RNA primers must be laid down and the new DNA be made in many short pieces that are later joined.These short nucleic acid pieces, each composed of a small stretch of RNA primer and about 1000-2000 DNA nucleotides, are called Okazaki fragments, for Reiji Okazaki, the scientist who first demonstrated their existence.

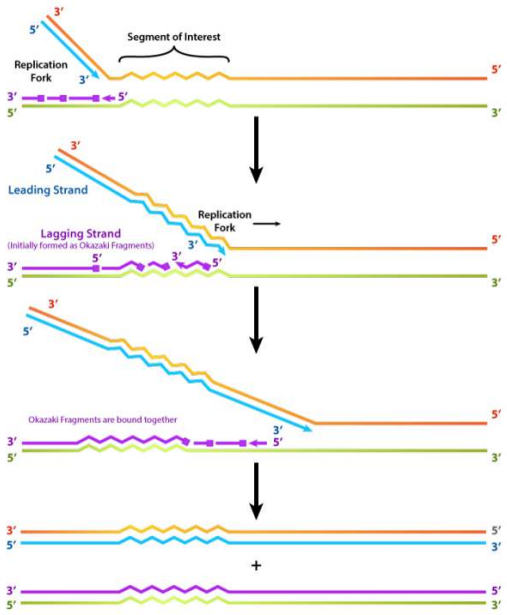


Figure 5.1.5: *Leading and lagging strand replication*

- The use of RNA primers requires that the RNA nucleotides must be removed and replaced with DNA nucleotides.
- We have seen that each newly synthesized piece of DNA starts out with an RNA primer, effectively making a new nucleic acid strand that is part RNA and part DNA. The finished DNA strand cannot be allowed to have pieces of RNA attached. o the RNA nucleotides are removed and the gaps are filled in with DNA nucleotides (by DNA polymerase I in E. coli). The DNA pieces are then joined together by the enzyme DNA ligase.

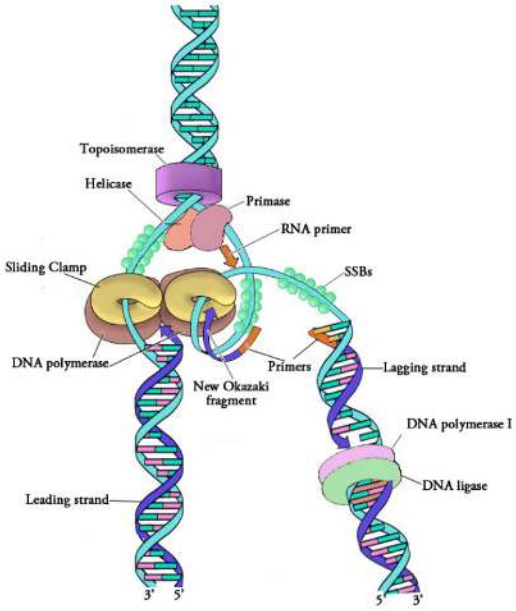


Figure 5.1.6: *Proteins at a replication fork*

The steps outlined above essentially complete the process of DNA replication. Figure 5.1.6 shows a replication fork, complete with the associated proteins that form the replisome.

- Ensuring accuracy in the copying of so much information

How accurate is the copying of information in the DNA by DNA polymerase? As you are aware, changes in DNA sequence (mutations) can change the amino acid sequence of the encoded proteins and that this is often, though not always, deleterious to the

functioning of the organism. When billions of bases in DNA are copied during replication, how do cells ensure that the newly synthesized DNA is a faithful copy of the original information?

DNA polymerases, as we have noted earlier, work fast (averaging 50 bases a second in human cells and up to 20 times faster in E. coli). Yet, both human and bacterial cells seem to replicate their DNA quite accurately. This is because of the proof-reading function of DNA polymerases. The proof-reading function of a DNA polymerase enables the polymerase to detect when the wrong base has been inserted across from a template strand, back up and remove the mistakenly inserted base. This is possible because the polymerase is a dual-function enzyme. It can extend a DNA chain by virtue of its 5' to 3' polymerase activity but it can also backtrack and remove the last inserted base because it has a 3' to 5' exonuclease activity (an exonuclease is an enzyme that removes bases, one by one, from the ends of nucleic acids). The exonuclease activity of the DNA polymerase allows it to excise a wrongly inserted base, after which the polymerase activity inserts the correct base and proceeds with extending the strand.

In other words, DNA polymerase is monitoring its own accuracy (also termed its fidelity) as it makes new DNA, correcting mistakes immediately before moving on to add the next base. This mechanism, which operates during DNA replication, corrects many errors as they occur, reducing by about 100-fold the mistakes made when DNA is copied.

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17.8.2: DNA Repair

Maintaining the Integrity of the Cell's Information: DNA Repair

In the last section we considered the ways in which cells deal with the challenges associated with replicating their DNA, a vital process for all cells. It is evident that if DNA is the master copy of instructions for an organism, then it is important not to make mistakes when copying the DNA to pass on to new cells. Although proofreading by DNA polymerases greatly increases the accuracy of replication, there are additional mechanisms in cells to further ensure that newly replicated DNA is a faithful copy of the original, and also to repair damage to DNA during the normal life of a cell.

All DNA suffers damage over time, from exposure to ultraviolet and other radiation, as well as from various chemicals in the environment. Even chemical reactions naturally occurring within cells can give rise to compounds that can damage DNA. As you already know, even minor changes in DNA sequence, such as point mutations can sometimes have far-reaching consequences. Likewise, unrepaired damage caused by radiation, environmental chemicals or even normal cellular chemistry can interfere with the accurate transmission of information in DNA. Maintaining the integrity of the cell's "blueprint" is of vital importance and this is reflected in the numerous mechanisms that exist to repair mistakes and damage in DNA.

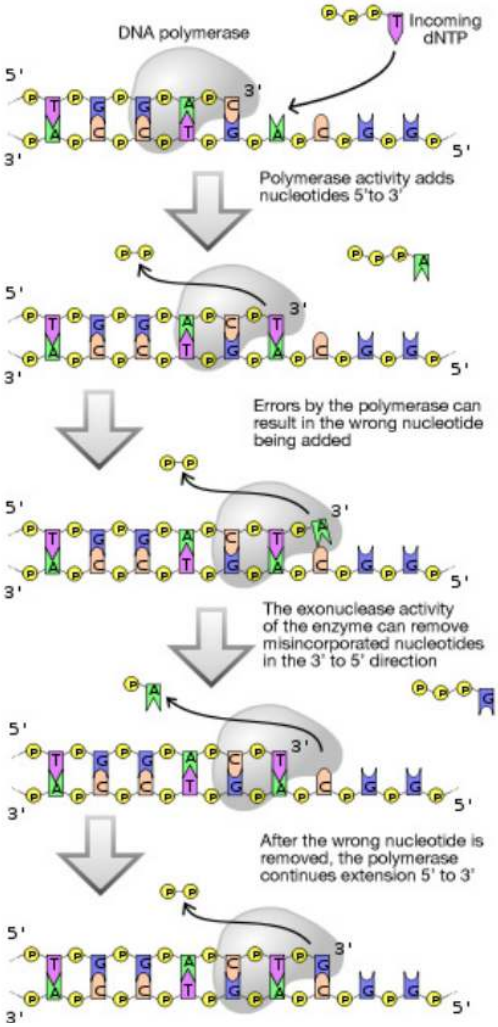


Figure **17.8.2.1**: *Example of DNA correction*

Post-Replicative Mismatch Repair

We earlier discussed proof-reading by DNA polymerases during replication. Does proofreading eliminate all errors made during replication. No. While proof-reading significantly reduces the error rate, not all mistakes are fixed on the fly by DNA polymerases. What mechanisms exist to correct the replication errors that are missed by the proof-reading function of DNA polymerases.

Errors that slip by proofreading during replication can be corrected by a mechanism called mismatch repair. While the error rate of DNA replication is about one in 10^7 nucleotides in the absence of mismatch repair, this is further reduced a hundred-fold to one in \)10^9\) nucleotides when mismatch repair is functional.

What are the tasks that a mismatch repair system faces. It must:

- Scan newly made DNA to see if there are any mispaired bases (e.g., a G paired to a T)
- Identify and cut out the region of the mismatch.
- Correctly fill in the gap created by the excision of the mismatch region.

Importantly, the mismatch repair system must have a means to distinguish the newly made DNA strand from the template strand, if replication errors are to be fixed correctly. In other words, when the mismatch repair system encounters an A-G mispair, for example, it must know whether the A should be removed and replaced with a C or if the G should be removed and replaced with a T.

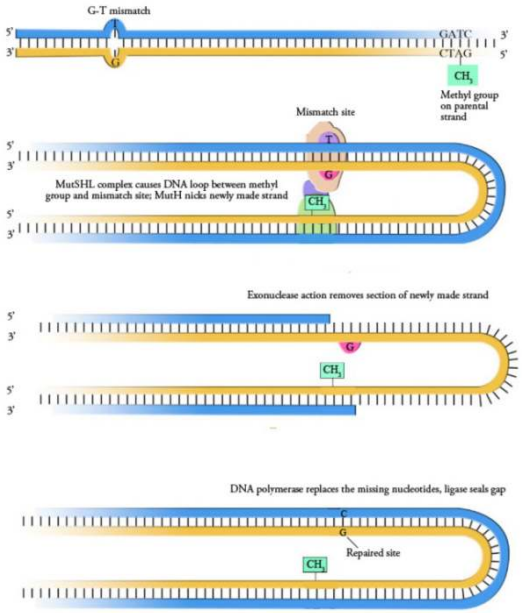


Figure 17.8.2.1: *Mismatch repair*

Mismatch repair has been well studied in bacteria, and the proteins involved have been identified. Eukaryotes have a mismatch repair system that repairs not only single base mismatches but also insertions and deletions. In bacteria, mismatch repair proteins are encoded by a group of genes collectively known as the mut genes. Some of the most important components of the mismatch repair machinery are the proteins MutS, L and H. MutS acts to recognize the mismatch, while MutL and MutH are recruited to the mismatch site by the binding of Mut S, to help cut out the region containing the mismatch. A DNA polymerase and ligase fill in the gap and join the ends, respectively.

But how does the mismatch repair system distinguish between the original and the new strands of DNA? In bacteria, the existence of a system that methylates the DNA at GATC sequences is the solution to this problem. *E.coli* has an enzyme that adds methyl groups on the to adenines in GATC sequences. Newly replicated DNA lacks thismethylation and thus, can be distinguished from the template strand, which is methylated. In Figure 17.8.2.2, the template strand shown in yellow is methylated at GATC sequences. The mismatch repair proteins selectively replace the strand lacking methylation, shown in blue in the figure, thus ensuring that it is mistakes in the newly made strand that are removed and replaced. Because methylation is the criterion that enables the mismatch repair system to choose the strand that is repaired, the bacterial mismatch repair system is described as being methyl-directed.

Eukaryotic cells do not use this mechanism to distinguish the new strand from the template, and it is not yet understood how the mismatch repair system in eukaryotes "knows" which strand to repair.

Systems to Repair Damage to DNA

In the preceding section we discussed mistakes made when DNA is copied, where the wrong base is inserted during synthesis of the new strand. But even DNA that is not being replicated can get damaged or mutated. These sorts of damage are not associated with DNA replication, rather they can occur at any time.

What causes damage to DNA? Some major causes of DNA damage are:

- Radiation (e.g., UV rays in sunlight, in tanning booths)
- Exposure to damaging chemicals (such as benzopyrene in car exhaust and cigarette smoke)
- Chemical reactions within the cell (such as the deamination of cytosine to give uracil).

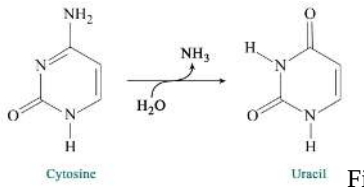


Figure 17.8.2.3: *Deamination of cytosine*

This means the DNA in your cells is vulnerable to damage simply from normal sorts of actions, such as walking outdoors, being in traffic, or from the chemical transformations occurring in every cell as part of its everyday activities. (Naturally, the damage is much worse in situations where exposure to radiation or damaging chemicals is greater, such as when people repeatedly use tanning beds or smoke.)

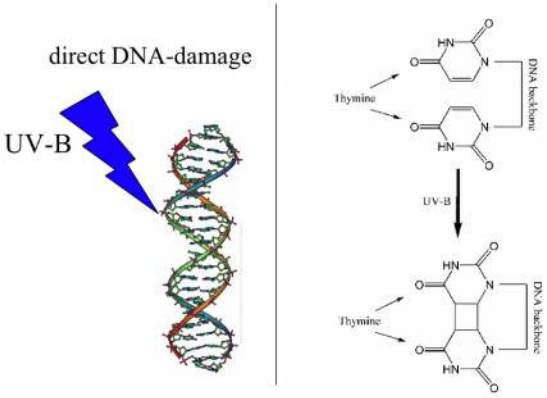


Figure 17.8.2.4: *Thymine dimer formation*

What kinds of damage do these agents cause? Radiation can cause different kinds of damage to DNA. Sometimes, as with much of the damage done by UV rays, two adjacent pyrimidine bases in the DNA will be cross-linked to form pyrimidine dimers (note that we are talking about two neighboring pyrimidine bases on the same strand of DNA). This is illustrated in the figure on the previous page where two adjacent thymines on a single DNA strand are cross-linked to form a thymine dimer. Radiation can also cause breaks in the DNA backbone.

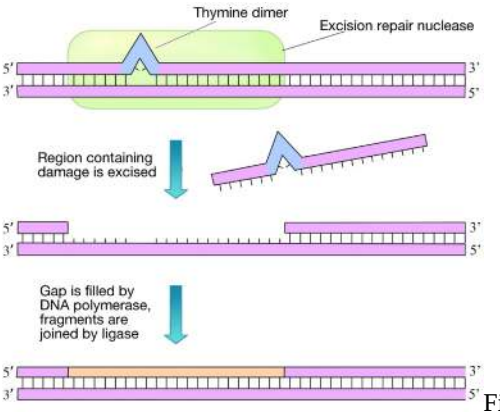


Figure 17.8.2.5: *Thymine dimer removal*

Chemicals like benzopyrene can attach themselves to bases, forming bulky DNA adducts in which large chemical groups are linked to bases in the DNA. The formation of chemical adducts can physically distort the DNA helix, making it hard for DNA and RNA polymerases to copy those regions of DNA.

Chemical reactions occurring within cells can cause cytosines in DNA to be deaminated to uracil, as shown in Figure **17.8.2.3**.

Other sorts of damage in this category include the formation of oxidized bases like 8-oxo-guanine. These do not actually change the physical structure of the DNA helix, but they can cause problems because uracil and 8-oxo-guanine pair with different bases than the original cytosine or guanine, leading to mutations on the next round of replication.

How do cells repair such damage? Cells have several ways to remove the sorts of damage described above, with excision repair being a common strategy. Excision repair is a general term for the cutting out and re-synthesis of the damaged region of the DNA. There are a couple of varieties of excision repair:

Nucleotide Excision Repair (NER)

This system fixes damage by chemicals as well as UV damage. As shown in the figure on the previous page, in nucleotide excision repair, the damage is recognized and a cut is made on either side of the damaged region by an enzyme called an excinuclease (shown in green). A short portion of the DNA strand containing the damage is then removed and a DNA polymerase fills in the gap with the appropriate nucleotides. The newly made DNA is joined to the rest of the DNA backbone by the enzyme DNA ligase. In E. coli, NER is carried out by a group of proteins encoded by the uvrABC genes. As you can see, NER is similar, in principle, to mismatch repair. However, in NER, the distortion of the helix, caused by the DNA damage, clearly indicates which strand of the DNA needs to be removed and replaced.

Base Excision Repair (BER)

BER deals with situations like the deamination of cytosine to uracil. As noted earlier, cytosines in DNA sometimes undergo deamination to form the base uracil.

Because cytosines pair with guanines and uracils pair with adenine, the conversion of cytosine to uracil in the DNA would lead to the insertion of an A in the newly replicated strand instead of the G that should have gone in across from a C. To prevent this from happening, uracils are removed from DNA by base excision repair.

In base excision repair, a single base is first removed from the DNA, followed by removal of a region of the DNA surrounding the missing base. The gap is then repaired.

The removal of uracil from DNA is accomplished by the enzyme uracil DNA glycosylase, which breaks the bond between the uracil and the sugar in the nucleotide.

The removal of the uracil base creates a gap called an apyrimidinic site (AP site). The presence of the AP site triggers the activity of an AP endonuclease that cuts the DNA backbone.

A short region of the DNA surrounding the site of the original uracil is then removed and replaced.

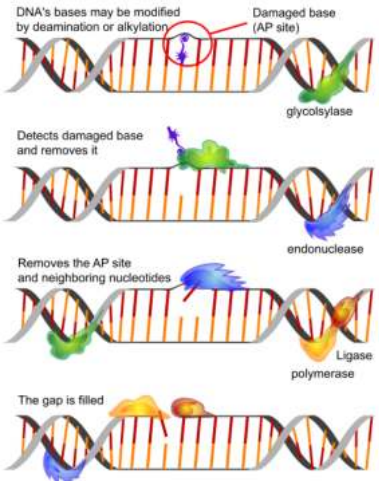


Figure **17.8.2.6**: *Base excision repair*

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17.8.3: Transcription

In the preceding sections, we have discussed the replication of the cell's DNA and the mechanisms by which the integrity of the genetic information is carefully maintained. What do cells do with this information? How does the sequence in DNA control what happens in a cell? If DNA is a giant instruction book containing all of the cell's "knowledge" that is copied and passed down from generation to generation, what are the instructions for? And how do cells use these instructions to make what they need?

You have learned in introductory biology courses that genes, which are instructions for making proteins, are made of DNA. You also know that information in genes is copied into temporary instructions called messenger RNAs that direct the synthesis of specific proteins. This description of flow of information from DNA to RNA to protein, shown on the previous page, is often called the Central Dogma of molecular biology and is a good starting point for an examination of how cells use the information in DNA.

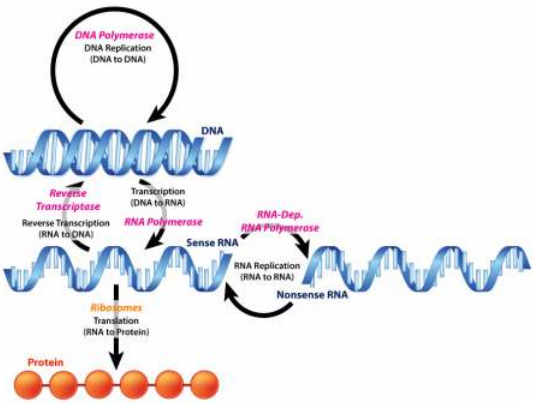


Figure 5.3.1: *Central dogma*

Consider that all of the cells in a multicellular organism have arisen by division from a single fertilized egg and therefore, all have the same DNA. Division of that original fertilized egg produces, in the case of humans, over a trillion cells, by the time a baby is produced from that egg (that's a lot of DNA replication!). Yet, we also know that a baby is not a giant ball of a trillion identical cells, but has the many different kinds of cells that make up tissues like skin and muscle and bone and nerves. How did cells that have identical DNA turn out so different.

The answer lies in gene expression, which is the process by which the information in DNA is used. Although all the cells in a baby have the same DNA, each different cell type uses a different subset of the genes in that DNA to direct the synthesis of a distinctive set of RNAs and proteins. The first step in gene expression is transcription, which we will examine next.

What is transcription? Transcription is the process of copying information from DNA sequences into RNA sequences. This process is also known as DNA-dependent RNA synthesis. When a sequence of DNA is transcribed, only one of the two DNA strands is copied into RNA.

General Features of Transcription

- The process of making RNA copies using a DNA as template is known as transcription
- The process of transcription produces all sorts of RNAs (mRNA, tRNA, rRNA, etc)
- One strand of the DNA serves as a template for the synthesis of RNA
- Enzymes that synthesize RNA are called RNA polymerases
- RNA polymerases synthesize RNA in the 5' to 3' direction
- RNA polymerases do not need a primer
- RNA polymerases uses rNTPs (ATP,GTP,UTP and CTP) to build the new RNA strand
- RNA polymerases bind at specific DNA sequences called promoters to start transcription
- RNA polymerases stop RNA synthesis when they reach sequences called terminators

Figure 5.3.2: *General Features of Transcription*

But, apart from copying one, rather than both strands of DNA, how is transcription different from replication of DNA. DNA replication serves to copy all the genetic material of the cell and occurs before a cell divides, so that a full copy of the cell's genetic information can be passed on to the daughter cell. Transcription, by contrast, copies short stretches of the coding regions of DNA to make RNA. Different genes may be copied into RNA at different times in the cell's lifecycle. RNAs are, so to speak, temporary copies of instructions of the information in DNA and different sets of instructions are copied for use at different times.

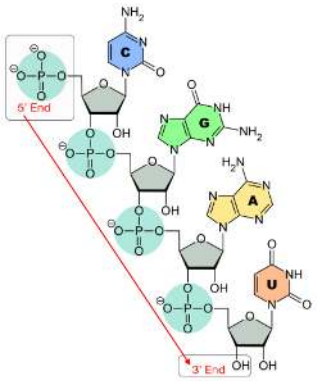
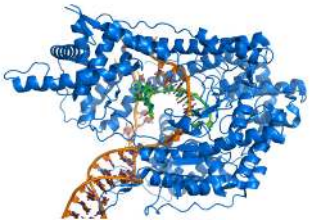


Figure 5.3.3: *RNA structure*

Cells make several different kinds of RNA:

- mRNAs that code for proteins
- rRNAS that form part of ribosomes
- tRNAs that serve as adaptors between mRNA and amino acids during translation
- Micro RNAs that regulate gene expression
- Other small RNAs that have a variety of functions.

Building an RNA strand is very similar to building a DNA strand. This is not surprising, knowing that DNA and RNA are very similar molecules. What enzyme carries out transcription? Transcription is catalyzed by the enzyme RNA Polymerase. "RNA polymerase" is a general term for an enzyme that makes RNA. There are many different RNA polymerases.


Figure 5.3.4: *T7 RNA Polymerase (blue) making RNA (green) using DNA template (brown)*

Like DNA polymerases, RNA polymerases synthesize new strands only in the 5' to 3' direction, but because they are making RNA, they use ribonucleotides (i.e., RNA nucleotides) rather than deoxyribonucleotides. Ribonucleotides are joined in exactly the same way as deoxyribonucleotides, which is to say that the 3'OH of the last nucleotide on the growing chain is joined to the 5' phosphate on the incoming nucleotide.

One important difference between DNA polymerases and RNA polymerases is that the latter do not require a primer to start making RNA. Once RNA polymerases are in the right place to start copying DNA, they just begin making RNA by stringing together RNA nucleotides complementary to the DNA template.

This, of course, brings us to an obvious question- how do RNA polymerases "know" where to start copying on the DNA. Unlike the situation in replication, where every nucleotide of the parental DNA must eventually be copied, transcription, as we have already noted, only copies selected genes into RNA at any given time.

Consider the challenge here: in a human cell, there are approximately 6 billion basepairs of DNA. Most of this is non- coding DNA, meaning that it won't need to be transcribed. The small percentage of the genome that is made up of coding sequences still amounts to between 20,000 and 30,000 genes in each cell. Of these genes, only a small number will need to be expressed at any given time.

What indicates to an RNA polymerase where to start copying DNA to make a transcript? Signals in DNA indicate to RNA polymerase where it should start (and end) transcription. These signals are special sequences in DNA that are recognized by the RNA polymerase or by proteins that help RNA polymerase determine where it should bind the DNA to start transcription. A DNA sequence at which the RNA polymerase binds to start transcription is called a promoter.

A promoter is generally situated upstream of the gene that it controls. What this means is that on the DNA strand that the gene is on, the promoter sequence is "before" the gene. Remember that, by convention, DNA sequences are read from 5' to 3'. So the

promoter lies 5' to the start point of transcription.

Also notice that the promoter is said to "control" the gene it is associated with. This is because expression of the gene is dependent on the binding of RNA polymerase to the promoter sequence to begin transcription. If the RNA polymerase and its helper proteins do not bind the promoter, the gene cannot be transcribed and it will therefore, not be expressed.



Figure 5.3.5: *Promoter Sequences*

What is special about a promoter sequence? In an effort to answer this question, scientists looked at many genes and their surrounding sequences. It makes sense that because the same RNA polymerase has to bind to many different promoters, the promoters should have some similarities in their sequences. Sure enough, common sequence patterns were seen to be present in many promoters. We will first take a look at prokaryotic promoters. When prokaryotic genes were examined, the following features commonly emerged (Figure 5.3.5):

- A transcription start site (this the base in the DNA across from which the first RNA nucleotide is paired).
- A -10 sequence: this is a 6 bp region centered about 10 bp upstream of the start site. The consensus sequence at this position is TATAAT. In other words, if you count back from the transcription start site, which by convention, is called the +1, the sequence found at -10 in the majority of promoters studied is TATAAT).
- A -35 sequence: this is a sequence at about 35 basepairs upstream from the start of transcription. The consensus sequence at this position is TTGACA.

What is the significance of these sequences? It turns out that the sequences at -10 and -35 are recognized and bound by a subunit of prokaryotic RNA polymerase before transcription can begin.



Figure 5.3.6: *Promoter sequence elements*

The RNA polymerase of E. coli, for example, has a subunit called the sigma subunit (or sigma factor) in addition to the core polymerase, which is the part of the enzyme that actually makes RNA. Together, the sigma subunit and core polymerase make up what is termed the RNA polymerase holoenzyme. The sigma subunit of the polymerase (shown in brown in Figure 5.3.7) can recognize and bind to the -10 and -35 sequences in the promoter, thus positioning the RNA polymerase (shown in green) at the right place to initiate transcription. Once transcription begins, the core polymerase and the sigma subunit separate, with the core polymerase continuing RNA synthesis and the sigma subunit wandering off to escort another core polymerase molecule to a promoter. The sigma subunit can be thought of as a sort of usher that leads the polymerase to its "seat" on the promoter.

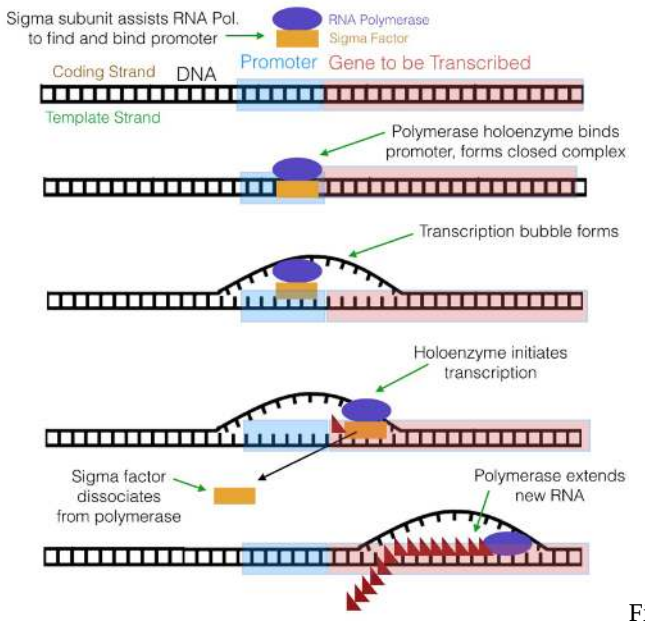


Figure 5.3.7: *Transcription initiation in E. coli*

As already mentioned, an RNA chain, complementary to the DNA template, is built by the RNA polymerase by the joining of the 5' phosphate of an incoming ribonucleotide to the 3'OH on the last nucleotide of the growing RNA strand. How does the polymerase know where to stop? A sequence of nucleotides called the terminator is the signal to the RNA polymerase to stop transcription and dissociate from the template.

Although the process of RNA synthesis is the same in eukaryotes as in prokaryotes, there are some additional issues to keep in mind in eukaryotes. One is that in eukaryotes, the DNA template exists as chromatin, where the DNA is tightly associated with histones and other proteins. The "packaging" of the DNA must therefore be opened up to allow the RNA polymerase access to the template in the region to be transcribed.

A second difference is that eukaryotes have multiple RNA polymerases, not one as in bacterial cells. The different polymerases transcribe different genes. For example, RNA polymerase I transcribes the ribosomal RNA genes, while RNA polymerase III copies tRNA genes. The RNA polymerase we will focus on most is RNA polymerase II, which transcribes protein-coding genes to make mRNAs.

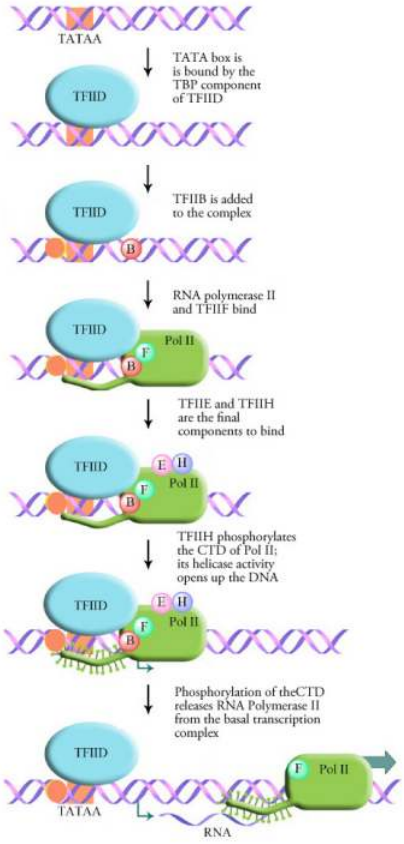


Figure 5.3.8: *Assembly of basal transcription complex and initiation of transcription*

All three eukaryotic RNA polymerases need additional proteins to help them get transcription started. In prokaryotes, RNA polymerase by itself can initiate transcription (remember that the sigma subunit is a subunit of the prokaryotic RNA polymerase). The additional proteins needed by eukaryotic RNA polymerases are referred to as transcription factors. We will see below that there are various categories of transcription factors.

Finally, in eukaryotic cells, transcription is separated in space and time from translation. Transcription happens in the nucleus, and the mRNAs produced are processed further before they are sent into the cytoplasm. Protein synthesis (translation) happens in the cytoplasm. In prokaryotic cells, mRNAs can be translated as they are coming off the DNA template, and because there is no nucleus, transcription and protein synthesis occur in a single cellular compartment.

Like genes in prokaryotes, eukaryotic genes also have promoters. Eukaryotic promoters commonly have a TATA box, a sequence about 25 basepairs upstream of the start of transcription that is recognized and bound by proteins that help the RNA polymerase to position itself correctly to begin transcription. (Some eukaryotic promoters lack TATA boxes, and have, instead, other recognition sequences to help the RNA polymerase find the spot on the DNA where it spot on the DNA where it binds and initiates transcription.)

We noted earlier that eukaryotic RNA polymerases need additional proteins to bind promoters and start transcription. What are these additional proteins that are needed to start transcription? General transcription factors are proteins that help eukaryotic RNA polymerases find transcription start sites and initiate RNA synthesis. We will focus on the transcription factors that assist RNA polymerase II. These transcription factors are named TFIIA, TFIIB and so on (TF= transcription factor, II=RNA polymerase II, and the letters distinguish individual transcription factors).

Transcription in eukaryotes requires the general transcription factors and the RNA polymerase to form a complex at the TATA box called the basal transcription complex or transcription initiation complex. This is the minimum requirement for any gene to be transcribed. The first step in the formation of this complex is the binding of the TATA box by a transcription factor called the TATA Binding Protein or TBP. Binding of the TBP causes the DNA to bend at this spot and take on a structure that is suitable for the binding of additional transcription factors and RNA polymerase. As shown in the figure at left, a number of different general transcription factors, together with RNA polymerase (Pol II) form a complex at the TATA box.

The final step in the assembly of the basal transcription complex is the binding of a general transcription factor called TFIIH. TFIIH is a multifunctional protein that has helicase activity (i.e., it is capable of opening up a DNA double helix) as well as kinase activity. The kinase activity of TFIIH adds a phosphate onto the C-terminal domain (CTD) of the RNA polymerase. This phosphorylation appears to be the signal that releases the RNA polymerase from the basal transcription complex and allows it to move forward and begin transcription.

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17.8.4: Regulation of Transcription

The processes described above are required whenever any gene is transcribed. But what determines which genes are transcribed at a given time. What are the molecular switches that turn transcription on or off? Although there are entire books written on this one topic, the basic mechanism by which transcription is regulated depends on highly specific interactions between transcription regulating proteins and regulatory sequences on DNA.

We know that promoters indicate where transcription begins, but what determines that a given gene will be transcribed? In addition to the promoter sequences required for transcription initiation, genes have additional regulatory sequences (sequences of DNA on the same DNA molecule as the gene) that control when a gene is transcribed. Regulatory sequences are bound tightly and specifically by transcriptional regulators, proteins that can recognize DNA sequences and bind to them. The binding of such proteins to the DNA can regulate transcription by preventing or increasing transcription from a particular promoter.

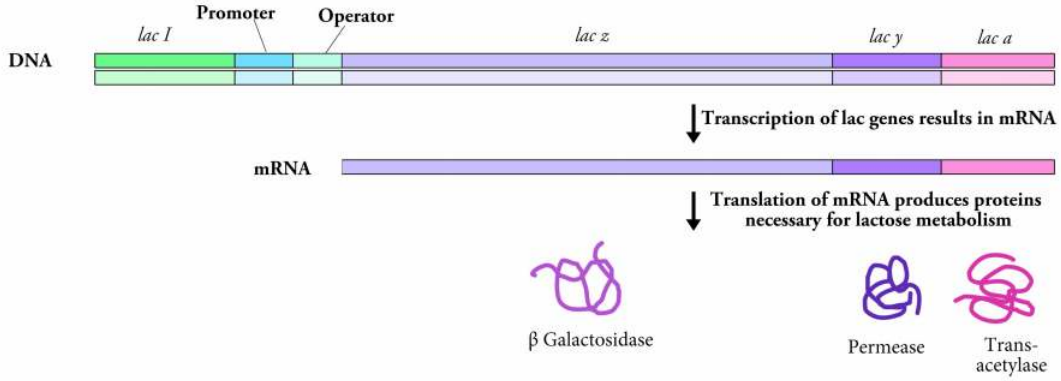


Figure 5.4.1: *The genes lac z, lac y, and lac a are all under the control of a single promotor in the lac operon*

Regulation in Prokaryotes

Let us first consider an example from prokaryotes. In bacteria, genes are often clustered in groups, such that genes that need to be expressed at the same time are next to each other and all of them are controlled as a single unit by the same promoter. The lac operon, shown in Figure 5.4.2, is one such group of genes that encode proteins needed for the uptake and breakdown of the sugar lactose. The three genes of the lac operon, lac z, lac y and lac a are controlled by a single promoter.

Bacterial cells generally prefer to use glucose for their energy needs, but if glucose is unavailable, and lactose is present, the bacteria will take up lactose and break it down for energy. Since the proteins for taking up and breaking down lactose are only needed when glucose is absent and lactose is available, the bacterial cells need a way to express the genes of the lac operon only under those conditions. At times when lactose is absent, the cells do not need to express these genes.

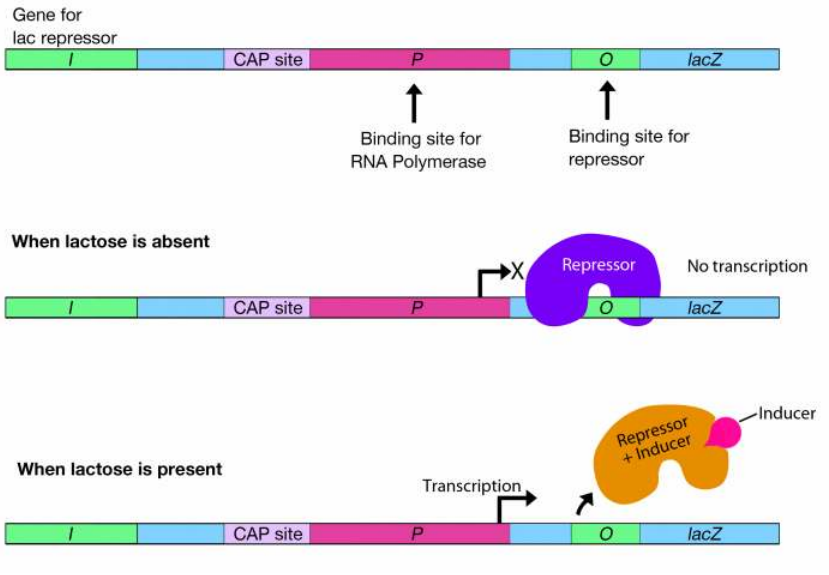


Figure 5.4.2: *Lac operon regulation*

How do bacteria achieve this? Transcription of the lac cluster of genes is primarily controlled by a repressor protein that binds to a region of the DNA just downstream of the -10 sequence of the lac promoter. Recall that the promoter is where the RNA polymerase must bind to begin transcription. The place where the repressor is bound is called the operator (labeled O in the figure). When the repressor is bound at this position, it physically blocks the RNA polymerase from transcribing the genes, just as a vehicle blocking your driveway would prevent you from pulling out.

Obviously, if you want to leave, the vehicle that is blocking your path must be removed. Likewise, in order for transcription to occur, the repressor must be removed from the operator to clear the path for RNA polymerase. How is the repressor removed?

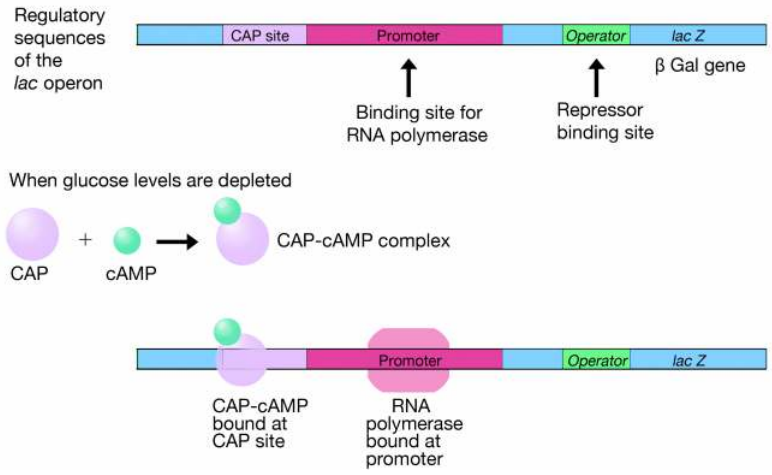


Figure 5.4.3: *Lac operon activation*

When the sugar lactose is present, it binds to the repressor, changing its conformation so that it no longer binds to the operator. When the repressor is no longer bound at the operator, the "road-block" in front of the RNA polymerase is removed, permitting the transcription of the genes of the lac operon.

Because the binding of the lactose induces the expression of the genes in the lac operon, lactose is called an inducer. (Technically, the inducer is allolactose, a molecule made from lactose by the cell, but the principle is the same.)

What makes this an especially effective control system is that the genes of the lac operon encode proteins that break down lactose. Turning on these genes requires lactose to be present. Once the lactose is broken down, the repressor binds to the operator once more and the lac genes are no longer expressed. This allows the genes to be expressed only when they are needed.

But how do glucose levels affect the expression of the lac genes? We noted earlier that if glucose was present, lactose would not be used. A second level of control is exerted by a protein called CAP that binds to a site adjacent to the promoter and recruits RNA

polymerase to bind the lac promoter. When glucose is depleted, there is an increase in levels of cAMP which binds to CAP. The CAP cAMP complex then binds the CAP site, as shown in Figure 5.4.3. The combination of CAP binding and the lac repressor dissociating from the operator when lactose levels are high ensures high levels of transcription of the lac operon just when it is most needed. The CAP protein binding may be thought of as a green light for the RNA polymerase, while the removal of repressor is like the lifting of a barricade in front of it. When both conditions are met, the RNA polymerase transcribes the downstream genes.

The lac operon we have just described is a set of genes that are expressed only under the specific conditions of glucose depletion and lactose availability. Other genes may be expressed unless a particular condition is met. An example of this is the trp operon in bacterial cells, which encodes enzymes necessary for the synthesis of the amino acid tryptophan. These genes are expressed at all times, except when tryptophan is available from the cell's surroundings. This means that these genes must be prevented from being expressed in the presence of tryptophan. This is achieved by having a repressor protein that will bind to the operator only in the presence of tryptophan.

Regulation in Eukaryotes

Transcription in eukaryotes is also regulated by the binding of proteins to specific DNA sequences, but with some differences from the simple schemes outlined above. For most eukaryotic genes, general transcription factors and RNA polymerase (i.e., the basal transcription complex) are necessary, but not sufficient, for high levels of transcription.

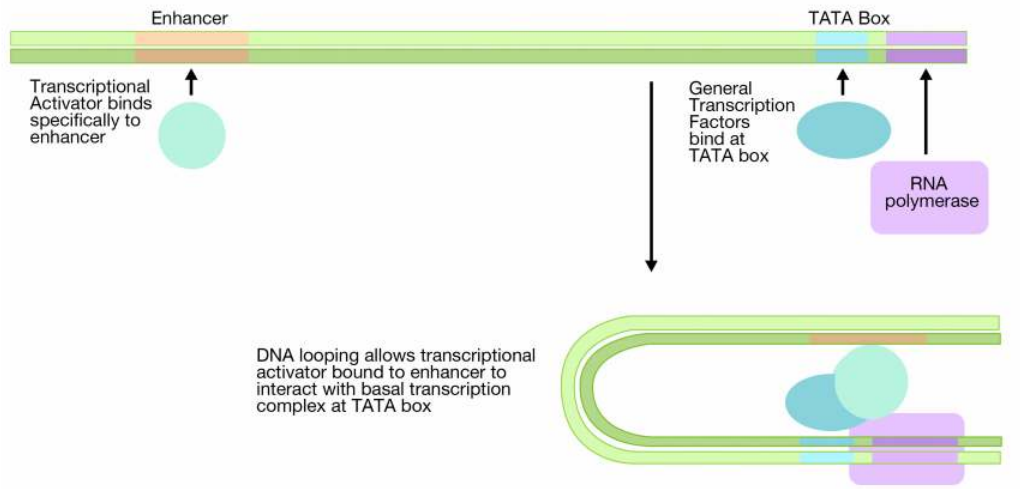


Figure 5.4.4: *Enhancer Mechanism*

In eukaryotes, additional regulatory sequences called enhancers and the proteins that bind to the enhancers are needed to achieve high levels of transcription. Enhancers are DNA sequences that regulate the transcription of genes. Unlike prokaryotic regulatory sequences, enhancers don't need to be next to the gene they control. Often they are many kilobases away on the DNA. As the name suggests, enhancers can enhance (increase) transcription of a particular gene.

How can a DNA sequence far from the gene being transcribed affect the level of its transcription?

Enhancers work by binding proteins (transcriptional activators) that can, in turn, interact with the proteins bound at the promoter. The enhancer region of the DNA, with its associated transcriptional activator(s) can come in contact with the basal transcription complex that is bound at a distant TATA box by looping of the DNA (previous page). This allows the protein bound at the enhancer to make contact with the proteins in the basal transcription complex.

One way that the transcriptional activator bound to the enhancer increases the transcription from a distant promoter is that it increases the frequency and efficiency with which the basal transcription complex is formed at the promoter.

Another mechanism by which proteins bound at the enhancer can affect transcription is by recruiting to the promoter other proteins that can modify the structure of the chromatin in that region. As we noted earlier, in eukaryotes, DNA is packaged with proteins to form chromatin. When the DNA is tightly associated with these proteins, it is difficult to access for transcription. So proteins that can make the DNA more accessible to the transcription machinery can also play a role in the extent to which transcription occurs.

In addition to enhancers, there are also negative regulatory sequences called silencers. Such regulatory sequences bind to transcriptional repressor proteins. Transcriptional activators and repressors are modular proteins- they have a part that binds DNA and a part that activates or represses transcription by interacting with the basal transcription complex.

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17.8.5: RNA Processing

So far, we have looked at the mechanism by which the information in genes (DNA) is transcribed into RNA. The newly made RNA, also known as the primary transcript (the product of transcription is known as a transcript) is further processed before it is functional. Both prokaryotes and eukaryotes process their ribosomal and transfer RNAs.

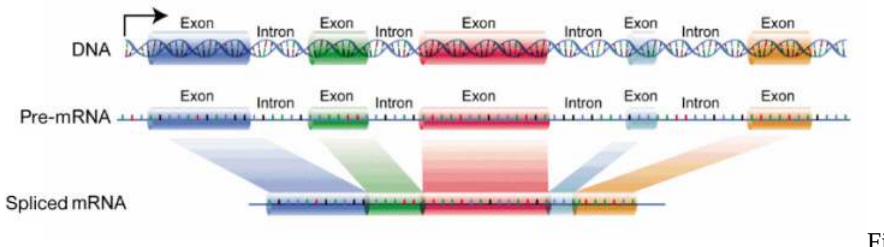


Figure 5.5.1: *RNA splicing*

The major difference in RNA processing, however, between prokaryotes and eukaryotes, is in the processing of messenger RNAs. We will focus on the processing of mRNAs in this discussion. You will recall that in bacterial cells, the mRNA is translated directly as it comes off the DNA template. In eukaryotic cells, RNA synthesis, which occurs in the nucleus, is separated from the protein synthesis machinery, which is in the cytoplasm. In addition, eukaryotic genes have introns, noncoding regions that interrupt the gene's coding sequence. The mRNA copied from genes containing introns will also therefore have regions that interrupt the information in the gene. These regions must be removed before the mRNA is sent out of the nucleus to be used to direct protein synthesis. The process of removing the introns and rejoining the coding sections or exons, of the mRNA, is called splicing. Once the mRNA has been capped, spliced and had a polyA tail added, it is sent from the nucleus into the cytoplasm for translation.

The initial product of transcription of a protein coding gene is called the pre-mRNA (or primary transcript). After it has been processed and is ready to be exported from the nucleus, it is called the mature mRNA or processed mRNA.

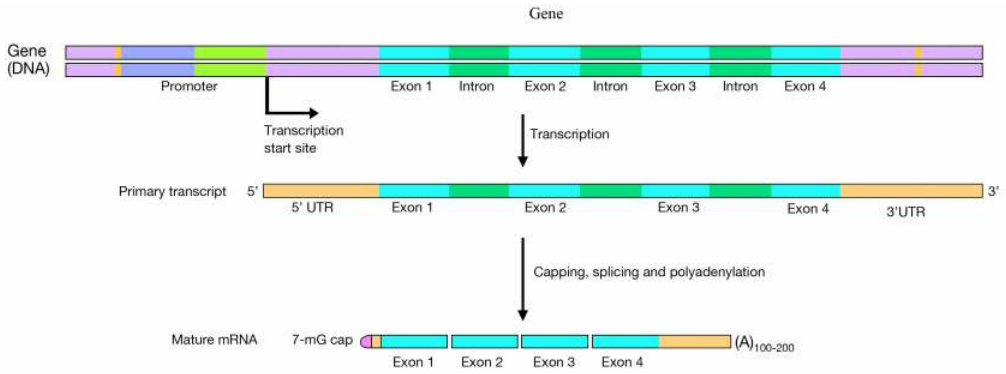


Figure 5.5.2: *Steps in processing eukaryotic messenger RNAs*

What are the processing steps for messenger RNAs?
In eukaryotic cells, pre-mRNAs undergo three main processing steps:

- Capping at the 5' end
- Addition of a polyA tail at the 3' end. and
- Splicing to remove introns

In the capping step of mRNA processing, a 7-methyl guanosine (shown at left) is added at the 5' end of the mRNA. The cap protects the 5' end of the mRNA from degradation by nucleases and also helps to position the mRNA correctly on the ribosomes during protein synthesis.

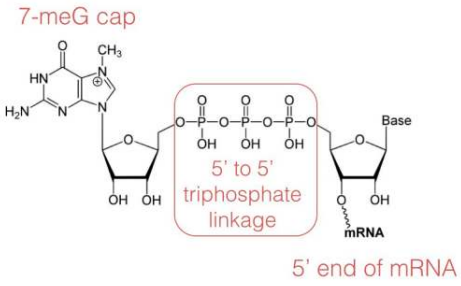


Figure 5.5.3: *mRNA capping structure*

The 3' end of a eukaryotic mRNA is first trimmed, then an enzyme called PolyA Polymerase adds a "tail" of about 200 ‘A’ nucleotides to the 3' end. There is evidence that the polyA tail plays a role in efficient translation of the mRNA, as well as in the stability of the mRNA. The cap and the polyA tail on an mRNA are also indications that the mRNA is complete (i.e., not defective). Introns are removed from the pre-mRNA by the activity of a complex called the spliceosome. The spliceosome is made up of proteins and small RNAs that are associated to form protein-RNA enzymes called small nuclear ribonucleoproteins or snRNPs (pronounced SNURPS). The splicing machinery must be able to recognize splice junctions (i.e., the end of each exon and the start of the next) in order to correctly cut out the introns and join the exons to make the mature, spliced mRNA.

What signals indicate where an intron starts and ends? The base sequence at the start (5' or left end, also called the donor site) of an intron is GU while the sequence at the 3' or right end (a.k.a. acceptor site) is AG. There is also a third important sequence within the intron, called a branch point, that is important for splicing.

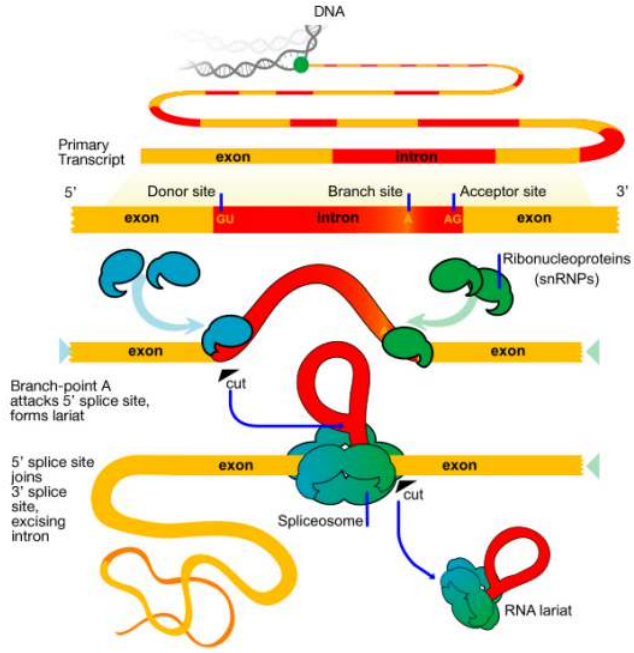


Figure 5.5.4: *Splicing*

There are two main steps in splicing:

- In the first step, the pre-mRNA is cut at the 5' splice site (the junction of the 5' exon and the intron). The 5' end of the intron then is joined to the branch point within the intron. This generates the lariat-shaped molecule characteristic of the splicing process
- In the second step, the 3' splice site is cut, and the two exons are joined together, and the intron is released.

Many pre-mRNAs have a large number of exons that can be spliced together in different combinations to generate different mature mRNAs. This is called alternative splicing, and allows the production of many different proteins using relatively few genes, since a single RNA can, by combining different exons during splicing, create many different protein coding messages. Because of alternative splicing, each gene in our DNA gives rise, on average, to three different proteins. Once protein coding messages have been processed by capping, splicing and addition of a poly A tail, they are transported out of the nucleus to be translated in the cytoplasm.

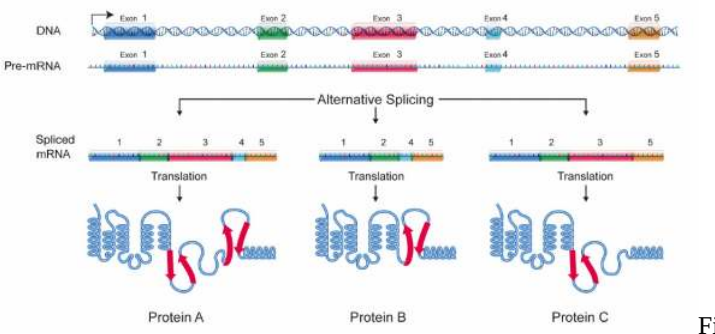


Figure 5.5.5: *Splicing and protein diversity*

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17.8.6: Translation

Translation is the process by which information in mRNAs is used to direct the synthesis of proteins. As you have learned in introductory biology, in eukaryotic cells, this process is carried out in the cytoplasm of the cell, by large RNA-protein machines called ribosomes. Ribosomes contain ribosomal RNAs (rRNAs) and proteins. The proteins and rRNAs are organized into two subunits, a large and a small. The large subunit has an enzymatic activity, known as a peptidyl transferase, that makes the peptide bonds that join amino acids to make a polypeptide. The small and large subunits assemble on the mRNA at its 5'end to initiate translation. Ribosomes function by binding to mRNAs and holding them in a way that allows the amino acids encoded by the RNA to be joined sequentially to form a polypeptide.

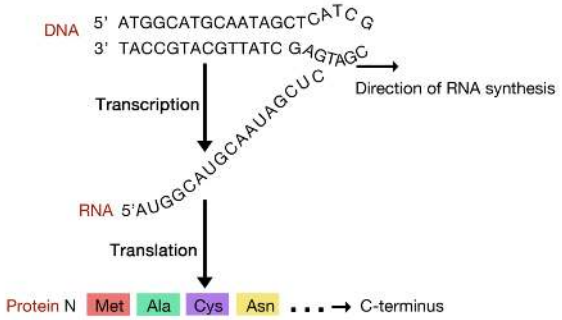


Figure 5.6.1: *Coupled transcription and translation in prokaryotes*

The sequence of an mRNA directly specifies the sequence of amino acids in the protein it encodes. Each amino acid in the protein is specified by a sequence of 3 bases called a codon in the mRNA. For example, the amino acid tryptophan is encoded by the sequence 5'UGG3' on an mRNA. Given that there are 4 bases in RNA, the number of different 3-base combinations that are possible is $\mathbf{4^3}$, or 64. There are, however, only 20 amino acids that are used in building proteins. This discrepancy in the number of possible codons and the actual number of amino acids they specify is explained by the fact that the same amino acid may be specified by more than one codon. In fact, with the exception of the amino acids methionine and tryptophan, all the other amino acids are encoded by multiple codons. The figure above shows the codons that are used for each of the twenty amino acids.

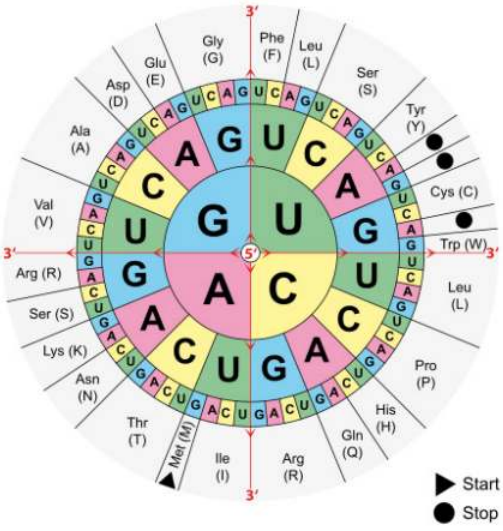


Figure 5.6.2: *The genetic code*

Three of the 64 codons are known as termination or *stop codons* and as their name suggests, indicate the end of a protein coding sequence. The codon for methionine, AUG, is used as the start, or initiation, codon.

This ingenious system is used to direct the assembly of a protein in the same way that you might string together colored beads in a particular order using instructions that used symbols like 111 for a red bead, followed by 222 for a green bead, 333 for yellow, and so on, till you came to 000, indicating that you should stop stringing beads.

While the ribosomes are literally the protein factories that join amino acids together using the instructions in mRNAs, another class of RNA molecules, the transfer RNAs (tRNAs) are also needed for translation. Transfer RNAs (see figure, left) are small RNA molecules, about 75-80 nucleotides long, that function to 'interpret' the instructions in the mRNA during protein synthesis. In terms of the bead analogy above, someone, or something, has to be able to bring a red bead in when the instructions indicate 111, and a green bead when the instructions say 222. Unlike a human, who can choose a red bead when 111 is present in the instructions, neither ribosomes nor tRNAs can think. The system, therefore, relies, like so many processes in cells, solely on molecular recognition.

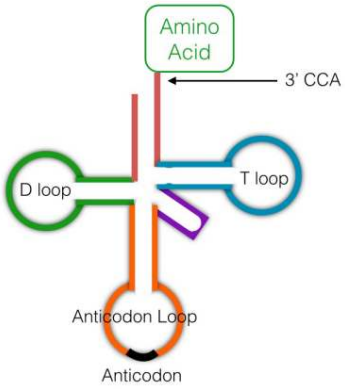


Figure 5.6.3: *tRNA structure*

A given transfer RNA is specific for a particular amino acid. It is linked covalently to this amino acid at its 3' end by an enzyme called aminoacyl tRNA synthetase. There is an aminoacyl tRNA synthetase specific for each amino acid. A tRNA with an amino acid attached to it is said to be charged. Another region of the tRNA has a sequence of 3 bases, the anticodon, that is complementary to the codon for the amino acid it is carrying. When the tRNA encounters the codon for its amino acid on the messenger RNA, the anticodon will base-pair with the codon, and the amino acid attached to it will be brought in to the ribosome to be added on to the growing protein chain.

With an idea of the various components necessary for translation we can now take a look at the process of protein synthesis. The main steps in the process are similar in prokaryotes and eukaryotes. As we already noted, ribosomes bind to mRNAs and facilitate the interaction between the codons in the mRNA and the anticodons on charged tRNAs.

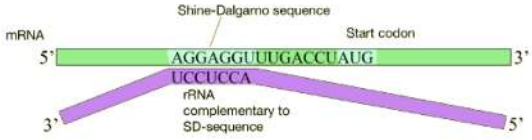


Figure 5.6.4: *mRNA alignment by Shine-Dalgamo sequence*

In bacterial cells, translation is coupled with transcription and begins even before the mRNA has been completely synthesized. How does the ribosome recognize and bind to the mRNA.

A variation of this process of ribosome assembly operates in eukaryotic cells. We already know that in eukaryotic cells, processed mRNAs are sent from the nucleus to the cytoplasm. The small and large subunits of ribosomes, each composed of characteristic rRNAs and proteins are found in the cytoplasm and assemble on mRNAs to form complete ribosomes that carry out translation.

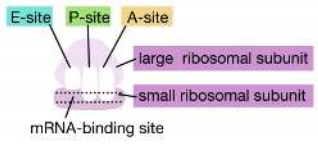


Figure 5.6.6: *A, P, and E sites of the ribosome*

Protein synthesis in eukaryotes starts with the binding of the small subunit of the ribosome to the 5' end of the mRNA. The assembly of the translation machinery begins with the binding of the small ribosomal subunit to the 7-methyl guanosine cap on the 5'end of an mRNA. Meanwhile, the initiator tRNA pairs with the start codon. (Recall that the start codon is AUG, and codes for

methionine. The initiator tRNA carries the amino acid methionine). The large subunit of the ribosome then joins the complex, which is now ready to start protein synthesis.

Ribosomes have two sites for binding charged tRNAs, each of which is positioned to make two adjacent codons on the mRNA available for binding by tRNAs. The initiation codon occupies the first of these ribosomal sites, the P-site. The anticodon complementary to this is on the initiator tRNA, which brings in the first amino acid of the protein. This initial phase of translation is called initiation and requires the help of protein factors called initiation factors.

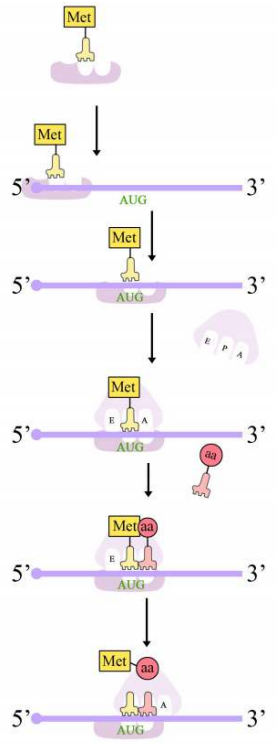


Figure 5.6.7: *Initiation of translation*

The second codon of the mRNA is positioned adjacent to the second site on the ribosome, the A site. This is where the tRNA carrying the amino acid specified by the second codon binds. The binding of aminoacyl tRNA to the A-site is mediated by proteins called elongation factors and requires the input of energy. Once the appropriate charged tRNAS have "docked" on the codons by base-pairing between the anticodon on the tRNA and the codon on the mRNA, the ribosome joins the amino acids carried by the two tRNAs by making a peptide bond (see figure at right).

Interestingly, the formation of the peptide bond is catalyzed by a catalytic RNA (the 23S rRNA in prokaryotes) rather than by a protein enzyme.

This and subsequent steps in the synthesis of the polypeptide are called the elongation phase of translation. Once the first two amino acids are linked , the first tRNA dissociates, and moves out of the P-site and into the E, or Exit site. The second tRNA then moves into the P-site, vacating the A-site for the tRNA corresponding to the next codon.

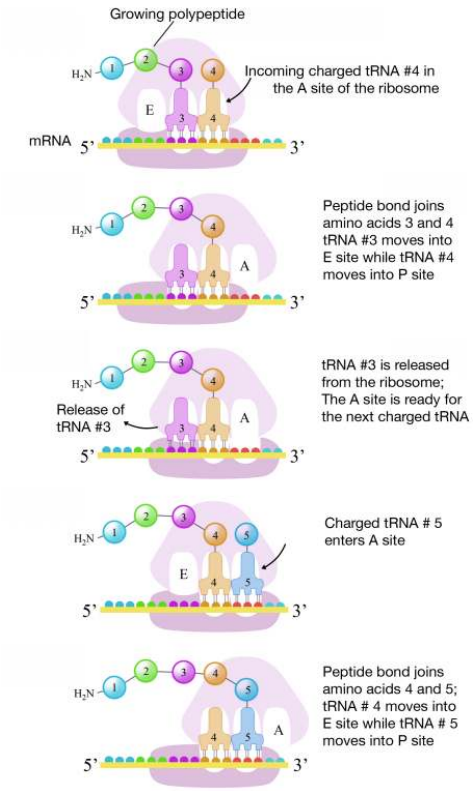


Figure 5.6.8: *Elongation of translation*

The process repeats till the stop codon is in the A-site. At this point, a release factor binds at the A-site, adds a water molecule to the polypeptide at the P-site, and releases the completed polypeptide from the ribosome, which itself, then dissociates into subunits.

As described in Chapter 3, polypeptides made in this way are then folded into their three dimensional shapes, post-translationally modified and delivered to the appropriate cellular compartments to carry out their functions.

Contributors

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17.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

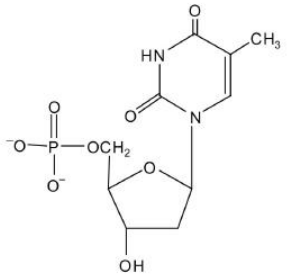
Answers

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

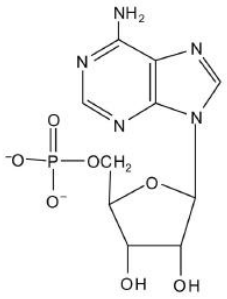
Exercises

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.

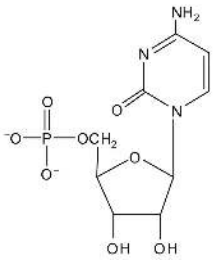
   a.

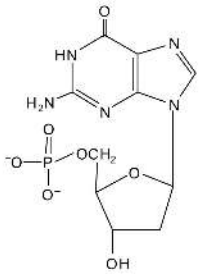


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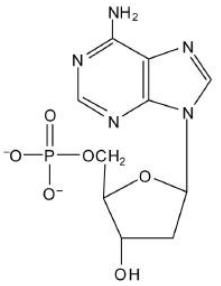
b. 

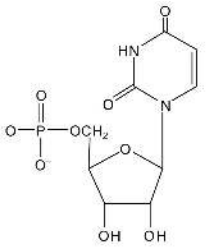
4. For each structure, circle the sugar unit and identify the nucleotide as a ribonucleotide or a deoxyribonucleotide.

a. 

b. 

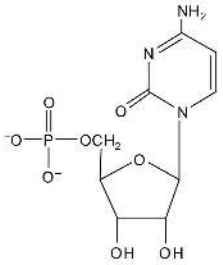
5. For each structure, circle the nitrogenous base and identify it as a purine or pyrimidine.

a. 

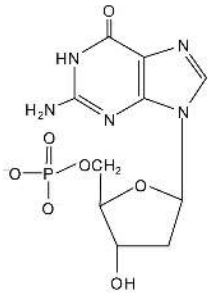
b. 

6. For each structure, circle the nitrogenous base and identify it as a purine or pyrimidine.

a.



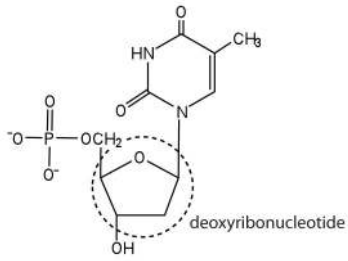
b.



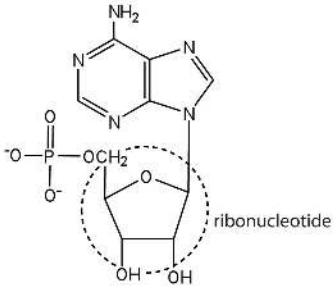
Answers

1. a. ribose
   b. deoxyribose

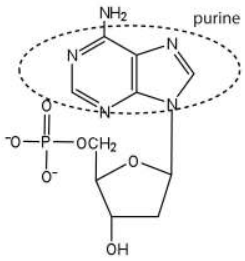
3. a.



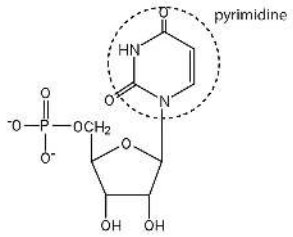
b.



a.



b.



19.2: Nucleic Acid Structure

Concept Review Exercises

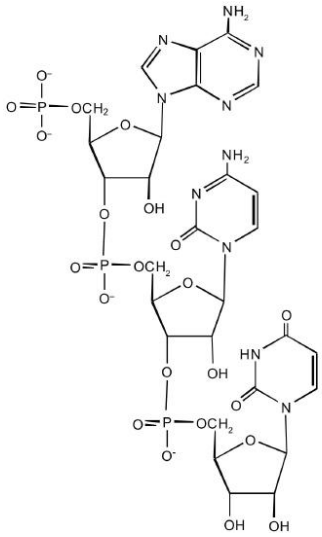
1. a. Name the two kinds of nucleic acids.
   b. Which type of nucleic acid stores genetic information in the cell?
2. What are complementary bases?
3. Why is it structurally important that a purine base always pair with a pyrimidine base in the DNA double helix?

Answers

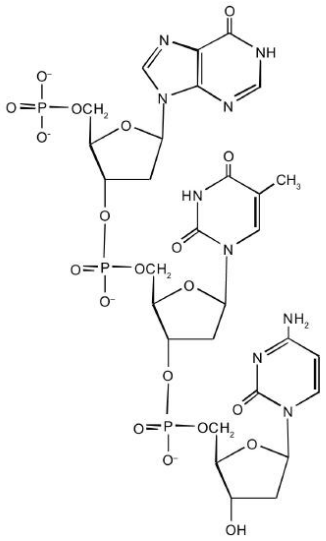
1. a. deoxyribonucleic acid (DNA) and ribonucleic acid (RNA)
   b. DNA
2. the specific base pairings in the DNA double helix in which guanine is paired with cytosine and adenine is paired with thymine
3. The width of the DNA double helix is kept at a constant width, rather than narrowing (if two pyrimidines 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.

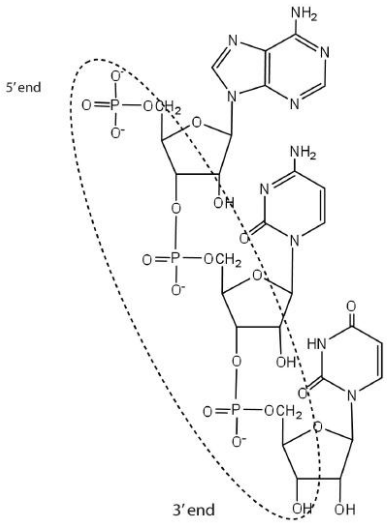


3. Which nitrogenous base in DNA pairs with each nitrogenous base?
    a. cytosine
    b. adenine
    c. guanine
    d. thymine
4. Which nitrogenous base in RNA pairs with each nitrogenous base?
    a. cytosine
    b. adenine
    c. guanine
    d. thymine
5. How many hydrogen bonds can form between the 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 **17.*E*.3** to identify the amino acids carried by each tRNA molecule in Exercise 1.
6. Use Figure **17.*E*.3** to identify the amino acids carried by each tRNA molecule in Exercise 2.
7. Use Figure **17.*E*.3** to determine the amino acid sequence produced from this mRNA sequence: 5′-AUGAGCGACUUUGCGGGAUUA-3′.
8. Use Figure **17.*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

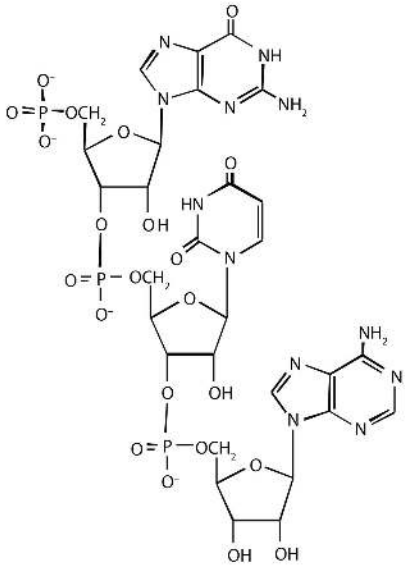
1. Describe the general structure of a virus.
2. How does a DNA virus differ from an RNA virus?
3. Why is HIV known as a retrovirus?
4. Describe how a DNA virus invades and destroys a cell.
5. a. Describe how an RNA virus invades and destroys a cell.
   b. How does this differ from a DNA virus?
6. What 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. -

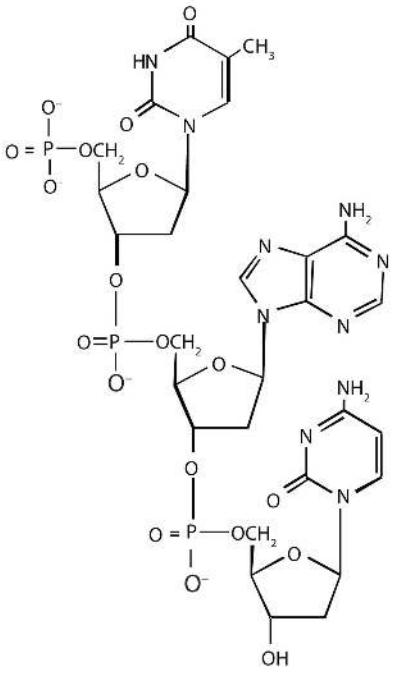
Additional Exercises

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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17.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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