Introduction to Biological Chemistry

Reza Karimi

CHAPTER 1

CHAPTER OUTLINE

1. Learn about the basic chemistry related to atoms and molecules. Understand the roles of orbitals and lone-pair electrons in a few common atoms (e.g., N, F, C, O) and comprehend nucleophilic/electrophilic attacks and their impact on oxidation, reduction, addition, and substitution reactions.
2. List and explain the importance of medicinal functional groups that commonly are found in drug molecules and appreciate the important roles that drug structures play in pharmaceutical sciences.
3. Understand basic concepts in acid–base theory and their roles in the structures of drug molecules.
4. Learn about salt formation, ionization, and water solubility of drug molecules, and explain the role of medicinal functional groups in ionization, salt formation, salt hydrolysis, and water solubility of drug molecules.
5. Implement a series of Learning Bridge assignments at your experiential sites to bridge your didactic learning with your experiential experiences.

OBJECTIVES

1. **Brønsted-Lowry acid–base:** definition used to express the acidic or basic properties of acids and bases.
2. **Buffer:** a mixture of an acid and its conjugate base in a solution that causes the solution to resist a pH change.
3. **Compound:** a combination of two or more substances, ingredients, or elements. While the majority of drugs on the market are compounds, not all compounds are drugs.
4. **Conjugate acid:** a base that has gained a proton.
5. **Conjugate base:** an acid that has lost its proton.
6. **Covalence:** the number of covalent bonds present.
7. **Covalent bonding:** bonding in which atoms in a molecule share electrons to fill their outermost shells.
8. **Electrolyte:** a compound that, when dissolved in a solvent (usually water), conducts electricity because it dissociates into ions (charged species).
9. **Electrophile:** an "electron-loving" species.
10. **Functional group:** a group of atoms attached to a molecule that plays an important role in the structure and function of that molecule.
11. **Henderson-Hasselbalch equation:** an equation that is useful when preparing buffer solutions in biochemistry and pharmaceutics. This equation also can be used to estimate the ionization of weakly acidic or basic drugs.
12. **IUPAC:** International Union of Pure and Applied Chemistry; the organization that oversees the rules and guidelines in regard to chemical nomenclature in chemical sciences and makes recommendations on how the nomenclature should be applied.

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13. **Lone-pair electrons:** pairs of electrons in the valence shell that are not involved in a bond.
14. **Noncovalent bonds:** weak interactions between ions, atoms, and molecules.
15. **Nucleophile:** a "nucleus-loving" species. Its electrons can be used to form a covalent bond with a positively charged molecule.
16. **Octet rule:** atoms have a tendency to lose, gain, or share electrons to reach the same number of electrons as the noble gases (i.e., they try to have eight electrons in their outermost valence shell).
17. **Orbital:** a region in space around the nucleus in which an electron is most likely to be found at any given time.
18. **Oxidation:** a chemical process in which an atom or a molecule loses one or two electrons.
19. **Physical properties:** characteristics of an atom or a molecule that are observed without any chemical change of the atom or molecule.
20. **Reduction:** a chemical process in which an atom or a molecule gains one or two electrons.
21. **Salt hydrolysis:** the reaction of the ions of a salt with water.
22. **Shell:** the grouping of electrons with similar energy into an energy level.
23. **Titration:** an analytical procedure in which a solution (often a base) with known volume and known concentration is added to another solution (an acid) with known volume but unknown concentration. The goal often is to calculate the unknown concentration.
24. **Valence electrons:** the electrons in the outermost shell that determine the chemical properties of the elements.

Introduction

"Introduction to biological chemistry" is an integrated topic that combines the organic chemistry of atoms and molecules with the biological roles that molecules play in our everyday lives. Understanding the science of chemistry begins with atoms, whereas understanding the science of biology begins with molecules. By definition, the smallest object that has a chemical identity is an atom (an element is an atom that has a known atomic number and specific placement in the periodic table). In the essential paths where atoms become molecules and where molecules display their biological and physiological characteristics, the roles of biological chemistry become perceptible. For this reason, it is important not only to appreciate the nature and characteristics of atoms, but also to understand how molecules are built and how the bonds that maintain the integrity of molecules are formed.

Medicinal functional groups are the cornerstone of biological chemistry. Pharmacy students need to fully understand the scope of medicinal functional groups and the key roles they play in pharmaceutical sciences. An understanding of medicinal functional groups is the first instrumental step in comprehending the pharmaceutical topics that will be discussed in this book. The role of medicinal functional groups in pharmacy education remains critical. Indeed, it is these medicinal functional groups that can assist pharmacy students in appreciating the roles that acids and bases play in ionization, salt formation, salt hydrolysis, and water solubility of drug molecules. Similarly, it is the medicinal functional groups that can assist students in predicting which biological role a compound might play. Therefore, learning medicinal functional groups assists students in building a strong foundation to comprehend absorption, distribution, metabolism, and elimination of drug molecules.

This chapter seeks to apply the science of organic chemistry to biological chemistry by addressing important and relevant points without overwhelming students with chemical reactions or detailed biological pathways.

Backbones of Molecules

Chemistry

Chemistry is a science that describes how atoms and molecules react with each other to produce new molecules with unique properties that are different from those of their parent atoms or molecules. While the atoms may be rearranged and redistributed to form new molecules, the chemical nature of the atoms remains the same. For instance, one molecule of acetic acid can be mixed with one molecule of salicylic acid to form acetylsalicylic acid (aspirin). The nature of the oxygen, carbon, and hydrogen atoms remains the same, but the new molecule (aspirin) has different physical and chemical properties than either acetic acid or salicylic acid (**Figure 1.1**).

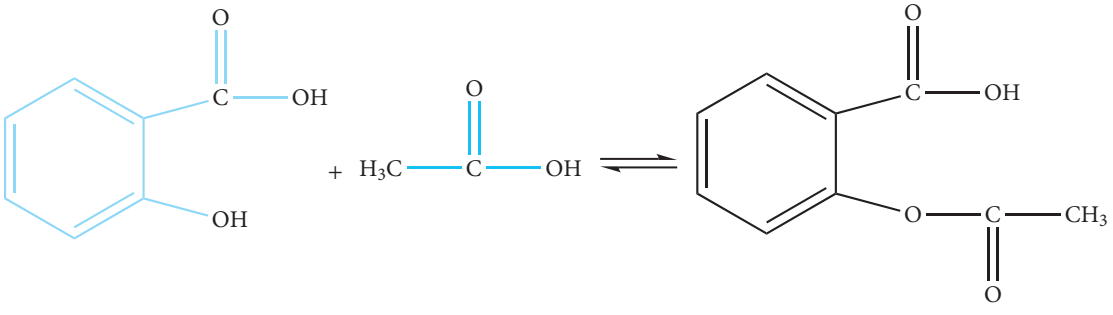
Physical and Chemical Properties

Physical properties refer to when an atom or a molecule is observed without any chemical change of the substance. For instance, boiling point, melting point, color, and odor are physical properties. Practical examples are when aspirin melts at 143 °C, acetic acid melts at 16.5 °C, and salicylic acid melts at 158 °C. On the other hand, chemical properties are characteristics of an atom or a molecule that can be observed by chemical change of the atom or molecule. For example, the fact that aspirin undergoes hydrolysis is a chemical property that aspirin has.

Compound and Element

Any pure material that can be broken down into simpler substances by a chemical means (but not by a physical means) is a compound. For example, acetylsalicylic acid is a compound that upon hydrolysis (chemical means) is broken into acetic acid and salicylic acid (see the reverse reaction in Figure 1.1). In contrast, a pure substance that cannot be broken down chemically into simpler substances is an element, like Na, C, N, or O.

An atom is the smallest particle of an element that can exist and still retain the chemical properties of that element. An atom consists of (1) electrons (negative electrical charges), found outside the nucleus, and (2) a nucleus that comprises protons (positive electrical charges) and neutrons (no electrical charge) (**Figure 1.2**).



Salicyclic acid Acetic acid Acetylsalicylic acid

Figure 1.1 Acetic acid (reactant) in a reaction with another reactant, salicylic acid, forms acetylsalicylic acid (product), which has different chemical and physical properties than the two reactants.

The Periodic Table

The order of elements in the periodic table is based on atomic number, which is the same as the number of protons. For instance, while carbon (C) has atomic number 6 (and 6 protons), nitrogen (N) has atomic number 7 (and 7 protons). Given that the numbers of electrons and protons are the same for each element, C has 6 electrons and N has 7 electrons. The periodic table (**Figure 1.3**) can be divided into four sections:

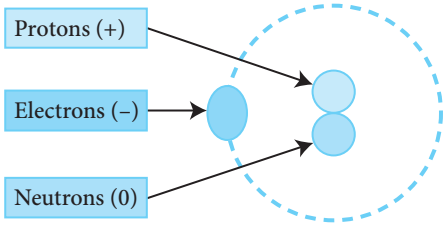


Figure 1.2 An atom with its constituents.

1. Metals: Elements (e.g., Fe, Mg, Ni) are shiny and can conduct electricity.
2. Nonmetals: Nonmetal elements (e.g., C, N, O) have a tendency to gain electrons and become negative ions. They are not shiny and cannot conduct electricity.
3. Metalloids: Metalloids or semimetals (e.g., As, B, Si) have both metallic and nonmetallic properties.
4. Noble gases: Noble gases (e.g., Ne, He, Rn) have a tendency not to combine with any other atoms. As will be discussed later, these elements have a complete set of valence electrons (see octet rule discussed later in this chapter).

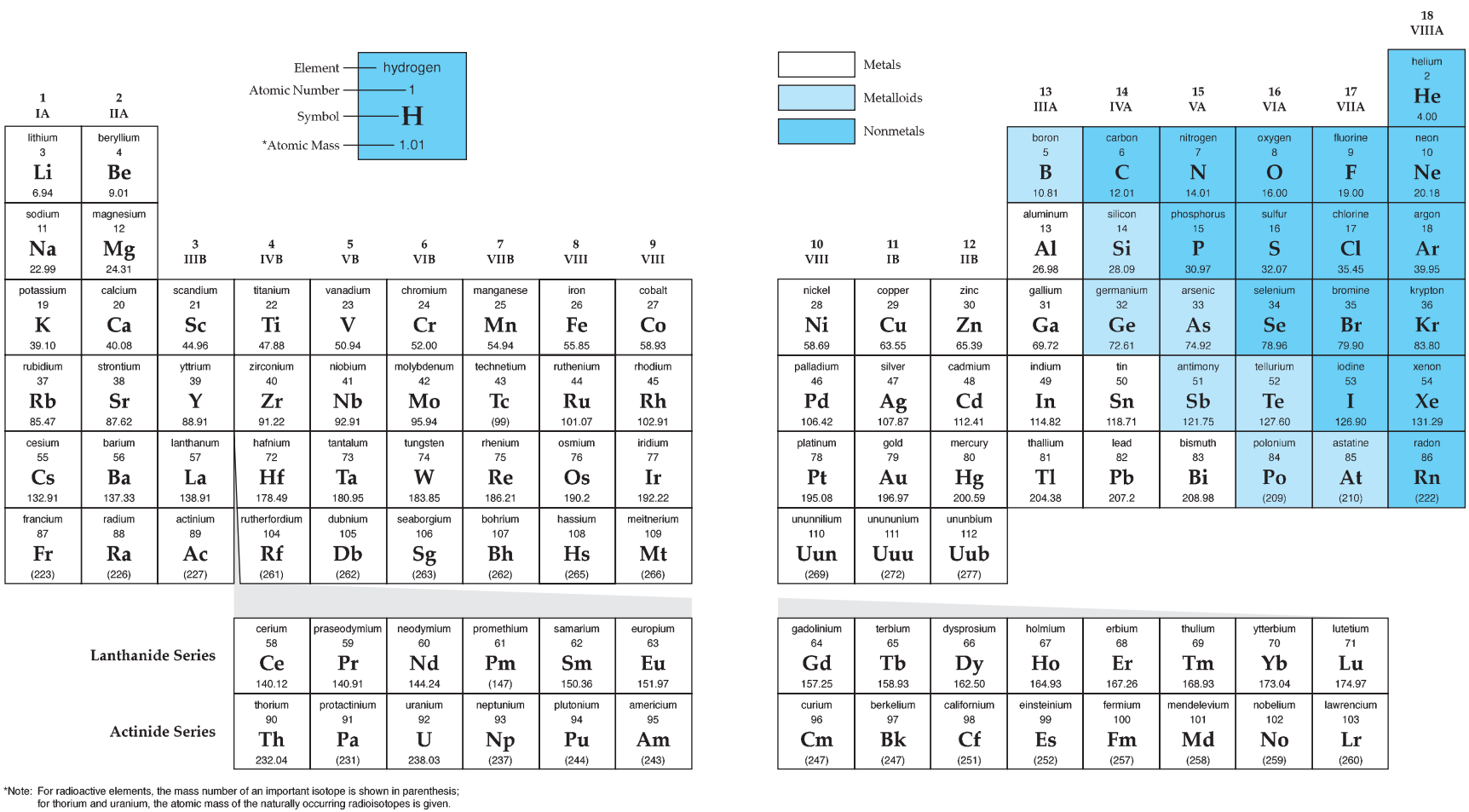
Horizontal direction across the periodic table indicates elements with the same valence shells; that is, all of these elements have their valence electrons in the same energy level. For instance, K and Ca have their valence electrons in the same energy level (in this case, in the fourth shell). Vertical direction down the periodic table indicates elements with the same number of electrons in their valence shells. For instance, F and Cl have the same number of electrons in their valence shells.

The atomic number is equal to the number of protons in the nucleus of an atom. Since an atom is electrically neutral, it indicates that the number of protons and electrons must be equal in an atom (so that + and – charges cancel each other and give no net charge). With this definition, one important piece of information comes into view: The atomic number also represents the number of electrons. For instance, the atomic number for carbon is 6 (see the periodic table in Figure 1.3), which means it has 6 protons and 6 electrons. Neutrons have no electrical charges, so their number in an atom is not necessarily the same as the number of protons or electrons. Except for hydrogen atoms, all atoms have protons and neutrons in their nuclei.

The elements in the periodic table are organized into periods and groups. Specifically, there are 7 horizontal rows (periods) and 18 vertical columns (groups). The elements in each group have similar chemical properties. For instance, carbon (C) and silicon (Si) have the same chemical properties.

Electronegativity

The electronegativity concept measures the ability of an atom to attract electrons in a chemical bond. Elements with high electronegativity (such as nonmetals) have a greater ability to attract electrons than elements with low electronegativity (such as metals). The most electronegative elements are found on the upper-right panel of the periodic table (N, O, F, and Cl); they readily accept electrons to become anions. The least electronegative elements are placed on the lower-left panel of the periodic table (Na, K, Rb, Cs, Ba, Fr, and Ra); they readily donate electrons to become cations. A compound such as sodium chloride (NaCl) is formed between electropositive Na and electronegative Cl. Keep in mind that the metals (e.g., Fe, Mg, Ni) are electropositive elements, whereas the nonmetals (e.g., C, N, O) are electronegative elements. The metalloids (e.g., As, B, Si) have intermediate electronegativities. As a rule of thumb, electronegativity increases as you go horizontally from left to right across the periodic table and decreases as you go vertically down the periodic table.



*Note: For radioactive elements, the mass number of an important isotope is shown in parenthesis; for thorium and uranium, the atomic mass of the naturally occurring radioisotopes is given.

Figure 1.3 Elements of the periodic table with their symbols and atomic number and weight.

What happens if the atoms in a molecule have the same electronegativity? This is the case when two atoms of the same element combine (as in H_2 or Cl_2). Because both Cl atoms have the same electronegativity, both have the same ability to attract the bonding pair of electrons. Electronegativity plays an important role in determining whether a bond is covalent, polar, or ionic (see the discussion of chemical bonds later in this chapter).

The Chemistry of Carbon

The chemistry of carbon compounds is called organic chemistry, and the element carbon is the cornerstone of organic chemistry. The interesting question you might ask is why only carbon, out of the 118 known elements, is the heart of organic chemistry? The answer is simple. If you look at the periodic table, you will find carbon in group 4A (or IVA) (whose members have four valence electrons). In addition, due to its ability to form four hybrid orbitals (see the next section), the carbon atom has the ability to form four strong covalent bonds. Carbon atoms can also react with each other to form long chains of molecules, a phenomenon that is critical in building macromolecules, such as fatty acids, carbohydrates, and nucleic acids (discussed later in this book). Other elements with four valence electrons (e.g., silicon) did not evolve to form macromolecules such as DNA or proteins for the following reasons:

1. Si is larger than the carbon atom and has a lower electronegativity than carbon.
2. When Si reacts with four hydrogen atoms, it forms a silane molecule (SiH_4) that is similar to methane (CH_4). Silane, however, is a very reactive molecule—upon reacting with oxygen (from the air), it explodes immediately. In contrast, methane is a gas that does not explode when it reacts with oxygen.
3. During the oxidation of carbohydrates, the human body produces carbon dioxide (CO_2), a molecule that is readily removed from the lungs by exhalation. When Si is oxidized, it becomes a solid—SiO_2 (silica)—which obviously makes it difficult to exhale from the lungs.
4. Silicon-based molecules are unstable. For example, the largest silicon molecule that has been observed by scientists has only six silicon atoms. This short-length molecule could not contribute to or support the structure of DNA and proteins that have long chains of carbons.

Let's go through some basic concepts in organic chemistry that you will encounter many times throughout this chapter (and even this book):

1. Hybrid orbitals
2. Oxidation–reduction reactions
3. Nucleophiles and electrophiles
4. Chemical bonds
5. Resonance structures

Hybrid Orbitals

Electrons that have similar energy are clustered in an energy level called a shell. The maximum number of electrons in each shell is indicated by the formula $2n^2$, where n is the number of the energy level. For instance, the maximum number of electrons in shell 2 will be 8 and the maximum number in shell 3 will be 18 (**Figure 1.4**).

An orbital is a region in a space around the nucleus where an electron is most likely to be found at any given time. Each orbital can hold a maximum of two electrons with opposite spins. In each shell, there are different types of orbitals (except in shell 1). In shell 1, there is one orbital called *s*; in shell 2, there are one *s* orbital and three *p* orbitals; and so on (**Table 1.1**).

Table 1.1 The Number of Orbitals in an Atom

Shell Number	1	2	3	4
Orbital's name	*s*	*s, p*	*s, p, d*	*s, p, d, f*
Number of orbitals	1	1, 3	1, 3, 5	1, 3, 5, 7

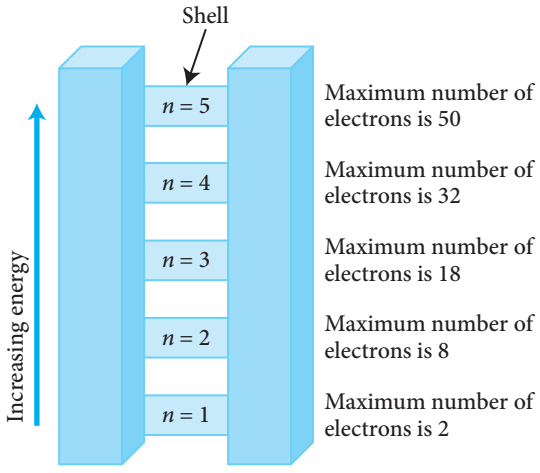


Figure 1.4 The capacity of different energy levels (shells) that can be occupied by electrons.

Adapted from Timberlake KC. Organic and biological chemistry: structures of life. San Francisco: Benjamin Cummings; 2001.

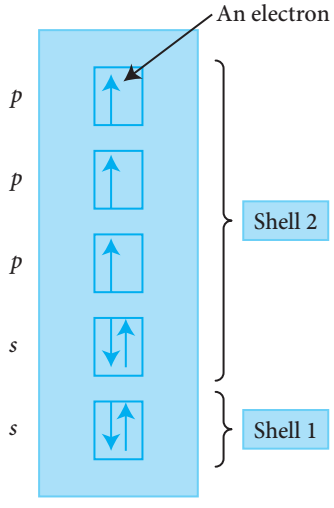


Figure 1.5 Distribution of electrons among the shells in an orbital diagram for a nitrogen atom.

The distribution of electrons among the shells in an orbital diagram (**Figure 1.5**) follows a logic pattern. For example, nitrogen (N) atom has seven electrons (see the arrows in the boxes). The electrons must occupy the lowest-energy orbital available first (in Figure 1.5, *s* in shell 1) before they move over to the next lowest-energy orbital (*s* and *p* in shell 2). Here, electrons fill the *p* orbital one at a time before any *p* orbital is completely filled. There is, however, an exception to this rule (see the discussion of hybrid orbitals).

The electrons in the outermost shell determine the chemical properties of the element. These influential electrons, called valence electrons, are located in the valence shell, which is the outermost energy level of an atom. Valence electrons are found in either *s* or *p* orbitals, or both. The maximum number of electrons in a valence shell is eight. Nitrogen has five valence electrons, whereas fluorine has seven (**Figure 1.6**).

Octet Rule

The octet rule applies when atoms have a tendency to lose, gain, or share electrons to reach the same number of electrons as the noble gases (i.e., they try to have eight electrons in their outermost valence shell). This tendency or rule is applied by an atom as it attempts to become more stable. For instance, an atom with seven electrons (such as fluorine) in its outermost shell would become more stable if it captured another electron.

One of the factors that influences the strength of chemical bonds is the distance of a bond's electrons from each nucleus. **Figure 1.7** demonstrates how the nucleus of chlorine is farther away from the bond pair with a hydrogen atom (compare it with the nucleus of fluorine). The comparison between these two molecules, HF and HCl, indicates that the hydrogen atom is more attracted to the F atom than to the Cl atom.

Hybridized Orbitals and the Lone-Pair Electrons

The topic "hybrid orbitals" is an important concept for understanding many chemical functions and reactions that you will encounter in this chapter. For instance, many enzymes catalyze reactions through nucleophilic or electrophilic attacks. In addition, many drugs are prone to

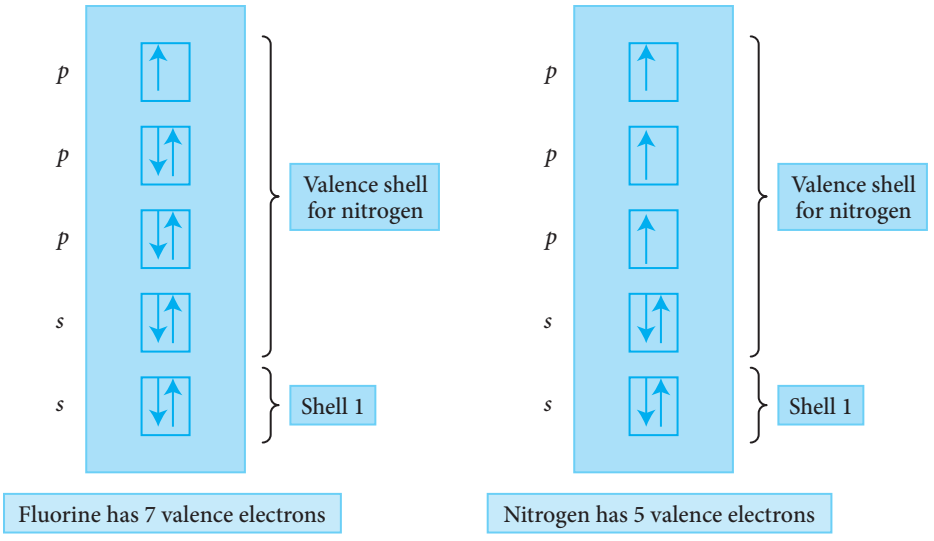


Figure 1.6 Two typical atoms (F and N) and the distribution of their valence electrons.

hydrolysis or metabolism—chemical reactions that are affected by an electrophilic or nucleophilic attack. Furthermore, the way acids and bases accept or donate electrons is related to their existence as electrophiles or nucleophiles. The hybrid orbitals clarify why this behavior occurs: Carbon does not have lone-pair electrons, for example, but nitrogen or oxygen atoms do. The instrumental roles that these lone-pair electrons play in drug action and metabolism are discussed in this chapter.

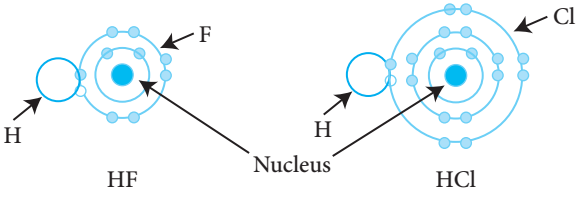


Figure 1.7 The distance between a bond's electrons and the F or Cl nucleus.

Hybrid Orbitals

Hybrid orbitals form when atomic orbitals in an atom mix together to enhance its bonding to other atoms. Of particular interest for us here are C, N, and O atoms. Let's return to the carbon atom to explore this concept.

The *s* and *p* orbitals of carbon's second shell (i.e., the valence shell) have very similar energies. As a result, carbon can adapt (hybridize) these orbitals to form the maximum number of chemical bonds. In carbon's hybrid orbitals, a new set of atomic orbitals is constructed so that carbon has four half-filled valence electrons. This makes carbon capable of sharing its electrons with four other atoms. Carbon can enter any of three hybridized atomic states—sp^3, sp^2, and *sp*—to bind to other elements. **Figure 1.8** illustrates the electron distributions for carbon in its three hybridized atomic states. Of particular interest is the valence electron distribution in the sp^3 hybridized atomic state (the framed boxes represent orbital diagrams for valence electrons).

Single Bond

Analysis of the methane molecule in its sp^3 hybridized state shows how the orbital diagram, which identifies the valence electrons, is filled with four hydrogen electrons (see the light teal arrows in **Figure 1.9**) when carbon atom is bound to four hydrogen atoms to form methane. As Figure 1.9 indicates, the sp^3 orbitals of methane represent a mixture of one 2*s* orbital with three 2*p* orbitals. The bonds between the carbon and hydrogen are called σ (sigma) bonds. All four bonds are equal in regard to strength, bond length, and bond angle.

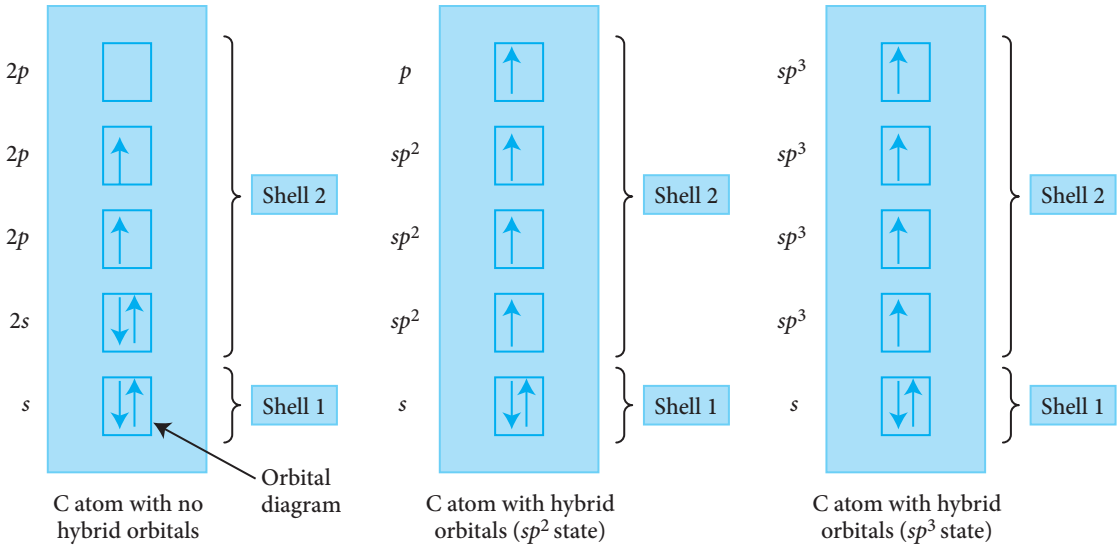


Figure 1.8 Carbon's three hybridized atomic states. Each hybridized state is associated with a unique orbital diagram for the valence electrons.

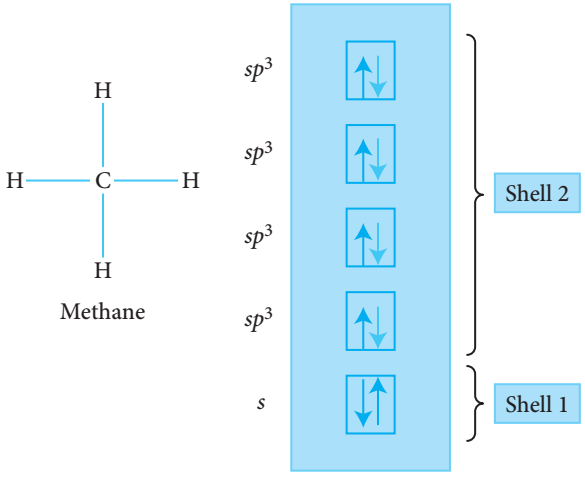


Figure 1.9 The sp^3 orbitals of methane. The orbital diagrams possess valence electrons from both carbon and hydrogen atoms.

Double Bond

In a double bond (for instance, in an ethylene molecule), sp^2 orbitals are present. In carbon, one *s* orbital is mixed with two *p* orbitals to form three sp^2 orbitals in the second shell. Two of the sp^2 orbitals, containing one electron each, form a sigma (σ) bond with other carbon atoms (or hydrogen atoms). The third sp^2 also forms a sigma bond with another carbon (for instance, in an ethylene molecule). The last *p* orbital forms a pi (π) bond with another carbon to form a double bond (**Figure 1.10**).

The electrons in the π bond are not located along an axis between the two carbon atoms, but rather are shared above and below (like a cloud) the sigma bond. Because the electrons in the π bond are above and below the bond, they are more readily donated (**Figure 1.11**).

Ethene (or ethylene) is the simplest alkene molecule. If you place a ripe banana among green tomatoes, you will notice that the green tomatoes undergo the ripening process more rapidly. The reason is that the ripe banana produces ethene, which serves as a plant growth substance. Commercial application of ethene allows many producers to sell fresh fruits. Farmers pick the fruits while they are not mature and ship them to other cities without being worried about the ripening process under the delivery time frame. When the fruits reach their destination, they can be exposed to ethene gas to ripen the fruits.

Triple Bond

In a triple bond (for instance, in an acetylene molecule), the *s* orbital is mixed with one *p* orbital to form two *sp* orbitals in the second shell. The two *sp* orbitals, which contain one electron each,

form a σ bond with a carbon atom and another σ bond with a hydrogen atom. The third and fourth orbitals (*p* orbitals; **Figure 1.12**) form two π bonds with another carbon to create a triple bond. The electrons in the π bonds are not located along an axis between the two carbon atoms, but rather are shared above and below the sigma bond.

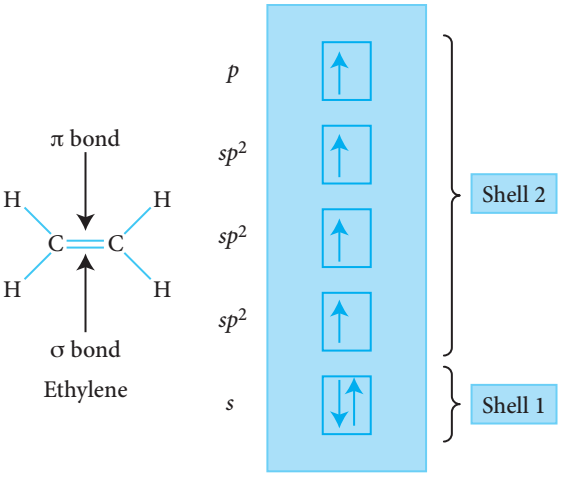


Figure 1.10 Mixing one *s* orbital with two *p* orbitals in the second shell of a carbon atom generates an sp^2 hybridization state.

Use of *s* and *p* Orbitals

When bonds are formed, energy is released and the molecule becomes more stable. For example, two times more energy will be released if carbon binds with four hydrogen atoms than if it binds with two hydrogens (i.e., if it forms CH_4 instead of CH_2). This is one reason carbon atoms try to enter a hybridized state—to form four bonds instead of two bonds, thereby becoming more stable. The new hybrid orbitals are neither *s* nor *p* orbitals, but rather a mixture of the two (hybrid orbitals). The bonds that result from the hybrid orbitals are stronger than the bonds from either *s* or *p* orbitals. Simply put, hybridization provides a means to mix atomic orbitals of slightly different energies to form new orbitals with equal energies. Keep in mind that hybridization occurs within one shell (because of the minimal energy variations among that shell) as opposed to between two shells (because of the large energy variation between shells).

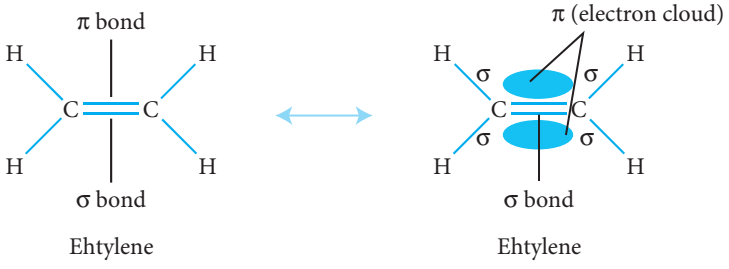


Figure 1.11 Electron cloud in the π bond of an ethylene molecule.

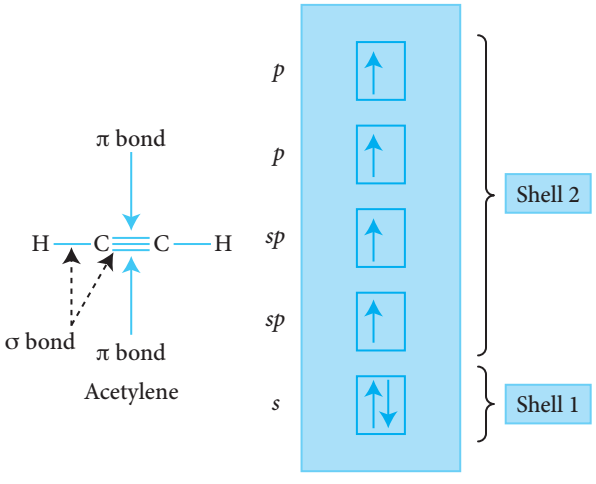


Figure 1.12 Triple bonding and orbital diagrams for an acetylene molecule.

Atoms that bind with just a σ bond (single bond) can rotate about the bond, whereas atoms that bind with a π bond cannot do so unless the π bond is broken. Therefore, a molecule with a double or triple bond is more rigid than a molecule with just a single bond. In addition, multiple bonds result in shorter and shorter bonds; that is, a triple bond is shorter than a double bond, which in turn is shorter than a single bond.

Hybridized States for Nitrogen and Oxygen

The sp^3 hybridized state also applies to nitrogen (N) and oxygen (O). Let's look at nitrogen first. Nitrogen is in group 5A (or VA, see the periodic table in Figure 1.3, which means it has five valence electrons. The electron configuration for nitrogen is shown in **Figure 1.13A**. Nitrogen, like oxygen, tries to adapt to a hybridized state.

Orbital hybridization for nitrogen gives four hybrid orbitals (**Figure 1.13B**). One sp^3 orbital is filled (two electrons) and, therefore, cannot be shared by another element (because it has already the maximum number of electrons that an orbital can have). These two nonbonding electrons are called lone-pair electrons and are not involved in covalent bond formation. (Lone-pair electrons are also called nonbonding electrons and unshared electrons.) The other three sp^3 hybrid orbitals (see the orbital diagrams in Figure 1.13B), each of which has one electron, can be shared with three hydrogen atoms to form ammonia (**Figure 1.14**). Remember, a hybrid orbital can hold only up to two electrons, exactly like a normal orbital. The lone-pair electrons in ammonia are available to be donated to an electron-deficient atom (like H^+). This is why ammonia has basic properties (we will return to basic properties in another section of this chapter).

Note when the lone-pair electrons are shown as dots around an atom, the model of that atom or molecule is called *Lewis structure.* The ammonia structure shown in Figure 1.14 is a typical Lewis structure.

You might ask why nitrogen's orbitals undergo hybridization when the distribution of electrons in Figure 1.13A is exactly the same as that in Figure 1.13B. Actually, there is a slight energy difference between *s* and *p* orbitals, even within the same shell. Nitrogen, by forming hybrid orbitals, will have four hybridized orbitals (sp^3) with exactly the same amount of energy and strength in each of them.

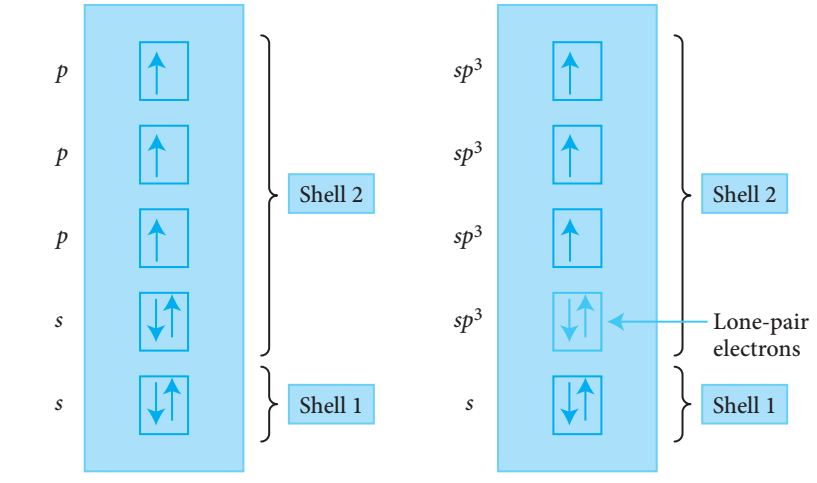


Figure 1.13 (A) Nitrogen atom in an isolated form (i.e., without a hybridized state). (B) Nitrogen atom with hybrid orbitals. The lone-pair electrons in the first orbital diagram (sp^3) do not form a covalent bond with other elements, but the electrons in other sp^3 orbitals have the capability to be shared with three other elements.

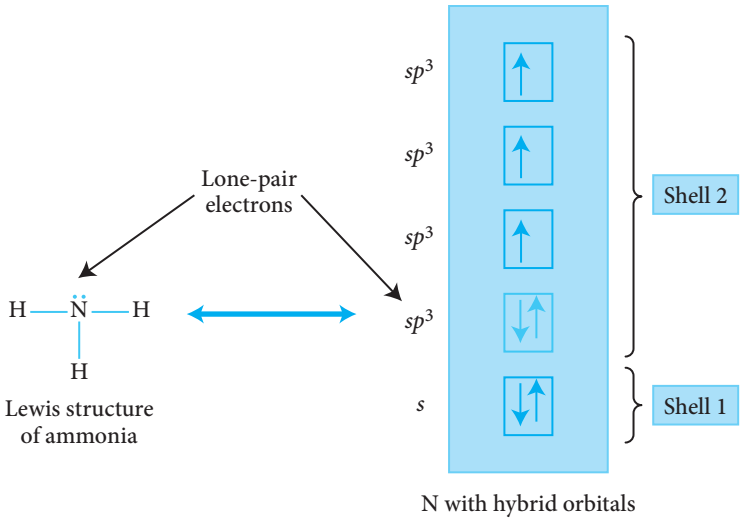


Figure 1.14 The Lewis structure of ammonia with lone-pair electrons and the hybrid atomic orbitals in ammonia.

Oxidation and Reduction Reactions

Oxidation means a loss of electrons; reduction means a gain of electrons. Free electrons are unstable (do not occur), so whenever an electron is released by an oxidation of a molecule, that electron must be accepted in a reduction reaction by another molecule (**Figure 1.15**).

If a carbon atom from an organic compound forms a bond to a more electronegative atom (e.g., to oxygen), the carbon will be oxidized. This occurs because the electrons in the carbon–oxygen bond are drawn ("lost") toward oxygen (recall the electronegativity of oxygen and carbon). Conversely, if the same carbon is bound to hydrogen ("gained"), the carbon atom is reduced.

In the cells of the body, oxidation of organic (carbon) compounds involves the transfer of hydrogen atoms (H), each of which is composed of an electron and a proton. In biochemical reactions, in addition to loss or gain of electrons, a loss of hydrogen may be described as oxidation and a gain of hydrogen as reduction (**Figure 1.16**). More information about biological oxidation–reduction reactions is provided in the *Introduction to Biochemistry* chapter.

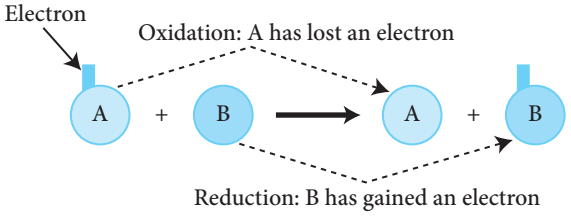


Figure 1.15 In an oxidation reaction, molecule A loses its electron to molecule B, which results in A being oxidized and B being reduced.

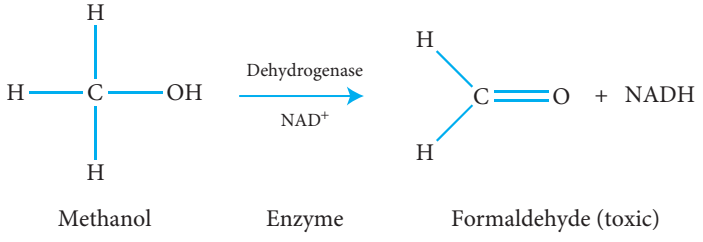


Figure 1.16 The alcohol dehydrogenase enzyme catalyzes the oxidation reaction by transferring two hydrogen atoms from methanol to NAD^+ and the surrounding media.

Important Facts About Alcohols

Alcohols are readily available in many countries and are the most widely encountered poisons in the developed countries. The four alcohols most commonly noted in poisonings are methanol, ethanol, isopropanol, and ethylene glycol. Let's see why these alcohols can be poisonous.

Methanol (CH_3—OH)

Methanol is a clear, colorless liquid that is found in cleaning materials, paints, antifreeze, and windshield washer fluid. It is a toxic solution (causes central nervous system [CNS] depression, blindness, and death) in small amounts of as little as a single mouthful. Methanol forms toxic substances such as formaldehyde and formic acid (see also Figure 1.16). The cause of poisoning is often accidental ingestion due to confusion of this substance with ethanol.

Ethanol (CH_3—CH_2—OH)

Ethanol is a colorless liquid found in many products, ranging from mouthwashes to over-the-counter (OTC) medications to alcoholic beverages. Ethanol is toxic when it is used in high doses. This alcohol is readily absorbed by the stomach and small intestine. Upon digestion, ethanol is oxidized to acetaldehyde by the alcohol dehydrogenase enzyme in hepatocytes, and then further oxidized to acetic acid, which finally is converted to CO_2 and water. This acetaldehyde is believed to give an individual the well-known headache and vomiting symptoms after alcohol consumption. The following reaction shows the metabolism of alcohol by the alcohol dehydrogenase enzyme and aldehyde dehydrogenase enzymes that are found largely in the liver and to some extent in the stomach and brain:

CH_3—CH_2—OH (ethanol) → CH_3—CHO (acetaldehyde) → CH_3—COOH (acetic acid) → CO_2 and H_2O

While the alcohol dehydrogenase enzyme catalyzes formation of acetaldehyde, the aldehyde dehydrogenase enzyme catalyzes formation of acetate (acetic acid). Due to genetic variations among individuals for expression of the alcohol dehydrogenase enzyme, different individuals may be influenced by different amounts of alcohol consumption. For instance, it has been suggested that women have less of gastric alcohol dehydrogenase than men do. This reduced amount of the alcohol dehydrogenase enzyme results in a longer duration of alcohol in the body, which in turn causes more intoxication among women than among men.

Certain agents can inhibit the alcohol metabolism reaction. For instance, fomepizole (Antizol) is known to inhibit alcohol dehydrogenase, which would otherwise catalyze the metabolism of ethanol, ethylene glycol, and methanol. Consequently, fomepizole is indicated in the treatment of methanol or ethylene glycol poisoning. In contrast, disulfiram (Antabuse), which inhibits the aldehyde dehydrogenase enzyme, is indicated for the treatment of chronic alcoholism. The oral dose is 500 mg/day for 1 to 2 weeks, and this agent should not be taken if ethanol has been consumed within the last 12 hours. Disulfiram prevents oxidation of acetaldehyde to acetic acid, leading to accumulation of acetaldehyde in the blood, which in turn leads to nausea, flushing, headache, palpitation, and vomiting. Because these effects are unpleasant, the patient is less likely to consume alcohol when taking disulfiram.

A few other drugs, when combined with alcohol, also produce a "disulfiram-like" effect. Examples include chloramphenicol (Chloromycetin in Canada), trimethoprim-sulfamethoxazole (Bactrim), cephalosporins, and metronidazole (Flagyl). Given these effects, the drugs should not be taken within 48 hours of alcohol consumption.

Because disulfiram is a hydrophobic agent, it is readily stored in adipose tissue (which makes disulfiram undergo a slow elimination process) and can cross the blood–brain barrier (**Figure 1.17**).

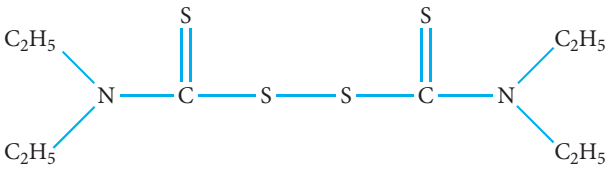


Figure 1.17 Structure of disulfiram, a highly lipid-soluble agent.

The effects of alcohol in lactic acid formation and hypoglycemia are discussed in the *Introduction to Biochemistry* and *Introduction to Pharmacology and Pathophysiology* chapters.

It is interesting to know about the history behind the discovery of disulfiram's healthcare application. In the past, tetraethylthiuram disulfide was used as an antioxidant in some rubber industries. In the early 1900s, workers from rubber industries who were exposed to tetraethylthiuram disulfide developed adverse reactions when they ingested ethanol. Later, tetraethylthiuram disulfide was used as a compound to synthesize the FDA-approved drug disulfiram, which entered the U.S. market in 1951. In addition to inhibiting the aldehyde dehydrogenase enzyme, disulfiram inhibits the dopamine β-hydroxylase enzyme, which is necessary for norepinephrine synthesis from dopamine. As a result, the CNS concentration of dopamine increases and the concentrations of epinephrine and norepinephrine decrease (as you will see in the *Introduction to Pharmacology and Pathophysiology* chapter, dopamine is a precursor to epinephrine and norepinephrine). The latter effect results in a decreased level of norepinephrine and an accumulation of acetaldehyde. Acetaldehyde is an effective vasodilator; the vasodilation, in turn, leads to hypotension.

Isopropanol [CH_3—CH(OH)—CH_3]

Isopropanol is found in antifreeze, skin lotions, home cleaning products, and rubbing alcohol (70% isopropyl alcohol). Its effect in causing hypotension and CNS and respiratory depression is two to three times more powerful than that of ethanol. Upon isopropanol ingestion, patients are intoxicated but do not have an odor of ethanol.

Ethylene Glycol (HO—CH_2—CH_2—OH)

Ethylene glycol is found in fire extinguishers, adhesives, air conditioners, and automobile antifreeze. This clear, colorless, sweet-tasting liquid is viscous at room temperature. The enzyme alcohol dehydrogenase converts it to a toxic substance: glycoaldehyde (HO—CH_2—COH). The symptoms of ethylene glycol toxicity include focal or generalized seizures, abdominal pain, nausea, vomiting, and coma.

Learning Bridge 1.1

Joe Smith has been using alcohol for the last 6 months. He has lost his job, and recently his wife filed a divorce petition. However, Joe has been thinking about quitting drinking alcohol and has been seeking help to cope with his alcohol consumption. On a Monday morning, he comes to your pharmacy to fill his disulfiram prescription. While you are asking his date of birth, you notice that he smells of alcohol. The patient denies that he has been drinking alcohol during the last 2 days.

What would you do as an intern pharmacist to help Joe with his medication?

Nucleophiles and Electrophiles

A nucleophile is an electron-rich and a "nucleus-loving" species. It has electrons that can be used to form a covalent bond to an electrophile. Nucleophilic species are either fully negative ions (such

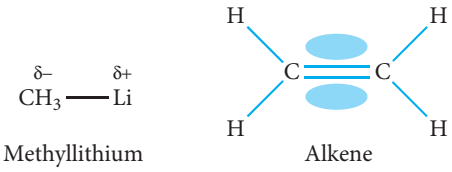


Figure 1.18 The methyl group in methyllithium has higher electron density and is a nucleophile. Similarly, the π bond in the alkene molecule functions as an electron donor, so this molecule is also a nucleophile.

as F^-, I^-, and OH^-); or contain a fairly negative region somewhere in a molecule because of a polar bond (e.g., methyllithium in **Figure 1.18**); or, in the alkene π bond, function as an electron donor (because the electrons in π bonds are above and below the bond, they are more available to be donated, Figure 1.18).

In contrast to a nucleophilic species, an electrophilic species is an electron-deficient and an "electron-loving" species. **Figure 1.19** demonstrates how the positively charged carbon is an electron seeker. A carbocation is an example of an electrophile and carries a positive charge. A neutral carbon atom has four valence electrons, while a charged carbon (C^+) has three valence electrons. C^+ tries to have maximum bonding, so it undergoes rearrangement to form sp^2 hybrid orbitals (Figure 1.19A). The valence electrons for C^+ (three electrons) are distributed among sp^2 orbitals, which can share electrons with other species (Figure 1.19B). Such an interaction leaves the last unhybridized *p* orbital empty (Figure 1.19C). As shown in Figure 1.19C, the vacant *p* orbital has a high tendency to accept two electrons so as to follow the octet rule and have a total of eight electrons in the valence shell.

The carbocation is among the most powerful electrophiles; halide anions are among the most powerful nucleophiles. When these two powerful species see each other, they rapidly react with each other (because a nucleus-loving species satisfies an electron-loving species, and vice versa) (**Figure 1.20**). The binding of the Cl anion to the carbocation is called nucleophilic attack, whereas the binding of the carbocation to the Cl anion is called electrophilic attack.

The chemistry of carbonyl compounds is dominated by the polarity of the carbonyl bond. The carbonyl carbon carries a partial positive charge, which makes it highly susceptible to attack by nucleophiles (**Figure 1.21**). Hydroxide ion (a nucleophile) attacks at the electrophilic carbon of the ester C=O, breaks the π bond, and creates a tetrahedral intermediate. This reaction leads to formation of carboxylic acid and an alcohol. This nucleophilic attack explains why esters are prone to hydrolysis (**Figure 1.22**). As you will learn in this chapter, ester is a common functional group for many drugs and a target for hydrolysis and metabolism.

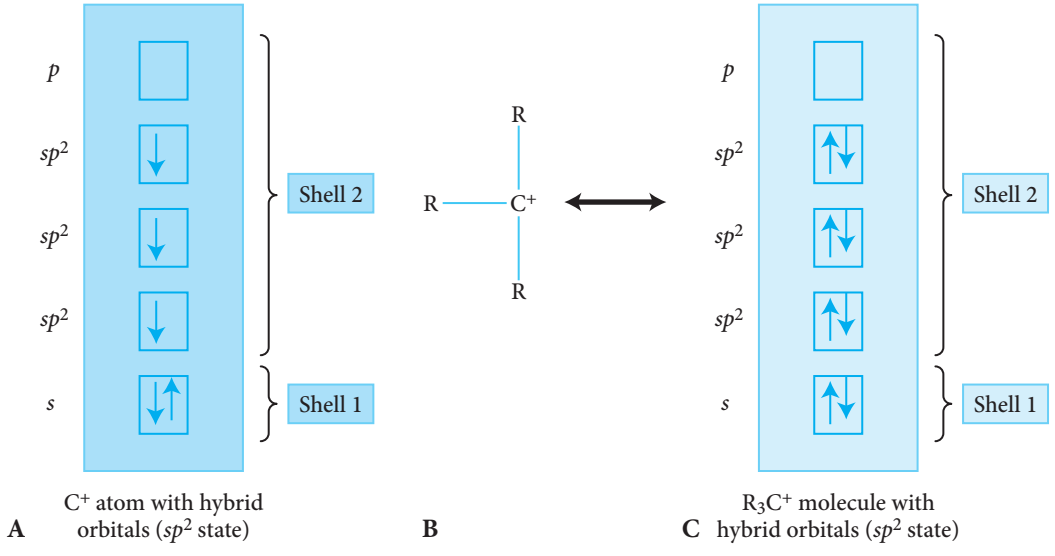


Figure 1.19 **(A)** The valence electrons for C^+ (three electrons) are distributed among sp^2 orbitals. **(B)** The electron-deficient C^+ has interacted with three other carbon atoms. **(C)** The last unhybridized *p* orbital is empty and has a high tendency to accept two electrons.

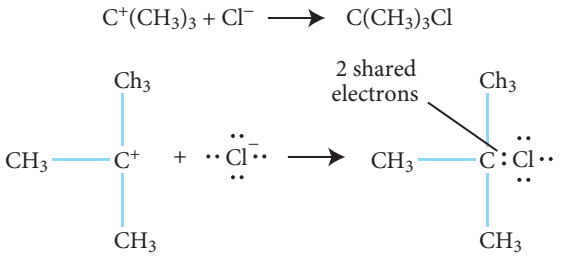


Figure 1.20 When a powerful electrophile (carbocation) meets a powerful nucleophile (halide anion), they rapidly react with each other.

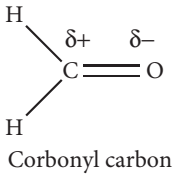


Figure 1.21 Structure of and polarity of the carbonyl carbon.

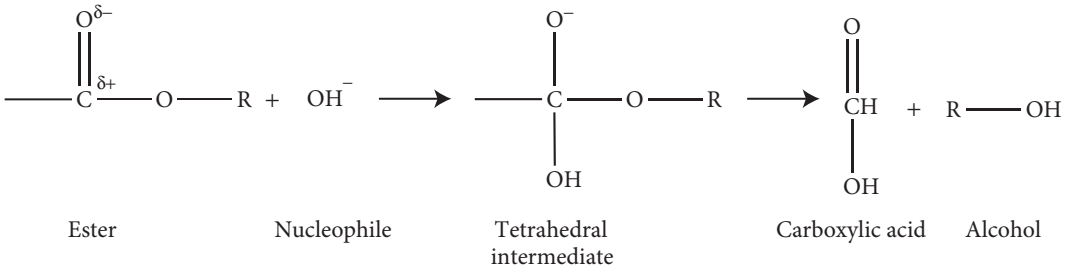


Figure 1.22 Ester molecules are prone to nucleophilic attack and, as a result, are susceptible to hydrolysis.

Learning Bridge 1.2

While you are completing your last day at your introductory pharmacy practice experience (IPPE), a patient is brought to the hospital with signs and symptoms of methanol poisoning—headache, lethargy, blurred vision, vomiting, abdominal pain, and confusion. The patient admits that he drank one mouthful of methanol that he mistakenly believed was ethanol. At the hospital, the attending physician prescribes fomepizole (Antizol).

A. Explain how fomepizole helps to detoxify the methanol poisoning.
B. Why didn't the physician prescribe disulfiram?

Chemical Bonds

The strength of bonds is expressed in units of kilojoules per mole (kJ/mol). The bond energy is the amount of energy that is required to break one mole of the bond. Similarly, it is the amount of energy that is gained when one mole of a bond is formed. For example, 400 kJ/mol of energy is required to break one mole of C—C covalent bonds. To give a simpler example, you need energy to break your pencil into two parts.

Chemical bonds can be divided into two major classes: covalent bonds and noncovalent bonds.

Covalent Bonds

In a covalent bond, atoms in a molecule share electrons to fill their outermost shell. Covalent bonds are responsible for holding atoms together as molecules (**Figure 1.23**). A typical example of a covalent bond is the hydrogen atom that is attached to an oxygen atom to form O—H. The most important covalent bonds in biology (C—C and C—H) have bond energies in the range of 300–400 kJ/mol; they are very strong. Some atoms can form more than one covalent bond. For example, the carbon atom can form four covalent bonds. It is the electron configuration of the atom that

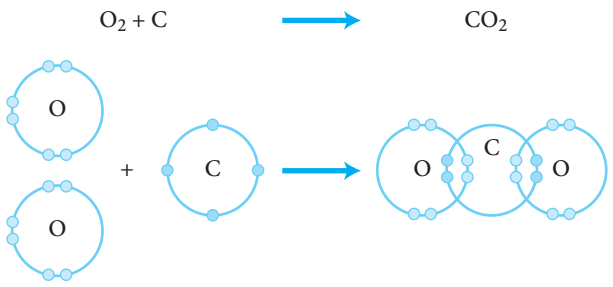


Figure 1.23 A carbon atom and oxygen atoms share their electrons to fill their outermost shells and, as a result, build a covalent bond.

ultimately determines the number of covalent bonds that are possible. The number of covalent bonds is referred to as covalence.

The covalent bond explains the strong bonding that occurs between hydrogen atoms and oxygen in a water molecule. Covalent bonding also explains why two identical atoms (e.g., Cl_2, H_2) or two atoms with similar electronegativity (C—H) form a molecule. In such a case, because the electronegativity of the atoms is identical or similar, there is no electron that transfers between atoms; instead, electrons are shared between these atoms—a unique characteristic of the covalent bond. When a covalent bond has an unequal sharing of a pair of electrons, it forms a dipole. For instance, hydrogen atoms have much less electronegativity than the oxygen atom in a water molecule. Because of this large electronegativity difference, the oxygen atom draws electrons from the hydrogen atoms, which in turn makes the hydrogen atoms partially positively charged and the oxygen atom partially negatively charged (**Figure 1.24**). This process makes water a dipole molecule. As the name indicates, the dipole molecule has two poles, one positive and one negative. Not all covalent bonds, however, produce dipole molecules.

Polar Bonds

Two identical atoms (such as two carbons) share an electron pair equally, something two unlike atoms cannot do. In a covalent bond between identical atoms, the bound electrons are symmetrically distributed. This bond is also known as a nonpolar covalent bond. By comparison, shared electrons between unlike atoms are found closer to the atom with the higher attraction for the electrons—that is the atom with higher electronegativity. When two atoms share their electrons unequally, they form a polar bond. This bond is also known as a polar covalent bond. Consider HCl. Chlorine is more electronegative (see the periodic table) than hydrogen. Chlorine's electronegativity is not sufficient for Cl to take an electron from hydrogen (otherwise, it would be ionized—see the discussion of ionic bonding later in this section). The bound electrons are shared between H and Cl, but because Cl is more electronegative than H, the shared electrons are pulled toward Cl. The imbalanced electronegativity among Cl and H atoms results in the Cl atom attaining a fractional negative charge (δ^-); for the same reason, the H atom attains a fractional positive charge (δ^+). The structure of this polar bond is shown in **Figure 1.25**.

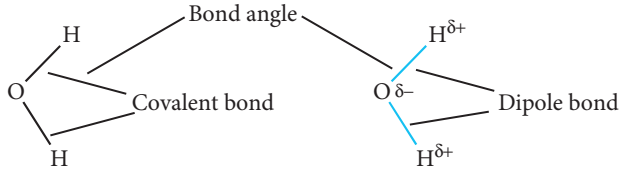


Figure 1.24 A dipole bond is formed when two atoms with different electronegativities share electrons with each other. When an atom is shared between two other atoms, it builds a bond angle. The bond distance is the distance between the nuclei of the bound atoms. Both bond angles and distances characterize the geometry of a molecule.

As you can see, HCl has two electrically distinguishable ends (much like two ends of a magnet). HCl is a dipole (it has two poles). Polar and dipole bonds, however, are different: A polar bond is a type of covalent bond, whereas a dipole is a moment when there are two poles on a molecule. The covalent bond within the HCl molecule is a polar bond but the HCl is a dipole molecule as well. The greater the difference between the electronegativities of the bound atoms, the more polar the bond formed. Keep in mind that the H and carbon atoms have similar electronegativities, so they cannot form a polar bond.

Figure 1.25 The structure of a polar bond. The arrow represents a dipole molecule and the direction of a dipole (direction from the positive pole to the negative pole).

Noncovalent Bonds

Noncovalent interactions (also known as noncovalent bonds) are weak interactions that occur between ions, atoms, and molecules. Such bonds assist some molecules and ions in maintaining their shape and structural integrity. For instance, DNA is composed of two intertwined chains of polynucleotides. While covalent bonds are responsible for holding together the atoms of the nucleotides in each DNA strand, the forces that hold the two strands together are noncovalent hydrogen bonds. The weak hydrogen bond forces are strong enough to keep the two DNA strands attached to each other, yet weak enough to allow the cell to separate the DNA strands from each other to carry out DNA replication and transcription. As another example, consider how amino acids embedded within a protein interact to maintain the structure and function of a protein. In contrast to the covalent bond, no electron sharing occurs between atoms in a noncovalent bond. Instead, in a noncovalent bond, electrons are transferred. As a consequence, a noncovalent bond is not as strong as a covalent bond. Four types of noncovalent bonds exist: ionic bonds, ion–dipole bonds, hydrogen bonds, and van der Waals forces.

Ionic Bonds

Ionic bonds form when one or more electrons are transferred from one atom to another. The ionic bond is the strongest noncovalent bond; it occurs between fully charged positive and negative ions, and it is very common in salt-formed molecules. Molecules that ionize entirely in solutions are electrolytes (a typical example is NaCl). In contrast, molecules that do not ionize in solutions but are very water soluble are nonelectrolytes (polar organic molecules like glucose).

Figure 1.26 depicts a typical ionic bond between Na and Cl ions. In the figure, Na has released one valence electron from its third shell so as to have eight electrons in its second shell and become more stable. Therefore, Na is a good electron donor. In contrast, Cl has seven electrons in its third shell; by gaining one electron, it will complete its valence shell with eight electrons (recall the octet rule) and become more stable. Therefore, Cl is a good electron acceptor. If you mix these two ions, the opposite ions will attract each other—a phenomenon called electrostatic force—leading to the formation of the NaCl salt. This reaction also indicates that an interaction between metals and nonmetals tends to form an ionic bond. However, if a salt with an ionic bond comes in contact

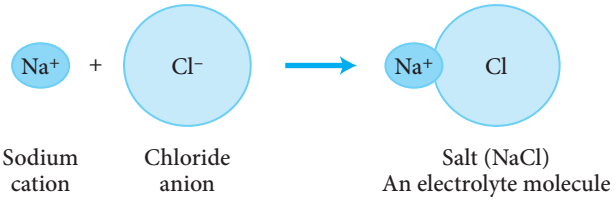


Figure 1.26 Na^+ and Cl^- ions interact with each other to form an ionic bond.

with water, and the attraction between the ions and water subsequently overcomes the attraction between the two ions in an ionic bond, the salt will dissolve into water.

Ion–Dipole Bonds

When an ion (cation or anion) binds to a dipole, it forms an ion–dipole bond (**Figure 1.27**). The ion–dipole bond plays an important role in the water solubility of drugs. Drugs that have free acidic or basic groups have poor aqueous solubility. Salt formation by these groups often improves their solubility, albeit only if the salt is able to dissociate in water (salt formation is explained in another section of this chapter). The topic of solubility is described in detail in the *Introduction to Pharmaceutics* chapter. For now, recognize that the definition of solubility is the amount (gram) of a compound that dissolves in 100 mL of a given solvent (usually in water) and at a specific temperature. For instance, the solubility of sucrose is defined as when 204 grams of sucrose dissolves in 100 mL of water at 20°C.

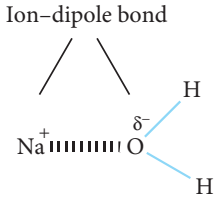


Figure 1.27 A dipole molecule such as water can form an ion–dipole bond with an ion.

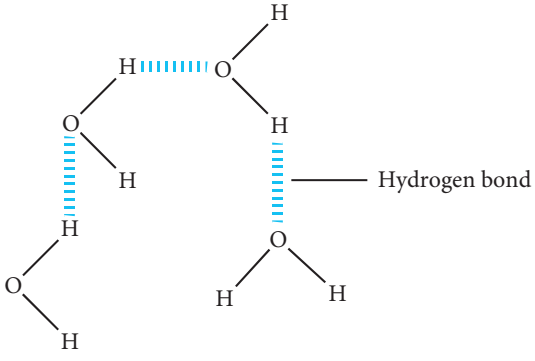


Figure 1.28 Water has a high boiling point (100°C) because of the large number of hydrogen bonds that exist in water.

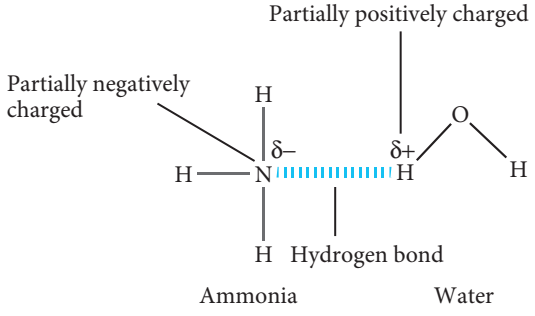


Figure 1.29 The partially negatively charged nitrogen of an ammonia molecule interacts with the partially positively charged hydrogen of a water molecule to form a hydrogen bond.

Hydrogen Bonds

Hydrogen bonds are strong chemical bonds. Indeed, it is the hydrogen bonds that explain how water molecules interact with each other to produce a high boiling point (**Figure 1.28**). As explained previously, when a covalent bond forms (like the one between the two hydrogen atoms and one oxygen atom in a water molecule), a dipole bond forms (because of the large electronegativity difference between hydrogen and oxygen). The partially positively charged hydrogen atoms in a dipole molecule (such as in water) can interact with a partially negatively charged atom from another molecule (such as oxygen from another water molecule).

Another example of a hydrogen bond is the interaction that occurs between a water molecule and ammonia—another molecule that contains hydrogen. **Figure 1.29** illustrates how the partially negatively charged nitrogen (of an ammonia molecule) interacts with the partially positively charged hydrogen (of a water molecule). Because both molecules (ammonia and water) are dipoles, the resulting bond is called a dipole–dipole bond as well. However, in a hydrogen bond one of the dipole molecules must contain an electropositive hydrogen—in other words, a hydrogen atom that is bound to an electronegative atom. In the hydrogen bond example shown in Figure 1.28, the hydrogen atom is partially electropositive because it is bound to an electronegative oxygen atom. As mentioned earlier, hydrogen bonds play important roles in stabilizing many macromolecules (e.g., RNA, DNA, proteins).

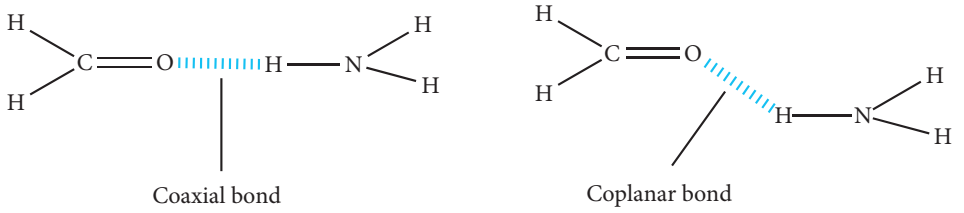


Figure 1.30 Structures of coaxial and coplanar hydrogen bonds.

There are two forms of hydrogen bonds: coaxial and coplanar (**Figure 1.30**). Coaxial hydrogen bonds are stronger than coplanar hydrogen bonds.

Van der Waals Forces

van der Waals forces are the weakest type of interaction between molecules. On average, at any given time the electrons in a nonpolar molecule or atom are distributed around the nucleus. Electrons may, in one instant, be slightly accumulated on one side of the molecule, which results in a small temporary dipole. A temporary dipole may influence the electron distribution of a nearby molecule or atom so that the nearby atom or molecule becomes a dipole—a process called induced dipole. The momentary polarization that causes (forces) attraction between a temporary dipole and an induced dipole is called a London force (**Figure 1.31**). In turn, all molecules in close vicinity, and regardless of their structure, experience London forces.

Although London forces may occur between any two molecules in close vicinity to each other, dipole–dipole forces occur only between polar molecules. However, London forces and dipole–dipole forces make up van der Waals forces. The London forces are temperature dependent (their role becomes more important at low temperatures). This last observation makes sense because, at high temperatures, molecules are not close enough to each other to produce an induced dipole moment. In addition, a steric hindrance negatively affects London forces (i.e., London forces require tight packing of molecules).

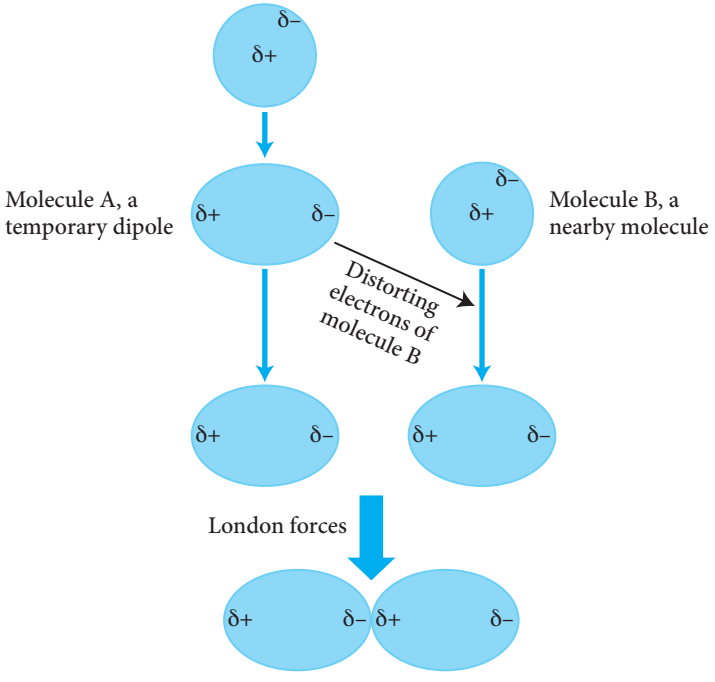


Figure 1.31 London forces. The constant motion and distribution of electrons within the molecule produce momentary polarizations in two nearby molecules (molecules A and B). These polarization processes force molecules A and B to interact with each other.

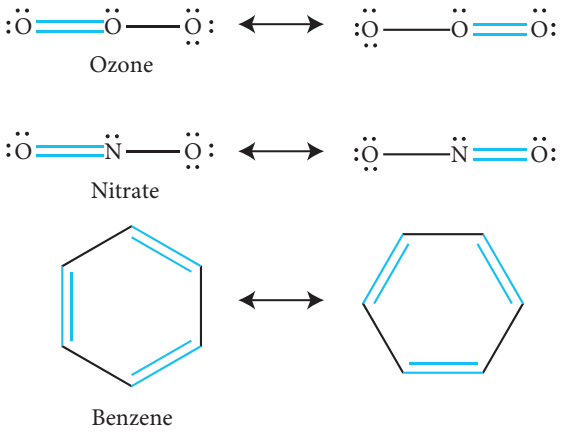


Figure 1.32 A few examples of molecules that have resonance structures.

Resonance Structures

A resonance structure describes a molecule for which two or more structures with identical arrangements of atoms but different arrangements of electrons can be drawn. **Figure 1.32** demonstrates electron rearrangements in a few examples of molecules with resonance structures.

As an example, let's look at the structure of ozone (O_3). In the ozone molecule shown in Figure 1.32, the electrons in the π bond are not always located between the two atoms of the original bond, but instead are delocalized. This delocalization process enhances the stability of the molecule.

Another example of a molecule with resonance structures is nitrite (NO_2). The electrons in nitrite have been delocalized over the oxygen atoms (as in the ozone molecule). Electrons can be delocalized over many atoms.

Another example of a molecule with resonance structures is a benzene ring. Like the ozone and nitrite molecules, the benzene ring is represented by two resonance structures. In this case, the double-bond electrons are not kept between any two carbons of the ring, but rather are free to move over the entire ring.

Learning Bridge 1.3

Today is your first day of your introductory pharmacy practice experience (IPPE) in a community pharmacy. A grandmother comes to your pharmacy and asks you where she can find aspirin for her 5-year-old granddaughter, Emily. She mentions that Emily has had a low fever since early this morning.

Originally, the customer wanted to give her granddaughter the aspirin tablets that she kept in her medicine cabinet in her bathroom. When she opened the aspirin bottle, however, she noticed a sharp odor of vinegar. The woman noticed immediately that the aspirin tablets' expiration date was 6 months ago. She didn't want to give Emily an old aspirin, so that is why she is at your store today.

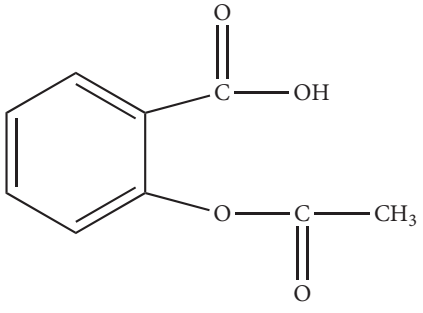


Exhibit 1.1 Acetylsalicylic acid.

The structure of acetylsalicylic acid is shown in **Exhibit 1.1**.

A. How would you explain the vinegar odor of the expired aspirin?

B. What is your reaction when the woman asks you to help her find aspirin for Emily?

Medicinal Functional Groups

Functional groups play important roles in reading structures, categorizing drugs into various classes, and to some extent predicting the pharmacological mechanisms of drugs. This introduction

to the organic functional groups provides an overview of the functional groups most commonly encountered in medicinal chemistry. The medicinal functional groups presented here are referred to in many chapters of this book to explain structure–activity relationships (SAR) and to assist students in understanding the principal roles of functional groups. In addition, the functional groups' physicochemical properties in the biochemical and pharmacological realms and their applications in the medical fields, particularly the pharmacy profession, are emphasized.

Nomenclature

The International Union of Pure and Applied Chemistry (IUPAC) is the organization that oversees the rules and guidelines in regard to chemical nomenclature in chemical sciences and makes recommendations on how that nomenclature should be applied. Although this section does not attempt to introduce students to the field of nomenclature for chemical structures, the IUPAC terminology is used to identify and indicate functional groups.

Many molecules are referred to by their common names rather than their IUPAC names. These molecules were identified as pure compounds before their structures were known, so their common names do not provide any information about their structures. Examples of compounds with such names include methane, ethane, benzene, furan, chloroform, and acetic acid. Likewise, many natural compounds are still used under their common names rather than their UIPAC names, such as morphine and limonene.

The following six functional groups are discussed in this chapter:

1. Alkanes, alkenes, halogenated hydrocarbons, and aromatic hydrocarbons
2. Alcohols, phenols, and ethers
3. Aldehydes and ketones
4. Amines, carboxylic acid, and functional derivatives of carboxylic acids
5. Sulfonic acids, sulfonamide, and thioethers
6. The nitro group

Before we go through each functional group, a brief introduction to metabolism will facilitate the discussion of the functional groups' metabolic pathways. A more detailed discussion of metabolism is presented in the *Introduction to Medicinal Chemistry* chapter.

Drug Metabolism

Drug metabolism describes the process in which a drug, through a biological reaction, is transformed into other metabolites. The formation of these metabolites can occur before or after the drugs have reached their sites of action. The metabolism of drugs occurs by more than one pathway. Each pathway consists of a series of metabolic enzymes that catalyze the metabolic reactions. Metabolic reactions of drugs and xenobiotics (foreign chemicals or drugs) take place in two major pathways: Phase I and Phase II. Drug metabolism occurs mainly in the liver, but also to some extent in the blood, kidney, intestine, brain, and lungs. Generally, metabolism of a drug reduces or completely eliminates the drug's pharmacological effect. However, exceptions exist with prodrugs—drugs that become active after they are administered to the body and undergo a metabolic reaction. You will see many examples of prodrugs throughout this book.

Undesirable metabolites are one of the major reasons why a drug may fail to reach the U.S. market—the Food and Drug Administration (FDA) will not approve a drug that produces a toxic metabolite. Therefore, obtaining information about metabolic stability, metabolite formation, and interaction with metabolic enzymes is crucial during the development of a drug. Many

pharmaceutical companies have incorporated data analysis regarding metabolites into the discovery phase while developing new drugs.

A major goal of drug metabolism is to make drugs more hydrophilic (water soluble) so that they can be readily excreted by the kidneys. Cytochrome P450 (CYP450) refers to a family of isozymes (also called microsomal enzymes) that are mainly located on the smooth endoplasmic reticulum of the liver. Isozymes are two or more enzymes that catalyze the same reaction but are expressed by different genes.

At least 15 CYP450 isozymes are involved in the metabolism of drugs. Therefore, they are of particular importance when studying drug metabolism and drug interaction. While CYP450 isozymes are mostly seen in the liver, they exist in the intestinal walls as well (albeit in concentrations 20 times less than those found in the liver). The largest amount of these intestinal isozymes is found in the villi of the small intestine.

The hydroxylation reactions of aliphatic compounds, aromatic compounds, and phenols, along with the dealkylation of amines, are catalyzed by CYP450 isozymes. Within the CYP450 system, CYP1A2, CYP2C9, and CYP3A4 are the most abundant isozymes in the liver and account for the metabolism of many drugs. Each CYP450 isozyme is unique and has a distinct role. Drug interactions involving the CYP450 system are common and generally result from either isozyme inhibition or induction. For example, if a drug is a potent CYP450 inhibitor, it may inhibit the metabolism of a co-administered drug, producing a severe adverse effect. Certain foods can enhance or inhibit CYP450 isozyme activity as well.

One of the major roles of the CYP450 system is to facilitate metabolism and detoxification of xenobiotics. As noted earlier, xenobiotic metabolism is divided into two phases: Phase I and Phase II.

Phase I

Phase I introduces new functional groups into the xenobiotics through oxidation, reduction, and hydrolysis by microsomal isozymes. One or more of the CYP450 isozymes may be involved in this pathway. One of the most significant roles played by these isozymes is hydroxylation. Such isozymes (or enzymes) are referred to as mixed-function oxidases or monooxygenases, in recognition of the fact that they catalyze incorporation of one atom of molecular oxygen into the substrate and one atom into water. More detailed information is provided in the *Introduction to Medicinal Chemistry* chapter.

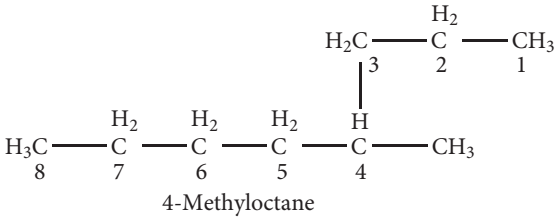
Phase II

Conjugation reactions occur when the xenobiotics react with glucuronic acid, sulfate, or a few amino acids. This pathway usually follows the Phase I reactions. Enzymes involved in Phase II reactions are largely located in the cytosol.

Alkanes

The "-ane" suffix indicates that a molecule is an alkane. Two typical examples are methane (CH_4) and ethane (CH_3—CH_3). In naming an alkane molecule, the name of the longest alkane chain is the parent (base) name for the molecule. In the example shown in **Figure 1.33**, the longest chain is an octane (it has eight carbons), so "octane" will be the parent name for the shown molecule. The lowest number in a chemical structure is given to the substituent (i.e., the methyl group in Figure 1.33).

Alkanes are unable to form hydrogen bonds, ionic bonds, or ion–dipole bonds (recall that there is a very small electronegativity difference between carbon and hydrogen in an alkane molecule). The van der Waals forces are the only forces that drive alkane molecules to interact with each other.



4-Methyloctane

Figure 1.33 Structure and the IUPAC name of an alkane molecule. The branched carbon (carbon 4) receives the lowest number. The longest continuous chain is used as the parent name.

Obviously, van der Waals forces exist only for molecules with more than four carbons, as an alkane with four or fewer carbons always takes a gaseous form (e.g., propane). Because alkanes cannot form hydrogen bonds with water molecules, they are water-insoluble molecules (i.e., they are lipid soluble or hydrophobic). Alkanes are colorless, and their melting and boiling points are relatively low. However, as the carbon chain length increases, the melting and boiling points increase due to the involvement of van der Waals forces. In contrast, as the amount of branching increases, the boiling point decreases due to lower van der Waals forces (recall that a steric hindrance reduces van der Waals forces).

Alkanes are mostly excreted as unchanged molecules because they are nonreactive. However, there is an exception: Oxidation of an alkane may occur at the end of the hydrocarbon chain.

Alkenes

The "-ene" suffix indicates that the molecule has a double bond. A typical example is propylene: CH2=CH—CH_3. As explained earlier, the name of the longest chain is the parent name for the molecule. The chain is numbered so that the double bond receives the lowest number. Some alkene compounds have more than one double bond (polyenes). A typical example is arachidonic acid, whose structure includes four double bonds inside the arachidonic molecule. Because each double bond decreases the number of hydrogen atoms in the molecule by 2, the general formula for an alkene molecule is C_nH_{2n} (**Figure 1.34**).

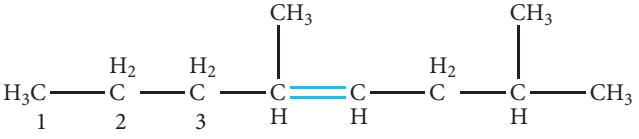
Two terms are used to identify the isomers of an alkene molecule:

- *cis* alkene (has the larger substituent on the same side)
- *trans* alkene (has the larger substituent across the double bond)

Despite the fact both maleic acid and fumaric acid have the same number of carbons and double bonds, they have different cellular functions in the citric acid cycle owing to their *cis* and *trans* configurations, respectively (**Figure 1.35**; see also the *Introduction to Biochemistry* chapter).

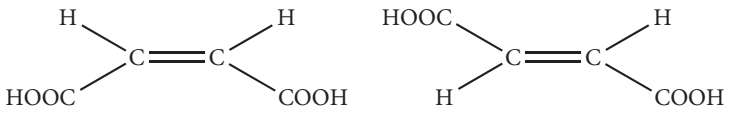
Alkenes are prone to oxidation (**Figure 1.36**), leading to peroxide formation—a serious pharmaceutical problem. However, the peroxide formation does not affect the *cis* or *trans* configuration of the compound.

Unlike in alkanes, the double bonds in alkenes do not have free bond rotation because of the rigidity of the double bond. As mentioned earlier, double bonds have shorter bond lengths



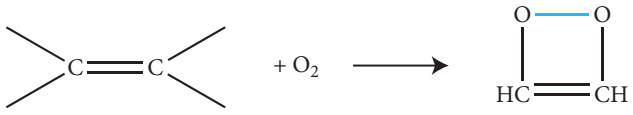
4,7-Dimethyl-4-octene

Figure 1.34 Structure and IUPAC name of an alkene molecule.



Maleic acid (*cis*) Fumaric acid (*trans*)

Figure 1.35 Both maleic acid and fumaric acid have the exact same number of carbon, hydrogen, and oxygen atoms. However, due to their *cis* and *trans* configurations, they have totally different cellular functions.



Alkene Oxygen Peroxide

Figure 1.36 Incorporation of oxygen into the alkene molecule during an oxidation reaction.

compared with single bonds. Due to alkenes' lack of water solubility, they dissolve in nonpolar solvents (e.g., fat, oil) and are flammable in the presence of oxygen and sparks. Endogenous alkenes (fatty acids from the human body) are reactive (i.e., they undergo hydration, reduction, and epoxidation), with the "addition reaction" being an especially common chemical reaction for these molecules. One example of an addition reaction involving alkenes is hydration of fatty acids (i.e., formation of an alcohol in the presence of water). As mentioned earlier, this reaction occurs because the π bond serves as a nucleophile and, as a result, is vulnerable to electrophilic attack. Just mixing an alkene with water will not cause hydration to occur and produce an alcohol; instead, an enzyme in the body or a strong acid such as H_2SO_4 in an experiment must be present to convert an alkene to an alcohol (**Figure 1.37**). Indeed, the latter experiment is how ethyl alcohol (or ethanol) is produced from ethylene.

Halogenated Hydrocarbons

Halogenated hydrocarbons are molecules in which a halogen atom such as fluorine (F), chlorine (Cl), bromine (Br), or iodine (I) has replaced a hydrogen atom. An example is ethyl bromide (CH_3CH_2Br). Halogenated hydrocarbons are polar molecules because halogen atoms are much more electronegative than carbon. To name a halogenated hydrocarbon, first find the longest chain (parent) and then locate the position of halogen. If halogen is the only substituent, give the halogen group the lowest possible number when naming the molecule (**Figure 1.38**).

Alkyl halides have an important place in the development of a pharmaceutical agent because they can be used as starting compounds for the preparation of other functionally substituted compounds. Monohaloalkanes have a permanent dipole character because of the strongly electronegative halide. However, because alkyl halides are electron-rich molecules, they do not

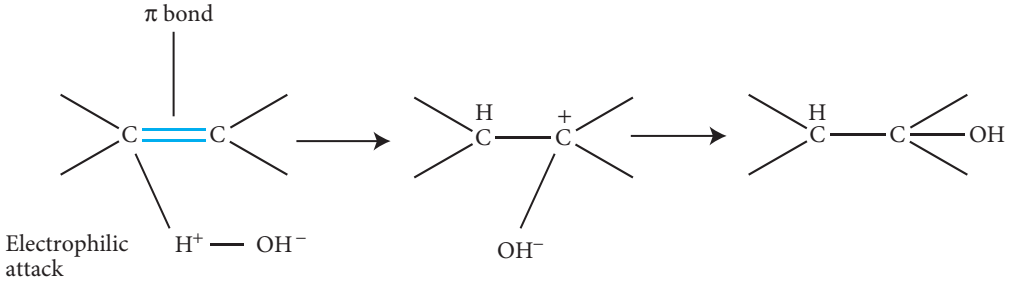


Figure 1.37 The π bond of an alkene molecule serves as a nucleophile and is prone to electrophilic attack.

readily interact with other dipole molecules (such as water) and, as a result, they have poor water solubility (in other words, they are lipid soluble). However, these compounds interact with other molecules through van der Waals forces. In addition, the high lipid solubility of halogens causes halogenated drugs to be reabsorbed from kidney tubules. This physiological process may explain their long duration of action (i.e., reduced renal elimination) and their drug toxicity due to their accumulation in the body. Halogen atoms also can be attached to an alkene to form a vinylic or allylic molecule (**Figure 1.39**).

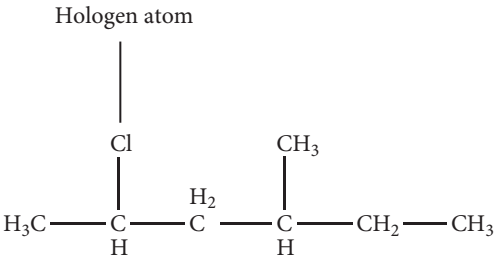


Figure 1.38 Structure and IUPAC name of a halogenated hydrocarbon.

Ethyl chloride (Gebauer's Ethyl Chloride) is an anesthetic spray that is used for relief of the skin pain associated with an intravenous (IV) injection or minor sport injury. Because ethyl chloride evaporates rapidly, it cools the skin to reduce pain (which explains why the duration of action is 1 minute or less).

Aromatic Hydrocarbons

Aromatic hydrocarbons have chemistry similar to that of the benzene molecule. These compounds are classified into two categories: benzenoid (or arenes) or nonbenzenoid. Whereas benzenoid aromatic hydrocarbons contain benzene ring(s), nonbenzenoid aromatic hydrocarbons have rings that are either smaller or larger than the benzene ring. The term "aromatic" was used to describe these hydrocarbons because many compounds that have a benzene ring produce an aroma. Not all aromatic hydrocarbons have an aroma, however. For instance, acetylsalicylic acid, ibuprofen, and acetaminophen all have a benzene ring but no aroma (**Figure 1.40**).

Benzene is the most common aromatic parent structure; it has the molecular formula C_6H_6 and is highly unsaturated due to its three double bonds. Substituents on a benzene ring are identified by a unique numbering process that gives the substituents the lowest possible numbers. A prefix is used when only two substituents are attached to a benzene ring: *ortho-* (*o-*): (1–2 placement), *meta-* (*m-*): (1–3 placement), and *para-* (*p-*): (1–4 placement). **Figure 1.41** indicates ortho, meta, and para positions on a benzene ring.

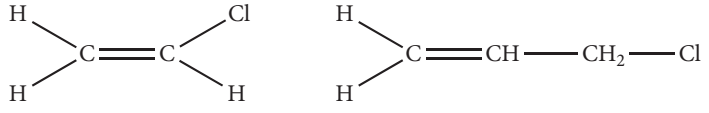


Figure 1.39 Structures of vinylic and allylic molecules.

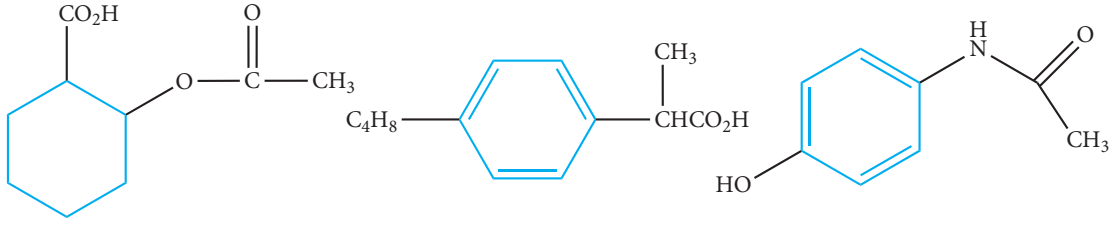


Figure 1.40 A few commonly used analgesic drugs that contain aromatic hydrocarbons.

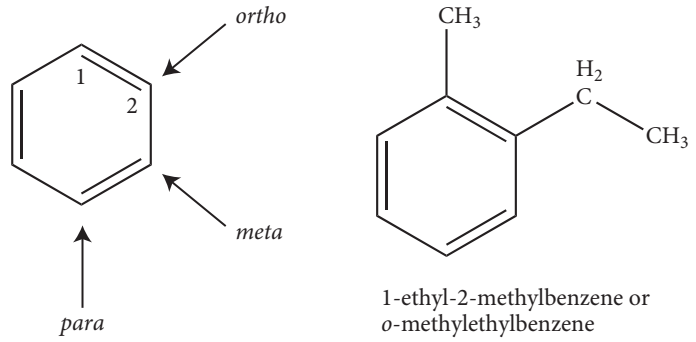


Figure 1.41 Benzene rings are prone to substitution reactions involving the *ortho*, *meta*, or *para* carbon of the benzene ring. The numbering and IUPAC name are shown here.

Because aromatic rings have double bonds, they have a cloud of π electrons above and below the ring (recall the π bonds). Electrophiles, in turn, attack the electron-dense cloud of the benzene ring. **Figure 1.42** shows how the NO_2^- ion, as an electrophile molecule, attacks the double bond and substitutes the hydrogen atom, a mechanism called electrophilic substitution.

Hydroxylation

Hydroxylation of aromatic rings (aromatic hydroxylation) occurs commonly in the liver's microsomal enzymes (i.e., in vivo) during Phase I metabolism. A typical example of a hydroxylation reaction is shown in **Figure 1.43**.

Alcohols

When a hydroxyl group (OH) is the major functional group, the "e" from alkane is dropped and is replaced by "ol." A typical example is methanol (from methane, CH_4, to methanol, CH_3—OH). In

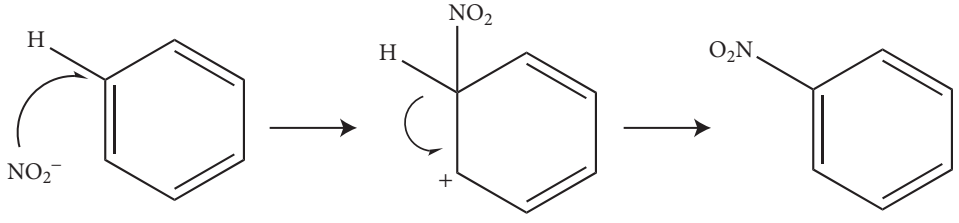


Figure 1.42 Electrophilic substitution reaction on a benzene ring by a nitrite ion.

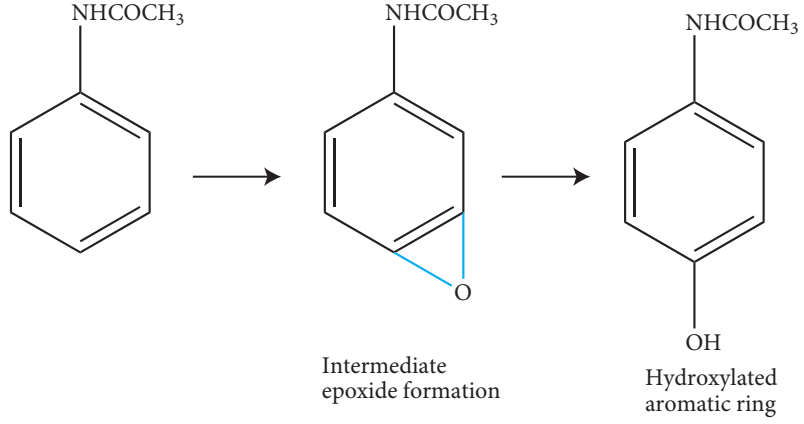
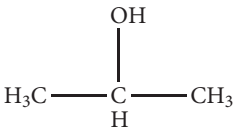


Figure 1.43 Hydroxylation of an aromatic ring includes formation of an intermediate epoxide.

giving a name to an alcohol molecule, designate the hydroxyl group to have the lowest possible number. When OH is the only functional group, the carbon number that has this group is placed in the front of the chain name (see **Figure 1.44**).



2-Propanol

Figure 1.44 Structure of a primary alcohol.

The hydrogen atom attached to the oxygen atom causes alcohols to be dipole molecules. Alcohols are weak acids, are less volatile than the corresponding hydrocarbon, and are water soluble. The water solubility, however, depends on the length of the hydrocarbon attached to the OH group. **Figure 1.45** shows three types of alcohol chains: primary, secondary, and tertiary.

An OH group centered in the molecule has higher water solubility than an OH at the end of the molecule. If a second OH group is added, the water solubility of the alcohol increases. Conversely, the more hydrocarbons are added to the OH functional group, the less water soluble the alcohol is. The C—O bonds of alcohols are polarized because of the electronegative oxygen. This polarization makes the O slightly negative and, therefore, a nucleophile.

Alcohols are readily metabolized in the body. Both primary and secondary alcohols are prone to oxidation (by oxidase enzymes) to form carboxylic acids and ketones. However, tertiary alcohols are stable to oxidation.

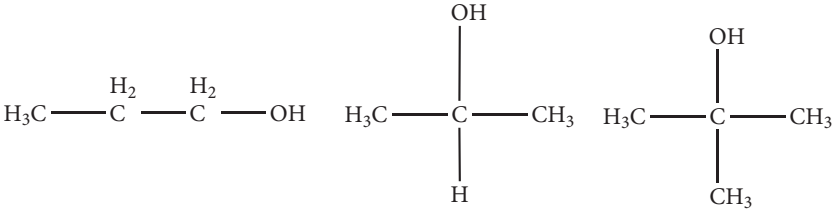
Phenol

Phenol is a benzene ring with an attached OH group (**Figure 1.46**). Mono-substituted phenols are named using the prefix *ortho-* (*o-*), *meta-* (*m-*), or *para-* (*p-*) due to the position of the substituent from the phenol's hydroxyl group.

The polar nature of the OH bond, due to the electronegativity difference of the atoms, promotes the formation of hydrogen bonds with other phenol molecules—which also explains why phenol has a high boiling point. Because of the same OH group, and therefore the hydrogen bonds, phenol is highly water soluble as well.

Because of the resonance phenomenon, phenols are more acidic than alcohols: Phenols are at least 100 times more acidic than alcohols. According to an acid definition—that is, the Brønsted-Lowry definition (addressed later in this chapter)—an acid is a substance that donates a hydrogen ion to another molecule or ion. Recall that the hydrogen atom is made of one electron and one proton, so a hydrogen ion (H^+) is a proton. Consequently, an acid is a proton donor. Simply put, both alcohol and phenol, because of the H atoms on their OH groups, can donate protons and thereby act as weak acids, albeit to different extents.

The most important factor that contributes to the fact that phenols are more acidic than alcohols is the aromatic ring system (**Figure 1.47**). Both alcohol and phenol can dissociate protons (being acidic). The negative ion on oxygen in ethoxide (i.e., when ethanol has lost a proton) is localized



A. Primary alcohol B. Secondary alcohol C. Tertiary alcohol

Figure 1.45 (A) Primary alcohol, where the OH group is at the end of a hydrocarbon chain. (B) Secondary alcohol, where the OH group is in the middle of the chain. (C) Tertiary alcohol, where the OH group is attached to a carbon atom that carries no H atoms.

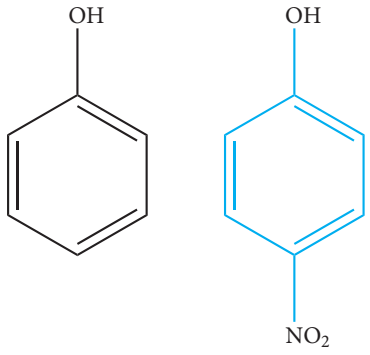


Figure 1.46 Structures of phenols.

only on the oxygen, and nowhere else. In contrast, the negative ion on a phenoxide ion is delocalized and overlaps with the π electrons (the clouds above and below the aromatic ring). Because of this delocalization, the negative ion is not readily available to attract a proton. This functional property of phenols makes them more acidic than alcohols.

Any electron-withdrawing group such as NO_2 or an aromatic ring (aryl group) will draw electrons from an oxygen atom and make the electrons above the oxygen atom less available to attract a proton. This results in a higher acidity. In contrast, an electron-releasing group (alkyl) makes the electrons on oxygen more available to attract a proton, which results in a lower acidity (**Figure 1.48**).

Keep in mind that the addition of a methyl or a halogen (e.g., Cl, F) reduces the water solubility of phenol. The addition of a second OH group (anywhere other than the *ortho* position), however, increases the water solubility of phenol. Salt formation (with Na^+ or K^+) is an important pharmaceutical reaction because the phenolate ion (phenoxide ion) will interact with water (recall the process of ion–dipole bonding). The liver is the primary site for metabolism of phenol-containing drugs. The metabolism of these drugs is very much like that of alcohols—that is, upon hydroxylation they produce diphenolic substances. Conjugation to glucuronic acid (forming glucuronide) and sulfonation (to produce sulfate conjugate) are the two most common metabolic pathways that occur for phenols during Phase II metabolism (**Figure 1.49**).

Ether

Ether is characterized by having an oxygen atom that links two hydrocarbon groups. Ether has an important place in pharmaceutical industries as a solvent in the preparation of many synthetic drugs. The widely used form of ether is ethyl ether.

The various types of ether are named by naming the two alkyl groups in alphabetic order as separate words and then adding the word "ether" at the end. Most ethers, however, are called by their common names; the IUPAC names are used only when their name is complicated. When both alkyl groups are the same, the prefix "di-" is used in the front of the alkyl name. An example is diethyl ether, which is also simply called ether (**Figure 1.50**).

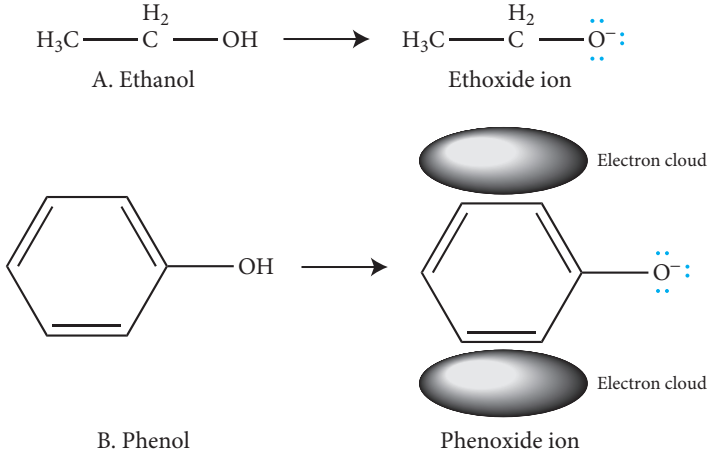


Figure 1.47 Alcohols (A) are less acidic than phenols (B) because the negative ion on a phenoxide ion is delocalized and overlaps with the π electrons.

The majority of drugs that contain ether are in the form of aromatic ether (**Figure 1.51**). Examples are codeine (Codeine, Contin, in Canada) and verapamil (Calan).

Ethers have a low boiling point (owing to van der Waals attractions) and poor water solubility (they lack an OH group). Moreover, as the length of the carbon chain increases, the solubility of ethers decreases. Compared with alcohols, ethers are less soluble in water, although they mix well with many organic solvents. Ethers with short carbon chains can form hydrogen bonds to water because the oxygen on ether has lone-pair electrons that bind the hydrogen atom of a water molecule. Ether in contact with O_2 (air) forms peroxides (if peroxide is concentrated, it may explode).

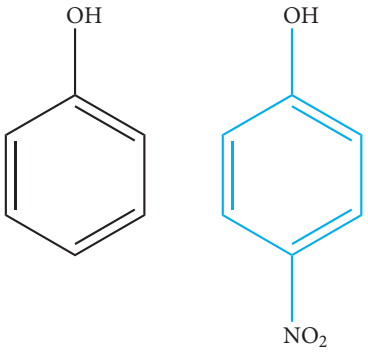


Figure 1.48 Two phenol groups with different acidity strengths.

Ether is a colorless liquid, stable, but is light and air sensitive. It is extremely volatile and flammable and, as a result, must be stored carefully. In the 1940s and 1950s, ether was a popular anesthesia agent, but now its use is strongly discouraged. This compound is toxic if ingested, inhaled, or absorbed through skin contact. The anesthetic effect occurs because ether accumulates in the lipids of the neurons and reduces nerve impulse transmission. In general, ethers are excreted unchanged, with one exception: dealkylation, when a short alkyl such as a methyl or ethyl group is lost by enzymatic oxidation in Phase I metabolism (**Figure 1.52**).

Aldehydes and Ketones

Aldehydes and ketones are closely related to each other, in that both contain a carbonyl group. Aldehydes have a high chemical reactivity and, as a result, are important intermediates in the pharmaceutical industry. The longest chain containing the aldehyde group provides the base name for the compound, with the aldehyde group as the first carbon. The suffix "-e" in alkane is replaced by "-al." Aldehydes are produced by oxidation of primary alcohols. As a result, they are easily oxidized to carboxylic acids (**Figure 1.53**). Therefore, aldehydes are sensitive to air oxidation and should not be stored for long periods.

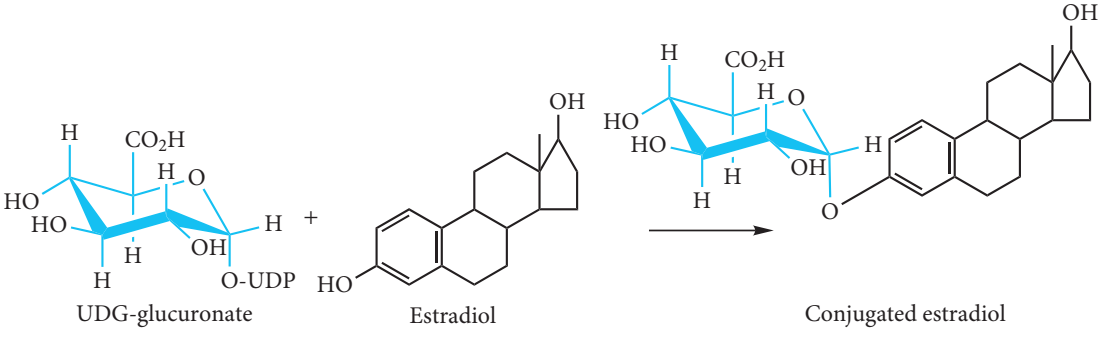


Figure 1.49 Glucuronidation of ibuprofen during hepatic Phase II metabolism.

Diethyl ether Methyl propyl ether

Figure 1.50 Ether names are often designated by common names instead of IUPAC names. They have the chemical structure R—O—R, in which the R can be identical or different aromatic or aliphatic hydrocarbons.

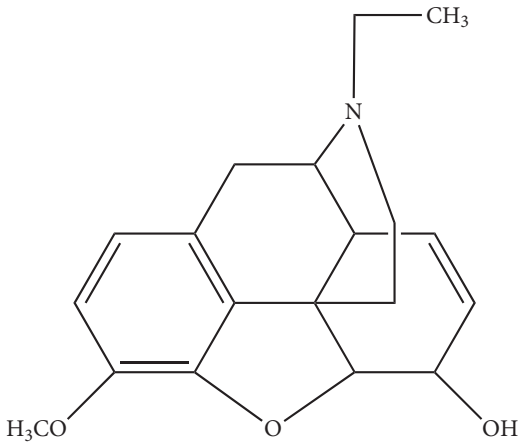


Figure 1.51 Structure of an aromatic ether (codeine).

In naming ketones, you find the longest chain and give the lowest number to the carbonyl group (C=O). The suffix "-e" in alkane is replaced by "-one" (**Figure 1.54**).

The carbonyl group present in aldehydes and ketones is a polar functional group. Ketones have a higher boiling point than other molecules with equal molecular weight. The reason is the dipole–dipole interaction between the carbonyl groups that occurs between the ketone molecules (**Figure 1.55**).

Ketones can form hydrogen bonds to the hydrogen atoms in water, making them water soluble to some extent. As usual, as the length of the chain increases (hydrophobic moiety increases), the water solubility decreases. While aldehydes are reactive to air oxidation (which leads to carboxylic acid formation), ketones are relatively nonreactive. The simplest aldehyde is formaldehyde, a colorless gas with a strong odor. Formaldehyde is toxic; if it comes in contact with the skin, it can cause severe skin irritation, or an ingestion of formaldehyde can lead to coma or death. An aqueous solution of formaldehyde is formalin (containing 37% formaldehyde), which has germicide effects (i.e., kills viruses, bacteria, and fungi) and is used to preserve biological specimens. The germicide effect arises because the aldehyde group of formalin interacts with the amino group of amino acids and thereby changes the structure and function of many essential proteins in viruses, bacteria, and fungi.

The simplest ketone is acetone, a colorless liquid that is used as a solvent in cleaning fluids. In humans, severe starvation or untreated type 1 and 2 diabetes leads to overproduction of a series of

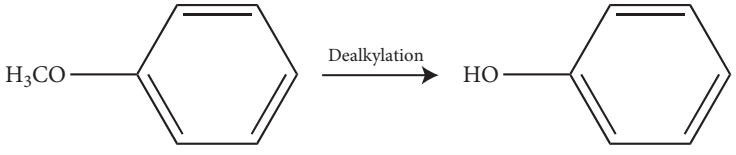


Figure 1.52 Enzymatic oxidation (dealkylation) of an ether during Phase I hepatic metabolism.

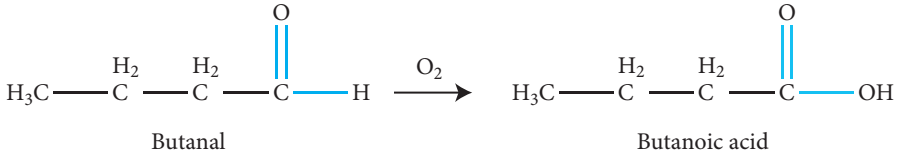


Figure 1.53 Oxidation of an aldehyde molecule (butanal) to a carboxylic acid (butanoic acid).

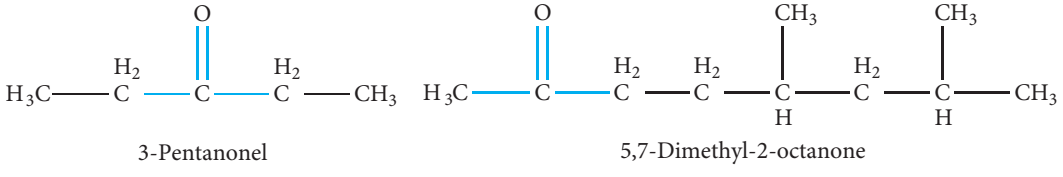
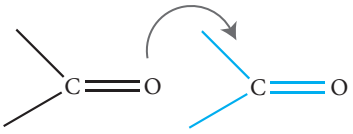


Figure 1.54 In the IUPAC system for naming ketones, the suffix "-e" in alkane is replaced by "-one."

acidic molecules called ketone bodies, which can cause a life-threatening condition called diabetic ketoacidosis (see also the *Introduction to Biochemistry* and *Introduction to Pharmacology and Pathophysiology* chapters). Acetone is a ketone body that gives a characteristic odor to the breath, which is sometimes useful in diagnosing untreated diabetes.



Dipole–dipole interaction

Figure 1.55 Dipole–dipole interaction between two carbonyl groups.

Amines

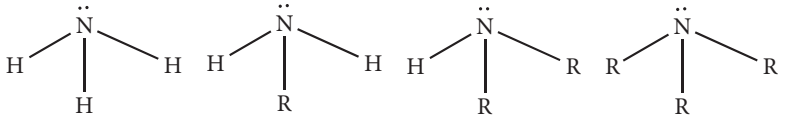
Most amines are bases (albeit with different strengths) because they can accept a proton. However, while amines usually do not donate a proton, one can find acidic amines such as phenobarbital. Amines are widely used in the structural design of drugs to not only produce a pharmacological effect, but also, due to their basicity, make salts from water-insoluble compounds. The lone pair of electrons on the amine nitrogen plays an important role in the basicity of amines.

Many plants' leaves, roots, and fruits are rich in nitrogen-containing compounds; because their water-based solutions increase the pH of the solutions, they are referred to as alkaloids. Many of these alkaloids are toxic and have a bitter taste—in essence, a warning signal from nature. Some alkaloids are used as analgesics and for the creation of euphoria. You will encounter many examples in this book. The names of amines are similar to the names of alcohols, except that the "e" in the parent alkane name is replaced by "amine." Amines are classified as primary, secondary, and tertiary (similar to alcohols) based on how many alkyl groups are bound to the nitrogen atom (**Figure 1.56**).

In naming amines, you number the carbon chain so as to give the lowest number to the amine group. In secondary and tertiary amines, the largest alkyl group attached to the nitrogen is named as the parent amine. The smaller alkyl groups are named with the prefix "*N*-" followed by the alkyl name, and are listed alphabetically. Common names are used for many aromatic and heterocyclic amines—as is the case for aniline, for instance (**Figure 1.57**).

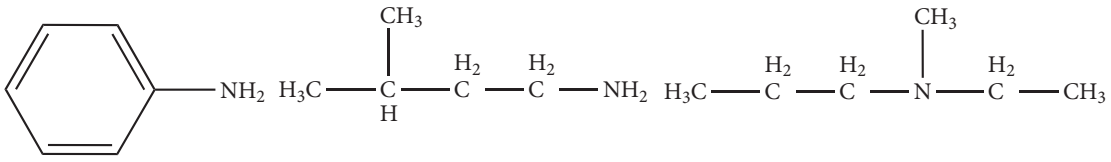
The most important characteristic of amines is their lone-pair electrons. The melting and boiling points of amines are higher than those of alkanes of similar size because of their hydrogen bonds. The effect of the carbon chain's length on the physical properties is the same as for alkanes—namely, the longer the chain, the higher the boiling point. However, despite the fact that amines are polar molecules, they do not have boiling points as high as those of alcohols. In primary and secondary amines, the hydrogen is bound to nitrogen, which is not as electronegative as oxygen. This characteristic leads to a weak dipole moment. The lowest boiling point is found with tertiary amines, because no hydrogen bonding takes place between the two tertiary amines.

Like alcohols, small amines, including tertiary amines, are soluble in water due to the hydrogen bonds they form with water (**Figure 1.58**). Nevertheless, amines with fewer than six carbons are less water soluble because of the hydrophobic effect from the hydrocarbon chain. The water solubility rank for amines is as follows: primary > secondary > tertiary. This order reflects the fact



Ammonia Primary amine Secondary amine Tertiary amine

Figure 1.56 Amines are designated as primary, secondary, and tertiary based on the replacement of one, two, or three hydrogen atoms, respectively, on an ammonia molecule.



Aniline 3-Methyl-l-butanamine *N*-Ethyl-*N*-Methyl-l propanamine

Figure 1.57 The parent name of molecules containing an amine is the largest alkyl group attached to the nitrogen atom. Common names are also used to name aromatic and heterocyclic amines (e.g., aniline).

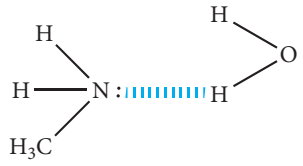


Figure 1.58 Hydrogen bonding between a primary amine and water.

that the nitrogen atom loses its hydrogen atom as it goes from a primary structure to a secondary or tertiary structure.

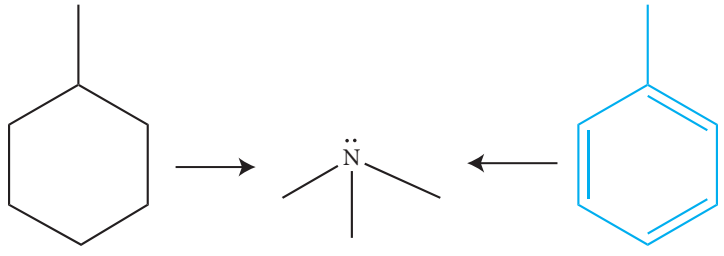
According to the Brønsted-Lowry definition, a base is a substance that accepts a proton (H^+). Because of amine's lone-pair electrons, amines have the ability to accept a proton. Indeed, this property assists amines in the formation of salts (i.e., amines will react with strong acids to form alkyl ammonium salts). Salt formation is a very important process for many drugs if they are to be water soluble, albeit subject to one important condition: The salt should be able to dissociate in water. Among the common acids used for salt formation by drugs containing amines are hydrochloric acid (HCl), sulfuric acid (H_2SO_4), and phosphoric acid (H_3PO_4).

The basicity of amines depends on the electron-releasing effect of the functional group that binds to the amines. For instance, electron-releasing groups (alkyl) increase the basicity of amines, whereas electron-withdrawing groups (aryl) reduce the basicity of amines (**Figure 1.59**).

When the aryl groups are attached to the amino group, the electron-withdrawing property of the aryl molecule pulls at the lone-pair electrons of the amine and makes them less available for accepting protons (recall the properties of a weak base). In contrast, the more readily available the lone-pair electrons are, the stronger the base is. In general, basicity declines in the following order:

$(CH_3)_3N > (CH_3)_2NH > CH_3—NH_2 > NH_3 \rightarrow$ Reduced basicity

Dealkylation is one of the major metabolic pathways for secondary and tertiary amines; it results in the formation of aldehyde or ketone groups (**Figure 1.60**). The dealkylation reaction increases the water solubility of an amine-based drug. Recall that a similar mechanism operates with ethers. In contrast, deamination (**Figure 1.61**) often occurs with primary amines, frequently catalyzed by an enzyme called monoamine oxidase (MAO; see the *Introduction to Pharmacology and Pathophysiology* chapter).



Alkyl group Aryl group

Figure 1.59 Alkyls are electron-releasing groups and aryls are electron-withdrawing groups. While the former increase the basicity of amines, the latter make amines less basic.

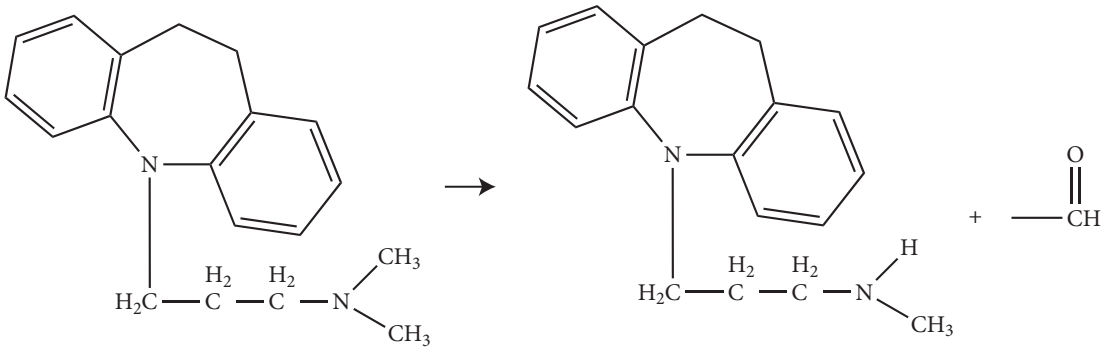


Figure 1.60 Dealkylation of amino groups is a common pathway in the metabolism of secondary and tertiary amines.

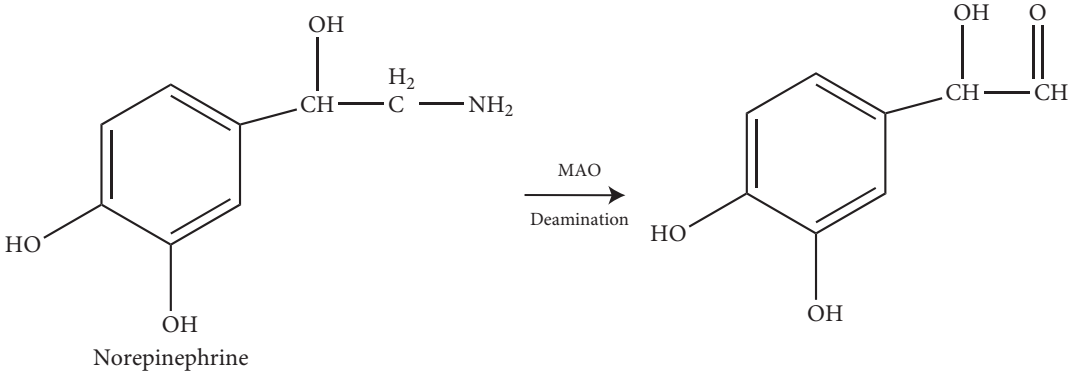


Figure 1.61 Deamination of a primary amine (norepinephrine) by monoamine oxidase (MAO) enzyme.

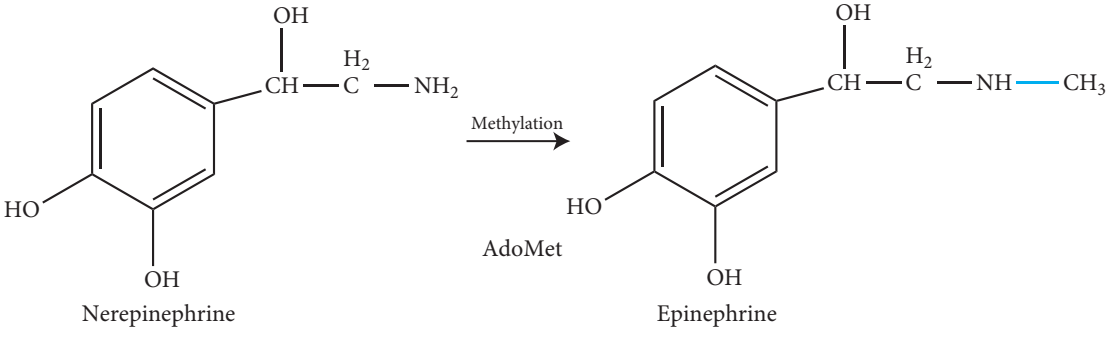


Figure 1.62 Enzymatic methylation of a primary amine (norepinephrine) in the presence of *S*-adenosylmethionine (AdoMet), which functions as a methyl donor.

A minor metabolic pathway for amines is methylation. Similar to the deamination reaction, the methylation reaction can occur with primary amines (**Figure 1.62**).

Glucuronic acid reacts (conjugates) with primary and secondary amines during Phase II hepatic metabolism, which in turn increases the water solubility of amines (**Figure 1.63**).

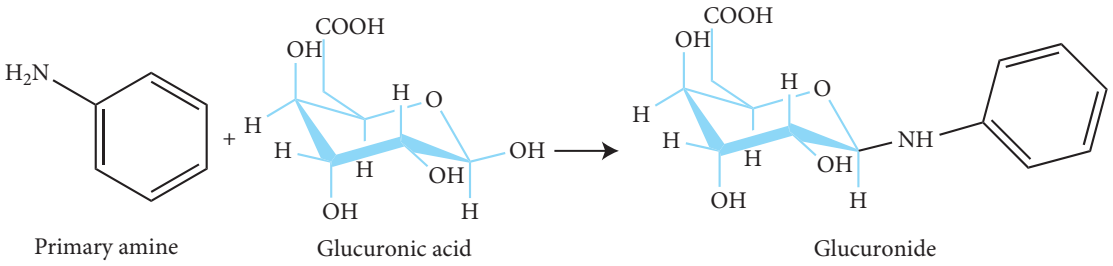


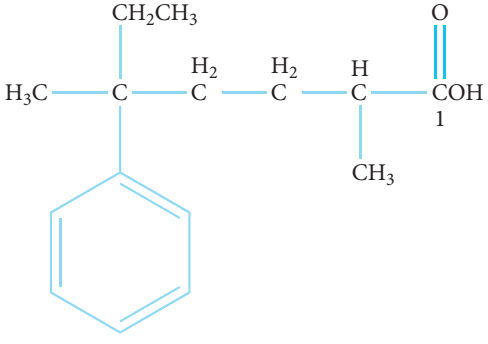
Figure 1.63 Both primary and secondary amines undergo conjugation reaction during Phase II hepatic metabolism, which increases their water solubility.

Learning Bridge 1.4

Amy likes to eat poppy seed bread for breakfast occasionally. Amy's employer implemented a random drug screening test for company employees yesterday. The drug screening test indicated that Amy had morphine in her blood sample. She has never used morphine in her entire life and claimed that the lab result was not accurate. A second lab analysis, however, confirmed the first finding. Amy knows that you are a pharmacy student and hopes that you can assist her in understanding why the drug screening showed traces of morphine. What would be your answer?

Carboxylic Acids

When naming carboxylic acids, the longest chain that contains the carboxyl group is used as the parent name for the molecule; numbering begins from the carbonyl carbon. Carboxylic acids are named by replacing the "e" of the alkane root name with "oic" and adding the word "acid" thereafter (**Figure 1.64**).



2,5-dimethyl-5-phenylheptanoic aci d

Figure 1.64 IUPAC name of a carboxylic acid molecule.

A carboxylic acid has a relatively high boiling point and high water solubility because of its polar carboxyl group, which enables it to form a hydrogen bond with another carboxyl group. However, as the length of the hydrocarbon chain increases, the water solubility of the carboxylic acid decreases.

Carboxylic acids are acidic due to the resonance stabilization of the carboxylate ion. The available electrons (or the negative charge) are shared equally between the two oxygen atoms. The arrow in **Figure 1.65** indicates the delocalization of electrons; neither of the two oxygen atoms is able to significantly attract a proton.

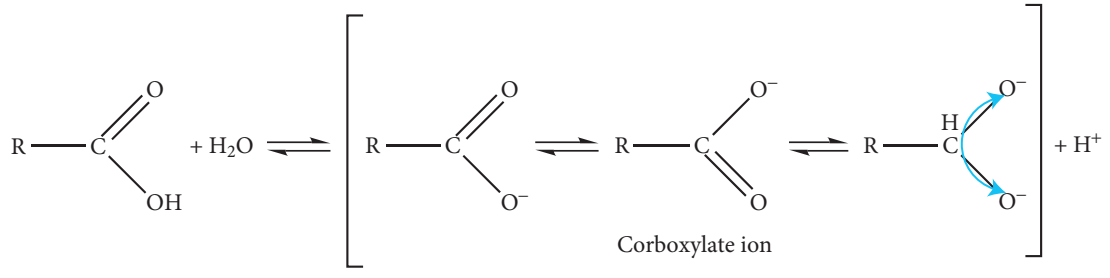


Figure 1.65 Resonance stabilization of the carboxylate ion in a carboxylic acid molecule.

In comparing a carboxylic acid to an alcohol and phenol, the carboxylic acid and alcohol have the highest acidity and lowest acidity, respectively. Carboxylic acid is more acidic than phenol because none of the oxygen atoms in the carboxylic acid significantly attracts a proton. In contrast, in phenol, the oxygen atom is the single most negatively charged species and, therefore, is able to attract, to some weak extent, a proton. Therefore, phenol is a weaker acid than a carboxylic acid.

Similar to amines, the acidity of carboxylic acid depends on the electronic effect of the groups that are attached to the carboxyl group. Electron-releasing groups (alkyls) decrease acidity, whereas electron-withdrawing groups (aryls) increase acidity (**Figure 1.66**); compare this effect with that noted for amino groups.

Because carboxylic acids are acidic molecules, a reaction with a strong base (NaOH) produces a carboxylate salt (**Figure 1.67**). The salt formation increases the water solubility of carboxylic acids. Keep in mind that the salt should be able to dissociate in water to increase the water solubility of the molecule.

It is common for carboxylic acids to undergo Phase II metabolism to conjugate with glycine or glucuronic acid and thereby increase their *in vivo* water solubility.

Functional Derivatives of Carboxylic Acids

Esters

Esters are much less polar than alcohols or carboxylic acids (a polar alcohol is combined with a polar acid to produce a much less polar molecule, so that the two hydroxyl groups disappear), leading to decreased water solubility. The boiling point for esters is low compared with the boiling points for alcohols or carboxylic acids with the same molecular weight. Esters are, however, more soluble in alcohols than in water.

When naming esters, the suffix "-ic" of the carboxylic acid is replaced by "-ate." Esters have two carbon chains separated by an "ether" oxygen; as a result, one has to name both chains separately in the full ester name (**Figure 1.68**). It is the position of the carbonyl group in an ester molecule that dictates which part is the alkyl group and which part is the alkanoate group.

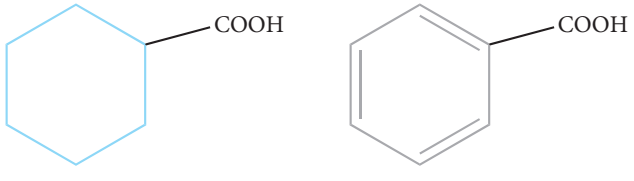


Figure 1.66 Alkyl and aryl groups act as electron-releasing and electron-withdrawing groups to carboxylic acids, respectively.

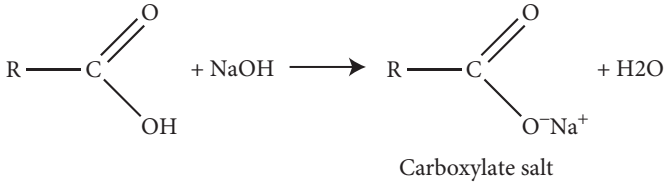


Figure 1.67 Due to the acidic properties of carboxylic acids, they are able to form salts when they are combined with bases.

In a reaction called esterification, a carboxylic acid reacts with an alcohol in the presence of an acid (usually H_2SO_4), which also causes a water molecule to be eliminated from the reaction. Keep in mind that esters are also produced by other pairs of compounds such as an acid anhydride and an alcohol, or an acid chloride and an alcohol, or simply by two different esters. When esters are split apart, in a reaction called hydrolysis, carboxylic acid and an alcohol are formed. Hydrolysis of esters occurs in the presence of water and strong acids such as H_2SO_4 and HCl or esterase enzymes. As a result, esters are prone to hydrolysis, which presents a stability problem that shortens the shelf-life of ester-based drugs.

Many plants and flowers owe their pleasant smells to esters. For instance, methyl butanoate gives the odor to an apple, and pentyl ethanoate gives the odor to a banana (**Figure 1.68**).

In the presence of a strong base (NaOH), ester is converted into a carboxylate salt. This reaction is a typical soap formation (from fats that contain ester groups). The hydrolyzing enzyme, esterase, catalyzes the hydrolysis of the ester to carboxylic acid and alcohol (**Figure 1.69**).

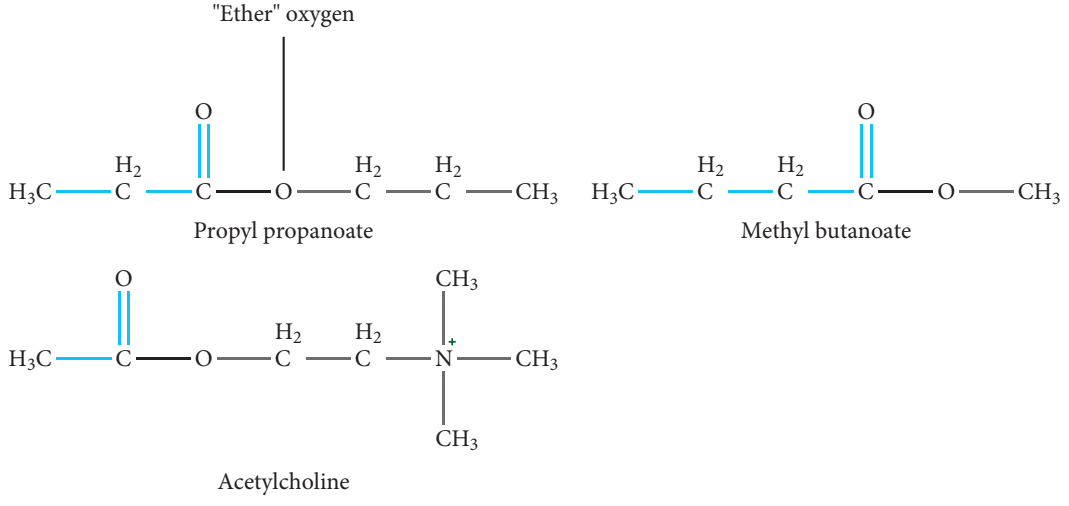


Figure 1.68 Structures of two esters produced by propanol and propanoic acid (propyl propanoate) and by methanol and butyric acid (methyl butanoate). In addition, the structure of the neurotransmitter ester, acetylcholine, is shown.

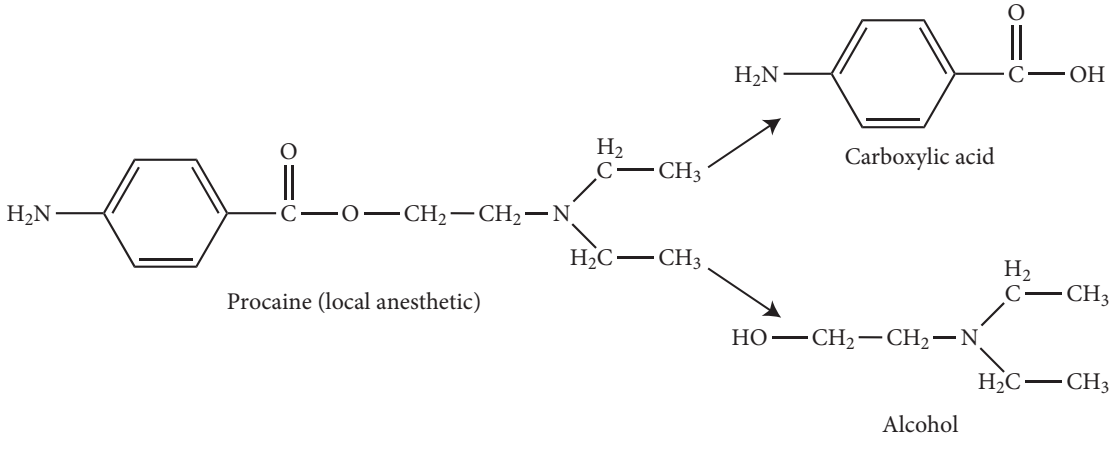
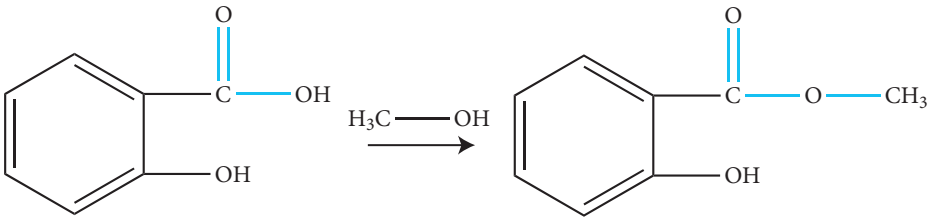
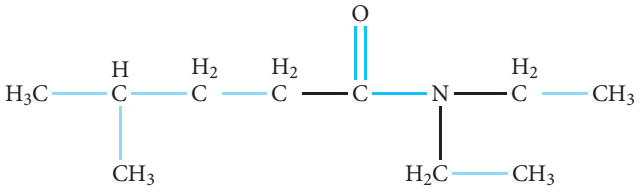


Figure 1.69 Hydrolysis of procaine by esterase enzymes results in the production of alcohol and carboxylic groups.



Salicylic acid Methyl salicylate (wintergreen)

Figure 1.70 Interaction between an acid (salicylic acid) and methanol that produces methyl salicylate.



N, *N*-Diethyl-3-methylbutanamide

Figure 1.71 The IUPAC name of an amide. An amide-containing compound has a characteristic chemical structure that is indicated by the attachment of a nitrogen atom to a carbonyl group.

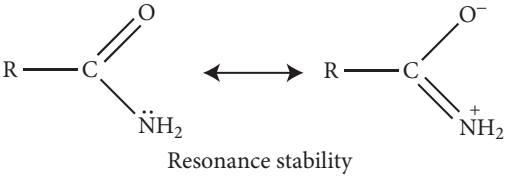
As shown in **Figure 1.70**, when an acid (salicylic acid) and an alcohol (methanol) interact with each other, an ester (methyl salicylate) is produced. Methyl salicylate (BenGay) is used as a topical drug to temporarily relieve minor muscle pain. Even though it is a topical formulation, if applied extensively to children, this product can result in salicylate poisoning. Heat, young age, and inflammation are all factors that can increase topical salicylate absorption, thereby increasing the risk of salicylate poisoning.

Amides

Amides are derivatives of carboxylic acids in which the hydroxyl group is replaced by a nitrogen group. In naming amides, you find the longest carbon chain and give the lowest number to the carbonyl group. Change the name of the acid by dropping the "oic" or "ic" ending and adding the suffix "-amide" (**Figure 1.71**).

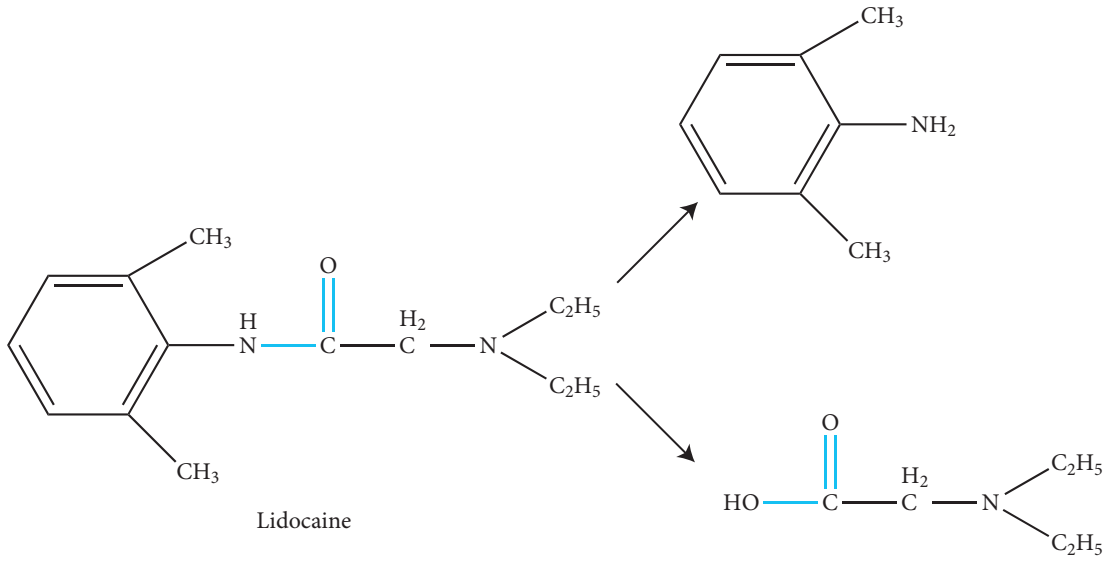
Most amides are solids at room temperature. They have high boiling points, but as more hydrogen atoms are replaced on the nitrogen atom, the boiling point decreases. Regardless of any hydrogen substitution on nitrogen, the carbonyl group is still present—which leads to a dipole–dipole interaction (recall that this property applies to the aldehyde and ketone groups as well). As a result, both substituted and unsubstituted amides can form hydrogen bonds to water, thereby being water soluble. Unlike amines, amides are not bases due to their resonance stability (**Figure 1.72**).

Amides are relatively stable to acid–base hydrolysis due to their resonance stability (the unshared electrons are no longer located solely on N but rather are spread over O, C, and N). This is an advantage when seeking to synthesize drugs with prolonged activity (see the sulfanilamide example in this chapter). Hydrolysis by amidase enzymes can occur, which yields a carboxylic acid (similar to hydrolysis of esters) and an amino group. A typical example is the hydrolysis of lidocaine (Lidoderm) (**Figure 1.73**).



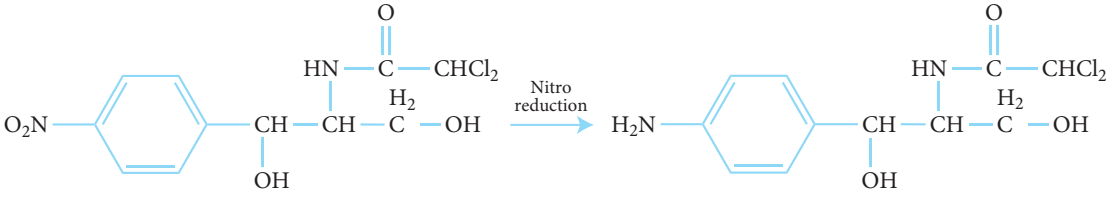
Resonance stability

Figure 1.72 Resonance stability of amides.



Lidocaine

Figure 1.73 Hydrolysis of amides occurs by amidase enzymes during Phase I reactions.



Chloramphenicol

Figure 1.74 Reduction of a nitro group to an amino group is the usual metabolic pathway for nitro groups.

Nitro Groups

Nitro groups consist of a nitrogen atom joined to two oxygen atoms; that is, NO_2. The nitrogen atom is positively charged and the oxygen atoms are partially negatively charged. Nitro groups have a powerful attraction for electrons, meaning that they are strong electron-withdrawing groups. Such groups are commonly found in aromatic chemistry but much less commonly encountered in aliphatic chemistry. Reduction of the nitro group to the corresponding amine is the usual metabolic pathway for drugs that possess a nitro group (**Figure 1.74**). A typical example is the chloramphenicol antibiotic (Chloromycetin, from Canada).

Sulfonic Acids and Sulfonamides

Sulfonic acids are named by first naming the hydrocarbon group as a separate word and then following it with the words "sulfonic acid." Because of the electron-withdrawing property of the SO_2 group, sulfonic acid has a higher acidity than either phenol or carboxylic acid (**Figure 1.75**). Similar to sulfonic acid, a sulfonamide can be named by first naming the carbon group as a separate word and then following it with the word "sulfonamide."

A wide range of drugs contain sulfonamide; these so-called sulfa drugs include diuretics, oral antidiabetic agents, antibiotics, and carbonic anhydrase inhibitors. Sulfa drug antibiotics work by inhibiting nucleic acid (DNA and RNA) synthesis. Such drugs are used to treat a variety of infections—for example, urinary tract infections, infections of the mucous membranes, gut infections, and pneumonia. Today, the antibiotic sulfonamides have largely been replaced by newer antibiotics

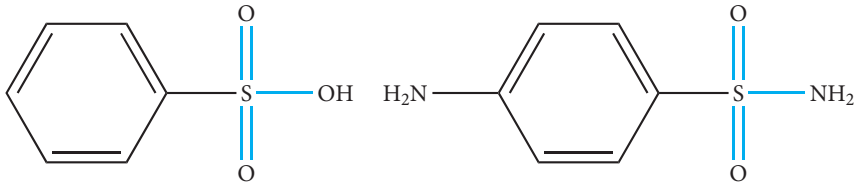


Figure 1.75 Structures of sulfonic acids and sulfonamides.

owing to the development of bacterial resistance to the older agents. However, a few sulfonamides, including mafenide acetate (Sulfamylon), are still used to treat second- and third-degree burns.

Sulfanilamide (Prontosil) was introduced in the 1930s by the pharmaceutical company Bayer as an antibiotic agent to treat bacterial infections. Prontosil had been shown to inhibit the growth of streptococci. The discovery of Prontosil led to Gerhard Domagk receiving the Nobel Prize in medicine in 1939. When Domagk checked Prontosil on a bacterial culture, the drug did not show any antibacterial effect. However, the research indicated that the drug should have an effective antibacterial effect in humans. Domagk showed that Prontosil was metabolized to sulfanilamide, which explained why Prontosil did not exert any antibacterial effect on a bacterial culture. Prontosil is no longer marketed.

Sulfonamides have low water solubility and weak acidity because the hydrogen attached to the nitrogen is made acidic by the strongly electron-withdrawing SO_2 group. This property ensures that sulfonamides readily form salts with bases. One of the major problems with sulfa drugs, which often justifies their discontinuation in human patients, is that they cause allergic reactions.

Learning Bridge 1.5

Lidocaine (Lidoderm) is a local topical anesthetic. Your job in a pharmaceutical company is to see if you can form a salt of a lidocaine powder. Pick up the lidocaine package insert from your pharmacy site and look at the structure of this compound. As you can see, there are two nitrogen atoms in lidocaine.

A. How would you form a salt of this drug?
B. Which amino group would you use to form the salt? Why?
C. Why do you want to form a salt of the lidocaine powder?

Thioethers

The names of thioethers (or thiols) are formed by using the prefix names for the groups R and R′ in alphabetical order as separate words, then adding the class name "sulfoxide" or "sulfone" (**Figure 1.76**). Thioethers are commonly oxidized to sulfoxide or sulfone (**Figure 1.77**).

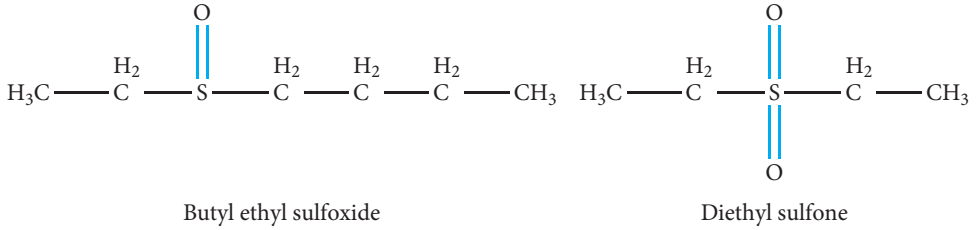


Figure 1.76 Structures of thioethers.

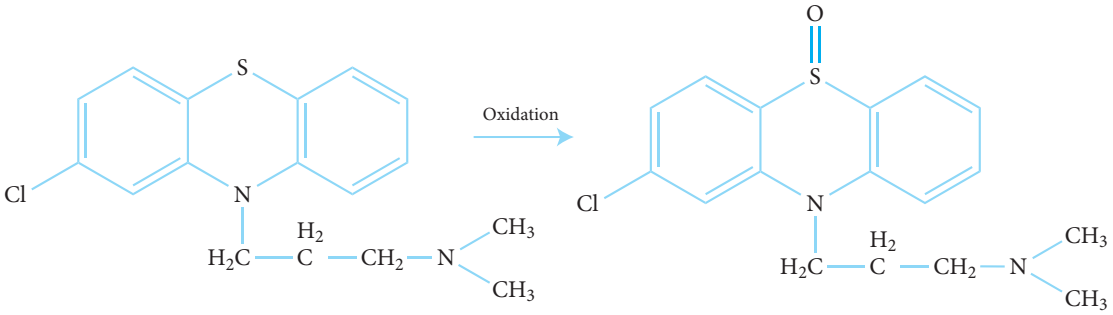


Figure 1.77 Thioethers are commonly oxidized to sulfoxide or sulfone. One example is chlorpromazine, which is used as an antipsychotic and antiemetic drug in the United States and Canada.

Disulfides play an important role in the stability of protein structures (their important biological role is discussed in the *Introduction to Biochemistry* chapter). The formula for disulfides is R—S—S—R. Disulfides are often prone to reduction, where the disulfide bridge is reduced by addition of hydrogen atoms:

$$R—S—S—R \rightarrow R—SH + R—SH$$

Drug Molecules as Acids and Bases

Most drugs are small organic molecules that act in solution as either weak acids or weak bases. To understand drugs and their actions, you must have a good command of acid–base theory. Let's start with the following concepts:

- Electrolytes
- Acid–base definitions
- Acid–base parameters (pH, K_a, and pK_a)

Electrolytes

An electrolyte is a compound that, when dissolved in a solvent (usually water), conducts electricity because it dissociates into ions (charged species). Negative ions move toward a positive terminal (or anode), while positive ions move toward a negative terminal (or cathode). This kind of ion movement allows the passage of electrical current through the solution.

There are two kinds of electrolytes:

- *Strong electrolytes*: These compounds dissociate almost completely into ions in solution, like HCl (a strong acid) or NaOH (a strong base).
- *Weak electrolytes*: These compounds dissociate only to small extent into ions in a solution, like acetic acid (a weak acid). Because many drugs are weak acids, you will find many of them function as weak electrolytes.

Three concepts are used to define acids and bases: (1) Arrhenius acid–base theory, (2) Brønsted-Lowry acid–base theory (often referred to as the Brønsted definition), and (3) Lewis acid–base theory.

Arrhenius Acid–Base Definition

With this concept, acids and bases are classified in terms of their formula and their behavior in water. According to the Arrhenius definition, an acid is a chemical substance that contains a hydrogen atom in its formula and dissociates in water to produce H_3O^+ (i.e., $H_2O + H^+$). Examples include HCl and HNO_3. A base is a chemical substance that contains an OH group in its formula and dissociates in water to yield OH^- (i.e., hydroxide). Examples include KOH and NaOH.

The Arrhenius definition does not include all bases, because some bases do not have any OH groups in their structure (e.g., ammonia, NH_3). The Brønsted-Lowry definition, in contrast, addresses this possibility.

Brønsted-Lowry Acid–Base Definition

With this concept, acids and bases are classified according to their ability to perform a proton (H^+) transfer. An acid is any species that donates a proton; it must have a hydrogen atom in its formula. Thus all Arrhenius acids are also Brønsted-Lowry acids. Examples include HCl and HNO_3. A base is any species that accepts a proton; the base must have lone-pair electrons to accept that proton. Thus all Arrhenius bases are also Brønsted-Lowry bases.

Lewis Acid–Base Definition

The Lewis acid–base definition highlights the role of electron pairs. An acid is any species that accepts an electron pair; an example is the electron-deficient hydrogen ion (H^+). A base is any species that donates an electron pair; an example is the electron-rich ammonia, NH_3:

$$NH_3 + H^+ \rightarrow NH_4^+$$

In this example, H^+ acts as a Lewis acid and accepts a pair of electrons from ammonia. Ammonia is a Lewis base because it donates a pair of electrons to H^+.

The Lewis acid–base definition is much broader than the Brønsted definition. In other words, it includes acids and bases that neither the Arrhenius nor Brønsted definition covers. For example, when an electron-poor molecule, such as BF_3, reacts with ammonia, the BF_3 acts as an acid—a condition that cannot be explained by the Arrhenius and Brønsted definitions (**Figure 1.78**).

In the Lewis model, electron pairs in an acid–base reaction are not given away from base to acid, but rather are shared. Two important conclusions emerge from this model:

1. An electrophile is also an electron-pair acceptor; that is, it is also a Lewis acid.
2. A nucleophile is also an electron-pair donor; that is, it is also a Lewis base.

In this textbook, we will use only the Brønsted-Lowry definition to define an acid or a base.

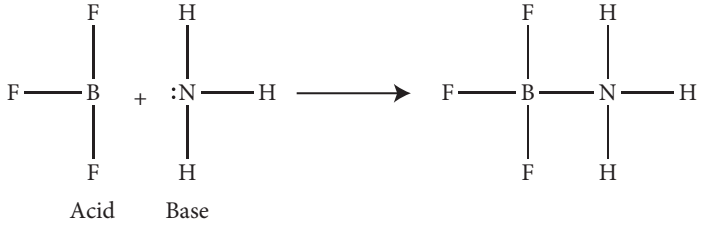


Figure 1.78 BF_3 is a Lewis acid because it is an electron-poor molecule and, as a result, accepts a pair of electrons from ammonia. Ammonia is a Lewis base because it donates a pair of its electrons to BF_3.

Acid–Base Parameters (pH, K_a, and pK_a)

It is important to emphasize a few parameters and concepts in acid–base theory to understand how drugs behave as acids or bases in a solution. Pure water, like any weak acid, slightly dissociates into ions (i.e., OH^- and H_3O^+):

$$H_2O \leftrightarrows OH^- + H_3O^+ \quad (1.1)$$

Because the dissociation process gives one H_3O^+ ion and one OH^- ion, the concentrations of these two ions are identical. From now on, for simplicity, we will use H^+ instead of H_3O^+. The equilibrium constant for Equation 1.1 is given by the following expression:

$$K_{eq} = \frac{[H^+][OH^-]}{[H_2O]} \quad (1.2)$$

which can be rearranged to give:

$$K_{eq}\,[H_2O] = [H^+] \times [OH^-] \quad (1.3)$$

The K_{eq} value for water is known (1.8×10^{-16} M). In pure water, the concentration of water is very high: $[H_2O] = 55.5$ M. If we plug these numbers into Equation 1.3, we obtain the ion product of water, K_w:

$$K_{eq}\,[H_2O] = K_w = [H^+] \times [OH^-] \quad (1.4)$$

$K_w = 1.8 \times 10^{-16}\ M \times 55.5\ M = 1 \times 10^{-14}\ M^2 = [H^+] \times [OH^-]$

As mentioned earlier, in pure water, $[H^+] = [OH^-]$. The last calculation indicates

$1 \times 10^{-14}\ M^2 = [H^+] \times [OH^-] = [1 \times 10^{-7}\ M] \times [1 \times 10^{-7}\ M]$

The importance of Equation 1.4 is that it applies to all aqueous solutions that include water. Because K_w is constant for any solution, we can determine the concentration of one species if we know the concentration of the other species. For instance, if an acid is present in water, the concentration of H^+ must be large and the concentration of OH^- must be small.

Example 1.1: The concentration of H^+ in milk is 4.5×10^{-7} M. What is the concentration of OH^- in milk?

Answer: According to Equation 1.4:

$1 \times 10^{-14}\ M^2 = 4.5 \times 10^{-7}\ M \times [OH^-]$

$[OH^-] = 1 \times 10^{-14}\ M^2 / 4.5 \times 10^{-7}\ M = 2.2 \times 10^{-8}\ M$

It is easier to work with the logarithm (log) of $[H^+]$ to avoid the negative power of 10 (e.g., 1×10^{-x}). Therefore pH = –log $[H^+]$. The pH for milk in the previous example is

$pH = -\log [H^+] = -\log (4.5 \times 10^{-7}) = 6.3$

As you can see, it is easier to say 6.3 than to say the concentration of H^+ is 4.5×10^{-7} M.

If you know the concentration of H^+, you can easily calculate the pH; conversely, if you know the pH, you can easily calculate the concentration of H^+.

$pH = -\log [H^+]$

$[H^+]$ = antilog of (–pH)

Example 1.2: The large intestine is the most alkaline part of the gastrointestinal tract (its pH is 8.5). What is the concentration of H^+ in the large intestine?

Answer:

$[H^+]$ = antilog of (–8.5) = 3.16×10^{-9} M

The reaction of a weak acid (like acetic acid, hereafter, artificially, called HAc) with water, like any chemical equilibrium, can be expressed by an equation similar to the one that we wrote for water:

$$H_2O + HAc \leftrightarrows AC^- + H_3O^+ \qquad (1.5)$$

Again, for simplicity, we will use H^+ instead of H_3O^+.

In the same way we expressed the equilibrium constant for water, we can express the equilibrium constant for the reaction of an acid with water. In other words, if we multiply the equilibrium constant K_{eq} with the concentration of water, $[H_2O]$, we make a new parameter called K_a.

$$K_{eq} = \frac{[H^+][Ac^-]}{[H_2O][HAc]} \qquad (1.6)$$

$$K_{eq}[H_2O] = \frac{[H^+][Ac^-]}{[HAc]} = K_a \qquad (1.7)$$

K_a is the dissociation or ionization constant for dissociation of a weak acid—for instance, the dissociation of HAc, acetic acid. Therefore the new reaction at equilibrium will be $HAc \leftrightarrows AC^- + H_3O^+$ and the ionization constant for this reaction can be expressed as follows:

$$K_a = \frac{[H^+][Ac^-]}{[HAc]} \qquad (1.8)$$

As Equation 1.8 indicates, K_a is given by the concentration of the products (H^+ and Ac) divided by the concentration of the reactant (HAc). For the same reason that we mentioned in conjunction with the pH, it is easier to work with the log of K_a to avoid the negative power of 10:

$pK_a = -\log K_a$

Strong acids are the acids that completely ionize in a solution. When a strong acid such as HCl dissociates in a solution, the concentrations of the H^+ and conjugate base (Cl^-) are equal to the concentration of the acid:

$$HCl \leftrightarrows Cl^- + H^+$$

For instance, if you start with 0.7 M HCl, the concentrations of H^+ and Cl^- will be 0.7 M as well. Thus, to measure the pH of a solution containing a strong acid (or base), you need to know only the concentration of that acid (or base).

Example 1.3: What is the pH of a solution when you add 0.3 M nitric acid (a strong acid, HNO_3) into water?

$$HNO_3 \leftrightarrows NO_3^- + H^+$$

Answer: If you start with 0.3 M HNO_3, the concentrations of H^+ and NO_3^- will be 0.3 M, too.

$pH = -\log [H^+]$

$-\log 0.3 = 0.52$

Another way to calculate the pH with higher accuracy is to consider the activity of H^+:

$$pH = -\log(\gamma^+ \times [H^+]) \quad (1.9)$$

where γ^+ is the activity coefficient—that is, the fraction of the actual concentration of the proton that is active. Generally, when you are dealing with nonideal solutions (i.e., solutions with a high concentration of acid or solutions containing many salts), the effective concentration of H^+ is lower than the actual concentration.

Example 1.4: Calculate the pH of 0.1 M HCl with the activity coefficient of 0.83.

Answer: According to Equation 1.9:

$pH = -\log (\gamma^+ \times [H^+])$

$pH = -\log (0.83 \times 0.1\ M) = 1.08$

Now that you have learned how to express the dissociation constant, K_a, for weak acids, let's use this constant to calculate the pH of a weak acidic solution. K_a is a constant for a given compound, at a given temperature, and for a weak acid is much less than 1.

Example 1.5: What is the pH of a solution when you add 0.2 M acetic acid (a weak acid, HAc) to water? K_a for acetic acid is 1.74×10^{-5}.

Answer: HAc is a weak acid and will *partially dissociate* in water; that is, HAc (undissociated) will continue to be a significant species in the solution. Thus the solution will contain HAc, Ac^-, and H^+ (**Figure 1.79**).

First write the reaction for the system:

$HAc \leftrightarrows AC^- + H_3O^+$

Next, write the dissociation constant (K_a) for the system:

$$K_a = \frac{[H^+][Ac^-]}{[HAc]}$$

Also write the total concentration of both species in the solution (C_a):

$C_a = [HAc] + [Ac^-]$

which we can rewrite as

$[HAc] = C_a - [Ac^-]$

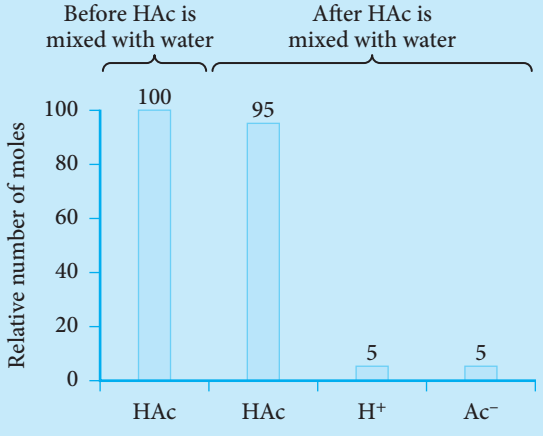


Figure 1.79 When a weak acid is added to water, it will dissociate to only some extent (≤5%). The remaining acid (≥95%) will remain intact.

Here you are dealing with a weak acid that does not dissociate completely. This means you have to take into account the concentration of HAc because there is a lot of undissociated HAc in the solution (in other words, if all of the HAc was dissociated into Ac^-, no HAc would be left).

Let's rewrite the dissociation constant according to Equation 1.8:

$$K_a = \frac{[H^+][Ac^-]}{C_a - [AC^-]} \quad (1.10)$$

The concentration of $[Ac^-]$ will be the same as the concentration of $[H^+]$ in the solution, so we can express it as follows:

$$K_a = \frac{[H^+][H^+]}{C_a - [H^+]} \quad (1.11)$$

which gives

$$[H^+]^2 = K_a\,(C_a - [H^+]) \quad (1.12)$$

The square root of Equation 1.12 gives Equation 1.13:

$$[H^+] = \sqrt{K_a (C_a - [H^+])} \quad (1.13)$$

If the extent of dissociation is small—that is, when you have a weak acid, only 5% of C_a will dissociate ($[H^+] << C_a$)—then we have

$$[H^+] = \sqrt{K_a \times C_a} \quad (1.14)$$

Now let's go back to the original question: What is the pH of a solution when you add 0.2 M acetic acid (a weak acid, HAc) to water? K_a for acetic acid is 1.74×10^{-5}. According to Equation 1.14:

$$H^+ = \sqrt{1.74 \times 10^{-5} \times 0.2\ M} = 1.86 \times 10^{-3}$$

$pH = -\log [H^+]$; $pH = -\log 1.86 \times 10^{-3} = 2.73$

Check the assumption you made earlier, which was $[H^+] << C_a$: $1.8 \times 10^{-3} << 0.2$.

In Example 1.5, we did not consider the concentration of H^+ that was contributed by water. Water, as a weak acid, also dissociates; thus the H^+ from water will add to the H^+ that comes from the acid. However, you do not need to account for the concentration of H^+ from water unless you are dealing with a very dilute solution.

Salt Formation, Ionization, and Water Solubility of Drug Molecules

Salt Formation

A salt is formed when an acid is mixed with a base. In such a reaction, the hydrogen atom of the acid is replaced by the cation of the base. Because there are many acids and bases, so there are also many salts. The following reaction is a typical acid–base interaction to form a salt:

$HCl + NaOH \rightarrow NaCl + H_2O$

Acid + Base → Salt + Water

Figure 1.80 shows a salt formation reaction in which a weakly acidic drug is mixed with a strong base (NaOH). Keep in mind that the majority of drugs behave as either weak acids or weak bases.

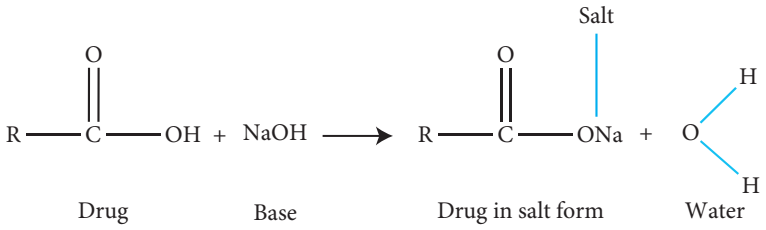


Figure 1.80 Formation of a salt when a weakly acidic drug is mixed with a strong base (NaOH).

Salt Hydrolysis

Most salts are strong electrolytes that completely dissociate into ions in water. When the ions of the salt react with water, the process is called salt hydrolysis. When you think about a salt, realize that the salt, upon dissociation in a solution, changes the pH of the solution. The stronger partner from which the salt is made dominates in the resulting solution. For example, when a salt is formed from a strong acid and a weak base, the salt produces an acidic solution (lower pH of the solution). In other words, the strong acid in this example decrees the final fate of the solution—a low pH.

A few examples of how salts can change the pH of a solution are described here.

Acidic Salt

NH_4Cl (ammonium chloride) is made by mixing a strong acid (HCl) with a weak base (NH_3). If you dissolve NH_4Cl in water, the solution becomes acidic. NH_4Cl, upon dissociation into water, produces NH_4^+, which acts as an acid (because it donates H^+ to the solution) and thereby increases the amount of H^+ in the solution (lowering the pH). In this example, the NH_4Cl is an acidic salt.

$$NH_4Cl\ (\text{solid}) \rightarrow NH_4^+\ (\text{aqueous}) + Cl^-\ (\text{aqueous})$$

$$NH_4^+ + H_2O \leftrightarrow NH_3 + H^+$$

Basic Salt

If a salt is formed by mixing a strong base with a weak acid, the salt in the solution produces a basic solution (increases the pH of the solution). An example is NaAc (sodium acetate), which is made from a strong base (sodium hydroxide, NaOH) and a weak acid (acetic acid, HAc). The basic (high pH) solution results because Ac^- accepts H^+ from water, which increases the amount of OH^- in the solution. In this case, the NaAc salt is a basic salt.

$$NaAc\ (\text{solid}) \rightarrow Ac^-\ (\text{aqueous}) + Na^+\ (\text{aqueous})$$

$$Ac^- + H_2O \leftrightarrow HAc + OH^-$$

If the salt results from the reaction of a strong acid and a strong base, the salt will not change the pH of the solution. An example is table salt, NaCl, which is made from NaOH and HCl. If the salt results from the reaction of a weak acid and a weak base, it will be difficult to predict if the salt will be acidic or basic. Later in this chapter, we show how to calculate the ratio between an acid and its conjugate base by using the Henderson-Hasselbalch equation.

It is important to recognize the conjugate base of an acid. **Table 1.2** identifies a few acids and their conjugate bases.

Table 1.2 Conjugate Bases of a Few Acids

Acid	Conjugate Base
RCOOH	$RCOO^-$
RNH_3^+	RNH_2
H_3PO_4	$H_2PO_4^-$
H_2CO_3	HCO_3^-

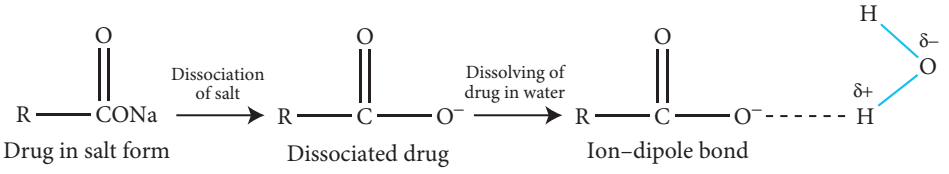


Figure 1.81 Formation of an ion–dipole molecule in a salt hydrolysis process.

Many drugs are provided in the form of salts to increase their water solubility. To confirm this fact, the next time you go to a pharmacy, look at some of the OTC products and see how many of them have "hydrochloride" or "sodium" in their names. When a drug is mixed with NaOH, the drug's name includes "sodium" (e.g., levothyroxine sodium). When a drug is mixed with HCl, the drug's name includes "hydrochloride" (e.g., minocycline hydrochloride).

Figure 1.81 shows how a drug in salt form dissociates first before it interacts with water to form an ion–dipole bond. As seen in the figure, the anion (oxygen) of the drug binds to the electron-deficient region (hydrogen atom) of water.

Example 1.6: Calculate the pH of an 0.3 M solution of NH_4Cl (salt). K_b for NH_3 is 1.8×10^{-5}.

Answer: NH_4Cl is a salt of a weak base (NH3) and a strong acid (HCl). We first write the reaction:

$$NH4Cl\,(solid) \rightarrow NH_4^+\,(aqueous) + Cl^-\,(aqueous)$$

$$NH_4^+ + H_2O \leftrightarrows NH_3 + H^+$$

The first thing you should think about is whether the salt will act as an acid or a base. In this case, it will work as an acid (see the preceding reaction). Thus what you need to know is K_a, not K_b. The dissociation constant for the acid is

$$K_a = \frac{[NH_3][H^+]}{[NH_4^+]}$$

We utilize the ion product of water to calculate K_a:

$$K_w = K_a \times K_b$$

$$K_a = K_w / K_b$$

We know that $K_w = 1 \times 10^{-14}$ (from the previous section), which in turns means

$$K_a = (1 \times 10^{-14}) / (1.8 \times 10^{-5}) = 5.56 \times 10^{-10}$$

Similar to how we solved the problem for a weak acid (recall the previous section), we can now solve the problem at hand:

$$[H^+] = \sqrt{K_a \times C_a}$$

$$pH = -\log [H^+] = 4.89$$

Example 1.7: What is the pH of an 0.20 M solution of sodium acetate (NaAc)? $K_b = 5.75 \times 10^{-10}$.

Answer: Think about whether the salt will act as an acid or a base. Here, it acts as a base:

$$NaAc\ (solid) \rightarrow Ac^-\ (aqueous) + Na^+\ (aqueous)$$

$$AC^- + H_2O \leftrightarrows HAC + HO^-$$

$$K_b = \frac{[HAc][OH^-]}{[AC^-]}$$

$$[OH^-] = \sqrt{K_b \times C_b}$$

Recall that you have the concentration of OH^-, but not H^+.

$$[OH^-] = 1.07 \times 10^{-5}$$

To know the pH, you should have the concentration of H^+:

$$K_w = [H^+] \times [OH^-]$$

$$[H^+] = K_w/[OH^-]$$

Now one can easily calculate the concentration of H^+ and thereby the pH:

$$[H^+] = 1 \times 10^{-14}/[OH^-]$$

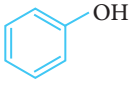
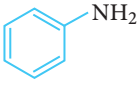
$$pH = -\log [H^+] = 9.03$$

So far, you have learned how you can calculate the pH of a solution containing a weak acid. You also have learned that if the extent of dissociation of H^+ is low, you can assume that the total concentration of acid in the solution is much higher than the concentration of the dissociated H^+ (i.e., Ca >> H^+).

But what if you have to deal with an acid for which you have no idea of the extent of H^+ dissociation? Could you use the same assumption as we did in the past examples? The short answer is no: If you make the same assumption, you may end up with an incorrect calculation of the pH. If the initial concentration of the weak acid (i.e., when the acid has not yet been in contact with your solution) is at least 100 times higher than its K_a, you can assume that the concentration of H^+ that dissociates is negligible compared to the initial concentration of the acid. For instance, in Example 1.6, the initial concentration of the acid (0.3 M) was more than 100 times higher than its K_a (5.56×10^{-10}).

Table 1.3 indicates the strengths of commonly used acidic and basic functional groups. The pK_a values are indicated for the acidic functional groups and for the conjugate acids of the basic functional groups.

Table 1.3 Acid/base Strengths, Based on pK_a Numbers, of Commonly Used Functional Groups in Drug Molecules

Acidic Functional Group	pK_a	Basic Functional Groups	pK_a of Conjugate Acid
R—SO_3H	1	R—NH_2	10–11
R—C(=O)—OH	4–5	R—C(=NH)—NH_2	9–10
	8–11		1–5

Adapted from Lemke T, Roche V, and Zito W. Review of Organic Functional Groups: Introduction to Medicinal Organic Chemistry. Lippincott Williams & Wilkins; 5th edition (2011).

Ionization

Generally, the drugs that are hydrophobic (un-ionized) cross cell membranes more readily than those that are hydrophilic (ionized). Important concepts regarding the acid–base properties of these drugs include the following:

1. Henderson-Hasselbalch equation
2. Titration curve
3. Buffer capacity

Henderson-Hasselbalch Equation

The Henderson-Hasselbalch equation is used to express and calculate the pH of a solution, and thereby to calculate the ionization of a weak acid or base. It fits very well to an acid–base titration curve.

To understand this expression, let's go back to the acetic acid (HAc) ionization and its dissociation constant:

$$HAc \leftrightarrows AC^- + H^+$$

Because we are interested in knowing the concentration of H^+, we can express the dissociation constant as follows:

$$K_a = \frac{[H^+][Ac^-]}{[HAc]} \qquad (1.15)$$

which can be rearranged to this expression:

$$[H^+] = K_a \frac{[HAc]}{[Ac^-]} \qquad (1.16)$$

We can solve for $[H^+]$ by using the negative logarithm of all terms in Equation 1.16:

$$-\log[H^+] = -\log K_a - \log([HAc]/[Ac^-]) \qquad (1.17)$$

To cancel the negative sign, we rewrite the last equation to get the Henderson-Hasselbalch equation:

$$pH = pK_a + \log([Ac^-])/[HAc]) \qquad (1.18)$$

Equation 1.18 is the same as Equation 1.19, which is also referred to as the Henderson-Hasselbalch equation:

$$\text{pH} = \text{p}K_a + \log \frac{[\text{Conjugate base}]}{[\text{Acid}]} \tag{1.19}$$

The Henderson-Hasselbalch equation is a very practical tool when preparing and calculating buffer solutions in a biochemical or compounding laboratory. This equation can be used to estimate the ionization of weakly acidic or basic drugs as well. When a weakly acidic or basic drug is administered and dissolves in the body, the drug ionizes to some extent depending on its pK_a and the pH of the body fluid in which the drug is dissolved in.

We can use the Henderson-Hasselbalch equation to estimate the percentage of ionization of HAc as follows:

For acidic drugs:

$$\%\ \text{ionized} = \frac{1 \times 100}{\text{Antilog}\,(\text{p}K_a - \text{pH}) + 1} \tag{1.20}$$

For basic drugs:

$$\%\ \text{ionized} = \frac{1 \times 100}{\text{Antilog}\,(\text{pH} - \text{p}K_a) + 1} \tag{1.21}$$

A few examples will serve to demonstrate how useful Equation 1.20 and Equation 1.21 are.

Example 1.8: What is the percentage ionization of indomethacin (Indocin) (pK_a = 4.5; i.e., an acidic drug) in the large intestinal tract (pH = 8.0)?

Answer: We are dealing with an acidic drug, so we use Equation 1.20:

$$\%\ \text{ionized} = \frac{1 \times 100}{\text{Antilog}\,(4.5 - 8) + 1} = 99.97\%$$

Example 1.9: What is the percentage ionization of ephedrine (pK_a = 9.5; i.e., a basic drug) in the large intestinal tract (pH = 8.0)?

Answer: We are dealing with a basic drug, so we use Equation 1.21:

$$\%\ \text{ionized} = \frac{1 \times 100}{\text{Antilog}\,(8 - 9.5) + 1} = 97\%$$

It is very important to know the percentage ionization for a drug. Oral administration of a drug (e.g., tablet, capsule, solution) results in a rapid passage of the drug through the esophagus and into the stomach; upon dissolving there, the drug finds its way quickly into the epithelial cells lining the intestines. The absorption of the drug occurs through the epithelial cells into the blood capillaries of the lamina propria. The blood containing the drug then travels via capillaries to reach the drug's sites of action (see the *Introduction to Pharmacodynamics* and *Introduction to Pharmacokinetics* chapters for more details of drug absorption).

An acidic drug will be un-ionized in an acidic milieu but will become ionized in an alkaline environment. Therefore, an acid in a basic milieu will carry a charge and be unable to directly

penetrate cell membranes; by the same token, a base will become ionized in an acidic milieu. Assuming an oral administration of a drug, the drug must go from the lumen of the gastrointestinal (GI) tract to the circulation on the other side of the GI tract. Membranes of the epithelial cells lining the lumen of the GI tract are lipophilic. Un-ionized drugs cross these lipophilic membranes, but ionized drugs do not (**Figure 1.82**). Keep in mind that ionized drugs are hydrophilic, whereas a cell membrane is made of many hydrophobic molecules (see also the *Introduction to Cell Biology* chapter).

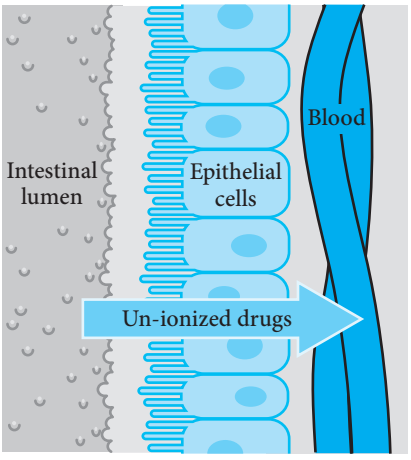


Figure 1.82 An un-ionized drug can readily cross the cell membranes of epithelial cells in the GI tract.

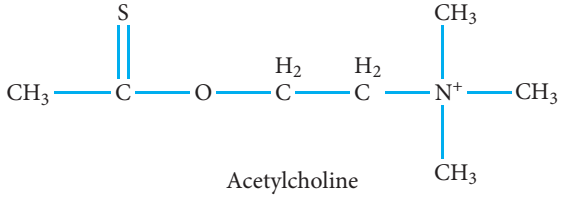
Titration and Buffer Capacity

Titration is an analytical procedure where a solution (often a base) with known volume and known concentration is added to another solution (an acid) with known volume but unknown concentration. This procedure is continued until the acid with unknown concentration has completely reacted with the base. At this point, an equivalence point is reached, where the number of moles of OH^- ions added to the solution equals the number of moles of H^+ ions originally present in the solution. In other words, when you do a titration of a weak acid, the acid dissociates in the solution to yield a small amount of H^+ ions. If you add a base (OH^-) to this solution, the OH^- ions react with the H^+ ions to form water (H_2O). Consequently, more H^+ ions dissociate and more OH^- ions react with H^+ to form more water, until you reach the equivalence point where there is no further H^+ left from the acid to be dissociated.

Learning Bridge 1.6

On the last day of your introductory pharmacy practice experience (IPPE), your preceptor gives you two assignments to see how you would apply your basic sciences knowledge to solve a water solubility problem.

A. Acetylcholi ne has an amino group and is a neurotransmitter that is involved in muscle contraction. Your preceptor asks you this question: If you were in charge of increasing the water solubility of acetylcholine, what could you do to make a salt of this neurotransmitter compound? She asks you to justify your answer. The structure of acetylcholine is shown in **Exhibit 1.2**.



Acetylcholine

Exhibit 1.2 Acetylcholine.

B. Levothyroxine is a thyroid hormone that is used to treat hypothyroidism. A solution contains levothyroxine and its salt, levothyroxine sodium. Explain what would happen if an acetic acid solution was added to this solution. The structures of free levothyroxine and its salt form (levothyroxine sodium) are shown in **Exhibit 1.3**.

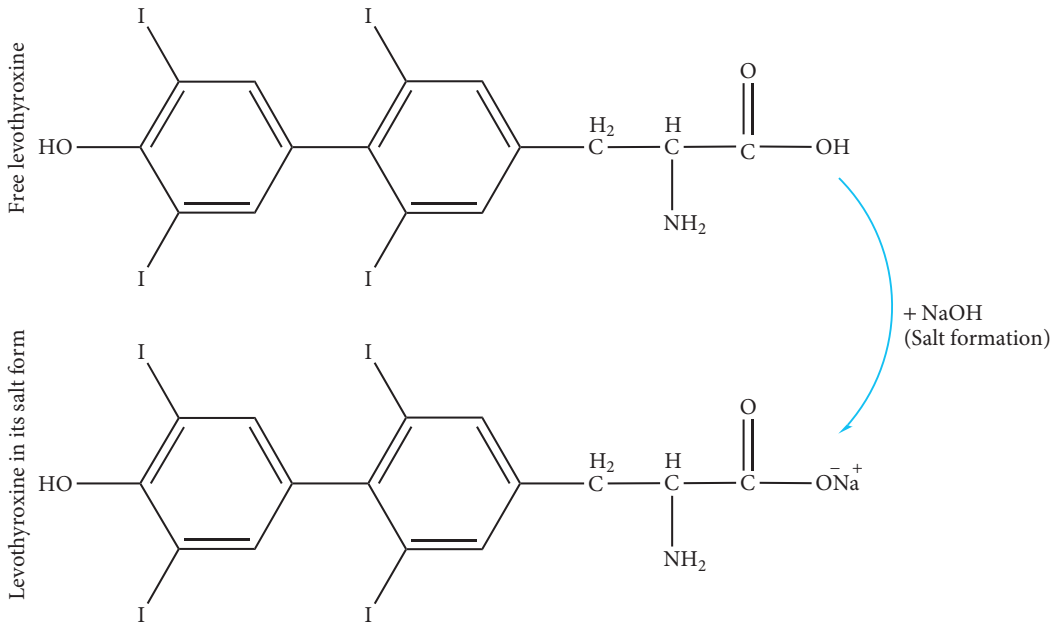


Exhibit 1.3 Free levothyroxine and its salt form (levothyroxine sodium).

Figure 1.83 demonstrates how a titration curve behaves during an acid–base titration experiment. As indicated, when 0.5 NaOH mole equivalent is added, half of the acetic acid has been dissociated so that the concentration of the proton acceptor (the conjugate base, Ac^-) is equal to the concentration of the proton donor (HAc). Based on the titration curve and the Henderson-Hasselbalch equation, if the concentration of the conjugate base is equal to the concentration of the acid, the pH of a solution is exactly the same as the pK_a of the acid (as shown in Figure 1.19 and **Figure 1.84**).

A titration curve shows the buffering range of a solution—that is, the points where the pH changes are minimal upon addition of an acid or a base to the solution. Such a curve allows you to calculate the concentration of an acid or base in a solution and assists you in calculating the pK_a value.

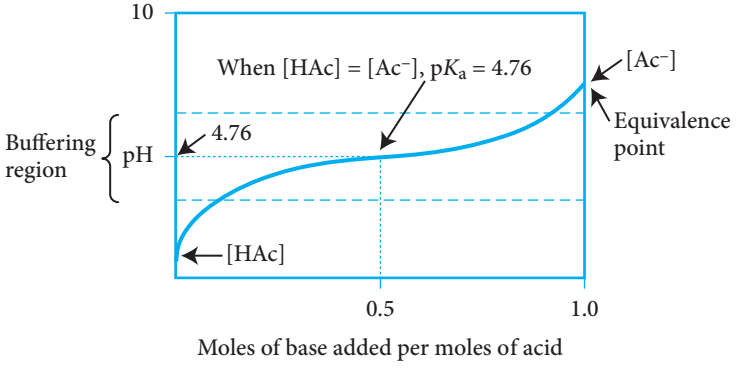


Figure 1.83 A titration curve is produced when a known concentration of strong base (NaOH) is titrated with an unknown concentration of a weak acid (HAc).

$$\frac{[Ac^-]}{[HAc]} = 1$$

$$pH = pK_a + \log \frac{[Ac^-]}{[HAc]} \xrightarrow{\log 1 = 0} pH = pK_a$$

Figure 1.84 In a buffer solution, when the concentration of an acid equals the concentration of its conjugate base, the pK_a of the acid equals the pH of the solution.

Learning Bridge 1.7

Suppose you have been asked to calculate the concentration of 10 mL vinegar in one of the compounding labs at your pharmacy program. One technique to measure the concentration of an acid (or a base) is to do a titration experiment. Suppose you add NaOH to the vinegar solution until you reach the equivalence point (you notice the equivalence point by using a pH paper that shows you a pH of 7.0—that is, it identifies when the vinegar is neutralized). To reach the equivalence point, you add 60 mL of 0.1 M NaOH. How would you calculate the concentration of the unknown acid (vinegar)?

Let's go back to Figure 1.83 and see how this titration curve can help us to identify two important pieces of data. First, the region in which the pH changes very little (i.e., –1 and +1 of the pK_a), which in our case is between 3.76 and 5.76, is called the buffering region. Second, the buffering capacity is highest when pH is equal to pK_a—that is, when HAc = Ac^-. Thus, when a drug's pK_a is equal to the pH of its milieu (the milieu could be a solution in a beaker, in your blood, in your stomach, or something else), the drug exists as 50% ionized and 50% un-ionized. In other words, the pK_a indicates the form (ionized or un-ionized) that a drug has at a given pH value.

The buffer capacity (β) describes how effectively a buffer can resist changes in the pH of a solution. It can be calculated for a solution by using Equation 1.22, where C is the molar concentration of the acid in the buffered solution. Assuming a constant concentration of C, the closer the dissociation constant (K_a) is to the concentration of the proton (H^+) in the solution, the higher the buffer capacity (β) is. In other words, Equation 1.22 indicates that the highest β is achieved when the pK_a of an acid equals the pH of the solution.

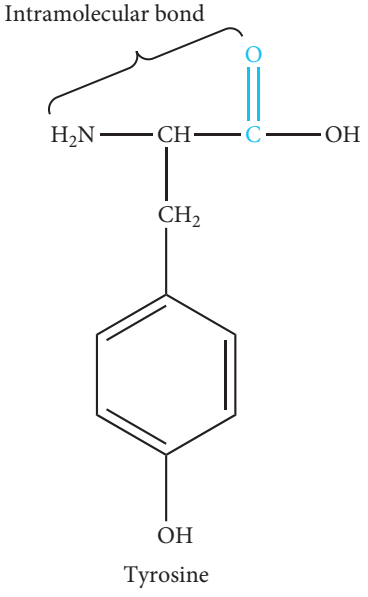


Figure 1.85 The intramolecular bond highlighted here does not allow the amino and carbonyl groups of the amino acid tyrosine to interact with water molecules.

$$\beta = \frac{2.3\,C\,K_a[H^+]}{(K_a + [H^+])^2} \qquad (1.22)$$

Example 1.10: Assume 0.20 M of an acetic acid solution is added to a solution that has a pH of 3.0. Calculate the buffer capacity for (1) the new solution, (2) a solution that has a pH of 4.76, and (3) a solution that has a pH of 5.76. The pK_a for acetic acid is 4.76.

Answer: First, take the –antilog of pK_a and pH to calculate K_a and $[H^+]$, respectively. Second, use Equation 1.22 to calculate the buffer capacity.

1. 0.008

2. 0.11

3. 0.04

As the results indicate, the highest buffer capacity is achieved when the pK_a is equal to the pH of the solution (i.e., answer 2).

Maintenance of the correct pH in the body is vital because pH alters the ionization of amino acids, the building blocks of proteins. As discussed in the *Introduction to Biochemistry* chapter, a change in the amino acid structure of a protein may change the ionization of the protein and, as a result, lead to inactivation of the protein. The body can tolerate a very small change in the blood's pH (pH 7.4 ± 0.3). A pH outside this range is life threatening because vital proteins lose the integrity of their structures and functions. In addition, distortion of the pH of blood leads to acidosis or alkalosis. The pH of body fluids is maintained by three major buffer systems: (1) HCO_3^-/H_2CO_3, (2) organic phosphates, and (3) proteins. All three buffers are present in the intracellular and extracellular fluids. The concepts of acidosis and alkalosis and the importance of maintaining a buffer system in the human body are discussed in the *Introduction to Nutrients* chapter.

Learning Bridge 1.8

Buffering dosage forms are used as antacids to neutralize "heartburn." While antacids neutralize the excess acid, they do not eliminate the "heartburn" condition. As a result, they should not be used for more than 2 weeks. During one of your intern hours at your introductory pharmacy practice experience (IPPE) site, one of the pharmacy technicians asks you to help her understand how some of the antacids work. She asks you two questions:

A. How does the antacid milk of magnesia work?

B. Alka-Seltzer (Alamag) is an analgesic OTC drug that contains a mixture of sodium bicarbonate ($NaHCO_3$), aspirin, and citric acid. Which of these three components acts as an antacid, and why?

Help the pharmacy technician to understand how the above antacids work.

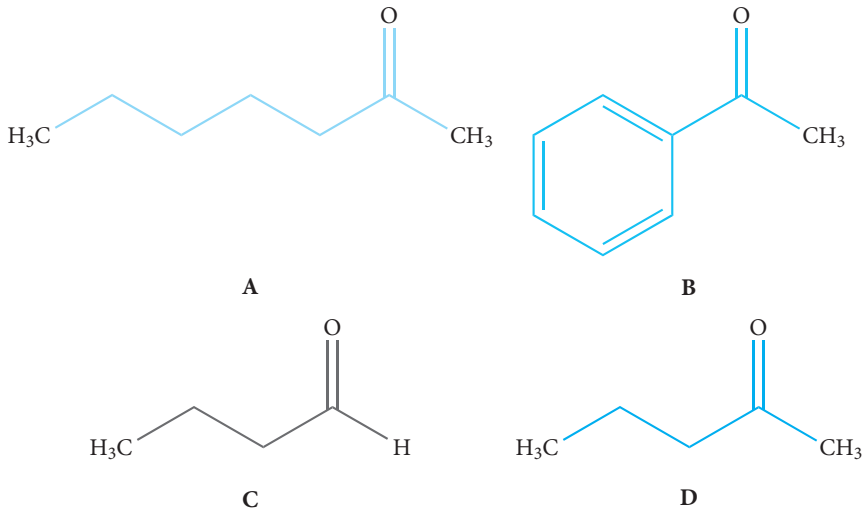


Figure 1.86 Four different molecules with different solubilities in water.

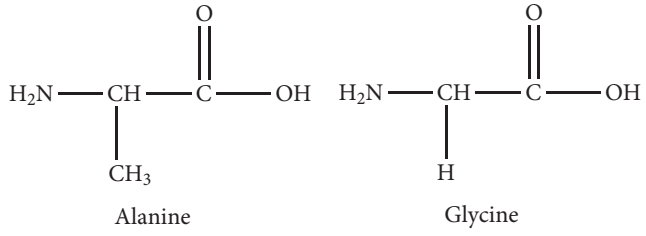


Figure 1.87 The side chains (CH_3 and H) are bound to a similar electronegative atom (C) in both amino acids. No electron attraction occurs between these atoms (between C and H); as a result, their side chain is nonpolar.

Water Solubility of Drug Molecules

For a molecule (drug) to be able to dissolve in water, the intramolecular and intermolecular bonds must first be broken so that water molecules can bind to the functional groups of the drug. Water is an ideal solvent because it is inexpensive, it is inert (i.e., has no pharmacological activity of its own), it is widely available, and its physical and chemical characteristics are well known.

Let's look at the structure of the amino acid tyrosine (**Figure 1.85**). The carboxyl group and amino group of tyrosine have opposite charges and, therefore, can interact with each other (i.e., intramolecular bonding). This means a water molecule cannot undertake an ion–dipole interaction to dissolve tyrosine. The phenol group by itself cannot dissolve tyrosine in water. As a result, tyrosine has a poor solubility in water. To break down the intramolecular bond, one can add NaOH or HCl (salt formation). This reaction enhances the water solubility of the salt.

Let's look at the structure of the four molecules in **Figure 1.86** to see which one has the highest water solubility and which one has the lowest water solubility. Molecule A has the longest carbon groups and, therefore, is hydrophobic (water insoluble). Molecule B has a benzene ring, so it is also hydrophobic. Molecules C and D are both less hydrophobic than A and B. In general, small ketones are more water soluble than small aldehydes. Molecule A is the least water-soluble molecule, and molecule D is the most water-soluble molecule. Generally speaking, functional groups

such as amino, hydroxyl, ester, nitro, and amide groups increase the water solubility of a drug, whereas aliphatic carbons, benzene rings, and halogens decrease the water solubility of a drug.

Greater water solubility, to some degree, will usually improve a drug's distribution within the circulatory system and increase its action. Drugs that are administered orally as solids or in the suspension form must be dissolved in the body's gastric fluid (an aqueous milieu) before they can be absorbed and transported to their site of action. The process in which the drug is dissolved in gastric fluid is called dissolution. The rate of dissolution depends on a few chemical and physical factors (these factors are discussed in the *Introduction to Pharmaceutics* chapter). However, the extent of dissolution depends only on the solubility of the drug, which in turn depends on the structure of the drug. Keep in mind that sometimes it is essential for drugs to have poor water solubility to achieve the best effect; for instance, if a drug has to pass through a membrane, it must be significantly hydrophobic.

Let's look at the structure of amino acids alanine and glycine. The R chain plays an important role in the solubility of an amino acid. The R chains of both alanine and glycine are nonpolar, which explains why these two amino acids are not water soluble (**Figure 1.87**).

Learning Bridge 1.9

Amy comes to your pharmacy to ask you about her concern regarding an OTC product that she has been using during the last two days. Amy has been using Anbesol (benzocaine with 0.5% phenol) to relieve the temporary pain of her orthodontic irritation. She just read the label for Anbesol and noticed that it contains phenol. Because Amy knows that phenol is a toxic molecule, she is worried that the phenol may have caused some damage to her mouth.

In addition, Amy mentions that last weekend while she was hiking, she came in contact with poison ivy. She has some skin irritation as a result of this contact and asks you if there is any OTC product to treat the poison ivy exposure.

A. How would you answer Amy's question about Anbesol?
B. How would you answer her question about relief from the poison ivy skin irritation?

Golden Keys for Pharmacy Students

1. Pharmacy education requires a solid foundation in chemistry. The more familiar you are with organic and inorganic chemistry, the better and faster you will understand many pharmaceutical topics, such as medicinal chemistry, biochemistry, pharmacology, and pharmaceutics.
2. Oxidation and reduction are very common reactions in biochemistry and metabolism of drugs. You must learn the basic concepts and mechanisms behind these two types of reactions.
3. Alcohols are readily available in many Western countries, are components of a few medications, and are the most widely available poison in the world.
4. Chemical bonds are divided into two major classes: covalent and noncovalent bonds. Pay special attention to ion–dipole and hydrogen bonds, which play important roles in salt hydrolysis of drugs and the structure and function of proteins, respectively.

5. It is important to recognize the different medicinal functional groups. These functional groups often maintain the integrity, stability, and pharmacological functionality of drugs.
6. Amines and carboxyl groups are the two most commonly encountered functional groups in drug structures. Both of these functional groups are important for salt formation, salt hydrolysis, and water solubility of drugs.
7. It is important to recognize the differences and similarities between amine and amide functional groups.
8. Alkyls are electron-releasing groups; aryls are electron-withdrawing groups. Attachment of these two functional groups to amines and carboxylic acids alters their basicity and acidic strength, respectively.
9. Esters are prone to hydrolysis. Hydrolysis of esters occurs in the presence of water, strong acids such as HCl, and esterase enzymes. Upon hydrolysis of an ester, an alcohol and a carboxylic acid are formed.
10. The Brønsted-Lowry acid–base definition is commonly used to express the acidic or basic properties of acids and bases. One simple reason why this definition is employed is because the proton transfer is readily visible in reaction schemes and equations when basic and acidic drugs participate in salt formation and salt hydrolysis, and for the indication of water solubility.
11. K_a is the dissociation or ionization constant for dissociation of a weak acid. The negative logarithm of K_a and the concentration of protons (H^+) are used in the form of pK_a and pH, respectively.
12. The equation $H^+ = \sqrt{K_a \times C_a}$ is very useful to calculate the pH of a weak acidic solution.
13. The equation $[OH^-] = \sqrt{K_b \times C_b}$ is very useful to calculate the pH of a weak basic solution.
14. A salt is formed when an acid is mixed with a base. Formation of a salt is often used to increase the water solubility of drugs in the pharmaceutical industry. However, if the salt cannot be hydrolyzed in water (i.e., if salt hydrolysis does not occur), the drug will not dissolve in water.
15. If a salt is formed by mixing a strong acid and a weak base, the salt, upon hydrolysis in a solution, reduces the pH of the solution. Conversely, if a salt is formed by mixing a weak acid and a strong base, the salt, upon hydrolysis in a solution, increases the pH of the solution.
16. If the initial concentration of the weak acid (i.e., when the acid has not been in contact with the new solution yet) is at least 100 times higher than its K_a, you can assume that the concentration of dissociated H^+ is negligible.
17. Hydrophobic (un-ionized) drugs cross cell membranes better than hydrophilic (ionized) drugs.
18. The Henderson-Hasselbalch equation is used to calculate the pH of a solution and to calculate the ionization of a weak acid or weak base. It fits very well to an acid–base titration curve. $\text{pH} = \text{p}K_a + \log \dfrac{[\text{Conjugate base}]}{[\text{Acid}]}$.
19. The percentage of ionization of acidic and basic drugs can be estimated by using two equations: for acidic drugs, $\%\ \text{ionized} = \dfrac{1 \times 100}{\text{Antilog}\,(\text{p}K_a - \text{pH}) + 1}$, and for basic drugs, $\%\ \text{ionized} = \dfrac{1 \times 100}{\text{Antilog}\,(\text{pH} - \text{p}K_a) + 1}$.

20. Titration is an analytical procedure where a solution (often a base) with known volume and known concentration is added to another solution (an acid) with known volume but unknown concentration. This procedure is continued until the number of moles of OH^- ions added to the solution is equal to the number of moles of H^+—that is, until an equivalence point is reached.

21. An acidic drug will be un-ionized in an acidic milieu but will ionize in an alkaline environment. Therefore, an acid in a basic milieu will carry a charge and be unable to directly penetrate cell membranes; by the same token, a base will ionize in an acidic milieu.

22. Attachment of functional groups such as amino, hydroxyl, ester, nitro, and amide groups to the structure of drugs increases the water solubility of the drugs. Conversely, attachment of functional groups such as aliphatic carbons, benzene rings, and halogens decreases the water solubility of drugs.

23. If you know the concentration of OH^- but not H^+, use the ion product of water to calculate the concentration of the H^+: $[K_w] = H^+ \times OH^- = 1 \times 10^{-14}$.

24. A solution containing a strong acid is not a buffer, and its pH can be calculated directly from the acid concentration alone. All of the strong acid dissociates into H^+. The following equation can be used directly: $pH = -\log [H^+]$.

25. A solution containing a strong base is not a buffer, and the $[OH^-]$ can be calculated directly from the base concentration alone. If you know $[OH^-]$, use K_w to calculate $[H^+]$.

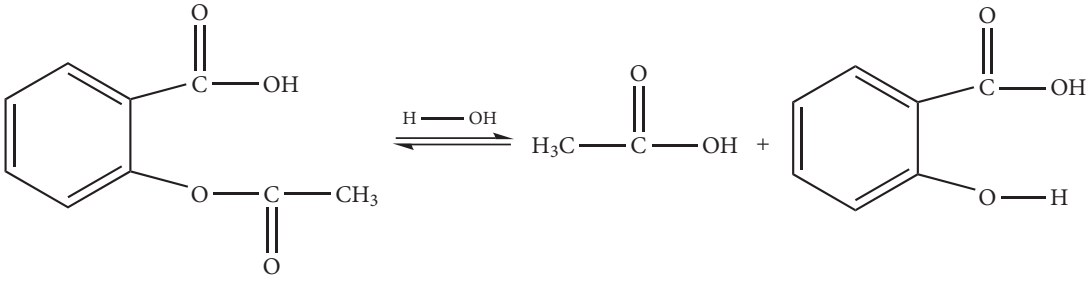
Learning Bridge Answers

1.1 You should refuse to fill this individual's medication, as there is a potential risk for severe nausea, tachycardia and orthostatic hypotension, palpitations, chest pain, and dyspnea. The most alarming side effect is the orthostatic hypotension, which can be fatal. Ask the patient to come back after 24 hours and be observant to ensure that he does not smell of alcohol before you fill his medication. It is very important to be familiar with drugs that produce a "disulfiram-like" effect so that you can counsel patients to avoid using alcohol while taking these medications.

1.2 **A.** In 2001, the FDA approved fomepizole for the treatment of methanol and ethylene glycol poisoning. This drug acts by blocking the alcohol dehydrogenase enzyme, thereby inhibiting oxidization of ethylene glycol and methanol. It has been suggested, based on *in vitro* studies, that fomepizole has approximately 8,000 times higher affinity than ethanol for alcohol dehydrogenase. Sometimes ethanol is given to methanol-intoxicated patients to counteract the effect of methanol, because ethanol has 10–20 times greater affinity for alcohol dehydrogenase than methanol does (a competitive inhibitor of alcohol dehydrogenase enzyme; see the *Introduction to Biochemistry* chapter). This inhibition blocks methanol's access to this enzyme, which in turn impairs the metabolism of methanol (i.e., ethanol or fomepizole keeps the enzyme busy). Recall that it is not the methanol itself that is a killer, but rather its metabolites (formaldehyde and formic acid).

B. Fomepizole (Antizol) is known to inhibit alcohol dehydrogenase, which otherwise catalyzes the metabolism of ethanol, ethylene glycol, and methanol. As a result, fomepizole is indicated in the treatment of methanol or ethylene glycol poisoning. Disulfiram (Antabuse) inhibits the aldehyde dehydrogenase enzyme, so it is not helpful in the case of methanol poisoning.

1.3 A. Because acetylsalicylic acid is an ester molecule, it is prone to nucleophilic attack by OH^- from the bathroom's moisture (see **Exhibit 1.4**). Aspirin, upon hydrolysis, is broken down into acetic acid (a carboxylic group) and an alcohol group (salicylic acid). Vinegar has 5–10% acetic acid, so the carboxylic acid part (acetic acid) is responsible for the odor of vinegar. Acetic acid is used for formation of acetylsalicylic acid (aspirin) from salicylic acid. When the concentration of acetic acid is greater than 50%, however, the solution can damage the skin, eyes, nose, and mouth.

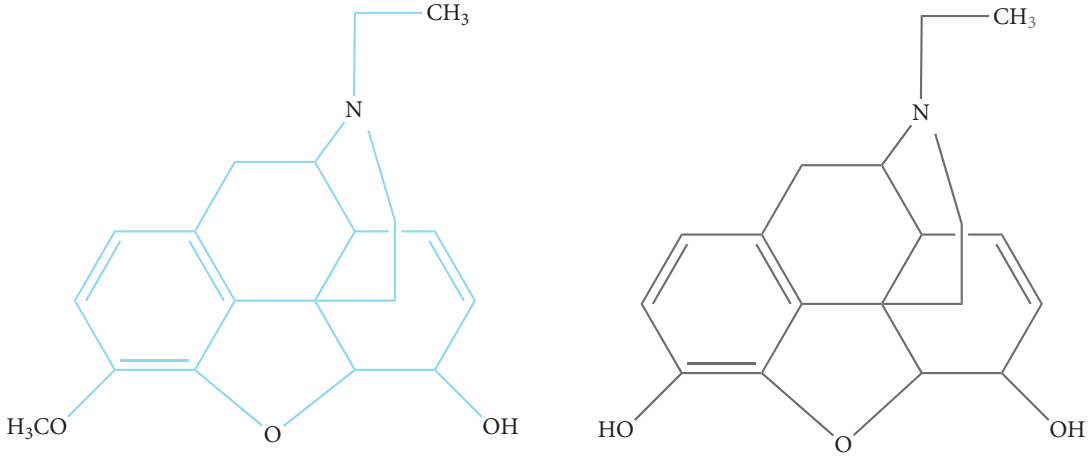


Acetylsalicylic acid (aspirin) Acetic acid (in vinegar) ~~Salicyclic~~ acid

Exhibit 1.4 Hydrolysis of an ester bond in acetylsalicylic acid (aspirin) produces an acid (a carboxylic group) and an alcohol group (salicylic acid).
Adapted from Timberlake KC. Organic and biological chemistry: structures of life. San Francisco: Benjamin Cummings; 2001.

B. You should advise the woman to not give any aspirin-containing agent to Emily. Aspirin belongs to the category of nonsteroidal anti-inflammatory drugs (NSAIDs). It is most commonly used for its anti-inflammatory effects, but is not recommended for children's fever because it has been associated with Reye syndrome in children. Reye syndrome is a rare, but sometimes fatal condition in children and young adults with viral infection. It may lead to liver damage, cerebral edema, and death. Children with fever should receive acetaminophen or ibuprofen instead of aspirin.

1.4 The opium poppy contains at least 20 alkaloids (e.g., codeine, morphine) (**Exhibit 1.5**). All parts of the poppy, including the seeds, contain morphine. Eating poppy seeds from bread is sufficient to put morphine in Amy's blood sample.



Codeine Morphine

Exhibit 1.5 Many alkaloids are used as analgesics and for the creation of euphoria.

1.5 The structure of lidocaine is shown in **Exhibit 1.6**.

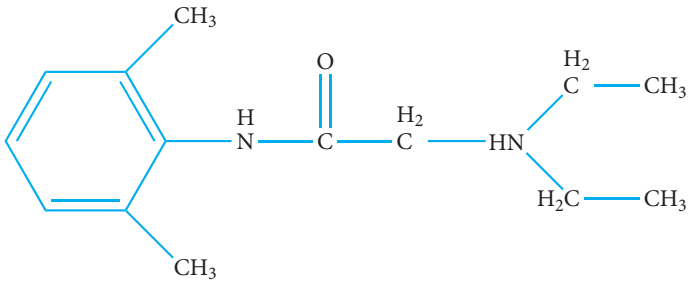


Exhibit 1.6 Lidocaine.

A. Since this drug has a basic amino group, it must work as a basic drug, too. If you mix a base with an acid, you make a salt. Use HCl to make the salt.

B. Unlike amines, amides do not have the basicity property; thus the nitrogen atom in the amide group will not interact with an acid to form a salt.

C. An amine salt is soluble in body fluids (i.e., the salt formation increases the water solubility of the drug).

1.6 **A.** The quaternary nitrogen has no lone-pair electrons that can bind to H^+ from an acid (i.e., it cannot be considered a base). If it is not a base, it cannot make a salt with an acid.

B. This solution has both free levothyroxine and its salt. Acetic acid dissociates to place H^+ into the solution, which will react with levothyroxine sodium to produce more free levothyroxine.

1.7 First write the reaction scheme:

$$HAc + NaOH \rightarrow NaAc + H_2O$$

To determine the molarity (concentration) of the vinegar solution, you need to know the number of moles of acetic acid dissolved in 10 mL of sample; that is, you have the volume but you are looking for the number of moles. First, find out how many moles of NaOH you used to reach the equivalence point. At the equivalence point, the ratio of moles of NaOH added to the moles of acid is 1. Moles of NaOH used: $60 \text{ mL} \times 0.1 \text{ mol/L} = 6 \times 10^{-3}$ mol. This number (6×10^{-3} mol) is exactly the same number of moles of acetic acid used to reach the equivalence point. Now you can calculate the molarity of your sample:

$$6 \times 10^{-3} \text{ mol}/10 \text{ mL} = 0.60 \text{ mol/L} = 0.60 \text{ M}$$

1.8 **A.** Each molecule of milk of magnesia, $Mg(OH)_2$, is able to collect two protons from the stomach, thereby neutralizing the stomach H^+ by the following reaction:

$$Mg(OH)_2(s) + 2H^+(aq) \rightarrow Mg_2^+(aq) + 2H_2O(l)$$

B. Antacids are bases that neutralize part of the excess stomach acid. Aspirin alone, however, is sufficient to provide the needed analgesic effect. The antacid molecule in Alka-Seltzer is $NaHCO_3$, which is a salt. The $NaHCO_3$ molecule upon dissolving in water, will produce HCO_3^-, which then serves as a base (accepting protons from the HCl found in the stomach) to form carbonic acid, H_2CO_3. The latter molecule breaks down rapidly to CO_2 and water. Alka-Seltzer in this reaction reduces the H^+, thereby neutralizing the stomach acid.

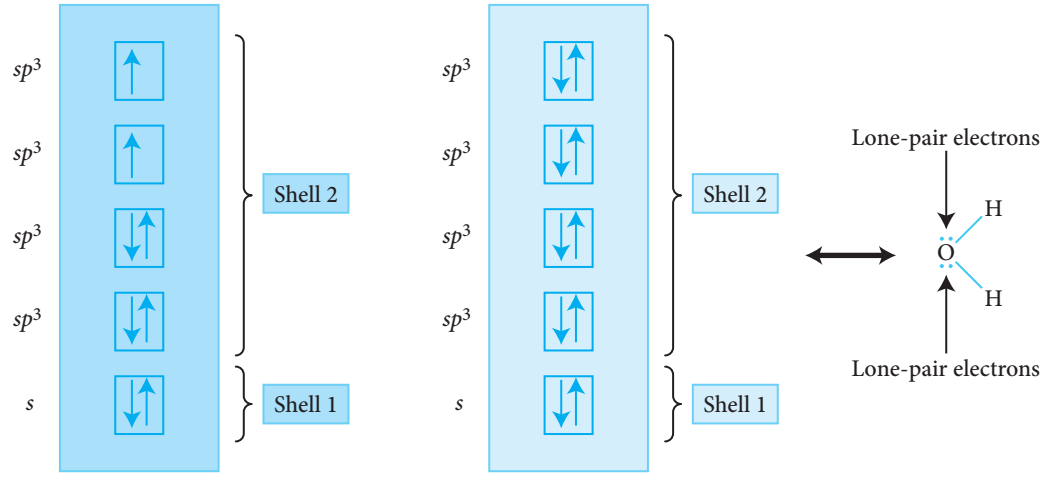
1.9 A. Anbesol contains 0.5% phenol. This relatively small amount of phenol, when the product is used for 1 or 2 days, will not harm either children or adults. The 0.5% phenol has both anesthetic and antibacterial effects.

B. The patient does not need to buy an OTC product to treat her skin irritation; instead, she can simply wash the affected area with a mixture of soap, water, and a basic solution such as baking soda. The molecule in poison ivy that causes skin irritation includes urushiol, a characteristic phenol group attached to a long hydrophobic alkyl group. In other words, urushiol is a phenol with a weak acidic property as well as an amphipathic with both hydrophilic and hydrophobic properties. If you add baking soda (bicarbonate) to a solution of water and soap, the bicarbonate will increase the pH of the solution. Washing the affected area with this solution will ionize the phenol group (through the increased pH) and emulsify the long hydrophobic alkyl group (by the soap through micelle formation). Thus you dissolve the hydrophobic chain with soap, and the phenol ring with water. The overall effect is to wash away the poison ivy from the affected area. Alternatively, you can suggest Ivy Dry, a topical OTC product to apply to the affected area as needed.

Problems and Solutions

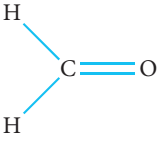
Problem 1.1 Oxygen has six valence electrons. Draw the electron configurations in an orbital diagram for oxygen and for a water molecule with hybrid orbitals. In addition, draw the Lewis structure of water and show how many lone-pair electrons can be found on a water molecule.

Solution 1.1 The six valence electrons of oxygen are distributed between four sp^3 hybrid atomic orbitals of the oxygen atom. Oxygen, because of its six electrons, ends up with two lone-pairs and two singly occupied sp^3 hybrid atomic orbitals (figure A). The single occupied orbitals can each overlap with a hydrogen atom to form two O—H bonds (figures B and C).



A Oxygen with hybrid orbitals **B** Water with hybrid orbitals **C**

Problem 1.2 Draw the Lewis structure and orbital diagram for the formaldehyde molecule (structure shown here). Which kind of hybrid orbitals can you find in the carbon atom of the formaldehyde molecule?

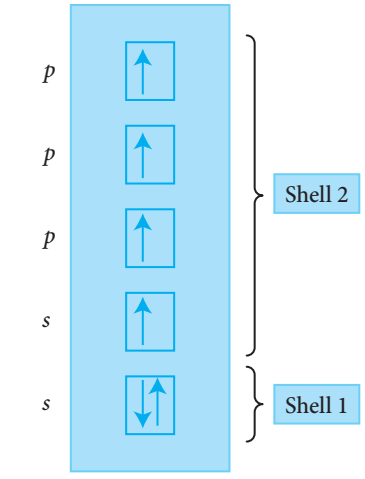


Lewis structure of formaldehyde

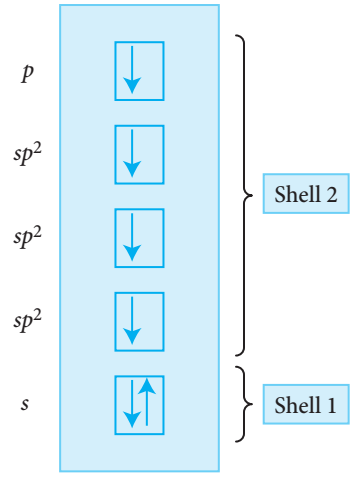
Solution 1.2 To predict hybridization in a molecule that has multiple bonds, one can apply the following rules:

1. If the central atom forms a double bond (like O or C in our example), it has sp^2 hybrid orbitals.
2. If the central atom forms two double bonds or has a triple bond, it has sp hybrid orbitals.

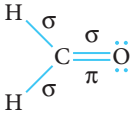
Because the carbon atom in the formaldehyde molecule has two hydrogen bonds, the carbon forms a double bond with the oxygen atom. As you can see from the carbon's orbital diagrams (figures A and B) and the Lewis structure (figure C), two of the carbon's sp^2 hybrid orbitals form two σ bonds with two hydrogen atoms (figure C). The third sp^2 hybrid orbital forms a σ bond with an sp^2 hybrid orbital of the oxygen atom (figures C and F). Similarly, the p orbital of the carbon atom (figure B) overlaps with the p orbital of the oxygen atom (figure E) and forms a π bond (figure F).



A Carbons without hybrid orbitals

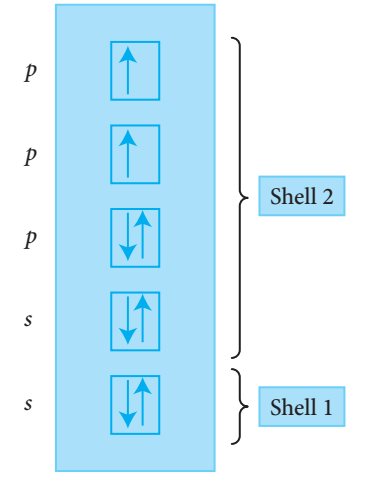


B Carbons with double bond in hybrid orbitals

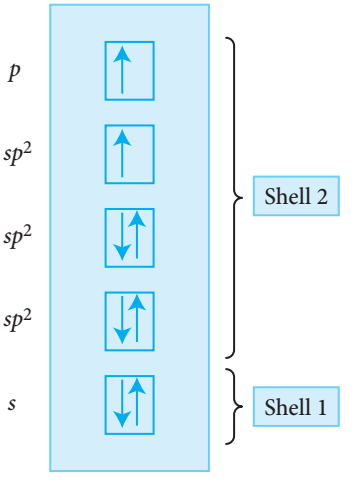


Lewis structure of formaldehyde

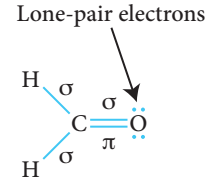
C



D Oxygen without hybrid orbitals



E Oxygen with double bond in hybrid orbitals

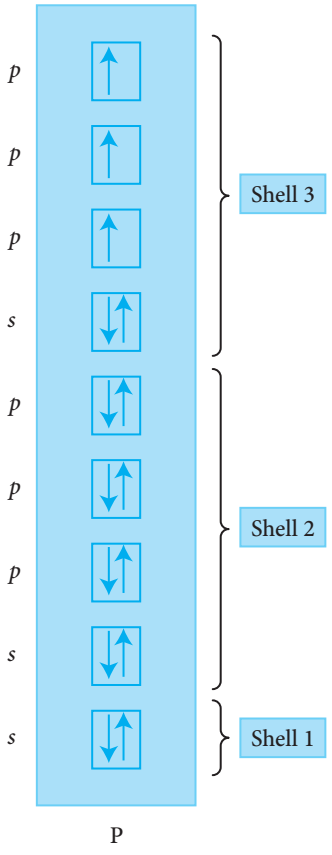


Lewis structure of formaldehyde

F

Problem 1.3 Use an orbital diagram to depict how the electrons in each orbital of a phosphorus (P) atom are filled.

Solution 1.3



Problem 1.4 How many electrons are present in an atom that has its first and second shells filled and has five electrons in its third shell? Name the element.

Solution 1.4 The first shell of an atom holds two electrons in its *s* orbital, and eight electrons in the second shell (i.e., the second shell has two electrons in the *s* orbital and six electrons in three *p* orbitals). Therefore this element has 2 + 8 + 5 = 15 electrons; it is phosphorus (see also Problem 1.4).

Problem 1.5 How many electrons does the calcium (Ca^{2+}) ion have in its outermost shell?

A. 2
B. 3
C. 4
D. 5
E. 6

Solution 1.5 A is correct.

Problem 1.6 What is an orbital?

Solution 1.6 An orbital is a region in a space around the nucleus where an electron is most likely to be found. Each orbital can hold a maximum of two electrons. Each shell is populated by different types of orbitals.

Problem 1.7 How would you show the shared and unshared electrons for the H_2S molecule?

Solution 1.7 Recall that sulfur and oxygen are in the same column (group) in the periodic table. As a result, sulfur, like oxygen, has six valence electrons. Two of the six electrons are involved with bonds to the hydrogen atoms, so two electron pairs are unbound (four unshared electrons).

Problem 1.8 The atomic orbitals for carbon of methane are considered:

A. *sp* hybridized

B. sp^2 hybridized

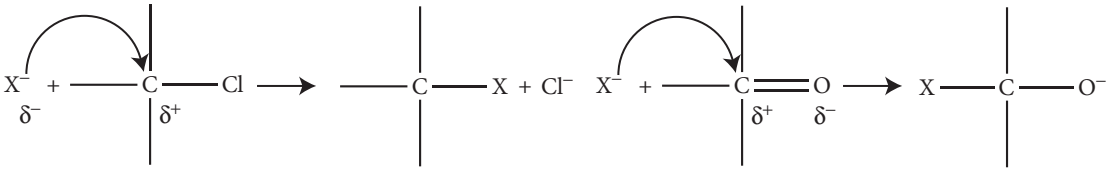
C. sp^3 hybridized

D. unhybridized

Solution 1.8 C; carbon has four valence electrons, with two electrons in the *s* orbital (second shell) and two in the *p* orbital (second shell). Hybridization maximizes the overlap of atomic orbitals when forming bonds. The *s* orbital is mixed with the three *p* orbitals to form a total of four sp^3 orbitals.

Problem 1.9 What is a nucleophile? Give an example.

Solution 1.9 A nucleophile is a molecule or ion that donates an electron pair to form a new covalent bond. Any molecule, ion, or atom that has electrons that can be shared can be a nucleophile. Examples include Br^-, OH^-, and NH_3 (see X^- in the figure). Pay attention to why the carbon is partially positively charged (think about the electronegativity difference between C and Cl). The reaction in the figure is also called a substitution reaction (because X displaces Cl). Recall that nucleophiles in the substitution reaction attack the sigma bond (single bond). If they attack the pi (π) bond (double bond), instead, the reaction will be considered an addition reaction.



Problem 1.10 Why would a water molecule act as both a nucleophile and an electrophile?

Solution 1.10 The oxygen atom of water has two lone pairs and a partial negative charge (δ^-). The oxygen is more electronegative than hydrogen, so water can behave as a nucleophile. A water molecule also can behave as an electrophile because each hydrogen atom bears a δ^+ charge. Only a few molecules can be both nucleophiles and electrophiles.

Problem 1.11 In each of the following instances, indicate whether the substance gains or loses electrons in a redox reaction.

A. A substance undergoing oxidation

B. A substance undergoing reduction

Solution 1.11 A: loses electrons; B: gains electrons.

Problem 1.12 Which of the following molecules has the highest boiling point?

A. Unbranched hexane

B. Branched hexane

C. Unbranched butane

D. Branched ethane

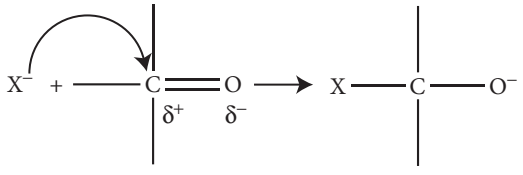
Solution 1.12 A; an unbranched alkane has higher boiling point than a branched alkane because van der Waals attractions are greater for the unbranched alkane than for the branched alkane (the branch acts as a "sticking arm" to increase the intermolecular distances). Remember that as the molecular weight increases, the boiling point increases as well, due to the increased van der Waals attraction between the molecules (however, as mentioned earlier, branching reduces the boiling point).

Problem 1.13 The following formulas are incorrect: N_2H_5, CCl_3. What is wrong with each of these two molecules?

Solution 1.13 Nitrogen forms three bonds and carbon forms four bonds.

Problem 1.14 What is an addition reaction?

Solution 1.14 In an addition reaction, hydrogen (H_2) or a halogen (Cl_2 or Br_2), water (HOH), or a hydrogen halide (HCl or HBr) is added. In an addition reaction, a nucleophile or an electrophile is added to a molecule containing a double bond. In the case of a nucleophile, the double bond is usually between carbon and oxygen (see the figure). In the case of an electrophile, the double bond is between one carbon and another carbon.

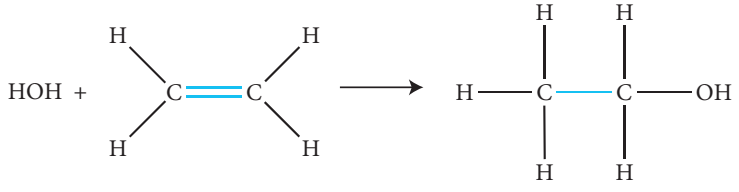


Nucleophile

The bottom line: When a nucleophile attacks a sigma bond (single bond), the reaction is a substitution reaction. When the nucleophile (or electrophile) attacks a pi bond (double bond), the reaction is an addition reaction. When an electrophile attacks a double bond in an aromatic ring, the reaction is a substitution reaction. The aromatic ring maintains its double bonds, so it is easier to understand why substitution occurs with an aromatic ring rather than an addition reaction.

Problem 1.15 What is a hydration reaction?

Solution 1.15 A hydration reaction is basically the same as an addition reaction with one exception: Water is added to an alkene (double-bond) molecule. Compare it with the addition reaction.



Water Alkene Alcohol

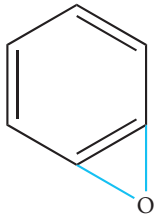
Problem 1.16 Aromatic hydrocarbons have double bonds similar to alkene molecules, however, they are not as prone as alkene to enter into an addition reaction. Why?

Solution 1.16 Aromatic hydrocarbons (aromatic rings) have pi (π) bonds because of the double bonds. The electrons of these double bonds are delocalized, which means they have much more space to move in an aromatic hydrocarbon than if the electrons were in a double bond like that in an alkene molecule. Because electrons repel each other, they are more stable when they have more space to occupy (i.e., the more space electrons have, the less they repel each other). This phenomenon results in more resistance to addition reactions (i.e., makes the aromatic hydrocarbon more stable).

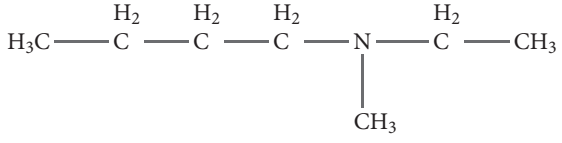
Problem 1.17 One of the common metabolic problems with drugs containing a benzene ring is they can produce a carcinogenic intermediate metabolite during the hydroxylation process. Which of the following reactions is responsible for the carcinogenic intermediate metabolite? Draw the structure of this metabolite.

A. Peroxidation
B. Hydrogenation
C. Epoxidation
D. Reduction
E. Oxidation

Solution 1.17 C is correct.



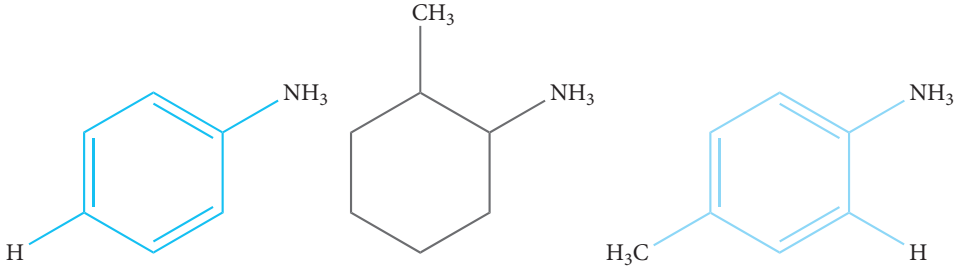
Problem 1.18 What is the IUPAC name for the structure shown?



A. *N*-propyl-*N*-ethyl-1-methanamine
B. *N*-ethyl-*N*-methyl-1-butanamine
C. *N*-butyl-*N*-methyl-1-ethananamine
D. *N*,*N*-ethylmethylpropylamine
E. *N*-methyl-*N*-ethyl-1-propanamine
F. Tetra-*N*-ethylmethylpropylamine

Solution 1.18 B is correct.

Problem 1.19 Rank the following amines in order of increasing base strength.



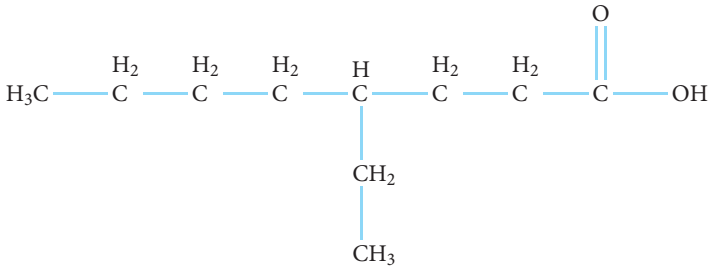
1 **2** **3**

Adapted from Bresnick S. Columbia review: high-yield organic chemistry. Baltimore, MD: Williams and Wilkins; 1996.

A. 1, 2, 3
B. 2, 1, 3
C. 3, 1, 2
D. 2, 3, 1
E. 1, 3, 2

Solution 1.19 E is correct. The lone-pair electrons of the nitrogen atom of compound 1 are delocalized over the aromatic ring, so they are not readily available for accepting protons (decreased basicity). Compound 3 is a stronger base than compound 1 because it has an electron-releasing group (alkyl) on the ring. The strongest base is 2 because it has a longer electron-releasing group (alkyl) in addition to a methyl group, which is also an electron-releasing group. The electron-releasing effect makes the lone-pair electrons on the nitrogen readily available for accepting a proton (increasing the basicity of amines).

Problem 1.20 What is the IUPAC name for the structure shown here?



Solution 1.20 4-Ethyloctanoic acid.

Problem 1.21 Which of the following amines is soluble in water?

A. Methylamine

B. Dimethylamine

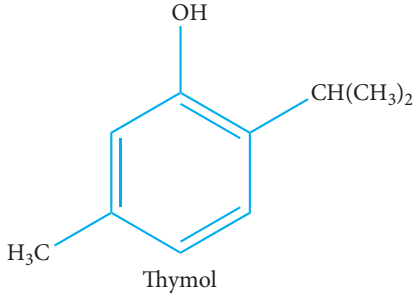
C. Trimethylamine

D. All of the above

E. None of the above

Solution 1.21 D; small, low-molecular-weight amines are water soluble because they are able to undergo hydrogen binding with water molecules. They do so because the lone-pair electrons on the nitrogen are available to the hydrogen atom from the water molecule.

Problem 1.22 Thymol has a pleasant minty taste. This compound is used by dentists to sterilize a tooth prior to filling it; in addition, it is used in some cough drops. Write the IUPAC name and name the class of compound to which thymol belongs.



Thymol

Solution 1.22 2-Isopropyl-5-methylphenol; it belongs to the phenol group.

Problem 1.23 Aldehydes undergo oxidation, whereas ketones do not. Why?

Solution 1.23 The carbon–carbon bonds in ketones must be broken for oxidation to occur—a process that requires a lot of energy.

Problem 1.24 Dimethyl ether and ethanol both have a molecular weight of 46 g/mol. Ethanol has a higher melting point than dimethyl ether. Why?

Solution 1.24 Ethanol molecules can form hydrogen bonds with each other, whereas dimethyl ether cannot. Therefore, a higher temperature is required to break down the hydrogen bonds between ethanol molecules.

Problem 1.25 Which of the following answers is (are) correct regarding the ketone and aldehyde functional groups?

I. Both can attract nucleophiles.

II. Both can attract electrophiles.

III. Both can undergo addition reactions.

IV. While a ketone undergoes an addition reaction, an aldehyde undergoes a substitution reaction.

A. I, II

B. I, II, III

C. I, IV

D. II, IV

E. I, II, III, IV

Solution 1.25 B; nucleophiles attack C=O at the carbonyl carbon, which is positively polarized, and electrophiles (particularly protons, H^+) attack oxygen, which is negatively polarized. The addition reaction can occur because in a nucleophilic attack, the nucleophile will be added to the carbonyl carbon.

Problem 1.26 What is the concentration of HNO_3 (a strong acid) in a solution that has a pH of 4.0?

Solution 1.26 As the question stated, HNO_3 is a strong acid—and a strong acid dissociates all of its H^+. Thus the concentration of the acid will be the same as the concentration of H^+, which is what you need to calculate pH. To determine the concentration of H^+, you can directly use the pH:

$pH = -\log [H+]$

$[H+] =$ antilog of $-pH$

$[H+] =$ antilog of $-4 = 1 \times 10^{-4}$ M

Be careful with the units of your answer. In this question, the answer should be in the concentration unit, molarity (M).

Problem 1.27 Acetylsalicylic acid (aspirin) is a weak acid with a pK_a of 3.5. Calculate the pH of an 0.05 M solution of aspirin.

Solution 1.27 As the question states, aspirin is a weak acid; as the presented data indicate, you are dealing with a weak acid that weakly (i.e., 5% or less) dissociates H^+. Whenever you deal with a "weak acid" and low dissociation rate for H^+, immediately use the following equation:

$$[H^+] = \sqrt{K_a C_a}$$

Be careful here: You don't have K_a but rather pK_a, so you must convert pK_a to K_a first:

$pK_a = -\log K_a$

$K_a =$ antilog of $-pK_a$

$K_a =$ antilog of $-3.5 = 3.16 \times 10^{-4}$

$pH = -\log [H+] = 2.40$

Problem 1.28 Erythromycin is an antibiotic that kills the bacteria that cause Legionnaires' disease. Erythromycin is a weak base with a dissociation constant (K_b) of 6.3×10^{-6}. Calculate the pH of an 0.2 M solution of erythromycin.

Solution 1.28 Here you are dealing with a base, so the value of K_b will help you to calculate the pH. When you think about a base, think about the artificial conjugate acid, Ac^-, which reacts with water.

$$Ac^- + H_2O \leftrightarrow HAc + OH^-$$

$$K_b = \frac{[HAc] \times [OH^-]}{[AC^-]}$$

In the same way you solved Problem 1.5, you can solve Problem 1.6, but this time using the following equation:

$$[OH^-] = \sqrt{K_b\, C_b} = 1.12 \times 10^{-3}\ M$$

Remember this number is $[OH^-]$, and not $[H^+]$. Thus, to know pH, you must know $[H^+]$:

$$K_w = [H^+] \times [OH^-] = 1 \times 10^{-14}\ M^2$$

$$[H^+] = 1 \times 10^{-14}\ M^2/[OH^-] = 8.91 \times 10^{-12}\ M$$

$$pH = -\log [H^+] = 11$$

Problem 1.29 How is K_a defined? Write the equation for K_a for the generic weak acid, HAc.

Solution 1.29 K_a is the dissociation constant or ionization constant for an acid and is expressed as follows:

$$K_a = \frac{[H^+] \times [AC^-]}{[HAc]}$$

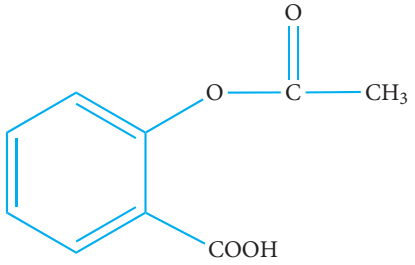
Problem 1.30 Calculate the pH of a solution of acetic acid, HAc ($pK_a = 4.76$), that contains 0.50 M HAc and 0.05 M Ac^-.

Solution 1.30 Here we can use the Henderson-Hasselbalch equation to calculate the pH:

$HAc = 0.50$ M and $Ac^- = 0.05$ M

$$pH = pK_a + \log \{[Ac^-]/[HAc]\} = 4.76 + \log \{[0.05]/[0.50]\} = 3.76$$

Problem 1.31 Acetylsalicylic acid (aspirin) is a weak acidic drug with pK_a of 3.5. The pH of the small intestine is 5.5 and the pH of the stomach is 1.5.



Aspirin

A. What is the percentage ionization in the stomach?

B. What is the percentage ionization in the small intestine?

C. Which of these two sites is the absorption site for aspirin? Why?

Solution 1.31 Aspirin is an acidic drug and you want to know the percentage ionization. Thus you should use the equation that gives % ionization of an acid:

$$\%\ \text{ionized} = \frac{1 \times 100}{\text{Antilog}\,(\text{p}K_a - \text{pH}) + 1}$$

A. 0.99%

B. 99%

C. In the stomach, because aspirin will be almost 100% un-ionized; as an un-ionized molecule, it will penetrate the cell membrane to reach the blood and go to its site of action.

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