

# The Chemistry of Life

## CHAPTER

# 1

### 1.1 Introduction

Biology is the study of life, a self-replicating and evolving system of enormous complexity. The large, complex molecules of living cells facilitate their own reproduction and allow for genetic continuity through generations. Nonliving systems can also exhibit forms of self-replication, as exemplified by the growth of a crystal lattice, but such systems do not evolve in ways to meet new challenges. Another important property of life is the capacity of living organisms to capture energy. In a cell, thousands of chemical reactions occur simultaneously at any instant of time. To maintain life, an organism repairs or replaces its structures. These and other life processes require a continuous supply of energy. The primary source of energy comes from sunlight. Plants and some microorganisms capture the energy of light and transform it into heat and chemical energy. Chemical energy derived from sunlight is then used to sustain tissues, reproduction, and growth. Many of the processes involved in living systems are highly complex, even in the simplest organisms.

Radioisotope studies suggest that the molecules that form living beings appeared gradually in our planet after it cooled billions of years ago. At some point during the hundreds of millions of years since then, an appropriate environment might have come into being for a particular “soup” of these molecules to form units able to reproduce themselves. Today there exist over 30 million types of organisms. Despite this diversity, common molecular patterns and principles underlie all expressions of life. Organisms as different as bacteria and humans use the same building blocks to construct proteins, lipids, and carbohydrates. The flow of information from genes to proteins is essentially the same in all organisms. Moreover, living systems on earth use a common currency of energy called ATP. These observations provide support to the thesis that life on our planet evolved from a common origin.

Living systems have many levels of hierarchy, beginning with nonliving particles—atoms and molecules—and moving on to living cells, multicellular organisms,

TABLE 1.1

<b>Atomic Composition of Living Organisms* and the Earth's Crust†</b>				
Element	Human	Alfalfa	Bacteria	Earth's Crust
Oxygen (O)	62.8%	77.9%	73.7%	50%
Carbon (C)	19.4%	11.34%	12.14%	0.2%
Hydrogen (H)	9.3%	8.7%	9.9%	0.9%
Nitrogen (N)	5.1%	0.8%	3.0%	1.3%
Phosphorus (P)	0.6%	0.7%	0.6%	0.12%
Sulfur (S)	0.6%	0.1%	0.3%	0.12%
Total	97.9%	99.6%	99.72%	52.6%

\*Living organisms also contain a number of mineral ions such as iron, calcium, and magnesium. These minerals account for as much as 2 percent of the human body weight.

†The Earth's crust includes the atmosphere, oceans and lakes, and the first 10 miles of solid matter.

families, and societies. Studies of fossils indicate that life on Earth has always consisted of a relatively small number of elements. Six elements out of more than a hundred make up 98 percent of the mass of any living organism: hydrogen (H), carbon (C), nitrogen (N), oxygen (O), phosphorus (P), and sulfur (S) (see Table 1.1). Moreover, with the exception of oxygen and calcium, the biologically most abundant elements are but minor components of the Earth's crust. The elements that constitute life, when combined with each other, produce an astonishing number of different molecules with diverse structures and functions. The capacity to achieve complexity out of a simple set of building blocks is one of the most intriguing properties of living systems.

## 1.2 Atoms

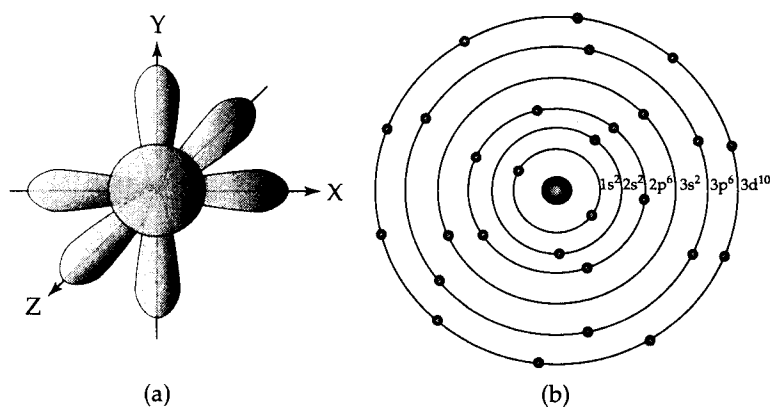
### 1.2.1 Physical Properties of Atoms

All matter, living and nonliving, is composed of atoms, which are the smallest units of matter. In the following we present a brief review of atomic structure and its impact on the chemical properties of elements. Atoms consist of a dense, positively charged nucleus and a cloud of one or more negatively charged electrons (Fig. 1.1). The nucleus is made of two different types of particles: protons and neutrons. These particles have the same mass of  $1.67 \times 10^{-24}$  g. Protons have a positive charge of  $1.60 \times 10^{-19}$  coulomb and neutrons have no charge. Electrons have negligible mass compared to protons and neutrons ( $9.1 \times 10^{-28}$  g). The number of electrons in an atom is equal to the number of protons in the atom, and because the negative charge of an electron is equal in magnitude to the positive charge of a proton, an atom has no net charge. By convention, the charge of a proton is shown as +1 and that of an electron as -1.

Atoms vary in mass and volumetric size. An *element* is matter that is made up of only one kind of atom and cannot be decomposed by chemical reaction into substances of simpler composition. The number of protons in an atom (the *atomic number*) determines the identity of the element. The atomic number increases by one in the sequence of elements in the Periodic Table (Fig. 1.2). There are over 100 elements

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**FIGURE**  
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**FIGURE 1.1** Outer-shell atomic orbitals of carbon (a). The nucleus of the carbon atom is at the origin of the Cartesian coordinate system ( $x, y, z$ ). The nucleus is surrounded by the spherical  $1s$  and  $2s$  orbitals and the three mutually orthogonal dumbbell shaped  $2p$  orbitals ( $2p_x, 2p_y, 2p_z$ ). Schematic diagram of orbitals around a nucleus (b). The orbitals are shown as circles around the spherical nucleus. The symbols identifying various orbitals are defined in the text.

on earth. The most abundant molecules of living systems (hydrogen, carbon, nitrogen, and oxygen) have low atomic numbers.

*Atomic mass number* refers to the number of protons and neutrons in the nucleus of an atom. Not all atoms of an element have the same atomic mass number. For example, different atomic forms of a single element, *isotopes*, differ in the number of neutrons in the atomic nucleus. The dominant isotope of oxygen has eight protons and eight neutrons. This isotope is assigned an *atomic mass unit* (amu) of 16. By definition, then, an atomic mass unit is 1/16 of the mass of

Group	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		
Period																				
1	1 H																	2 He		
2	3 Li	4 Be											5 B	6 C	7 N	8 O	9 F	10 Ne		
3													11 Na	12 Mg	13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
4			21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr		
5	37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe		
6	55 Cs	56 Ba	* 71 Lu	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn		
7	87 Fr	88 Ra	* 103 Lr	104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Uun	111 Uuu	112 Uub	113 Uut	114 Uuq	115 Uup	116 Uuh	117 Uus	118 Uuo		
*Lanthanides	* 57 La	58 Ce	59 Pr	60 Nd	61 Pm	62 Sm	63 Eu	64 Gd	65 Tb	66 Dy	67 Ho	68 Er	69 Tm	70 Yb						
**Actinides	* 89 Ac	90 Th	91 Pa	92 U	93 Np	94 Pu	95 Am	96 Cm	97 Bk	98 Cf	99 Es	100 Fm	101 Md	102 No						

**FIGURE 1.2** Periodic table indicating the atomic properties of all elements found on Earth. (From <http://www.genome.ad.jp/kegg/catalog/elements.html>.)

the most common isotope of an oxygen atom. The choice of oxygen as the standard is arbitrary. Nevertheless, it can be justified by the fact that oxygen forms compounds with most elements. *Atomic mass* is the average atomic mass number in a large collection of atoms of an element. Because there may be multiple isotopes of an element in the collection of atoms, the element's atomic mass is not necessarily an integer number. The atomic mass of hydrogen is 1.008 amu and that of sulfur is 32.006 amu.

Since atoms are extremely small, any laboratory experiment dealing with chemicals involves large numbers of atoms. One *gram-atom* is defined as the collection of atoms whose total mass in grams is numerically equal to the atomic mass of the atom. For example, 32.066 g of sulfur is equal to 1 gram-atom of sulfur. The number of atoms in one gram-atom of an element is always equal to  $6.0235 \times 10^{23}$ . This number is called the *Avogadro number*.

### 1.2.2 Electron Configurations

The extent with which an atom interacts with other atoms depends on the configuration of the cloud of electrons surrounding its nucleus. The precise location of a given electron in an atom at any time is impossible to determine, but it is possible to specify a region where the electron is likely to be at least 90 percent of the time. Such a region is called an *orbital* (Fig. 1.1), which can be occupied by at most, two electrons. The two electrons in an orbital spin about their own axes with equal speed, but in opposite directions.

An electron in an atom can only have certain specific levels of energy. Furthermore, the energy of an electron in a given orbital remains constant. Thus, orbitals constitute a series of constant-energy electron shells around the nucleus (Fig. 1.1b). The innermost electron shell is associated with the lowest energy, and the energy levels increase with increasing orbital numbers. The only way an electron can change its energy is to shift from one discrete energy level (orbital) to another. When an electron jumps to a lower energy level, it radiates energy, and if no lower energy level is available, the electron cannot get any closer to nucleus. An electron will jump to a higher energy orbit when its energy is increased due to increase in temperature or radiation.

Chemists classify the electron orbitals around the nucleus into shells and subshells according to their energy levels (Fig. 1.1b). Because electrons in an orbital have constant energy, schematic diagrams show orbitals as circles of varying radii around a centrally located nucleus. The larger the radius of the orbital, the greater is the energy of electrons in that orbital. The *principal quantum number* identifies the shell to which an electron belongs. This parameter is represented by the letter *n*. Its lowest value is one, and it increases by one for the next energy level. The number of subshells in a shell is always equal to *n*. These subshells are identified with small letters s, p, and d in the order of increasing energy levels. The s orbital forms a spherical surface around the nucleus. The p orbitals resemble that of two spheres, one on each side of the nucleus (Fig. 1.1a). An electron in a p orbital has an equal probability of being found in either half of the orbital. A p subshell is constructed of three p orbitals perpendicular to each other. The spatial distribution of electrons in the higher order subshells are considerably more complicated.

### 1.2.3 Chemical Reactivity and the Octet Rule

The electrons of an atom fill the orbitals from the lowest to the highest energy levels. The shell with the lowest overall energy ( $n = 1$ ) has only one subshell identified as 1s. The integer in front of the subshell symbol  $s$  identifies the principal quantum number  $n$ . The 1s subshell can contain up to 2 electrons. The L shell ( $n = 2$ ) has the next lowest energy level. It is composed of two subshells: 2s (containing up to two electrons) and 2p (which has 3, 2p orbitals and can hold six electrons). Electrons in the 2p orbital have higher energy than the 2s orbital. In the M shell ( $n = 3$ ), there are three subshells, 3s, 3p, and 3d, each of which can hold 2, 6, and 10 electrons, respectively. Because the energy level of the 4s orbital is slightly smaller than the energy level of orbital 3d, atoms with atomic numbers greater than 18 begin to fill 4s before filling 3d. The six atoms most commonly found in biomolecules have atomic numbers less than 18. Their electronic configurations are shown in Table 1.2.

The terms 1s, 2s, 2p, 3s, and 3p refer to electron orbits written in the order of increasing energy levels. The integers 1, 2, and 3 identify the orbit and the letters  $s$  and  $p$  the orbital belonging to the orbit;  $s$  orbitals can accommodate up to two electrons and  $p$  orbitals up to six electrons. In general, atoms (with atomic numbers greater than 2) form molecules that have eight electrons in their outermost orbitals. Therefore, the number of electrons in the outermost shell is an important determinant of the chemical properties of an atom. These electrons are called *valence electrons*. They are responsible for the *combining capacity* of atoms. In the periodic table presented in Fig. 1.2, elements are grouped into vertical columns according to the number of valence electrons. The tendency for eight electrons in the outermost orbitals is called the *octet rule*. Atoms that already have eight electrons in their outermost shell such as argon do not interact with other elements. They are said to be *inert*. In *electron dot formulas*, *valence* electrons are shown with dots surrounding the symbol of the atom:



The symbols H, C, N, O, P, and S denote, respectively, hydrogen, carbon, nitrogen, oxygen, phosphorus, and sulfur. *Hydrogen* is the simplest element on earth. It forms the bulk of the matter of the sun, but exists only in small amounts in an uncombined form on Earth, suggesting that the Earth's gravity is not strong enough to

TABLE 1.2

<b>Electronic Composition of Bioelements</b>							
Z*	Element	1s	2s	2p	3s	3p	4s
1	Hydrogen (H)	1					
6	Carbon (C)	2	2	2			
7	Nitrogen (N)	2	2	3			
8	Oxygen (O)	2	2	4			
15	Phosphorus (P)	2	2	6	2	3	
16	Sulfur (S)	2	2	6	2	4	
20	Calcium (Ca)	2	2	6	2	6	2

\*Z: Atomic Number [number of protons (electrons) in an element].

keep large amounts of hydrogen gas in the atmosphere. Hydrogen has a single valence electron. In forming a stable compound, hydrogen must either empty its electron orbital by giving up its electron to another atom (ionic bond) or fill the orbital by sharing electrons with another atom (covalent bond).

The organic element with the second smallest atomic number is *carbon*. There are six protons in each carbon atom and most carbon atoms have six neutrons. About 1.1 percent of carbon atoms have seven neutrons and a tiny fraction have eight. Carbon has four valence electrons: therefore, its outermost orbitals are exactly half filled. The possession of a half-filled outermost orbit allows carbon to engage in the formation of chemical bonds with many other atoms. The resulting chemical versatility is essential for the reactions of biological metabolism and propagation. Silicon also has four valence electrons and also serves as the backbone of molecules that are large enough to carry biological information. On the other hand, silicon interacts with only a few other atoms, and the large silicon molecules are monotonous compared with the combinatorial universe of carbon-based organic molecules. Carbon is present as carbon dioxide in the atmosphere and is found dissolved in natural waters. It is also abundant in living organisms and in organic matter such as coal and petroleum. Carbon is also one of the most abundant of the higher elements in our solar system.

*Nitrogen* occupies 78 percent of the volume of the atmosphere. In plants and animals, nitrogen is found in proteins and in the genetic material DNA and RNA. Approximately, 16 percent of the weight of proteins is due to nitrogen. Nitrogen atoms have seven protons and five valence electrons. This corresponds to an outer electron orbit, which is only slightly more than half filled. The compounds of nitrogen, though not as numerous as those of carbon, are just as varied in function. *Phosphorus* has 15 protons and five valence electrons. It is abundant in rock formations in the form of calcium phosphate. This inorganic salt also constitutes 60 percent of bones in the human body.

*Oxygen* and *sulfur* both have six valence electrons. Oxygen is the most abundant element in the earth's crust. It is found in water, rocks, living organisms, and in the atmosphere. Oxygen has eight protons and six valence electrons in its outermost shell. It can gain two electrons to achieve the stable *octet* configuration. In so doing, it combines with all other elements except inert helium, neon, and argon. *Sulfur* is found in the free-element form in large beds several hundred feet underground. As discussed in the next chapter, sulfur atoms, when present in the amino acid cysteine, play a fundamental role in determining the three-dimensional shapes of many proteins.

### 1.3 Molecules and Covalent Bonds

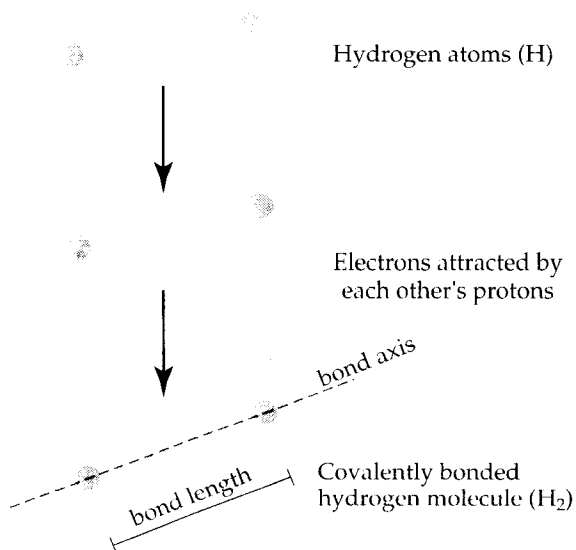
Atoms interact with each other by forming bonds of different types such as covalent bonds, ionic bonds, and hydrogen bonds. These various bond configurations will be discussed in this section and the following sections. Two atoms form *covalent bonds* by sharing one or more pairs of electrons in order to have a complete set in their outer shell at least some of the time. For most elements found in living systems this means eight electrons in the outermost orbitals (octet rule). The only exception is hydrogen, which has one valence electron in a single outermost orbital. In a hydrogen

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**FIGURE 1.3** Sharing of electron pairs in covalent bonds. Two hydrogen atoms form a covalent bond when they come close enough that the electron orbitals in the  $n = 1$  (M) shell overlap. Each electron is attracted to both protons of the opposing hydrogen atoms repulse each other and the balance of these opposing forces are the determinants of the resulting molecular structure.

molecule ( $\text{H}_2$ ), the two hydrogen nuclei share the two electrons equally and completely (Fig. 1.3).

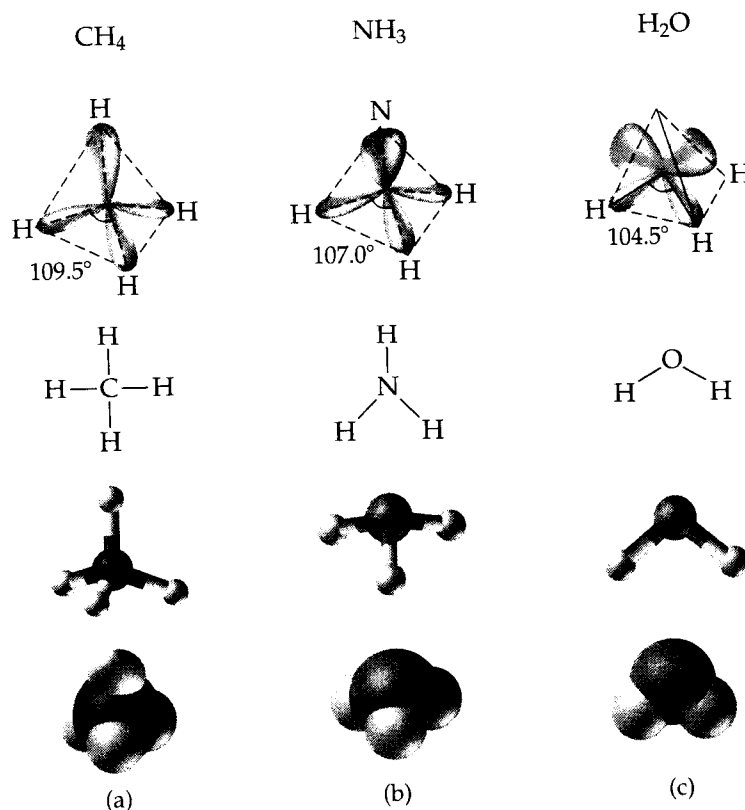
A *covalent bond* is formed when an outer orbital of one atom containing an electron overlaps an outer orbital of another atom also containing a single electron. These two atoms begin sharing the electron pair (Fig. 1.3). The overlapping orbitals deform as a result of the interaction. The nuclei of the interacting atoms are electrically attracted to the mutually shared electron pair. This attraction results in what is called the *covalent bond*. The line joining the nuclei of two covalently bonded atoms is called the *bond axis* and the distance between the nuclei is called the *bond length* (Fig. 1.3). The bond length is not fixed, and the bond acts much as if it were a stiff spring. Figure 1.4 shows the orbitals of the shared electrons for three commonly known molecules: methane ( $\text{CH}_4$ ), ammonia ( $\text{NH}_3$ ), and water ( $\text{H}_2\text{O}$ ).

A combination of atoms held together by covalent bonds is called a *molecule*. A molecule is identified by the symbols of elements that constitute it. The subscript associated with each element refers to the number of atoms of that element in the molecule. For example, the oxygen molecule ( $\text{O}_2$ ) is composed of two oxygen atoms. Carbon dioxide is formed when two oxygen atoms share some of their electrons with a carbon atom; and thus the symbol  $\text{CO}_2$ . The quantity of molecules in a given volume is typically expressed in terms of moles, or M. The unit M represents one mole per liter. Like the number of atoms in one gram-atom, the number of molecules in one *mole* of matter is equal to the *Avogadro* number,  $6.0235 \times 10^{23}$ .

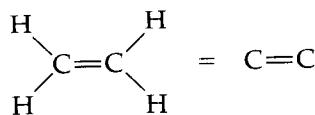
### 1.3.1 Double and Triple Bonds

Bonds in which a single pair of electrons is shared between two atoms are called *single bonds*. A single bond is represented by a straight-line segment connecting two atoms.

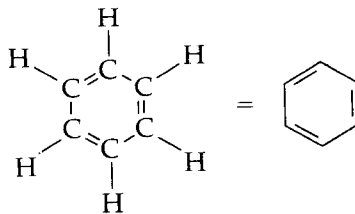
**FIGURE 1.4** Structural representation of simple molecules. Top row: Methane ( $\text{CH}_4$ ) molecules assume the shape of a tetrahedron with bond angles equal to  $109.5^\circ$  (a). Ammonia ( $\text{NH}_3$ ) also takes the shape of a tetrahedron, with the unshared electron pair occupying one corner of the tetrahedron (b). Water ( $\text{H}_2\text{O}$ ) is triangular in shape, with the bond angle between the two hydrogen-oxygen covalent bonds equal to  $104.5^\circ$  (c). Note that the clouds of unshared electrons are larger than those of shared electrons. The charge clouds of nonbonded electrons push the bonded pairs toward each other. The middle and bottom rows show the ball-and-stick and space-filling models of these three molecules.



When four electrons are shared between two atoms, the covalent link is called a *double bond*. A double bond is represented by a double-line segment. This is illustrated for ethylene ( $\text{C}_2\text{H}_4$ ):



Shown in the left is the standard structural formula of ethylene. On the right is the simplified diagram that masks the presence of  $\text{C}-\text{H}$  bonds. Since carbon will form four bonds with neighboring atoms, it is implicitly assumed that the bonds not shown are  $\text{C}-\text{H}$  bonds. Another example of a six-carbon hydrocarbon is as follows:



Double bonds between carbon atoms occur often in biological compounds (Fig. 1.5).



Class of Molecules	Functional Group	Example	Ball - Stick
Ethanol (Alcohols)	Hydroxyl —OH	$\begin{array}{c} \text{H} \quad \text{H} \\   \quad   \\ \text{H}-\text{C}-\text{C}-\text{OH} \\   \quad   \\ \text{H} \quad \text{H} \end{array}$	
Acetaldehyde (Aldehydes)	Carbonyl —CHO	$\begin{array}{c} \text{H} \quad \text{O} \\   \quad // \\ \text{H}-\text{C}-\text{C} \\   \quad \backslash \\ \text{H} \quad \text{H} \end{array}$	
Acetone (Ketones)	Carbonyl 	$\begin{array}{c} \text{H} \quad \text{O} \quad \text{H} \\   \quad    \quad   \\ \text{H}-\text{C}-\text{C}-\text{C}-\text{H} \\   \quad \quad   \\ \text{H} \quad \quad \text{H} \end{array}$	
Acetic Acid (Carboxylic Acids)	Carboxyl —COOH	$\begin{array}{c} \text{H} \quad \text{O} \\   \quad // \\ \text{H}-\text{C}-\text{C} \\   \quad \backslash \\ \text{H} \quad \text{OH} \end{array}$	
Methylamine (Amines)	Amino —NH <sub>2</sub>	$\begin{array}{c} \text{H} \quad \text{H} \\   \quad   \\ \text{H}-\text{C}-\text{N} \\   \quad \backslash \\ \text{H} \quad \text{H} \end{array}$	
3-Phosphoglycic Acid (Organic Phosphates)	Phosphate —OPO <sub>3</sub> <sup>2-</sup>	$\begin{array}{c} \text{HO} \quad \text{O} \\ \diagdown \quad // \\ \text{C} \\   \\ \text{H}-\text{C}-\text{OH} \\   \\ \text{H}-\text{C}-\text{O}-\text{P}-\text{O}^- \\   \quad \quad    \quad \quad   \\ \text{H} \quad \quad \text{O} \quad \quad \text{O}^- \end{array}$	
Mercaptoethanol (Thiols)	Sulfhydryl —SH	$\begin{array}{c} \text{H} \quad \text{H} \\   \quad   \\ \text{HO}-\text{C}-\text{C}-\text{SH} \\   \quad   \\ \text{H} \quad \text{H} \end{array}$	

**FIGURE 1.5** Examples of small carbon molecules observed frequently in organic compounds. Double bonds are shown with two line segments and single bonds with a single connecting line segment.

Atoms connected by a single bond can rotate freely about the bond axis; however, atoms connected by double bond cannot rotate about the bond axis. Because a double bond occupies more space than a single bond, it is more repulsive. As a result, the H—C—H bond angle is  $116^\circ$  whereas H—C=O angle is  $122^\circ$ .

A *triple bond* involves the sharing of six electrons between two atoms. An important example of a triple bond is the covalent bond between two nitrogen atoms in a nitrogen molecule ( $N_2$ ). This is a very stable bond. Triple bonds are rarely observed in organic materials. Most nitrogen compounds involve single bonds and are relatively unstable. The precursors of these molecules are produced from atmospheric nitrogen by the nitrogen-fixing bacteria present in the roots of nitrogenous plants such as legumes (peas and beans). These bacteria convert molecular nitrogen to a form that can be used readily by plants.

### 1.3.2 Three-Dimensional Structure of an Organic Molecule

The pair of electrons involved in covalent bonding is called a *shared pair*. The pairs of outermost electrons not involved in bonding are called *unshared pairs*. Each bond and each unshared pair in the outer level of an atom form a charge cloud that repels all other charge clouds. The repulsions between the charge clouds determine the three-dimensional shape of the molecules.

The physical rules that dictate the three-dimensional shape of a molecule can be listed as follows:

1. In a molecule, atoms are oriented so that repulsion between electron pairs (either bonding or unshared) around an atom is minimized. In other words, electron pairs spread as far apart as possible to minimize repulsive forces.
2. Repulsive forces between various electron pairs in a molecule are not equal in strength. An unshared pair is acted upon by only one nucleus, and its cloud occupies more space compared to that of a shared pair. The repulsive forces between the unshared pairs of electrons are greater than the repulsive forces between two shared pairs.

The geometry of a molecule is a fundamental determinant of its chemical properties. Biologists use various representations to capture the three-dimensional shapes of molecules. Figure 1.4 shows four of these representations for the molecules methane ( $CH_4$ ), ammonia ( $NH_3$ ), and water ( $H_2O$ ). The top row indicates the three-dimensional shapes of the shared and unshared outer orbitals. The second row presents the planar sketches of the molecules. The third row represents molecules as if they were composed of balls and sticks. Balls represent the locations of the nuclei of atoms in the molecule and sticks represent the covalent bonds along the bond axes. The bottom row shows the space-filling models of these three molecules. In methane, the central carbon atom forms covalent bonds with four hydrogen atoms in order to have eight electrons in its outermost shell. Because this results in four pairs of electrons equally repelling each other, the shape of the methane molecule is a tetrahedron. The angle the two adjoining bonds make (bond angle) is  $109.5^\circ$  in this case. In the ammonia molecule ( $NH_3$ ), the three pairs of bonded electrons and one unshared pair must be positioned to reduce repulsion to a minimum. The resulting structure is again a tetrahedron, but the unshared pair occupies more space than the other three electron pairs. The angle between the bond pairs is  $107^\circ$  in ammonia.

Two unshared pairs of outer electrons of oxygen are present in a water molecule: Both of these clouds are larger than the clouds of bonded electrons. This additional cloud size results in a reduction in the bond angle ( $104.5^\circ$ ) between the bond axes connecting O to H atoms. Again the electron clouds are tetrahedral, the molecule (lines connecting the nuclei) is V-shaped.

The three-dimensional structure of thousands of small organic molecules and information on their chemical properties can be found by using the compound search engine of the Kyoto University KEGG Web site <http://www.genome.ad.jp/dbget/ligand.html>. Another highly used site is that of the Protein Data Bank or PDB, which is the single worldwide repository for the processing and distribution of three-dimensional biological macromolecular structure data (<http://www.rcsb.org/pdb/>).

One can search for the molecular structure and other information by typing the name of the compound in the ligand search engine. KEGG provides structural formulas in their simplified form. For example, the benzene molecule ( $C_6H_6$ ) that forms a carbon ring is shown in KEGG simply as a hexagonal ring with no symbols attached, as shown earlier.

In general, KEGG masks the symbols for carbon and hydrogen atoms. All corners with no symbol attached represent the locations of carbon atoms. The presence of hydrogen bonds is implied when a carbon atom has less than four explicitly drawn bonds. A more detailed description of the KEGG representation is presented in Chapter 2.

### 1.3.3 Physical Strength of a Covalent Bond

Covalent bonds constitute stable links between atoms and are the strongest of bonds connecting molecules. The strength of a covalent bond is measured by the energy required to break it. Rupture of covalent bonds can occur in two ways: The linkage between two atoms may be broken symmetrically to provide a pair of free radicals whose reactivity is derived from the unpaired spins of their electrons. This mode of cleavage is often observed in the breaking of identical or similar atoms. Alternatively, the bond may be broken asymmetrically to produce a pair of ions, one of which is electron deficient and the other, electron rich. The bond strengths of some covalent bonds important in biological systems are shown in Table 1.3.

In general, the energy required to break a covalent bond is much greater than the internal (thermal) energy available at body temperature (0.6 kcal/mol). Chemical changes between molecules take place when the energy needed to break bonds is supplied by some other source, such as the energy released by the formation of new bonds.

As Table 1.3 indicates, covalent bonds between carbon atoms are highly stable. This property enables carbon to form more than seven million chemical compounds. Although silicon also has four valence electrons, silicon's larger atomic radius prevents two silicon atoms from approaching each other closely enough to form stable bonds with each other. Both nitrogen and phosphorus are electron-rich atoms having five valence electrons. The repulsive forces between the unshared pairs of electrons make the N—N bonds less stable than C—C bonds. As a result, the bond energy of an N—N bond is about half the bond energy of a C—C bond. This is why extended chains of bonded N atoms are unstable compared to carbon compounds. Since phosphorus has a larger diameter than nitrogen, it forms even less stable chains of covalent bonds.

TABLE 1.3

<b>Energy Required to Break Covalent Bonds (kcal/M)</b>			
Bond	Energy	Bond	Energy
C=O	170	C—H	99
C=N	147	C—O	84
C=C	146	C—C	83
P=O	120	S—H	81
O—H	110	C—N	70
H—H	104	C—S	62
P—O	100	N—O	53

Next on the periodic table, with six valence electrons, are oxygen and sulfur. Oxygen can make only two covalent bonds; it is involved in most important biochemical reactions, but does not form the backbone of biomolecules. The concentration of sulfur is much lower than oxygen in living systems. Sulfur is also less electronegative than oxygen. Sulfur bonds play a fundamental role in the determination of the three-dimensional shape of a protein. Some of the frequently observed covalent bond groups in organic compounds are illustrated in Fig. 1.5.

### 1.3.4 Electronegativity and Polar Bonds

The capacity of an atom to attract electrons from a neighboring atom is called *electronegativity* and is measured on a scale from 4 (fluorine, the most electronegative element) to a hypothetical 0 (Table 1.4). Table 1.4 shows oxygen as highly electronegative in comparison to carbon and hydrogen.

Covalent bonds between two atoms with comparable electronegativity (such as that between C and H) correspond to an equal sharing of electrons between the two nuclei. When highly electronegative atoms form covalent bonds with atoms of weaker electronegativity, shared electrons spend more of their time closer to the atom with stronger electronegativity. The resulting bond is called a *polar covalent bond* or simply a *polar bond*. Thus, covalent bonds can have partial charges when the atoms involved have different electronegativity. The symbols  $\delta^+$  and  $\delta^-$  are used to indicate partial charges located at different parts of the molecule. For example, the water molecule can be shown in this notation as

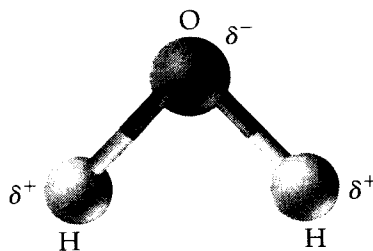


TABLE 1.4

#### Electronegativity of Bioelements

Element	Number	Electronegativity
Hydrogen (H)	1	2.1
Carbon (C)	6	2.5
Nitrogen (N)	7	3.0
Oxygen (O)	8	3.5
Phosphorus (P)	15	2.1
Sulfur (S)	16	2.5
Calcium (Ca)	20	1.0

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## 1.4

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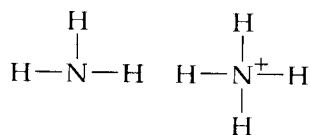
In the water molecule, the oxygen atom exerts a stronger attraction to the bonding electrons than the hydrogen atoms do, resulting in unequal sharing of bonded electrons. When oxygen binds to hydrogen, the bonding electrons spend much more time near the oxygen nucleus than the hydrogen nucleus. Consequently, the oxygen end of the molecule is slightly negative and the hydrogen end slightly positive. Unequal sharing of electrons between two atoms in a molecule results in charge polarity. As discussed later in this chapter, *polar* molecules dissolve easily in water and interact with other polar molecules. In contrast, *nonpolar* molecules dissolve better in a nonpolar environment such as acetone or ethanol.

## 1.4 Ionic Compounds and Electrostatic Bonds

Consider a compound in which one of the two interacting atoms is much more electronegative than the other. In such a compound, one or more electrons from the outer shell of the less electronegative atom are transferred to the more electronegative atom. The result is two electrically charged particles, which are called *ions*. An ion with a positive charge such as  $\text{Ca}^{2+}$  or  $\text{H}^+$  is called a *cation*. An ion with negative charge, such as the hydroxyl ion  $\text{OH}^-$ , is called an *anion*. The net charge of an ion is shown at the superscript immediately to the right of the name of the atom from which it was derived. An electrostatic force holds two ions together due to their differing charges. This force is called the *ionic bond*. The electrostatic force between two ions is large enough to make ionic compounds stable substances. Ionic compounds have high melting points, conduct electricity in the molten state, and tend to be soluble in water.

An example of ionic bond is found in table salt. A sodium atom (Na) has only one electron in its outermost shell of electrons and a chlorine atom (Cl) has seven electrons in its outermost orbits. When the two atoms meet, the highly electronegative chlorine atom takes the single unstable electron from the sodium, producing two ions,  $\text{Na}^+$  and  $\text{Cl}^-$ . Another example of an ionic bond is found in calcium phosphate [ $\text{Ca}_3^{2+}(\text{PO}_4)_2^{3-}$ ], major component of bone. The calcium atom has two electrons in its outermost shell and becomes an anion ( $\text{Ca}^{2+}$ ) by losing two electrons. The phosphate ion  $\text{PO}_4^{3-}$  is a complex ion, meaning that it is a group of covalently bonded atoms that carry an electrical charge.

An example of a covalent bond between a molecule and an ion is exhibited in the ammonium ion ( $\text{NH}_4^+$ ):



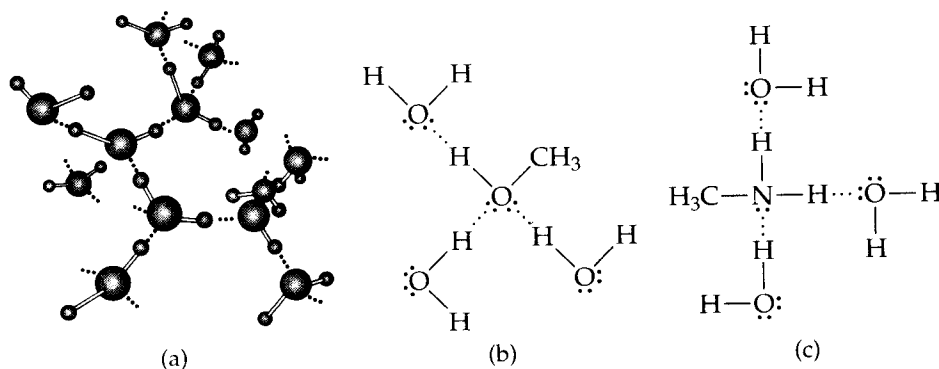
In ammonia ( $\text{NH}_3$ ), the nitrogen forms three covalent bonds with three hydrogen atoms. One of the outermost electron pairs of nitrogen is not involved in a covalent bond; thus, this electron pair is not shared. When dissolved in water, ammonia

picks up a hydrogen ion ( $H^+$ ) to become an ammonium ion ( $NH_4^+$ ), which has a net positive charge of 1. The recruited hydrogen ion shares a previously unshared bond. Again the outermost shell of nitrogen is filled with eight electrons. Because ammonia is highly reactive when dissolved in water, it is used as a main ingredient in many cleaning reagents. Other molecules also become ions when immersed in certain solvents. Consider for example the case of ethanol. Ethanol has no charge, whereas ionized ethanol has a charge of  $-1$ . This transformation depends on the acidity of the medium, a topic discussed later in the chapter.

## 1.5 Water and Hydrogen Bonds

At room temperature, oxygen and hydrogen exist in gaseous form. The water molecules they form, however, are mostly in the liquid state under the same physical conditions. This is in contrast with gaseous carbon dioxide, another compound formed by two elements. Water has important physical properties that make life possible on Earth. It has the ability to dissolve many other substances. As a result, it serves as a medium in which a great variety of chemical changes occur. These special properties of water are due to the *hydrogen bonding* between water molecules (Fig. 1.6). If hydrogen bonds did not exist, water would be a gas at room temperature, very much like other gases such as ammonia and carbon dioxide.

Hydrogen bonding is caused by the polar nature of covalent  $H-O$  bonds that hold together water molecules. In liquid water, the hydrogen atoms of water molecules are attracted to the unshared electrons of oxygen atoms of adjacent water molecules. In chemical diagrams, hydrogen bonds are represented by a series of three dots. The polarity of water molecules leads to extensive interactions between them. The mutual attraction between water molecules causes water to have melting and boiling points at least  $100^\circ$  higher than they would be if water molecules were nonpolar.



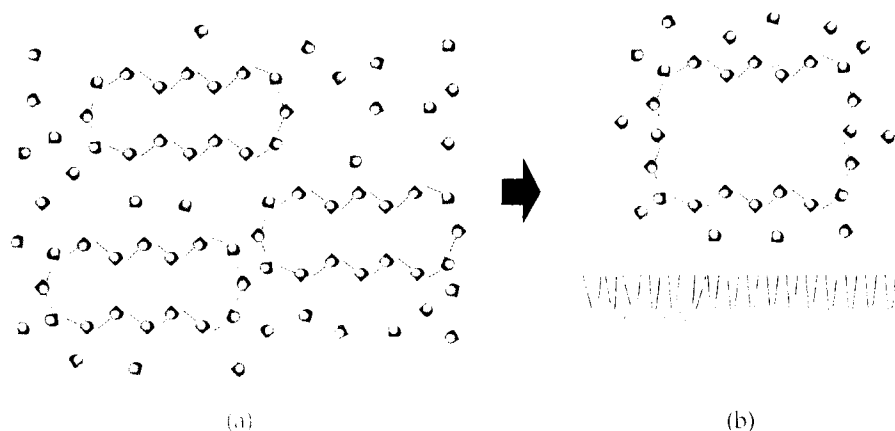
**FIGURE 1.6** Hydrogen bonding. Bonding is maximal when two oxygen atoms and a hydrogen atom fall into a straight line (a). In liquid water, water molecules form transient hydrogen bonds with several others, creating a fluid network (b). Hydrogen bonds between methanol ( $CH_3OH$ ) and water, and methylamine ( $CH_3NH_2$ ) and water (c). Each of the two pairs of nonbonding oxygen electrons can accept a hydrogen atom in a hydrogen bond. The single pair of unshared electrons in the nitrogen outer shell is also capable of becoming an acceptor in a hydrogen bond.

Water molecules form hydrogen bonds with other *polar* molecules including those of nitrogen and oxygen compounds. Both nitrogen and oxygen are considerably more electronegative than hydrogen. Because all covalent N—H and O—H bonds are polar bonds, the H atoms in these bonds can participate in hydrogen bonding. The two atomic groups that often engage in hydrogen bonding in living systems are the amino ( $-\text{NH}_2$ ) and hydroxyl ( $-\text{OH}$ ) groups (Fig. 1.5). Thus, the presence of amino or hydroxyl groups makes many molecules soluble in water. When table salt dissolves in water, the negative (oxygen) ends of the water molecules surround the sodium ions ( $\text{Na}^+$ ). On the other hand, the chloride ions ( $\text{Cl}^-$ ) are surrounded by the H atoms of the polar water molecules. Thus, water molecules cluster around cations and anions in solutions, blocking their association into a solid. Hydrogen bonds also form between different parts of large polar molecules such as proteins (Fig. 1.6). A hydrogen bond is much weaker than a covalent bond in physical strength and duration. However, because many hydrogen bonds can form between different parts of a molecule, they can greatly influence the physical properties of biological substances.

## Lipids and van der Waals Attraction

Carbon and hydrogen share bonding electrons equally. Hydrocarbons, compounds of carbon and hydrogen, are therefore nonpolar. When hydrocarbons are dispersed in water, they slowly come together to form aggregates (Fig. 1.7).

These aggregates take the form of droplets that join to form larger drops. The separate grouping of nonpolar substances in an aqueous environment is due to the inability of nonpolar hydrocarbon molecules to form hydrogen bonds with water. Their presence distorts the usual water structure. The disruption decreases upon formation of a hydrogen-bonded cage surrounding nonpolar hydrocarbons. The cage compresses nonpolar molecules and separates them from the water molecules. In other words, nonpolar solute molecules are driven together in water not primarily because they have high affinity for each other, but because water bonds strongly to itself. Because they do not dissolve in water, nonpolar substances such as olive oil are also called *hydrophobic* or water fearing. Nonpolar molecules do not interact with ionic particles or polar molecules of any type.



**FIGURE 1.7** Nonpolar molecules disturb the hydrogen bonds between water molecules, forcing water to form a cage around them (a). More stable clusters of nonpolar molecules form as the surface area of cage is minimized. As a result, these molecules are pushed together to form larger and larger droplets. Oil forms a single thin layer on the air-water interface (b). The hydrophobic tails of oil molecules extend into the air to avoid contact with water.

The hydrophobic effect drives a number of very important biological phenomena. For example, the formation of cell membranes by lipid bilayers as discussed in Chapter 2 is driven by the hydrophobic nature of the hydrocarbon chains of the lipids that make up the bilayer. The hydrocarbon chains interact with one another, but not with the polar environment. Consequently, lipid bilayers have a hydrophobic core with the hydrophilic heads facing the polar environments outside or inside the cell. Even though the formation of an organized bilayer would appear to impose more order, the entropy (disorder) of the system actually increases because restrictions on the movement of neighboring water molecules decreases with the formation of a lipid bilayer.

Similar hydrophobic effects drive the folding of proteins, the molecular machines of life. In this case, regions rich in hydrophobic amino acids (building blocks of proteins) tend to fold away from more polar regions and from the outer surface of the protein in contact with the polar environment. In some proteins, this leads to the formation of hydrophobic pockets or clefts, which often provide a binding site for small hydrophobic molecules such as steroid hormones.

When molecules come very close to each other, whether they are pushed toward each other by water or any other mechanism, the random variations in the electron distribution of one molecule creates an opposite charge distribution in the adjacent molecule. The result is a brief, weak attraction called *van der Waals* interactions. Although each such interaction is brief and weak at any one site, the summation of many such interactions over the entire surface of a molecule can produce substantial interaction. Van der Waals forces act on nonpolar molecules brought together by a polar solvent.

## 1.7 | Acids and Bases

An *acid* is a substance that can donate protons ( $H^+$ ), and a base is a substance that can accept protons. An example of an acid is hydrochloric acid (HCl), which dissolves in water to generate  $H^+$  and  $Cl^-$  ions. Molecules having a carboxyl group ( $-COOH$ ) are also acidic because  $COOH$  tends to dissociate in water to form  $COO^-$  and  $H^+$ . Ammonia ( $NH_3$ ) is a base because it readily picks up a hydrogen ion to become an ammonium ion ( $NH_4^+$ ). Many important biological molecules have an amino group ( $-NH_2$ ) associated with them. Like ammonia ( $NH_3$ ),  $-NH_2$  is also a base because it can take up a hydrogen ion to become  $-NH_3^+$ . Acids and bases have distinct physical features. Acids in water have sour taste and cause the purple dye litmus to turn red. *Bases* taste bitter, feel slippery, and turn the purple litmus paper blue.

Biological molecules bear functional groups that can undergo acid-base reactions in living systems. Important properties of such molecules vary with the acidities of the solutions in which they are immersed. The main ingredient of the liquid phase of biological organisms is water. A small fraction of water molecules dissociate into positively charged hydrogen ions ( $H^+$ ) and negatively charged hydroxyl ions ( $OH^-$ ). When an acid is added to water, the concentration of  $H^+$  increases, and conversely when a base is added the concentration of  $H^+$  decreases. The hydrogen ion concentration affects the rates of chemical reactions that occur in aqueous medium. In pure water at  $25^\circ C$ , the concentration of hydrogen ions  $[H^+]$  is equal to  $10^{-7}$  mol/L. Since there are  $6.0235 \times 10^{16}$  (*Avogadro* number) ions in one mole of  $H^+$ , this concentration amounts to the same number of hydrogen ions per liter. The



concentration of hydrogen ions in a solution is expressed as

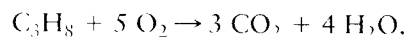
$$\text{pH} = -\log[\text{H}^+],$$

where  $\log$  denotes 10-based logarithm and  $[\text{H}^+]$  is the concentration of  $[\text{H}^+]$  in moles per liter (or M). The pH of water at 25°C is 7. The pH of cell fluid (cytoplasm) is normally about 7.2. Values of pH below 7 indicate acidic solutions and values above 7 indicate basic solutions. Gastric fluids, vinegar, soda, lemon juice, and contracting muscle cell fluid are acidic whereas sweat, human blood ( $[\text{H}^+] = 4 \times 10^{-8}$  M) and household ammonia are basic.

Small shifts in cellular pH play an important role in the regulation of a number of cellular phenomena including cell division and cell growth. The relative number of acidic and basic amino acids (building blocks of proteins) in different proteins varies significantly. Although many proteins are denatured by acidic conditions, some proteins, such as gastric enzymes and lysosomal enzymes, are in their most active state at low pH. In contrast, enzymes in the small intestine are most active in somewhat basic conditions. Some cellular membranes have the ability to pump protons from one side to the other and create a pH gradient. As we discuss later, such a proton gradient serves an important function in mitochondria where it is an important component in the generation and storage of energy.

## Chemical Reactions

A chemical reaction occurs when atoms combine or change binding partners. In a chemical reaction, one form of matter is changed into another. Consider the combustion reaction that takes place when propane ( $\text{C}_3\text{H}_8$ ) reacts with  $\text{O}_2$  in a stove, the resulting equation can be written as



In this equation, propane and oxygen are the reactants, and carbon dioxide and water are the products. The arrow shows the direction of the chemical reaction. Numbers preceding the molecular formulas indicate the proportions of the number of molecules reacting or produced. Subscripts indicate the number of a certain atom type in a molecule. Since matter is neither created nor destroyed in a chemical reaction, the number of atoms of a given type on the left-hand side of the equation equals that on the right-hand side.

## Energetics of Chemical Reactions

The forces of thermodynamics were instrumental in the evolutionary development of living cells. In thermodynamics, a “system” is defined as the part of the universe that is of interest. Examples of a system include an isolated tumor, a cell, or even a single protein molecule. The rest of the universe is then called the “surroundings.” A system is said to be open if it can exchange matter and energy with its surrounding. Living cells are open systems as they take up nutrients, release waste products, and generate work and heat. On the other hand, an organism that was frozen for research purposes can be idealized as a closed system.

The first law of thermodynamics is also referred to as the conservation of energy law and states that energy can be neither destroyed nor created. There are many forms of energy such as mechanical energy, electrical energy, and chemical energy. In a

chemical reaction, energy is merely transformed from one form to another. Let  $\Delta U$ ,  $q$ , and  $w$  denote, respectively, the energy gained by an open system, the heat absorbed by the surroundings, and the work done by the system on the surroundings. Then the first law can be written as follows:

$$\Delta U = q - w. \quad (1.1)$$

Heat is a consequence of random molecular motion, whereas work is associated with organized motion (force) and can be mechanical, electrical, or chemical in nature. The energy of a system depends only on its current properties (state) and not on how it reached that state, whereas both heat and work are path dependent. The processes in which the system releases heat ( $q < 0$ ) are called *exothermic* processes, and those in which the system gains heat are known as *endothermic* processes.

The *second law of thermodynamics* states that in all processes, some of the energy involved irreversibly loses its ability to do work. The disorder of the universe (its entropy) increases with each ongoing process. For a system 1 and its surroundings, the second law of thermodynamics can be written in the form

$$\Delta S_1 + \Delta S_2 = \Delta S_u > 0. \quad (1.2)$$

In this equation,  $S$  refers to entropy, which is the measure of disorder in a system. The terms  $S_1$ ,  $S_2$ , and  $S_u$  represent the entropies of the system, surroundings, and the universe, respectively. The inequality (1.2) indicates that the change in entropy of the system ( $\Delta S_1$ ) could be positive or negative, but the overall change of the entropy of the universe must always be positive. For simple systems such as a gas in a chamber, entropy can be estimated by counting the number of different ways gas particles can exist. However, estimation of entropy using combinational probability is much more difficult in more complex media such as the cytoplasm of a cell.

In closed systems, the entropy of the system must increase with time. Therefore, any spontaneous process must lead to an increase in the entropy of the system. Such a spontaneous process occurs when oil drops in water merge to form a separate phase from that of water. Nonpolar molecules composing oil drops cannot form hydrogen bonds with water and therefore distort the usual water structure, forcing the water to make a cage of hydrogen bonds around it. Formation of such cages restricts the motion of adjacent water molecules and thereby increases the structural organization of water. When nonpolar molecules cluster together, the structural organization of the water is reduced and the overall entropy of the system increases.

The first and the second laws of thermodynamics can be combined in the following form when chemical reactions are considered:

$$\Delta H = \Delta G + T \Delta S. \quad (1.3)$$

In this equation,  $\Delta H$  is the overall change in bond energy due to reaction (kcal/mol),  $\Delta S$  is the change in entropy (a measure of the energy lost to disorder in the system), and  $\Delta G$  is defined as the change in free energy, first introduced into the thermodynamics literature by J. Willard Gibbs in 1878. Of the energy that is released by a chemical reaction, only a certain percentage can be used to do work, no matter how efficient the process. The energy that can be used to do work is called the free energy. For spontaneous chemical processes that occur at constant temperature, the following relation holds:

$$\Delta S_1 \geq q/T. \quad (1.4)$$

In this relation,  $q$  refers to heat imported into the system and  $T$  is the absolute temperature. Equality holds only at equilibrium, where changes could occur infinitesimally. For systems that can only do pressure–volume work at constant pressure and temperature, the criterion of spontaneity can then be written as

$$\Delta G \leq 0. \quad (1.5)$$

Again,  $\Delta G$  denotes the change in free energy. To gain insights into the preferred direction of chemical reactions, consider a chemical reaction in which  $A$  and  $B$  react to produce  $C$  and  $D$ :

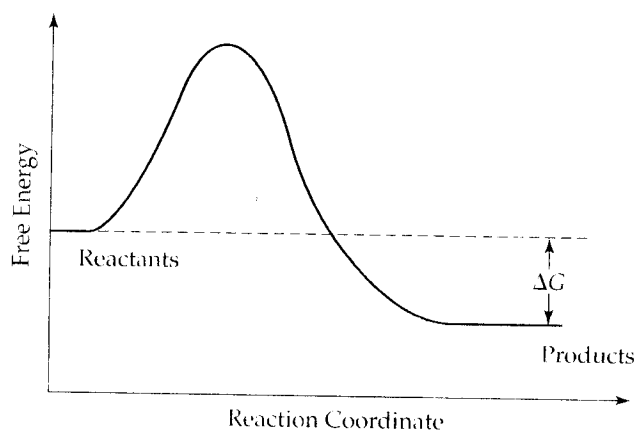


In this equation, the double arrow indicates that the reaction proceeds in both directions. Whether the reaction will proceed overall in the forward or reverse direction depends on the change in free energy due to the reaction.

The parameter  $\Delta G$  is an indicator of spontaneity for constant-temperature and pressure processes (Fig. 1.8):

1. If  $\Delta G < 0$ , then the free energy of the products is less than the free energy of the reactants, and the forward reaction will tend to occur spontaneously. This type of reaction is said to be *exergonic* or energetically favorable.
2. If  $\Delta G > 0$ , then the reverse reaction tends to occur. Such a reaction is said to be *endergonic*.
3. If  $\Delta G = 0$ , both forward and reverse reactions occur at equal rates; the reaction is at steady state. If the reaction occurs in an isolated chamber, then the steady state corresponds to *chemical equilibrium*. However, living systems are not in chemical equilibrium. Cells are not isolated chambers, and there is continuous exchange of mass and energy across the cell membrane between the cell interior and the external environment.

There are two parts to the free-energy change that occurs in a chemical reaction. One part is called the *change in standard free energy*, and it is represented by the symbol  $\Delta G^\circ$ . The other part depends on the concentrations of reactants and products. For a chemical reaction of the form



**FIGURE 1.8** Free-energy change during an energy-releasing reaction expressed as a function of the progress of reaction. The conversion of substrate to product will only occur if it results in the loss of potential energy.

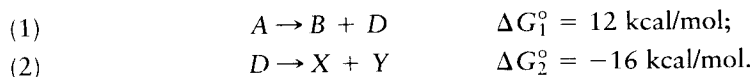
the change in free energy is given by the equation

$$\Delta G = \Delta G^\circ + RT \ln \left\{ \frac{[C][D]}{[A][B]} \right\}, \quad (1.8)$$

where  $\ln$  denotes natural logarithm,  $R = 1.987$  cal/mol is the gas constant and  $T = 273.15^\circ + C^\circ$  is the temperature measured in degrees Kelvin. The terms in brackets represent the volumetric concentrations of the reactants and the products in M. The standard free energy  $\Delta G^\circ$  is the free-energy change of the reaction when all reactants and products are in a standard state. For biochemical reactions, the standard state means restricting initial concentrations of the chemicals to unit values (1 mol/L), the temperature to  $25^\circ\text{C}$ , and the pH to 7.0. Standard free energy is an intrinsic property of the chemical reaction itself and can be determined experimentally by measuring the equilibrium concentrations of the products and reactants under standard conditions. Standard free-energy changes have been measured and tabulated for many biochemical reactions. For the oxidation reaction of glucose, the standard free-energy change  $\Delta G^\circ = -686$  kcal/mol. Thus, when 1 mol of glucose reacts with oxygen under standard conditions, 686 kcal of energy is released.

The second part of the free-energy change is dependent on temperature and the concentrations of reactants and products. The free-energy change ( $\Delta G$ ) increases with increasing temperature and increasing concentrations of reactants. The change in free energy decreases with increasing concentration of the products. The net reaction proceeds in the forward direction when the sum of the two components of free-energy change is less than zero.

Many chemical reactions in biological systems are *endergonic* reactions where the change in free energy  $\Delta G > 0$  and therefore the forward reaction is not favored. How do such reactions proceed in the forward direction? The answer lies in the additive property of free energy. A chemical reaction with a positive  $\Delta G$  may be coupled to a reaction that has a negative  $\Delta G$  of a larger magnitude, so that the sum of the two reactions has a negative  $\Delta G$ . Consider, for example, the following two-step reaction process:

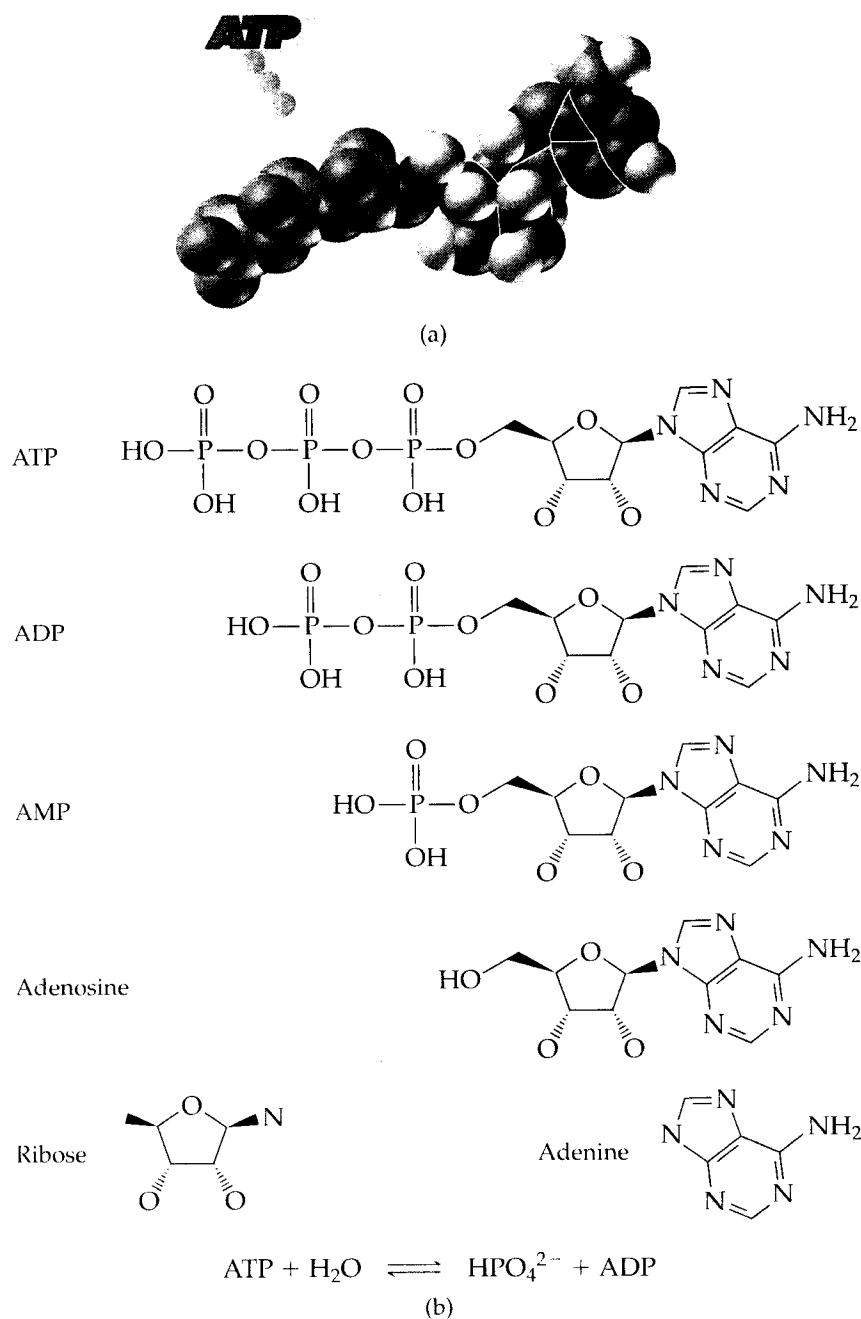


Reaction (1) would not occur spontaneously under standard conditions because  $\Delta G_1^\circ > 0$ . When reaction (1) is coupled to reaction (2), however, the net change in standard free energy becomes negative ( $\Delta G_1^\circ + \Delta G_2^\circ = -4$  kcal/mol). As Reaction (2) converts  $D$  into products, the concentration of  $D$  is reduced to values that make the free energy change negative [see Eq. (1.1).] Reaction (1) will operate in the forward direction in order to replenish the equilibrium concentration of  $D$ . As a rule, as long as the overall pathway is *exergonic* ( $\Delta G_3 = \Delta G_1 + \Delta G_2 < 0$ ), the sequence of reactions will operate in the forward direction.

The standard free-energy change  $\Delta G^{\circ'}$  is related to the equilibrium constant  $K_{\text{eq}}$  of a reaction by the equation

$$\Delta G^{\circ'} = -RT \ln K_{\text{eq}},$$

in which  $\ln$  denotes natural logarithm. A chemical reaction having a positive  $\Delta G^{\circ'}$  can proceed spontaneously if it is coupled with a reaction having a negative  $\Delta G^{\circ'}$  of a larger value. This exergonic reaction is most often the hydrolysis of ATP. Endergonic organic reactions are coupled to the energy-releasing properties of ATP, a molecule that is considered the universal energy currency of living systems (Fig. 1.9).



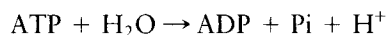
**FIGURE 1.9** Structures of ATP, ADP, and AMP (a). The hydrolysis of ATP releases free energy (b). An ATP molecule consists of the base adenine bonded by three phosphate groups. In the chemical conditions in a living cell, the phosphate groups are ionized and bear negative charges that repel one another. When ATP hydrolyzes and the phosphate group breaks away, the charges are spread over two molecules that are free to move apart from each other. Hydrolysis of ADP to AMP also releases energy, but this reaction does not occur often in cells. Hydrolysis of the last phosphate group does not spread the negative charges apart, so the change in free energy is small.

### 1.8.2 ATP: The Standard Energy Carrier

Most food products would readily burn in the presence of oxygen to produce carbon dioxide, water, heat, and light. The metabolic machinery of the cell traps a significant portion of the chemical energy of foodstuffs into a more readily usable form stored in ATP. ATP consists of the nucleotide, adenine, the sugar ribose, and a triphosphate unit and participates in most cellular reactions and processes that require energy. The energy-extracting processes of cells are extremely complex, involving large numbers of enzymes and ligands. Nevertheless, this multistep process can be divided into distinct pathways that can be independently analyzed by explicitly listing inputs and outputs.

ATP is a very stable molecule: One will find bottles of ATP stored at room temperature in any biochemistry laboratory. However, when catalyzed by the appropriate enzyme (an ATPase), ATP can undergo the so-called hydrolysis reaction  $\text{ATP} \rightarrow \text{ADP} + \text{P}_i + \text{H}_2\text{O}$ , where ADP and  $\text{P}_i$  represent respectively, adenosine diphosphate and  $\text{PO}_4^{3-}$ . ATP hydrolysis has very high activation energy and releases 7.2 kcal/mol of energy that can be used to drive energy requiring cellular processes. Endergonic reactions coupled to ATP hydrolysis include the synthesis of large macromolecules, contraction of muscle cells, and the transport of molecules in and out of a cell against a concentration gradient.

The hydrogen atoms shown in the figure as bound to phosphate groups represent protons in the cytosol that associate with the electronegative oxygens of the phosphate groups. The active form of ATP is a complex of ATP with  $\text{Mg}^{2+}$  or  $\text{Mn}^{2+}$ . In this complex, the positively charged divalent cation interacts with oxygen by replacing two of the hydrogen atoms in the outer phosphate groups. The chemical reaction



is called ATP hydrolysis.

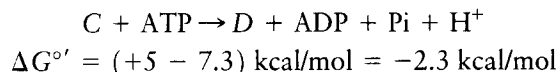
The change in free energy as ATP is converted to ADP represents that portion of the total energy, which is available for doing work. The free energy  $G$  is a quantity (always a positive scalar) similar to gravitational potential energy and the elastic energy of a spring. In ATP hydrolysis, the term change in free energy ( $\Delta G$ ) refers to the free energy of  $\text{ADP} + \text{P}_i$  minus the free energy of ATP. The hydrolysis of ATP results in a change of free energy ( $\Delta G$ ) of  $-12$  kcal/mol under physiological conditions. The standard free energy  $\Delta G^{\circ'}$  is  $-7.3$  kcal/mol for hydrolysis of ATP to ADP.

The four hydrogen ions associated with the triphosphate of ATP dissociate easily from the molecule, leaving the negative charges on the oxygen ions unmasked. Electrostatic repulsive forces arising from these negative charges stretch the molecule and increase its potential energy. These repulsive forces are reduced when the outer inorganic phosphate group detaches from the rest of the molecule. This is one reason why conversion of ATP to ADP results in a reduction of free energy. One other factor contributing to the energy-carrying capacity of ATP is that ATP-ADP turnover increases entropy. ADP and the orthophosphate have many more possible positional configurations when compared with the structural configurations that are possible for ATP.

Let us next illustrate how ATP hydrolysis could drive a reaction that requires energy input. Suppose that the free energy of the conversion of  $A$  into  $B$  is  $+4$  kcal/mol, as in



Because standard free energy is positive, conversion from  $A$  to  $B$  does not go forward under the standard conditions. Let us now couple this reaction with ATP hydrolysis:



The standard free-energy change for the coupled reactions is equal to the standard free-energy change due to ATP hydrolysis plus the change due to the conversion of  $A$  into  $B$ . The resulting standard free-energy change is negative and the conversion of  $A$  to  $B$  goes forward.

In biological systems, the concentration of ATP is maintained at a much higher level than that of ADP. The ATP-generating system of cells maintains the ratio  $\{[\text{ATP}]/[\text{ADP}][\text{Pi}]\}$  of the order of 500. In a typical cell, an ATP molecule is consumed within a minute following its formation. Even though ATP is inherently stable, the turnover of the ATP-ADP cycle is very high: A resting human converts about 40 kg of ATP to ADP in 24 hours. This massive hydrolysis of ATP is catalyzed by enzymes known as ATPases, which are involved in almost all energy-requiring reactions. Some reactions in the living systems are driven by nucleotides other than ATP. Guanosine triphosphate (GTP) drives synthesis of peptides and also plays an important role in supplying the energy needed for signal transduction. The structure of GTP is very similar to that of ATP, and GTP hydrolysis is catalyzed by enzymes known as GTPases.

Enzymes catalyze the transfer of the terminal phosphoryl group from one nucleotide to another:



The standard free-energy change from GTP to GDP is comparable to that of ATP to ADP. Other nucleotides such as uridine triphosphate (UTP) and cytidine triphosphate (CTP) also drive energy-requiring biosynthetic processes. The reader could refer to *Kyoto Encyclopedia of Genes and Genomes* (KEGG) database by the Institute of Chemical Research, Kyoto University and utilize the search engine at <http://www.genome.ad.jp/dbget/ligand.html> to learn about the pathways that involve the hydrolysis of UTP and CTP. It is interesting to note, however, that most of the central molecules involved in energy transfer in living systems are nucleotides that contain the five-carbon sugar ribose rather than deoxyribose. A likely explanation for this phenomenon is that RNA evolved before proteins and DNA. When proteins replaced RNA as the major catalysts to achieve greater versatility, these enzymes utilized ribonucleotides because they were already well adapted to their metabolic roles. The role of energy-carrying ribonucleotides in metabolism is further illustrated in Chapter 3.

Besides ATP and GTP, a large number of biological molecules contain high-energy bonds. Why is it then that ATP and similar molecules such as GTP are used as the standard energy source in biological reactions? The answer to this question is that the free energy of hydrolysis of ATP (also GTP) is sufficient to drive most of the coupled reactions in living systems. Higher release of free energy would be wasted as heat. The situation is comparable to using currency to buy goods. If commerce were restricted in a way that no change is returned after a purchase, one would be tempted to use smaller bills rather than a hundred-dollar bill in purchasing an item that costs four dollars. Otherwise, much of the effort spent in earning a hundred-dollar bill would have been wasted.

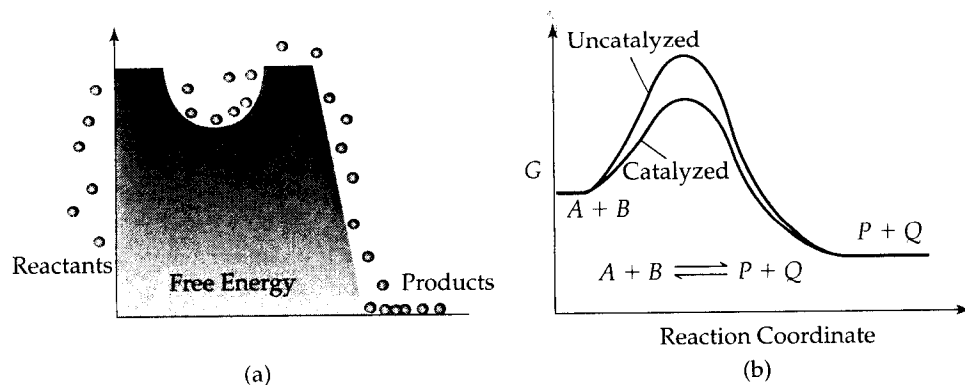
## 1.9 Enzymes

Burning of propane gas ( $C_3H_8O_2$ ), although energetically favorable, does not occur spontaneously. One has to use a flame to ignite propane and initiate burning. Most chemical reactions require an initial input of energy to get started. The added energy increases the kinetic energy of the molecules and thereby increases the frequency of collision. Collision is needed to overcome the repulsive forces between the electrons surrounding molecules and to break existing chemical bonds with the molecules. *Activation energy* is defined as the energy barrier that needs to be overcome for a reaction to proceed (Fig. 1.10). Burning of propane involves breaking of covalent bonds between carbon and hydrogen and between two oxygen atoms. As presented in Table 1.3, the dissociation of bonds requires infusion of energy. The activation energy for this reaction is supplied by the flame used to initiate burning. The energy released in the forward reaction in the form of heat is sufficient to overcome the activation energy barrier at later times. The importance of activation energy on the progression of the reaction is illustrated graphically in Fig. 1.10. Consider two molecules  $A$  and  $B$  reacting to form  $P$  and  $Q$ :  $A + B \rightarrow P + Q$ . For this reaction to occur,  $A$  and  $B$  must approach closely enough so that an unstable (high-energy) complex (say,  $X^*$ ) forms. The intermediate product  $X^*$  is called the transition state. This product is so high in free energy that it is unstable and eventually breaks down to give  $P$  and  $Q$ . When the free energy of the reactants and products are shown as a function of the reaction coordinate (measuring the extent in which the reaction proceeded), the transition state lies at the crest of the energy profile curve in Fig. 1.10. The rate of reaction is considerably enhanced when heat is supplied to overcome the activation barrier.

Chemical substances called catalysts provide an alternative way of overcoming activation energy. A catalyst is a substance, present in small amounts relative to the reactants, that accelerates a reaction without being consumed in the process. Catalysts form complexes with reactants and lower the activation energy barrier for the reaction being catalyzed (Fig. 1.10). Because the forward and reverse reactions are catalyzed to the same extent, the reaction equilibrium is not disturbed. Catalysts have no effect on the  $\Delta G$  of the reaction.

Biological catalysts are called enzymes. In a living cell, thousands of reactions can occur at constant temperature at any instant of time. Any extraction or infusion of heat would affect these reactions indiscriminately. A flux of heat also breaks the

**FIGURE 1.10** Enzymes overcome the energy of activation and facilitate a chemical reaction to go forward. Not all reactant molecules have the same levels of kinetic energy. Some molecules surmount the energy barrier and react, thereby forming products (a). An enzyme reduces the activation energy barrier of a chemical reaction (b).

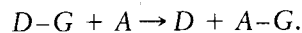




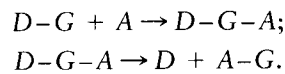
hydrogen bonds between various parts of proteins—molecular machines of life—and has other destructive effects.

Even if a biological reaction is *exergonic* (negative free-energy change), it does not proceed in the absence of enzymes. For example, digestion of proteins is an energetically favorable process in which the peptide bonds between the monomers (amino acids) of a protein molecule are broken. Nevertheless, in a sterile aqueous solution at room temperature, hardly any degradation would occur over days or even months. This is because the activation energy for breaking the peptide bonds is high enough to prevent all but a few protein molecules from engaging in the forward reaction of degradation. In biological systems, in reactions where covalent bonds are made and broken, differences in energy between reactants and products range from 1 to 20 kcal/mol. On the other hand, the activation energy associated with a bioreaction can be on the order of 100 kcal/mol. As a result, the covalent bonds of structural molecules remain intact over very long periods of time.

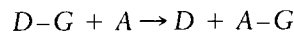
Let us now illustrate the effect of an enzyme on a simple chemical reaction in which a covalent group  $G$  is transferred from donor  $D$  to acceptor  $A$ :



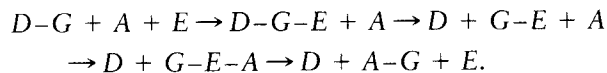
This overall reaction proceeds via two half reactions: (1) the formation of the transition state and (2) the decay of the transition state to form products. These reactions proceed as follows:



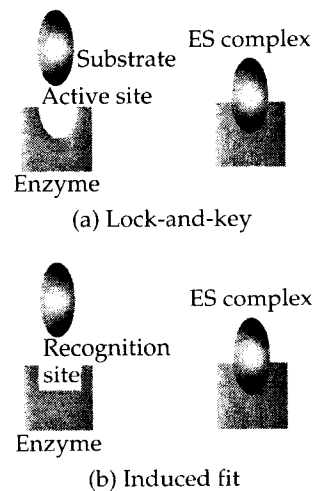
In these equations,  $D-G-A$  represents the transition state where  $D$ ,  $G$ , and  $A$  are bound to each other for a brief period. The free energy of the transition state is typically higher than the free energy of the reactants, creating an *energy barrier* against the forward reaction. An enzyme alters the transition state through which a reaction must proceed by temporarily binding to one or more of the reactants (substrates) through multiple weak interactions. Remarkably, many enzymes have evolved to bind (and stabilize) the transition-state conformation of the reactant rather than the starting substrate. Consequently, the transition states that occur in the presence of an enzyme have considerably lower free energy, thus allowing the reaction to proceed. For example, the reaction



is transformed into a set of intermediate reactions in the presence of enzyme  $E$ :



In the first reaction, enzyme  $E$  combines with  $D-G$ . In the second reaction,  $D$  detaches from  $E-G$ . Another transition product,  $E-G-A$ , is subsequently produced, and in the last step, enzyme detaches from the acceptor molecule  $A$ . Thus, the concentration of enzyme  $E$  is not changed by the resultant chemical reaction. As illustrated in this example, much of the catalytic power of enzymes comes from their bringing substrates together in favorable orientations in *enzyme-substrate* complexes. In doing so, enzymes may utilize a lock-and-key type mechanism where the substrate binds to a site of exact complementary fit (Fig. 1.11a). Alternatively, an enzyme



**FIGURE 1.11** Enzyme-substrate interactions. In the lock-and-key mechanism, binding of substrate to the complementary active site positions it for catalysis (a). In enzymes with induced fit action, binding of substrate induces a conformational change in the enzyme that brings the part of the enzyme site involved in catalysis to the proximity of the substrate (b).

may induce strain or distortion of the substrate to promote catalysis. In such cases, enzyme–substrate interaction may occur according to induced fit action where the binding of substrate induces a conformational change in the enzyme that brings part of the enzyme site involved in catalysis to the proximity of the substrate (Fig. 1.11b). Studies of protein structure by X-ray crystallography have indicated that the active sites of most enzymes are largely preformed; however, in most cases, conformational changes are induced by substrate binding.

Essentially all biochemical reactions are enzyme catalyzed. Enzymes are reaction-specific catalysts. Each enzyme binds only a small number of reactants, and frequently just one reactant. Many diseases are due to genetically determined abnormalities in the synthesis of a few enzymes. Quite often, the rate of an enzyme-catalyzed reaction is  $10^6$  to  $10^{12}$  times that of an uncatalyzed reaction under otherwise similar conditions.

### 1.9.1 Factors Affecting Enzyme Activity

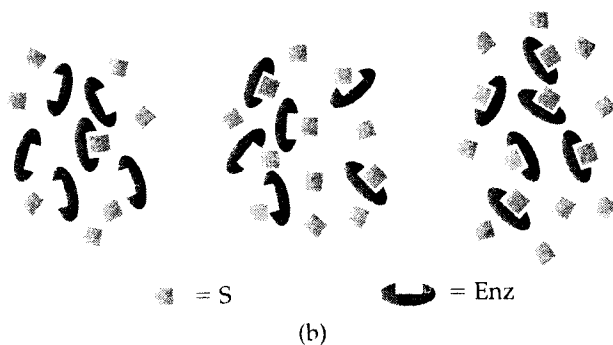
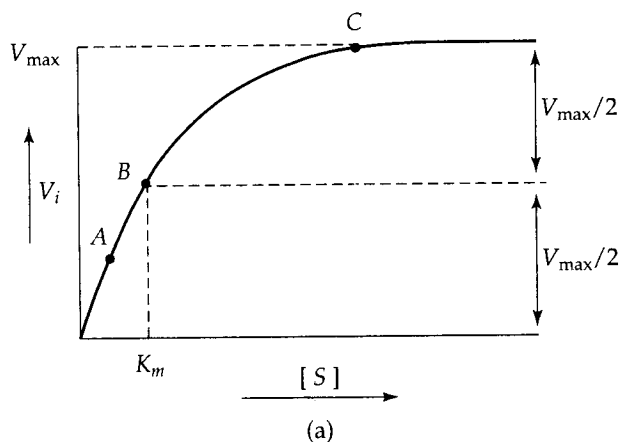
Concentrations of substrates and enzymes in an enzyme-mediated reaction, the temperature, pH, and the presence of enzyme inhibitors are among the major factors affecting enzymatic activity. Rates of biological reactions double with a  $10^\circ\text{C}$  increase in temperature, hence the increase in heart rate with increasing room temperature. For most enzymes, maximum activity is observed between pH values of 5 and 9, and many enzymes denature at extremely low and high pH values. Moderate changes in pH may also have significant effects on the ionic state of the enzyme and the substrate. Changes in pH could alter the charge distribution on the binding site, resulting in a change in the efficiency of catalytic activity.

As mentioned earlier, enzyme concentrations are typically much lower than the concentrations of reactants. In enzyme-mediated reactions, the rate of reaction increases in proportion to enzyme concentration. The rate of reaction shows hyperbolic behavior, on the other hand, with respect to substrate concentration. This is illustrated in Fig. 1.12 for the reaction  $S \rightarrow P$ . The figure shows that the rate of reaction is proportional to substrate concentration at low substrate concentrations, but becomes concentration independent (zero order) at high concentrations. The hyperbolic dependence of rate of reaction on substrate concentration reflects the fact that when all the enzyme molecules available are already combined with substrate molecules, increasing substrate concentration does not increase the rate of reaction.

The equation for the rate of product formation  $V = d[P]/dt$  can be written as

$$V = k_{\text{cat}}[E_t][S]/\{[S] + K_m\}, \quad (1.9)$$

where  $V$  is typically identified as the velocity of reaction and  $[E_t]$  and  $[S]$  are the concentrations of the enzyme (bound or unbound) and the substrate, respectively. The parameters  $k_{\text{cat}}$  and  $K_m$  refer to time constants involving the enzyme-mediated reaction. In particular, the dimensionless rate constant  $K_m$  is equal to the half maximal velocity of the reaction. This equation is called the Michealis–Menten equation. Linear double reciprocal plots using this equation present a straight line where slope and intercept can be deduced by computing the rate of reactions at alternate  $S$  values for constant  $[E]$ . It is important to note that even in the face of marked changes in the rates at which reactions occur, enzyme-mediated catalysis does not change reaction equilibria, both forward and reverse reactions are catalyzed



**FIGURE 1.12** Effect of substrate concentration on the velocity of an enzyme-catalyzed reaction (a). The velocity of reaction  $S \rightarrow P$  is defined as the time rate of formation of product  $P$ . The points A, B, and C in graph (a) represent low, medium, and high concentrations of the enzyme relative to the substrate concentration (b).

equally well. Enzyme concentration or activity is often the point of regulation of chemical reaction pathways in biological systems. Examples of control of cellular activity with modification of enzyme concentration will be discussed in Chapter 4.

## 1.10 | More on Bioelements

1. Discuss the possible reasons why elements with atomic numbers 2 to 5 do not constitute important components of living systems. The element with atomic number 2 is helium with an electron configuration of  $1s^2$ . This electron configuration is stable, making the helium atom inert. Helium is not capable of bonding with other atoms and therefore would not be a good building block in a living system, which requires the building of complex molecules. The element with atomic number 3 is lithium with an electron configuration  $1s^2 2s^1$ . Lithium has one electron in its outer shell and is more likely to lose the lone electron rather than attract electrons to achieve a full outer shell. Because lithium has lower electronegativity (0.98) than hydrogen (2.1), it would give the electron rather than share it with other atoms. Hydrogen, on the other hand, can form covalent bonds with organic elements such as carbon, nitrogen, and oxygen and in solution. Compounds of lithium such as lithium carbonate and lithium sulfate are used as antidepressants. Because lithium has similar electron configuration

as sodium and it is a smaller atom, it can use the sodium/potassium channels to enter living cells from blood flow. Precisely how lithium affects brain cells to alleviate mental disorders is not known. However, the effect of lithium can be attributed to its action on receptor-mediated neuronal pathways.

The element with atomic number 4 is beryllium with an electronic configuration of  $1s^2 2s^2$ . Because beryllium's  $s$  subshells are filled, this element is relatively inert compared to other alkali elements. Beryllium is not a building block of complex molecules; it does not react with water even at very high temperatures. The element with atomic number 5 is boron, with the electron configuration  $1s^2 2s^2 2p^1$ . Boron has three valence electrons. However, its electronegativity (2.04) is less than that of hydrogen (2.1) and of nitrogen (3.0). The atomic radius of boron (1.17 Å) is larger than carbon (0.91 Å) and nitrogen (0.75 Å). A large atomic radius indicates that the outer subshell electrons are relatively far from the nucleus. Thus, in a living system, molecules containing boron would be more loosely held than those molecules containing carbon or nitrogen. The weak bonding capacity would not favor the longevity of complex molecules in a living system. Nevertheless, boron is a trace mineral that is essential for plants. In minute amounts, boron may also be essential for humans and animals in energy utilization and the development and maintenance of bone. Animal studies show that boron improves the production of antibodies that help fight infection and markedly decreases peak secretion of insulin from pancreas.

2. *Fluorine is the most electronegative element and yet it is not part of life. Why?* The extremely high electronegativity of fluorine makes it a very reactive element. It partakes in ionic bonding, but not covalent bonds. In a living system, fluorine would strip electrons from atoms, thus destroying bonds that keep complex molecules intact.
3. *Discuss the differences between covalent bonds and metallic bonds.* In metallic bonds, electrons in the outer shell form a cloud around the lattice of nuclei. A covalent bond, on the other hand, is the sharing of one or more electrons between two atoms. In metallic bonding, each atom is bound to several neighboring atoms. The bound electrons are relatively free to move throughout the three-dimensional structure of the lattice of atoms, a property that makes metals good conductors of electricity.
4. *Why do heavy elements form covalent bonds much less frequently than lighter elements?* The electrostatic force by which electrons are attracted to the nucleus is inversely proportional to the square of the distance between the nucleus and the electron. Typically, heavy elements have a larger atomic radius than lighter elements. Therefore, the outer shells of heavy elements are held less tightly than those shells of lighter elements. The more easily the electrons in the outer shell part from the rest of the atom, the less likely the atom is to have covalent bonding.
5. *Describe the various isotopes of oxygen and carbon and their significance for living systems.* Isotopes of an element differ in the number of neutrons in nucleus. There are four naturally occurring isotopes of oxygen. These isotopes are  $O^{15}$  with a half-life equal to 122.2 s and the three stable isomers  $O^{16}$ ,  $O^{17}$ , and  $O^{18}$ . The most abundant isotope is  $O^{16}$ . The naturally occurring oxygen in air and water is a combination of the three stable isotopes.

## 1.11

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The isotopes of carbon include  $C^{11}$  with half-life of 20.3 min,  $C^{12}$  (stable),  $C^{13}$  (stable),  $C^{14}$  with half-life equal to 5730 years, and  $C^{15}$  with half-life of 2.5 s. The three principal isotopes of carbon that occur naturally are  $C^{12}$  (98.89%),  $C^{13}$  (1.11%), and  $C^{14}$ . Plants and animals utilize carbon within the biological food chain and as a consequence take up  $C^{14}$  as well as the other two isotopes. Since there is no incorporation of radioactive  $C^{14}$  after an organism dies, measuring the concentration of  $C^{14}$  in a fossil helps determine its age.

6. Provide examples of nutrients rich in (a) nitrogen, (b) phosphorus, and (c) sulfur. Nitrogen is found in all proteins, most vitamins, and hormones. Nitrogen accounts for approximately 16 percent of all proteins by weight. It is also found in fertilizer products in the form of ammonia, nitric acid, and urea. Phosphorus is found in some proteins in milk, eggs, fish, poultry, legumes, nuts, and whole grains. Similarly, meat, milk, eggs, and legumes are rich in sulfur-containing amino acids.
7. Estimate the number of different types of enzymes in a typical bacteria. One of the most heavily studied bacterial genomes is that of *Escheria coli* (*E. coli*). The *E. coli* genome has 4290 genes. Another bacterium, *Haemophilus influenza*, has 1743 genes. Not all of these genes encode enzymes. *E. coli* has approximately 2000 enzymes. The list of these enzymes can be found in the EcoCyc database.
8. Why is ammonia a good cleaning agent? Ammonia has the chemical formula  $NH_3$  and is a good cleaning agent because of its ability to attract protons associated with dirt. When aqueous ammonia comes into contact with dirt, it takes a proton and is converted to the ammonium ion  $NH_4^+$ . Once the dirt particle loses a proton, it becomes negatively charged and becomes soluble in water. The dirt then detaches from what it was initially attached to and is swept away by the drained water.

## 1.11 ASSIGNMENTS

1.1 Brief Quiz: (a) What are the elements that make up organic materials? Discuss their chemical properties. (b) What is chemical reactivity? What is the octet rule? (c) Discuss the four types of bonds between atoms and/or ions. (d) Why do fatty acids cluster when immersed in water? (e) What are enzymes, and what role do they play in living systems? (f) Why is sulfur less electronegative than oxygen? (g) What significant role does sulfur play in living organisms?

1.2 Determine the chemical and structural formulas of the organic compounds *glyceraldehyde 3-phosphate*, *succinate*, and *glutamine* using the ligand/compound database called the *Kyoto Encyclopedia of Genes and Genomes (KEGG)* by the Institute of Chemical Research of the Kyoto University. Specifically, go to the Web site <http://www.genome.ad.jp/dbget/ligand.html>, and press

“Search enzymes and compounds.” In the next page, input your search keywords (the name of the compound) into the search box, and then press “Submit.” The next page will present you with a list of enzymes that interact with the compound (those lines that begin with *ec:*) and the different forms and variations of the compound itself (*cpd:*). When this search was conducted in October 2000, there were 36 entries for glutamine, 21 of which were enzymes. The compound name glutamine appeared 23rd on the list. When this line was entered, the next page provided the structural as well as the chemical formula of the glutamine ( $C_5H_{10}N_2O_3$ ).

1.3 The energy required to break a covalent bond must be equal to the work done against forces of interaction between the two atoms. The atomic force microscope is being increasingly used in the quantification of