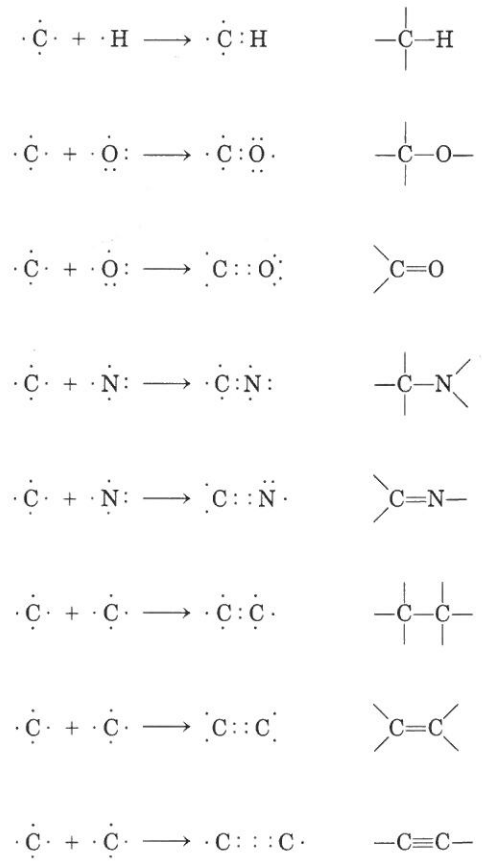
Biomolecules Are Compounds of Carbon

The chemistry of living organisms is organized around carbon, which accounts for more than half the dry weight of cells. Carbon can form single bonds with hydrogen atoms, and both single and double bonds with oxygen and nitrogen atoms (Fig. 3–3). Of greatest significance in biology is the ability of carbon atoms to share electron pairs with each other to form very stable carbon–carbon single bonds. Each carbon atom can form single bonds with one, two, three, or four other carbon atoms. Two carbon atoms also can share two (or three) electron pairs, thus forming double (or triple) bonds (Fig. 3–3).

The four single covalent bonds that can be formed by a carbon atom are arranged tetrahedrally, with an angle of about 109.5° between any two bonds (Fig. 3–4) and an average length of 0.154 nm. There is free rotation around each single bond unless very large or highly charged groups are attached to both carbon atoms, in which case rotation may be restricted. A double bond is shorter (about 0.134 nm) and rigid and allows little rotation about its axis.

Covalently linked carbon atoms in biomolecules can form linear chains, branched chains, and cyclic structures. To these carbon skeletons are added groups of other atoms, called **functional groups,** which confer specific chemical properties on the molecule. Molecules with covalently bonded carbon backbones are called **organic compounds;** they occur in limitless variety. Most biomolecules are organic compounds; we can therefore infer that the bonding versatility of carbon was a major factor in the selection of carbon compounds for the molecular machinery of cells during the origin and evolution of living organisms. No other chemical element can form molecules of such widely different sizes and shapes or with such a variety of functional groups.

figure 3–3
Versatility of carbon in forming covalent single, double, and triple bonds (in red), particularly between carbon atoms. Triple bonds occur only rarely in biomolecules.



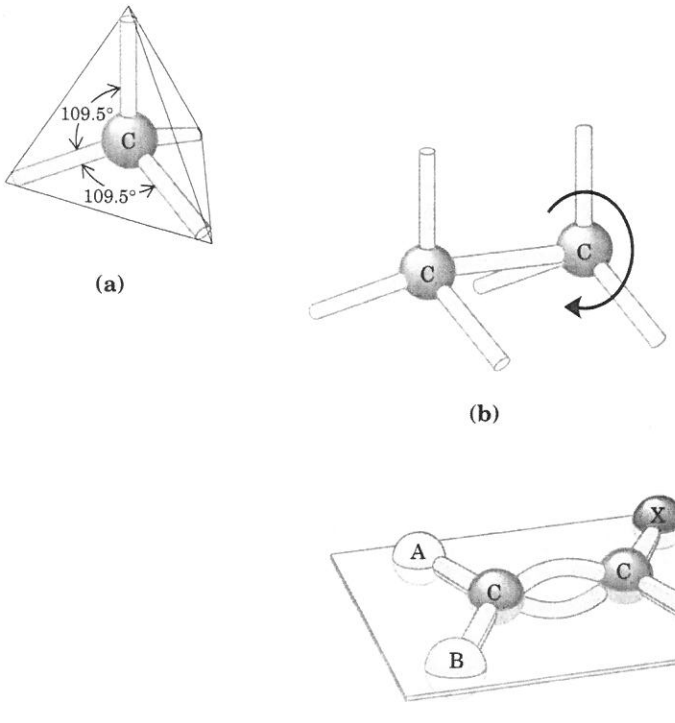


figure 3–4
Geometry of carbon bonding. (a) Carbon atoms have a characteristic tetrahedral arrangement of their four single bonds, which are about 0.154 nm long and at an angle of 109.5° to each other. **(b)** Carbon–carbon single bonds have freedom of rotation, as shown for the compound ethane (CH_3—CH_3). **(c)** Double bonds are shorter and do not allow free rotation. The single bonds on each doubly bonded carbon make an angle of 120° with each other. The two doubly bonded carbons and the atoms designated A, B, X, and Y all lie in the same rigid plane.

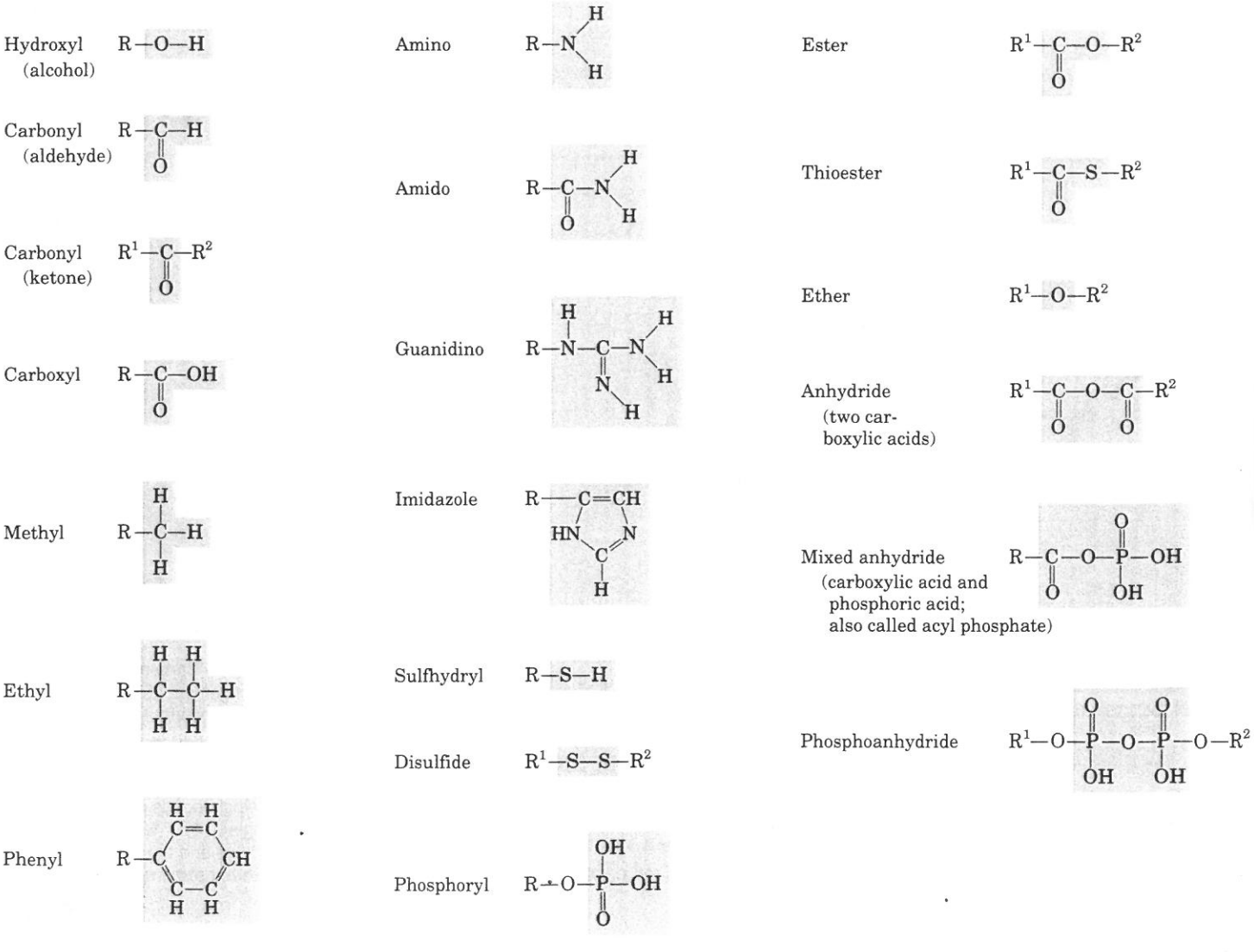
Functional Groups Determine Chemical Properties

Most biomolecules can be regarded as derivatives of hydrocarbons, compounds with a covalently linked carbon backbone to which only hydrogen atoms are bonded. The backbones of hydrocarbons are very stable. The hydrogen atoms may be replaced by a variety of functional groups to yield different families of organic compounds. Typical of these are alcohols, which have one or more hydroxyl groups; amines, which have amino groups; aldehydes and ketones, which have carbonyl groups; and carboxylic acids, which have carboxyl groups (Fig. 3–5).

Many biomolecules are polyfunctional, containing two or more different kinds of functional groups (Fig. 3–6), each with its own chemical characteristics and reactions. The chemical "personality" of a compound such as epinephrine or acetyl-coenzyme A is determined by the chemistry of its functional groups and their disposition in three-dimensional space.

figure 3–5

Some common functional groups of biomolecules. All groups are shown in their uncharged (nonionized) form. In this figure and throughout the book, we use R to represent "any substituent." It may be as simple as a hydrogen atom, but typically it is a carbon-containing moiety. When two or more substituents are shown in a molecule, we designate them R^1, R^2, and so forth.



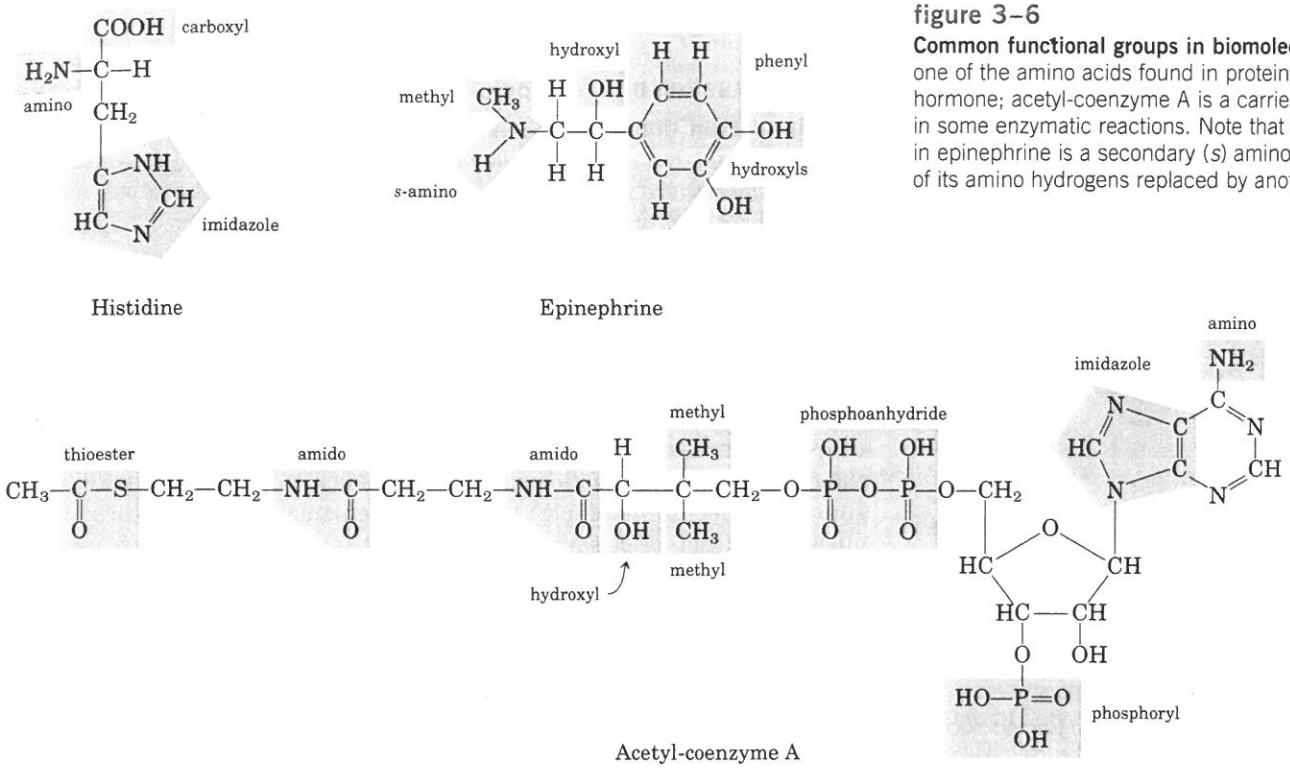


figure 3–6
Common functional groups in biomolecules. Histidine is one of the amino acids found in proteins; epinephrine is a hormone; acetyl-coenzyme A is a carrier of acetyl groups in some enzymatic reactions. Note that the amino group in epinephrine is a secondary (*s*) amino group, with one of its amino hydrogens replaced by another group.

Three-Dimensional Structure: Configuration and Conformation

Although the covalent bonds and functional groups of a biomolecule are central to its function, the arrangement of the molecule's constituent atoms in three-dimensional space—its stereochemistry—is also crucially important. Compounds of carbon commonly exist as **stereoisomers,** different molecules in which the order of bonding is the same, but the spatial relationship among the atoms is different. Molecular interactions between biomolecules are invariably stereospecific; that is, they require specific stereochemistry in the interacting molecules.

Figure 3–7 shows three ways to illustrate the stereochemical configuration of simple molecules. The perspective diagram specifies configuration unambiguously, but bond angles and center-to-center bond lengths are better represented with ball-and-stick models. In space-filling models, the radius of each atom is proportional to its van der Waals radius (Table 3–1), and the contours of the molecule represent the outer limits of the region from which atoms of other molecules are excluded.

table 3–1

Van der Waals Radii and Covalent (Single-Bond) Radii of Some Elements*

Element	Van der Waals radius (nm)	Covalent radius for single bond (nm)
H	0.1	0.030
O	0.14	0.074
N	0.15	0.073
C	0.17	0.077
S	0.18	0.103
P	0.19	0.110
I	0.22	0.133

*Van der Waals radii describe the space-filling dimensions of atoms. When two atoms are joined covalently, the atomic radii at the point of bonding are less than the van der Waals radii, because the joined atoms are pulled together by the shared electron pair. The distance between nuclei in a van der Waals interaction or in a covalent bond is about equal to the sum of the van der Waals radii or the covalent radii, respectively, for the two atoms. Thus the length of a carbon–carbon single bond is about 0.077 nm + 0.077 nm = 0.154 nm.

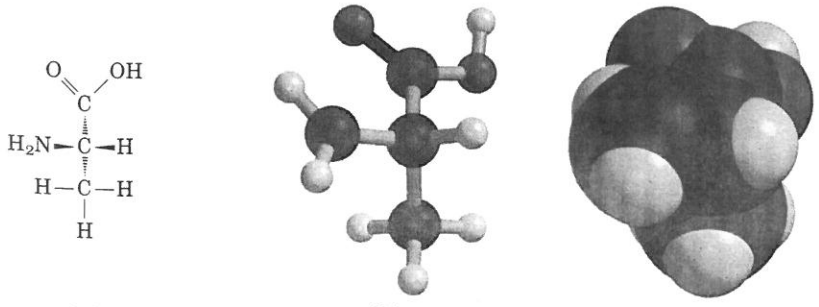


figure 3–7
Three ways to represent the structure of the amino acid alanine. **(a)** Structural formula in perspective form: a solid wedge (—) represents a bond in which the atom at the wide end projects out of the plane of the paper, toward the reader; a dashed wedge (┅) represents a bond extending behind the plane of the paper. **(b)** Ball-and-stick model, showing relative bond lengths and the bond angles. **(c)** Space-filling model, in which each atom is shown with its correct relative van der Waals radius (see Table 3–1).

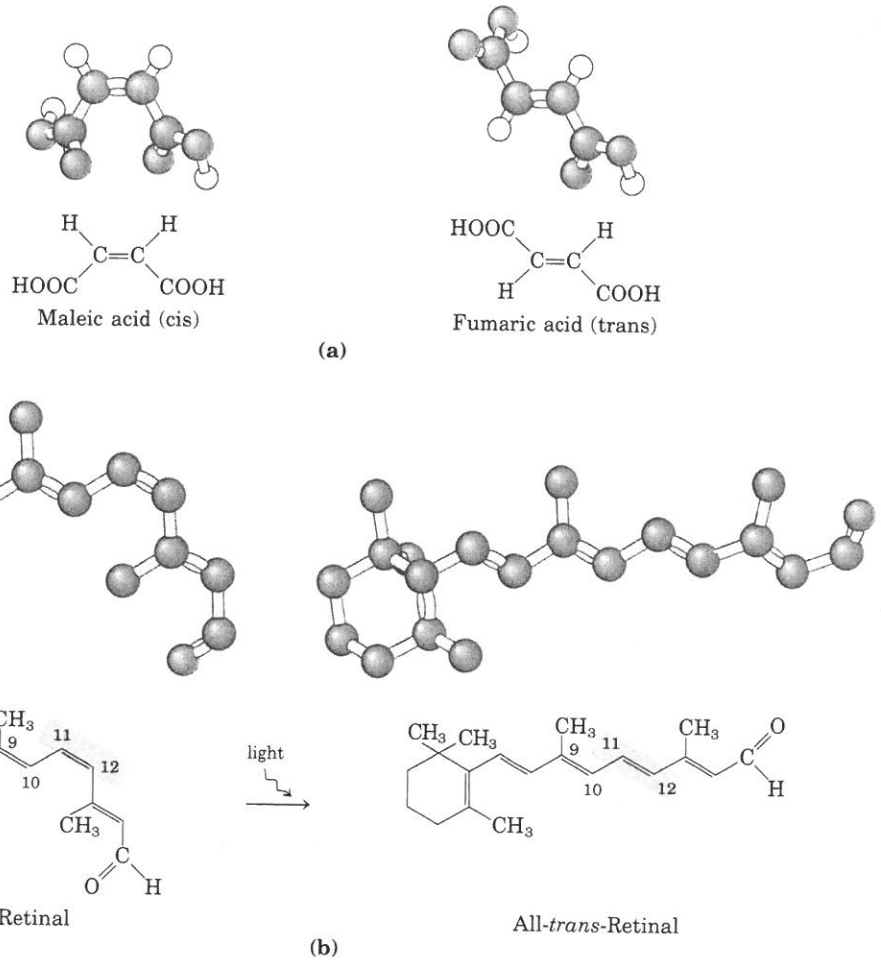
The Configuration of a Molecule Is Changed Only by Breaking a Bond

Configuration denotes the fixed spatial arrangement of atoms in an organic molecule that is conferred by the presence of either (1) double bonds, around which there is no freedom of rotation, or (2) chiral centers, around which substituent groups are arranged in a specific sequence. The identifying characteristic of configurational isomers is that they cannot be interconverted without temporarily breaking one or more covalent bonds.

Figure 3–8a shows the configurations of maleic acid and its isomer, fumaric acid. These compounds are **geometric** or **cis-trans isomers;** they differ in the arrangement of their substituent groups with respect to the nonrotating double bond. Maleic acid is the cis isomer and fumaric acid the trans isomer; each is a well-defined compound that can be separated from the other, and each has its own unique chemical properties. A binding site (on an enzyme, for example) that is complementary to one of these molecules would not be a suitable binding site for the other, which explains why these compounds have distinct biological roles despite their similar chemistry.

figure 3–8

Configurations of geometric isomers. (a) Isomers such as maleic acid and fumaric acid cannot be interconverted without breaking covalent bonds, which requires the input of much energy. **(b)** In the vertebrate retina, the initial event in light detection is the absorption of visible light by 11-*cis*-retinal. The energy of the absorbed light (about 250 kJ/mol) converts 11-*cis*-retinal to all-*trans*-retinal, triggering electrical changes in the retinal cell that lead to a nerve impulse.



Four different substituents bonded to a tetrahedral carbon atom may be arranged two different ways in space (i.e., have two configurations; Fig. 3–9), yielding two stereoisomers with similar or identical chemical properties, but differing in certain physical and biological properties. A carbon atom with four different substituents is said to be asymmetric, and asym-

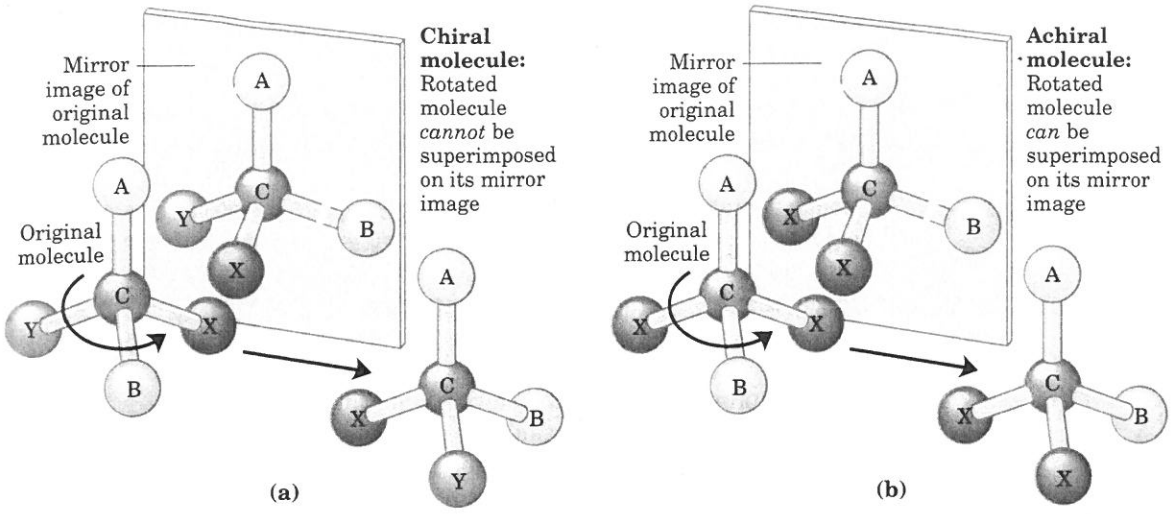


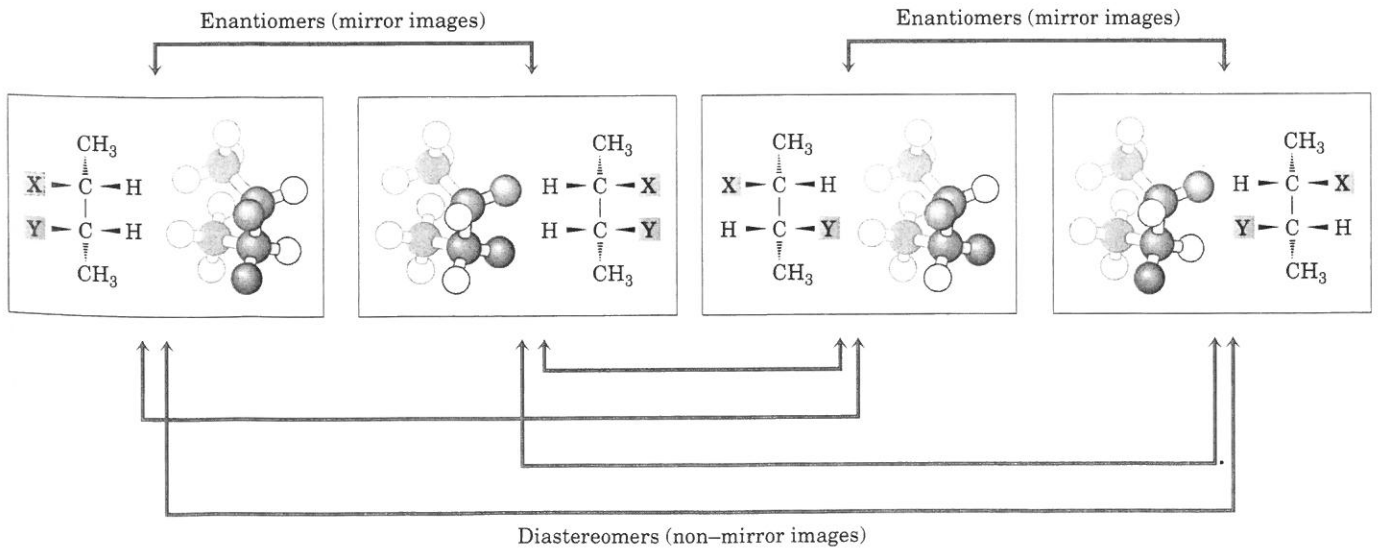
figure 3–9

Molecular asymmetry: chiral and achiral molecules. **(a)** When a carbon atom has four different substituent groups (A, B, X, Y), they can be arranged in two ways that represent nonsuperimposable mirror images of each other (enantiomers). Such a carbon atom is asymmetric and is called a chiral atom or chiral center. **(b)** When a tetrahedral carbon has only three dissimilar groups (i.e., the same group occurs twice), only one configuration is possible and the molecule is symmetric, or achiral. In this case the molecule is superimposable on its mirror image: the molecule on the left can be rotated counterclockwise (when looking down the vertical bond from A to C) to create the molecule in the mirror.

metric carbons are called **chiral centers** (Greek *chiros*, "hand"; some stereoisomers are related structurally as the right hand is to the left). A molecule with only one chiral carbon can have only two stereoisomers, but when two or more (n) chiral carbons are present, there can be 2^n stereoisomers. Some stereoisomers are mirror images of each other; they are called **enantiomers** (Fig. 3–9). Pairs of stereoisomers that are not mirror images of each other are called **diastereomers** (Fig. 3–10).

figure 3–10

Two types of stereoisomers. There are four different 2,3-disubstituted butanes (n = 2 asymmetric carbons, hence 2^n = 4 stereoisomers). Each is shown in a box as a perspective formula and a ball-and-stick model, which has been rotated to allow the reader to view all the groups. Some pairs of stereoisomers are mirror images of each other, and thus enantiomers. Other pairs are not mirror images; these are diastereomers. (Adapted from Carroll, F. (1998) *Perspectives on Structure and Mechanism in Organic Chemistry*, p. 63, Brooks/Cole Publishing Co., Pacific Grove, CA.)

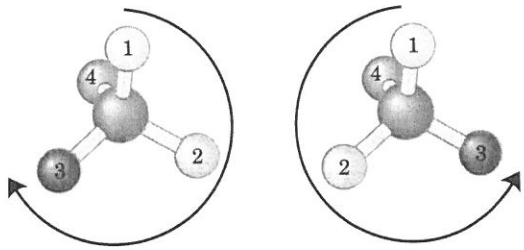


As Louis Pasteur observed (Box 3–1), enantiomers have nearly identical chemical properties but differ in a characteristic physical property, their interaction with plane-polarized light. In separate solutions, two enantiomers rotate the plane of plane-polarized light in opposite directions, but equimolar solutions of the two enantiomers (**racemic mixtures,** in the terminology of Pasteur) show no optical rotation. Compounds without chiral centers do not rotate the plane of plane-polarized light.

Biological interactions (between enzyme and substrate, receptor and hormone, or antibody and antigen, for example) are stereospecific: the "fit" in such interactions must be stereochemically correct. We must therefore name and represent the structure of a biomolecule so as to make its stereochemistry unambiguous. For compounds with more than one chiral center, the RS system of nomenclature is often more useful than the D and L system described in Chapter 5. In the RS system, each group attached to a chiral carbon is assigned a *priority.* The priorities of some common substituents are

$$-OCH_2 > -OH > -NH_2 > -COOH > -CHO > -CH_2OH > -CH_3 > -H$$

The chiral atom is viewed with the group of lowest priority (4) pointing away from the viewer. If the priority of the other three groups (1 to 3) decreases in clockwise order, the configuration is (*R*) (Latin *rectus*, "right"); if in counterclockwise order, the configuration is (*S*) (Latin *sinister*, "left").



Clockwise (*R*) Counterclockwise (*S*)

In this way each chiral carbon is designated as either (*R*) or (*S*), and the inclusion of these designations in the name of the compound provides an unambiguous description of the stereochemistry at each chiral center.

Molecular Conformation Is Changed by Rotation about Single Bonds

Molecular **conformation** refers to the spatial arrangement of substituent groups that, without breaking any bonds, are free to assume different positions in space because of the freedom of bond rotation. In the simple hydrocarbon ethane, for example, there is nearly complete freedom of rotation around the C—C bond. Many different, interconvertible conformations of the ethane molecule are therefore possible, depending on the degree of rotation (Fig. 3–11). Two conformations are of special interest: the staggered, which is more stable than all others and thus predominates, and the eclipsed, which is least stable. It is not possible to isolate either of these conformational forms, because they are freely interconvertible. However, when one or more of the hydrogen atoms on each carbon is replaced by a functional group that is either very large or electrically charged, freedom of rotation around the C—C bond is hindered. This limits the number of stable conformations of the ethane derivative.

box 3–1

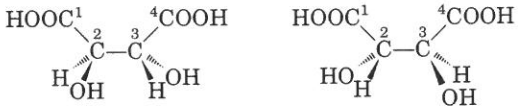
Louis Pasteur and Optical Activity: *In Vino, Veritas*

Louis Pasteur
1822–1895

Louis Pasteur encountered the phenomenon of **optical activity** in 1843, during his investigation of the crystalline sediment that accumulated in wine casks ("paratartaric acid," also called racemic acid, from Latin *racemus*, "bunch of grapes"). He used fine forceps to separate two types of crystals identical in shape, but mirror images of each other. Both types proved to have all the chemical properties of tartaric acid, but in solution one type rotated polarized light to the left (levorotatory), the other to the right (dextrorotatory). Pasteur later described the experiment and its interpretation:

> In isomeric bodies, the elements and the proportions in which they are combined are the same, only the arrangement of the atoms is different. . . . We know, on the one hand, that the molecular arrangements of the two tartaric acids are asymmetric, and, on the other hand, that these arrangements are absolutely identical, excepting that they exhibit asymmetry in opposite directions. Are the atoms of the dextro acid grouped in the form of a right-handed spiral, or are they placed at the apex of an irregular tetrahedron, or are they disposed according to this or that asymmetric arrangement? We do not know.*

Now we do know. X-ray crystallographic studies in 1951 confirmed that the levorotatory and dextrorotatory forms of tartaric acid are mirror images of each other at the molecular level, and established the absolute configuration of each (Fig. 1). The same approach has been used to demonstrate that although the amino acid alanine has two stereoisomeric forms (designated D and L), alanine in proteins exists exclusively in one form (the L isomer; see Chapter 5).



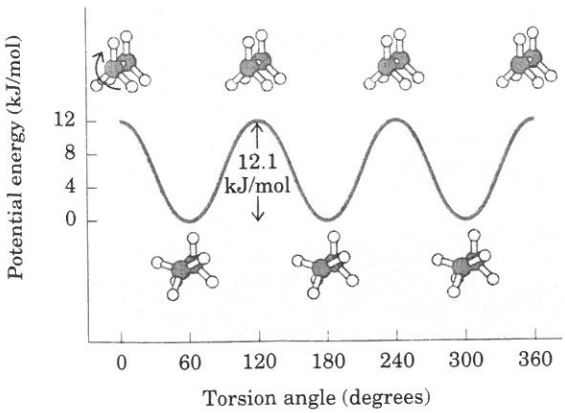
(2*R*,3*R*)-Tartaric acid (dextrorotatory)

(2*S*,3*S*)-Tartaric acid (levorotatory)

figure 1

Pasteur separated crystals of two stereoisomers of tartaric acid and showed that solutions of the separated forms rotated polarized light to the same extent but in opposite directions. These dextrorotatory and levorotatory forms were later shown to be the (*R*,*R*) and (*S*,*S*) isomers represented here. The RS system of nomenclature is described in the text.

* From Pasteur's lecture to the Société Chimique de Paris in 1883, quoted in DuBos, R. (1976) *Louis Pasteur: Free Lance of Science*, p. 95, Charles Scribner's Sons, New York.



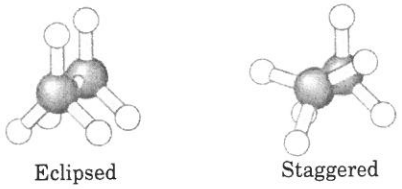


figure 3–11

Many conformations of ethane are possible because of freedom of rotation around the C—C bond. When the front carbon atom (as viewed by the reader) with its three attached hydrogens is rotated relative to the rear carbon atom, the potential energy of the molecule rises in the fully eclipsed conformation (torsion angle 0°, 120°, etc.), then falls in the fully staggered conformation (torsion angle 60°, 180°, etc.). Because the energy differences are small enough to allow rapid interconversion of the two forms (millions of times per second), the eclipsed and staggered forms cannot be separately isolated.