Chapter 5

Stereochemistry: Chiral Molecules

The Handedness of Life

Molecules of the amino acids of which our proteins are built have the property of being nonsuperposable on their mirror image. Because of this, they are said to be chiral, or to possess “handedness.” Although both mirror image forms are theoretically possible, such as those for the amino acid alanine above, life on Earth has evolved in a way that amino acids are mainly of the mirror image form said to be “left-handed” (designated L). The reason that most amino acids are of the left-handed form is not known, however. In the absence of an influence that possesses handedness such as a living system, chemical reactions produce an equal mixture of both mirror image forms. Since almost all theories about the origin of life presume that amino acids and other molecules central to life were present before self-replicating organisms came into being, it was assumed that they were present in equal mirror image forms in the primordial soup. But could the mirror image forms of these molecules actually have been present in unequal amounts before life began, leading to some sort of preference as life evolved? A meteorite discovered in 1970, known as the Murchison meteorite, fueled speculation about this topic. Analysis of the meteorite...
showed that amino acids and other complex molecules associated with life were present, proving that molecules required for life could arise outside the confines of Earth. But even more interesting, recent experiments have shown that a 7–9% excess of four L-amino acids is present in the Murchison meteorite. The origin of this unequal distribution is uncertain, but some scientists speculate that electromagnetic radiation emitted in a cork-screw fashion from the poles of spinning neutron stars could lead to a bias of one mirror image isomer over another when molecules form in interstellar space.

5.1 Isomerism: Constitutional Isomers and Stereoisomers

Isomers are different compounds that have the same molecular formula. In our study of carbon compounds, thus far, most of our attention has been directed toward those isomers that we have called constitutional isomers.

Constitutional isomers are isomers that differ because their atoms are connected in a different order. They are said to have a different connectivity. Examples of constitutional isomers are the following:

<table>
<thead>
<tr>
<th>Molecular Formula</th>
<th>Constitutional Isomers</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₂H₆O</td>
<td>CH₃OCH₃ and CH₃CH(OH)</td>
</tr>
<tr>
<td>C₃H₇Cl</td>
<td>CH₃CHCl₂ and CH₃CHCl₂</td>
</tr>
<tr>
<td>C₄H₁₀</td>
<td>CH₃CH₂CH₃ and CH₃CH₂CH₂</td>
</tr>
</tbody>
</table>

Stereoisomers are not constitutional isomers—they have their constituent atoms connected in the same sequence. Stereoisomers differ only in arrangement of their atoms in space. The cis and trans isomers of alkenes are stereoisomers (Section 1.13B); we can see that this is true if we examine cis- and trans-1,2-dichloroethene:

![cis-1,2-Dichloroethene and trans-1,2-Dichloroethene](image)

 cis-1,2-Dichloroethene and trans-1,2-dichloroethene are isomers because both compounds have the same molecular formula (C₂H₄Cl₂), but they are different. They cannot be easily interconverted because of the large barrier to rotation of the carbon–carbon double bond. Stereoisomers are not constitutional isomers, because the order of connections of the atoms in both compounds is the same. Both compounds have two central carbon atoms joined by a double bond, and both compounds have one chlorine atom and one hydrogen atom attached to the two central atoms. The cis-1,2-dichloroethene and trans-1,2-dichlo-
roethene isomers differ only in the arrangement of their atoms in space. In cis-1,2-dichloroethene the hydrogen atoms are on the same side of the molecule, and in trans-1,2-dichloroethene the hydrogen atoms are on opposite sides. Thus, cis-1,2-dichloroethene and trans-1,2-dichloroethene are stereoisomers (see Section 1.13B).

Stereoisomers can be subdivided into two general categories: enantiomers and diasteromers. **Enantiomers** are stereoisomers whose molecules are non-superposable mirror images of each other. **Diastereomers** are stereoisomers whose molecules are not mirror images of each other.

Molecules of cis-1,2-dichloroethene and trans-1,2-dichloroethene are not mirror images of each other. If one holds a model of cis-1,2-dichloroethene up to a mirror, the model that one sees in the mirror is not trans-1,2-dichloroethene. But cis-1,2-dichloroethene and trans-1,2-dichloroethene are stereoisomers and, since they are not related to each other as an object and its mirror image, they are diastereomers.

Cis and trans isomers of cycloalkanes furnish us with another example of stereoisomers that are diastereomers of each other. Consider the following two compounds.

These two compounds are isomers of each other because they are different compounds that are not interconvertible, and because they have the same molecular formula (C₇H₁₄). They are not constitutional isomers because their atoms are joined in the same sequence. They are therefore stereoisomers. They differ only in the arrangement of their atoms in space. They are not enantiomers because their molecules are not mirror images of each other. They are therefore diastereomers. (In Section 5.13 we shall find that trans-1,2-dimethylcyclopentane also has an enantiomer.)

Cis–trans isomers are not the only kind of diastereomers that we shall encounter. In Section 5.11 we shall study diastereomers that are not cis–trans isomers. The essential requirements that must be fulfilled for two compounds to be diastereomers of each other are that the two compounds be stereoisomers of each other, and that they not be mirror images of each other.

**SUBDIVISION OF ISOMERS**

**ISOMERS** (Different compounds with same molecular formula)

- **Constitutional isomers** (Isomers whose atoms have a different connectivity)
- **Stereoisomers** (Isomers that have the same connectivity but that differ in the arrangement of their atoms in space)

- **Enantiomers** (Stereoisomers that are non-superposable mirror images of each other)
- **Diastereomers** (Stereoisomers that are not mirror images of each other)
5.2 ENANTIOMERS AND CHIRAL MOLECULES

Enantiomers occur only with those compounds whose molecules are chiral. A chiral molecule is defined as one that is not identical with its mirror image. The chiral molecule and its mirror image are enantiomers, and the relationship between the chiral molecule and its mirror image is defined as enantiomeric.

The word chiral comes from the Greek word *cheir*, meaning “hand.” Chiral objects (including molecules) are said to possess “handedness.” The term chiral is used to describe molecules of enantiomers because they are related to each other in the same way that a left hand is related to a right hand. When you view your left hand in a mirror, the mirror image of your left hand is a right hand (Fig. 5.1). Your left and right hands, moreover, are not identical, and this can be shown by observing that they are not superposable* (Fig. 5.2).

Many familiar objects are chiral and the chirality of some of these objects is clear because we normally speak of them as having “handedness.” We speak, for example, of nuts and bolts as having right- or left-handed threads or of a propeller as having a right- or left-handed pitch. The chirality of many other objects is not obvious in this sense, but becomes obvious when we apply the test of nonsuperposability of the object and its mirror image.

Objects (and molecules) that are superposable on their images are achiral. Most socks, for example, are achiral, whereas gloves are chiral.

Classify each of the following objects as to whether it is chiral or achiral:

(a) A screwdriver  (d) A tennis shoe  (g) A car
(b) A baseball bat  (e) An ear  (h) A hammer
(c) A golf club  (f) A wood screw

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Problem 5.1

Figure 5.1 The mirror image of a left hand is a right hand.

Figure 5.2 Left and right hands are not superposable.

* Remember: To be superposable means that we can place one thing on top of the other so that all parts of each coincide (cf. Section 1.13B).
The chirality of molecules can be demonstrated with relatively simple compounds. Consider, for example, 2-butanol.

\[
\text{CH}_3\text{CH}(_2)\text{CH}(_2)\text{OH} \\
\text{2-Butanol}
\]

Until now, we have presented the formula just written as though it represented only one compound and we have not mentioned that molecules of 2-butanol are chiral. Because they are, there are actually two different 2-butanols and these two 2-butanols are enantiomers. We can understand this if we examine the drawings and models in Fig. 5.3.

If model I is held before a mirror, model II is seen in the mirror and vice versa. Models I and II are not superposable on each other; therefore they represent different, but isomeric, molecules. Because models I and II are nonsuperposable mirror images of each other, the molecules that they represent are enantiomers.

**Figure 5.3** (a) Three-dimensional drawings of the 2-butanol enantiomers I and II. (b) Models of the 2-butanol enantiomers. (c) An unsuccessful attempt to superpose models of I and II.
If models are available, construct the 2-butanols represented in Fig. 5.3 and demonstrate for yourself that they are not mutually superposable. (a) Make similar models of 2-bromopropane. Are they superposable? (b) Is a molecule of 2-bromopropane chiral? (c) Would you expect to find enantiomeric forms of 2-bromopropane?

How do we know when to expect the possibility of enantiomers? One way (but not the only way) is to recognize that a pair of enantiomers is always possible for molecules that contain one tetrahedral atom with four different groups attached to it. In 2-butanol (Fig. 5.4) this atom is C2. The four different groups that are attached to C2 are a hydroxyl group, a hydrogen atom, a methyl group, and an ethyl group.

An important property of enantiomers such as these is that interchanging any two groups at the tetrahedral atom that bears four different groups converts one enantiomer into the other. In Fig. 5.3b it is easy to see that interchanging the hydroxyl group and the hydrogen atom converts one enantiomer into the other. You should now convince yourself with models that interchanging any other two groups has the same result.

Because interchanging two groups at C2 converts one stereoisomer into another, C2 is an example of what is called a stereocenter. A stereocenter is defined as an atom bearing groups of such nature that an interchange of any two groups will produce a stereoisomer. Carbon-2 of 2-butanol is an example of a tetrahedral stereocenter. Not all stereocenters are tetrahedral, however. The carbon atoms of cis- and trans-1,2-dichloroethene (Section 5.1) are examples of trigonal planar stereocenters because an interchange of groups at either atom also produces a stereoisomer (a diastereomer). In general, when referring to organic compounds, the term stereocenter implies a tetrahedral stereocenter unless otherwise specified. (A carbon atom that is a stereocenter can also be called a stereogenic carbon.)

When we discuss interchanging groups like this, we must take care to notice that what we are describing is something we do to a molecular model or something we do on paper. An interchange of groups in a real molecule, if it can be done, requires breaking covalent bonds, and this is something that requires a large input of energy. This means that enantiomers such as the 2-butanol enantiomers do not interconvert spontaneously.

We shall see later that enantiomers are also possible for molecules that contain more than one tetrahedral atom with four different groups attached to it, but some of these molecules (Section 5.11A) do not exist as enantiomers.
At one time, tetrahedral atoms with four different groups were called chiral atoms or asymmetric atoms. Then, in 1984, K. Mislow (of Princeton University) and J. Siegel (now at the University of California, San Diego) pointed out that the use of such terms as this had represented a source of conceptual confusion in stereochemistry that had existed from the time of van’t Hoff (Section 5.4). Chirality is a geometric property that pervades and affects all parts of a chiral molecule. All of the atoms of 2-butanol, for example, are in a chiral environment and, therefore, all are said to be chirotopic. When we consider an atom such as C2 of 2-butanol in the way that we describe here, however, we are considering it as a stereocenter and, therefore, we should designate it as such, and not as a “chiral atom.” Further consideration of these issues is beyond our scope here, but those interested may wish to read the original paper; see Mislow, K.; Siegel, J. J. Am. Chem. Soc. 1984, 106, 3319–3328.

Figure 5.5 demonstrates the validity of the generalization that enantiomeric compounds necessarily result whenever a molecule contains a single tetrahedral stereocenter.
Demonstrate the validity of what we have represented in Fig. 5.5 by constructing models. Demonstrate for yourself that III and IV are related as an object and its mirror image and that they are not superposable (i.e., that III and IV are chiral molecules and are enantiomers). (a) Now take IV and exchange the positions of any two groups. What is the new relationship between the molecules now? (b) Now take either model and exchange the positions of any two groups. What is the relationship between the molecules now?

If all of the tetrahedral atoms in a molecule have two or more groups attached that are the same, the molecule does not have a stereocenter. The molecule is superposable on its mirror image and is achiral. An example of a molecule of this type is 2-propanol; carbon atoms 1 and 3 bear three identical hydrogen atoms and the central atom bears two identical methyl groups. If we write three-dimensional formulas for 2-propanol, we find (Fig. 5.6) that one structure can be superposed on its mirror image.

Thus, we would not predict the existence of enantiomeric forms of 2-propanol, and experimentally only one form of 2-propanol has ever been found.

5.3 The Biological Importance of Chirality

Chirality is a phenomenon that pervades the universe. The human body is structurally chiral, with the heart lying to the left of center, and the liver to the right. For evolutionary reasons, far from understood, most people are right handed. Helical seashells are chiral, and most spiral like a right-handed screw. Many plants show chirality in the way they wind around supporting structures. The honeysuckle, *Lonicera sempervirens*, winds as a left-handed helix; bindweed, *Convolvulus sepium*, winds in a right-handed way. Most of the molecules that make up plants and animals are chiral, and usually only one form of the chiral molecule occurs in a given species. All but one of the 20 amino acids that make up naturally occurring proteins are chiral, and all of them are classified as being left handed.
The molecules of natural sugars are almost all classified as being right handed, including the sugar that occurs in DNA.* DNA, itself, has a helical structure, and all naturally occurring DNA turns to the right.

The origin of biological properties relating to chirality is often likened to the specificity of our hands for their respective gloves; the binding specificity for a chiral molecule (like a hand) at a chiral receptor site (a glove) is only favorable in one way. If either the molecule or the biological receptor site had the wrong handedness, the natural physiological response (e.g., neural impulse, reaction catalysis) will not occur. A diagram showing how only one amino acid in a pair of enantiomers can interact in an optimal way with a hypothetical binding site (e.g., in an enzyme) is shown in Fig. 5.7. Because of the tetrahedral stereo-center of the amino acid, three-point binding can occur with proper alignment for only one of the two enantiomers.

Chiral molecules can show their different handedness in many ways, including the way they affect human beings. One enantiomeric form of a compound called limonene (Section 23.3) is primarily responsible for the odor of oranges, and the other enantiomer, for the odor of lemons.

Enantiomeric forms of limonene

One enantiomer of a compound called carvone (Problem 5.14) is the essence of caraway, and the other, the essence of spearmint.

The activity of drugs containing stereocenters can similarly vary between enantiomers, sometimes with serious or even tragic consequences. For several years before 1963 the drug thalidomide was used to alleviate the symptoms of morning sickness in pregnant

women. In 1963 it was discovered that thalidomide was the cause of horrible birth defects in many children born subsequent to the use of the drug.

Even later, evidence began to appear indicating that whereas one of the thalidomide enantiomers (the right-handed molecule) has the intended effect of curing morning sickness, the other enantiomer, which was also present in the drug (in an equal amount), may be the cause of the birth defects. The evidence regarding the effects of the two enantiomers is complicated by the fact that under physiological conditions, the two enantiomers are interconverted. Now, however, thalidomide is approved under highly strict regulations for treatment of a serious complication associated with leprosy. Its potential for use against other conditions including AIDS, brain cancer, and rheumatoid arthritis is also under investigation. We shall consider other aspects of chiral drugs in Section 5.10.

Problem 5.5
Which atom is the stereocenter (a) of limonene and (b) of thalidomide? Draw bond-line formulas for the limonene and thalidomide enantiomers, showing the stereocenter in each using wedge–dashed wedge notation (Section 1.17E).

5.4 Historical Origin of Stereochemistry

In 1877, Hermann Kolbe (of the University of Leipzig), one of the most eminent organic chemists of the time, wrote the following:

Not long ago, I expressed the view that the lack of general education and of thorough training in chemistry was one of the causes of the deterioration of chemical research in Germany. . . . Will anyone to whom my worries seem exaggerated please read, if he can, a recent memoir by a Herr van’t Hoff on “The Arrangements of Atoms in Space,” a document crammed to the hilt with the outpourings of a childish fantasy. . . . This Dr. J. H. van’t Hoff, employed by the Veterinary College at Utrecht, has, so it seems, no taste for accurate chemical research. He finds it more convenient to mount his Pegasus (evidently taken from the stables of the Veterinary College) and to announce how, on his bold flight to Mount Parnassus, he saw the atoms arranged in space.

Kolbe, nearing the end of his career, was reacting to a publication of a 22-year-old Dutch scientist. This publication had appeared earlier, in September 1874, and in it, van’t Hoff had argued that the spatial arrangement of four groups around a central carbon atom is tetrahedral. A young French scientist, J. A. Le Bel, had independently advanced the same idea in a publication in November 1874. Within 10 years after Kolbe’s comments, however, abundant evidence had accumulated that substantiated the “childish fantasy” of van’t Hoff. Later in his career (in 1901), and for other work, van’t Hoff was named the first recipient of the Nobel Prize in Chemistry.
Together, the publications of van’t Hoff and Le Bel marked an important turn in a field of study that is concerned with the structures of molecules in three dimensions: stereochemistry. Stereochemistry, as we shall see in Section 5.15, had been founded earlier by Louis Pasteur.

It was reasoning based on many observations such as those we presented earlier in this chapter that led van’t Hoff and Le Bel to the conclusion that the spatial orientation of groups around carbon atoms is tetrahedral when a carbon atom is bonded to four other atoms. The following information was available to van’t Hoff and Le Bel.

1. Only one compound with the general formula CH₃X is ever found.
2. Only one compound with the formula CH₂X₂ or CH₂XY is ever found.
3. Two enantiomeric compounds with the formula CHXYZ are found.

By working Problem 5.6 you can see more about the reasoning of van’t Hoff and Le Bel.

**Problem 5.6**

Show how a square planar structure for carbon compounds can be eliminated from consideration by considering CH₂Cl₂ and CH₂BrCl as examples of disubstituted methanes. (a) How many isomers would be possible in each instance if the carbon had a square planar structure? (b) How many isomers are possible in each instance if the carbon is tetrahedral? Consider CHBrClF as an example of a trisubstituted methane. (c) How many isomers would be possible if the carbon atom were square planar? (d) How many isomers are possible for CHBrClF if carbon is tetrahedral?

### 5.5 Tests for Chirality: Planes of Symmetry

The ultimate way to test for molecular chirality is to construct models of the molecule and its mirror image and then determine whether they are superposable. If the two models are superposable, the molecule that they represent is achiral. If the models are not superposable, then the molecules that they represent are chiral. We can apply this test with actual models, as we have just described, or we can apply it by drawing three-dimensional structures and attempting to superpose them in our minds.

**Figure 5.8** (a) 2-Chloropropane has a plane of symmetry and is achiral. (b) 2-Chlorobutane does not possess a plane of symmetry and is chiral.
There are other aids, however, that will assist us in recognizing chiral molecules. We have mentioned one already: the presence of a single tetrahedral stereocenter. The other aids are based on the absence in the molecule of certain symmetry elements. A molecule will not be chiral, for example, if it possesses a plane of symmetry.

A plane of symmetry (also called a mirror plane) is defined as an imaginary plane that bisects a molecule in such a way that the two halves of the molecule are mirror images of each other. The plane may pass through atoms, between atoms, or both. For example, 2-chloropropane has a plane of symmetry (Fig. 5.8a), whereas 2-chlorobutane does not (Fig. 5.8b). All molecules with a plane of symmetry are achiral.

**Problem 5.7** Which of the objects listed in Problem 5.1 possess a plane of symmetry and are, therefore, achiral?

**Problem 5.8** Write three-dimensional formulas and designate a plane of symmetry for all of the achiral molecules in Problem 5.4. (In order to be able to designate a plane of symmetry you may have to write the molecule in an appropriate conformation. This is permissible with all of these molecules because they have only single bonds and groups joined by single bonds are capable of essentially free rotation at room temperature. We discuss this matter further in Section 5.11.)

### 5.6 Nomenclature of Enantiomers: The \((R−S)\) System

The two enantiomers of 2-butanol are the following:

![Structure of 2-butanol enantiomers](image)

If we name these two enantiomers using only the IUPAC system of nomenclature that we have learned so far, both enantiomers will have the same name: 2-butanol (or sec-butyl alcohol) (Section 4.3F). This is undesirable because each compound must have its own distinct name. Moreover, the name that is given a compound should allow a chemist who is familiar with the rules of nomenclature to write the structure of the compound from its name alone. Given the name 2-butanol, a chemist could write either structure I or structure II.

Three chemists, R. S. Cahn (England), C. K. Ingold (England), and V. Prelog (Switzerland), devised a system of nomenclature that, when added to the IUPAC system, solves both of these problems. This system, called the \((R−S)\) system, or the Cahn–Ingold–Prelog system, is now widely used and is part of the IUPAC rules.

According to this system, one enantiomer of 2-butanol should be designated \((R)-2\)-butanol and the other enantiomer should be designated \((S)-2\)-butanol. \((R)\) and \((S)\) are from the Latin words *rectus* and *sinister*, meaning right and left, respectively. These molecules are said to have opposite configurations at C-2.
(R) and (S) configurations are assigned on the basis of the following procedure.

1. Each of the four groups attached to the stereocenter is assigned a priority or preference \( a, b, c, \) or \( d \). Priority is first assigned on the basis of the atomic number of the atom that is directly attached to the stereocenter. The group with the lowest atomic number is given the lowest priority, \( d \); the group with next higher atomic number is given the next higher priority, \( c \); and so on. (In the case of isotopes, the isotope of greatest atomic mass has highest priority.)

We can illustrate the application of the rule with the 2-butanol enantiomer, I.

![Diagram of 2-butanol enantiomer](image)

Oxygen has the highest atomic number of the four atoms attached to the stereocenter and is assigned the highest priority, \( a \). Hydrogen has the lowest atomic number and is assigned the lowest priority, \( d \). A priority cannot be assigned for the methyl group and the ethyl group by this approach because the atom that is directly attached to the stereocenter is a carbon atom in both groups.

2. When a priority cannot be assigned on the basis of the atomic number of the atoms that are directly attached to the stereocenter, then the next set of atoms in the unassigned groups are examined. This process is continued until a decision can be made. We assign a priority at the first point of difference.

When we examine the methyl group of enantiomer I, we find that the next set of atoms consists of three hydrogen atoms \((H, H, H)\). In the ethyl group of I the next set of atoms consists of one carbon atom and two hydrogen atoms \((C, H, H)\). Carbon has a higher atomic number than hydrogen so we assign the ethyl group the higher priority, \( b \), and the methyl group the lower priority, \( c \) \((C, H, H) \gg (H, H, H)\).

3. We now rotate the formula (or model) so that the group with lowest priority \( d \) is directed away from us.

\[ \text{The rules for a branched chain require that we follow the chain with the highest priority atoms.} \]

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5.6 Nomenclature of Enantiomers: The (R–S) System

Then we trace a path from \( a \) to \( b \) to \( c \). If, as we do this, the direction of our finger (or pencil) is clockwise, the enantiomer is designated \( \text{(R)} \). If the direction is counterclockwise, the enantiomer is designated \( \text{(S)} \). On this basis the 2-butanol enantiomer \( I \) is \( \text{(R)} \)-2-butanol.

Write the enantiomeric forms of bromochlorofluoromethane and assign each enantiomer its correct \( \text{(R)} \) or \( \text{(S)} \) designation.

Give \( \text{(R)} \) and \( \text{(S)} \) designations for each pair of enantiomers given as answers to Problem 5.4.

The first three rules of the Cahn–Ingold–Prelog system allow us to make an \( \text{(R)} \) or \( \text{(S)} \) designation for most compounds containing single bonds. For compounds containing multiple bonds one other rule is necessary.

4. Groups containing double or triple bonds are assigned priorities as if both atoms were duplicated or triplicated, that is,

\[
\begin{align*}
\text{C} &= \text{Y} \quad \text{as if it were} \quad \text{C} \quad \text{Y} \\
& \quad \text{and} \quad \text{Y} \quad \text{C} \\
\text{C} &= \text{Y} \quad \text{as if it were} \quad \text{C} \quad \text{Y} \\
& \quad \text{and} \quad \text{Y} \quad \text{C}
\end{align*}
\]
where the symbols in parentheses are duplicate or triplicate representations of the atoms at the other end of the multiple bond.

Thus, the vinyl group, \(-\text{CH}==\text{CH}_2\), is of higher priority than the isopropyl group, \(-\text{CH}(\text{CH}_3)_2\). That is,

\[
\begin{array}{c}
\text{H} \\
\text{C} \\
\text{H} \\
\text{C} \\
\text{H}
\end{array}
\]

which has higher priority than

\[
\begin{array}{c}
\text{H} \\
\text{C} \\
\text{H} \\
\text{C} \\
\text{H}
\end{array}
\]

because at the second set of atoms out, the vinyl group (see the following structure) is \(\text{C}, \text{H}, \text{H}\), whereas the isopropyl group along either branch is \(\text{H}, \text{H}, \text{H}\). (At the first set of atoms both groups are the same: \(\text{C}, \text{C}, \text{H}\).)

\[
\begin{array}{c}
\text{H} \\
\text{C} \\
\text{H} \\
\text{C} \\
\text{H}
\end{array}
\]

\(
\text{Vinyl group} > \text{Isopropyl group}
\)

Other rules exist for more complicated structures, but we shall not study them here.*

**Problem 5.11**

List the substituents in each of the following sets in order of priority, from highest to lowest:

(a) \(-\text{Cl}, -\text{OH}, -\text{SH}, -\text{H}\)
(b) \(-\text{CH}_3, -\text{CH}_2\text{Br}, -\text{CH}_2\text{Cl}, -\text{CH}_2\text{OH}\)
(c) \(-\text{H}, -\text{OH}, -\text{CHO}, -\text{CH}_3\)
(d) \(-\text{CH}(\text{CH}_3)_2, -\text{C}(\text{CH}_3)_2, -\text{H}, -\text{CH}==\text{CH}_2\)
(e) \(-\text{H}, -\text{N}(\text{CH}_3)_3, -\text{OCH}_3, -\text{CH}_3\)

**Problem 5.12**

Assign (\(R\)) or (\(S\)) designations to each of the following compounds:

(a) \(\text{CH}_2==\text{CH}\) \(\text{CH}_3\)
(b) \(\text{CH}_3==\text{CH}\) \(\text{OH}\)
(e) \(\text{H}==\text{C}==\text{C}==\text{CH}_3\)

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*Further information can be found in the Chemical Abstracts Service Index Guide.*
Sample Problem

Consider the following pair of structures and tell whether they represent enantiomers or two molecules of the same compound in different orientations.

Answer:

One way to approach this kind of problem is to take one structure and, in your mind, hold it by one group. Then rotate the other groups until at least one group is in the same place as it is in the other structure. (Until you can do this easily in your mind, practice with models.) By a series of rotations like this you will be able to convert the structure you are manipulating into one that is either identical with or the mirror image of the other. For example, take B, hold it by the Cl atom and then rotate the other groups about the bond until the bromine is at the bottom (as it is in A). Then hold it by the Br and rotate the other groups about the C*-Br bond. This will make B identical with A.

Another approach is to recognize that exchanging two groups at the stereocenter inverts the configuration of that carbon atom and converts a structure with only one stereocenter into its enantiomer; a second exchange recreates the original molecule. So we proceed this way, keeping track of how many exchanges are required to convert B into A. In this instance we find that two exchanges are required, and, again, we conclude that A and B are the same.

A useful check is to name each compound including its (R±S) designation. If the names are the same, then the structures are the same. In this instance both structures are (R)-1-bromo-1-chloroethane.

Another method for assigning R and S configurations using one’s hands as chiral templates has been described (Huheey, J. E. J. Chem. Educ. 1986, 63, 598–600). Groups at a stereocenter are correlated from lowest to highest priority with one’s wrist, thumb, index finger, and second finger, respectively. With the ring and little finger closed against the palm and viewing one’s hand with the wrist away, if the correlation between the stereocenter is with the left hand the configuration is S, and if with the right hand, R.
Problem 5.13

Tell whether the two structures in each pair represent enantiomers or two molecules of the same compound in different orientations.

(a) \( \text{Br}_2 \text{H}_2 \text{F} \) and \( \text{Br}_2 \text{H}_2 \text{Cl} \)

(b) \( \text{F}_2 \text{H}_2 \text{Cl} \) and \( \text{H}_3 \text{F}_2 \text{Cl} \)

(c) \( \text{H}_3 \text{F}_2 \text{OH} \) and \( \text{H}_3 \text{F}_2 \text{OH} \)

5.7 Properties of Enantiomers: Optical Activity

The molecules of enantiomers are not superposable one on the other and, on this basis alone, we have concluded that enantiomers are different compounds. How are they different? Do enantiomers resemble constitutional isomers and diastereomers in having different melting and boiling points? The answer is no. Enantiomers have identical melting and boiling points. Do enantiomers have different indexes of refraction, different solubilities in common solvents, different infrared spectra, and different rates of reaction with achiral reagents? The answer to each of these questions is also no.

Many of these properties (e.g., boiling points, melting points, and solubilities) are dependent on the magnitude of the intermolecular forces operating between the molecules (Section 2.14), and for molecules that are mirror images of each other these forces will be identical.

We can see an example if we examine Table 5.1 where some of the physical properties of the 2-butanol enantiomers are listed:

Enantiomers show different behavior only when they interact with other chiral substances. Enantiomers show different rates of reaction toward other chiral molecules—that is, toward reagents that consist of a single enantiomer or an excess of a single enantiomer. Enantiomers also show different solubilities in solvents that consist of a single enantiomer or an excess of a single enantiomer.

One easily observable way in which enantiomers differ is in their behavior toward plane-polarized light. When a beam of plane-polarized light passes through an enantiome-

<table>
<thead>
<tr>
<th>Physical Property</th>
<th>((R))-2-Butanol</th>
<th>((S))-2-Butanol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boiling point (1 atm)</td>
<td>99.5°C</td>
<td>99.5°C</td>
</tr>
<tr>
<td>Density (g mL(^{-1}) at 20°C)</td>
<td>0.808</td>
<td>0.808</td>
</tr>
<tr>
<td>Index of refraction (20°C)</td>
<td>1.397</td>
<td>1.397</td>
</tr>
</tbody>
</table>
mer, the plane of polarization rotates. Moreover, separate enantiomers rotate the plane of plane-polarized light equal amounts but in opposite directions. Because of their effect on plane-polarized light, separate enantiomers are said to be optically active compounds.

In order to understand this behavior of enantiomers we need to understand the nature of plane-polarized light. We also need to understand how an instrument called a polarimeter operates.

5.7A Plane-Polarized Light

Light is an electromagnetic phenomenon. A beam of light consists of two mutually perpendicular oscillating fields: an oscillating electric field and an oscillating magnetic field (Fig. 5.9).

If we were to view a beam of ordinary light from one end, and if we could actually see the planes in which the electrical oscillations were occurring, we would find that oscillations of the electric field were occurring in all possible planes perpendicular to the direction of propagation (Fig. 5.10). (The same would be true of the magnetic field.)

When ordinary light is passed through a polarizer, the polarizer interacts with the electrical field so that the electrical field of the light that emerges from the polarizer (and the magnetic field perpendicular to it) is oscillating only in one plane. Such light is called plane-polarized light (Fig. 5.11).

![Figure 5.9](image-url) The oscillating electric and magnetic fields of a beam of ordinary light in one plane. The waves depicted here occur in all possible planes in ordinary light.

![Figure 5.10](image-url) Oscillation of the electrical field of ordinary light occurs in all possible planes perpendicular to the direction of propagation.
The lenses of Polaroid sunglasses have this effect. You can demonstrate for yourself that this is true with two pairs of Polaroid sunglasses. If two lenses are placed one on top of the other so that the axes of polarization coincide, then light passes through both normally. Then if one lens is rotated 90° with respect to the other, no light passes through.

5.7B The Polarimeter

The device that is used for measuring the effect of plane-polarized light on optically active compounds is a polarimeter. A sketch of a polarimeter is shown in Fig. 5.12. The principal working parts of a polarimeter and the measurement of optical rotation, (From Holum, J.R., *Organic Chemistry: A Brief Course*; Wiley: New York, 1975; p 316.)
working parts of a polarimeter are (1) a light source (usually a sodium lamp), (2) a polarizer, (3) a tube for holding the optically active substance (or solution) in the light beam, (4) an analyzer, and (5) a scale for measuring the number of degrees that the plane of polarized light has been rotated.

The analyzer of a polarimeter (Fig. 5.12) is nothing more than another polarizer. If the tube of the polarimeter is empty, or if an optically inactive substance is present, the axes of the plane-polarized light and the analyzer will be exactly parallel when the instrument reads 0°, and the observer will detect the maximum amount of light passing through. If, by contrast, the tube contains an optically active substance, a solution of one enantiomer, for example, the plane of polarization of the light will be rotated as it passes through the tube. In order to detect the maximum brightness of light the observer will have to rotate the axis of the analyzer in either a clockwise or counterclockwise direction. If the analyzer is rotated in a clockwise direction, the rotation, \( \alpha \) (measured in degrees), is said to be positive (+). If the rotation is counterclockwise, the rotation is said to be negative (−). A substance that rotates plane-polarized light in the clockwise direction is also said to be dextrorotatory, and one that rotates plane-polarized light in a counterclockwise direction is said to be levorotatory (Latin: dexter, right, and laevus, left).

**5.7C Specific Rotation**

The number of degrees that the plane of polarization is rotated as the light passes through a solution of an enantiomer depends on the number of chiral molecules that it encounters. This, of course, depends on the length of the tube and the concentration of the enantiomer. In order to place measured rotations on a standard basis, chemists calculate a quantity called the *specific rotation*, \([\alpha]\), by the following equation:

\[
[\alpha] = \alpha / c \cdot l
\]

where

- \([\alpha]\) = the specific rotation
- \(\alpha\) = the observed rotation
- \(c\) = the concentration of the solution in grams per milliliter of solution (or density in g mL\(^{-1}\) for neat liquids)
- \(l\) = the length of the tube in decimeters (1 dm\(^{10}\) cm)

The specific rotation also depends on the temperature and the wavelength of light that is employed. Specific rotations are reported so as to incorporate these quantities as well. A specific rotation might be given as follows:

\[
[\alpha]_D = +3.12^\circ
\]

This means that the D line of a sodium lamp (\(\lambda = 589.6\) nm) was used for the light, that a temperature of 25°C was maintained, and that a sample containing 1.00 g mL\(^{-1}\) of the optically active substance, in a 1-dm tube, produced a rotation of 3.12° in a clockwise direction.*

---

* The magnitude of rotation is dependent on the solvent when solutions are measured. This is the reason the solvent is specified when a rotation is reported in the chemical literature.
The specific rotations of \((R)-2\)-butanol and \((S)-2\)-butanol are given here.

\[
\begin{align*}
(R)-2\text{-Butanol} & : \quad [\alpha]_{D}^{25} = +13.52^\circ \\
(S)-2\text{-Butanol} & : \quad [\alpha]_{D}^{25} = +13.52^\circ
\end{align*}
\]

The direction of rotation of plane-polarized light is often incorporated into the names of optically active compounds. The following two sets of enantiomers show how this is done.

\[
\begin{align*}
(R)-(+)\text{-2-Methyl-1-butanol} & : \quad [\alpha]_{D}^{25} = +5.756^\circ \\
(S)-(+)\text{-2-Methyl-1-butanol} & : \quad [\alpha]_{D}^{25} = +5.756^\circ \\
(R)-(+)\text{-1-Chloro-2-methylbutane} & : \quad [\alpha]_{D}^{25} = -1.64^\circ \\
(S)-(+)\text{-1-Chloro-2-methylbutane} & : \quad [\alpha]_{D}^{25} = +1.64^\circ
\end{align*}
\]

The previous compounds also illustrate an important principle: No obvious correlation exists between the configurations of enantiomers and the direction \((+\text{ or } -)\) in which they rotate plane-polarized light.

\((R)-(+)\text{-2-Methyl-1-butanol}\) and \((R)-(+)\text{-1-chloro-2-methylbutane}\) have the same configuration, that is, they have the same general arrangement of their atoms in space. They have, however, an opposite effect on the direction of rotation of the plane of plane-polarized light.

\[
\begin{align*}
(R)-(+)\text{-2-Methyl-1-butanol} & : \quad ([\alpha]_{D})^{25} = +13.52^\circ \\
(S)-(+)\text{-1-Chloro-2-methylbutane} & : \quad ([\alpha]_{D})^{25} = -1.64^\circ
\end{align*}
\]

These same compounds also illustrate a second important principle: No necessary correlation exists between the \((R)\) and \((S)\) designation and the direction of rotation of plane-polarized light. \((R)-2\text{-Methyl-1-butanol}\) is dextrorotatory \((+\text{ or } +)\), and \((R)-1\text{-chloro-2-methylbutane}\) is levorotatory \((-\text{ or } -)\).

A method based on the measurement of optical rotation at many different wavelengths, called optical rotatory dispersion, has been used to correlate configurations of chiral molecules. A discussion of the technique of optical rotatory dispersion, however, is beyond the scope of this text.
Problem 5.14

Shown below is the configuration of (+)-carvone. (+)-Carvone is the principal component of caraway seed oil and is responsible for its characteristic odor. The fact that the carvone enantiomers do not smell the same suggests that the receptor sites in the nose for these compounds are chiral, and only the correct enantiomer will fit its particular site (just as a hand requires a glove of the correct chirality for a proper fit). Give the correct \((R)\) and \((S)\) designations for \((+)-\) and \((-)-\)carvone.

5.8 The Origin of Optical Activity

It is not possible to give a complete, condensed account of the origin of the optical activity observed for separate enantiomers. An insight into the source of this phenomenon can be obtained, however, by comparing what occurs when a beam of plane-polarized light passes through a solution of achiral molecules with what occurs when a beam of plane-polarized light passes through a solution of chiral molecules.

Almost all individual molecules, whether chiral or achiral, are theoretically capable of producing a slight rotation of the plane of plane-polarized light. The direction and magnitude of the rotation produced by an individual molecule depend, in part, on its orientation at the precise moment that it encounters the beam. In a solution, of course, many billions of molecules are in the path of the light beam and at any given moment these molecules are present in all possible orientations. If the beam of plane-polarized light passes through a solution of the achiral compound 2-propanol, for example, it should encounter at least two molecules in the exact orientations shown in Fig. 5.13. The effect of the first encounter might be to produce a very slight rotation of the plane of polarization to the right. Before the beam emerges from the solution, however, it should encounter at least one molecule of 2-propanol that is in exactly the mirror-image orientation of the first. The effect of this

Figure 5.13 A beam of plane-polarized light encountering a molecule of 2-propanol (an achiral molecule) in orientation (a) and then a second molecule in the mirror-image orientation (b). The beam emerges from these two encounters with no net rotation of its plane of polarization.
second encounter is to produce an equal and opposite rotation of the plane: a rotation that exactly cancels the first rotation. The beam, therefore, emerges with no net rotation.

What we have just described for the two encounters shown in Fig. 5.13 can be said of all possible encounters of the beam with molecules of 2-propanol. Because so many molecules are present, it is statistically certain that for each encounter with a particular orientation there will be an encounter with a molecule that is in a mirror-image orientation. The result of all of these encounters is such that all of the rotations produced by individual molecules are canceled and 2-propanol is found to be optically inactive.

What, then, is the situation when a beam of plane-polarized light passes through a solution of one enantiomer of a chiral compound? We can answer this question by considering what might occur when plane-polarized light passes through a solution of pure (R)-2-butanol. Figure 5.14 illustrates one possible encounter of a beam of plane-polarized light with a molecule of (R)-2-butanol.

When a beam of plane-polarized light passes through a solution of (R)-2-butanol, no molecule is present that can ever be exactly oriented as a mirror image of any given orientation of a (R)-2-butanol molecule. The only molecules that could do this would be molecules of (S)-2-butanol, and they are not present. Exact cancellation of the rotations produced by all of the encounters of the beam with random orientations of (R)-2-butanol does not happen and, as a result, a net rotation of the plane of polarization is observed. (R)-2-Butanol is found to be optically active.

**5.8A Racemic Forms**

The net rotation of the plane of polarization that we observe for a solution consisting of molecules of (R)-2-butanol alone would not be observed if we passed the beam through a solution that contained equimolar amounts of (R)-2-butanol and (S)-2-butanol. In the latter instance, molecules of (S)-2-butanol would be present in a quantity equal to those of (R)-2-butanol, and for every possible orientation of one enantiomer, a molecule of the other enantiomer would be in a mirror-image orientation. Exact cancellations of all rotations would occur, and the solution of the equimolar mixture of enantiomers would be optically inactive.

An equimolar mixture of two enantiomers is called a racemic form (either a racemate or a racemic mixture). A racemic form shows no rotation of plane-polarized light; as
such, it is often designated as being (±). A racemic form of (R)-(-)-2-butanol and (S)-(+)-2-butanol might be indicated as (±)-2-Butanol or as (±)-CH$_2$CH$_2$CHOHCH$_3$.

### 5.8B Racemic Forms and Enantiomeric Excess

A sample of an optically active substance that consists of a single enantiomer is said to be enantiomerically pure or to have an enantiomeric excess of 100%. An enantiomerically pure sample of (S)-(+)-2-butanol shows a specific rotation of +13.52° ([α]$_D$ = +13.52°). On the other hand, a sample of (S)-(+)-2-butanol that contains less than an equimolar amount of (R)-(-)-2-butanol will show a specific rotation that is less than +13.52° but greater than 0°. Such a sample is said to have an enantiomeric excess less than 100%. The enantiomeric excess (ee) is defined as follows:

\[
\text{% Enantiomeric excess} = \frac{\text{moles of one enantiomer} - \text{moles of other enantiomer}}{\text{total moles of both enantiomers}} \times 100
\]

The enantiomeric excess can be calculated from optical rotations:

\[
\% \text{ Enantiomeric excess}^* = \frac{\text{observed specific rotation}}{\text{specific rotation of the pure enantiomer}} \times 100
\]

Let us suppose, for example, that a mixture of the 2-butanol enantiomers showed a specific rotation of +6.76°. We would then say that the enantiomeric excess of the (S)-(+)-2-butanol is 50%.

\[
\text{Enantiomeric excess} = \frac{+6.76°}{+13.52°} \times 100 = 50\%
\]

When we say that the enantiomeric excess of this mixture is 50% we mean that 50% of the mixture consists of the (+) enantiomer (the excess) and the other 50% consists of the racemic form. Since for the 50% that is racemic, the optical rotations cancel one another out, only the 50% of the mixture that consists of the (+) enantiomer contributes to the observed optical rotation. The observed rotation is, therefore, 50% (or half) of what it would have been if the mixture had consisted only of the (+) enantiomer.

#### Sample Problem

What is the actual stereoisomeric composition of the mixture referred to above?

**Answer:**

Of the total mixture, 50% consists of the racemic form, which contains equal numbers of the two enantiomers. Therefore, half of this 50% or 25%, is the (-) enantiomer and 25% is the (+) enantiomer. The other 50% of the mixture (the excess) is also the (+) enantiomer. Consequently the mixture is 75% (+) enantiomer and 25% (-) enantiomer.

---

* This calculation should be applied to a single enantiomer or to mixtures of enantiomers only. It should not be applied to mixtures in which some other compound is present.
5.9 The Synthesis of Chiral Molecules

5.9A Racemic Forms

Many times in the course of working in the organic laboratory a reaction carried out with reactants whose molecules are achiral results in the formation of products whose molecules are chiral. In the absence of any chiral influence (from the solvent or a catalyst), the outcome of such a reaction is the formation of a racemic form. In other words, the chiral molecules of the product are obtained as a mixture of enantiomers.

An example is the synthesis of 2-butanol by the nickel-catalyzed hydrogenation of 2-butanone. In this reaction the hydrogen molecule adds across the carbon–oxygen double bond in much the same way that it adds to a carbon–carbon double bond (Section 4.18A).

\[
\begin{align*}
\text{2-Butanone} & \quad \text{Hydrogen} \\
\text{achiral molecules} & \quad \text{achiral molecules} \\
\overset{\text{Ni}}{\text{H}} & \quad \overset{\text{H}}{\text{H}} \\
\overset{\text{2-Butanol}}{\text{chiral molecules}} & \quad \overset{(\pm)-2-Butanol}{\text{but 50:50 mixture (R) and (S)}}
\end{align*}
\]

Molecules of neither reactant (2-butanone nor hydrogen) are chiral. The molecules of the product (2-butanol) are chiral. The product, however, is obtained as a racemic form because the two enantiomers, \((R)-2\)-butanol and \((S)-2\)-butanol, are obtained in equal amounts.

This is not the result if reactions like this are carried out in the presence of a chiral influence such as an optically active solvent or, as we shall see below, an enzyme. The nickel catalyst used in this reaction does not exert a chiral influence.

Figure 5.15 shows why a racemic form of 2-butanol is obtained. Hydrogen, adsorbed on the surface of the nickel catalyst, adds with equal facility at either face of 2-butanone. Reaction at one face produces one enantiomer; reaction at the other face produces the other enantiomer, and the two reactions occur at the same rate.

5.9B Enantioselective Syntheses

If a reaction that leads to the formation of enantiomers produces a preponderance of one enantiomer over its mirror image, the reaction is said to be enantioselective. For a reaction to be enantioselective, a chiral reagent, solvent, or catalyst must assert an influence on the course of the reaction.

In nature, where most reactions are enantioselective, the chiral influences come from protein molecules called enzymes. Enzymes are biological catalysts of extraordinary efficiency. They not only have the ability to cause reactions to take place much more rapidly than they would otherwise, they also have the ability to assert a dramatic chiral influence on a reaction. Enzymes do this because they, too, are chiral, and they possess an active site where the reactant molecules are bound, momentarily, while the reaction takes place. This active site is chiral, and only one enantiomer of a chiral reactant fits it properly and is able to undergo reaction.
Many enzymes have also found use in the organic chemistry laboratory, where organic chemists take advantage of their properties to bring about enantioselective reactions. One enzyme used frequently in this way is an enzyme called lipase. Lipase catalyzes a reaction, called hydrolysis, whereby esters (Section 2.11C) react with a molecule of water and are converted to a carboxylic acid and an alcohol. (This is the reverse of a reaction by which esters are synthesized.)

\[
\begin{align*}
\text{Ester} & \quad \text{Water} \\
\text{Carboxylic acid} & \quad \text{Alcohol}
\end{align*}
\]

Hydrolysis, which means literally cleavage (lysis) by water, can be carried out in the laboratory in a variety of ways that do not involve the use of an enzyme. However, use of the enzyme lipase allows the hydrolysis to be used to prepare almost pure enantiomers. The following hydrolysis using lipase is a good example.

**Figure 5.15** The reaction of 2-butanoate with hydrogen in the presence of a nickel catalyst. The reaction rate by path (a) is equal to that by path (b). (R)-(+)-2-Butanol and (S)-(+)-2-butanol are produced in equal amounts, as a racemate.

\[
\begin{align*}
\text{Ethyl (±)-2-fluorohexanoate} & \quad \text{Ethyl (R)-(+)-2-fluorohexanoate} \\
\text{[an ester that is a racemate of (R) and (S) forms]} & \quad \text{(>99% enantiomeric excess)}
\end{align*}
\]
The \((R)\) enantiomer of this ester does not fit the active site of the enzyme and is, therefore, unaffected. Only the \((S)\) enantiomer of the ester fits the active site and undergoes hydrolysis. After the reaction is over, therefore, one can isolate the unchanged \((R)\)-ester in 99% enantiomeric purity. This method also has the added benefit of producing the \((S)-(+)\) acid in 69% enantiomeric purity. Other enzymes called dehydrogenases have been used to effect enantioselective versions of carbonyl reductions like that in Section 5.9A. We shall have more to say about this in Chapter 12.

5.10 CHIRAL DRUGS

Of much recent interest to the pharmaceutical industry and the U.S. Food and Drug Administration is the production and sale of “chiral drugs,” that is, drugs that contain a single enantiomer rather than a racemate.* In some instances a drug has been marketed as a racemate for years even though only one enantiomer is the active agent. Such is the case with the antiinflammatory agent \textit{ibuprofen} (Advil, Motrin, Nuprin). Only the \((S)\) isomer is effective. The \((R)\) isomer has no antiinflammatory action, and even though the \((R)\) isomer is slowly converted to the \((S)\) isomer in the body, a medicine based on the \((S)\) isomer alone takes effect more quickly than the racemate.

\[
\text{Ibuprofen}
\]

The antihypertensive drug \textit{methyldopa} (Aldomet) also owes its effect exclusively to the \((S)\) isomer.

\[
\text{Methyldopa}
\]

And, with penicillamine, the \((S)\) isomer is a highly potent therapeutic agent for primary chronic arthritis; the \((R)\) isomer has no therapeutic action, and it is highly toxic.

**Problem 5.16**

Write three-dimensional formulas for the \((S)\) isomers of (a) \textit{ibuprofen} (b) \textit{methyldopa}, and (c) \textit{penicillamine}.

There are many other examples of drugs like these, including drugs where the enantiomers have distinctly different effects. The preparation of enantiomerically pure drugs, therefore, is one factor that makes enantioselective synthesis (Section 5.9B) and the resolution of racemic drugs (separation into pure enantiomers, Section 5.15) active areas of research today.

There are chemists who are deliberately synthesizing the unnatural enantiomer of certain proteins. These proteins are called "D-proteins" because they are made from D-amino acids, the enantiomeric form of natural L-amino acids. D-Proteins are somewhat resistant to breakdown by proteolytic (protein-digesting) enzymes because they do not have the proper chirality to fit in the active site of natural enzymes. This fact, however, opens up the intriguing possibility that for certain drugs that are proteins, the D-protein should have a longer lifetime in the blood. The effect of a given dose of a D-protein drug would thus be prolonged. This technology is being explored at the present for protein drugs where the action of the drug does not depend on the specific mirror-image form of the enzyme but where its degradation would be slowed by being present in the unnatural mirror-image form. An example is superoxide dismutase, an enzyme that can eliminate harmful superoxide radicals ($O_2^-$).

5.11 Molecules with More Than One Stereocenter

So far all of the chiral molecules that we have considered have contained only one stereocenter. Many organic molecules, especially those important in biology, contain more than one stereocenter. Cholesterol (Section 23.4B), for example, contains eight stereocenters. (Can you locate them?) We can begin, however, with simpler molecules. Let us consider 2,3-dibromopentane shown here—a structure that has two stereocenters.

$$\text{CH}_3\text{CH(CH}_2\text{CH}_2\text{Br}_2$$

2,3-Dibromopentane

A useful rule gives the maximum number of stereoisomers: In compounds whose stereoisomerism is due to tetrahedral stereocenters, the total number of stereoisomers will not exceed $2^n$, where $n$ is equal to the number of tetrahedral stereocenters. For 2,3-dibromopentane we should not expect more than four stereoisomers ($2^2 = 4$).

Our next task is to write three-dimensional formulas for the stereoisomers of the compound. We begin by writing a three-dimensional formula for one stereoisomer and then by writing the formula for its mirror image.

It is helpful to follow certain conventions when we write these three-dimensional formulas. For example, we usually write our structures in eclipsed conformations. When we do this we do not mean to imply that eclipsed conformations are the most stable ones—they most certainly are not. We write eclipsed conformations because, as we shall see...
later, they make it easy for us to recognize planes of symmetry when they are present. We also write the longest carbon chain in a generally vertical orientation on the page; this makes the structures that we write directly comparable. As we do these things, however, we must remember that molecules can rotate in their entirety and that at normal temperatures rotations about all single bonds are also possible. If rotations of the structure itself or rotations of groups joined by single bonds make one structure superposable with another, then the structures do not represent different compounds; instead, they represent different orientations or different conformations of two molecules of the same compound.

Since structures 1 and 2 are not superposable, they represent different compounds. Since structures 1 and 2 differ only in the arrangement of their atoms in space, they represent stereoisomers. Structures 1 and 2 are also mirror images of each other; thus 1 and 2 represent enantiomers.

Structures 1 and 2 are not the only possible structures, however. We find that we can write a structure 3 that is different from either 1 or 2, and we can write a structure 4 that is a nonsuperposable mirror image of structure 3.

Structures 3 and 4 correspond to another pair of enantiomers. Structures 1–4 are all different, so there are, in total, four stereoisomers of 2,3-dibromopentane. Essentially what we have done above is written all the possible structures that result by successively interchanging two groups at all stereocenters. At this point you should convince yourself that there are no other stereoisomers by writing other structural formulas. You will find that rotation of the single bonds (or of the entire structure) of any other arrangement of the atoms will cause the structure to become superposable with one of the structures that we have written here. Better yet, using different colored balls, make molecular models as you work this out.

The compounds represented by structures 1–4 are all optically active compounds. Any one of them, if placed separately in a polarimeter, would show optical activity. The compounds represented by structures 1 and 2 are enantiomers. The compounds represented by structures 3 and 4 are also enantiomers. But what is the isomeric relation between the compounds represented by 1 and 3?

We can answer this question by observing that 1 and 3 are stereoisomers and that they are not mirror images of each other. They are, therefore, diastereomers. Diastereomers have different physical properties—different melting points and boiling points, different solubilities, and so forth. In this respect these diastereomers are just like diastereomeric alkenes such as cis- and trans-2-butene.
Problem 5.17

(a) If 3 and 4 are enantiomers, what are 1 and 4? (b) What are 2 and 3 and 2 and 4? (c) Would you expect 1 and 3 to have the same melting point? (d) The same boiling point? (e) The same vapor pressure?

5.11A Meso Compounds

A structure with two stereocenters does not always have four possible stereoisomers. Sometimes there are only three. This happens because some molecules are achiral even though they contain stereocenters.

To understand this, let us write stereochemical formulas for 2,3-dibromobutane shown here.

\[
\begin{align*}
\text{CH}_3 & \\
\text{CH}_3 & \\
\text{H} & \\
\text{H} & \\
\text{Br} & \\
\text{Br} & \\
\end{align*}
\]

2,3-Dibromobutane

We begin in the same way as we did before. We write the formula for one stereoisomer and for its mirror image.

\[
\begin{align*}
\text{CH}_3 & \\
\text{CH}_3 & \\
\text{H} & \\
\text{H} & \\
\text{Br} & \\
\text{Br} & \\
\text{C} & \\
\end{align*}
\]

Structures A and B are nonsuperposable and present a pair of enantiomers. When we write structure C (see below) and its mirror image D, however, the situation is different. The two structures are superposable. This means that C and D do not represent a pair of enantiomers. Formulas C and D represent two different orientations of the same compound.

The molecule represented by structure C (or D) is not chiral even though it contains tetrahedral atoms with four different attached groups. Such molecules are called meso compounds. Meso compounds, because they are achiral, are optically inactive.

The ultimate test for molecular chirality is to construct a model (or write the structure) of the molecule and then test whether or not the model (or structure) is superposable on its mirror image. If it is, the molecule is achiral. If it is not, the molecule is chiral.

We have already carried out this test with structure C and found that it is achiral. We can also demonstrate that C is achiral in another way. Figure 5.16 shows that structure C has a plane of symmetry (Section 5.5).

Figure 5.16  The plane of symmetry of meso-2,3-dibromobutane. This plane divides the molecule into halves that are mirror images of each other.
The following two problems relate to compounds A–D in the preceding paragraphs.

Problem 5.18
Which of the following would be optically active?
(a) A pure sample of A
(b) A pure sample of B
(c) A pure sample of C
(d) An equimolar mixture of A and B

Problem 5.19
The following are formulas for three compounds, written in noneclipsed conformations. In each instance tell which compound (A, B, or C) each formula represents.

Problem 5.20
Write three-dimensional formulas for all of the stereoisomers of each of the following compounds. Label pairs of enantiomers and label meso compounds.
(a) CH\(_2\)CHClCHClCH\(_3\)
(b) CH\(_2\)CHOHCH\(_2\)CHOHCH\(_3\)
(c) CH\(_2\)ClCHFCHFCH\(_2\)Cl
(d) CH\(_2\)CHOHCH\(_2\)CHOHCH\(_3\)
(e) CH\(_2\)ClBrCHFCH\(_3\)

5.11B Naming Compounds with More than One Stereocenter

If a compound has more than one tetrahedral stereocenter, we analyze each center separately and decide whether it is \((R)\) or \((S)\). Then, using numbers, we tell which designation refers to which carbon atom.

Consider the stereoisomer A of 2,3-dibromobutane.

When this formula is rotated so that the group of lowest priority attached to C2 is directed away from the viewer it resembles the following.
The order of progression from the group of highest priority to that of next highest priority (from —Br, to —CHBrCH₃, to —CH₃) is clockwise. So C₂ has the (R) configuration.

When we repeat this procedure with C₃ we find that C₃ also has the (R) configuration.

Compound A, therefore, is (2R,3R)-2,3-dibromobutane.

Give names that include (R) and (S) designations for compounds B and C in Section 5.11A.

Give names that include (R) and (S) designations for your answers to Problem 5.20.

Chloramphenicol (below) is a potent antibiotic, isolated from Streptomyces venezuelae, that is particularly effective against typhoid fever. It was the first naturally occurring substance shown to contain a nitro (—NO₂) group attached to an aromatic ring. Both stereocenters in chloramphenicol are known to have the (R) configuration. Identify the two stereocenters and write a three-dimensional formula for chloramphenicol.

5.12 Fischer Projection Formulas

In writing structures for chiral molecules so far, we have used only three-dimensional formulas, and we shall continue to do so until we study carbohydrates in Chapter 22. The reason: Three-dimensional formulas are unambiguous and can be manipulated on paper in any way that we wish, as long as we do not break bonds. Their use, moreover, teaches us to see molecules (in our mind’s eye) in three dimensions, and this ability will serve us well.
Chemists sometimes represent structures for chiral molecules with two-dimensional formulas called Fischer projection formulas. These two-dimensional formulas are especially useful for compounds with several stereocenters because they save space and are easy to write. They are widely used to depict acyclic forms of simple carbohydrates. (See the Learning Group Problem, Part 2). Their use, however, requires a rigid adherence to certain conventions. Used carelessly, these projection formulas can easily lead to incorrect conclusions.

The Fischer projection formula for (2R,3R)-2,3-dibromobutane is written as follows:

![Fischer projection formula for (2R,3R)-2,3-dibromobutane](image)

By convention, Fischer projections are written with the main carbon chain extending from top to bottom and with all groups eclipsed. Vertical lines represent bonds that project behind the plane of the paper (or that lie in it). Horizontal lines represent bonds that project out of the plane of the paper. The intersection of vertical and horizontal lines represents a carbon atom, usually one that is a stereocenter. By not writing the carbon at the intersections in a Fischer projection, we know that we can interpret the formula as indicating the three-dimensional aspects of the molecule. If the carbons were shown (as in Problem 5.23) the formula would not be a Fischer projection and we could not ascertain the stereochemistry of the molecule.

In using Fischer projections to test the superposability for two structures, we are permitted to rotate them in the plane of the paper by 180° but by no other angle. We must always keep them in the plane of the paper, and we are not allowed to flip them over.

![Rotation of Fischer projections](image)

Your instructor will advise you about the use you are to make of Fischer projections.
5.13 STEREOISOMERISM OF CYCLIC COMPOUNDS

Because the cyclopentane ring is essentially planar, cyclopentane derivatives offer a convenient starting point for a discussion of the stereoisomerism of cyclic compounds. For example, 1,2-dimethylcyclopentane has two stereocenters and exists in three stereoisomeric forms 5, 6, and 7.

\[ \text{Enantiomers} \]

\[ \text{Meso compound} \]

The trans compound exists as a pair of enantiomers 5 and 6. cis-1,2-Dimethylcyclopentane (7) is a meso compound. It has a plane of symmetry that is perpendicular to the plane of the ring.

(a) Is trans-1,2-dimethylcyclopentane (5) superposable on its mirror image (i.e., on compound 6)? (b) Is cis-1,2-dimethylcyclopentane (7) superposable on its mirror image? (c) Is cis-1,2-dimethylcyclopentane a chiral molecule? (d) Would cis-1,2-dimethylcyclopentane show optical activity? (e) What is the stereoisomeric relationship between 5 and 7? (f) Between 6 and 7?

Problem 5.24

Write structural formulas for all of the stereoisomers of 1,3-dimethylcyclopentane. Label pairs of enantiomers and meso compounds if they exist.

Problem 5.25

5.13A CYCLOHEXANE DERIVATIVES

1,4-DIMETHYLCYCLOHEXANES If we examine a formula of 1,4-dimethylocyclohexane we find that it does not contain any tetrahedral atoms with four different groups. However, we learned in Section 4.12 that 1,4-dimethylocyclohexane exists as cis--trans isomers. The cis and trans forms (Fig. 5.17) are *diastereomers*. Neither compound is chiral and, therefore, neither is optically active. Notice that both the cis and trans forms of 1,4-dimethylocyclohexane have a plane of symmetry.
1,3-Dimethylcyclohexane has two stereocenters; we can, therefore, expect as many as four stereoisomers (\(2^2 = 4\)). In reality there are only three. **cis**-1,3-Dimethylcyclohexane has a plane of symmetry (Fig. 5.18) and is achiral. **trans**-1,3-dimethylcyclohexane does not have a plane of symmetry and exists as a pair of enantiomers (Fig. 5.19). You may want to make models of the **trans**-1,3-dimethylcyclohexane enantiomers. Having done so, convince yourself that they cannot be superposed as they stand, and that they cannot be superposed after one enantiomer has undergone a ring flip.

1,3-Dimethylcyclohexanes 1,3-Dimethylcyclohexane has two stereocenters; we can, therefore, expect as many as four stereoisomers (\(2^2 = 4\)). In reality there are only three. **cis**-1,3-Dimethylcyclohexane has a plane of symmetry (Fig. 5.18) and is achiral. **trans**-1,3-dimethylcyclohexane does not have a plane of symmetry and exists as a pair of enantiomers (Fig. 5.19). You may want to make models of the **trans**-1,3-dimethylcyclohexane enantiomers. Having done so, convince yourself that they cannot be superposed as they stand, and that they cannot be superposed after one enantiomer has undergone a ring flip.

**Figure 5.17** The cis and trans forms of 1,4-dimethylcyclohexane are diastereomers of each other. Both compounds are achiral.

**Figure 5.18** **cis**-1,3-Dimethylcyclohexane has a plane of symmetry and is therefore achiral.

**Figure 5.19** **trans**-1,3-Dimethylcyclohexane does not have a plane of symmetry and exists as a pair of enantiomers. The two structures (a and b) shown here are not superposable as they stand, and flipping the ring of either structure does not make it superposable on the other. (c) A simplified representation of (b).
1,2-Dimethylcyclohexanes 1,2-Dimethylcyclohexane also has two stereocenters, and again we might expect as many as four stereoisomers. There are four; however, we find that we can isolate only three stereoisomers. trans-1,2-Dimethylcyclohexane (Fig. 5.20) exists as a pair of enantiomers. Its molecules do not have a plane of symmetry.

With cis-1,2-dimethylcyclohexane, the situation is somewhat more complex. If we consider the two conformational structures (c) and (d) shown in Fig. 5.21, we find that these two mirror-image structures are not identical. Neither has a plane of symmetry and each is a chiral molecule, but they are interconvertible by a ring flip. Therefore, although the two structures represent enantiomers they cannot be separated because at temperatures even considerably below room temperature they interconvert rapidly. They simply represent different conformations of the same compound. In effect (c) and (d) comprise an interconverting racemic form. Structures (c) and (d) are not configurational stereoisomers; they are conformational stereoisomers. This means that at normal temperatures there are only three isolable stereoisomers of 1,2-dimethylcyclohexane.

5.14 Relating Configurations through Reactions in Which No Bonds to the Stereocenter Are Broken

If a reaction takes place in a way so that no bonds to the stereocenter are broken, the product will of necessity have the same general configuration of groups around the stereocenter as the reactant. Such a reaction is said to proceed with retention of configuration. Consider as an example the reaction that takes place when (S)-(-)-2-methyl-1-butanol is heated with concentrated hydrochloric acid.

Problem 5.26
Write formulas for all of the isomers of each of the following. Designate pairs of enantiomers and achiral compounds where they exist.
(a) 1-Bromo-2-chlorocyclohexane
(b) 1-Bromo-3-chlorocyclohexane
(c) 1-Bromo-4-chlorocyclohexane

Give the (R,S) designation for each compound given as an answer to Problem 5.26.

Problem 5.27
We do not need to know now exactly how this reaction takes place to see that the reaction must involve breaking of the CH₂OH bond of the alcohol because the CH₂OH group is replaced by a CH₂Cl. There is no reason to assume that any other bonds are broken. (We shall study how this reaction takes place in Section 11.13.) Since no bonds to the stereocenter are broken, the reaction must take place with retention of configuration, and the product of the reaction must have the same configuration of groups around the stereocenter that the reactant had. By saying that the two compounds have the same configuration we simply mean that comparable or identical groups in the two compounds occupy the same relative positions in space around the stereocenter. (In this instance the CH₂OH group and the CH₂Cl are comparable and they occupy the same relative position in both compounds; all the other groups are identical and they occupy the same positions.)

Notice that in this example while the (R–S) designation does not change [both reactant and product are (S)] the direction of optical rotation does change [the reactant is (−) and the product is (+)]. Neither occurrence is a necessity when a reaction proceeds with retention of configuration. In the next section we shall see examples of reactions in which configurations are retained and where the direction of optical rotation does not change. The following reaction is an example of a reaction that proceeds with retention of configuration but involves a change in (R–S) designation.

In this example the (R–S) designation changes because the CH₂Br group of the reactant changes to a CH₂H group in the product (CH₂Br has a higher priority than CH₂CH₃, and CH₂H has a lower priority than CH₂CH₃).

### 5.14A Relative and Absolute Configurations

Reactions in which no bonds to the stereocenter are broken are useful in relating configurations of chiral molecules. That is, they allow us to demonstrate that certain compounds have the same relative configuration. In each of the examples that we have just cited, the products of the reactions have the same relative configurations as the reactants.

Before 1951 only relative configurations of chiral molecules were known. No one prior to that time had been able to demonstrate with certainty what the actual spatial arrangement...
of groups was in any chiral molecule. To say this another way, no one had been able to
determine the absolute configuration of an optically active compound.

Configurations of chiral molecules were related to each other through reactions of
known stereochemistry. Attempts were also made to relate all configurations to a single
compound that had been chosen arbitrarily to be the standard. This standard compound
was glyceraldehyde.

\[
\begin{align*}
&\text{Glyceraldehyde} \\
&\quad \begin{array}{c}
\text{CHOH} \\
\text{CH}_2\text{OH}
\end{array}
\end{align*}
\]

Glyceraldehyde molecules have one tetrahedral stereocenter; therefore, glyceraldehyde
exists as a pair of enantiomers.

\[
\begin{align*}
\text{(R)-Glyceraldehyde} & \quad \text{(S)-Glyceraldehyde} \\
\begin{array}{c}
\text{CHOH} \\
\text{CH}_2\text{OH}
\end{array} & \quad \begin{array}{c}
\text{CHOH} \\
\text{CH}_2\text{OH}
\end{array}
\end{align*}
\]

In the older system for designating configurations, (R)-glyceraldehyde was called D-glyceraldehyde and (S)-glyceraldehyde was called L-glyceraldehyde. This system of nomenclature is still widely used in biochemistry.

One glyceraldehyde enantiomer is dextrorotatory (+) and the other, of course, is levorotatory (−). Before 1951 no one could be sure, however, which configuration belonged to which enantiomer. Chemists decided arbitrarily to assign the (R) configuration to the (+) enantiomer. Then, configurations of other molecules were related to one glyceraldehyde enantiomer or the other through reactions of known stereochemistry.

For example, the configuration of (−)-lactic acid can be related to (+)-glyceraldehyde through the following sequence of reactions.

\[
\begin{align*}
\text{H}_2\text{O} & \quad \text{HNO}_2 \\
\text{HNO}_2 & \quad \text{HBr}
\end{align*}
\]

5.14 Relating Configurations through Reactions in Which No Bonds to the Stereocenter Are Broken
The stereochemistry of all of these reactions is known. Because bonds to the stereocenter (shown in red) are not broken in any of them, they all proceed with retention of configuration. If the assumption is made that the configuration of \((+)-\text{glyceraldehyde}\) is as follows:

\[
\begin{align*}
\text{CH}_2\text{OH} \\
\text{CH}\text{OH} \\
\text{H} \\
\text{O} \\
(\text{R})(+)\text{-Glyceraldehyde}
\end{align*}
\]

then the configuration of \((-)-\text{lactic acid}\) is

\[
\begin{align*}
\text{O} \\
\text{H} \\
\text{OH} \\
\text{CH} \\
(\text{R})(-)\text{-Lactic acid}
\end{align*}
\]

Problem 5.28

Write three-dimensional formulas for the starting compound, the product, and all of the intermediates in a synthesis similar to the one just given that relates the configuration of \((-)-\text{glyceraldehyde}\) with \((+)-\text{lactic acid}\). Label each compound with its proper \((\text{R})\)–\((\text{S})\) and \((+)-(\text{-})\) designation.

The configuration of \((-)-\text{glyceraldehyde}\) was also related through reactions of known stereochemistry to \((+)-\text{tartaric acid}\).

\[
\begin{align*}
\text{CO}_2\text{H} \\
\text{H} \\
\text{OH} \\
(+)\text{-Tartaric acid}
\end{align*}
\]

In 1951 J. M. Bijvoet, the director of the van’t Hoff Laboratory of the University of Utrecht in the Netherlands, using a special technique of X-ray diffraction, was able to show conclusively that \((+)-\text{tartaric acid}\) had the absolute configuration shown above. This meant that the original arbitrary assignment of the configurations of \((+)-\) and \((-)-\text{glyceraldehyde}\) was also correct. It also meant that the configurations of all of the compounds that had been related to one glyceraldehyde enantiomer or the other were now known with certainty and were now absolute configurations.

Problem 5.29

How would you synthesize \((\text{R})\)-1-deuterio-2-methylbutane? [Hint: Consider one of the enantiomers of 1-chloro-2-methylbutane in Section 5.7C as a starting compound.]
5.15 Separation of Enantiomers: Resolution

So far we have left unanswered an important question about optically active compounds and racemic forms: How are enantiomers separated? Enantiomers have identical solubilities in ordinary solvents, and they have identical boiling points. Consequently, the conventional methods for separating organic compounds, such as crystallization and distillation, fail when applied to a racemic form.

5.15A Pasteur’s Method for Separating Enantiomers

It was, in fact, Louis Pasteur’s separation of a racemic form of a salt of tartaric acid in 1848 that led to the discovery of the phenomenon called enantiomerism. Pasteur, consequently, is often considered to be the founder of the field of stereochemistry. (+)-Tartaric acid is one of the by-products of wine making (nature usually only synthesizes one enantiomer of a chiral molecule). Pasteur had obtained a sample of racemic tartaric acid from the owner of a chemical plant. In the course of his investigation Pasteur began examining the crystal structure of the sodium ammonium salt of racemic tartaric acid. He noticed that two types of crystals were present. One was identical with crystals of the sodium ammonium salt of (+)-tartaric acid that had been discovered earlier and had been shown to be dextrorotatory. Crystals of the other type were non-superposable mirror images of the first kind. The two types of crystals were actually chiral. Using tweezers and a magnifying glass, Pasteur separated the two kinds of crystals, dissolved them in water, and placed the solutions in a polarimeter. The solution of crystals of the first type was dextrorotatory, and the crystals themselves proved to be identical with the sodium ammonium salt of (+)-tartaric acid that was already known. The solution of crystals of the second type was levorotatory; it rotated plane-polarized light in the opposite direction and by an equal amount. The crystals of the second type were of the sodium ammonium salt of (−)-tartaric acid. The chirality of the crystals themselves disappeared, of course, as the crystals dissolved into their solutions but the optical activity remained. Pasteur reasoned, therefore, that the molecules themselves must be chiral.

Pasteur’s discovery of enantiomerism and his demonstration that the optical activity of the two forms of tartaric acid was a property of the molecules themselves led, in 1874, to the proposal of the tetrahedral structure of carbon by van’t Hoff and Le Bel.

Unfortunately, few organic compounds give chiral crystals as do the (+)- and (−)-tartaric acid salts. Few organic compounds crystallize into separate crystals (containing separate enantiomers) that are visibly chiral like the crystals of the sodium ammonium salt of tartaric acid. Pasteur’s method, therefore, is not generally applicable to the separation of enantiomers.

5.15B Current Methods for Resolution of Enantiomers

One of the most useful procedures for separating enantiomers is based on allowing a racemic form to react with a single enantiomer of some other compound. This changes a racemic form into a mixture of diastereomers; and diastereomers, because they have different melting points, different boiling points, and different solubilities, can be separated by conventional means. Diastereomeric recrystallization is one such process. We shall see how this is done in Section 20.3E. Another method is resolution by enzymes, whereby an enzyme selectively converts one enantiomer in a racemic mixture to another compound, after which the unreacted enantiomer and the new compound are separated.

The reaction by lipase in Section 5.9B is an example of this type of resolution. Chromatography using chiral media is also widely used to resolve enantiomers. This approach is applied in high-performance liquid chromatography (HPLC) as well as in other forms of chromatography. Diastereomeric interactions between molecules of the racemic mixture and the chiral chromatography medium cause enantiomers of the racemate to move through
the chromatography apparatus at different rates. The enantiomers are then collected separately as they elute from the chromatography device. (See "The Chemistry of . . . HPLC Resolution of Enantiomers," Section 20.3.)

5.16 COMPOUNDS WITH STEREOCENTERS OTHER THAN CARBON

Any tetrahedral atom with four different groups attached to it is a stereocenter. Shown here are general formulas of compounds whose molecules contain stereocenters other than carbon. Silicon and germanium are in the same group of the periodic table as carbon. They form tetrahedral compounds as carbon does. When four different groups are situated around the central atom in silicon, germanium, and nitrogen compounds, the molecules are chiral and the enantiomers can, in principle, be separated. Sulfur oxides, like certain examples of other functional groups where one of the four groups is a nonbonding electron pair, are also chiral. This is not the case for amines, however (Section 20.2B).

\[
\begin{align*}
\text{Si} & \quad R_1 \quad R_2 \quad R_3 \quad R_4 \\
\text{Ge} & \quad R_1 \quad R_2 \quad R_3 \quad R_4 \\
\text{N} & \quad R_1 \quad X \quad R_2 \quad R_3 \\
\text{SO} & \quad R_1 \quad O \quad R_2 
\end{align*}
\]

5.17 CHIRAL MOLECULES THAT DO NOT POSSESS A TETRAHEDRAL ATOM WITH FOUR DIFFERENT GROUPS

A molecule is chiral if it is not superposable on its mirror image. The presence of a tetrahedral atom with four different groups is only one locus that can confer chirality on a molecule. Most of the chiral molecules that we shall encounter do have such stereocenters. Many chiral molecules are known, however, that do not. An example is 1,3-dichloroallene (Fig. 5.22).

Allenes are compounds whose molecules contain the following double bond sequence:

\[
\text{CC} \quad \text{C}
\]

The planes of the \(\pi\) bonds of allenes are perpendicular to each other.

This geometry of the \(\pi\) bonds causes the groups attached to the end carbon atoms to lie in perpendicular planes, and, because of this, allenes with different substituents on the end carbon atoms are chiral (Fig. 5.22). (Allenes do not show cis–trans isomerism.)

![Figure 5.22 Enantiomeric forms of 1,3-dichloroallene. These two molecules are nonsuperposable mirror images of each other and are therefore chiral. They do not possess a tetrahedral atom with four different groups, however.](image-url)
Key Terms and Concepts

Stereochemistry

Sections 5.1, 5.4

Isomers

Sections 1.13B, 5.1

Constitutional isomers

Sections 1.3A, 4.2, 5.1

Stereoisomers

Sections 5.1, 5.13

Chirality

Sections 5.2, 5.3, 5.5

Chiral molecule

Section 5.2

Enantiomers

Sections 5.1, 5.2, 5.6, 5.7, 5.15

Diastereomers

Section 5.1

Achiral molecule

Sections 5.2, 5.11

Stereocenter

Sections 5.2, 5.11, 5.16

Plane of symmetry

Sections 5.5, 5.11A

Configuration

Sections 5.6, 5.14

Racemic form (racemate or racemic mixture)

Sections 5.8A, B

Meso compound

Section 5.11A

Fischer projection formulas

Section 5.12

Enantioselective reaction

Section 5.9B

Resolution

Section 5.15

Additional Problems

5.30 Which of the following are chiral and, therefore, capable of existing as enantiomers?

(a) 1,3-Dichlorobutane
(b) 1,2-Dibromopropane
(c) 1,5-Dichloropentane
(d) 3-Ethylpentane
(e) 2-Bromobicyclo[1.1.0]butane
(f) 2-Fluorobicyclo[2.2.2]octane
(g) 2-Chlorobicyclo[2.1.1]hexane
(h) 5-Chlorobicyclo[2.1.1]hexane

5.31 (a) How many carbon atoms does an alkane (not a cycloalkane) need before it is capable of existing in enantiomeric forms?

(b) Give correct names for two sets of enantiomers with this minimum number of carbon atoms.

5.32 (a) Write the structure of 2,2-dichlorobicyclo[2.2.1]heptane.

(b) How many stereocenters does it contain?

(c) How many stereoisomers are predicted by the 2ⁿ rule?

(d) Only one pair of enantiomers is possible for 2,2-dichlorobicyclo[2.2.1]heptane. Explain.

5.33 Shown below are Newman projection formulas for (R,R)-, (S,S)-, and (R,S)-2,3-dichlorobutane.

(a) Which is which?

(b) Which formula is a meso compound?

5.34 Write appropriate structural formulas for

(a) a cyclic molecule that is a constitutional isomer of cyclohexane,

(b) molecules with the formula C₆H₁₂ that contain one ring and that are enantiomers of each other,

(c) molecules with the formula C₆H₁₂ that contain one ring and that are diastereomers of each other,

(d) molecules with the formula C₆H₁₂ that contain no ring and that are...
enantiomers of each other, and (e) molecules with the formula $C_6H_{12}$ that contain no ring and that are diastereomers of each other.

5.35 Consider the following pairs of structures. Identify the relationship between them by describing them as representing enantiomers, diastereomers, constitutional isomers, or two molecules of the same compound.

(a) $\text{CH}_3\text{CH}_3\text{Br}$ and $\text{CH}_3\text{Br}\text{CH}_3$
(b) $\text{CH}_3\text{Br}$ and $\text{CH}_3\text{H}$
(c) $\text{F}$ and $\text{H}$
(d) $\text{CF}_3\text{CH}_3\text{H}$ and $\text{CH}_3\text{H}$
(e) $\text{F}$ and $\text{CF}_3\text{H}$
(f) $\text{CF}_3\text{CH}_3\text{H}$ and $\text{CH}_3\text{H}$
(g) $\text{Br}$ and $\text{F}$
(h) $\text{Br}$ and $\text{Cl}$
(i) $\text{H}$ and $\text{Cl}$
(j) $\text{Cl}$ and $\text{Cl}$
(k) $\text{Cl}$ and $\text{Cl}$
(l) $\text{Cl}$ and $\text{Cl}$
(m) $\text{H}$ and $\text{Br}$
(n) $\text{H}$ and $\text{Br}$

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5.36 Discuss the anticipated stereochemistry of each of the following compounds.
(a) ClCH\(_2\)C\(=\)C\(=\)CHCl (c) ClCH\(_2\)C\(=\)CCl
(b) Cl\(_2\)C\(=\)C\(=\)CHCl

5.37 There are four dimethylcyclopropane isomers. (a) Write three-dimensional formulas for these isomers. (b) Which of these isomers are chiral? (c) If a mixture consisting of 1 mol of each of these isomers were subjected to simple gas chromatography, how many fractions would be obtained and which compounds would each fraction contain? (d) How many of these fractions would be optically active?

5.38 (Use models to solve this problem.) (a) Write a conformational structure for the most stable conformation of trans-1,2-diethylcyclohexane and write its mirror image. (b) Are these two molecules superposable? (c) Are they interconvertible through a ring "flip"? (d) Repeat the process in part (a) with cis-1,2-diethylcyclohexane. (e) Are these structures superposable? (f) Are they interconvertible?

5.39 (Use models to solve this problem.) (a) Write a conformational structure for the most stable conformation of trans-1,4-diethylcyclohexane and for its mirror image. (b) Are these structures superposable? (c) Do they represent enantiomers? (d) Does trans-1,4-diethylcyclohexane have a stereoisomer, and if so, what is it? (e) Is this stereoisomer chiral?

5.40 (Use models to solve this problem.) Write conformational structures for all of the stereoisomers of 1,3-diethylcyclohexane. Label pairs of enantiomers and meso compounds if they exist.

5.41 Tartaric acid [HO\(_2\)CCH(OH)CH(OH)CO\(_2\)H] was an important compound in the history of stereochemistry. Two naturally occurring forms of tartaric acid are optically inactive. One form has a melting point of 206°C, the other a melting point of 140°C. The inactive tartaric acid with a melting point of 206°C can be separated into two optically active forms of tartaric acid with the same melting point (170°C). One optically active tartaric acid has \([\alpha]_D^\circ = +12^\circ\), and the other, \([\alpha]_D^\circ = -12^\circ\). All attempts to separate the other inactive tartaric acid (melting point 140°C) into optically active compounds fail. (a) Write the three-dimensional structure of the tartaric acid with melting point 140°C. (b) What are possible structures for the optically active tartaric acids with melting points of 170°C? (c) Can you be sure which tartaric acid in (b) has a positive rotation and which has a negative rotation? (d) What is the nature of the form of tartaric acid with a melting point of 206°C?
*5.42 (a) An aqueous solution of pure stereoisomer X of concentration 0.10 g/mL had observed rotation $\alpha$ in a 1.0-dm tube at 589.6 nm (the sodium D line) and 25°C. What do you calculate its $\alpha_D$ to be at this temperature?

(b) Under identical conditions but with concentration 0.050 g/mL, a solution of X had observed rotation $\alpha$ in a 1.0-dm tube at 589.6 nm (the sodium D line) and 25°C. Rationalize how this could be and recalculate $\alpha_D$ for stereoisomer X.

(c) If the optical rotation of a substance studied at only one concentration is 0°, can it definitely be concluded to be achiral? Racemic?

*5.43 If a sample of a pure substance that has two or more stereocenters has an observed rotation of 0°, it could be a racemate. Could it possibly be a pure stereoisomer? Could it possibly be a pure enantiomer?

*5.44 Unknown Y has a molecular formula of C$_3$H$_6$O$_2$. It contains one functional group that absorbs infrared radiation in the 3200 to 3550 cm$^{-1}$ region (when studied as a pure liquid; i.e., “neat”), and it has no absorption in the 1620 to 1780 cm$^{-1}$ region. No carbon atom in the structure of Y has more than one oxygen atom bonded to it, and Y can exist in two (and only two) stereoisomeric forms. What are the structures of these forms of Y?