Organic Chemistry, *Fourth Edition*

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Chapter 5
Stereochemistry

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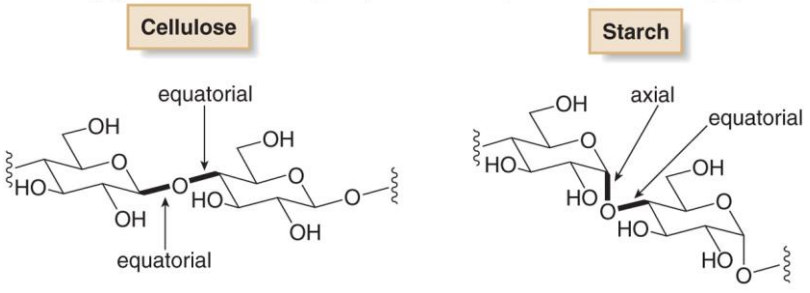
Stereochemistry

- **Stereochemistry refers to the three-dimensional structure of a molecule.**
- **As a consequence of stereochemistry, apparently minor differences in 3-D structure can result in vastly different properties.**
- **We can observe this by considering starch and cellulose, which are both composed of the same repeating unit.**

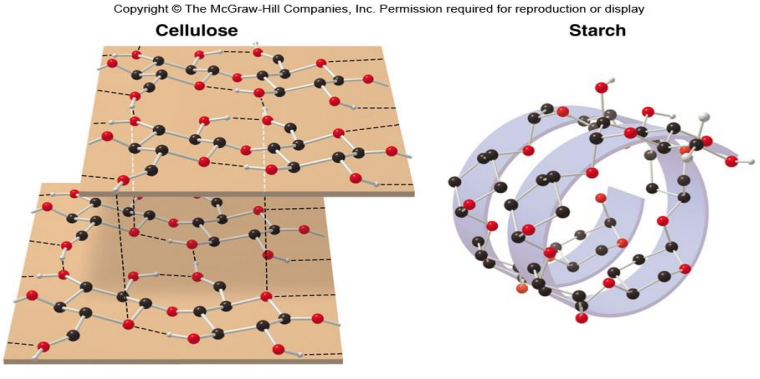
Stereochemistry of Starch and Cellulose

- **In cellulose, the O atom joins two rings using equatorial bonds.**
- **In starch, the O atom joins two rings using one equatorial and one axial bond.**
- **Due to these differences in stereochemistry, humans can metabolize starch for energy but we cannot digest cellulose.**



3-D Structure of Starch and Cellulose

Figure 5.2



Cellulose consists of an extensive three-dimensional network held together by hydrogen bonds.

The starch polymer is composed of chains that wind into a helix.

Constitutional Isomers

- **Isomers are different compounds with the same molecular formula.**
- **The two major classes of isomers are constitutional isomers and stereoisomers.**
  - **Constitutional/structural isomers have:**
    - **different IUPAC names**
    - **same or different functional groups**
    - **different physical properties**
    - **different chemical properties**

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Stereoisomers

- **Stereoisomers:**
  - **Differ only in the way the atoms are oriented in space.**
  - **Have identical IUPAC names (except for a prefix like *cis* or *trans*).**
  - **Always have the same functional group(s).**
  - **Differ in configuration (three-dimensional arrangement).**

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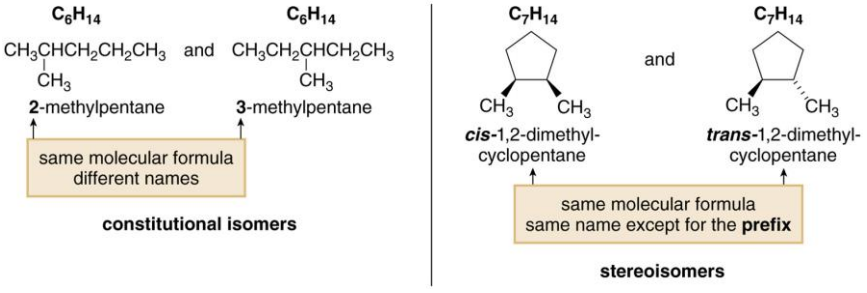
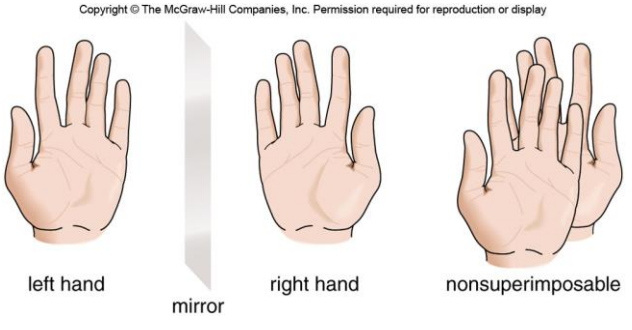
Constitutional and Stereoisomers

Figure 5.3



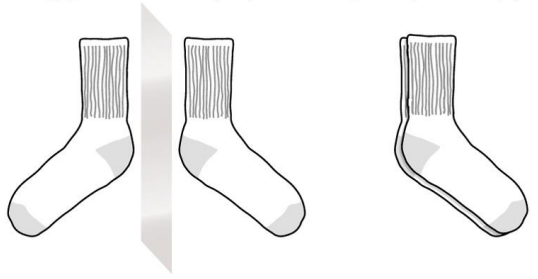
Nonsuperimposable Mirror Images

- **Although everything has a mirror image, mirror images may or may not be superimposable.**
  - **To superimpose means to align all parts of two objects**
- **Some molecules are like hands. Left and right hands are mirror images, but they are not identical, or superimposable.**
- **A molecule (or object) that is not superimposable on its mirror image is said to be chiral.**



Superimposable (Achiral) Objects

- **Other molecules are like socks.**
  - **Two socks from a pair are mirror images that are superimposable.**
  - **A sock and its mirror image are identical.**
- **A molecule or object that is superimposable on its mirror image is said to be achiral.**



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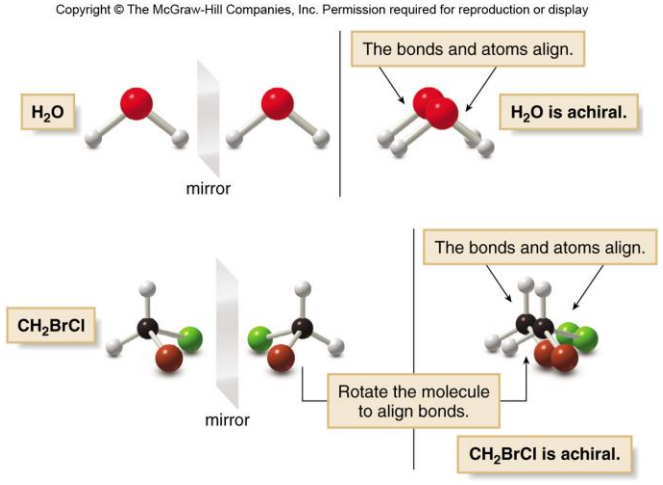
Achiral Molecules

- **We can now consider several molecules to determine whether or not they are chiral.**



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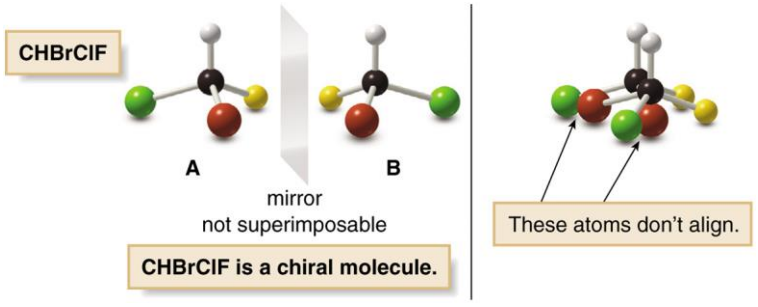
Chiral Molecules

- The molecule labeled A and its mirror image labeled B are not superimposable.
  - No matter how you rotate A and B, all the atoms never align.
  - Thus, CHBrClF is a chiral molecule, and A and B are different compounds.
- A and B are stereoisomers—specifically, they are enantiomers.
- A carbon atom with four different groups is a tetrahedral stereogenic center.



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Stereogenic Centers

- In general, a molecule with no stereogenic centers will not be chiral (exceptions to this will be considered in section 17.5).
- With one stereogenic center, a molecule will always be chiral.
- With two or more stereogenic centers, a molecule may or may not be chiral.

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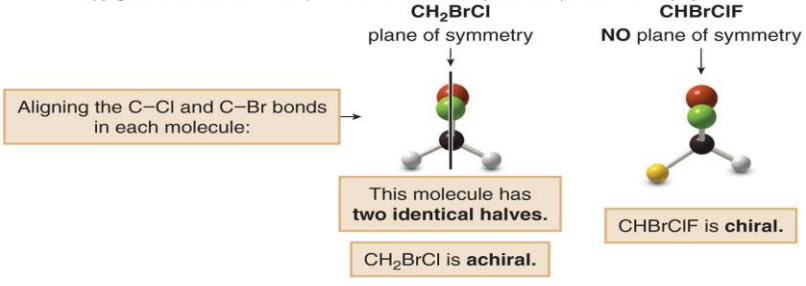
Planes of Symmetry

- A plane of symmetry is a mirror plane that cuts the molecule in half, so that one half of the molecule is a reflection of the other half.
- Achiral molecules usually contain a plane of symmetry but chiral molecules do not.



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Summary of Chirality

- Everything has a mirror image.
- The fundamental question is whether a molecule and its mirror image are superimposable.
  - If not, they are chiral and do not contain a plane of symmetry.
  - If they are superimposable, they are achiral and will contain a plane of symmetry.
- The terms stereogenic center and chiral molecule are related but distinct.
- A chiral molecule must have one or more stereogenic centers.

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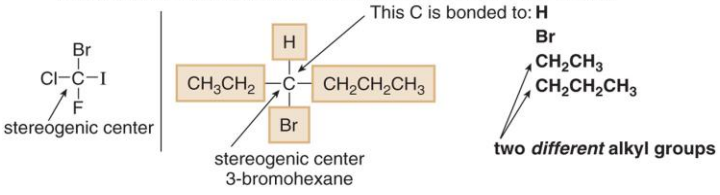
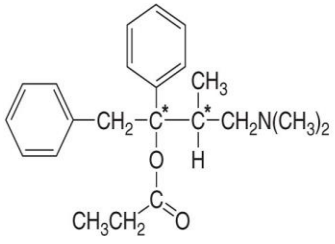
Stereogenic Centers

- **To locate a stereogenic center, examine each tetrahedral carbon atom in a molecule, and look at the four groups—not the four atoms—bonded to it.**
- **Always omit from consideration all C atoms that cannot be tetrahedral stereogenic centers. These include:**
  - **CH_2 and CH_3 groups**
  - **Any *sp* or sp^2 hybridized C**

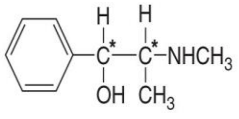


Multiple Stereogenic Centers

- **Larger organic molecules can have two, three, or even hundreds of stereogenic centers.**

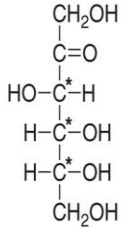


propoxyphene
Trade name: Darvon
(analgesic)



ephedrine
(bronchodilator, decongestant)

[* = stereogenic center]

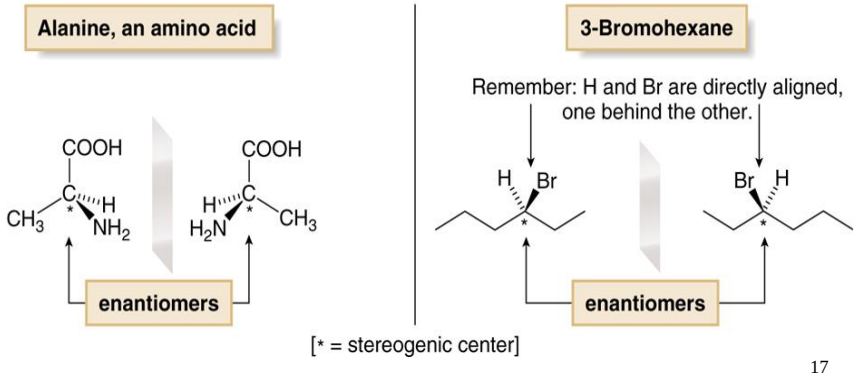


fructose
(a simple sugar)

Enantiomers

- **Enantiomers are non-superimposable mirror image molecules.**
- **Any molecule with one stereogenic center exists as a pair of enantiomers.**

Figure 5.5



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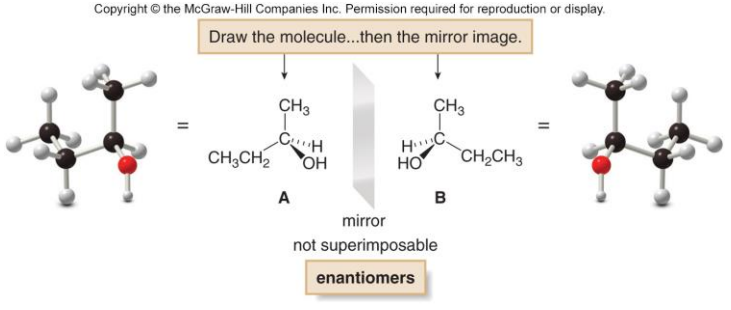
Drawing Enantiomers

- **To draw both enantiomers of a chiral compound such as 2-butanol, use the typical convention for depicting a tetrahedron.**
  - **To form the first enantiomer, arbitrarily place the four groups—H, OH, CH_3 and CH_2CH_3—on any bond to the stereogenic center.**
  - **Then draw the mirror image.**



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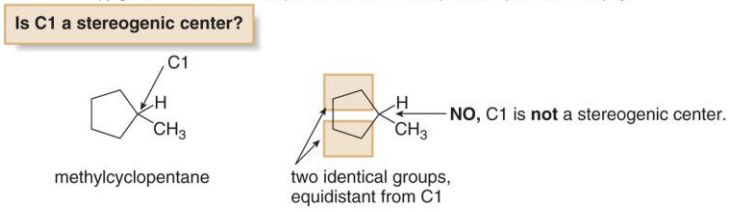
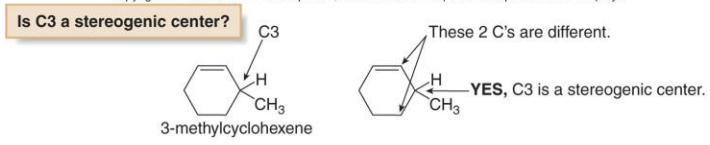
Stereogenic Centers in Cyclic Compounds

- **Stereogenic centers may also occur at carbon atoms that are part of a ring.**
- **To find stereogenic centers on ring carbons, always draw the rings as flat polygons, and look for tetrahedral carbons that are bonded to four different groups.**





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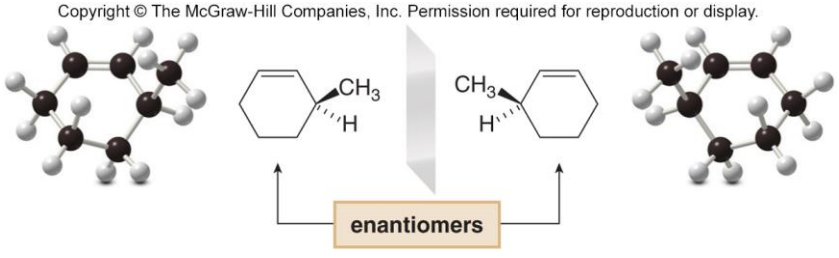
Stereogenic Centers

- **In 3-methylcyclohexene, the CH_3 and H substituents that are above and below the plane of the ring are drawn with wedges and dashes as usual.**



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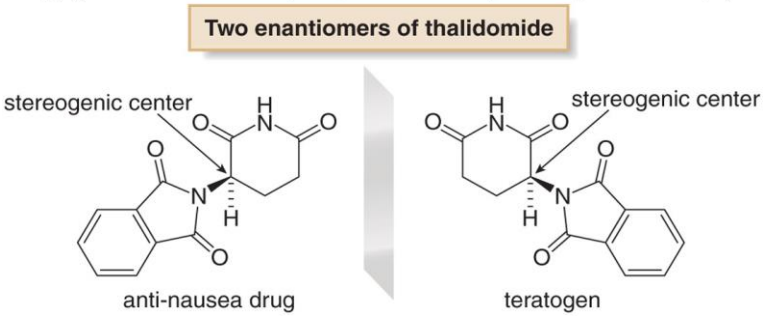
Some Biologically Active Molecules with Stereogenic Centers on Rings



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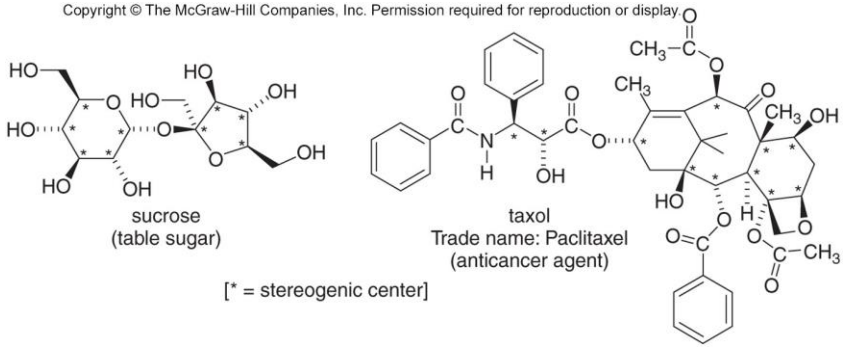
Some Biologically Active Molecules with Stereogenic Centers on Rings



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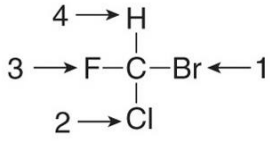
Labeling Stereogenic Centers with *R* or *S*

- **Since enantiomers are two different compounds, they need to be distinguished by name.**
  - **This is done by adding the prefix *R* or *S* to the IUPAC name of the enantiomer.**
  - **A counterclockwise direction is an S (Latin for *sinister*, left) configuration. A clockwise direction is an R (Latin for *rectus*, right) configuration**
- **RULE 1: To designate enantiomers as *R* or *S*, priorities must be assigned to each group bonded to the stereogenic center, in order of decreasing atomic number.**
- **The atom of highest atomic number gets the highest priority (1).**



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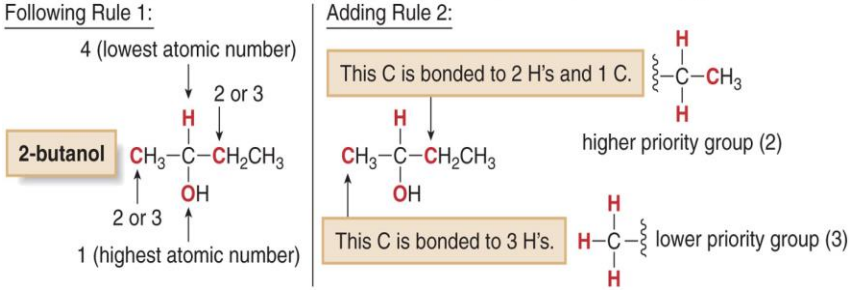
Assigning Priority for *R* and *S*

- **RULE 2: If two atoms on a stereogenic center are the same, assign priority based on the atomic number of the atoms bonded to these atoms.**
- **One atom of higher atomic number determines the higher priority.**



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Assigning Priority for *R* and *S*–Isotopes

- **RULE 3: If two isotopes are bonded to the stereogenic center, assign priorities in order of decreasing mass number.**
- **Thus, in comparing the three isotopes of hydrogen, the order of priorities is:**

	Mass number	Priority
T (tritium)	3 (1 proton + 2 neutrons)	1
D (deuterium)	2 (1 proton + 1 neutron)	2
H (hydrogen)	1 (1 proton)	3

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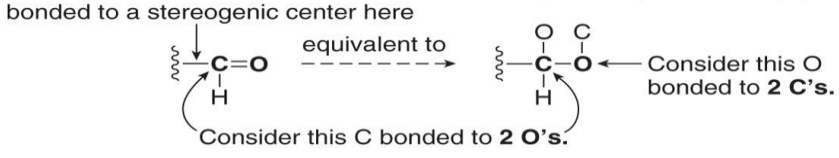
Assigning Priority for *R* and *S*–Multiple Bonds

- **RULE 4: To assign a priority to an atom that is part of a multiple bond, treat a multiply bonded atom as an equivalent number of singly bonded atoms.**
- **For example, the C of a C=O is considered to be bonded to two O atoms.**



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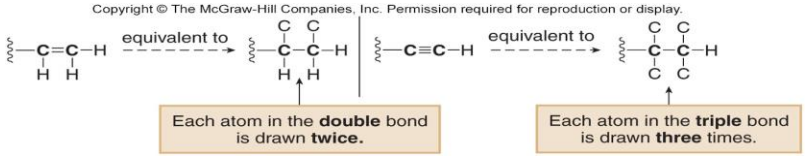
Assigning Priority for *R* and *S*–Multiple Bonds

- **Other common multiple bonds are drawn below:**



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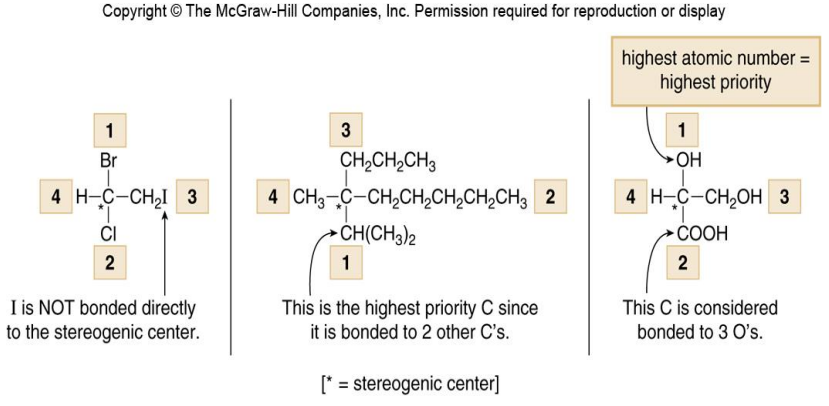
Assigning Priorities to Stereogenic Centers

Figure 5.6



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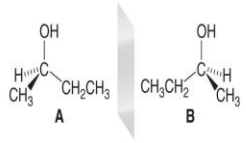
How To Assign *R* or *S*

HOW TO Assign *R* or *S* to a Stereogenic Center

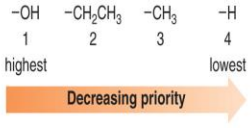
Example Label each enantiomer as *R* or *S*.



two enantiomers of 2-butanol

Step [1] Assign priorities from 1 to 4 to each group bonded to the stereogenic center.

- The priorities for the four groups around the stereogenic center in 2-butanol were given in Rule 2, on page 171.



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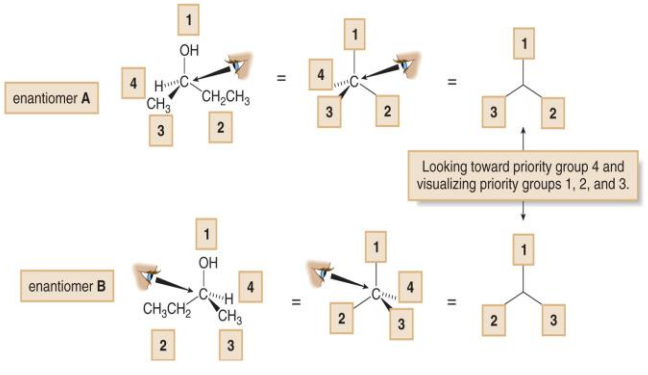
How To Assign *R* or *S*

HOW TO, continued . . .

Step [2] Orient the molecule with the lowest priority group (4) *back* (on a *dash*), and visualize the relative positions of the remaining three groups (priorities 1, 2, and 3).

- For each enantiomer of 2-butanol, look toward the lowest priority group, drawn behind the plane, down the C – H bond.



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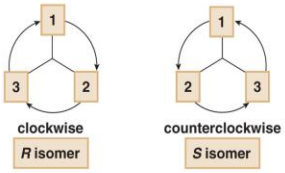
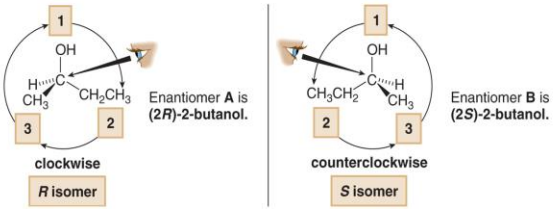
How To Assign *R* or *S*

Step [3] Trace a circle from priority group 1 → 2 → 3.

- If tracing the circle goes in the **clockwise** direction—to the right from the noon position—the isomer is named ***R***.
- If tracing the circle goes in the **counterclockwise** direction—to the left from the noon position—the isomer is named ***S***.



- The letters *R* or *S* precede the IUPAC name of the molecule. For the enantiomers of 2-butanol:



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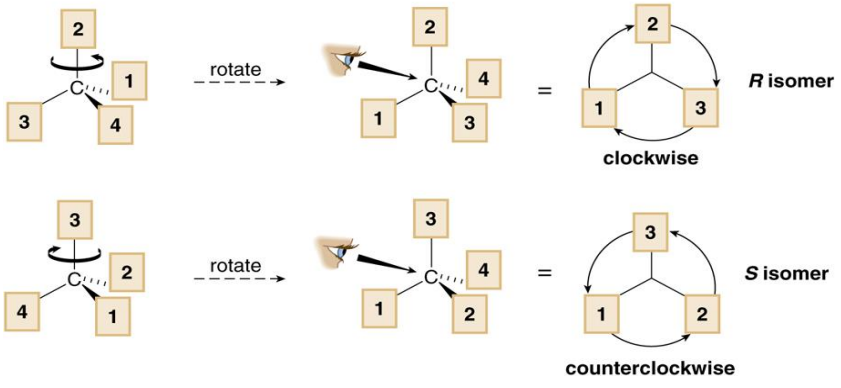
Orienting the Lowest Priority Group in Back

- **If the lowest priority group is not facing towards back, rotate the molecule 120º around a stationary bond axis.**

Figure 5.7



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Diastereomers

- For a molecule with *n* stereogenic centers, the maximum number of stereoisomers is 2^n.
- When *n*=2, $2^2 = 4$.
  - With two stereogenic centers there are 4 stereoisomers that can be drawn, although some of them may be the same molecule.
  - Some of the stereoisomers will not be mirror images of each other.
  - Diastereomers are non-mirror image stereoisomers.

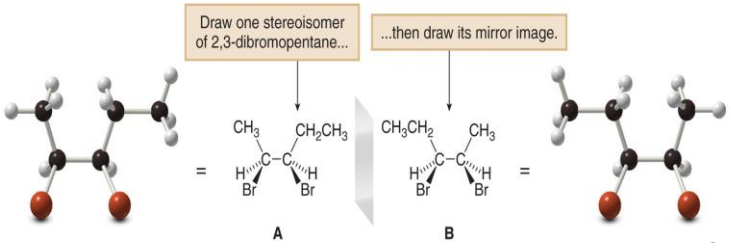
Finding All Possible Stereocenters

Example 1: stereoisomers of 2,3-dibromopentane

- Let us consider the stepwise procedure for finding all the possible .

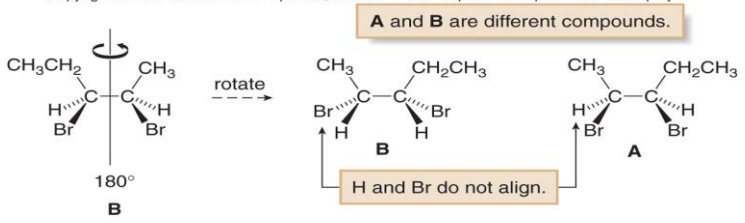
HOW TO Find and Draw All Possible Stereoisomers for a Compound with Two Stereogenic Centers

Step [1] Draw one stereoisomer by arbitrarily arranging substituents around the stereogenic centers. Then draw its mirror image.



Finding All Possible Stereocenters

- **After drawing the compound and the mirror image, place B directly on top of A; and rotate B 180° and place it on top of A to see if the atoms align.**



- **In this case, the atoms of A and B do not align, making A and B nonsuperimposable mirror images—i.e., enantiomers.**
- **A and B are two of the four possible stereoisomers of 2,3-dibromopentane.**

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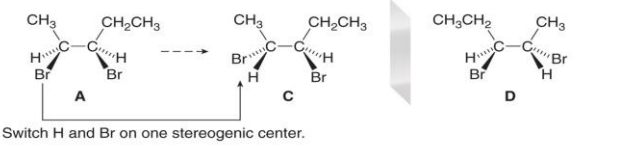
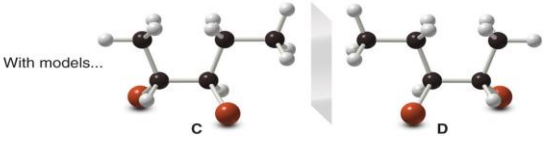
Finding All Possible Stereocenters

- **Switching the positions of H and Br (or any two groups) on one stereogenic center of either A or B forms a new stereoisomer (labeled C in this example), which is different from A and B.**
- **The mirror image of C is labeled D.**

HOW TO, continued . . .





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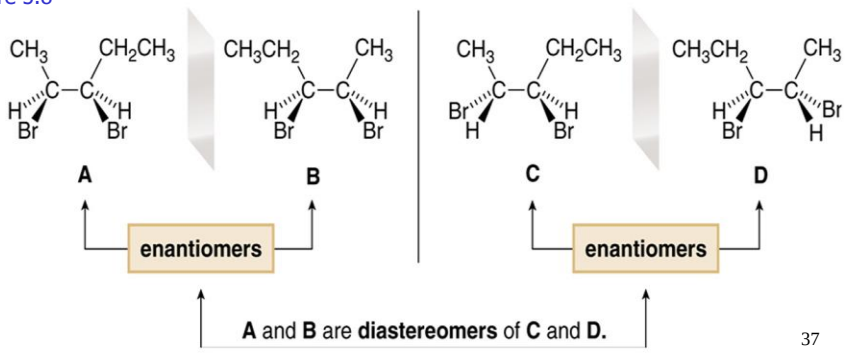
Summary of Stereoisomers of 2,3-dibromopentane

- **A and B are enantiomers. C and D are enantiomers.**
- **A and C are diastereomers. A and D are diastereomers. B and C are diastereomers. B and D are diastereomers.**

Figure 5.8



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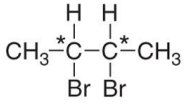
Example 2: stereoisomers of 2,3-dibromobutane

- **Since this molecule has two stereogenic centers, the maximum number of stereoisomers is 4.**



2,3-dibromobutane

[* = stereogenic center]

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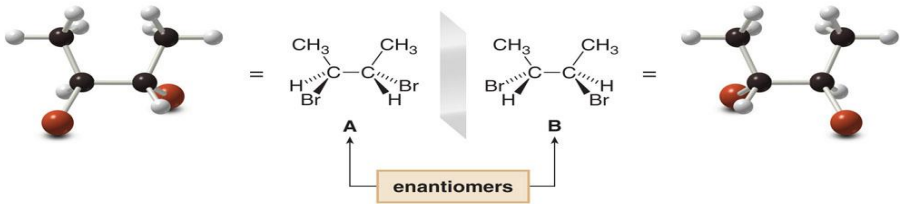
Stereoisomers of 2,3-dibromobutane

- **To find all the stereoisomers of 2,3-dibromobutane, arbitrarily form one stereoisomer A, and then draw its mirror image, B.**



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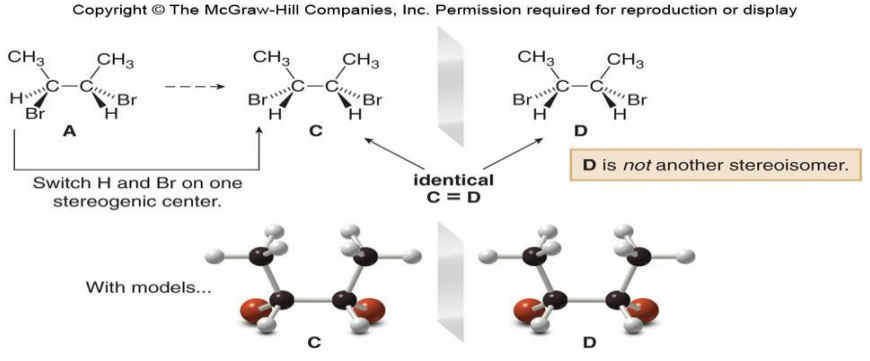
Stereoisomers of 2,3-dibromobutane

- **To find the other two stereoisomers if they exist, switch the position of two groups on one stereogenic center of one enantiomer only.**
- **Switching the positions of H and Br on one stereogenic center of A forms C, which is different from both A and B.**



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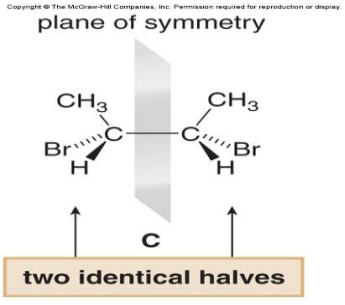
Meso Compounds

- **Compound C contains a plane of symmetry, and is achiral.**
- **A meso compound is an achiral compound that contains tetrahedral stereogenic centers. C is a meso compound.**
- **Meso compounds generally contain a plane of symmetry so that they possess two identical halves.**



- **Because one stereoisomer of 2,3-dibromobutane is superimposable on its mirror image, there are only three stereoisomers, not four.**

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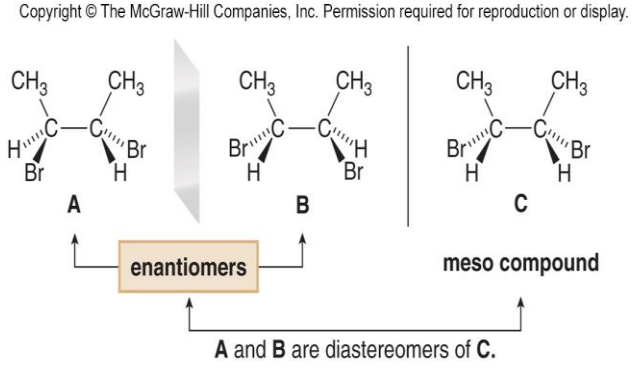
Stereoisomers of 2,3-dibromobutane

Figure 5.9



Pair of enantiomers: A and B
Pairs of diastereomers: A and C; B and C

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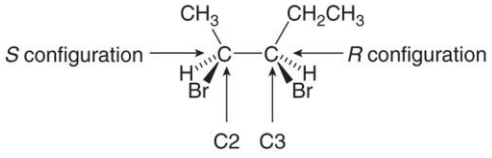
R and *S* Assignments in Compounds with Two or More Stereogenic Centers

- When a compound has more than one stereogenic center, *R* and *S* configurations must be assigned to each of them.



One stereoisomer of 2,3-dibromopentane

(2*S*,3*R*)-2,3-dibromopentane

- **Identical compounds have the *same R,S* designations at every tetrahedral stereogenic center.**
- **Enantiomers have exactly *opposite R,S* designations.**
- **Diastereomers have the *same R,S* designation for at least one stereogenic center and the *opposite* for at least one of the other stereogenic centers.**

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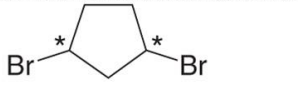
Example 3: 1,3-Dibromocyclopentane Stereoisomers

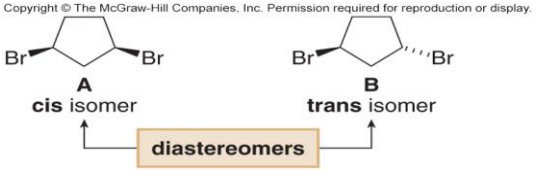
- **Since it has two stereogenic centers, it has a maximum of four stereoisomers.**



1,3-dibromocyclopentane

[* = stereogenic center]

- **Disubstituted cycloalkanes can have two substituents on the same side of the ring (*cis* isomer, A) or on opposite sides of the ring (*trans* isomer, B).**
- **These compounds are stereoisomers but not mirror images.**



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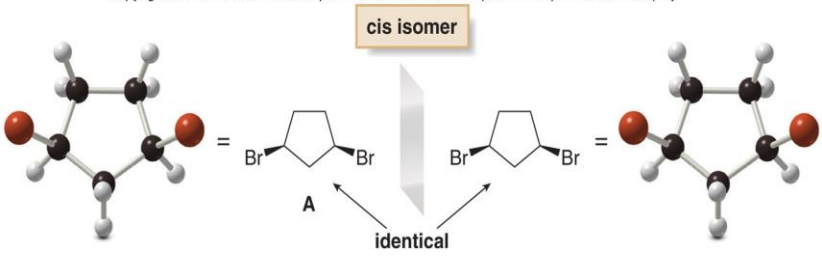
Cis-1,3-Dibromocyclopentane Structures

- **To find the other two stereoisomers if they exist, draw the mirror images of each compound and determine whether the compound and its mirror image are superimposable.**



- **The *cis* isomer is superimposable on its mirror image, making the images identical.**
- **A is an achiral meso compound.**

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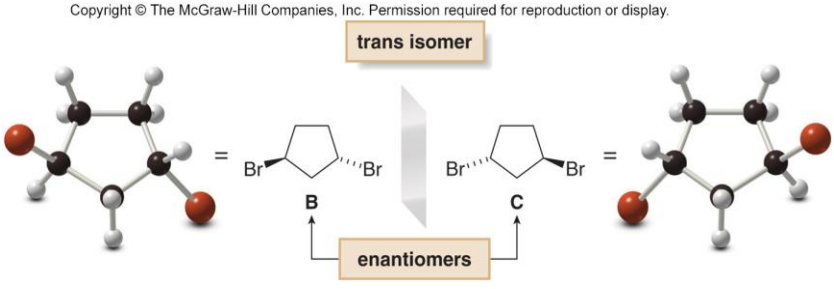
Trans-1,3-Dibromocyclopentane Structures

- **The trans isomer is not superimposable on its mirror image, labeled C, making B and C different compounds.**
- **B and C are enantiomers.**



- **Because one stereoisomer of 1,3-dibromocyclopentane is superimposable on its mirror image, there are only three stereoisomers, not four.**

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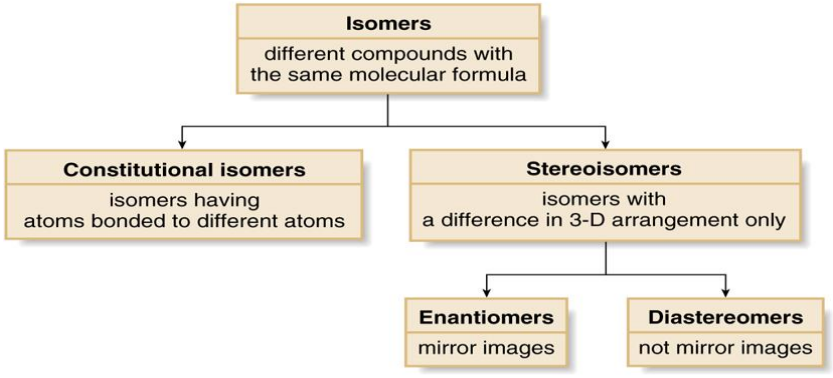
Summary–Types of Isomers

Figure 5.10



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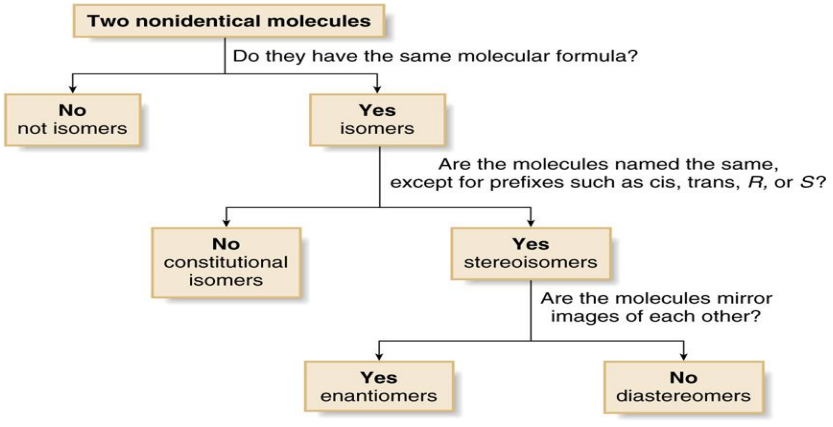
Determining the Relationship Between Molecules

Figure 5.11



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Optical Activity

- **The chemical and physical properties of two enantiomers are identical except in their interaction with chiral substances.**
- **They have identical physical properties, except for how they interact with plane-polarized light.**
- **Plane-polarized (polarized) light is light that has an electric vector that oscillates in a single plane.**
- **Plane-polarized light arises from passing ordinary light through a polarizer.**
- **A polarimeter is an instrument that allows polarized light to travel through a sample tube containing an organic compound and permits the measurement of the degree to which an organic compound rotates plane-polarized light.**

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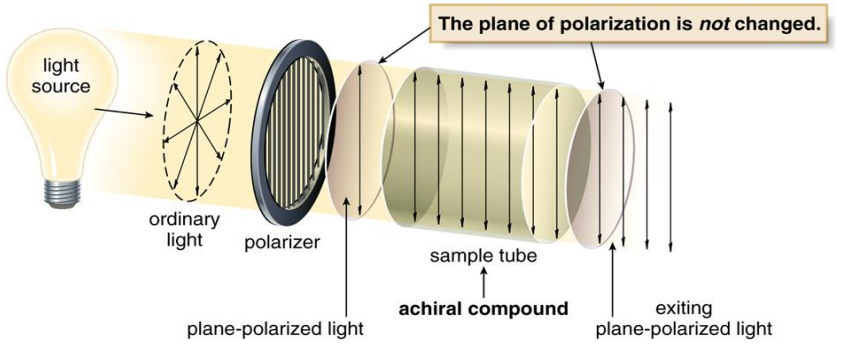
Plane-Polarized Light

- **With achiral compounds, the light that exits the sample tube remains unchanged.**
- **A compound that does not change the plane of polarized light is said to be optically inactive.**



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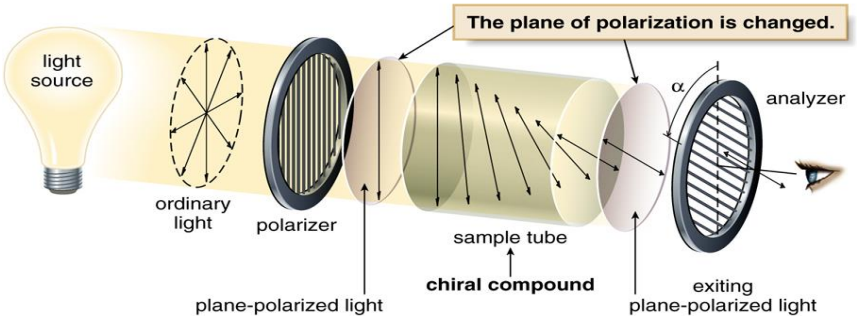
Rotation of Plane-Polarized Light

- With chiral compounds, the plane of the polarized light is rotated through an angle α.
- The angle α is measured in degrees (°), and is called the observed rotation.
- A compound that rotates polarized light is said to be optically active.



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Optical Activity Summary

- The rotation of polarized light can be clockwise or counterclockwise.
- If the rotation is clockwise, the compound is called dextrorotatory. The rotation is labeled *d* or (+).
- If the rotation is counterclockwise, the compound is called levorotatory. The rotation is labeled *l* or (-).
- Two enantiomers rotate plane-polarized light to an equal extent but in opposite directions.
  - (e.g., if enantiomer A rotates polarized light +5°, the same concentration of enantiomer B rotates it –5°)
- No relationship exists between *R* and *S* prefixes and the (+) and (-) designations that indicate optical rotation.

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Racemic Mixtures

- **An equal amount of two enantiomers is called a racemic mixture or a racemate.**
- **A racemic mixture is optically inactive.**
- **Because two enantiomers rotate plane-polarized light to an equal extent but in opposite directions, the rotations cancel, and no rotation is observed.**

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Racemic Mixtures

Table 5.1 The Physical Properties of Enantiomers A and B Compared

Property	A alone	B alone	Racemic A + B
Melting point	identical to **B**	identical to **A**	may be different from **A** and **B**
Boiling point	identical to **B**	identical to **A**	may be different from **A** and **B**
Optical rotation	equal in magnitude but opposite in sign to **B**	equal in magnitude but opposite in sign to **A**	0°

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Specific Rotation

- **Specific rotation is a standardized physical constant for the amount that a chiral compound rotates plane-polarized light.**
- **Specific rotation is denoted by the symbol [α] and defined using a specific sample tube length (*l*, in dm), concentration (*c* in g/mL), temperature (25°C) and wavelength (589 nm).**

$$\text{specific rotation} = [\alpha] = \frac{\alpha}{l \times c}$$

α = observed rotation (°)
l = length of sample tube (dm)
c = concentration (g/mL)

[dm = decimeter
1 dm = 10 cm]

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Optical Purity

- **Enantiomeric excess (optical purity) is a measurement of how much one enantiomer is present in excess of the racemic mixture.**
- **It is denoted by the symbol *ee*.**

***ee* = % of one enantiomer - % of the other enantiomer**

- **Consider the following example—If a mixture contains 75% of one enantiomer and 25% of the other, the enantiomeric excess is 75% - 25% = 50%.**
- **Thus, there is a 50% excess of one enantiomer over the racemic mixture or 50% *ee*.**

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Enantiomeric Excess

- **The enantiomeric excess can also be calculated if the specific rotation [α] of a mixture and the specific rotation [α] of a pure enantiomer are known.**

ee **= ([α] mixture/[α] pure enantiomer) x 100%**

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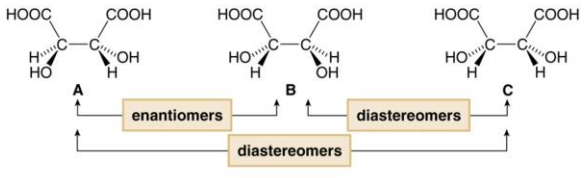
Physical Properties of Stereoisomers

- **Since enantiomers have identical physical properties, they cannot be separated by common physical techniques like distillation.**
- **Diastereomers and constitutional isomers have different physical properties, and therefore can be separated by common techniques.**

Figure 5.12



Property	A	B	C	A + B (1:1)
melting point (°C)	171	171	146	206
solubility (g/100 mL H_2O)	139	139	125	139
[α]	+13	−13	0	0
R,S designation	*R,R*	*S,S*	*R,S*	—
d,l designation	*d*	*l*	none	*d,l*

- The physical properties of **A** and **B** differ from their diastereomer **C.**
- The physical properties of a racemic mixture of **A** and **B** (last column) can also differ from either enantiomer and diastereomer **C.**
- **C** is an achiral meso compound, so it is optically inactive; [α] = 0.

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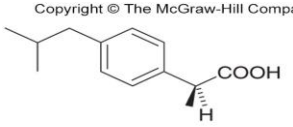
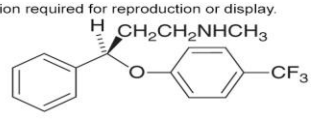
Chemical Properties of Enantiomers

- **Two enantiomers have exactly the same chemical properties except for their reaction with chiral, non-racemic reagents.**
- **Many drugs are chiral and often must react with a chiral receptor or chiral enzyme to be effective.**
- **(*S*)-ibuprofen is the active component agents in Motrin and Advil.**
- **(R)-fluoxetine is the active component in Prozac.**



(*S*)-ibuprofen
anti-inflammatory agent



(*R*)-fluoxetine
antidepressant

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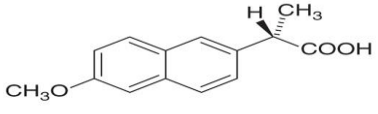
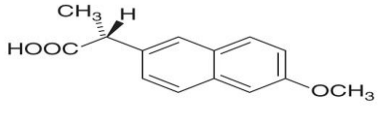
Chemical Properties of Enantiomers

- **One enantiomer of a drug may effectively treat a disease whereas its mirror image may be ineffective or toxic.**
- **Changing the orientation of the substituents on naproxen converts it from a common anti-inflammatory agent into a harmful liver toxin.**



(*S*)-naproxen
anti-inflammatory agent



(*R*)-naproxen
liver toxin

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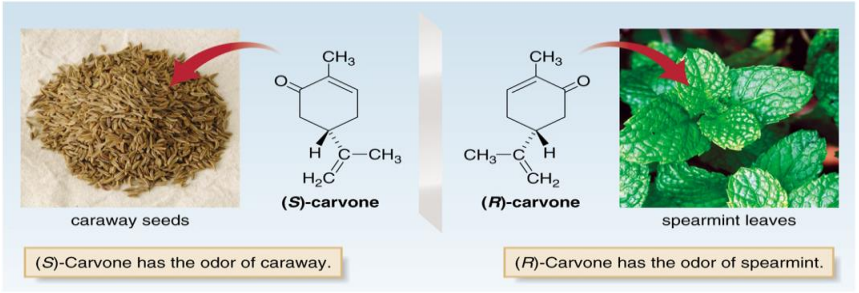
Enantiomers and the Sense of Smell

- **Research suggests that the odor of a particular molecule is determined more by its shape than by the presence of a particular functional group.**
- **Because enantiomers interact with chiral smell receptors, some enantiomers have different odors.**



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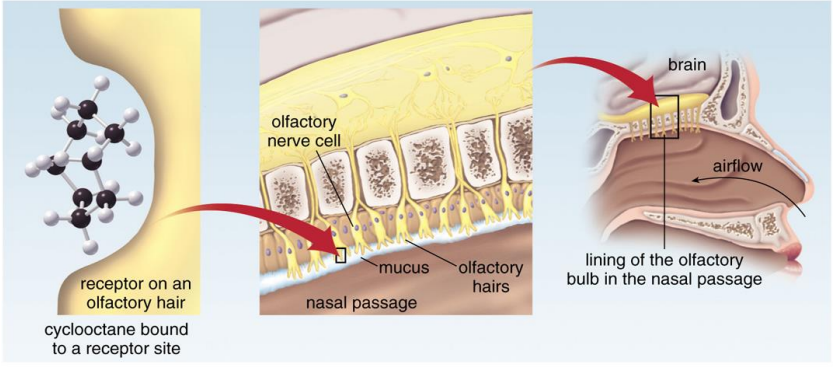
Molecular Shape and the Sense of Smell

Figure 5.13



Cyclooctane and other molecules similar in shape bind to a particular olfactory receptor on the nerve cells that lie at the top of the nasal passage. Binding results in a nerve impulse that travels to the brain, which interprets impulses from particular receptors as specific odors.

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