Chapter 6. Stereochemistry

Stereochemistry is the branch of chemistry concerned with **the three-dimensional structure of molecules**.

The difference in shape between “left-handed” and “right-handed” molecules can have significant biological consequences, particularly in medicine.

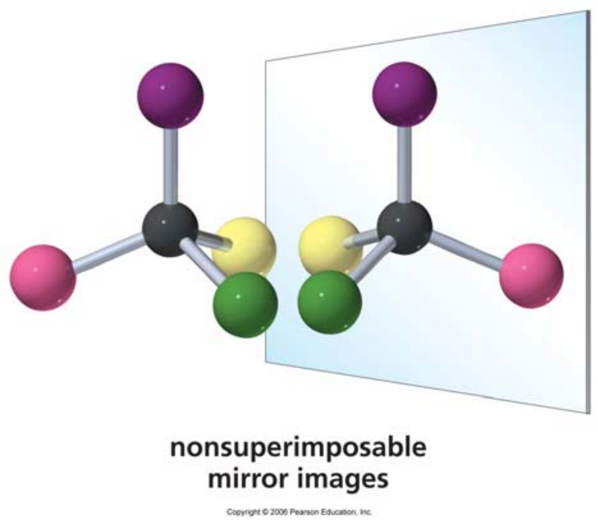
6.1 Stereochemistry and the Tetrahedral Carbon

Right and left hands are **mirror images** of each other. This **handedness**, or **chirality**, has profound implications.

Many biologically important molecules provide a **chiral environment** that will **selectively recognize a molecule of one handedness, but not its mirror image**.

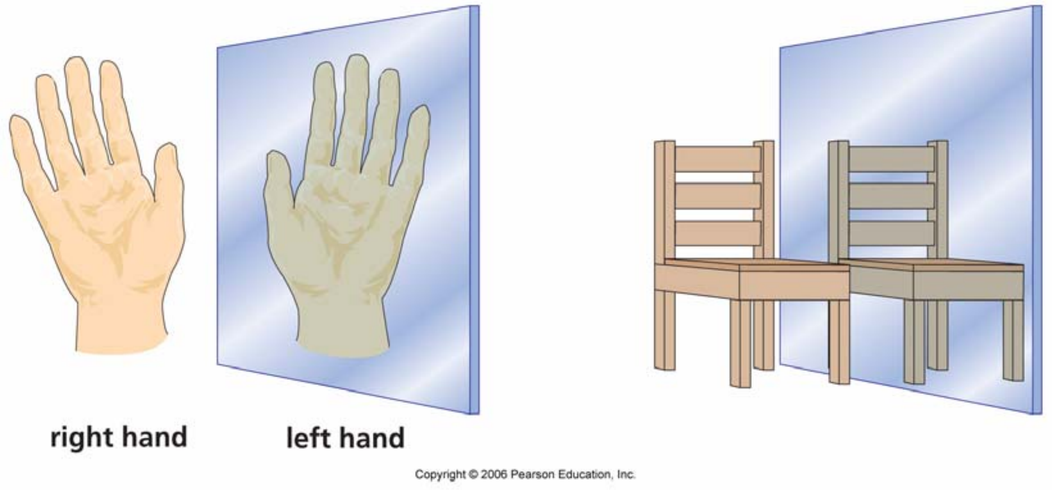
What makes the molecules chiral?

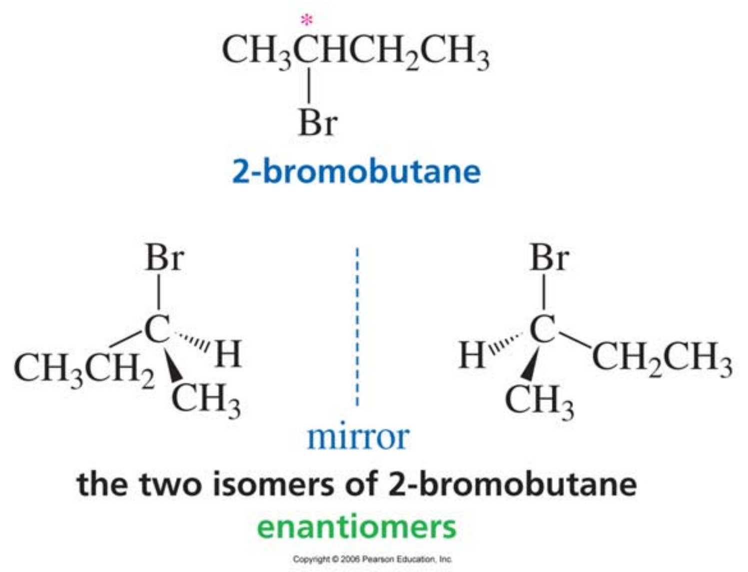
Tetrahedral carbon



A molecule containing **a carbon with four different substituents** is not identical to its mirror image. The molecule can not be superimposed on its mirror image.

A molecule that is not identical to its mirror image is a kind of stereoisomer called **enantiomer** (in Greek “opposite”).





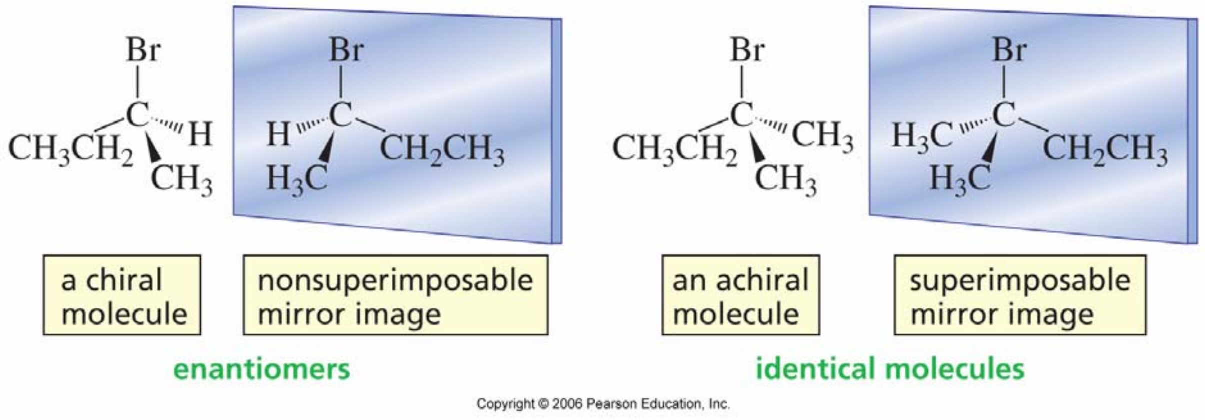
6.2 Finding Handedness in Molecules

Stereocenter (chirality center): a carbon atom bonded to four different groups

Note that CH_2, CH_3, C=C, and C=O carbons can not be stereocenters because they have at least two identical bonds.

A plane of symmetry is a plane that cuts through the middle of a molecule or other object so that one half of the object is a mirror image of the other half.

A molecule that has a plane of symmetry in any of its possible conformations must be identical to its mirror image and hence must be **nonchiral**, or **achiral**.



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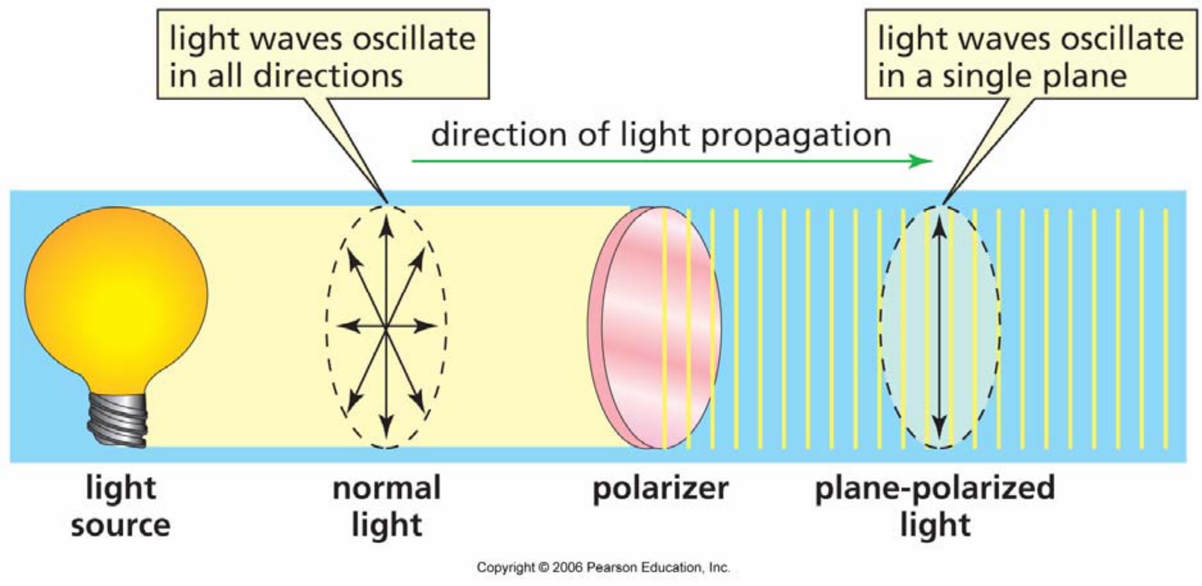
6.3 Optical Activity

Jean Baptiste Biot studied stereochemistry in the nature of ***plane-polarized light***.

A beam of ordinary light consists of electromagnetic waves that oscillate in an infinite number of planes at right angles to the direction of light travel.

When a beam of ordinary light passes through a device called **a polarizer**, only the light waves oscillating in a single plane pass through and the light is said to be **plane-polarized**.



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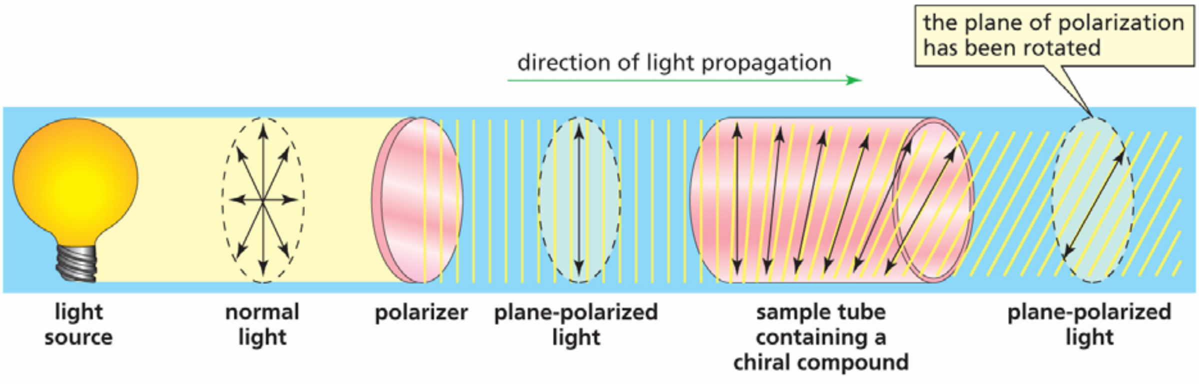
When a beam of plane-polarized light passes through a solution of chiral molecules, the plane of polarization is rotated. The molecules are said to be **optically active**.



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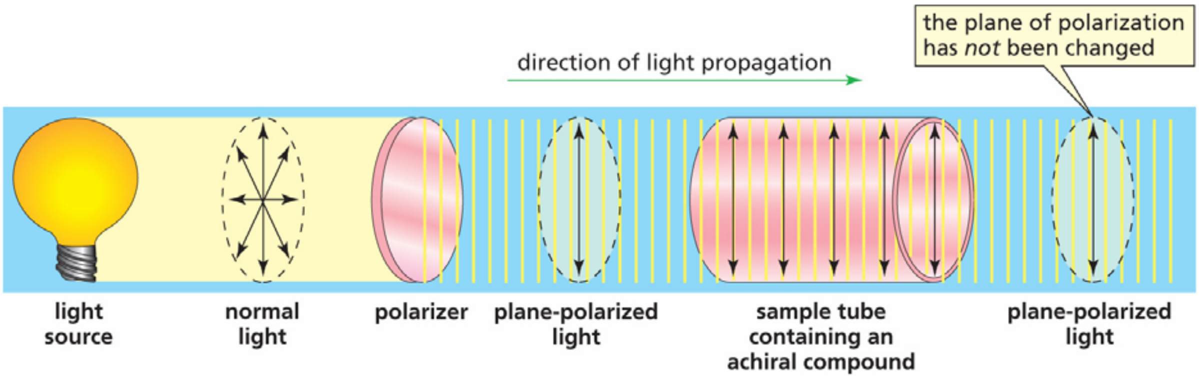

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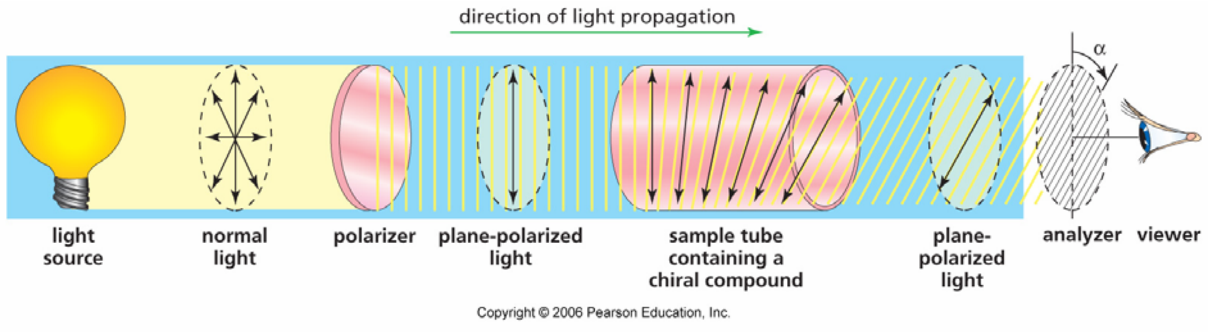
The amount of rotation can be measured with an instrument called **a polarimeter**, and is denoted by α in degree.

The direction of rotation – from the vantage point of the observer

Levorotatory (–): rotate plane-polarized light to the left (counterclockwise).

Dextrorotatory(+): rotate plane-polarized light to the right (clockwise).



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6.4 Specific Rotation

The degree of rotation in a polarimeter depends on **the structure** of sample molecules, and on **the number (concentration** and **sample path length)** of molecules encountered by the light beam.

Specific rotation ($[\alpha]_D$): the observed rotation when light of 589.6 nanometer wavelength (sodium D line) is used with a sample path length (*l*) of 1 decimeter and a sample concentration (*c*) of 1 g/mL.

$$[\alpha]^{T}_{\lambda} = \frac{\alpha}{l \times c}$$

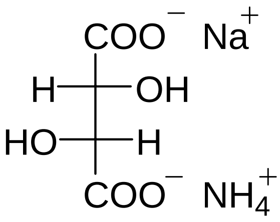
α: observed rotation (degree)
l: path length (dm)
c: concentration (g/mL)

The specific rotation is a physical constant characteristic of a given optically active compound.

6.5 Pasteur’s Discovery of Enantiomers

1848, Louis Pasteur studied crystalline tartaric acid salts derived from wine, and found and separated two distinct kinds of crystals which were mirror images.

The original sample (a 50:50 mixture of right and left) was optically inactive but solutions of crystals from each of the separated one were optically active. **Their specific rotations were equal in amount but opposite in sign**.



Racemic mixture (racemate): the symbol **(±)** indicates that racemate contains equal amounts of dextrorotatory and levorotatory enantiomers. Racemate shows **no optical activity** because (+) rotation from one enantiomer exactly cancers (–) rotation from the other.

Enantiomers (optical isomers) have identical physical properties but differ in the direction in which their solutions rotate plane-polarized light.

6.6 Sequence Rules for Specifying Configuration

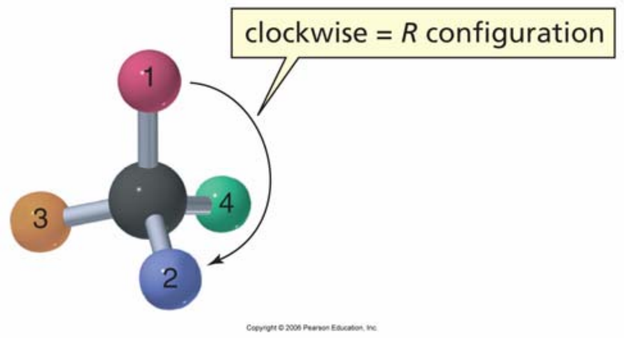
The method for specifying the three dimensional structure employs the sequence rule.

Sequence rule

Rule 1. Look at the four atoms directly attached to the stereocenter, and assign priorities in order of decreasing atomic number.

Rule 2. If a decision can not be reached, look at the second, third, or fourth atoms outward until the first difference is found.

Rule 3. Multiple-bonded atoms are equivalent to the same number of single-bonded atoms.



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The stereochemical configuration around the carbon

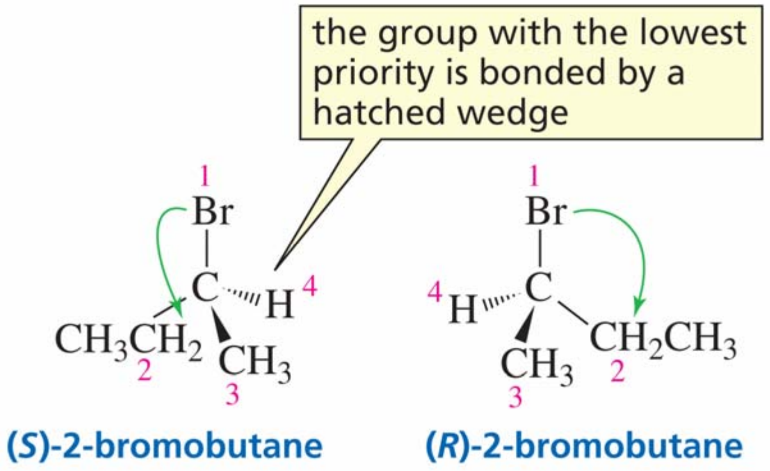
1. Place the molecule so that the group of lowest priority is pointing directly back, away from you.

2. Look at the three remaining substituents.

If a curved arrow drawn from the highest- to second-highest- to third-highest-priority substituent (1-2-3) is **clockwise**, then the stereocenter has an ***R* configuration** (Latin *rectus*, meaning right).

If an arrow from 1-2-3 is **counterclockwise**, the stereocenter has an ***S* configuration** (Latin *sinister*, meaning left).

The sign of optical rotation, (+) or (–), is not related to the *R*, *S* designation.



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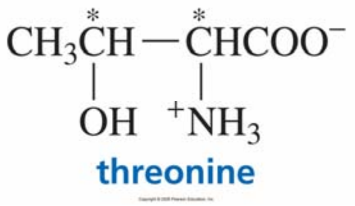
6.7 Enantiomers and Diastereomers

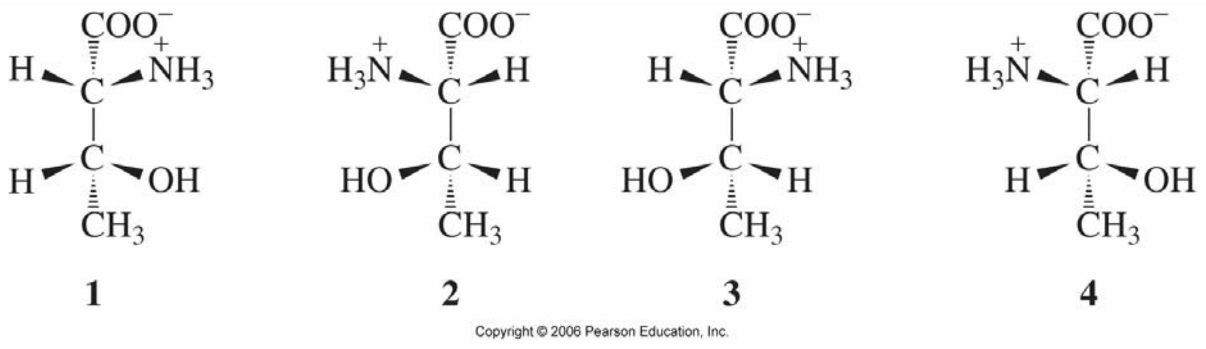


$$\mathrm{CH_3\underset{OH}{\overset{*}{C}H}-\underset{{}^+NH_3}{\overset{*}{C}H}COO^-}$$

threonine

Diastereomers: stereoisomers that are not mirror images.

Diastereomers have opposite configurations at some stereocenters but the same configuration at others.



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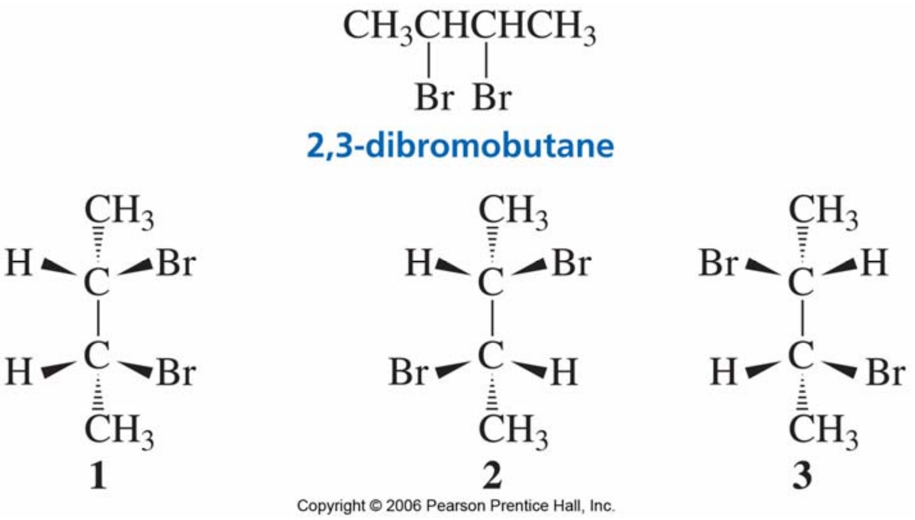
(2*R*, 3*R*) **(2*S*, 3*S*)** **(2*R*, 3*S*)** **(2*S*, 3*R*)**

Natural form

6.8 Meso Compounds

Meso compounds: compounds that are achiral, yet contain stereocenters.



$$\mathrm{CH_3\underset{Br}{C}H\underset{Br}{C}HCH_3}$$

2,3-dibromobutane

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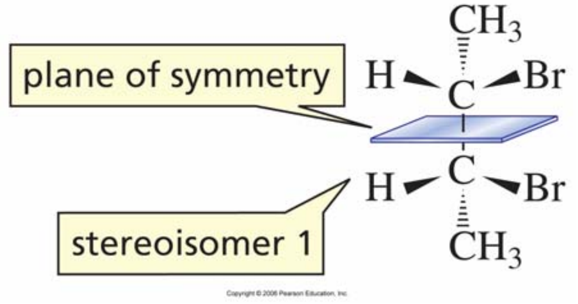
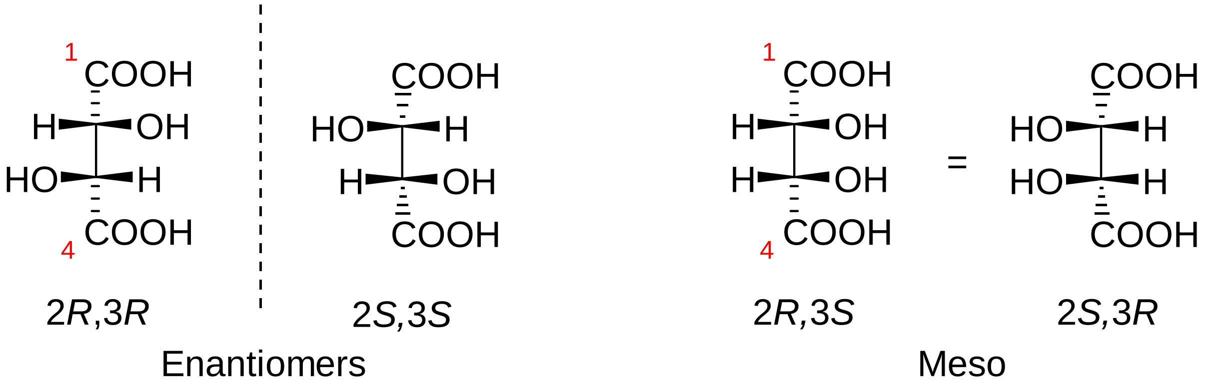
(2S, 3R), (2R, 3S) **(2S, 3S)** **(2R, 3R)**

The (2S, 3R) and (2R, 3S) structures are identical because the molecule has a plane of symmetry and is therefore achiral, even though it has two stereocenters.



Tartaric acid



Some Properties of the Stereoisomers of Tartaric Acid

Stereoisomer	M.P. (°C)	$[\alpha]_D$ (°)	Density (g/cm^3)	Solubility at 20 °C (g/100mL H_2O)
(+)	167-170	+12	1.7598	139.0
(–)	167-170	–12	1.7598	139.0
Meso	146-148	0	1.6660	125.0
(±)	206	0	1.7880	20.6

The (+) and (–) enantiomers have identical melting points, solubilities, and densities. They differ only in the sign of their rotation of plane-polarized light.

The diastereoisomeric meso compound is a different compound and has different physical properties.

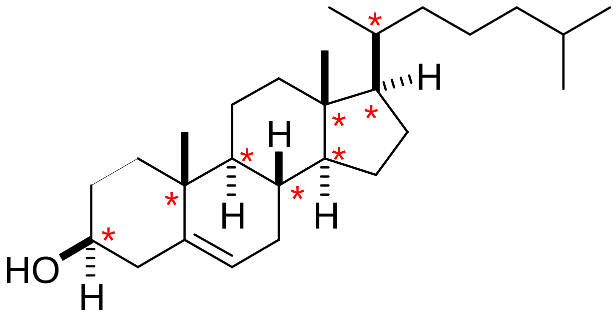
The racemates, although mixtures of enantiomers, act as though they were pure compounds, different from either enantiomer or from the meso form.

6.9 Molecules with More Than Two Stereocenters

One stereocenter gives rise to two stereoisomers.

A molecule with n stereocenters has a maximum of 2^n stereoisomers.

Cholesterol has eight stereocenters, and 256 stereoisomers are possible in principle. Only one, however, is produced in nature.

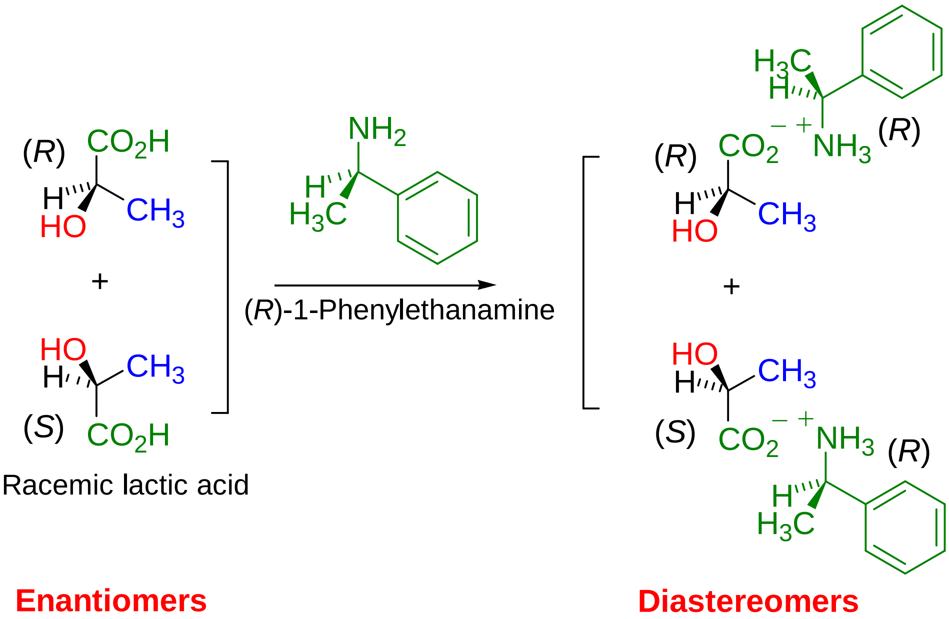


6.10 The Chiral Environment

Enantiomers have identical physical properties, but **diastereomers** behave as completely different molecules.

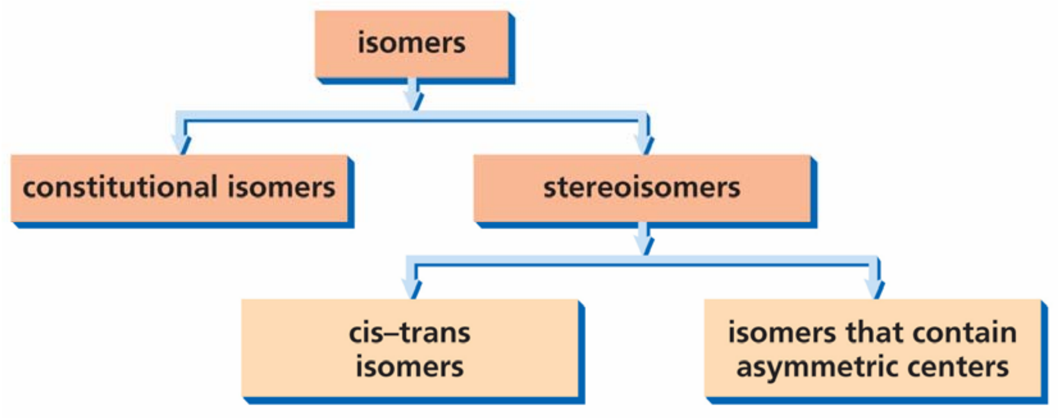
Enantiomers exhibit very different properties in the presence of another source of chirality (a chiral environment) – the different actions of the enantiomers of thalidomide are a result of the chiral environment inside a living cell.

The resolution of racemic mixtures of carboxylic acids by generating a chiral environment – **using a single enantiomer of an amine to yield diastereomeric ammonium salts**.



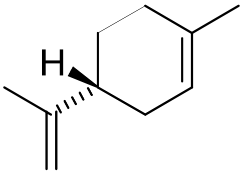
The two resulting salts are diastereomers and have different chemical and physical properties. It is possible to separate them. Once separated, acidification of the two diastereomeric salts with HCl then allows to isolate the two pure enantiomers of lactic acid and to recover the chiral amine.

6.11 A Brief Review of Isomerism

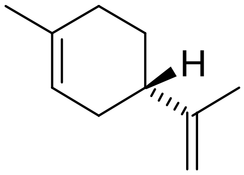


6.12 Chirality in Nature

Different stereoisomeric forms of a chiral molecule have different biological properties.

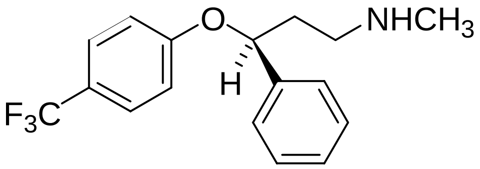


(+)-Limonene
(in orange)



(–)-Limonene
(in lemons)

Fluoxetine (Prozac), a commonly prescribed medication



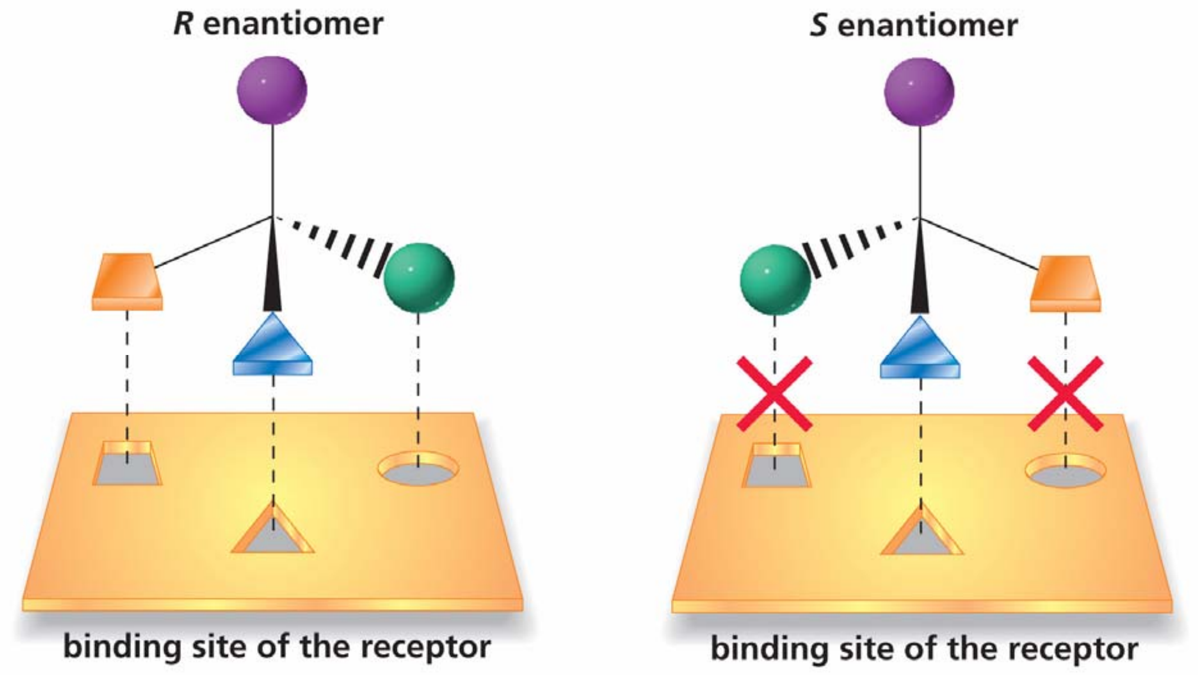
(*S*)-Fluoxetine

Racemic fluoxetine is an effective antidepressant, but it has no activity against migraine.

The pure S enantiomer works well in preventing migraine.

Why do different stereoisomers have different biological properties?

A chiral molecule must fit into a chiral receptor at a target site for biological actions. A particular stereoisomer can fit only into a receptor having the proper complementary shape.



A reaction which generates an asymmetric center