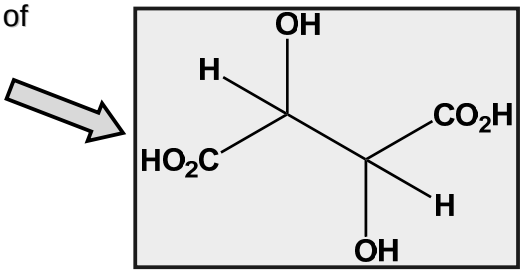
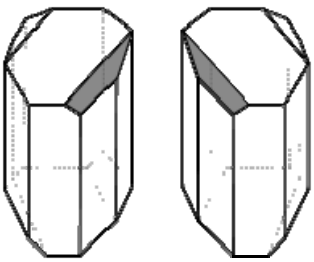
Stereoisomerism and Chirality

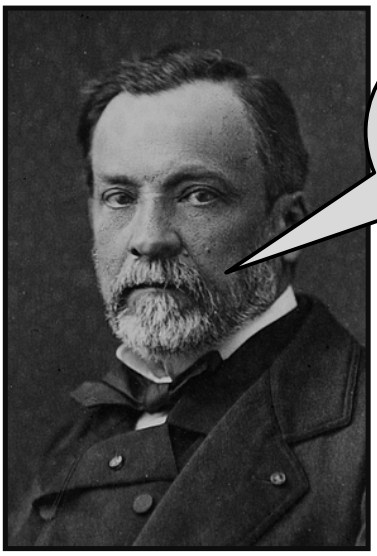
Chapter 3

Jean Baptiste Biot,1832 observed rotation of tartaric acid.

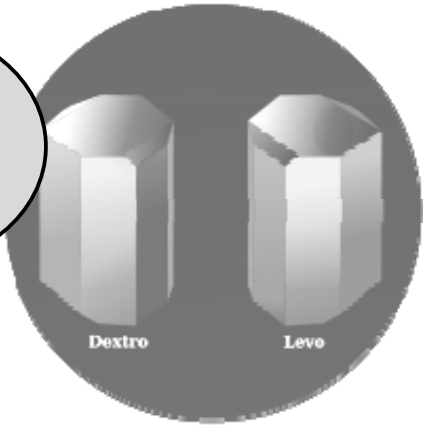


Louis Pasteur continued this research in 1847 by investigating the shapes of ammonium sodium tartrate crystals, which he found to be chiral. By manually sorting the differently shaped crystals under magnification, Pasteur was the first to produce a pure sample of levotartaric acid.

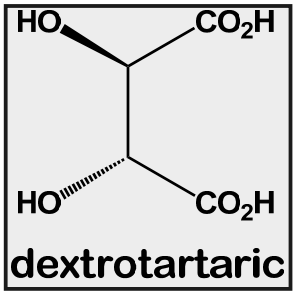




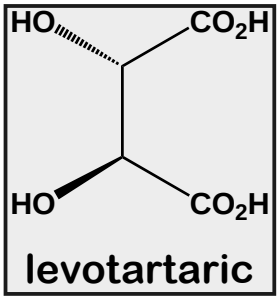
O-Chem rocks!



"In the field of observation, chance favors only the prepared mind."



dextrotartaric



levotartaric

Isomers

- Isomers: Different compounds with the same molecular formula.
- Constitutional isomers: Isomers with a different connectivity.
- Stereoisomers: Isomers with the same connectivity but a different orientation of their atoms in space.

Chirality

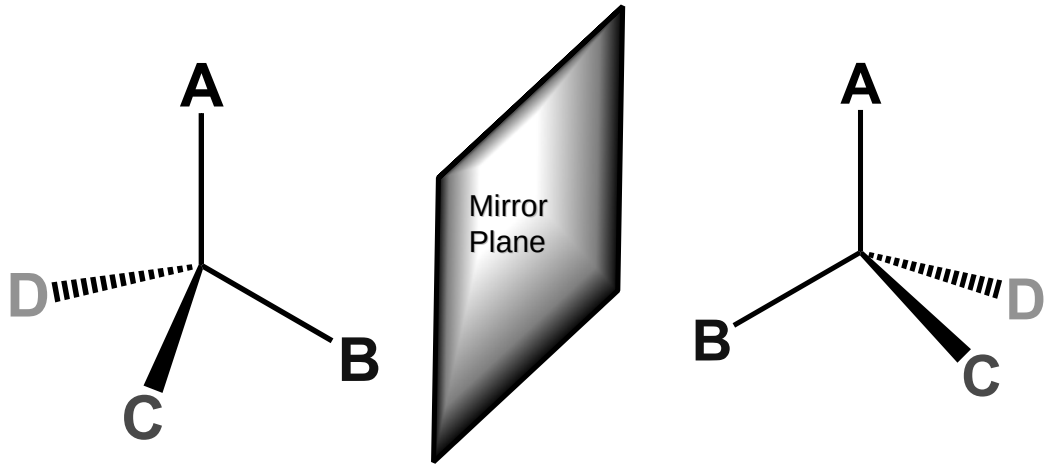
- Chiral: From the Greek, *cheir*, hand
  - an object that is not superposable on its mirror image.
- Achiral: An object that lacks chirality; one that lacks handedness.
  - An achiral object has at least one element of symmetry.

Chirality

- An achiral object has at least one element of symmetry:
- Plane of symmetry: An imaginary plane passing through an object dividing it so that one half is the mirror image of the other half.
- Center of symmetry: A point so situated that identical components of the object are located on opposite sides and equidistant from that point along any axis passing through it.

Stereocenter

- **The most common (but not the only) cause of chirality in organic molecules is a tetrahedral atom, most commonly carbon, bonded to four different groups.**
- A carbon with four different groups bonded to it is called a **chiral center.**
  - All chiral centers are stereocenters, but not all stereocenters are chiral centers.
  - **Enantiomers**: Stereoisomers that are nonsuperposable mirror images.
  - Refers to the relationship between pairs of objects.

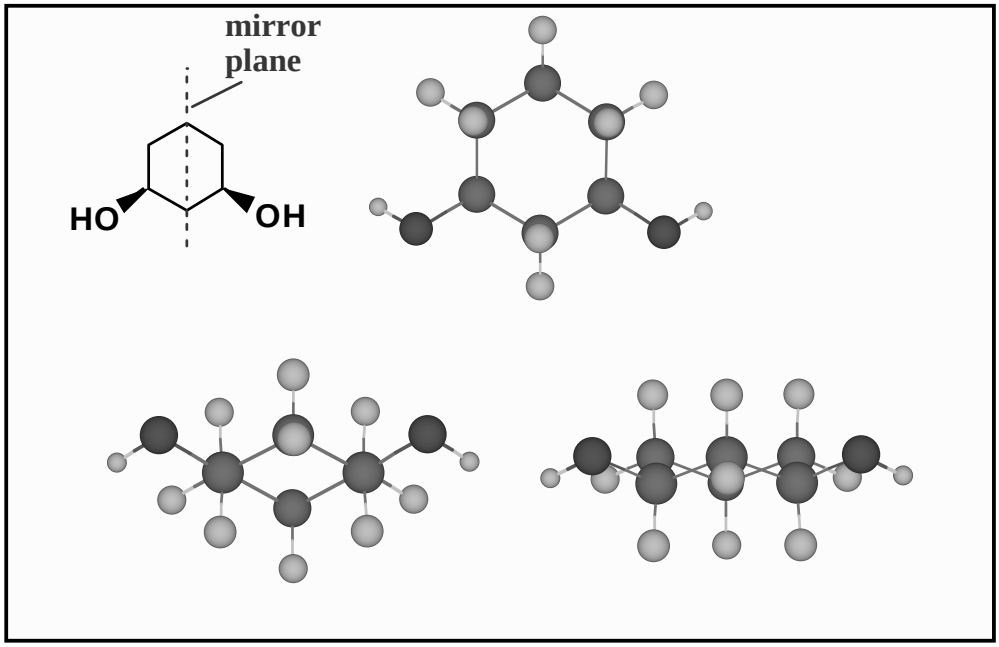


A compound with 4 different substitutents

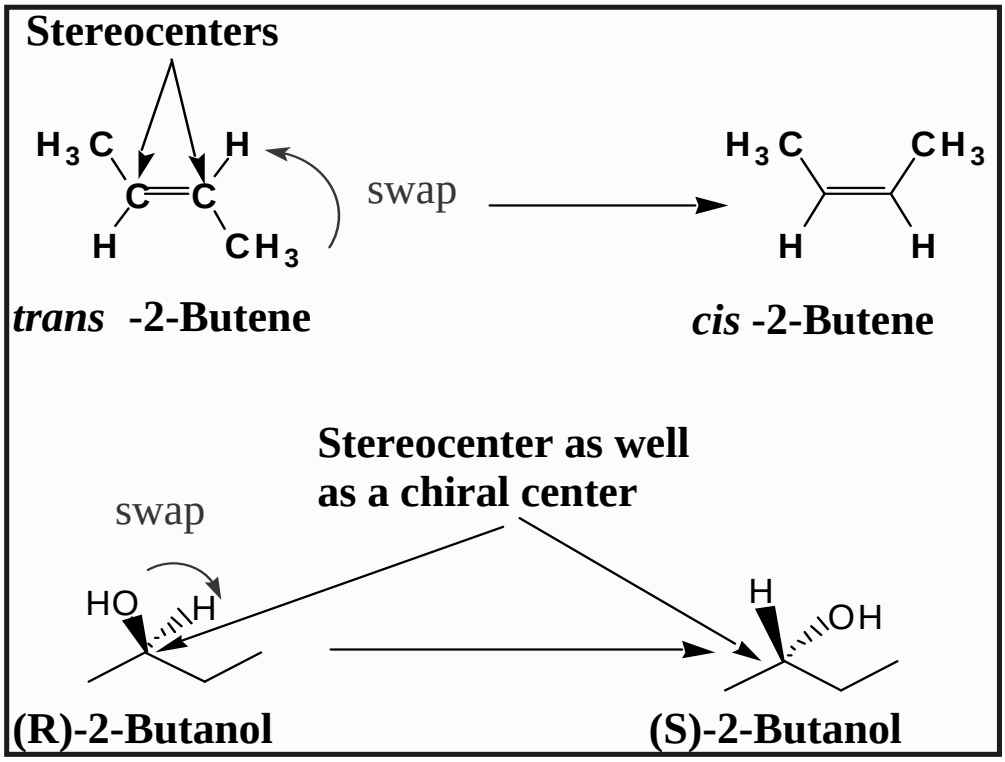
Its stereoisomer- NOT superimposable

These are called enantiomers

Elements of Symmetry

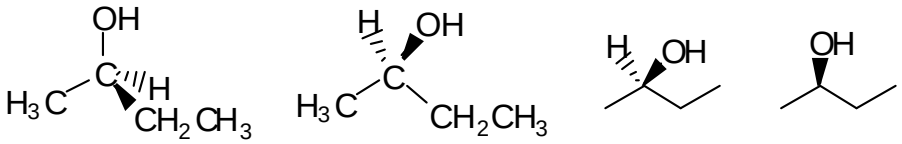


Stereocenter & Chiral Centers



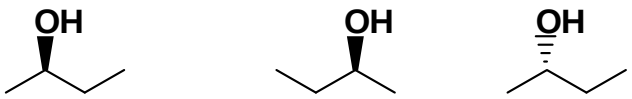
Enantiomers

- 2-Butanol
  - Has one stereocenter.
  - Here are four representations for one enantiomer.



(1) (2) (3) (4)

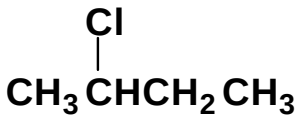
  - Here are two representations for the enantiomer of (4).

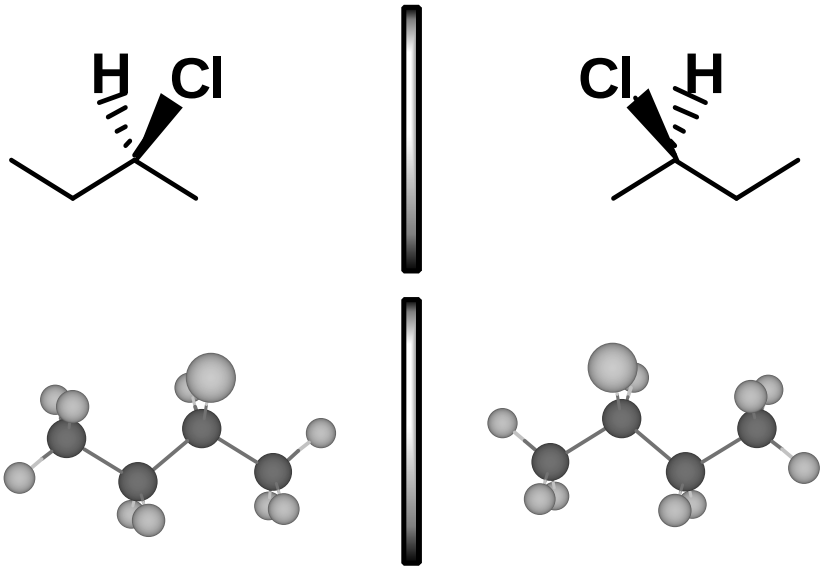


(4) **representations for the enantiomer of (4)**

Enantiomers

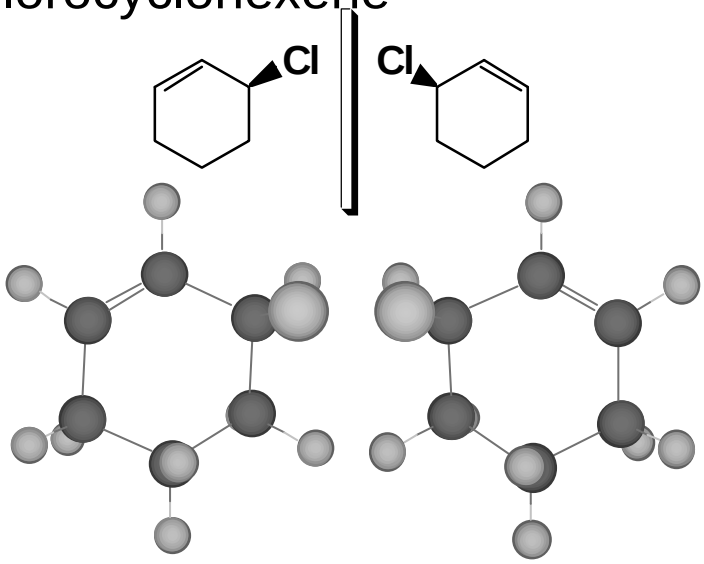
- 2-Chlorobutane





Enantiomers

- 3-Chlorocyclohexene



R & *S* Convention

- Priority rules
  1. Each atom bonded to the chiral center is assigned a priority based on atomic number; the higher the atomic number, the higher the priority.

(1)	(6)	(7)	(8)	(16)	(17)	(35)	(53)
-H	$-CH_3$	$-NH_2$	-OH	-SH	-Cl	-Br	-I

Increasing priority

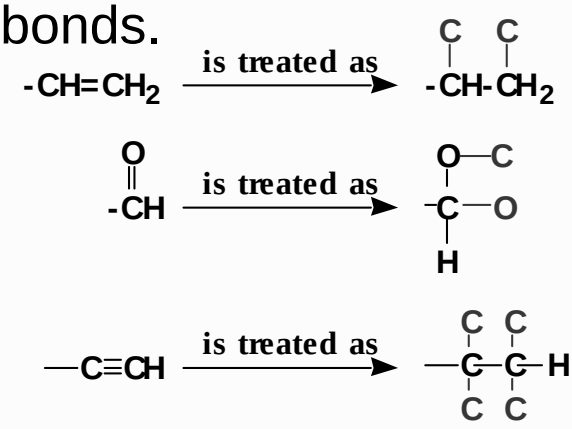
  2. If priority cannot be assigned per the atoms bonded to the chiral center, look to the next set of atoms; priority is assigned at the first point of difference.

(1)	(6)	(7)	(8)
$-CH_2-H$	$-CH_2-CH_3$	$-CH_2-NH_2$	$-CH_2-OH$

Increasing priority

R & *S* Convention

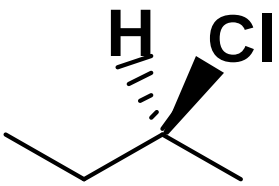
3. Atoms participating in a double or triple bond are considered to be bonded to an equivalent number of similar atoms by single bonds.

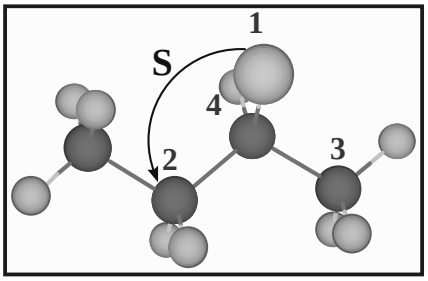


Naming Chiral Centers

1. Locate the chiral center and identify its four substituents.
2. Assign priority from 1 (highest) to 4 (lowest) to each substituent.
3. Orient the molecule so that the group of lowest priority (4) is directed away from you.

(*S*)-2-Chlorobutane

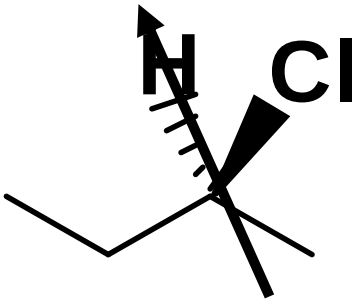


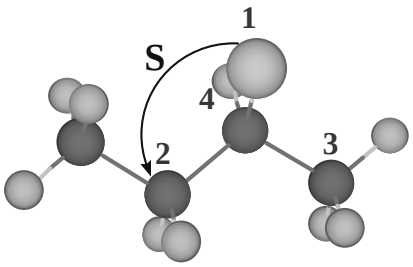


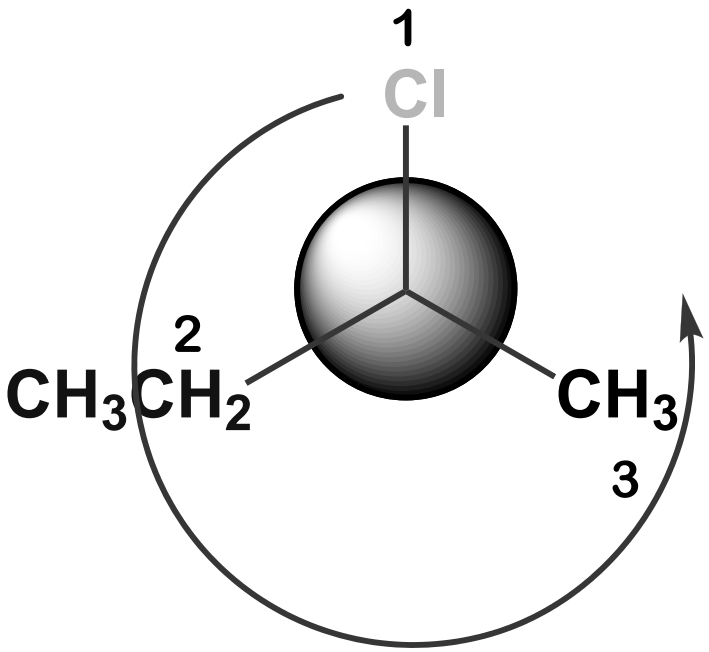
Naming Chiral Centers

4. Read the three groups projecting toward you in order from highest (1) to lowest priority (3).
5. If the groups are read clockwise, the configuration is *R;* if they are read counterclockwise, the configuration is *S*.

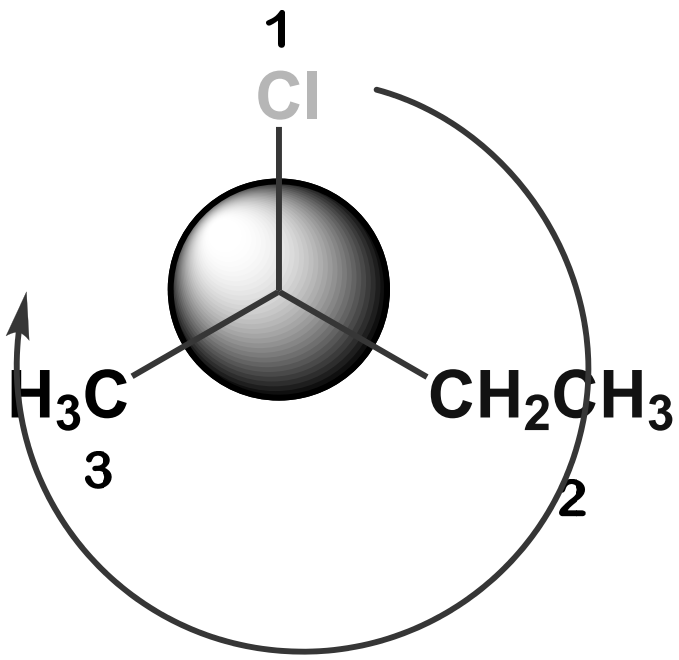
(*S*)-2-Chlorobutane







Counter clockwise movement-
i.e to the “left” is the S configuration



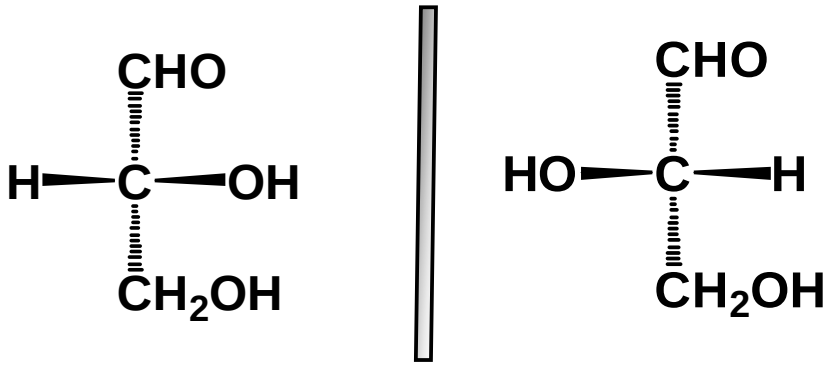
Clockwise movement-
i.e to the “right” is the R configuration

Enantiomers & Diastereomers

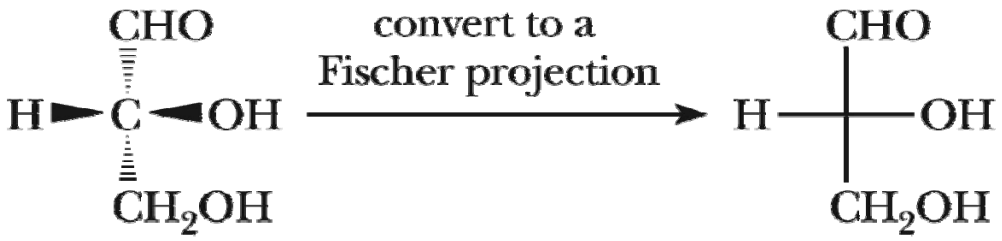
- For a molecule with 1 chiral center, $2^1 = 2$ stereoisomers are possible.
- For a molecule with 2 chiral centers, a maximum of $2^2 = 4$ stereoisomers are possible.
- **For a molecule with *n* chiral centers, a maximum of 2^n stereoisomers are possible.**

Fischer Projections

- The use of two-dimensional representations to show the configuration of molecules with multiple chiral centers are called **Fischer projections**.



Fischer Projections



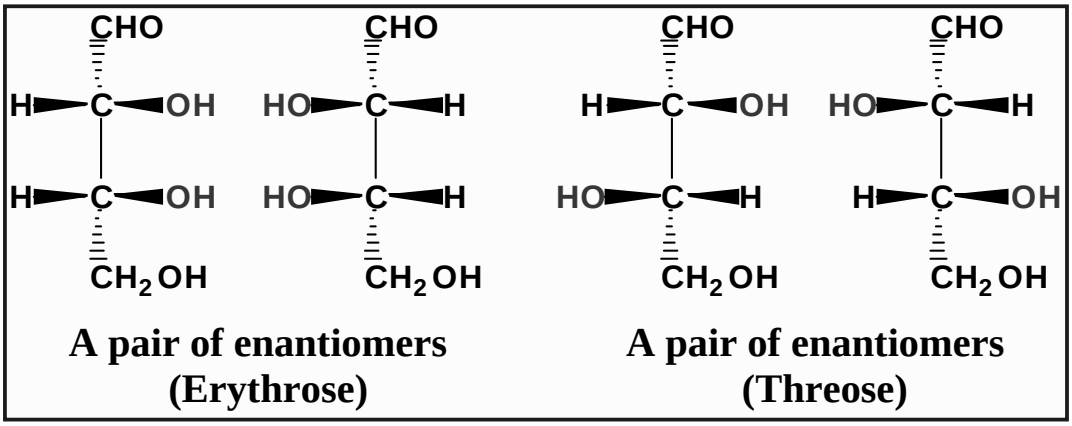
(*R*)-Glyceraldehyde (three-dimensional representation)

(*R*)-Glyceraldehyde (Fischer projection)

The horizontal segments represent bonds toward you.
The vertical segments represent bonds directed away from you.

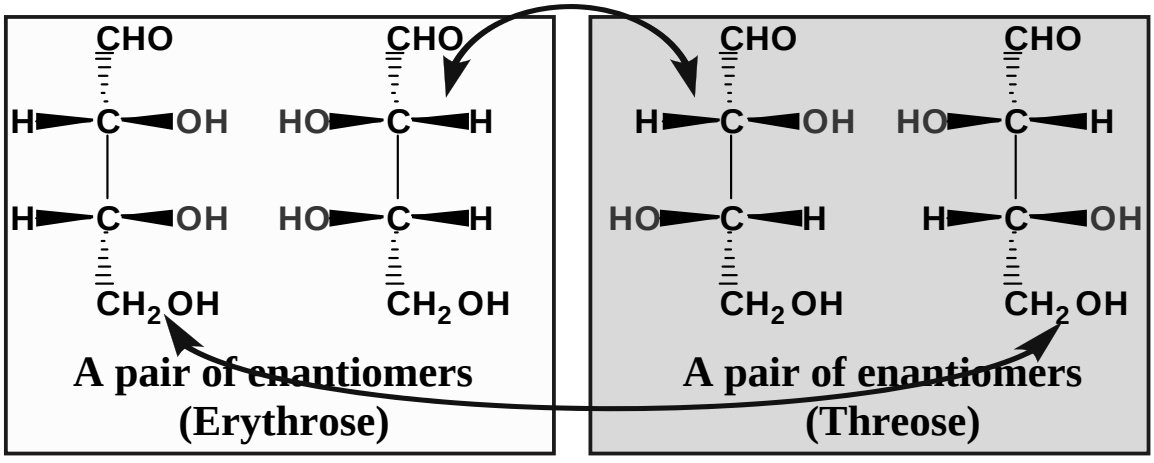
Enantiomers & Diastereomers

- 2,3,4-Trihydroxybutanal
  - two chiral centers.
  - $2^2 = 4$ stereoisomers exist; two pairs of enantiomers.



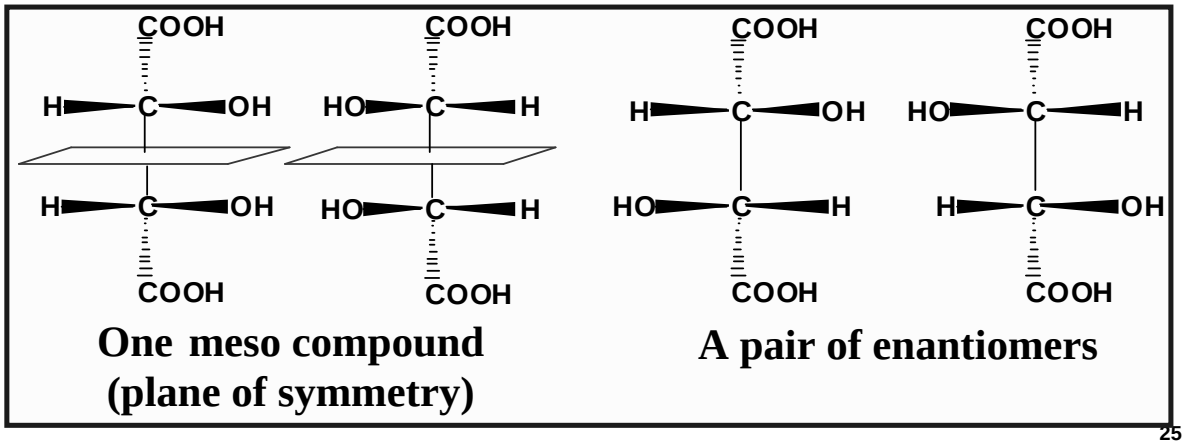
Enantiomers & Diastereomers

- Diastereomers:
  - Stereoisomers that are not mirror images.
  - Refers to the relationship among two or more objects.



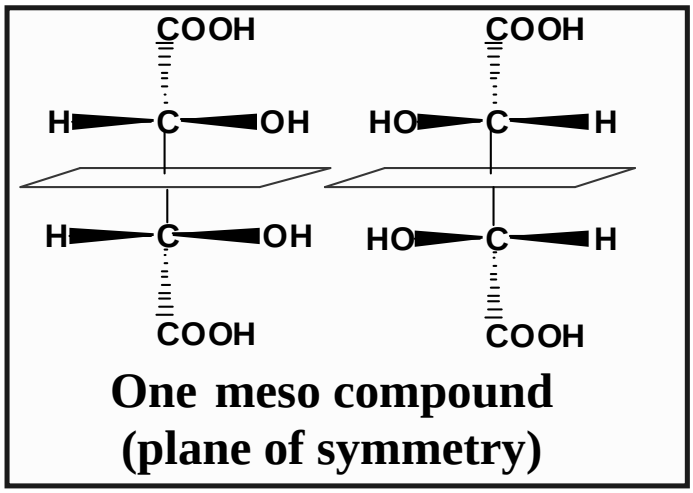
Enantiomers & Diastereomers

- Another e.g.--2,3-Dihydroxybutanedioic acid (tartaric acid)
  - two chiral centers; $2^n = 4$, **but only three stereoisomers exist**



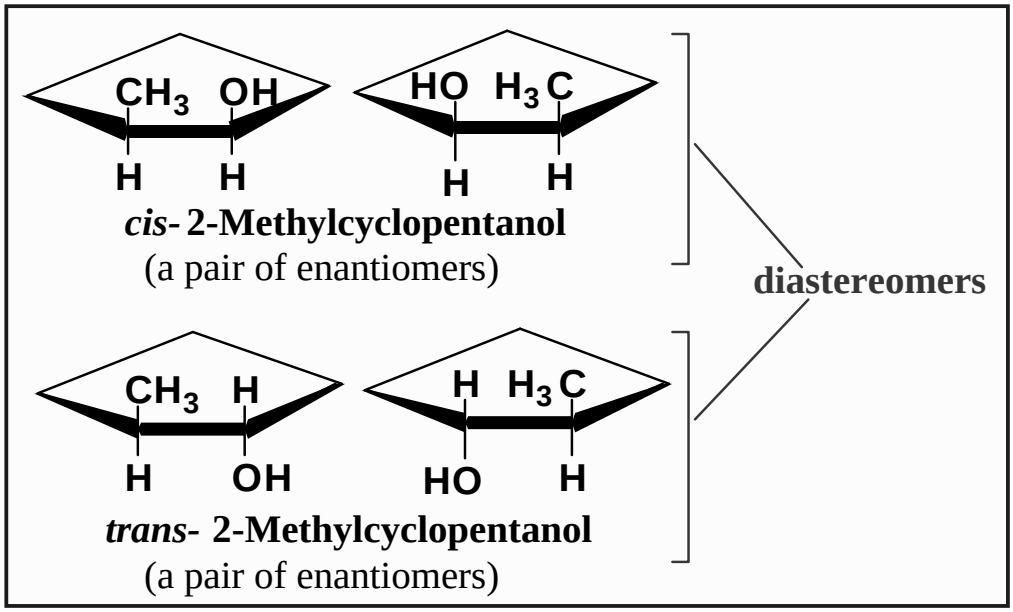
Enantiomers & Diastereomers

Meso compound: An achiral compound possessing two or more chiral centers that also has chiral isomers.

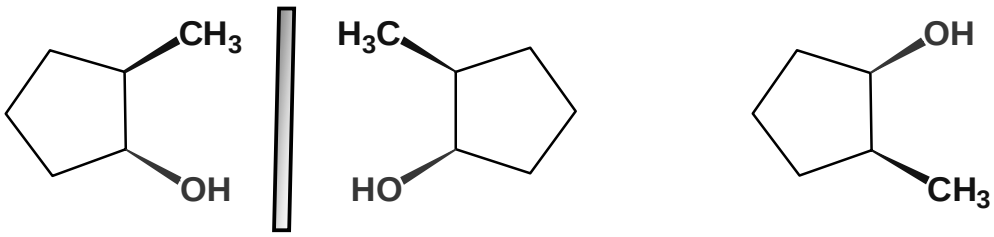


Enantiomers & Diastereomers

- 2-Methylcyclopentanol

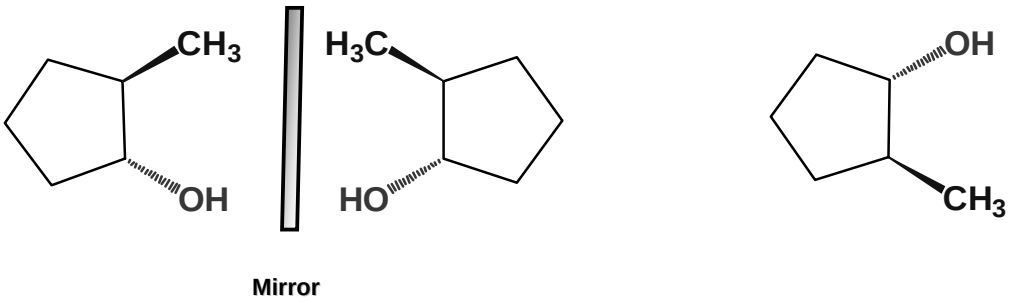


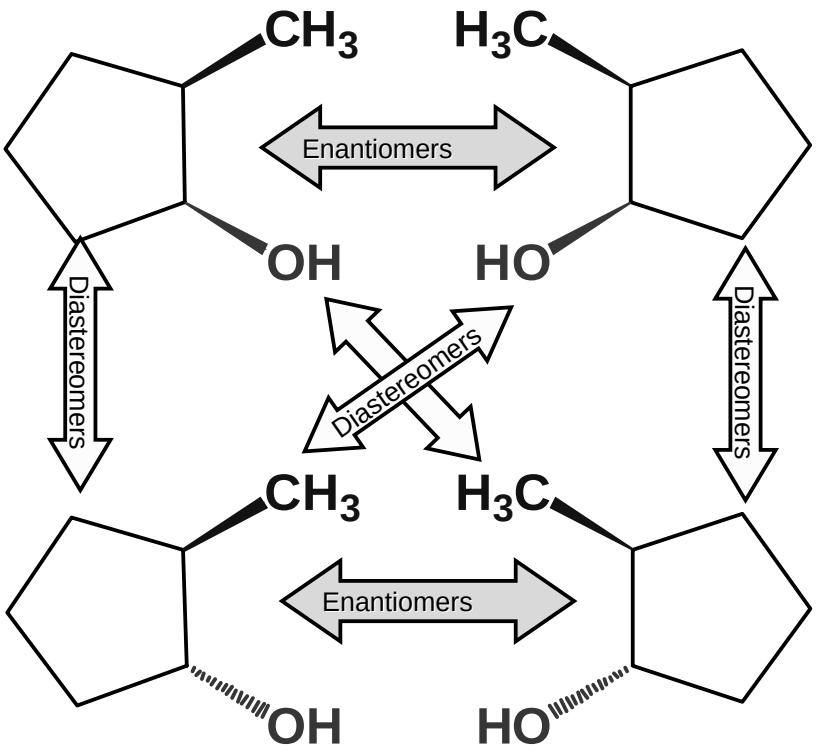
cis-2-Methylcyclopentanol



Mirror

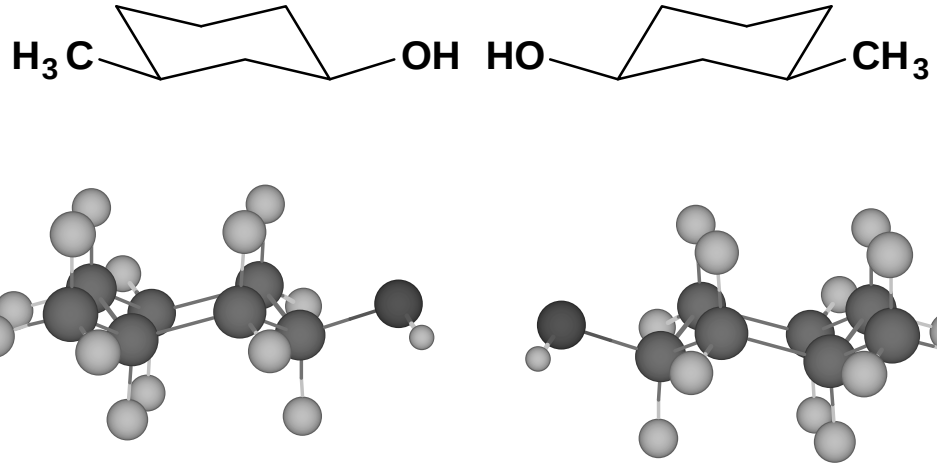
trans-2-Methylcyclopentanol





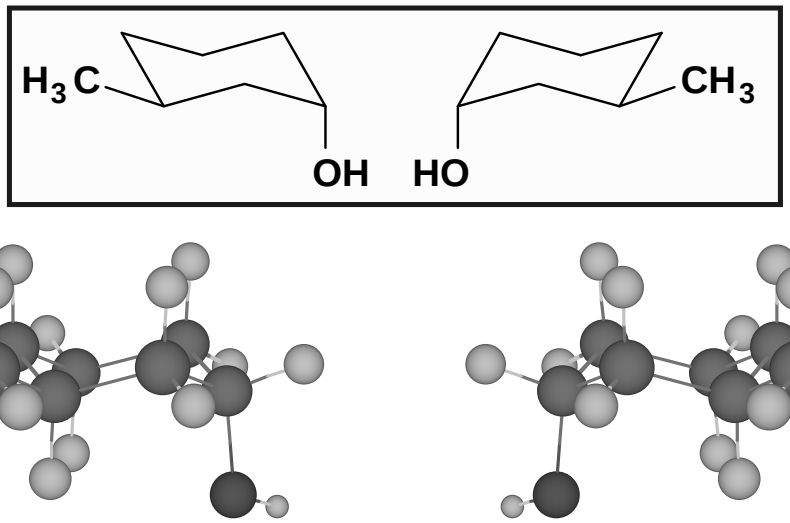
Enantiomers & Diastereomers

- *cis*-3-Methylcyclohexanol (a pair of enantiomers)

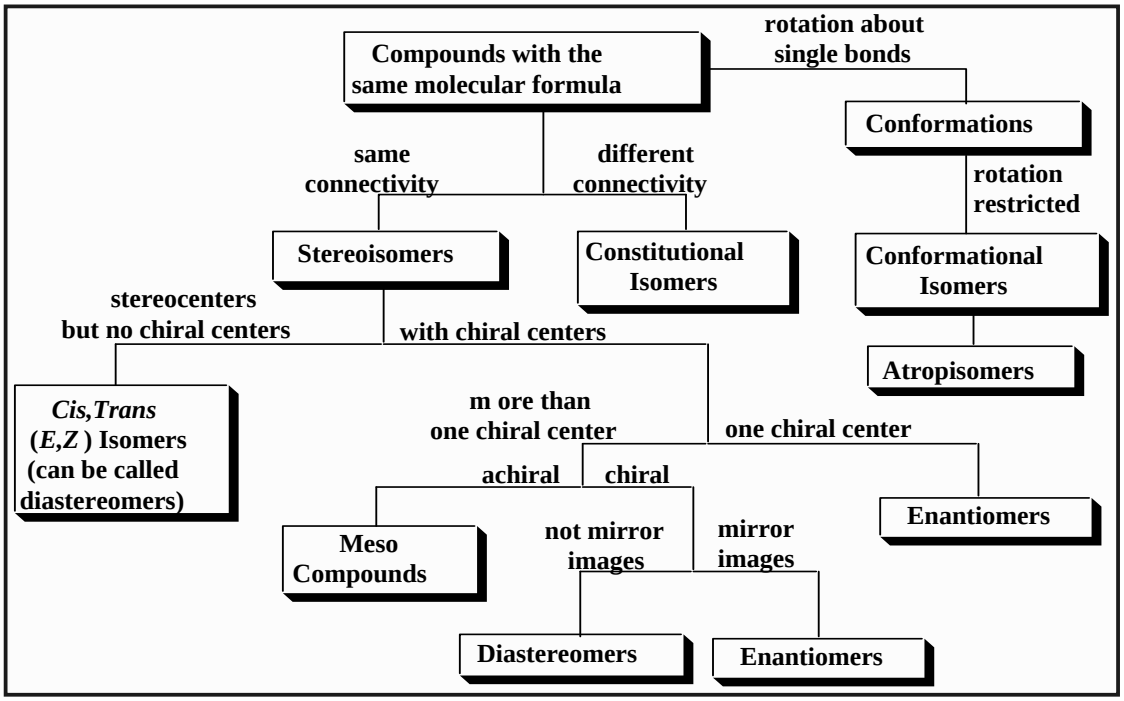


Enantiomers & Diastereomers

- *trans*-3-Methylcyclohexanol (a pair of enantiomers)

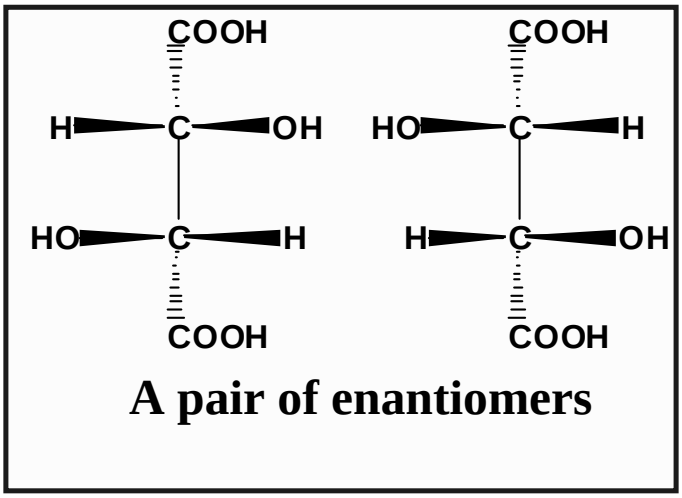


Isomers



Properties of Stereoisomers

- Enantiomers have **identical** physical and chemical properties in achiral environments.
- E.G. tartaric acid:

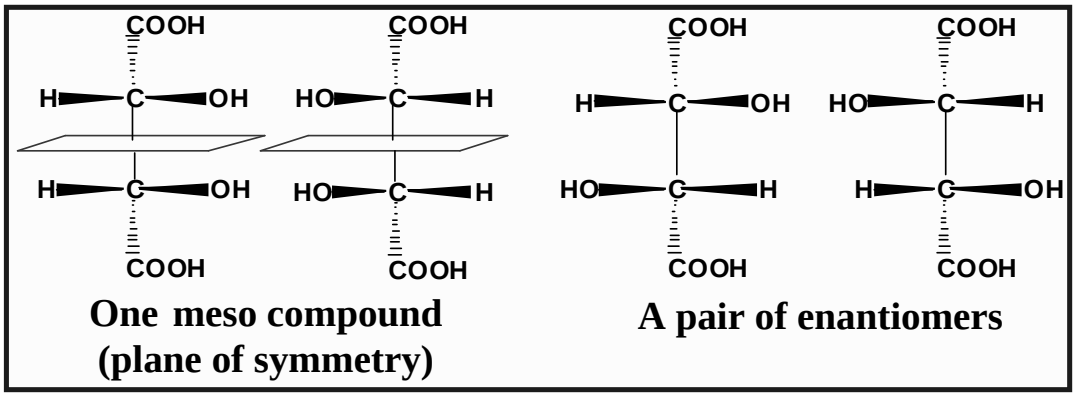


A pair of enantiomers

Properties of Stereoisomers

- **Diastereomers are different compounds** and have different physical and chemical properties.

  meso tartaric acid, for example, has different physical and chemical properties from the R,R and S,S enantiomers:

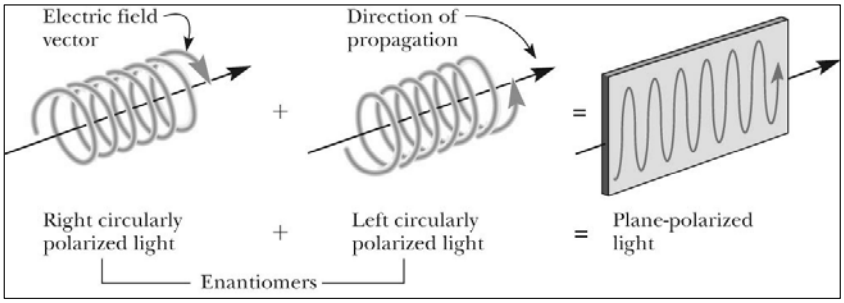


Plane-Polarized Light

- Ordinary light: Light oscillating in all planes perpendicular to its direction of propagation.
- Plane-polarized light: Light oscillating only in parallel planes.
- Optically active: Refers to a compound that rotates the plane of plane-polarized light.

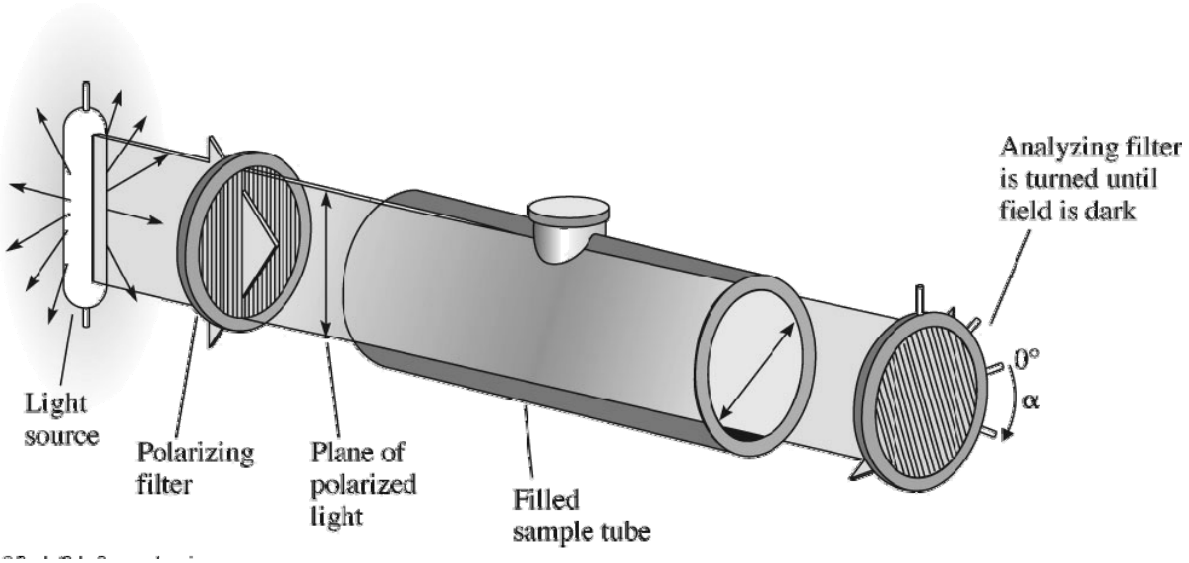
Plane-Polarized Light

- Plane-polarized light is the vector sum of left and right circularly polarized light.
- Circularly polarized light interacts one way with an *R* chiral center, and the opposite way with its enantiomer.
- **The result of interaction of plane-polarized light with a chiral compound is rotation of the plane of polarization.**



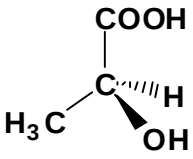
Plane-Polarized Light

- Polarimeter: A device for measuring the extent of rotation of plane-polarized light.



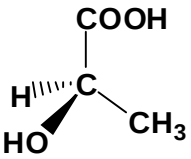
Optical Activity

- Observed rotation: The number of degrees, α, through which a compound rotates the plane of polarized light.
- **Dextrorotatory (+):** Refers to a compound that rotates the plane of polarized light to the right.
- **Levorotatory (-):** Refers to a compound that rotates the plane of polarized light to the left.



(*S*)-(+)-Lactic acid

$[\alpha]_D^{21} = +2.6°$

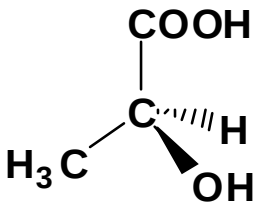


(*R*)-(-)-Lactic acid

$[\alpha]_D^{21} = -2.6°$

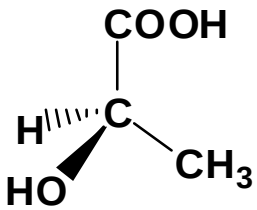
Optical Activity

- **Specific rotation:** Observed rotation for a sample in a tube **1.0 dm in length and at a concentration of 1.0 g/mL;** for a pure liquid, concentration is expressed in g/mL (density).



(*S*)-(+)-Lactic acid

$[\alpha]_D^{21} = +2.6°$



(*R*)-(-)-Lactic acid

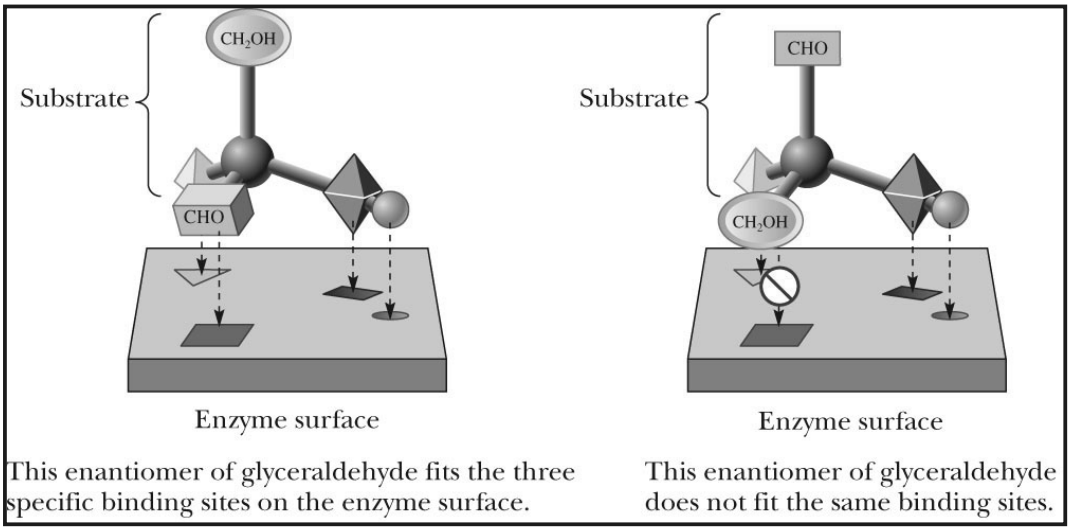
$[\alpha]_D^{21} = -2.6°$

Chirality in the Biological World

- Enzymes are like hands in a handshake.
  - The **substrate fits into a binding site** on the enzyme surface.
  - A left-handed molecule, like hands in gloves, will only fit into a left-handed binding site and
  - a right-handed molecule will only fit into a right-handed binding site.
  - Because of the differences in their interactions with other chiral molecules in living systems, **enantiomers have different physiological properties.**

Chirality in the Biological World

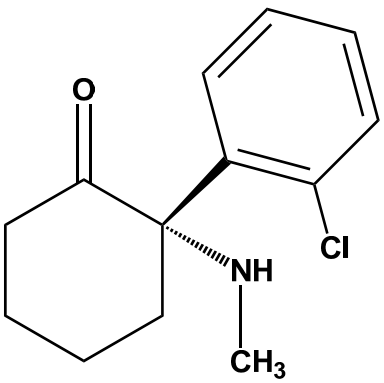
- A schematic diagram of an enzyme surface capable of binding with (*R*)-glyceraldehyde but not with (*S*)-glyceraldehyde.



Resolution

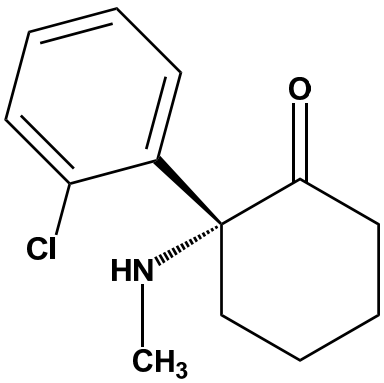
- Racemic mixture: An equimolar mixture of two enantiomers.
  - because a racemic mixture contains equal numbers of dextrorotatory and levorotatory molecules, **its specific rotation is zero.**
- Resolution: The separation of a racemic mixture into its enantiomers.

Chirality in Medicinal Chemistry



(S)-ketamine

Dissociative anesthesia
4X affinity for PCP site
More potent analgesic
Does not lower BP
Or respiration



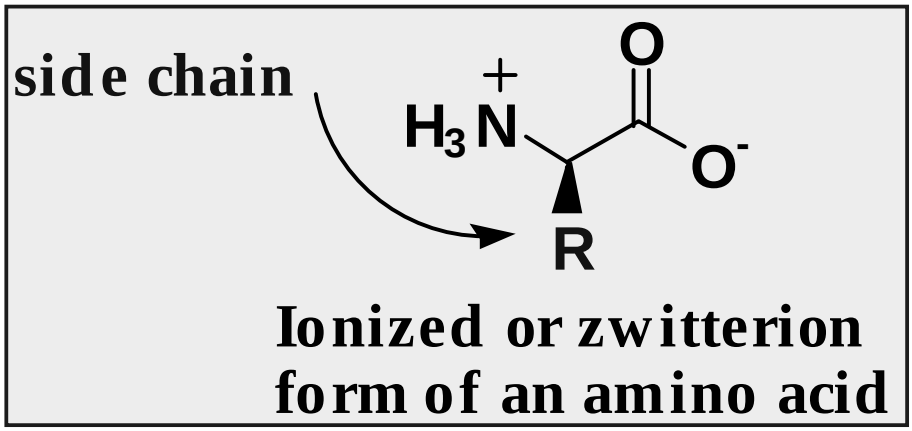
(R)-ketamine

hallucinogen
Dissociative anesthesia
analgesic

Amino Acids

– the 20 most common amino acids have a central carbon, called an α-carbon, bonded to an NH_2 group and a COOH group.

– in 19 of the 20, the α-carbon is a chiral center.



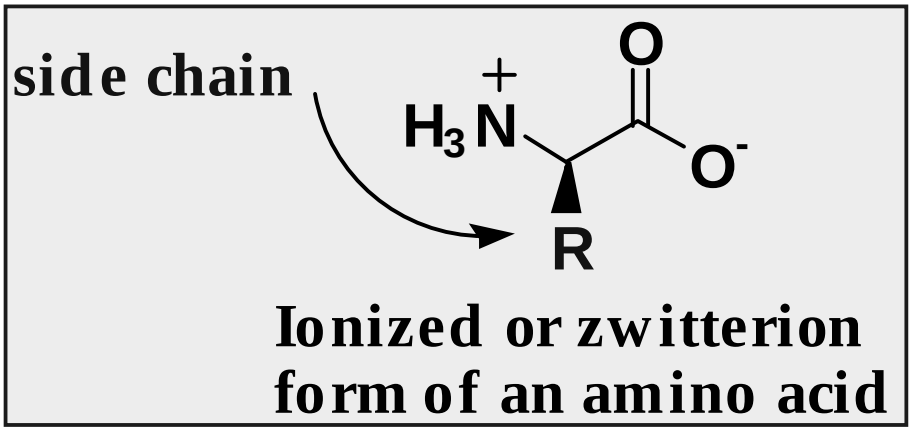
Ionized or zwitterion form of an amino acid

Amino Acids

18 of the 19 α-carbons have the *R* configuration, one has the *S* configuration.

– at neutral pH, an amino acid exists as an internal salt.

– in this structural formula, the symbol R = a side chain.



Ionized or zwitterion form of an amino acid