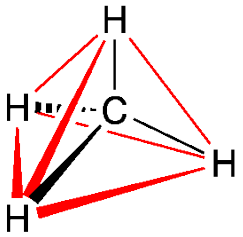
Stereochemistry

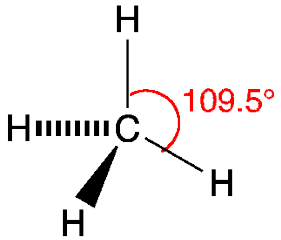
A study of the three-dimensional (3D) structure of molecules.

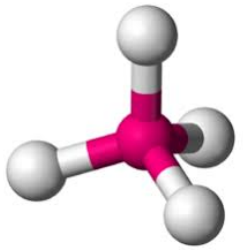
J. H. van't Hoff

J. A. Le Bel

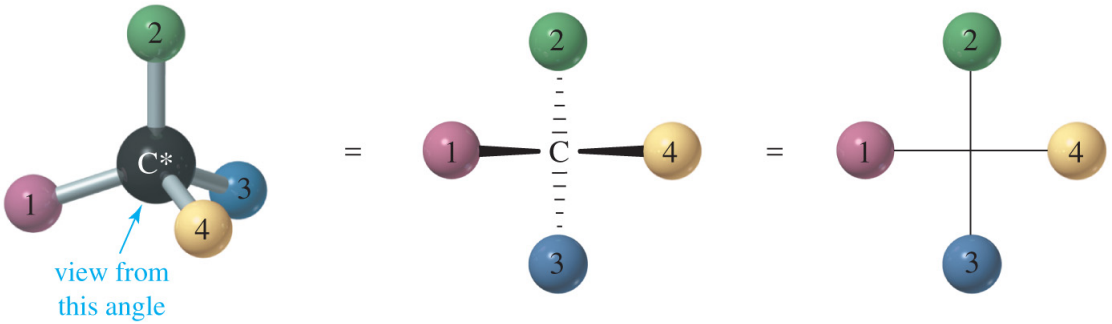
First predicting the structure of tetrahedral carbon atom in 1874. The Nobel Prize in Chemistry 1901. (Founders of stereochemistry)



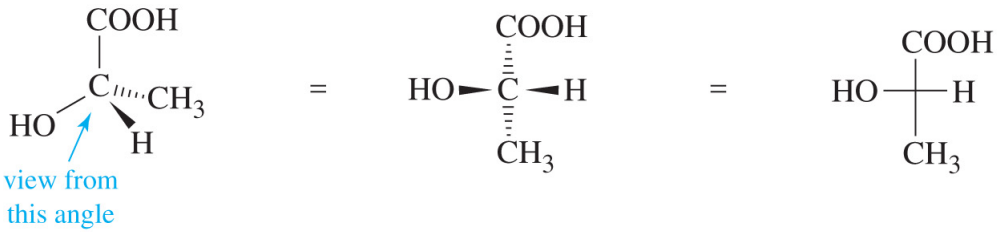




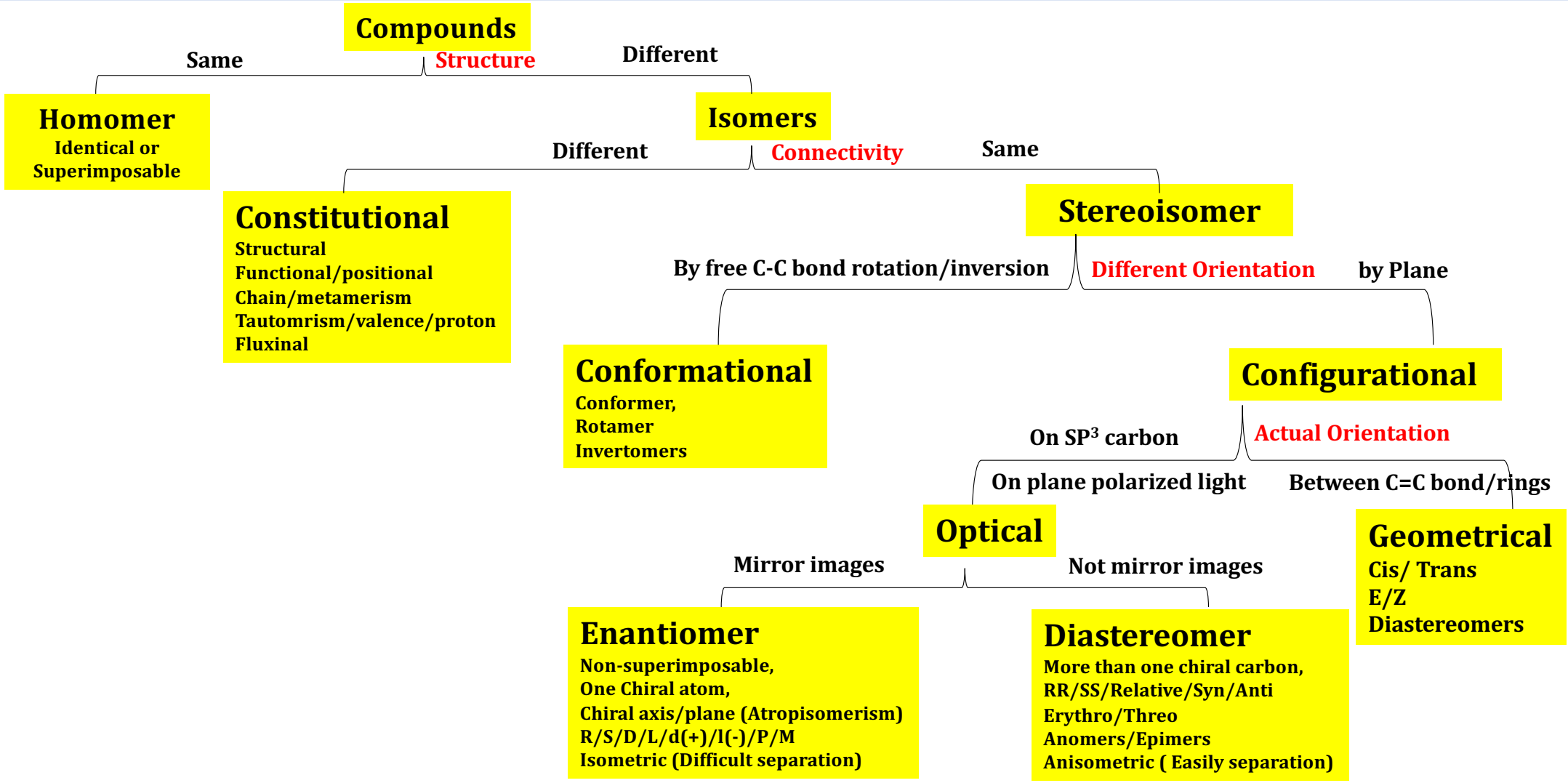
3D View



The study of spatial/actual arrangements of groups in 3D.

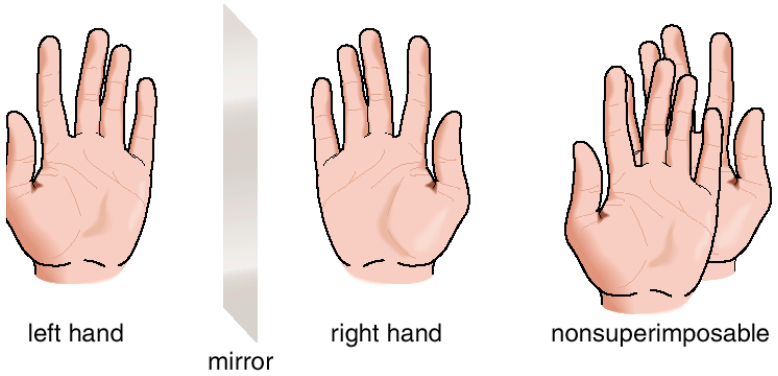


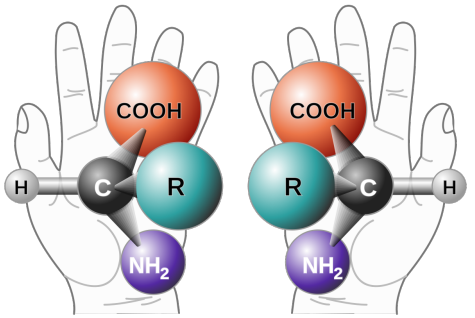
Classification of organic compounds



Concept of Chirality

A molecule/ion/object that is not-superimposable on its mirror image is said to be chiral.





Pair of Enantiomers (R/S)

The property was first observed by Jean-Baptiste Biot in 1815

- ✓ **Chirality** is a geometric property which influences and affects all parts of chiral molecules.
- ✓ Chirality is not only depends on single atom or groups but also nature of all molecules.
- ✓ The term *chirality* is derived from the Greek word Kheir for hand.
- ✓ The mirror images of a chiral molecule or ion are called enantiomers or **optical isomers.**
- ✓ The presence of an asymmetric carbon center is one of several structural features that induce chirality in organic and inorganic molecules.
- ✓ Chiral molecules and ions are able to rotate plane-polarized light.

Definitions

Chiral, or asymmetric carbon - A tetrahedral carbon atom bearing four different substituents.

Chirality centers, or stereocenters - Asymmetrically substituted atoms in a molecular structure.

The most common type encountered in this course will be the chiral carbon described above.

Enantiomers - Nonsuperposable mirror images, or chiral molecules which are mirror images.

Diastereomers - Stereoisomers which are not enantiomers (or mirror images).

Meso compounds, or meso forms - Symmetric, or achiral molecules that contain stereocenters.

Meso compounds and their mirror images are not stereoisomers, since they are identical.

Optical activity - The ability of chiral substances to rotate the plane of polarized light by a specific angle.

Dextrorotatory - Ability of chiral substances to rotate the plane of polarized light to the right.

Levorotatory - Ability of chiral substances to rotate the plane of polarized light to the left.

Specific rotation - The measured angle of rotation of polarized light by a pure chiral sample under

Racemic mixture, racemic modification, or racemate - A mixture consisting of equal amounts
of enantiomers. A racemic mixture exhibits no optical activity because the activities of the
individual enantiomers are equal and opposite in value, therby canceling each other out.

Optical purity - The difference in percent between two enantiomers present in a mixture in unequal amounts. For example, if a mixture contains 75% of one enantiomer and 25% of the other, the optical purity is 75-25 = 50%.

Absolute configuration - A description of the precise 3-dimensional topography of the molecule.

Relative configuration - A description of the 3-dimensional topography of the molecule relative to an arbitrary standard. Absolute and relative configurations may or may not coincide.

Stereochemistry

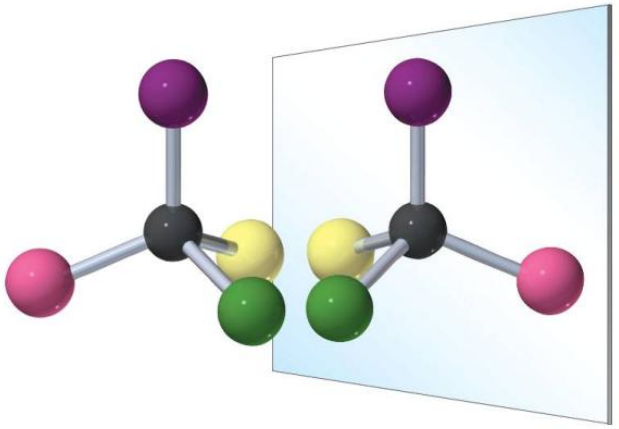
- Diastereomers have different physical properties, so they can be easily separated.
- Enantiomers differ only in reaction with other chiral molecules and the direction in which polarized light is rotated.
- Enantiomers are difficult to separate.
- Convert enantiomers into diastereomers to be able to separate them.

- Molecules with two or more chiral carbons.
- Stereoisomers that are not mirror images.

- When compounds have two or more chiral centers they have enantiomers, diastereomers, or meso isomers.
- Enantiomers have opposite configurations at each corresponding chiral carbon.
- Diastereomers have some matching, some opposite configurations.
- Meso compounds have internal mirror planes.
- Maximum number of isomers is 2^n, where n = the number of chiral carbons.

6.2 Chirality

- ***Chiral*** – Nonsuperimposable on its mirror image.
- ***Achiral*** – Superimposable on its mirror image.
- If a molecule (or object) has a mirror plane or an inversion center, it cannot be chiral.



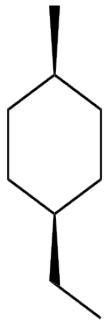
nonsuperimposable mirror images

Chiral

Chiral molecules have **point chirality** at a single *stereogenic* atom, which has four different substituent.

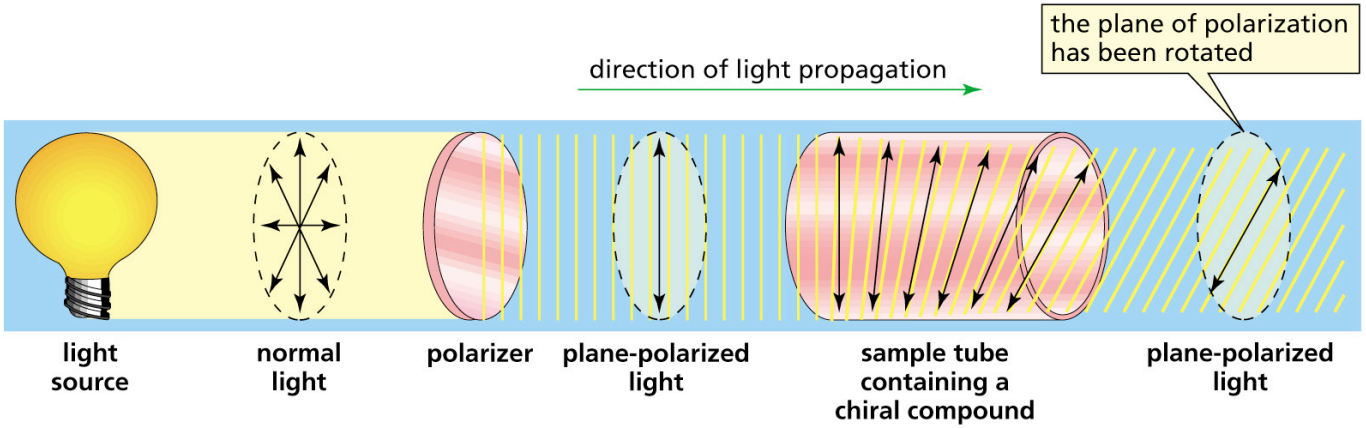
pseudochirality

two of the ligands differ from each other by being mirror images of each other. When this happens, the mirror image of the molecule is identical to the original, and the molecule is achiral.



(1*s*,4*s*)-1-ethyl-4-methylcyclohexane

Chiral compounds are optically active; they rotate the plane of polarized light.



Clockwise (+) Counterclockwise (-)

Different from *R,S* configuration

Achiral compounds do not rotate the plane of polarized light. They are optically inactive.

A polarizer measures the degree of optical rotation of a compound

The observed rotation (α)

$$[\alpha]_{\lambda}^{T} = \frac{\alpha}{lxc}$$

$[\alpha]_{\lambda}^{T}$ = *specific rotation*

T is the temp in °C

λ is the wavelength

α is the measured rotation in degrees

l is the path length in decimeters

c is the concentration in grams per mL

Each optically active compound has a characteristic specific rotation

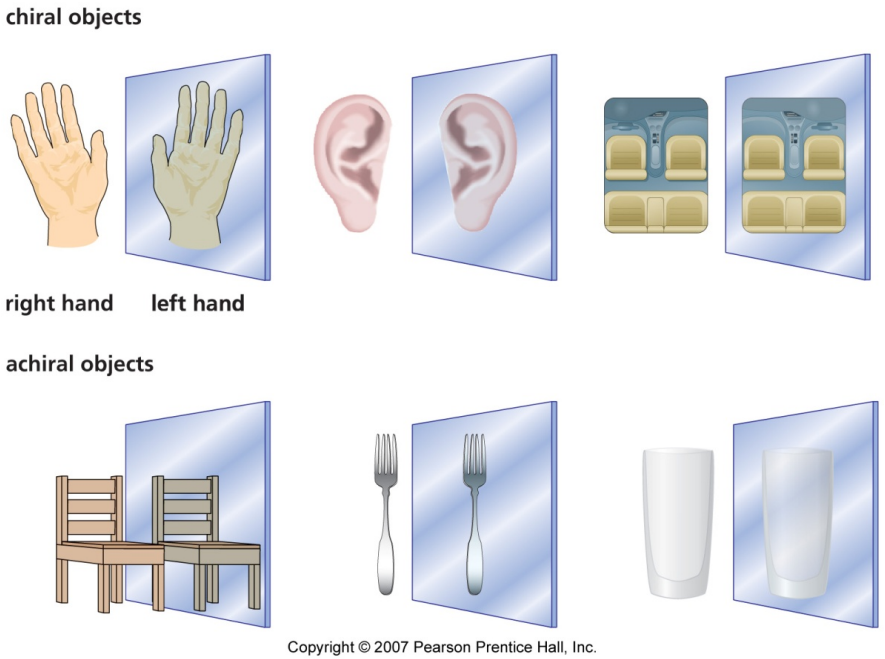
A racemic mixture, which contains an equal amount of the two enantiomers, is optically inactive

$$\text{optical purity} = \frac{\text{observed specific rotation}}{\text{specific rotation of the pure enantiomer}}$$

$$\text{enantiomeric excess} = \frac{\text{excess of a single enantiomer}}{\text{entire mixture}}$$

Nonsuperimposable Mirror Images

“Handedness” - hands (gloves) and feet (shoes) have right- and left-handed forms

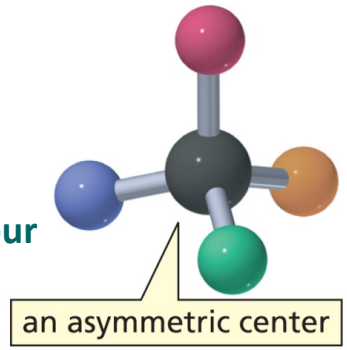


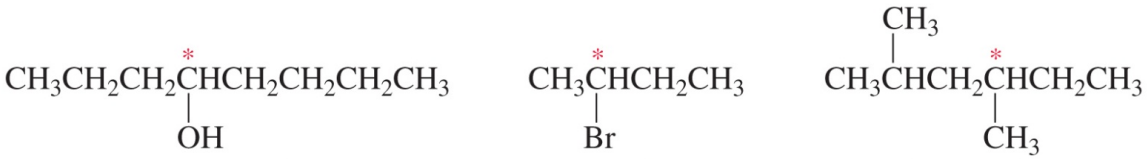
RULE - look for symmetry in a molecule - symmetry breaks chirality

Asymmetric Centers

Chiral molecules - generally molecules containing an asymmetric center

Asymmetric (chiral) center - tetrahedral atom bonded to four different groups - indicated with an *asterisk (*)*





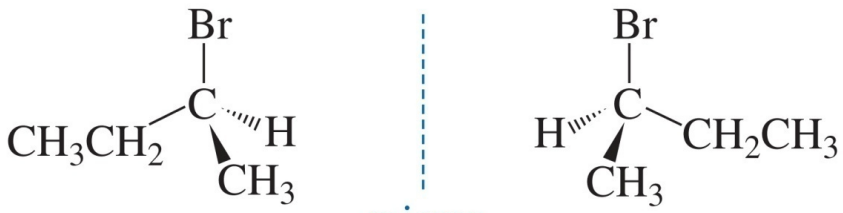
RULE - only sp^3 hybridized atoms can be chiral

NOTE - molecules may not appear to be different until you go out several atoms

One Asymmetric Center

Molecules with one asymmetric center can exist as 2 stereoisomers

2-bromobutane



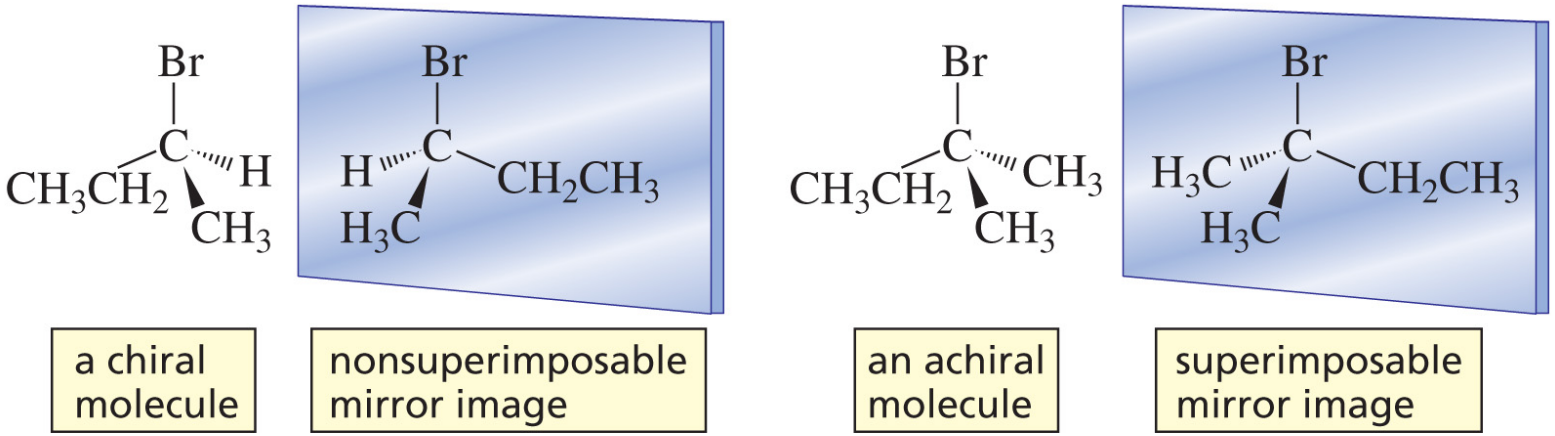
the two isomers of 2-bromobutane

enantiomers

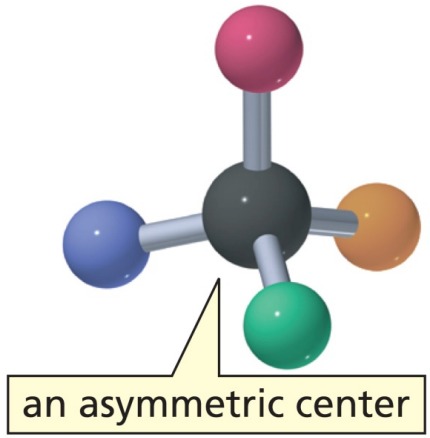
These Two Enantiomers are chiral compounds-

Achiral Molecules

Have superimposable mirror images



Build a Molecule and Prove it to yourself

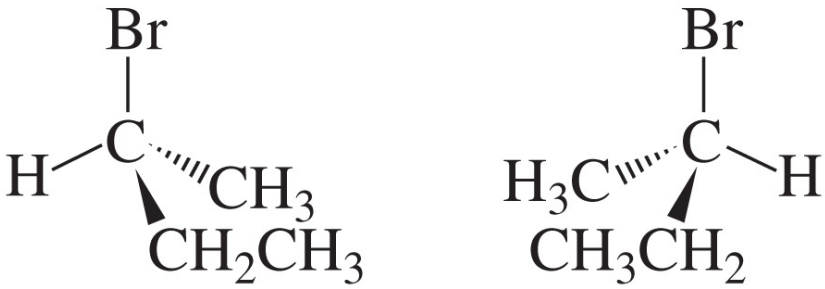


Drawing Enantiomers

Solid lines – bonds in the plane of the paper

Solid Wedge – coming out of the paper toward you

Hatched Wedge – going back into space behind the paper



perspective formulas of the enantiomers of 2-bromobutane

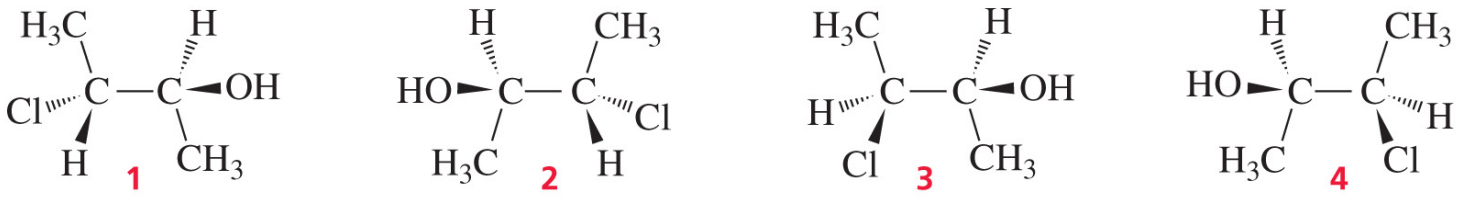
Properties of Enantiomers

- Same boiling point, melting point, density
- Same refractive index
- Different direction of rotation in polarimeter
- Different interaction with other chiral molecules
  - Enzymes
  - Taste buds, scent

=>

Diastereomers

- Sterioisomers - that are not enatiomers.



erythro enantiomers

threo enantiomers

perspective formulas of the stereoisomers of 3-chloro-2-butanol (staggered)

Properties of Diastereomers

- Diastereomers have different physical properties: m.p., b.p.
- They can be separated easily.
- Enantiomers differ only in reaction with other chiral molecules and the direction in which polarized light is rotated.
- Enantiomers are difficult to separate.

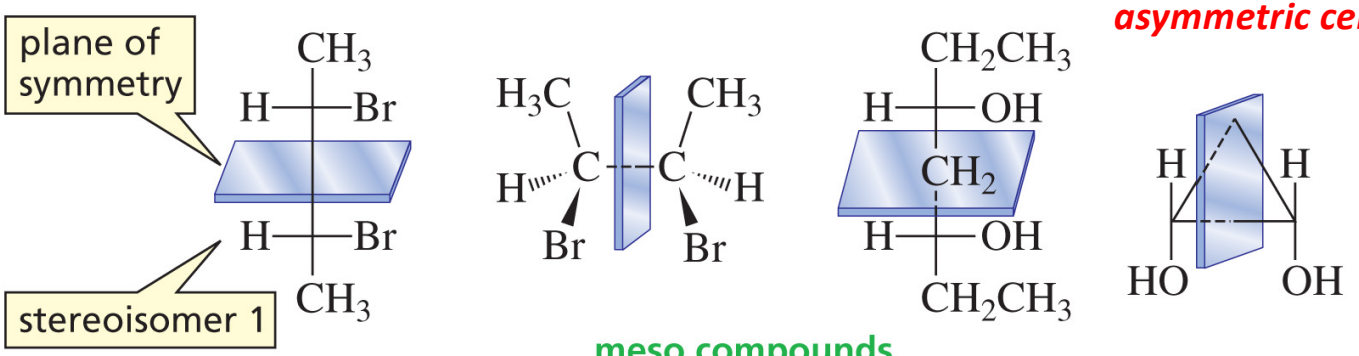
Meso Compound

- **Compound that contains an asymmetric center and a plane of symmetry.**
- **The four groups bonded to each asymmetric center are the same**

Meso Compounds

A compound with 2 or more asymmetric centers, and a **plane of symmetry** - cuts molecule in half so that one half of the molecule is the mirror image of the other

Symmetry plane not drawn through ***asymmetric centers***

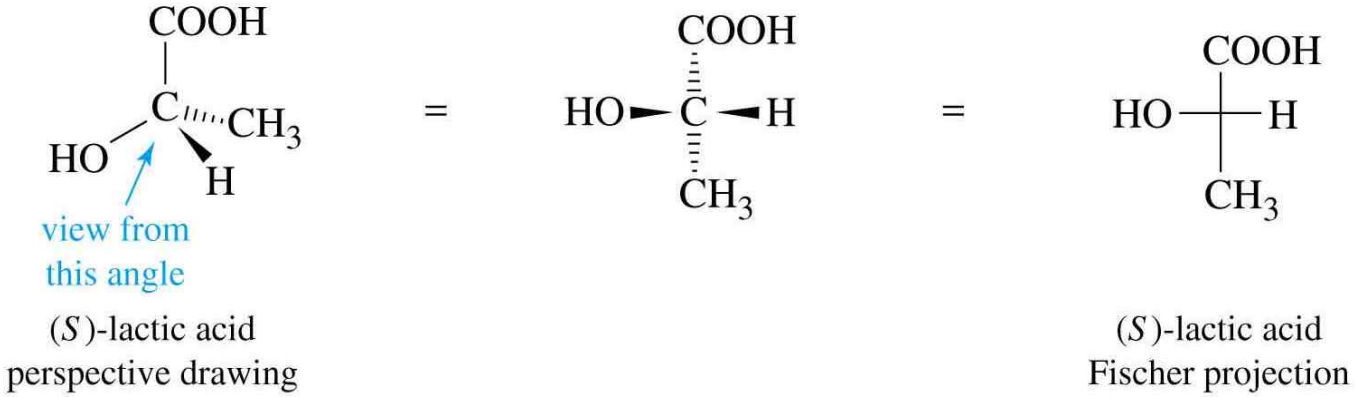


meso compounds

Note this plane of symmetry does not eliminate the presence of stereocenters (you still have sp^3 carbon atoms with four different atoms attached - you just have multiple stereocenters with the same four atoms!)

Fischer Projections

- Flat drawing that represents a 3D molecule
- A chiral carbon is at the intersection of horizontal and vertical lines.
- Horizontal lines are forward, out-of-plane.(Above the plane)
- Vertical lines are behind the plane.(Below the plane)

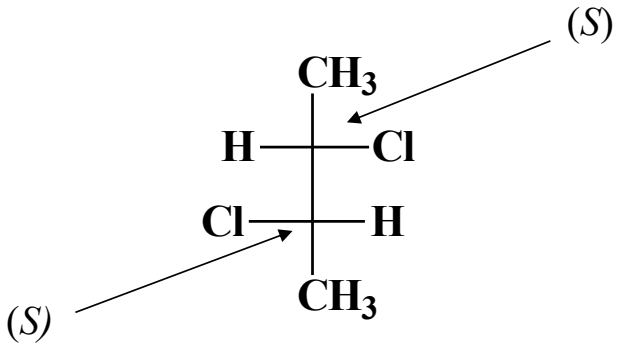


(*S*)-lactic acid
perspective drawing

(*S*)-lactic acid
Fischer projection

Fischer (*R*) and (*S*)

- Lowest priority (usually H) comes above the plane , so assignment rules are reverse!
- Clockwise 1-2-3 is (*S*) and counterclockwise 1-2-3 is (*R*).
- Example:



R- and S- nomenclature of chirality centers

The Cahn-Ingold-Prelog priority rules are used for naming chirality centers and geometric isomer (*e.g.* E- or Z-alkenes)

Then at each chirality center....
•Assign the priority (high = 1 to low = 4) to each group attached to the chirality center based on atomic number.

•Reposition the molecule so that the **lowest priority group** *is away from you* (below the plane)

•Determine the relative direction of the priority order of the three higher priority groups (1 to 2 to 3)

•If this is **clockwise** then it is the **R**-stereoisomer (Latin; *rectus* = right handed)

•If this is **counter-clockwise** then it is the **S**-stereoisomer (Latin; *sinister* = left handed)

•If there is more than one stereocenter, then the location needs to be included with the locant, *e.g.* (2R)-

Subrules:

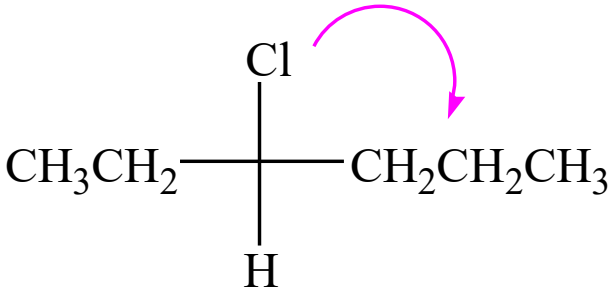
•Isotopes: H vs D ? Since isotopes have identical atomic numbers, the mass number is used to discriminate them so D >H

•If the same atom is attached, then look for the first point of difference by moving out **one atom** at a time.

•If a multiple bond is encountered, treat it as if the atoms are attached by the same number of single bonds *e.g.* C=C is treated a 2 C-C and C=O is 2 C-O

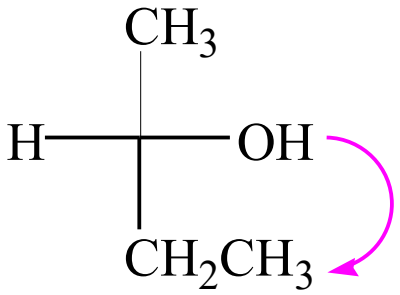
Naming from the Fischer Projection

1. Rank the groups (or atom) that are bonded to the asymmetric carbon and draw an arrow with the highest priority to the lowest priority

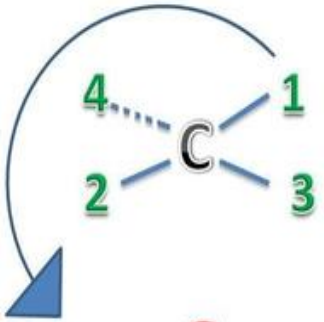


(*R*)-3-chlorohexane

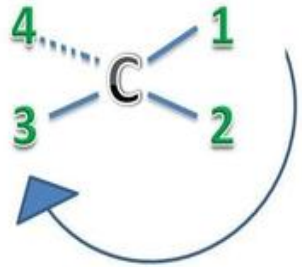
2. If the lowest priority is on a horizontal bond, the naming is opposite to the direction of the arrow



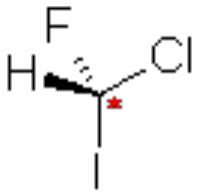
(*S*)-2-butanol



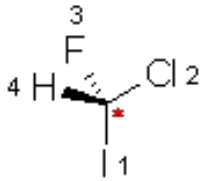
S



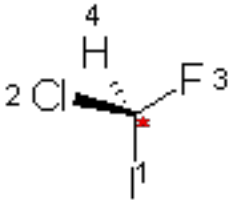
R



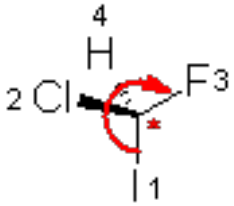
identify the chirality center(s)



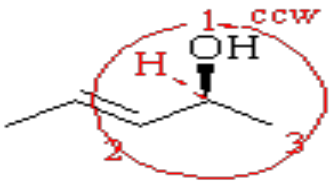
assign the relative priorities



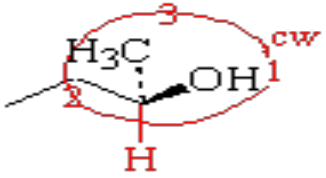
rotate the low priority group away



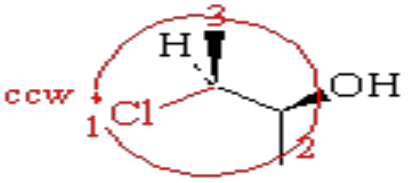
determine the sense of groups 1 -> 3
clockwise = R


1
ccw
OH
H
2
3

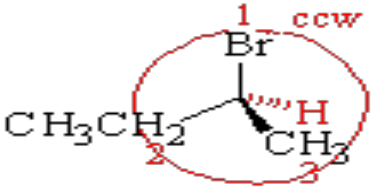
S


3
cw
H3C
OH
1
2
H

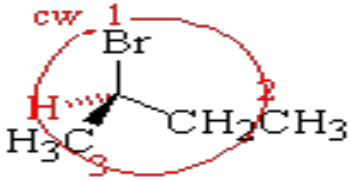
R


3
H
ccw
Cl
1
OH
2

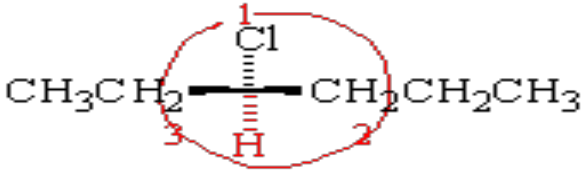
S


1
ccw
Br
CH3CH2
H
CH3
2
3

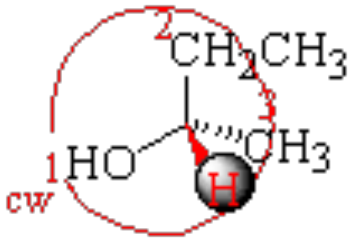
S


cw
1
Br
H
H3C
CH2CH3
2
3

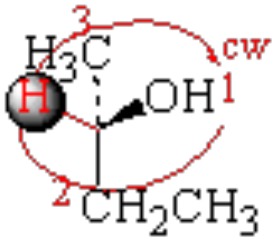
R


1
Cl
CH3CH2
CH2CH2CH3
3
H
2

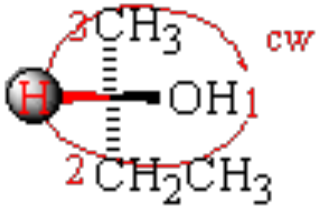
R


2
CH2CH3
3
CH3
1HO
cw
H

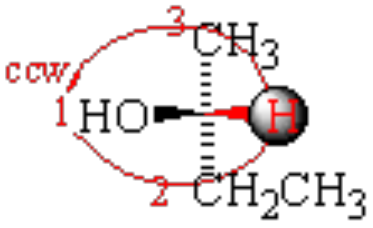
S


3
H3C
cw
H
OH1
2
CH2CH3

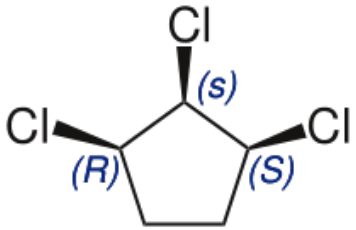
S


3
CH3
cw
H
OH1
2
CH2CH3

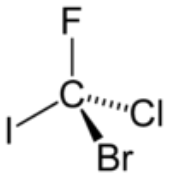
S


3
CH3
ccw
1
HO
H
2
CH2CH3

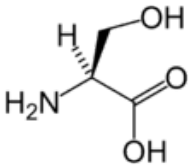
R



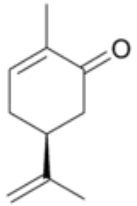
(1*R*,2*s*,3*S*)-1,2,3-trichlorocyclopentane



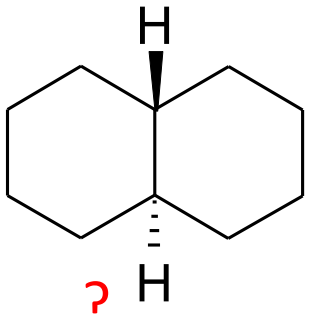
?



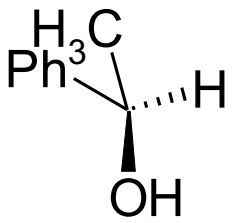
?



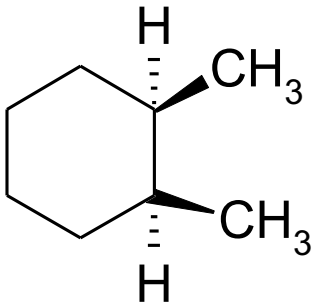
?



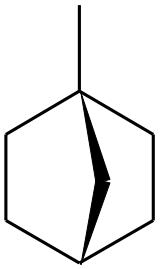
?



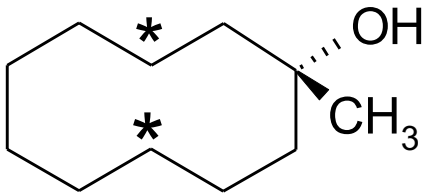
?



?



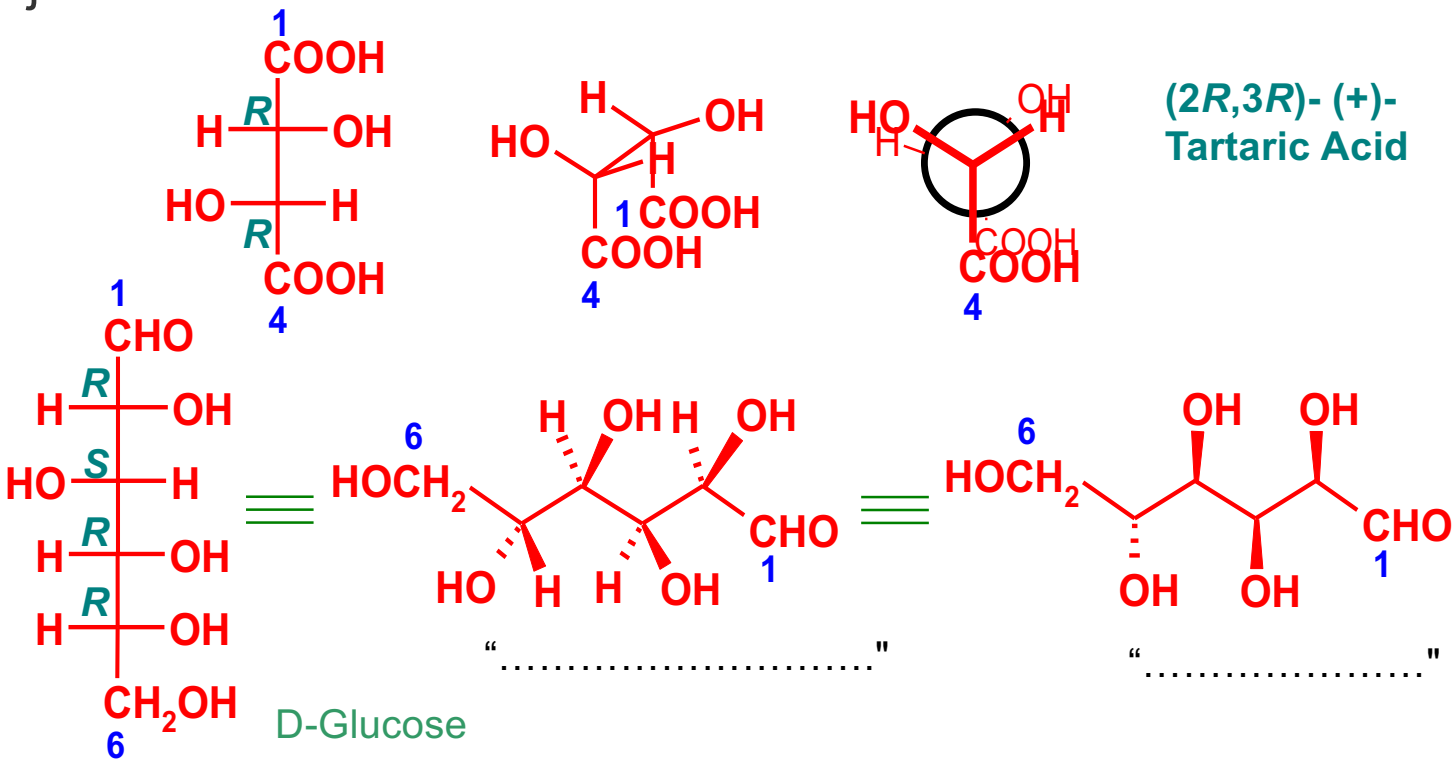
?



?

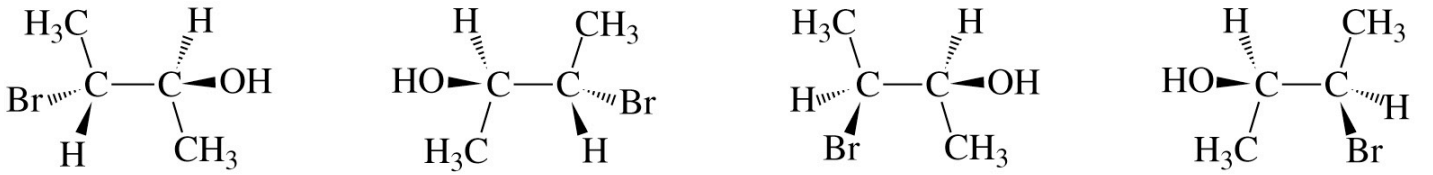
Structural Representations (cont.)

Relationship between Fischer, Newman, sawhorse, other projections

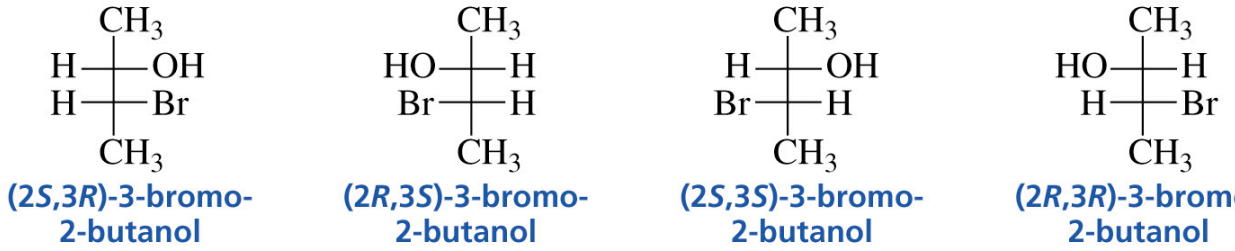


'……..' or '……' projections used for depicting stereostructures of reaction products or natural products!

The *R,S* nomenclature of isomers with more than one asymmetric carbon

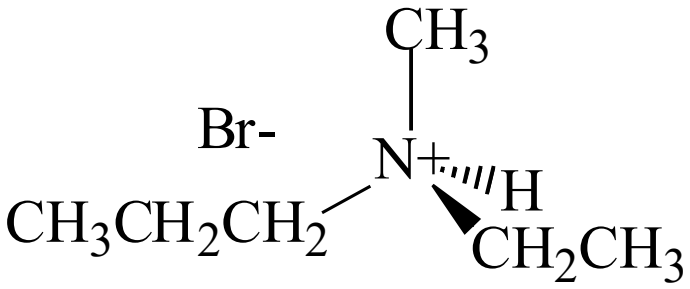


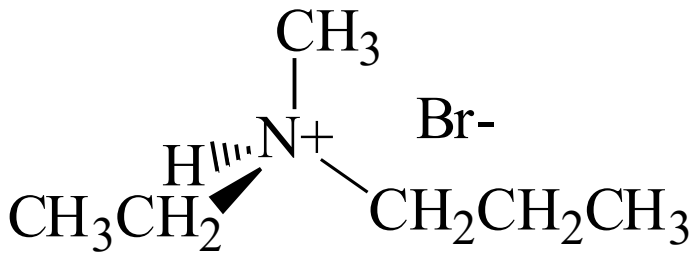
perspective formulas of the stereoisomers of 3-bromo-2-butanol

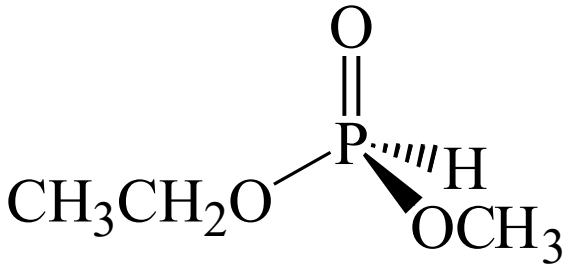


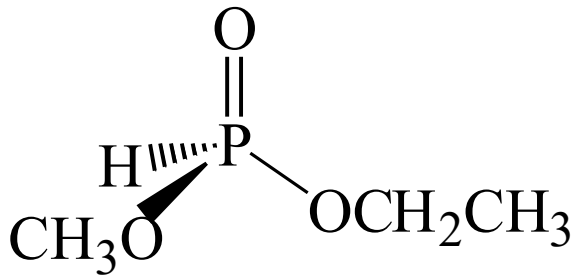
Fischer projections of the stereoisomers of 3-bromo-2-butanol

Atoms other than carbon can be asymmetric

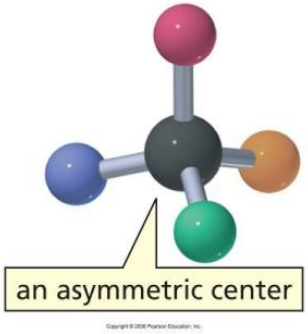


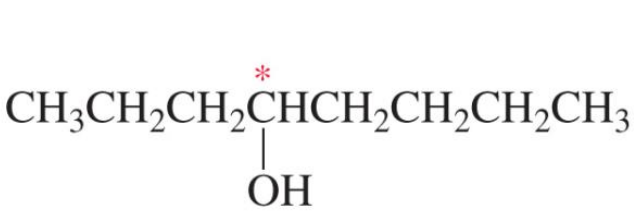




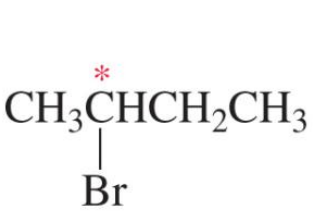


- An **asymmetric center** is an atom that is bonded to four different groups.

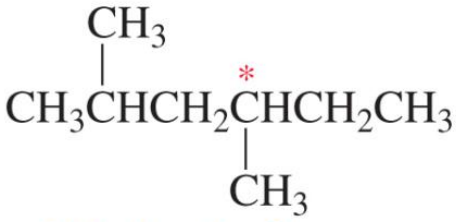




4-octanol

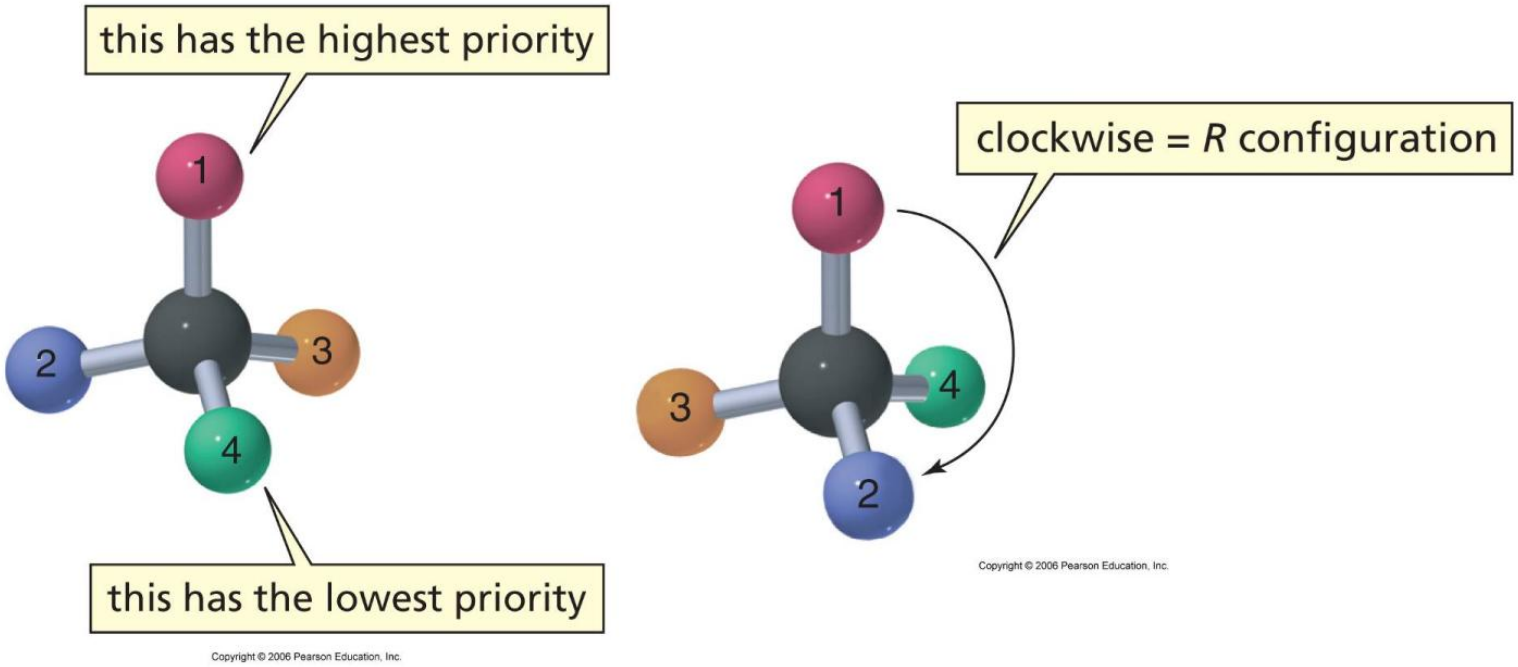


2-bromobutane

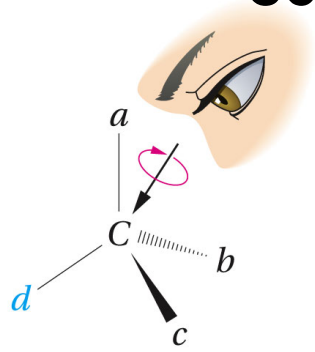


2,4-dimethylhexane

6.6 Naming enantiomers: the *R*,*S* system

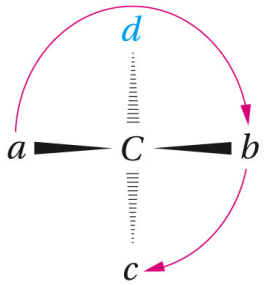


Configuration and the R-S Convention

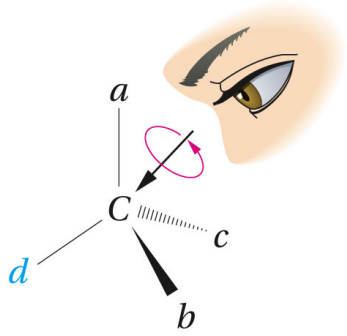


$a \rightarrow b \rightarrow c$ clockwise
R

or

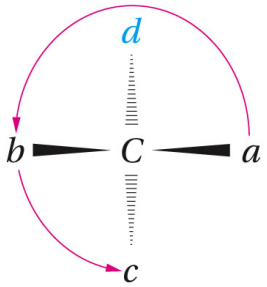


$a \rightarrow b \rightarrow c$ clockwise
R

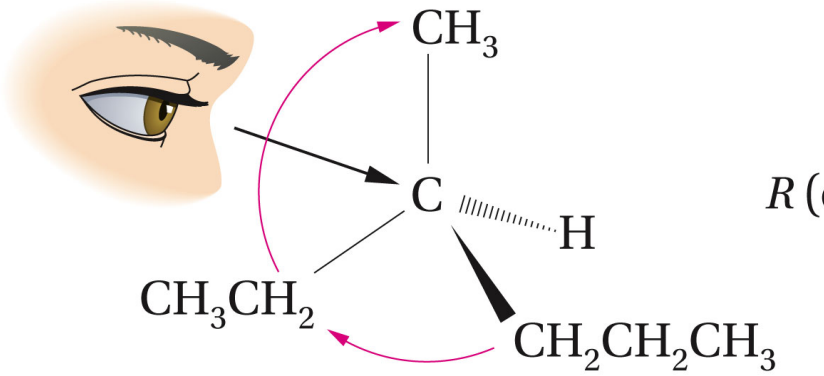


$a \rightarrow b \rightarrow c$ counterclockwise
S

or



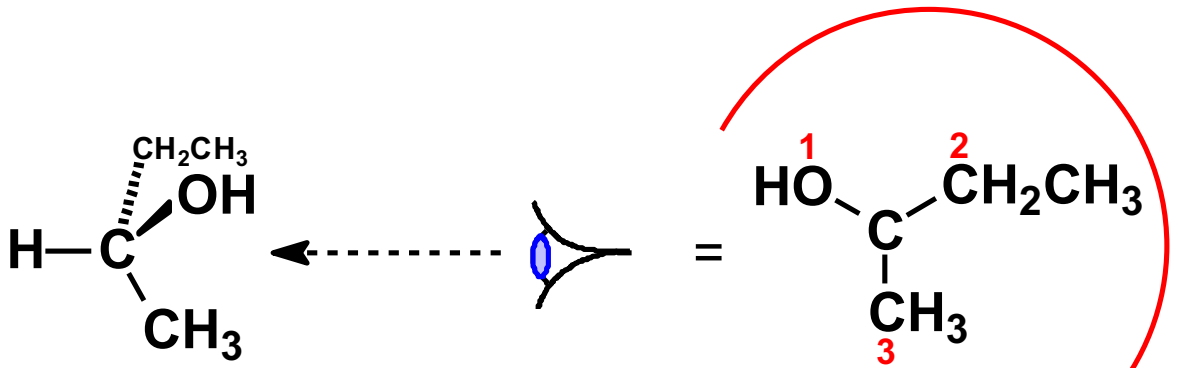
$a \rightarrow b \rightarrow c$ counterclockwise
S



R (clockwise)

Absolute Configuration

- ***R*** and ***S***
  - Assign priorities to the remaining groups based on atomic numbers.
  - Clockwise (highest to lowest priority) ⇒ ***R***
  - Counterclockwise ⇒ ***S***



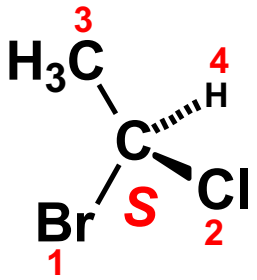
(*R*)-2-butanol

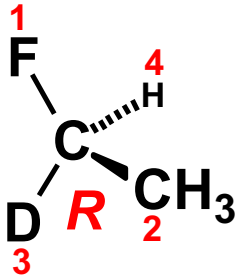
Absolute Configuration

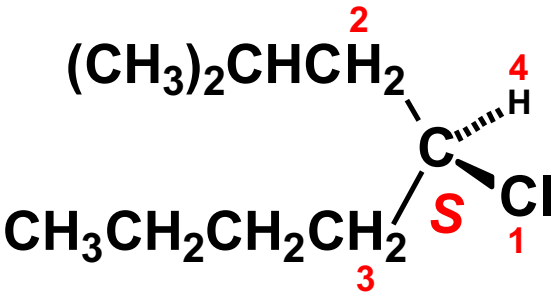
- Assign priority:
  - Atomic number of atom directly bonded.
  - If the same atom is bonded, go to the next atom, etc.
  - Groups containing multiple bonds are treated as though multiple atoms were attached:

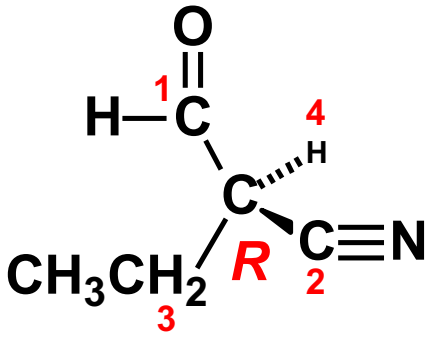
Absolute Configuration

- Determine the absolute configuration of the following compounds:



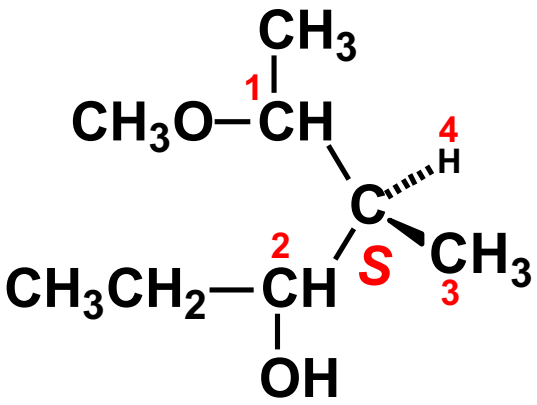


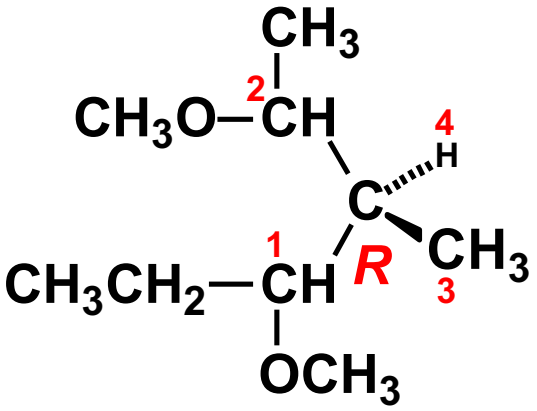


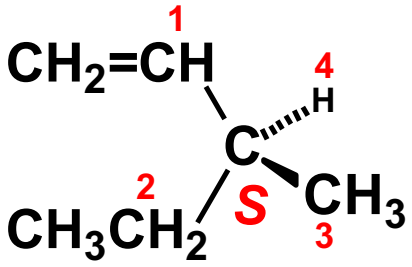


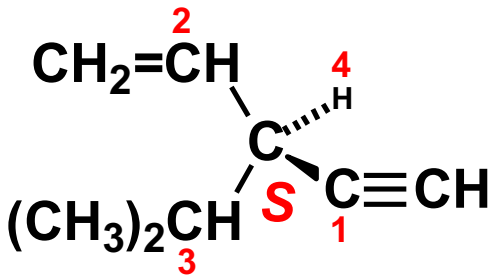
Absolute Configuration

- Determine the absolute configuration of the following compounds:

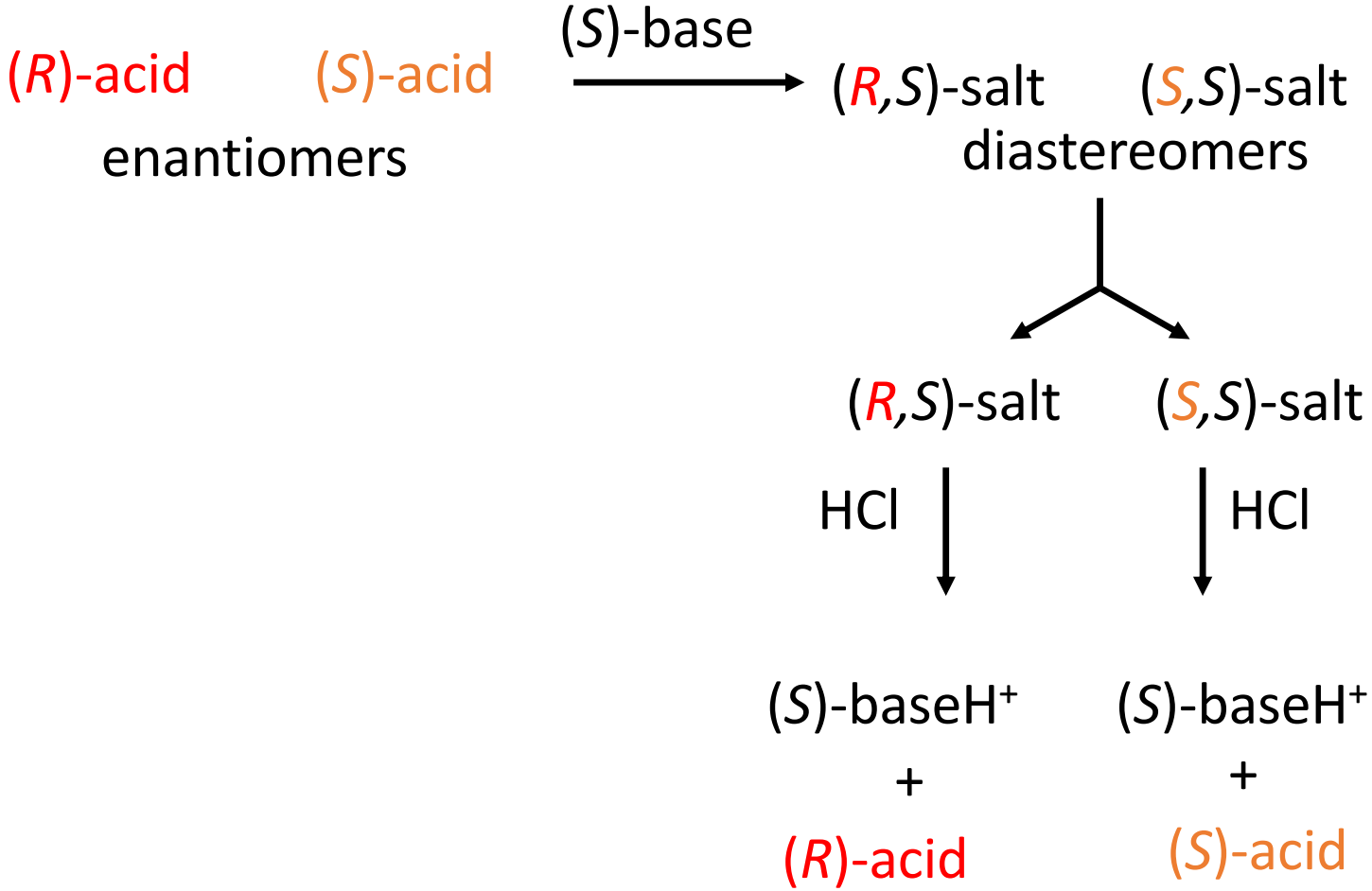


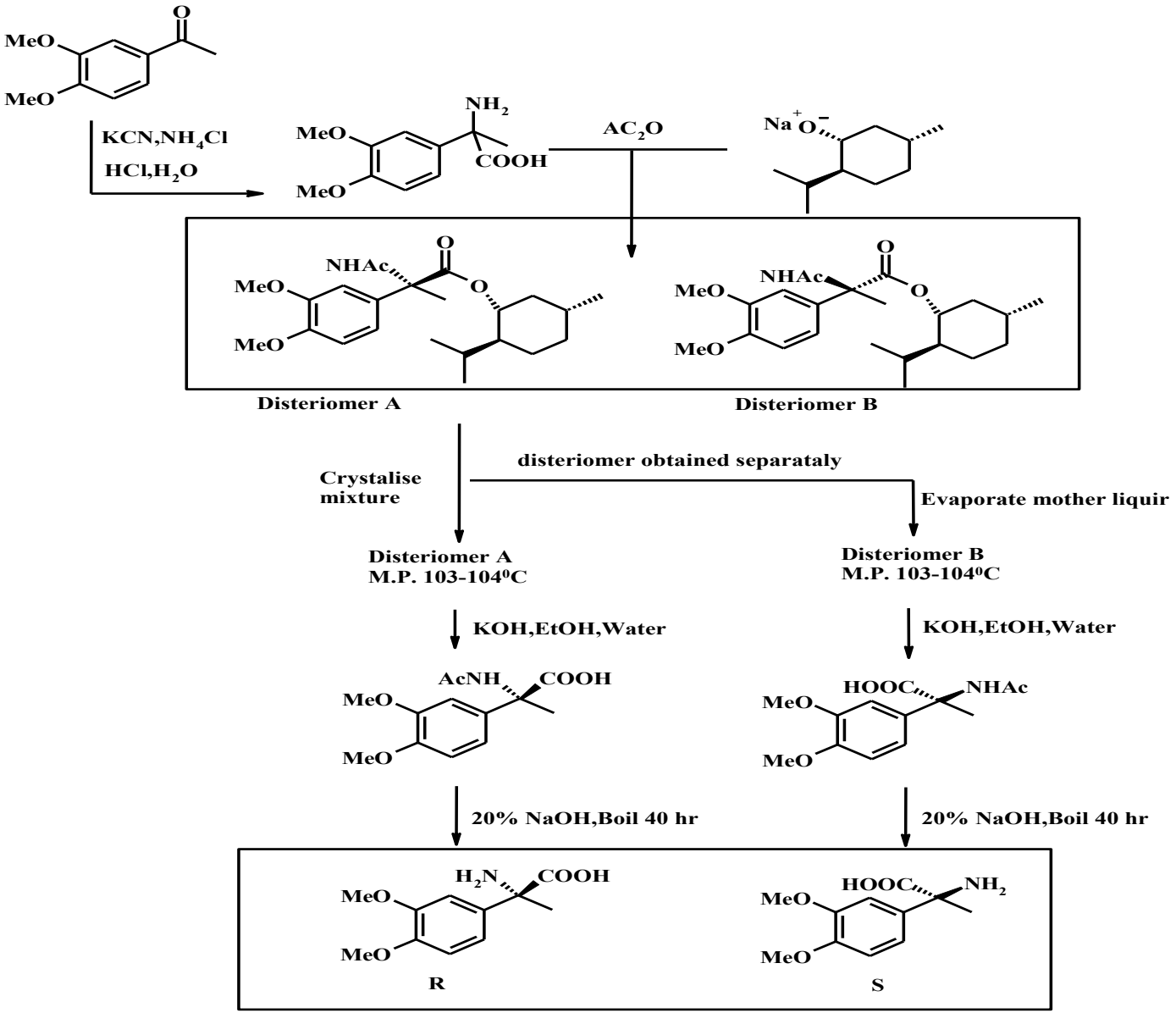




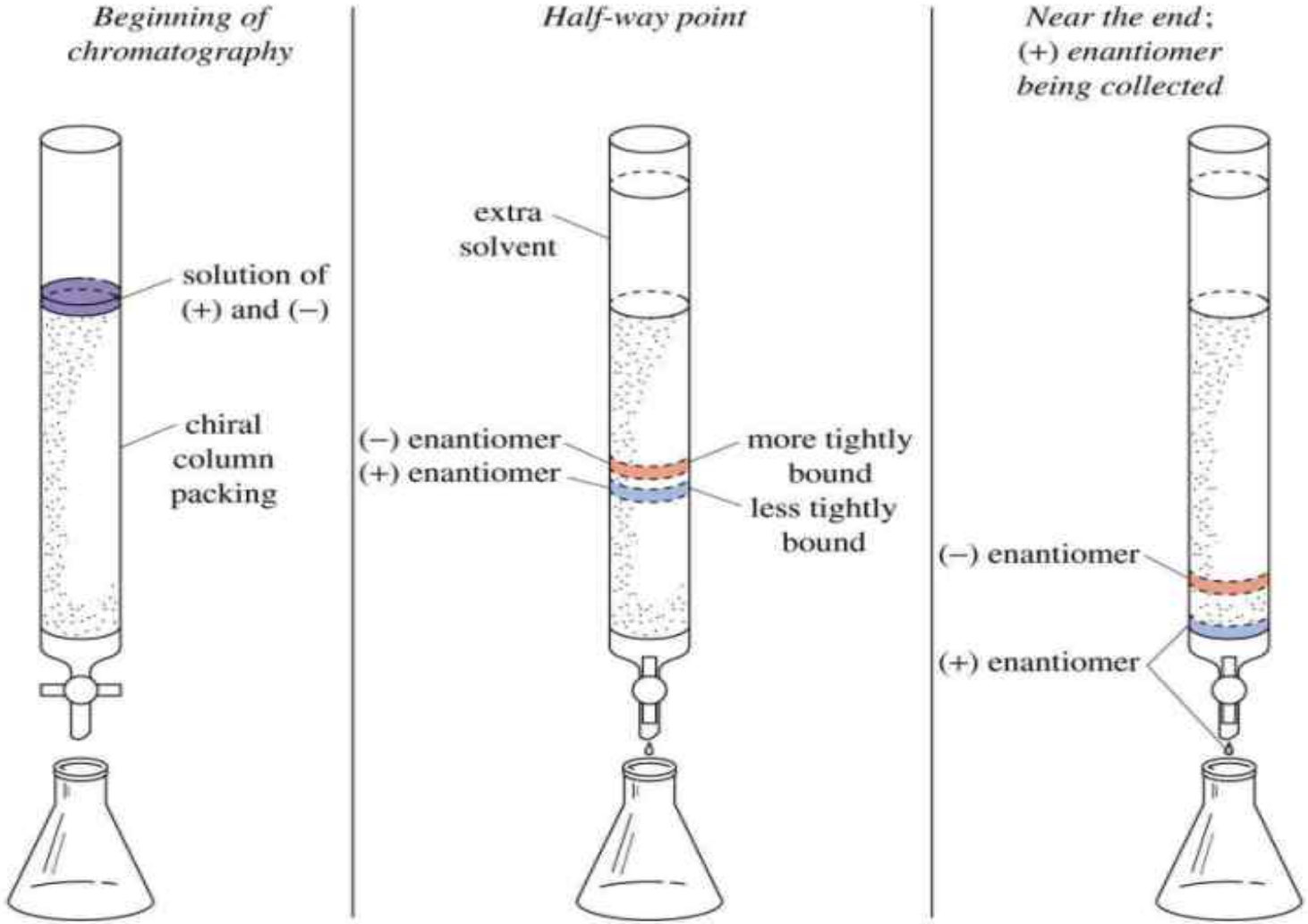


Resolution of a Racemic Mixture




MeO
MeO
O
KCN,NH4Cl
HCl,H2O
NH2
COOH
AC2O
Na+ O−
NHAc
O
Disteriomer A
Disteriomer B
Crystalise mixture
disteriomer obtained separataly
Evaporate mother liquir
Disteriomer A
M.P. 103-104⁰C
Disteriomer B
M.P. 103-104⁰C
KOH,EtOH,Water
AcNH
HOOC
20% NaOH,Boil 40 hr
H2N
NH2
R
S

Chromatographic Resolution of Enantiomers



Discrimination of Enantiomers by Biological Molecules