Topic II

Stereochemistry of Organic Molecules

Lecture slides are courtesy of : Prof. R.B Sunoj, IIT Bombay
Prof. Peter Volhardt, UC Berkeley
Prof. J. M McBride, Yale University
Oxford University Press

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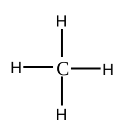
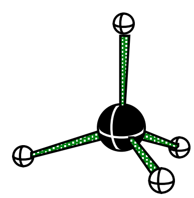
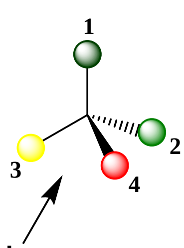
Representation of three dimensional structures-METHANE



2D drawing



3D drawing



view

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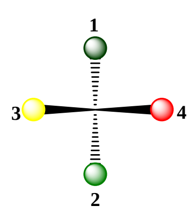

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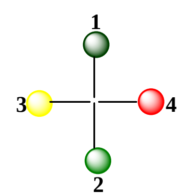

Fischer Projection

Perspective drawing
Or Flying-wedge formula

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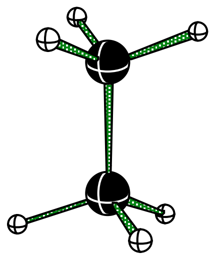
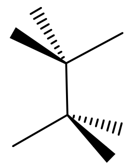
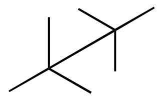
Representation of three dimensional structures-ETHANE



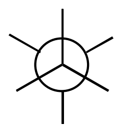
3D Image



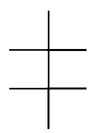
Flying-wedge formula



Sawhorse formula



Newman Projection



Fischer Projection

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Isomers

Isomers are different compounds with the same molecular formula

Isomers can differ in,

(1) Constitution: connectivity between atoms are different

Constitutional isomers (Structural isomers)

(2) Orientation (configuration) of atoms in space:

Stereoisomers

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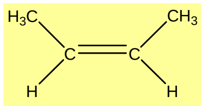
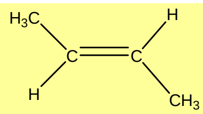
Isomers

E.g., C_4H_8



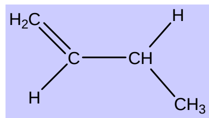
cis-2-butene



trans-2-butene

Stereo

Constitutional



1-butene

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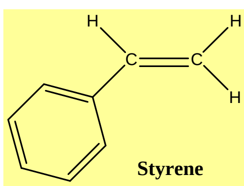
Isomers

CH103
R. B. Sunoj

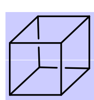
E.g., C_8H_8



Styrene

Used for making polymers

Constitutional



Cubane

Used as solid propellants (strain energy of 166 kcal/mol)

Polynitro cubane is an explosive!

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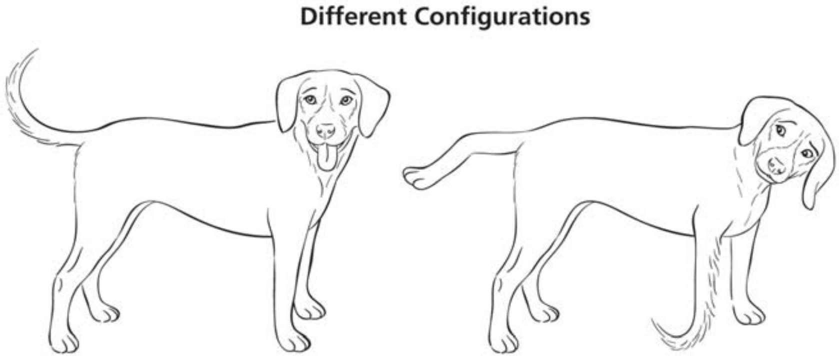
Different Configurations



Compounds with different configurations can be separated.

Cis–trans isomers have different configurations.

Chirality

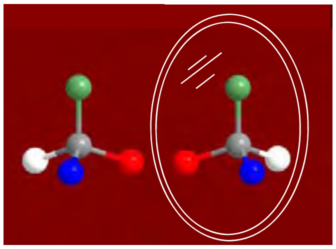
The word ‘chiral’ is derived from Greek word ‘cheir = handed

Human hands have OBJECT and MIRRO IMAGE relationship and they are NON SUPERIMPOSABLE

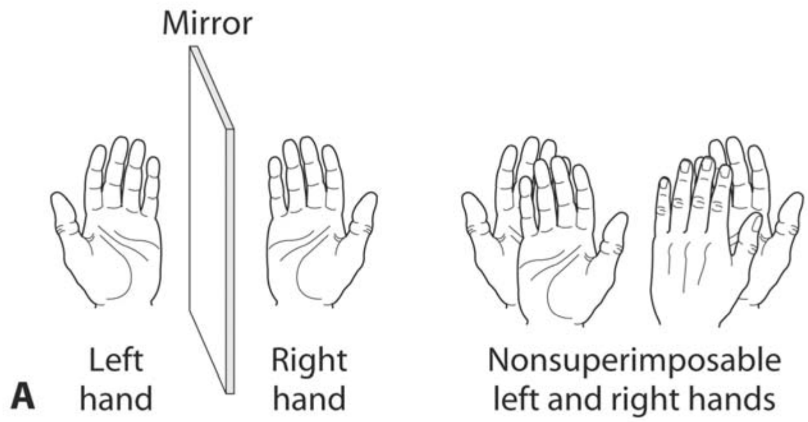
Examples: Shoe, scissors, screw

Chiral Molecules

Chiral center has four different groups attached to a tetrahedral center



Objects are Chiral and Achiral



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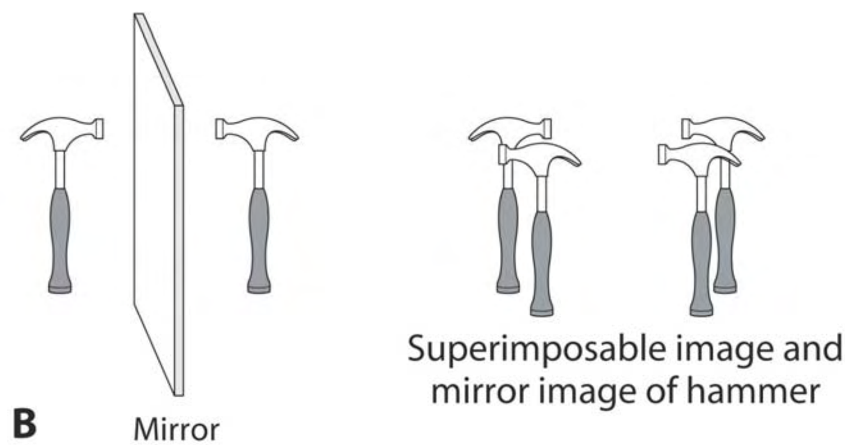
Objects are Chiral and Achiral



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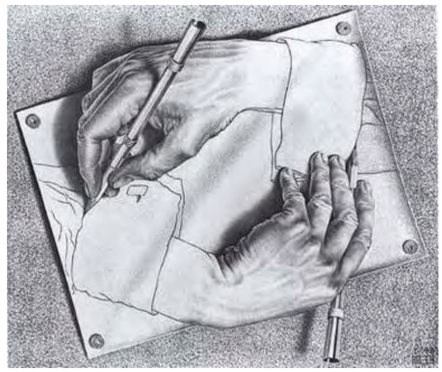
Symmetry in Art: M. C. Escher



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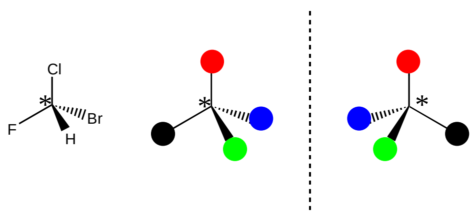
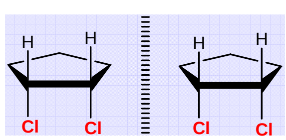
Chiral Molecules-Enantiomers

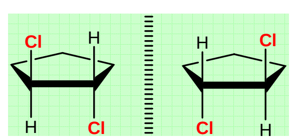
Presence of a stereo center (chiral center) is neither necessary nor sufficient requirement for molecular chirality

chiral



Isomers that are non-superimposable mirror images are called ENANTIOMERS





Identical

Enantiomers

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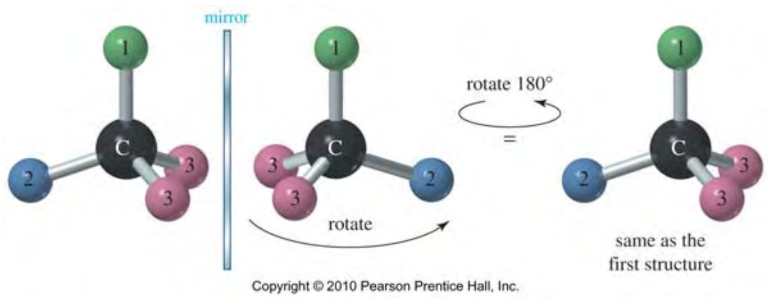
Same physical and chemical properties

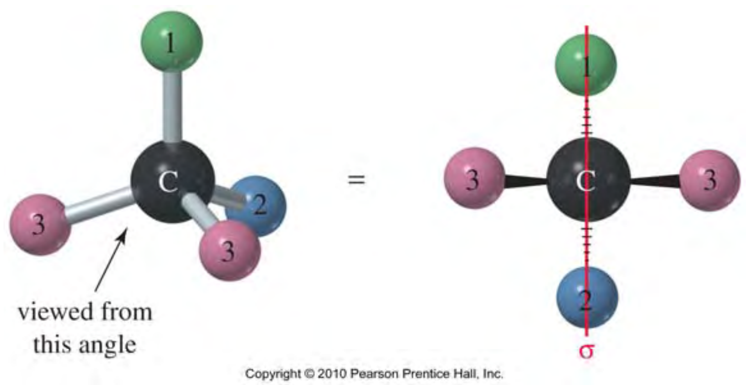
Achiral Compounds



Take this mirror image and try to superimpose it on the one to the left matching all the atoms. Everything will match.

When the images can be superposed the compound is ***achiral***.

Planes of Symmetry



- A molecule that has a plane/centre of symmetry is ***achiral***.

Properties of Enantiomers

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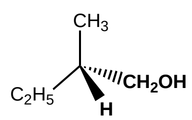
R. B. Sunoj

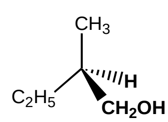
1. **Enantiomers are chiral**
2. **Pure sample of single enantiomer is optically active**
3. **Enantiomers have <u>identical physical and chemical properties</u> in an achiral environment**
4. **Different biological properties**

Example

(+) or dextro



(-) or laevo



	(+) or dextro	(-) or laevo
[α]	+5.9	-5.9
BP	128.9	128.9
μ	1.4107	1.4107

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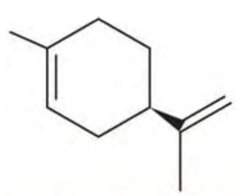
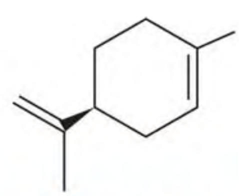
Oranges and Lemons



(+)-limonene

found in oranges



(–)-limonene

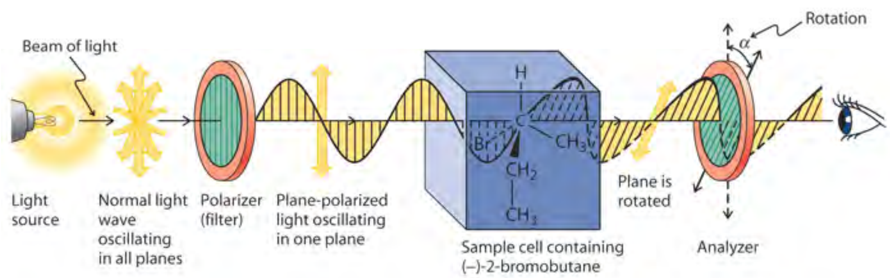
found in lemons

Stereoisomerism & Optical Activity

Enantiomers: Which is which? Absolute configuration.

1. **X-ray crystal structure. "Photo."**
2. **Polarimeter: Optical rotation of plane polarized light:**
   Image → dextrorotatory (clockwise), (+)-enantiomer

Mirror image → levorotatory (counter-clockwise), (-)-enantiomer.



Enantiomers are optically active

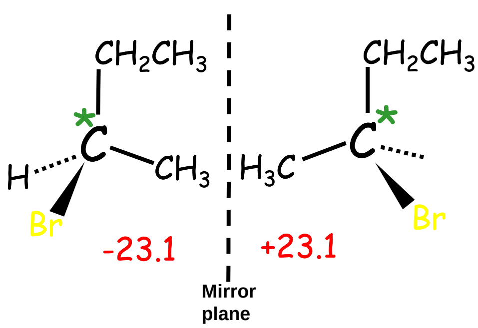
Optical rotation:

$$[\alpha]_{\lambda}^{t(°C)} = \frac{\alpha}{lc}$$

Measured rotation

Length of vessel (in dm usually)

Concentration (g ml^{-1})



[α] is called *specific rotation*.

Note: Sign of rotation does not tell you absolute configuration

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Optical Purity

- **Optical purity (o.p.) is sometimes called enantiomeric excess (e.e.).**
- **One enantiomer is present in greater amounts.**

$$\text{o.p.} = \frac{\text{observed rotation}}{\text{rotation of pure enantiomer}} \times 100$$

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Calculate % Composition

The specific rotation of (*S*)-2-iodobutane is +15.90°. Determine the % composition of a mixture of (*R*)- and (*S*)-2-iodobutane if the specific rotation of the mixture is -3.18°.

Sign is from the enantiomer in excess: levorotatory.

$$\textbf{o.p.} = \frac{\mathbf{3.18}}{\mathbf{15.90}} \times \mathbf{100} = \mathbf{20\%}$$

$$2l = 120\% \qquad l = 60\% \qquad d = 40\%$$

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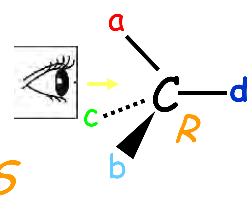
Naming Enantiomers (Absolute Configuration)

Cahn-Ingold-Prelog *R*,*S*-Nomenclature

Label all substituents at stereocenter, starting at point of attachment, according to the sequence rules in order of decreasing priority: a, b, c, d (note color scheme). Look down C-d bond:

a, b, c clockwise : *R*

a, b, c counterclockwise : *S*



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Cahn-Ingold-Prelog

1966

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Vladimir Prelog, ETH Zurich
Nobel Prize in Chemistry (1975)
for Stereochemistry

H.G Khorana, MIT
Nobel Prize in Medicine (1968)
for Genetic Code

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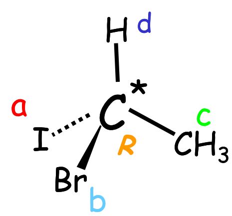
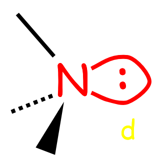
Sequence Rules

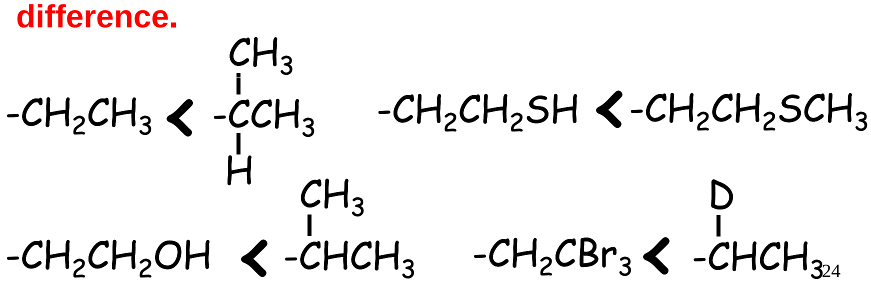
1. Order by atomic number, i.e. H = 1, lowest.



Exception: lone pair, # "zero". E.g., amines:



2. If same priority at first atom: Go to first point of difference.



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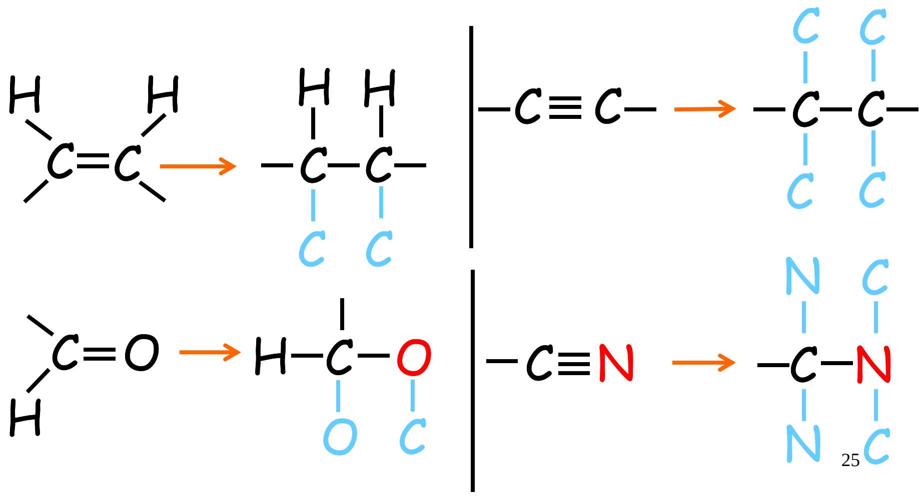
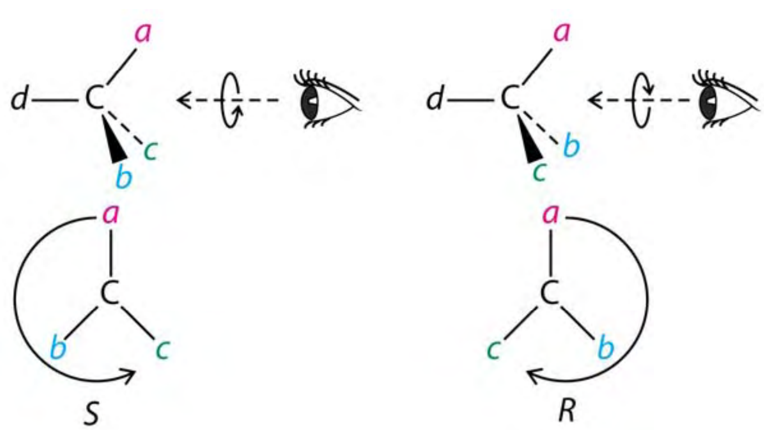
3. Multiple bonds: Add double or triple representations of atoms at the respective other end of the multiple bond.



Procedure for Assignment of *R*, *S*



HINT

If the lowest-priority atom (usually H) is oriented toward you, you don't need to turn the structure around. You can leave it as it is with the H toward you and apply the *R/S rule backward*.

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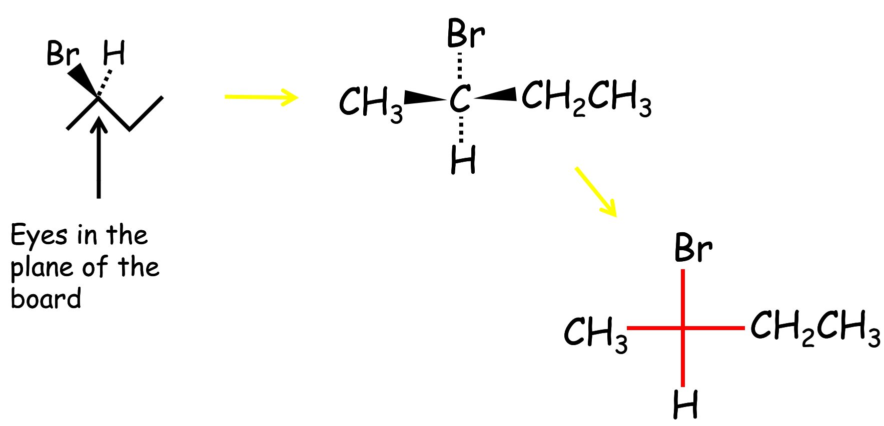
Fischer Projection: A flat stencil



Depending on your starting dashed-wedged line structure, several Fischer projections are possible for the same molecule.

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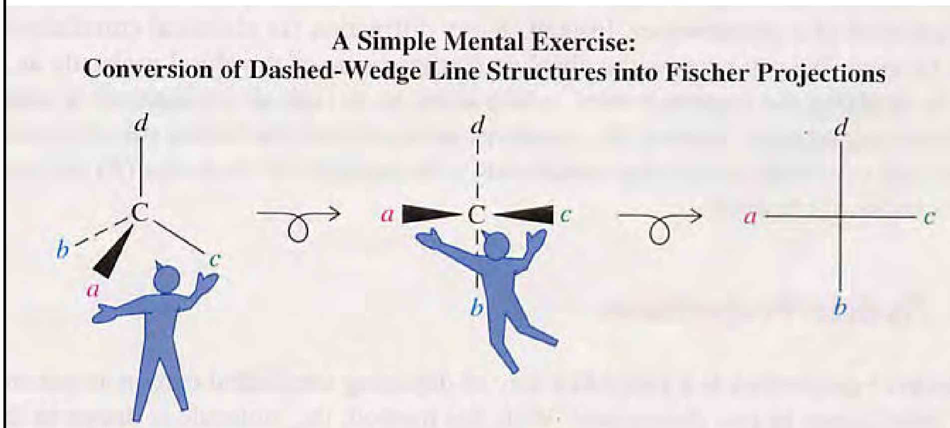
Fischer Projections



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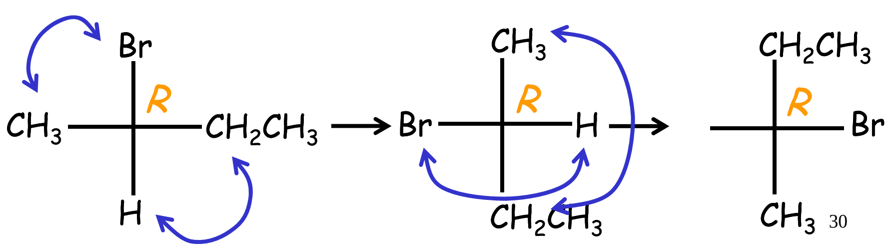
Rules for handling Fischer projections:

1. Don't rotate.
2. The mutual exchange of any pair gives the other enantiomer

Therefore: Two exchanges leave absolute configuration. Example: (2*R*)-Bromobutane



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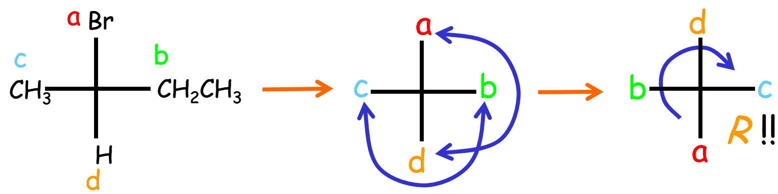
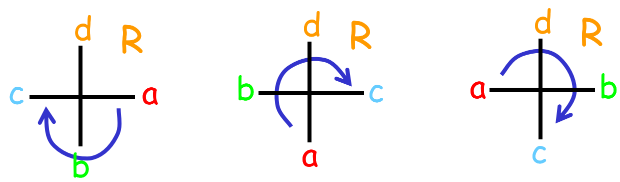
This procedure can be used to readily assign *R,S*:

Do double exchanges to place d on top.

Example:



Note: There are three possible arrangements for each, *R* or *S*, e.g., *R*:



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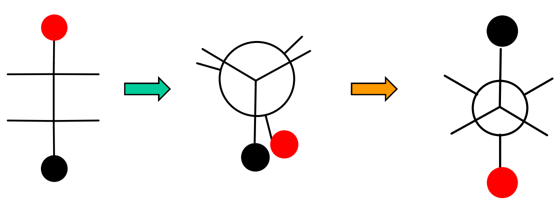
Projection Formulae Inter-conversion

Fischer Projection ⇄ **Newman Projection**



Fischer projection refers to eclipsed conformation

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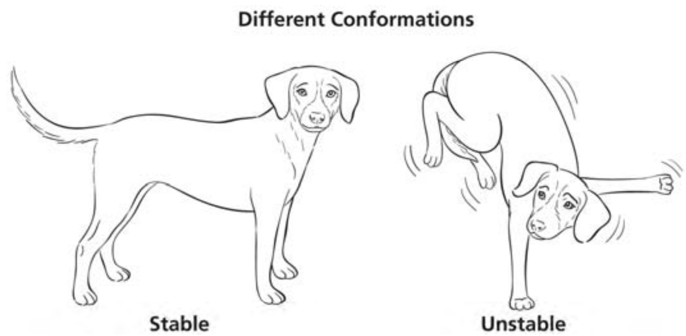
Different Conformations



Compounds with different conformations (conformers) cannot be separated in most cases.

Diastereomers

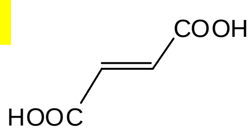
Diastereomers are stereoisomers that are not enantiomers

They are chemically (and physically) different

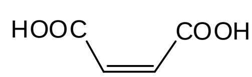
OR

Stereoisomers that are <u>not mirror images</u>

E.g.,1



Fumaric Acid



Maleic Acid

MP: 299-300 ºC

MP: 140-142 ºC

Forms anhydride upon heating

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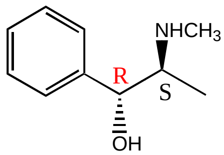
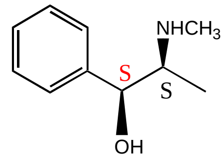
Diastereomers

Example 1:





Ephedrine

pseudoephedrine

(+)-ephedrine is used in traditional medicine

(as a nasal decongestant)

Diastereomers can be chiral or achiral

E.g., cis-trans geometrical isomers

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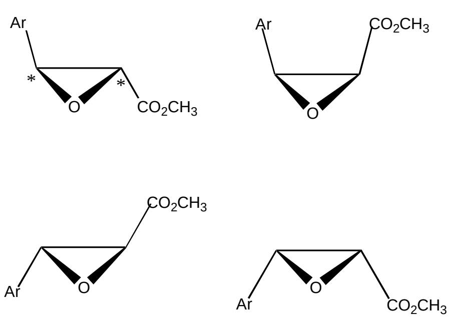
Diastereomers

Diastereomers can be chiral or achiral

Large number of diastereomers are available which are compounds containing two or more chiral centers (usually asymmetric carbon atoms)

E.g.,2

SR



SS

Enantio

Enantio

RS

RR

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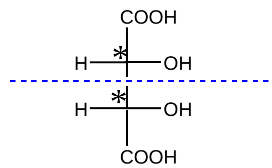
Optically Inactive!

Presence of a stereo center not a <u>sufficient requirement</u> for molecular chirality

Though the following stereoisomer of tartaric acid possesses two chiral centers, a pure sample of this compound is optically inactive: MESO

Internal Compensation OR presence of plane of symmetry!

achiral



meso

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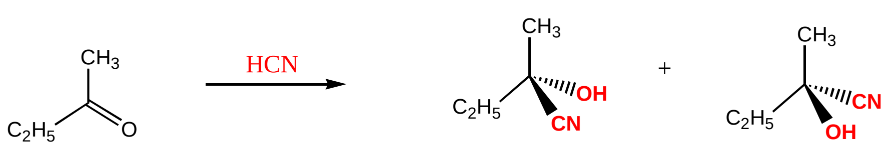
Chiral Molecules-Optically Inactive

When there is <u>equal composition</u> (1:1) of enantiomers in the mixture, the resulting solution is optically inactive

External compensation OR cancellation due to opposite optical rotations: RACEMIC MIXTURE



1 (50%) **1'** (50%)

Achiral chiral chiral

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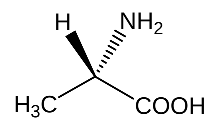
Nature's perfection

When one tries to generate optically active molecules in the laboratory, the problem of racimisation is always a challenge

Example 1: The amino acids found in living systems are enantiometically pure! (L-family)

(*S*)-alanine



Example 2: The lactic acid fatigue
(produced in human muscles when working under insufficient oxygen supply)

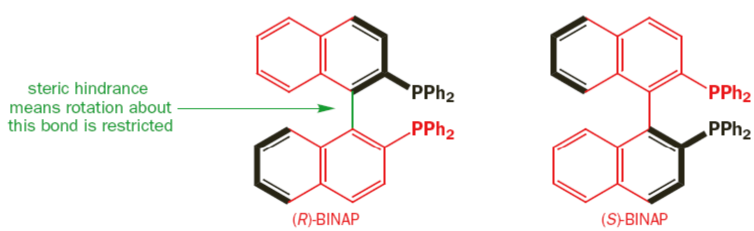
(*S*)-lactic acid

Chiral Molecules-with no chiral centers

The property of chirality is determined by overall molecular topology

There are many molecules that are chiral even though they do not possess a chiral center (asymmetric carbon)

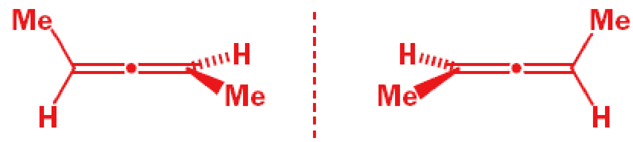
Example 1:



These molecules are axially chiral (axial asymmetry) arises due to restricted rotation around the C-C bond

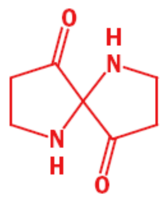
Chiral Molecules-with no chiral centers

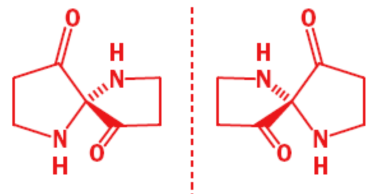
Example 2:



a chiral allene

Example 3:





nonsuperimposable enantiomers

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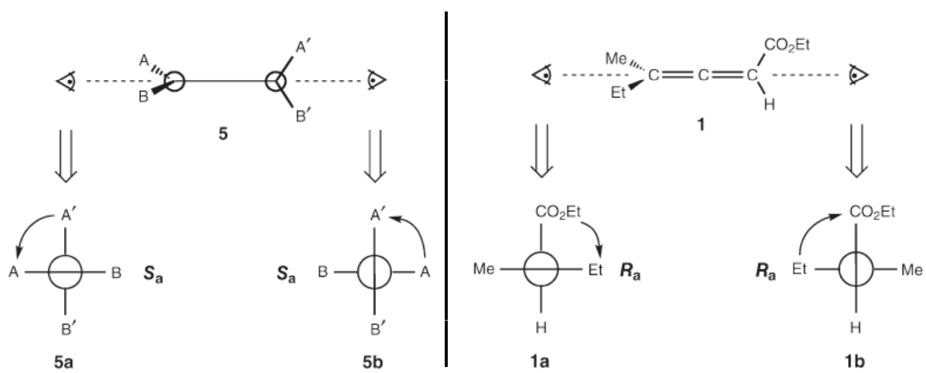
Absolute configuration of molecules with an axis of chirality



Journal of Chemical Education **2011, *88*, 299**

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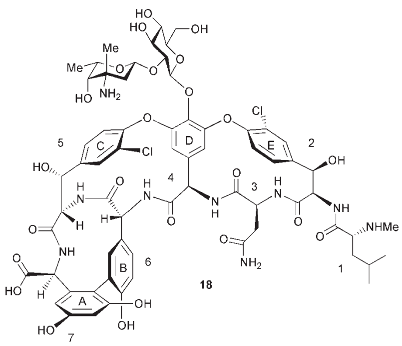
Atropisomers

Stereoisomers resulting from hindered rotation about single bonds (due to high steric strain to rotation)

Vancomycin is naturally occurring atropisomer



Used against bacterial infections

(also known as drug of last resort)

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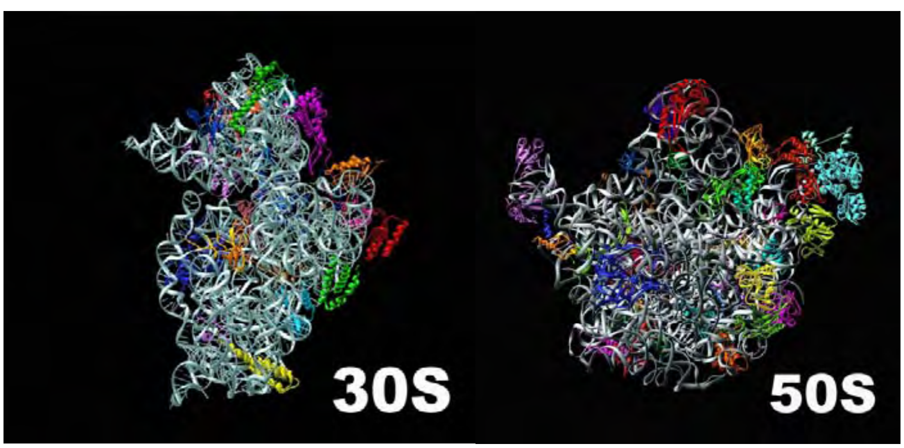
Ribosome Structure (X-Ray)



Nobel Prize in Chemistry 2009

Photo: U. Montan

Venkatraman Ramakrishnan

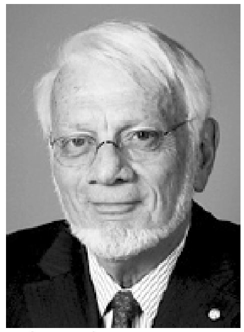


Photo: U. Montan

Thomas A. Steitz

Photo: U. Montan

Ada E. Yonath

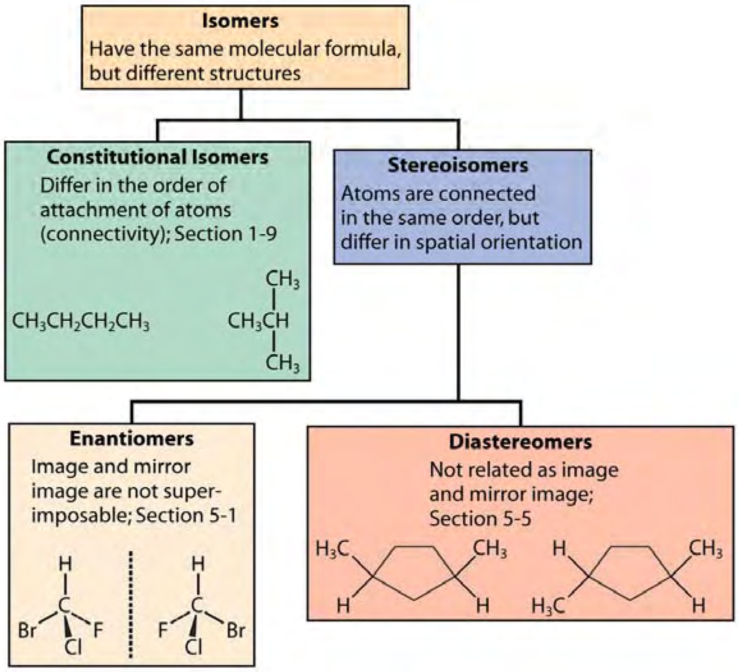
The Nobel Prize in Chemistry 2009 was awarded jointly to Venkatraman Ramakrishnan, Thomas A. Steitz and Ada E. Yonath *"for studies of the structure and function of the ribosome"*.

Doing Science for Nobel Prize

Q: How students could aim to emulate him and "win a Nobel for India,"?

Dr. Ramakrishnan answered emphatically: "That is the wrong question to ask…You can't go into science thinking of a Nobel Prize. You can only go into science because you're interested in it."

From Chidambaram to Cambridge: A life in science



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Two or More Chiral Carbons

- 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.

Chapter 5

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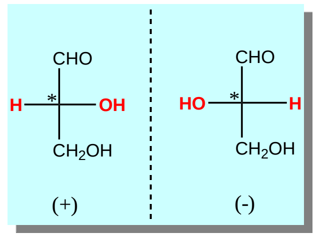
Relative Configuration

CH103
R. B. Sunoj

Glyceraldehyde is one of the simplest chiral molecule– sugar (carbohydrate)

D-(+)-glyceraldehyde



L-(-)-glyceraldehyde

Glyceraldehyde is used as a standard for assigning ***relative configurations***

Any enantiomerically pure compound that could be related to the configuration of

D-(+)-glyceraldehyde is labeled as D
and
L-(-)-glyceraldehyde is labeled as L

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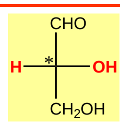
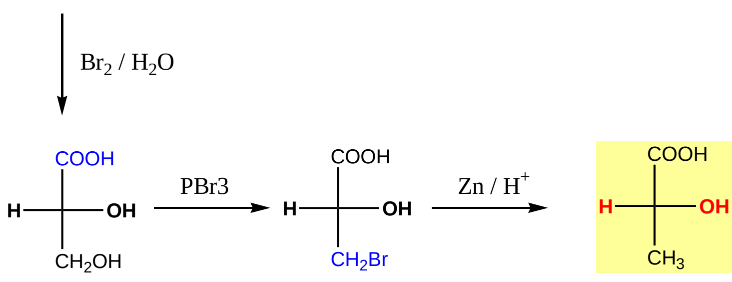
Important: note the use of capital letters

Relationship with Glyceraldehyde



D-(+)-glyceraldehyde



D-Lactic acid

Maintaining the basic connectivity, D-lactic acid is related to D-glyceraldehyde

D-optical family

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Optical Families

D-(+)-glyceraldehyde

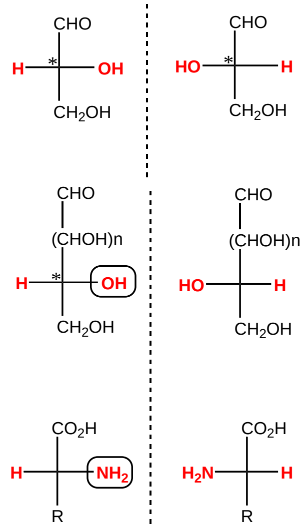
L-(-)-glyceraldehyde

D-sugars

L-sugars

D-amino acids

L-amino acids



R/S (absolute) versus D/L (relative)

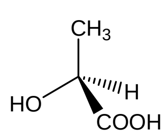
There is NO direct relationship between the configurational descriptors R/S or D/L

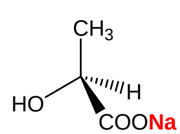
and

The sign of rotation

Sign of rotation of a sample should be measured using a polarimeter.

Lactic acid





Sodium lactate

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

The universe is asymmetric and I am persuaded that life, as it is known to us, is a direct result of the asymmetry of the universe or of its indirect consequence.

"Chance favors the prepared mind."

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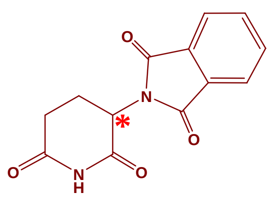
Properties of Enantiomers differ in Chiral medium

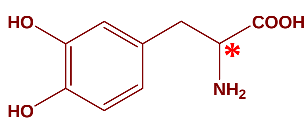
Biological properties of enantiomers are different, as the receptor sites are chiral

E.g., 1 **Thalidomide**



- R against nausea
- S cause fetal damage

E.g., 2 **DOPA**



- L treatment of Parkinson's disease
- D biologically inactive !

E.g., 3

(+)-glucose is metabolized by animals but NOT (-) glucose!

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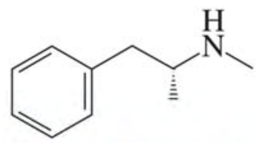
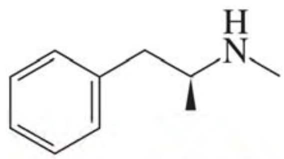
Physiological Properties of Enantiomers



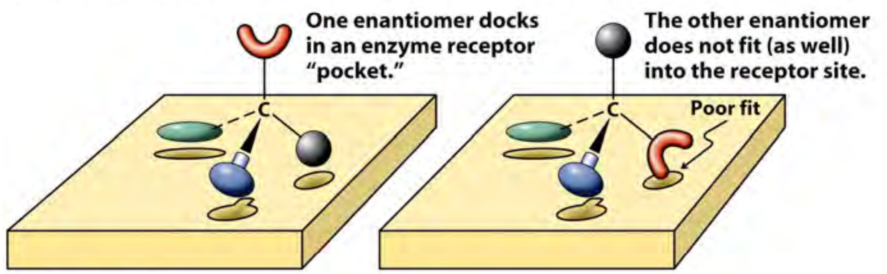
the active ingredient
in Vicks Vapor Inhaler®



methamphetamine
"speed"

Enantiomers can have very different physiological properties.

Biological Targets are Chiral!



Unnumbered figure pg 198b
Organic Chemistry, Fifth Edition

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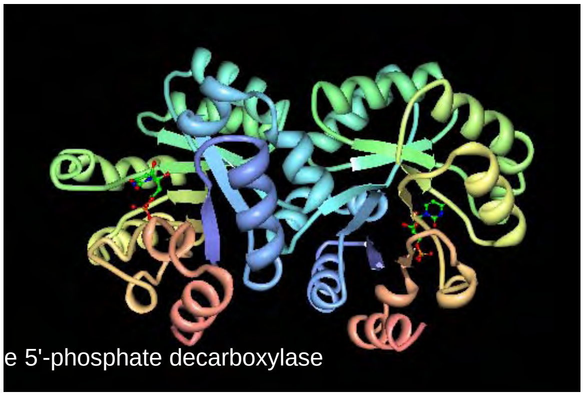
Enzymes are Chiral!



No of amino Acid- 228 residues (Chain A)
Function-Involved in pyrimidine metabolism. The enzyme converts orotidine monophosphate (OMP) to uridine monophosphate (UMP) by liberating carbon dioxide. It is known for being an extraordinarily efficient catalyst capable of accelerating the uncatalyzed reaction rate by a factor of 10^{17}

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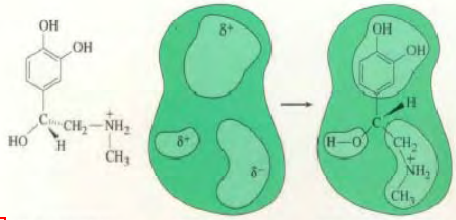
Taken from the Protein Data Bank

Biological Targets are Chiral!

Substrate specific binding is key to drug action

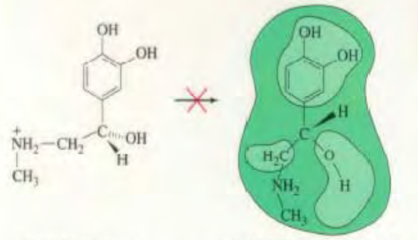
active *R*-isomer of ephinephrine



(*R*)-(−)-epinephrine natural epinephrine

enzyme active site

enzyme–substrate complex



(*S*)-(+)-epinephrine unnatural epinephrine

does not fit the enzyme's active site

S-isomer inactive

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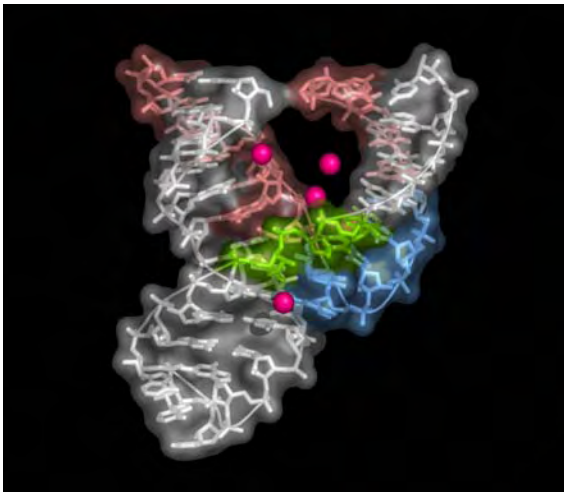
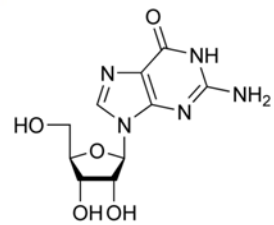
Courtesy L. G. Wade, Organic Chemistry, 4e, Pearson Education

Enzymes are Chiral!

RNA Enzyme: Ribozyme (Helical Chirality)





Resolution: Separation of Enatiomers

- **In 1848, Louis Pasteur noticed that a salt of racemic (±)-tartaric acid crystallizes into mirror-image crystals.**
- **Using a microscope and a pair of tweezers, he physically separated the enantiomeric crystals.**
- **Pasteur had accomplished the first artificial resolution of enantiomers.**

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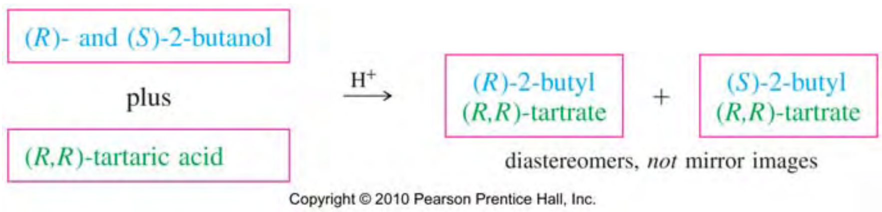
Resolution of Enantiomers



React the racemic mixture with a pure chiral compound, such as tartaric acid, to form diastereomers, then separate them.

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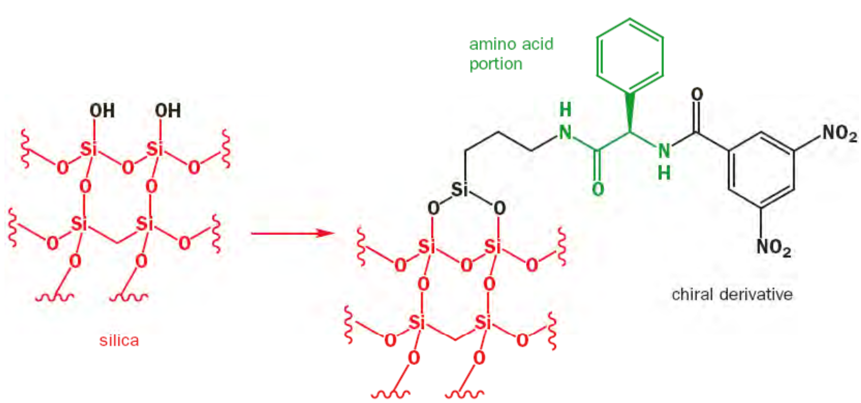
Resolution & Chiral HPLC



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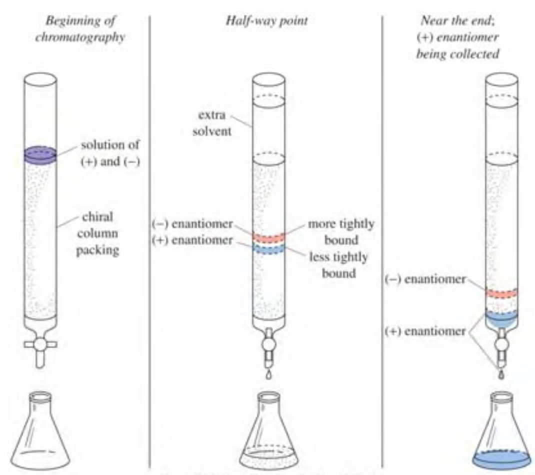
Chromatographic Resolution of Enantiomers



Comparing Structures

Are the structures connected the same?

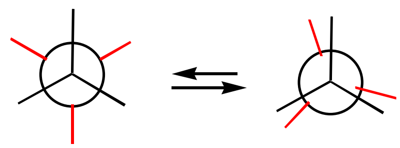
- **yes** → **Are they mirror images?**
  - **yes** → **Enantiomers** — *All chiral centers will be opposite between them.*
  - **no** → **Is there a plane of symmetry?**
    - **yes** → **Meso** — *superimposable*
    - **no** → **Diastereomers**
- **no** → **Constitutional Isomers**

Conformational Isomers

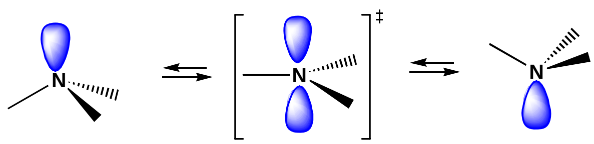
CH103
R. B. Sunoj

Conformational isomers: Stereoisomers that can interconvert rapidly at room temperature. Conformers cannot be separated.They arise due to

(a) rotation about single bonds (b) Amine inversion



Staggered Eclipsed



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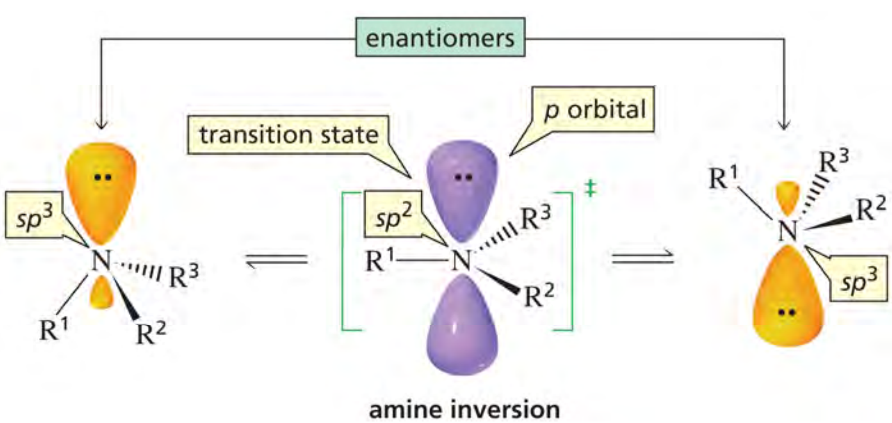
Amine Inversion



If one of the four groups attached to N is a lone pair, because they interconvert as a result of amine inversion.

The Mars Exploration Rover searching for life.

Unnumbered figure pg 199
Organic Chemistry, Fifth Edition

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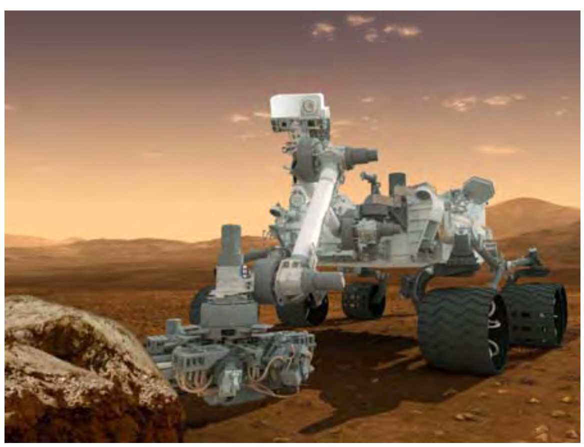

Ultimate Mars Challenge + You Tube

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