

INTRODUCTION TO CHEMISTRY

CML-101



**Dr. Chinmoy K. Hazra
Department of Chemistry
IIT Delhi**

12-12-2020

Course Instructor

Instructor: Chinmoy K. Hazra

Office: Main Building, 6th floor, MS 721,

Department of Chemistry

Contact Number: +9111-2654-8408

Email: chinmoy@chemistry.iitd.ac.in

Lab: Block VI, Ground floor, Room No: 134

Syllabus

Importance of stereochemistry in drug action (warfarin, thalidomide, naproxen); R/S nomenclature, Fisher, Sawhorse, and Newmann projections

Kinetic versus thermodynamic control: selected examples using MO theory (DAR, 1,3-butadiene addition, enolate alkylation, naphthalene sulfonation)

Determination of reaction mechanism: kinetic methods, isotope effects, intermediate trapping, the stereochemical outcome in reactions (NGP and elimination reaction)

Spectroscopic methods of structure determination

Syllabus

Importance of stereochemistry in drug action (warfarin, thalidomide, naproxen); R/S nomenclature, Fisher, Sawhorse, and Newmann projections

Kinetic versus thermodynamic control: selected examples using MO theory (DAR, 1,3-butadiene addition, enolate alkylation, naphthalene sulfonation)

Determination of reaction mechanism: kinetic methods, isotope effects, intermediate trapping, the stereochemical outcome in reactions (NGP and elimination reaction)

Spectroscopic methods of structure determination

References

- 1. Solomons's Organic Chemistry, Global Edition Paperback – 1 January 2017 by T. W. Graham Solomons, Craig B. Fryhle, Scott A. Snyder.**

- 2. Organic Chemistry 2nd Ed. (J. Clayden, N. Greeves and S. Warren, Oxford University Press, 2012, ISBN 978-0-19-927029-3).**

- 3. Guidebook to Mechanism in Organic Chemistry (6th Edition) by Peter Sykes.**

What is organic chemistry?

Organic chemistry is a branch of chemistry that studies the structure, properties and reactions of organic compounds, which contain carbon in covalent bonding. Study of structure determines their chemical composition and formula.

History

In 1828 Friedrich Wöhler produced the organic chemical **urea** (carbamide), a constituent of urine, from inorganic starting materials (the salts potassium cyanate and ammonium sulfate).

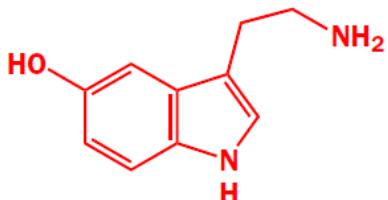


Friedrich Wöhler

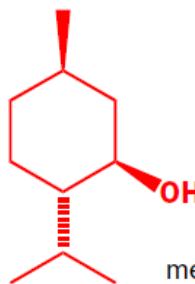
Importance

- 1. Pharmaceutical industry**
- 2. Petrochemicals**
- 3. Industrial and commercial products:** plastics, synthetic rubber, organic adhesives, catalysts
- 4. Clean energy: Hydrogen gas (H_2)**
etc

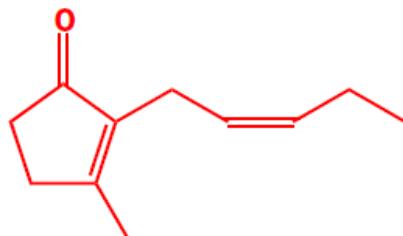
Importance



serotonin
human neurotransmitter



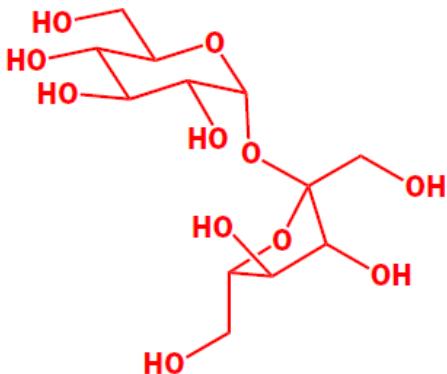
menthol



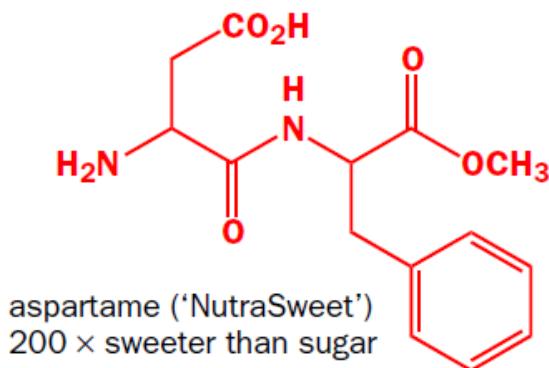
cis-jasmone



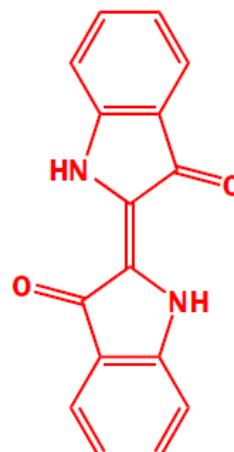
quinine



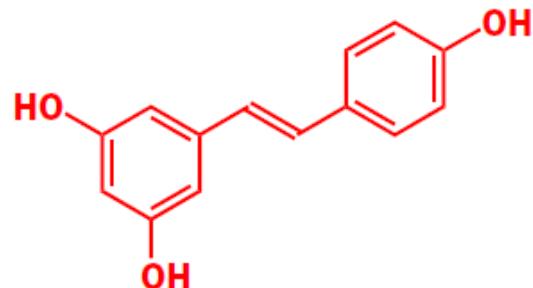
sucrose – ordinary sugar
isolated from sugar cane
or sugar beet
white crystalline solid



aspartame ('NutraSweet')
200 × sweeter than sugar



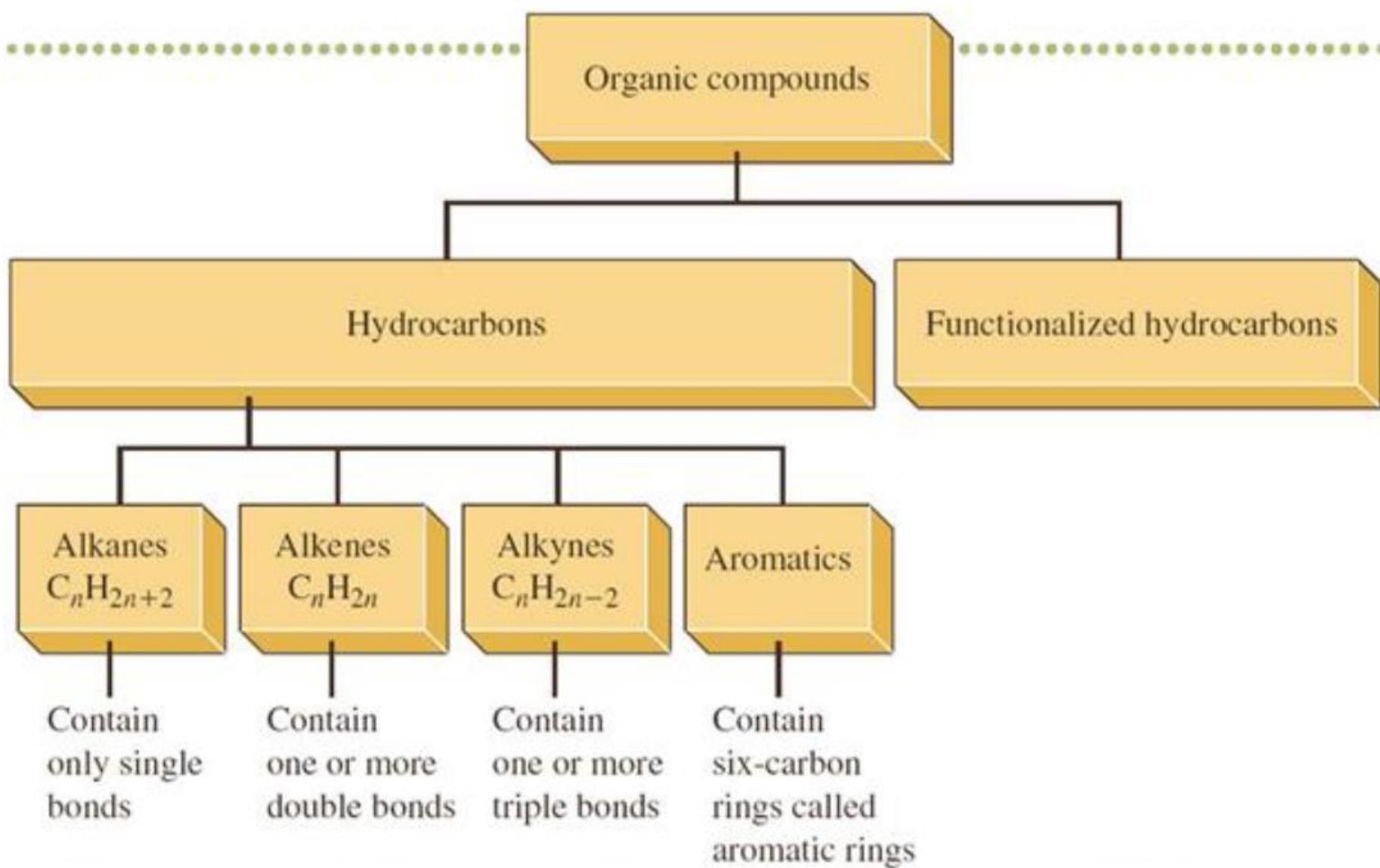
indigo
the colour of blue jeans



resveratrol from the skins of grapes
is this the compound in red wine
which helps to prevent heart disease?



Remdesivir



Basic Naming of Hydrocarbons

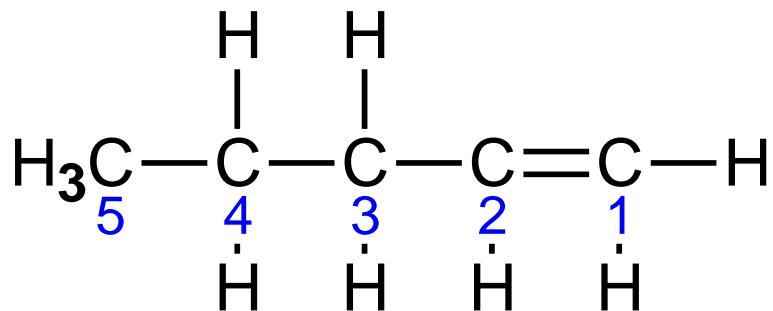
Hydrocarbon names are based on: 1) type, 2) # of carbons, 3) side chain type and position

1) name will end in -ane, -ene, or -yne

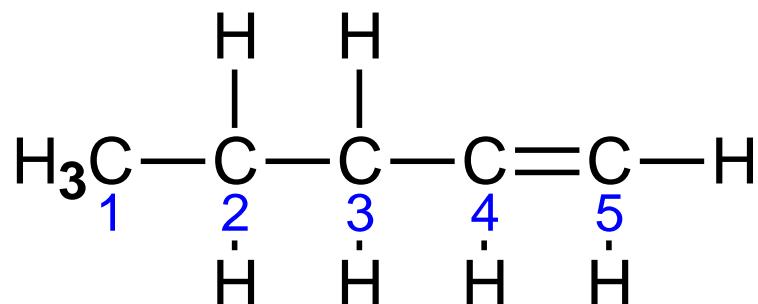
2) the number of carbons is given by a “prefix”

1 meth- 2 eth- 3 prop- 4 but- 5 pent- 6 hex- 7 hept- 8 oct- 9
non- 10 dec- etc.

Numbering Carbons

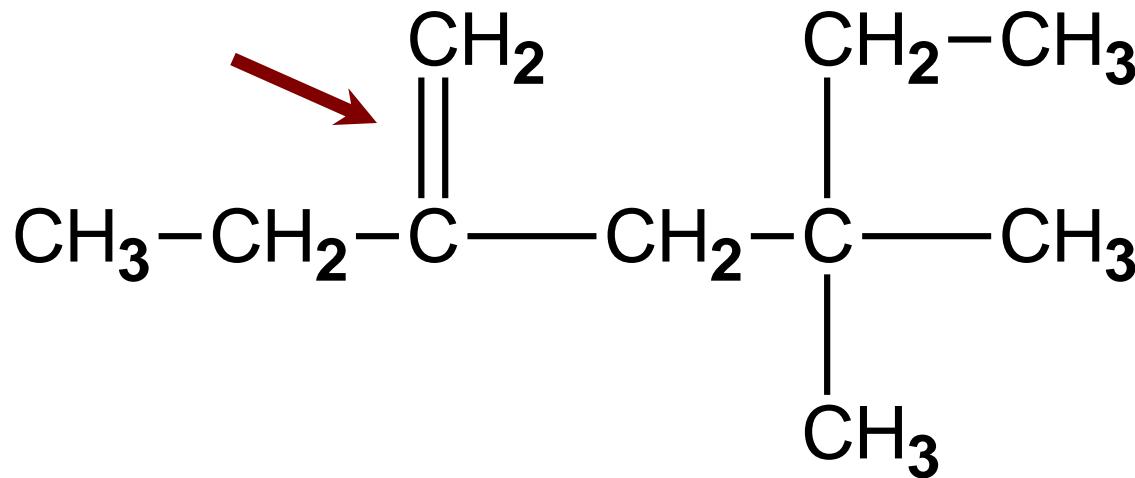


1-pentene



Naming Side Chains

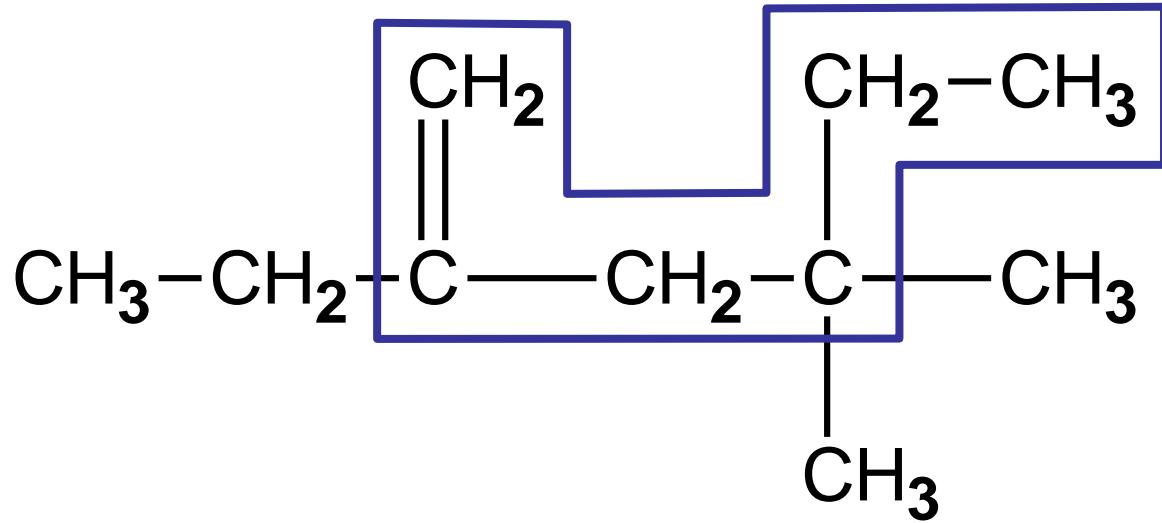
Example: use the rules on this handout
to name the following structure



Rule 1: choose the correct ending

ene

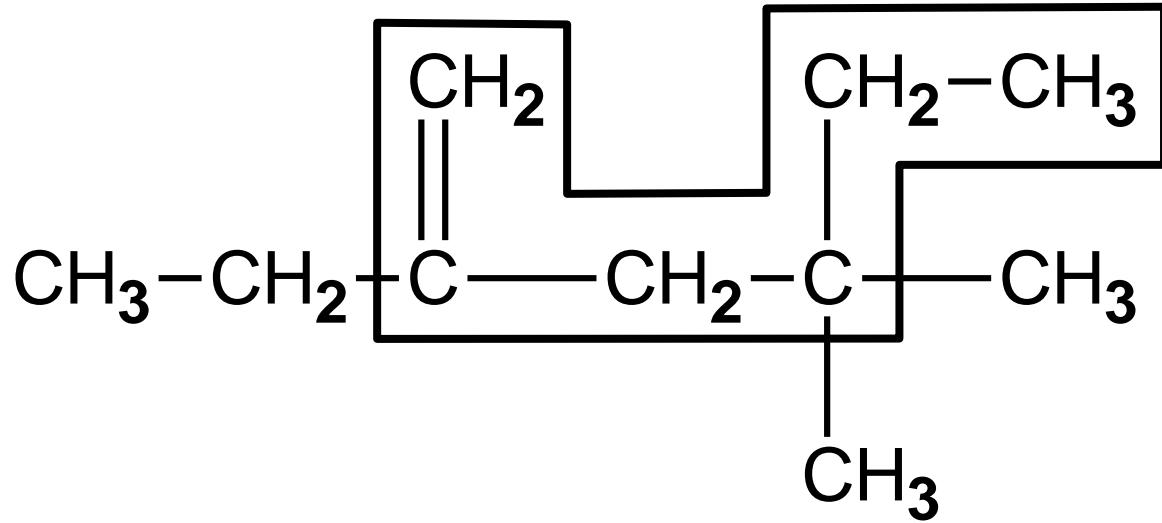
Naming Side Chains



Rule 2: determine the longest carbon chain

ene

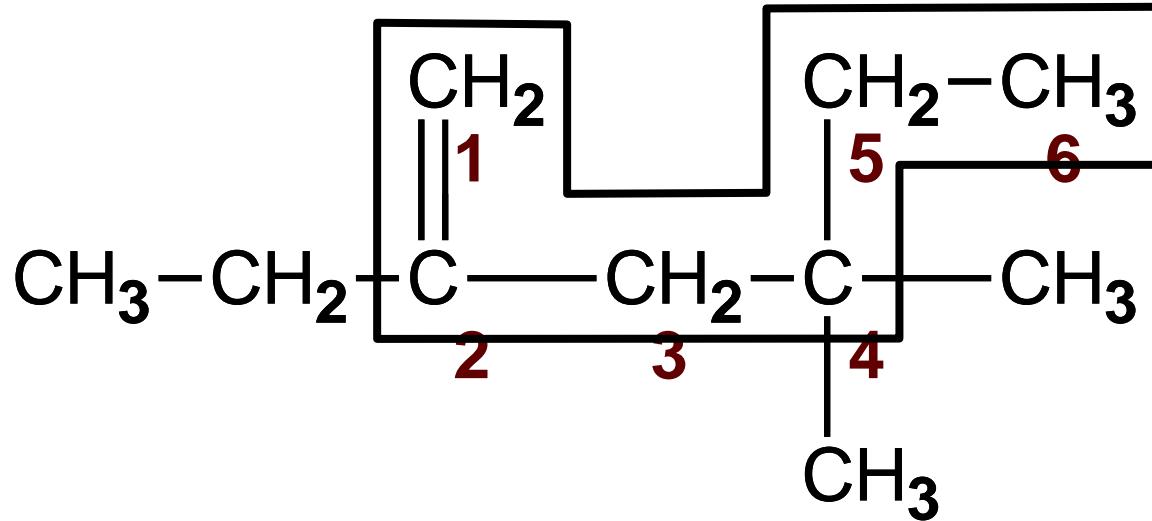
Naming Side Chains



Rule 3: Assign numbers to each carbon

ene

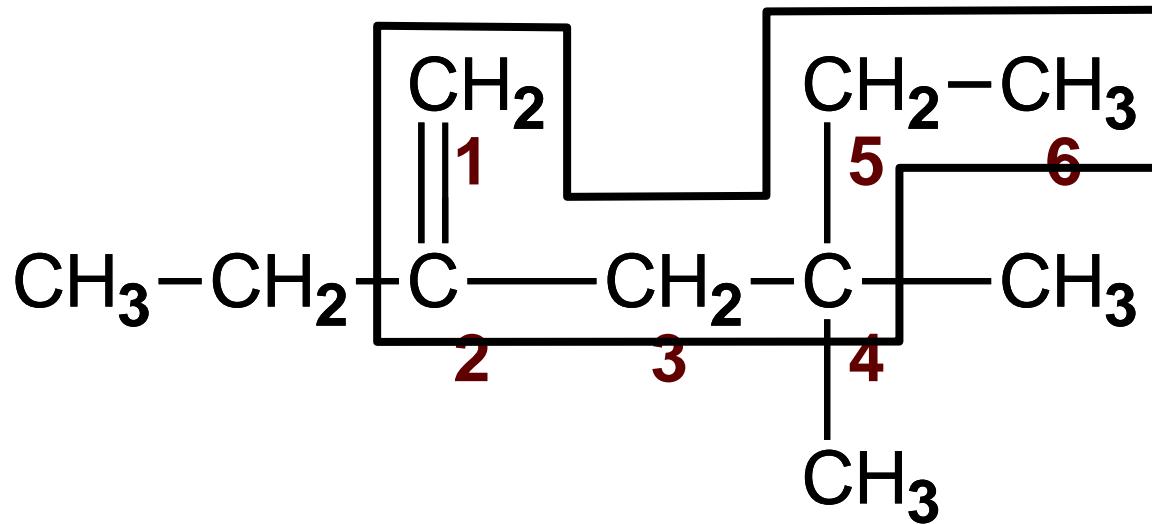
Naming Side Chains



Rule 3: Assign numbers to each carbon

ene

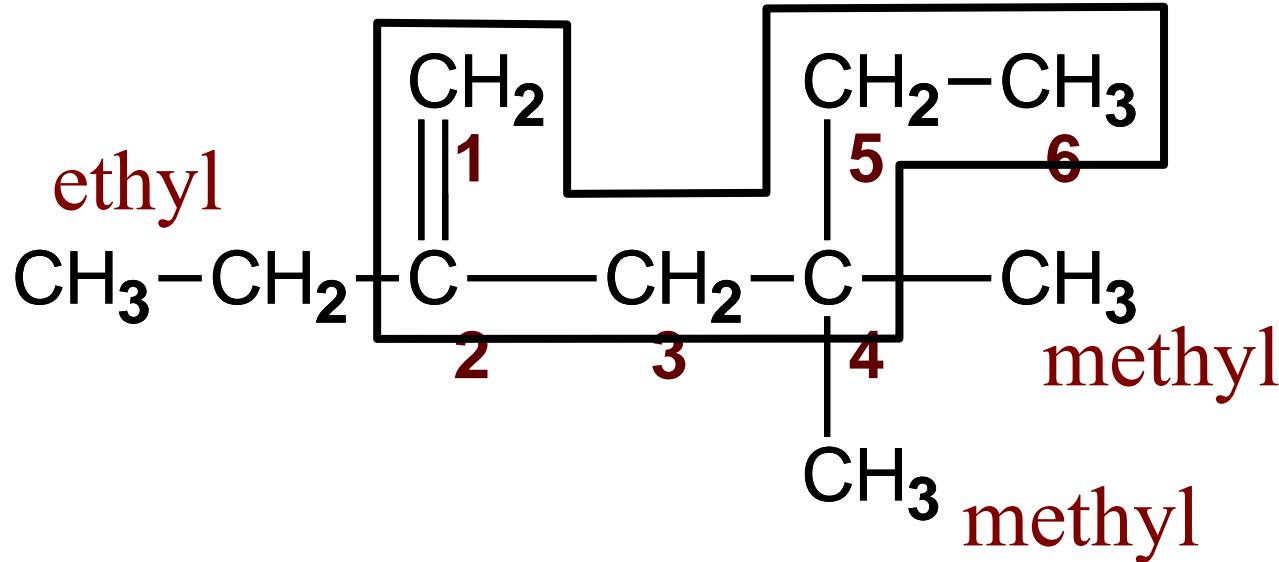
Naming Side Chains



Rule 4: attach prefix (according to # of Cs)

1-hexene

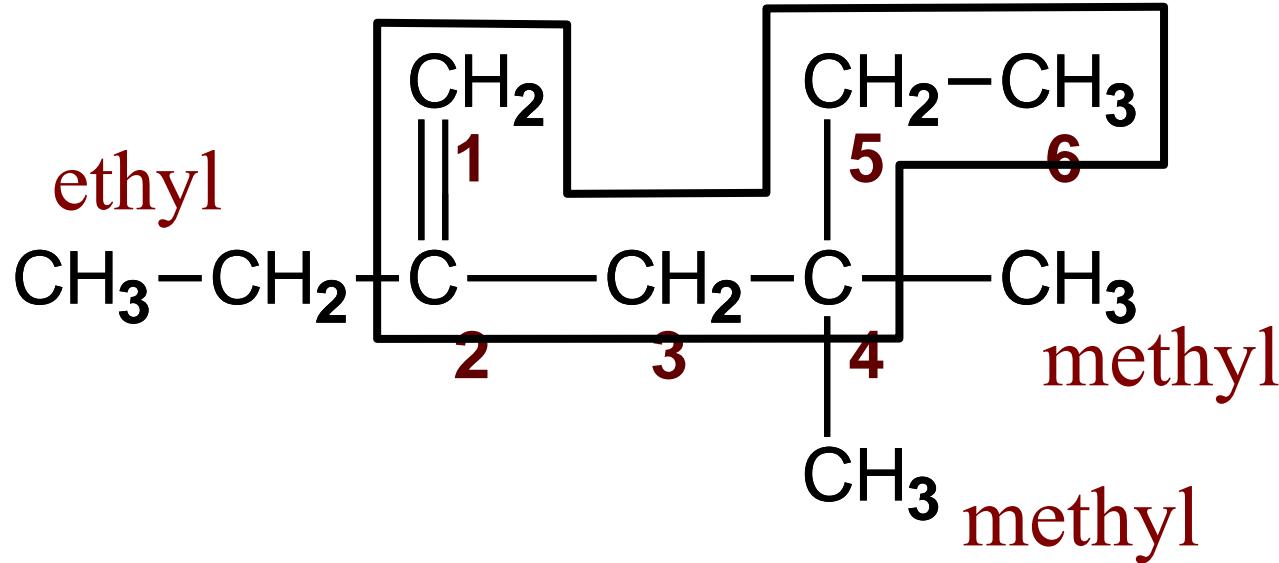
Naming Side Chains



Rule 5: Determine name for side chains

1-hexene

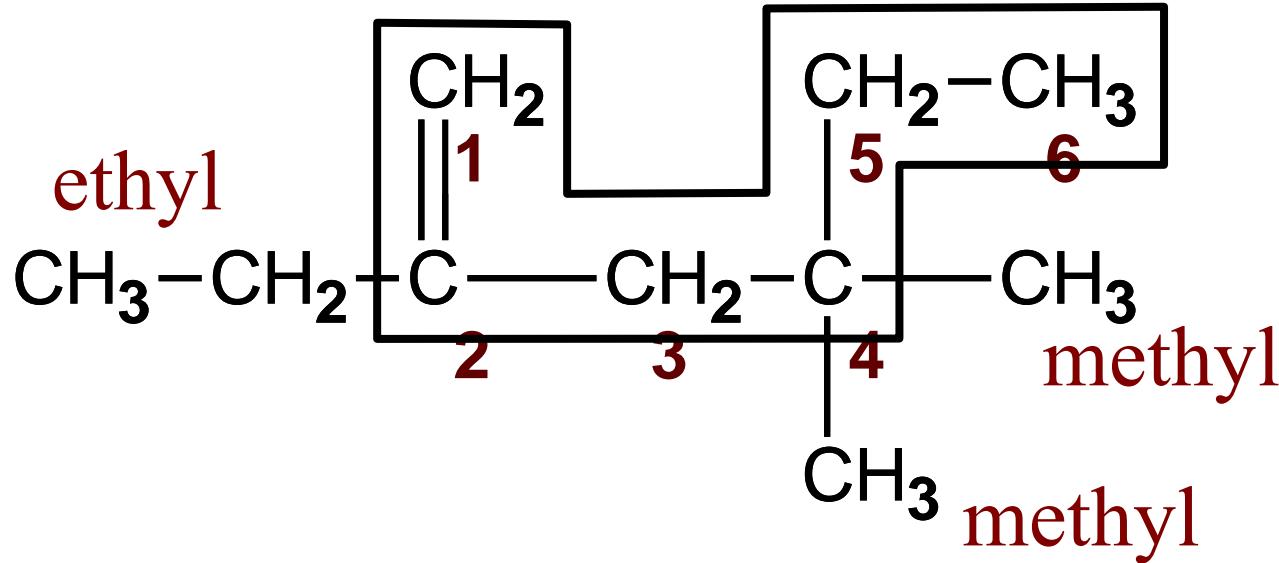
Naming Side Chains



Rule 6: attach name of branches alphabetically

2-ethyl-4-methyl-4-methyl-1-hexene

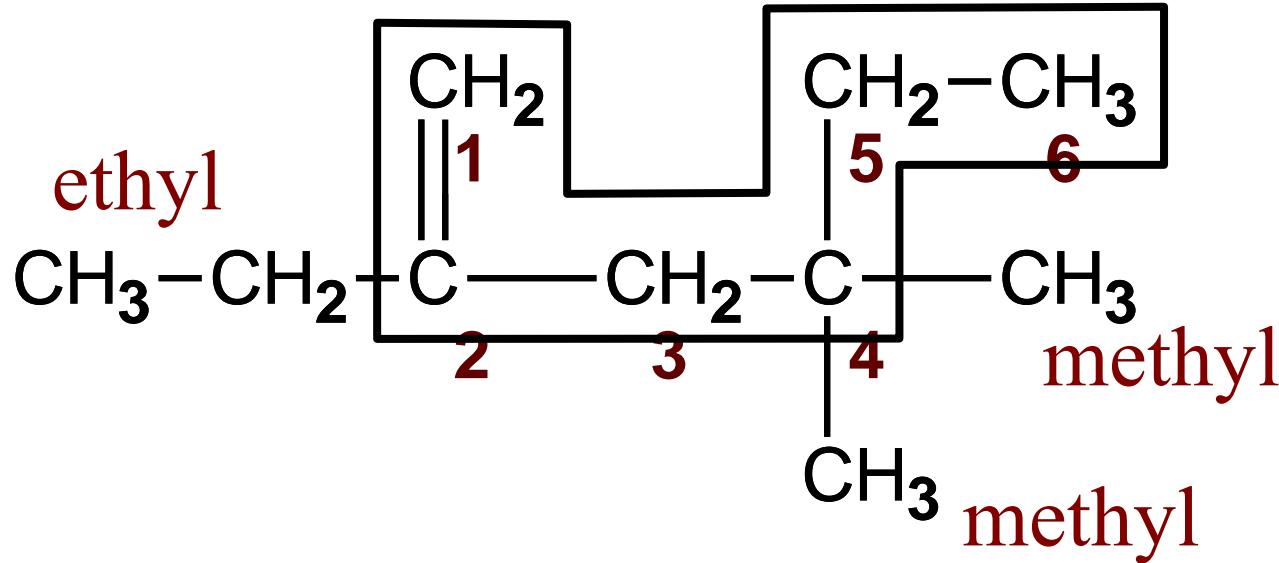
Naming Side Chains



Rule 7,8: group similar branches

2-ethyl-4-methyl-4-methyl-1-hexene

Naming Side Chains



Rule 7,8: group similar branches

2-ethyl-4,4-dimethyl-1-hexene

2. STEREOISOMERISM

- Isomers which have the same molecular formula and same structural formula but differ in the manner their atoms or groups are arranged in the space are called **stereoisomers**. It is of two types:

I **Configurational Isomerism**

II **Conformational Isomerism**

I. Configurational Isomerism

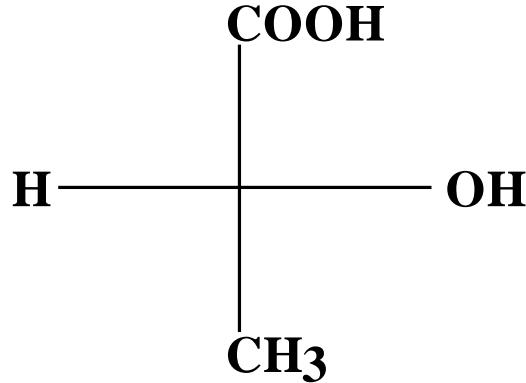
- *The stereoisomers which cannot be interconverted unless a covalent bond is broken are called configurational isomers. These isomers can be separated under normal conditions.*
- *The configurational isomerism is again of two types:*
 - a) *Optical Isomerism or Enantiomerism*
 - b) *Geometrical Isomerism*

a) Optical Isomerism or Enantiomerism

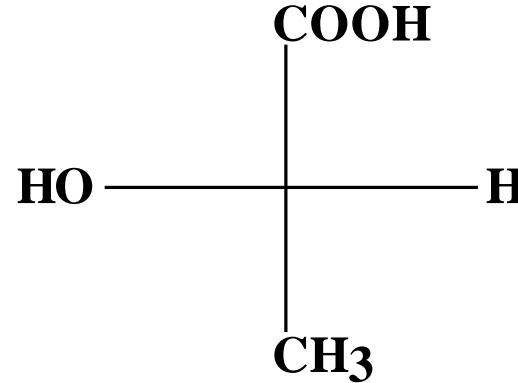
- The stereoisomers which are related to each other as an object and its non-superimposable mirror image are called *optical isomers* or *enantiomers* (Greek: enantion means opposite).
- The optical isomers can also rotate the plane of polarised light to an equal degree but in opposite direction.
- *The property of rotating plane of polarised light is known as optical activity.*
- *The optical isomers have similar physical and chemical properties.*

For example,

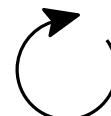
- Molecular formula $C_3H_6O_3$ represents two enantiomeric lactic acids as shown below:



(Rotates the plane of polarized light towards left hand side i.e. anticlockwise)

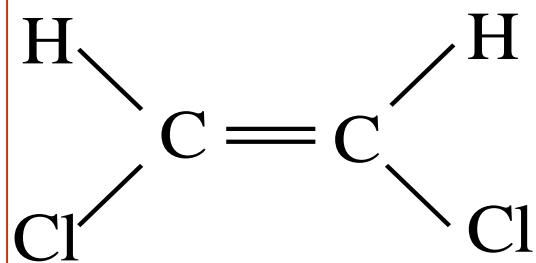


(Rotates the plane of polarized light towards right hand side i.e. clockwise)

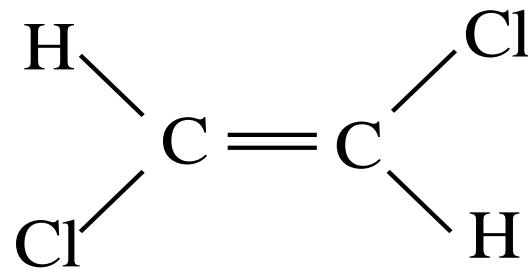


b) Geometrical Isomerism

- **Geometric isomers** are the stereoisomers which differ in their spatial geometry due to restricted rotation across a double bond.
- These isomers are also called as *cis-trans* isomers. For example, molecular formula $C_2H_2Cl_2$ corresponds to two geometric isomers as follows:



cis-1,2-Dichloroethene



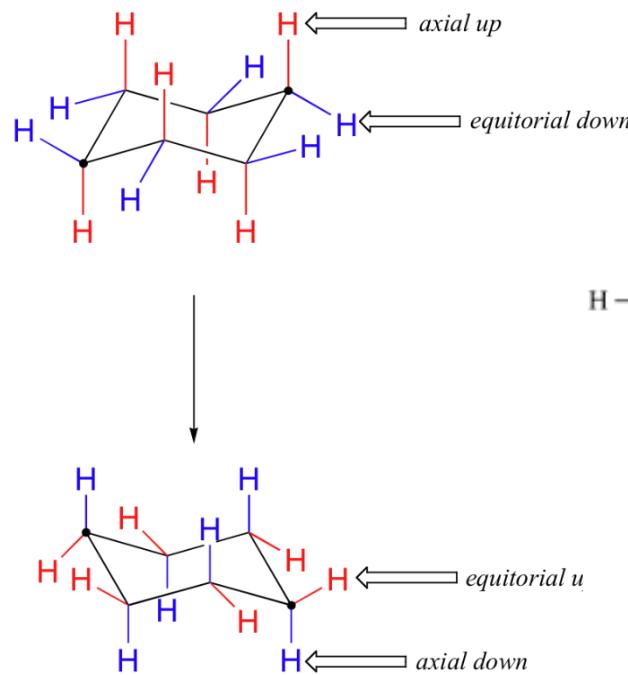
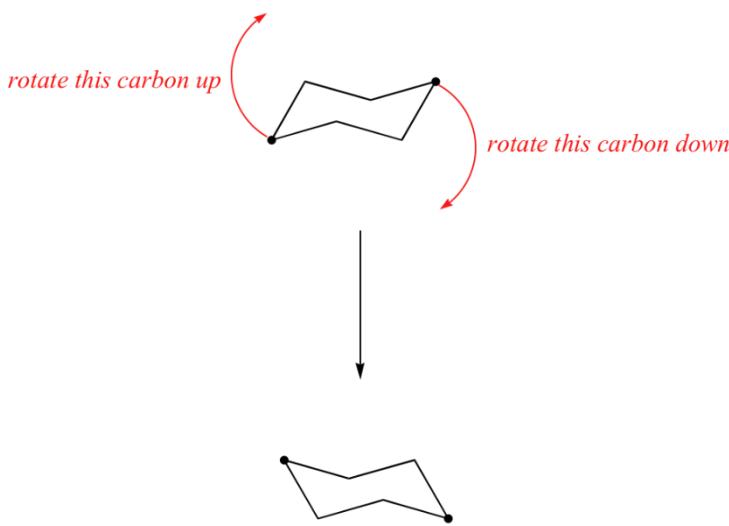
trans-1,2-Dichloroethene

II. Conformational Isomerism

- The stereoisomers which can be interconverted rapidly at room temperature without breaking a covalent bond are called conformational isomers or conformers.
- Because such isomers can be **readily interconverted**, they cannot be separated under normal conditions.
- Two types of conformational isomers are:
 - a) *Conformational isomers resulting from rotation about single bond*
 - b) *Conformational isomers arising from amine inversion*

a) Conformational isomers resulting from rotation about single bond

- Because the single bond in a molecule rotates continuously, the compounds containing single bonds have many interconvertible conformational isomers. e.g, '*boat*' and '*chair*' forms of cyclohexane.

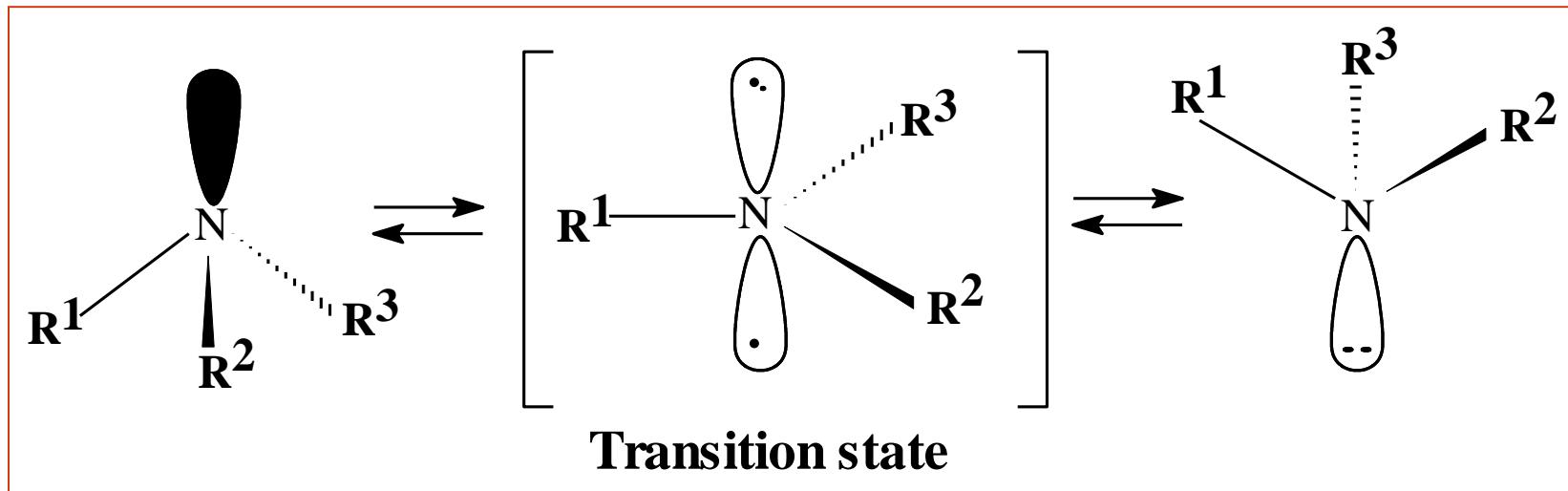


Cyclohexane
(chair form)

Cyclohexane
(boat form)

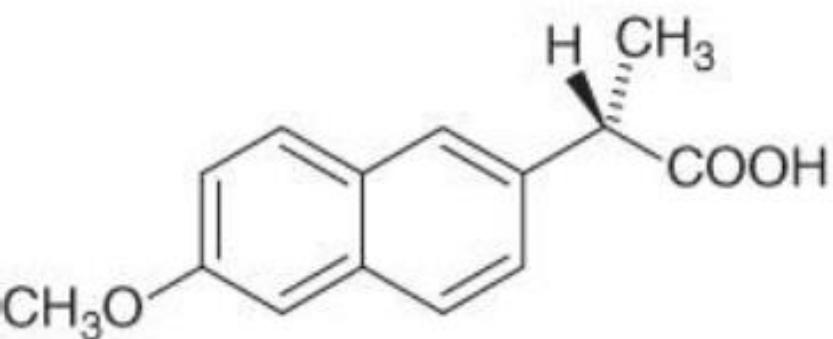
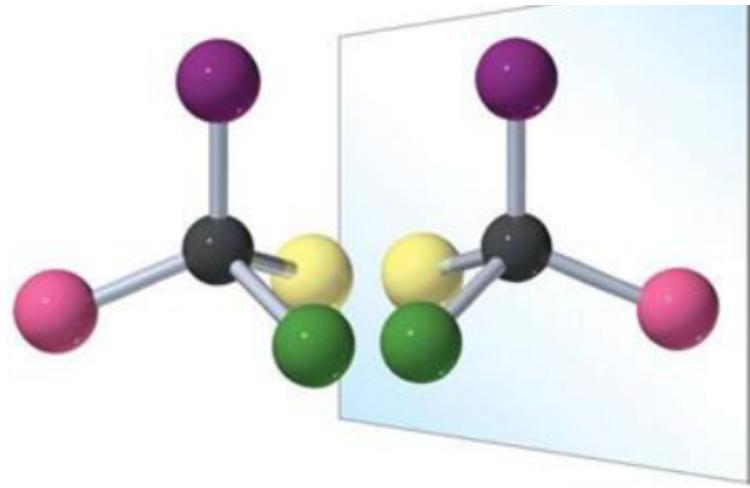
b) Conformational isomers arising from amine inversion

- Nitrogen atom of amines has a pair of non-bonding electrons which allow the molecule to turn "*inside out*" rapidly at room temperature. This is called **amine inversion** or **Walden inversion**.

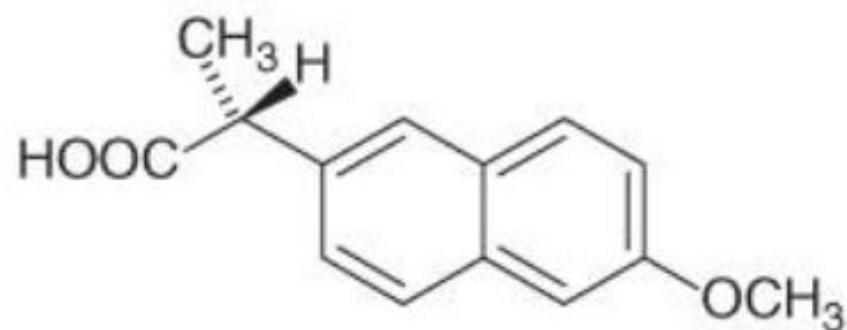


Stereochemistry

The branch of chemistry concerned with the three-dimensional arrangement of atoms and molecules and the effect of this on chemical reactions.



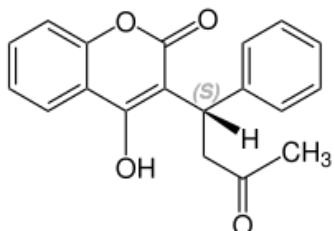
(S)-naproxen
anti-inflammatory agent



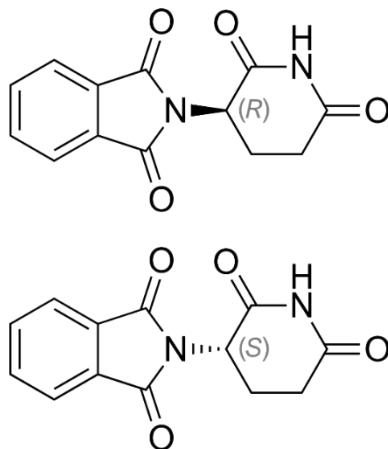
(R)-naproxen
liver toxin

Importance of Stereochemistry

Structure of Warfarin



Structure of Thalidomide



Uses of Thalidomide & its analogues

FDA approved :ENL

Multiple Myeloma :
Myelodysplastic syndrome

Promising uses

- Prostate cancer
- Aphthous ulcers (in HIV)
- Anti-neoplastic effects :**
 - AIDS related Kaposi's sarcoma

Potential uses

- Autoimmune conditions**
- GVHD
- RA & Ankylosing Spondylitis
- Inflammatory bowel disease
- SLE & Bechet's disease

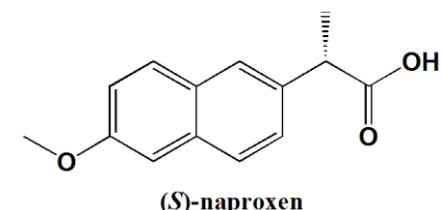
Cachexia and weight loss

- HIV associated
- Tuberculosis
- Cancer cachexia
- Heart failure

Dermatological conditions

- Discoid lupus erythematosus
- Actinic prurigo
- Prurigo nodularis
- pyoderma gangrenosum

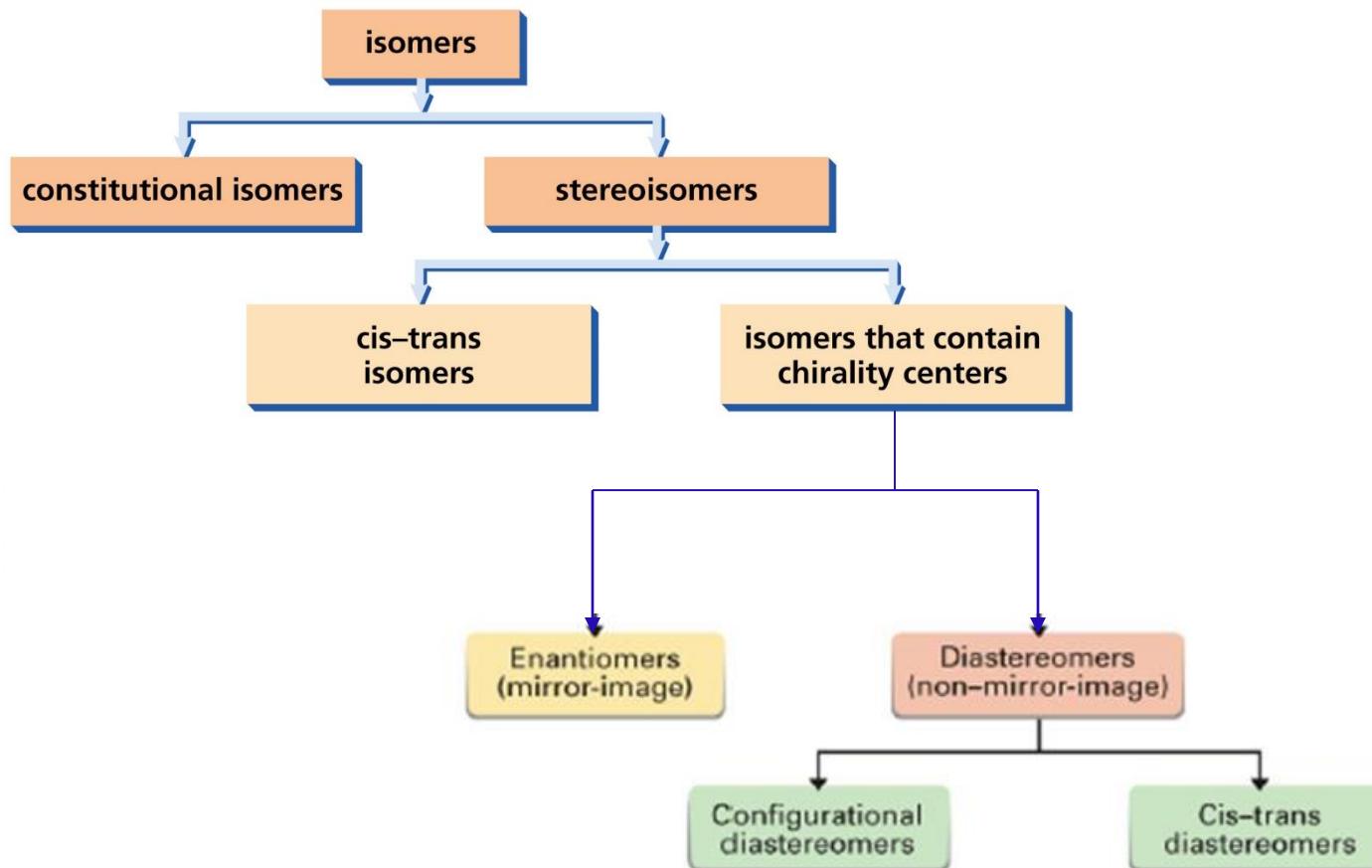
Structure of Naproxen



Naproxen is a medicine that reduces inflammation and **pain** in joints and muscles. It's used to treat diseases of joints, such as **rheumatoid arthritis**, **osteoarthritis** and **gout**. It's also used for period **pain** and muscle and bone disorders, such as back **pain** and sprains and strains.

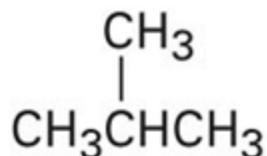
Isomerism

Isomers are different compounds that have the same molecular formula.

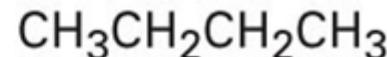


- **Constitutional isomers** are isomers that differ because their atoms are connected in a different order.

Different carbon skeletons



and



2-Methylpropane

Butane

Different functional groups



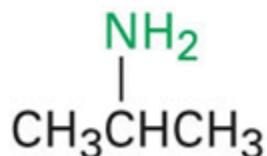
and



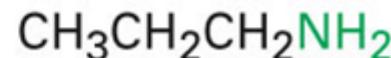
Ethyl alcohol

Dimethyl ether

Different position of functional groups



and



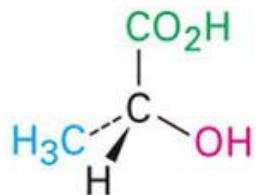
Isopropylamine

Propylamine

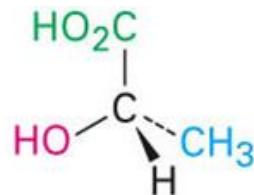
-
- **Stereoisomers** have their atoms connected in the same sequence (the same Constitution), but differ in the arrangement of their atoms in space.
 - **Stereoisomers** can be either **enantiomers** or **diasteromers**.
 - **Enantiomers** are stereoisomers whose molecules are nonsuperimposable mirror images of each other.
 - All other Stereoisomers are diasteromers.
 - **Diasteromers** are stereoisomers whose molecules are not mirror images of each other. Includes cis, trans and configurational.

Enantiomers

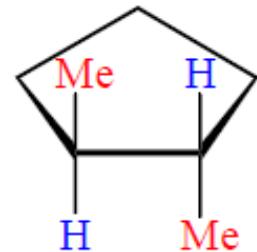
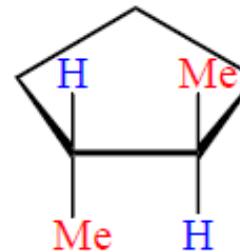
(nonsuperimposable
mirror-image
stereoisomers)



(R)-Lactic acid



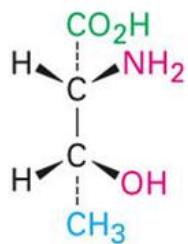
(S)-Lactic acid



trans-1,2-Dimethylcyclopentane

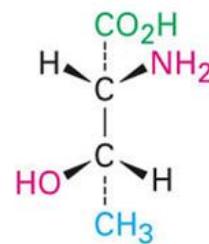
Diastereomers

(nonsuperimposable,
non-mirror-image
stereoisomers)

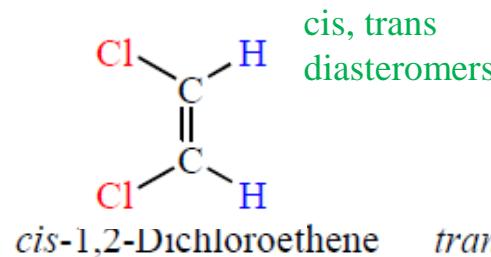


2*R*,3*R*-2-Amino-3-hydroxybutanoic acid

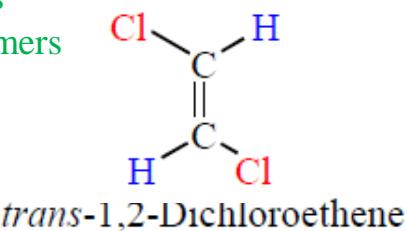
Configurational
diastereomers



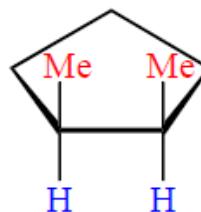
2*R*,3*S*-2-Amino-3-hydroxybutanoic acid



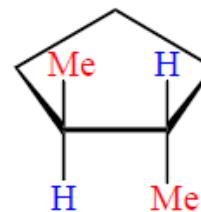
cis-1,2-Dichloroethene



trans-1,2-Dichloroethene



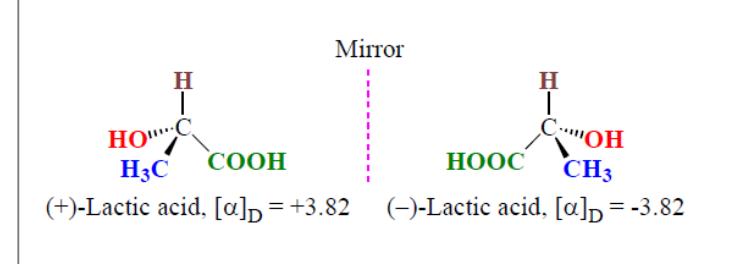
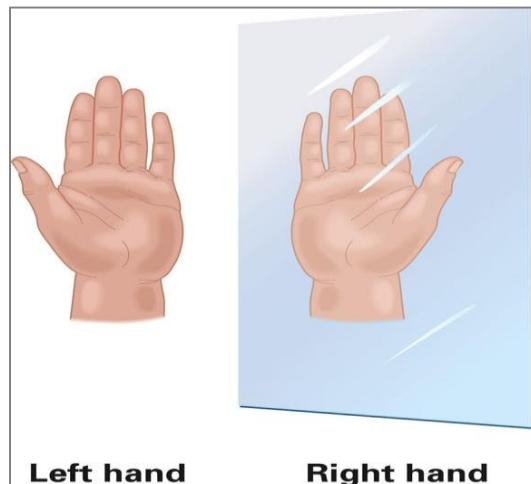
cis-1,2-Dimethylcyclopentane

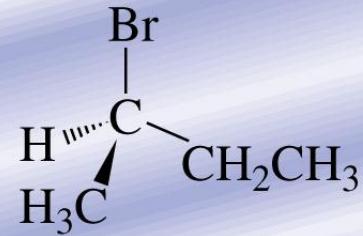
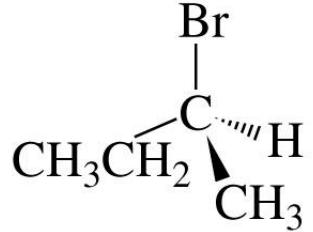


trans-1,2-Dimethylcyclopentane

Enantiomers and Chiral Molecules

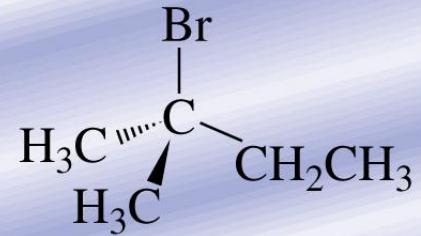
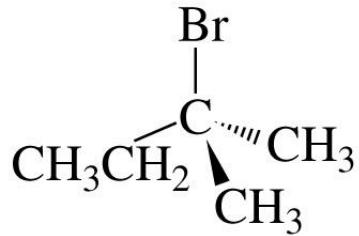
- **Enantiomers** occur only with compounds whose molecules are **chiral**.
- A **chiral molecule** is one that is not superposable on its mirror image (have handedness).
- The relationship between a chiral molecule and its mirror image are said to be **enantiomers** of each other.





a chiral molecule

enantiomers



an achiral molecule

identical molecules

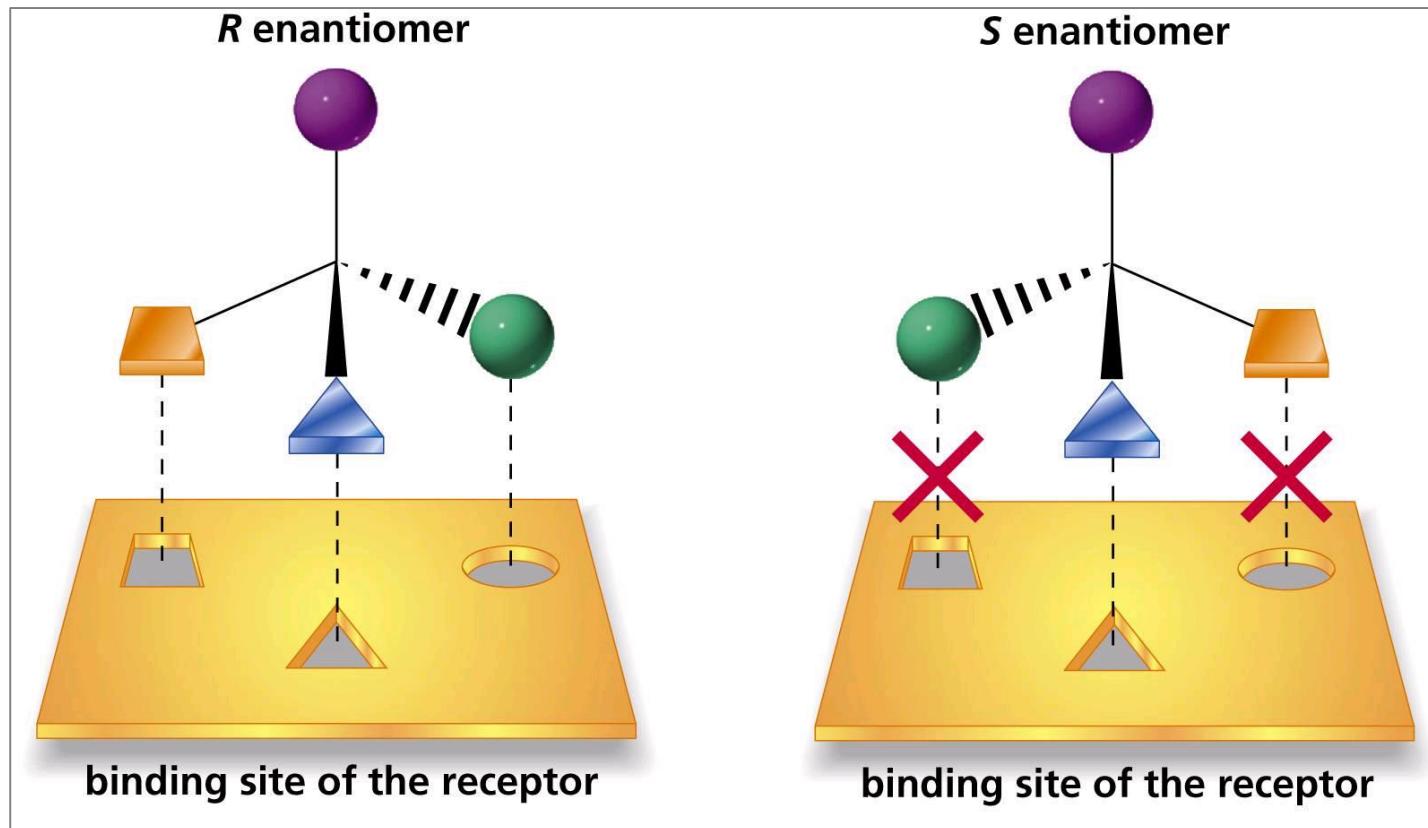
superimposable mirror image

Achiral compounds have superimposable mirror images

Chiral compounds have nonsuperimposable mirror images

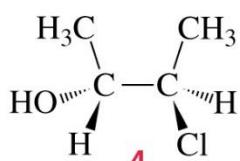
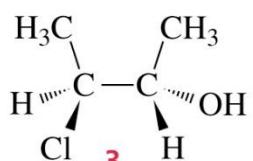
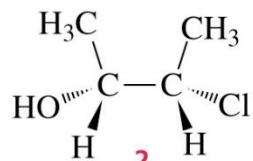
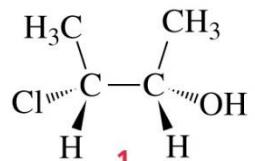
The Biological Importance of Chirality

- Only one of the two enantiomers shown (the right-hand one) can achieve three-point binding with hypothetical binding site (e.g., in an enzyme)



Drawing Enantiomers

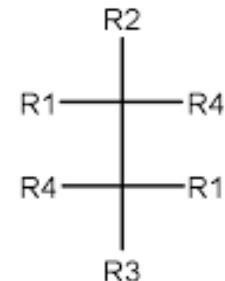
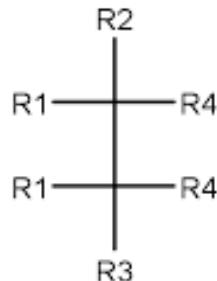
Perspective formula



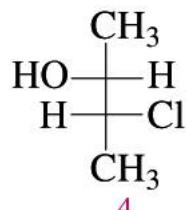
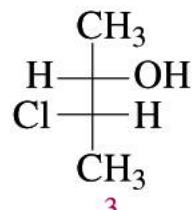
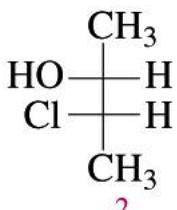
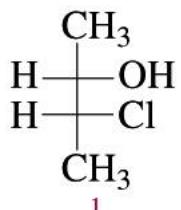
erythro enantiomers

threo enantiomers

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



Fischer projection



erythro

threo

erythro enantiomers

threo enantiomers

Properties of Enantiomers: Optical Activity

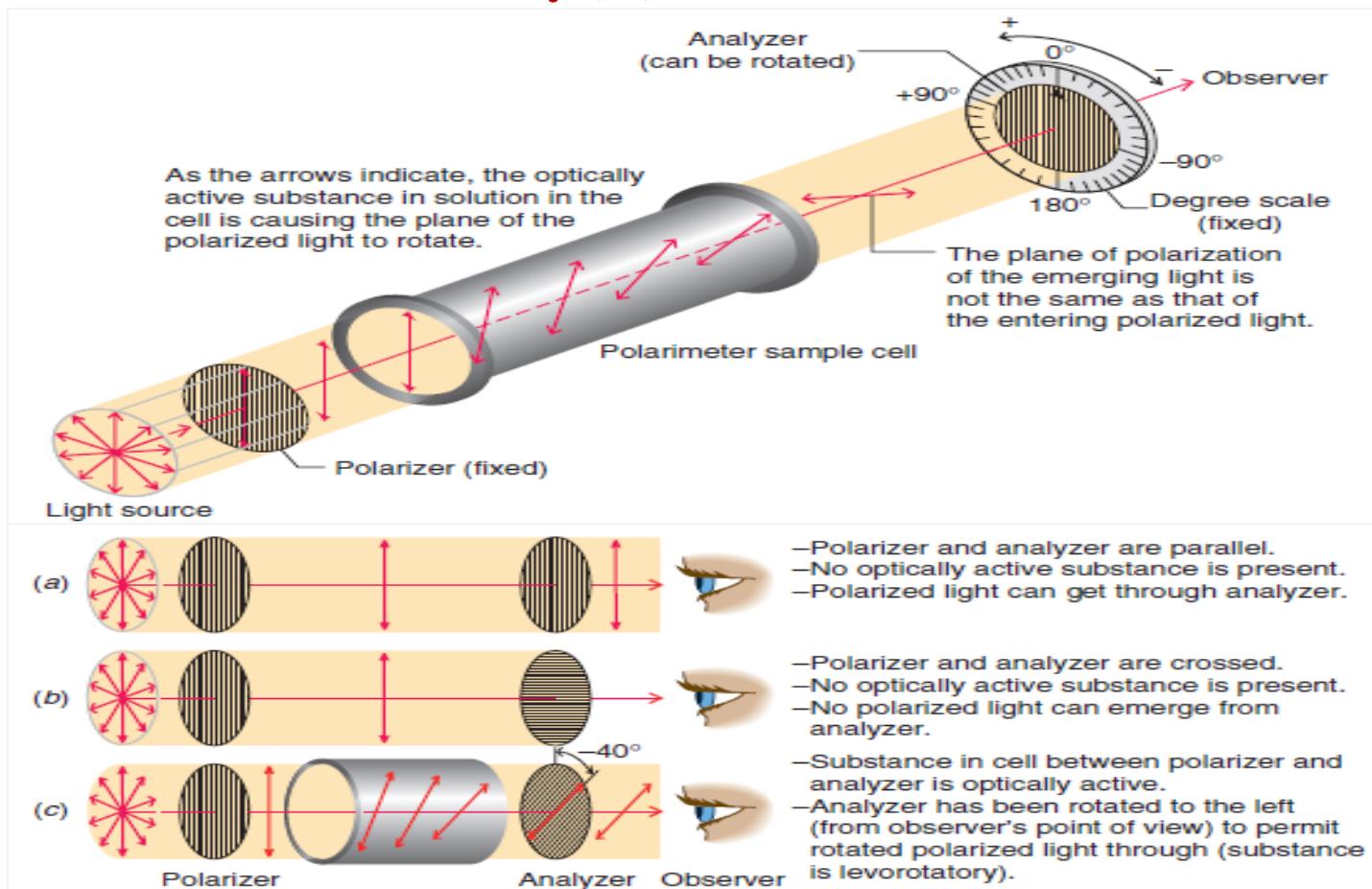
- **Enantiomers** have identical physical properties such as boiling points, melting points, refractive indices, and solubilities in common solvents **except optical rotations**.
- **Enantiomers** rotate the plane of plane-polarized light in equal amounts but in opposite directions.
- **Plane-Polarized Light**

The light used to measure optical activity has two properties:
consists of a single wavelength And it is plane-polarized.

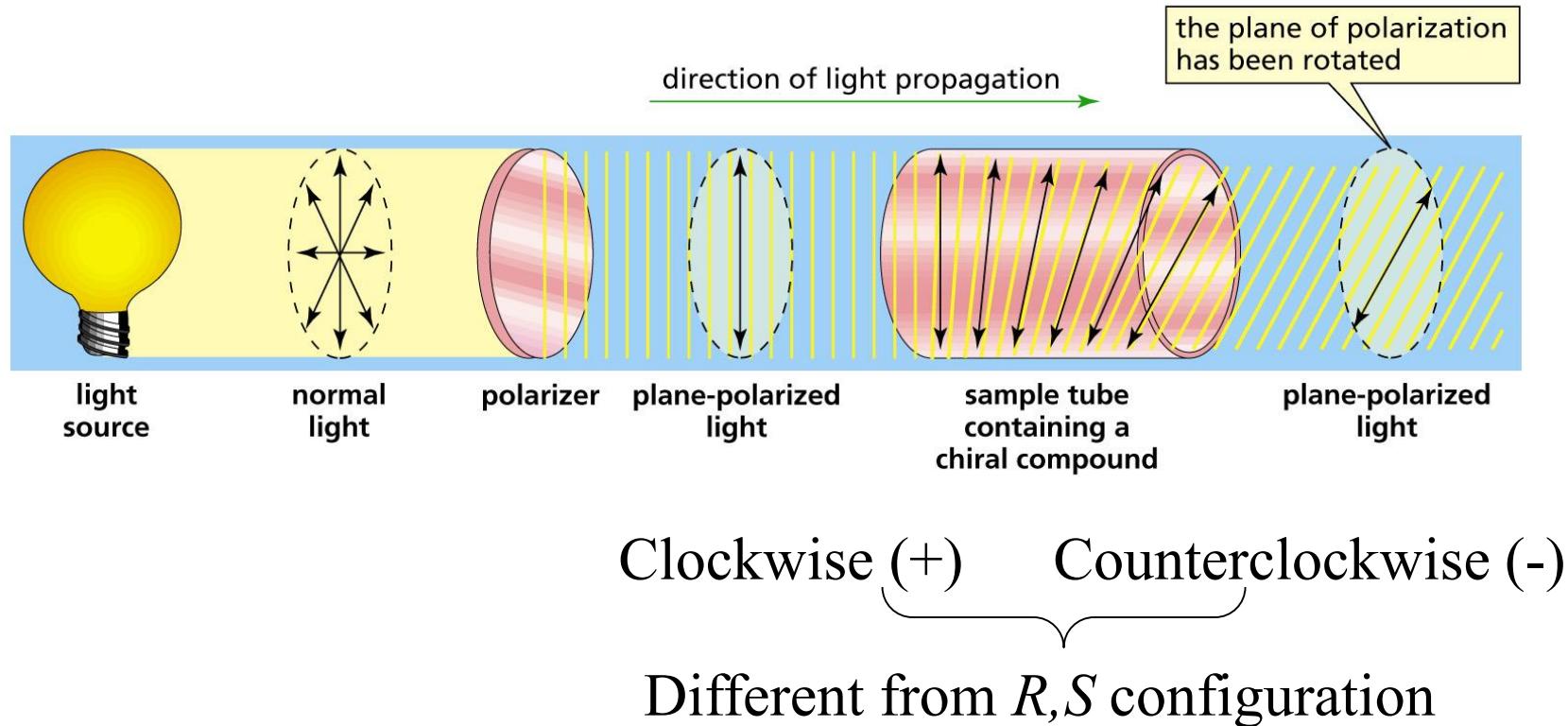
- **Optical activity** is the ability of a chiral substance to rotate the plane of plane-polarized light and is measured using an instrument called **Polarimeter**.

Polarimeter

- A **polarimeter** measures the rotation of plane-polarized light that has passed through a solution.
- The angle between the entrance and exit planes is the optical rotation.
- Rotation, in degrees, is $[\alpha]$
- Clockwise rotation is called **dextrorotatory** (+)
- Anti-clockwise is **levorotatory** (-)



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



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)

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

$[\alpha]_T^T$ = 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

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

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

Physical Properties of Stereoisomers—Optical Purity

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

$$ee = \% \text{ of one enantiomer} - \% \text{ of the other enantiomer.}$$

- Consider the following example—if a mixture contains 75% of one enantiomer and 25% of the other, the enantiomeric excess is $75\% - 25\% = 50\%$. Thus, there is a 50% excess of one enantiomer over the racemic mixture.
- The enantiomeric excess can also be calculated if the specific rotation $[\alpha]$ of a mixture and the specific rotation $[\alpha]$ of a pure enantiomer are known.

$$ee = ([\alpha] \text{ mixture}/[\alpha] \text{ pure enantiomer}) \times 100.$$

Examples



(R)-2-Butanol
 $[\alpha]_D^{25} = -13.52$



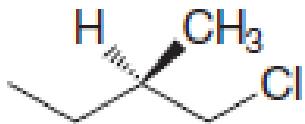
(S)-2-Butanol
 $[\alpha]_D^{25} = +13.52$



(R)-(+)-2-Methyl-1-butanol
 $[\alpha]_D^{25} = +5.756$



(S)-(-)-2-Methyl-1-butanol
 $[\alpha]_D^{25} = -5.756$

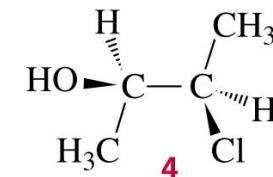
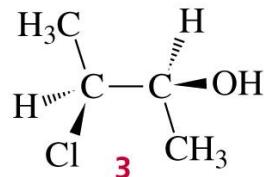
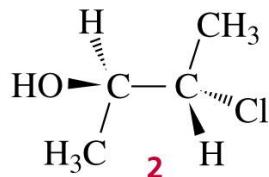
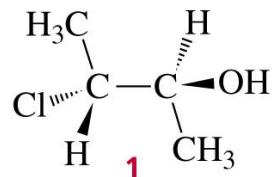
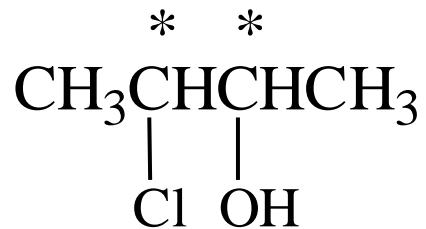


(R)-(-)-1-Chloro-2-methylbutane
 $[\alpha]_D^{25} = -1.64$



(S)-(+)-1-Chloro-2-methylbutane
 $[\alpha]_D^{25} = +1.64$

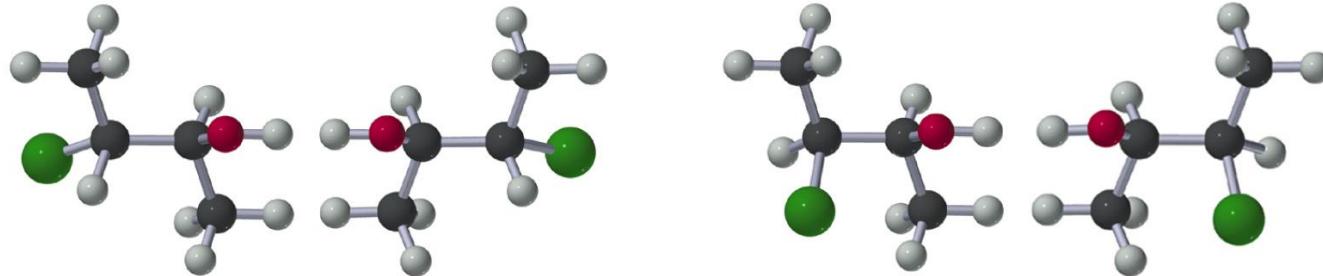
Isomers with more than one chiral carbon: a maximum of 2^n stereoisomers can be obtained



erythro enantiomers

threo enantiomers

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

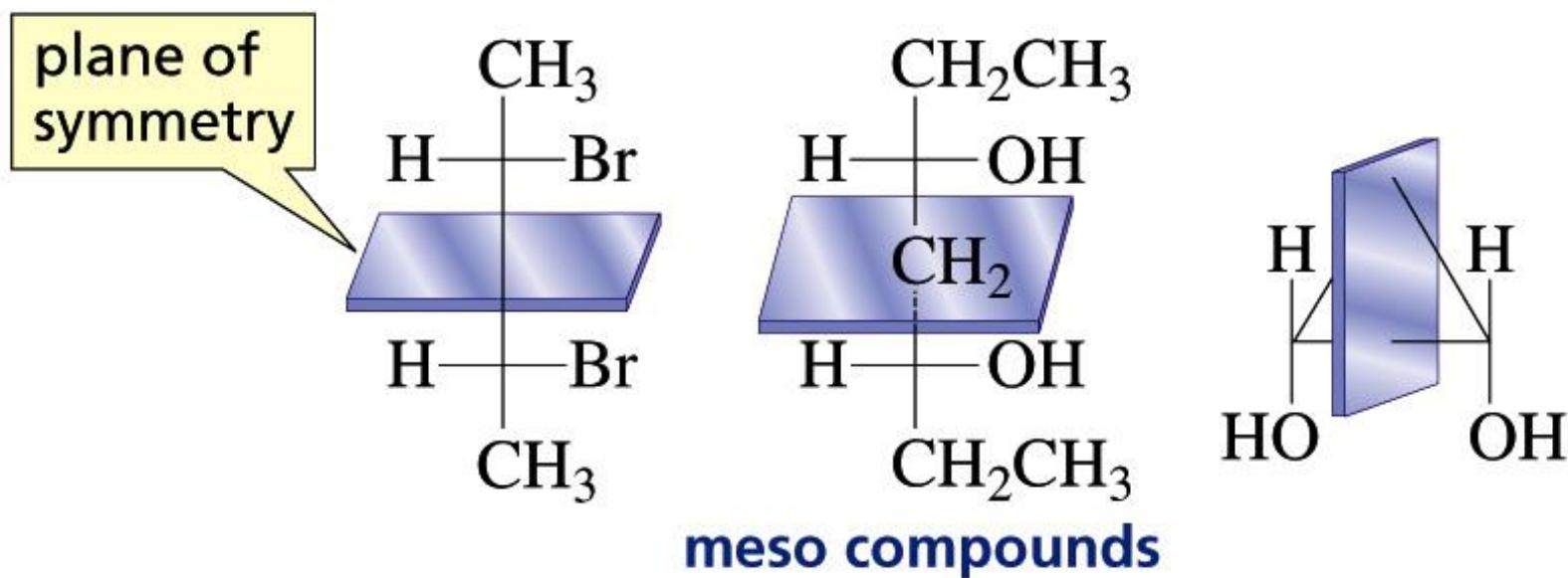


stereoisomers of 3-chloro-2-butanol

Diastereomers are stereoisomers that are not enantiomers

Meso Compounds

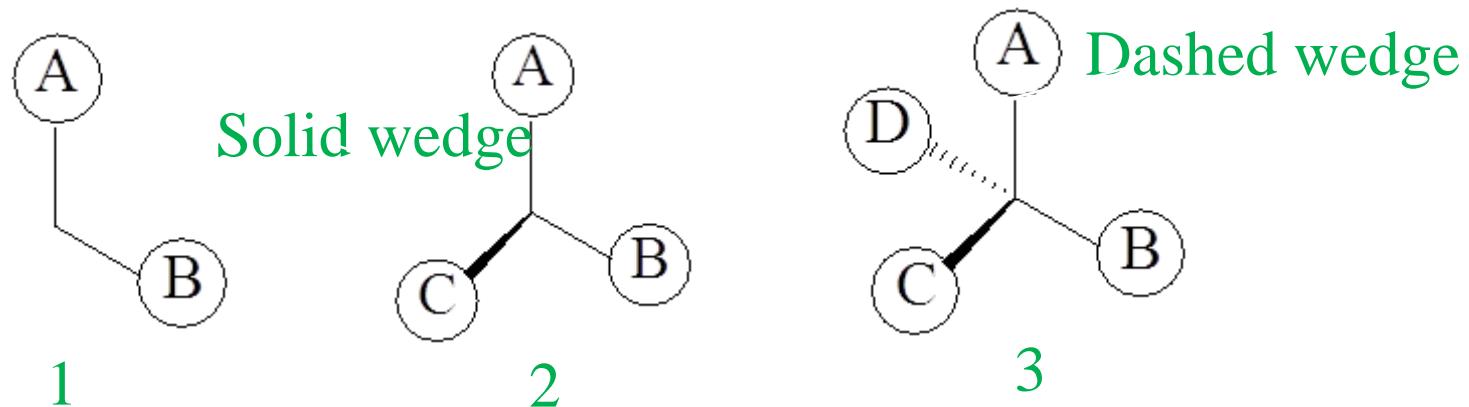
Have two or more asymmetric carbons and a plane of symmetry



They are achiral molecules

Naming Enantiomers: The R,S-System or Cahn-Ingold-Prelog System

How to draw Three-Dimensional Formulas



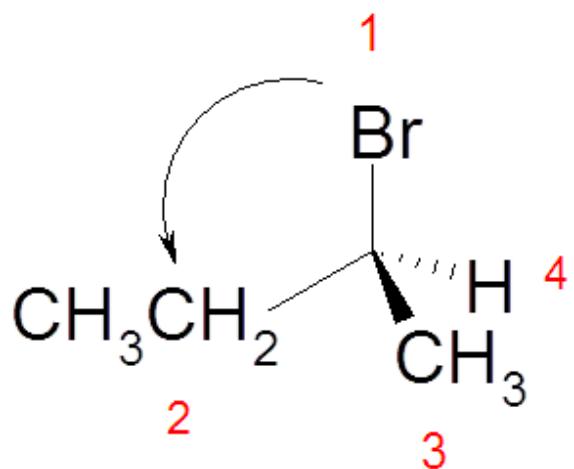
(R) and (S) are from the Latin words *rectus* and *sinister*:

- **R** configuration: clockwise (*rectus*, “**right**”)
- **S** configuration: counterclockwise (*sinister*, “**left**”)

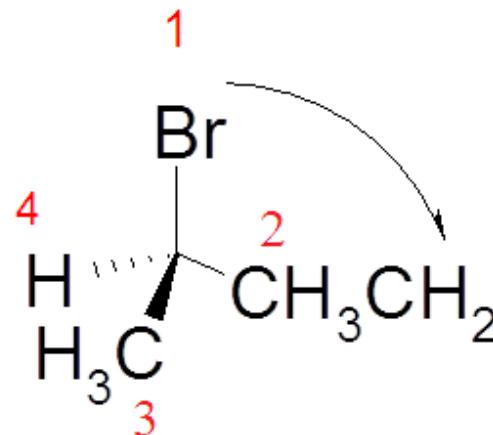
How to Assign (R) and (S) Configurations

- 1- Each of the four groups attached to the stereo center is assigned a priority.
- 2- Priority is first assigned on the basis of the atomic number of the atom that is directly attached to the stereo center.
- 3- The group with the lowest atomic number is given the lowest priority, (4); the group with next higher atomic number is given the next higher priority, (3); and so on.
- 4- The group or atom with the lowest priority has to be bonded to a dashed wedge.
- 5- If the direction from highest priority (1) to the next highest (2) to the next (3) is **clockwise**, the enantiomer is designated **R**.
- 6- If the direction is **countrerclockwise**, the enantiomer is designated **S**.

7- If the group with the lowest priority (**4**) is not bonded with a dashed wedge, switch two groups to make it bonded with a dashed wedge and switch again for any two groups without switching the lowest priority (**4**). As you switched the groups, also switch the configurations, i.e. if the molecule appears to be S then it is originally R , and if it appears to be R then it was originally S.



(S)-2-bromobutane



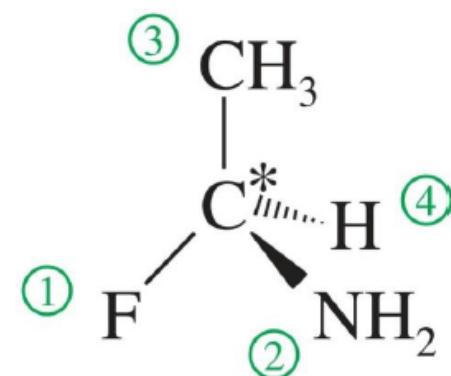
(R)-2-bromobutane

- Assign a relative “priority” to each group bonded to the asymmetric carbon. Group 1 would have the highest priority, group 2 second, etc.
- Atoms with higher atomic numbers receive higher priorities.



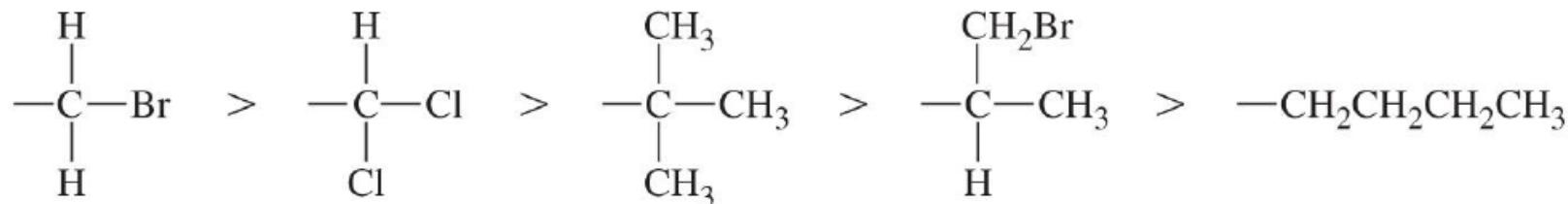
Atomic number: F > N > C > H

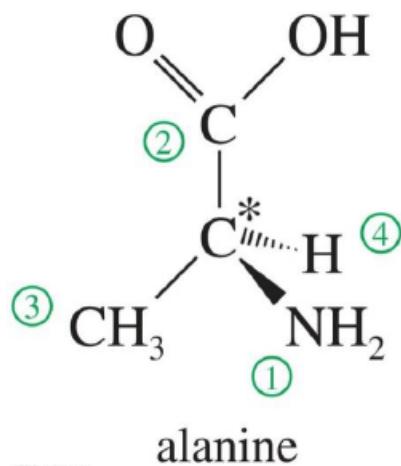
(R) and (S) Configuration: Breaking Ties



In case of ties, use the next atoms along the chain of each group as tiebreakers.

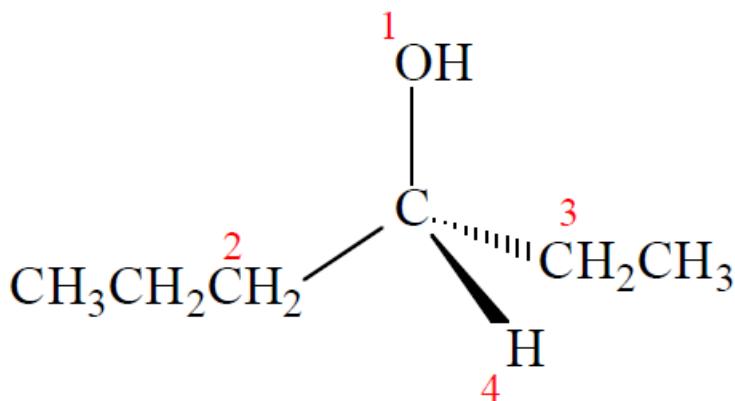
Examples



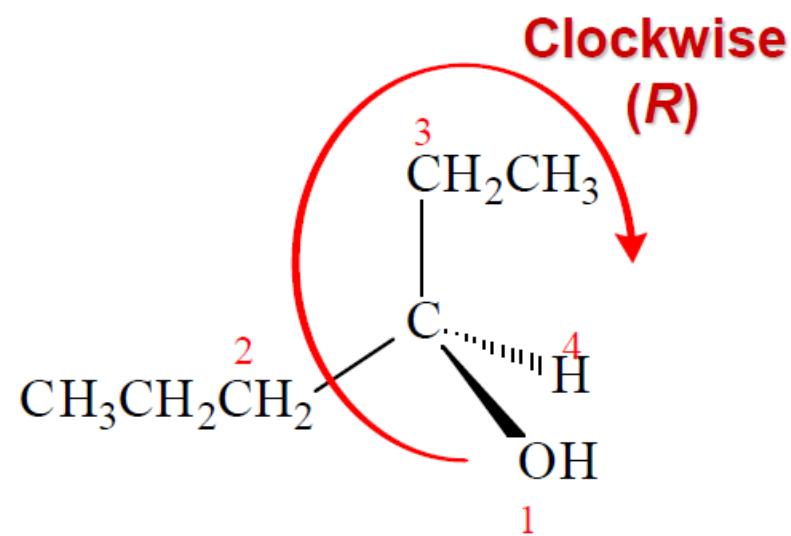
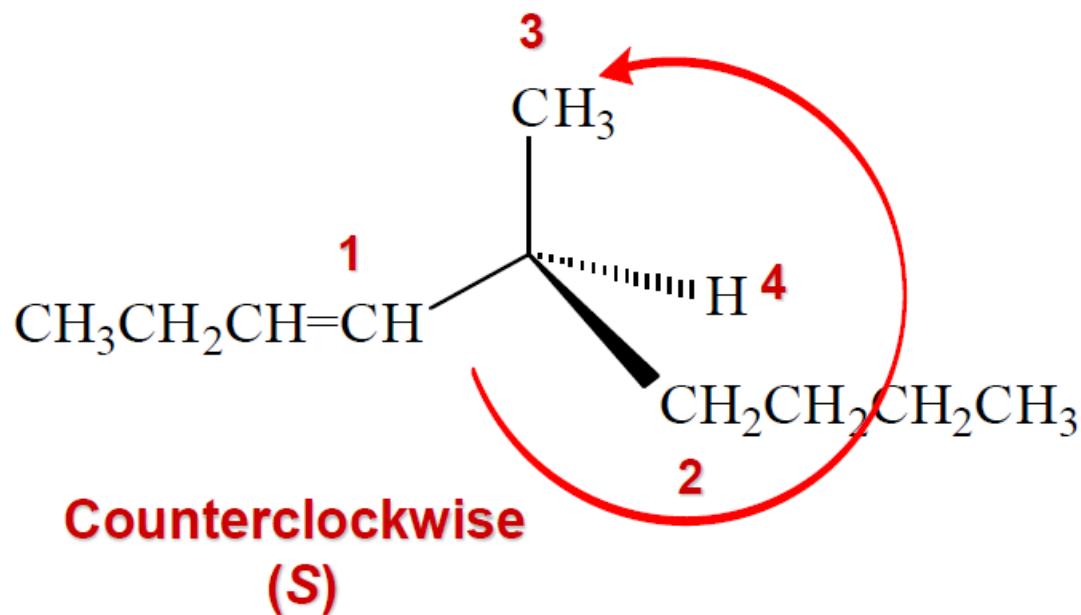


Counterclockwise

(S)

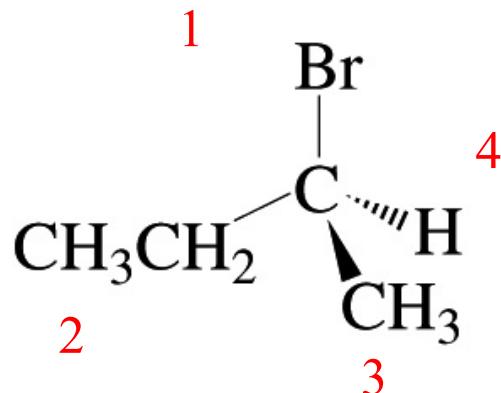


rotate →

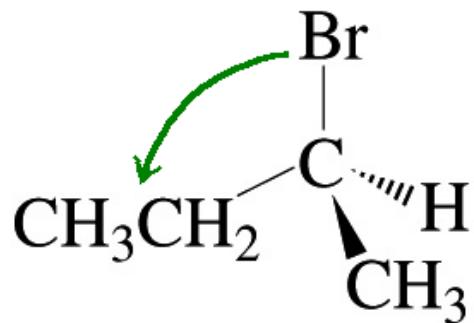


Naming from the Perspective Formula

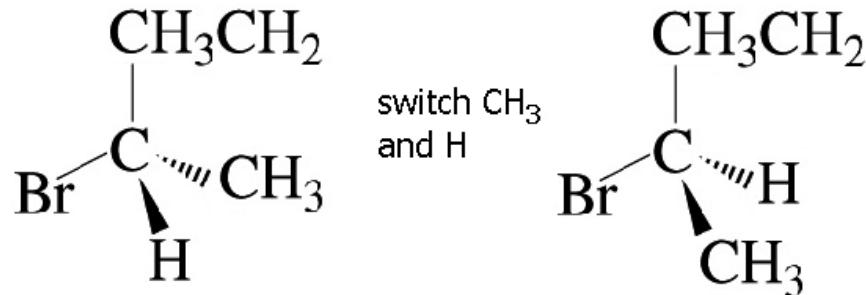
1. Rank the groups bonded to the asymmetric carbon



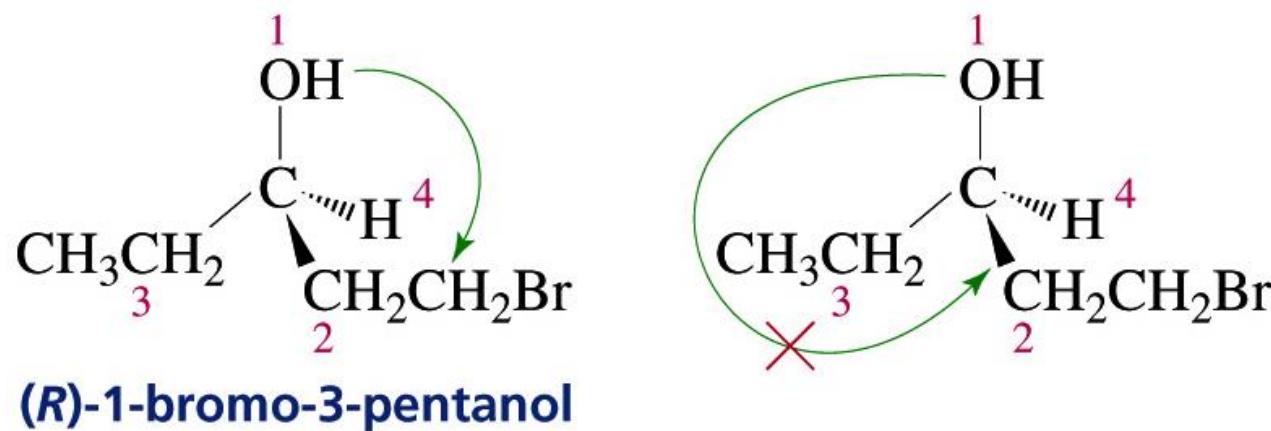
2. If the group (or atom) with the lowest priority is bonded by hatched wedge,



3. If necessary, rotate the molecule so that the lowest priority group (or atom) is bonded by a hatched wedge



4. You can draw group 1 to group 2, passing group 4, but never 3



Molecules with More than One Stereocenter

Molecules with 1 stereocenter
can be R or S

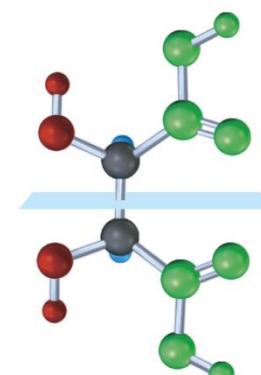
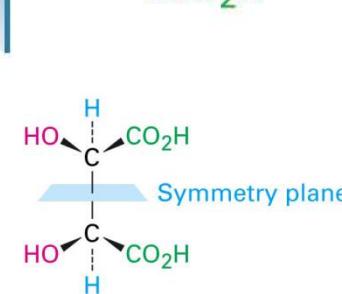
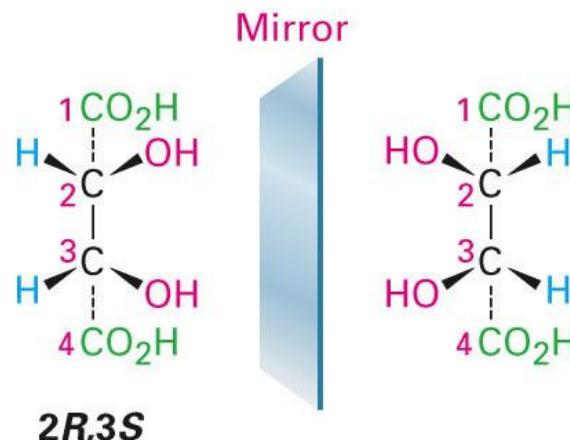
→ 2 possible
stereoisomers

Molecules with n stereocenters
can have all the possible
combinations of R and S for
each stereocenter

→ 2^n possible
stereoisomers

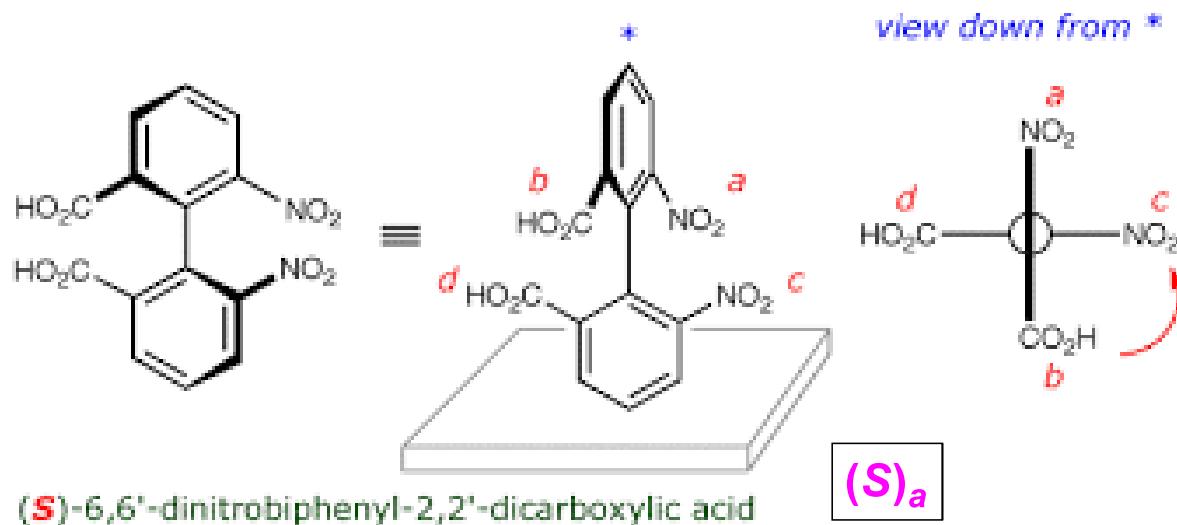
Example:

- Tartaric acid has two chirality centers
- One form is chiral and the other is achiral, but both have two chirality centers
- An achiral compound with chirality centers is called a Meso Compound – it has a plane of symmetry
- The two structures on the right in the figure are identical so the compound (2R, 3S) is achiral

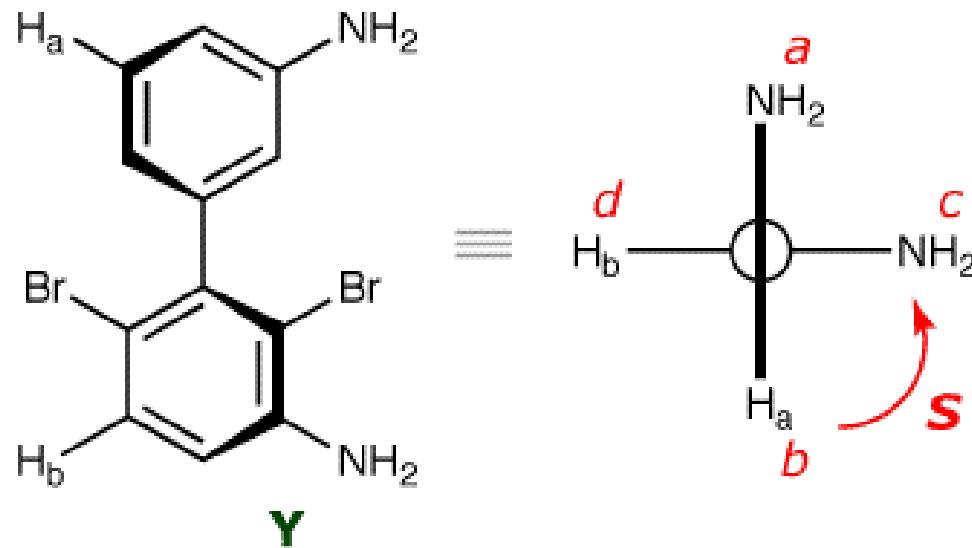


Atropisomerism chirality

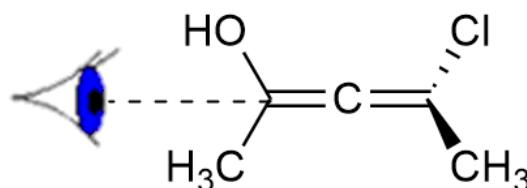
- These molecules show chirality or dissymmetry and hence enantiomerism. Examples of such compounds are *o*-substituted biphenyls.



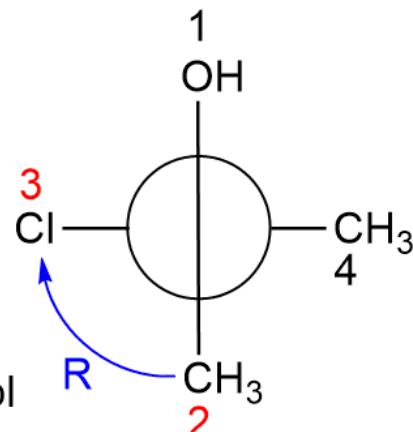
Atropisomerism chirality



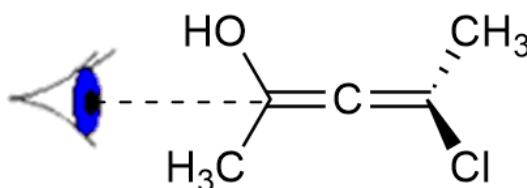
$(S)_a$



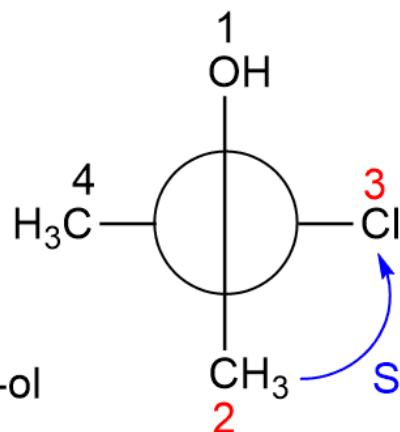
(*R*)-4-chloropenta-2,3-dien-2-ol



Clockwise = (*R*)



(*S*)-4-chloropenta-2,3-dien-2-ol

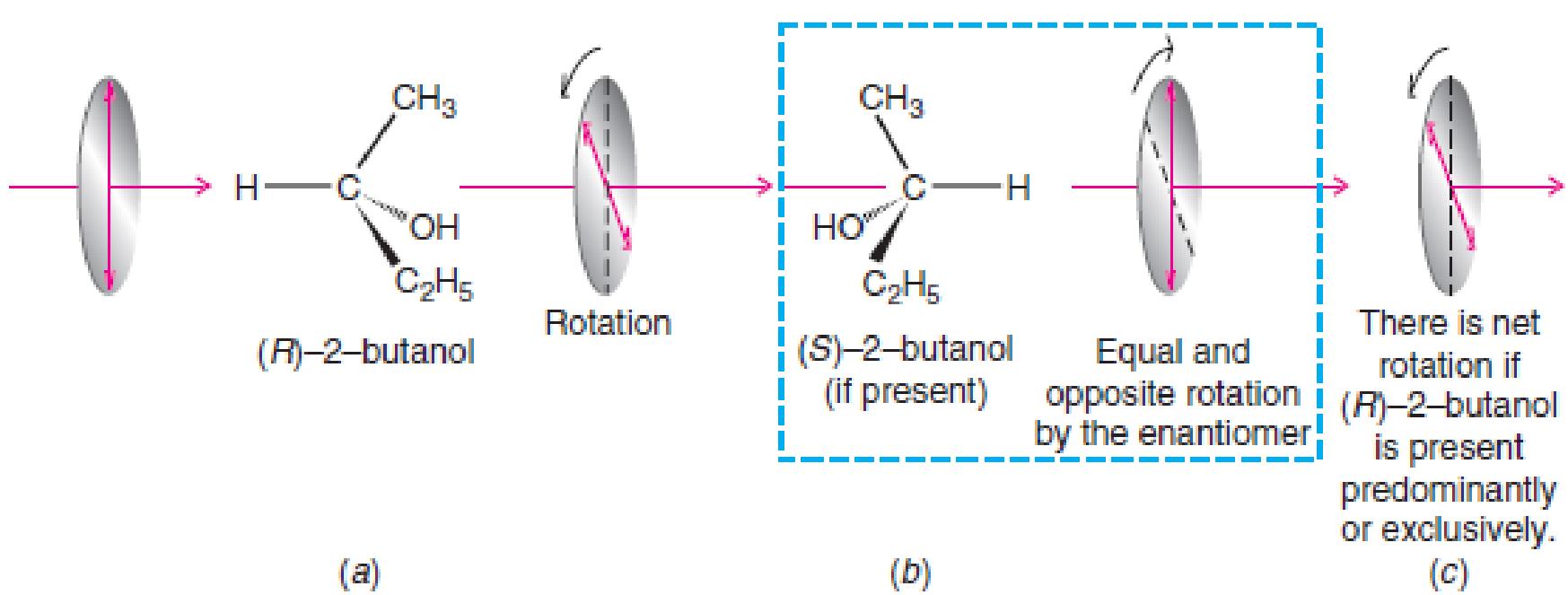


Anti-Clockwise = (*S*)

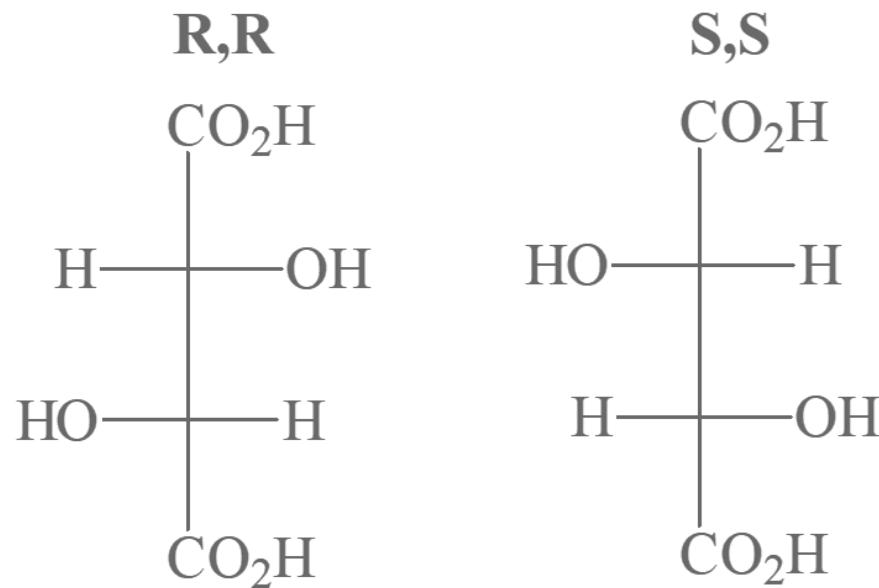
Due to *sp* hybridization of central carbon which forms two p-bonds perpendicular to each other and thus the two groups attached to terminal carbon atoms are also *orthogonal*. Due to this arrangement the molecule of allene is devoid of symmetry and hence is chiral.

Racemic Mixture

- A 50:50 mixture of two enantiomers is called a **racemic mixture** (or racemate or racemic form).
- A racemic mixture causes no net rotation of plane-polarized light.



Example:



Racemic Mixture (Racemate): 50/50 mixture of enantiomers

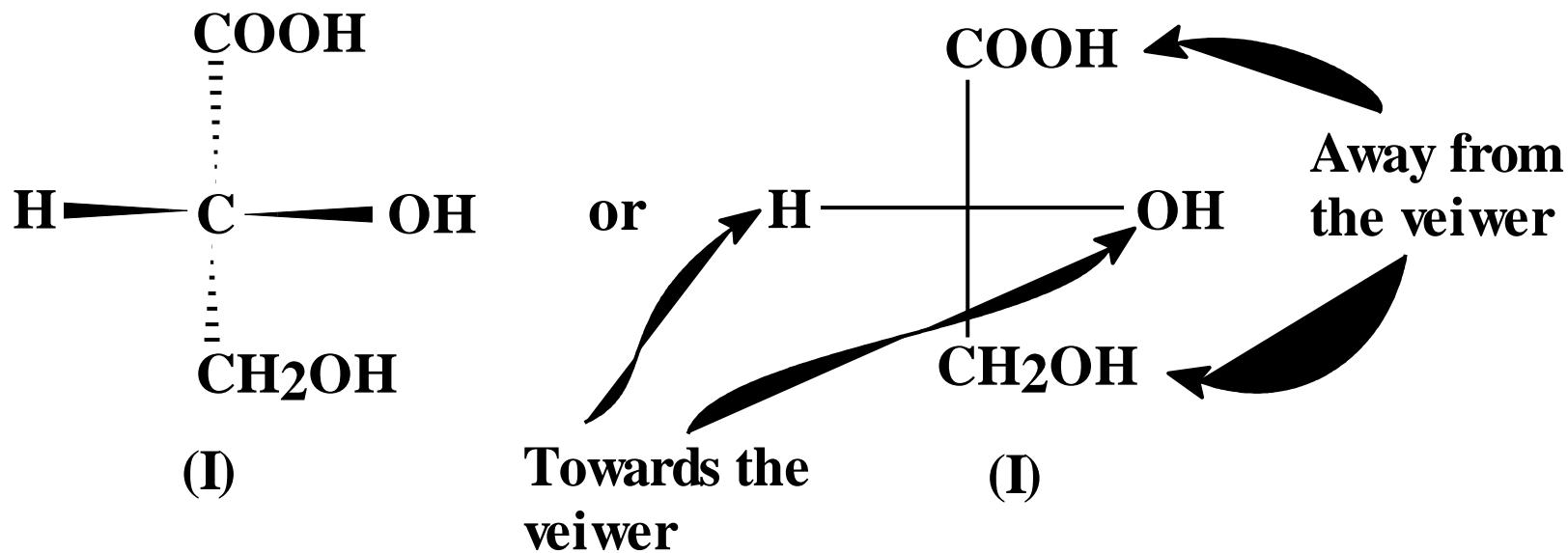
<u>(R,R) Tartaric acid</u>	<u>(S,S) Tartaric Acid</u>	<u>(+/-) Tartaric acid</u>
----------------------------	----------------------------	----------------------------

m.p. C	168-170	168-170	210-212
[α] (degrees)	- 12	+ 12	0
ρ (g/mL)	1.7598	1.7598	1.7723

3.4 PROJECTION FORMULAS OF CHIRAL MOLECULES

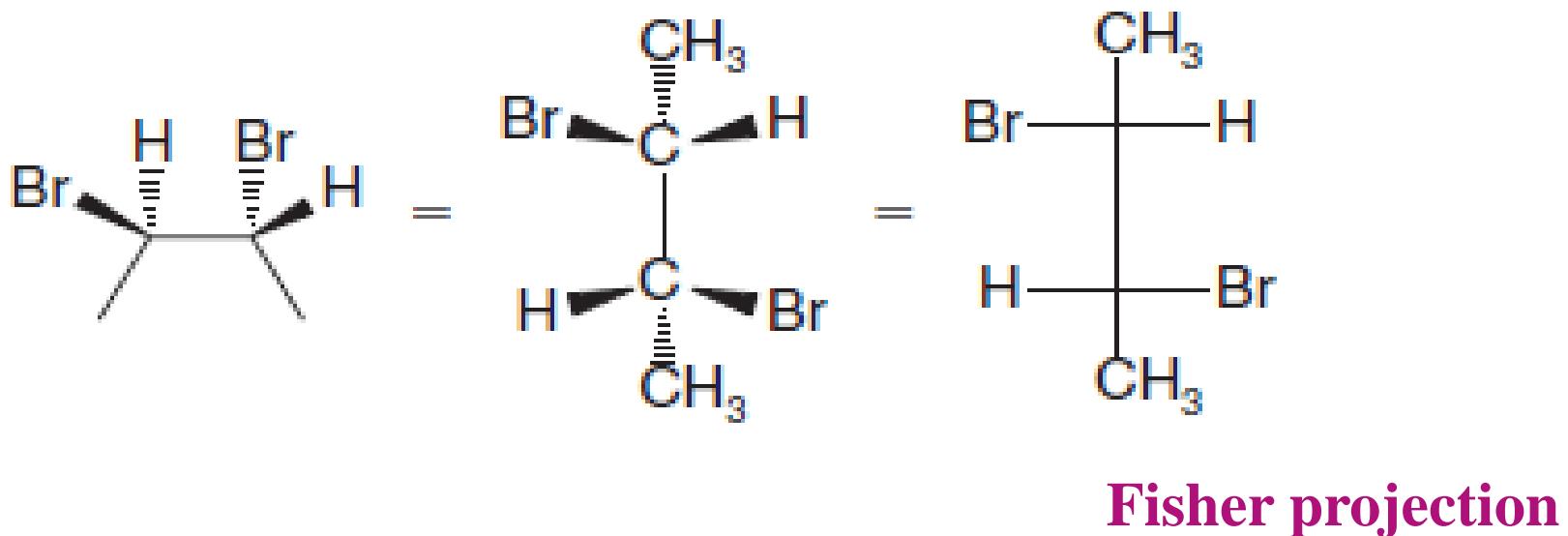
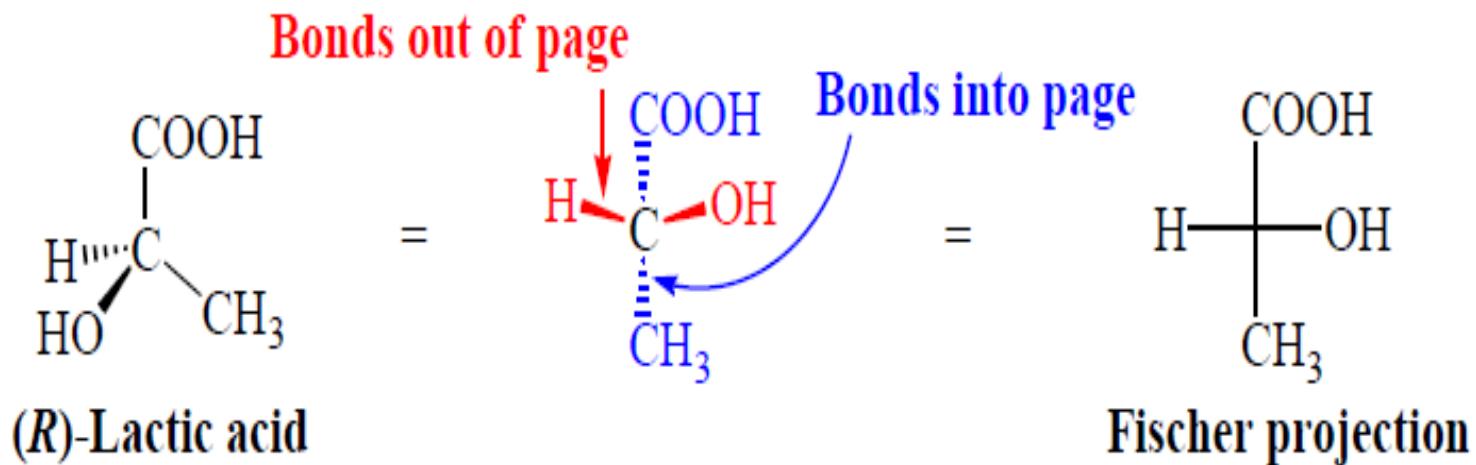
- Configuration of a chiral molecule is three dimensional structure and it is **not very easy to depict it on a paper** having only two dimensions. To overcome this problem the following four two dimensional structures known as projections have been evolved.
- 1. Fischer Projection
- 2. Newman Projection
- 3. Sawhorse Formula
- 4. Flying Wedge Formula

1. Fischer Projection



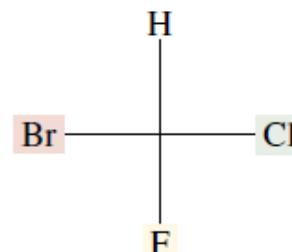
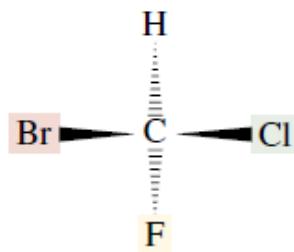
- **Characteristic features of Fischer projection:**
Rotation of a Fischer projection by an angle of 180° about the axis which is perpendicular to the plane of the paper gives identical structure. However, similar rotation by an angle of 90° produces non - identical structure.

Fischer Projection Formulas

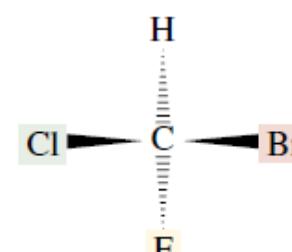


Assigning R,S Configuration to Fischer Projections

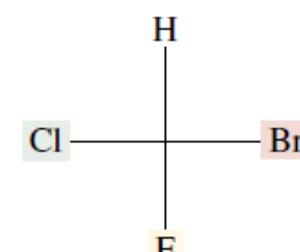
- 1- Assign priorities to the four substituents.
- 2- The group of the lowest priority has to be at the top.
- 3- Determine the direction of rotation in going from priority 1 to 2 to 3, and assign R or S configuration.
- 4- If the group with the lowest priority (4) is not at the top, switch two groups to make it on the top and switch again for any two groups without switching the lowest priority (4).



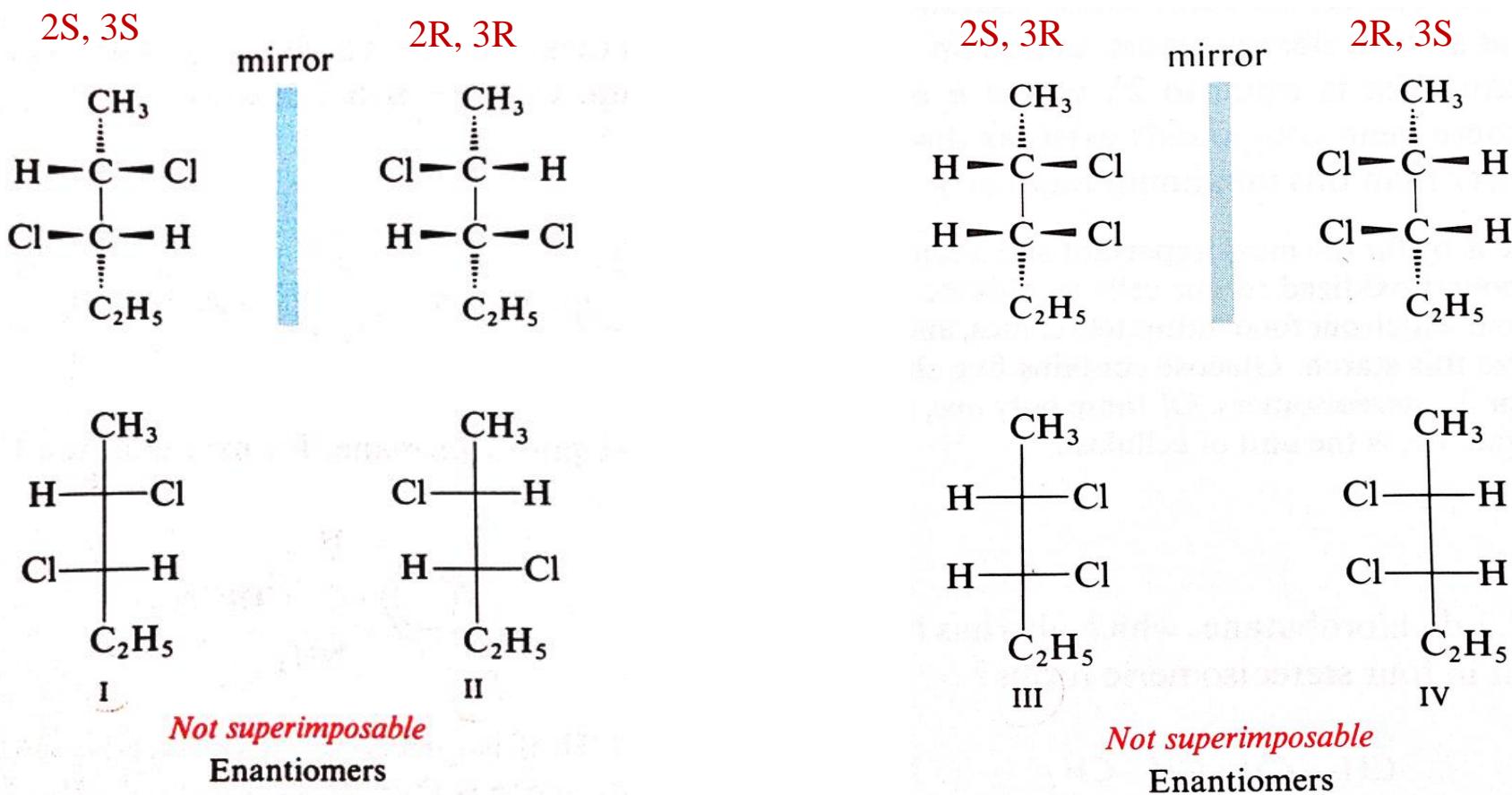
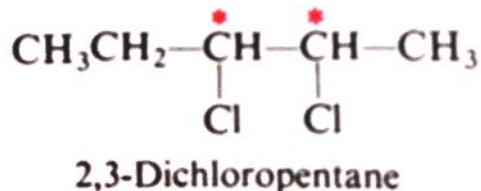
(R)-Bromochlorofluoromethane



(S)-Bromochlorofluoromethane



Example:

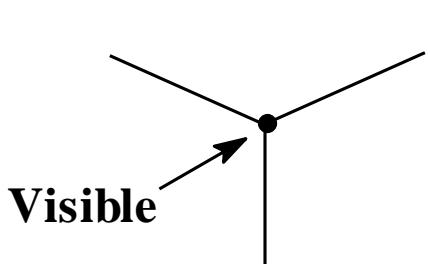


2. Newman Projection

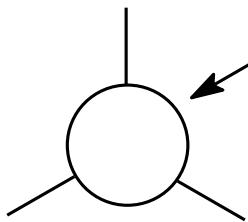
- In Newman projection we look at the molecule down the length of a particular carbon - carbon bond. The carbon atom away from the viewer is called '**rear**' carbon and is represented by **a circle**. The carbon atom facing the viewer is called '**front**' carbon and is represented as **the centre** of the above circle which is shown by dot. The remaining bonds on each carbon are shown by small straight lines at angles of 120° as follows:

- i) Bonds joined to 'front' carbon intersect at the central dot.
- ii) Bonds joined to 'rear' carbon are shown as emanating from the circumference of the circle.

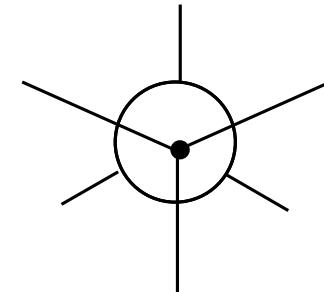
The concept of Newman projection for *n*-butane can be understood by the following drawings:



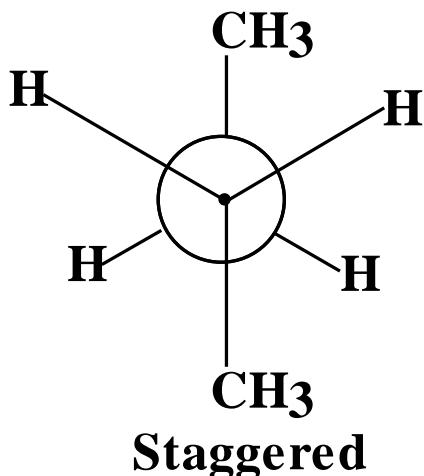
Front Carbon



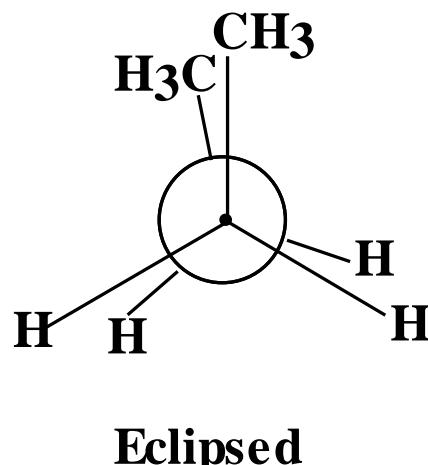
Rear Carbon



Newman Projection



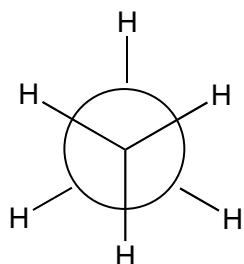
Staggered



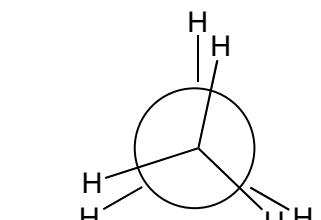
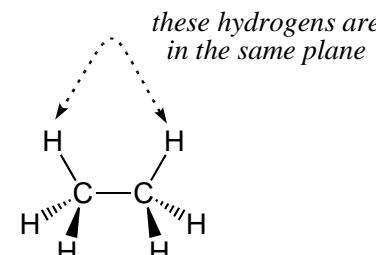
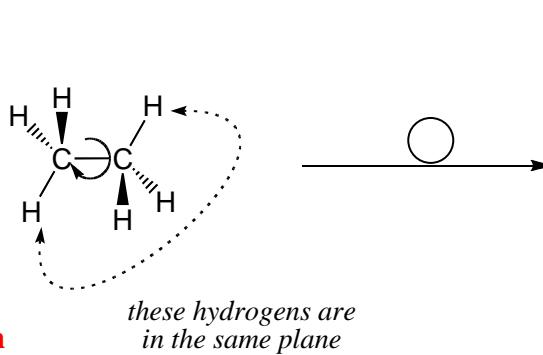
Eclipsed

These conformations arise due to free rotation about the carbon - carbon single bond (front and rear carbon atoms).

Newman projection Ethane



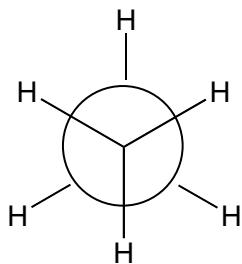
The "staggered" conformation



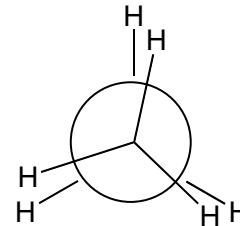
The "eclipsed" conformation

The staggered conformation is the lowest energy conformation

The eclipsed conformation is the highest energy conformation



The energy minimum

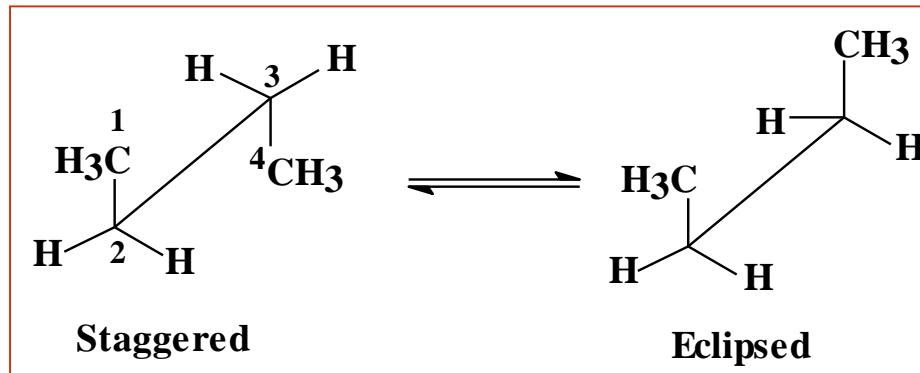


The energy maximum

Molecules that differ by only rotations around single bonds are **conformational Isomers**.

3. Sawhorse projection

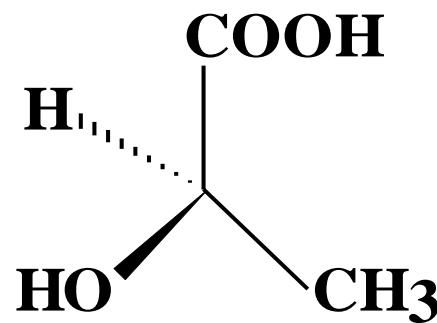
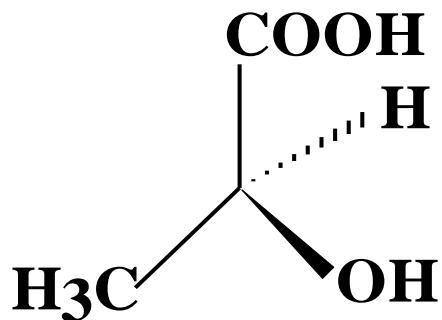
- The bond between two carbon atoms is shown by a longer diagonal line because we are looking at this bond from an oblique angle. The bonds linking other substituents to these carbons are shown projecting above or below this line.



- Due to free rotation along the central bond two extreme conformations are possible - the staggered and the eclipsed

4. Flying Wedge Formula

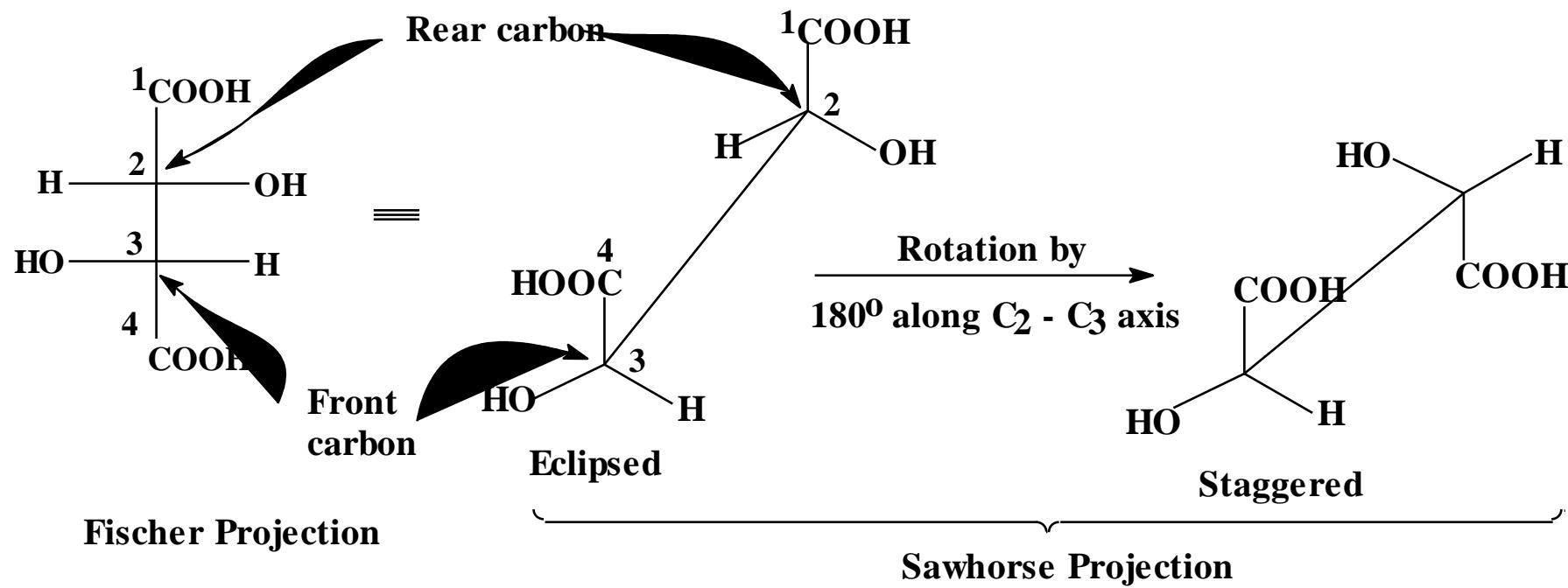
- It is a three dimensional representation.
- The flying wedge formulas of two enantiomeric lactic acids are shown below:



- Both these structure are mirror image of each other.
- (Note: The main functional group is generally held on the upper side in the vertical plane.)

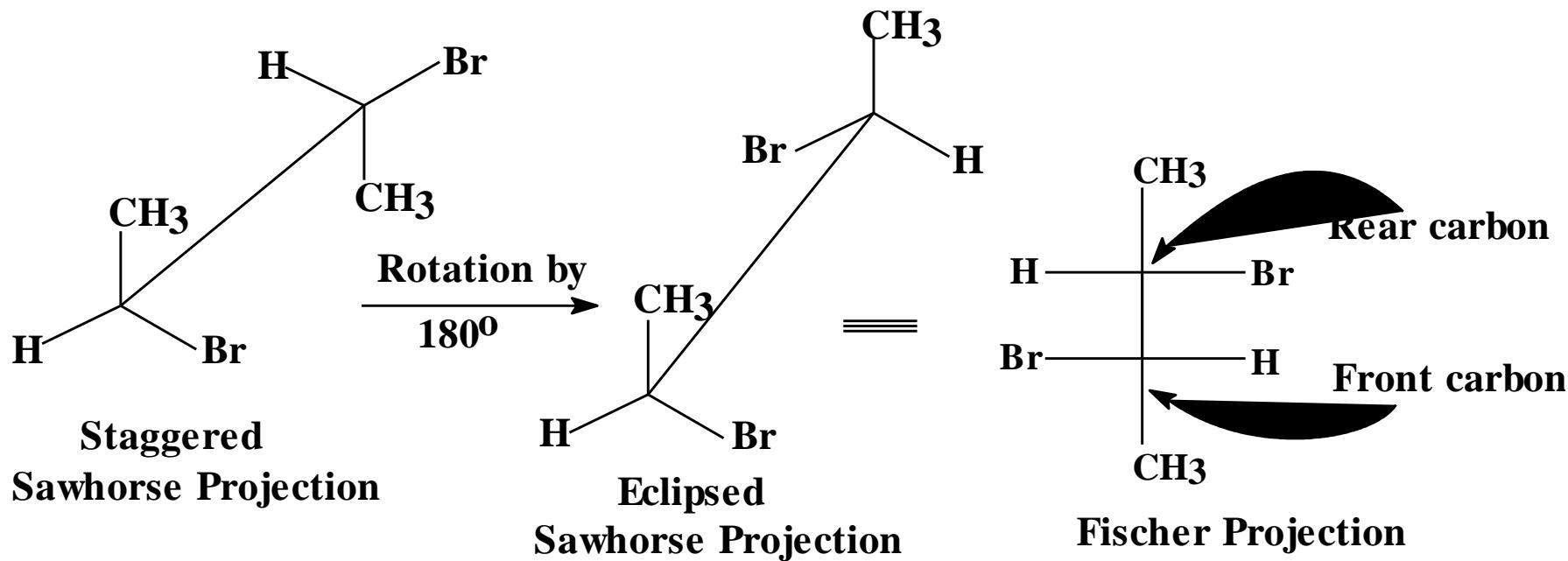
Conversion of Fischer Projection into Sawhorse Projection

- Fischer projection of a compound can be converted into sawhorse projection first in the eclipsed form by holding the model in horizontal plane in such a way that the groups on the vertical line point above and the last numbered chiral carbon faces the viewer. Then one of the two carbons is rotated by an angle of 180° to get staggered form (*more stable or relaxed form*).

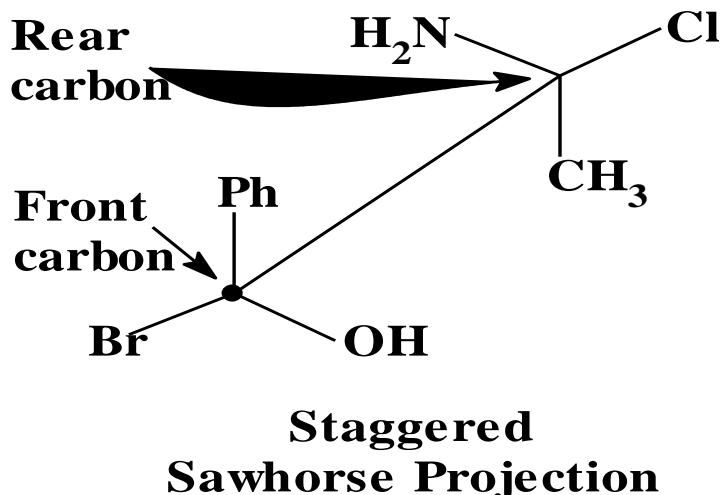


Conversion of Sawhorse projection into Fischer projection

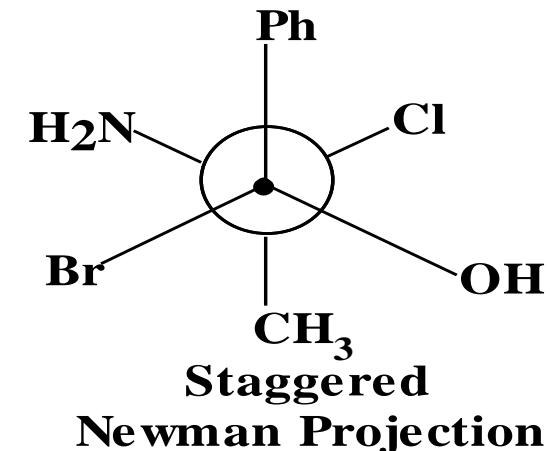
- First the staggered sawhorse projection is converted in eclipsed projection. It is then held in the vertical plane in such a manner that the two groups pointing upwards are away from the viewer i.e. both these groups are shown on the vertical line. Thus, for 2,3-dibromobutane.



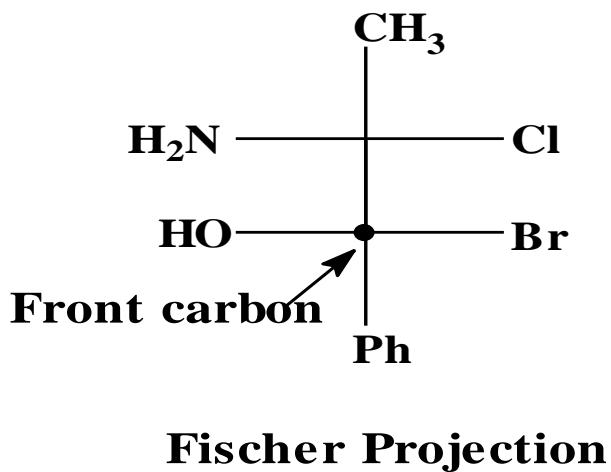
Conversion of Sawhorse to Newman to Fischer Projection



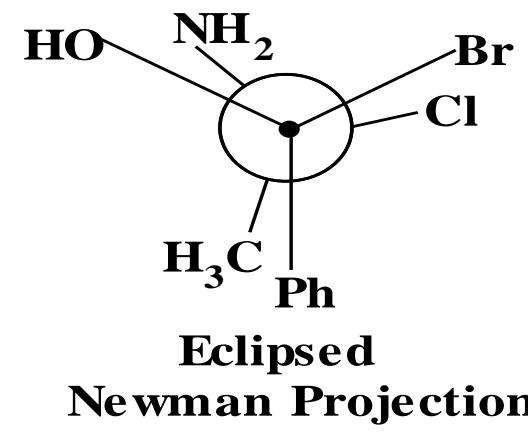
**View through
the front carbon**



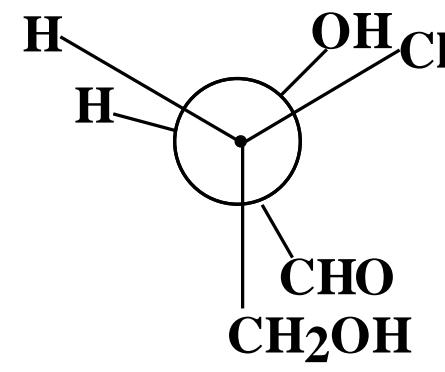
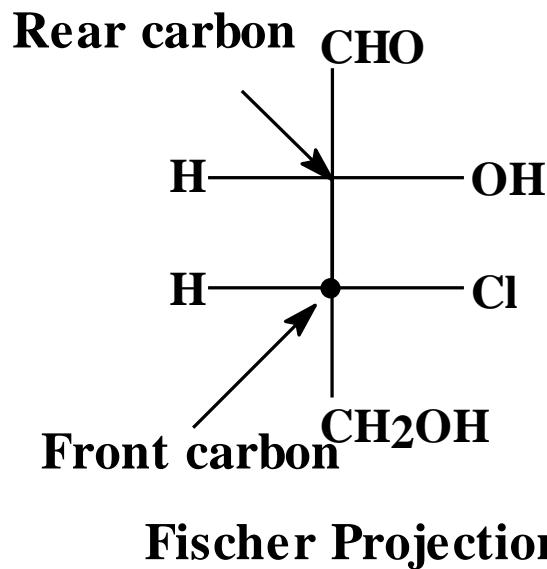
**Rotate the front carbon
along the central
bond by 180°**



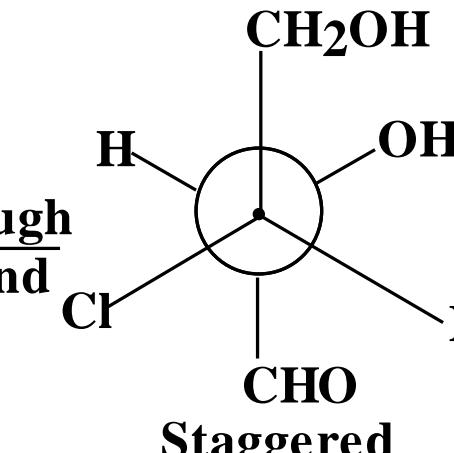
**Hold in vertical plane
keeping front carbon as the
lowest**



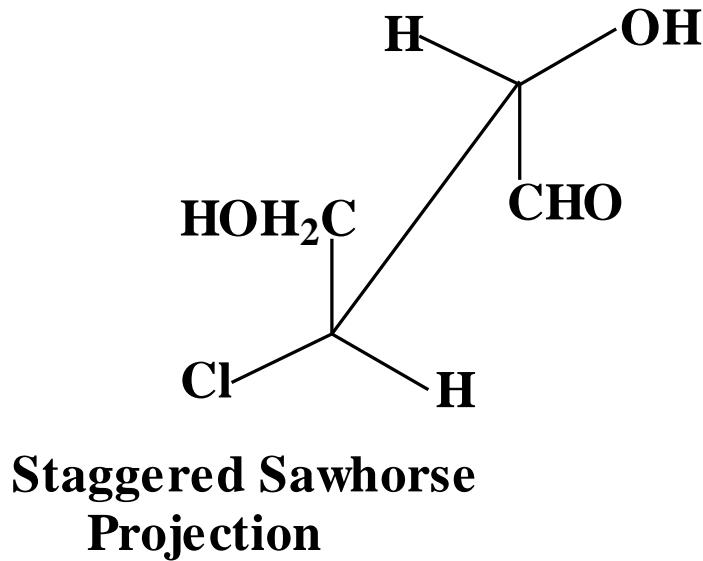
Conversion of Fischer to Newman to Sawhorse Projection



Rotate front
carbon by 180°

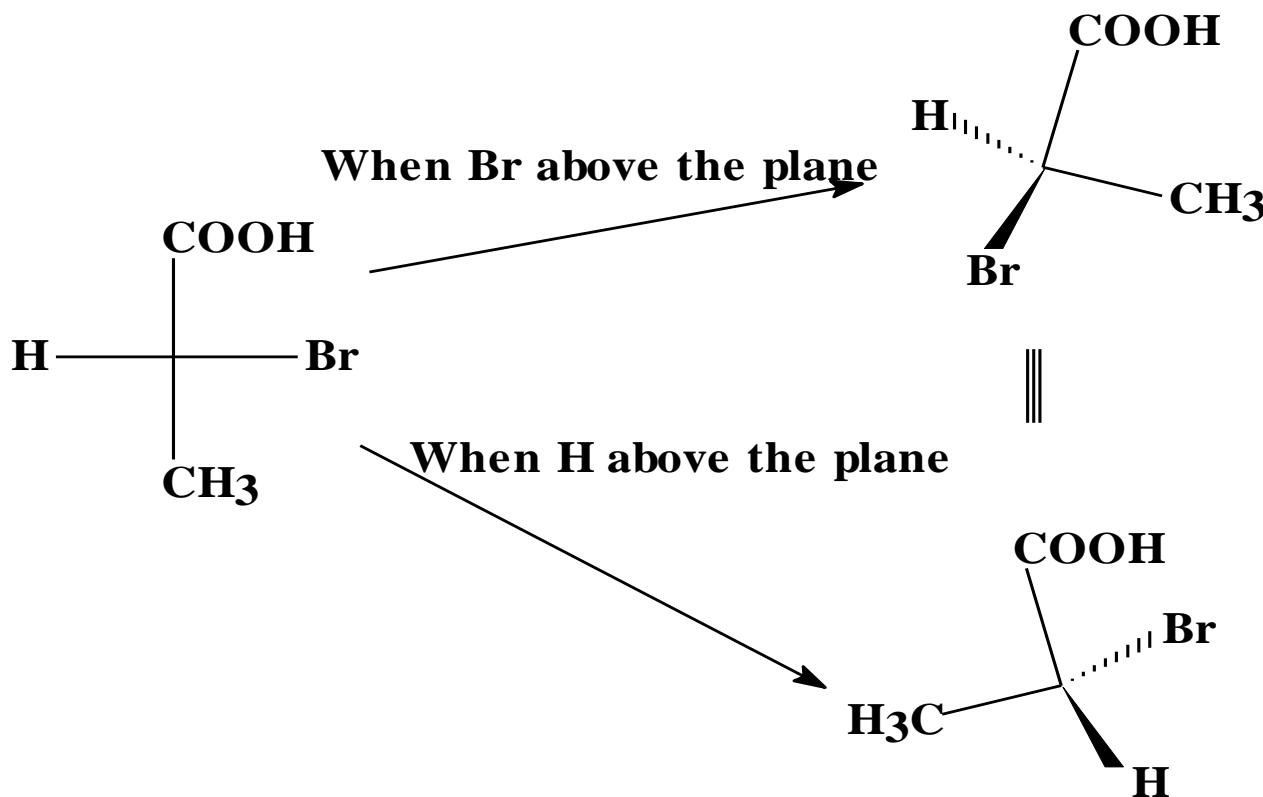


View through
central bond



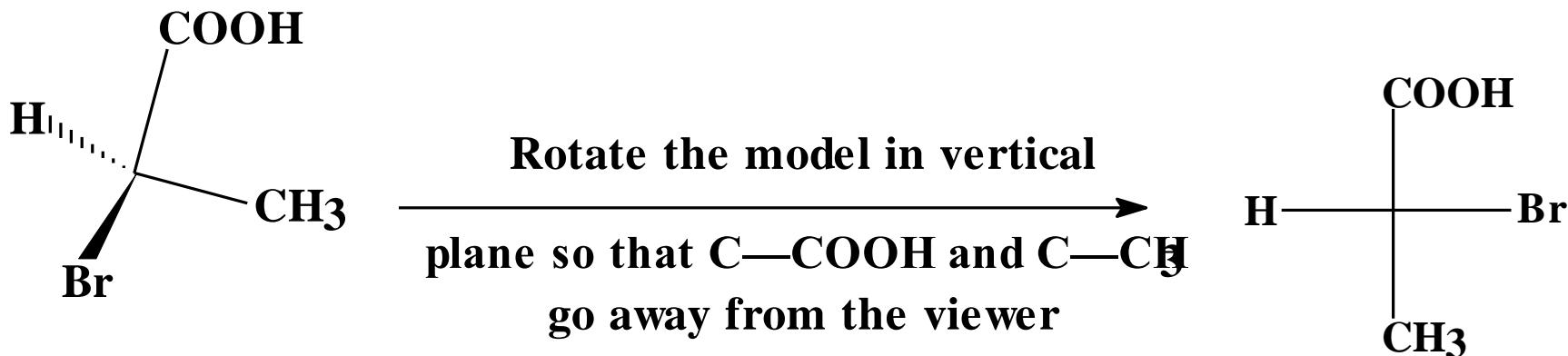
Conversion of Fischer Projection into Flying Wedge

- The **vertical bonds** in the Fischer projection are drawn in the plane of the paper using simple lines (—) consequently **horizontal bonds will project above and below the plane.**



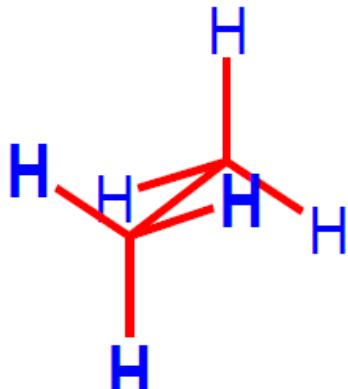
Conversion of Flying Wedge into Fischer Projection

- The molecule is rotated (in the vertical plane) in such a way that the bonds shown in the plane of the paper go away from the viewer and are vertical.

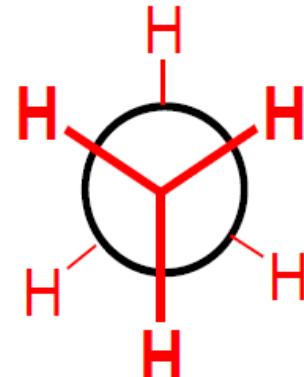


Conformers of Alkanes

- We do not observe perfectly free rotation
- There is a barrier to rotation, and some conformers are more stable than others
- **Staggered**- most stable: all 6 C-H bonds are as far away as possible
- **Eclipsed**- least stable: all 6 C-H bonds are as close as possible to each other

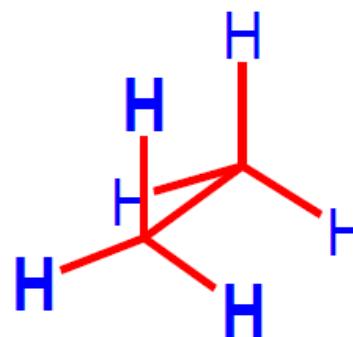


sawhorse

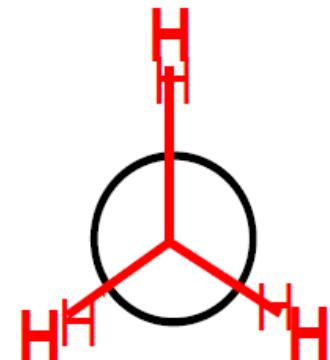


Newman

staggered



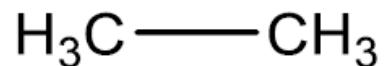
sawhorse



Newman

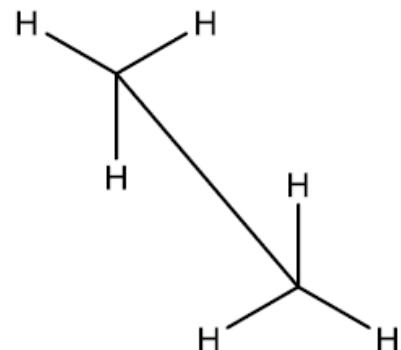
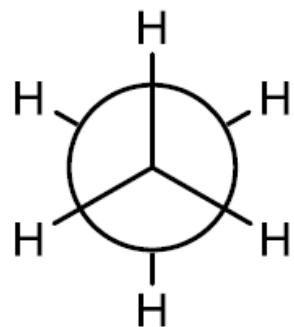
eclipsed

Conformations of ethane



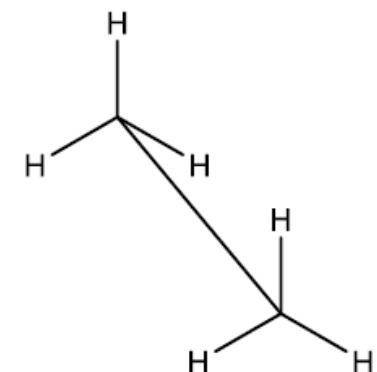
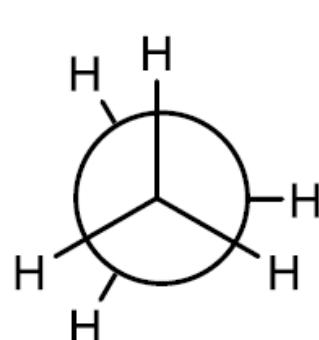
ethane

Staggered
conformation
of ethane



Newman
Projection

Eclipsed
conformation
of ethane



Sawhorse
Representation

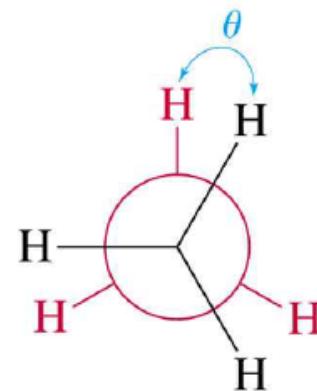
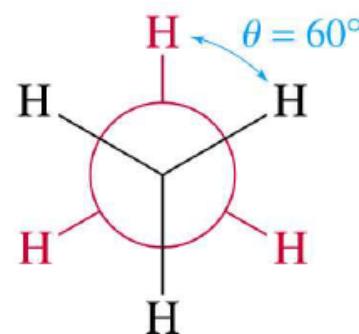
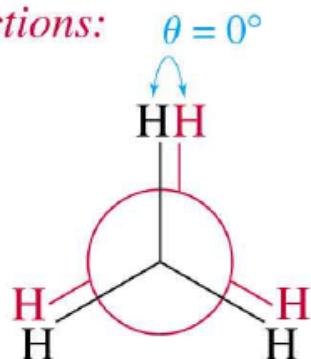
Newman
Projection

Sawhorse
Representation

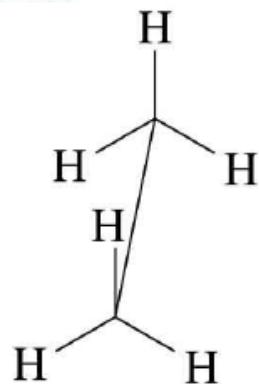
Ethane Conformers

- Staggered conformer: Lowest energy; Dihedral angle = 60°
- Eclipsed conformer has highest energy; Dihedral angle = 0°

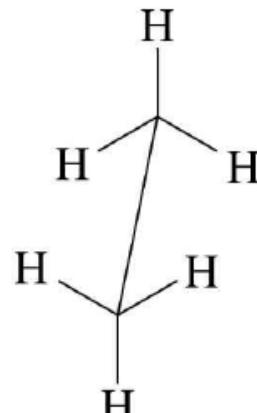
Newman projections:



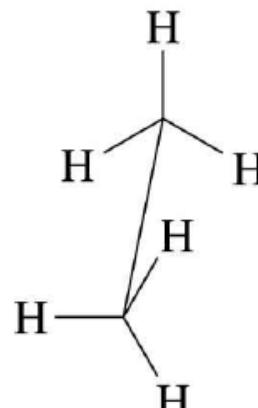
Sawhorse structures:



eclipsed, $\theta = 0^\circ$



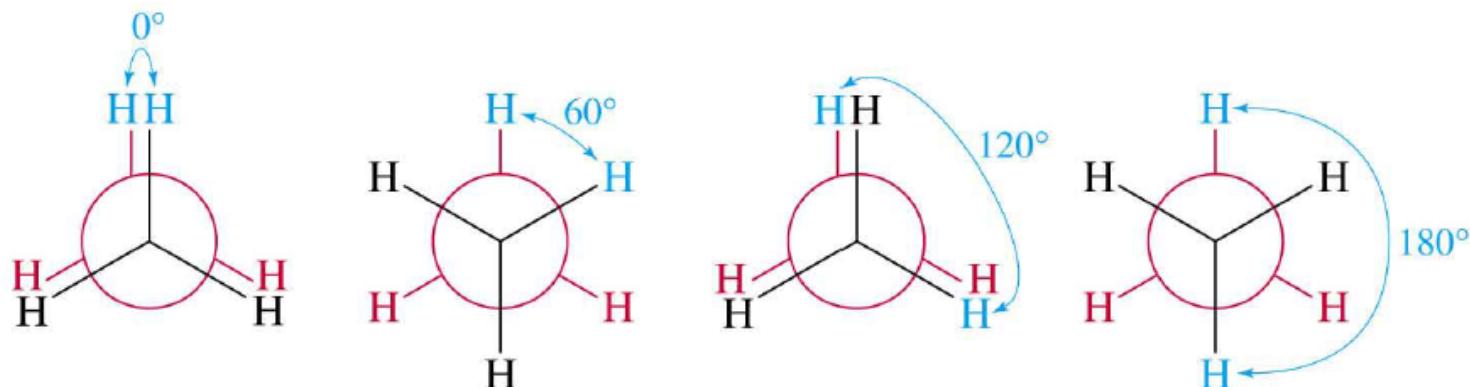
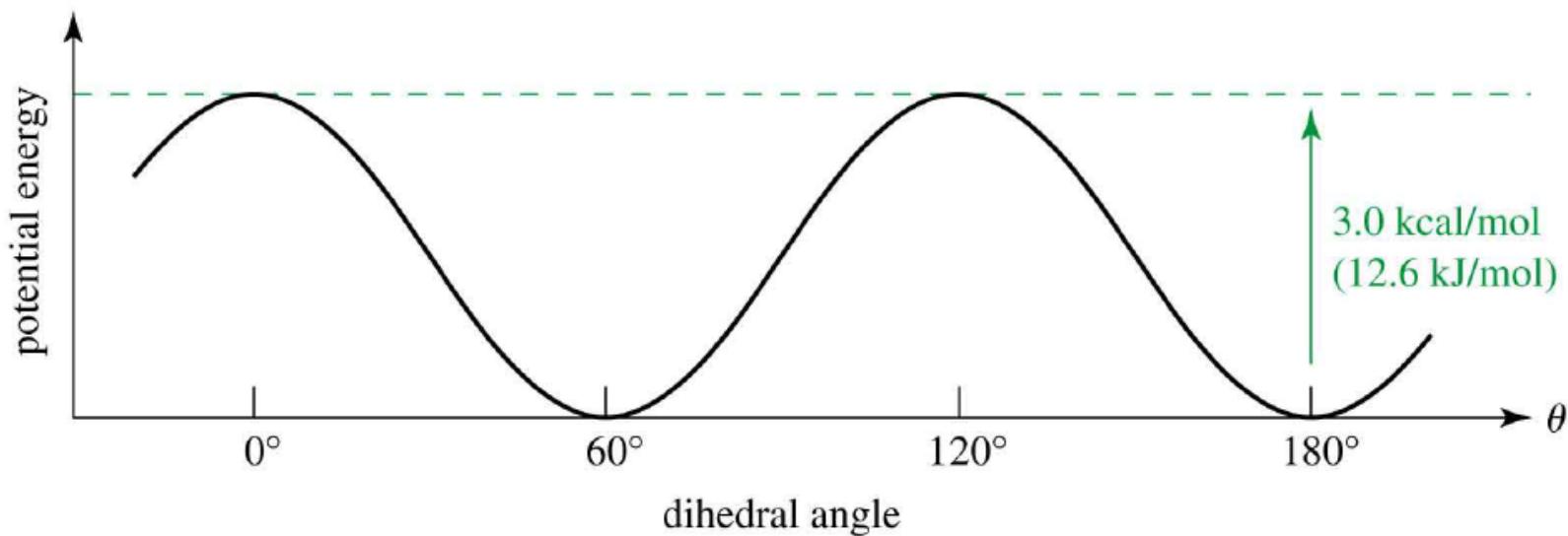
staggered, $\theta = 60^\circ$



skew, $\theta = \text{anything else}$

Conformational Analysis

- Torsional strain: resistance to rotation.
- For ethane, only 3.0 kcal/mol



ELEMENTS OF SYMMETRY

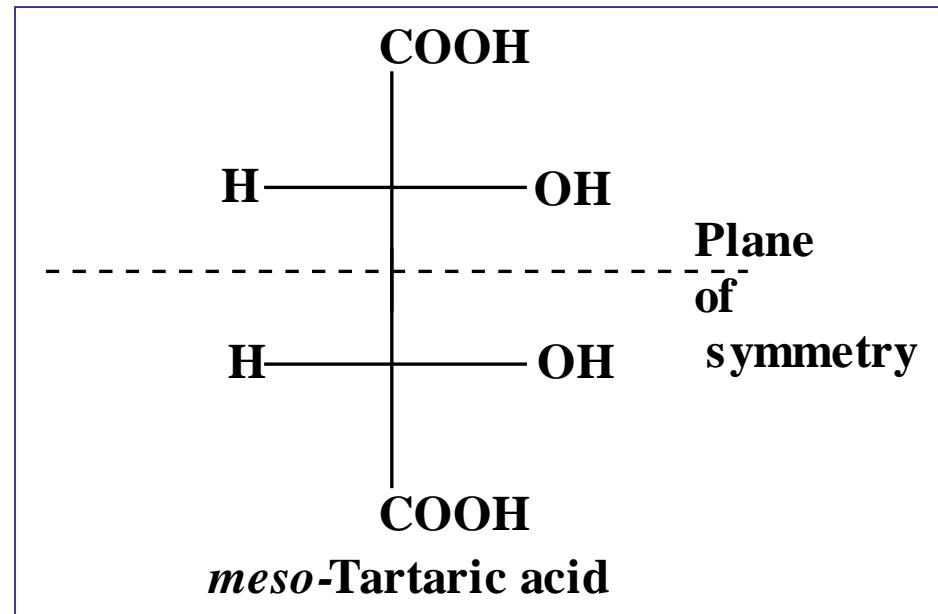
- Enantiomerism depends on whether a molecule is not superimposable on its mirror image. If it is superimposable, the molecule is optically inactive otherwise is optically active. The most convenient method of inspecting superimposability is to determine whether the molecule has any of the following four elements of symmetry:

1. Plane of symmetry (s)
2. Centre of symmetry (i)
3. Simple or proper axis of symmetry (C_n)
4. Alternating or improper axis of symmetry (S_n)

1. Plane of symmetry (s)

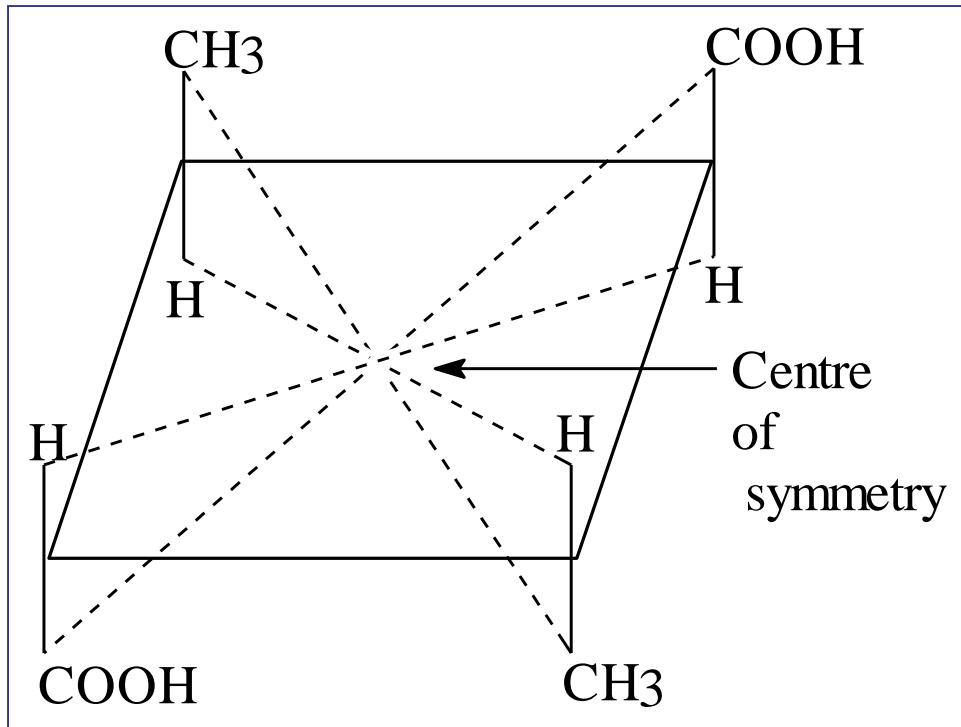
- A plane of symmetry is defined as an imaginary plane which divides a molecule in such a way that one half is mirror image of the other half.
- A molecule with atleast a plane of symmetry can be superimposed on its mirror image and is achiral. A molecule that does not have a plane of symmetry is usually chiral; it cannot be superimposed upon its mirror image.

• A plan of symmetry may pass through atoms, between atoms or both.



2. Centre of symmetry or *inversion* (*i*) or (C_i)

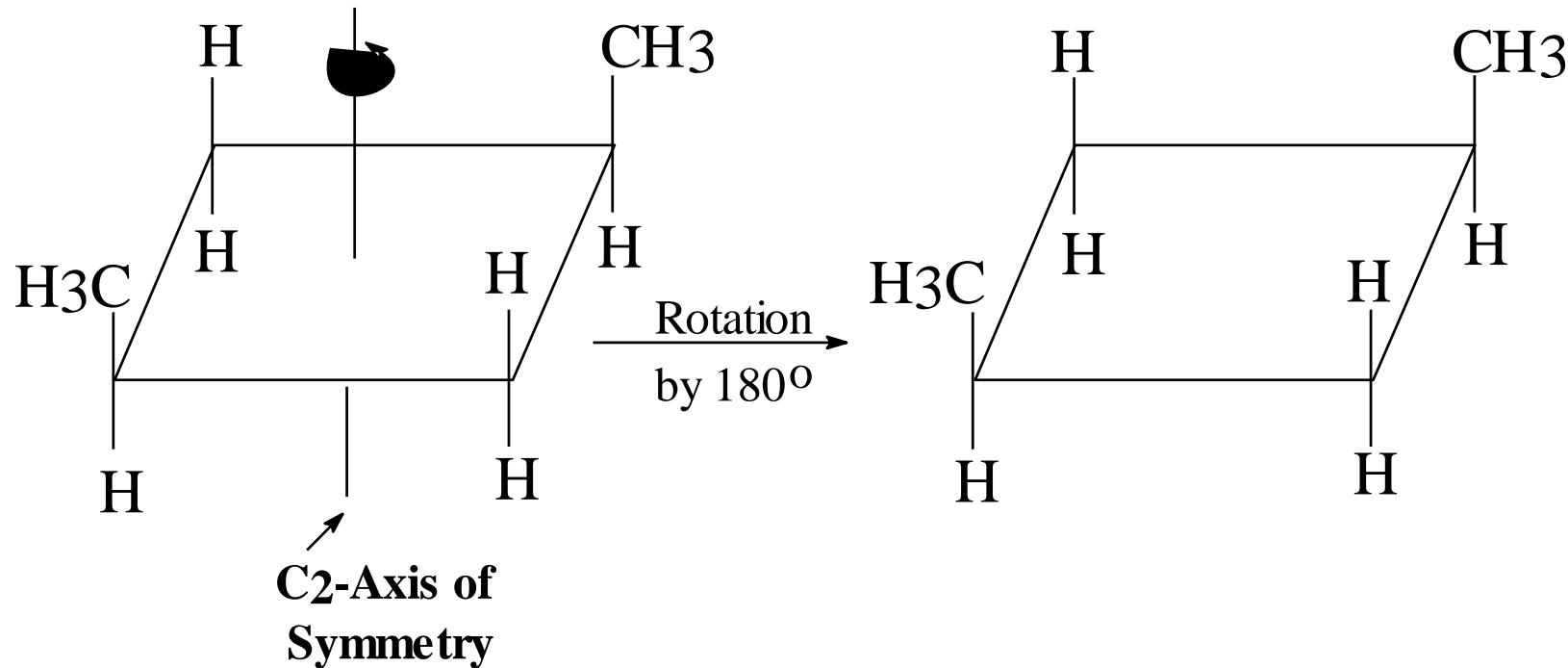
- A centre of symmetry (centre of inversion) is defined as a point within the molecule such that if an atom is joined to it by a straight line which if extrapolated to an equal distance beyond it in opposite direction meets an equivalent atom. In other words it is a point at which all the straight lines joining identical points in the molecule cross each other.*



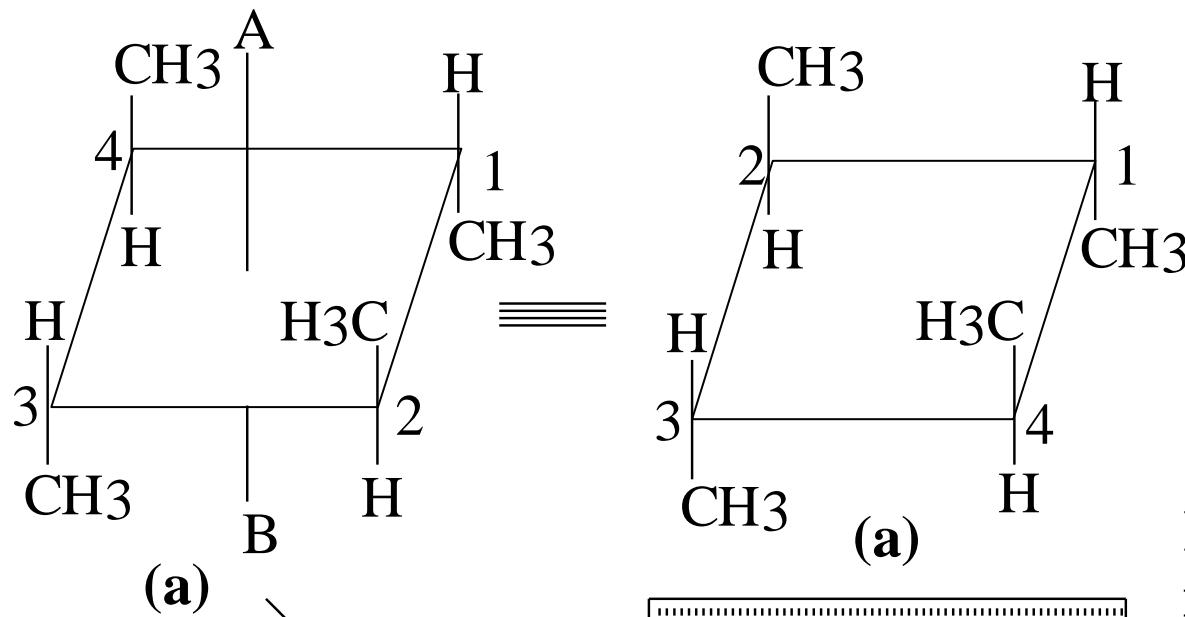
2,4-Dimethylcyclobutane -
1,3-dicarboxylic acid has C_i

3. Simple or proper axis of symmetry (C_n)

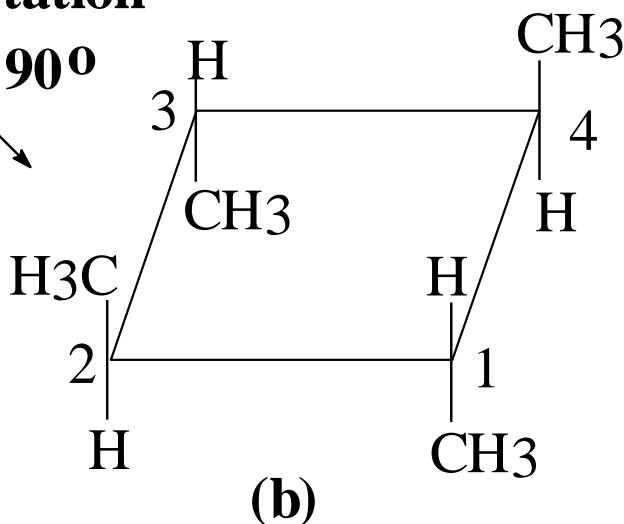
- An imaginary line passing through the molecule in such a way that when the molecule is rotated about it by an angle of $360^\circ/n$, an arrangement indistinguishable from the original is obtained. Such an axis is called **n-fold axis of symmetry**. For example, *cis*-1,3-dimethylcyclobutane has a two fold axis of symmetry (C_2) i.e. rotation by 180° gives indistinguishable appearance.



4. Alternating or improper axis of symmetry (S_n)



**Rotation
by 90°**



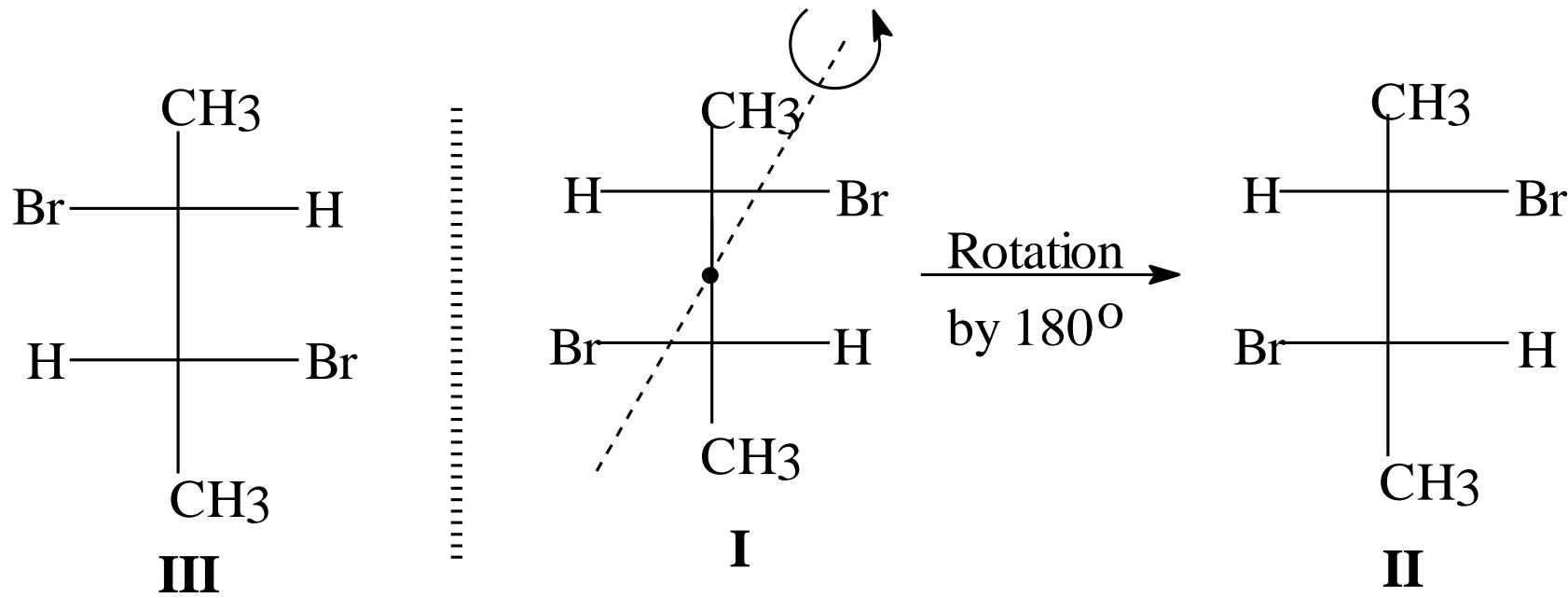
1,2,3,4-Tetramethyl-
cyclobutane has S_4

**Refraction through
mirror plane
perpendicular to
axis of rotation**

Asymmetry v/s Dissymmetry

- In general the term *asymmetry* is used for those optically active compounds which have none of the four elements of symmetry.
- In contrast the term *dissymmetry* is used for all stereoisomeric compounds which are capable of existing as pairs of non-superimposable mirror images despite the presence of some elements of symmetry.
- In other words the term dissymmetry is applicable to all stereoisomers, which are related to each other as non-superimposable mirror images of each other, e.g. 2,3-dibromobutane possesses a C_2 axis of symmetry in the molecule at right angle to the plane of the paper.

Since structures I and II are indistinguishable, the molecule has C_2 axis of symmetry. But it is non-superimposable on its mirror image so it is dissymmetric and not asymmetric and exhibits optical activity.



All asymmetric molecules are dissymmetric but all dissymmetric molecules are not asymmetric. However, both these types of molecules show optical activity and are chiral. Hence, to avoid any confusion, in using these terms, - asymmetry or dissymmetry - the term chirality is used.

RACEMIC MIXTURE

an equimolar (50/50) mixture of enantiomers

$$[\alpha]_D = 0^\circ$$

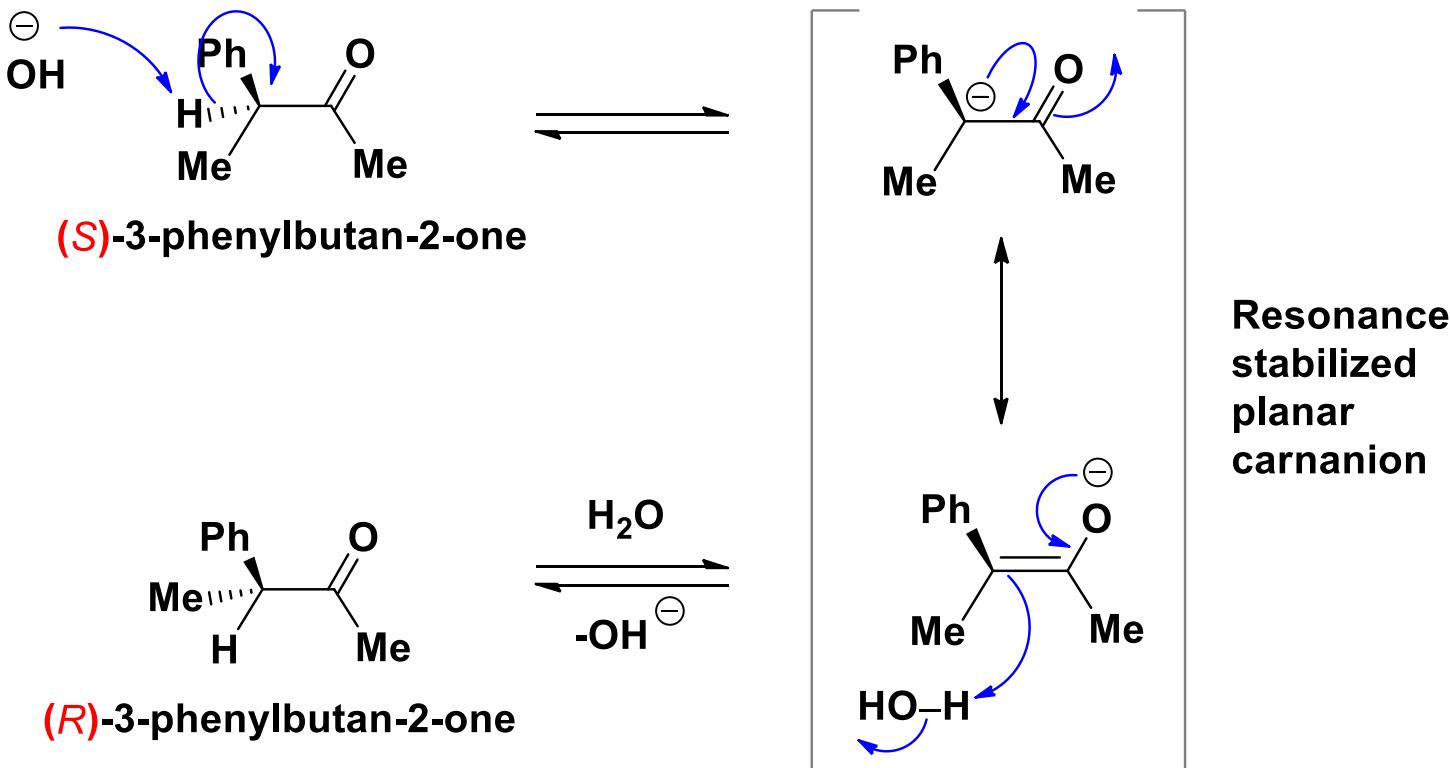
the effect of each molecule is
cancelled out by its enantiomer

Methods of Racemisation

- 1. Racemisation involving a carbanion as an intermediate**
- 2. Racemisation involving a carbocation as an intermediate (SN1 mechanism)**
- 3. Racemisation involving Walden Inversion (SN2 mechanism)**
- 4. Racemisation involving rotation about carbon - carbon single bond**

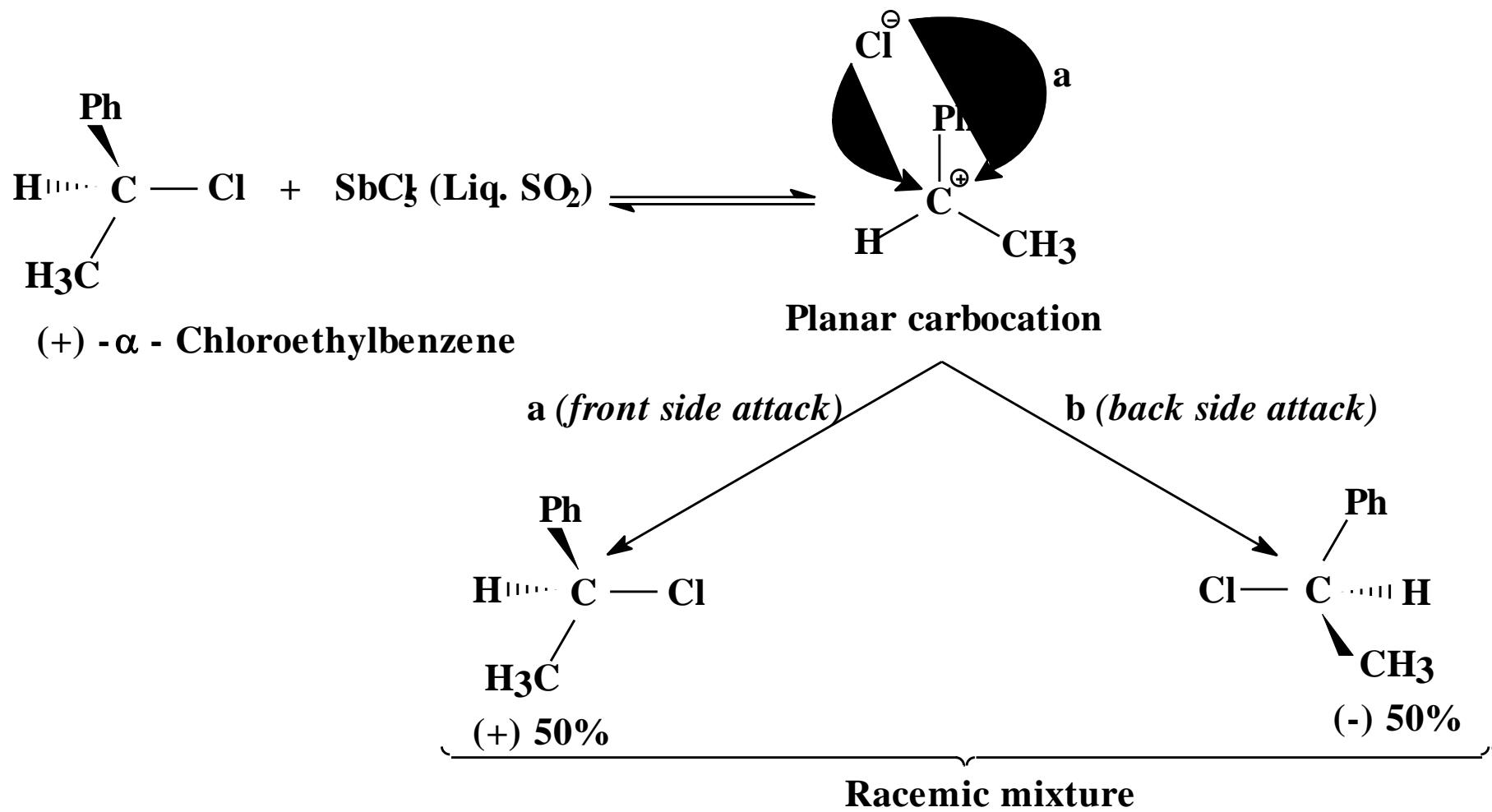
1. Racemisation involving a carbanion as an intermediate

When an optically active aldehyde or ketone having a hydrogen atom on the α -carbon, which is chiral, is treated with an acid or a base, it produces racemate.



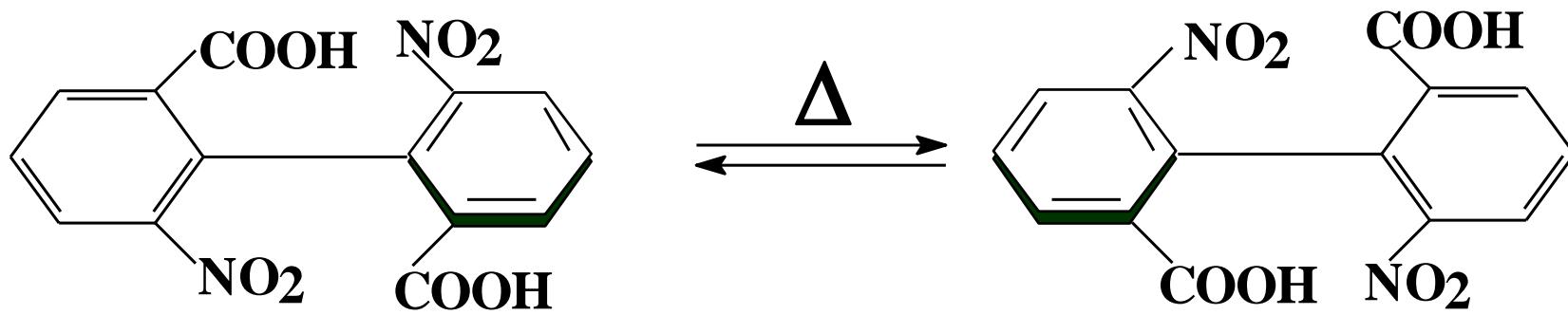
2. Racemisation involving a carbocation (*SN*1 mechanism)

- Carbocations are **planar** and hence achiral. Recombination of an anion can take place from either side of the carbocation with equal ease thereby leading to racemisation.



4. Racemisation involving rotation about C - C single bond

- Optical activity of biphenyls arises due to restricted rotation. It is, therefore, reasonable to believe that if the rings of such biphenyl derivatives become planar their optical activity should be lost. In agreement with this it has been found that a number of optically active compounds can be racemised under suitable conditions, e.g., heating which overcomes the energy barrier between two enantiomers.

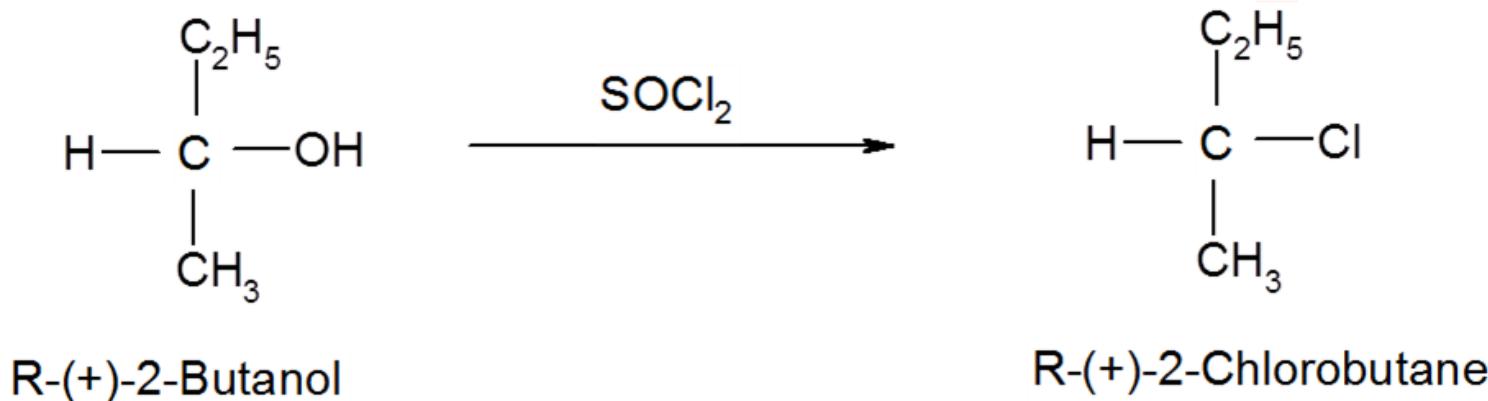


**6, 6'-Dinitrodiphenic acid
(Racemic mixture)**

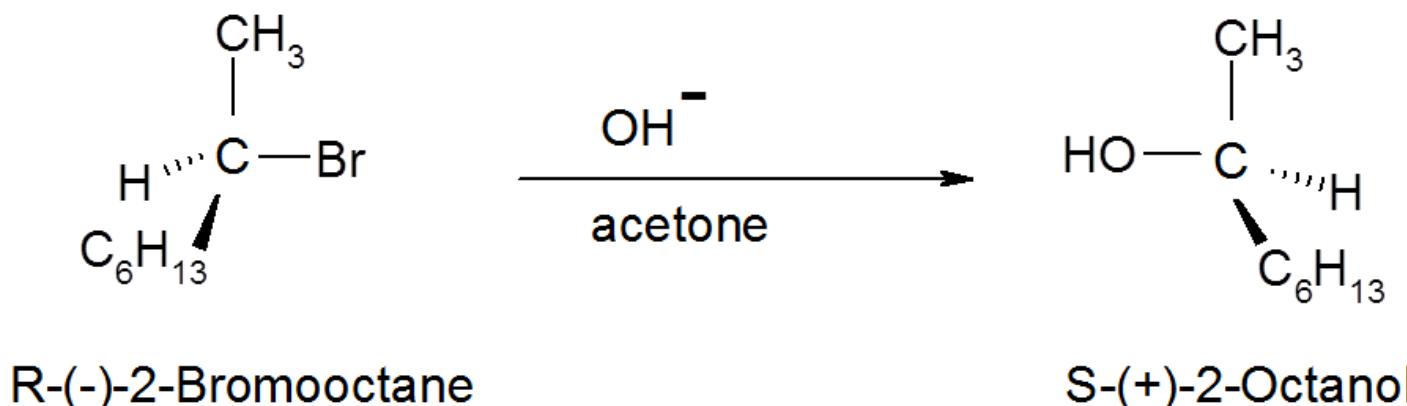
Coalescence temperature ?

Stereochemistry of Organic Reactions

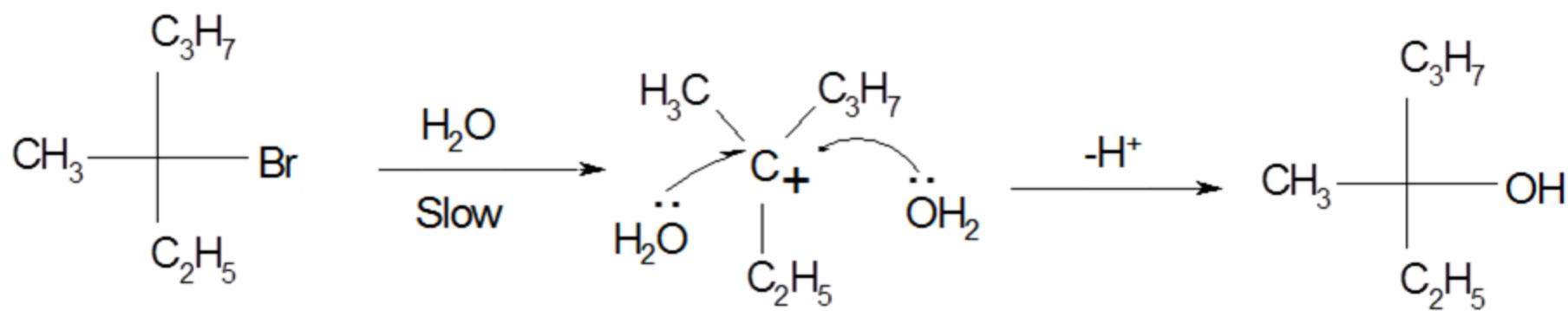
1- Retention of configuration:



2- Inversion of configuration: $\text{S}_{\text{N}}2$ Reactions



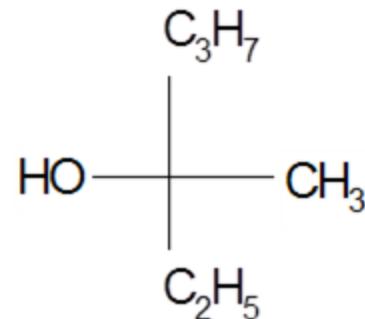
3- Racemization: S_N1 Reactions



R-(+)-3-Bromo-3-methylhexane

R-(+)- 50%

+



S(-)- 50%