Stereochemistry

For
Cheminformatics

Introduction

The branch of chemistry treating of the space relations of atoms in molecules.

Definition

- The branch of chemistry that deals with spatial arrangements of atoms in molecules and the effects of these arrangements on the chemical and physical properties of substances.
- The study of the three-dimensional arrangement of atoms or groups within molecules and the properties which follow from such arrangement.

The importance of stereochemistry

- The importance of stereochemistry in drug action is gaining greater attention in medical practice, and a basic knowledge of the subject will be necessary for clinicians to make informed decisions regarding the use of single-enantiomer drugs. Many of the drugs currently used in psychiatric practice are mixtures of enantiomers. For some therapeutics, single-enantiomer formulations can provide greater selectivities for their biological targets, improved therapeutic indices, and/or better pharmacokinetics than a mixture of enantiomers.

Importance of stereochemistry

- Many biologically active synthetic drugs contain chiral centers, although they are used as racemic mixtures. Enantiomers are hard to distinguish in the chemical laboratory but are readily discriminated in the body and differ in their biological activities and disposition. The pharmacokinetic profiles of enantiomers can be variable, especially for drugs with a first-pass effect and enantioselective pharmacokinetic monitoring should be carried out. Ultimately, whether to exploit a racemate or a single enantiomer in therapy is a multi-faceted decision to which drug disposition data have important contributions to make.

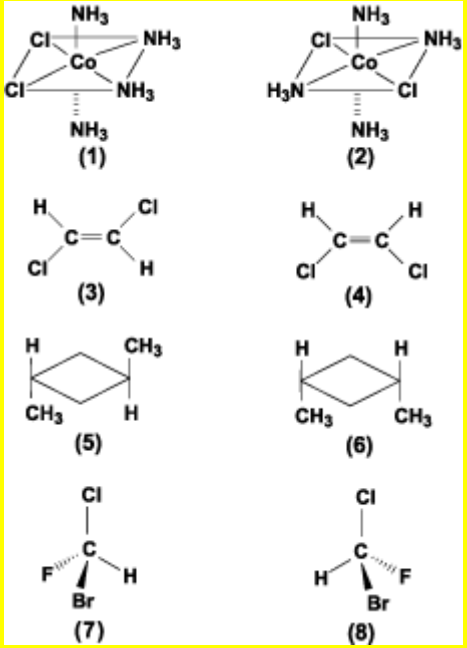
Stereoisomers and stereoisomerism

- Molecules that have identical molecular structures but differ in the relative spatial arrangement of component parts are stereoisomers.

- Inorganic and organic compounds exhibit stereoisomerism.

- Examples are structures (**1**)–(**8**).

Examples


NH3
Cl
NH3
Co
Cl
NH3
NH3
(1)
NH3
Cl
NH3
Co
H3N
Cl
NH3
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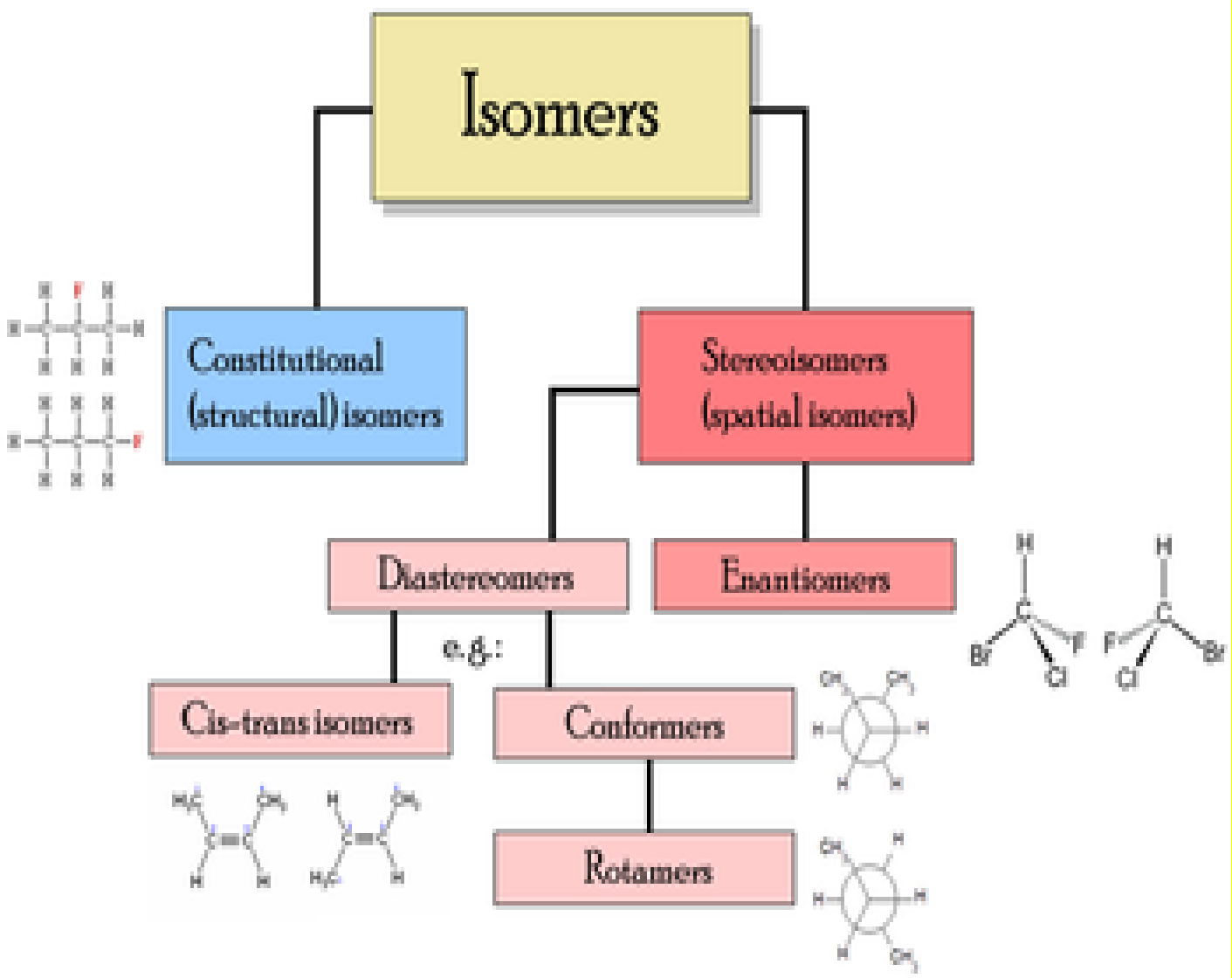
H
Cl
C
C
Cl
H
(3)
H
H
C
C
Cl
Cl
(4)
H
CH3
CH3
H
(5)
H
H
CH3
CH3
(6)
Cl
C
F
H
Br
(7)
Cl
C
H
F
Br
(8)

Isomerism

- Central to stereochemistry is the concept of isomerism.

- Isomers are sets of chemical compounds having identical atomic composition but different structural properties.

Classification of Isomers



Geometrical isomers

- With geometric isomers, the differences arise from the atoms being bonded in different sequences or patterns.
- An example is *ortho*- and *para*-dichlorobenzene; the former has chlorine atoms replacing adjacent carbon atoms in a benzene ring while the latter has chlorine atoms replacing opposing carbon atoms.

Optical isomers

- Optical isomers are pairs of molecules that differ in the same way that a left hand and right hand screw differ; i.e., they are mirror images of each other. Such molecules with a “handedness” typically rotate the plane of polarization of light that passes through them, but in opposite directions.
- The sugars glucose and dextrose are a pair of optical isomers; glucose rotates the plane of polarization to the left and dextrose to the right.

Origin of stereochemistry

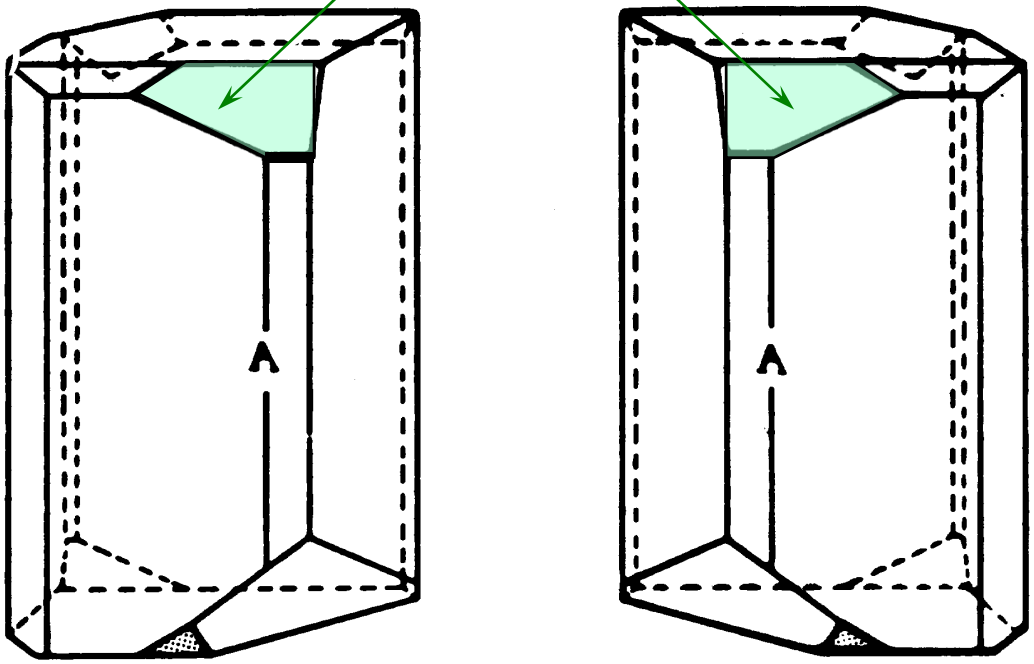
- Louis Pasteur could rightly be described as the first stereochemist, having observed in 1849 that salts of tartaric acid collected from wine production vessels could rotate plane polarized light, but that salts from other sources did not. This property, the only physical property in which the two types of tartrate salts differed, is due to optical isomerism. In 1874, Jacobus Henricus van 't Hoff and Joseph Le Bel explained optical activity in terms of the tetrahedral arrangement of the atoms bound to carbon.

Crystals of Sodium Ammonium Tartrate

Pasteur found two different crystals.

hemihedral faces

mirror images



Biot's results : (+) (-)

Louis Pasteur separated these and gave them to Biot to measure.

Origin of stereochemistry

- Cahn-Ingold-Prelog priority rules are part of a system for describing a molecule's stereochemistry. by R-S and E-Z Nomeclature.
- Fischer projection is a simplified way to depict the stereochemistry around a stereocenter.

Thalidomide

The significance of stereochemistry

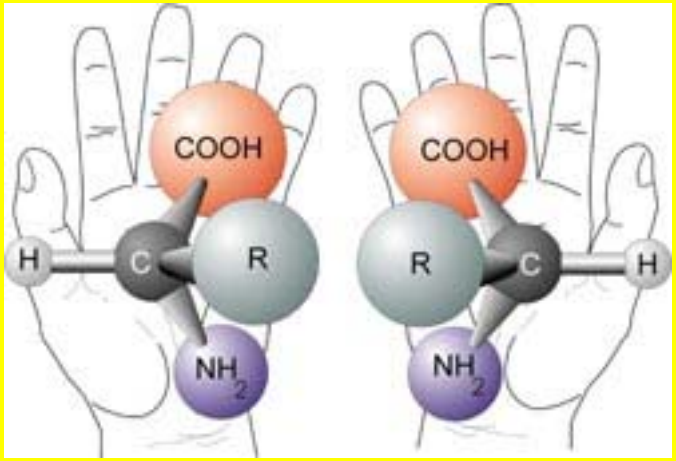
- One of the most infamous demonstrations of the significance of stereochemistry was the thalidomide disaster. Thalidomide is a drug, first prepared in 1957 in Germany, prescribed for treating morning sickness in pregnant women. The drug however was discovered to cause deformation in babies. It was discovered that one optical isomer of the drug was safe while the other had teratogenic effects, causing serious genetic damage to early embryonic growth and development.
- In the human body, thalidomide undergoes racemization: even if only one of the two stereoisomers is ingested, the other one is produced.
- Thalidomide is currently used as a treatment for leprosy and must be used with contraceptives in women to prevent pregnancy-related deformations. This disaster was a driving force behind requiring strict testing of drugs before making them available to the public.

Types of stereoisomerism

- Atropisomerism
- *Cis-trans* isomerism
- Conformational isomerism
- Diastereomers
- Enantiomers
- Rotamers

Chiral

- The term **chiral** is used to describe an object that is non-superposable on its mirror image.
- Human hands are perhaps the most universally recognized example of chirality: The left hand is a non-superposable mirror image of the right hand; no matter how the two hands are oriented, it is

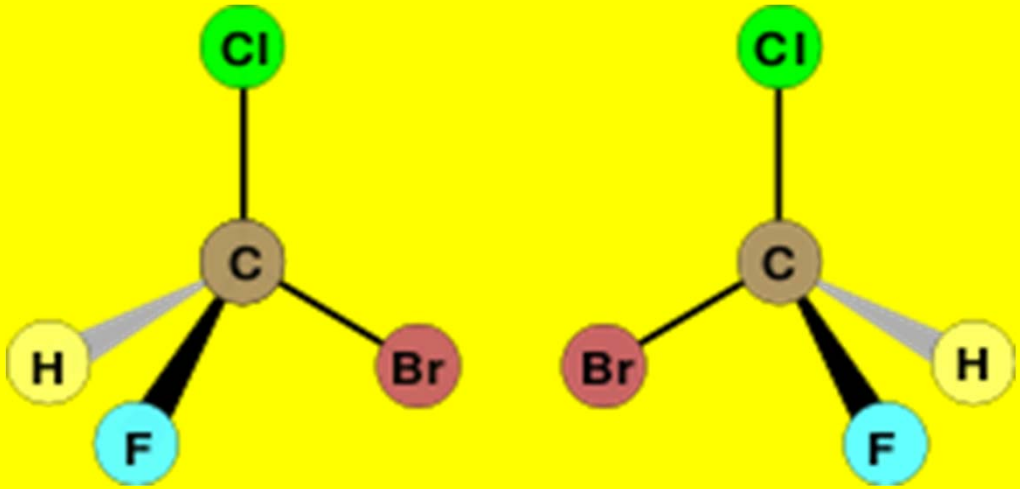


Chirility or optical activity

- Tetrahedral carbon attached to four different atoms or groups producing nonsuperimposable mirror images is called chiral carbon. Compound having chiral carbon is chiral compound.
- Nonsuperimposable mirror images are a pair of enatiomers, which has ability to rotate plane of polarized light to the right or the left. This property is known as optical activity.
- If it rotate plane of polarized light to the right or in clockwise direction it is symbolized by ‘d’ or + sign and termed as dextro isomer.
- If it rotate plane of polarized light to the left or in anticlockwise direction it is symbolized by ‘l’ or - sign and termed as levo isomer.

Enantiomers or optical isomers

- When used in the context of chemistry, chirality usually refers to molecules. Two mirror images of a molecule that cannot be superposed onto each other are referred to as enantiomers or optical isomers.
- The two enantiomers of bromochlorofluoromethane

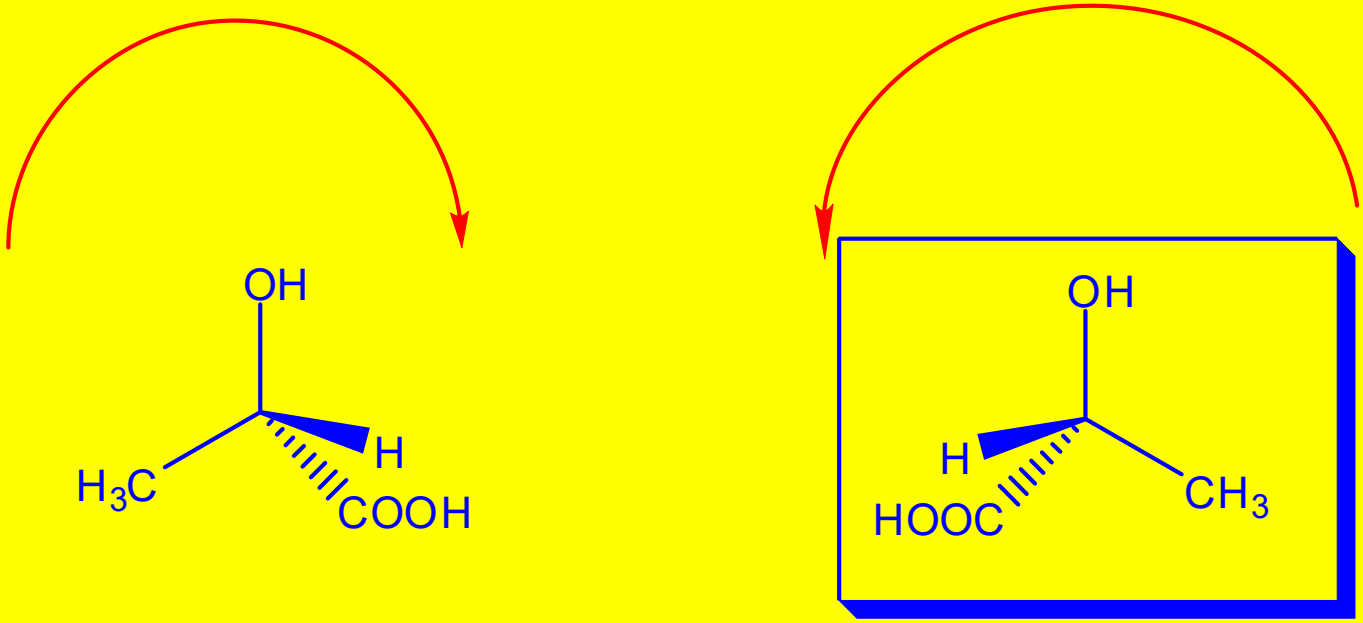


Racemic mixture

- A mixture of equal amounts of the two enantiomers is said to be a racemic mixture. Racemic mixtures are not optically active as rotation caused by one isomer is equally cancelled by another isomer.

Optical activity in Lactic Acid

- $CH_3C^*H(OH)COOH$, Acc' to 2^n rule $2^1=2$ isomers are possible (n= no of chiral carbon)



d/(+)-Lactic acid

I

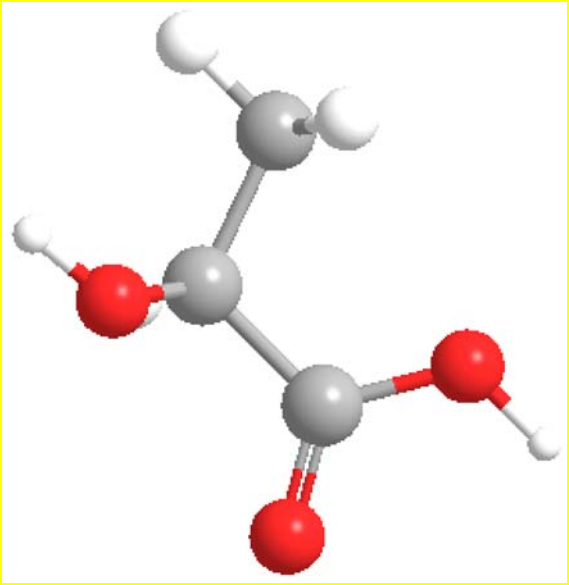
l/(-)-Lactic acid

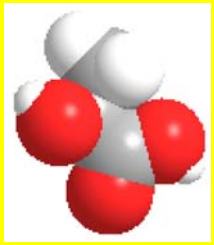
II

nonsuperimposale mirror images, dl pair

a pair of inantiomers, optically active

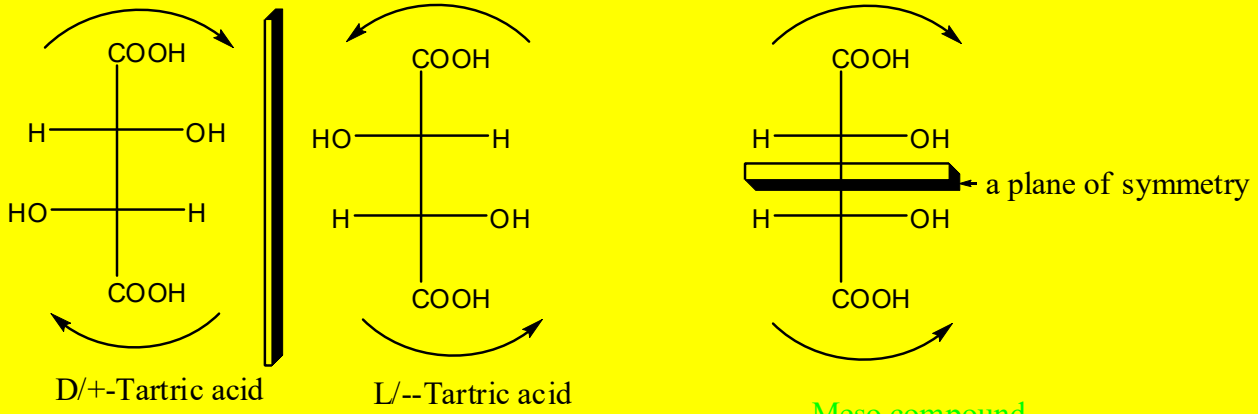
Ball and stick model & Space filling model





Optical activity in Tartric Acid

HOOCC*H(OH) C*H(OH)COOH, Acc' to 2n rule 2^2=4 isomers are possible (n= no of chiral carbon) using Fischer model



I **nonsuperimposale mirror images, dl pair a pair of inantiomers, optically active**

II

III Meso compound optically inactive

Tartric Acid

- Enantiomers: Stereoisomers that are nonsuperimposable mirror images. I and II are nonsuperimposable mirror images and are enantiomers and are chiral.
- They roatate plane of polarized light to the right or the left. I is dextro and II is levo isomerof tartric acid.
- Distereoisomers: Stereoisomers that are not the mirror images. It has atleast 2 chiral carbons. I and III & II and III are distereoisomers. It has atleast 2 chiral carbons.
- Meso compound: One half of a molecule is the mirror image of other part. It has plane of symmetry. It is optically inactive as rotation caused by one half is equally cancelled by another. III is the meso compound.
- Racemic mixture: Equal parts of enatiomers (I and II) forms Racemic mixture which is optically inactive as as rotation caused by one isomer is equally cancelled by another.

Conformational Analysis

- Different arrangements of atoms or groups arise due to allowed free rotation about single bond is known as Conformation
- When atoms or groups rotate about single bond due to allowed free rotation energy changes is taking place which is known as Conformation
- E.g. Conformational Analysis of ethane, n-butane and cyclohexane

Factors affecting the stability of conformation

- Angle Strain
- Rotational or Torsional Strain
- Steric Strain
- Wander waal strain

Angle Strain

- For sp3 hybridised td carbon atom bond angle of 109 28’ is the normal bond angle. Any deviation from this angle is accompanied by angle strain.
- E.g. half chair conformation

Rotational or Torsional Strain

- **Any two non bonded atoms tends to have their bonds staggered. Staggered arrangement is the normal arrangement. Any deviation from this arrangement is accompanied by Rotational or Torsional Strain. E.g. eclipsed ethane**

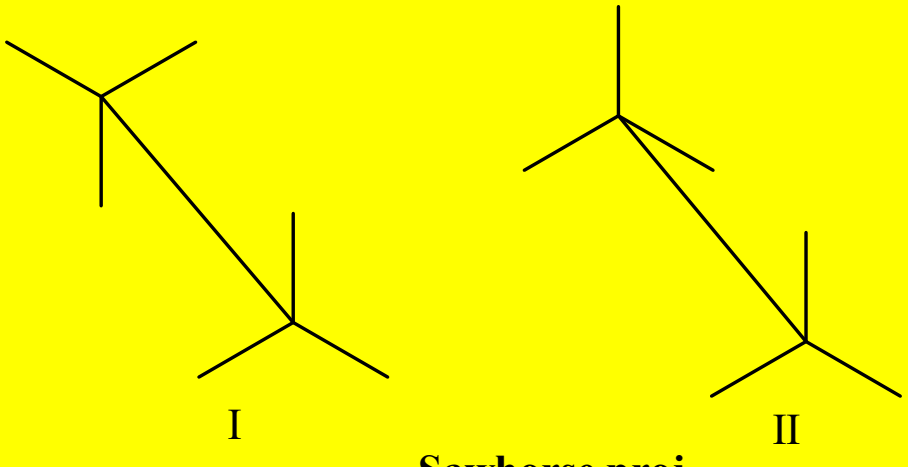
Steric strain

- **Any two nonbonded atoms tends to remain as far as possible. If distance between them is less than their Van der waal radai causes repulsion. Such an interaction is called steric effect. E.g. flag pole hydrogens in boat conformation.**

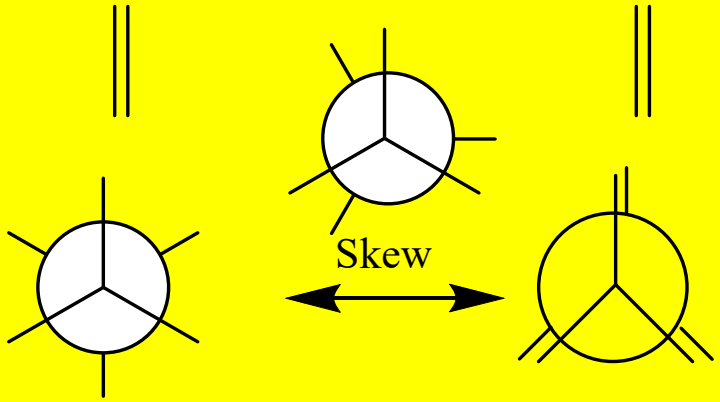
Dipole-dipole interaction

- **H bonding is the very good example of Dipole-dipole interaction**

Conformational Analysis of ethane



Sawhorse proj.



Ia stageered
stable

IIa eclipsed
unstable

Newmann proj.

Conformational Analysis of ethane

- In staggered conformation all H atoms are as far as possible. There is maximum separation and minimum repulsion. As it is free from angle, torsional and steric strain it is the most stable arrangement.

- While in eclipsed conformation 3 H atoms present on front carbon atom collide with three H atoms present on back side carbon atom. Angle between colliding H atom is 0^0. So energy increases by 0.9 x 3 = 2.7 kcal/mole and it becomes least stable conformation.

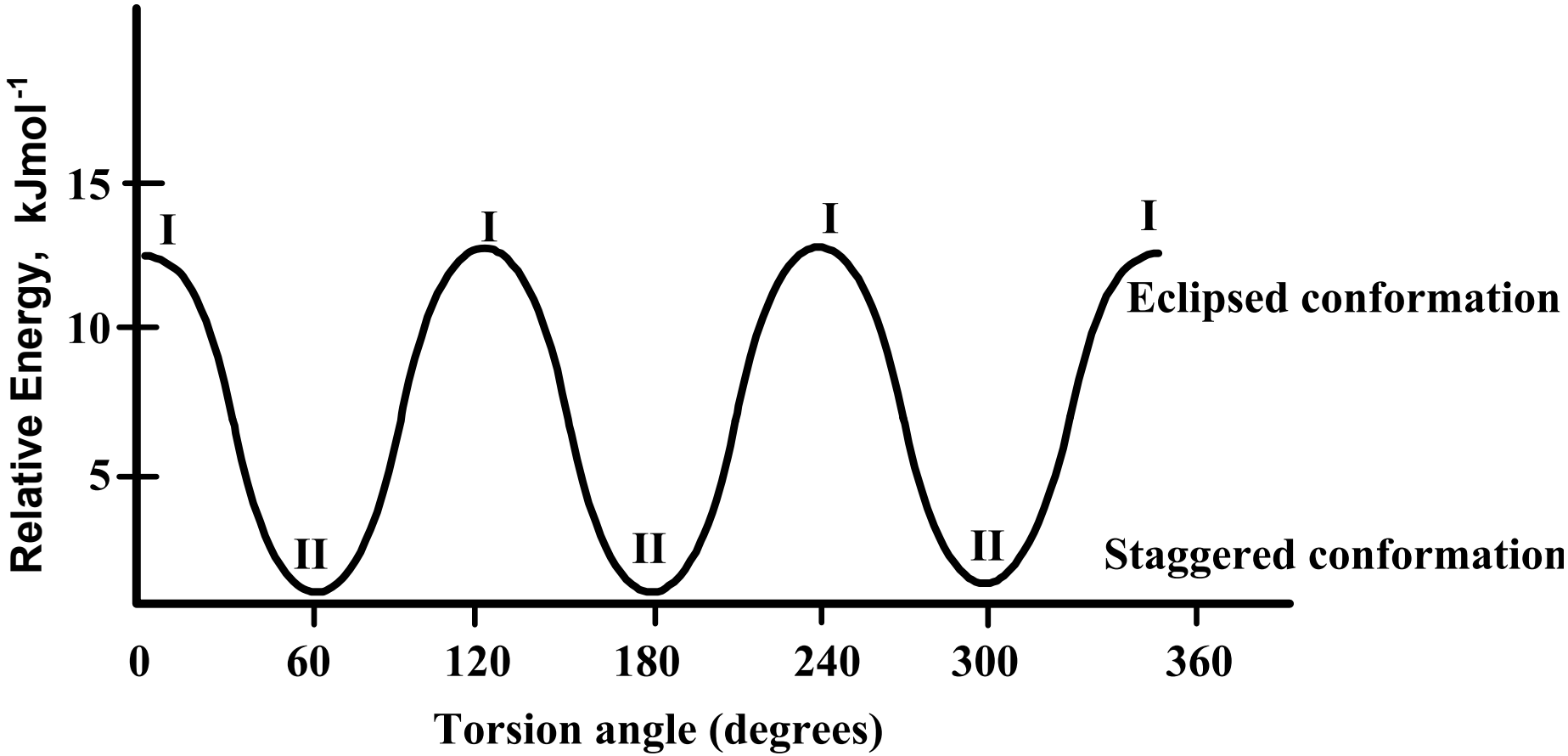
Conformational Analysis of ethane

- **In between eclipsed and staggered conformation there are no of possible conformations known as skew conformations.**

Skew

Conformational Analysis of ethane

- **In eclipsed conformation 3 H atoms present on front carbon atom collide with three H atoms present on back side carbon atom. Angle between collinding H atom is 0^0. So energy increases by 0.9 x 3 = 2.7 kcal/mole and it becomes least stable conformation.**



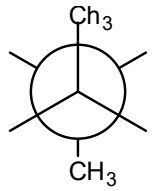
I at 0^{o}, 120^{o} and 240^{o}

II at 60^{o}, 180^{o} and 300^{o}

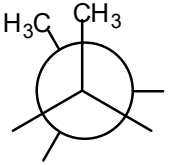
Fig. 3.7 Rotational or torsional energy in ethane

Conformational Analysis of n-butane

- In n-butane one H of each c atom of ethane is replaced by bulky -CH3 group and the conformation studyof n-butane becomes complex than that of ethane
- There are several conformations possible



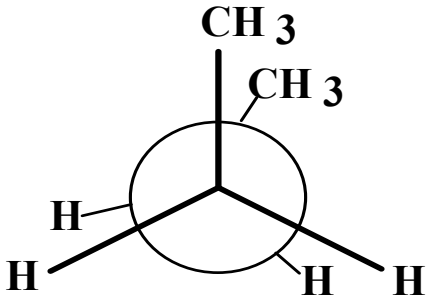
- Four main conformations are
- Anti or fully staggered
- Gauche
- Partially eclipsed



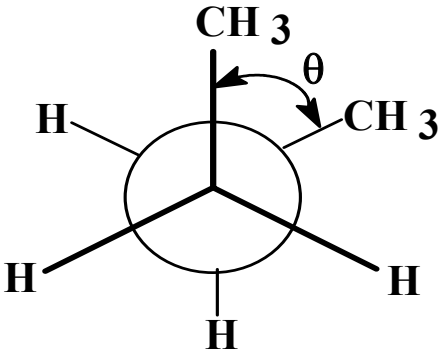
- Fully eclipsed
- In staggered conformation both CH3 groups are as far as possible. There is maximum separation and minimum repulsion. As it is free from angle, torsional and steric strain it is the most stable arrangement.

While in eclipsed conformation - CH3 group present on front carbon atom collide with other CH3 group present on back side carbon atom. Angle between colliding H atom is 0^0. So energy increases by 0.9 x 4 = 3.6 kcal/mole and it becomes least stable conformation.

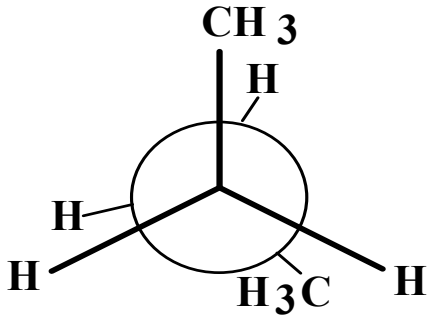
Conformations of *n*-Butane



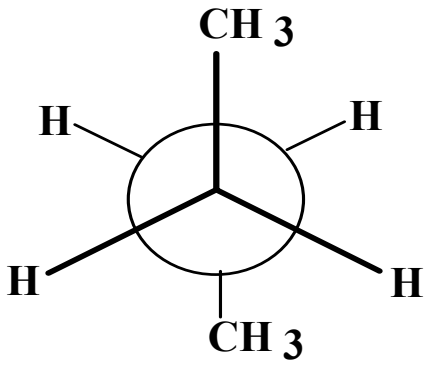
I
Fully Eclipsed
(θ = 0 ^{o})



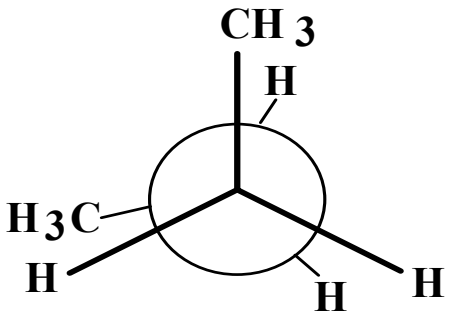
II
Gauche (θ = 0 ^{o})



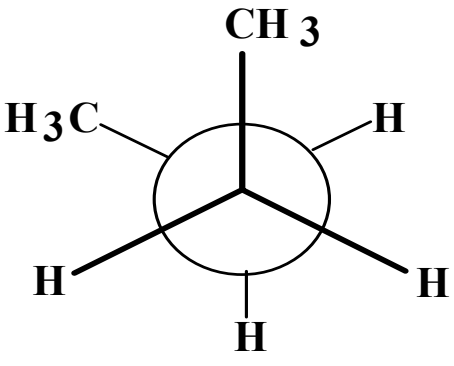
III
Partially Eclipsed
(θ = 120 ^{o})



IV
Anti or *Trans* (θ = 180 ^{o})



V
Partially Eclipsed
(θ = 240 ^{o})



VI
Gauche (θ = 300 ^{o})

Due to congestion in space a repulsive force acts between the methyl groups which is called van der Waals strain or steric hindrance. In butane, *gauche* conformation is less stable than *anti*-conformation due to vander Waals strains i.e. *n*-butane gauche (or skew) intraction.

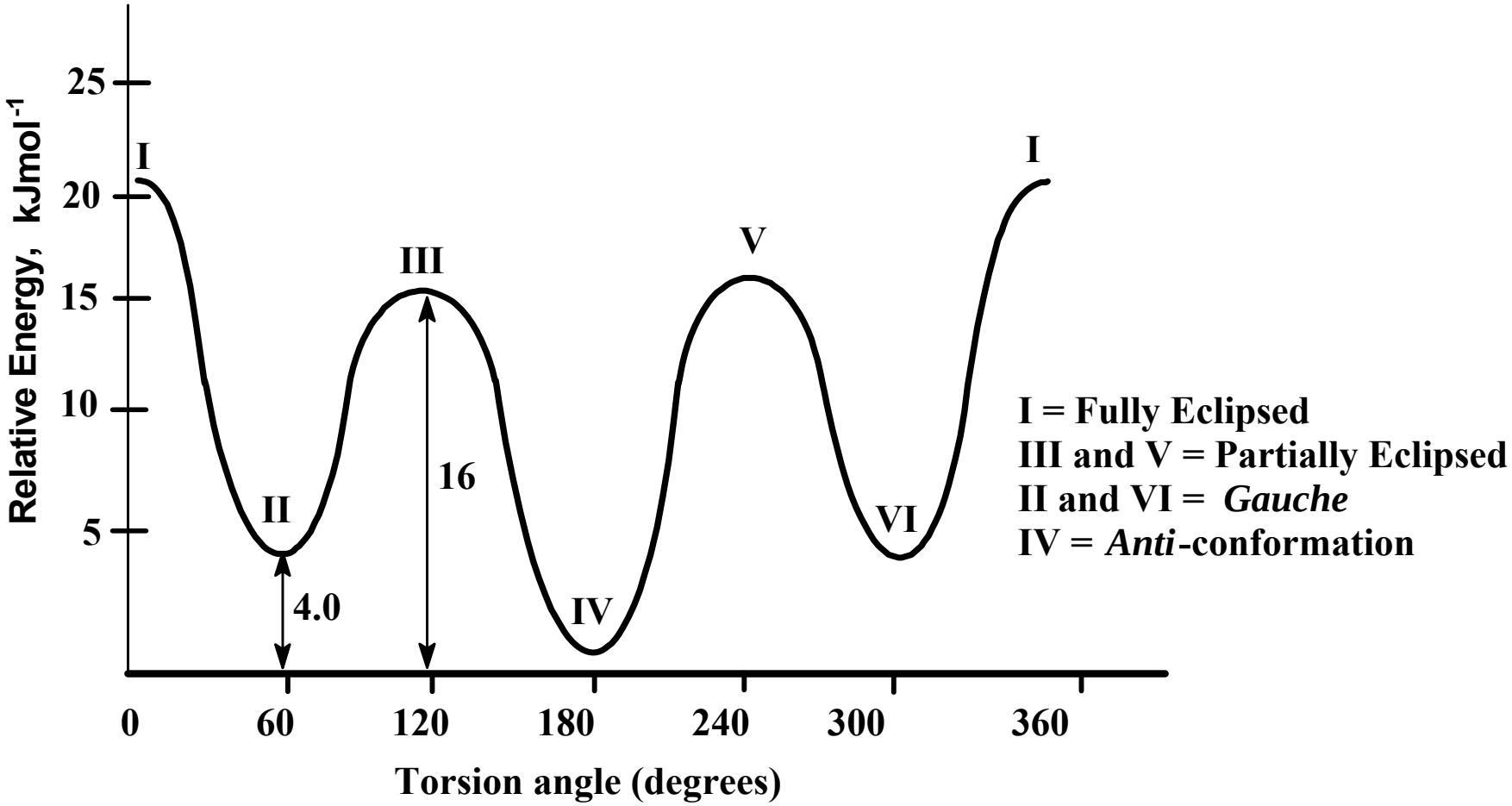


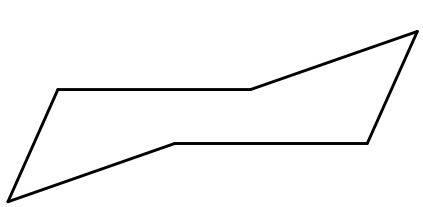
Fig. 3.8 Rotational or torsional energy in *n*-butane

I 18-26, II 3-4, III 14-16

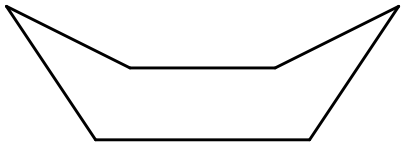
At room temperature, almost all molecules exist in staggered conformation and amongst staggered conformations 78% exist in *anti* and 22% in *gauche* conformations.

Alicyclic System: Cyclohexane

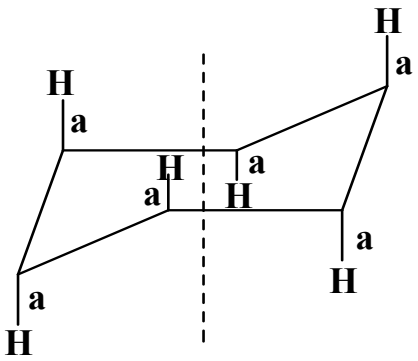
- **Cyclohexane can have two conformations free from Baeyer or angle strain, called the *chair* form (I) and the *boat* form (II), respectively.**

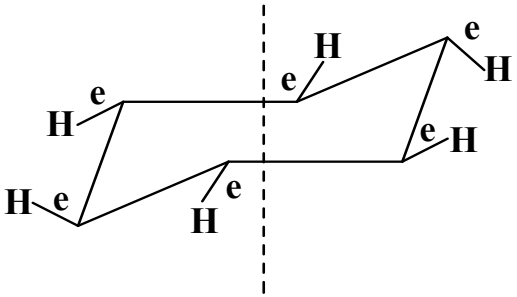


I

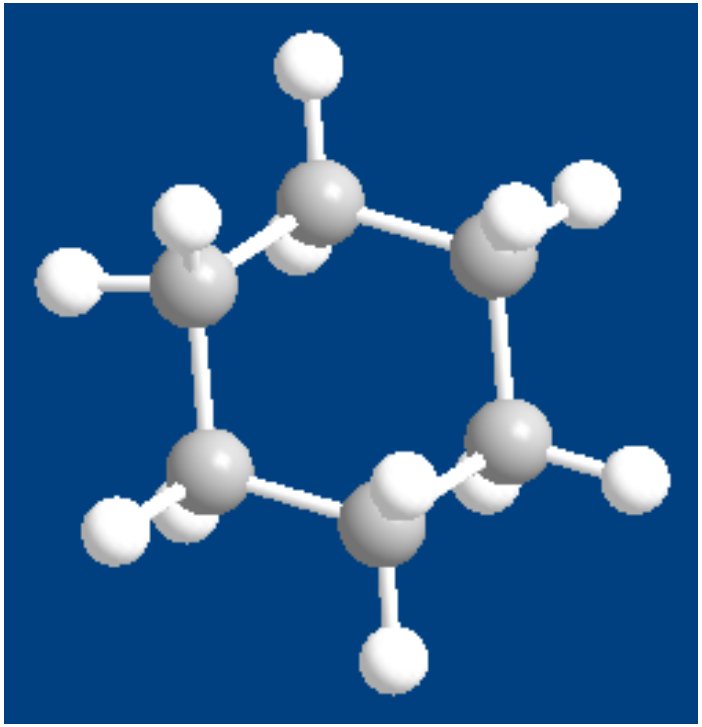


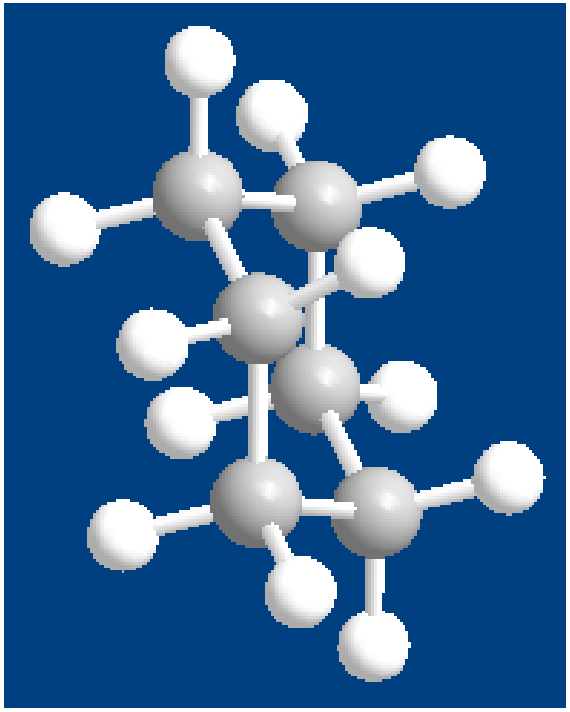
II

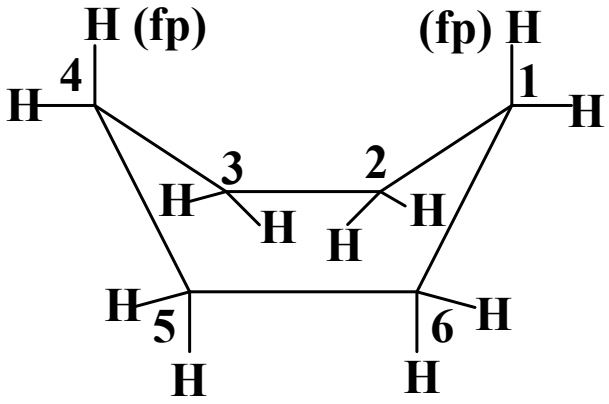




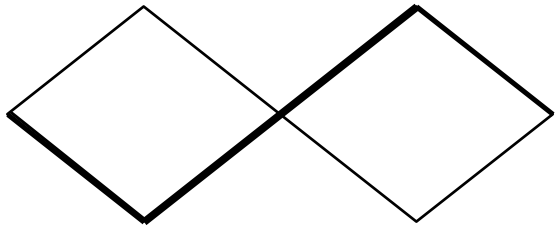
Chair conformations of cyclohexane with axial and equatorial bonds



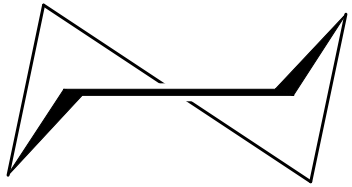




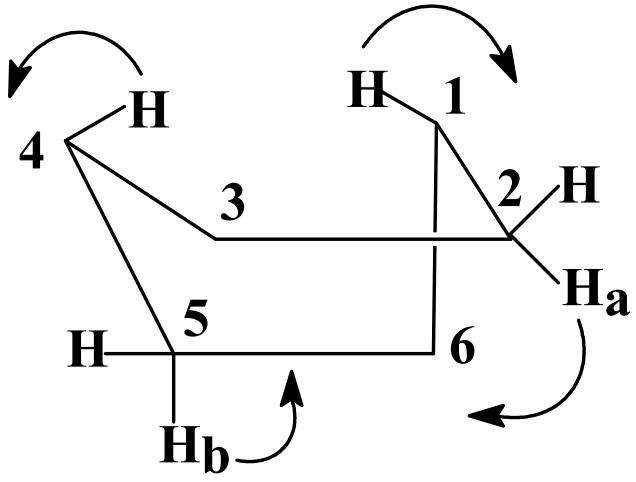
Boat



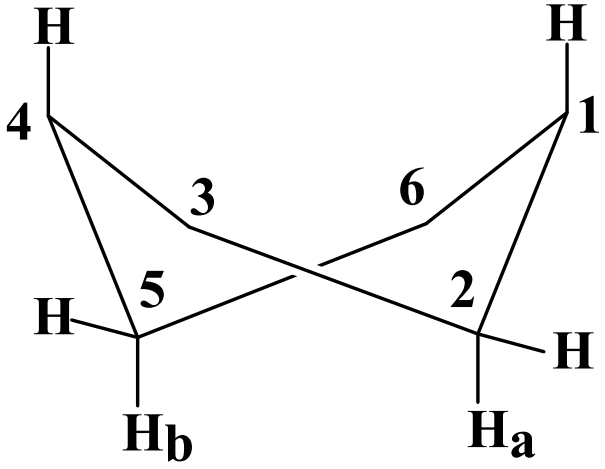
Twist Boat



Twist chair



Boat



Twist boat

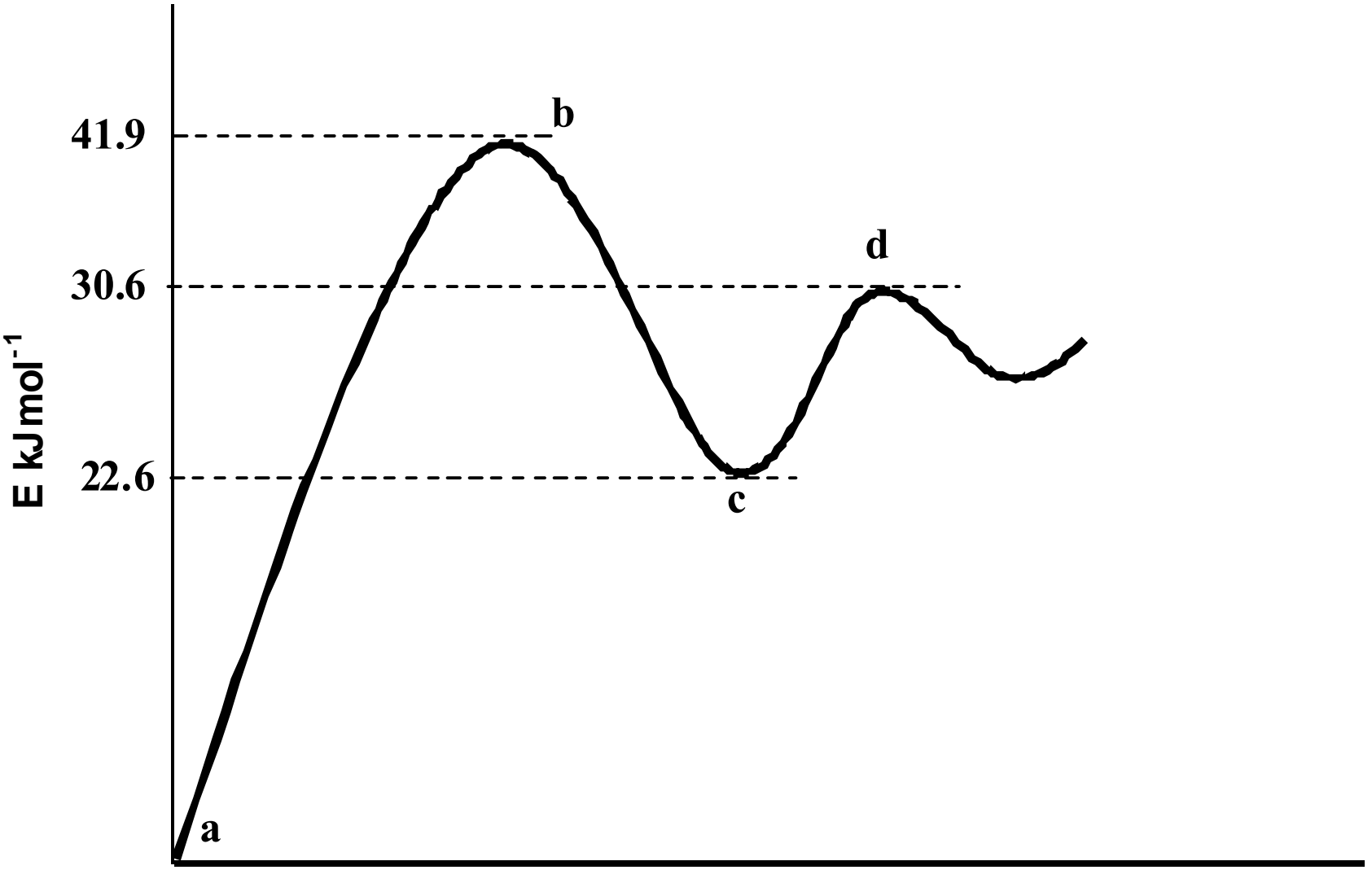
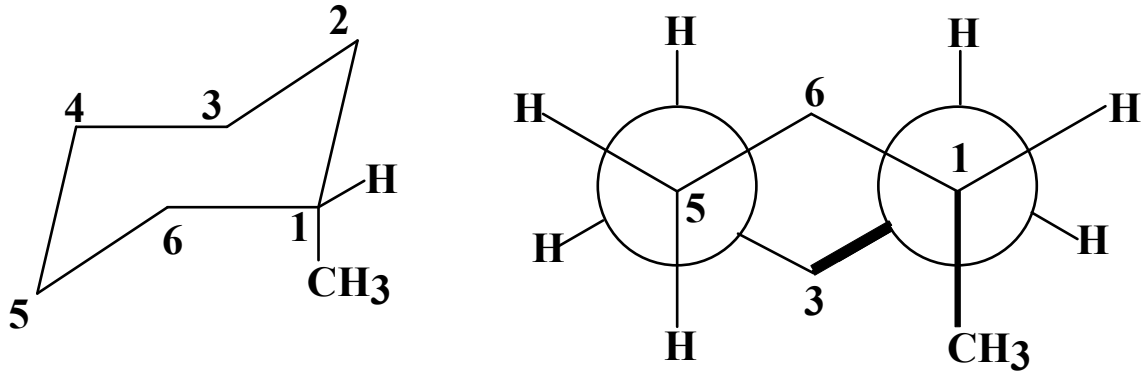


Fig. 3.10 Potential energy of cyclohexane, a, chair; b, twist chair; c twist boat; d, boat.

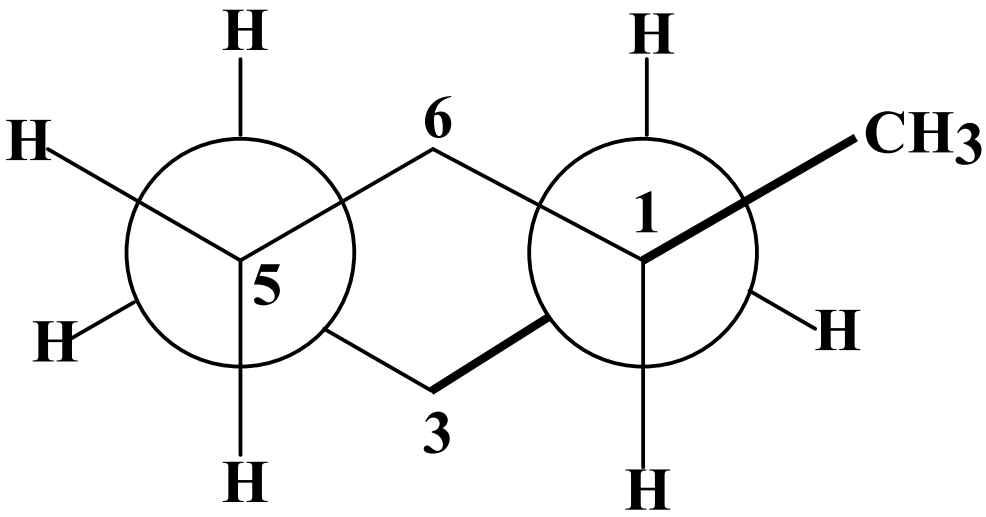
Cyclohexane Derivatives

- In methylcyclohexane, the axial conformer will have two more *n*-butane skew interactions (7.54 kJ mol^{-1}) whereas in the equatorial conformer no additional interaction or torsional strain is introduced since the two new *n*-butane segments in it are both fully staggered (*anti*).

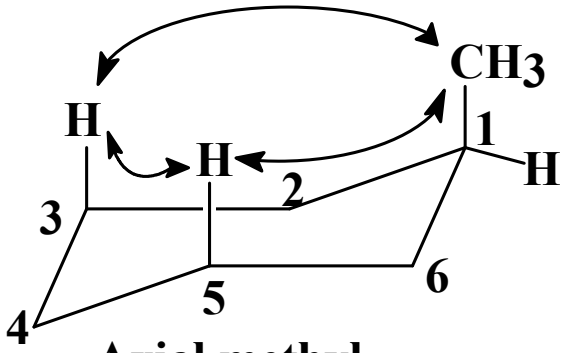


The two new skew (gauche) interactions in the axial conformer are best demonstrated by drawing the Newman projection formula for the *n*-butane segment, CH_3, C_1, C_2, C_3 and CH_3, C_1, C_6, C_5.

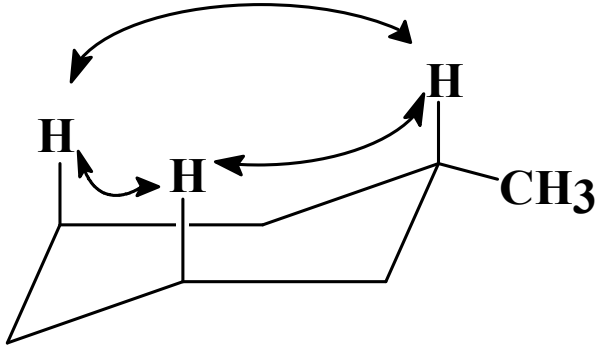
Newman projection for the equatorial conformer, as shown below, clearly shows the absence of any additional skew interaction.



We reach the same conclusion if we consider that in the axial conformer the two axial hydrogens on C_3 and C_5 are closer to the axial than to the equatorial methyl group.



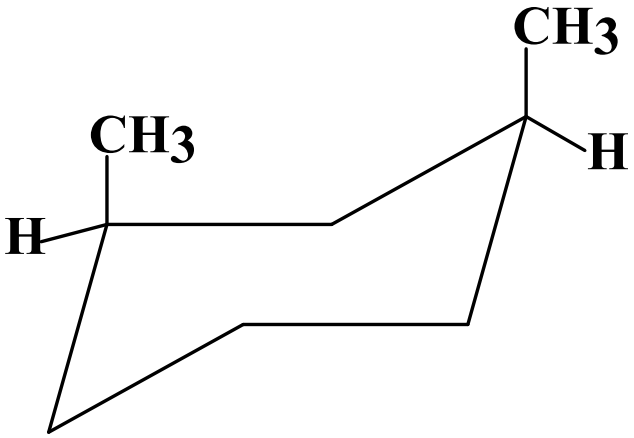
Axial methyl



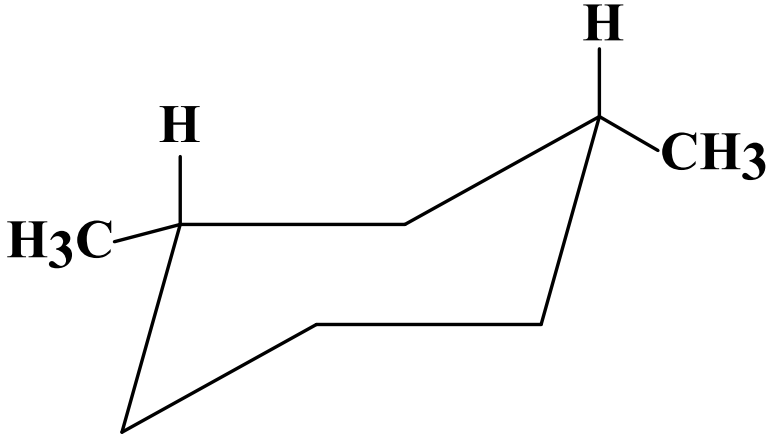
Equatorial methyl

Cis 1,3-dimethylcyclohexane

- **The interactions between the axial atoms or groups at 1- and 3- or 5-positions are called *1,3-diaxial interactions* and in the case of 1,3-dimethylcyclohexane, the 1,3-diaxial interaction has been assigned the value of 22.6kJmol^{-1}. Thus *cis* 1,3-dimethylcyclohexane exists at room temperatures almost wholly in the diequatorial conformation.**



cis* 1,3-Dimethylcyclohexane *(diaxial conformer; much less stable)



cis* 1,3-Dimethylcyclohexane *(diequatorial conformer; much more stable)

Methods of Resolution

Usual methods of separation such as fractional distillation, fractional crystallization or adsorption techniques cannot be used for the separation of enantiomers. Therefore, some special procedures are needed for resolution of racemic mixtures. Some of the more important methods are:

1. **Mechanical Separation**
2. **Preferential Crystallization**
3. **Biochemical Method**
4. **Resolution through the formation of diastereomers: The Chemical Method**
5. **Chromatographic Method**

1 Mechanical Separation

- **Pasteur (1948) proved that the compound called "racemic acid" is actually an equimolecular mixture of (+) and (-) tartaric acids. He found that when racemic sodium ammonium tartarate was crystallized below 300K, two types of crystals, were obtained. These crystals had distinguishable hemihedral faces and were non-superimposable. He separated them with tweezers and magnifying glass.**

Limitations:

(i) This method is painstaking and time consuming.

(ii) It is of limited use being applicable to those compounds only which can crystallize as two well defined types of crystals.

2 Preferential Crystallization

- **Preferential crystallization is closely related to mechanical separation of crystals.**
- **A supersaturated solution of the racemic mixture is inoculated with a crystal of one of the enantiomers or an isomorphous crystal of another chiral compound. For example, when the saturated solution of (±) sodium ammonium tartarate is seeded with the crystal of one of the pure enantiomer or a crystal of (–) asparagine, (–) sodium ammonium tartarate crystalises out first.**
- **This method is also called as entrainment and the seed crystal is called entrainer.**

3 Biochemical Method

- **Microorganisms or enzymes are highly stereoselective.**
- **Fermentation of (±) tartaric acid in presence of yeast or a mold, e.g., *Pencillium glaucum*. The (+) tartaric acid is completely consumed leaving behind (–) tartaric acid.**
- **(±) Amino acids can be separated using *hog-kidney acylase* until half of acetyl groups are hydrolysed away, only acetyl derivative of L-amino acid is hydrolysed leaving behind acetyl derivative of D-amino acid.**

Limitations:

(i) These reactions are to be carried out in dilute solutions, so isolation of products becomes difficult.

(ii) There is loss of one enantiomer which is consumed by the microorganism. Hence only half of the compound is isolated (*partially destructive method*).

4 The Chemical Method

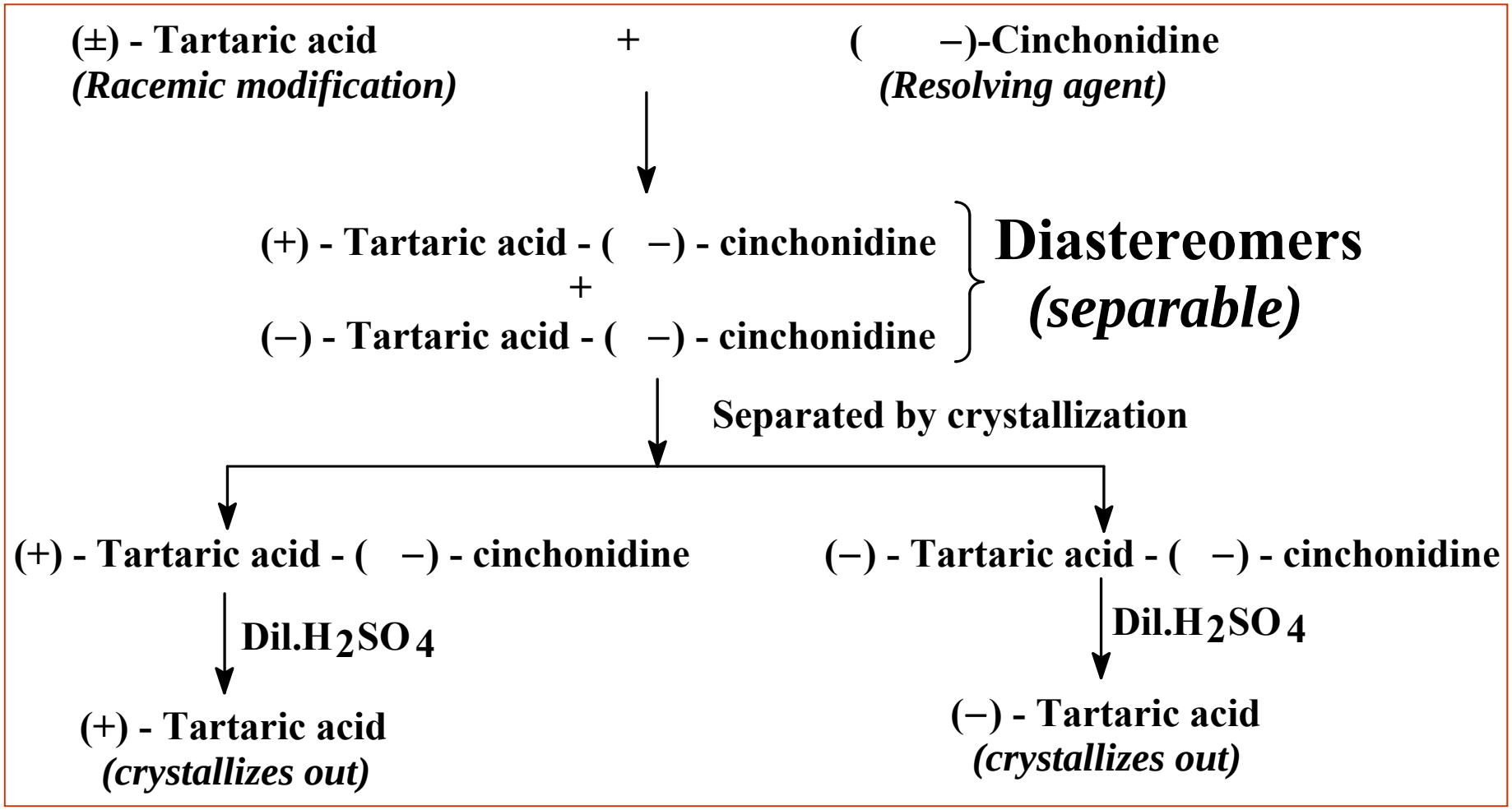
Basic Principle

Step 1. A *racemic mixture (±)*-A reacts with an optically pure reagent (+) or (–)-B to give a mixture of two products which are diastereomers. The reagent (+) or (–)-B is called the resolving agent.

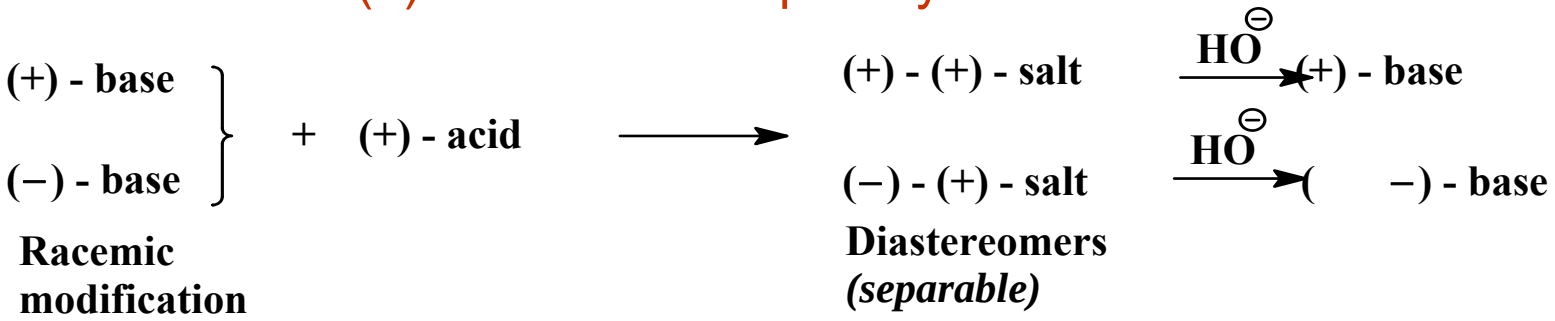
(±) - A + (+)-B → (+)A(+)B + (-)A(+)B

Step 2. The mixture of diastereomers obtained above can be separated using the methods of fractional distillation, fractional crystallization, etc.

Step 3. The pure diastereomers are then decomposed each into the corresponding enantiomer and the original optically active reagent, which are then separated.



Similarly resolution of a (±) base with an optically active acid.



- For neutral compounds acid handles are introduced and resolution is done as per chiral acid, then reacted e. g. hydrolyzed to remove acid functional group.
- R-OH+AC

Advantages of chemical method

The chemical method of resolution is widely used and has the advantage that both the enantiomers are obtained. This method will be successful if the following conditions are fulfilled:

(i) The resolving agent should be optically pure.

(ii) The substrate (racemic mixture) and the resolving agent should have suitable functional groups for reaction to occur.

(iii) The resolving agent should be cheap and be capable of regeneration and recycling.

(iv) The resolving agent should be such which produces easily crystallizable diastereomeric products.

(v) The resolving agent should be easily separable from pure enantiomers.

5 Chromatographic Method

- The rates of movement of the two enantiomers through the column should be different (due to difference in the extent of adsorption). They should thus be separable by elution with suitable solvent.
- This method has an advantage over chemical separation as the enantiomers need not be converted into diastereomers.
- The techniques used include paper, column, thin layer, gas and liquid chromatography.