Stereochemistry M.Sc F.Y (I sem) Munde Mam

MAHAGURU Page No. Date

★ Conformational Analysis :

→ The isomers produced by c-c rotation, ring flippi pyramidal inversion are known as Conformers.

→ The study of physical & chemical properties of Conformers of a molecule is known as Conformation analysis

→ Internal motion of a molecule is not free by attaining suitable stable Conformer molecule is fixed

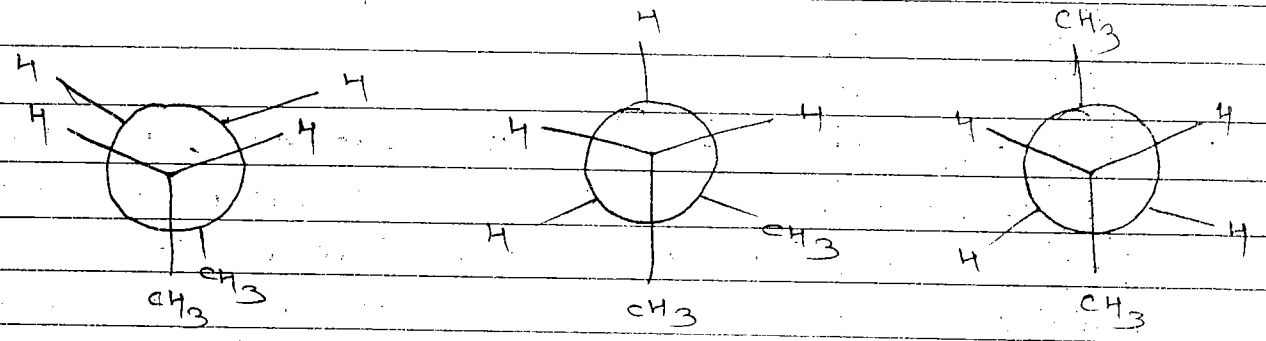
→ The angle of rotation performed in c-c bond to give new conformer is known as dihedral angle.

→ The no. of Conformers produced by a molecule depends on dihedral angle.

→ The suitable projection for Conformers are 'Newmann projection'.

Conformational Analysis of Butane

$CH_3 - CH_2 - CH_2 - CH_3$



Eclipsed Gauche Staggered

→ In eclipsed Conformation, eclipsed strain is present

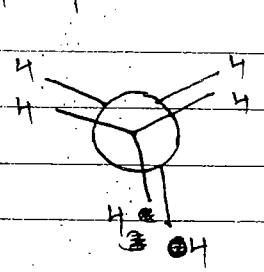
→ In Gauch Conformation: Vandeewall's repulsion is present between two methyl groups.

→ In Staggered Conformation: No strain, No repulsion highly stable.

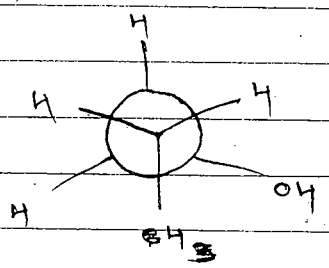
★ Conformational Analysis of Mono & disubstituted hydroxy:

→ Whenever –OH groups are there in the molecule, the relative stability of the molecule is given on the basis of intramolecular H-bonding.

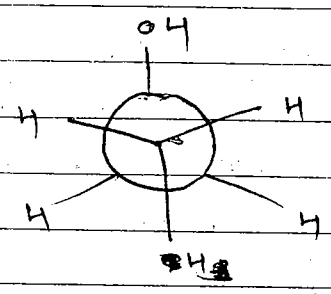
→ In mono-substituted hydroxyl molecule, there is no other –OH group is present, therefore H-bonding does not occur & Hence staggered is more stable than gauch & gauch is more stable than eclipsed. in ~~1-propanol~~ ethanol



Eclipsed



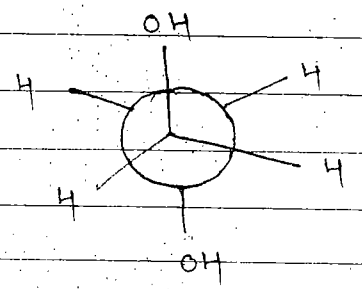
Gauch



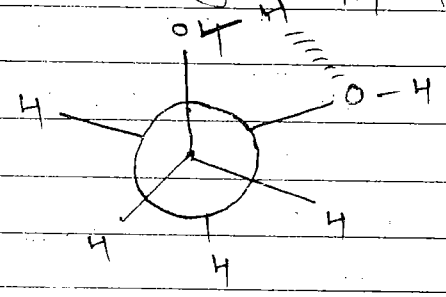
~~Staggered~~ Gauch

– For effective intramolecular H-bonding, the two –OH groups must be close to each other which is possible in eclipsed Conformation & gauch Conformation

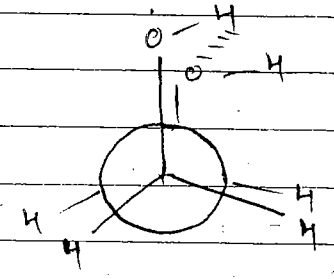
– Whereas in staggered Conformers the H-bonding does not takes place. eg. Glycol



Staggered



Gauch



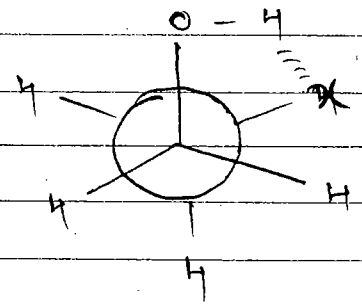
Eclipsed

– In eclipsed Conformer, intramolecular H-bonding occurs but due to eclipsed strain Conformer becomes unstable

- In eclipsed Conformation, the two atoms come within Contact, so Vander Waal's repulsive forces come into play & make the Conformation unstable.

- In Gauche Conformation with a torsional angle 60°-70° has intra-molecular H-bonding.

- H-bonding can also be shown between -OH & -X usually the dihedral angle is slightly higher than 60°. Therefore H-bond is always stronger.



X → -OH, $-NH_2$, -F, -Cl, -Br, -I
$-OCH_3$ etc.

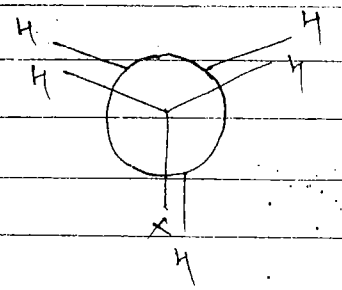
★ Conformational Analysis of Mono Haloalkanes :

In Conformations of Haloethane, we have two Conformations eclipsed & ~~staggered~~ / gauch

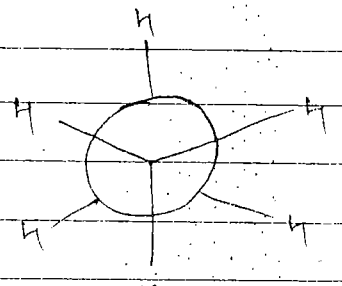
eg.

CH_3-CH_2-X

X → F, Cl, Br, I



eclipsed

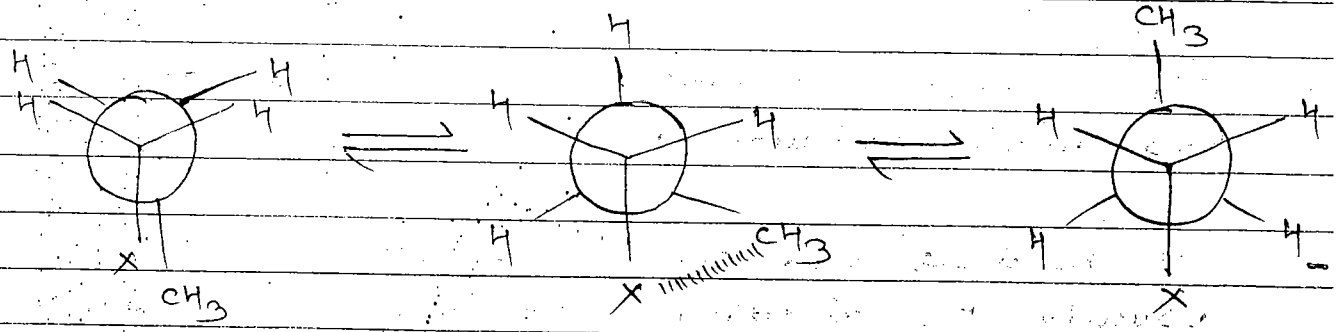


~~staggered~~ Gauch

- In this example, the eclipsed Conformation is least stable than ~~staggered~~ / gauch Conformation because in eclipsed Conformation the dihedral angle between substitution of two carbons is 0° therefore there is a presence of eclipsed ~~strain~~ strain giving unstability, whereas in staggered Conformation, eclipsed strain is absent giving/result in more stable Conformation.

→ But in Case of 1-Halopropane, the gauche Conformation is more stable than staggered.

$CH_3-CH_2-CH_2-X$:



Eclipsed Gauche staggered

— In ~~monoalkane~~ Monohaloalkane, having more than 2-carbons Gauche Conformer is more stable than staggered Conformer due to Vanderwaal's attraction

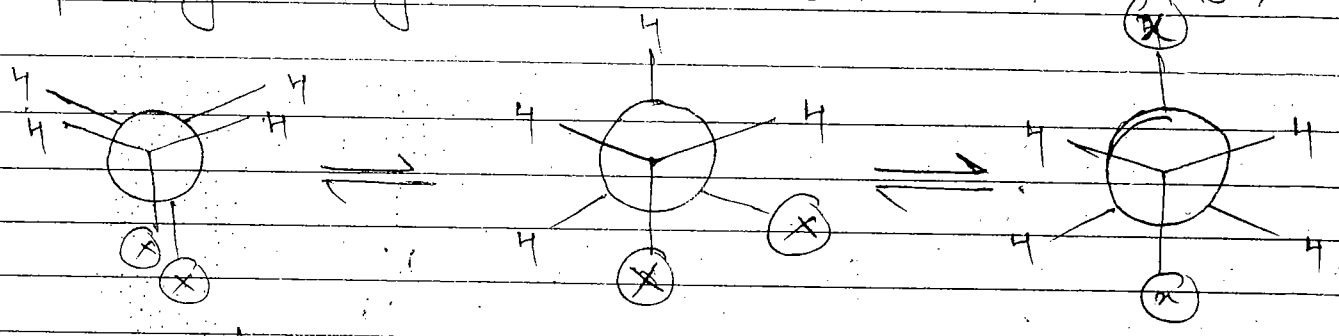
— In above example, Vanderwaal's attraction occurs between halogen & methyl group in eclipsed & Gauche Conformation, but in eclipsed Conformation eclipsed strain gives unstability.

— Stability order : Gauche > staggered > Eclipsed.

★ Conformational Analysis of Dihaloalkanes :

In Conformations of 1,2-dihaloalkane ethane have been studied on the basis of physical method like dipole measurements, Raman, IR & microwave Spectroscopy.

In gaseous state (22°c) 1,2 dichloro & 1,2-dibromo ethane Contains 73% & 85% of the anticonformers respectively. and gauche Conformer Contains 27% & 15% -



Eclipsed Gauche staggered

x → cl, br

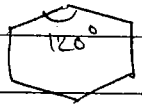
→ In both the examples, the antiform / staggered Conformati is highly stable over gauche Conformation due Combined effect of steric (effect) factor. (Br - Br & cl - cl having repulsion between atoms due to larger size as well as same electronegativity) i.e. electronic interaction.

→ In the liq. state or in polar solvent the electronic dipole - dipole repulsion decreases due to high dielectric Constant of the medium & therefore gauche interaction increases but still less or equal to than staggered Conformation.

→ In dichloroethane, the two Conformers are almost equally populated in liq. state whereas in dibromoethane the gauche population will be 35%.

→ Similarly for 1,2 - diiodoethane, the anticonformation predominate in the gaseous state but the gauche forms become more is liq. state.

★ Conformation of Cyclohexane :



$\theta = 120^\circ$

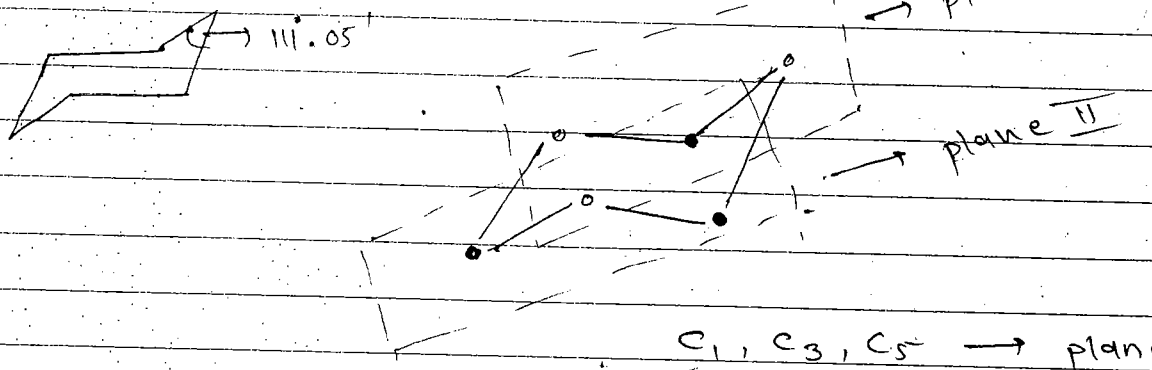
Angle strain & Eclipsed strain

→ Planar cyclohexane is suffering from eclipsed & angle strain
→ Eclipsed strain due to C's & H's
→ In order to reduced strain involve in non - planar arrangement.
→ As no. of 'C' increases, flexibility increases, Conformers also increases.
→ Cyclohexanes produce 5 types of non - planar arrangement or puckered structure

1) chair 2) Boat 3) Twist boat 4) Half chair 5) Half Boat.

→ x - ray & electronic diffraction study Conformers that chair conformation is highly stable at room temp.

1) chair form :



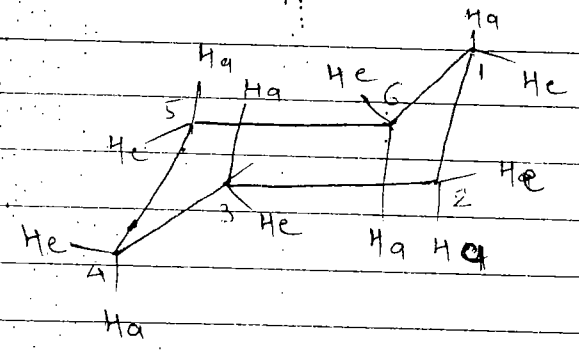
C_1, C_3, C_5 → plane I
C_2, C_4, C_6 → plane II

→ chair form of cyclohexane exhibits 2 types of carbon in 2 different planes providing free from eclipsed strain.

→ In chair conformer adjacent C-H are away from eclipsed interaction.

→ Bond angle (angle strain) reduced from 120° - 111.05'

→ 1,3 & 1,5 diaxial interactions are completely ignored due to free from Vandeewal's repulsion.



(1)

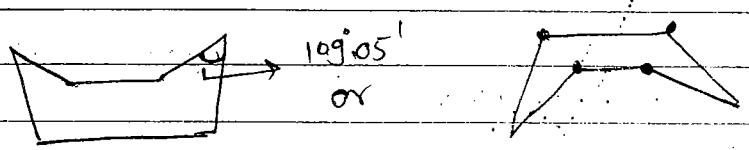
1,2 ⇒ Ha, Ha } Trans
1,2 ⇒ He, He }
1,2 ⇒ Ha, He } cis
1,2 ⇒ He, Ha }

(2)

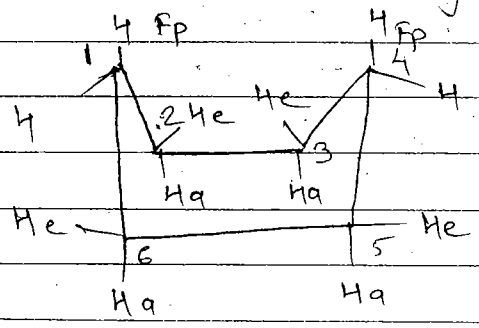
1,3 ⇒ Ha, Ha } cis
1,3 ⇒ He, He }
1,3 ⇒ Ha, He } trans
1,3 ⇒ He, Ha }

(3) 1,4 ⇒ Ha, Ha } Traws
1,4 ⇒ He, He }
1,4 ⇒ Ha, He } cis
1,4 ⇒ He, Ha }

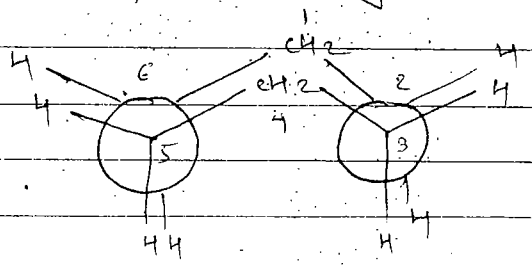
2) Boat form :



— The 4 c's are inplane & 2 c's are above the plane/ below the plane
— unstable Conformer due to eclipsed strain
— Angle strain is Completely reduce.



H Fp → Flag pole

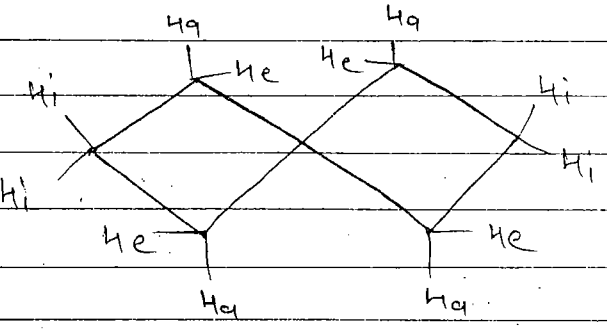


⟶ It is unstable due to Fp - Fp repulsion & 4 pairs of H's in eclipsed strain
⟶ Individual eclipsed interaction increases energy about 18 KJ/mole

4 × 18 KJ/mole = 72 KJ/mole

3) Twist boat :

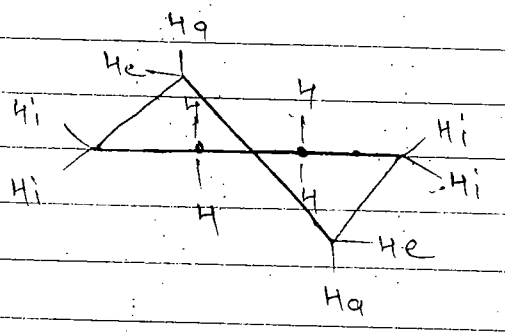
Free from eclipsed & angle strain



Hi = Isoclinical
↓
Neither axial/equitorial

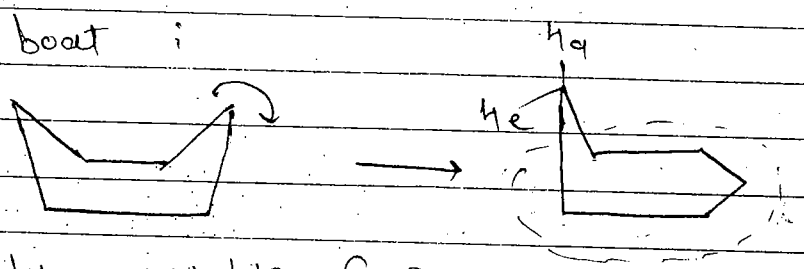
→ Absence of $F_p - F_p$ repulsion.
→ No eclipsed interaction with 4 pairs of H's.
→ Stable Conformer over boat form

4) Half chair :



→ unstable Conformer
→ Eclipsed strain present
→ 4 c's are present in plane
→

5) Half boat :



→ Highly unstable Conformer
→ 5 c's are present in plane
→ Highly eclipsed strain.

Order of Stability :

chair > Twist boat > boat > Half chair > Half boat

→ At room temp. most of Cyclohexane molecules (99.9%) exist in the most stable chair conformation.
→ As potential energy of Conformer increases results in the formation of unstable Conformer.

3, 4, 12, 13, 14, 15, 16, 18, 19, 20, 22, 24, 32, 36, 37, 38, 42, 46, 47, 48, 50, 51, 53, 54, 55, 56, 58, 59, 60, 61

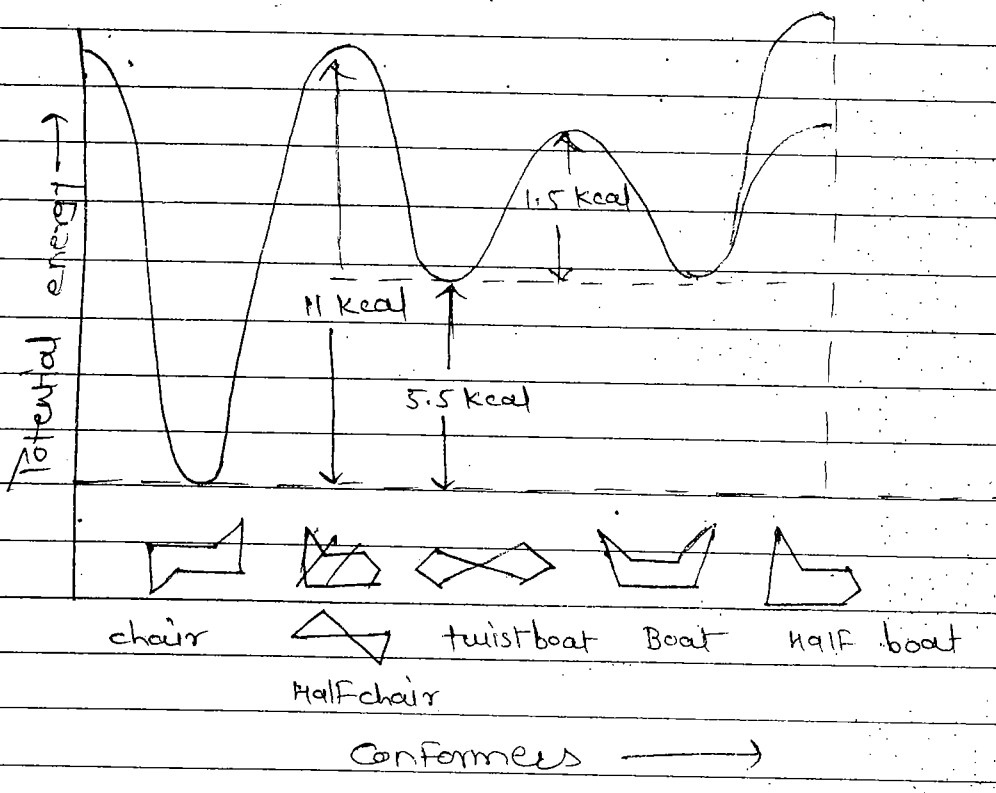


fig. Potential energy relationships among Conformations of Cyclohexane.

★ Conformational Analysis of Monosubstituted Cyclohexane :

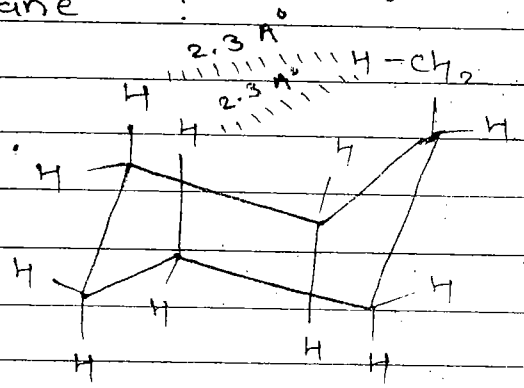


fig. Axial methyl Cyclohexane

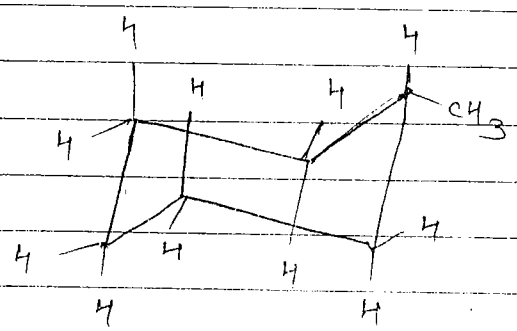
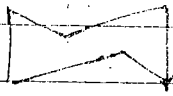


fig. Equitorial methyl cyclohexane



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Conformational Analysis of monosubstituted cyclohexane :-

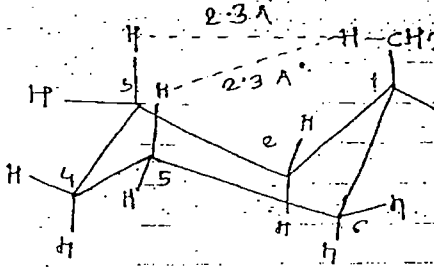
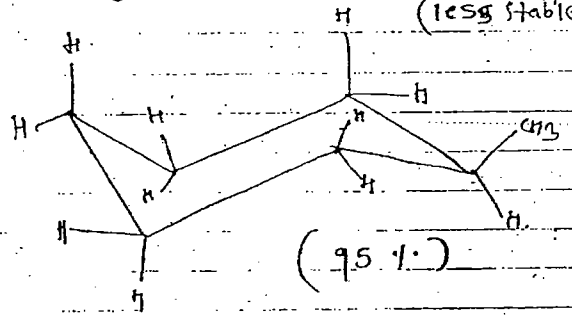
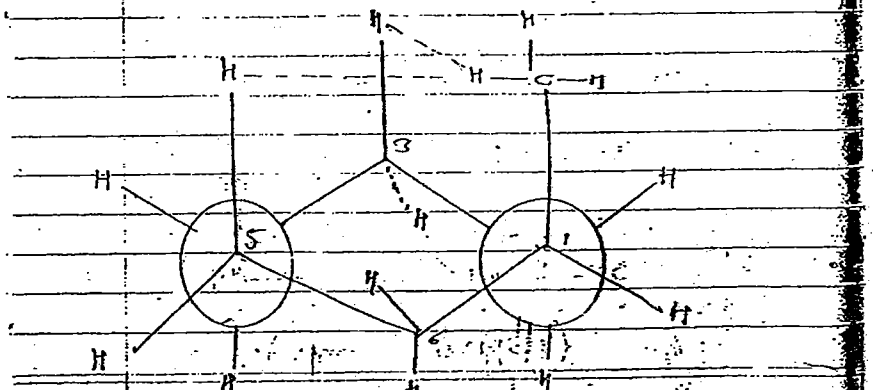


Fig ④ Axial Methyl cyclohexane (less stable 5%)



(95%)

Fig ⑤ Equatorial methyl cyclohexane



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(1) In the axial conformation of methyl cyclohexane, the axial $-CH_3$ group on C_1 is close to the two axial H atom on C_3 and C_5 which develop repulsive forces or steric strain in the molecule. repulsive force (steric strain) in betn axial $-CH_3$ group and axial H atom present in the 1,3 position to each other such non bonded interaction is called as 1,3 diaxial interaction 2) The distance betn H of $-CH_3$ at C_1 and H at C_3 is 2.3 A° which is less than the sum of vander wall's radii of two H atom (2.5 A°). it causes steric strain in the form of 1,3 diaxial interaction also called as 'trans-annular effect'. Each such 1,3 diaxial interaction increases the energy of the molecule by 0.9 kcal. Another 1,3 diaxial interaction takes place between H of CH_3 at C_1 and H at C_5 which again increases energy of molecules by 0.9 kcal. Hence, these two diaxial interaction increases energy of axial methyl cyclohexane by $0.9 \times 2 \simeq 1.8$ kcal.

3) In equatorial methyl cyclohexane there is absence of such 1,3 diaxial interaction therefore, equatorial methyl cyclohexane gets more stabilized by 1.8 kcal than

axial methyl cyclohexane.
(95% equatorial & 5% of axial)

Imp

* Conformational Analysis of di-substituted cyclohexane :-

Dimethyl Cyclohexane exist in the form of following stereo isomers.

(i) 1,2 dimethyl cyclohexane
(ii) 1,3 dimethyl cyclohexane
(iii) 1,4 dimethyl cyclohexane.

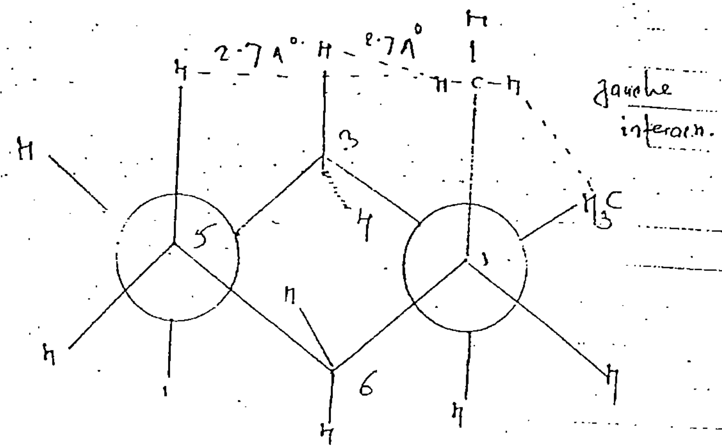
(1) Conformational Analysis of 1,2 Dimethyl Cyclohexane :-

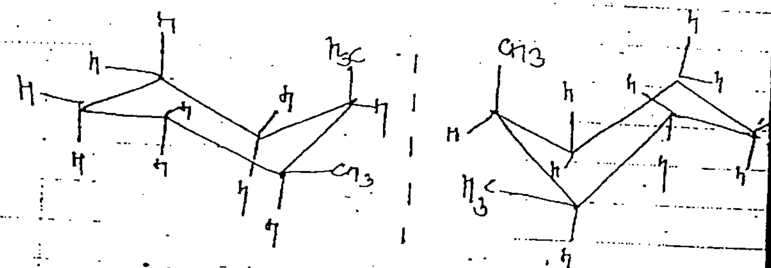
1,2 Dimethyl cyclohexane exist in the form of following four conformations -

i) cis ae 1,2 Dimethyl cyclohexane
ii) cis ea -1-
iii) trans aa -1-
iv) trans ee -1-

In both, cis ae and cis ea conformations, 1-methyl group is axial which causes two 1,3 diaxial CH_3 / H interactions. i.e also one gauche interaction betn two - CH_3 group. These three interaction increases the energy of cis conformation (ea, ae) by

$0.9 \times 3 = 2.7$ Kcal m^{-1}. Thus, both cis ae and cis ea conformations are equally stable.





cis ae

Fig (a) conformational enantiomer.

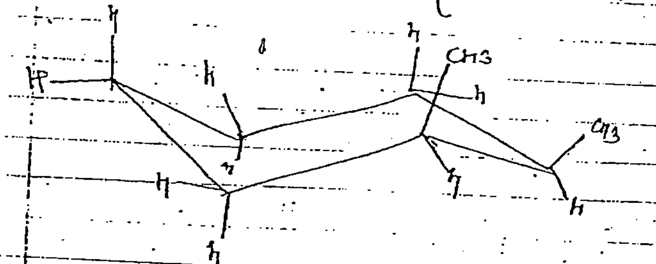
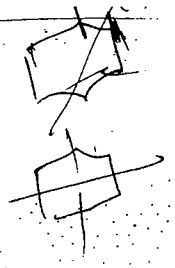
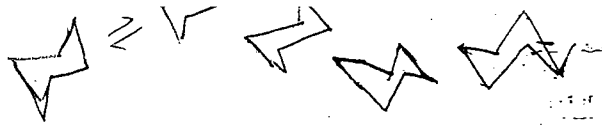


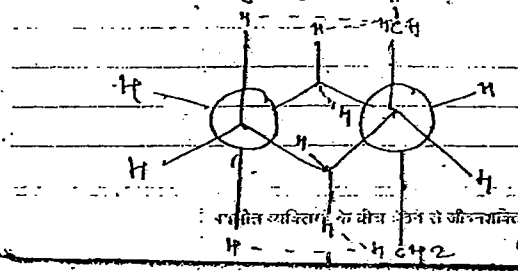
Fig (b) cis ea





cis e,e and cis a,a conformations are mirror images of each other and non-superimposable hence, they are interconvertible at ordinary temp. hence, they are known as conformational enantiomer (which are non resolvable therefore cis 1,2 dimethyl cyclohexane isomer exist as a non-resolvable racemic modification which is optically inactive even though it poses two stereogenic (chiral) centers.)

In trans a,a 1,2 dimethyl cyclohexane both methyl groups are axial which ~~are~~ causes both 1,3 diaxial CH_3 / H interaction. 1,3 diaxial interaction increases the energy of trans a,a conformation by $0.9 \times 4 = 3.6$ kcal/mol. it is optically active due to the presence of two chiral centers. two stereo isomer are mirror images of each other and non-superimposable but they are not interconvertible hence, they are known-as configurational enantiomer.



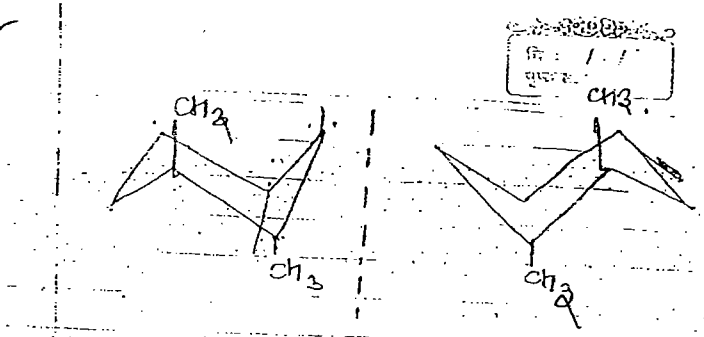
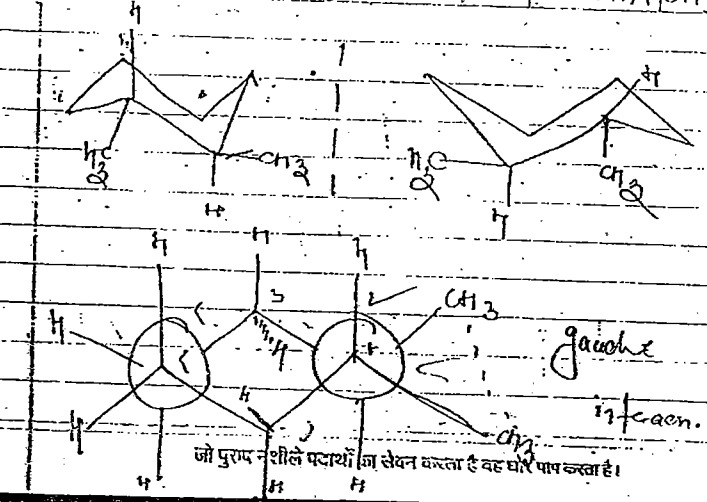


Fig: Configurational Enantiomer.

trans e,e 1,2 dimethyl cyclohexane conformation, both CH_3 groups are equatorial there is no any 1,3 diaxial CH_3 / H interaction, there is one CH_3 / CH_3 gauche interaction which increases the energy of trans e,e conformation by 0.9 kcal/mol. It is optically active due to the presence of two chiral center. two isomer (stereo) is mirror images of each other and non superimposable but they are not interconvertible. Hence, they are known-as configurational enantiomer



trans ee conformation gets interconverted into trans aa conformation. trans ee and trans aa conformations are not mirror images of each other. and not non-superimposable but they are interconvertible Hence, they are known-as conformational diastereomers. Thus, each isomer trans ee and trans aa is optically active and their racemic modification is resolvable.

cis and trans isomers of 1,2 dimethyl cyclohexane are not mirror images of each other and non superimposable moreover they are not interconvertible Hence they are configurational diastereomer.

trans ee conformations is more stable than cis ae / ea conformation by $2.7 - 0.9 = 1.8$ kcal/mol. trans ee is also more stable than trans aa conformation by $3.6 - 0.9 = 2.7$ kcal/mol Hence, order of relative stability of conformations of 1,2 dimethyl cyclohexane can be represented as

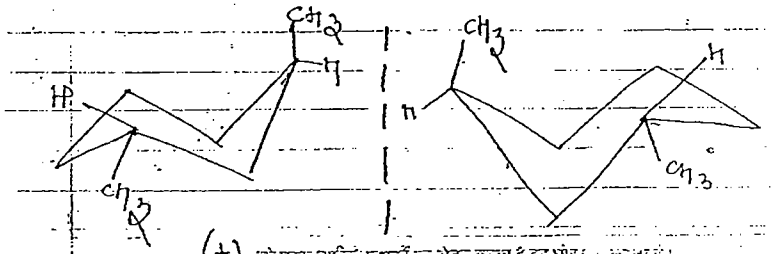
trans ee > cis ae ≅ cis ea > trans aa

(1) Conformational analysis 1,3 dimethyl cyclohexane and their relative stability :-

1,3 dimethyl cycloheptane exist in the form of following four conformations.

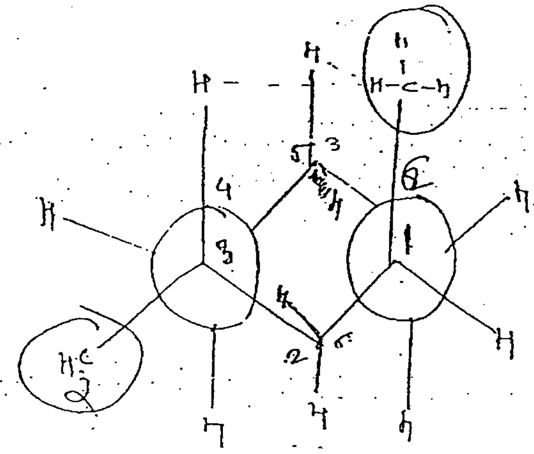
(i) trans a e 1,3 dimethyl cyclohexane
(ii) trans e a —1—
(iii) cis a a —1—
(iv) cis e e —1—

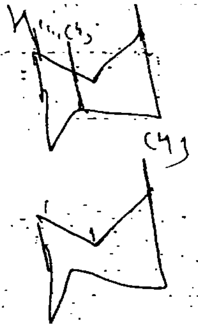
In both, trans a.e & trans e a conformations one CH_3 group is axial it causes two 1,3 diaxial CH_3/H interaction which increases the energy of trans ae & trans ea by $0.9 \times 2 = 1.8$ kcal/mol these conformations (trans ae/ea) poses two chiral centers and do not poses any element of symmetry. Hence trans ae & trans ea conformations are optically active. two stereoisomer are mirror images of each other & non superimposable & not interconvertible. Hence they are configurational enantiomer hence and each dl pair is resolvable.



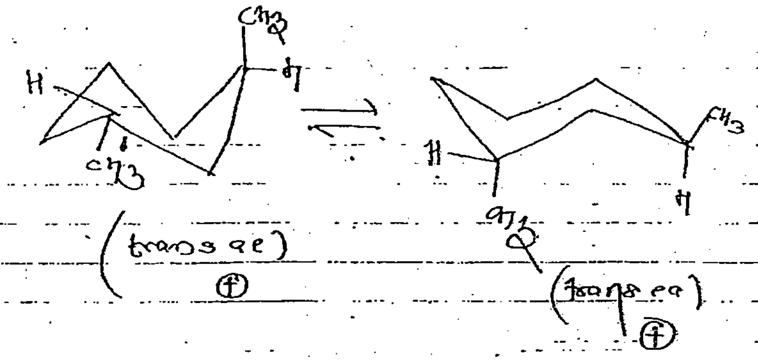
(+) जो पुरुष नशीले पदार्थों का सेवन करता है वह धोर... करता है।

(-)

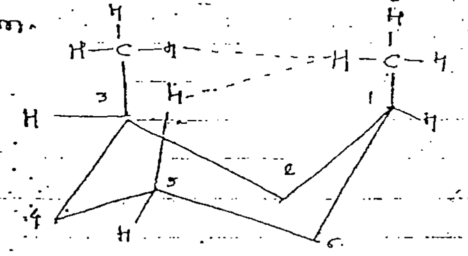


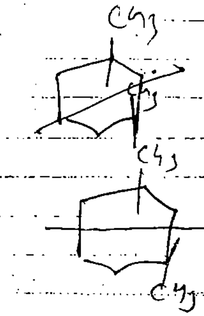


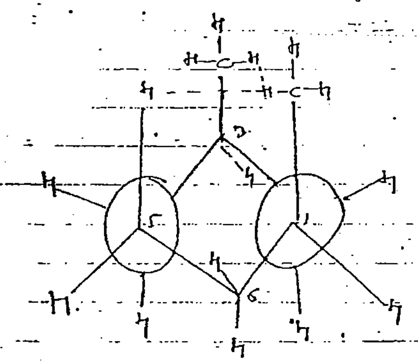
Ring Flipping of trans a,a conformation converts it into trans e a conformations which are not mirror images of each other and non super imposable Hence they are conformational diastereomers. Ring inversion converts dextro into dextro and levo into levo. The process is called as "topomerisation"

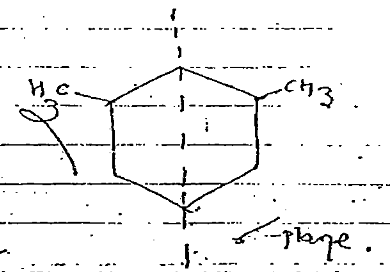


In cis a a conformations two CH_3 groups are axial. Hence, there are two CH_3 / H and one CH_3 / CH_3 1,3 diaxial interaction which increase the energy of molecule by $3 \times .9 = 2.7$ Kcal/mol. cis a a conformation have plane of symmetry Hence, it is optically inactive even though it poses two chiral centers i.e cis a,a conformation is meso form.

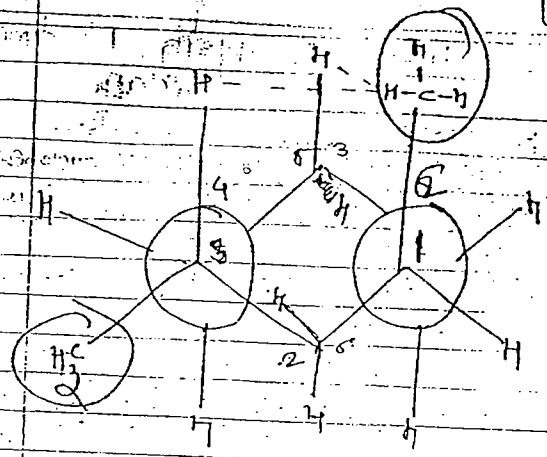




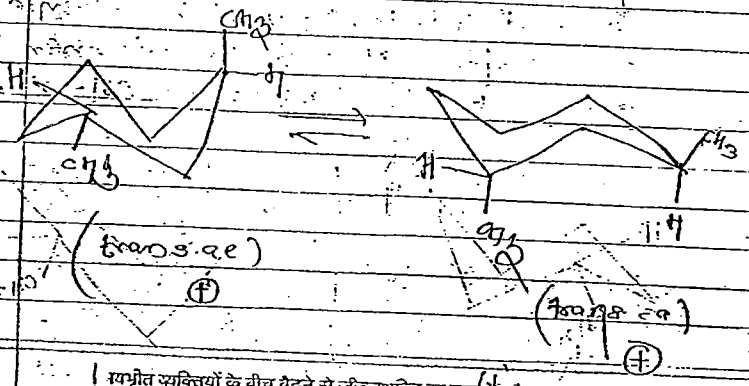




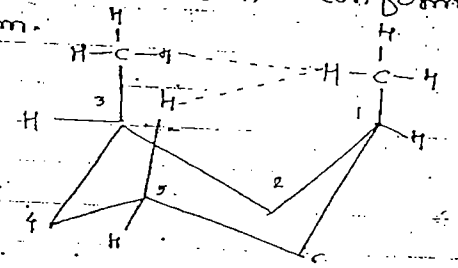
Meso form.

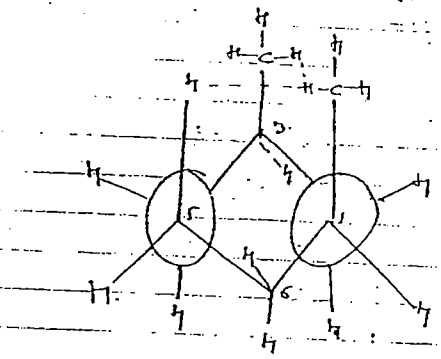


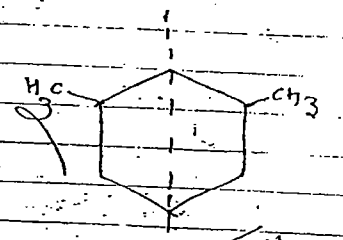
Ring Flipping of trans aa conformation converts it into trans ee conformations which are not mirror images of each other and non super imposable Hence they are conformational diastereomers. Ring inversion converts dextro into dexo and levo into levo. The process is called as "topomerisation"



In cis aa conformation two CH_3 groups are axial. Hence there are two CH_3 / H and one CH_3 1,3 diaxial interaction which increase the energy of molecule by 3x = 2.7 kcal/mol. cis aa conformation has plane of symmetry Hence, it is optically inactive even though it poses two chiral centers i.e cis a,a conformation is meso form.



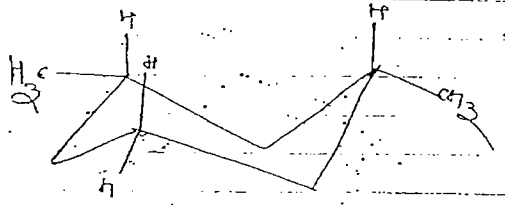


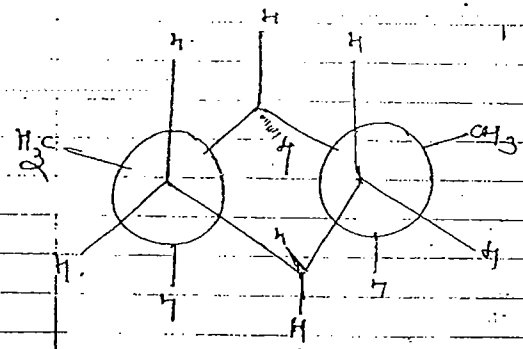


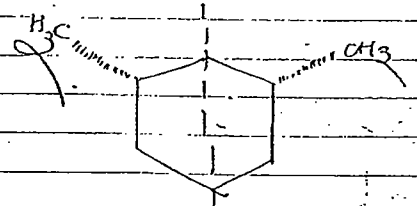
plane.

meso form.

In cis ee 1,3 dimethyl cyclo hexane two methyl groups are equatorial. Hence, there is no any CH_3/H or CH_3/CH_3 1,3 diaxial interacn which makes the molecule to poses less energy. cis ee conformation poses plane of symmetry. Hence it is optically inactive even though it has two chiral center (meso form).







cis ee

Meso form.

cis aa and cis ee conformations are not mirror images of each other and non superimposable but they are interconvertible. Hence, they are called as conformational diastereomers.

cis ee is more stable than trans ae / trans ea conformations by 1.8 kcal/mol. cis ee is also more stable than cis aa conformation by 2.7 kcal/mol. Thus, order of relative stability of 1,3 dimethyl cyclohexane can be represented as,

cis ee > trans ae ≅ trans ea > cis aa.

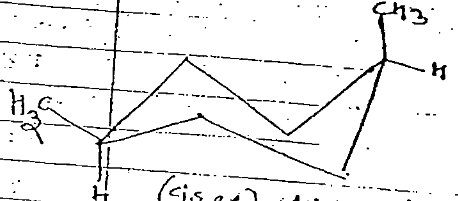
★ Conformational Analysis of 1,4 dimethyl cyclohexane :-

1,4 dimethyl cyclo hexane exist in the following four conformations.

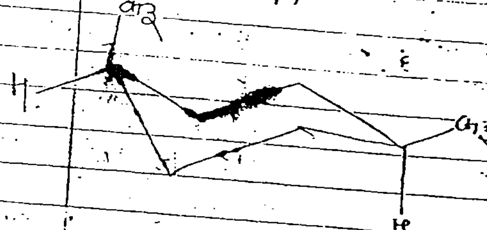
(i) cis ae 1,4 dimethyl cyclohexane.
(ii) cis ea
(iii) trans aa
(iv) trans ee

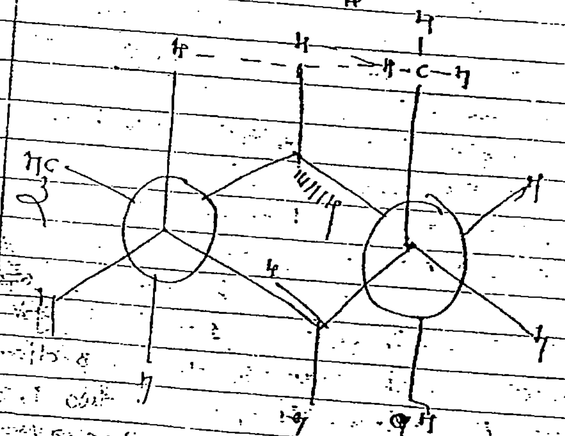
In both cis ae / ea cis ea conformations are 1 methyl group is axial which causes two 1,3 diaxial CH_3/H interaction. Each two 1,3 diaxial interacn increase the energy of cis ae / cis ea conformation by $0.9 \times 2 = 1.8$ kcal/mol. In both cis ae & cis ea conformations, a plane passes through

C_1 & C_4 Hence it poses plane of symmetry which makes it optically inactive even though it has two chiral centers.



(cis a,e)

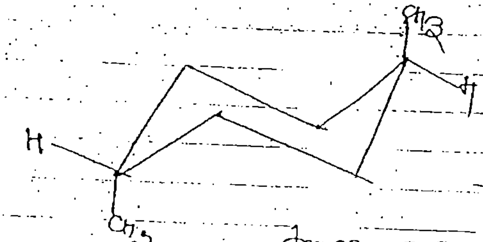




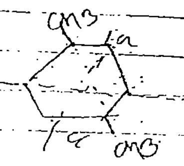
In trans a a there are four 1,3 diaxial CH_3/H interaction which increase the energy of

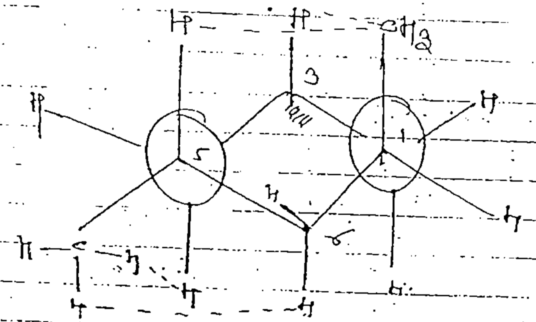
molecules by $0.9 \times 4 = 3.6$ Kcal/mol

In trans aa σ plane passes through C_1 and C_4 Hence it poses plane of symmetry it makes optically inactive.

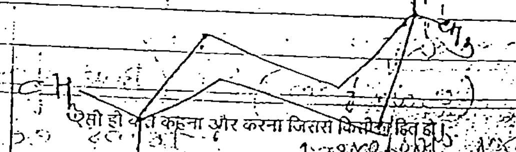


trans a a

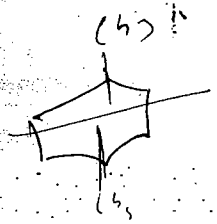


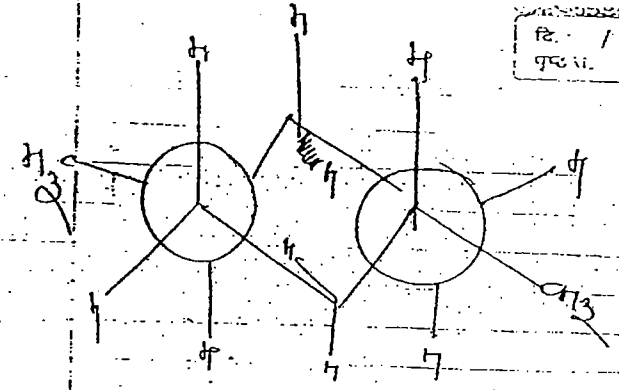


In trans ee 1,4 dimethyl cyclohexane conformation, both methyl groups are equatorial. Hence there is a no any 1,3 diaxial interaction which makes it to poses less energy. In trans ee conformation σ plane passes through C_1 & C_4. Hence it poses plane of symmetry it makes optically inactive



trans ee

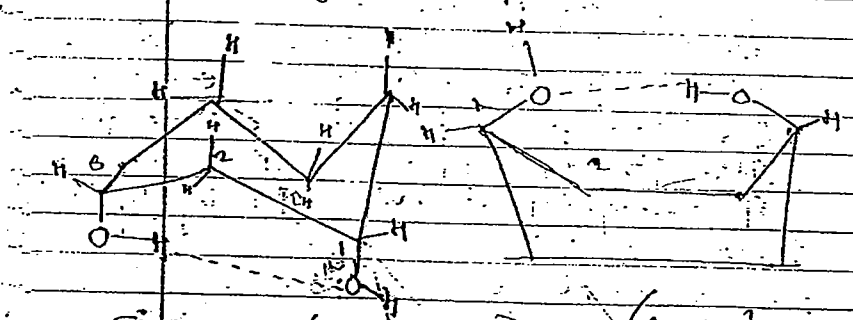




trans ee conformation is more stable than cis ae / cis ea conformation by 1.8 Kcal^{-1} Moreover trans ee is also more stable than trans aa conformations by 3.6 Kcal^{-1} Hence order of relative stability of conformations of 1,4 dimethyl cyclohexane can be represented as,

trans ee > cis ee ≃ cis ea > trans aa

★ Conformational Analysis of 1,3 dihydroxy cyclohexane :-

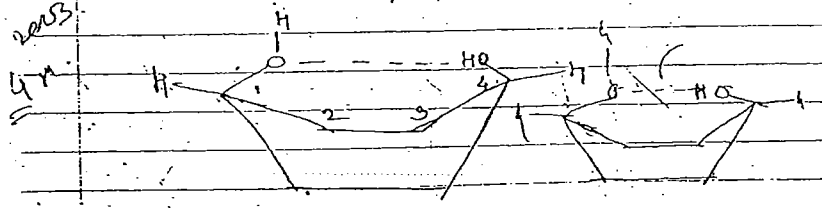


cis aa (chair form) (Boat form)

1,3 dihydroxy cyclohexane trans ee

cis 1,3 dihydroxy cyclohexane is exceptionally more stable because in this conformation two -OH groups are axial (α and β-axial). This conformation gets more stability due to the presence of intermolecular hydrogen bonding between two axial -OH groups such type of intermolecular H bonding is absent in another / other conformation like cis ee, trans ae and trans ea which makes them less stable.

★ 1,4 Dihydroxy cyclohexane :-



(Boat form)

Boat form of 1,4 dihydroxy cyclohexane is exceptionally more stable because in this boat form conformation two -OH groups are present at dipole positions of cyclohexane ring. Hence two OH group becomes close to each other resulting in the formation of intermolecular H-bonding and this intermolecular H-bonding gives more stability to the Boat form of 1,4 dihydroxy cyclohexane than its chair form.

Shreyou Pandey

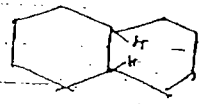
1 Imp ★

4th

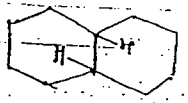
Conformations of Bicyclic Compounds

Decalin (saturated naphthalein)

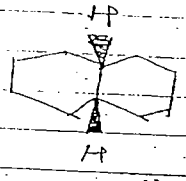
There are two conformations of Decalin.



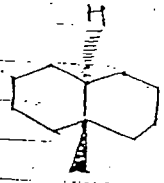
Cis Decalin



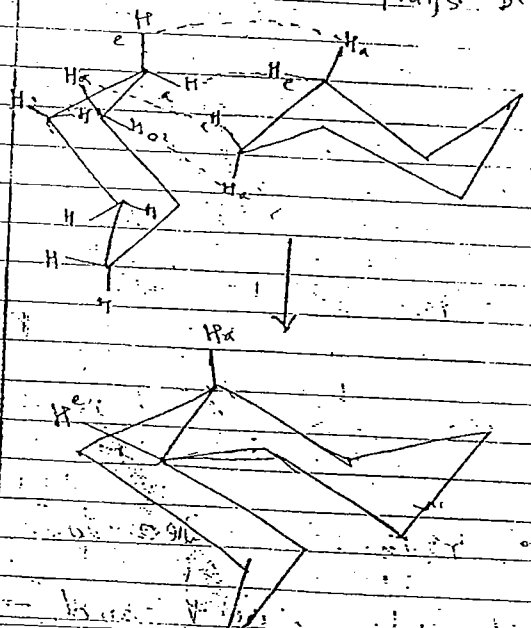
Trans Decalin



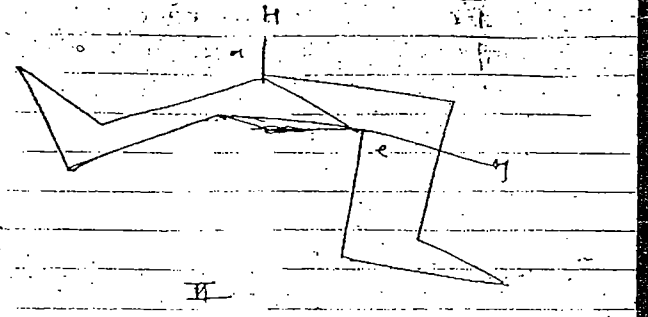
Cis-Decalin



Trans Decalin



Cis-Decalin

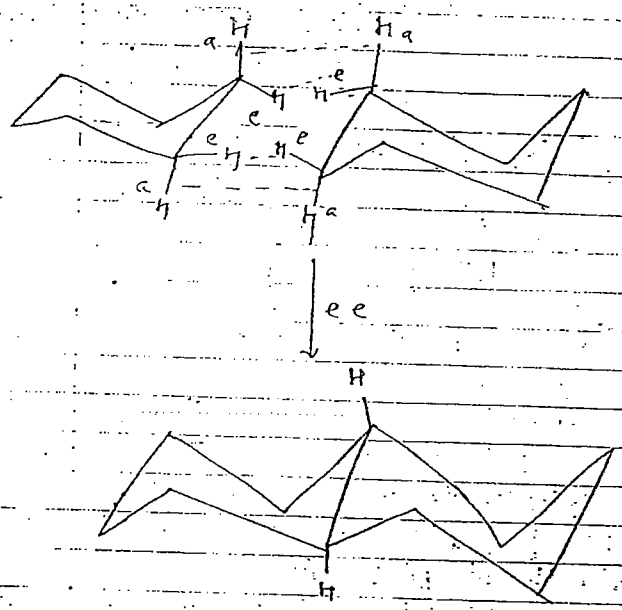


Two cyclohexane ring in Decalin get fused in two ways resulting in the formation of cis and trans conformations of Decalin. In both form of Decalin joining betn two cyclohexane ring takes place in chair conformation.

In cis Decalin chair forms of two cyclohexane rings have been found to be fused together in ae form (Axial bond of 1 chair form get fused with equatorial bond of another chair form). The fusion betn two chair form of two cyclohexane rings through ae bonds resulting in the formation of cis-Decalin can be represented as above. As ring fusion in cis decalin involve equatorial and axial bonds the more becomes flexible and undergoes interchange very easily with the other cis form i.e cis decalin exist in I & II forms.

Trans Decalin is formed due to the fusion betn chair form of two

cyclohexane rings two ee bonds i.e each cyclohexane ring is fused with the other by equatorial bonds.



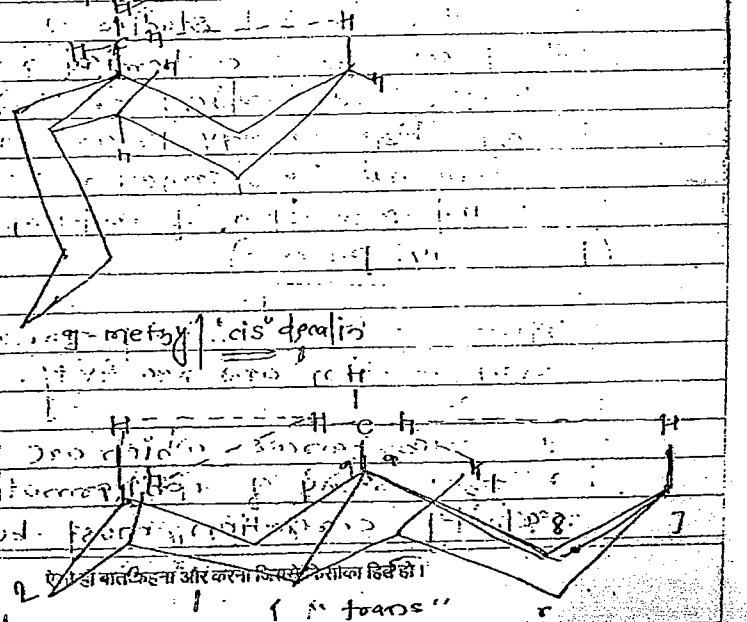
Trans - Decalin

Trans Decalin is formed due to the fusion of two cyclohexane rings through ee bonds therefore it does not undergo ring flipping Hence trans decalin is a rigid molecule and exist only in one form. Trans Decalin possesses centre of symmetry and plane of symmetry. Hence it is optically inactive. However both conformations of cis decalin possesses two chiral centers. Each conformations exists in the form of two enantiomers but they are interconvertible hence they are conformational enantiomer. Cis decalin exist in the form of dl pair which is non resolvable.

★ Monosubstituted Decalin :-

9 - methyl cis decalin is more stable than 9-methyl trans decalin even though trans decalin is more stable than cis decalin

Cis Decalin possesses 2.7 kcal/mol more energy than trans decalin Hence trans decalin is more stable than cis decalin



दि.: / /
पृष्ठ सं.:

Stereoselective Reaction & Stereospecific reaction :-

Organic reactions often gives a mixture of products. The products may be structural isomers or stereoisomers. In such cases the stereochemical nature of the products depends upon the stereochemical nature of the reactant as well as the reaction path depending upon the stereochemical path followed, the reactions are classified into the following two ways.

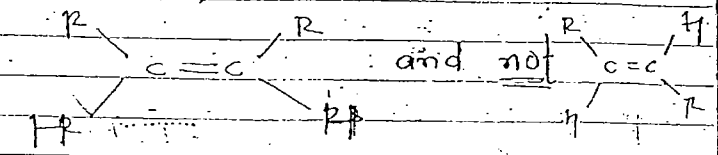
① Stereoselective Reactions :-

A stereoselective reaction is a reaction which affords predominantly only one diastereomers of a set of diastereomeric form of the product regardless of the stereochemistry of the reactant. Following are some of the examples of stereoselective reaction.

② Hydrogenation of alkynes (except acetylene and mono-substituted acetylene) in the presence of palladium suspended over barium sulphate gives selectively cis-alkenes and not trans alkenes.

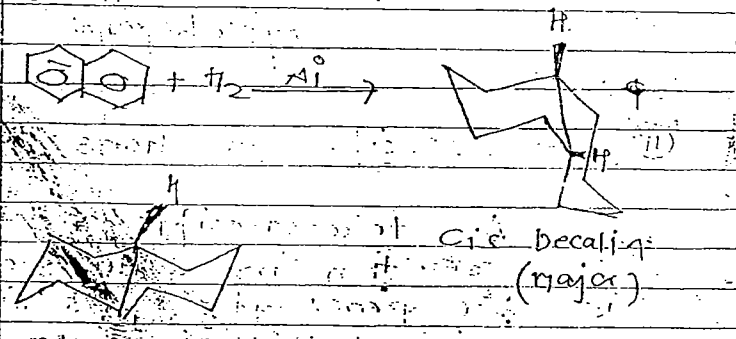
In this reaction H atoms are added from the same side.

$$R-C\equiv C-R + H + H_2 \xrightarrow[\Delta]{Pd\ /\ BaSO_4}$$



cis alkene trans-Alkene

③ Catalytic hydrogenation of naphthalene gives cis-decalin as the major product and not the trans-decalin.

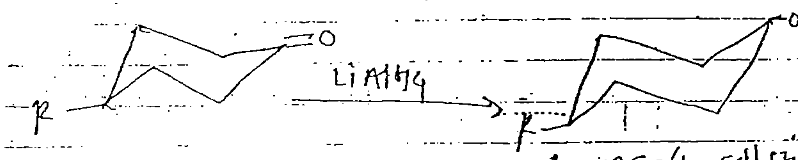


वयस्क व्यक्तियों के बीच बैठने से जीवनशक्ति का ह्रास होता है।

जो पुरुष नशीले पदार्थों का सेवन करता है वह घोर पाप करता है।

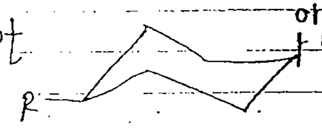
Shabdasm C_2H_5 ...

(c) Reduction of a substituted cyclic ketones like 4-substituted cyclohexanone with Li aluminium hydride produces selectively trans isomer and not the cis-isomer.



trans-4-substituted cyclohexanol.

and not



cis-4-substituted cyclohexanol

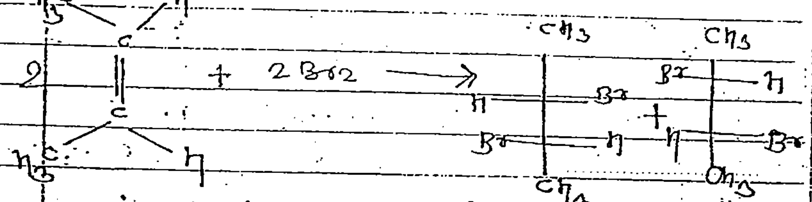
(ii) Stereospecific reactions :-

A stereospecific reaction is a reaction in which stereoisomeric reactants gives diastereochemically different products, that is one stereoisomer of the reactant gives specific diastereomer of the product.

The polar or ionic addition reactions across double bond of alkenes are highly stereospecific reactions. A cis-alkene gives one stereomer as the product while the trans-alkene forms another stereomer as the product as shown in following reactions.

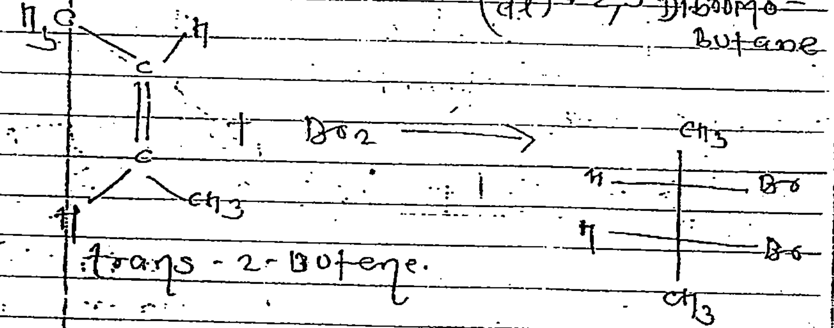
(a) The addition of halogens to alkene is a stereospecific reaction.

For eg :- The reaction of cis-2-Butene with bromine gives (dl)-2,3 dibromo butane, whereas trans 2-butene gives meso-2,3 dibromobutene.



cis 2 Butene

(dl)-2,3 Dibromo-Butane



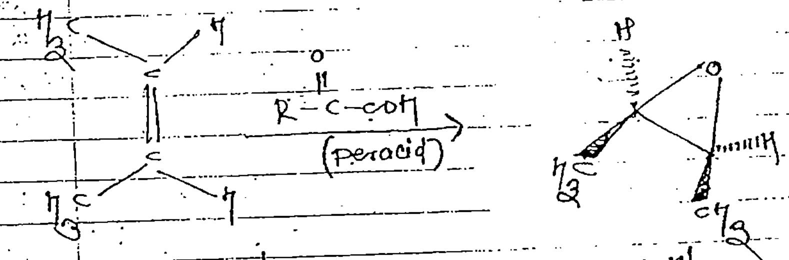
trans-2-Butene.

Meso-2,3 Dibromo Butane.

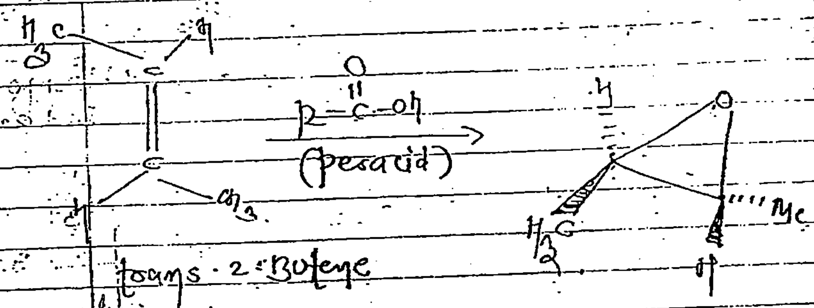
Stereochemically diff. reactant givens diff. product

(b) The reaction of alkenes with peracid to give epoxide is a stereospecific reaction.

eg:- cis 2-butene with peracid gives cis 2,3 dimethyl oxirane while trans 2-butene on the other hand furnishes trans 2,3 dimethyl oxirane:



cis-2-Butene. cis-2,3 Dimethyl oxirane.



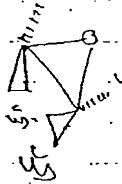
trans-2-Butene

trans-2,3 Dimethyl oxirane.

★ Asymmetric Synthesis :-

Synthesis of an optically active compound from optically inactive compound with or without use of optically active reagent is called as asymmetric synthesis.

There are two types of Asymmetric synthesis.

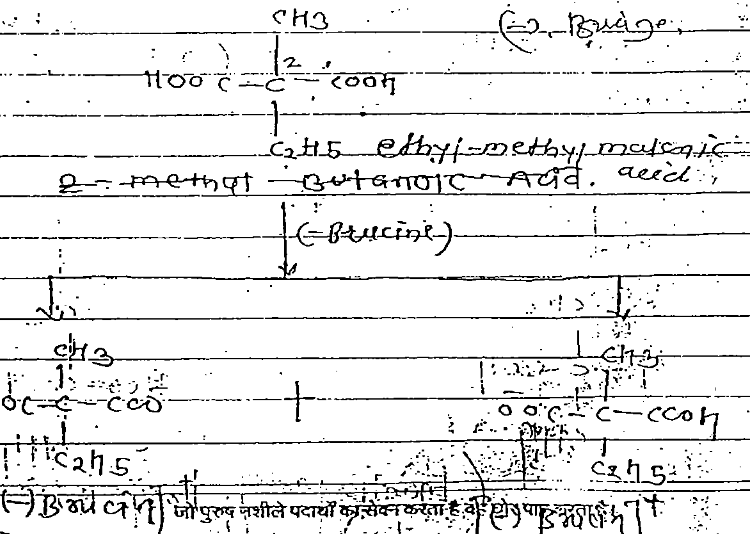


(1) Partial asymmetric synthesis :-

Synthesis of an optically active compounds from optically inactive compound with the use of optically active reagent is called as partial asymmetric synthesis.

For eg :-

2-methyl Butanoic Acid can be prepared from ethyl methyl malonic acid by using optically active reagent like (-) Brucine.



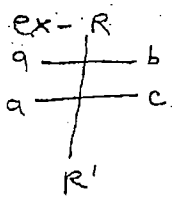
[(-) Brucine H]⁺ [(-) Brucine H]⁺

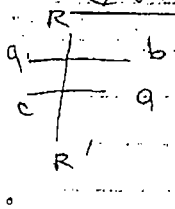
Erythro And Threo: Isomers:

In oldest system, the diasterisomers are represented as Erythro and threo in analogy with erythrose and threose.

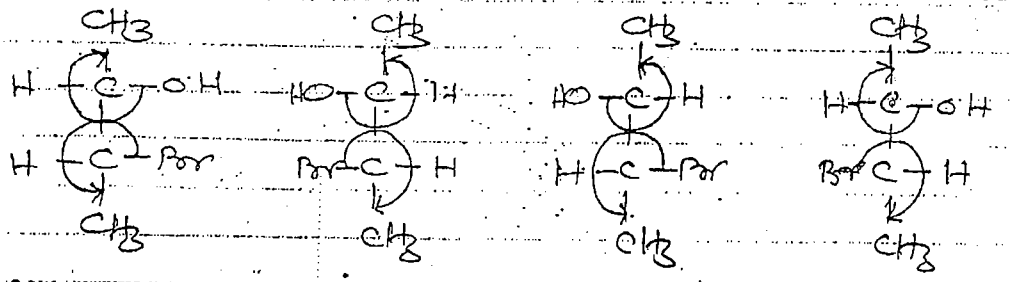
The diastereoisomers in which two like group are on same side of Fischer projection is called erythro forms. whereas the diastereoisomers in which two like groups are on opposite side of Fischer projection is called as threo forms. The nomencleature is derived from names of c-sugar threos and erythro

Example: 3-bromo 2-butanol



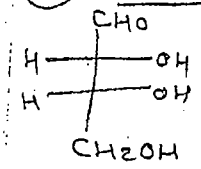


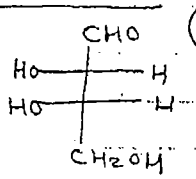
erythro Threo



(2S, 3R) (2R, 3S) (2R, 3R) (2S, 3S)

(ex)- Aldotetrose

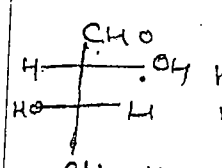


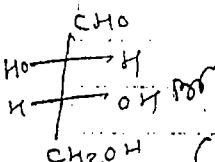


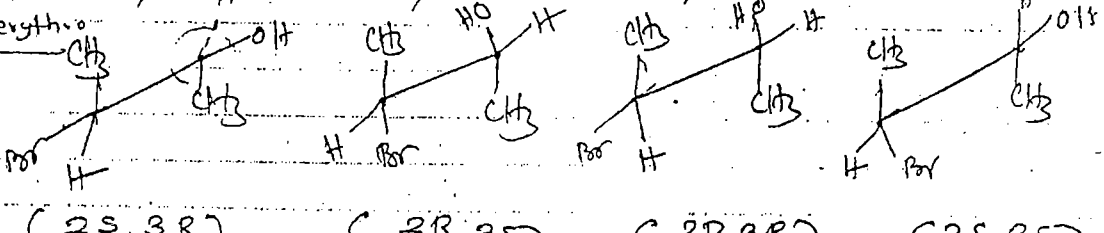
Ia II(b) II(a) II(b)

180° 180° 180° 180°

DC-) erythro LC+) erythro







(2S, 3R) (2R, 3S) (2R, 3R) (2S, 3S)

LC+) Threo DC-) Threo

(±) Erythro form (±) threo form.

The erythro form is one in which two terminal group and two like group have the same relative stereochemistry. (anti or gauche), and

The threo form is one which the two pairs of group have diff. relative stereochemistry (anti or gauche).

Thanks
Shabdashri

Optical ~~Activity~~ Purity :-

The optical purity (OP) of a chiral compound is expressed as the percentage ratio of the rotation observed and the maximum rotation (rotation of pure enantiomers) and is usually equal to enantiomeric excess (ee). The following eq^n (1) shows a relationship.

$$O_p = \frac{[\alpha]_{obsd}}{[\alpha]_{max}} \times 100 = ee = \frac{|[R] - [S]|}{[R] + [S]} \times 100$$

where [R] and [S] represents the mole fraction of the R and S enantiomers so that, [R] + [S] = 1. The percentage of R and S enantiomers can be calculated from the above equation as follows:

$$\% \text{ of } R \text{ (or } S) = ee + \% \text{ of } S \text{ (or } R)$$

$$= ee + 100 - \% \text{ of } R \text{ (or } S)$$

$$= \frac{ee + 100}{2} \text{ (for major enantiomers)}$$

Similarly,

$$\% \text{ of } S \text{ (or } R) = \frac{100 - ee}{2} \text{ (for minor enantiomers)}$$

Determination of O_p or ee of a chiral comp. is an essential part of any resolution method or asymetric synthesis. Since it gives the composition of the product.

In majority of cases, polarimetric measurements gives the true value of O_p or ee.

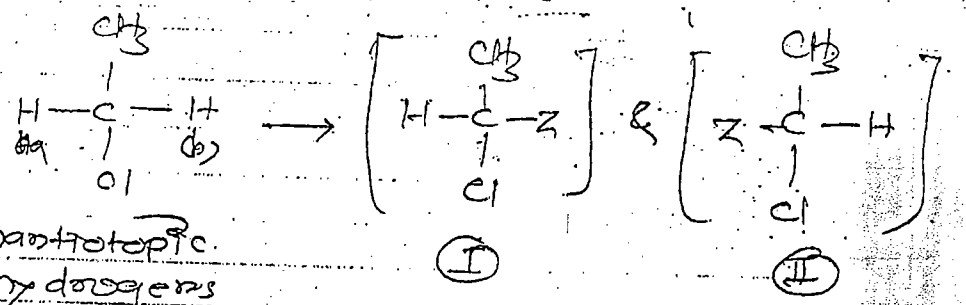
One of best way to know whether a compound is enantiomerically pure or not is to crystallise it several times & check the m.p and optical rotation.

Another alternative is to procure the optical antipode - preferably by another route - and to see whether it has exactly equal & opposite rotation.

Enantiotopic And Diastereotopic Ligands: (atom and group) :-

We had to decide wheather certain l and - atom or group that were equivalent i chemical composition and location on a cham ring were or were not stereochemically equivate

Let us take a simple molecule like eth chloride. Let us imagine that one of these hydrog is replaced by some other atom or group. (Z) Depending upon which hydrogen replace, w get two isomers. (I) and (II)



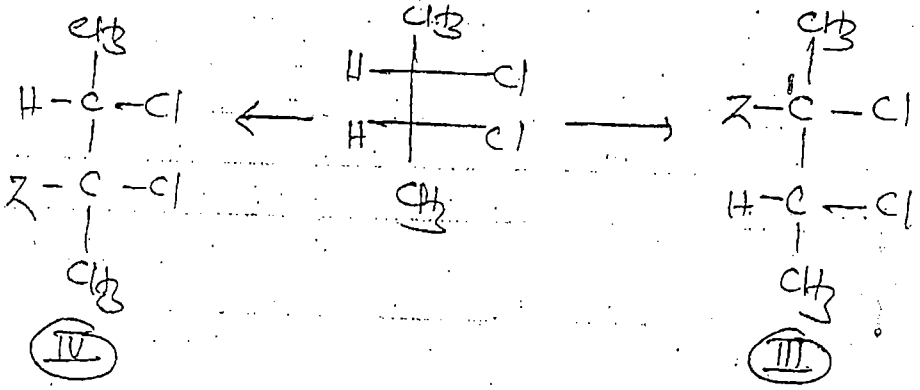
Enantiotopic hydrogens

(I) (II)

Since the product are not identical, but are stere isomeric, the two hydrogens are not stereochemica equivalent. such pairs of ligand are said to Enantiotopic : replacement of one or the other of them give one or the other of pair of enan tiomers.

Now consider second example: In meso, 2,3-dichlorobutane.

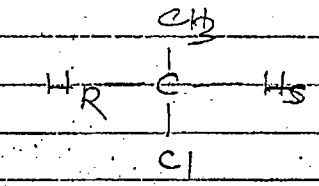
In these molecule hydrogen atom is on diff. carbon atom. The replacement of hydrogen on diff carbon atom give again two isomers. III and (IV).



(IV) (III)

[A carbon to which a pairs of enantiotopic ligand are attached is called as prochiral centre., since replacement of one of its ligand would convert the carbon into a chiral centre. ie. CWXYZ is a chiral centre and CWXXY is called prochiral centre.]

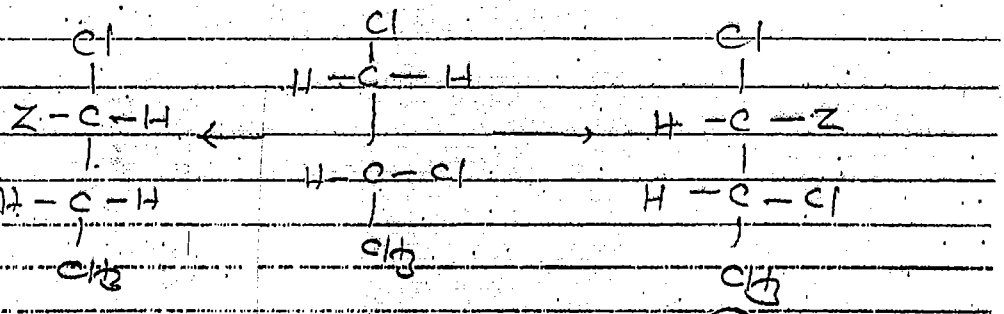
In the replacement of ligand concerned give the R-configuration, the ligand is specified as pro-R if the S-configuration then pro-S.



Enantiotopic hydrogen pro R & pro S:

Diastereotopic ligand (atom or group):-

Now, consider a molecule: 1,2, dichloropropane. Let us imagine that one of these hydrogens is replaced by Z. Depending upon which of H hydrogen is replaced, we obtain V and VI stereoisomers are diastereomeric

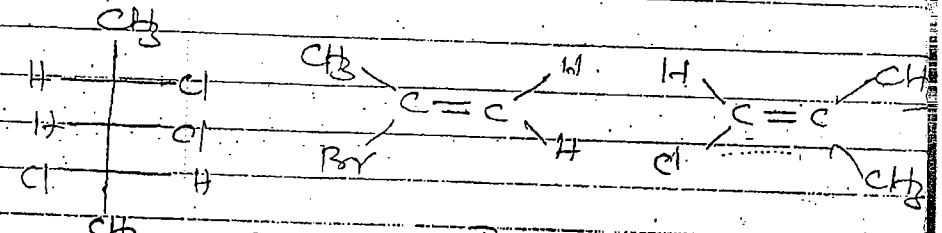


(VI) (V)

Again two hydrogens being replaced are stereochimically non-equivalent but in a way that is different from what we saw before. Such pairs of ligand are said to be Diastereotopic: replacement of one or the other of them gives one or other of a pairs of diastereomers

By apping our replacement tests we find that a set of diastereotopic ligands are sometimes attached to diff carbon within a molecule and sometime to the same double bonded carbon. geometric isomers.

For example:



Diastereotopic Ligand.

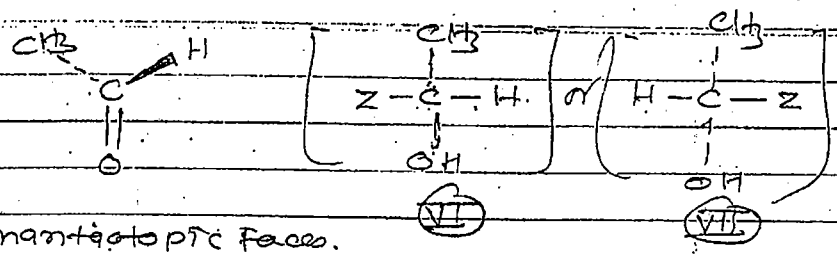
The together, enantiotopic and diastereotopic ligand are known as Hetrotopic ligand. ie. ligand in diff places and same ligand in identical stereochemical environment. ligand whose imaganary replacement leads to identical product are called homotopic ligand. ie. ligand in same pla

Enantiotopic And Diastereotopic Faces:-

Now, we started bout to examine the stereochemical relation between diff pairs faces of the same molecule.

If two faces of a molecule are truly equivalent, attachment of an atom or group to either will gives the same product. Let us, consider a simple molecule Acetaldehyde. it undergoes nucleophilic addition. ie. Z nucleophile. be come attached to the carbonyl carbon and a proton becomes attached to carbonyl oxygen.

A Acetaldehyde is flad molecule We can attach Z to one of other of its Fuce depending upon which faces we obtain two isomers. VI and VII



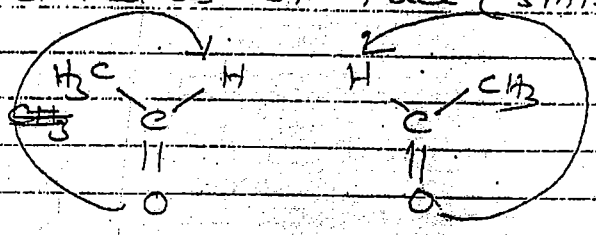
Enantiotopic faces.

Since the product are not identical, but are stereoisomeric, the two faces not stereochemically equivant. They are example of enantiotopic faces: attachement of ligand to one or the other of them gives rise to one or the other of pairs of enantiomers.

To specify the particular faces of an enantiotopic pair, we again adapt Cahn-Ingold prelog procedure:

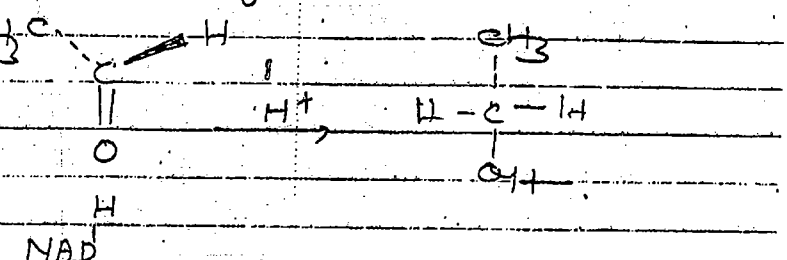
If in degreasing priority of ligand our eye travels in clockwise direction, the faces term upward toward us is specified as Re-face. if in anticlockwise it is specified as Si-Face (sinister).

ex:



Re-face. Si-face

In enzyme reduction of acetaldehyde to ethanol NADH transfer H to only one of the faces of aldehyde. give Re-face Since the ligand being attached H is the same as one already present in molecule enantiomers are not formed.



Attach only Re-face.

Depending upon the stereoric of the rest of the molecule, there can be also be diastereo Faces: attachment of a ligand to one of the other of them gives rise to one of the other pairs of diastereomers.

Together enantiotopic & diastereo faces are called heterotopic Faces. Face that are not heterotopic are sterochemically equivalent are called homotopic.

Table: Atoms and groups with increasing priority:

1. $-H$	(10) $-CH=CH_2$	(19) CO_2R
2. $-D$	11) $-C(CH_3)_3$	20) NH_2
3. $-CH_3$	12) $-C\equiv CH$	21) $NHCH_3$
4. $-CH_2-CH_3$	13) $-C_6H_5$	22) $N(CH_3)_2$
5. $-CH_2(CH_2)_nCH_3$	14) $-CH_2OH$	23) NO
6 $-CH_2-CH=CH_2$	15) $CH=O$	24) NO_2
7 $-CH_2-C\equiv CH$	16) COR	25) OH
8 $-CH_2-C_6H_5$	17) $CONH_2$	26) $O(CH_3)$
9 $-CH(CH_3)_2$	18) CO_2H	27) $O-C_6H_5$

28) $OCOR$	32) SOR	36) I	
29) F	33) SO_2R		
30) SH	34) Cl		
31) SR	35) Br		

Asymethric Synthesis.

" The direct (without resolution) synthesis of an optically active compound from a symmetric compound (optically inactive) with or without the use of partically active reagent is known as Asymetric Synthesis."

It is of two type

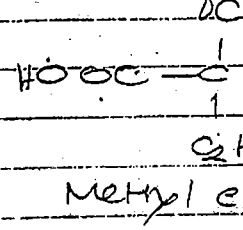
a) Partial asymetric synthesis.

b) Absolute asymetric synthesis.

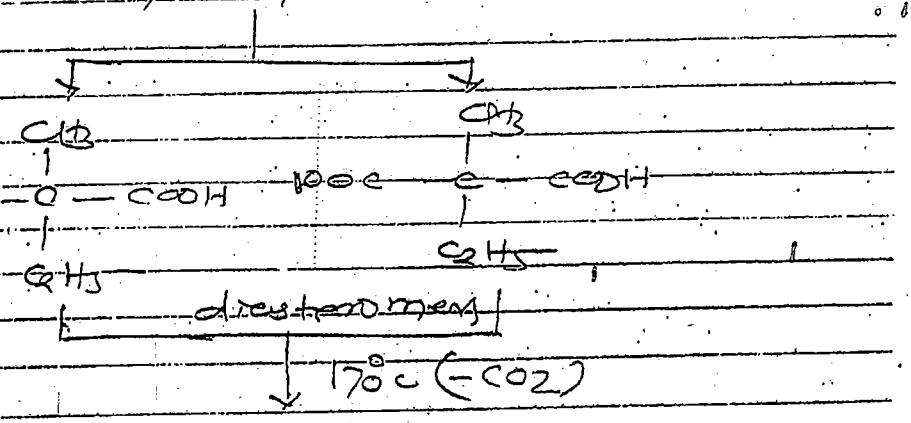
(A) Partial Asymetric Synthesis :-

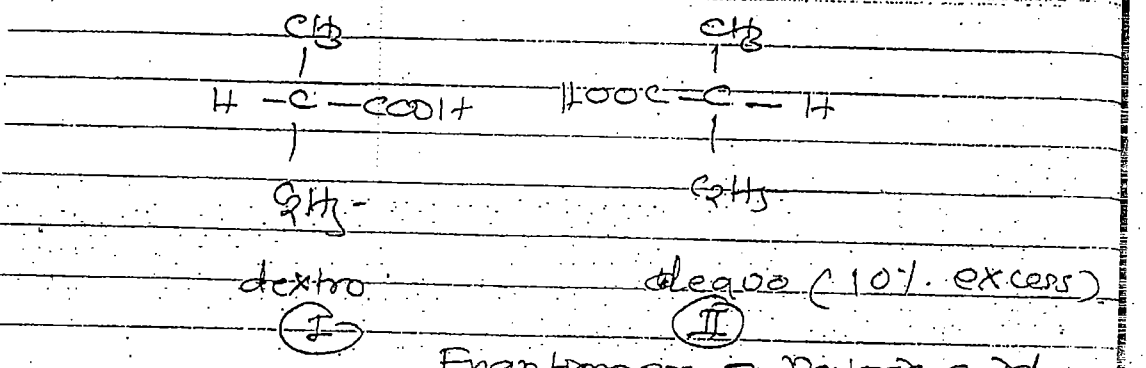
Marckwald (1904) observed that an optically active compound can also be synthesis (d methy (without resolution) from a symetrical compound by the intermediate use of some optically active comp. this phenomena is known as Partial asysymetric Synthesis.

e.g. The synthesis of optically active (Valeric acid) from Methyl ethyl Malonic acid with aid of (-) brucine which is as



Methyl ethyl Malonic acid.



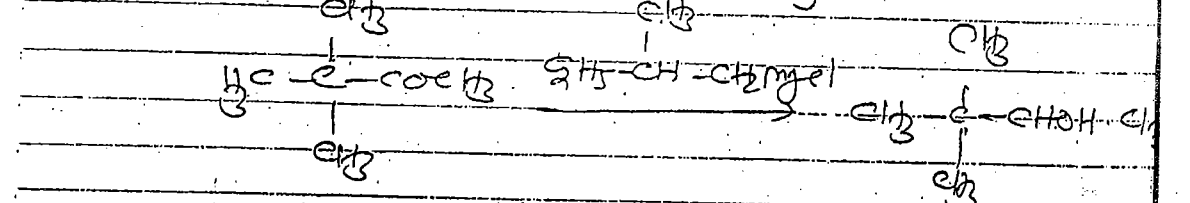


Enantiomers of lactic acid.

As resulting product is levorotatory the two enantiomers must be present in unequal amount.

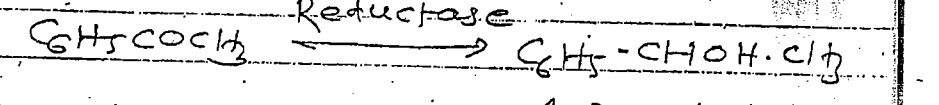
ex: 2

(II) Reduction of 3,3 dimethyl butan-2-one to (+) 3,3 dimethyl butan-2-ol in presence of (+)-2methyl butyl magnesium chloride



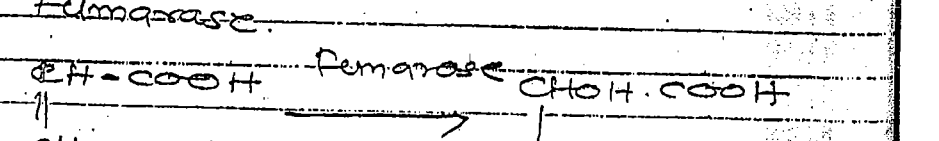
3,3 dimethyl butan-2-one 3,3 dimethyl butan-2-ol.

ex: 3 Formation of (-) 1-phenylethanol from acetophenone in presence of reductase.



Acetophenone 1-phenyl ethanol

ex: 4 Fumaric acid into (-) Malic acid by Fumarase.

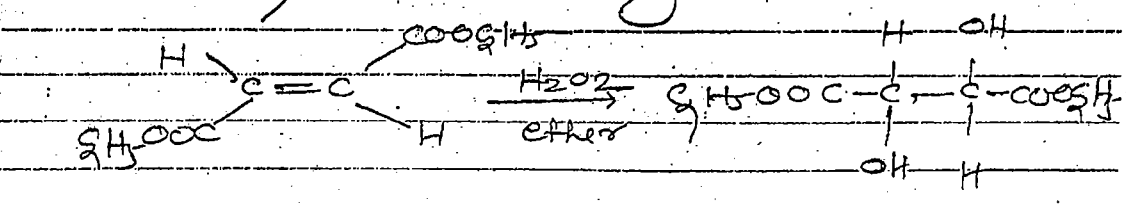


Fumaric acid Maleic acid

(B) Absolute asymetric synthesis:-

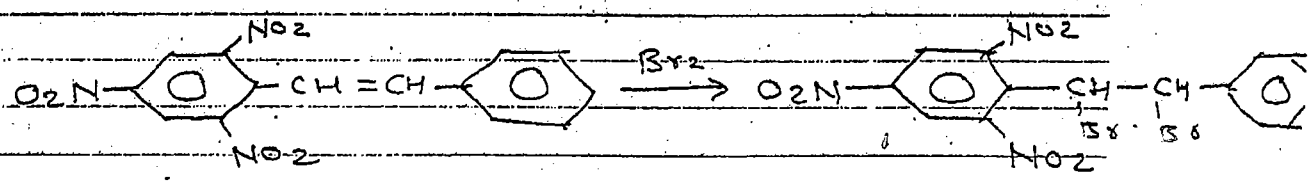
The formation of an optically active compound from inactive one, without the intermediate use of optically active reagent is known as Absolute asymetric synthesis or Absolute decomposition.

i) example: The d-or(+)-diethyl tartaric acid can be synthesised, from ethyl fumarate, and H_2O_2 under the influence of dextro-circularly polarised light.



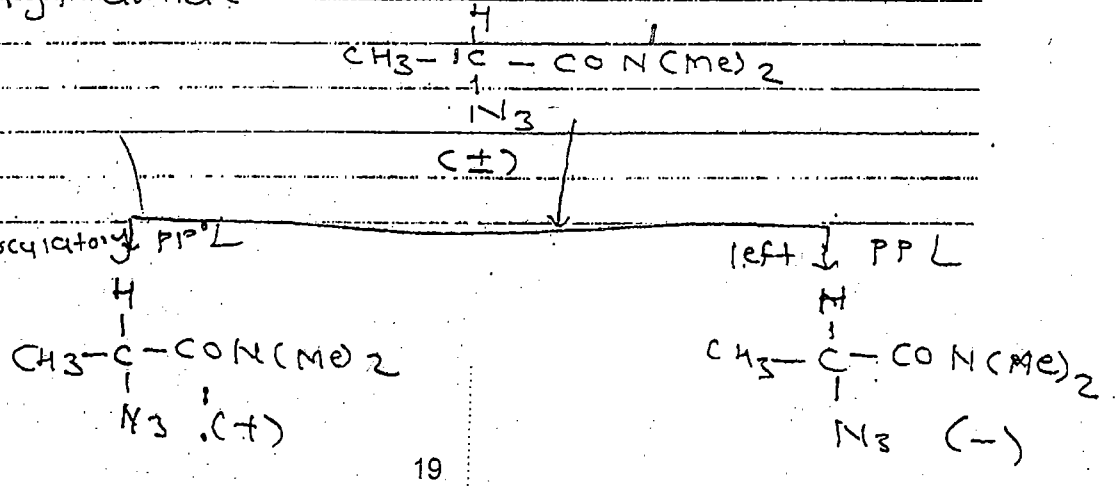
Ethyl Fumarate d(+)Diethyl tartaric acid

ii) Example:- Addition of bromine to 2,4,6 trinitrostilbene in beam of right-circularly polarised light gave dextrorotatory product.



(+)-rotation.

iii) Example:- α-methyl Azido propionic dimethyl amide.



Meso - Tartaric acid :-

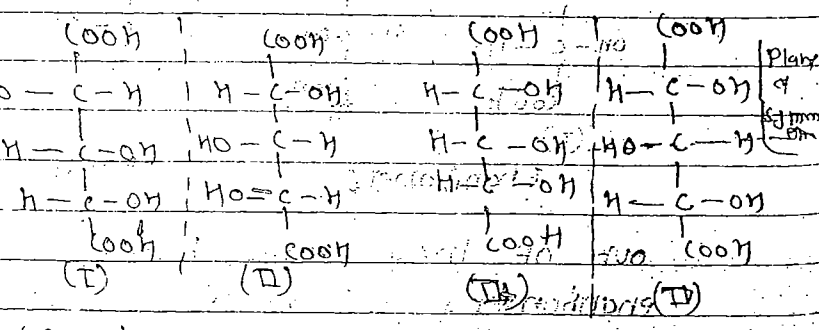
Meso- tartaric acids contain two asymmetric or chiral carbons then also it is optically inactive optical inactivity of meso-tartaric acid is due to presence of plane of symmetry.

Hence tartaric acid is present in 4 forms.

i) (+) tartaric acid - dextro rotatory
ii) (-) Tartaric acid - laevo rotatory
iii) (I) Tartaric acid - optically inactive
iv) meso form - optically inactive

β) Molecules with odd nos of chiral centres :-
no. of steriomer isomers = $2^{(n-1)}$
meso form = $2^{(n-1)}$

eg: hydroxy glutaric acid (n=2)



(Enantiomers) meso meso

Resolution :-

Synthesis of optically active comp. produces a mix. of both (+) & (-) isomers in equal amounts. Such a mix. is called a racemic mix. The separation of racemic mix. in to its (+) & (-) isomers is known as Resolution.

As stated above, racemic mix. contains equal amounts of the two enantiomers. In resolution process, mix. of two enantiomers can be seperated.

Two important methods to resolve racemic mix. are

Biochemical method :-

In this method with the help of selected micro organisms such as bacteria, enzymes one unrequired optical isomers is destroyed from racemic mix.

eg: To isolate (-) tartaric acid from racemic mix. of tartaric acid penicillium glaucum. (+) enzyme is used. This enzyme destroys (+) tartaric acid from racemic mix. Hence we will get (-) tartaric acid.

limitations :-

1) since, one of the enantiomers is destroyed this method is not satisfactory
2) selection of micro organism is difficult

3) micro organism is difficult process therefore the yield of the product is small.

2) Chemical method :-

This is most widely used method for seperating racemic mix. This method is based upon the principle that when a racemic mix. is treated with an optically active reagent it gives a mix. of two diastereomers.

Since, diastereomers have diff physical properties such as melting pt. boiling pt. solubilities etc. and hence they can be seperated by physical method such as fractional crystallization.

Fractional distillation etc. Each diastereomers is converted seperately into corresponding enantiomers.

Consider the resolution of (±) racemic acid when it is treated with optically active base such as (+) brucine (+) tartaric acid gives mix. of two diastereomers.

(+) tartaric acid - (+) brucine & (-) tartaric acid - (+) brucine.

These two diastereomers are seperated by fractional crystallization.

After the seperation, each diastereomer is treated seperately with HCl to regenerate the

(±tartaric acid) X (+) Brucine

↓

(+)tartaric acid, (+)Brucine & (-)tartaric acid, (+)Brucine

| crystallization / Distillation

(+)tartaric acid-(+)Brucine (-) Tartaric acid (+) Brucine

↓ HCl ↓ HCl

+Tartaric acid (-) Tartaric acid.

3) Mechanical method :-

This method is most classical method and used pasteur to seperate the enantiomers. The seperation is carried out by hand using magnifying glass and small forceps. This method is two active diastereomers for practical purpose and is now historical importance only because it was the method of resolution by which pasteur used for seperation of (±) sodium ammonium tartarate.

4) Chromatography :-

Racemic mix. can also be seperated by chromatography using an optically active adsorbent such as starch, lactose etc. where one of the enantiomers gets selectively adsorbed. elution of the column with suitable solvent 1st gives the enantiomer which is not adsorbed strongly on Suse subsequently the more strongly adsorbed enantiomers. In this way the