Rule 2: If two or more than two isotopes of the same element is present, the isotope of higher mass receives the higher priority. ${}_{1}H^{1}{}_{1}H^{2}{}_{1}H^{3}$

Rule 3: If two or more of the atoms directly bonded to the chiral carbon are identical, the atomic number of the next atoms are used for priority assignment. If these atoms also have identical atoms attached to them, priority is determined at the first point of difference along the chain. The atom that has attached to it an atom of higher priority has the higher priority.

In this example the atoms connected directly to the chiral carbon are iodine and three carbons. Iodine has the highest priority. Connected, to the three carbons are 2H and Br, 2H and C and 2H and C. Bromine has the highest atomic number amongst C,H and Br and thus CH_2Br has highest priority among these three groups (*i.e.*, priority no. 2). The remaining two carbons are still identical (C and 2H) connected to the second carbons of these groups are 2H and I and 2H and aC. Iodine has highest priority amongst these atoms, so that $-CH_2 - CH_2 - I$ is next in the priority list and $CH_2 - CH_2 - CH_3$ has the last priority.

$$I - CH_2 - CH_2 - CH_2 - CH_2 - Br = (3) + (2)$$

Rule 4 : If a double or a triple bond is linked to chiral centre the involved atoms are duplicated or triplicated respectively.

$$- \underset{|}{C} = O \equiv - \underset{|}{C} - O; \ - C \equiv N \equiv - \underset{|}{C} - N; \ - C = OH \equiv - \underset{|}{C} - OH = - \underset{|}{C} - OH$$

By this rule, we obtained the following priority sequence :

$$-CH = CR_2,$$

Step 2: The molecule is then visualised so that the group of lowest priority (4) is directed away from the observes (At this position the lowest priority is at the bottom of the plane). The remaining three groups are in a plane facing the observer. If the eye travels clockwise as we look from the group of highest priority to the groups of second and and third priority (*i.e.*, $1 \rightarrow 2 \rightarrow 3$ with respect to 4) the configuration is designated *R*. If arrangement of groups is in anticlocwise direction, the configuration designated *S*.

For example:



Let us apply the whole sequence to bromochlorofluoro methane.

This Fischer projection the least priority number is not at the bottom of the plane.

In such cases the Fischer projection formula of the compound is converted into another equivalent projection formula in such a manner that atom or group having the lowest priority is placed vertically downward. This may be down by two **interchanges** between four priority numbers. The first interchange involves the two priority numbers, one is the least priority number and other is the priority number which is present at the bottom of the plane. In the above case first interchanges will takes place between 2 and 4.



First interchange of two groups at the chiral centre inverts the configuration and this gives enantiomer of the original compound. Thus (A) and (B) are enantiomer. The second interchange involves the remaining two groups.

Glyceraldehyde (For example) has one asymmetric carbon, hence it has two configurational isomers (I) and (II).

СНО	СНО		
H - C - OH	HO - C - H		
$\dot{C}H_2OH$	CH_2OH		
(R)glyceral dehyde	(S)glyceral dehyde		
(I)	(II)		

One can draw a number other configurations for glyceraldehyde but each of them will be a repetition of either (I) or (II). In this connection it is important to note that if two projection formulae of differ by an odd number of interchagnes (1, 3, 5, 7,) of positions of groups on the chiral carbon, they are different, but if the two differ by an even number of interchanges $(2, 4, 6, \ldots)$ they are identical.

For example :

Thus (I), (III) and (V) are identical. Similarly (II) and (IV) are identical.

(11) **Resolution of racemic modifications :** The separation of racemic mixture into its enantiomers is known as resolution. The following methods are used for resolution.

(i) **Resolution by mechanical separation**: Since (+) and (-) forms have opposite crystalline shapes, this property can be used in the separation of the two forms from a racemic mixture.

(ii) **Biochemical separation**: When a living organism is added to or developed to a racemic mixture, they eat up one of the enantiomers preferentially leaving the other behind. Thus, resolution of forms can be done using this specific property of living organisms. For example, **Penicillium glaucum** can be used to remove (d)-ammonium tartrate from the racemic mixture to leave back only the (1)-ammonium tartrate after a suitable time interval.

(iii) **Separation by conversions into diasteremoers** : Enantiomers have identical physical properties while diastereomers have different physical properties. This fact is utilised in separation of enantiomers from racemic mixture. The racemic mixtrue to be resolved is allowed to react with an optically active compound. This leads to the formation of two diastereomers. These have different physical properties, so both diastereomers can be separated by physical methods. Each of the enantiomers may then be regenerated and isolated from the diastereomers. Resolution of enantiomers through the use of diastereomers is given below:

Pair of diastereomers. Top of the molecules are
mirror images but bottom s are not.

$$B B B$$

$$A - C - D D - C - A$$

$$A - C - D D - C - A$$

$$A - C - D D - C - A$$

$$M + W$$

$$A - C - D D - C - A$$

$$M + W$$

$$A - C - D D - C - A$$

$$M + W$$

$$CR$$

$$Chemical reconversion$$

$$CR$$

$$Chemical reco$$

e optically

Note :
Group X reacts with group O to give new group W.

(12) Asymmetric synthesis and Walden inversion

(i) **Asymmetric synthesis**: The synthesis of an optically active compound (asymmetric) from a symmetrical molecule (having no asymmetric carbon) without resolution to form (+) or (-) isomer directly is termed

asymmetric synthesis. For example the reduction of pyruvic acid $(CH_3 - C - COOH)$ in presence of nickel catalyst gives (±) lactic acid (racemic mixture). On the other hand, pyruvic acid is reduced to (–) lactic acid only by yeast.



(ii) **Walden inversion**: The conversion of (+) form into (-) form and vice-versa is called **Walden inversion**. When an atom or group directly linked to an asymmetric carbon atom is replaced (inverse); the configuration of the new compound may be opposite to that of the original, *i.e.*,

CH_3	CH_3	СООН	СООН	СООН
H - C - OH - C	$\xrightarrow{PCl_5} Cl - C - H$	$\xrightarrow{AgOH} HO - \stackrel{ }{C} H$	$\xrightarrow{PCl_5} H - \stackrel{ }{C} - Cl$	$\xrightarrow{AgOH} H - \stackrel{ }{C} - OH$
(+) Malic acid	(–) Chloro succinic acid	LH2COOH (-)Malic acid	(+) Chloro succinic acid	CH2COOH (+)Malic acid

Conformational isomerism .

(1) **Definition :** The different arrangement of atoms in a molecule which can be obtained due to rotation about carbon-carbon single bond are called conformational isomers (conformers) or rotational isomers (rotamers). This type of isomerism is found in alkanes and cycloalkanes and their substituted derivatives.

It may be noted that rotation around a C-C sigma bond is not completely free. It is in fact hindered by an energy barrier of 1 to 20 kJ mol⁻¹ in different bonds. There is a possibility of weak repulsive interactions between the bonds or electron pairs of the bonds on adjacent carbon atoms. Such type of repulsive interaction is known as **torsional strain**.

(2) **Difference between conformation and configuration :** The term conformation should not be confused with the configuration which relates to those spatial arrangements of the atoms of a molecule that can be changed only by the breaking and making of bonds whereas the spatial arrangements in conformation are changed simply by rotation about a single bond.

(3) **Representation of conformations :** Represent conformations we can draw three dimensional pictures. However, chemists represent conformations in two simple ways. These are : (i) Saw horse representation and (ii) Newman projection



(i) **Saw horse representation**: In this projection, the molecule is viewed along the axis of the model from an oblique angle. The central carbon-carbon bond (C-C) is draw as a straight line slightly tilted to right for the sake of clarity. The front carbon is shown as the lower left hand carbon and the rear carbon is shown as the upper right hand carbon. The three bonds around each carbon atom (C-H) in ethane or C-C in higher alkanes) are shown by three lines.

(ii) **Newman projection** : This is a simple method to represent the conformations. In this method, he molecule is viewed from the front along the carbon-carbon bond axis. The two carbon atoms forming the σ -bond are represented by two circles; one behind the other so that only the front carbon is seen. The front carbon atom is shown by a point whereas the carbon further from the eye is represented by the circle. Therefore, the C - H bonds of the front carbon are depicted from the centre of the circle while C - H bonds of the back carbon are drawn from the circumference of the circle at an angle of 120° to each other.

(4) Conformation in alkanes

(i) Conformations of ethane : When one of the carbon atom is kept fixed and other is rotated about C-C bond an infinite numbers of isomers possible. Out of all the conformations for ethane, only two extreme conformations are important and these are: (a) Staggered conformation (b) Eclipsed conformation

(a) Staggered conformation : In this arrangement, the



hydrogens of he two carbon atoms are staggered with respect to one another. As a result, they are at maximum distance apart and have minimum repulsion between them.

(b) Eclipsed conformation : In this conformation, the hydrogens of one carbon atom are directly behind those of the other. Consequently, the repulsion in these atoms is maximum. The saw horse projections of these conformations are represented in fig.

Saw horse representation of staggered and eclipsed conformations of ethane



Newman projections for staggered and eclipsed conformations of ethane

The Newman projections for staggered and eclipsed conformations of ethane are shown in figure. It is clear that when the staggered conformation is rotated through angle of 60°, it changes to eclipsed conformation and similarly, when eclipsed conformation is rotated through the same angle, it gives back the staggered conformation.

Relative stabilities of the conformations of ethane : The

two conformations of differ in ethane their relative stabilities. The conformation staggered has minimum repulsions between the H-atoms attached tetrahedrally to the two carbon atoms. On the other hand. the eclipsed conformation has maximum force of between Hrepulsion atoms. Therefore. the staggered conformation is stable than more the



eclipsed conformation. The difference in the energy contents of the staggered and eclipsed conformations is 12.5 kJ mol⁻¹. This small barrier to rotation is also called **torsional barrier** of the single bond. However, **this energy difference is not large enough to prevent rotation**. Even at ordinary temperatures, the molecules have thermal of kinetic energy to overcome this energy barrier. Therefore, the two conformations of ethane go on changing from one form to another and consequently, it is not possible to isolate the different conformations of ethane.

The variation of energy versus rotation about the C-C bond has been shown in figure.

(ii) **Conformations of propane** : The next higher member in alkane series, propane $(CH_3 - CH_2 - CH_3)$ has also two extreme conformations, staggered conformation and eclipsed conformation. In figure only Newman projections are shown for simplicity. However, the energy barrier in propane is 14 kJ mol⁻¹, which is slightly higher than that in ethane.



In the eclipsed conformation of the propane, there are two ethane type H - H interactions and an additional interaction between C - H bond and C - C bond (of methyl group). The variation of energy versus rotation about C - C bond as shown in fig.

(iii) **Conformations of butane** : As the alkane molecule becomes larger, the conformation situation becomes more complex. In butane $(CH_3 - CH_2 - CH_2 - CH_3)$, for example, the rotation about the single bond between two inner atoms (C_2 and C_3) is considered. In this case, all the staggered as well as eclipsed conformations will not have same stability and energy because of different types of interaction between C - C (Of methyl) and C - H bonds.

The lowest energy conformation will be the one, in which the two methyl groups are as far apart as possible *i.e.*, 180° away form each other.

This conformation will be maximum staggered and is Different conformations of butane called **anti conformation** (marked I). Other conformations can be obtained by rotating one of the C_2 or C_3 carbon atoms through an angle of 60° as shown ahead.

As is clear from the above Newman projection the Gauche or Skew conformations (III and V) are also staggered. However, in these conformations, the methyl groups are so close that they repel each other. This repulsion causes gauche conformations, to have about 3.8 kJ mol⁻¹ more energy than anti conformation. This conformations II and VI are **eclipsed conformations**. These are unstable because of repulsions. These are 16 kJ mol⁻¹ less stable than anti conformation. Conformation IV is also eclipsed and it is least stable having energy 19 kJ mol⁻¹ more than anti conformation. This is because of repulsion between methyl-methyl groups which are very closed together. It is called **fully eclipsed conformation**.

The **order of stability** of these conformations is, Anti > Skew or Gauche > Eclipsed > Fully eclipsed.

The energy differences between various conformations is shown in figure.

(5) Conformations in cycloalkanes

 (i) Stability of cycloalkanes : Compounds with three and four membered rings are not as stable as compounds with five or six membered rings.

The German chemist Baeyer was the first to suggest that the instability of these small rings compounds was due to angle strain. This theory is known as **Baeyer-strain theory**.







Baeyer strain theory was based upon the assumption that when an open chain organic compound having the normal bond angle 109.5° is convert into a cyclic compound, a definite distortion of this normal angle takes place leading to the development of a strain in the molecule.

Baeyer assumed that cyclic rings are planar. Assuming that the rings are planar, the amount of strain in various cycloalkanes can be expressed in terms of angle of deviation (d).

$$d = \frac{1}{2} \left[109.5 - \frac{2(n-2)}{n} \times 90 \right] \quad \text{or} \quad d = \frac{1}{2} [109.5 - \alpha]$$

where n = number of carbon-carbon bonds in cycloalkane ring; $\alpha =$ inner bond angle in the cycloalkane ring.

Angle strain $\propto d \propto \frac{1}{\text{inner angle}}$; Stability $\propto \frac{1}{d} \propto \text{inner angle}(\alpha)$

Now let us take the case of three to eight membered cyclic compounds.



The positive and negative values of (*d*) indicate whether the inner angle is less than or more than the normal tetrahedral value.

Beayer thus predicted that a five membered ring compound would be the most stable. He predicted that six membered ring compounds would be less stable and as cyclic compound became larger than five membered ring they would become less and less stable.

Contrary to what Baeyer predicted, however cyclohexane is more stable than cyclopentane. Furthermore, cyclic compounds do not become less and less stable as the number of sides increase. Thus Baeyer strain theory is applicable only to **cyclopropane**, **cyclobutane and cyclopantane**.

The mistake that Baeyer made was to assume that all cyclic compounds are planar. In real only cyclopropane is planar and other cycloalkanes are not planar. Cyclic compounds **twist** and **bend** in order to achieve structure that minimises the three different kinds of strain that can destabilise a cyclic compound.

(a) **Angle strain** is the strain that results when the bond angle is different from desired tetrahedral bond angle of 109.5°.

(b) **Torsional strain** is caused by repulsion of the bonding electrons of one substituent with bonding electrons of a nearby substituent.

(c) **Steric strain** is caused by atoms or groups of atoms approaching each other too closely.

(ii) **Conformation of cyclohexane**: Despite Baeyer's prediction that five-membered cyclic compounds would be the most stable, the six membered cyclic compound is the most stable. Six membered cyclic compound are most stable because they can exist in a conformation that is almost completely free of strain. This conformation is called the **chair conformation**. In a chair conformation of cyclohexane all bond angles are 111° which is very close to the 109.5° and all the adjacent carbon-hydrogen bonds are staggered.





Chair conformation of cyclohexane

Newmann projection of the chair conformation

- \Rightarrow Each carbon in chair conformation has an axial bond and an equatorial bond.
- \Rightarrow Axial bonds are perpendicular to the plane of the ring equatorial bonds are in the plane of the ring.
- ⇒ If axial bond on carbon-1 is above the plane of the ring then axial bond on carbon-2 will be below the plane of the ring. Thus a
 - C-1, C-3 and C-5 axial bonds are above

C-2, C-4 and C-6 axial bonds are below



- \Rightarrow Thus C-1 axial and C-2 axial are *trans* to each other. Similarly C-1 and C-5 axials are *cis* to each other.
- ⇒ If axial bond on carbon-1 will be above the plane then equatorial bond on this carbon will be below the plane. Above



- (a) Thus C-1 equatorial and C-2 equatorial bonds are trans.
- (b) C-1 axial and C-2 equatorial will be *cis*.
- ⇒ As a result of rotation abut carbon-carbon single bonds cyclohexane rapidly interconverts between two stable chair conformations. This interconversion is know as ring –flip. When the two chair forms interconvert, axial bonds become equatorial and equatorial bonds become axial.



⇒ Cyclohexane can also exist in a boat conformation. Like the chair conformation, the boat conformation is free of angle strain. However, the boat conformation is less stable than the chair conformation by 11 *kcal/mole*. Boat conformation is less stable because some of the carbon-hydrogen bonds in boat conformation are eclipsed.





conformation

The boat conformations is further destabilised by the close proximity of the flagpole hydrogens. These hydrogens are 1.8 Å apart but the vander Waal's radii is 2.4 Å. The flagpole hydrogens are also known as *trans* nuclear hydrogens.

Note : The selective stabilities of the four conformations of cyclohexane decrease in the order:

Chair > twist boat > boat > half chair.

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