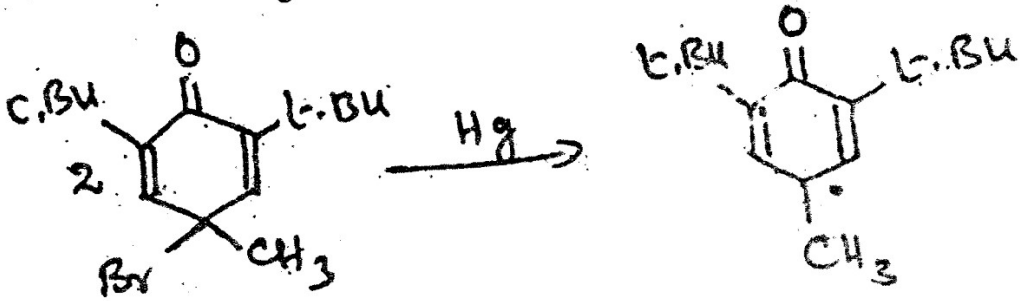
c) Organic Methods

Triphenyl methyl radical was generated using metallic silver.

$$(C_6H_5)_3CCl \xrightarrow[\text{benzene}]{Ag} (C_6H_5)_3C^{\bullet} + AgCl$$

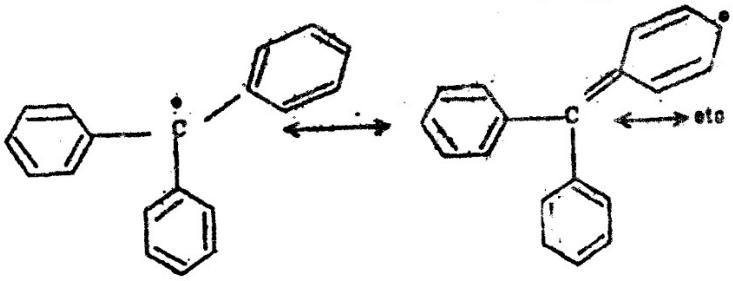
Other metals such as Hg and Zn have also been used in free radical generation.



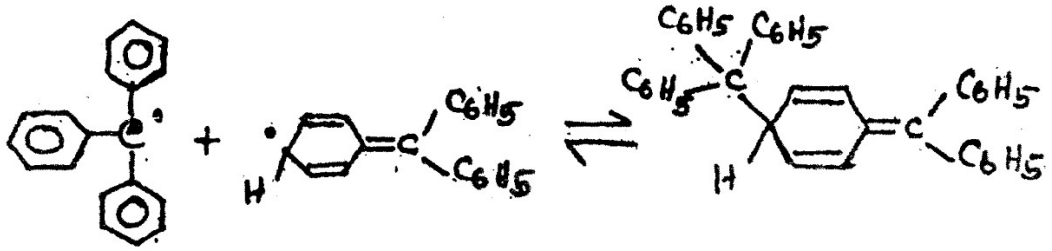
Stability of Free Radicals

The major factors operating in the stabilization of free radicals are, a) resonance b) steric effects c) hyperconjugation and d) aromaticity

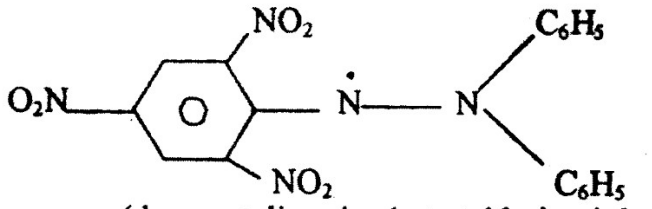
Normally the stability of the radical is decided by the extent of delocalization within the molecule. One of the markedly stabilized free radicals is the triphenylmethyl, which receives resonance contribution from several structures and the radical is found to absorb visible light appearing yellow in colour.



The stability also results due to the relieving of strain from the SP^3 hybridization in the triphenyl methane to SP^2 (109.5° ⟶ 120°) in the radical. However, the radical undergoes dimerisation readily in benzene solution in equilibrium with the following molecule.

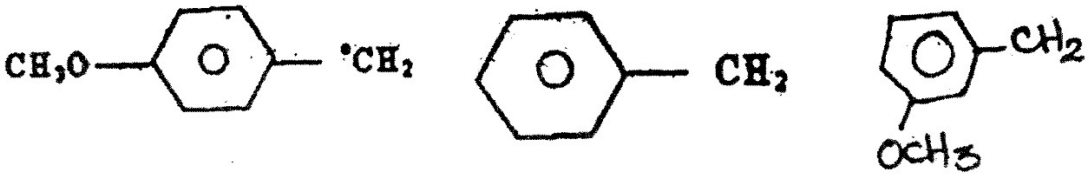


But ortho substituted phenyl groups do not favour dimerisation due to steric repulsion and destabilize the radical as the rings are twisted out of plane. Still, the resonance effects are found to be twice more effective than steric effects.

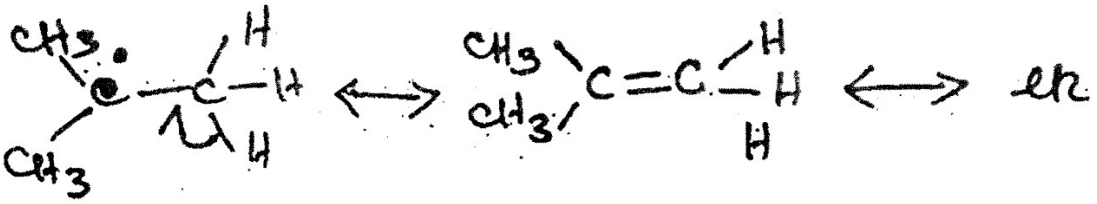


(does not dimerise but stable in violet colour)

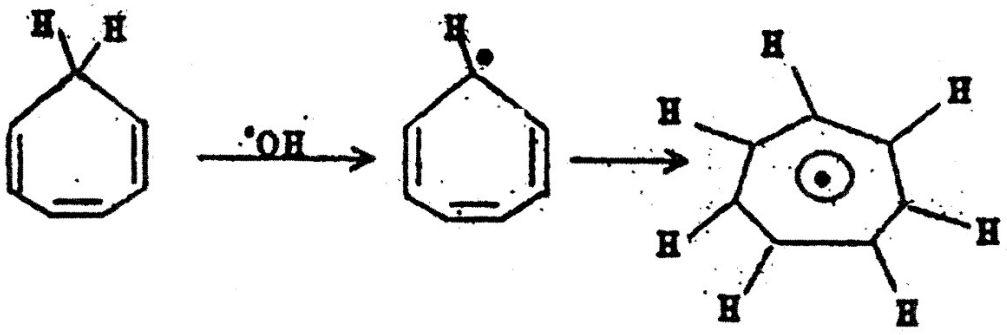
Similar resonance stabilization is found in benzylic and allylic radicals. Any group capable of resonating with the free electron will enhance the stability of the radical. Hence hyperconjugative stability is reflected in the stability sequence of the following radicals:



The tert. butyl free radical is the most stabilized similar to the respective carbonium ion, as it contains the maximum number of α - hydrogen atoms which participate in hyperconjugation

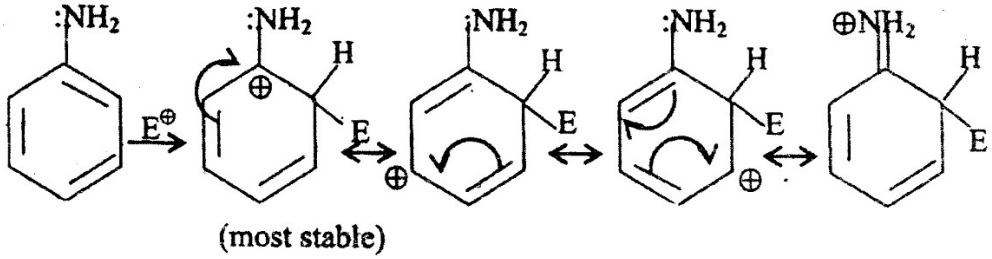


Development of aromaticity in molecules specially contribute to formation of stable radical species (e.g) cycloheptatriene readily loses a H• when reacted with •OH, to form a free radical when the odd electron is resonating with the aromatic system, with perfect delocalization.

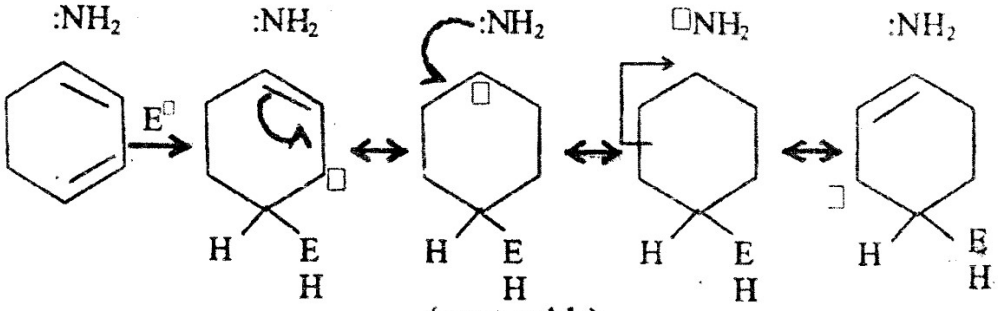


Aromatic Electrophilic Disubstitution

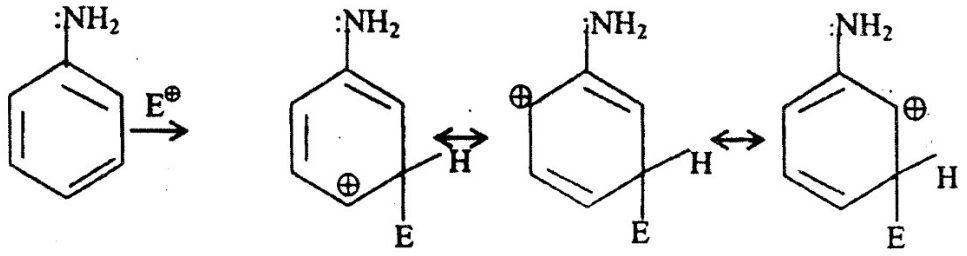
Electrophilic attack on a pure benzene nucleus will result in a single product as all the six positions are identical. When the ring is further substituted, the incoming electrophile could attack one of the two Ortho positions, one of the two meta positions or the para position. This selectivity of the electrophile is due to its tendency to attack the position of high electron density, which depends on the activating or deactivating ability of the group already present. It has been observed that electron releasing groups favour an electrophilic attack at the Ortho and Para positions whereas the electron withdrawing groups prefer the meta position. This could be explained on the basis of the stability of the σ - complex formed.



(most stable)

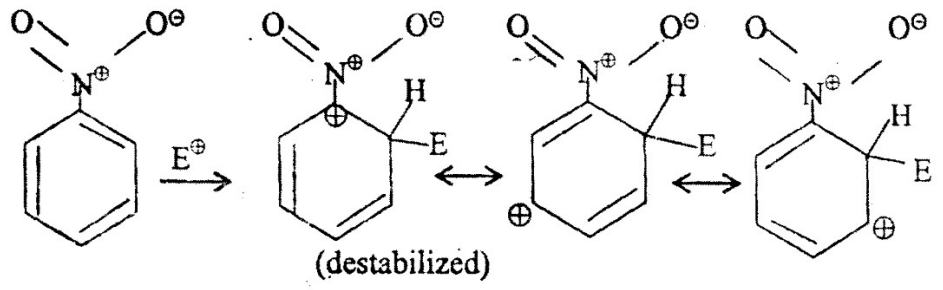


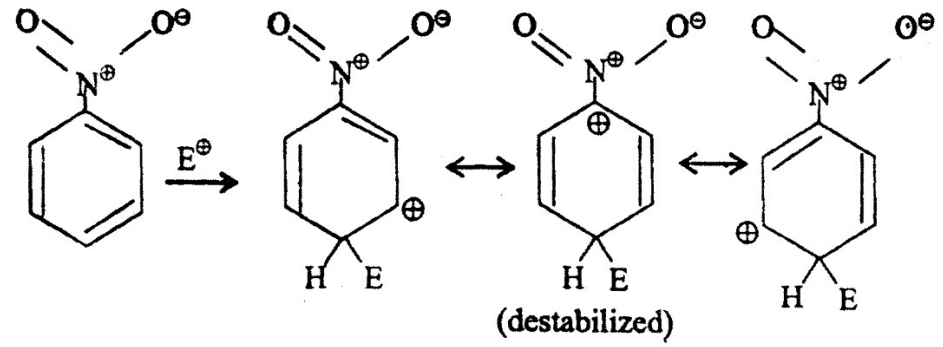
(most stable)

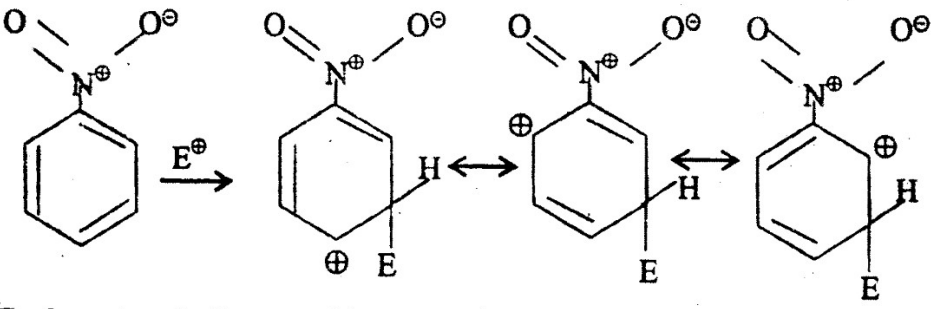


Several carbonium ions are formed, of which the tertiary carbonium ion is the most stabilized in the case of σ - complexes for Ortho and Para products. Such a carbonium ion is not formed in the case of the meta product, hence less stable. Moreover, the electron releasing group could not be involved in resonance with the benzene ring to stabilize the σ - complex whereas it is possible in the Ortho and Para complexes.

Similarly, an examination of the σ - complexes for an electron withdrawing group indicates that the Ortho and Para substitution results in the destabilization of the σ - complexes, but not affecting the stability of those of the meta product



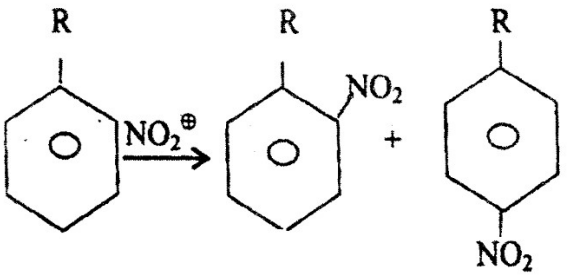




The formation of adjacent positive charges in at least one of the σ - complexes for Ortho as well as Para substitution, destabilize them, but no σ - complex structure is destabilized for meta product though not stabilized. Hence the entering electrophile attacks the meta position, which has not been much affected due to deactivation.

Ortho – Para Ratio

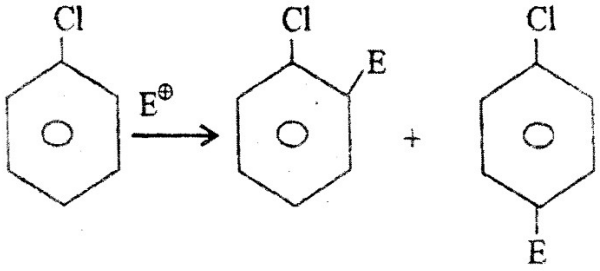
In the absence of any other effect operating in the molecule, purely on statistical basis an Ortho isomer must be formed in double the quantity compared to the Para isomer. (ie) the O/P ratio must be 2/1. In practice, this ratio is never achieved, as the % of the Ortho isomer is considerably less in most of the molecules. This could be due to the steric effect exerted by the group already present as well as the entering electrophile, the polar effect of the substituent (already present) solvent effect, temperature effect and the electrostatic forces operating between the substrate and the electrophile when they approach each other. The O/P ratio in the Nitration of a series of alkyl benzenes establishes the steric influence of the alkyl group (already present) in the given order.



R	O / P
CH_3	1.57
CH_2CH_3	0.92
$CHMe_2$	0.48
CMe_3	0.22

The % of the para product drastically increases with the increase in size of the alkyl group (37%, 49%, 62%, 73% respectively)

The steric effect due to the entering electrophile, is equally apparent in the various substitution reaction in the chloro benzene nucleus

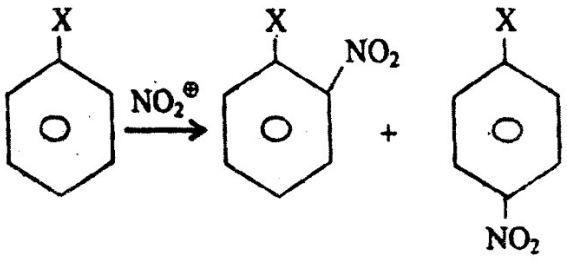


$E^{\oplus}$	O / P
Cl	0.71
NO_2	0.43
Br	0.14
SO_3H	0.01

In the above said illustrations, the increasing size of the substituent and the electrophile, retards the stability of the σ - complex of the Ortho product.

Polar Effect & Steric Effect

In the nitration of various halobenzens, despite the steady increase in the steric factor, the % of the Ortho product is found to increase and the O/P ratio also increases.

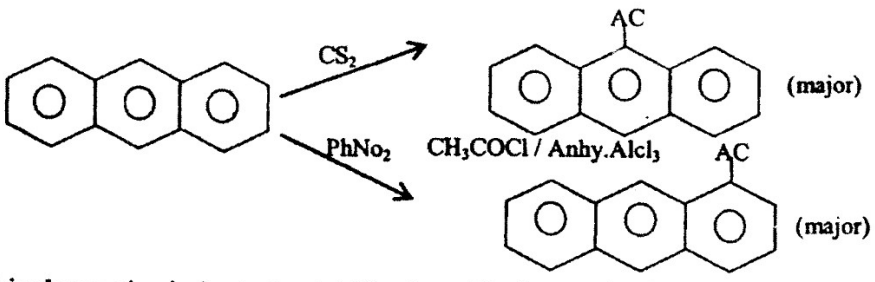


X	O / P
F	0.14
Cl	0.44
Br	0.60
I	0.63

Hence it is reasonable to suppose that the operating steric effect is far out weighed by the –I effect the halogen, which decrease with distance (from the Ortho to Para)

Solvent Effect

The Friedel crafts acetylation of anthracene occurs at 1 - position in Nitro benzene solvent where as at 9 – position with carbon disulphide as the solvent.



This observation is due to the stabilization of the large solvolyzed [CH_3 COCl–$AlCl_3$] complex in Nitrobenzene favouring the less hindered 1 – position but not the more hindered 9 – position.

Partial Rate Factor

The ratio of the rate of electrophilic substitution at a given position in a substituted benzene derivative compared to that in benzene is called partial rate factor. Since the entering substituent selectively attacks a position, the partial rate factors are different for different positions. They are represented as o_f^R, m_f^R, and P_f^R, for the Ortho, meta and para position respectively. In general, they may be formulated based on statistical considerations as follows:

$$O_f^R = \frac{K_{PhR}}{K_{PhH}/6} \times \frac{\%\ \text{Ortho isomer}}{2 \times 100}$$

$$m_f^R = \frac{K_{PhR}}{K_{PhH}/6} \times \frac{\%\ \text{metaisomer}}{2 \times 100}$$

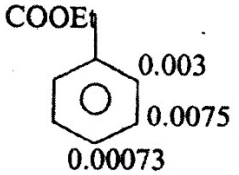
$$P_f^R = \frac{K_{PhR}}{K_{PhH}/6} \times \frac{\%\ \text{Paraisomer}}{100}$$

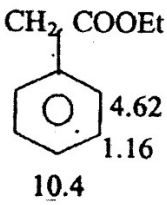
Since there are six equivalent positions in benzene, the K_{phH} has to be divided by 6, and 2 equivalent ortho and meta positions have necessitated division by 2.

The significance of partial rate of factors may be illustrated for the nitration of toluene (HNO_3/AC_2O) at O°c. Any of the five positions in toluene nucleus is found to be 27 times more active than any position in benzene. hence $K_{ph.Me} = 27$. The % of the O, m & p – products are, 61.5, 1.5 and 37.0, hence the calculated partial rate factors:

$O_f^R = 50$, $m_f^R = 1.3$ and $P_f^R = 60$

When the factor is greater than 1, it is understood that the particular position is activated by the substituent present in the nucleus. When it is less than 1, it indicates the deactivating influence of the group at that position. The values for the nitration of ethyl benzoate and ethyl phenyl acetate has established the combined –I and –M effect of the group in deactivating various positions in the nucleus.





When the carbethoxy group is insulated from the nucleus by the $-CH_2$ group, the hyperconjugative effect predominates, with the overall activation of the various positions.

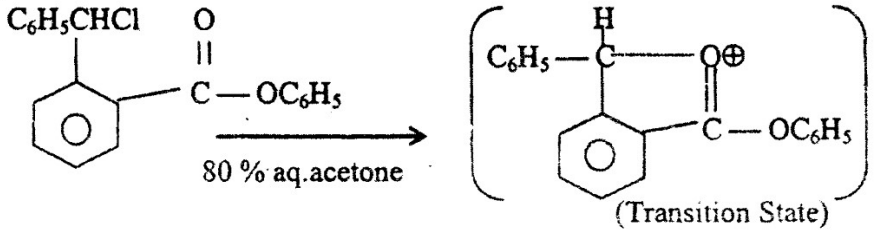
Study of Organic Reaction Mechanism

It is possible, the path of a chemical reaction could be explained by more than one mechanism, but the one which explains all the experimental observations is considered to be the plausible one. To follow the path of a chemical reaction, both kinetic and non-kinetic methods are employed.

Kinetic Methods

Study of Abnormal Reaction Rates

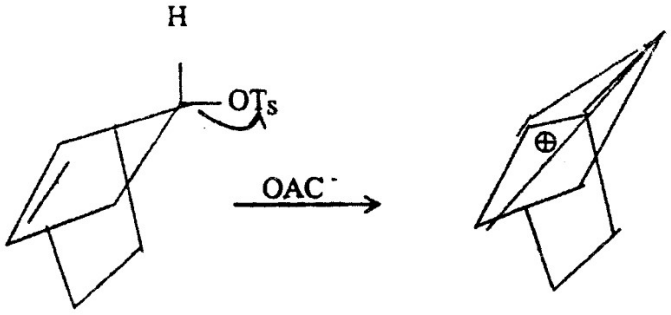
A reaction whose rate is unexpectedly faster or slower than similar reactions under the same experimental conditions, suggests the operation of a different or modified pathway from the expected one, (e.g) The rate of hydrolysis of Ortho carbophenoxy benzhydryl chloride is found to be several orders of magnitude higher than that of the para isomer, in 80% aq. acetone.



(Transition State)

The abnormal rate of the reaction has thrown suspicion on the normal course of an SN^1 process. Hence it is concluded that the reaction follows an SN^2 mechanism when the transition state is stabilized through an intramolecular chelation process, which is not possible in the para isomer.

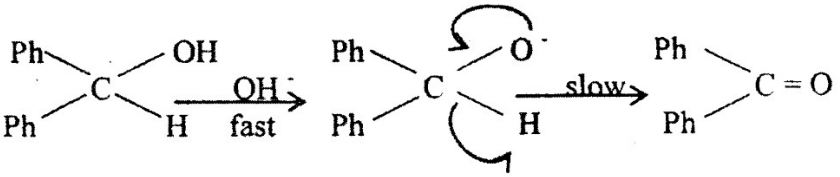
The acetolysis of anti – 7 norbornyl para toluene sulphorate is 10^{11} times faster than the corresponding saturated ester.



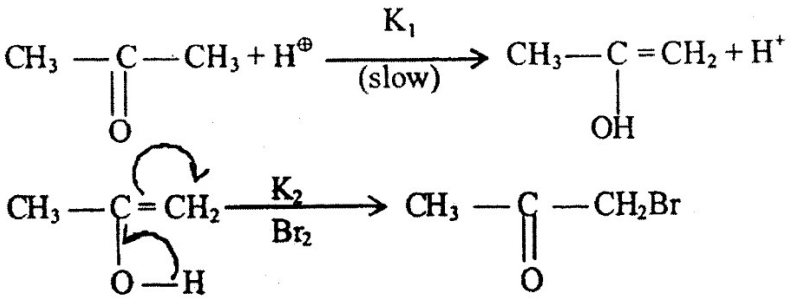
This abnormal reaction rate again suggests that the reaction path is different from the normal SN^1 mechanism. It has now been concluded that a non-classical carbonium ion intermediate formed is stabilized in the course of the reaction, due to neighbouring group participation

2) Kinetic Isotopic Effect

A C – H bond is broken easily compared to a C – D bond. The ratio of their rate constants ($^{KH}/_{KD}$) should be ~ 7. In reactions where the cleavage of a C – H bond forms the rate determining step, a kinetic isotopic effect is observed as indicated by the $^{KH}/_{KD}$ value. When the value is around unity, no such effect is involved and it may be concluded that the rate determining step doesn't involve C – H bond breaking. (e.g) The oxidation of diphenyl carbinol is found 6.5 times faster than the labeled alcohol. This suggests that C – H bond breaks at the rate determining step.

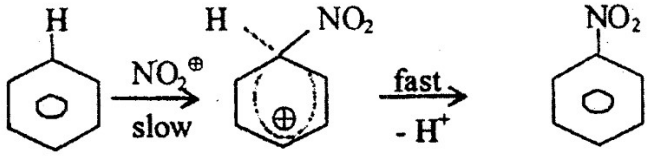


Similarly acid catalysed bromination of acetone has as $^{KH}/_{KD}$ value of 7.5



The observed $^{KH}/_{KD}$ value is in agreement with the mechanism in which the bromine plays no part in the kinetics and the rate is decided by the concentration of acetone and of the protons in solution.

Again, nitration of benzene shows no primary kinetic isotopic effect as hexa deutrobenzene as well as benzene undergo nitration at the same rate $^{KH}/_{KD} = 1$. Hence the mechanism must not involve the breaking of C – H bond at the rate determing step. According the mechanism is:

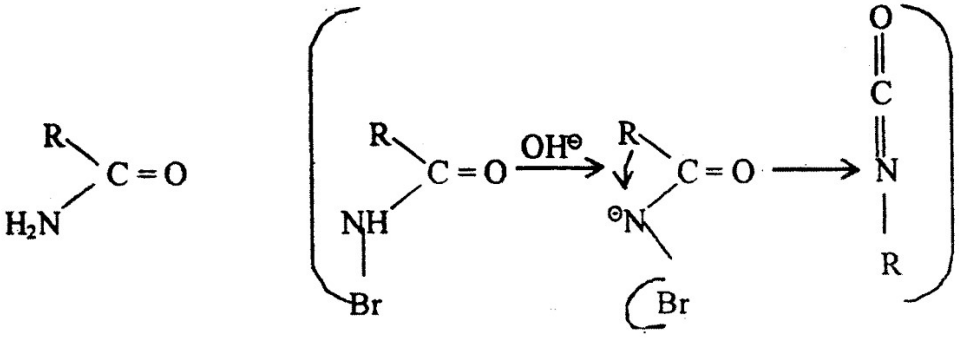


Non Kinetic Methods

Most of the reactions proceed through the formation of at least one intermediate, which if isolated serves as an incontrovertible evidence for the proposed mechanism.

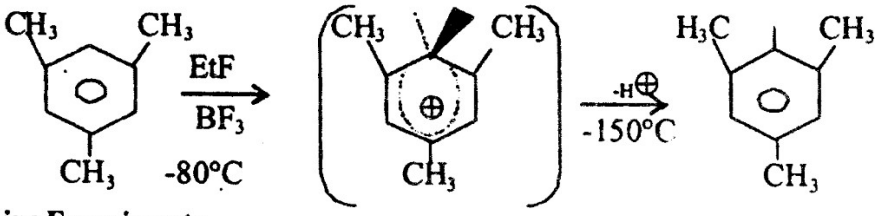
1) Isolation of Intermediate

The Hoffman rearrangement involves the formation of 3 intermediates the N – bromoamide, its anion and isocyanate, which on hydrolysis yields the amine.



All these intermediates have been isolated by carefully controlling the reaction conditions and the suggested mechanism is thus well documented.

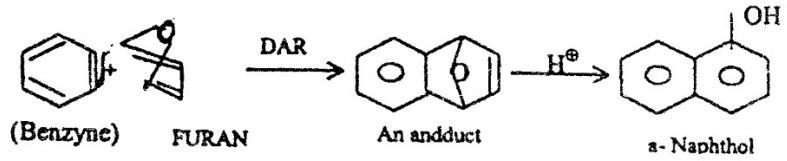
In the Friedel – crafts alkylation, the final product is formed through a wheland intermediate. This has been isolated as an organge crystalline solid which melts with decomposition at – 15°c to give the product, thus confirming the mechanism.



2) Trapping Experiments

In cases where the isolation of the intermediate is not possible due to its transient nature, such intermediates have been trapped using a suitable molecule.

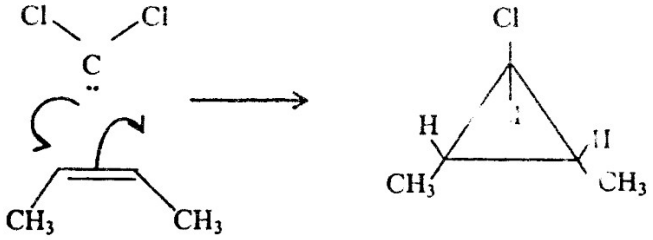
Aromatic nucleophilic substitution reactions proceed through the formation of an aryne intermediate which defies any isolation, but it undergoes a Diels – Alder type of reaction with alicydic as well as aromatic dienes.



Furan acts as a trap to incorporate the molecule to form an adduct which readily undergoes hydrolysis to form α - Naphthol.

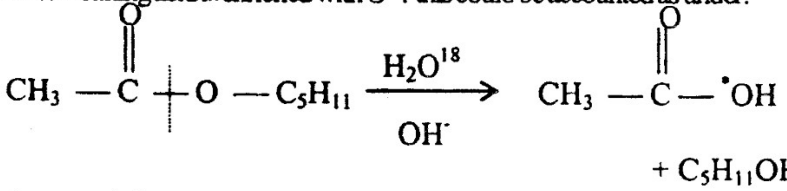
Similarly an aryne can be trapped using Anthracene which forms triptycene as the adduct.

The highly electron deficient reactive intermdiate dichlorocarbene has been trapped by introducing into the reaction mixture, an electron rich molecule cis - 2- butene.



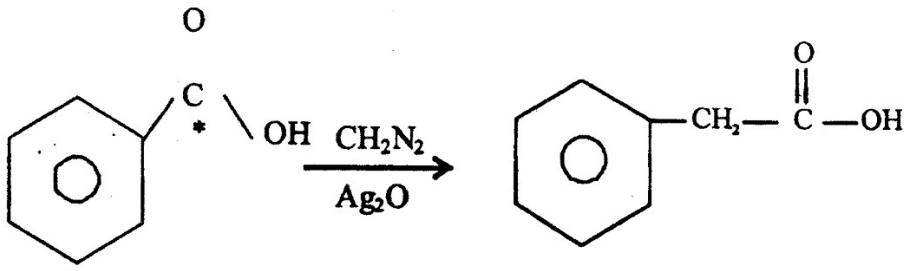
3) Isotopic Labelling

A well documented case of using labeled isotopes is the base catalysed hydrolysis of n – aryl acetate which may undergo cleavage either at acyl oxygen bond or the alkyl oxygen bond, to form an acid and alcohol. However, the use of water enriched with H_2O^{18}, has shown that the cleavage occurs at the acyl oxygen bond as the resulting acid is enriched with O^{18}. this could be accounted as under:



Hence in esters it is acyl oxygen cleavage and not the alkyl oxygen cleavage is involved in base hydrolysis.

Similar dispute arises in the mechanism of Arndt – Eistert synthesis of a higher homologue of an aromatic carboxylic acid

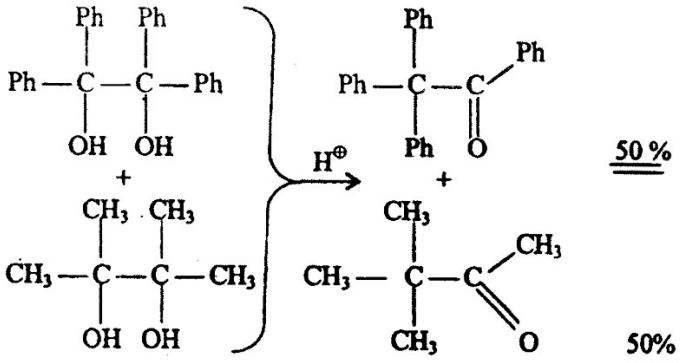


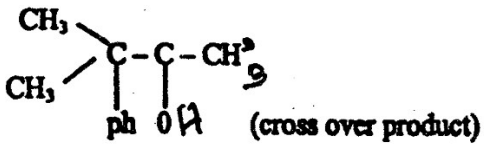
It is whether the carboxyl carbon in the phenyl acetic acid is the same as that in benzoic acid or from the diazomethane. The C^{13} labelling of the carboxyl carbon in benzoic acid and the isolation of the final product indicates that the C^{13} is retained in the carboxyl group.

4) Cross Over Experiments

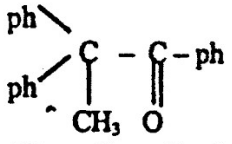
Such experiments are carried out to test whether a mechanism proceeds intermolecularly or intramolecularly, by mixing a molecule during the course of the reaction similar to the substrate molecule undergoing the reaction. This verification is required very commonly in molecular rearrangements which are mostly intra – molecular. In case the rearrangement is intermolecular, cross products are formed.

The pinnacol – pinnacolone rearrangement, proceeds through the formation of a carbonium ion through migration of an alkyl or aryl group. It is possible during migration the group may or may not completely detach from the rest of the molecule. If there is complete detachment, the group can migrate into the neighbouring molecule also, apart from attacking the same molecule. In that case, cross over products are possible. In the following example two pinnacols are mixed and the rearrangement carried out.





(cross over product)



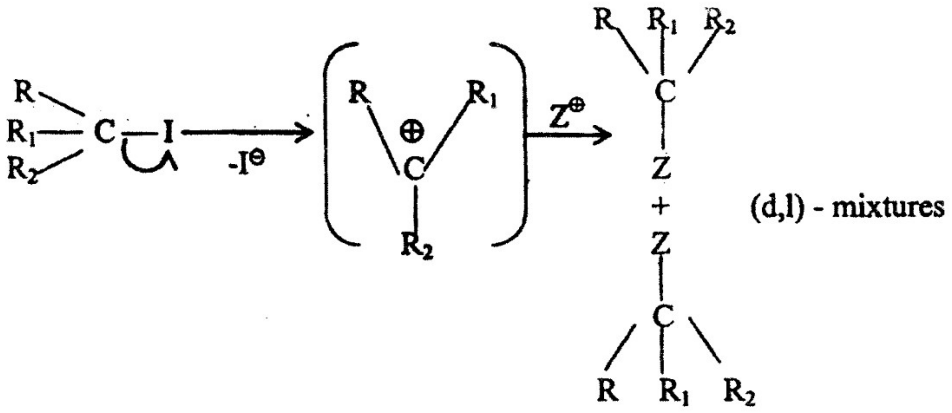
Nil

(Cross Over Product)

However, no cross product has been formed, confirming the intra – molecular nature of the rearrangement.

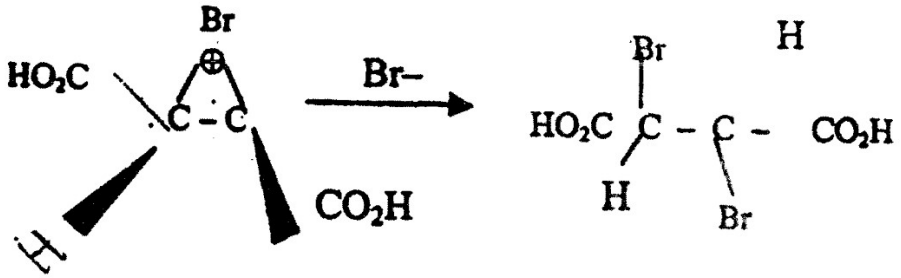
5) Stereo chemical Evidence

Besides the kinetic and chemical methods of studies, stereochemistry of the final product provides wide support for the mechanism, in a variety of reactions. SN^1 and SN^2 processes can be differentiated through the stereochemistry of the final product, as the SN^1 mechanism proceeds through the formation of a planar carbonium ion, which is attacked by the nucleophile to produce a 50:50 mixture of the d and l isomers. (ie) an optically inactive racemic mixture is formed, provided the substrate carbon is asymmetric, as in the given example.



However, when SN^2 mechanism operates in molecules, the products are completely inverted, as Walden inversion occurs and the final product is optically active.

Similarly, the addition of Br_2 to fumaric acid is believed to proceed through a cyclic bromonium ion intermediate which is confirmed through the formation of a meso product.



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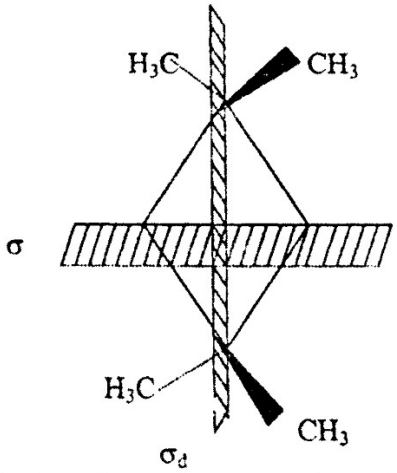
UNIT II
STEREO CHEMISTRY

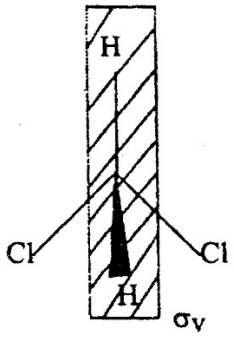
Symmetry of Molecules

The Symmetry properties of a given molecule are directly related to its stereochemistry. When molecules possess elements of symmetry they are called symmetric. Since symmetric molecules do not exhibit any optical isomerism it is mandatory to verify the presence or absence of any elements of symmetry, before attempting on the stereochemistry of such molecules.

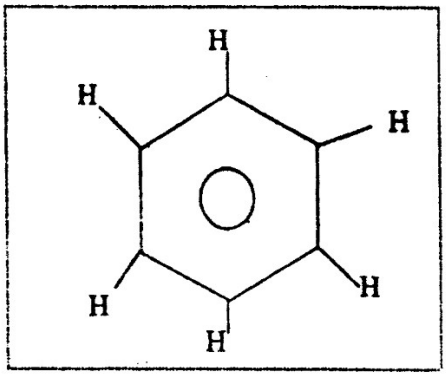
Plane of Symmetry (σ)

It is any plane passing through a given molecule such that it bisects the molecule in to equal halves which are mirror images of each other (e.a)





Any molecule where the atoms or groups lie on the same plane will automatically have a horizontal plane of symmetry. More symmetric molecules may have more number of planes of symmetry. Benzene molecule has several vertical planes of symmetry (σ_v) and one horizontal plane of symmetry (σ_h), which is cutting along the edges of the molecule.



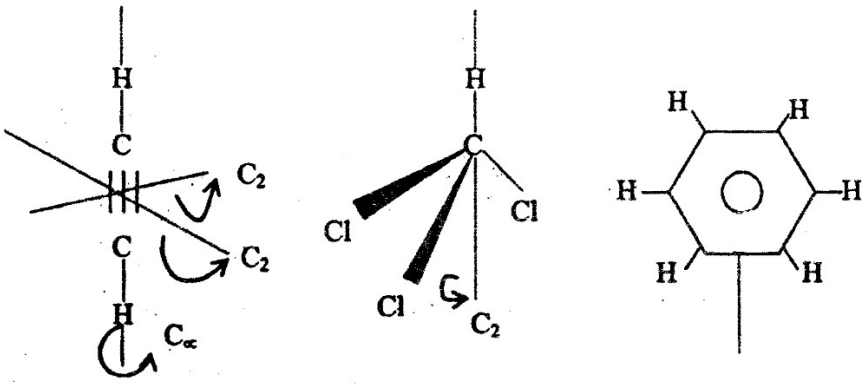
σ_h

In the cyclobutane derivative given above, the plane passing along the diagonals of the molecule could also be designated as diagonal planes of symmetry (σ_d)

Simple Axis of Symmetry (C_n)

(Proper Rotation Axis)

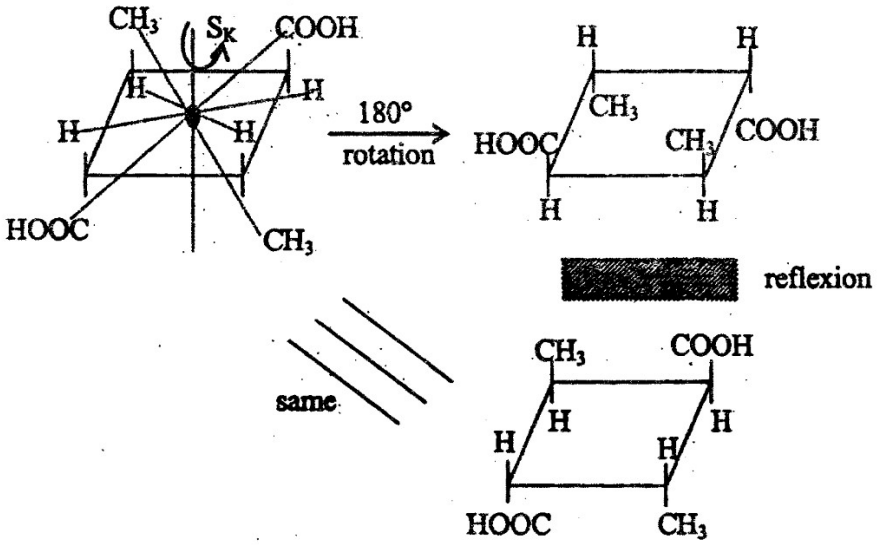
It is any axis passing through the molecule such that when it is rotated through an angle of 360° /n, produces n number of identical arrangements as the original molecule.



A molecule of acetylene has infinite number of axes of symmetry (C∞) when rotated through any angle, but benzene has a 6 – fold axis of symmetry as it produces 6 identical appearances when rotated through 360°.

Centre of Symmetry (i)
(inversion centre)

It is a point in the molecule through which when lines are drawn on opposite sides, meet identical atoms or groups at the same distance from the point. Inversion of all atoms (groups) in the molecule through the point gives an original arrangement. Hence it is also called an inversion centre.



Rotation – Reflexion Axis (Sn)
(Alternating axis of symmetry)

It is an axis passing through the molecule such that a rotation around an angle 360°/n followed by reflexion through a mirror kept at 90° to the axis produces an image identical to the original molecule. In the cyclo butane derivative given above, there is a centre of symmetry as well as a 2 – fold alternating axis of symmetry denoted as S_2. An all molecules possessing an S_2 will have automatically a centre of inversion, since S_2 operation brings about the exchange of like groups across the centre. Similarly operation of an S_1 axis consists of C_1 and σ (rotation and reflexion). Since C_1 operation leaves the molecule unchanged, the S_1 axis can be equated to σ. Hence a molecule possessing a plane of symmetry must have an S_1 axis.

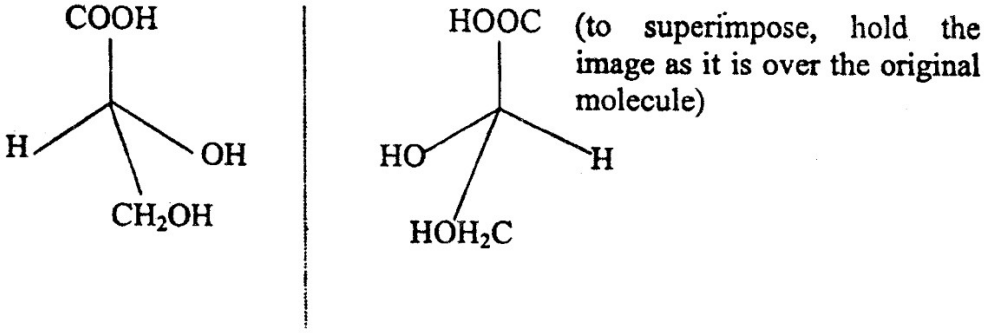
From the nature of the various symmetry elements, it is clear that an alternating axis of symmetry is more fundamental in deciding the symmetry of a molecule. Hence to hold a molecule symmetric it is enough to verify the presence of an alternating axis of any order, normally S_1 (σ) or S_2 (i). Absence of these elements in a molecule may give rise to optical isomerism and such molecules may be classified as asymmetric and dissymmetric.

Asymmetric molecules should not have any element of symmetry except the trivial C_1 axis and these molecules can exhibit optical isomerism.

Dissymmetric molecules should have no S_n axis but a C_n axis may be present, still exhibiting optical isomerism.

Chirality and Optical Isomerism

An asymmetric molecule or a dissymmetric molecule can give rise to a mirror image which is nonsuperimposable with the original molecule. Such molecules are called Chiral, and they may (or may not) have a Chiral centre. A Chiral carbon will have an SP^3 hybridization and all the four groups different.

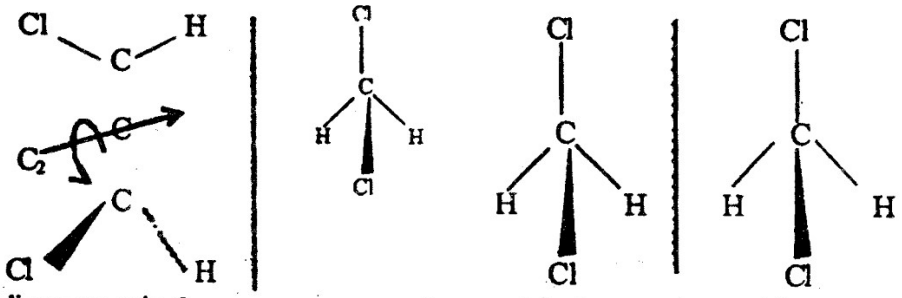


(to superimpose, hold the image as it is over the original molecule)

d & l forms of glyceric acid

The original molecule and its mirror image are nonsuperimposable, hence the molecule is said to be optically active and chiral. The molecule and its image constitute two different isomers, the dextro and the levo forms (d & l) called optical isomers, or enantiomers.

A symmetric molecule however has its image, superimposable with the original molecule, hence termed achiral. But a dissymmetric molecule though possesses a simple axis of symmetry is termed Chiral, since its mirror image is nonsuperimposable with the object.

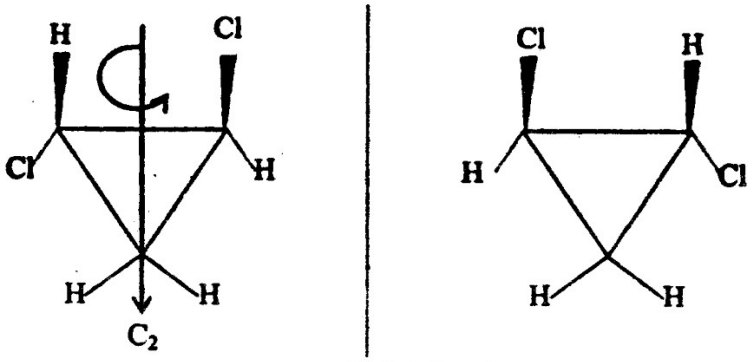


(dissymmetric & non super imposable Chiral molecule)

(symmetric & super imposable A Chiral molecule)

From the above discussions it is increasingly clear that Chirality is the necessary and sufficient condition for enantiomorism or optical isomerism exhibited by molecules, and not the asymmetry or dissymmetry of a molecule. However, all asymmetric molecules are chiral, but chiral molecules need not be asymmetric, since even molecules possessing C_n axis are found to be Chiral as seen from the nonsuperimposability of the image, in the given 1,3 dichlro allene.

Another example of a chiral molecule which does not possess a chiral centre still possessing a C_2 axis, is the dissymmetric molecule trans 1,2 dichlorocyclopropane. Hence the fundamental crieterian for optical activity is chirality and not a chiral centre or asymmetry.



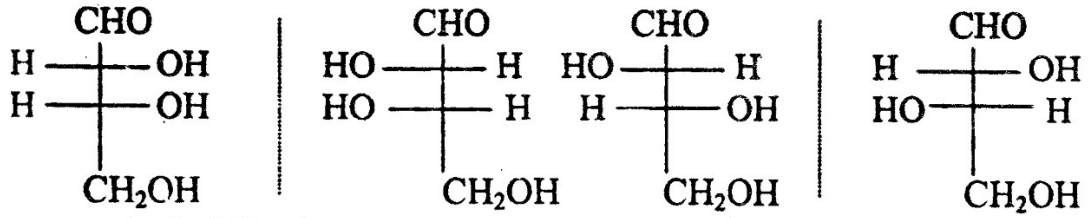
(d & l form)

Molecules Possessing 2 or more Chiral Centres

Even though the possession of a Chiral centre is not a criterian for optical activity, the number of optical isomers in a molecule is decided by the number of Chiral centers present in the molecule. For a molecule with n number of distinctly different asymmetric centers, 2^n optical isomers are possible.

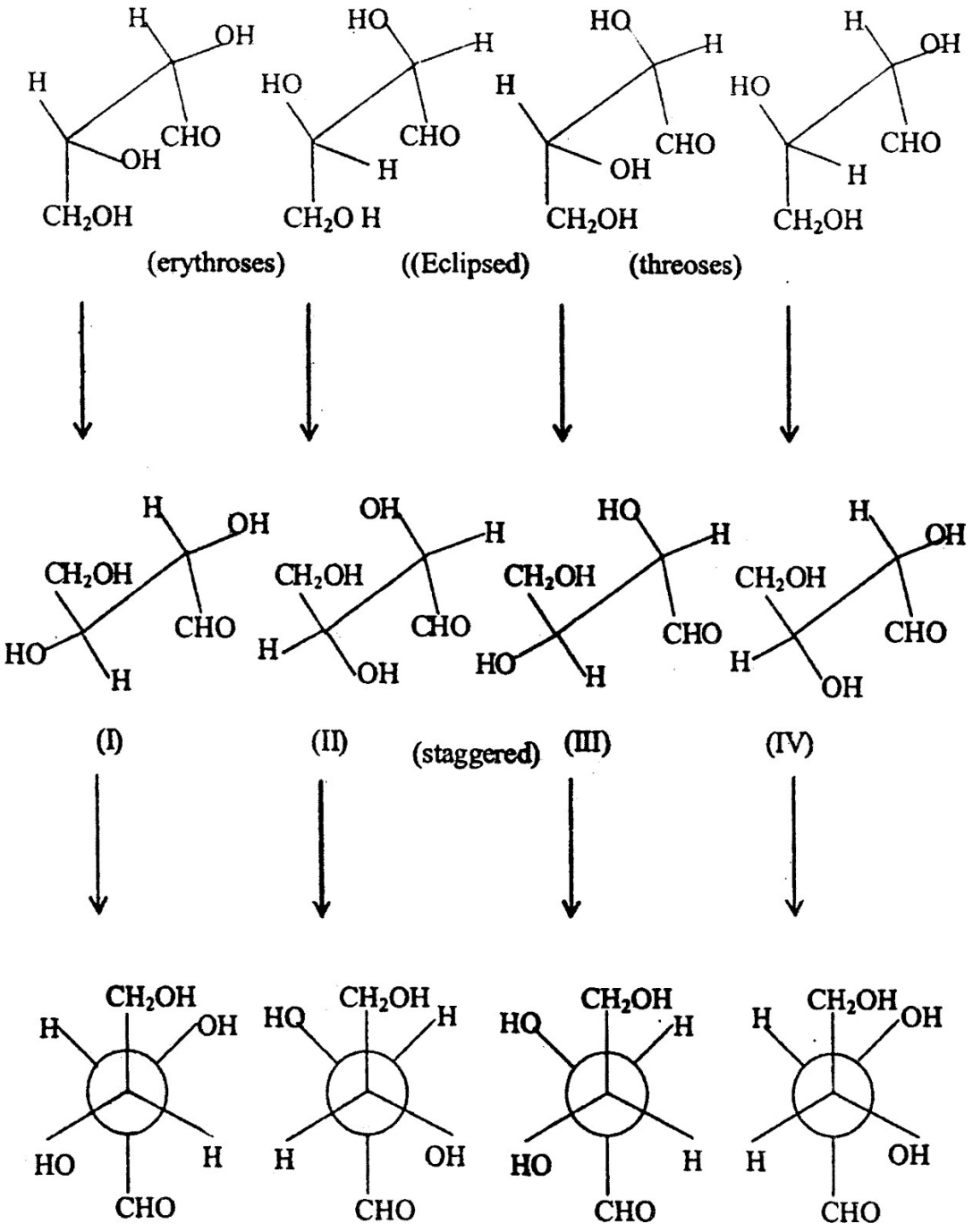
Molecules with Unequal Asymmetric Centres

Consider the aldotetroses with 2 unlike asymmetric centers. They exist in 4 different stereo isomeric forms, with 2 pairs of enantiomers. Their Fischer projection formulae are as under:

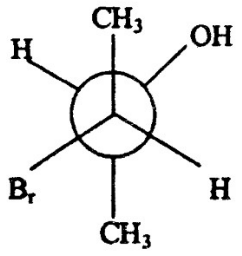


(+ & -) Erythroses (+ & -) Threoses

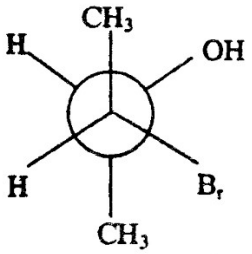
These sterioisomers given in Fischer projections are representing only the most unstable conformer viz. the eclipsed form, hence they are best represented by the sawhorse formula or the Newman formula. The Fischer projections (eclipsed) are directly translated as under into the Sawhorse Formula



The C – C bond in the molecules are rotated through an angle of 180°, to stagger the molecules from the eclipsed forms. The configurations of the 2 pairs of enantiomers are clearly depicted in the Newman projection formula. Any molecule possessing 2 or more number of unequal asymmetric centers could be represented in the Erythro form or the threo form, using these prefixes. Hence the stereo isomeric forms of one of the erythro forms and threo forms are as under:



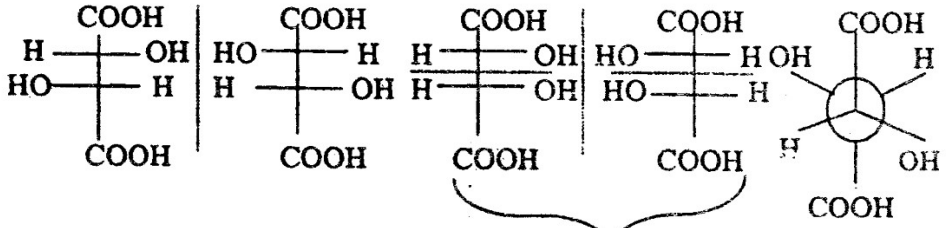
Erythro-form)



(Threo-form)

Molecules with like Asymmetric Centres

2,3 dihydroxy succinic acid (Tartaric acid) molecule contains 2 asymmetric centers but symmetrical with respect to each other. It can exist only in 3 stero isomeric forms of which one is an optically inactive meso form, the other two being a pair of enantiomers.



(+ & - form) identical (meso form)

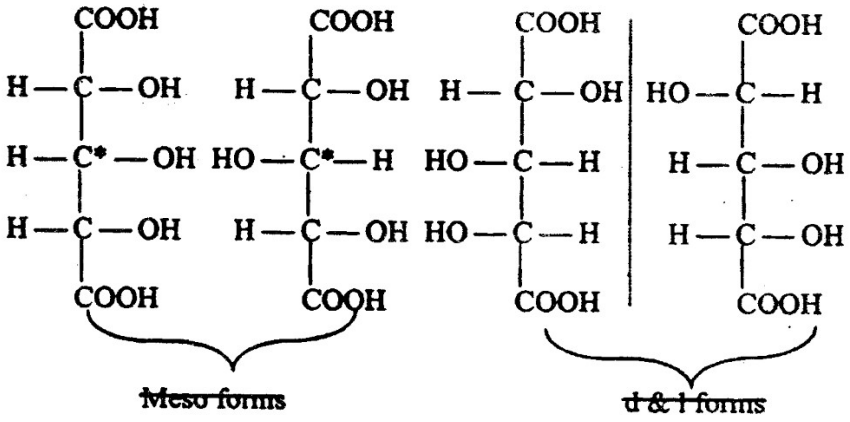
I II III IV

While molecules I & II possess enantiomeric relationship, stereo isomers I & II as well as II & III are not related through object – mirror image relationship and are called diastereoisomers.

Similar diastereoisomeric relationship exists between the (+) erythrose and (+) threose, (+) erythrose and (-) threose, ( ) erythrose and (+) threose as well as (-) erythrose and (-) threoses).

Molecule III is identical with IV, since 180° rotation of any one of them makes it identical with the other. Again, the molecule has 2 constitutionally symmetrical chi enters whose configurations are opposite in nature (R & S) or (S & R), hence internally compensated and opti ally inactive. Moreover, the staggered form of the molecule has a centre of symmetry (i) and the eclipsed form has a plane of symmetry which make the molecule achiral.

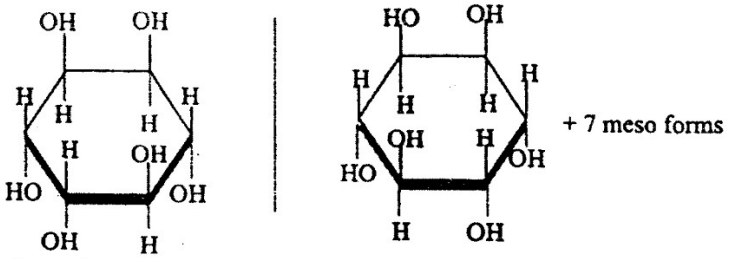
Another molecule with 2 like asymmetric centers and a pseudoasymmetric centre is 2,3,4 trihydroxy glutaric acid.



~~Meso forms~~ ~~d & l forms~~

Both the meso forms have a pseudo asymmetric carbon, the other two chiral centers having opposite configuration, one of the centers rotating the plane polarized light to the right and stereo isomeric forms are optically inactive.

Cyclic compounds normally possess greater symmetry and exhibit lesser number of stereo isomers than predicted. The naturally occurring inositol containing six chiral centers exists in 8 stereo isomeric forms of which only one is resolvable into enantiomeric pairs.



The meso forms have one or more σ planes rendering them irresolvable.

Axial Chirality

Most of the examples discussed so far, contain chiral centers or stereo centres, with a tetrahedral orientation. A class of molecules where there is a stereo axis giving rise to optical activity has been identified in allenes, biphenyls and spiranes. If the single tetrahedral centre is replaced by a linear group such as C – C as in biphenyls or C = C = C as in allenes and spiranes, the tetrahedron is elongated along an axis. This tetrahedron is more asymmetric than the normal tetrahedron, as it is enough if any of the two end groups are different to make the whole molecule chiral. Such an axis present in these groups of chiral allenes, sprianes and biphenyls is called a Chiral Axis, and the phenomenon known as Axial chirality.

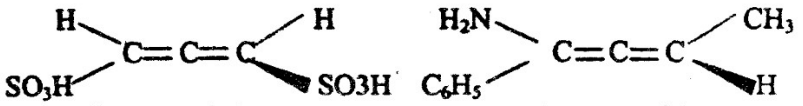
Stereo Chemistry of Allenes

The allenes correspond to the general formula bbC = C = Caa or aaC = C = Cbd or baC = C = Cab or edC = C = Cab, where the two double bonds are perpendicular to each other. The first two types of allenes are totally symmetric and achiral the third type dissymmetric and the fourth type asymmetric.

(achiral) σ_h & σ_v present

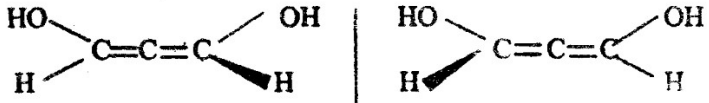
chiral – dissymmetric chiral – asymmetric

If any two extreme groups are identical, the allene is rendered achiral if the end groups are distinguishable, the molecule is chiral. Normally the substituents are amino alkyl, aryl, hydroxyl carboxyl, carboalkoxy, alkoxy, sulphonic acid etc.



(disymmetrict) (asymmetric)

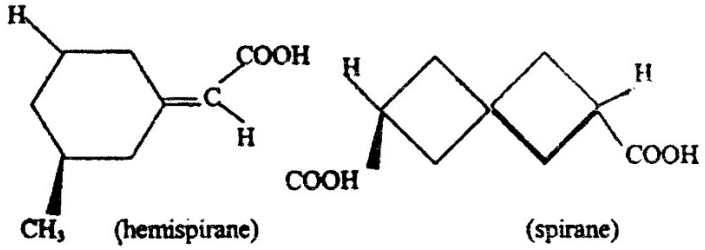
Hence, due to the presence of achiral axis, the entire molecule is rendered asymmetric, since it possesses object – mirror image relationship.



(Non superimposable)

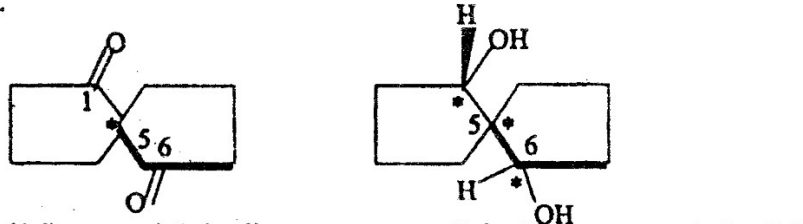
Spiranes:

Replacing one or both the double bonds in allenes by rings can give rise to hemispiranes or spirances, without changing the stereo chemistry of the molecule. Hence the spiranes behave very similar to allenes towards exhibiting stereoisomerism.



(hemispirane) (spirane)

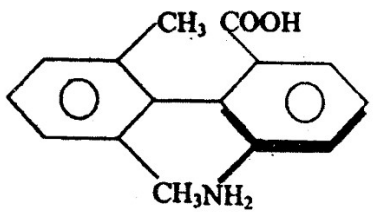
4 – methyl cyclohexylidene acetic acid is an example of a hemispirane and Spiro (3,3) heptane 2,6 dicarboxylic acid is a spirane. Both are axially chiral, the hemispirane bing asymmetric and the spirane, dissymmetric due to the different groups attached at the extreme carbon atoms as in allenes. However, spiranes which are chiral due to the presence of one or more chiral centres are also known.



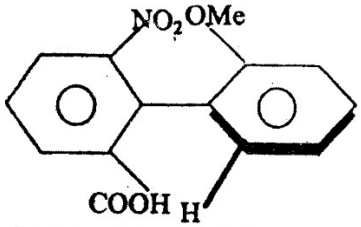
Spiro (4,4) nonane – 1,6 – dione Spiro (4,4) nonane – 1, 6 – diol

Biphenyls (Atropisomerism)

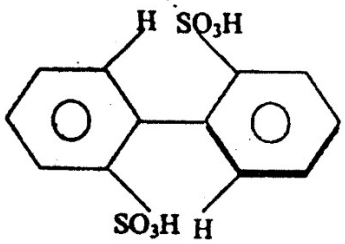
A biphenyl molecule cannot exhibit any sterioisomerism as long as the two rings are on the same plane. However, when the Ortho positions are substituted by bulky groups, restricted rotation around the C – C axis is achieved. This causes the two rings tilting out of plane giving rise to chirality in the molecule, and the C – C axis is rendered a chiral axis. The type of chirality due to the restricted rotation around a single bond is otherwise known as atropisomerism, and the molecule and the image are called atroprisomers. As in the case of allenes, the 4 positions in biphenyls could be asymmetrically or dissymmetrically substituted, to induce chirality in the molecule. Introduction of identical groups in one of the rings would automatically introduce a plane of symmetry in the molecule even though the rings are out of plane. Examples of chiral and achiral biphenyls are as under:



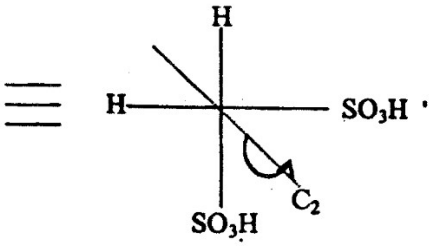
(achiral)



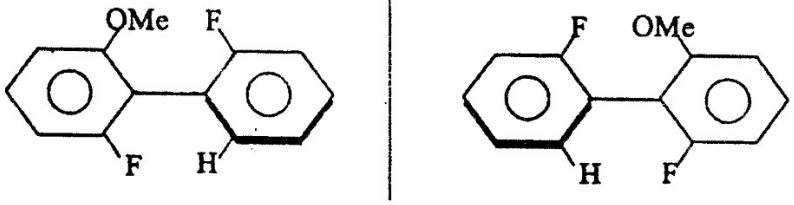
(asymmetric – chrial)



(chiral axis – dissymmetric)



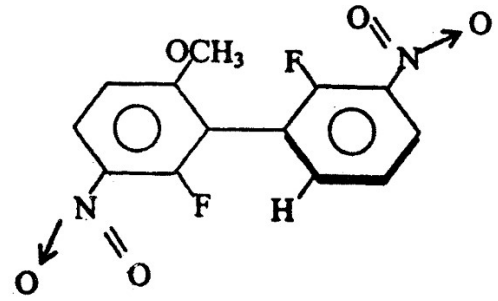
When the Ortho positions are filled with less bulkier groups, then the rate of interconversion of the d and l forms is much faster and racemisation occurs easily. Bulkier the ortho substituents, greater is the energy barrier for interconversion, and easier the resolution into d & l forms.



(d & l forms – readily racemises)

But introduction of a bulkier group of the meta position arrests the rate at which free rotation occurs, as the ortho substituents cannot easily bend backwards during fast rotation. This effect is called buttressing effect. (e.g) 3 – Nitro derivative of the above molecule.

When the orthro positions are filled with less bulkier groups, when the rate of inter conversion of the d and l forms is much faster and racemisation occurs readily. Bulkier the ortho substituents, greater is the energy barrier for interconversion, and easier would be the resolution in d & l forms.



Buttressing effect introduced in the molecule has enhanced the configurational stability of the isomers and arrested the rate of racemisation.

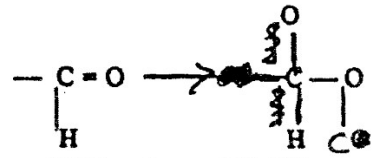
R.S. Configuration

According to Cahn, Ingold and Prelog, the configuration notation of three dimentional structures of molecules with chiral centres could be given by assigning priority sequence to the various valencies attached to the centre. The atom or group with least priority is kept away from the sight of the observer and if the priority of the other three group falls (decreases) along the clockwise direction the centre has R – configuration; if it falls along the anticlockwise direction it has an S – configuration. This system is also called the CIP system of nomenclature.

The priorities of the group are fixed based on a set of rules called sequence rules.

1. The near end always precedes over the far end.
2. The highest atomic number (of the atom directly attached to the centre) precedes over the lower atomic number (O>N>C etc)
3. An atom of heavier isotope takes preference over the lighter. (O^{18}>O^{16})
4. Cis – configuration (Z) is preferred over the trans – configuration (E)
5. R has preference over S.

The priority if disputed over the same atom for two groups, it decided by passing over to the next atom or atoms along the chain, until it is settled based on sequence rules. When the centre is attached to an atom multiply bonded, the atom is considered duplicated or triplicates as case may be. Hence the following considerations are made.



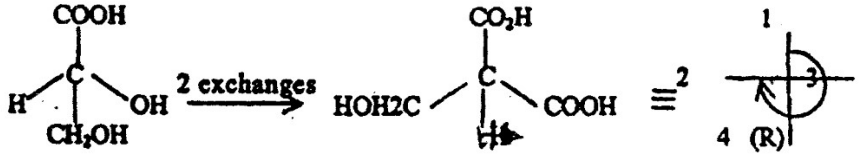
Hence

— CHO > — CH_2OH

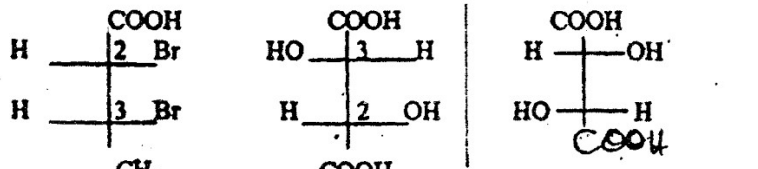
— C ≡ N > — $CH_2N(CH_3)_2$

— $C(CH_3)_3$ > — CH = CH_2

Accordingly, the configurations of the following molecules are fixed, by making even number of exchanges aroung the chiral centre.



if required, to keep the group of least priority away from the sight (ie) bottom position in a Fischer projection formula. In molecules with multichiral centers, every centre should be treated separately.

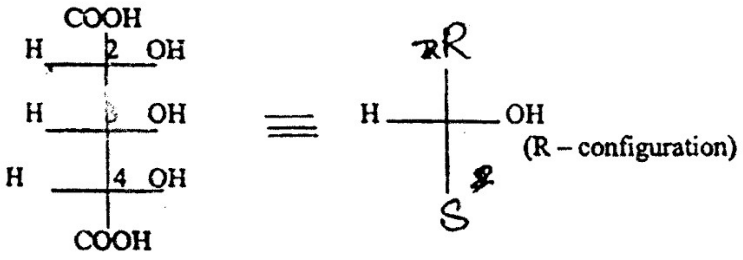


[2(S),3(R) - - 2,3dibromobutanal]

[2(S), 3(S) - -Tartaric acid]

[2(R) , 3(R) - Tartaric acid]

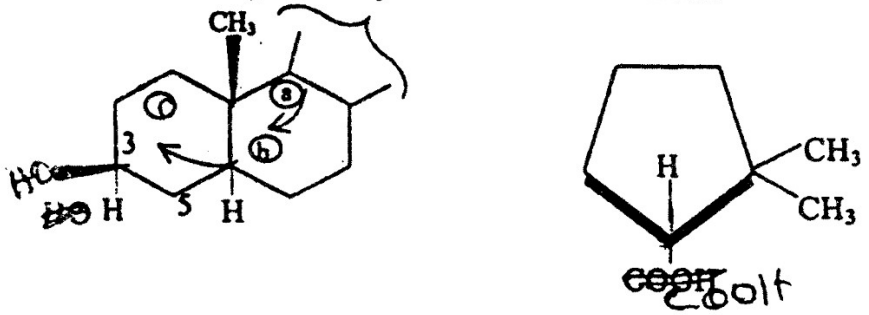
In tartaric acid, - COOH is preferred over – CHOH – COOH. The meso tartaric acid has the C_2 and C_3, opposite configuration so that the molecule is internally compensated. In trihydroxy glutaric acid the pseudo asymmetric centre has either R or S configuration in both the meso forms (e.g.)



In this example, the R takes precedence over the S configuration.

In cyclic molecules, the chiral centre is projected on the plane of the paper so that one of the group (reference group) lies above or below the plane, the other 3 groups being on the plane. The 3 groups are counted clockwise or anticlockwise as the case may be in the order of decreasing priority. The configuration could be R or S depending on the number and sign of the group which alternates according to the formula; 4B(+), 3B(-), 2B(+), IB (-) and 4F(-), 3F(-), 3F(+), 2F(-) and IF(+). If the particular reference group has (+) sign, the configuration arrived at is correct and (-) sign indicates that the configuration is just opposite to what is arrived at (e.g)

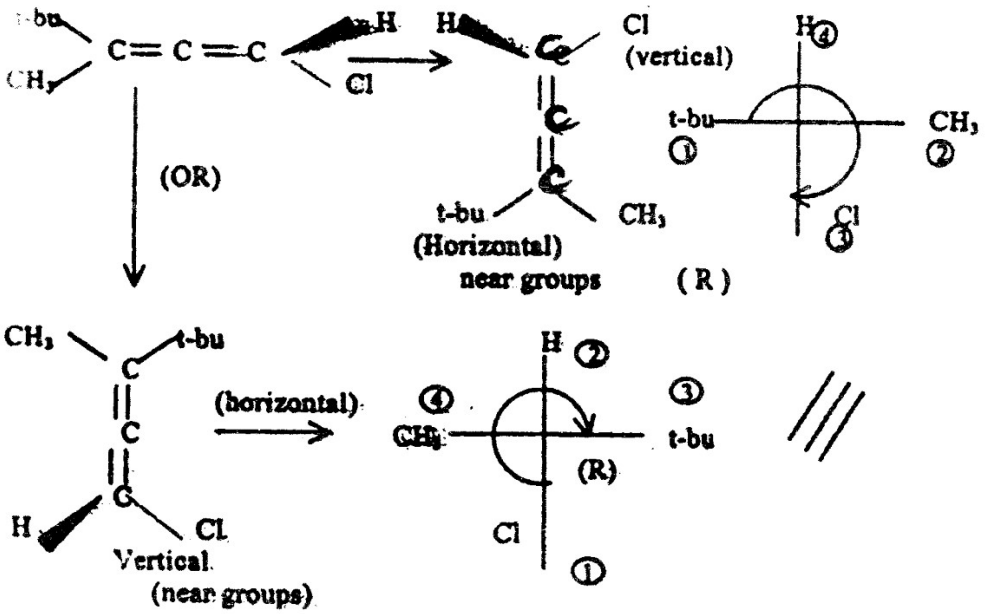
Consider the following steroidal system with three chiral centers.



1(R), 2,2 dimethyl cyclo pentane carboxylic acid

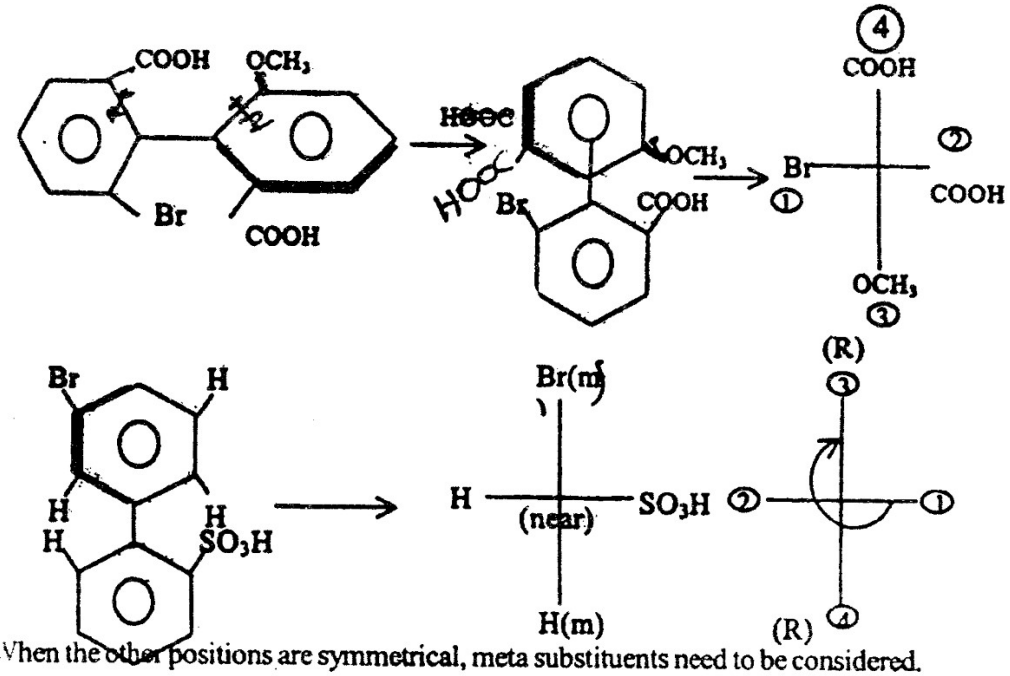
The angular CH_3 group may be taken as the reference group at C_{10} position. It is on the front of the plane and its number is 4F(-), the number 4 being the order of priority, and F for the front position. The other three groups are in a clockwise direction and the configuration must be R. but the sign being negative on the reference group 4F(-) the actual configuration of C_{10} is S. similar conclusion may be arrived at considering the C_3 and C_5 position, where the rear H – atom may be taken as the 4B(+) position. Accordingly the C_3 as well as C_5 have S configuration,. The cyclopentane carboxyloic acid has the COOH group clearly, below the place of the ring taking the priority number IB (-). Hence the configuration is R.

The configuration of the axially chiral molecules, allenes, spiranes & biphenyl could be fixed by holding the molecule vertically along the chiral axis so that two groups fall on the vertical plane and other two on the horizontal plane. Now either the vertical or the horizontal groups form the 'near groups' which precede over the 'far groups'.

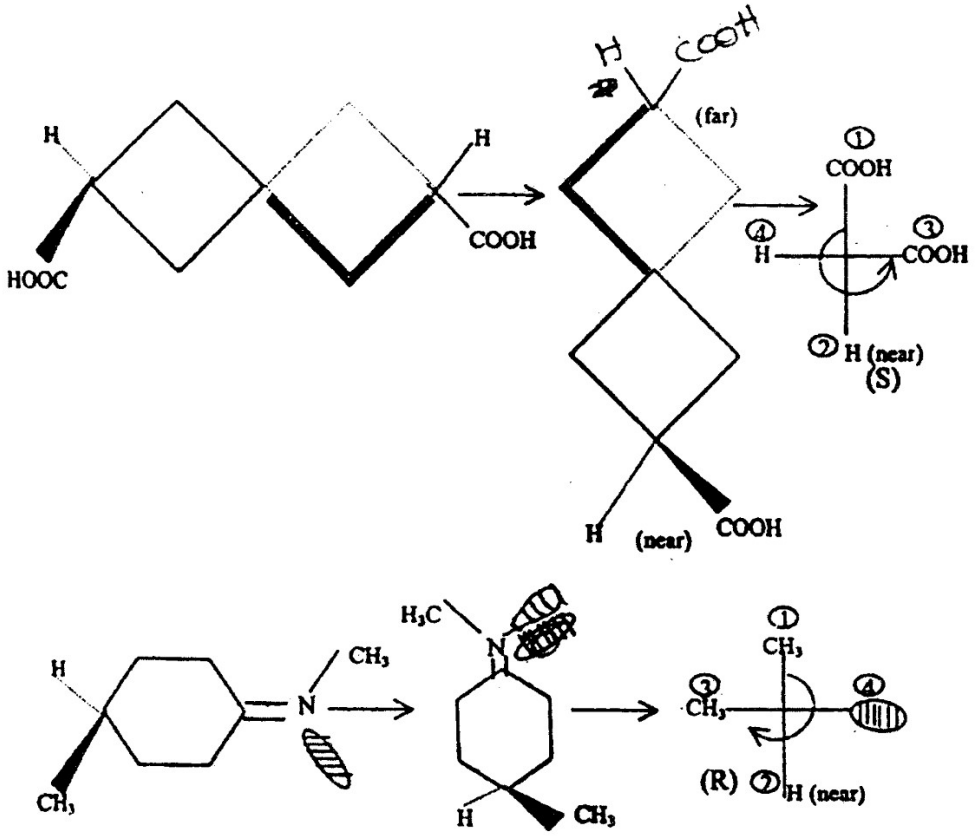


Among the vertical groups, that which is above the plane, form the top and that below the plane takes the bottom position is the Fischer projection. The priority is given to the near groups irrespective of the atomic number of the atoms concerned in the far groups. The least preferred group need not be considered for deciding the direction of rotation.

The spiranes and biphenyls are also projected vertically along the chiral axis and translated into



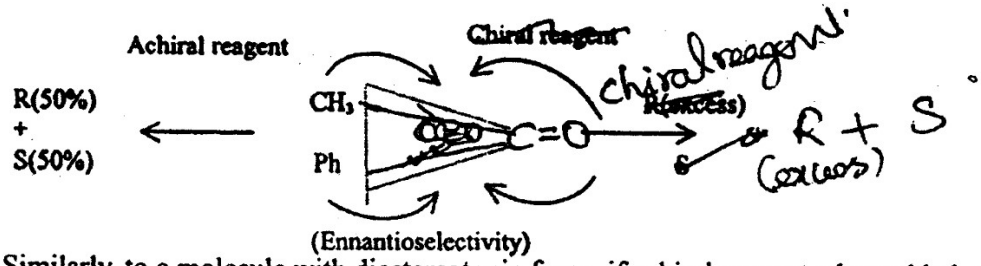
When the other positions are symmetrical, meta substituents need to be considered.



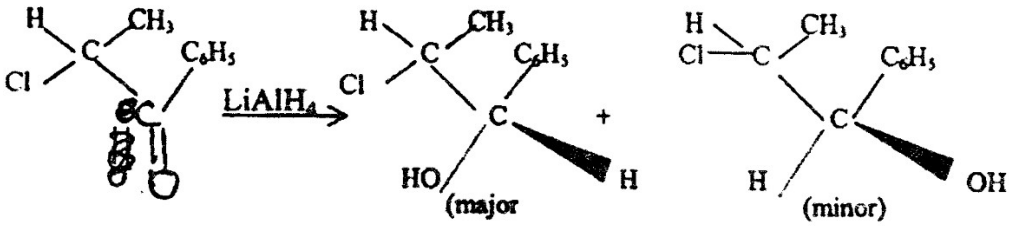
When the fourth substituent is absent, the lone pair over the atom may be considered, assigning least priority to the lone pair.

Stereoselectivity

The preferential formation of one of the stereoisomers selectively or exclusively in certain reactions, is termed stereo seolectivity. These reactions can be enantioselective or enantiotopic faces. (eg) When an achiral reagent is added to acetophenone the enantiomers are formed in equal quantities. But with a chiral reagent, the ketone gives rise to the formation of one of the enantiomers selectively (R Product Predominates). This is called enantionselectivity. It is due to the selective stabilization of one of the transition states, when asymmetry is introduced into the reaction system.



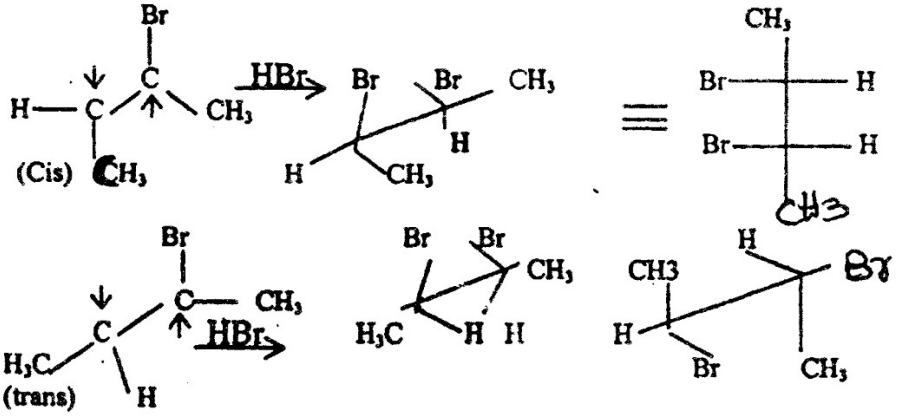
Similarly, to a molecule with diastereotopic faces, if achiral reagent when added, one of the diasteriosomers is formed exclusively or selectively. Since the molecule already has an asymmetric centre the two faces are no more symmetric and it results in the formation of one products selectively. This is called diastereoselectivity.



This an example for asymmetric induction, as a new asymmetric centre has been introduced or synthesized during the course of the reaction.

Stereospecificity

When stereochemically different starting materials give rise to stereochemically opposite products, the process is called stereospecific. For example the free radical addition of HBr to 2 – bromo -2 butene is stereospecific, since the cis-olefin gives the meso dibromide, whereas the trans olefin gives the (d,l) mixture.



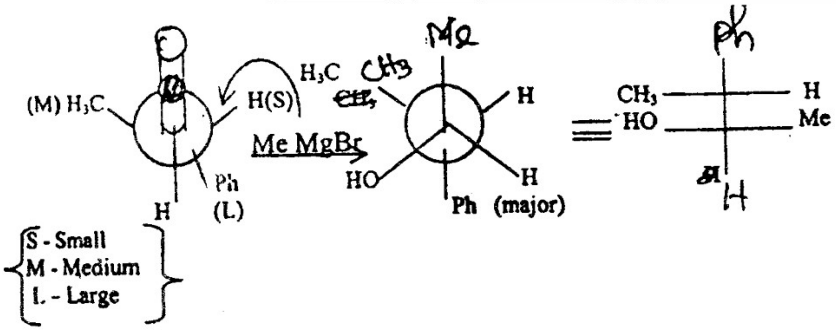
Similarly maleic acid on bromination gives a d,l - mixture whereas fumaric acid gives the meso form almost exclusively. It can also be observed that all these stereospecific processes are also stereoselective but the converse is not true.

Asymmetric Synthesis (Asymimetric Induction)

When an achiral reagent is added to a molecule with prochiral centre adjacent to an asymmetric centre, a pair of diastereoisomers is formed, of which one is found to be predominant. The diastereoisomers contain a new asymmetric centre, formed due to asymmetric induction by the existing asymmetric centre. This process of synthesis of an asymmetric centre in a molecule already containing a chiral centre is called asymmetric synthesis or asymmetric induction.

As already explained, the the process is highly stereoselective and the reason for the selectivity is offered by **Cram's rule**. According to this rule, when the existing asymmetric centre is so oriented that the prochiral carbonyl group is flanked between the smaller groups (M & S), the attacking nucleophile preferentially approaches the carbonyl group from the side of least resistance (S Side). However, when the reaction centre is much away from the chiral centre, the ratio of the products in nearing only.

Consider the grignard addition to the following aldehyde, by the Crams Open Chain Model.



Validity of Rule:

1. The rule is applicable only to reactions which are kinetically controlled (e.g)In he MPV reduction of a chiral ketone, the initial product formed is rate controlled and as predicted by the Cram's rule, but the subsequent product formed is thermodynamic controlled and the one not predicted by Cram's rule.

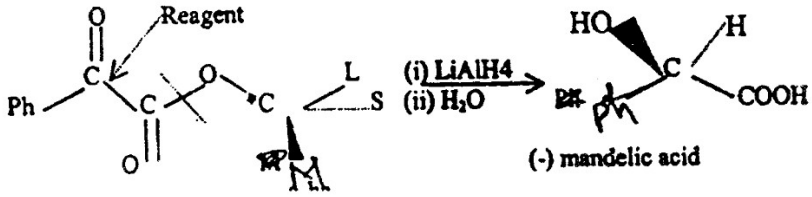
2. The rule does not apply to catalytic reduction and reactions where the small group(S) is OH, OR, NH_2 etc.

Application of C: am's Rule

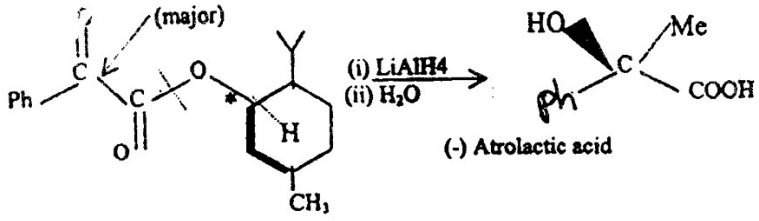
The relative configuration of the predominant, product is easily predicted by the Cram's rule, using an arbitrary model.

Prelog's Rule.

Another asymmetric synthesis of greater interest, is the reductive hydrolysis of (-) menthylphenylglyoxylate giving (-) mandelic acid, as the predominant isomer. Reduction is performed using Na/Hg, Lithium Aluminium hydride or sodium borohydride. This stereoselectivity is explained in terms of Prelog's rule, which specifies the orientation of various group in the molecule. According to one convention, the two carbonyl group in the phenylglyoxylate are written with an antiperiplanar symmetry, the largest group in the asymmetric alcohol (- Menthol) eclipsing the ketonic carbonyl group while the smallest group is at the back of the plane and the medium group projecting to the front. Now the attacking reagent enters through the side of minimum resistance (ie), along the side of the smallest group, as represented below.



Prelog's rule has very successfully predicated the major product and assigned its configuration also. Similar to the configuration of (-) mandelic acid, that of (-) Atrolactic acid has been established using Grignard addition on (-) menthylglyoxylate.

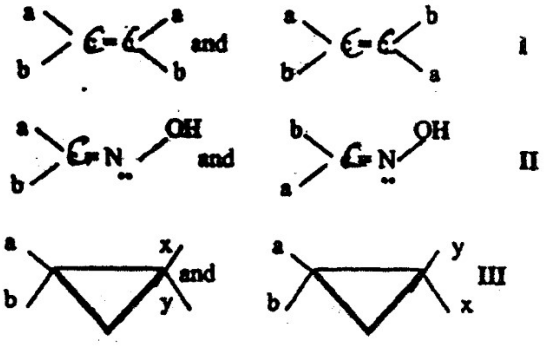


Since (-) atrolactic acid has been isolated a the major product, the configuration of the molecule should be as explained by the Prelog's rule. This method of configurational assignment has made possible the determination of absolute configuration in a number of molecules.

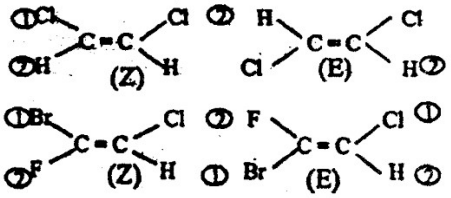
E – Z Normenclature of Geometrical Geometrical Isomers

Geometrical isomers constitute the other class of stercosomers which arise due to total restriction of rotation mostly around a C = C or C – N in acyclic system and rigidity of the geometry in cyclic systems.

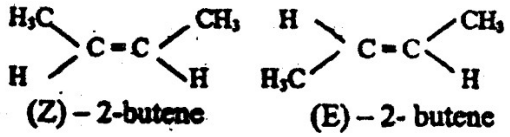
Such systems give rise to two different modifications of the groups around the rigid part of the system (e.a)



The older system of momenclature of these geometrical isomers viz. trans forms, hold good as long as the groups are of the type as in I, where identical groups are attached across the rigid part of the molecule. The system fails when the groups are non – identical as in III. Hence a common system of nomenclature based on the CIP system, has been evolved. Under this system, the two groups on each carbon (Nitrogen) across the rigid bond, are assigned the priority based on the sequence rules. The two highly preferred groups when they occupy the same side of the rigid bond, the arrangement is called 'Z' the when opposite to each other it is 'E' form.

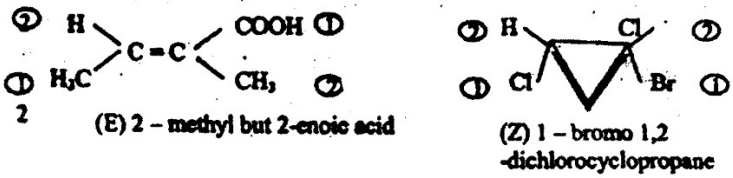


(Z4 = "Zusammen" means together E = "Entgegeu" means opposite (or) trans Both are derived from germn) the cis and trans 2 – butanes are now designated as:



(Z) – 2-butene **(E) – 2- butene**

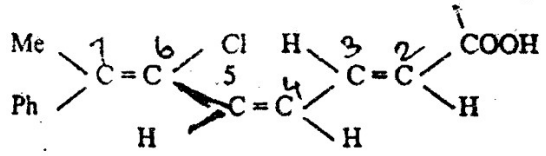
A cis isomer need not always have an Z configuration and a trans form, an E–configuration. e.g.



(E) 2 – methyl but 2-enoic acid

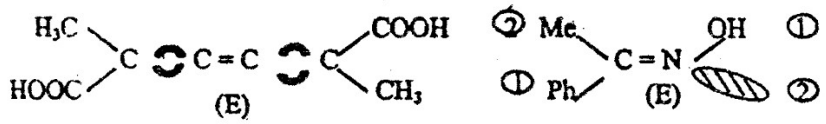
(Z) 1 – bromo 1,2 -dichlorocyclopropane

In molecules with more than one C = C bonds, the configuration of each must be assigned separately.



7-phenylocta - 2E, 4Z, 6E -- trienoic acid.

Cumulenes (with odd number of double bonds) as well as oximes could be designated as under.

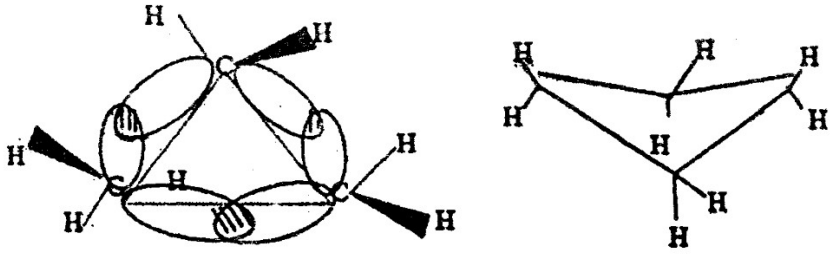


Phenylmethylketoxime

Conformational Analysis

According to Baeyer's strain theory the 3 & 4 membered rings are subject to maximum strain and are unstable as seen from the maximum heat of compared to any other ring system (38.6 & 27.2KJ) per mole of (CH_2). The 5 and 6 membered rings have minimum strain have high angle strain but have only smaller value for their heat of combustion. This contradictory behaviour could not be explained, hence the Baeyers strain theory had to be abandoned. This is because Baeyer failed to see the planar and puckered conformations of these ring systems.

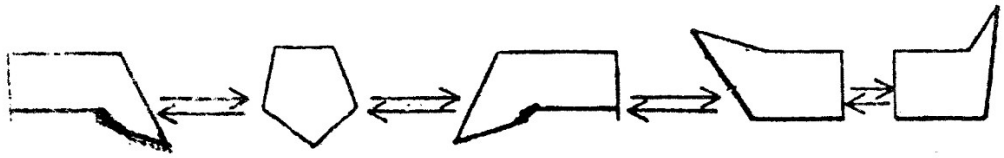
In cyclopropane, the C – C bonds do not lie along the lines connecting the carbon atoms but they fall outside the triangular lines, giving rise to bent bonds. In cyclobutane, the internuclear angles are not as small as in cyclopropane and the C – C bonds are not so bent, hence it has less strain per bond.



Conformations of cyclopropane and cyclobutane

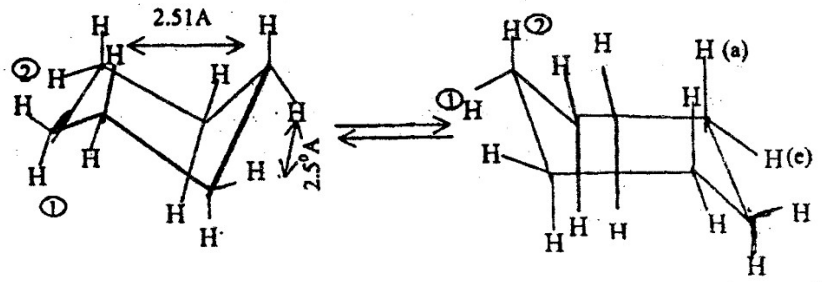
Hence cyclopropane framework has a planar structure, but cyclobutane exists in a non – planar conformation in which one of the methylene groups is bent at an angle of 25° from the plane of the other 3 methylene groups.

The actual structure of cyclopentane, is 'envelope' shaped, where one of the methylene groups is staggered out of plane. But twisting about the various C – C bonds, successive conformations are possible.

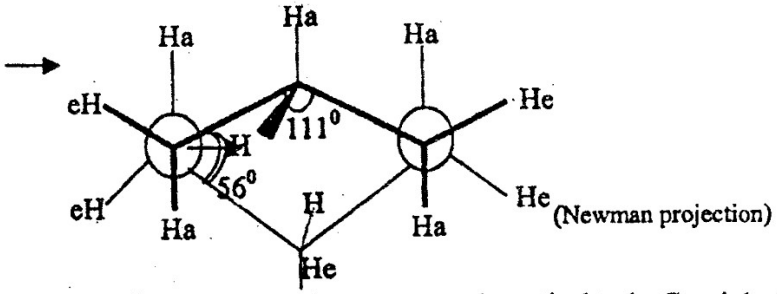


Conformation of Cyclohexane

It was first proposed by sachse that cyclohexane could exist in two non – planar conformations in which the bond angles are almost normal and free from Baeyer's strain. One of these forms is somewhat rigid in the chair like form and the other is more flexible boat form.

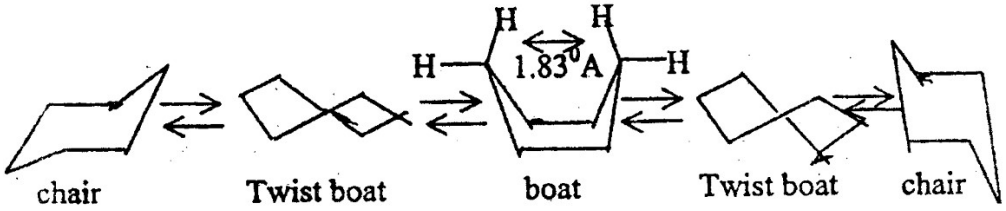


However, each of these two forms could flip over to at least two more forms of identical or almost identical energy. This one chair form rapidly gets converted to the other, the flipping taking place rapidly at room temperature when the axial bonds become equatorial and vice versa ($H_1 \rightarrow H_2$ and $H_2 \rightarrow H_1$). The dihedral angle is 56°.



and the C-C-C bond angle is 111°. The axial bonds are not exactly vertical to the C_3 axis but leaning away outwards by 7°.

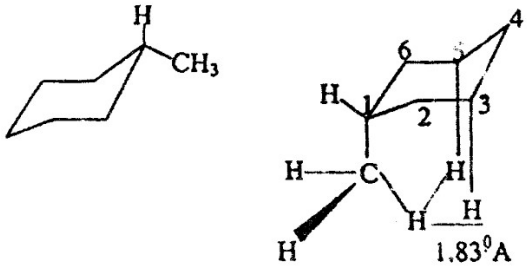
One of the chair forms can also flip over to the boat form before being converted to the other chair form.



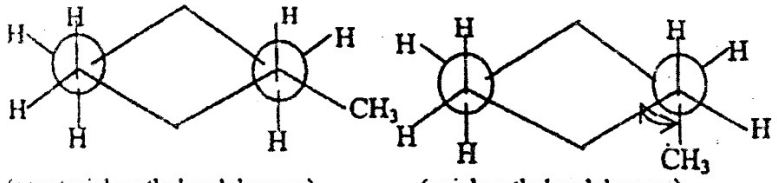
As seen from the proximity of the two 'flag pole' hydrogens in the boat form at the 1,3 – carbon atoms the boat conformation is less stable compared to the chair form by 6.5 k.cal/mol due to the flag pole interaction. The X – ray diffraction studies also show that cyclohexane exists mostly in the chair form, to the extent of 99.9% at equilibrium.

Monosubstituted Cyelohexanes

They exist in two non – equivalent distereoisomeric chair conformation where the substitutent takes either the axial or equatorial position. (c.a) In methyl cyclohexane, the axial conformation suffers from several unfavourable interactions.



There are two 1,3 diaxial interactions, due to the presence of C -H and C -H at an equidistance of 1.83° A which is much less than the 2.51° A in the cyclohexane. Moreover the axial isomer has two additional gauche butane interactions,

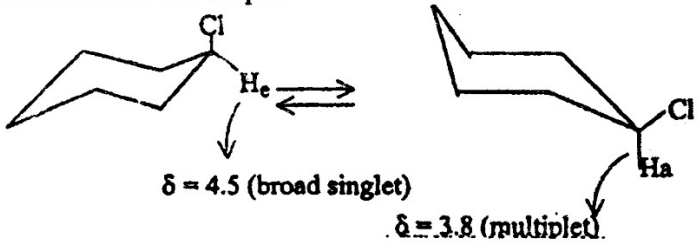


(equatorial methylcyclohexane) (axial methylcyclohexane)

in addtion to the normal gauche butane interactiosn present in the equatorial form. Hence the axial conformer is less populated (<5%) in the equilibrium mixture. For this reason, t-butyl, phenyl and isopropyl, and isopropyl chelohexanes get locked in the equatorial form, andtheir conformation free energies (- ΔG°) are very high (20.00, 12.6 and 9.00 respectively) compared to 7.5 KJ per mole in the methyl derivative. However, a few monosubstituted cyclohexanes exist in the axial form also since the energy difference between the axial & equatorial conformations is not much.

Characterisation and Separation of Conformers

In chloro, bromo Iodo, hydroxyl derivatives, a considerable proportion of the axial form is expected as seen from the NMR studies of these conformers. Normally below - 100°C the interconversion is restricted and the axial and equatorial protons give different signals. The axial hydrogen undergoes coupling with adjacent protons and forms a multiplet



The halflife of the equatorial chlorocyclohexane is a function of temperature as it has a halflife of 22 yrs at – 160°, but at 25°C, 10^{-5} sec. At – 150° the equatorial form crystallizers leaving the axial form in the mother liquor.

Disubstituted Cyclohexanes

When two substituents are attached to the ring it can be done in four different ways. (ie) 1,1 1,2 1,3 and 1,4 substitutions.

1.1 - Disubstitution

This will not lead to any configurational isomerism, but two interconvertibe conformers are formed only if the two substituents are different as in I – methyl cyclohexanol. The preferred conformer is the one with the bulkier CH_3 group at the equatorial position, and the conformers are in the ratio 70:30, in DMSO.