ORGANIC CHEMISTRY-I

M.Sc. CHEMISTRY

SEMESTER-I, PAPER-II

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M.Sc. CHEMISTRY: ORGANIC CHEMISTRY-I

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FOREWORD

Since its establishment in 1976, Acharya Nagarjuna University has been forging ahead in the path of progress and dynamism, offering a variety of courses and research contributions. I am extremely happy that by gaining 'A+' grade from the NAAC in the year 2024, Acharya Nagarjuna University is offering educational opportunities at the UG, PG levels apart from research degrees to students from over 221 affiliated colleges spread over the two districts of Guntur and Prakasam.

The University has also started the Centre for Distance Education in 2003-04 with the aim of taking higher education to the door step of all the sectors of the society. The centre will be a great help to those who cannot join in colleges, those who cannot afford the exorbitant fees as regular students, and even to housewives desirous of pursuing higher studies. Acharya Nagarjuna University has started offering B.Sc., B.A., B.B.A., and B.Com courses at the Degree level and M.A., M.Com., M.Sc., M.B.A., and L.L.M., courses at the PG level from the academic year 2003-2004 onwards.

To facilitate easier understanding by students studying through the distance mode, these self-instruction materials have been prepared by eminent and experienced teachers. The lessons have been drafted with great care and expertise in the stipulated time by these teachers. Constructive ideas and scholarly suggestions are welcome from students and teachers involved respectively. Such ideas will be incorporated for the greater efficacy of this distance mode of education. For clarification of doubts and feedback, weekly classes and contact classes will be arranged at the UG and PG levels respectively.

It is my aim that students getting higher education through the Centre for Distance Education should improve their qualification, have better employment opportunities and in turn be part of country's progress. It is my fond desire that in the years to come, the Centre for Distance Education will go from strength to strength in the form of new courses and by catering to larger number of people. My congratulations to all the Directors, Academic Coordinators, Editors and Lesson-writers of the Centre who have helped in these endeavors.

Prof. K. Gangadhara Rao
M.Tech., Ph.D.,
Vice-Chancellor I/c
Acharya Nagarjuna University.

M.Sc. CHEMISTRY

SEMESTER-I, PAPER-II

102CH24 - ORGANIC CHEMISTRY-I

SYLLABUS

Learning Objectives:

- ✓ To Know about Aromaticity in Benenoid compounds and Non-Benzenoid compounds.
- ✓ To know about basics on heterocyclic compounds, their synthesis and importance.
- ✓ To know the importance of natural products, their medicinal use.
- ✓ To know particularly about terpenoids and their classification and synthesis.
- ✓ To discuss stereochemistry more elaborately.
- ✓ To know about the conformations of acyclic, monocyclic and fused ring systems.

UNIT-I

Aromaticity Benzenoid & Non-Benzenoid: Concept of aromaticity, Huckel's rule for aromaticity in benzenoid compounds, Aromaticity of five membered, six membered rings and fused systems.

Non Benzonoid Aromatic Compounds: Cyclopropenyl cation, Cyclobutadienyl dication, cyclopentadienyl anion, tropyllium cation and cyclooctatetraenyl dianion. Ferrocene. Azulenes, Fulvenes, Annulenes, Fullerenes. Homo aromaticity, and Anti aromaticity.

UNIT-II

Heterocyclic Compounds and Natural Products:

a) Synthesis, Properties and Reactions of furan, thiophene, pyrrole, pyridine, quinoline, isoquinoline and indole; Skraup synthesis, Fisher indole synthesis.

b) Heterocyclic compounds more than one hetero atom-: synthesis, properties and reactions of Pyrazole, Imidazole, Oxazole Iso-Oxazole, Thiazole.

Natural Products: Importance of natural products as drugs.

Terpenoids: General methods in the structure determination of terpenes. Isoprene rule. Structure determination and synthesis of a-terpeniol, B-carotene, and camphor.

UNIT-III

Stereochemistry:

a) Molecular representations of organic molecules - Wedge, Fischer, Newman and Saw-horse formulae, their description and inter-conservation. Stereoisomerism-Definition, classification.

b) Concept of Chirality and Molecular Symmetry: Symmetry operations, Recognition of symmetry elements (Cn, Ci and Sn), Dissymmetric and asymmetric molecules. Chiral structures (one and more than one chiral centers); D-L and R-S nomenciature, diastereoisomerism; Threo and Erythro isomers, Racemic mixture, racemization and methods of resolution, stereo specific and stereoselective synthesis. Stereochemistry of compounds containing nitrogen, sulphur and phosphorous.

c) Geometrical isomerism-E, Z - nomenclature-Spectral and chemical methods of determining the configuration of geometrical isomers. Determination of configuration in aldoximes and ketoximes.

UNIT-IV

Conformational Analysis-I

a) Conformation of acyclic molecules - alkanes and substituted alkanes (Ethane and 1,2-disubstituted ethane derivatives like butane, dihalobutane halohydrin, ethylene glycol, butane-2,3-diol, amino alcohols and 1,1,2,2-tetrahalobutanes). Klyne-Prelog terminology for conformers and torsion angles.

b) Factors affecting the conformational stability and conformation equilibrium - Attractive and Repulsive interactions. Use of Physical and Spectral methods in conformational analysis.

c) Conformational effects on the stability and reactivity of diastereomers in cyclic molecules - steric and stereo electronic factors-examples.

UNIT-V

Conformational Analysis-II

a) Conformations of monocyclic compounds - cyclohexane-chair, boat and twist boat cyclohexanes, energy profile diagram-mono-and di-substituted cyclohexanes - conformations. Effect of conformation on stability and reactivity in mono and disubstituted cyclohexane derivatives.

b) Conformations of unsaturated acyclic compounds: Propylene, and 1-Butene

c) Elementary treatment of fused and bridged ring systems - Decalines and Bornanes. Conformation of sugars. Steric strain due to unavoidable crowding.

Reference Books:

1) Advanced organic chemistry - reaction, mechanism and structure, Jerry March, John Wiley.

2) Advanced organic chemistry, F.A. Carey and R.J. Sundberg, Plenum.

3) A guide book to Mechanism in organic chemistry, Peter Sykes, Longman.
4) Organic chemistry, I.L.Finar, Vol. I & II, Fifth ed. ELBS, 1975.
5) Organic chemistry, Hendrickson, Cram and Hammond (Mc Graw-Hill).
6) Stereo Chemistry of carbon compounds - E.L. Eliel.
7) Modern organic Reactions, H.O. House, Benjamin.
8) An introduction to chemistry of Heterocyclic compounds, R.M.Acheson.
9) Structure and mechanism in organic chemistry, C.K.Ingold, Cornell University Press.
10) Principles of organic synthesis, R.O.C.Norman and J.M.Coxon, Blakie Academic & Professional.
11) Reaction Mechanism in Organic Chemistry, S.M.Mukherji and S.P.Singh, Macmillan.
12) Basic Principles of Organic Chemistry by J. B. Roberts and M. Caserio.
13) Stereo Chemistry of Organic compounds, P. S. Kalsi, New Age International pubs.

Learning Outcomes:

- Students can able to understand aromaticity in Benenoid compounds and Non-Benzenoid compounds.
- Students are able to understand formation of various heterocyclic compounds and their synthesis and importance.
- Students can understand the importance of natural products in medicinal chemistry
- Students can able to write the stereo chemical forms for different organic molecules.
- Understand the conformations of acyclic, monocyclic and fused ring systems and applying it to organic compounds.

ACHARYA NAGARJUNA UNIVERSITY: CENTRE FOR DISTANCE EDUCATION

M.Sc. – Chemistry - Program code: 04

Program Structure

Program code	Program	Internal assessment	External exams	Max. Marks	credits
SEMISTER 1					
101CH24	Inorganic Chemistry-I	30	70	100	4
102CH24	Organic Chemistry-I	30	70	100	4
103CH24	Foundation for Chemistry	30	70	100	4
104CH24	Physical Chemistry-I	30	70	100	4
105CH24	Inorganic & Physical Chemistry **Practical-I**	30	70	100	4
106CH 24	Organic Chemistry **Practical-II**	30	70	100	4
SEMISTER 2					
201CH24	Physical Chemistry-II	30	70	100	4
202CH24	Organic Chemistry-II	30	70	100	4
203CH24	Essential Lab Techniques for Industry	30	70	100	4
204CH24	Inorganic Chemistry-II	30	70	100	4
205CH24	Inorganic & Physical Chemistry **Practical-I**	30	70	100	4
206CH24	Organic Chemistry **Practical-II**	30	70	100	4
SEMISTER 3					
301CH24	Applied Inorganic Analysis	30	70	100	4
302CH24	Analysis of Applied Industrial Products	30	70	100	4
303CH24	Optical Thermal & Radiochemical Methods of Analysis	30	70	100	4
304CH24	Principles and Techniques in Classical Analysis	30	70	100	4
305CH24	Classical Methods of Analysis **Practical-I**	30	70	100	4
306CH24	Instrumental Methods of Analysis **Practical-II**	30	70	100	4
SEMISTER 4					
401CH24	Advanced Methods of Analysis	30	70	100	4
402CH24	Analysis of Drugs, Foods, Diary Products & Biochemical Analysis	30	70	100	4
403CH24	Separation Techniques & Electro Analytical Techniques	30	70	100	4
404CH24	Environmental Chemistry & Analysis	30	70	100	4
405CH24	Classical & Instrumental Methods of Analysis **Practical-I**	30	70	100	4
406CH24	Spectral Problems **Practical-II**	30	70	100	4

(102CH24)

M.Sc. DEGREE EXAMINATION, MODEL QUESTION PAPER
M.Sc. CHEMISTRY - FIRST SEMESTER
PAPER-II: ORGANIC CHEMISTRY-I

Time: Three Hours **Maximum: 70 Marks**

UNIT-I

1 a) Define aromaticity and explain Hückel's rule with suitable examples. **[4]**

or

b) Differentiate between homoaromaticity and antiaromaticity with examples.

2 a) Discuss the concept of aromaticity in five-membered and six-membered rings. Explain with examples how fused systems exhibit aromaticity. **[10]**

or

b) Write a detailed account on non-benzenoid aromatic compounds with special reference to cyclopropenyl cation, tropyllium cation, and ferrocene.

UNIT-II

3 (a) Write short notes on Skraup synthesis and Fischer indole synthesis. **[4]**

or

(b) Explain the isoprene rule with examples from terpenoids.

4 (a) Discuss the synthesis, properties, and reactions of pyrrole, furan, and thiophene. Compare their aromatic character. **[10]**

or

(b) Write a detailed account on the importance of natural products as drugs. Discuss the structure determination and synthesis of camphor.

UNIT-III

5 (a) Explain the interconversion of Wedge, Fischer, Newman, and Saw-horse formulae with examples. **[4]**

or

(b) Differentiate between D-L and R-S nomenclature with suitable examples.

6 a) Discuss the concept of chirality and molecular symmetry. Explain the recognition of symmetry elements with examples. **[10]**

or

b) Elaborate on methods of resolution of racemic mixtures. Discuss stereospecific and stereoselective synthesis with examples.

UNIT-IV

7 a) Explain Klyne-Prelog terminology for conformers and torsion angles. **[4]**

or

b) Describe the factors affecting conformational stability in substituted ethanes.

8 a) Discuss the conformations of alkanes and substituted alkanes with special reference to ethane and 1,2-disubstituted ethane derivatives. **[10]**

or

b) Elaborate on the use of physical and spectral methods in conformational analysis. Explain with examples.

UNIT-V

9 a) Explain the conformations of cyclohexane with energy profile diagram. **[4]**

or

b) Describe the conformations of unsaturated acyclic compounds with examples.

10 a) Discuss the conformations of mono substituted cyclohexanes. Explain the effect of conformation on stability and reactivity. **[10]**

or

b) Elaborate on the conformational analysis of fused and bridged ring systems with special reference to decalines and bornanes.

CONTENTS

LESSON – 1

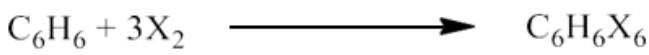
CONCEPT OF AROMATICITY

1.1 INTRODUCTION OF AROMATICITY:

The molecular formula of benzene has been found to be C_6H_6 from elemental analysis and molecular weight determination methods. Since the carbon to hydrogen ratio in this compound ismuch less than the corresponding alkane C_6H_{14}, it is expected to be highly unsaturated and should undergo addition reactions like alkenes & alkynes.

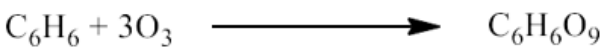
Following reactions show the presence of three double bonds and six membered carbocyclic rings.

- It adds three moles of halogen forming benzene hexachloride.



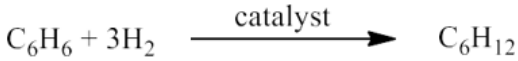
$$C_6H_6 + 3X_2 \longrightarrow C_6H_6X_6$$

- It forms atriozonide on ozonolysis.



$$C_6H_6 + 3O_3 \longrightarrow C_6H_6O_9$$

- It can be hydrogenated catalytically with three moles of hydrogen to yield cyclohexane.



$$C_6H_6 + 3H_2 \xrightarrow{\text{catalyst}} C_6H_{12}$$

Further studies have showed that the three double bonds of benzene are different from the ordinary double bonds and have a special type of arrangement which is responsible for "unusual" stability of this molecule. The high degree of stability of benzene molecule can be understood from the following facts.

a) Benzene remains unaffected on treatment with potassium permanganate under usual conditions.

b) In the presence of some suitable catalysts, it undergoes electrophilic substitution reactions rather than addition reactions like nitration, sulphonation, halogenation & Friedal Craft's reactions.

c) Halogen acid fails to add to the molecule of benzene.

Further benzene form only one mono-substituted and three di-substituted products. Inorder to account all these properties, the concept of "Aromaticity" has been introduced.

A most significant feature of benzene and other compounds containing this ring system or behave like benzene is that they are more stable in comparison to the corresponding acyclic polyenes. Such compounds possess large resonance energies and are called Aromatics. The extra stability of such compounds is ascribed to a special property referred to as Aromatic character or Aromaticity.

Originally the term Aromatic (or Aromaticity) was coined for odiferous compounds and referred to a classification of organic compounds based on the physiological property of odour. Many of these compounds resemble benzene in their chemical behavior particularly in undergoing substitution reactions despite of unsaturation in the molecule and are said to exhibit aromatic character or Aromaticity.

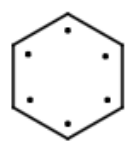
The term Aromaticity was used to describe all compounds that possessed the properties of Benzene. From the survey of literature, it has been found that the term Aromaticity is very elastic and no one complete or concrete definition was not given so far. Different meaning & definitions have been given various workers.

- Elidge and Jacks on defined an aromatic compound is one which contains an induced ring current.
- Badger defined aromatic compounds as those cyclic compounds which have large resonance energy and where all the annular atoms take part in a single conjugated system.

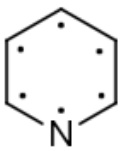
However certain theories are put forward to explain abnormal properties of several compounds called aromatics.

1.2 AROMATIC SEXTET THEORY (ROBINSON, 1925):

According to this theory, benzene ringh as six electrons more than required to link together the six carbon atoms. The six electrons, one contributed by each carbon atom, form a closed group commonly named as aromatic sextet. This aromatic sextet is responsible for the aromatic properties of benzene.



Benzene



Pyridine

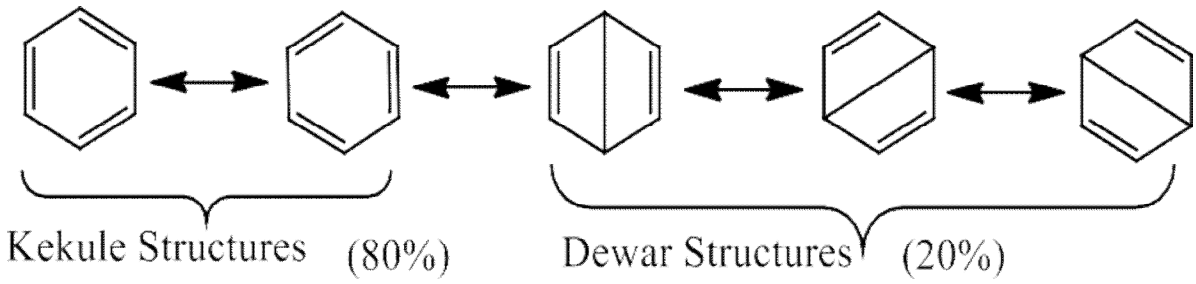
Furan

As this closed group of electrons is not possible in aliphatic and alicyclic compounds, they behave normally i.e. they easily undergo addition reactions. On the other hand, as thearomatic sextet is possible in heterocyclic compounds, they also exhibit aromatic properties.

1.2.1 Valence Bond Theory:

The Valence Bond Theory is based on the X-Ray analysis of benzene which revealed that all six hydrogen atoms of benzene lie in the same plane of the ring i.e. the benzene ring is planar, each C- C-H valency angle is 120^o and all C-C bond lengths are same viz. 1.397 A^o which is midway value between a single and double bond lengths.

This can only explain in terms of resonance due to which every C-C bond in benzene is neither single nor double.

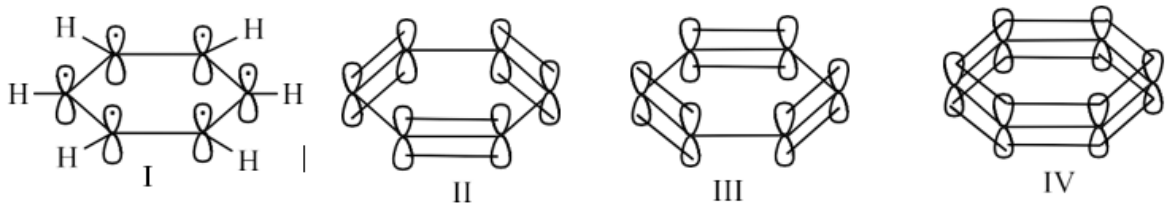


Due to the resonance, benzene molecule is stabilized as indicated by its high resonance energy (36 Kcal/mole) value which is much larger than the resonance energy (<5Kcal/mole) of open chain conjugated dienes. Similarly, Pyridine, Pyrrole etc. possess resonance energy of about 25 Kcal/mole.

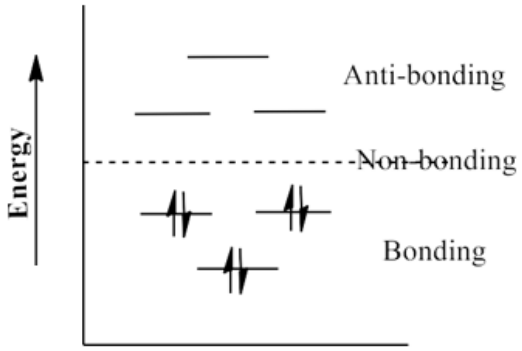
1.2.2 Molecular Orbital Theory:

Benzene is a regular flat hexagon in which all carbon atoms are in SP^2 hybridization. Hence in benzene every carbon atom forms three 'σ' bonds among which one is with 'H' atom and remaining two with adjacent 'C' atoms.

Each carbon atom yet contains un-hybridized 2Pz orbital with single electron; these are all parallel and perpendicular to the plane of ring (I). These can be overlapping in two ways, both being equally good (II & III).Each 2Pz orbital however, overlaps with its neighbors equally and therefore all six can be treated as forming a molecular orbital (IV) covering all six 'C' atoms, and so are completely delocalized.



Since six 2Pz orbitals are involved, six molecular orbitals are possible, among them three are bonding and three are anti-bonding. The arrangement of six molecular orbitals is like that, there is one molecular orbital of lowest energy which is followed by degenerate pairs of molecular orbitals in the increasing order of energy. There is one molecular orbital of highest energy. Electrons enter into these orbitals strictly according to Hund's Rule. So, in the ground state the six electrons (2Pz) of benzene will occupy the bonding molecular orbitals doubly. So, the molecule has a closed shell electronic configuration and will exhibit aromatic character.



Prof. V. Madhava Rao

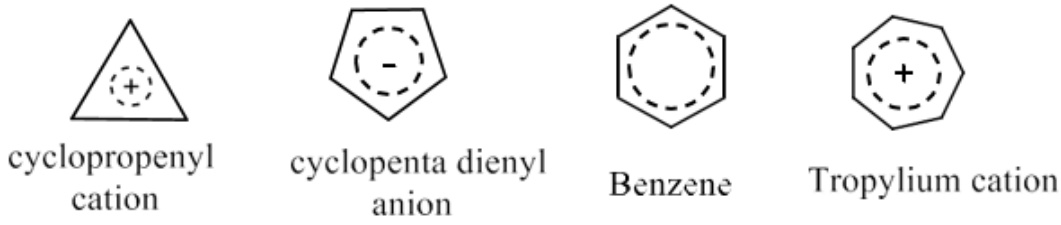
LESSON - 2

HUCKEL'S RULE FOR AROMATICITY

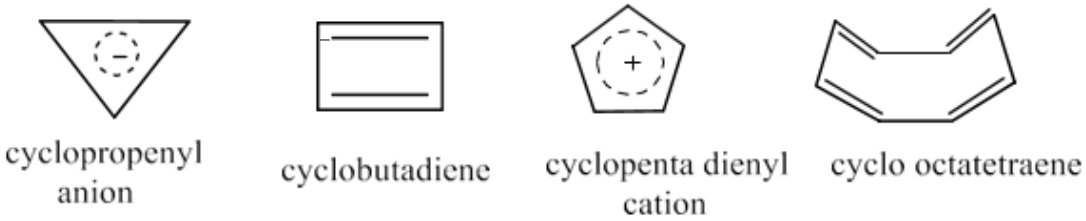
2.1 HUCKEL'S RULE (4N+2) Π RULE:

On the basis of molecular orbital calculations, Huckel in 1937 suggested that only those planar cyclic systems having conjugated double bonds display aromatic character, only if they contain **(4n+2) π** electrons. Where 'n' is an integer and may be 0, 1, 2, 3 etc.

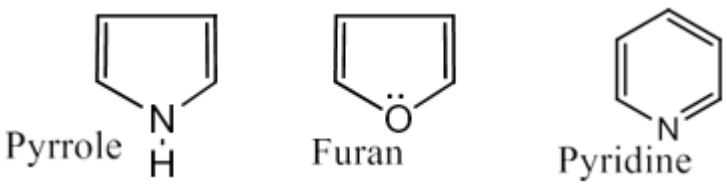
Thus, for a molecule to be aromatic, it must have **(4n+2) π** electrons i.e. 2 (n=0); 6 (n=1); 10 (n=2); 14 (n=3) etc. Pi **(π)** electrons quite ignoring the number of carbon atoms in the ring. Thus, the following entities which conform the **(4n+2) π** electrons rule are relatively stable and behave like aromatic compounds.



In marked contrast to the above examples, it has not been possible to demonstrate the stable existence of the following compounds, because they do not contain **(4n+2) π** electrons.



Huckel rule may be extended to the heterocyclic compounds as they contain planar structure with 6 π electrons.



Thus, in short, the Huckel rule states that fully conjugated, cyclic planar, polyene species possessing (4n+2) π electrons may have special aromatic stability.

So, an aromatic compound is characterized by the following facts.

i) It must be a planar cyclic molecule.

ii) Its conjugate dpi-bonds must be in delocalization.

iii) It must have a high resonance energy.

iv) Its number of pi-electrons must follow Huckel rule, $(4n+2)\ \pi$ electrons.

v) Aromatic compound preferably undergoes electrophilic substitution reactions rather than addition reactions.

2.1.1 Classification:

Mainly there are three classes of aromatic compounds.

a) Benzenoid aromatic compounds which contain at least one benzene ring.

b) Non-benzenoid aromatic compounds which possess planar cyclic carbon skeleton other than that of benzenoid type.

c) Heterocyclic compounds which similar to benzene.

2.2 AROMATICITY IN BENZENOID COMPOUNDS:

The compounds which contain benzene ring in their structure are called Benzenoid compounds.

Benzene and other organic compounds which resemble benzene in certain characteristic properties are called aromatic compounds. These properties are called aromatic properties which are as follows:

Unusual Stability: Aromatic compounds are highly stable due to the low heats of hydrogenation and low heats of combustion.

Substitution rather than Addition Reactions: Aromatic compounds although possess double bonds, they do not undergo addition reactions. But they undergo electrophilic substitutions like nitration, sulphonation etc.

Resistent to Oxidation:

These compounds are resistent to oxidation by aq. $KMnO_4$ and mild oxidising agents.

Cyclic Flat Molecules:

These compounds generally contain six membered rings and are found to be cyclic flat structures.

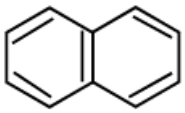
On the basis of molecular orbital treatment aromatic compounds must full fill the following requirements. i. It must have cyclic clouds of delocalized πelectrons above and below the plane of the molecule.

These compounds must contain a total of $(4n + 2)\pi$ electrons, where 'n' is an integer. This rule is known as Huckel rule. Thus, according to Huckel rule, the no. of π electrons in an aromatic compound may be 2, 6, 10, 12 etc.

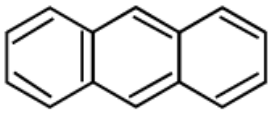
n = 1

Benzene $4n + 2 = 4 + 2 = 6\,\pi$ electrons.

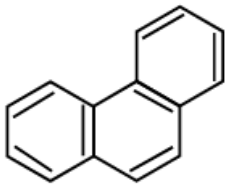
In systems of fused six membered aromatic rings. They obey Huckel's rule which can be shown as follows



Napthalein
n = 2
$4n + 2 = 10\,\pi e^-$



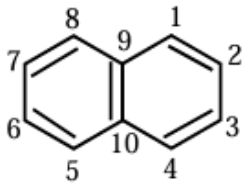
Anthracene
n = 3
$4n + 2 = 14\,\pi e^-$



Phenanthrene
n = 3
$4n + 2 = 14\,\pi e^-$

All these compounds follow the Huckel's rule and are aromatic.

In these systems, the principal canonical forms are usually not all equivalent.



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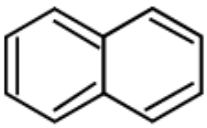
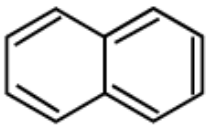


(II)

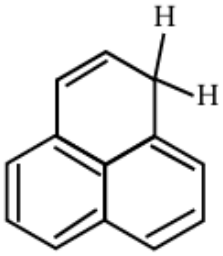


(III)

In the above examples I has a central double bond and different from II and III which are equivalent to each other. Molecular orbital calculations shows that bond orders and bond distances between 1, 2 & 2, 3 bonds are different. This non equivalency of bonds called partial bond fixation is found in nearly all fused aromatic systems.

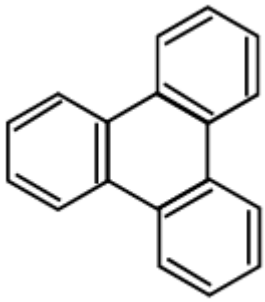
The resonance energies of the fused systems increase as the number of principal canonical forms increases. Resonance energies for fused systems can be estimated by counting canonical forms.

Not all the fused systems can be fully aromatic.



Phenalene

In a fused system there are not six electrons for each ring. In Naphthalene one of the ring has 6π electrons and other has four, and hence one is aromatic system and other resembles butadiene system. As a result of this the reactivity of the compound increases and this effect becomes extreme in case of triphenylene.



Triphenylene

In this compound there are 18π electrons which were distributed so as to give each of the outer rings a sextet, while the middle ring is empty. Since none of the outer rings need share any electron with an adjacent ring, they are as stable as benzene. Unlike other fused aromatic systems, it has low reactivity. This phenomenon, where some rings in fused systems give up part of their aromaticity to adjoint rings is called annellation.

LESSON - 3

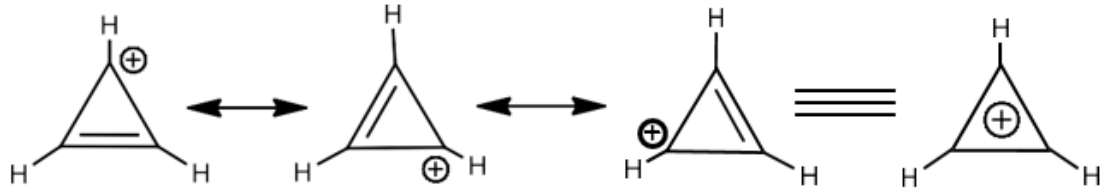
NON-BENZENOID AROMATIC COMPOUNDS

3.1 AROMATICITY OF NON-BENZENOIDCOMPOUNDS:

A compound which although does not contain a benzenoid ring yet exhibit a degree of aromatic character is called non-benzenoid aromatic compound.

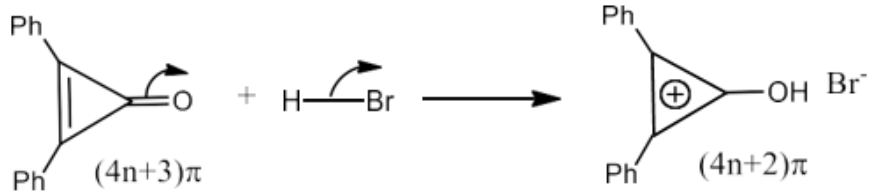
3.1.1 Three Membered Ring Compounds: Ex.Cyclopropenium salts.

Cyclopropene has a doubly filled bonding and singly occupied antibonding molecular orbital i.e. it is (4n+3) π electron molecule. But if the later electron is lost, the resulting cation becomes a closed shell (4n+2) π electron molecule. This is the cyclopropenyl cation, and may be represented as resonance hybrid.

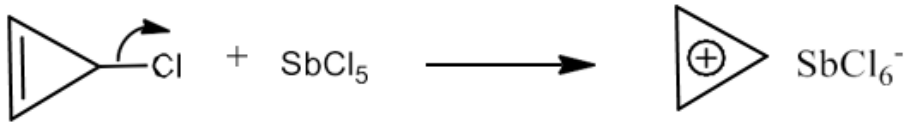


Many cyclopropenium salts have actually been prepared in a simple way as follows.

I. Hydroxy diphenyl cyclopropenyl bromide

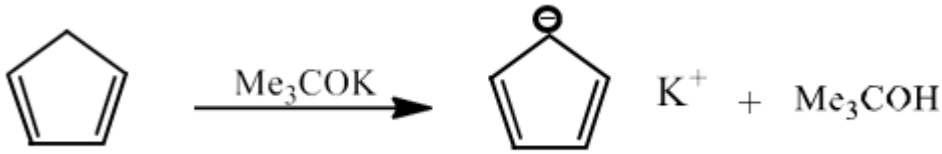


II. Cyclo propenyl hexa chloro antimonate

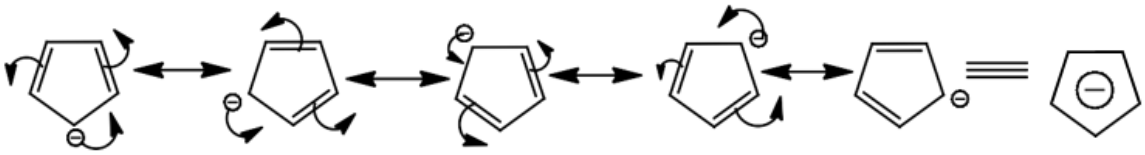


3.1.2 Five Membered Ring Compounds: Cyclopentadienide salts

Cyclopentadiene is a (4n+1) π electron molecule and the gain of one π electron in theformation of cyclopentadienyl anion, which now has three doubly filled molecular orbitals. This anion is a closed-shell (4n+2) π electron molecule & exhibit Aromaticity.



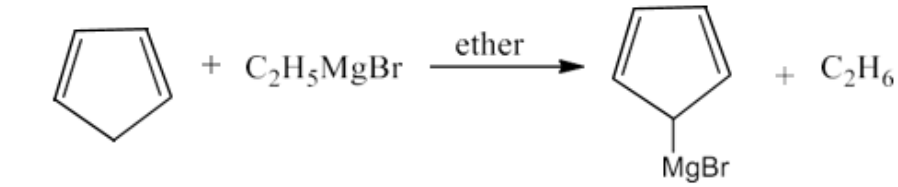
Ithas high resonance energy of about 42 K.Cal/mole.

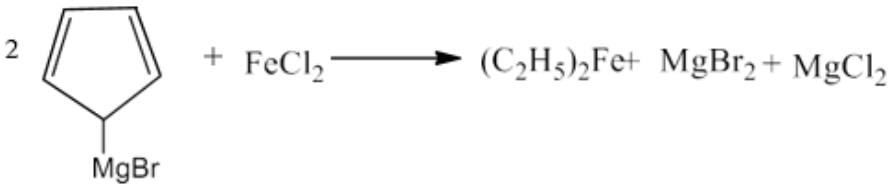


3.2 FERROCENE:

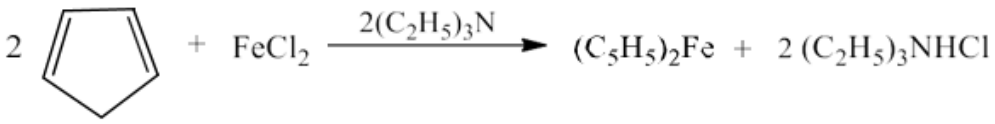
It is a one of member of five membered ring compounds. In this pi- complex is formed between the cyclopentadienyl anion and transitional metal like iron.

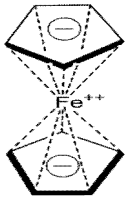
It was discovered by Kealy & Pausonin 1951.





Ferrocene may also be prepared by treating a mixture of cyclopentadiene and ferrous chloride with a base as triethylamine.

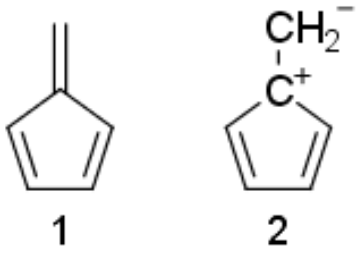




Its structure was established by x-ray crystallography as ferrous ion is Sandwichedbetweentwoparallelandequidistancecyclopentadienylanions placed about 3.4 A^o apart.

3.3 FULVENES:

Fulvenes are cyclic polyenes with an odd number of carbon atoms, and a prototype of a cross-conjugated hydrocarbon



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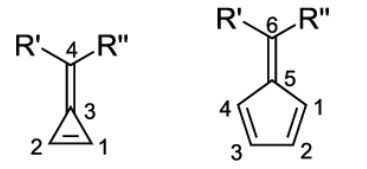
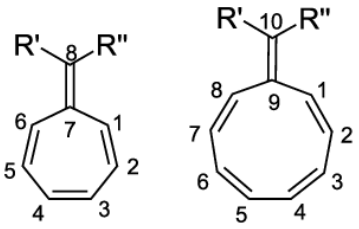
Fulvenes, while not strictly aromatic, exhibit varying degrees of aromatic character depending on their structure and substituents, with pentafulvenes showing the most aromatic character due to their ability to form resonance structures.



triafulvene pentafulvene

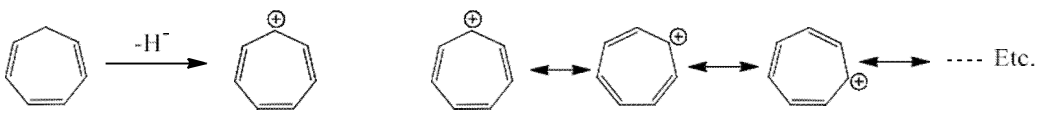


heptafulvene nonafulvene

3.4 SEVEN - MEMBERED RING COMPOUNDS:

For example, Tropylium cation

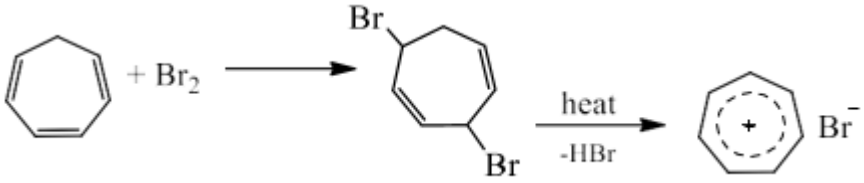
Cycloheptatriene behaves like a typical triene. Removal of a hydride ion leads to the formation of a carbonium ion known as cycloheptatrienylium or tropylium cation.



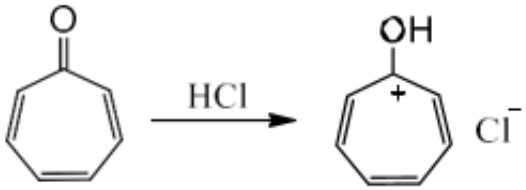
Tropylidine Tropylium Cation Resonance forms

Various tropylium salts have been prepared as follows:

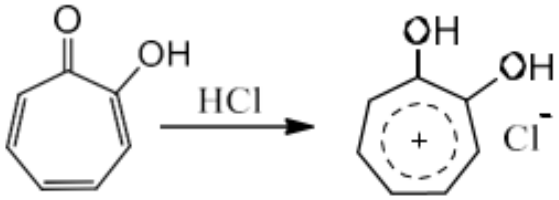
I. Tropylium bromide from cycloheptatriene:



II. Hydroxytropylium chloride from tropone:



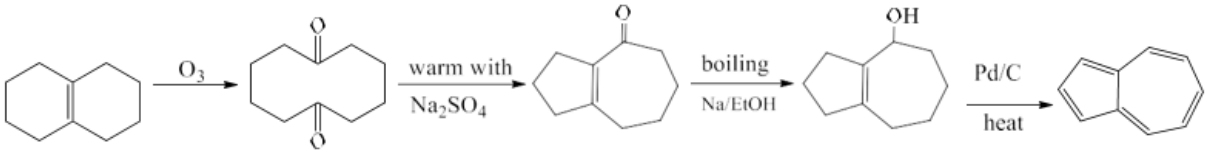
III. 1,2-dihydroxytropylium chloride from tropolone:



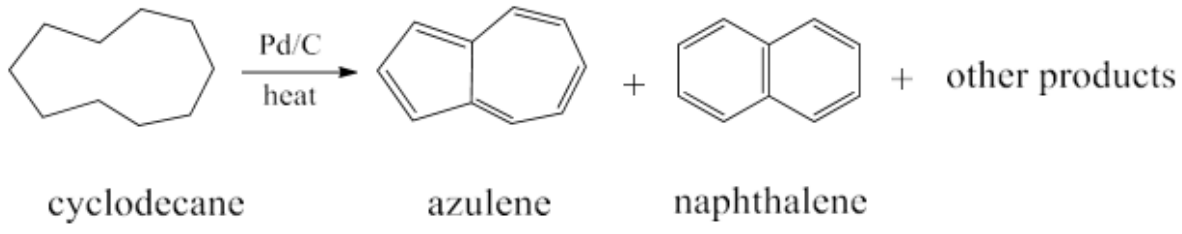
3.5 AZULENES:

The name azulene was given to a group of blue-coloured compounds found in certain essentialoils.

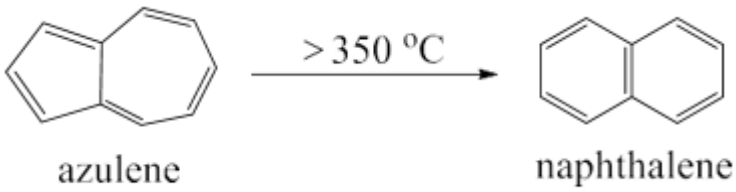
Plattner and St. Pfau synthesized azulene in 1937 from 9-decalene.



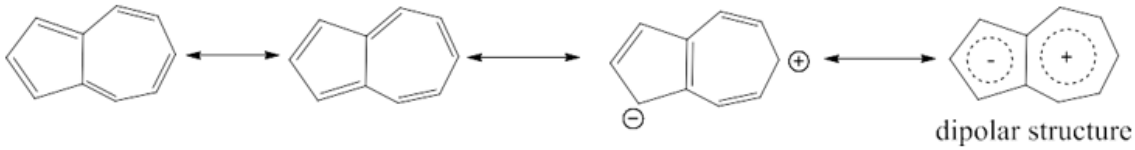
Azulene has also been prepared by the dehydrogenation of cyclodecane in the gas phase in the presence of palladium on charcoal.



Azulene is a deep blue compound (m.p.90 ^{o}C). It is isomeric with Naphthalene but less stable than it. It can isomerize to naphthalene quantitative lyon heating above350 ^{o}C in absenceofair. This suggesting that it possesses lower resonance energy (49 Kcal. /mol.) than naphthalene (77 Kcal. / mol.).



Azulene can be written as cyclopentadiene and cycloheptatriene rings, neither of which aloneis an aromatic. The 5-membered ring has five and 7-membered ring has seven π-electrons (two π electrons are common to both rings). If one π-electron is transferred from 7-membered to 5-membered ring, each will now have a closed shell of six π-electrons. In this condition, the molecule will have a dipolar structure.



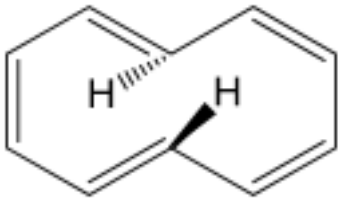
Azulene containing (4n+2) π electrons and behaves chemically as an aromatic compound i.e. it undergoes various substitution reactions such as bromination, nitration, Friedal Craft's reactions. Electrophilic substitution occurs preferentially in the 5membered ring, because it is electron rich than the 7-membered ring.

3.6 ANNULENES:

The ring compounds having an even number of methylene (-CH=units) represented as neutral polyenes (C_nH_n) are referred to as annulenes. In these n≥10 was prepared by 'Sondheimer' et al. Annulenes were named as [n]-annulenes, where 'n' referring to the number of carbon atoms in the ring.

Ex. Benzeneis[6]-annulene

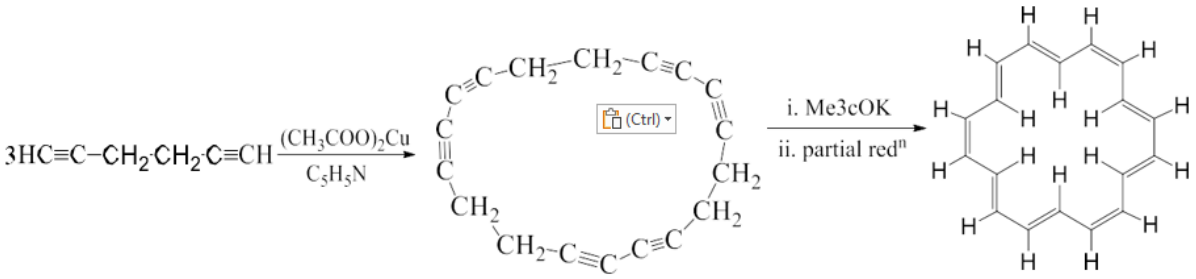
[10]-annulene (Cyclodecapentaene) is the simplest annulene, capable of possessing a strain less planar ring. This compound contains trans double bonds, but due to the interference between 1&6 'H' atoms it can't attain co-planarity i.e. it is non-planar and hence doesn't exhibit Aromaticity.



[10]-annulene

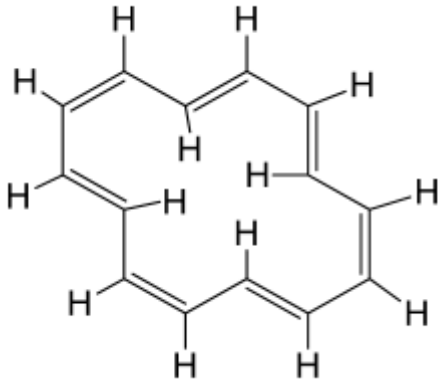
The annulenes so far prepared have n=12, 14, 16, 18, 20, 24 & 30, out of which only(14), (18) & (30) annulenes have (4n+2) π electrons, while others have (4n) π electrons and thus behave like olefins.

The key reaction in the synthesis of annulenes is oxidative coupling of acetylenes by cupric acetate in pyridine solution, followed by rearrangement with potassium tertiary but oxide (Me_3COK) via proto tropic shifts. Finally, the triple bonds are partially hydrogenated to double bonds.



[18]-annulene contains (4n+2) π electrons and in which the inside 'H' atoms are sufficiently far apart for the molecule to adopt a planar or a near-planar configuration. So, it should be anaromatic. It is reasonably stable in the presence of light and oxygen. Although [18]-annulene seems to be an aromatic, it behaves like an olefin.

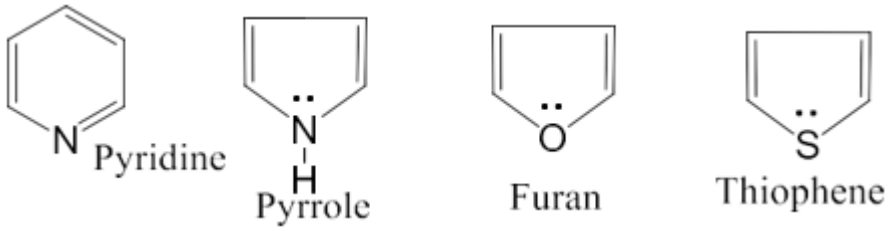
A similar synthetic route has afforded [14]-annulene, [30]-annulene with (4n+2) π electrons, exist in planar configuration, but less stable than [18]-annulene.



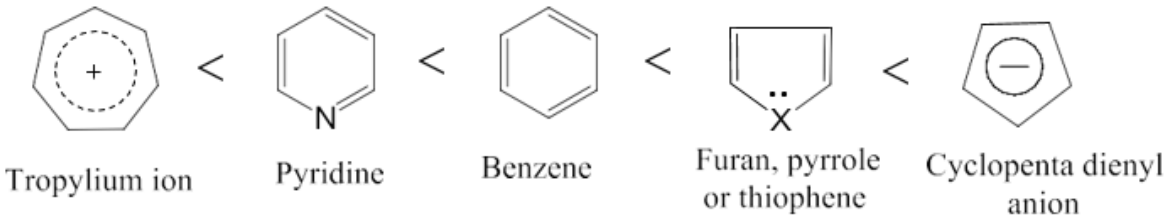
[14]-annulene

3.7 HETEROCYCLIC COMPOUNDS:

Heterocyclic compounds viz. pyrrole, furan, thiophene, pyridine etc. have sic-pi electronscloud (aromatic sextet), delocalized over all the atoms of the ring and thus obey Huckel's ((4n+2) π electrons) rule. The aromatic character of heterocyclic compounds is indicated by their stability, high resonance energy and electrophilic substitution reactions rather than addition reactions.



Five, six, seven membered carbo cyclic and heterocyclic systems show the following sequence of Aromaticity i.e. affinity for electrophilic reagents.



Prof. V. Madhava Rao

LESSON - 4

ANTI AROMATICITY AND HOMO AROMATICITY

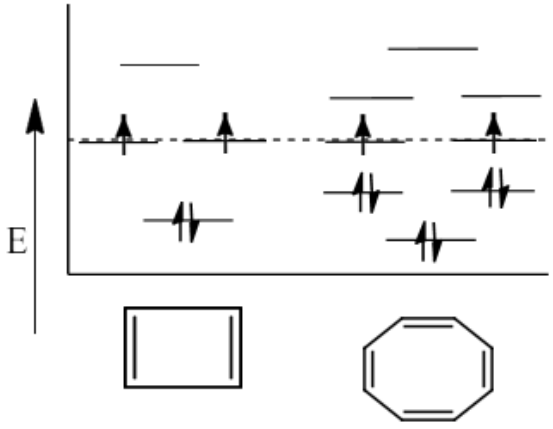
4.1 ANTI-AROMATICITY:

The cyclic conjugated species those which are less stable than corresponding acyclic unsaturated systems are called anti-aromatic. Molecular Orbital calculations have shown that such compounds have (4n) π electrons. So, conjugated cyclic compounds of high un-stability with 4n π electrons are called anti-aromatics and this characteristic is called anti-aromaticity.

Thus, although two equivalent contributing structures can be written for 1, 3 - cyclobutadiene, it is extremely unstable anti-aromatic compound, because it has 4n π electrons.

This shows that the ability to write equivalent contributing structures is not sufficient to predict the stability. It has experimentally been shown that conjugated rings with 2, 6, 10, & 14 electrons are aromatic, while those with 4, 8 12, 16 &20 are anti-aromatic.

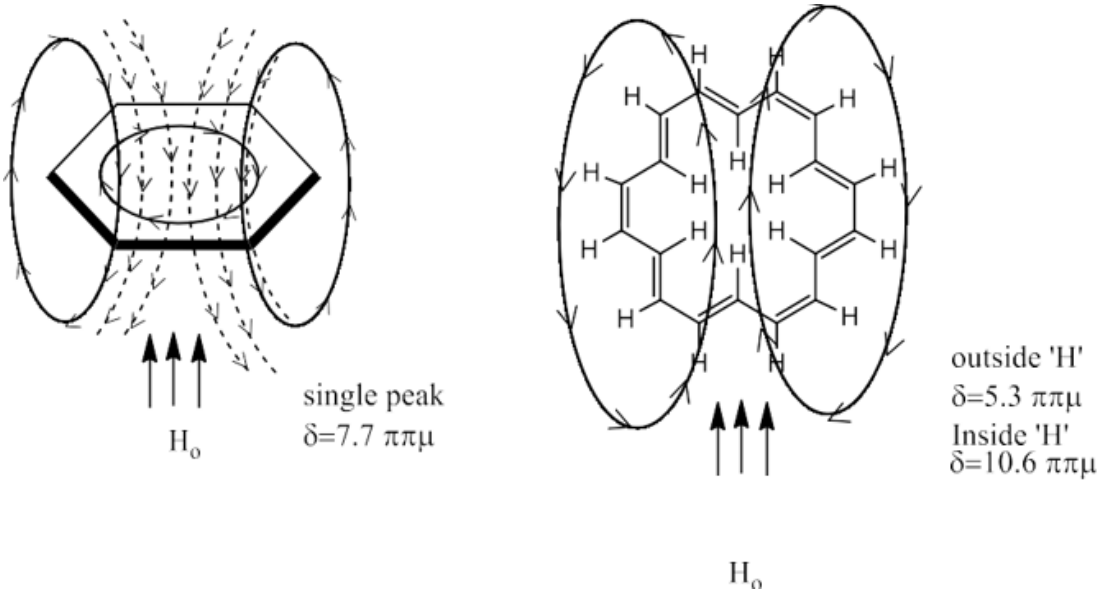
According to molecular orbital theory, in cyclobutadiene out of 4π electrons, two would fill the lowest orbital and the remaining two would go to the first pair of degenerate orbitals, each being singly occupied. As expected, cyclobutadieneis anti-aromatic compound. So, there will always be two singly occupied degenerate orbitals in such systems. Because of this arrangement of electrons, such systems are highly unstable and are termed as anti-aromatic.



It can also be explained by NMR spectral data. In [16]-annulene which is anti-aromatic,outside protons are more shielded and inside protons are less shielded.

But in benzene and [18]-annulene, outside protons are less shielded and inside protons are more shielded. This reversal of shielding and de-shielding region in going from [18] to [16]-annulenes can only mean that the directions of their induced magnetic fields are reversed.

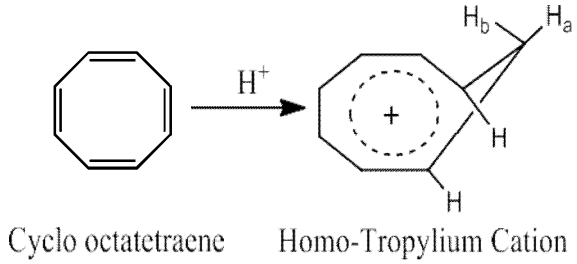
Thus [16]-annulene which is anti-aromatic is due to not only lack of aromatic ring current, but also its π-electrons produce exactly the opposite effect when place in external magnetic field.



4.2 HOMO-AROMATICITY:

The compound that contains one or more Sp3 hybridized carbon atoms in a conjugated cyclic system is known as homo-aromatic compound and the phenomenon is called as Homo - aromaticity.

When cyclo octatetraene is dissolved in concentrated sulphuric acid, a proton adds to one of the double bonds to form a Homo-tropylium ion.



In this ion an aromatic sextet is spread over seven carbon atoms as in the tropylium cation. The eight-carbon atom is an Sp3 carbon and so can't take part in the aromaticity. An NMR spectrum shows the presence of a diatropic ring current. H_b at δ= -0.3 ppm & H_a at δ= 5.1 ppm.

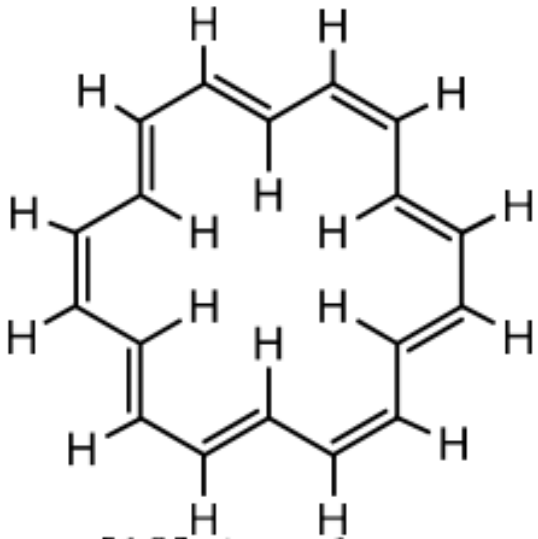
In order for the orbitals to overlap most effectively so as to close a loop, the Sp^3 atoms are forced to lie almost vertically above the plane of aromatic atom. In Homo-tropylium ion H_b is directly above the aromatic sextet and so is shifted for up field in the NMR.

All Homo-Aromatic compounds so far discussed are ions and it is questionable as to whether homo-aromatic character can exist only in uncharged systems. Homo-Aromatic ions of two and ten electrons are also known.

4.3 PSEUDO-AROMATICITY:

Pseudo-aromatic compounds are organic molecules that exhibit some characteristics of aromatic compounds but do not meet all the criteria of aromaticity. So, these compounds are often cyclic but may not be fully conjugated where the double bonds are not in a way that allows for full delocalization of π electrons. Hence the structure may not be planar, which can disrupt the conjugation necessary for true aromaticity.

The compound [18]-Annulene is showing pseudo-aromaticity i.e. 50% Aromaticity. It is red colour solid substance with nearly planar structure obeying Huckel rule i.e. it has (4n+2) π electrons, where n=4.



[18]-Annulene

But these compounds exhibit some olefinic characters as below:

i) It is readily hydrogenated to the corresponding cycloalkane

ii) It will not undergo nitration or sulphonation.

iii) This compound is higher member of the Aceno series, but highly reactive and unstable.

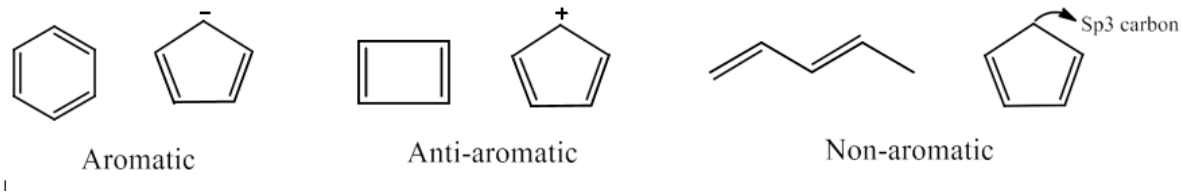
iv) Even though this compound obeys Huckel rule, but shows non- aromatic character.

v) So, it is called as Pseudo-Aromatic

4.4 NON-AROMATICITY:

Non-aromaticity is a term used to describe organic compounds that do not have the structural and electronic characteristics of aromatic compounds i.e. they do not hold a comprehensive conjugated π system inside the ring. Non-aromatic compounds can be non-cyclic, non-planar, or have a structure that doesn't allow for a continuous overlapping ring of p-orbitals.

A compound even if in a cyclic form that does not demand a continuous form of an overlapping ring of p-orbitals needs not be considered aromatic or even anti-aromatic.



Hence, these are termed as non-aromatic or aliphatic. The electronic energy of non-aromatic compounds is the same as its open-chain counterpart. Non-aromatics do not contain such a ring system with a delocalized electron cloud. We will learn about aromatic compounds and anti-aromatic compounds below. Non-aromatic compounds are those which do not satisfy the conditions applied to identify aromatic and anti-aromatic compounds.

So, non aromatic compounds are those which are not related to the aromatic and anti-aromatic compounds.

LESSON - 5

HETEROCYCLIC COMPOUNDS - I

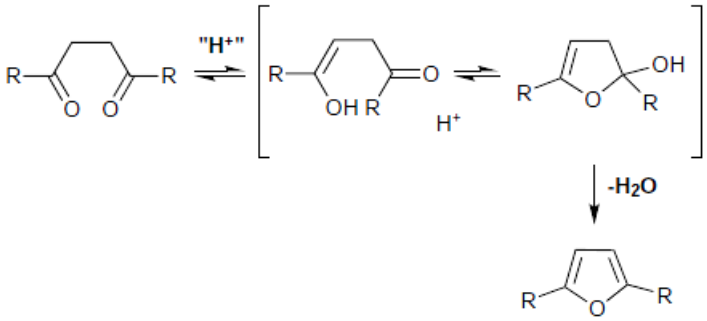
5.1 DEFINITION:

Heterocyclic compounds are organic compounds that contain a ring structure containing atoms in addition to carbon, such as sulfur, oxygen or nitrogen, as the heteroatom. The ring may be aromatic or non-aromatic.

5.2 SYNTHESIS AND REACTIONS OF FURAN:

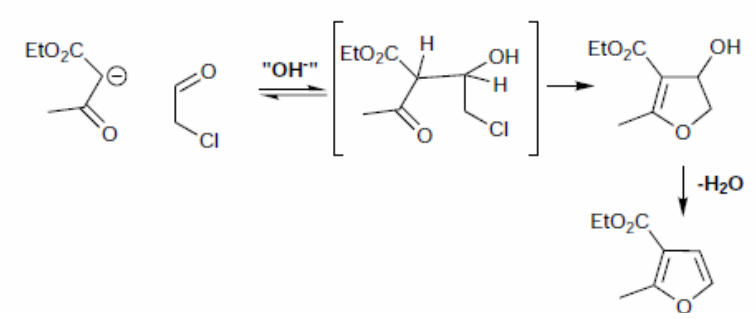
5.2.1 Paal - Knorr Synthesis:

Involves the dehydration of 1, 4 - dicarbonyl compounds (γ - hydoxy - α, β-unsaturated enones can also be employed) under non-aqueous acidic conditions.



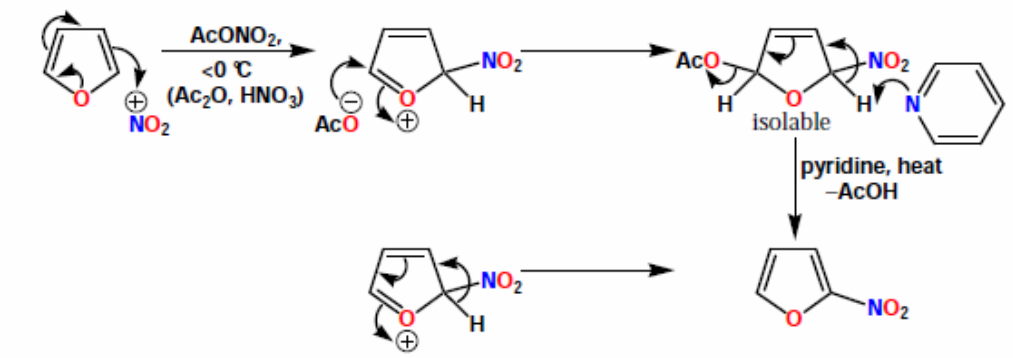
5.2.2 Feist - Benary Synthesis:

Involves an aldol addition of a (deprotonated) 1, 3 - dicarbonyl compound to an α- halocarbonyl moiety followed by subsequent ring closure.

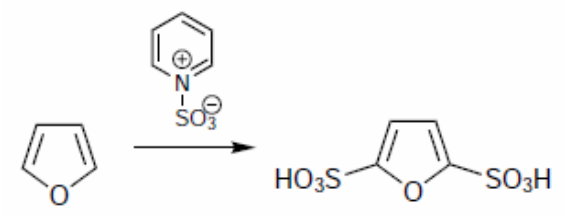


5.2.3 Nitration:

Nitration can occur by an addition-elimination process. When NO_2BF_4 is used as a nitrating agent, the reaction follows usual mechanism.

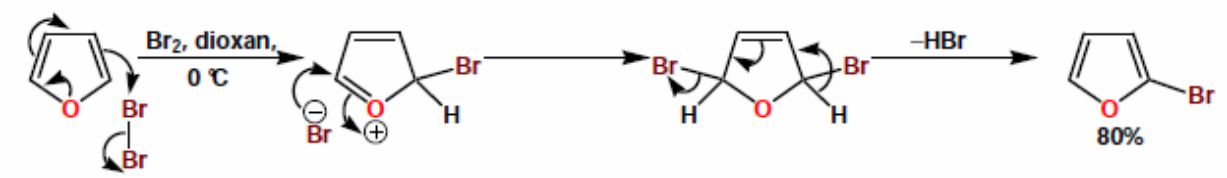


5.2.4 Sulphonation:



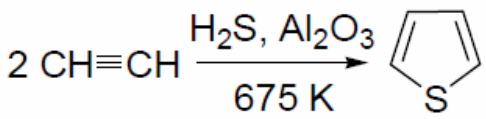
5.2.5 Bromination:

Furan reacts vigorously with Br2 or Cl2 at room temp. to give polyhalogenated products. It is possible to obtain 2-bromofuran by careful control of temperature.

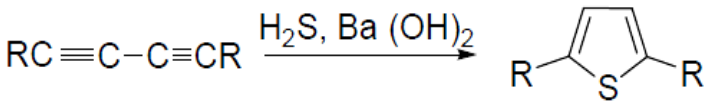


5.3 SYNTHESIS AND REACTIONS OF THIOPHENE:

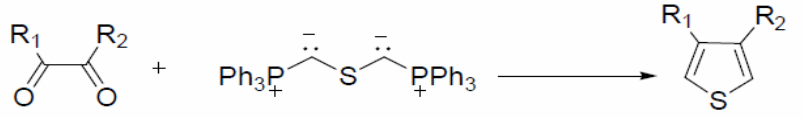
Thiophene can be generated by passing a mixture of ethyne and H_2S on Al_2O_3 at 675 K.



Substituted thiophenes can be obtained from 1,3 – diynes and H_2S.



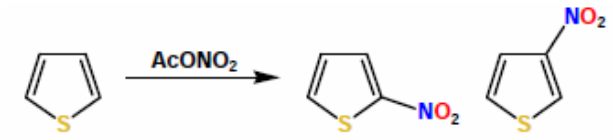
1,2 - diketones and diylide undergo cyclization to produce a variety of thiophenes.



5.3.1 Reactions of Thiophene:

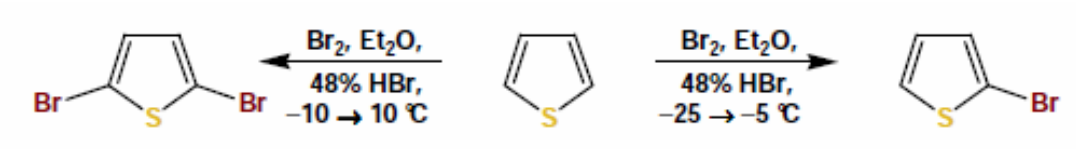
5.3.1.1 Nitration of Thiophenes:

Reagent AcONO2 generated *in situ* from c-HNO3 and Ac2O



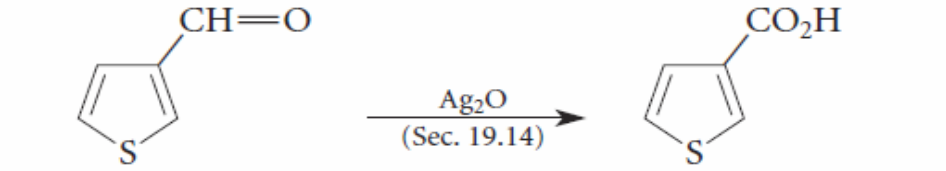
5.3.1.2 Halogenation of Thiophenes:

Occurs readily at room temperature and even at -30 °C. Careful control or reaction conditions is required to ensure mono-bromination



5.3.1.3 Side-Chain Reactions:

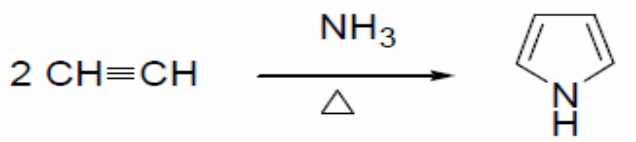
Many reactions occur at the side chains of heterocyclic compounds without affecting the rings, just as some reactions occur at the side chain of a substituted benzene.



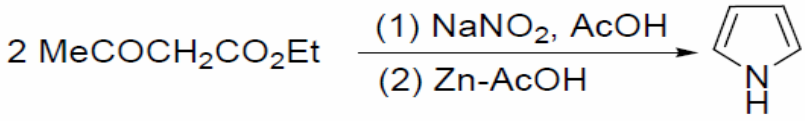
3-thiophenecarbaldehyde 3-thiophenecarboxylic acid (95–97% yield)

5.4 SYNTHESIS AND REACTIONS OF PYRROLE:

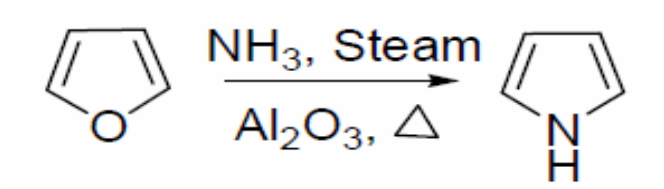
Pyrrole can be produced by passing a mixture of acetylene and ammonia through a red-hot tube.

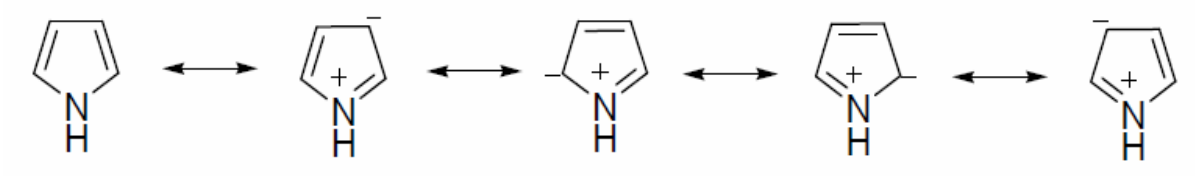


Knorr synthesis is the widely employed method for the synthesis of pyrrole using two equivalents of ethyl acetoacetate.



A mixture of furan, ammonia, and steam on Al_2O_3 at 675 K results in pyrrole.

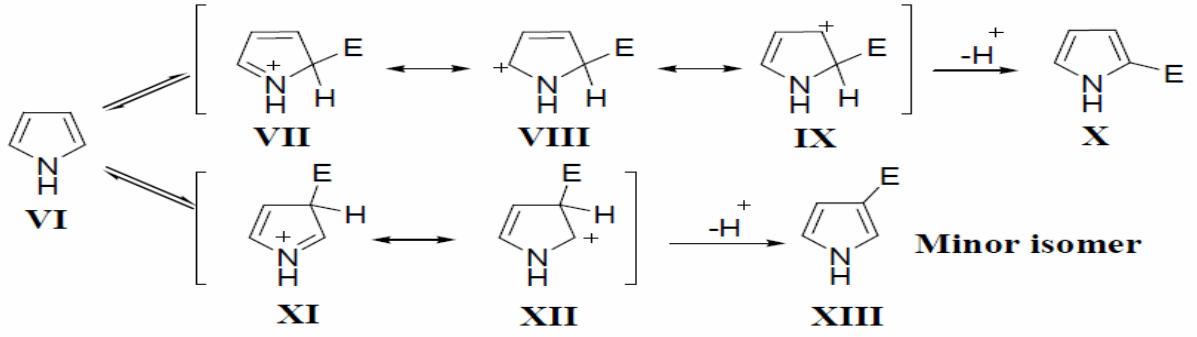




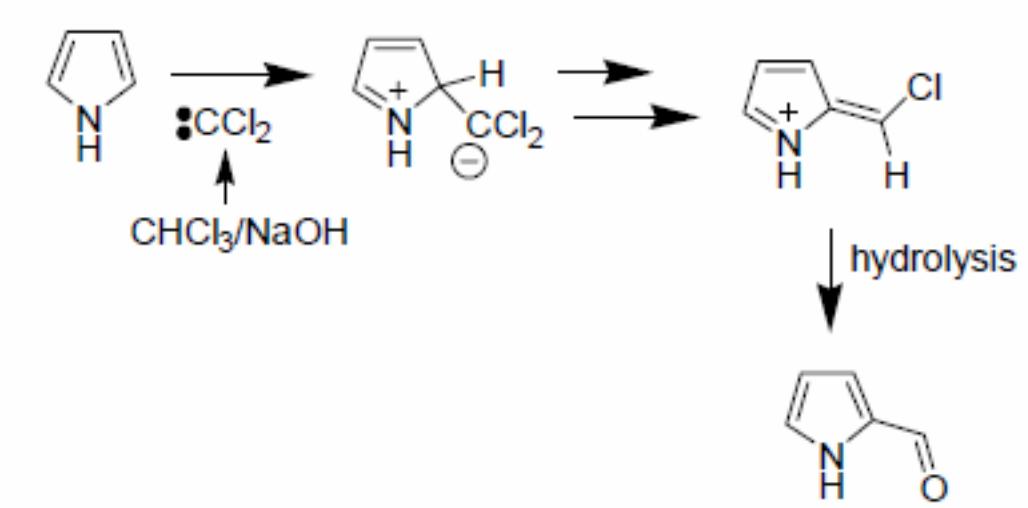
Resonance Forms of Pyrrole

5.4.1 Reactions of Pyrrole:

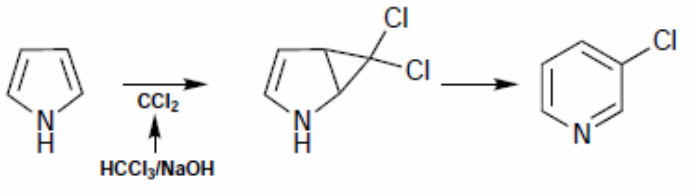
The attack of the electrophile generally proceeds as indicated in below. The major isomer **X** is generated through intermediates **VII – VIII – IX**, among which the isomer **VIII** contributes its major share to stabilize theintermediate. On the contrary, a minor isomer **XIII** is generated through the less stable intermediates, **XI** and **XII**.



5.4.1.1 Reimer-Tiemann Reaction:

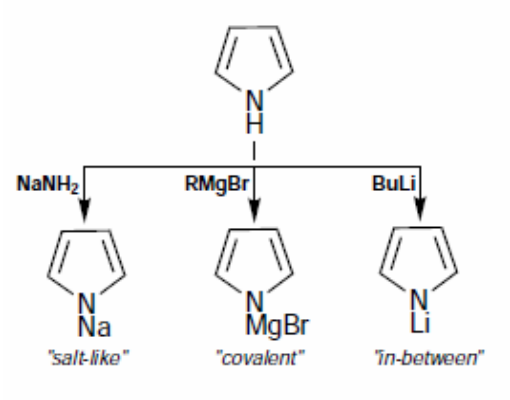


But under **non-aqueous** conditions:



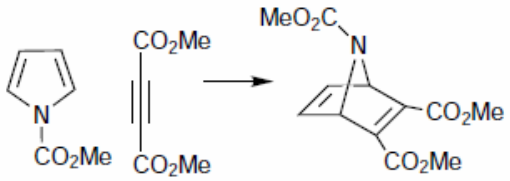
5.4.1.2 Reactions with Bases:

The NH proton is relatively acidic (pKa 17.5) and can be removed with bases.



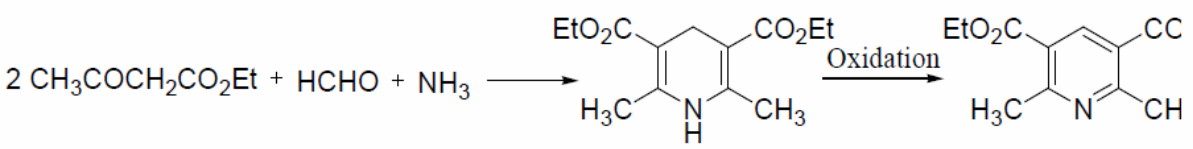
5.4.1.3 With Dienophiles:

Mainly Michael adducts, and only Diels-Alder reactions with electron withdrawing substituents on **N**.

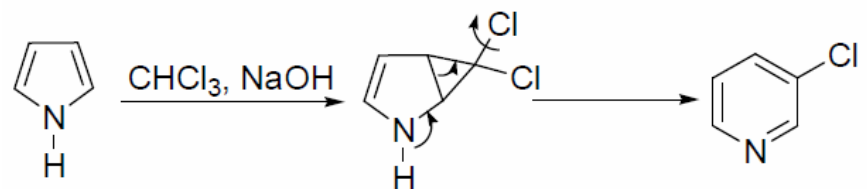


5.5 SYNTHESIS AND REACTIONS OF PYRIDINE:

5.5.1 Hantzch Synthesis: Hantzch method is one of the most convenient procedures for the synthesis of pyridine derivatives. The method involves the reaction of two equivalents of β – keto ester or other activated methylene derivatives with an aldehyde in the presence of ammonia to give dihydropyridine, which upon oxidation results in pyridine derivative.

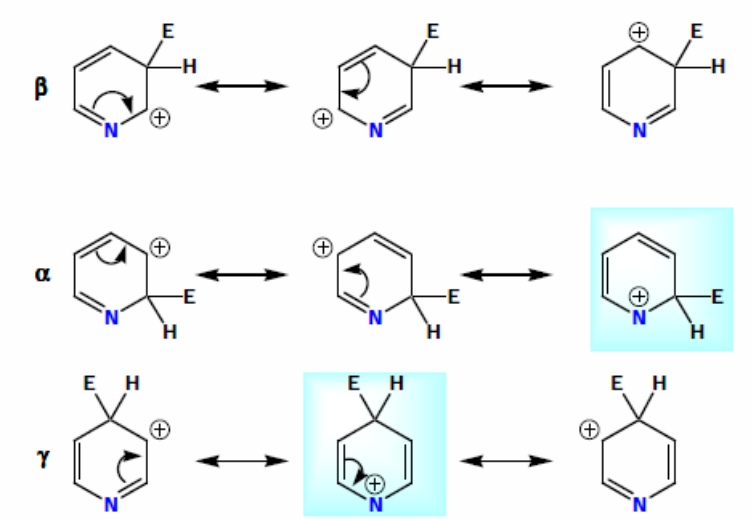


Pyrrole on reacting with dichlorocarbene undergoes ring expansion resulting in 3 – chloropyridine.



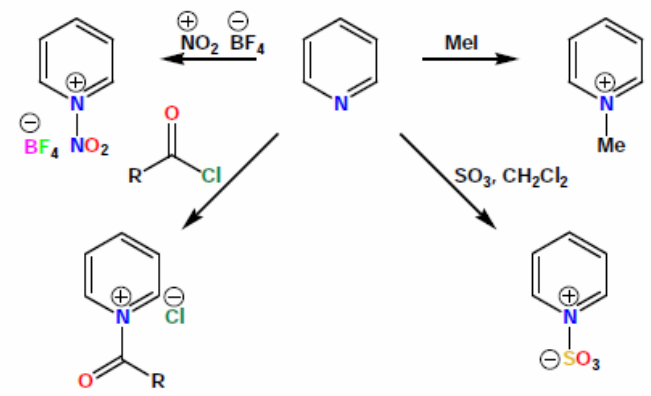
5.5.2 Reactions:

Regiochemical outcome of Electrophilic Substitution of Pyridines



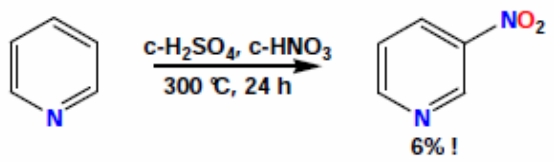
Resonance forms with a positive charge on *N* (i.e. 6 electrons) are very unfavourable the β-substituted intermediate, and the transition state leading to this product, have more stable resonance forms than the intermediates/transition states leading to the α/ϒ products.

5.5.2.1 N-Substitution:

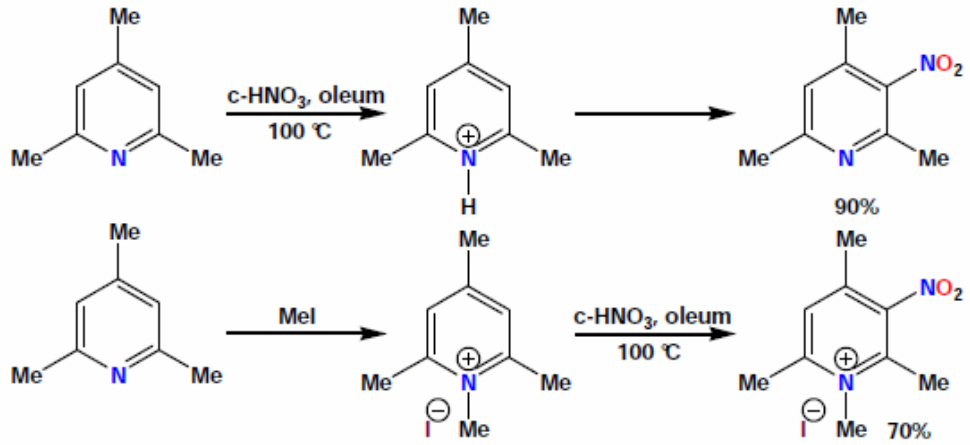


Reaction at *C* is usually difficult and slow, requiring forcing conditions. Friedel-Crafts reactions are not usually possible on free pyridines

5.5.2.2 Nitration of Pyridine:



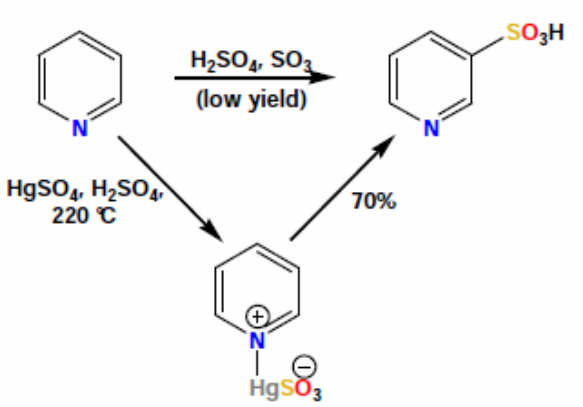
Use of Activating Groups



Multiple electron-donating groups accelerate the reaction. Both reactions proceed at similar rates which indicates that the protonation at *N* occurs prior to nitration in the first case.

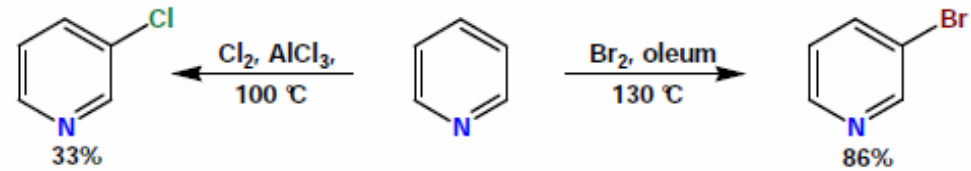
5.5.2.3 Sulfonation of Pyridine:

Low yield from direct nitration but good yield via a mercury intermediate.



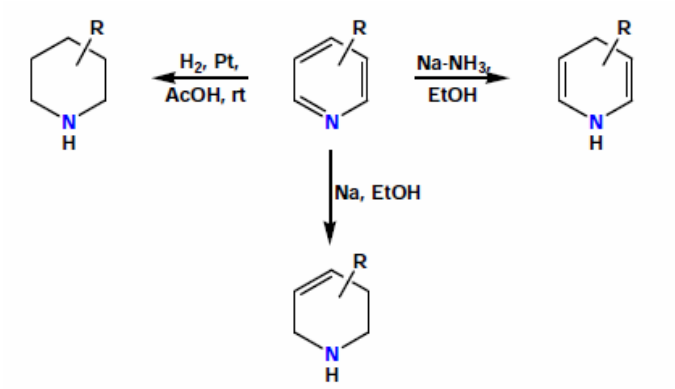
5.5.2.4 Halogenation of Pyridine:

Forcing reaction conditions are required for direct halogenations.



5.5.2.5 Full or Partial Reduction of Pyridines:

Pyridines generally resist oxidation at ring carbon atoms and will often undergo side-chain oxidation in preference to oxidation of the ring. Full or partial reduction of the ring is usually easier than in the case of benzene.

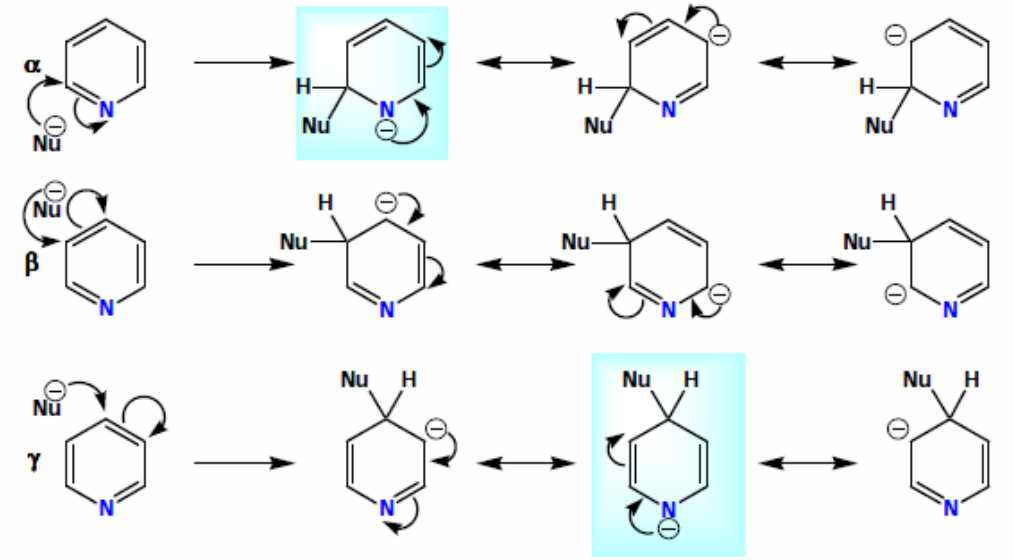


5.5.3 Pyridines - Nucleophilic Reactions:

Regiochemical Outcome of Nucleophilic Addition to Pyridines

Nitrogen acts as an electron sink

- Substitution is less favoured because there are no stable resonance forms with the negative charge on *N*
- Aromaticity will be regained by loss of hydride or a leaving group, or by oxidation

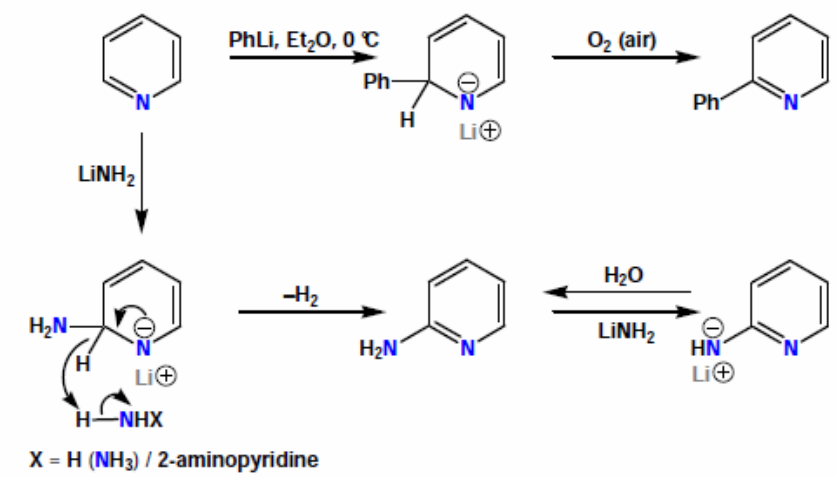


5.5.3.1 Chichibabin Reaction:

Nucleophilic Attack with Transfer of Hydride

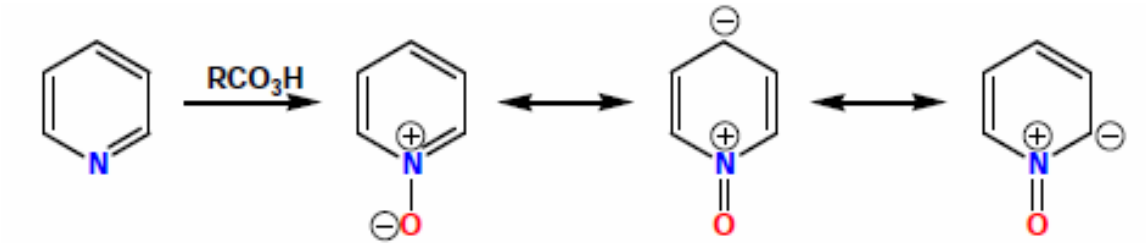
A hydride acceptor or oxidising agent is required to regenerate aromaticity.

The reaction with $LiNH_2$ is referred to as the Chichibabin reaction.



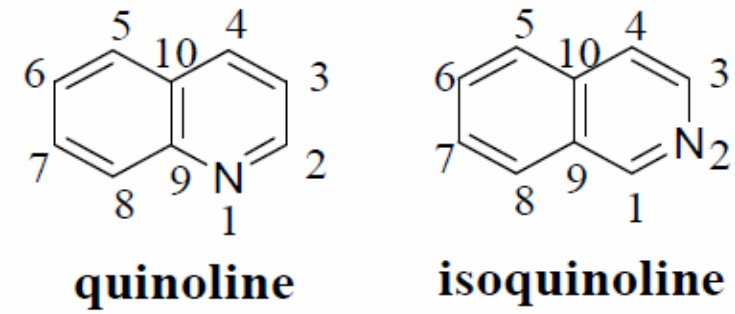
5.5.3.2 N-Oxide Formation:

The reactivity *N*-oxides differs considerably from that of pyridines or pyridinium salts. A variety of peracids can be used to oxidise *N* but *m*-CPBA is used most commonly.*N*-Oxide formation can be used to temporarily activate the pyridine ring to both nucleophilic and electrophilic attack.

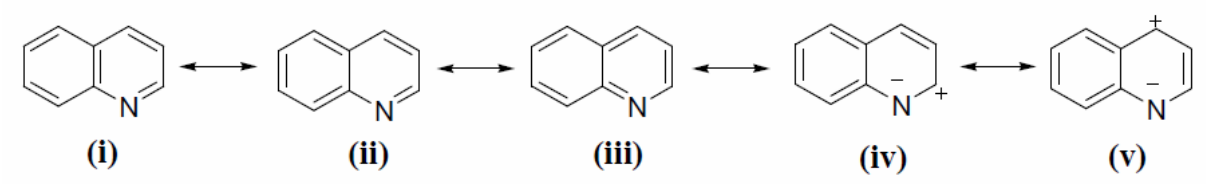


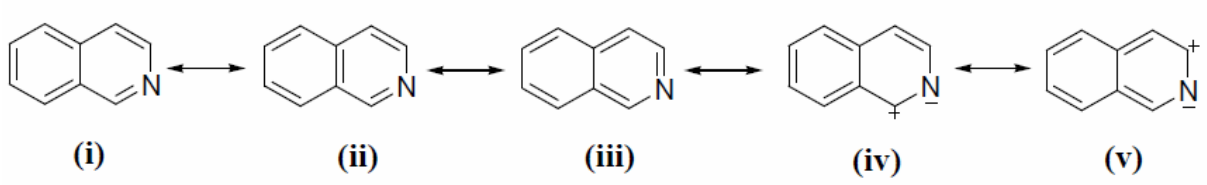
5.6 QUINOLINE AND ISOQUINOLINE:

Two faced heterocycles quinoline and Isoquinoline are formed by the unification of pyridine whereas isoquinoline is a low melting solid (M.P 265 ^{o}C, B.P 243^{0}C). All the atoms in quinoline and isoquinoline are sp2 hybridized with 10 π - electrons and furnish one electron each in orthogonal *p* - orbitals for delocalization over the rings.



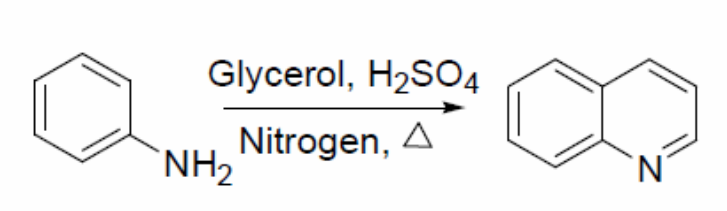
For both quinoline and isoquinoline, charge separated canonical forms can be written depicting the resonance energies of 198 and 143 KJ/mol., respectively. The first three resonance hybrids (**i - iii**) of both quinoline and isoquinoline are of low energy and contribute appreciably to aromatic character compared to the other charge separated structures (**iv -v**). Even though, quinoline and isoquinoline are slightly more basic in nature than pyridine but less basic than amines. This can be attributed to the sp2 hybridization of nitrogen in quinoline and isoquinoline compared to sp3 hybridized nitrogen of anilines, resulting in high electro negativity of the former. The dipole moment of isoquinoline (2.6 D) is greater than quinoline (2.1 D).



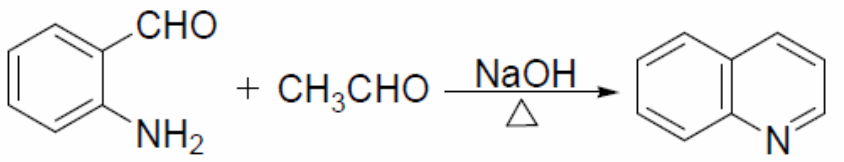


5.6.1 Synthesis of Quinoline:

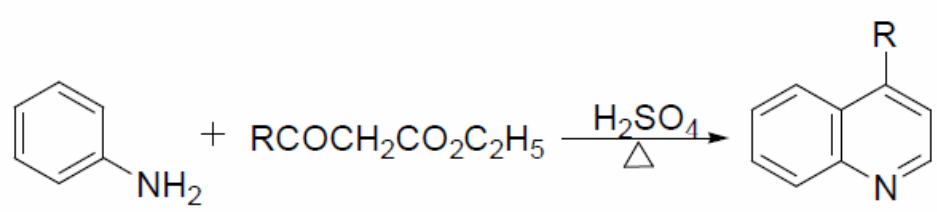
5.6.1.1 Skraup Synthesis: Skraup synthesis involves heating of aniline derivative having free ortho position with glycerol and sulfuric acid and an oxidizing agent like nitrobenzene. The acid functions as a dehydrating agent and an acid catalyst.



5.6.1.2 Friedlander Synthesis: Friedlander synthesis involves heating a mixture of *o* - amino benzaldehyde or *o* - aminoacetophenone with an aldehyde or ketone having an active methylene group in the presence of a base.

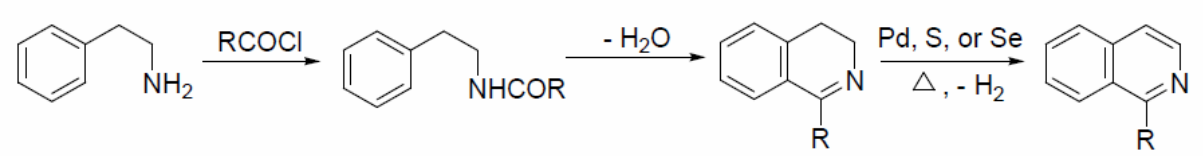


5.6.1.3 Knorr Quinoline Synthesis: Heating aniline with β -keto esters in the presence of acid results in 2 - substituted quinolines.

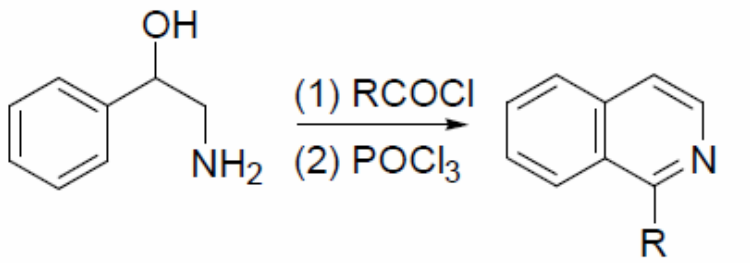


5.7 Synthesis of Isoquinoline:

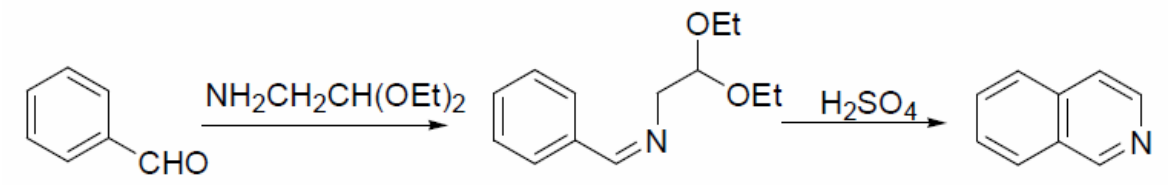
5.7.1 Bischler - Napieralski Synthesis: The synthesis involves the reaction of β - phenylethylamine with acyl chloride to give β - phenylethylamine which further undergoes cyclodehydration in the presence of POCl3, P2O5, H3PO4, or ZnCl2 to produce 3,4 - dihydro isoquinoline. 3,4 - dihydro isoquinoline on dehydration over Pd, S, or Se yields 1 - substituted isoquinoline.



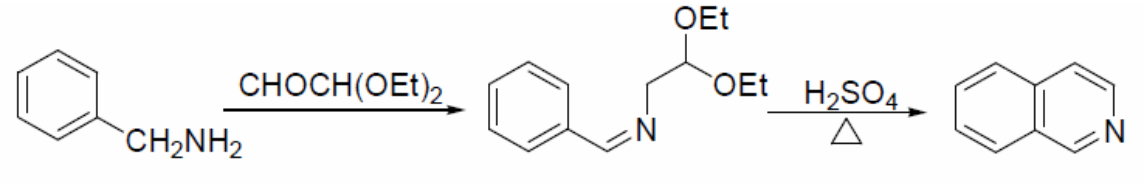
5.7.2 Pictat - Gam Synthesis: It is a modified Bischler - Napieralski synthesis except that a hydroxyl group is introduced in the starting material β - phenylethylamine.



5.7.3 Pomerantz - Fritsch Reaction: The method involves the condensation of an aromatic aldehyde with an amino acetal, which further undergoes cyclization in the presence of sulfuric acid yielding isoquinoline.



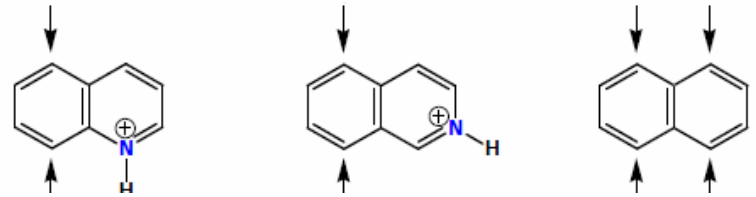
Condensation of benzylamine with acetal followed by cyclization yields isoquinoline.



5.7.4 Quinolines/Isoquinolines – Electrophilic Reactions:

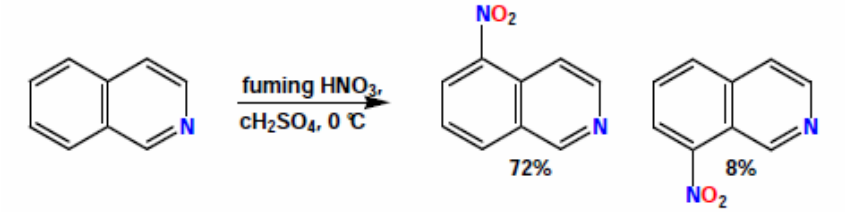
5.7.4.1 Regiochemistry:

Under strongly acidic conditions, reaction occurs *via* the ammonium salt. Attack occurs at the benzo - rather than hetero-ring. Reactions are faster than those of pyridine but slower than those of naphthalene.



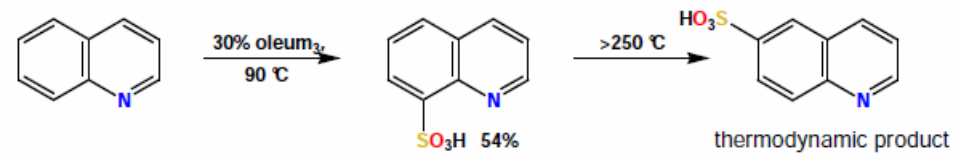
5.7.4.2 Nitration:

In the case of quinoline, equal amounts of the 5- and 8-isomer are produced



5.7.4.3 Sulfonation:

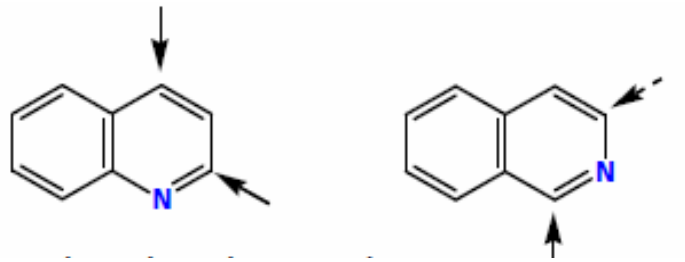
Halogenation is also possible but product distribution is highly dependent on conditions. It is possible to introduce halogens into the hetero-ring under the correct conditions. Friedel-Crafts alkylation/acylation is not usually possible.



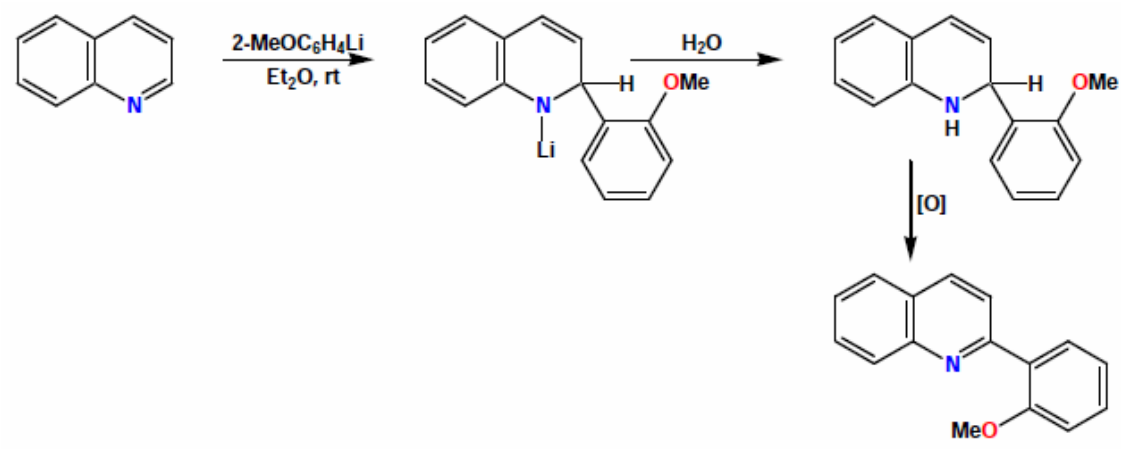
5.7.5 Quinolines / Isoquinolines - Nucleophilic Reactions:

5.7.5.1 Regiochemistry:

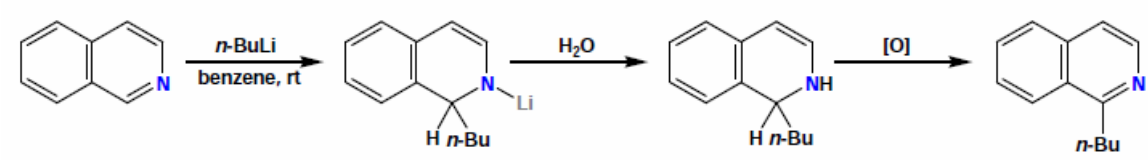
Attack occurs at hetero- rather than benzo-ring.They are enerally more reactive than pyridines to nucleophilic attack.



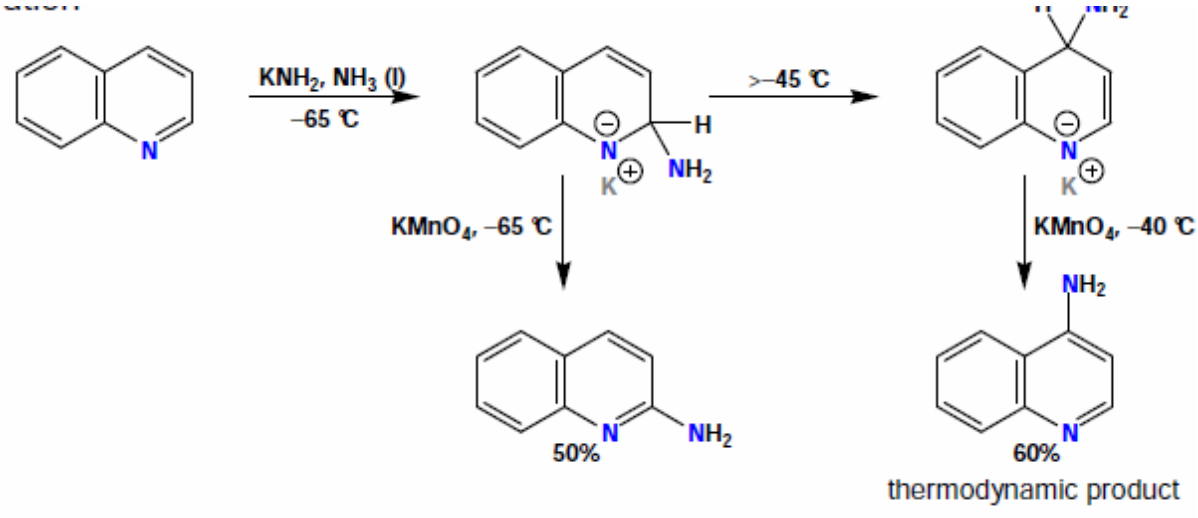
5.7.5.2 Carbon Nucleophiles:



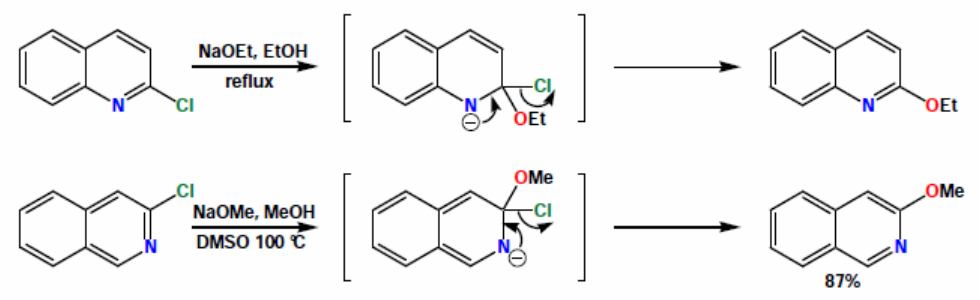
Oxidation is required to regenerate aromaticity



5.7.5.3 Amination:

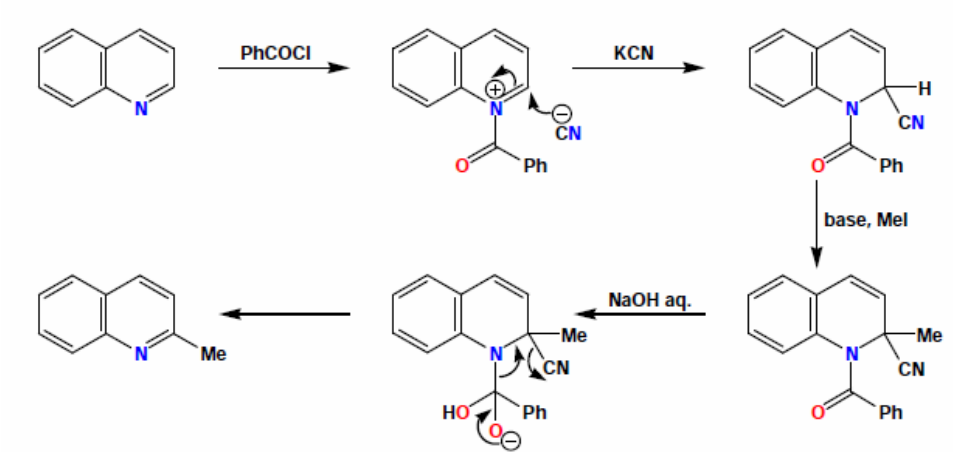


5.7.5.4 Displacement of Halogen:



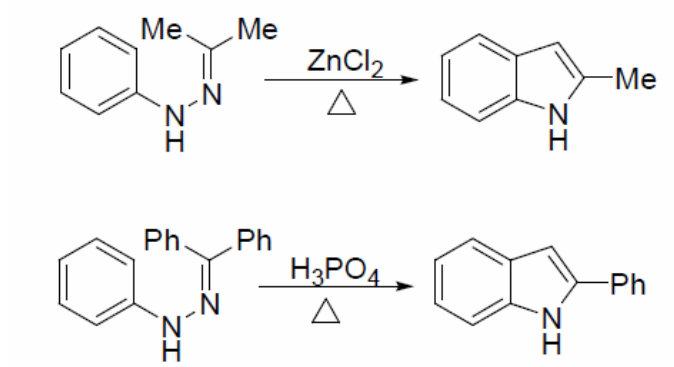
5.7.5.5 The Reissert Reaction:

The proton adjacent to the cyano group is extremely acidic. The reaction works best with highly reactive alkyl halides.

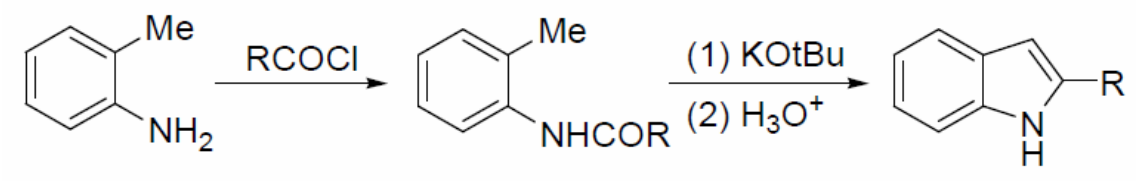


5.8 SYNTHESIS OF INDOLES:

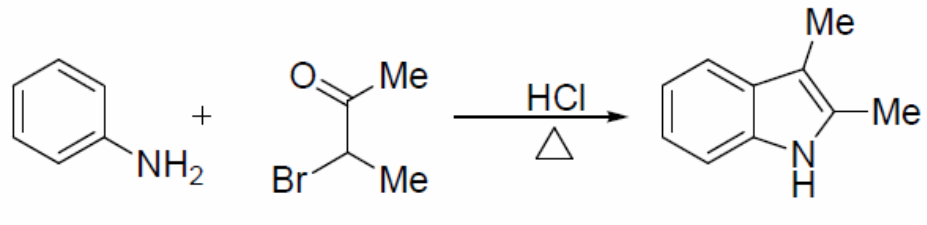
5.8.1 Fischer - Indole Synthesis: This is the most important and widely used method for the preparation of indoles. Thermal elimination of ammonia from phenylhydrazine or substituted hydrazine of an aldehyde or ketone. The reaction is catalyzed by phosphoric acid, sulphuric acid, ZnCl2 or BF3.



5.8.2 Madelung Synthesis: *O* - toluidine on reaction with acyl chloride results in *o* - acylamino toluene which undergoes cyclization in the presence of strong base followed by dehydration to give indole or 2 - substituted indole derivatives.



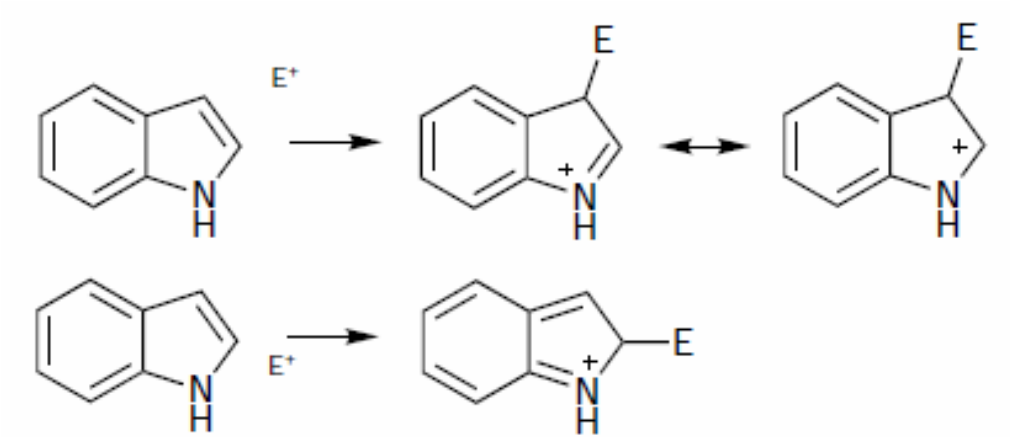
5.8.3 Bischler Synthesis: The method involves the reaction of aniline or substituted anilines with α - halo ketone or aldehyde to give α - arylamino ketone or aldehyde, which undergoes cyclization on heating with an acid or ZnCl2 to produce substituted indoles.



5.8.4 Indoles - Electrophilic Substitution:

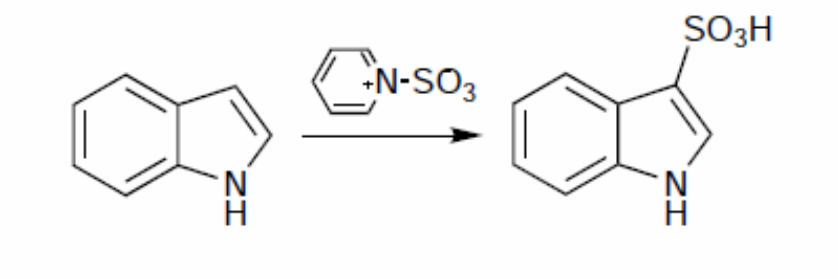
The pyrrolic ring in indole is electron rich and electrophilic substitution occurs preferentially in this ring (rather than the benzene ring). However, in direct contrast to pyrrole, substitution occurs at the **3-position**. This is a consequence of the stabilities of the Wheland intermediates where attack in the 2-position leads to loss of aromaticity in the benzenoid ring. When the indole is already substituted in the 3-position then apparent 2- substitution occurs but these products (normally) derive from a **migration** after initial attack at the 3-position.

2- vs 3-Position:



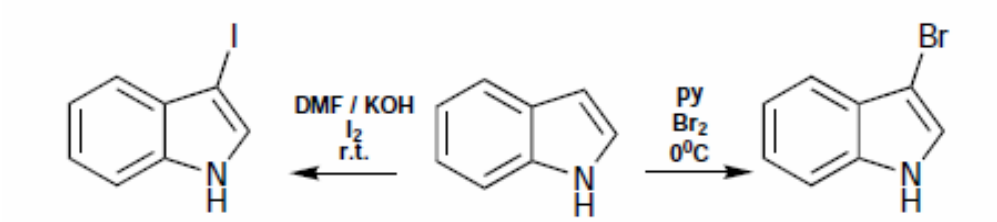
5.8.4.1 Sulphonation:

as with furan and pyrrole using pyridine/SO3 complex

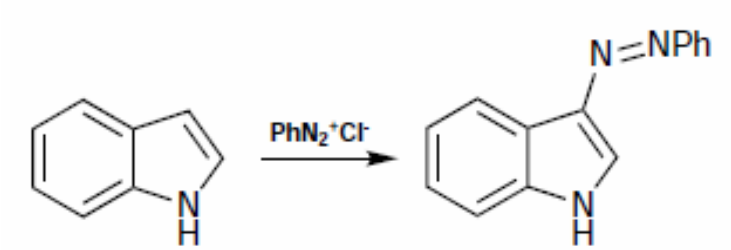


5.8.4.2 Halogenation:

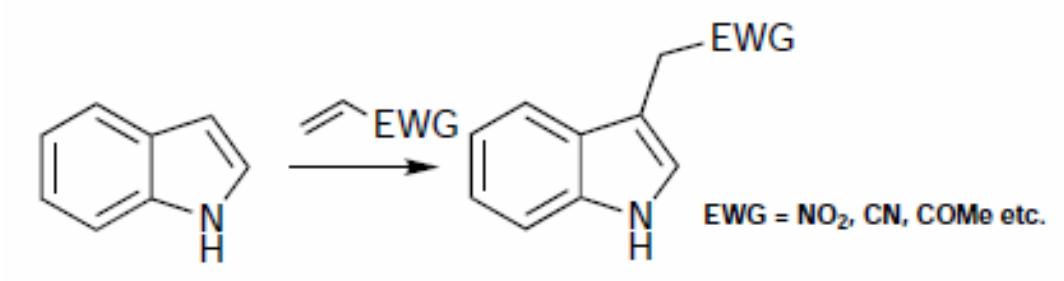
Mild conditions required. Haloderivatives are not very stable.



5.8.4.3 With Diazonium Salts:

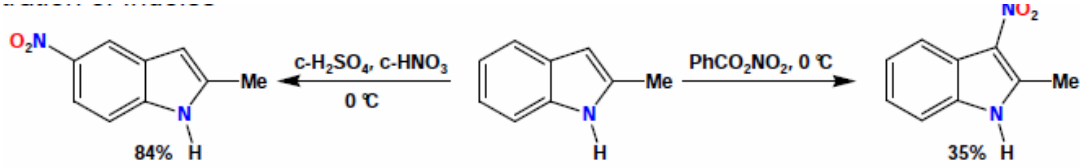


5.8.4.4 With Michael Acceptors:

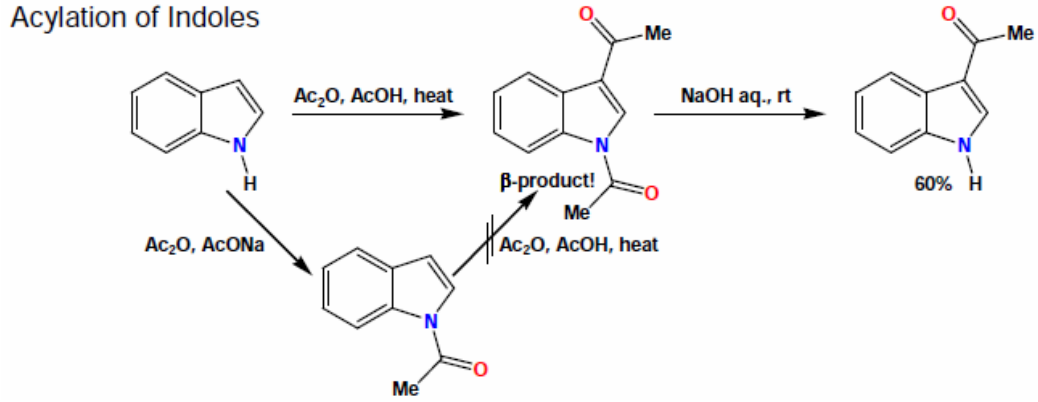


5.8.4.5 Nitration of Indoles:

Polymerisation occurs when there is no substituent at the 2-position. Halogenation is possible, but the products tend to be unstable.

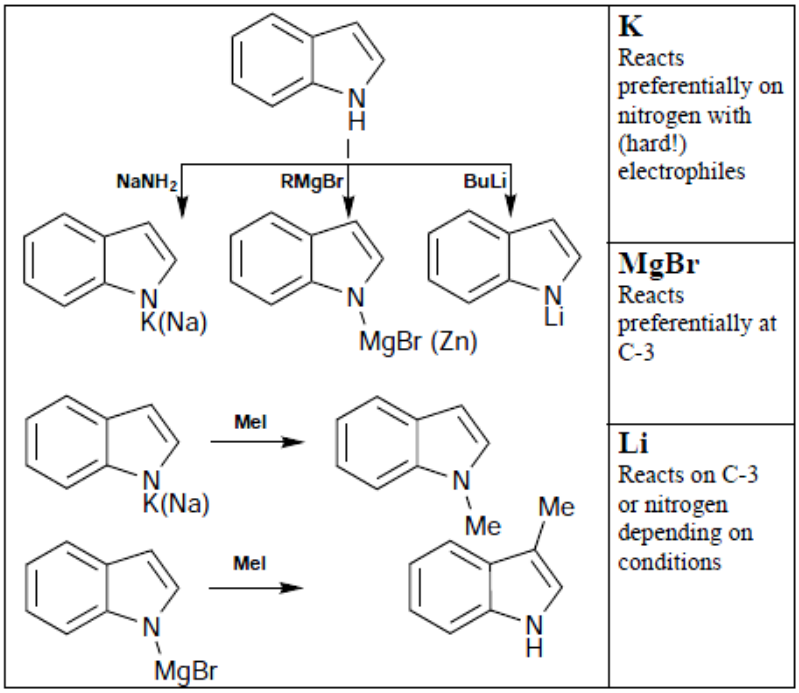


5.8.4.6 Acylation of Indoles:



Acylation occurs at *C* before *N* because the *N*-acylated product does not react

5.8.5 Reactions with Bases (Metallation):



Prof. D. Ramachandran

LESSON - 6

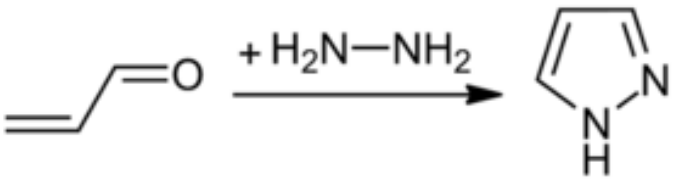
HETEROCYCLIC COMPOUNDS - II

6.1 PYRAZOLE:

Pyrazole is an organic compound with the formula $C_3H_3N_2H$. It is a heterocycle characterized by a 5-membered ring of three carbon atoms and two adjacent nitrogen atoms. Pyrazole is a weak base, with pK_b 11.5 (pK_a of the conjugated acid 2.49 at 25 °C). Pyrazoles are also a class of compounds that have the ring C_3N_2 with adjacent nitrogen atoms. Notable drugs containing a pyrazole ring are celecoxib (Celebrex) and the anabolic steroid stanozolol.

6.1.1 Synthesis:

Pyrazoles are synthesized by the reaction of α, β-unsaturated aldehydes with hydrazine and subsequent dehydrogenation.

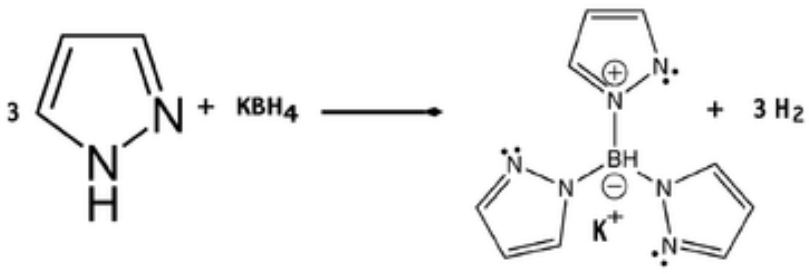


Substituted pyrazoles are prepared by condensation of 1,3-diketones with hydrazine (Knorr-type reactions).[5] For example, acetylacetone and hydrazine gives 3,5 dimethyl pyrazole.

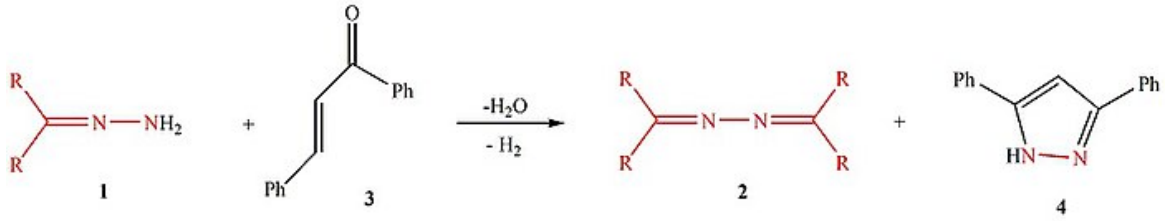
$$\mathbf{CH_3C(O)CH_2C(O)CH_3 + N_2H_4 \rightarrow (CH_3)_2C_3HN_2H + 2\,H_2O}$$

6.1.2 Reactions of Pyrazole:

Pyrazoles react with potassium borohydride to form a class of ligands known as scorpionate. Pyrazole itself reacts with potassium borohydride at high temperatures (~200 °C) to form a tridentate ligand known as Tp ligand.



3,5-Diphenyl-1*H*-pyrazole is produced when (*E*)-1,3-diphenylprop-2-en-1-one is reacted with hydrazine hydrate in the presence of elemental sulfur[9] or sodium persulfate,[10] or by using a hydrazone in which case an azine is produced as a by-product.



6.2 IMIDAZOLE:

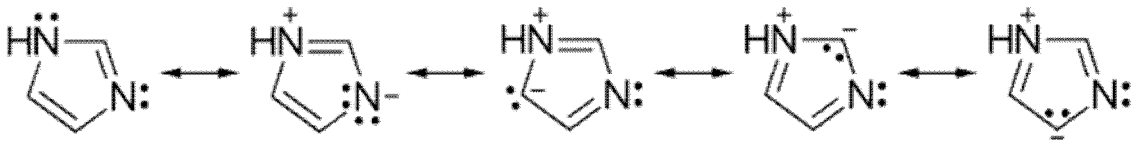
Imidazole is an organic compound with the formula $C_3N_2H_4$. It is a white or colourless solid that is soluble in water, producing a mildly alkaline solution. In chemistry, it is an aromatic heterocycle, classified as a diazole, and has non-adjacent nitrogen atoms.

Many natural products, especially alkaloids, contain the imidazole ring. These imidazoles share the 1,3-C_3N_2 ring but feature varied substituents. This ring system is present in important biological building blocks, such as histidine and the related hormone histamine. Many drugs contain an imidazole ring, such as certain antifungal drugs, the nitroimidazole series of antibiotics, and the sedative midazolam

When fused to a pyrimidine ring, it forms a purine, which is the most widely occurring nitrogen-containing heterocycle in nature.

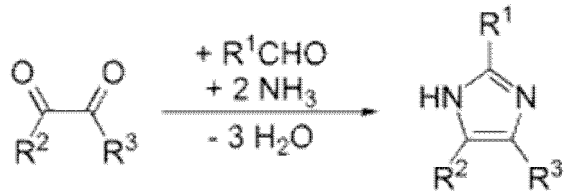
6.2.1 Structure and Properties:

Imidazole is a planar 5-membered ring. It exists in two equivalent tautomeric forms, because hydrogen can be bound to one or the other nitrogen atom. Imidazole is a highly polar compound, as evidenced by its electric dipole moment of 3.67 D. It is highly soluble in water. The compound is classified as aromatic due to the presence of a planar ring containing 6 π-electrons (a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring). Some resonance structures of imidazole are shown below.



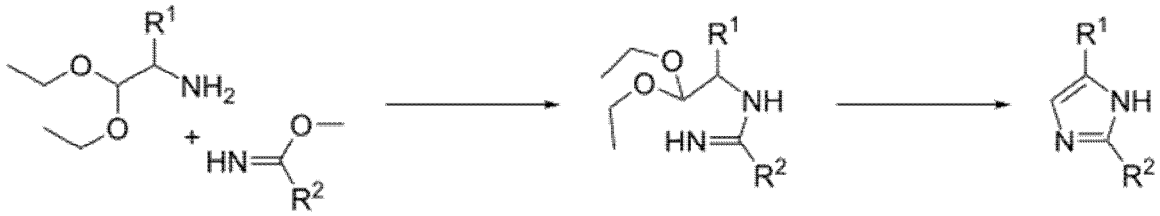
6.2.2 Synthesis:

Imidazole was first reported in 1858 by the German chemist Heinrich Debus, although various imidazole derivatives had been discovered as early as the 1840s. It was shown that glyoxal, formaldehyde, and ammonia condense to form imidazole (glyoxaline, as it was originally named).This synthesis, while producing relatively low yields, is still used for generating *C*-substituted imidazoles.



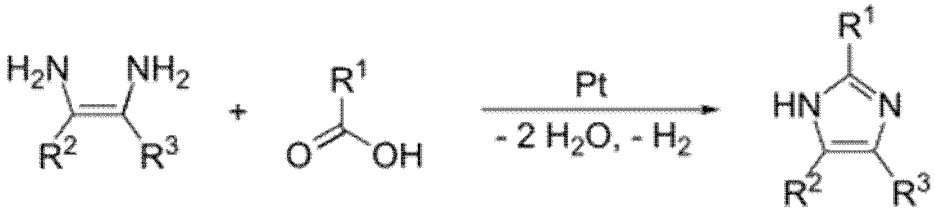
6.2.2.1 One Component:

The (1,5) or (3,4) bond can be formed by the reaction of an imidate and an α aminoaldehyde or α-aminoacetal. The example below applies to imidazole when R_1 = R_2 = hydrogen.



6.2.2.2 Two Component:

The (1,2) and (2,3) bonds can be formed by treating a 1,2-diaminoalkane, at high temperatures, with an alcohol, aldehyde, or carboxylic acid. A dehydrogenating catalyst, such as platinum on alumina, is required.

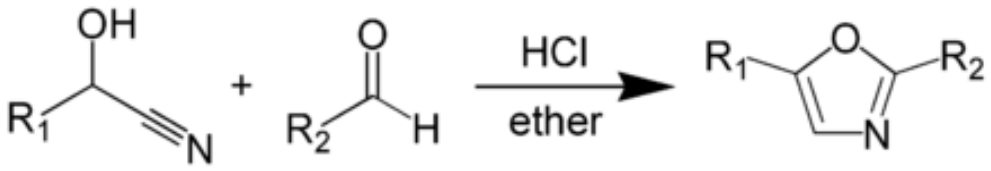


6.3 OXAZOLE:

Oxazole is the parent compound for a vast class of heterocyclic aromatic organic compounds. These are azoles with an oxygen and a nitrogen separated by one carbon. Oxazolesare aromatic compounds but less so than the thiazoles. Oxazole is a weak base; its conjugate acid has a pK_a of 0.8, compared to 7 for imidazole.

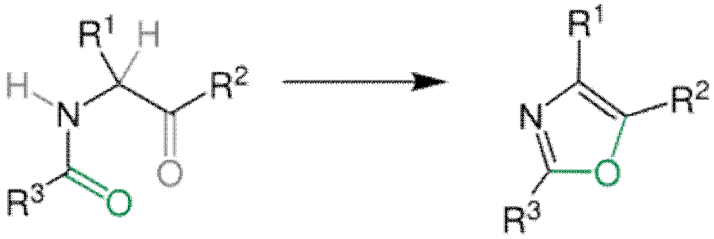
6.3.1 Fischer Oxazole Synthesis:

The **Fischer oxazole synthesis** is a chemical synthesis of an oxazole from a cyanohydrin and an aldehyde in the presence of anhydrous hydrochloric acid. This method was discovered by Emil Fischer in 1896.



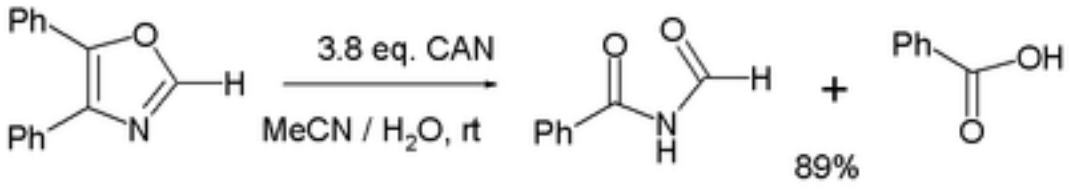
6.3.2 Robinson - Gabriel Synthesis:

The **Robinson - Gabriel synthesis** is an organic reaction in which a 2-acylamino-ketone reacts intramolecularly followed by a dehydration to give an oxazole. A cyclodehydrating agent is needed to catalyze the reaction[1][2][3] It is named after Sir Robert Robinson and Siegmund Gabriel who described the reaction in 1909 and 1910, respectively.

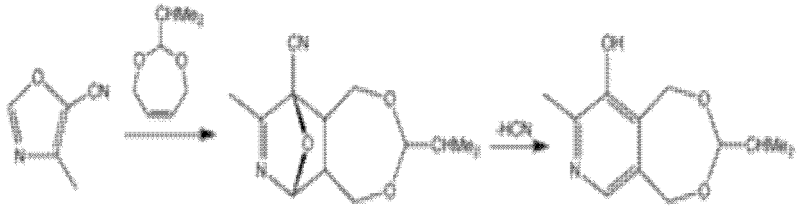


6.3.3 Reactions:

Various oxidation reactions. One studyreports on the oxidation of 4,5-diphenyloxazole with 3 equivalents of CAN to the corresponding imide and benzoic acid.



In the balanced half-reaction three equivalents of water are consumed for each equivalent of oxazoline, generating 4 protons and 4 electrons (the latter derived from Ce^{IV}).

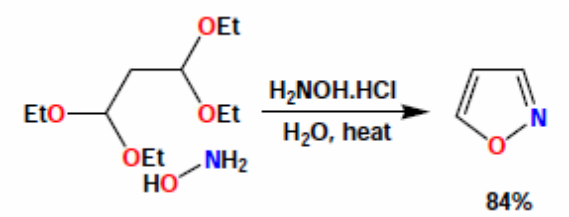


6.4 ISO-OXAZOLE:

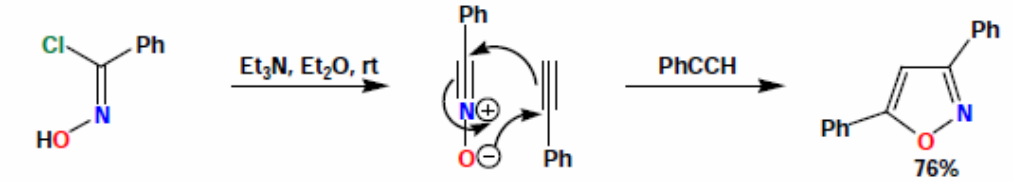
Isoxazole is an azole with an oxygen atom next to the nitrogen. It is also the class of compounds containing this ring. **Isoxazolyl** is the univalent radical derived from isoxazole.

6.4.1 Synthesis of Isoxazole:

Synthesis of Isoxazoles from 1,3-Dicarbonyl Compounds and Hydrazines or Hydroxylamines ("3+2").



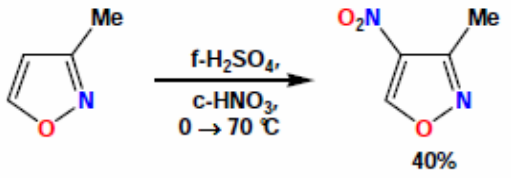
Mono-alkyl/-aryl alkynes react to give 3,5-disubstituted isoxazoles but when the alkyne possesses two substituents mixtures of 3,4- and 3,5-disubstituted isoxazoles are usually produced.



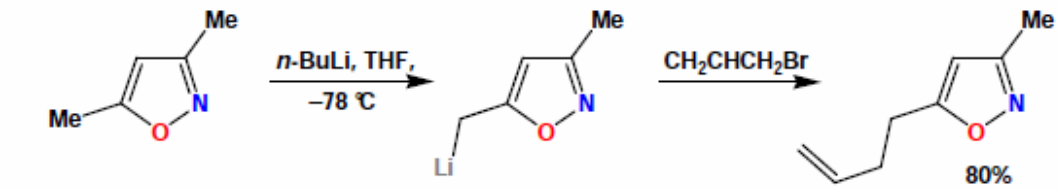
6.4.2 Reactions:

6.4.2.1 Nitration of Isoxazoles:

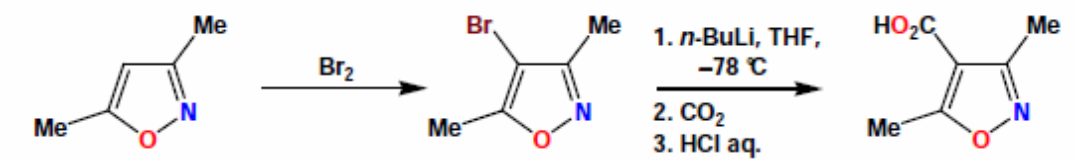
Isoxazole nitrates in very low yield, but 3-methylisoxazole is sufficiently reactive to undergo nitration at the 4-position.



Surprisingly, 3-methylisothiazole does not deprotonate as easily as 5-methylisothiazole and the same effect is found in isoxazoles.



Metal-halogen exchange can be used to avoid deprotonation of alkyl groups

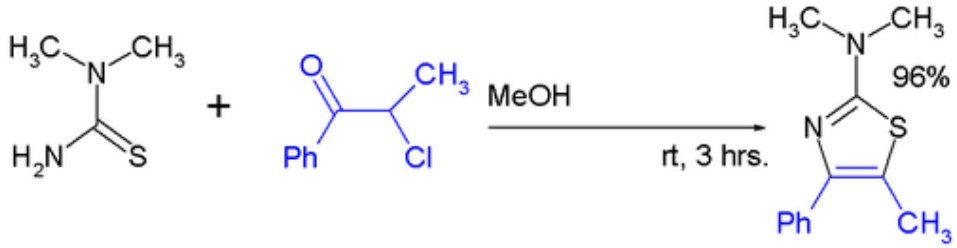


6.5 THIAZOLE:

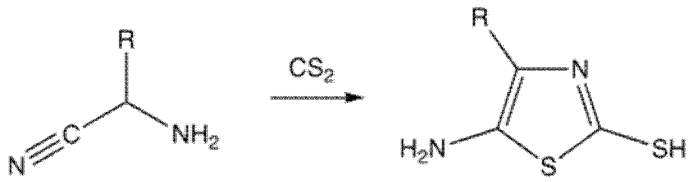
Thiazole, or **1, 3-thiazole**, is a heterocyclic compound that contains both sulfur and nitrogen; the term 'thiazole' also refers to a large family of derivatives. Thiazole itself is a pale yellow liquid with a pyridine-like odor and the molecular formula C_3H_3NS.[2] The thiazole ring is notable as a component of the vitamin thiamine (B_1).

6.5.1 Synthesis:

The Hantzsch thiazole synthesis (1889) is a reaction between haloketones and thioamides. For example, *2,4-dimethylthiazole* is synthesized from acetamide, phosphorus pentasulfide, and chloroacetone. Another example is given below

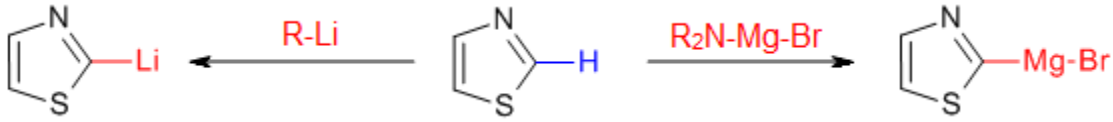


The **Cook–Heilbron thiazole synthesis** highlights the formation of 5-aminothiazoles through the chemical reaction of α-aminonitriles or aminocynoacetates with dithioacids, carbon disulphide, carbon oxysulfide, or isothiocynates at room temperature and under mild or aqueous conditions. Variation of substituents at the 2nd and 4th position of the thiazole is introduced by selecting different combinations of starting reagents.



6.5.2 Reactions:

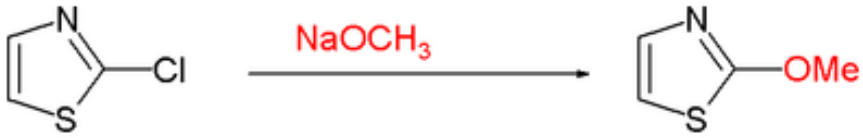
Deprotonation at C2: the negative charge on this position is stabilized as an ylide; Hauser bases and organolithium compounds react at this site, replacing the proton.



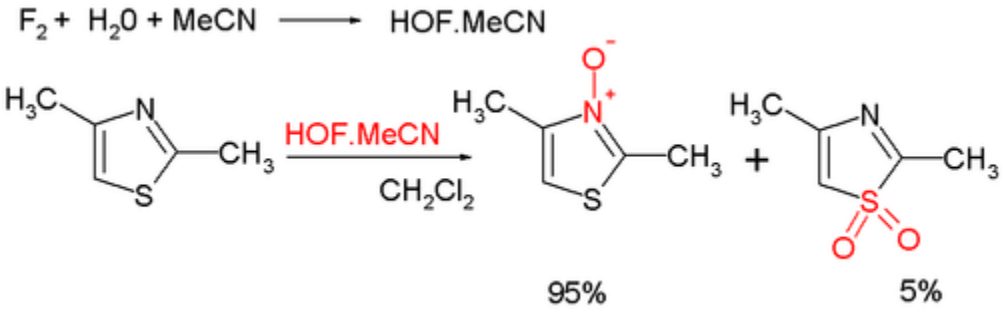
2-(trimethylsiliyl) thiazole (with a trimethylsilyl group in the 2-position) is a stable substitute and reacts with a range of electrophiles such as aldehydes, acyl halides, and ketenes.

Electrophilic aromatic substitution at C5 requires activating groups such as a methyl group in this bromination:

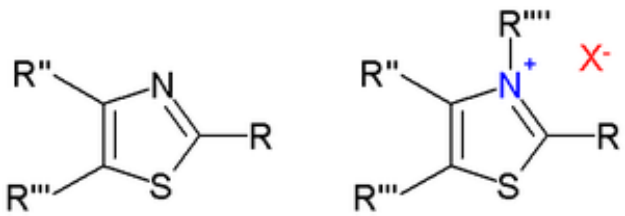
Nucleophilic aromatic substitution often requires a leaving group such as chlorine at C2 with



Organic oxidation at nitrogen gives the aromatic thiazole *N*-oxide; many oxidizing agents exist, such as mCPBA; a novel one is hypofluorous acid prepared from fluorine and water in acetonitrile; some of the oxidation takes place at sulfur, leading to non-aromatic sulfoxide/sulfone.



Alkylation of thiazoles at nitrogen forms a **thiazolium** cation. Thiazolium salts are catalysts in the Stetter reaction and the Benzoin condensation. Deprotonation of *N*-alkyl thiazolium salts give the free carbenes[9] and transition metal carbene complexes.



LESSON - 7

NATURAL PRODUCTS

7.1 THE IMPORTANCE OF NATURAL PRODUCTS AS DRUGS:

Natural products have played a crucial role in drug discovery and development throughout human history. Their importance spans from traditional medicine to modern pharmaceuticals.

7.1.1 Historical Significance:

Natural products have been the foundation of medicine for thousands of years. Traditional healing systems like Ayurveda, Traditional Chinese Medicine, and indigenous pharmacopeias all relied heavily on plant, fungal, and animal-derived substances. Many modern drugs trace their origins to these traditional remedies.

7.1.2 Key Contributions to Modern Medicine:

Natural products have contributed significantly to our current pharmacopeia:

- Approximately 50% of FDA-approved drugs from 1981-2019 were either natural products, derived from natural products, or inspired by natural product structures
- Many life-saving medicines originate from natural sources, including antibiotics, anticancer agents, immunosuppressants, and pain relievers
- Several blockbuster drugs like paclitaxel (Taxol, from yew trees), artemisinin (from sweet wormwood), and lovastatin (from fungi) came directly from nature

7.1.3 Unique Advantages:

Natural products offer several distinct advantages as drug sources:

- **Structural Complexity and Diversity:** Natural products often possess complex 3D structures that synthetic chemistry struggles to replicate, providing unique scaffolds for drug development
- **Biological Relevance:** Having evolved for specific biological functions, natural compounds often interact with cellular targets in ways synthetic molecules may not
- **Lead Compound Potential:** Even when not directly usable as drugs, natural products frequently serve as starting points for developing more effective medications

- **Novel mechanisms of action**: Natural products can reveal previously unknown biological pathways and mechanisms.

In conclusion, natural products are essential in the development of new drugs. They offer a diverse and rich source of bioactive compounds with therapeutic potential, helping to combat a wide range of diseases from bacterial infections to cancer. Their role in modern medicine continues to evolve, and they are central to the future of drug discovery.

7.2 INTRODUCTION OF TERPENOIDS:

There are many different classes of naturally occurring compounds. Terpenoids also form a group of naturally occurring compounds majority of which occur in plants, a few of them have also been obtained from other sources. Terpenoids are volatile substances which give plants and flowers their fragrance. They occur widely in the leaves and fruits of higher plants, conifers, citrus and eucalyptus.

The term ‘terpene’ was given to the compounds isolated from terpentine; a volatile liquid isolated from pine trees. The simpler mono and sesqui terpenes are chief constituent of the essential oils obtained from sap and tissues of certain plant and trees. The di and tri terpenoids are not steam volatile. They are obtained from plant and tree gums and resins. Tertraterpenoids form a separate group of compounds called ‘Carotenoids’

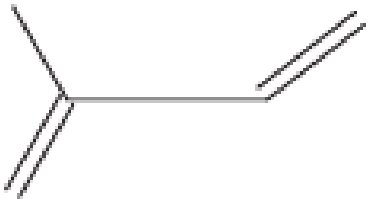
The term ‘terpene’ was originally employed to describe a mixture of isomeric hydrocarbons of the molecular formula $C_{10}H_{16}$ occurring in the essential oils obtained from sap and tissue of plants, and trees. But there is a tendency to use more general term ‘terpenoids’ which include hydrocarbons and their oxygenated derivatives. However the term terpene is being used these days by some authors to represent terpenoids.

By the modern definition: “Terpenoids are the hydrocarbons of plant origin of the general formula $(C_5H_8)n$ as well as their oxygenated, hydrogenated and dehydrogenated derivatives.”

7.3 ISOPRENE RULE:

Thermal decomposition of terpenoids give isoprene as one of the products. Otto Wallach pointed out that terpenoids can be built up of isoprene unit.

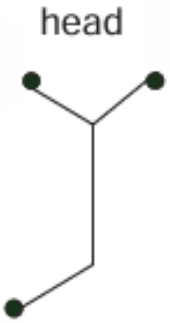
Isoprene rule stats that the terpenoid molecules are constructed from two or more isoprene unit.



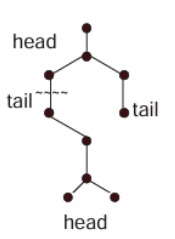
isoprene unit

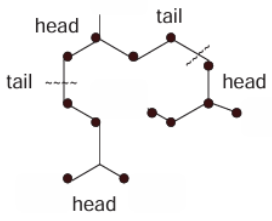
Further Ingold suggested that isoprene units are joined in the terpenoid via ‘head to tail’ fashion. Special isoprene rule states that the terpenoid molecule are constructed of two or more isoprene units joined in a ‘head to tail’ fashion.

But this rule can only be used as guiding principle and not as a fixed rule. For example, carotenoids are joined tail to tail at their central and there are also some terpenoids whose carbon content is not a multiple of five.

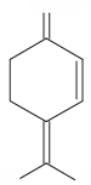


In applying isoprene rule we look only for the skeletal unit of carbon. The carbon skeletons of open chain monotrpenoids and sesqui terpenoids are,

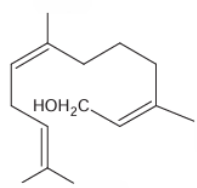




Examples.



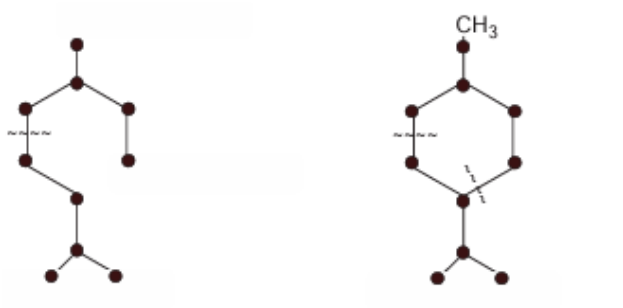
Myrcene
(monoterpene)



Farnesol (Sesquiterpene)

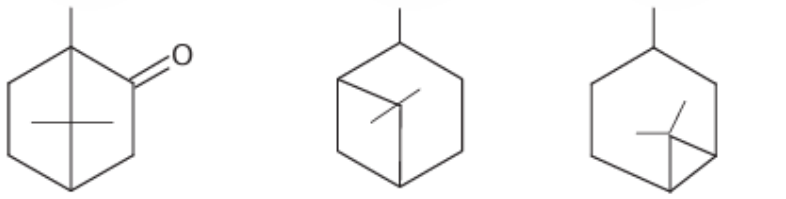
Ingold (1921) pointed that a gem alkyl group affects the stability of terpenoids. He summarized these results in the form of a rule called ‘gem dialkyl rule’ which may be stated as "Gem dialkyl group tends to render the cyclohexane ring unstable where as it stabilizes the three, four and five member rings.”

This rule limits the number of possible structures in closing the open chain to ring structure. Thus, the monoterpenoid open chain give rise to only one possibility for a monocyclic monoterpenoid i.e the p-cymene structure.



P-cymene structure

Bicyclic monoterpenodis contain a six member and a three-member ring. Thus, closure of the ten-carbon open chain monoterpenoid gives three possible bicyclic structures.



Camphor (6+5) system

Pinane (6+4) system

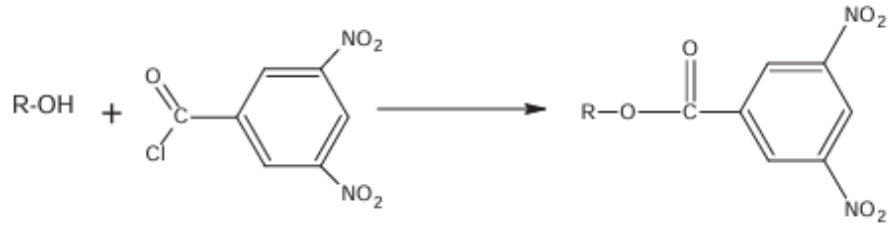
Carane (6+3) System

7.4 GENERAL METHODS OF STRUCTURE ELUCIDATION TERPENOIDS:

(i) Molecular Formula: molecular formula is determined by usual quantitative analysis and mol. Wt. determination methods and by means of mass spectrometry. If terpenoid is optically active, its specific rotation can be measured.

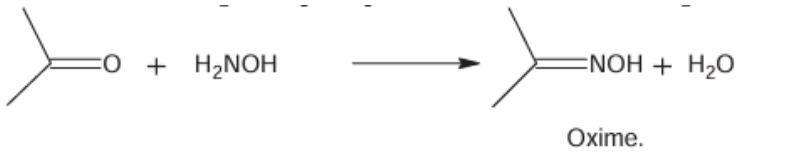
(ii) Nature of Oxygen Atom Present: If oxygen is present in terpenoids its functional nature is generally as alcohol aledhyde, ketone or carboxylic groups.

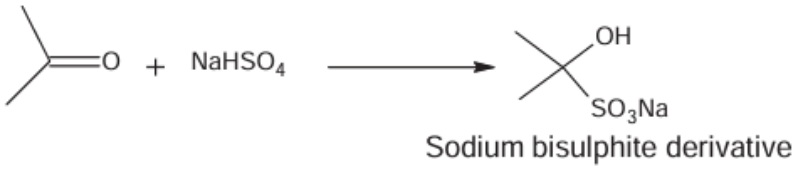
a) Presence of Oxygen Atom Present: Presence of –OH group can be determined by the formation of acetates with acetic anhydride and benzoyate with 3.5-dinitirobenzoyl chloride.



Primary alcoholic group undergo esterification more readily than secondary and tertiary alcohols.

b) Presence of >C=O group: Terpenoids containing carbonyl function form crystalline addition products like oxime, phenyl hydrazone and bisulphite etc.

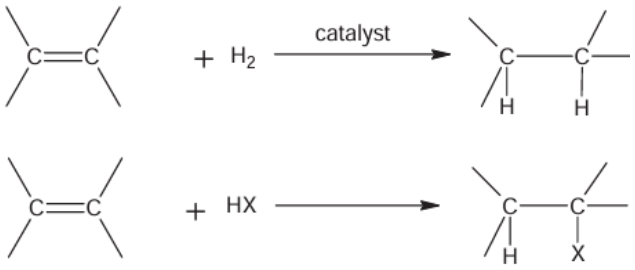




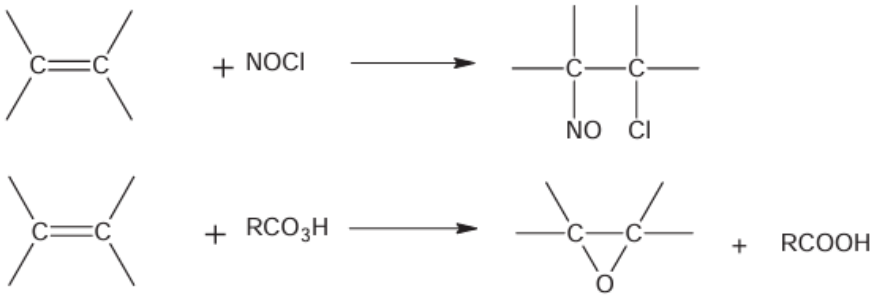
If carbonyl function is in the form of aldehyde, it gives carboxylic acid on oxidation without loss of any carbon atom whereas the ketone on oxidation yields a mixture of lesser number of carbon atoms.

iii) Unsaturation: The presence of olefinic double bond is confirmed by means of bromine, and number of double bond determination by analysis of the bromide or by quantitative hydrogenation or by titration with monoperpthalic acid.

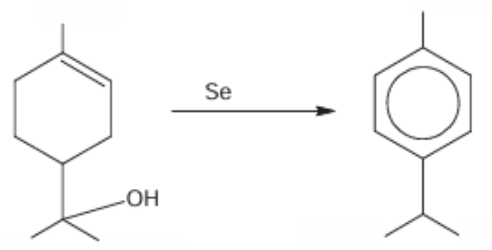
Presence of double bond also confirmed by means of catalytic hydrogenation or addition of halogen acids. Number of moles of HX absorbed by one molecule is equal to number of double bonds present.



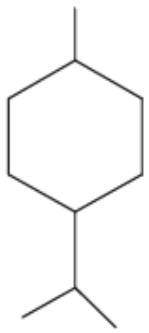
Addition of nitrosyl chloride (NOCl) (Tilden's reagent) and epoxide formation with peracid also gives idea about double bonds present in terpenoid molecule.



iv) **Dehydrogenation:** On dehydrogenation with sulphur, selenium, polonium or palladium terpenoids converted to aromatic compounds. Examination of these products the skelton structure and position of side chain in the original terpenoids can be determined. For example -terpenol on Se-dehydrogenation yields p-cymene.



Thus, the carbon Skelton of terpenol is as follows.



v) **Oxidative degradation:** Oxidative degradation has been the parallel tool for elucidating the structure of terpenoids. Reagents for degradative oxidation are ozone, acid, neutral or

alkaline potassium permanganate, chromic acid, sodium hypobromide, osmium tetroxide, nitric acid, lead tetra acetate and peroxy acids. Since oxidizing agents are selective, depending on a particular group to be oxidized, the oxidizing agent is chosen with the help of structure of degradation products.

vi) **Number of the Rings Present:** With the help of general formula of corresponding parent saturated hydrocarbon, number of rings present in that molecule can be determined.

vii) Relation between general formula of compound and type of compounds:

General formula of parent saturated Hydrocarbon	Type of structure
C_nH_{2n+2}	Acyclic
C_nH_{2n}	Monocyclic
C_nH_{2n-2}	Bicyclic
C_nH_{2n-4}	Tricyclic
C_nH_{2n-6}	Tetrayclic

For example, limonene (mol. formula. $C_{10}H_{16}$) absorbs 2 moles of hydrogen to give tetrahydro limonene (mol. Formula $C_{10}H_{20}$) corresponding to the general formula. C_nH_{2n}. It means limonoene has monocyclic structure.

viii) **Spectroscopic Studies:** All the spectroscopic methods are very helpful for the confirmation of structure of natural terpenoids and also structure of degradation products. The various methods for elucidating the structure of terpenoids are; UV Spectroscopy, IR Spectroscopy, NMR Spectroscopy, Mass Spectroscopy

ix) **X-ray Analysis:** This is very helpful technique for elucidating structure and stereochemistry of terpenoids.

x) **Synthesis:** Proposed structure is finally confirmed by synthesis. In terpenoid chemistry, many of the synthesis are ambiguous and, in such cases, analytical evidences are used in conjunction with the synthesis.

Prof. D. Ramachandran

LESSON - 8

STRUCTURAL DETERMINATION AND SYNTHESIS OF TERPENOIDS

8.1 STRUCTURE DETERMINATION AND SYNTHESIS OF α-TERPINEOL:

α-Terpineol is perhaps the most important monoterpenoid. It is naturally occurring optically active terpenoid whose (+) and (-) forms occur in nature. The melting Point of racemic form is 35°C and it is found in form of various esters or alone in various essential oils. The (+) form is found in petitgrain and neroli oils, the (–) form in camphor oil and the racemic form in cajeput oil.

8.1.1 Structural Elucidation:

1) Molecular formula of α-terpineol as determined by analytical data is $C_{10}H_{18}O$.

2) α-Terpineol adds two atoms of hydrogen or two atoms of bromine to give addition products showing thereby the presence of one double bond.

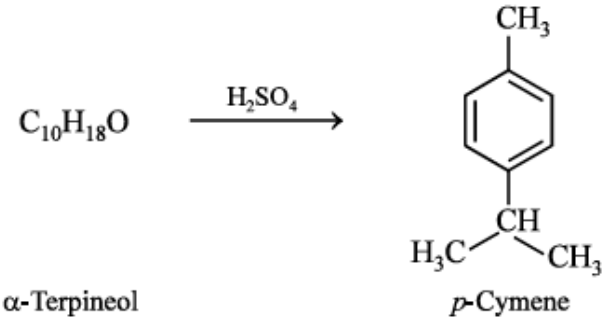
$$C_{10}H_{18}O.Br_2 \xleftarrow{Br_2} C_{10}H_{18}O \xrightarrow{H_2} C_{10}H_{20}O$$

3) α-Terpineol gets dehydrated to give an olefin which shows that alcoholic group is tertiary. Other reactions also prove that α-terpineol contains a tertiary alcoholic group.

$$C_{10}H_{18}O \xrightarrow{-H_2O} C_{10}H_{16}$$

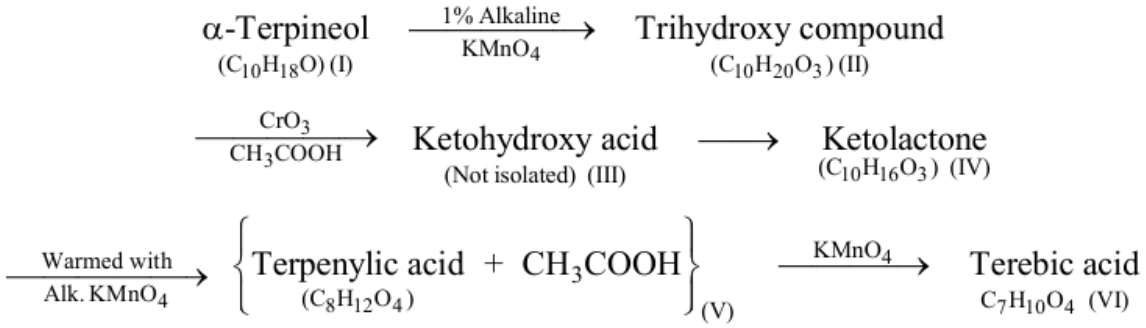
4) From the above facts it is clear that the parent saturated hydrocarbon of-terpineol α is $C_{10}H_{20}$ ($C_{10}H_{18}O$—OH gp + 1 hydrogen atom in place of OH gp + 2 hydrogen atoms for a double bond). This formula $C_{10}H_{20}$ has the form C_nH_{2n} which represents a monocyclic system.

5) On heating with sulphuric acid, α-terpineol forms p-cymene in low yield. Combining this fact with the observation that α-terpineol is monocyclic, leads to the conclusion that α-terpineol has p-cymene carbon skeleton.



α-Terpineol *p*-Cymene

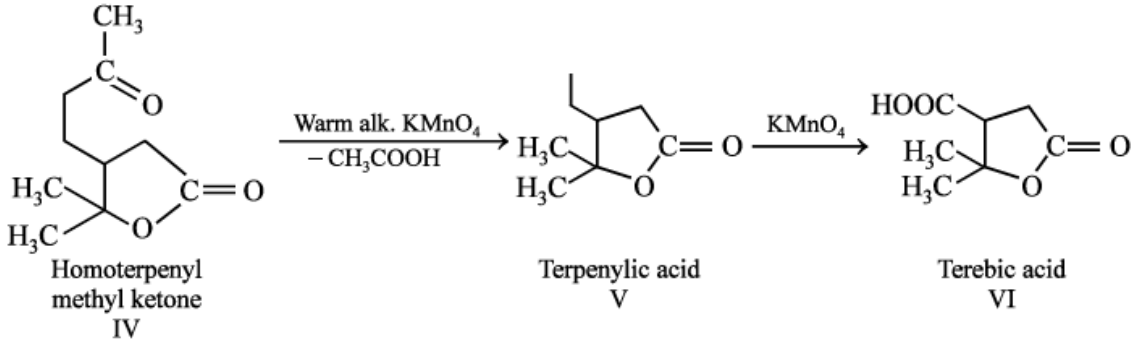
6) Thus, we can conclude that -terpineol α is p-methane with one double bond and a tertiary alcoholic group. The positions of these functional groups were ascertained by a series of graded oxidation reaction by Wallach (1893–1895). The reactions are as given below. Only number of carbon atoms in each product are given.



The oxidation of an α-terpineol with alkaline potassium permanganate must have hydroxylated the double bond to produce the trihydroxy compound C10H20O3 (II). This on oxidation with chromic acid produced the compound C10H16O3 (IV). Compound IV was neutral possessing a ketonic group. It did not react with sodium carbonate solution showing the absence of carboxyl group. However, IV on being refluxed with standard solution of sodium hydroxide, revealed that alkali has been consumed equivalent to one carboxyl group. Thus (IV) could be a lactone of the monocarboxylic acid which could not be isolated. The slow and spontaneous lactonisation indicates that the acid must have been a γ-hydroxy acid and hence IV is a γ-lactone. Oxidation of IV with alkaline potassium permanganate to yieldC8H12O4 (Terpenylic acid) and acetic acid points IV to be a methyl ketone having a CH3CO- group. The nature of IV was confirmed by its synthesis (Simonsen et. al. 1932) and could be called as homoterpenyl-methyl ketone.

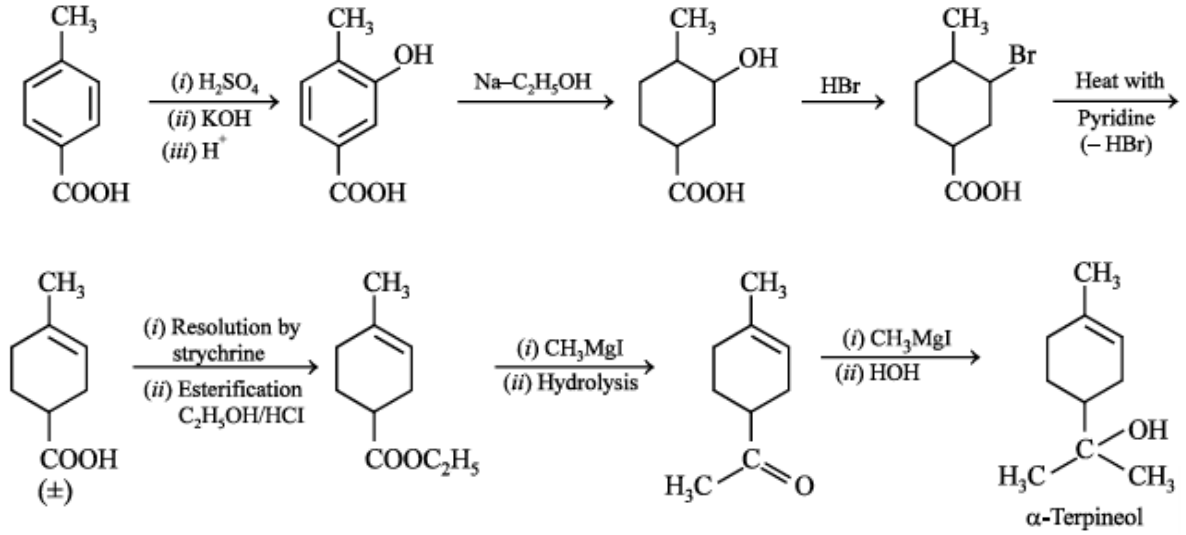
In the formation of the compound (IV) from (II) there has been no loss of carbon atoms hence the double bond must be in the ring and not outside. Had it been outside the number of carbon atoms in (IV) must have been less.

The oxidation of IV (which has been synthesised) to terpenylic acid (V) and terebic acids VI can be represented as given below.



8.1.2 Synthesis of α-Terpineol:

First synthesis of α-terpineol was accomplished in 1904 by Perkin Junior. After four years Perkin Junior, Meldrum and Fisher synthesised α-terpineol starting from p-toluic acid.

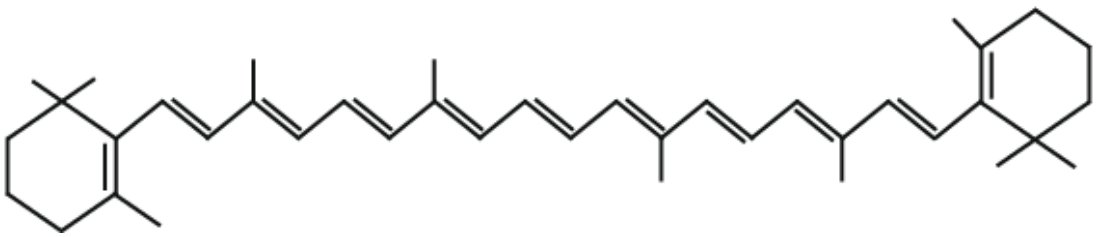


8.2 STRUCTURE DETERMINATION AND SYNTHESIS OF β-CAROTENE (C_{40} H_{56}):

8.2.1 Introduction:

Beta-carotene is found in pumpkins, sweet potatoes, carrots and winter squash. β-carotene is responsible for their orange yellow colour.

8.2.2 Structure:



Structure of Beta Carotenoid

8.2.3 Structure Elucidation of β-carotene:

(i) Molecular Formula: Molecular formula of β-carotene is C_{40} H_{56} which contain 8 isoprene units.

(ii) Determination of Unsaturation: By the catalytic hydrogenation of β-carotene, it is concluded that 11 double bonds are present in β-carotene.

$$\underset{\beta-\text{Carotene}}{C_{40}H_{56}+11H_2} \xrightarrow{Pt} \underset{\text{perhydro}-\beta-\text{carotene}}{C_{40}H_{78}}$$

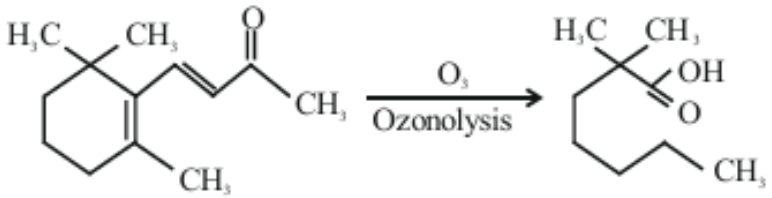
(iii) Bicyclic Ring: General formula $C_n H_{2n-2}$ tends it has two rings.

(iv) Presence of Five Conjugated Double Bonds: The characteristic reaction of conjugated double bond, the β-carotene form adducts with 5 maleic anhydride molecules. This show that there are five conjugated double bonds in β-carotene.

(v) Ozoanalysis: On ozonalysis, b-ionone gives one molecule of geronic acid, while β-carotene on ozonalysis gives two molecules of geronic acid. (Karror 1930).

$$\beta-\text{Carotene} \xrightarrow{\text{air}} \beta-\text{ionone}$$

$$\beta-\text{Carotene} \xrightarrow[[O]]{\text{Cold}} \beta-\text{ionone}$$

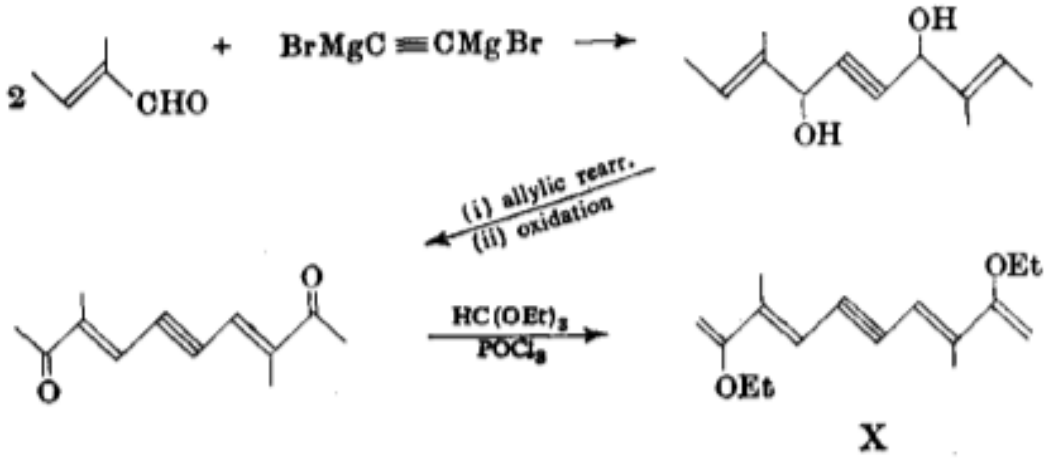


β-inone Geronic acid

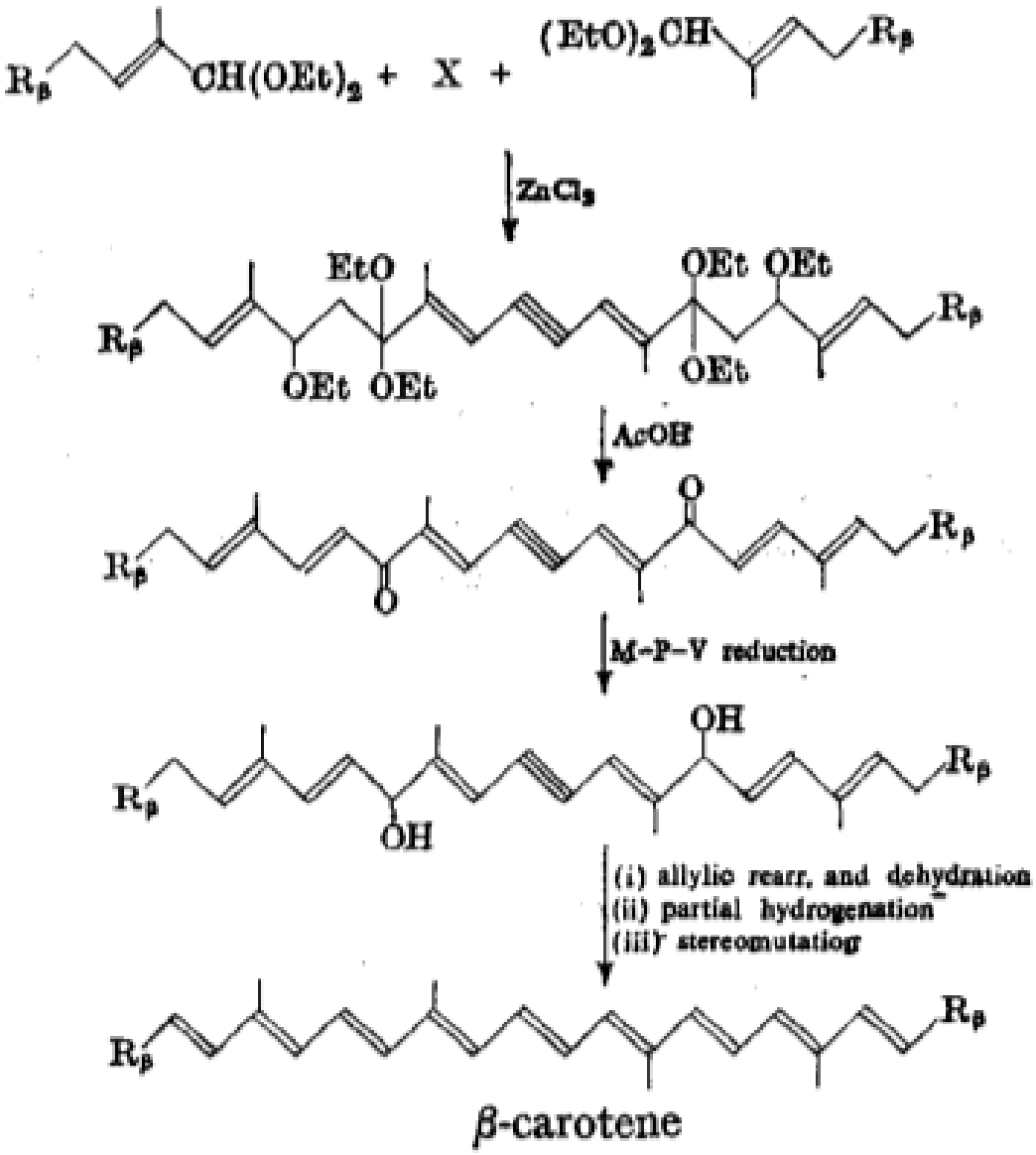
8.2.3 Synthesis:

The structure of β-carotenes is confirmed by the following synthesis:

An example of the synthesis of *β*-carotene by the third is that of Isler *et al.* (1957) [R_β = *β*-ionine ring]:



X



β-carotene

8.3 STRUCTURE DETERMINATION AND SYNTHESIS OF CAMPHOR:

Camphor occurs in camphor tree of Formosa and Japan. It is optically active; the (+) and (-) forms occur in nature. It is solid having m.p. 180oC. It is obtained by steam distillation of wood, leaves or bark of camphor tree. It sublimes at room temperature.

It is used in pharmaceutical preparation because of its analgesic, stimulant for heart muscles, expectorant and antiseptic properties. It is used in manufacture of celluloid, smokeless powder and explosives. It is also used as moth repellent.

8.3.1 Structure Determination:

(i) Molecular Formula: By usual method it was found to be C10H16O.

(ii) Saturated Nature: General reactions like formation of mono substituted products; mono bromo, monochloro camphor and molecular refraction show that it is saturated.

(iii)Nature of Oxygen Atom Present: Nature of Oxygen atom in camphor is found to be ketonic as it forms oxime with hydroxyl amine, and phenyl hydrozone with phenyl hydrazine.

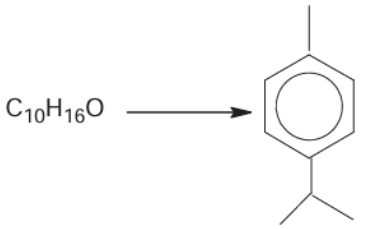
$$\underset{\text{Camphor}}{C_{10}H_{16}O} + H_2NOH \longrightarrow \underset{\text{Oxime}}{C_{10}H_{16}=N\text{-}OH}$$

$$\underset{\text{Camphor}}{C_{10}H_{16}O} + 2HN.NHC_6H_5 \longrightarrow \underset{\text{Phenyl hydrazone}}{C_{10}H_{16}=N\text{-}NH\text{-}C_6H_5}$$

(iv) Camphor when oxidised with nitric acid yields a dicarboxylic acid called camphoric acid, without loss of carbon atoms. On reduction with sodium amalgam, it gives secondary alcohol; borneol. Thus, oxo function in camphor is cyclic ketone.

(v) Presence of Bicyclic System: Molecular formula of saturated hydrocarbon of camphor (C10H16O) corresponds to the general formula of a bicyclic compound (CnH2n-2)

(vi)Presence of a Six Membered Ring: When distilled with zinc Chloride or phosphorous peroxide, it yields p-cymene. Formation of p-cymene confirms the presence of six-membered ring.



p-cymene

(vii)Nature of Carbon Frame: Bredt assigned the correct formula to camphor on the basis of above facts and also on the basis of oxidation products obtained from camphor. Oxidation of camphor with nitric acid gives camphoric acid, $C_{10}H_{16}O_6$ and further oxidation of camphoric acid gives camphoronic acid $C_9H_{14}O_6$.

$$C_{10}H_{16}O \xrightarrow[[O]]{HNO_3} \underset{\text{camphoric acid}}{C_{10}H_{16}O_4} \xrightarrow[[O]]{HNO_3} \underset{\text{camphoronic acid}}{C_9H_{14}O_6}$$

Camphoric acid is saturated dicarboxylic acid with the same number of carbon atoms as camphor, it suggests that keto group is present in one of ring and ring contain keto group is

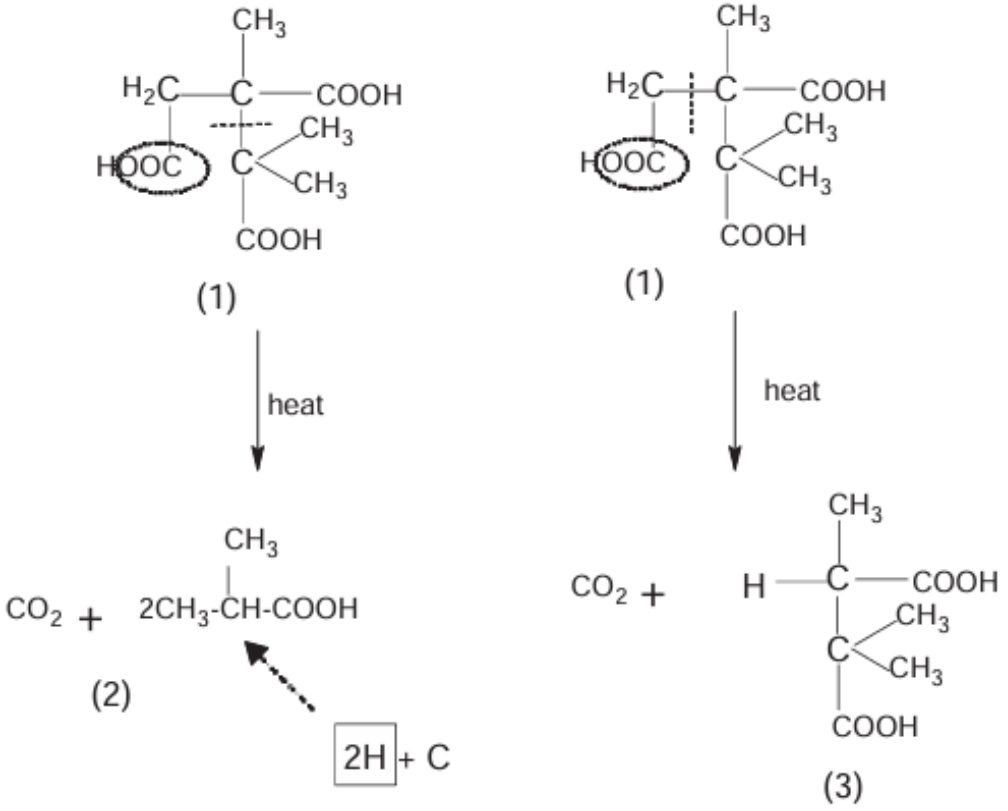
opened in the formation of camphoric acid. Thus, camphoric acid should be a monocyclic compound.

Camphoronic acid is tricarboxylic acid. In order to determine the structure of camphor, the structures of camphoric acid and camphoronic acid should be known.

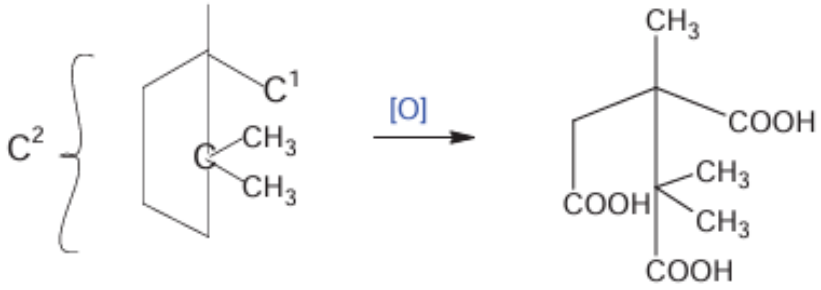
(viii) Structure of Camphoronic Acid and Camphoric Acid:

It was found to be staturated tricarboxylic acid, and on distillation at atmospheric pressure it gave (1) isobutyric acid (2) trimethyl succinic acid (3), carbondioxide, and carbon. But it does not undergo decarboxylation under ordinary condition it shows that three carboxylic groups are attached to the different carbon atoms.

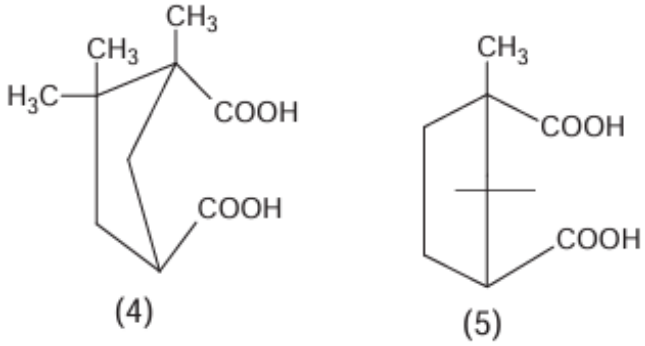
To explain the formation of carbon products Bredt suggested that camphoronic acid is a **α, β -** trimethyl tricarboxylic acid(1).



Above proposed structure for camphoronic acid is confirmed by its synthesis given by Perkin junior and Thorpe (1897). Camphoric acid was found to be saturated dicarboxylic acid. If above (1) structure of camphoronic acid should have three methyl groups. So camphoric acid is $(CH_3)_3C_5H_5(COOH)_2$. The saturated hydrocarbon of this (C_5H_{10}) corresponds to the general formula C_nH_{2n}. Thus, camphoric acid is cyclopentene derivative and oxidation of camphoric acid to camphoronic acid may be written as;

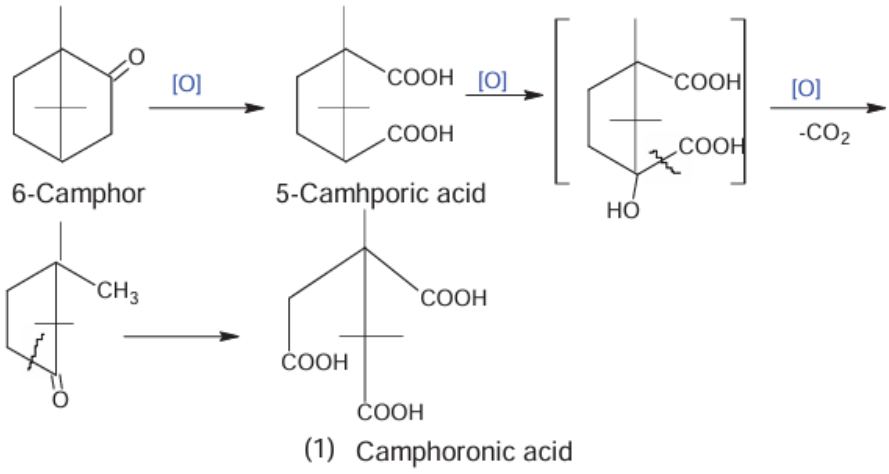


Camphoric anhydride form only one mono bromo derivative it means one –hydrogen is there in camphoric acid. Thus, the carbon atom of one carboxylic acid must be 1C. But question arises what should be the position of other –COOH group, when cyclopentane ring open on oxidation. It opens with loss of one carbon atom to give camphoronic acid. So, two structure (4) and (5) could be proposed for camphoric acid.

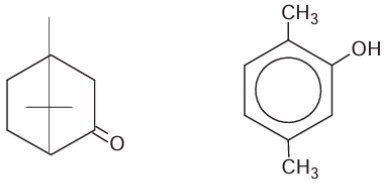


Structure (5) accounts for all the facts given in the foregoing discussion.

8.3.1.1 Structure of Camphor: Bredt therefore suggested that structure (5) was the structure camphoric acid and structure (6) was the structure of Camphor and proposed the following reaction.



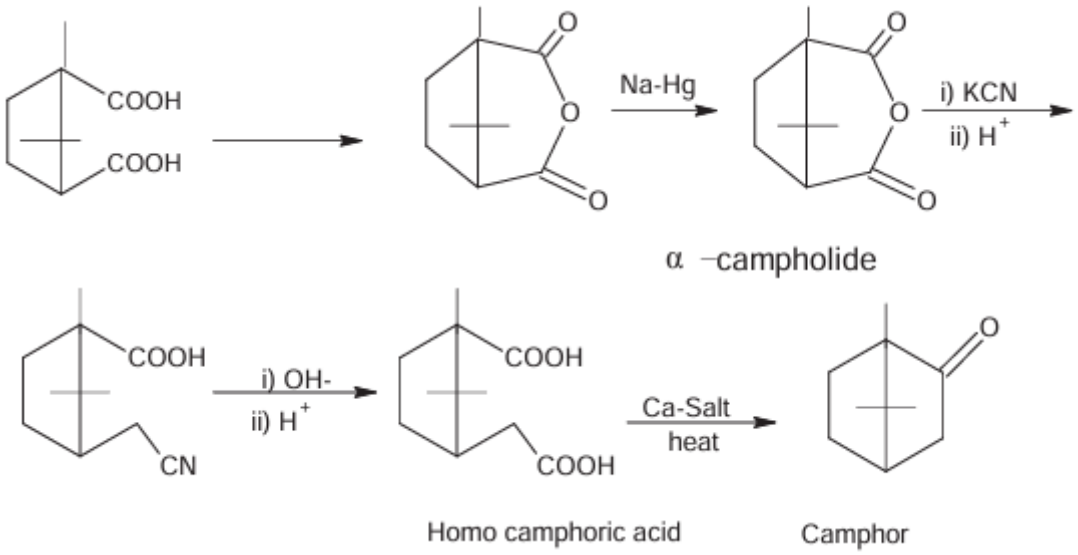
Bredt also proposed structure (7) for the camphor, but he rejected (7) in favor of (6) because camphor gives carvacrol (8). When distilled with iodine formation of which can be explained by assuming structure (6) for camphor.



(7) (8)

8.3.2 Synthesis: Finally, structure was confirmed by the synthesis.

Haller gave this synthesis of camphor from camphoric acid which was synthesized by Komppa.



Prof. D. Ramachandran

LESSON - 9

MOLECULAR REPRESENTATIONS OF ORGANIC MOLECULES

9.1 PROJECTION FORMULAE:

- To write the structure of methane, which has tetrahedral shape, we need length, breadth and also the height. So, we cannot justify writing these structures of these type of molecules on black board or paper. Some methods are used to justify the writing of structures of these molecules. These methods are called "projection formulae".
- "Writing of three-dimensional structures on two dimensional objects like paper or black board are called projection formulae".

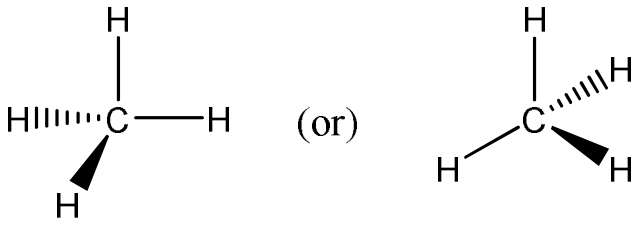
There are 4 types of projection formulae. They are:

- ➲ Wedge formulae
- ➲ Fischer projection formulae
- ➲ Newman projection formulae
- ➲ Saw-horse formulae

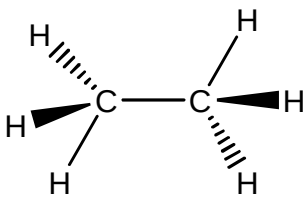
9.1.1 Wedge Formula:

Normal lines (–) are used to indicate the bonds which are present in the plane of the object. Solid wedge (▶) is used to represent the bonds which are above the plane forwards the observer. Broken wedge is used to indicate the bonds which are below the plane (away from the observer).

Ex: CH_4 (Methane)



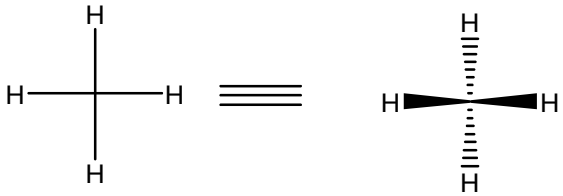
C_2H_6 (Ethane)



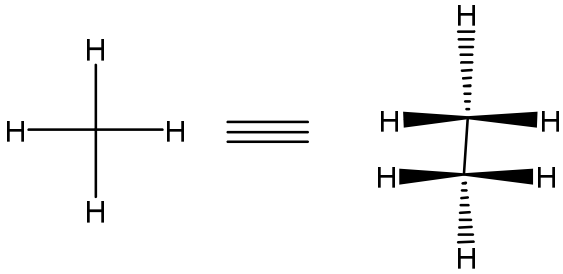
9.1.2 Fischer Projection Formula:

- A cross is used to represent the tetrahedral structures in Fischer projection formula.
- The groups which are in horizontal position are infront of paper plane, the groups which are in vertical position are behind the paper plane and the carbon atom to which 4 groups are attached is in the plane of the paper.

CH_4 (methane)



C_2H_6 (ethane)

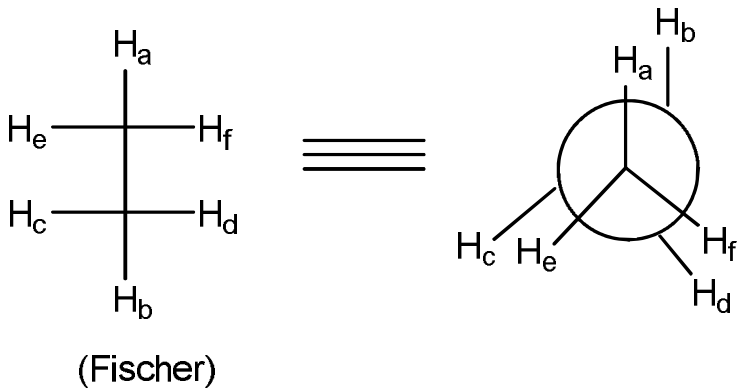


Note: (Fischer projection formula represents the molecule in eclipsed conformation)

9.1.3 Newman Projection Formula:

In Newman projection formula, the molecule is viewed from one end. The carbon atom near the eye is represented by a point and three atoms (or) groups attached to the carbon by three equally spaced radii (120°). The carbon atom away from the eye is designated by a circle and three atoms (or) groups attached to it by three equally spaced radii.

Newmann Projection for Ethane Molecule

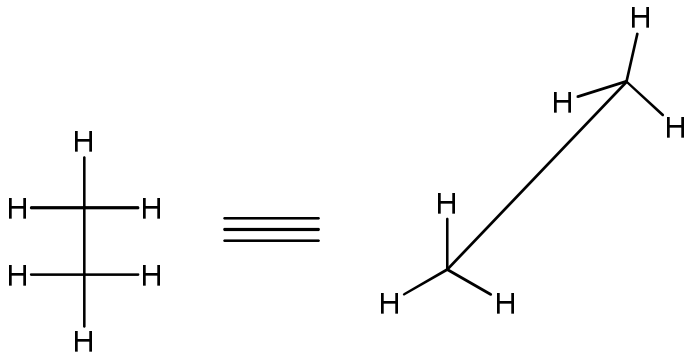


(Fischer)

9.1.4 Saw-Horse Formula:

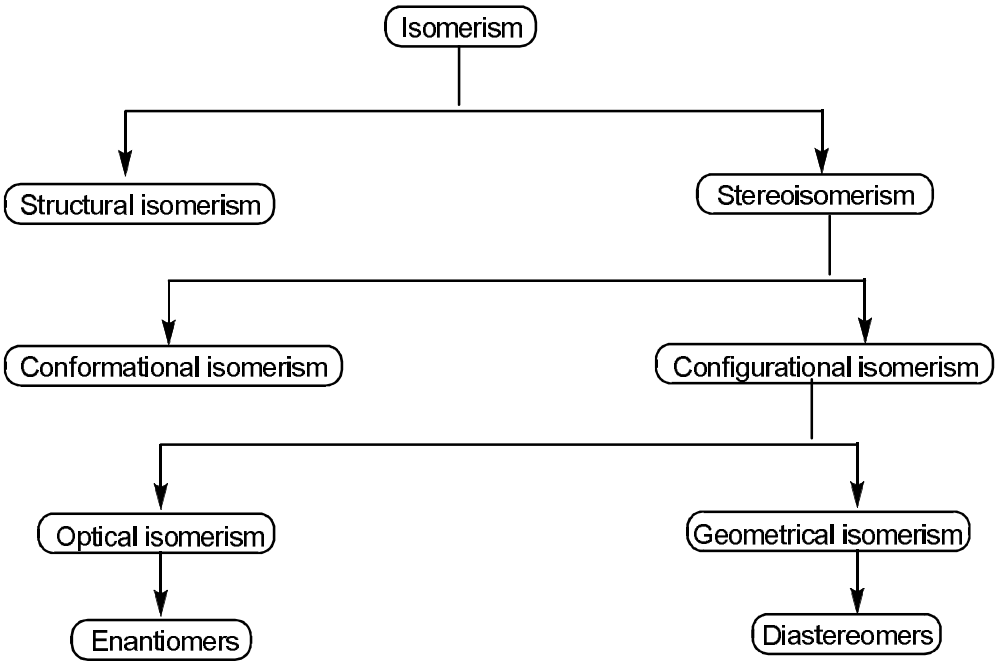
The saw-horse formula is the formula obtained when the fischer projection is viewed slightly from above in about 45° angle. The bond between two carbon atoms is drawn diagonally and is slightly elongated for clarity. The lower left hand carbon is considered to be towards front and upper right hand carbon towards back.

C_2H_6 (ethane)



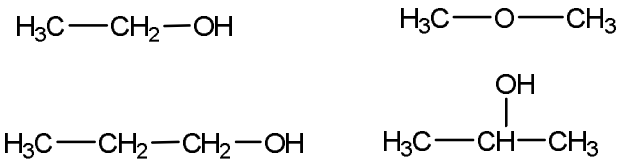
9.2 ISOMERISM:

Two or more compounds having the same molecular formula are called “isomers” and this phenomenon is called as “isomerism”.



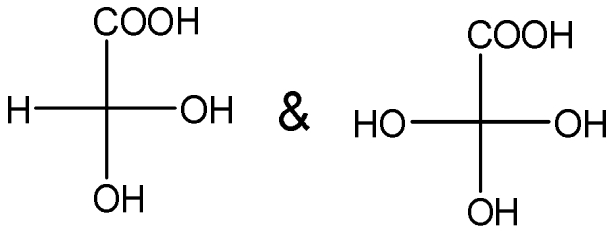
9.2.1 Structural Isomerism:

Two or more compounds having same molecular formula but differ in structural arrangement of atoms (or) groups are called “structural isomers” or “constitutional isomers”.



9.2.2 Stereoisomerism:

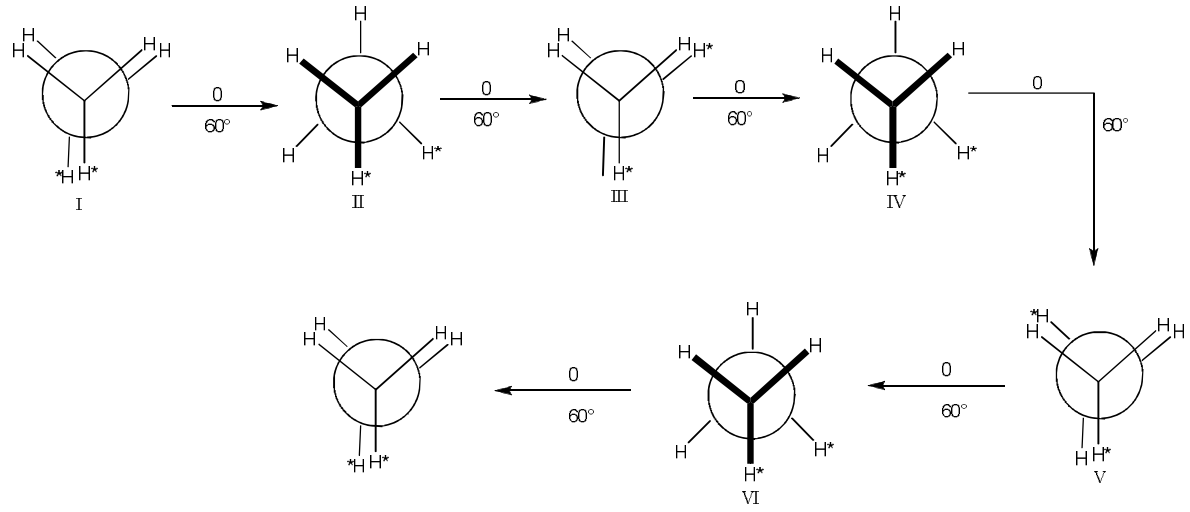
Two or more compounds having same molecular formulae as well as structural formulae, but differ in the arrangement of atoms (or) groups in space are called "stereoisomers" and this phenomenon is called as "stereoisomerism".



9.2.3 Conformational Isomerism:

Two or more stereoisomers which are interconvertable by C-C bond rotation at room temperature are called as "conformational isomers" and the phenomenon is called "conformation isomerism".

a) Conformations of Ethane:



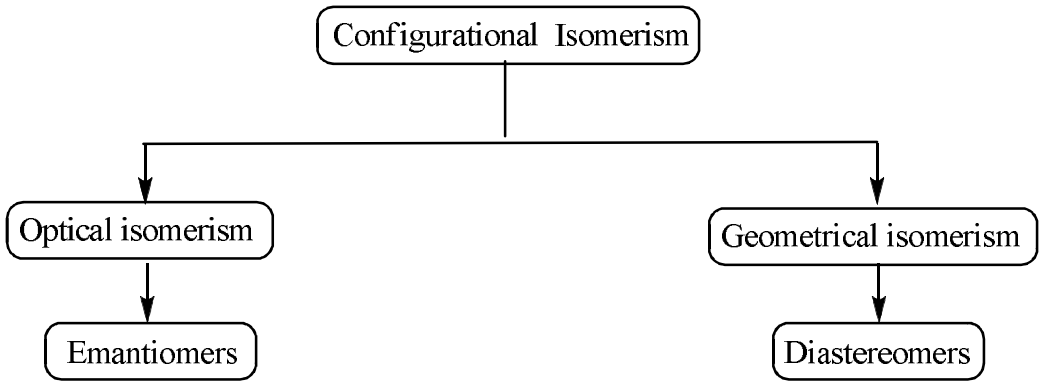
- The various conformations of ethane are obtained by fixing the front carbon and rotating the back carbon through an angle of 60° at a time.
- I, III, V conformers are called "eclipsed form".
- II, IV, VI conformers are called "staggered form".

- In eclipsed form, the bond pairs of C-H bonds of the two carbons are very close to each other. The energy of such arrangement is maximum when the bond pairs of two central carbon atoms are very close to each other. Hence eclipsed form is less stable.
- In staggered form, the bond pairs of the C-H bonds of the two carbons are far away from each other. The energy of such arrangement is minimum due to less repulsive forces between bond pairs of C-H bonds of two carbon atoms. Hence staggered form is stable form.

Stability ⇒ Staggered form > Eclipsed form

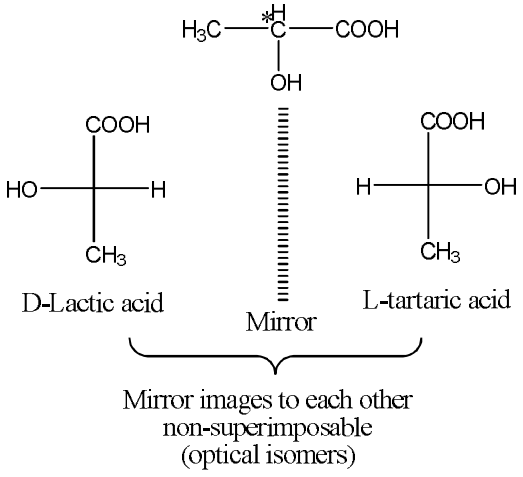
9.2.4 Configurational Isomerism:

Two or more stereoisomers which are not interconvertable at room temperature are called configurational isomers and the phenomenon is called "configurational isomerism".



9.2.4.1 Optical Isomerism:

If the two isomers are mirror images to each other and non-super imposable, then they are called "optical isomers" and the phenomenon is called "optical isomerism".



* Optical isomers differ in action on plane polarised light

* If one rotates plane polarised light to right and the other rotate it to left

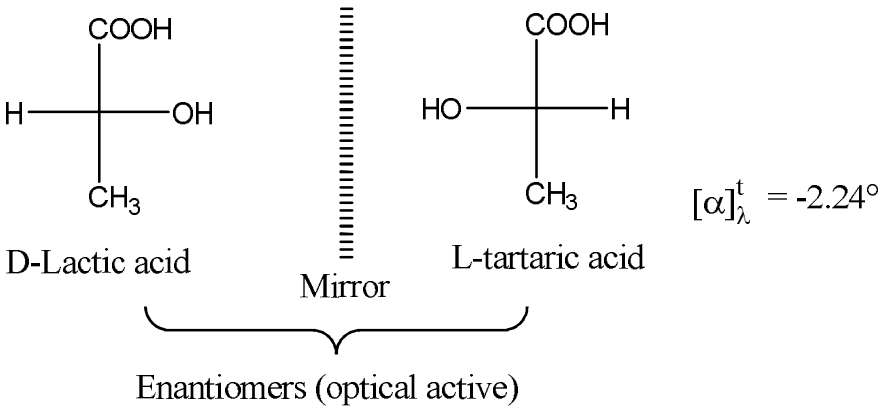
9.2.4.1.1 Enantiomers:

- Enantiomers are simplest type of optical isomers.
- "Enantiomers are the optical isomers which are non-superimposable mirror images of each other".

Characteristics:

- Enantiomers have same physical and chemical properties.
- Enantiomers rotate the plane polarized light in opposite directions but to the same extent.

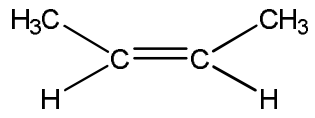
Example:



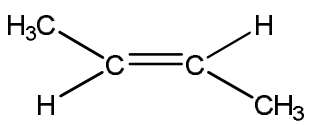
Conditions for Geometrical Isomerism:

- The molecule must have a C=C bond.
- There must be two different groups attached to each carbon atom of double bond.
- The isomer in which similar groups are present on one side of the double bond is called "Cis-isomer" and the isomer with similar groups on opposite side of double bond is called "trans-isomer".

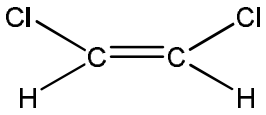
Example:



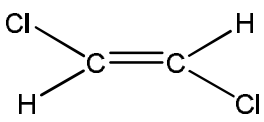
trans-1-butene



trans-2-butene



trans-1,2-dichloroethene



trans-1,2-dichloroethane

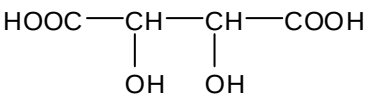
9.2.5 Diastereomers:

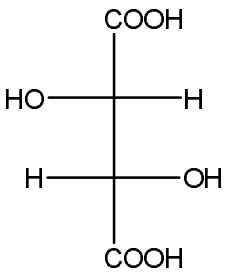
"Diastereomers are the stereoisomers which are not mirror images to each other".

Characteristics:

- Diastereomers have different physical properties.
- Diastereomers have different chemical properties.
- Diastereomers may have rotation in same or different direction to different extent.
- Diastereomers can be separated by physical methods like fractional crystallisation etc.

Example:

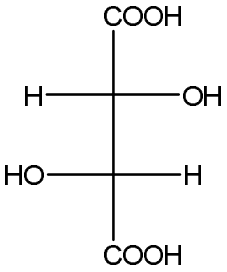
Consider tartaric acid,  which exists in three stereoisomers.



D-tartonic acid

I

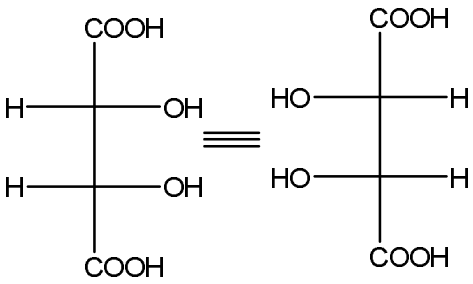
$[\alpha]^t_\lambda = +12°$



L-tartaric acid

II

$[\alpha]^t_\lambda = -12°$



Meso-tartoric acid

III

$[\alpha]^t_\lambda = 0°$

I, III = Diastereomers

II, III = Diastereomers

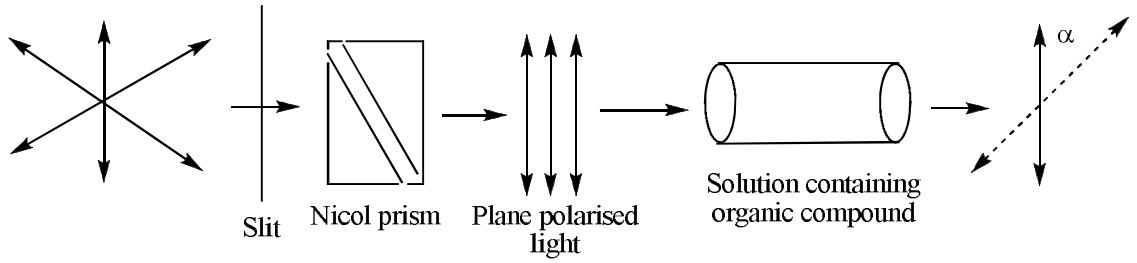
I, II = Enantiomers

LESSON - 10

CONCEPT OF CHIRALITY AND MOLECULAR SYMMETRY

10.1 OPTICAL ACTIVITY AND OPTICAL ROTATION:

An ordinary light vibrates in all the planes perpendicular to its path of propagation. This light is called "Non-plane polarised light". When the monochromatic light is passed through a nicol prism, the light vibrates in one plane and all other vibrations are stopped. Such a light is called "plane polarised light".



When plane polarised light is passed through solution of some carbon compounds, it may rotate the plane polarised light to left or right by some angle. Such carbon compounds are called "optically active compounds" and the phenomenon is called "optical activity".

- A substance which rotates the plane polarised light towards rights is called "dextro-rotatory" (d) and the one which rotates the plane polarised light towards left is called "Laevorotatory" (L).

  dextro-rotatory = d = +

  Laevo-rotatory = L = -

- The angle through which the plane polarised light is rotated by an optical active substance is called "optical rotation" (α).

  The optical rotation depends on

  i) Nature of the compound
  ii) Length of solution (Length of sample tube)
  iii) Temperature
  iv) Concentration of solution
  v) Wavelength of light used

- The optical activity of a substance is expressed in terms "specific rotation" which is constant.

$$[\alpha]_{\lambda}^{t} = \frac{\alpha}{l\,C}$$

Where; $[\alpha]_{\lambda}^{t}$ = Specific rotation

α= Angle of rotation (optical rotation)

l= Length of solution in sample tube (in decimetre)

C = Concentration of solution (in gm/CC)

Criterion for the Optical Rotation:

- Every object has its mirror image. Some objects are non-super imposable on their mirror images. So these two are different objects. This property is called "asymmetry". Asymmetry is the minimum condition for optical rotation.
- Any compound which is non-superimposable on its mirror image is optically active.
- Compounds with absence of plane of symmetry, centre of symmetry and n-fold alternating axis of symmetry are "asymmetric". Such compounds show optical activity.

Asymmetric ≡≡≡ Non-superimposable mirror image ≡≡≡ Absence of plane, centre and n-fold alternating axis of symmetry

⇓

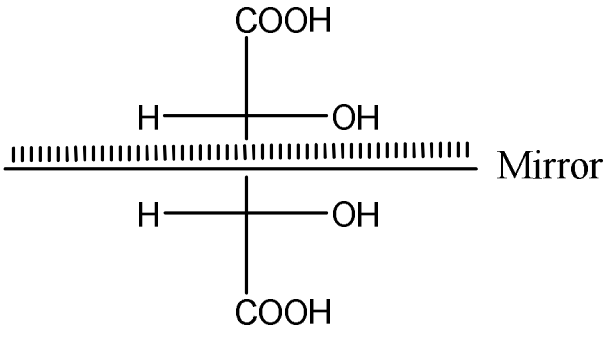
Optical activity

10.2 SYMMETRY OPERATIONS:

10.2.1 Plane of Symmetry (σ):

If an imaginary plane bisects the molecule into two equal halves which have object and mirror image relationship, such a plane is called "plane of symmetry".

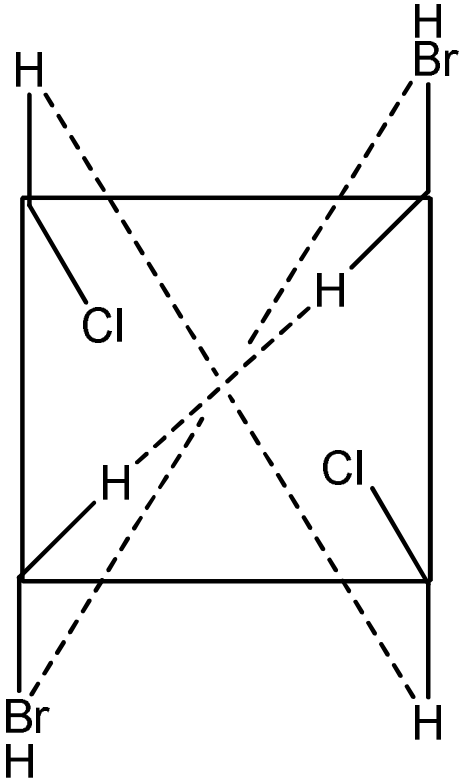
Ex: Meso-tartaric acid



(Optically inactive molecule)

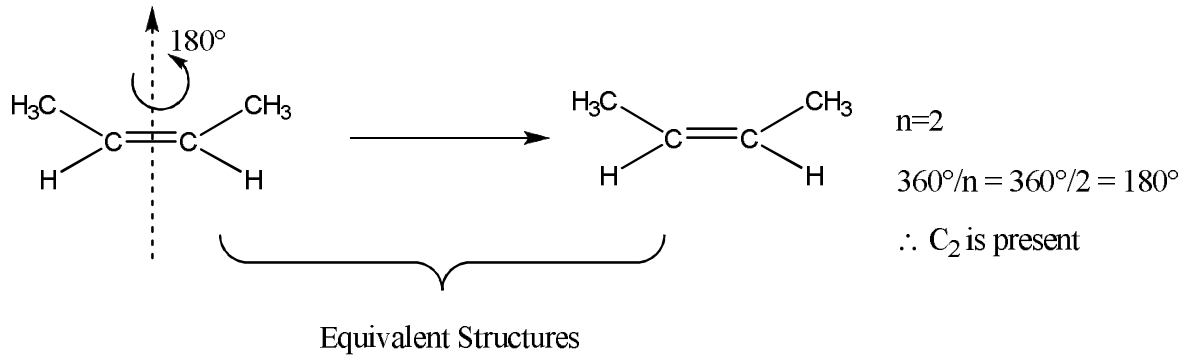
10.2.2 Centre of Symmetry (i):

Centre of symmetry is an imaginary point within an object such that a straight line drawn connecting the equivalent groups pass through it.



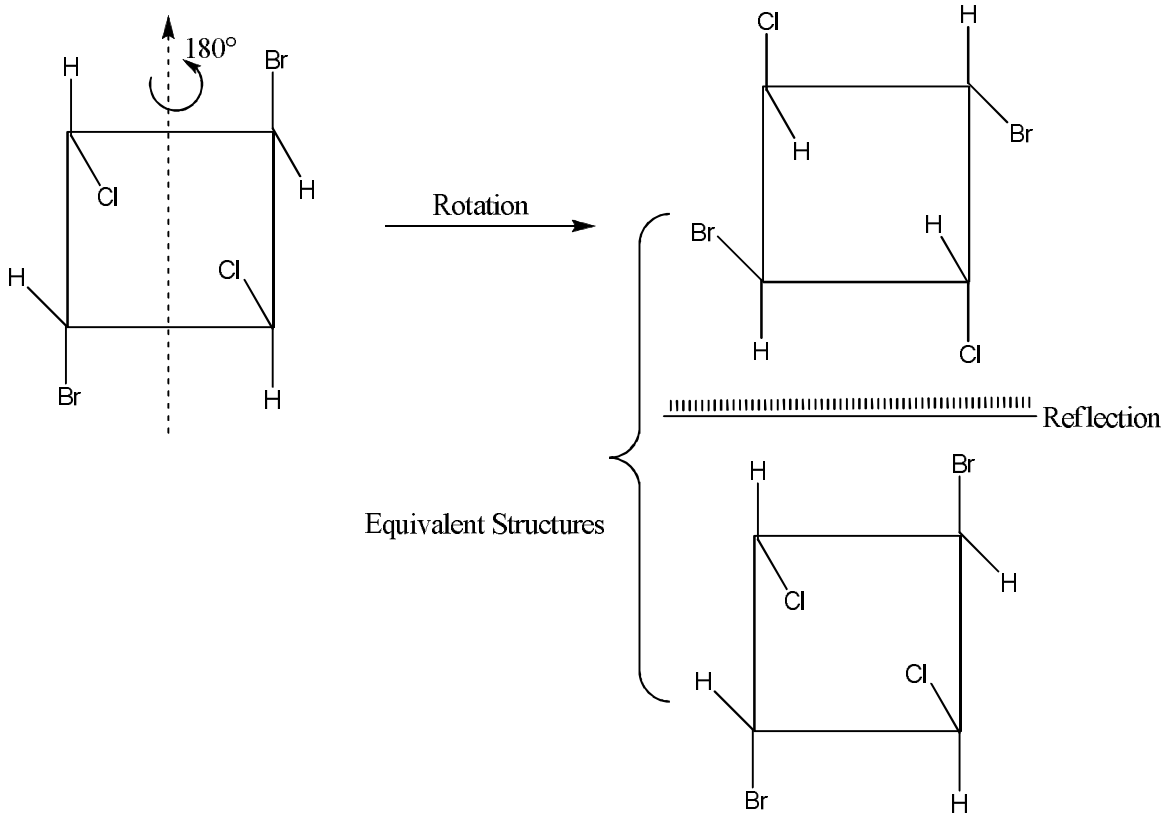
10.2.3 n-Fold Axis of Symmetry (Cn):

It is an imaginary axis through which a molecule is rotated by an angle 360°/n (n=2,3,4....) results in an equivalent structure.



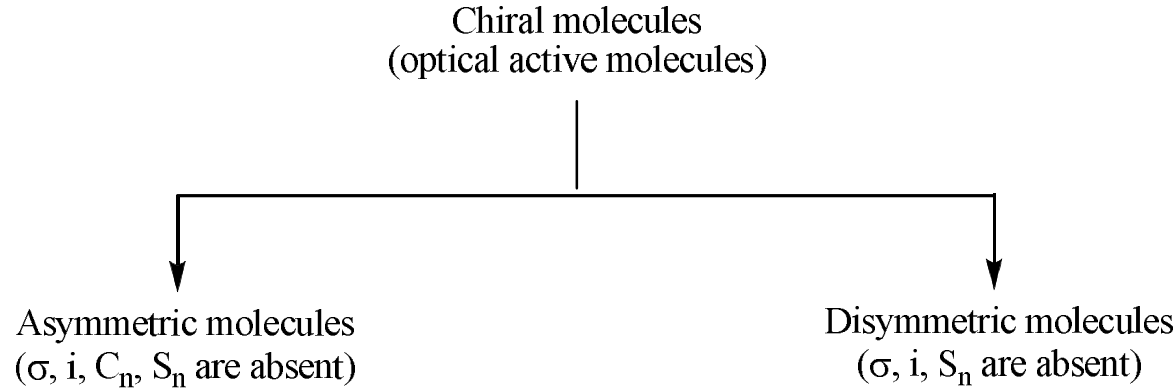
10.2.4 n-Fold Alternating Axis of Symmetry (Sn):

If a molecule is rotated through an imaginary axis by angle 360°/n (n=2,3,4....) followed by reflection across a plane perpendicular to the rotational axis results in equivalent structure, then the molecule is said to possess “n-fold alternating axis of symmetry”.



10.3 CHIRALITY (ASYMMETRIC CENTRE):

- A molecule is said to be chiral, if it has no elements of symmetry (i, Sn, σ) except Cn.

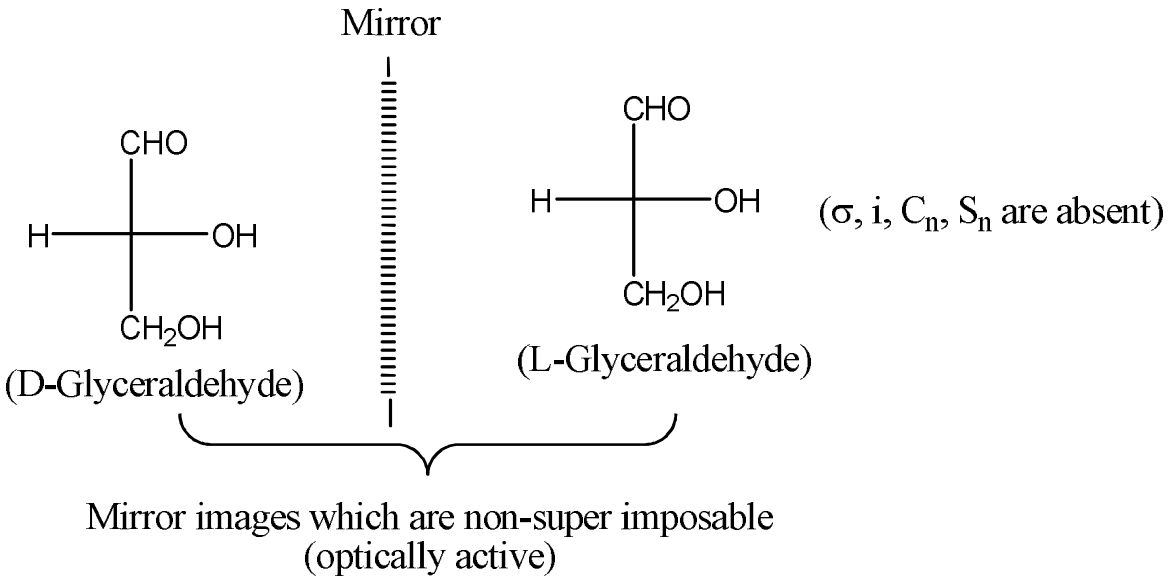


10.3.1 Chiral Molecules (Asymmetric Molecules) with One Chiral Centre:

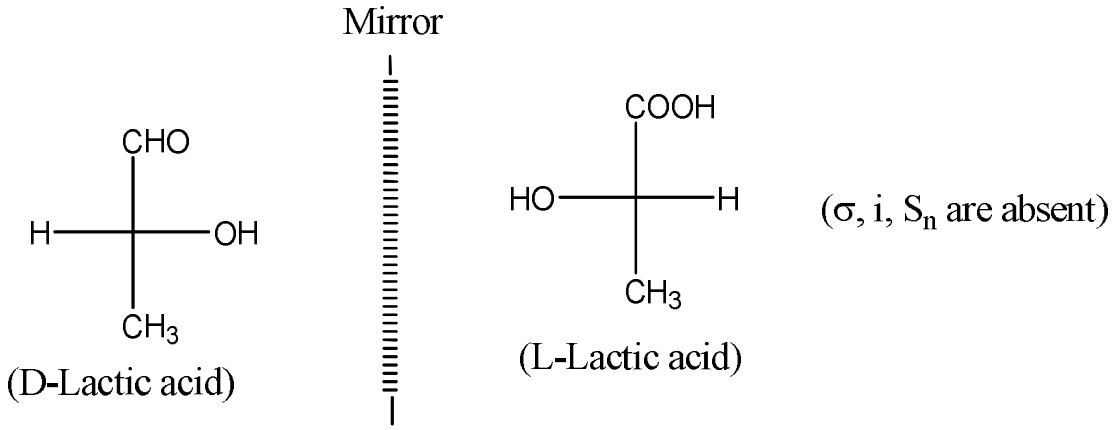
- Chiral centre means the arrangement of four different groups or atoms around the carbon.
- The compounds having a single chiral centre lack all symmetry elements and is asymmetric.
- Asymmetric molecules are optical active molecules.

Examples:

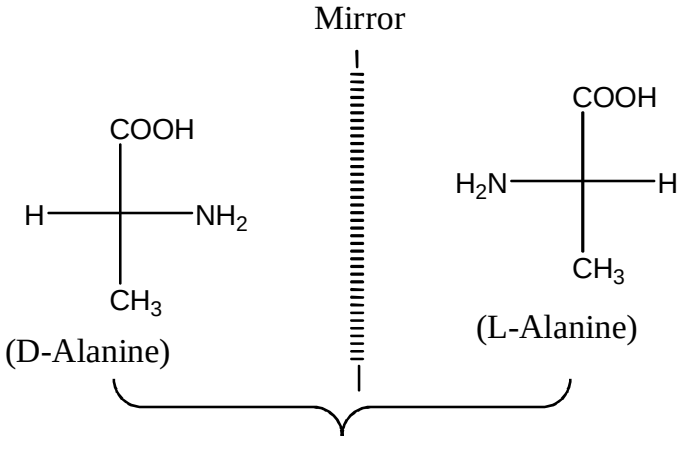
a) Glyceraldehyde



b) Lactic acid



c) Alanine

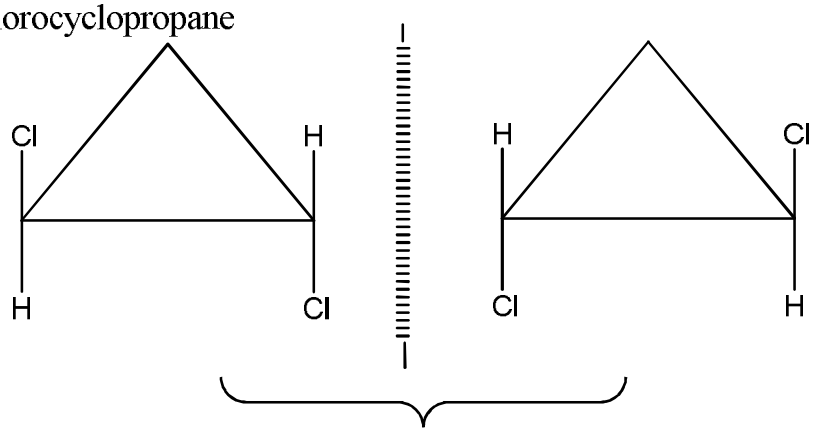


10.3.2 Disymmetric Molecules:

- Molecules having two similar chiral carbons may or may not exhibit optical activity.
- Structures having all of i, σ and Sn symmetric elements are called dissymmetric molecules.
- Molecules having one chiral carbon exhibit optical activity.

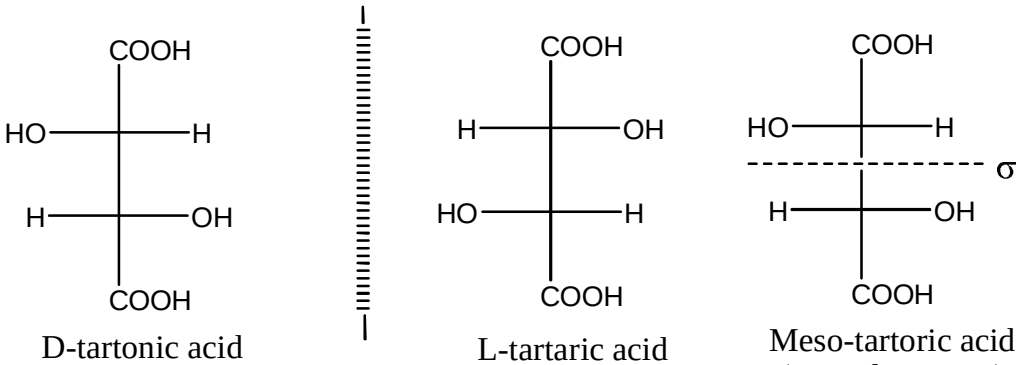
Example:

1) trans-1,2-dichlorocyclopropane



Object & mirror image are non-superimposable (optically active)

2) Tartaric acid



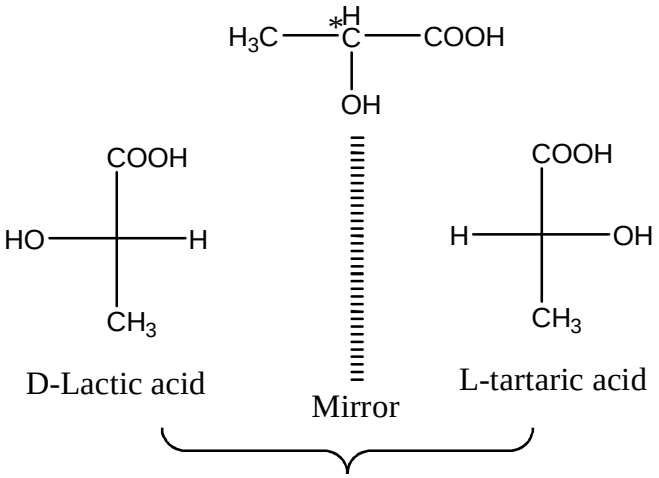
D-tartonic acid L-tartaric acid Meso-tartoric acid (optical inactive)

Optical active

10.3.3 Optical Isomerism:

- Optical isomerism is associated with chiral molecules.
- Optical active substances exist in two or more isomeric forms. If the two isomers are mirror images to each other and non-super imposable, then they are called “optical isomers” and the phenomenon is called “optical isomerism”.

Ex:



* Optical isomers differ in action on plane polarised light

* If one rotates plane polarised light to right and the other rotate it to left

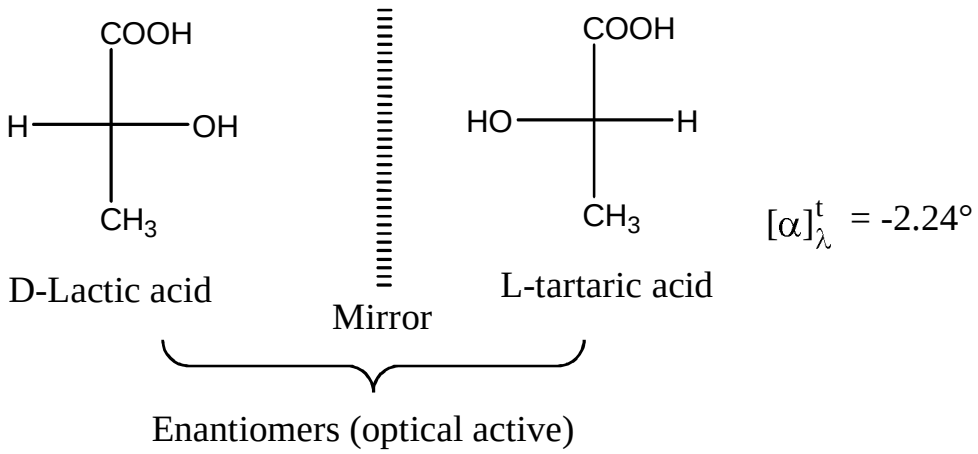
10.3.4 Enantiomers:

- Enantiomers are simplest type of optical isomers.
- "Enantiomers are the optical isomers which are non-superimposable mirror images of each other".

Characteristics:

- Enantiomers have same physical and chemical properties.
- Enantiomers rotate the plane polarized light in opposite directions but to the same extent.

Example:



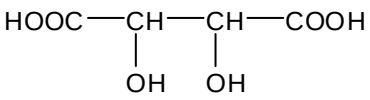
10.3.5 Diastereomers:

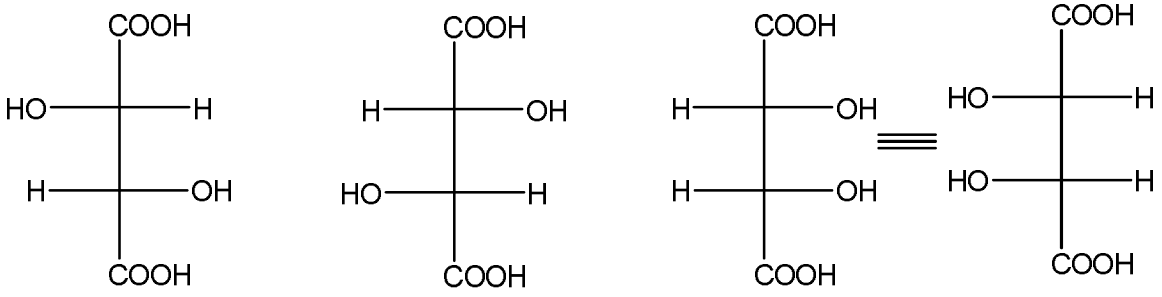
"Diastereomers are the stereoisomers which are not mirror images to each other".

Characteristics:

- Diastereomers have different physical properties.
- Diastereomers have different chemical properties.
- Diastereomers may have rotation in same or different direction to different extent.
- Diastereomers can be separated by physical methods like fractional crystallisation etc.

Example:

Consider tartaric acid,  which exists in three stereoisomers.



D-tartonic acid
I

L-tartaric acid
II

Meso-tartoric acid
III

$[\alpha]^t_\lambda = +12°$ $[\alpha]^t_\lambda = -12°$ $[\alpha]^t_\lambda = 0°$

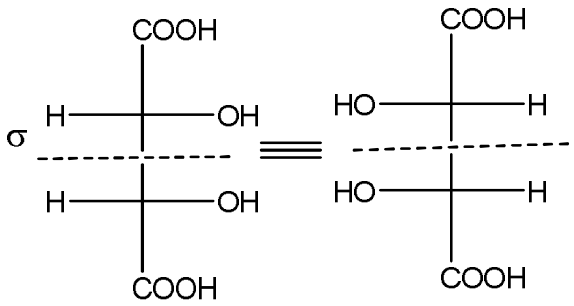
I, III = Diastereomers
II, III = Diastereomers
I, II = Enantiomers

10.3.6 Meso Compounds (Mesomers):

"Mesomers are the compounds which contain two or more chiral centres and are optically inactive due to the presence of plane of symmetry (σ).

Examples:

Meso-Tartaric Acid:



(Optically inactive due to σ)

$[\alpha]^t_\lambda = 0°$

10.3.7 Calculation of Enantiomers & Mesomers:

1) When the molecule is unsymmetrical and has 'n' chiral carbons

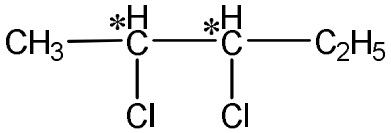
Enantiomers (or) Optically active isomers $= 2^n$

mesomers $= 0$

Total isomers $= 2^n$

Example: 1) 2,3-dichloropentane

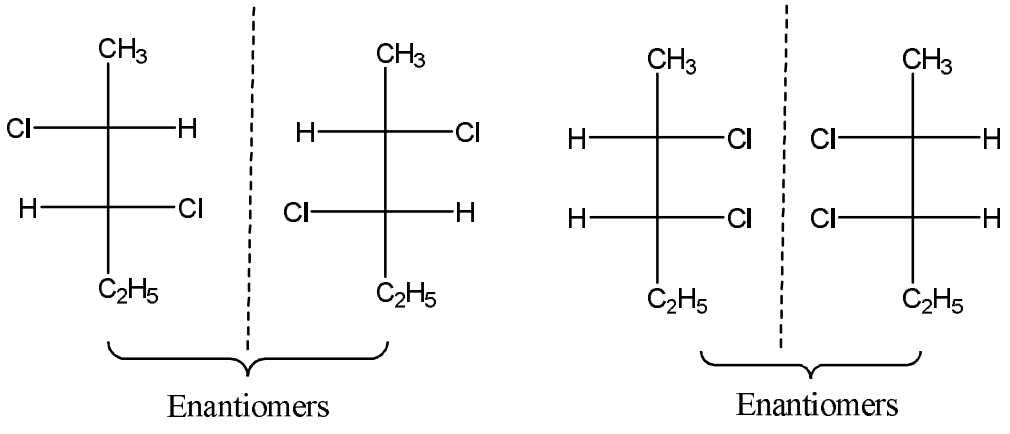
2) 2,3-dibromopentane



∴ Enantiomers $= 2^2 = 4$

Mesomers $= 0$

Total isomers $= 4$



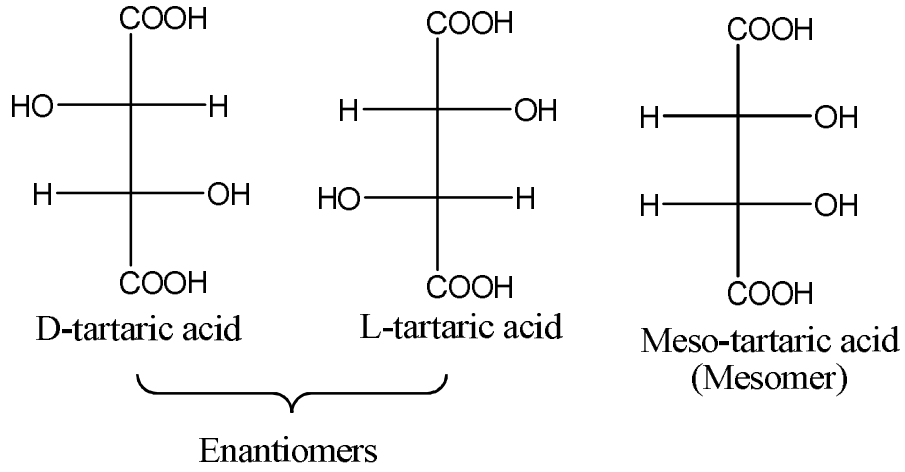
2) When the molecule is symmetric and has even number of chiral carbons

Enantiomers $= 2^{n-1}$

Mesomers $= 2^{n/2-1}$

Total isomers $= 2^{n-1} + 2^{n/2-1}$

Example: Tartaric acid



3) When the molecule is symmetric and has odd number of chiral carbon atoms

Enantiomers $= 2^{n-1} - 2^{n-1/2}$

Mesomers $= 2^{n-1/2}$

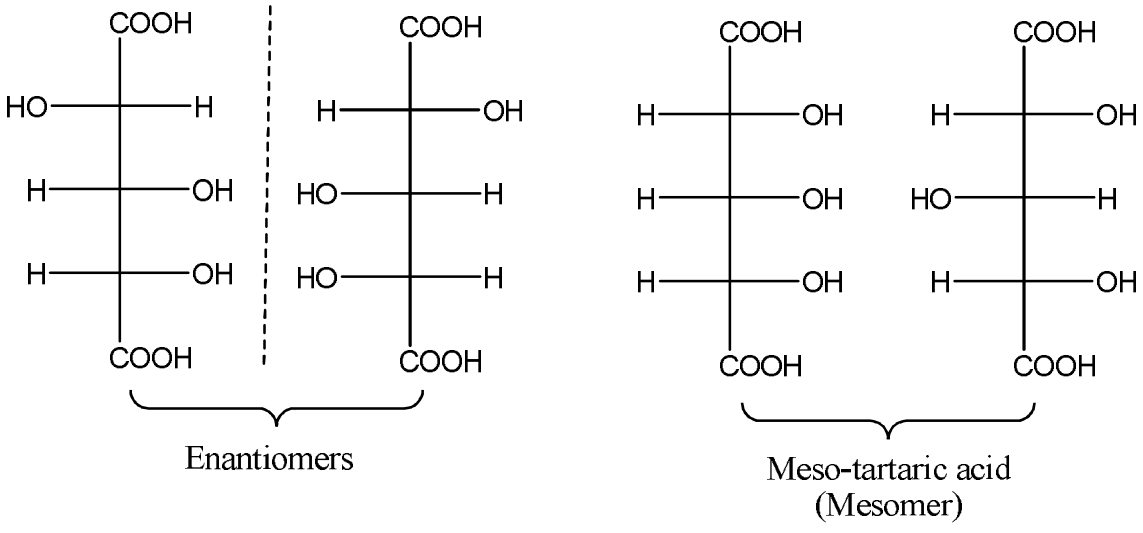
Total stereo-isomers $= 2^{n-1}$

Example: Glutaric acid

Enantiomers $= 2^{3-1} - 2^{3-1/2}$

Mesomers $= 2^{3-1/2} = 2$

Total $= 4$



10.4 CONFIGURATION:

"The stereochemical or three-dimensional arrangement of atoms or groups around a chiral carbon in a molecule is called as its configuration".

There are two methods in use to express the configuration.

They are:

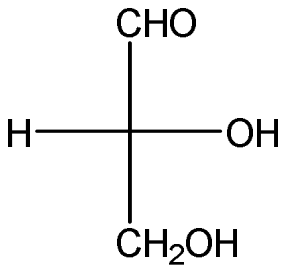
i) D,L – Configuration

ii) R,S – Configuration

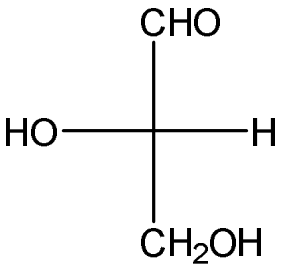
i) D, L – Configuration (Relative Configuration):

The two stereo-isomer of Glyceraldehyde are named as,

D (+) - glyceraldehyde

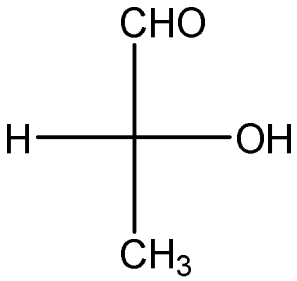


L(-)-Glyceraldehyde

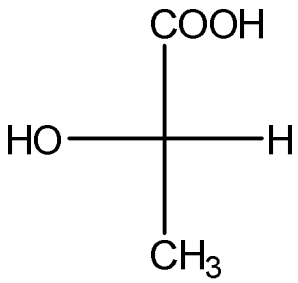


- Among the horizontal groups, the smaller group if present on right side, the isomer is assigned D-symbol and if it is present on the left side, the isomer is assigned L-symbol.
- The D- & L-Glyceraldehyde are the standard reference compounds in the D,L-configuration method.

Example:



(D-Lactic acid)



(L-Lactic acid)

- D, L-configuration is useful to know the configuration of last or bottom chiral carbon in molecules having more than one chiral centres.

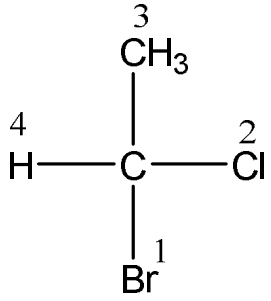
Examples: D – Glucose, L – Glucose

ii) R, S-Configuration (CIP Nomenclature):

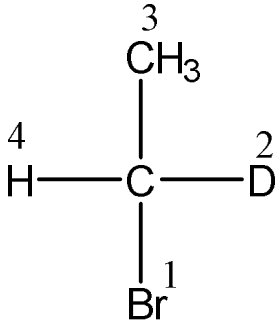
Cahn, Ingold and Prelog introduced a simple procedure to assign configuration for an optically active compounds, called as "RIS-Configuration" or "CIP nomenclature".

Step-1: Priorities are assigned to four atoms or groups directly attached a chiral carbon. This involves a set of rules known as sequence rules.

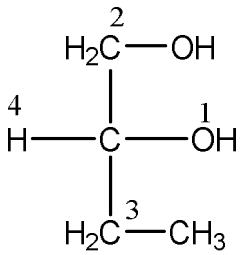
Rule-1: The atom with highest atomic number gets highest priority and atom with lowest atomic number gets least priority.



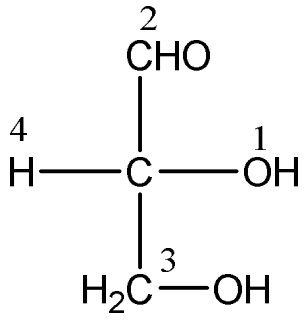
Rule-2: If the atoms are isotopes of same element, the atom of higher mass number gets highest priority.



Rule-3: If the first atom of two or more groups attached to chiral carbon is same, then relative priorities are given by comparing second or even third atoms of the respective groups.



Rule-4: If an atom is attached to a double bond, it is considered as two atoms and if an atom is attached to a triple bond, it is considered as three atoms.

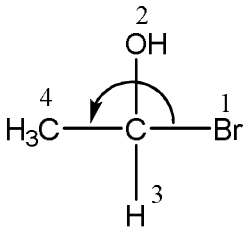


Step-2: The least priority group (4) should be written away from the eye in the molecule after assigning the priorities. The remaining three groups or atoms which are closer to the eye is now observed. The arrangement of groups from 1 → 2 → 3 is in clock wise, the compound is assigned "R-configuration". If it is anticlockwise, it is assigned "S-configuration".

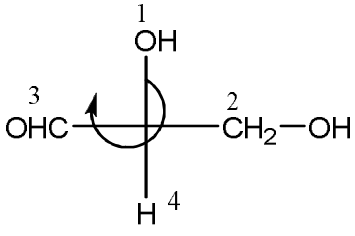
R = Rectus = Right side

S = Sinister = Left side

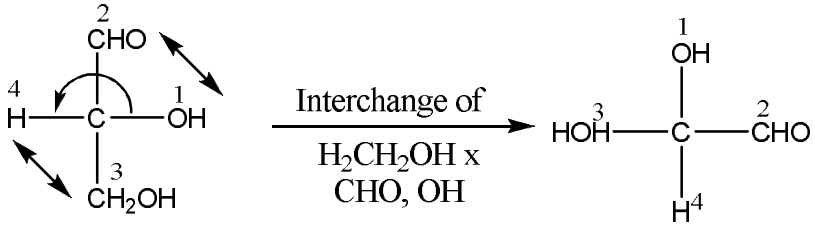
Examples:



(S)

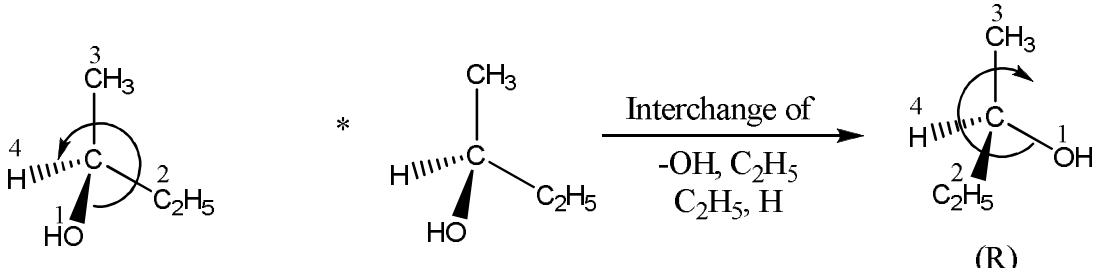


(R)



(Least priority group near the observer)

(R)



(Least priority group away from eye)

(S)

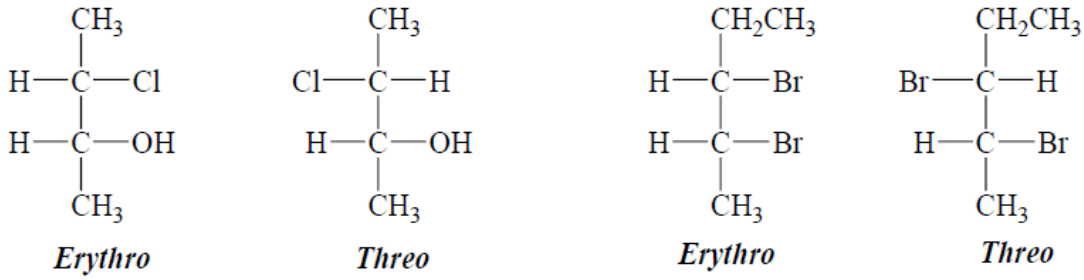
(R)

10.5 ERYTHRO (SYN) AND THREO (ANTI) DIASTEREOMERS:

- *Threo*and *erythro* nomenclature method is designated by organic chemists to assign appropriate name to diastereomers.
- The *threo*and *erythro* naming is given only to those diastereomers having two adjacent stereocentres.
- The nomenclature is applicable to these diastereomers if there are two common atoms/groups bonded to each adjacent stereo centre. In other words the terms *erythro*and *threo*are generally applied only to those molecules which do not have symmetric ends..
- If the similar groups/atoms on adjacent stereocentres of diastereomer are on same (*syn*) side it is designated as *erythro*, whereas if the similar groups/atoms on adjacent stereocentres of diastereomer are on opposite (*anti*) side the diastereomer is designated as *threo.*

Example: You can easily understand the erythro and threo nomenclature by taking examples of 3-bromo-2-butanol and 2,3-dibromo pentane.

Ex:



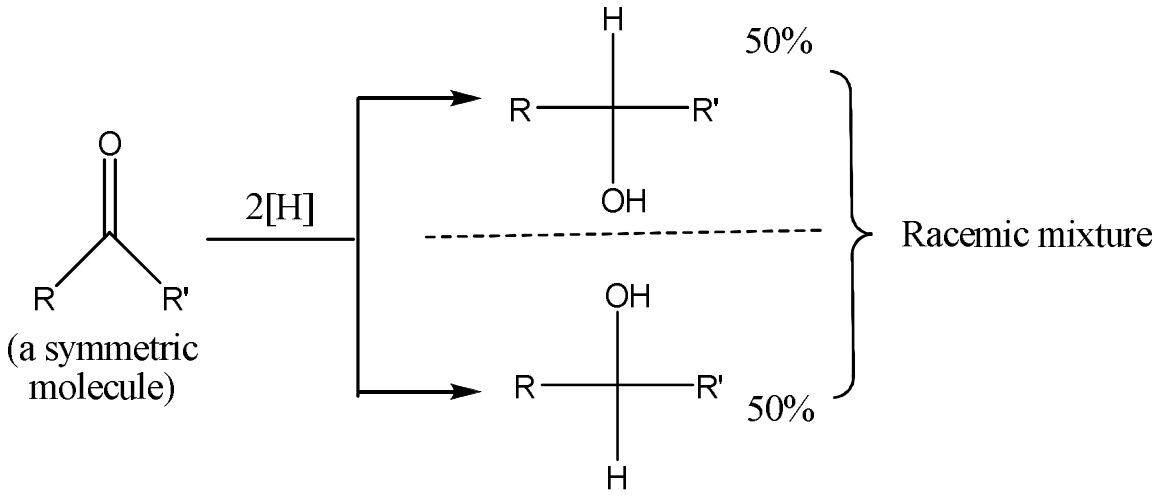
3-Chloro-2-butanol **2,3-Dibromopentane**

10.6 RACEMIC MIXTURE:

- Enantiomers rotate the plane polarised light in opposite direction, but amount of rotation is same.
- Mixing of enantiomers in equal quantities (1:1), results in zero optical rotation. Such type of mixtures are called “Racemic mixtures”. They are denoted by (±). The process of formation of racemic mixture is called “Racemisation”. These are formed by various ways.

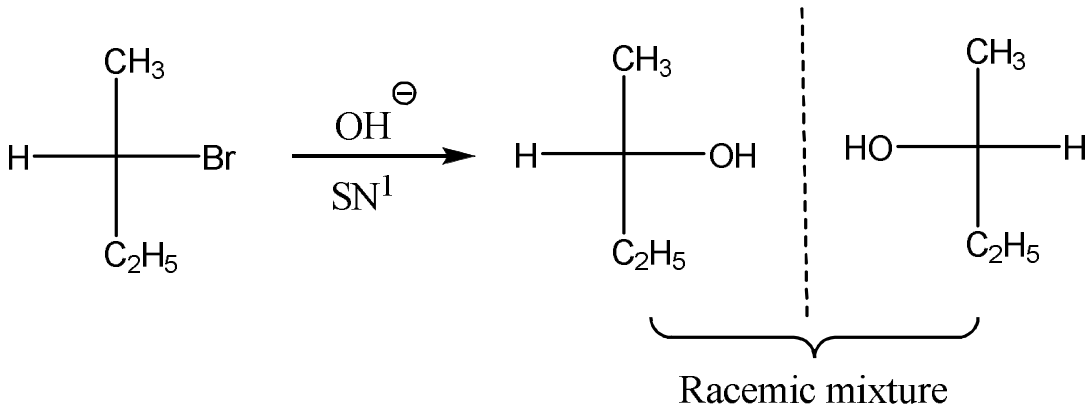
a) From Synthesis of Asymmetric (Chiral) Molecules from Symmetric Molecules (a chiral)

Ex:



b) By Racemisation Process:

Conversion of pure enantiomers into racemic mixture is called racemisation.



10.7 RESOLUTION:

Separation of pure enantiomers (+), (-) from a racemic mixture (±) is called "resolution". There are three methods for resolution.

a) Physical Method:

The racemic mixture of sodium ammonium tartarate has two distinct type of crystals which have object and mirror image relationship. Pasteur separated this mixture into two with the help of microscope with lot of patience. But this involves lot of time. Hence the physical method can be a universal method.

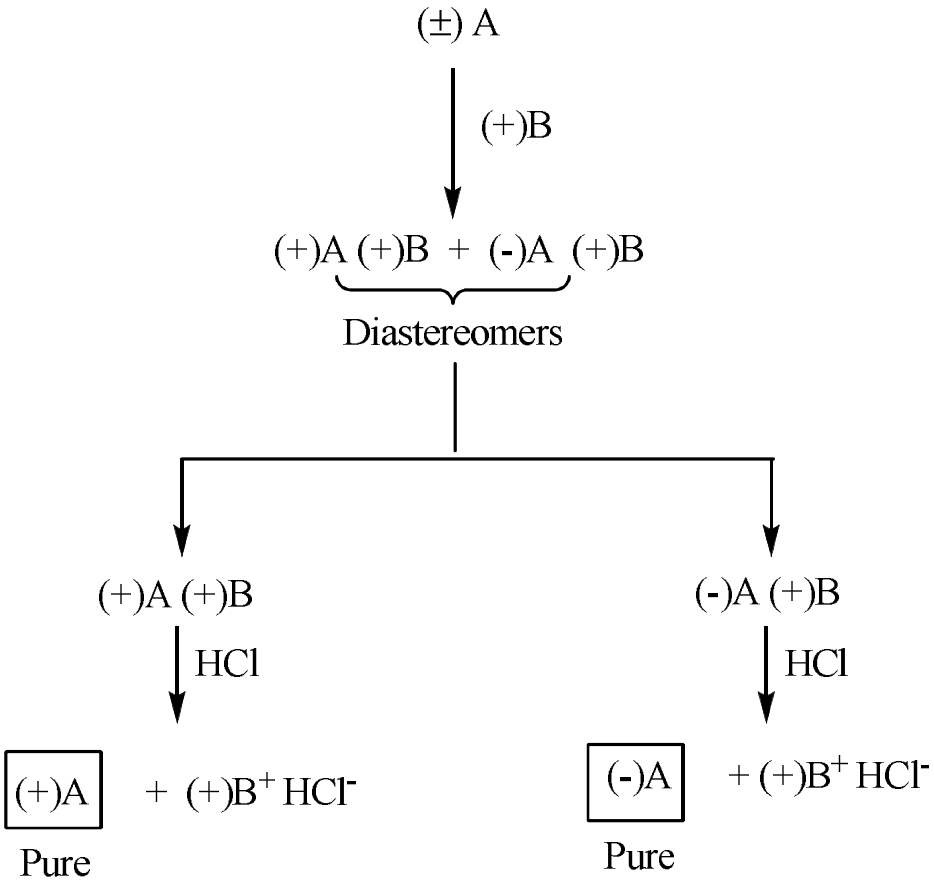
b) Biochemical Method:

In biochemical method, enzymes are used to separate the racemic mixture the enzyme consumers either (+) or (-) and leaves pure enantiomer.

Ex: The bacterium penicillium glaucum utilises the (+) isomer of (±) ammonium tartarate in its metabolic process. Hence (-) siomer is left out in the solution in pure form. By this method one enantiomer is lost. Hence this method is not recommended for resolution.

c) Diastereomer Formation Method or Chemical Method:

To separate the racemic mixture (±) of a carboxylic acid A, a base (+) B is allowed to react with (±) A. It forms (+) A (+B) salt and (-) A (+B) salt, which are disastereomers. Since the physical properties of diastereomers are different, they are separated easily. The salt are treated with strong acids like HCl to get pure enantiomers (+)A and (-)A.



d) Stereospecific Synthesis:

- A reaction where the **stereochemistry of the reactant determines the stereochemistry of the product** in a specific way.
- Only one specific **stereoisomer** is formed depending on the starting material.

- **Ex:** Consider a racemic mixture of **(R) and (S) alcohols** reacting with a **chiral acid** to form diastereomers.
- These diastereomers can then be separated due to their different physical properties (e.g., solubility or crystallization behavior).
- After separation, hydrolysis regenerates the pure enantiomer.

(R)−Alcohol+Chiral Acid→(R)−Ester (diastereomer)

(S)−Alcohol+Chiral Acid→(S)−Ester (diastereomer

Since diastereomers have different properties, they can be separated.

e) Stereoselective Synthesis:

- A reaction that **preferentially forms one stereoisomer** over another, but does not completely exclude the formation of the minor product.
- The reaction yields an **excess** of one enantiomer or diastereomer.
- Using a **chiral catalyst or enzyme** that selectively converts only one enantiomer into a product.
- The remaining enantiomer can be separated easily.

Ex:

- Suppose we have a racemic mixture of (R) and (S) alcohols.
- An enzyme (e.g., **lipase**) selectively reacts with **(R)-alcohol**, converting it into an ester, while (S)-alcohol remains unchanged.
- The unreacted (S)-alcohol can then be isolated in pure form.

(R)−Alcohol + Lipase→(R)−Ester + H2O(R)

(S)−Alcohol (unchanged)

LESSON - 11

STEREOCHEMISTRY OF COMPOUNDS CONTAINING N, P AND S

Like tetravalent carbon compounds, the nitrogen, phosphorous and sulphur containing compounds also exhibit stereochemical behaviour. Compounds of N, P and S show both enantiomerism and/or geometrical isomerism.

11.1 STEREOCHEMISTRY OF NITROGEN COMPOUNDS:

11.1.1 Geometrical Isomerism of Nitrogen Compounds:

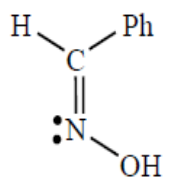
Nitrogen containing compounds like >C=N- as well as –N=N- bond also exhibit geometrical isomerism. The important classes of compounds that exhibit geometrical isomerism due to >C=N- bond are

i) Oximes

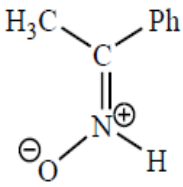
ii) Nitrones

iii) Semicarbazones

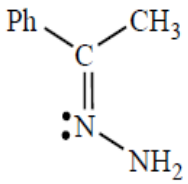
iv) Hydrazones



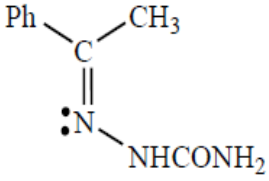
(*Z*)-benzaldehyde oxime



(*E*)-nitrone



(*E*)-1-(1-phenylethylidene) hydrazine

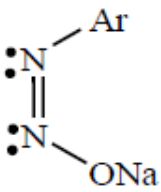


(*E*)-1-(1-phenylethylidene) semicarbazide

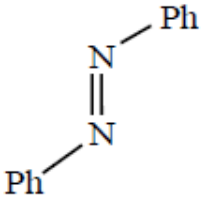
Geometrical Isomers of Compounds having >C=N:

Oximes are the most common compounds among all above classes. Both carbon and nitrogen atom in oxime are sp2 hybridized the C=N bond of oxime consists a sigma (σ) and a pi (π) bond. Therefore, there is no free rotation possible around C=N bond; hence, oximes of aldehyde and ketones (unsymmetrical) exhibit geometrical isomerism.

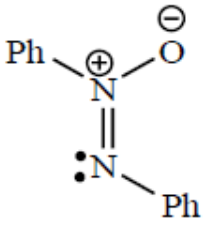
Examples of compounds exhibiting geometrical isomerism containing –N=N- are



(*Z*)-Diazoate



(*E*)-Azobenzene



(*E*)-Azoxybenzene

The configuration of such compounds is also based on priority of the groups/atoms attached to the double bonded carbon and nitrogen. Lone pair of the nitrogen always considered to be the lowest priority group. The priority of the groups/atoms is assigned as per the sequence rule. If the higher priority groups/atom on double bonded carbon and nitrogen are on same side of the double bond the isomer is considered as *Z*- isomer, whereas if the higher priority groups/atoms are on opposite side the isomer is considered as *E*-isomer.

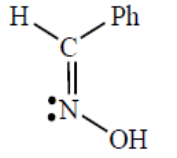
Example: E/Z isomerism is shown by

i) benzaldoxime,

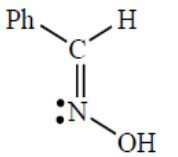
ii) ethylmethylketoxime and

iii) methylphenylketoxime

i)

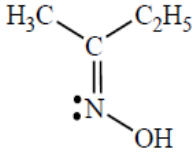


(*Z*)-benzaldehyde oxime

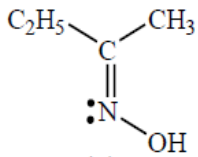


(*E*)-benzaldehyde oxime

ii)

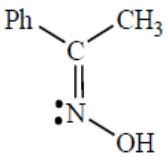


(*Z*)-ethylmethyl ketoxime

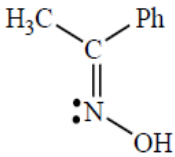


(*E*)-ethylmethyl ketoxime

iii)



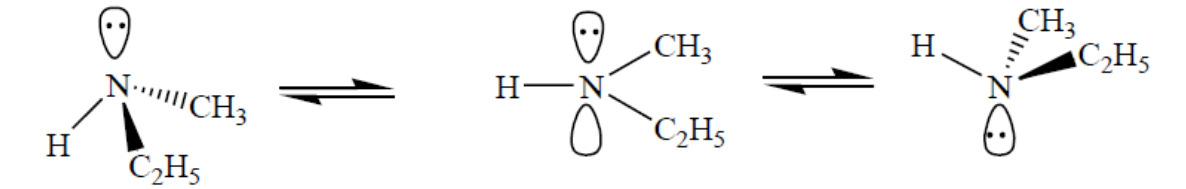
(*E*)-acetophenone oxime



(*Z*)-acetophenone oxime

11.1.2 Enantiomerism of Nitrogen Compounds: The tetrahedral concept of carbon has also been successfully extended to nitrogen containing compounds. The only difference in nitrogen compounds is that one of the sp^3hybridized orbital of nitrogen usually contains a lone pair of electrons which is not involved in bonding. Thus, nitrogen containing compound

have three ligands and one lone pair in sp^3orbital. Thus, in terms of a chiral center, nitrogen is analogous to carbon. The tertiary amines of with all three different atoms or groups attached with center nitrogen atom have chiral nitrogen, but do not have optical activity. Thus, is due to the rapid interconversion of lone pair from one face of the other resulting in rapid racemization shown in below figure. The amine interconversion is described as an inversion, such enantiomers are called invertomers.

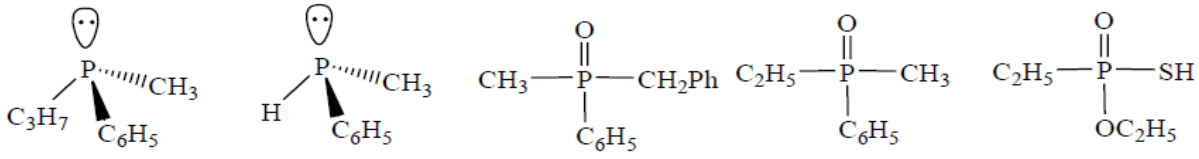


R-ethylmethylamine transition state is planar *S*-ethylmethylamine

Inversion of Lone Pair in Nitrogen Containing Compounds

11.2 STEREOCHEMISTRY OF COMPOUNDS CONTAINING P:

Phosphorous can also exhibit covalencies of 3, 4 and 5, hence they give rise to more possible configuration than nitrogen. In tetravalent phosphorous compounds the valence deposition is tetrahedral (sp^3hybridized) in which one sp^3orbital being occupied by lone pair, whereas, in quinquevalent (pentavalent) phosphorous compounds the valence deposition is trigonal bipyramidal (sp^3d). The following are examples of the various resolvable compounds of phosphorous in its different hybrid states.

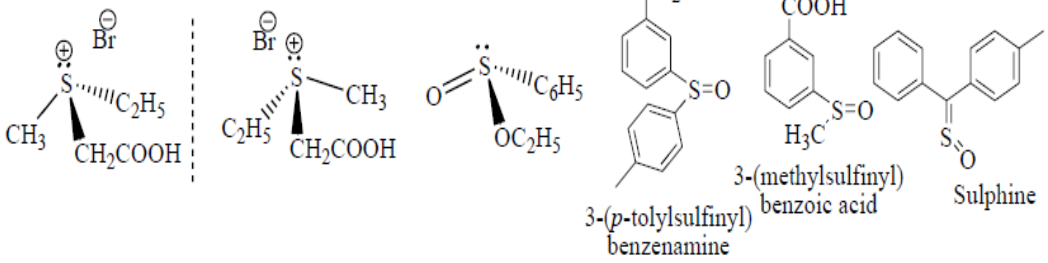


(*S*)-methyl(phenyl) (propyl)phosphine (*R*)-methyl(phenyl) phosphine

11.3 STEREOCHEMISTRY OF COMPOUNDS CONTAINING S:

Similar to nitrogen and phosphorous containing compounds, various sulphur containing compounds have also been identified to exhibit enantiomerism. Some common examples are Sulphonium salts, Sulphuris esters, Sulphoxides and Sulphines.

Examples:



Sulphonium Salts **Sulphonic Ester**

Mr. E. Ramanjaneyulu

LESSON - 12

GEOMETRICAL ISOMERISM

12.1 GEOMETRICAL ISOMERISM:

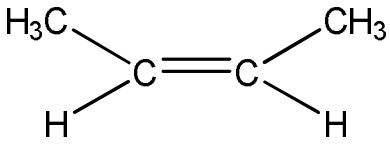
"The two stereoisomers which differ in the spatial arrangement of atoms or groups around carbon-carbon double bond are called Geometrical isomers" and the phenomenon is called Geometrical isomerism.

12.1.1 Conditions for Geometrical Isomerism:

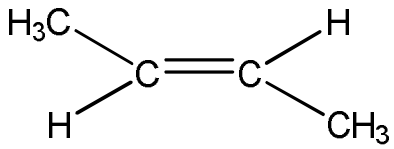
- The molecule must have a C=C bond.
- There must be two different groups attached to each carbon atom of double bond.

The isomer in which similar groups are present on one side of the double bond is called "Cis-isomer" and the isomer with similar groups on opposite side of double bond is called "trans-isomer".

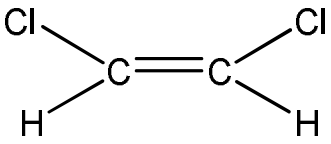
Example:



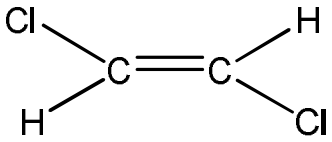
trans-1-butene



trans-2-butene



trans-1,2-dichloroethene



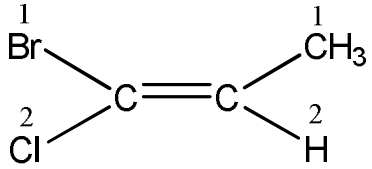
trans-1,2-dichloroethane

12.2 E, Z-NOMENCLATURE:

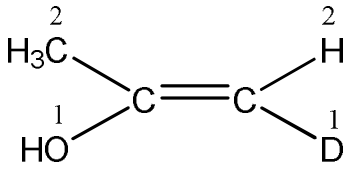
Cis-trans nomenclature cannot be used when C=C has four different groups. In such cases E, Z-nomenclature is used.

Step-I: Assign priority to the two groups attached to each of the doubly bonded carbon by using "sequence rules".

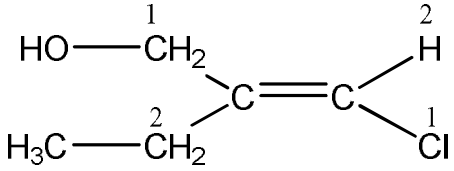
Rule-1: The atom or group with highest atomic number gets highest priority.



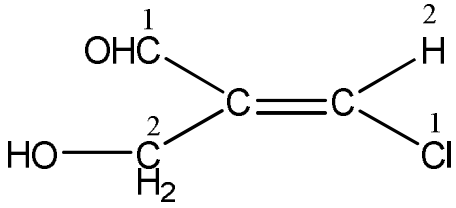
Rule-2: In case of isotopes, the isotope of highest mass number gets highest priority.



Rule-3: If two atoms directly attached to C=C are the same, then priorities are given by comparing second, third or fourth atoms of the respective groups.



Rule-4: A doubly or triply bonded atom is considered to be equivalent to two or three atoms.

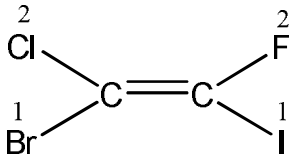


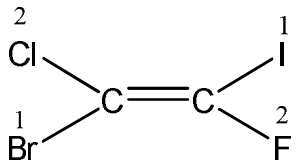
Step- II:

If the atoms or groups of highest priority are on the same side of double bond, the compound is assigned Z-configuration. If the atoms or groups of highest priority are on opposite sides of double bond, the compound is assigned E-configuration.

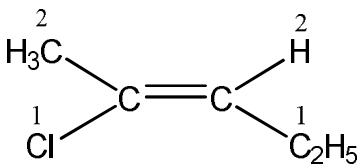
Examples:

1)

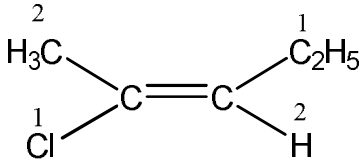




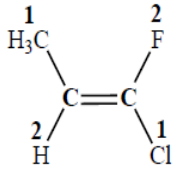
2)



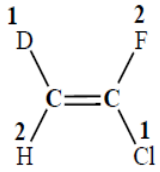
(Z-isomer)



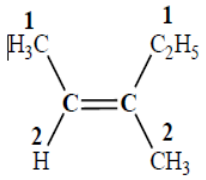
(Z-isomer)



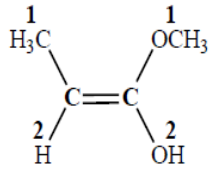
(*E*)-1-chloro-1-fluoroprop-1-ene



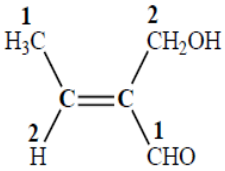
(*E*)-Deuterated1-chloro-1-fluoroprop-1-ene



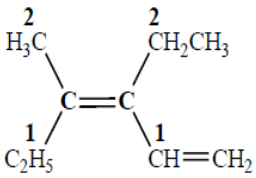
(*Z*)-3-methylpent-2-ene



(*Z*)-1-methoxyprop-1-en-1-ol



(*E*)-2-(hydroxymethyl)but-2-enal



(*Z*)-3-ethyl-4-methylhexa-1,3-diene

12.3 SPECTRAL AND CHEMICAL METHODS FOR DETERMINING THE CONFIGURATION OF GEOMETRICAL ISOMERS:

Geometrical isomers, also called cis-trans or E-Z isomers, differ in the spatial arrangement of substituent's around a double bond or a ring system. Their configurations can be determined using spectroscopic and chemical methods.

12.3.1 Spectral Methods:

(i) Infrared Spectroscopy (IR):

- Cis isomers show higher absorption in the C=C stretching region (~1650 cm^{-1}) due to steric strain.
- Trans isomers have lower absorption intensity due to better conjugation.

Ex:

- Maleic acid (cis) shows a broad and strong O-H stretching due to intramolecular hydrogen bonding.
- Fumaric acid (trans) lacks this interaction, leading to different IR bands.

(ii) Nuclear Magnetic Resonance (NMR) Spectroscopy:

a) ^{1}H-NMR Chemical Shift:

- Cis isomers have deshielded protons due to steric hindrance, leading to downfield shifts (higher δ values).
- Trans isomers have protons further apart, leading to upfield shifts (lower δ values).

b) Coupling Constants (J values):

- Cis isomer (Z-isomer): J = 6–12 Hz
- Trans isomer (E-isomer): J = 12–18 Hz (higher due to better orbital overlap).

Ex: 2-Butene

- Cis-2-butene: J ≈ 6–10 Hz
- Trans-2-butene: J ≈ 14–18 Hz

(iii) UV-Visible Spectroscopy

- Trans isomers exhibit higher λmax (longer wavelength) due to better conjugation and symmetry.
- Cis isomers have lower λmax due to steric strain and poor conjugation.

  Ex: β-Carotene derivatives:
- All-trans isomer absorbs at a longer wavelength due to extended conjugation.
- Cis isomer has a blue shift (lower wavelength absorption).

(iv) X-Ray Crystallography

- Provides direct structural evidence of cis and trans isomers by visualizing bond angles and distances.
- Cis isomers show shorter distances between substituents.
- Trans isomers have longer and more linear geometry.

  Ex:Maleic acid (cis) and fumaric acid (trans) can be clearly distinguished.

12.3.2 Chemical Methods:

(i) Bromine Addition Test:

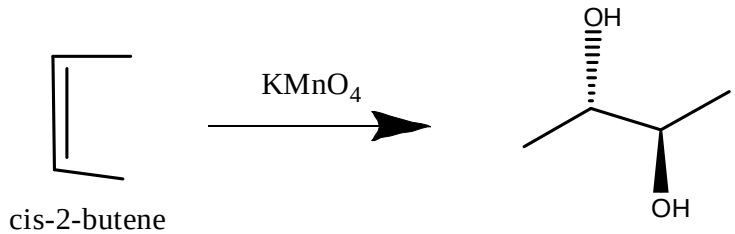
- Cis-alkenes react faster with Br_2 in CCl_4 due to steric hindrance, forming dibromo compounds with a syn addition mechanism.
- Trans-alkenes react slower due to less steric hindrance.

  Ex: Cis-2-butene reacts with Br_2 rapidly compared to trans-2-butene.

(ii) Oxidation with $KMnO_4$ (Baeyer Test)

- Cis alkenes undergo Syn hydroxylation with $KMnO_4$ forming cis-glycols.
- Trans alkenes give trans-glycols.

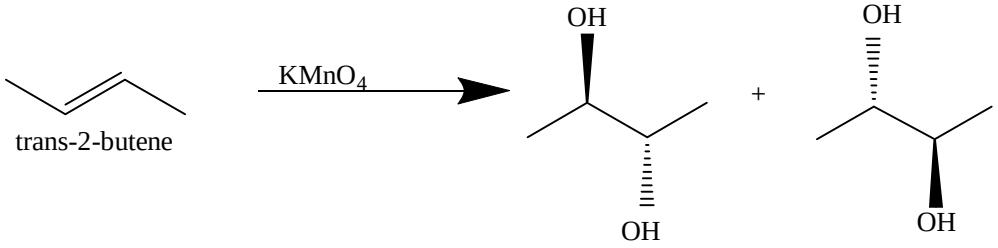
  Ex: Cis-2-butene gives meso-2,3-butanediol.



cis-2-butene

meso-2,3-butanediol

- Trans-2-butene gives enantiomeric 2,3-butanediols.



trans-2-butene

Enantiomeric 2,3-dimethylbutane

(iii) Reduction with Sodium in Liquid Ammonia (Birch Reduction):

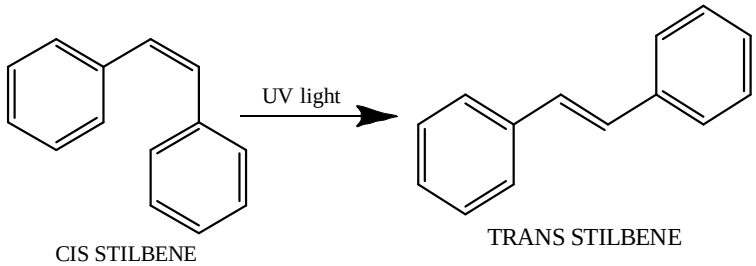
- Cis isomers hydrogenate faster than trans isomers due to less steric hindrance.

  Ex: Cis-stilbene reacts faster than trans-stilbene.

(iv) Thermal Isomerization:

- Cis isomers can thermally convert to trans isomers at high temperatures due to lower stability.
- Trans isomers are more thermodynamically stable and less likely to isomerize back.

  Ex: Cis-stilbene thermally converts to trans-stilbene under UV light.



CIS STILBENE

TRANS STILBENE

12.4 GEOMETRICAL ISOMERISM OF ALDOXIMES AND KETOXIMES:

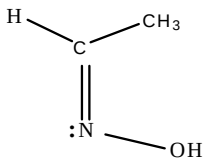
Geometrical isomerism (also called **cis-trans isomerism or E-Z isomerism**) in **aldoximes and ketoximes**arises due to the restricted rotation around the **C=N** in oximes. Both carbon and nitrogen atom in oxime are sp^2 hybridized. The C=N bond of oxime consists a sigma (σ) and a pi (π) bond. Therefore, there is no free rotation possible around C=N bond; hence, oximes of aldehyde and ketones (unsymmetrical) exhibit geometrical isomerism

- The configuration of such compounds is also based on priority of the groups/atoms attached to the double bonded carbon and nitrogen
- Lone pair of the nitrogen always considered to be the lowest priority group.
- The priority of the groups/atoms is assigned as per the sequence rule (CIP rules).
- If the higher priority groups/atom on double bonded carbon and nitrogen are on same side of the double bond the isomer is considered as *Z*- isomer, whereas if the higher priority groups/atoms are on opposite side the isomer is considered as *E*- isomer

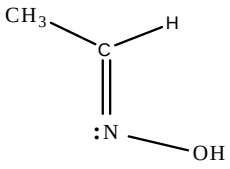
12.4.1 Aldoximes (RCH=NOH):

Aldoximes have one hydrogen and one alkyl (R) group attached to the carbon of the **C=N** bond.

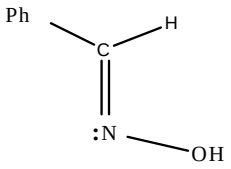
Examples:



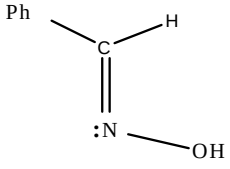
Z-Acetoldoxime



E-Acetoldoxime



Z-benzaldehyde oxime

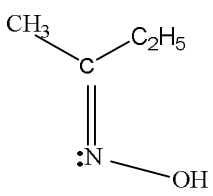


E-benzaldehyde oxime

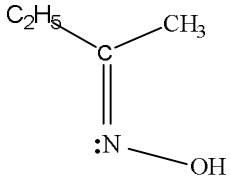
12.4.2 Ketoximes (R_2C=NOH):

Ketoximes have two different alkyl groups (**R and R'**) attached to the **C=N** bond.

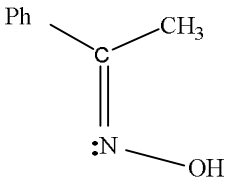
Examples:



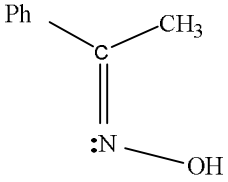
Z-ethylmethyl ketoxime



E-ethylmethyl ketoxime



Z-phenyl methyl ketoxime



E-phenyl methyl ketoxime

Mr. E. Ramanjaneyulu

LESSON - 13

CONFORMATION OF ACYCLIC MOLECULES-I

13.1 INTRODUCTION:

The different spatial arrangements of atoms in a molecule which are readily inter convertible by rotation about single bonds are called ***conformations;*** *'if* not, *configurations.* Conformations represent *conformers* which are readily inter convertible and thus non separable. The terms **conformational isomers** and **rotamers** are also used for **conformers.** Sometimes different conformations corresponding to energy minima are called **conformers.** The terms conformation and configuration are related to energy barrier for inter conversions of different spatial arrangements of atoms in a molecule. If the energy barrier for conversion of different spatial arrangements is between> 0.6and < 16 kcal/mole they are conformations (i.e., conformers), and if it is S 16 kcals/mole, they are configurations *(i.e.,* stereoisomers).If the energy barrier is 0.6 kcal/mole or less at room temperature, the rotation would be free because this amount of energy can be readily provided by the thermal energy of the molecule.

The study *of the* ***existence*** *of* ***preferred*** *conformations* ***in molecules,*** *and the* ***relating of physical and*** *chemical properties of a molecule to its preferred conformation are known as conformational* ***analysis.***

13.2 CONFORMATIONS OF ETHANE:

When an ethane molecule rotates about its carbon-carbon single bond, two extreme conformations can result: the **staggered conformation** and the **eclipsed conformation.** An infinite number of conformations between these two extreme conformations is also possible. These are called skew conformations. There are various ways to represent the three-dimensional conformations on the paper. Here we will use **New man projections** to discuss the conformations of acyclic compounds. The Newman projections for staggered and eclipsed conformations are given below:

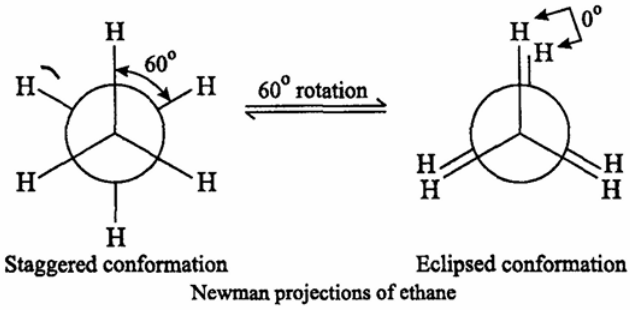


Fig. 13.1

13.2.1 Staggered Conformation: A conformation with a 60° dihedral (torsional) angle is known as staggered conformation. The angle between the atoms attached to the front and the rear carbon atoms is called the torsional angle.

13.2.2 Eclipsed Conformation: A conformation with a 0° torsional angle is known as eclipsed conformation.

The electrons in a carbon-hydrogen bond will repel the electrons in another carbon-hydrogen bond if the bonds get too close to each other. This is called torsional or bond opposition strain. Therefore, the staggered conformation is the most stable conformation because the carbon-hydrogen bonds are as far away from each other as possible, i.e., it has least torsional strain. The eclipsed conformation is the least stable conformation because the carbon- hydrogen bonds are closest. In staggered conformation the distance between the hydrogen nuclei is 2.55 &, but they are only 2.29 A apart in the eclipsed conformation. The rotational energy barrier in ethane is 2.9 kcal/mole. This rotational barrier can be described in terms of the change in potential energy of the molecule as a function of the change in torsional angle as shown in below Fig. 13.2.

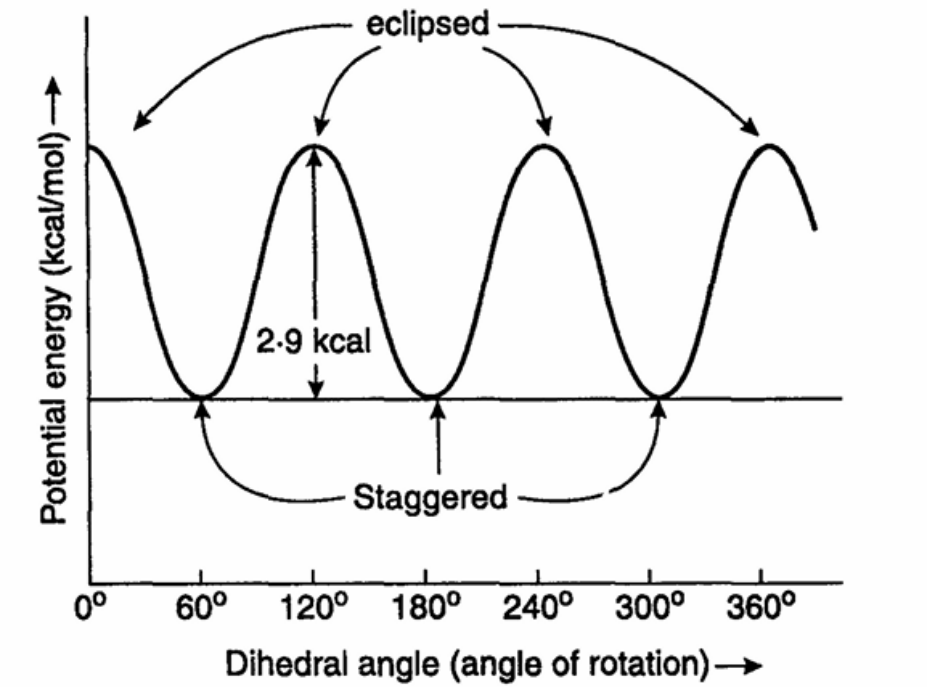


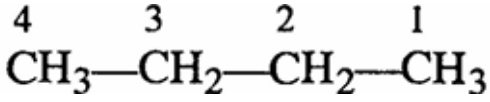
Fig. 13.2

The extra energy of the eclipsed conformation is called **torsional strain.** Torsional strain is the name given to the repulsion felt by bonding electrons of one substituent as they pass close the bonding electrons of another substituent. The energy barrier between staggered

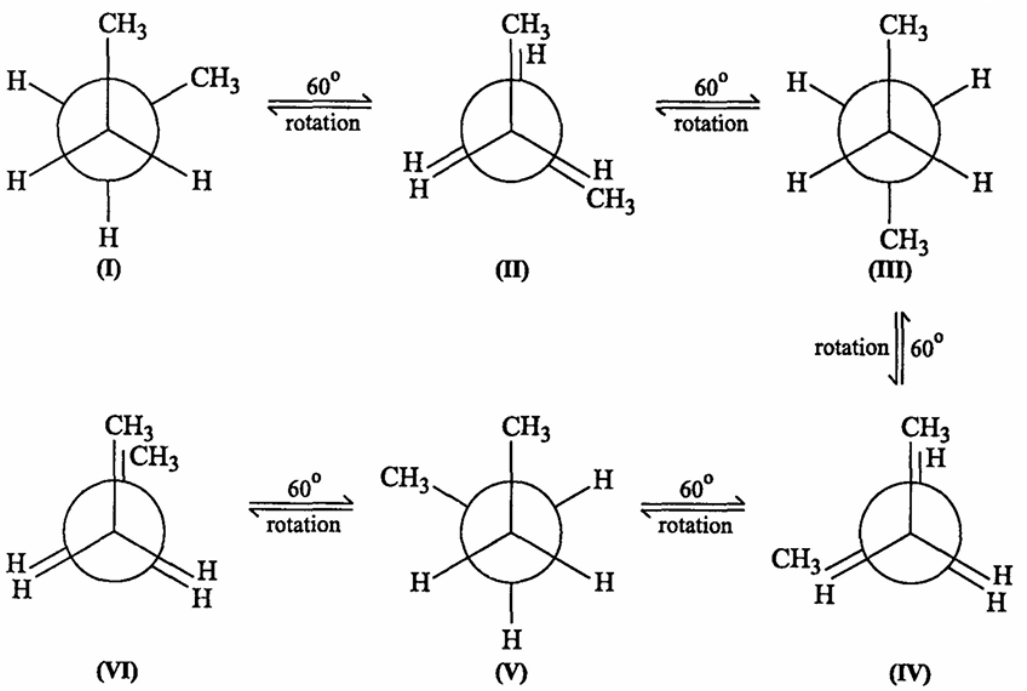
and eclipsed conformation in ethane molecule is 2.9 kcal/mole. This barrier is more than *RT* (=0.6 kcal/mole) at room temperature (energy for free rotation) and lessthan16-20kcal/mole (energy barrier for complete restricted rotation, *i.e.,* frozen rotation).Thus, the rotation about the carbon-carbon single bond is neither completely free nor frozen (completely restricted) but only restricted by 2.9 kcal/mole.

13.3 CONFORMATIONS OF N-BUTANE:

Butane has three carbon-carbon single bonds and the molecule can rotate about each of them.



If the rotation will be about C2and C3 bond then conformations will be symmetrical. For conformational analysis butane may be treated as the derivative of ethane where one hydrogen on each carbon is replaced by a methyl group. Different conformations of butane can be obtained by rotation about its middle carbon-carbon bond *(i.e.,* between C2 and C3 bond) as shown below.



Butane has three staggered conformers **(I, III** and V). Conformer **III, in** which the two methyl groups are as far a part as possible is more stable than the other two staggered conformers I and V. The most stable of the staggered conformers **(III)** is called the **anti *conformer*** and the other two staggered conformers (I and V) are called ***gauche conformers*** *(anti* is Greek for "opposite of", gauche is French for "left.")

13.3.1 Factors Affecting Stability:

In the anti conformer the largest substituents are opposite to each other; in the gauche conformer, they are adjacent. The two gauche conformers have the same energy but each is 0.9 kcal/mole less stable than the anti conformer.

***Anti* and gauche conformers** do not have the same energy because of the **stericstrain. Steric** strain or steric **hindrance** is the strain put on a molecule when its atoms or groups are large in size and due to this, they are too close to each other, which causes repulsion between the electrons of atoms or groups. There is more sterics train in the gauche conformer than in the *anti* because the two methyl groups are closer together in the gauche conformer. Stericstrain in gauche conformeris called **gauche interaction.**

The eclipsed conformer in which the two methyl groups are closest to each other (VI) is less stable than the other eclipsed conformers (II and IV). All these eclipsed conformers have both torsional and steric strain. Torsional strain is due to bond-bond repulsion and steric strain is due to the closeness of the eclipsing groups. In general, steric strain in the molecule is directly proportional to the size of the eclipsing groups. Eclipsed conformer VI is called the fully eclipsed conformer, while II and IV are called eclipsed conformers. The energy diagram for rotation about the C2-C3 bond of butane is shown in below figure 13.3.

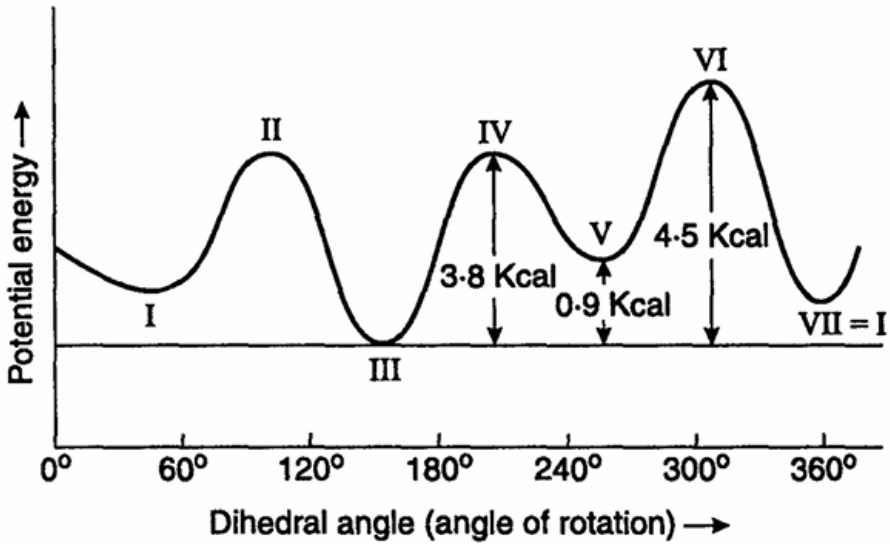


Fig. 13.3

Thus, the relative stabilities of the six conformers of n-butane in decreasing order is as follows:

$$\underset{\text{III}}{\textit{Anti}} > \underset{\text{I and V}}{\text{gauche}} > \underset{\text{II and IV}}{\text{eclipsed}} > \underset{\text{VI}}{\text{fully eclipsed}}$$

Molecules with carbon-carbon single bonds have many inter convertible conformers. Conformers cannot be separated because they rapidly interconvert.

13.4 CONFORMATIONAL ANALYSIS OF DIHALOBUTANE:

Conformational analysis refers to the study of the different spatial arrangements (conformations) that a molecule can adopt by rotation around its single bonds. In the case of **dihalobutane**, the focus is on how the two halogen substituents attached to the butane skeleton influence the stability and energy of different conformations.

13.4.1 Halogen Substituents in Dihalobutane:

Dihalobutane is a butane molecule where two hydrogen atoms have been replaced by halogen atoms (X = fluorine, chlorine, bromine, or iodine). The possible types of substitution patterns include:

(a) 1, 2-Dihalobutane: $^{1}CH_2(X) - {}^{2}CH(X) - {}^{3}CH_2 - {}^{4}CH_3$

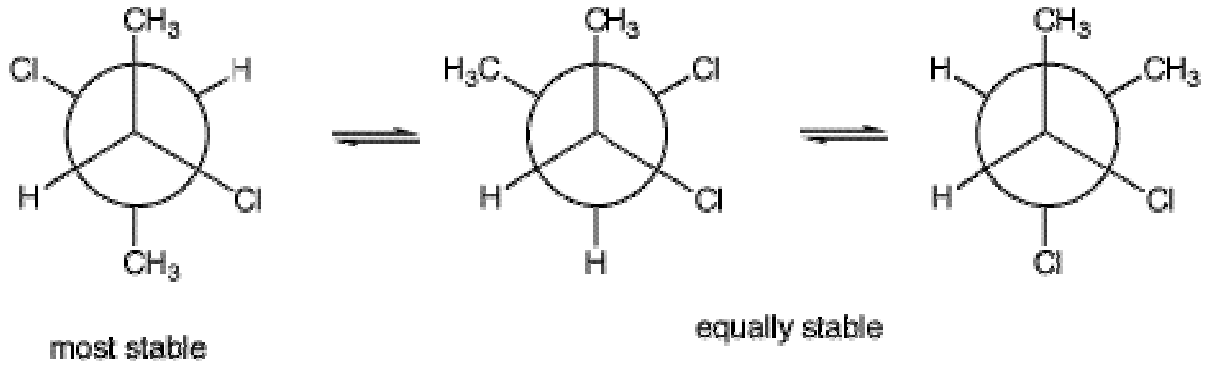
- Halogens are attached to adjacent carbon atoms (C1 and C2 or C2 and C3).
- The molecule can rotate around the C2–C3 bond, leading to different staggered and eclipsed conformations.
- Steric hindrance and dipole–dipole interactions between the halogen atoms will influence the conformer's stability.

(b) 1, 3-Dihalobutane: $^{1}CH_2(X) - {}^{2}CH_2 - {}^{3}CH(X) - {}^{4}CH_3$

- Halogens are separated by one carbon atom (attached at C1 and C3 or C2 and C4).
- This leads to interactions across the 1,3-distance (like syn-pentane interactions).
- Steric and electronic effects are less severe than in 1,2-dihalobutane, but still significant.

(c) 1, 4-Dihalobutane: $^{1}CH_2(X) - {}^{2}CH_2 - {}^{3}CH_2 - {}^{4}CH_2(X)$

- Halogens are attached at opposite ends of the chain (C1 and C4).
- The molecule prefers an extended anti-conformation to reduce steric and dipole–dipole interactions.
- This is the most stable of the three types due to the large distance between the substituents.



Newmann Projections for dichlorobutane

13.4.2 Factors Affecting Stability:

When halogens are introduced into butane, several new effects come into play:

i) Steric Hindrance:

- Halogen atoms are larger than hydrogen, with increasing size from **F < Cl < Br < I**.
- Larger halogens create greater van der Waals repulsion when they are close together.
- This favors conformations that keep the halogen substituents as far apart as possible (usually anti-conformation).

ii) Dipole–Dipole Interaction:

- Halogens are highly electronegative, creating permanent dipole moments in the C–X bonds.
- If two halogens are gauche or eclipsed, their dipole moments align, leading to repulsion and increased energy.
- Anti-conformation reduces this effect by placing the dipoles in opposite directions, minimizing the repulsion.

iii) Hyperconjugation and Inductive Effects:

- Halogens are electron-withdrawing via inductive effects (−I effect).
- This can stabilize or destabilize specific conformers depending on the orbital overlap and electron density distribution.

13.4.3 General Rules for Dihalobutane Conformations:

- Anti-conformations are generally most stable because they minimize steric and dipole–dipole repulsion.

- Gauche conformations are less stable due to steric and dipole interactions.
- Eclipsed conformations are least stable due to maximum torsional strain.
- Larger halogens enhance the stability of anti-conformers due to increased steric hindrance.
- Smaller halogens (like fluorine) allow more flexibility between anti and gauche forms.

13.5 CONFORMATIONAL ANALYSIS OF HALOHYDRINS:

Halohydrins are organic molecules containing both a hydroxyl group (-OH) and a halogen atom (X = F, Cl, Br, I) attached to adjacent carbon atoms. The presence of these two polar functional groups creates interesting stereoelectronic and steric interactions, making their conformational behavior particularly important in organic chemistry, especially in reaction mechanisms such as epoxide formation.

The study of halohydrin conformations involves analyzing the spatial arrangement of the hydroxyl and halogen groups around the C-C bond. The rotation about this single bond gives rise to different conformers, each with different stabilities due to factors like hydrogen bonding, dipole interactions, and steric hindrance.

Let's explore the conformational behavior of halohydrins, focusing on 2-chloroethanol ($Cl – CH_2 - CH_2 - OH$) as a representative example.

13.5.1 Structure of Halohydrins:

The general structure of a halohydrin is: $X\text{-}CH_2\text{-}CH_2\text{-}OH$

where: **X** = Halogen (F, Cl, Br, I) & **OH** = Hydroxyl group

For example, **2-chloroethanol** ($Cl\text{-}CH_2\text{-}CH_2\text{-}OH$) is a halohydrin where a chlorine atom is attached to one carbon and a hydroxyl group to the adjacent carbon.

The presence of a polar hydroxyl group and a polarizable halogen leads to a competition between different stabilizing and destabilizing factors, which influences the preferred conformation.

13.5.2 Types of Conformations in Halohydrins:

Since rotation about the C–C bond is possible, halohydrins can exist in several distinct conformations. The main conformations are defined by the dihedral angle (torsion angle) between the hydroxyl and halogen groups.

The three main conformations are:

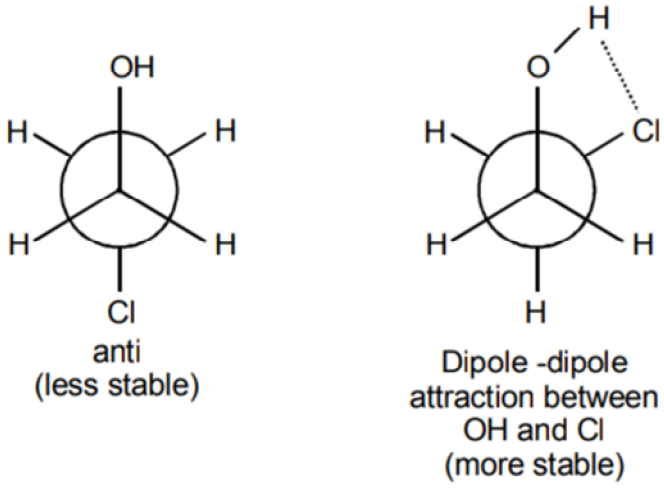
(a) Gauche Conformation:

- The hydroxyl and halogen groups are positioned at an angle of **around 60º** relative to each other.
- This arrangement creates a staggered conformation where the substituents are close but not directly aligned.
- The key stabilizing factor in the gauche conformation is **intra molecular hydrogen bonding** between the hydroxyl hydrogen and the lone pair on the halogen.

Example: In 2-chloroethanol, the hydroxyl proton can form a hydrogen bond with the lone pairs on chlorine: **Cl-CH_2-CH_2-OH**

- Chlorine is electronegative enough to accept a hydrogen bond from the hydroxyl group.
- This hydrogen bonding stabilizes the gauche conformation despite the slight steric hindrance from having the groups close together.
- Fluorine and chlorine strongly favor gauche conformations due to stronger hydrogen bonding.

Stability: The gauche conformation is generally **favored** for smaller halogens (F, Cl) because the stabilization from hydrogen bonding outweighs the steric hindrance.



Anti Conformation **Gauche Conformation**

Newmann Projections for 2-chloroethanol

(b) Anti Conformation:

- The hydroxyl and halogen groups are positioned at a dihedral angle of **around 180º** (on opposite sides of the C–C bond).
- This creates a staggered conformation where the bulky hydroxyl and halogen groups are as far apart as possible, minimizing steric hindrance.
- However, in this conformation, there is **no intramolecular hydrogen bonding** since the hydroxyl proton and halogen lone pairs are too far apart.

Example: In 2-chloroethanol, the anti conformation would look like this: Cl and OH are on opposite sides of the molecule.

The anti conformation is preferred when the halogen is large (Br, I) because the steric hindrance from large groups is minimized.

Stability:

- The anti conformation becomes more stable when the halogen is larger because the increase in steric bulk increases the penalty for keeping the groups close together in the gauche form.
- Therefore, bromoethanol and iodoethanol favor the anti conformation.

(c) Syn Conformation:

- The hydroxyl and halogen groups are positioned at a dihedral angle of **0º** (eclipsed).
- This creates a highly strained conformation due to torsional strain and steric hindrance.
- There is no intra molecular hydrogen bonding because the groups are too close and direct steric clash occurs.

Example: In 2-chloroethanol, the syn conformation would place Cl and OH directly next to each other, leading to repulsion:$Cl\text{-}CH_2\text{-}CH_2\text{-}OH$

Stability: This is the **least stable** conformation because of the high torsional strain and steric hindrance. Rarely observed in equilibrium mixtures.

15.5.3 Effect of Halogen Size on Conformation:

The size and electro-negativity of the halogen play a significant role in determining the preferred conformation:

Halogen	Gauche Stabilization	Anti Preference	Notes
F	Strong	Weak	Strong hydrogen bonding due to high electronegativity
Cl	Moderate	Moderate	Hydrogen bonding stabilizes gauche but steric clash favors anti
Br	Weak	Strong	Larger size favors anti-conformation
I	Very Weak	Very Strong	Large size strongly favors anti-conformation

- Fluoroethanol and chloroethanol **favor the gauche conformation** due to hydrogen bonding.
- Bromoethanol and iodoethanol**favor the anti conformation** due to steric hindrance from the larger halogen atom.

Dr. P. Bharath

LESSON - 14

CONFORMATION OF ACYCLIC MOLECULES - II

14.1 CONFORMATIONAL ANALYSIS OF ETHYLENE GLYCOL:

The conformational analysis of ethylene glycol ($HO{-}CH_2{-}CH_2{-}OH$) is interesting due to the presence of two polar hydroxyl (-OH) groups capable of intramolecular hydrogen bonding and the gauche effect. Rotation can occur around the C-C bond and the two C-O bonds, leading to several possible conformers. However, the most significant conformational preferences arise from rotation about the central C-C bond.

Newman Projections and Key Conformations (looking down the C-C bond):

We can consider the substituents on each carbon of the C-C bond: one -OH group and two hydrogen atoms. The main conformations are:

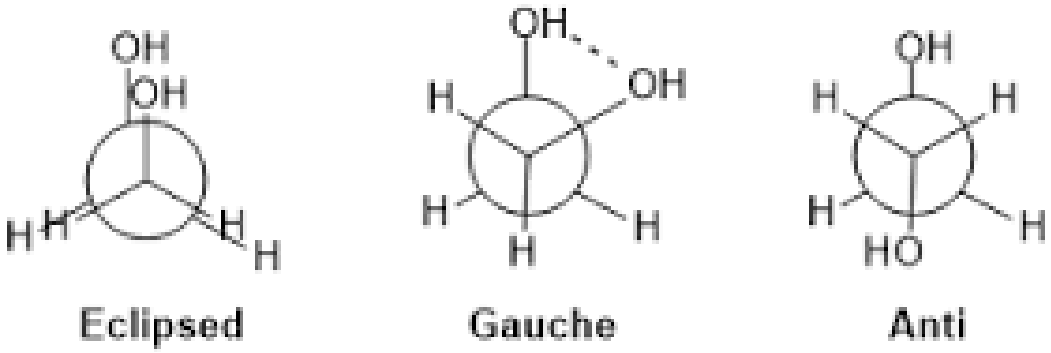
Anti (or Trans): The two -OH groups are 180^0 apart. This conformation minimizes steric repulsion between the relatively bulky hydroxyl groups.

Gauche: The two -OH groups are 60^0 apart. There are two enantiomeric gauche conformations.

Eclipsed: These are higher energy conformations where the bonds on the front and back carbons are aligned. There are three eclipsed conformations:

Fully eclipsed: The two -OH groups are eclipsed (0^0 dihedral angle). This is the highest energy conformation due to maximum steric and torsional strain.

Two other eclipsed forms where an -OH group is eclipsed with a hydrogen atom.



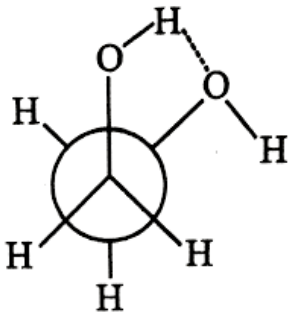
Newmann Projections for Ethylene Glycol

14.1.1 Factors Affecting Stability:

Unusual Stability: The Gauche Effect and Intramolecular Hydrogen Bonding

Ethylene Glycol Exhibits an Unusual Conformational Preference: The gauche conformation is more stable than the anti conformation in the gaseous and liquid states. This is primarily attributed to two factors:

i) Intramolecular Hydrogen Bonding: In the gauche conformation, the spatial arrangement of the two hydroxyl groups allows for the formation of an intramolecular hydrogen bond between the hydrogen of one -OH group and the oxygen of the other. This weak interaction provides a stabilizing effect that outweighs the steric strain associated with the gauche arrangement.



ii) Gauche Effect: This is a general stereoelectronic effect observed in molecules with electronegative substituents on adjacent carbons. It refers to the tendency for such substituents to prefer a gauche conformation over the anti conformation. In ethylene glycol, the oxygen atoms are electronegative. One explanation for the gauche effect involves hyperconjugation, where the electron density from a C-H σ bonding orbital can delocalize into a C-O σ antibonding orbital when the C-H and C-O bonds are gauche to each other. This interaction is stabilizing and is more effective in the gauche conformation compared to the anti conformation.

Stability Order:

Based on these factors, the general order of stability for the main conformations of ethylene glycol is: Gauche > Anti > Eclipsed (with the fully eclipsed being the least stable)

In summary, the conformational analysis of ethylene glycol is dominated by the stabilization offered by intramolecular hydrogen bonding and the gauche effect, making the gauche conformation the most stable, which is a deviation from the typical preference for anti conformations in other 1, 2-disubstituted ethanes where these specific stabilizing interactions are absent or weaker.

14.2 CONFORMATIONAL ANALYSIS OF BUTANE - 2, 3-DIOL:

The conformational analysis of butane-2, 3-diol ($^{1}CH_3$–$^{2}CH(OH)$–$^{3}CH(OH)$–$^{4}CH_3$) is particularly interesting due to the presence of two hydroxyl (-OH) groups on adjacent carbon

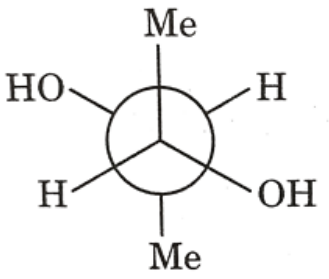
atoms. This allows for the possibility of intramolecular hydrogen bonding and the influence of the gauche effect, similar to ethylene glycol, but with the added steric bulk of methyl groups.

Butane-2, 3-diol exists in two stereoisomeric forms: the meso isomer and a pair of enantiomers. The conformational analysis differs slightly for each due to the spatial arrangement of the substituents. We primarily focus on the rotation around the central C2-C3 carbon-carbon bond.

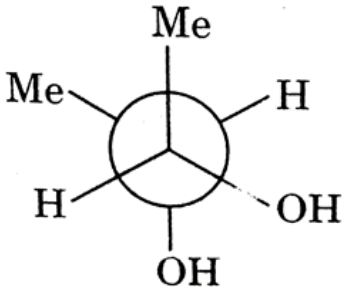
14.2.1 Newman Projections and Key Conformations (Looking Down the C2-C3 Bond):

The substituents on each carbon of the C2-C3 bond are a methyl group (CH3), a hydroxyl group (-OH), and a hydrogen atom (H). The main staggered conformations are:

i) Anti: The two largest non-hydrogen substituents are 180^0 apart. Depending on the isomer, this could be the two methyl groups (in chiral forms) or a methyl and a hydroxyl group (in meso form).



ii) Gauche: The two largest non-hydrogen substituents are 60^0 apart. Again, the specific groups that are gauche depend on the isomer.



iii) Eclipsed: These are higher energy conformations where the bonds on C2 and C3 are aligned.

14.2.2 Factors Affecting Stability:

The stability of the conformers of butane-2, 3-diol is determined by a combination of factors:

i) Steric Strain: Repulsion between bulky groups (CH3 and OH) when they are in close proximity (gauche or eclipsed).

ii) Torsional Strain: Resistance to twisting about the C-C bond, which is highest in eclipsed conformations.

iii) Intramolecular Hydrogen Bonding: The close proximity of the two -OH groups in certain gauche conformations allows for the formation of a stabilizing intramolecular hydrogen bond between the hydrogen of one hydroxyl group and the oxygen of the other.

iv) **Gauche Effect:** The preference for electronegative substituents (like oxygen in the -OH group) to be in a gauche conformation due to stabilizing hyper conjugation interactions.

14.2.3 Conformational Analysis of Meso-Butane-2,3-diol:

In the meso isomer, the two chiral centers have opposite configurations. The most stable conformation is generally considered to be a gauche conformation where the two hydroxyl groups are close enough to form an intramolecular hydrogen bond. This stabilization outweighs the steric repulsion between the methyl groups, which are also gauche in this conformation.

14.2.4 Conformational Analysis of Chiral Butane-2, 3-diol:

In the chiral enantiomers ((2R,3R) or (2S,3S)), the two chiral centers have the same configuration. For these isomers, the gauche conformation where the two hydroxyl groups are gauche and can form an intramolecular hydrogen bond is also often the most stable. In the anti conformation, the hydroxyl groups are too far apart for hydrogen bonding. While the anti conformation minimizes steric interactions between the methyl groups, the stabilization from intramolecular hydrogen bonding in the gauche form is significant.

14.3 CONFORMATIONAL ANALYSIS OF AMINO ALCOHOLS:

Amino alcohols are organic compounds that contain both an amine ($-NH_2$) and a hydroxyl (-OH) functional group attached to a hydrocarbon chain. The conformational behavior of amino alcohols is complex because of the ability of these two polar functional groups to interact with each other through **intramolecular hydrogen bonding** and other electronic effects. This leads to specific preferences for certain spatial arrangements (conformations) around the carbon-carbon and carbon-heteroatom single bonds.

To understand the conformational analysis of amino alcohols, it's important to consider:

i) The ability of the hydroxyl and amine groups to form hydrogen bonds.

ii) The steric hindrance created by substituents.

iii) The electronic effects that arise from dipole-dipole interactions between the amine and hydroxyl groups.

14.3.1 Types of Intramolecular Hydrogen Bonding in Amino Alcohols:

The formation of intramolecular hydrogen bonds is a key factor in determining the preferred conformation of amino alcohols.

(a) O–H···N Hydrogen Bonding:

- The hydroxyl proton (-OH) can form a hydrogen bond with the nitrogen lone pair of the amine.
- This stabilizes a specific conformation where the hydroxyl and amine groups are close together, typically leading to a **gauche conformation** (dihedral angle ~60º).
- This type of hydrogen bonding is highly stabilizing and lowers the overall energy of the molecule.

(b) N–H···O Hydrogen Bonding

- The amine proton (-NH2_2) can form a hydrogen bond with the oxygen lone pair of the hydroxyl group.
- This type of hydrogen bonding also promotes a gauche conformation since the donor and acceptor groups must be spatially close.

Hydrogen bonding favors gauche conformations because it brings the hydroxyl and amine groups closer together, resulting in an energetically favorable arrangement.

14.3.2 Rotational Freedom and Conformational Preferences:

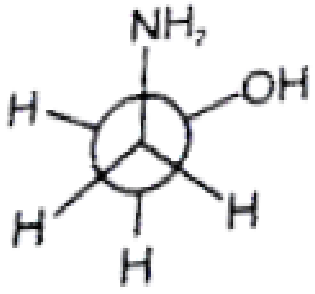
Rotation around the C–C and C–N bonds allow the amino alcohol molecule to adopt different conformations. However, not all conformations are equally stable due to steric, electronic, and hydrogen-bonding effects.

Key Torsional Angles: H–C–C–OH, H–C–C–NH_2, OH–C–C–NH_2

For example, we can study the Conformations of 2-Aminoethanol (Ethanolamine)

2-Aminoethanol (HO–CH_2–CH_2–NH_2) is the simplest amino alcohol and serves as a model system for understanding amino alcohol conformations.

Preferred Conformation:



i) The gauche conformation is strongly favored due to the formation of an intramolecular O–H···N hydrogen bond.

ii) The anti conformation is less stable by ~4–8 kJ/mol because the stabilizing hydrogen bond is lost.

Reasons Gauche is Favored:

i) The hydrogen bonding stabilizes the molecule and reduces torsional strain.

ii) The molecule sacrifices some steric repulsion to maximize hydrogen bonding.

14.3.3 Summary of Amino Alcohol Conformations:

Molecule	Preferred Conformation	Reason
2-Aminoethanol	Gauche	Strong intramolecular hydrogen bonding
2-Amino-1-propanol	Gauche	Hydrogen bonding + mild steric hindrance
2-Amino-2-methyl-1-propanol	Gauche (less stabilized)	H-bonding vs steric clash

The conformational analysis of amino alcohols is primarily influenced by hydrogen bonding and steric interactions. Gauche conformations are typically preferred due to the formation of stabilizing hydrogen bonds, but steric hindrance from larger substituents can shift the equilibrium toward anti conformations.

14.4 CONFORMATIONAL ANALYSIS OF 1,1,2,2-TETRAHALOBUTANES:

The conformational analysis of 1,1,2,2-tetrahalobutanes ($X_2{}^{1}CH-{}^{2}CHX_2-{}^{3}CH_2-{}^{4}CH_3$, where X is a halogen) is more complex than that of simpler alkanes due to the presence of four halogen atoms on the adjacent C1 and C2 carbons. These bulky and electronegative substituents introduce significant steric and electronic effects that dictate the preferred conformations around the C1-C2 bond.

To analyze the conformations, we primarily focus on the rotation around the central C1-C2 carbon-carbon single bond. We use Newman projections to visualize the different spatial arrangements of the substituents. Looking down the C1-C2 bond, the substituents on C1 are two halogen atoms (X) and a hydrogen atom (H), and the substituents on C2 are also two halogen atoms (X) and a −CH2CH3 (ethyl) group.

$X_2{}^{1}CH-{}^{2}CHX_2-{}^{3}CH_2-{}^{4}CH_3$ (Where X = halogen atom)

The different conformations are classified based on the **dihedral angle** between the two sets of halogen-substituted carbons (C1 and C2). The main conformations are:

1) **Staggered Conformations:** These are generally lower in energy than eclipsed conformations because the bonds on adjacent carbons are as far apart as possible, minimizing torsional strain. For 1,1,2,2-tetrahalobutanes, there are three staggered conformers:

a) **Anti:** The two largest groups on C1 and C2 are 180□ apart. In this case, we need to consider the relative sizes and electronic effects of X and −CH2CH3. There are two possible "anti-like" conformations depending on which pair of substituents are anti:
   - Halogen-Halogen anti and Halogen-Ethyl anti

b) **Gauche:** The two largest groups are 60^0 apart. There are two sets of gauche conformers depending on which substituents are gauche:
   - Two conformers with a halogen and the ethyl group gauche.
   - Two conformers with two halogen atoms gauche.

2. **Eclipsed Conformations:** These are higher in energy due to torsional strain, where the bonds on adjacent carbons are aligned. There are three eclipsed conformers:
   - Halogen-Halogen eclipsed.
   - Halogen-Ethyl eclipsed (two possibilities).
   - Hydrogen-Halogen eclipsed (two possibilities).

14.4.1 Factors Affecting Stability:

The relative stability of these conformers is determined by a balance of several factors:

14.4.1.1 Steric Strain: Repulsion between the electron clouds of bulky substituents. The large size of halogen atoms (especially Br and I) and the ethyl group will lead to significant steric strain in conformations where they are in close proximity (gauche and especially eclipsed).

14.4.1.2 Torsional Strain: Resistance to twisting about the C-C bond. Eclipsed conformations suffer from this due to the alignment of C-H, C-X, and C-C bonds on adjacent carbons.

14.4.1.3 Electrostatic Interactions (Dipole-Dipole Interactions): The C-X bonds are polar, with a partial negative charge on the halogen and a partial positive charge on the carbon. The alignment of these bond dipoles in certain conformations can lead to repulsive or attractive electrostatic interactions, affecting the stability. For example, conformations where several C-X bond dipoles are aligned in the same direction will be less stable due to dipole-dipole repulsion.

14.4.1.4 Gauche Interactions: Specific steric and electronic interactions that occur when two bulky groups are in a gauche relationship. The magnitude of these interactions depends on the nature of the halogen and the ethyl group.

Order of Energies: Anti < Gauche < Eclipsed

The energy difference between anti and gauche is usually around **3–4 kJ/mol**, while the difference between anti and eclipsed is around **12–14 kJ/mol**.

14.4.2 Effect of Halogen Size and Type:

The type of halogen significantly affects the preferred conformation:

Halogen Substitution	Preferred Conformation	Reason
1,1,2,2-Tetrafluorobutane	Anti	Minimizes dipole repulsion due to small fluorine size
1,1,2,2-Tetrachlorobutane	Anti	Minimizes steric hindrance between larger chlorine atoms
1,1,2,2-Tetrabromobutane	Anti	Steric clashes are greater with larger bromine atoms
Mixed halogens (e.g., 1,1-dichloro-2,2-difluorobutane)	Anti or Gauche	Depends on balance between size and dipole interactions

In Summary, **Anti-conformation** is the most stable due to minimized steric and dipole-dipole repulsion, **Gauche-conformation** is moderately stable but higher in energy due to increased steric and dipole repulsion, and **Eclipsed-conformation** is the least stable because of maximum steric and dipole interactions. The size of the halogen and its electronegativity strongly influence the conformational preference.

14.5 KLYNE-PRELOG TERMINOLOGY:

The Klyne-Prelog terminology provides a systematic way to describe the conformations around a single bond by specifying the torsion angle (also known as the dihedral angle). It divides the 360^0 of rotation into specific ranges and assigns descriptive terms.

Here's a breakdown of the Klyne-Prelog terminology for conformers based on their torsion angles (θ):

Ranges of Torsion Angles and Corresponding Terminology:

a) Syn (s): θ^0 between 0^0 and $\pm 90^0$

i) Synperiplanar (sp): θ^0 between 0^0 and $\pm 30^0$ (This includes the *eclipsed* conformation)

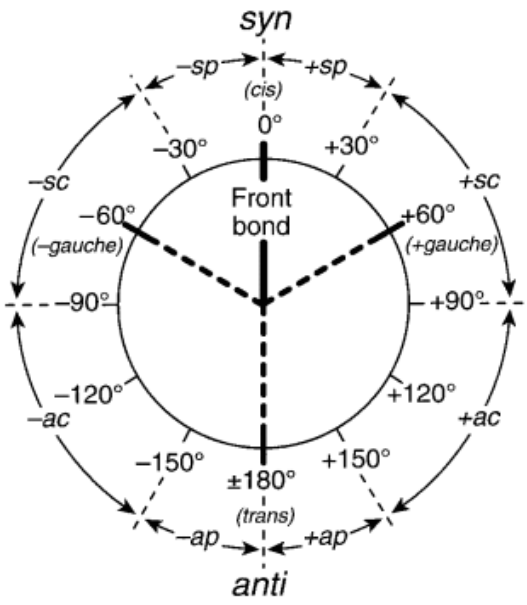
ii) Synclinal (sc): θ^0 between $\pm30^0$ and $\pm90^0$ (This is equivalent to the *gauche* or *skew* conformation)

b) Anti (a): θ^0 between $\pm90^0$ and 180^0

i) Anticlinal (ac): θ^0 between $\pm90^0$ and $\pm150^0$

ii) Antiperiplanar (ap): θ^0 between $\pm150^0$ and 180^0 (This is equivalent to the *anti* or *trans* conformation)

Visual Representation (Imagine looking down the C-C bond in a Newman projection):



sp – Synperiplanar

sc – Synclinical

ac – Anticlinical

ap – Antiperiplanar

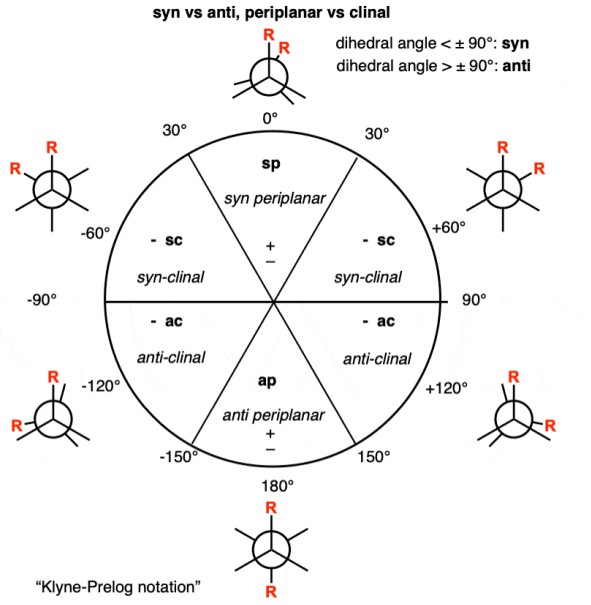
- The torsion angle (θ) is defined as the angle between the bonds to the substituents on the front and back atoms of the bond being viewed in a Newman projection. It's the angle between two planes, each containing three atoms.
- The sign of the torsion angle is determined by the direction of rotation needed to make the front substituent eclipse the rear substituent: clockwise is positive (+), and counterclockwise is negative (-). This is important for chiral molecules and specifying enantiomeric gauche or clinal conformers (e.g., +sc and -sc).
- The Klyne-Prelog system provides a more precise way to describe conformations than the general terms like eclipsed, staggered, gauche, and anti, especially when torsion angles deviate significantly from the ideal 0^0, 60^0, 120^0, and 180^0.
- The "clinal" term signifies that the torsion angle is neither periplanar (close to 0^0 or 180^0) nor exactly 60^0 or 120^0.

Example: Butane

For butane, looking down the C2-C3 bond:

Anti: The two methyl groups have a torsion angle of 180□, which is antiperiplanar (ap).

Gauche: The two methyl groups have torsion angles of approximately $+60^0$ or -60^0, which are synclinal (+sc or -sc).



Dihedral angle	Designation	Dihedral angle	Designation
0 ± 30°	± syn periplanar	180 ± 30°	± anti periplanar
+60° ± 30°	+ syn-clinal	-120° ± 30°	- anti-clinal
120 ± 30°	+ anti-clinal	-60 ± 30°	- syn-clinal

Eclipsed (methyls eclipsed with hydrogen): Torsion angles of 0^0 (methylssynperiplanar - sp), $+120^0$ (methyl eclipsed with hydrogen, anticlinal - +ac), and -120^0 (methyl eclipsed with hydrogen, anticlinal - -ac).

Fully Eclipsed (methyls eclipsed with methyl): Torsion angle of 0^0, synperiplanar (sp), highest energy conformation.

The Klyne-Prelog terminology is valuable for unambiguously describing and discussing the conformations of molecules, especially those with complex structures and non-ideal torsion angles.

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LESSON - 15

STABILITY AND ANALYSIS OF MOLECULAR CONFORMATIONS

15.1 FACTORS AFFECTING CONFORMATIONAL STABILITY AND CONFORMATION EQUILIBRIUM: ATTRACTIVE AND REPULSIVE INTERACTIONS:

The stability of different conformations of a molecule and the equilibrium distribution between them are governed by a variety of attractive and repulsive interactions. These interactions determine the potential energy of each conformer, with more stable conformers residing at lower energy minima.

Here's a breakdown of the key attractive and repulsive interactions influencing conformational stability and equilibrium:

15.1.1 Repulsive Interactions (Destabilizing Factors):

- **Steric Strain (Van der Waals Repulsion):** This arises from the repulsion between the electron clouds of atoms or groups that are forced too close to each other. Bulky substituents in close proximity (e.g., in eclipsed or gauche conformations) experience significant steric strain, increasing the energy of that conformer. The magnitude of steric strain depends on the size of the interacting groups and the distance between them.
- **Torsional Strain (Pitzer Strain):** This is the resistance to twisting about a bond. It is highest in eclipsed conformations where the bonds on adjacent atoms are aligned, leading to repulsion between their bonding electrons. Staggered conformations minimize torsional strain. The energy barrier to rotation around a single bond is primarily due to torsional strain.
- **Angle Strain (Baeyer Strain):** This occurs primarily in cyclic compounds where bond angles deviate from the ideal tetrahedral angle (approximately 109.5° for sp^3 hybridized carbons). This forces atoms closer together or further apart than their optimal non-bonding distance, leading to increased energy and decreased stability. While less directly relevant to acyclic conformational analysis around single bonds, it can influence the overall shape and flexibility of cyclic systems.
- **Dipole-Dipole Repulsion:** When polar bonds or groups are oriented such that their partial charges with the same sign are in close proximity, electrostatic repulsion occurs, destabilizing the conformer.

15.1.2 Attractive Interactions (Stabilizing Factors):

- **Intramolecular Hydrogen Bonding:** When a molecule contains both a hydrogen bond donor (e.g., -OH, -NH) and a hydrogen bond acceptor (e.g., -O-, -N:, halogens in some cases) within appropriate proximity and orientation, an intramolecular hydrogen bond can form. This attractive interaction lowers the energy of the conformer, often favoring specific gauche-like arrangements.
- **Dipole-Dipole Attraction:** Conversely, when polar bonds or groups are oriented such that their opposite partial charges are in close proximity, electrostatic attraction occurs, stabilizing the conformer.
- **Hyperconjugation:** This is a stabilizing interaction that involves the overlap of a filled sigma (σ) bonding orbital with an adjacent empty or partially filled antibonding sigma* (σ) or pi (□) orbital. In conformational analysis, hyperconjugation can favor certain staggered conformations where C-H σ bonds can interact with antibonding orbitals of adjacent C-C or C-heteroatom bonds. The gauche effect, where electronegative substituents on adjacent carbons prefer a gauche conformation, is often attributed in part to stabilizing hyperconjugation.
- **London Dispersion Forces (Van der Waals Attraction):** These are weak, short-range attractive forces arising from temporary fluctuations in electron distribution around atoms and molecules. While generally weaker than other interactions, they contribute to the overall stability of all conformers and can become significant for larger molecules with extensive surface areas.

15.1.3 Conformational Equilibrium:

The relative populations of different conformers at equilibrium are determined by the Boltzmann distribution, which depends on the energy difference (ΔG) between the conformers and the temperature (T):

$$\mathbf{K = [Conformer\ B] / [Conformer\ A] = \exp(-\Delta G / RT)}$$

Where,

- K is the equilibrium constant.
- [Conformer B] and [Conformer A] are the concentrations of the two conformers.
- ΔG is the difference in Gibbs free energy between the conformers ($\Delta G = \Delta H - T\Delta S$).
- R is the ideal gas constant.

Attractive interactions lower the enthalpy (H) and thus favor that conformer. Repulsive interactions increase the enthalpy and disfavor that conformer. Entropy (S), related to the number of accessible microstates, also plays a role. More symmetrical or less constrained conformers may have higher entropy, which can influence the equilibrium at higher temperatures.

The equilibrium between different conformers is governed by the balance of these attractive and repulsive forces. Factors that affect this equilibrium include:*Temperature, Substituent Effects, Solvent Effects, Conformational Barriers, and SubstituentInteractions.*

In summary, the conformational landscape of a molecule is a result of a delicate balance between various attractive and repulsive interactions. Understanding these interactions is crucial for predicting the preferred conformations and the distribution of conformers at equilibrium, which in turn influences the physical and chemical properties of the molecule.

15.2 USE OF PHYSICAL AND SPECTRAL METHODS IN CONFORMATIONAL ANALYSIS:

Several physical and spectroscopic techniques are employed to study and analyze the conformations of molecules, particularly in determining the relative populations of different conformers and understanding the factors that influence their stability.

A. NMR Spectroscopy:

Nuclear Magnetic Resonance (NMR) spectroscopy is one of the most widely used techniques in conformational analysis due to its ability to detect different environments of nuclei within a molecule, particularly hydrogens (1H NMR) and carbons (13C NMR).

Coupling Constants (J-values):

The scalar coupling constants between nuclei provide valuable information about the relative spatial positions of atoms. For example, **cis** (eclipsed) conformers typically have larger coupling constants than **trans** (staggered) conformers due to differences in their spatial arrangements.

Chemical Shifts:

The chemical shift of protons or carbons can shift depending on the environment of the atom, which can be influenced by the conformation of the molecule. For example, the proximity of electronegative groups like -OH may alter the chemical shifts of adjacent hydrogens.

NOE (Nuclear Overhauser Effect):

The NOE provides information about the spatial proximity between nuclei. This effect can be used to detect interactions between atoms in close proximity in space, even if they are far apart in terms of bond connectivity. By comparing NOE signals in different conformers, the preferred conformations can be deduced.

Exchange Processes:

Conformational interconversion can lead to chemical exchange, which can be observed in NMR spectra as broadened peaks or multiple signals for the same nuclei, indicating that the molecule is rapidly interconverting between different conformers.

B. X-ray Crystallography:

X-ray diffraction analysis provides high-resolution structural information, which is invaluable for determining the conformation of molecules in the solid state. This technique can reveal the precise three-dimensional arrangement of atoms, which helps in understanding the conformation and confirming whether a particular conformer is more stable than others.

C. Computational Methods:

Molecular Modeling:

Computational techniques, such as molecular mechanics (MM) and density functional theory (DFT), can be used to predict the most stable conformations of molecules by calculating the total energy of each possible conformer. These methods take into account the steric, electrostatic, and bonding interactions to predict the most stable conformation.

Monte Carlo Simulations:

These methods simulate the random movement of atoms or molecules over time, allowing the study of the conformational preferences of a molecule based on energy calculations.

D. Infrared (IR) Spectroscopy:

IR spectroscopy can provide information on the functional groups in different conformers. The stretching and bending frequencies of bonds like -OH, -NH, and -CH2 may shift depending on the conformation, due to different intermolecular forces, hydrogen bonding, and steric hindrance.

E. UV-Vis Spectroscopy

For molecules with conjugated systems (e.g., aromatic compounds), UV-Vis spectroscopy can be used to observe electronic transitions. Conformational changes that affect the conjugation or symmetry of the molecule can alter the absorption spectrum, providing insight into the molecule's conformation.

15.2.1 Conclusion:

The study of conformational stability and equilibrium is crucial in understanding the behavior and reactivity of molecules. Attractive and repulsive interactions govern the relative stabilities of conformers, with steric hindrance and electronic effects playing major roles. Physical and spectral methods such as NMR, X-ray crystallography, IR spectroscopy, and computational approaches provide valuable tools for determining the preferred conformations of molecules and for understanding the factors that influence their equilibrium. These techniques enable chemists to predict the most stable conformers and their relative populations, which is essential for understanding chemical reactivity, solubility, and other properties.

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LESSON - 16

CYCLIC DIASTEREOMER STABILITY & REACTIVITY: CONFORMATIONAL EFFECTS

16.1 CONFORMATIONAL EFFECTS ON THE STABILITY AND REACTIVITY OF DIASTEREOMERS IN CYCLIC MOLECULES:

Diastereomers are stereoisomers that are **not mirror images** of each other. In cyclic molecules, the spatial arrangement of substituents around the ring creates different diastereomers, which often exhibit significant differences in stability and reactivity due to **conformational effects**.

The key factors influencing the stability and reactivity of cyclic diastereomers are:

i) Ring strain

ii) Steric interactions

iii) Stereoelectronic effects

iv) Intramolecular hydrogen bonding or dipole interactions

i) Ring Strain in Cyclic Diastereomers:

Ring Size and Angle Strain:

i) Small rings (e.g., cyclopropane, cyclobutane) have **high angle strain** because their bond angles deviate significantly from the ideal tetrahedral angle (109.5°).

ii) Medium-sized rings (e.g., cyclopentane, cyclohexane) can reduce strain through puckering or adopting non-planar conformations.

iii) Large rings (e.g., 12-membered and larger) reduce strain, but introduce greater conformational flexibility, leading to increased entropy.

Example: cis- vs. Trans-Decalin

cis-Decalin - Both fused rings are in a cis relationship (hydrogens on the bridgehead carbons are on the same face).

- *Conformationally flexible*
- *Less stable due to increased steric hindrance*
- *More reactive due to ring strain*

trans-Decalin - Both fused rings are in a trans relationship (hydrogens on the bridgehead carbons are on opposite faces).

- *More stable due to favorable equatorial positioning*
- *Less reactive due to reduced ring strain*

Result: Trans-decalin is more stable than cis-decalin due to reduced steric clash and ring strain.

ii) Steric Interactions in Diastereomers:

Steric interactions arise from the spatial clash between substituents, which depends on their orientation (axial vs. equatorial) and the size of the substituents.

Cyclohexane Chair Conformations:

- Cyclohexane adopts a **chair conformation** to minimize torsional and angle strain.
- Substituents on cyclohexane rings prefer the **equatorial position** because axial substituents create **1, 3-diaxial interactions** (steric clashes between axial groups at C1, C3, and C5).

Example: cis- vs. trans-1, 2-dimethylcyclohexane:

cis-1, 2-dimethylcyclohexane

- One methyl group is axial, the other is equatorial.
- Increased steric hindrance due to 1, 3-diaxial interactions.
- Less stable.

trans-1, 2-dimethylcyclohexane

- Both methyl groups can occupy equatorial positions.
- More stable due to minimized steric hindrance.

Result: The trans-isomer is more stable due to minimized steric hindrance in the equatorial conformation.

iii) Stereoelectronic Effects

Stereoelectronic effects arise when the spatial orientation of substituents allows favorable or unfavorable orbital interactions, such as: Hyperconjugation, Anomeric effects, π–σ^* or σ–σ^* interactions.

Anomeric Effect:

- Common in cyclic acetals, cyclic ethers, and glycosides.
- When an electronegative substituent (like OR or F) occupies the axial position, lone pair donation into the adjacent σ* orbital leads to stabilization.

Example: α- vs. β-anomers of glucopyranose

α-glucopyranose – The hydroxyl at the anomeric position is axial, allowing favorable n → σ* donation (anomeric effect).

- More reactive toward hydrolysis due to increased ring strain and stereoelectronic alignment.

β-glucopyranose – The hydroxyl at the anomeric position is equatorial.

- More stable due to reduced steric clash.
- Less reactive due to absence of anomeric stabilization.

Result: α-anomers are more reactive due to the anomeric effect, while β-anomers are more stable.

iv) Intramolecular Hydrogen Bonding and Dipole Interactions

Hydrogen bonding and dipole interactions can stabilize or destabilize certain conformers or diastereomers.

Example: cis- vs. trans-2-fluorocyclohexanol

cis-2-fluorocyclohexanol – Fluorine and hydroxyl groups are positioned close enough to form an intramolecular hydrogen bond.

- Increased stability due to hydrogen bonding.
- Lower reactivity due to reduced nucleophilicity of hydroxyl.

trans-2-fluorocyclohexanol – Fluorine and hydroxyl groups are far apart, preventing hydrogen bonding.

- Less stable due to the absence of stabilizing interaction.
- Higher reactivity due to greater availability of the hydroxyl group.

Result: Intramolecular hydrogen bonding stabilizes the cis-isomer but reduces its reactivity.

iv) Effect on Reactivity:

Conformational effects also influence the reactivity of cyclic diastereomers by controlling the accessibility of reactive sites and transition state energies.

Example: Ester Hydrolysis in cis- vs. trans-2-methylcyclohexyl acetate

cis-ester - The ester group and nucleophile can align more easily in a favorable conformation, leading to faster hydrolysis.

trans-ester - Steric hindrance from equatorial substituents raises the activation barrier, slowing down the reaction.

Result: The cis-isomer reacts faster due to reduced steric hindrance and better orbital alignment.

16.2 CONFORMATIONAL EFFECTS ON THE STABILITY AND REACTIVITY OF DIASTEREOMERS IN CYCLIC MOLECULES - STERIC AND STEREO ELECTRONIC FACTORS:

The stability and reactivity of diastereomers in cyclic molecules are heavily influenced by their preferred conformations, which are determined by:

Steric Factors: Repulsive interactions due to the spatial arrangement of atoms (e.g., 1, 3-diaxial strain in cyclohexanes) directly impact stability and can hinder reaction pathways.

Stereo electronic Factors: Stabilizing or destabilizing interactions arising from the spatial arrangement of bonds and lone pairs (e.g., the anomeric effect, gauche effect, hyperconjugation) significantly affect conformational preference and thus reactivity.

Different conformations, dictated by these factors, lead to variations in:

Stability: Diastereomers favor conformations minimizing steric strain and maximizing stabilizing electronic interactions.

Reactivity: Conformation affects transition state energy, accessibility of reactive sites, and stereochemical outcomes.

Understanding these conformational effects is crucial for predicting and controlling the behavior of cyclic diastereomers in chemical processes.

16.3 SUMMARY TABLE OF CONFORMATIONAL EFFECTS ON DIASTEREOMERS:

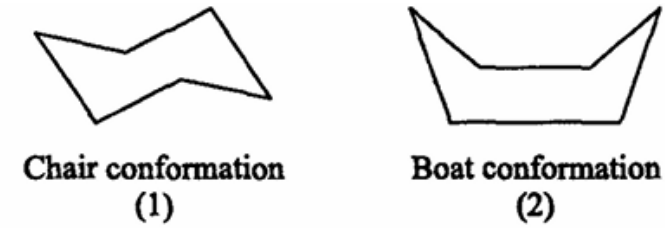
Effect	Influence on Stability	Influence on Reactivity	Example
Ring Strain	Increased strain reduces stability.	Increased strain raises reactivity due to higher energy transition state.	cis- vs. trans-decalin
Steric Hindrance	Substituents in axial positions reduce stability.	Increased steric hindrance raises the activation energy, reducing reactivity.	cis- vs. trans-1,2-dimethylcyclohexane
Stereoelectronic Effects	Favorable orbital interactions (e.g., anomeric effect) increase stability.	Aligning orbitals reduces activation energy, increasing reactivity.	α- vs. β-glucopyranose
Intramolecular Hydrogen Bonding	Stabilizes conformers through hydrogen bonding.	Reduces reactivity by reducing the availability of nucleophilic sites.	cis- vs. trans-2-fluorocyclohexanol

LESSON - 17

CONFORMATIONS OF MONOCYCLIC COMPOUNDS

17.1 CONFORMATION OF CYCLOHEXANE:

Sachse (1890) and Mohr (1931) assumed three-dimensional structure of alicyclic compounds. They pointed out that two forms are possible for cyclohexane if it has puckered conformation. These two forms are the chair and boat conformations of cyclohexane which are free from angle strain. Both forms are interconvertible into each other.



Chair conformation (1) **Boat conformation (2)**

The chair form is rigid (in the sense that it resists distortion) and when it is transformed into the boat form some angular deformation is necessary. The energy barrier in this process is about 9-11 kcal/mole. This value is large enough for each conformation to retain its identity, but is not large enough to prevent their rapid interconversion at room temperature. Thus, it is not possible to isolate each conformation. In 1947 Hassel established by means of electron diffraction studies that cyclohexane exists predominantly in the chair conformation.

The chair and boat forms are free from angle strain, (The angle between the carbon-carbon bonds is all 111° which is very close to tetrahedral angle **109-5°)** but because of differences in the steric strain and bond opposition strain, the two forms differ in energy content. Fig. 17.1 and 17.2 represent the chair and boat conformations and the direction of the C-H bonds.

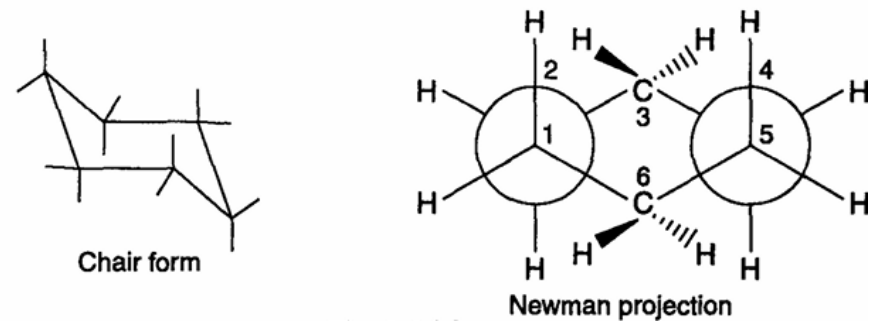


Figure 17.1

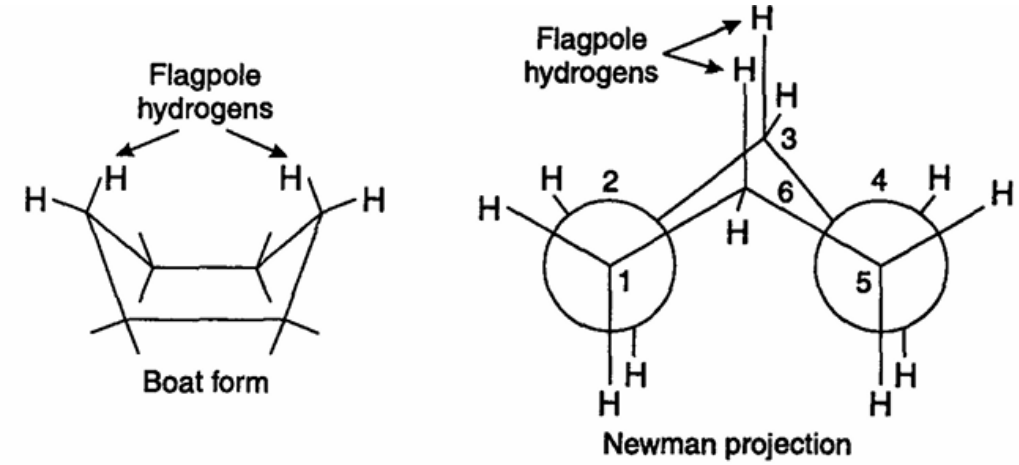


Figure 17.2

In the chair form Fig. (17.1) all the C-H bonds on adjacent carbons are in the skew position (The arrangement is skew as in the gauche form of n-butane). On the other hand, in the boat conformation there are four skew interactions (2, 3; 3, 4; 5, 6 and 6, 1) and two eclipsed interactions (1, 2 and 4, 5) Fig. 17.2.

Apart from the factor mentioned above there is one more factor which makes the boat conformation less stable. It is the repulsion between hydrogen atoms which are at the top of the boat. These hydrogens are known as flag pole hydrogens. The distance between their centres is only 1.83 & while the sum of the vander Waals radii of the two hydrogen atoms is 2.5 & This repulsion is called ***bow-sprint repulsion*** vander Waals or and contributes to increase the energy of the boat form Fig 17.3.

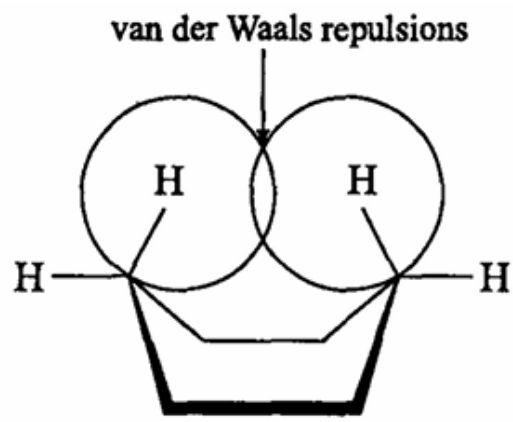


Figure 17.3

Thus, the total strain in the boat conformation is larger than that in the chair conformation and consequently the former is less stable than the latter. The boat form is however flexible and can readily be distorted into many shapes (Fig. 17.4).

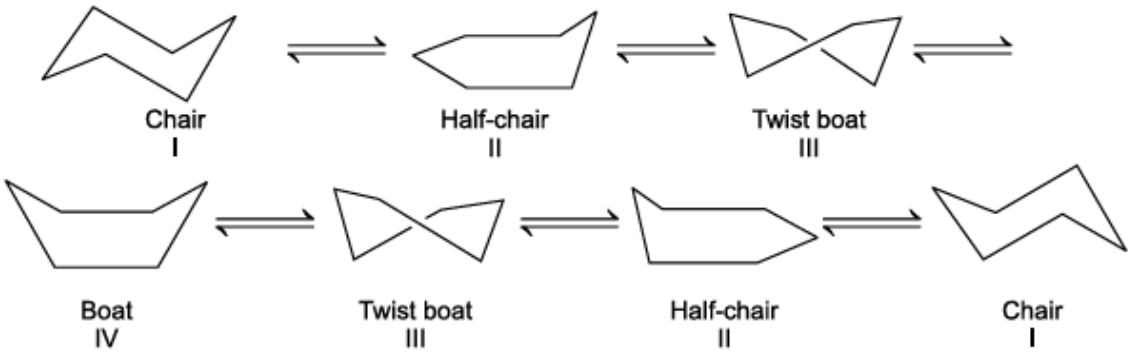


Fig. 17.4 Interconversion of Conformers of Cyclohexane

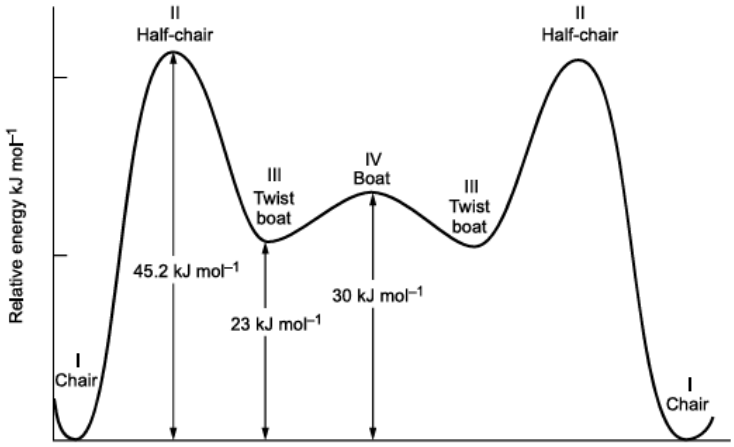


Fig. 17.5 Relative Energies of the Various Conformations of Cyclohexane

The relative energies of various conformations of cyclo hexane are depicted in Fig. 17.5. As seen (Fig.17.5), the energy barriers between the chair, boat and twist boat conformations of cyclohexane are low. This makes the separation of the conformations rather impossible at room temperature.

At room temperature, about 1 million interconversions occur each second and due to greater stability of the chair, more than 99% of the molecules are believed to be in the chair conformation at any time.

17.1.1 Axial and Equatorial Bonds in Cyclohexane:

The chair form of cyclohexane has two types of carbon-hydrogen bonds, viz., axial *(a)* and equatorial *(e)* The C-H bonds which are parallel to the axis are axial bonds (Fig.17.6) and the remaining six C-H bonds which extend outward at an angle of 109.5^{O} to the axis are equatorial bonds (Fig.17.6). The axial bonds are vertical to the plane of the ring and the Equatorial bonds are roughly in the plane of the rings.

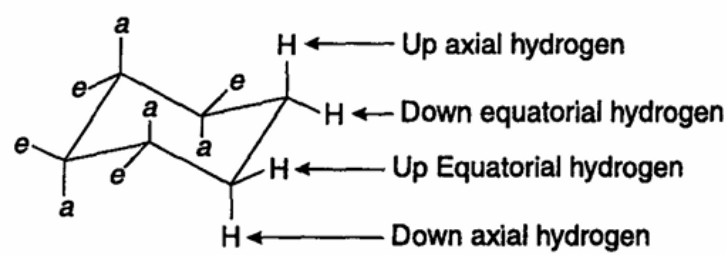


Fig. 17.6

When ring flipping takes place from one chair form to another, all the axial bonds become equatorial bonds and equatorial bonds become axial bonds.

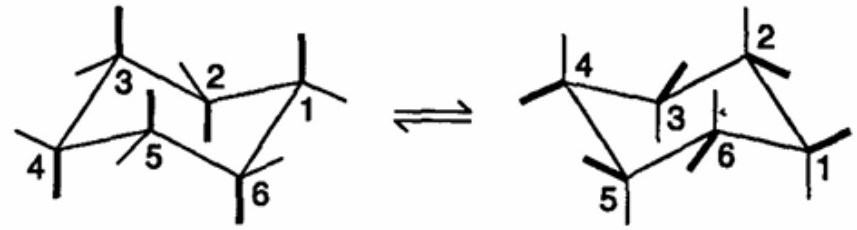


Fig. 17.7: Flipping of One Chair form to Another

In case of substituted cyclohexane's (mono or di), there will be two cyclohexane's, axial or equatorial. It is interesting to know why one form is more stable than the other. This forms the subject matter of the following sections.

17.2 CONFORMATIONS OF MONOSUBSTITUTED CYCLOHEXANE:

Monosubstituted cyclohexane, for example, methylcyclohexane has two chair conformations. In one form, methyl group is axial and in the other the methyl group is equatorial (Fig. 17.8). Both these forms are interconvertible by ring flipping. On the basis of studies, it has been shown that methyl cyclohexane with the methyl group equatorial is more stable than the conformation with methyl group axial by about 7.6 kJ mol^{-1}. In fact, the methyl cyclohexane with equatorial methyl is present to the extent of 95% in the equilibrium mixture. The greater stability of methyl cyclohexane with equatorial methyl is because in axial methyl group (in position 1),

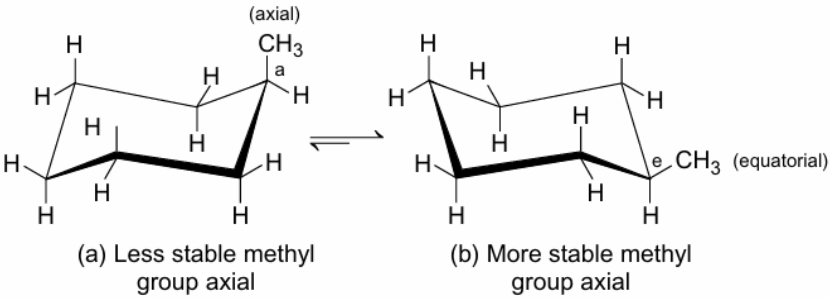


Fig. 17.8: Conformations of methyl-cyclohexane

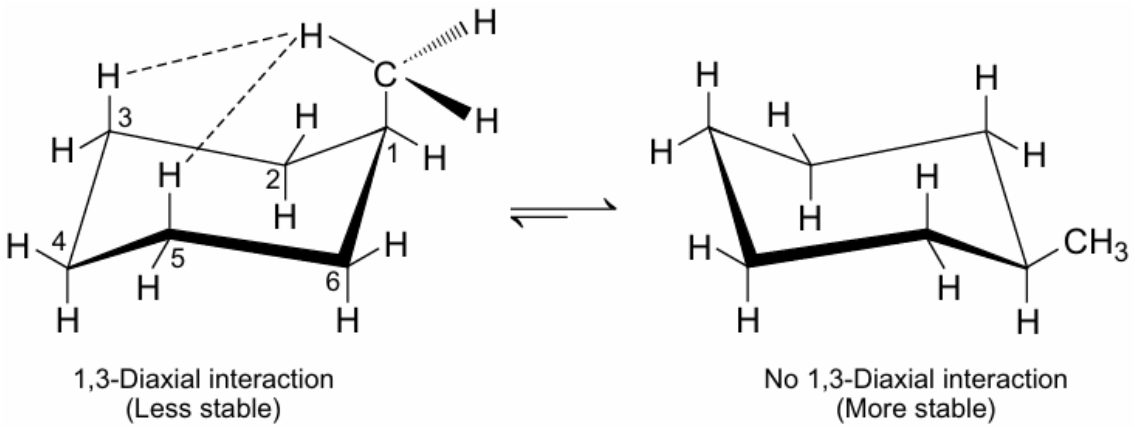


Fig. 17.9: Equatorial methylcyclohexane is more stable than axial methylcyclohexane

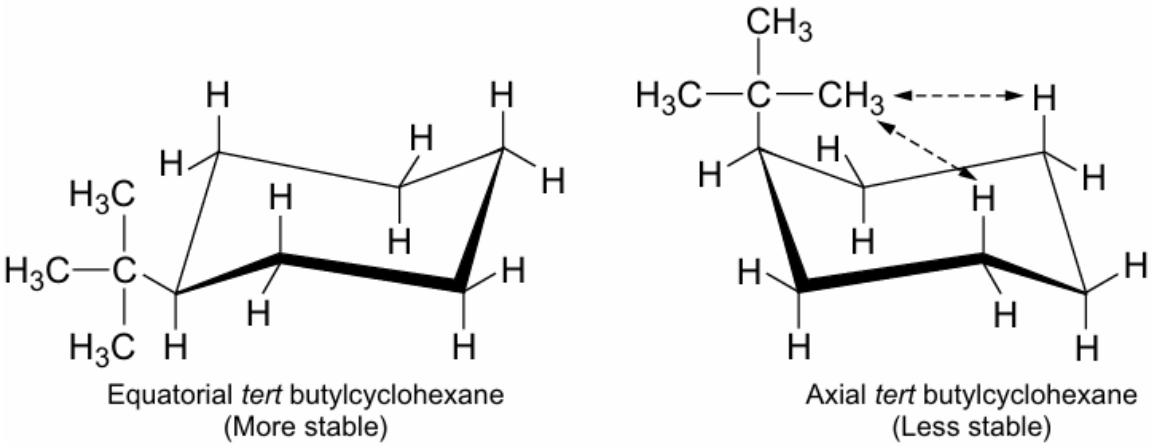


Fig. 17.20: Equatorial tert butylcyclohexane is more stable than axial tert butylcyclohexane

there is non-bonded interaction between CH_3 group and H atoms at positions 1 and 3, commonly knownas1,3-diaxial interaction. In this case, the distance between H of CH_3 and H at C-3 and C-5 is less than the sum of vander Waals radii of two hydrogens. This repulsion destabilises axial conformation of methylcyclohexane, whereas no such interaction is possible with equatorial conformation of methylcyclohexane making it a more stable conformation (Fig. 17.19).

In case, monosubstituted cyclohexane has a large alkyl substituent (e.g., tertiary butyl group), the strain caused by 1,3-diaxial interaction is much more pronounced. The conformation of tert-butylcyclohexane with tert-butyl group in equatorial is found to be more than 21 kJ mol–1 more stable than the axial form (Fig. 17.20).

At room temperature, 99.99% of equatorial tert-butylcyclohexane is present in the equilibrium mixture.

17.3 CONFORMATIONS OF DISUBSTITUTED CYCLOHEXANE:

Disubstituted cyclohexanes exhibit more complex conformational behavior than monosubstituted derivatives due to the interaction between two substituents. Their analysis is crucial for understanding the properties and reactivity of these important organic structures.

17.3.1 Types of Disubstituted Cyclohexanes: Disubstituted cyclohexanes are classified based on the relative positions of the two substituents:

I) **1,2-disubstituted** (vicinal): Substituents on adjacent carbon atoms

II) **1,3-disubstituted** (meta): Substituents separated by one carbon atom

III) **1,4-disubstituted** (para): Substituents on opposite sides of the ring

Each position relationship can be further classified as:

- **Cis**: Both substituents on the same side of the ring
- **Trans**: Substituents on opposite sides of the ring

I) Conformations of 1,2-Dimethylcyclohexane:

In case of 1,2 dimethylcyclohexane also there is a possibility of cis–trans isomerism. Letusfirstconsiderthecaseof1,2-dimethylcyclohexane,inwhichoneCH_3 group occupies axial position at C-1 and the second methyl group occupies an equatorial position at C–2. As both the methyl groups are on the same side, this is the cis arrangement (Fig. 17.21).

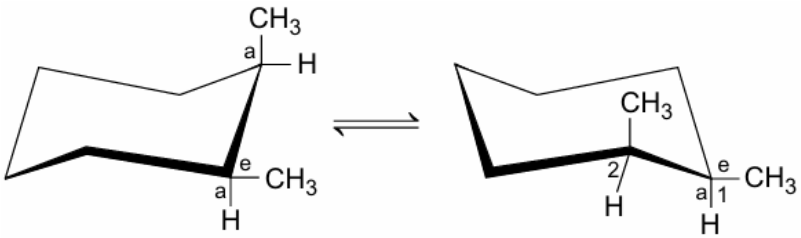


Fig. 17.21 Cis-1,2-Dimethylcyclohexane

In the above case, the two CH_3 groupsareclosertoeachother; there is a crowding between the hydrogens of the two methyl groups. Ring flipping of the cis form gives another equivalent cis form. However, this does not lead to any change as far as interactions between the hydrogens of the two methyl groups are concerned.

In case both the methyl groups occupy axial position, the arrangement is a trans arrangement of the groups. This trans conformation on ring flipping gives another trans configuration in which both the methyl groups occupy equatorial positions (Fig. 17.22).

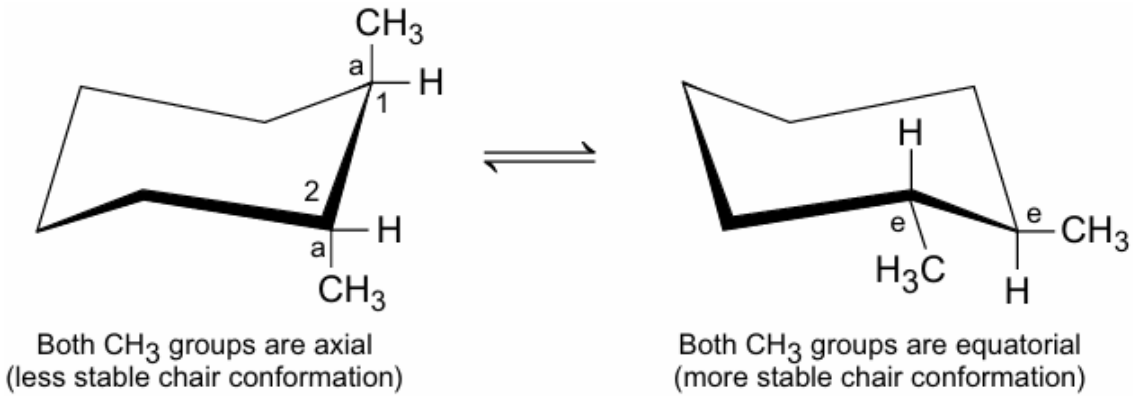


Fig. 17.22 Trans-1,2-Dimethylcyclohexane

In the above configuration, the axial —CH_3 group at C-1 faces van der Waals repulsion by axial hydrogens at C-3 and C-5 carbon atoms. Similar repulsion for the axial C-2 methyl group with hydrogens at C-4 and C-6 carbon atoms makes this diaxial trans conformation less stable compared to the diequatorial trans conformation. The equatorial positions are free from such interactions as the substituents project outward. As a general rule, any substituent is more stable in the equato rial position than in the axial position. Thus, trans diequatorial conformation of 1,2-dimethylcyclohexane is more stable than the trans diaxial cyclohexane.

II) Conformations of 1,3-Dimethylcyclohexane

In 1,3-dimethylcyclohexane, whenboththemethylgroupsareaxial,thearrangement is cis. This arrangement on ring flipping gives another cis form in which both the methyl groups occupy equatorial positions (Fig. 17.23).

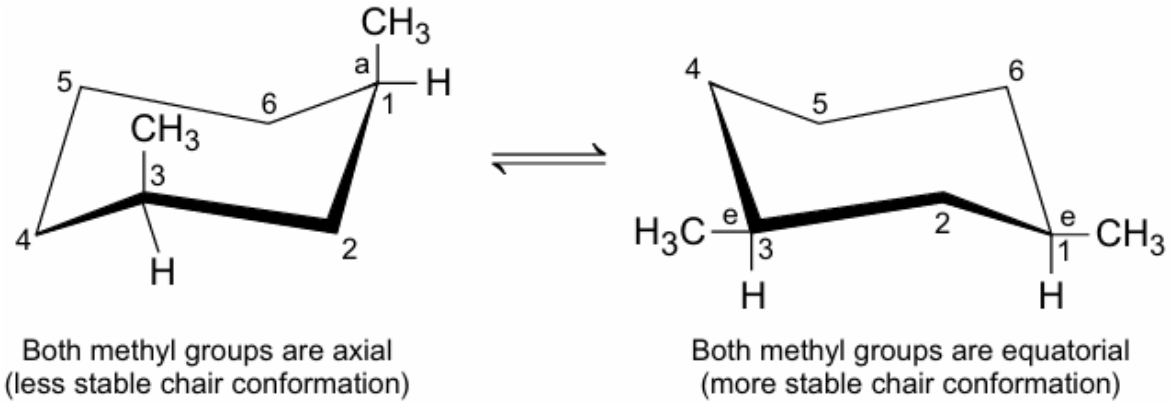


Fig. 17.23 Cis-1, 3-Dimethylcyclohexane

However, in case C-1 methyl is axial and C-3 methyl is equatorial (i.e., both the CH3 groups are trans to eachother), ring flipping gives another equivalent trans form (Fig. 17.23).

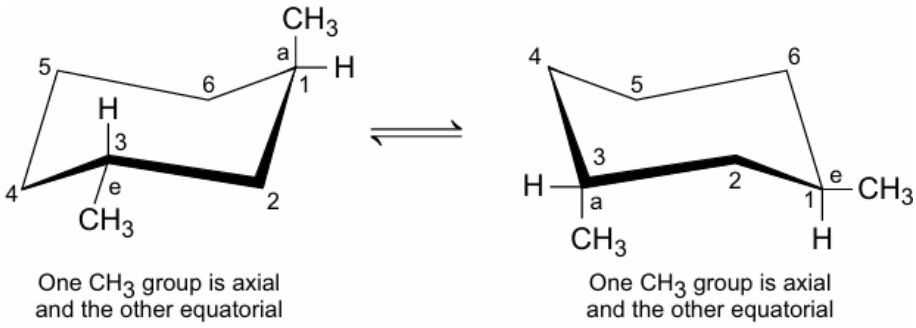


Fig. 17.24: Trans-1, 3-Dimethylcyclohexane

As seen, the trans form has one methyl group in equatorial position and the other methyl group in axial position compared to the cis form, which is its more stable conformation and both the methyl groups are in equatorial positions. So, in this case, the cis form with diequatorial substituents is more stable than the transform.

III) Conformations of 1,4-Dimethylcyclohexane:

In 1,4-dimethylcyclohexane, when both the methyl groups are axial, it leads to trans arrangement of methyl groups. The resulting diaxial arrangement of methyl groups on ring flipping is changed into another chair form having diequatorial arrangement of methyl groups (Fig. 17.25).

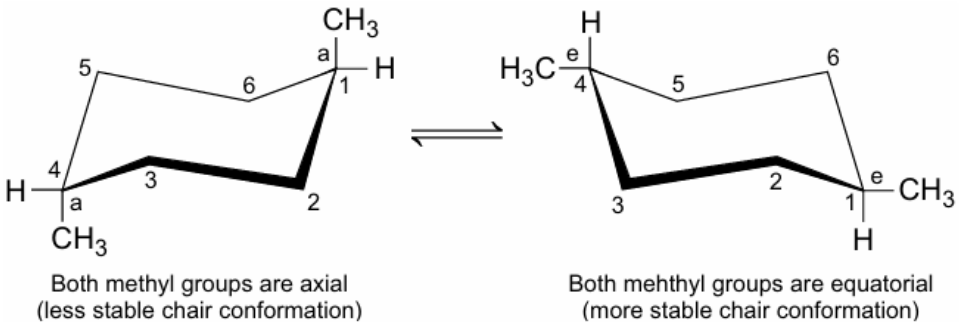


Fig. 17.25: Trans-1, 4-Dimethylcyclohexane

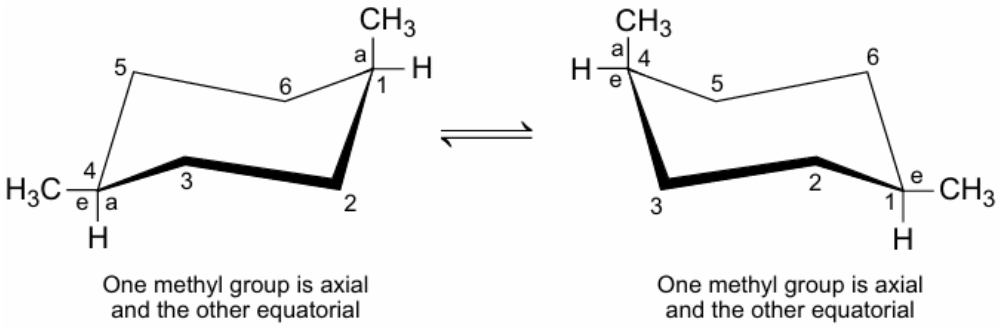


Fig. 17.26 Cis-1-,4-Dimethylcyclohexane

If one methyl at C-1 is axial and the other methyl at C-4 is equatorial, it leads to cis arrangement of methyl groups. The ring flipping gives another equivalent chair conformation (Fig. 17.26).

The cis-1,4-dimethylcyclohexane (Fig. 17.26) has two equivalent chair conformations having one axial and equatorial methyl substituent.

Comparison of the cis and trans conformations shows that in the trans conformation, both the methyl groups are equatorial and so it is more stable than the cis form which has one substituent each in the axial and equatorial positions.

Table 17.1 Conformations of dimethylcyclohexanes

Compound	Cis isomer	Trans isomer
1,2-dimethylcyclohexane	a, e or e, a	**e, e** or a, a
1,3-dimethylcyclohexane	**e, e** or a, a	a, e or e, a
1,4-dimethylcyclohexane	a, e or e, a	**e, e** or a, a

The different conformations of 1,2-, 1,3- and 1,4-dimethylcyclohexanes are summarised in Table 17.1. The more stable conformation, where one exists, is shown in bold underlined type.

As seen, the conformation in which both the methyl groups are in equatorial positions is more stable. In case, the disubstituted cyclohexanes have different substituents, the isomer with the larger substituent occupying the equatorial position is more stable.

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LESSON - 18

STABILITY AND REACTIVITY IN MONO AND DISUBSTITUTED CYCLOHEXANE DERIVATIVES

18.1 EFFECT OF CONFORMATION ON STABILITY AND REACTIVITY IN MONO AND DISUBSTITUTED CYCLOHEXANE DERIVATIVES:

The conformation of mono- and disubstituted cyclohexane derivatives significantly impacts their stability and reactivity.

18.1.1 Stability Effect:

18.1.1.2 Steric Strain: The primary factor influencing stability is steric strain, particularly 1,3-diaxial interactions. Axial substituents experience significant steric hindrance, raising the molecule's energy. And, the equatorial substituents minimize these interactions, leading to greater stability.

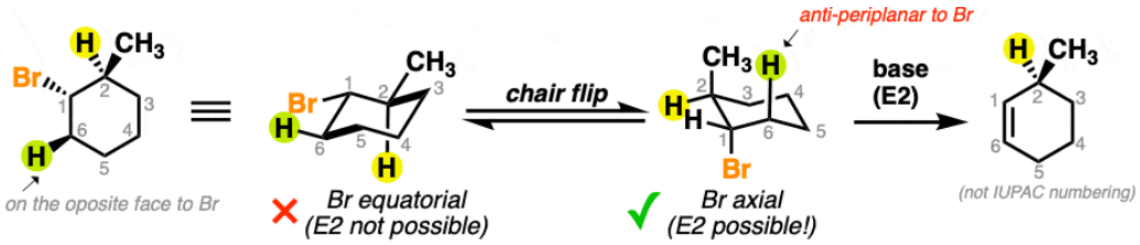
18.1.1.3 Monosubstituted Cyclohexanes: The equatorial conformation is generally more stable due to reduced 1,3-diaxial interactions.The size of the substituent dictates the degree of preference for the equatorial position. Larger substituents result in a greater energy difference between axial and equatorial conformations.

18.1.1.4 Disubstituted Cyclohexanes: The stability of disubstituted cyclohexanes depends on the relative positions (cis/trans, 1,2-, 1,3-, 1,4-) and sizes of the substituents. Generally, Diequatorial conformations are generally the most stable.When both axial and equatorial positions are occupied, the larger substituent tends to favor the equatorial position.

18.1.2 Reactivity:

18.1.2.1 Accessibility of Functional Groups: Conformation influences the accessibility of functional groups to reactants. Axial substituents can hinder reactions due to steric crowding and equatorial substituents are generally more accessible, facilitating reactions.

18.1.2.2 Elimination Reactions: In elimination reactions (e.g., E_2), the conformation plays a crucial role. For example, in cyclohexane systems, Axial substituents are often more **reactive** in reactions like **E_2 eliminations**, where the leaving group must be axial to align antiperiplanar to the β-H. This conformational requirement dictates the reaction's rate and stereochemistry.

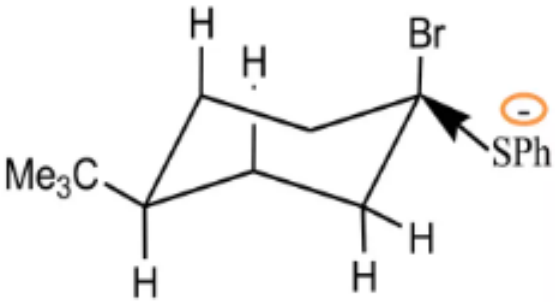


In cyclohexane rings, this can only happen when the leaving group and hydrogen are both axial and on opposite faces of the ring.

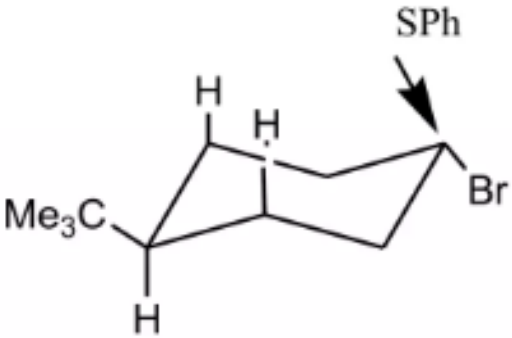
18.1.2.3 Substitution Reactions: Similarly, in substitution reactions (e.g., S_N1, S_N2), the conformation affects the approach of nucleophiles or electrophiles.

- S_N2 requires the nucleophile to approach from the opposite side (back side attack).
- When the leaving group is axial, the geometry aligns properly for this backside attack → favorable antiperiplanar arrangement between the leaving group and incoming nucleophile.
- If the leaving group is equatorial, the approach angle is poor, making S_N2 very slow or even impossible.

Example: axial cyclohexyl halides undergo S_N2 reactions faster than equatorial ones

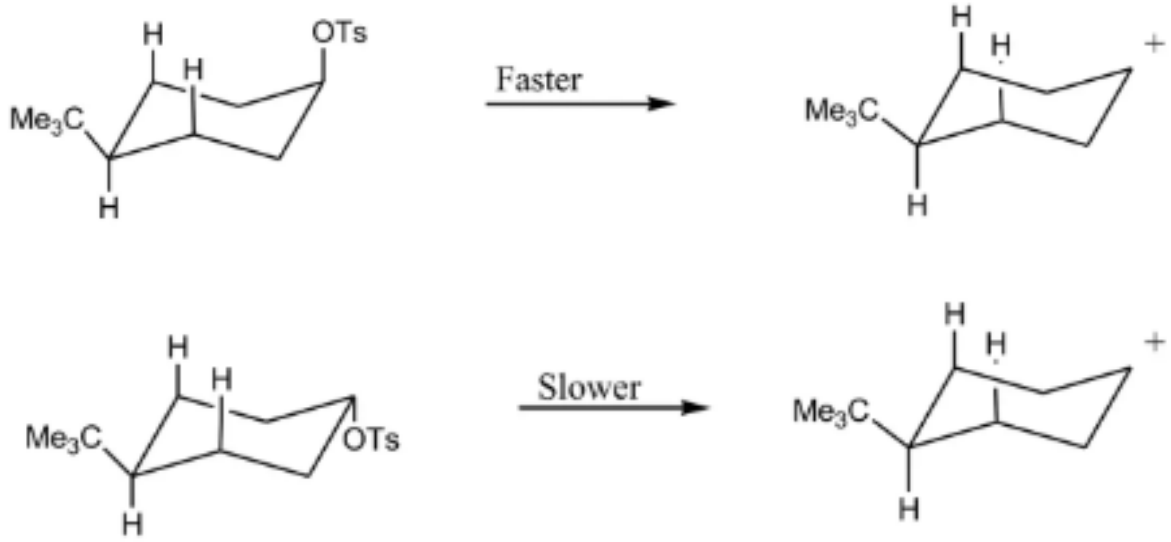


Axial Substituent is favored for S_N2 than equitorial



Equtorial Substituent

- **S_N2 reaction** is favored because the **Br is axial**, perfectly positioned for backside attack.
- S_N1 reactions can sometimes be slightly favored by axial substituents due to strain relief, but are more heavily influenced by overall carbocation stability. Once the leaving group departs, both axial and equatorial precursors form the same planar carbocation intermediate.



Cis-4-tert butyl cyclohexyl tosylate (both axial and equatorial tosylates)

- It's important to remember that these are general trends, and the specific outcome can depend on the size and nature of the substituents involved.

Table 18.1

Summary of Effect of Conformation on Stability and Reactivity in Cyclohexane Derivatives

Type	Substituent Orientation	Effect on Stability	Effect on Reactivity
Monosubstituted	Equatorial	Most stable (fewer steric interactions, especially avoids 1,3-diaxial interactions)	Generally lower reactivity in SN2 (poor orbital alignment)
Monosubstituted	Axial	Less stable (due to 1,3-diaxial interactions)	Favored in SN2 (good antiperiplanar alignment for backside attack)

Disubstituted (cis)	One axial, one equatorial	Moderate stability	Reactivity depends on which group is axial and the type of reaction
Disubstituted (trans)	Both equatorial (if possible)	Most stable configuration	Lower SN2 reactivity if leaving group is equatorial
Disubstituted (trans)	Both axial	Least stable (high steric strain)	High SN2 reactivity if one is a good leaving group in axial position

18.1.2.4 Influence on Reaction Pathways:

The conformation of a molecule can change the reaction pathway that a molecule will take. Because certain conformations are more or less stable, this will change the likelyhood of certain reaction products.

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LESSON - 19

CONFORMATIONS OF UNSATURATED ACYCLIC COMPOUND

19.1 INTRODUCTION:

Unsaturated acyclic compounds like propylene (propene) and 1-butene exhibit different conformational behaviors compared to saturated compounds due to the presence of carbon-carbon double bonds. These double bonds create rigidity and restrict rotation in specific parts of the molecule.

When discussing the conformations of unsaturated acyclic compounds like propylene and 1-butene, we need to consider the influence of the double bond on the molecule's shape and stability. The eclipsed and bisecting conformations in these unsaturated systems have split out here.

Eclipsed Conformation: In an eclipsed conformation, substituents on adjacent carbon atoms are as close to each other as possible.1 This leads to increased torsional strain.

Bisecting Conformation: In the context of alkenes, particularly with an adjacent alkyl group, the "bisecting" conformation refers to the arrangement where the alkyl group's bonds bisect the double bond's pi bond. This is a specific type of conformation related to how the alkyl group aligns with the double bond.

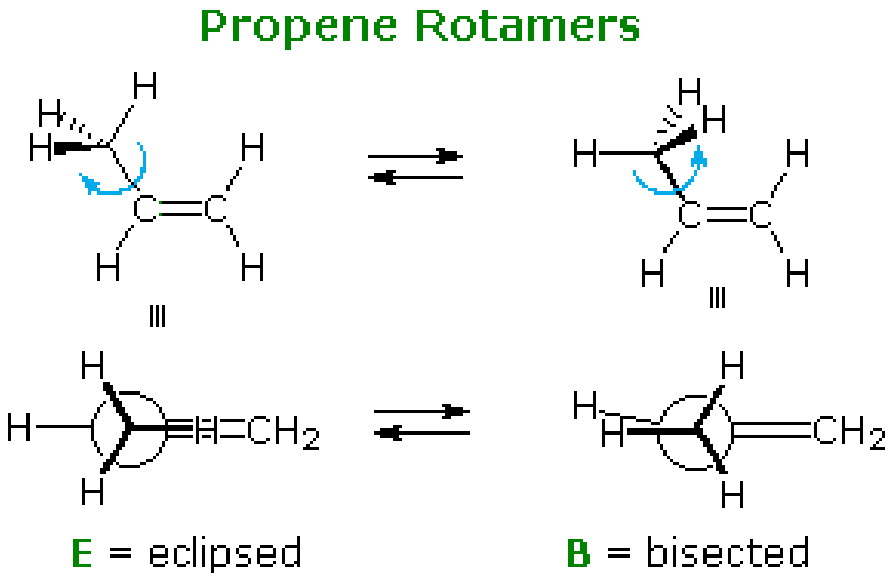
Hyperconjugation: A key factor in alkene conformation stability is hyperconjugation. This involves the overlap of sigma bonds (like C-H) with the pi bond of the alkene, which can stabilize certain conformations.

19.2 CONFORMATIONAL ANALYSIS OF PROPYLENE (PROPENE):

Propylene (CH_3-CH=CH_2) has a methyl group attached to a carbon-carbon double bond. The π bond prevents rotation around the C=C bond, While the double bond is rigid, the methyl group can freely rotate around the C-C single bond. This rotation has a relatively low energy barrier (~2 kcal/mol). The methyl group experiences minimal steric hindrance in all rotational positions

The rotation of a methyl group (or any alkyl group) relative to a double bond is an important conformational event. Propene provides a simple example, as shown below. In the course of the methyl rotation a C–H bond eclipses either a sp^2C–H bond or the C=CH_2 bond,

but not simultaneously. The energy of this rotation follows a simple sine-curve similar to the rotational barrier of ethane, with a smaller amplitude (ca. 2 kcal/mol). The conformer in which the $C=CH_2$ bond is eclipsed is the lower energy rotamer, possibly reflecting a stabilizing interaction between σ-C–H bonds of methyl and the π*-antibonding orbital. This conformer will be termed **eclipsed**, and the higher energy alternative **bisected**.

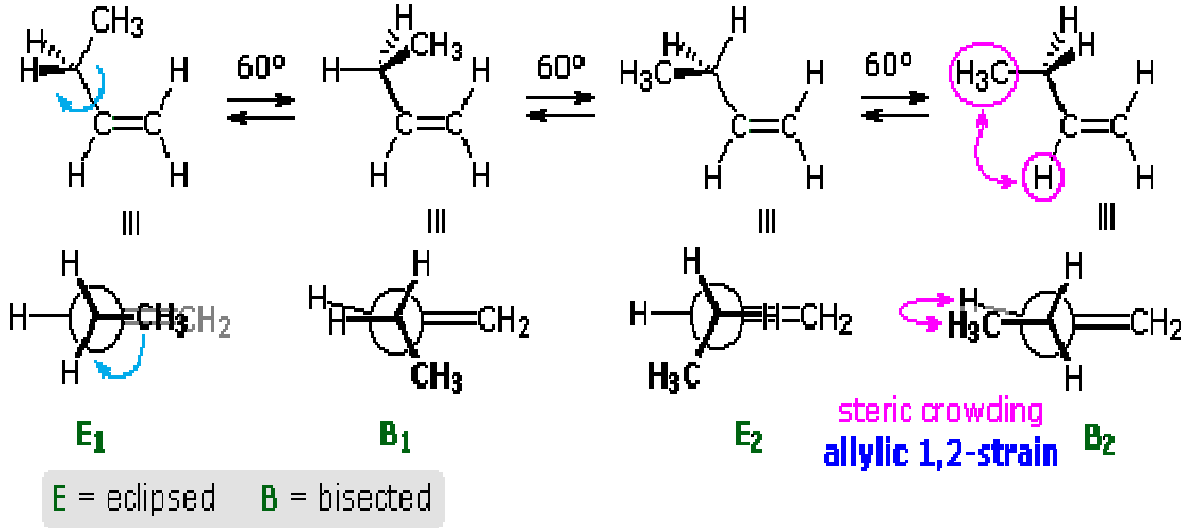


- In propylene, an "eclipsed" conformation refers to when the methyl group's C-H bonds are aligned with the double bond's pi bond.
- Interestingly, in propylene, the "eclipsed" conformation is the more stable conformation. This is due to a stabilizing effect called hyperconjugation, where there is an overlap between the C-H sigma bonds of the methyl group and the pi antibonding orbital of the double bond.
- The "bisecting" conformation is when the methyl group's C-H bonds are aligned with the plane that bisects the double bond.In propylene, the bisecting conformation is the less stable conformation.

19.3 CONFORMATIONAL ANALYSIS OF 1-BUTENE:

1-Butene (CH_3-CH_2-$CH=CH_2$) contains both an ethyl group and a terminal double bond. Similar to propylene, no rotation occurs around the C=C double bond. 1-butene introduces more complexity due to the ethyl group, the ethyl group can rotate around the C-C single bond attached to the double bond. This creates several possible conformations for the ethyl group relative to the double bond. Therefore, we have more eclipsed and bisecting possibilities.

Adding a methyl group to propene, as in 1-butene, doubles the number of eclipsed and bisected conformers. Interestingly, the overall rotational barrier is reduced, and the energy difference between the two eclipsed rotamers is over twenty times greater than the difference between the two bisected forms. This is illustrated in the following diagram. The eclipsing shown by arrows in conformer B_2 is referred to as allylic 1,2-strain (A 1,2-strain).



1-butene's conformational analysis is more complex due to the ethyl group. Again, hyperconjugation plays a significant role in determining the relative stabilities of these conformations. There are multiple eclipsed, and bisecting conformations, and their stability will be determined by the balance of steric hinderance, and hyperconjugation.The eclipsed conformations, where a C-H bond of the ethyl group is aligned with the alkene pi bond, will be more favored, due to hyperconjugation.

Important Considerations:

- The presence of the double bond alters the conformational preferences compared to saturated alkanes.
- Hyperconjugation is a significant factor in determining the stability of alkene conformations.
- Steric effects still play a role, but the favorable hyperconjugation can overcome some steric strain.

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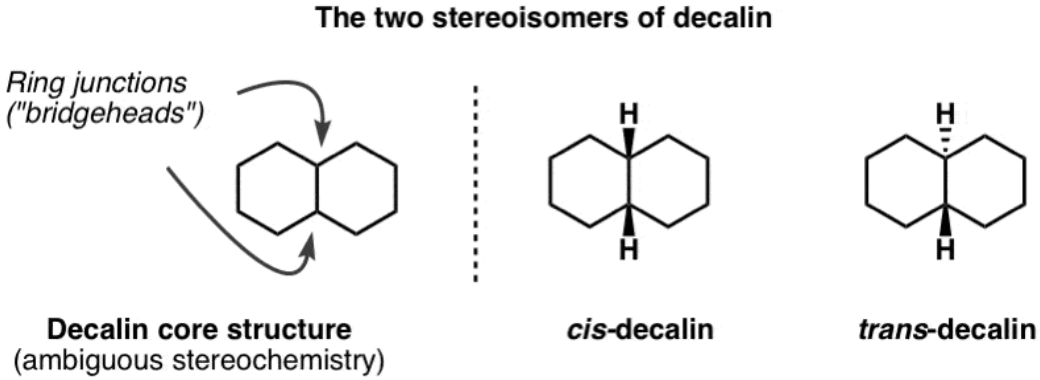
LESSON - 20

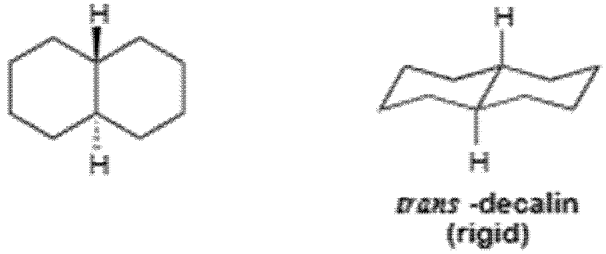
ELEMENTARY TREATMENT OF FUSED AND BRIDGED RING SYSTEMS

20.1 CONFORMATIONS OF DECALIN:

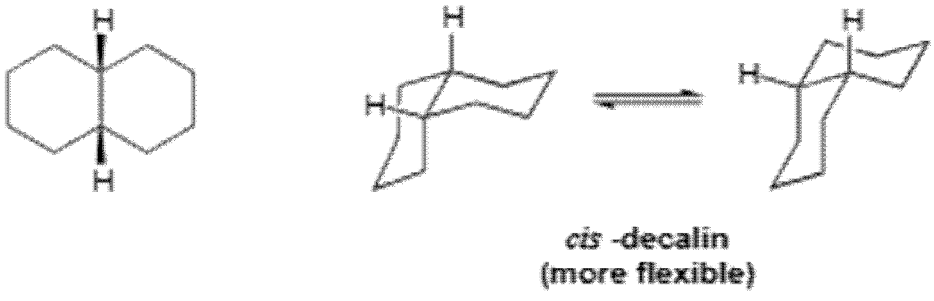
Decalin is a bicyclic compound. Generally, bicyclo [4,4,0] decane is known as decalin. Two cyclohexane rings are fused together in chair conformation to generate decalin.It exists in two diastereomeric forms (i.e. cis- and trans-decalins).



cis-decalin: When both the cyclohexane rings are fused together of one equatorial and one axial bond form the decalin thus formed is called cis-decalin.

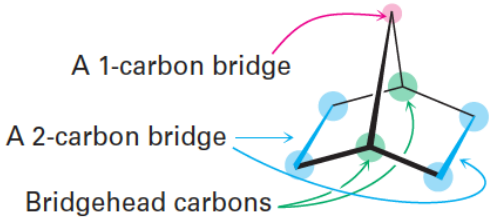


trans-decalin: However, when two cyclohexane rings are fused together in ee form the decalin thus formed is called trans-decalin



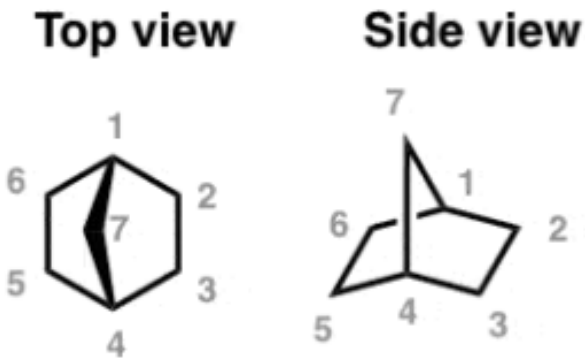
The trans-decalin is more stable than cis-decalin by 2.7 kcal/mol of energy. Thus cis-decalin can be easily converted in to trans-decalin but the reverse process is not possible. Due to flexibility in structure of cis-decalin, its ring flipping is possible. Thus cis-decalin exists in two interconvertible conformational isomers. In comparison to cis-decalin, the trans decalin is a rigid molecule. Due to the presence of two equatorial bonds the ring flipping of trans-decalin is not possible.

20.2 CONFORMATIONS OF NORBORNANE:



Norbornane
(bicyclo[2.2.1]heptane)

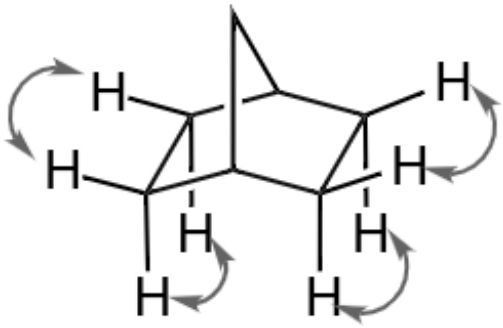
Norbornane is also known asbicyclo [2.2.1] heptane. Like decalin, norbornane is a bicycloalkane, so called because two rings would have to be broken open to generate an acyclic structure.



Its systematic name, bicycle [2.2.1] heptane, reflects the fact that the molecule has seven carbons, is bicyclic, and has three “bridges” of 2, 2, and 1 carbon atoms connecting the two bridgehead carbons.

Norbornane has a conformationally locked boat cyclohexane ring in which carbons 1 and 4 are joined by an additional CH_2 group. In drawing this structure, a break in the rear bond indicates that the vertical bond crosses in front of it. Making a molecular model is particularly helpful when trying to see the three-dimensionality of norbornane.

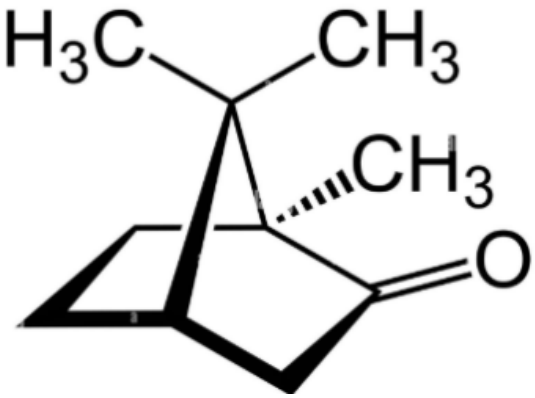
Norbornane is estimated to have 72 kJ/mol of ring strain which can be understood when viewing the contained rings. The carbon bridge in norbornane holds the cyclohexane ring at the bottom in a boat conformation creatingtorsional strain from eclipsing bonds along the edge.



Eclipsing Hydrogens of Norbornane

Also, the carbon bridge forms a cyclopentane ring with increased angle strain throughout the whole molecule.

Substituted norbornanes, such as camphor, are found widely in nature, and many have been important historically in developing organic structural theories.



Camphor

20.3 CONFORMATION OF SUGARS AND STERIC STRAIN DUE TO CROWDING:

Sugars (carbohydrates) exhibit complex conformational behavior due to their multiple stereogenic centers and the cyclization process that creates ring structures. The resulting conformational preferences are largely driven by steric effects that arise from unavoidable crowding of substituents.

Most monosaccharides (like glucose, galactose, etc.) cyclize into rings in solution. The two main ring forms are:

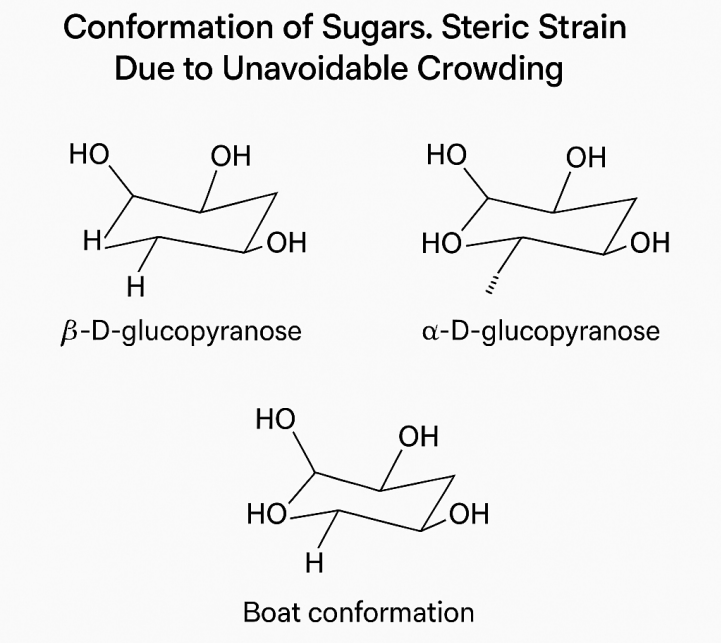
I) **Pyranoses**: 6-membered rings (more stable for most aldohexoses)

II) **Furanoses:** 5-membered rings (more common in ketohexoses and some ribose derivatives)

I) Pyranose Conformations:

In six-membered rings, like those formed by glucose and many other aldohexoses, the ring adopts a pyranose form. These rings are not flat; instead, they twist into more stable three-dimensional shapes to minimize strain. The most common and stable conformation is the chair form, which resembles the conformation adopted by cyclohexane rings.

In the chair conformation, substituents on the carbon atoms of the ring can occupy two types of positions: axial (pointing straight up or down from the ring plane) and equatorial (pointing outward, roughly parallel to the ring plane). These orientations are crucial in determining the stability of a sugar molecule.



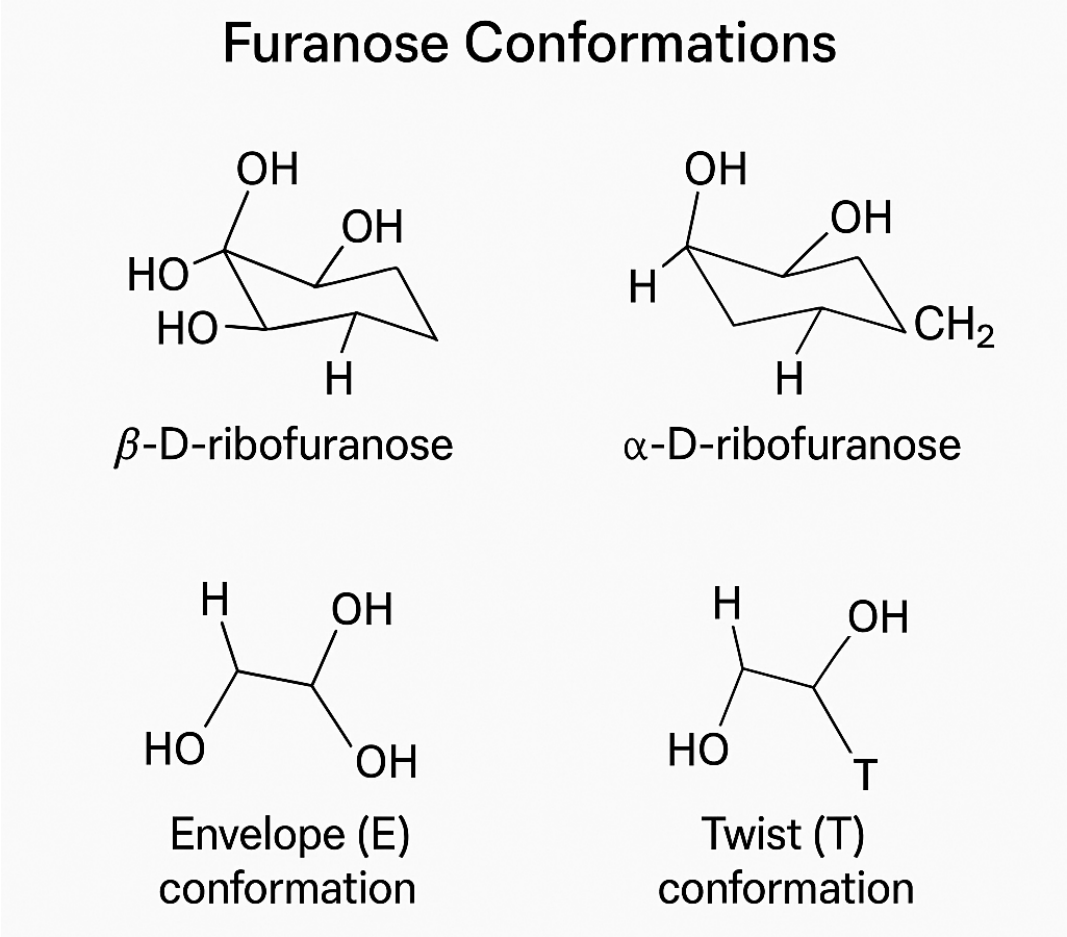
For instance, in β-D-glucopyranose, all of the bulky hydroxyl groups and the CH_2OH group are positioned in equatorial positions in the chair conformation. This minimizes steric hindrance and makes β-D-glucopyranose one of the most stable sugar conformations known. On the other hand, in α-D-glucopyranose, the hydroxyl group on the anomeric carbon (C-1) occupies an axial position. This can create steric strain due to close contact with other axial groups, particularly through 1,3-diaxial interactions - where axial substituents on carbon atoms separated by one carbon (like C-1 and C-3) clash with each other. These interactions increase steric crowding and decrease conformational stability.

Anomeric Effect and Conformational Preference:

Interestingly, despite the potential steric hindrance, some sugars like α-D-glucopyranose can still be significantly stable. This is due to the anomeric effect—a phenomenon where the axial orientation of the anomeric hydroxyl group is favored because of stabilizing electronic interactions. Essentially, the lone pair on the ring oxygen can overlap with the antibonding orbital of the axial C-OH bond, which gives some extra electronic stabilization.

II) Furanose Conformations:

Sugars like ribose (in RNA) or fructose can also form furanose rings, which are five-membered rings. These rings are more flexible than pyranose rings and do not adopt chair conformations. Instead, they adopt shapes like envelope and twist conformations to relieve strain.



However, because the ring is smaller, there's less room to arrange large substituents comfortably, and crowding becomes a bigger issue. This leads to steric hindrance, particularly when bulky groups are forced into close proximity.

Table 20: Summary of Steric Strain in Sugar Conformations

Type of Strain	Cause	Example
1,3-Diaxial interactions	Axial substituents clash on carbon 1 and 3	α-D-glucopyranose (less favored)
Anomeric effect	Stabilization of axial anomeric OH by lone pairs	α-D-glucopyranose can be stable
Steric hindrance in furanoses	Substituents in close proximity due to 5-member ring	Ribofuranose

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