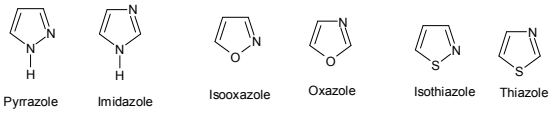


AZOLES

Azoles are five membered heterocyclics with hetero atoms of which one is nitrogen, depending on the position of hetero atoms 1,2 and 1,3 azole are possible.

Ex.

PYRAZOLE

This five membered heterocyclic contain two nitrogen atoms at 1,2 positions.

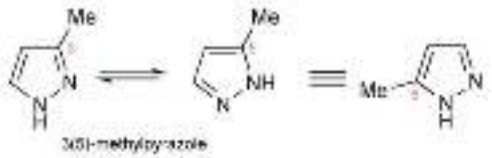
Pyrazole is a weak base, with pK_b 11.5 (pK_a of the conjugated acid 2.49 at 25 °C)

Structure and Aromaticity:

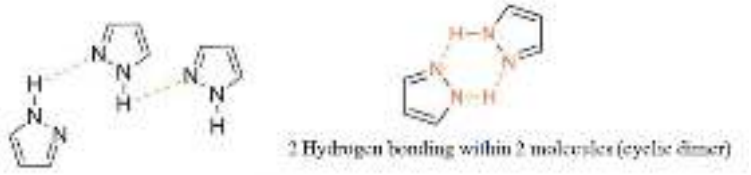
- Pyrazole have 3 C and 2 N , all are sp^2 hybridized
- sp^2 hybridization is planar, it makes a planar pyrazole ring structure.
- Each ring atoms also contains unhybridized p orbital that is perpendicular to the plane of σ bonds (plane of ring).
- Here p orbitals are parallel to each other, so overlapping btwn p orbitals is possible.
- the total no of non bonding e- are 6 (3 of three C, 1 from one N and 2 of other N)
- The resonance of 6 e- follows the Hückel's rule
- So the pyrazole is aromatic .

Properties

Tautomerism_ In Pyrazole the one of the sp2 hybrid nitrogen is bonded to hydrogen and another carries pi bond, so the migration of hydrogen and pi bond can result in different tautomeric structures.



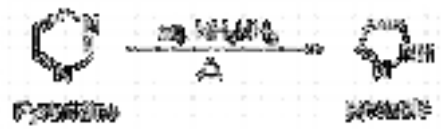
Due to the presence of this hydrogen they also undergo intermolecular hydrogen bonding thus have high boiling point and water solubility



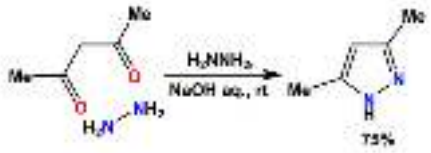
2 Hydrogen bonding within 2 molecules (cyclic dimer)

METHODS OF SYNTHESIS

1. From Pyrimidine



2. Knorr-Pyrazole synthesis: In volves the reaction of 1,3-dicarbonyl compound with hydrazine.



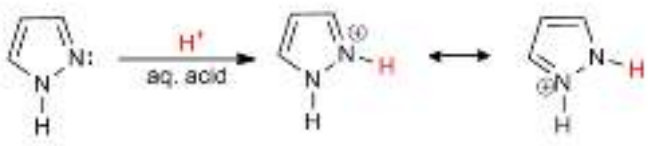
3. From Nitrile Imines

- Pyrazoles are produced by the dipolar cycloaddition btwn alkynes with nitrile imines

Reactions:

a. Protonation (basic property)

- Pyrazole accept proton, act as base.



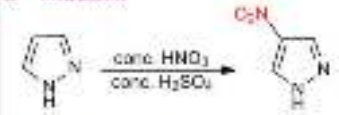
pyrazolium cation

B. Electrophilic substitution reactions

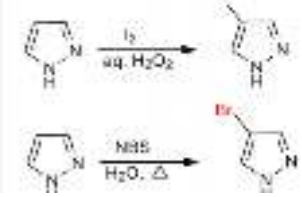
This aromatic heterocyclic compound undergoes electrophilic substitution preferably at C-4.

2. Electrophilic substitution to C

a. Nitration

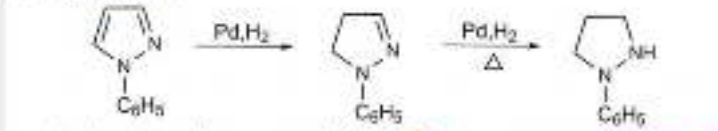


b. Halogenation



3. Oxidation

4. Reduction

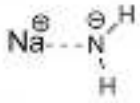


1-phenylpyrazole — 1-phenyl-4,5-dihydropyrazole — 1-phenylpyrazolidine

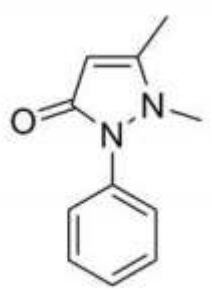
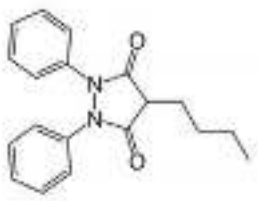
5. Ring opening

- *N*-substituted pyrazole reacted with strong base (sodamide) cause ring opening

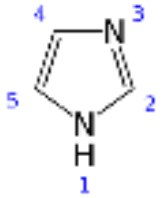
N-substitutedpyrazole — acrylonitrile derivative



Medicinal Compounds

 *antipyrine* Use: Antipyretic and analgesic	 *phenylbutazone* Use: anti-inflammatory agent

IMIDAZOLE



This five membered heterocyclic with two nitrogen and three carbon ring is isomer of pyrazole and differ in the position of nitrogen's it is 1,3 Azole.

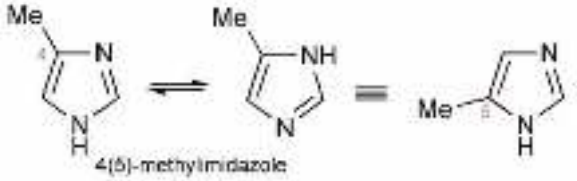
Properties

Aromaticity

Imidazole have 3 C and 2 N , all are sp^2 hybridized
sp^2 hybridization is planar, it makes a planar imidazole ring structure.
Each ring atoms also contains unhybridized p orbital that is perpendicular to the plane of σ bonds (plane of ring).
Here p orbitals are parallel to each other, so overlapping btwn p orbitals is possible.
the total nu of non bonding e- are 6 (3 of three C, 1 from one N and 2 of other N)
The resonance of 6 e- follows the Hückel's rule

2. Tautomerism

- Imidazole with a ring N- hydrogen are subject to tautomerism.

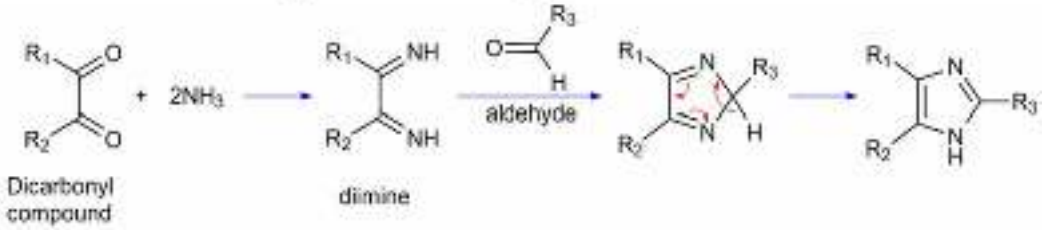


- 4 –methylimidazole equilibrium with 5 – methylimidazole

Methods of Synthesis

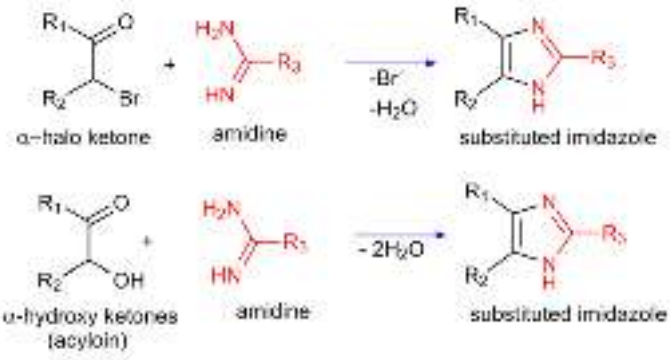
1. Radziszewski Imidazole synthesis

- Synthesis of imidazole from a dicarbonyl, an aldehyde & ammonia.
- The reaction completes in two stages.



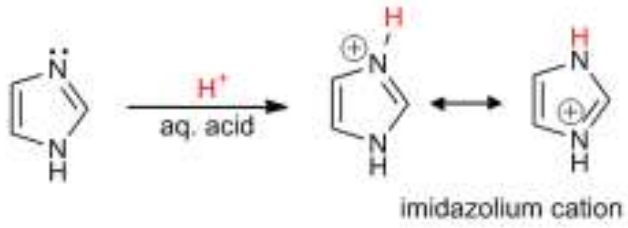
stage_1	stage_2
the dicarbonyl and ammonia *condense* to give an diimine	diimine condenses with the aldehyde

2. From an α- Halo - Carbonyl Component

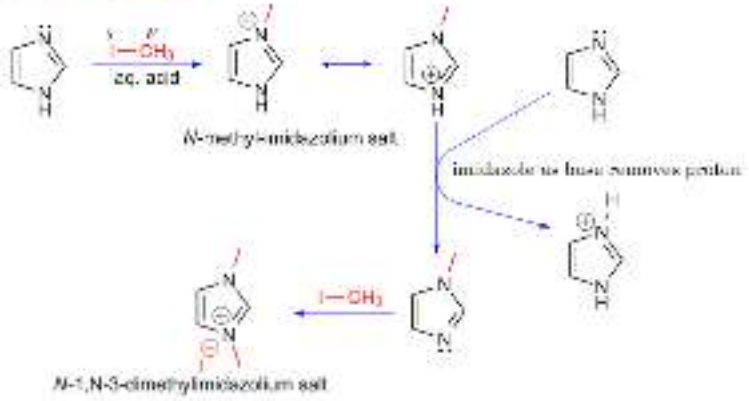


Reactions:

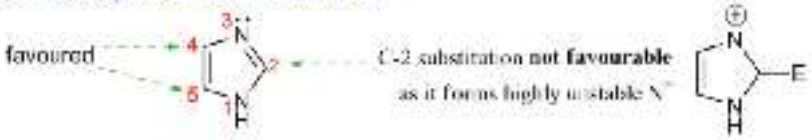
Basicity:



b. N-alkylation

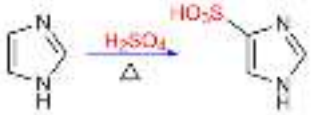


2. Electrophilic substitution to C

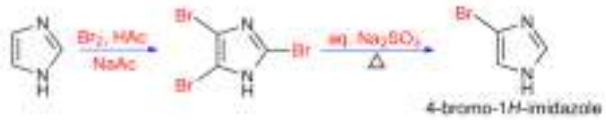


a. Nitration

b. sulphonation

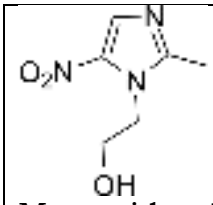
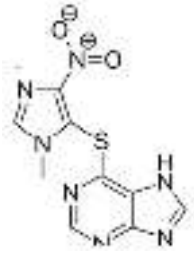


c. Halogenation

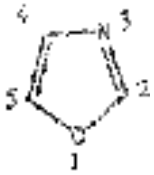


- Bromination gives 2,4,5-tribromomidazole
- 4(5)-Bromoimidazole can be obtained by reduction of tribromoimidazole with sodium sulfite.

MEDICINAL COMPOUNDS

 Metronidazole Uses: antibiotic used to treat protozoal infections	 Azathioprine Uses: Anticancer agent

OXAZOLE



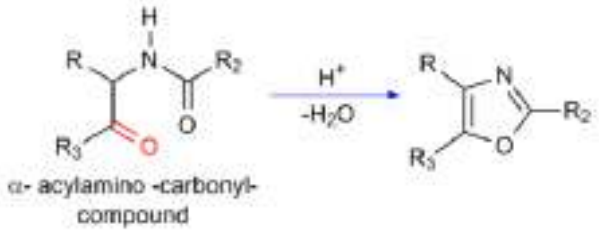
1,3-Azole with oxygen and nitrogen at 1,3 positions in five membered heterocyclic ring.

Aromatic with 6 delocalized pi electrons, obey Huckels rule.

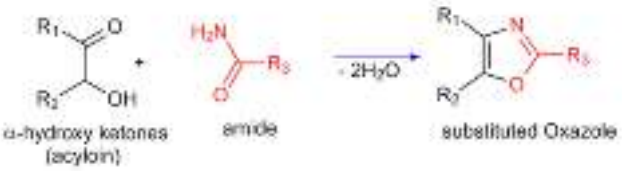
Methods of synthesis

1. Robinson-Gabriel Synthesis

Cyclising dehydration (acid - catalyzed closure) of an α- acylamino - carbonyl – compound.



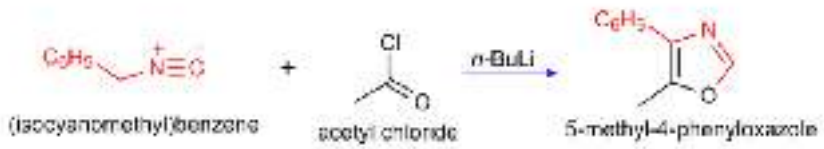
2. From an α- Hydroxy - Carbonyl Component



3. From Isocyanides

- Reaction of isocyanides with acid chlorides or anhydrides yields substituted oxazoles.

E.g.

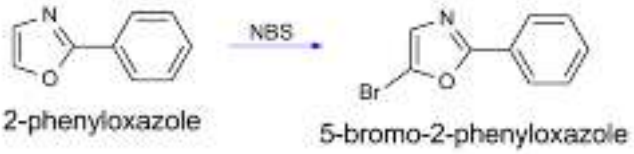


REACTIONS

2. Electrophilic substitution to C

- Less reactive due to O present in hetero skeletal
- Reaction is possible at 5th position, if ring is *activated by EDG.*
- Nitration and sulphonation are more difficult

E.g.

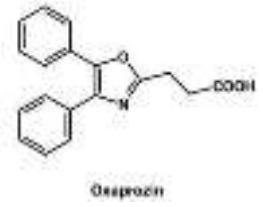
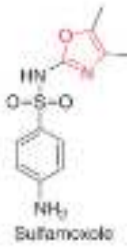


3. Diels-Alder Reaction

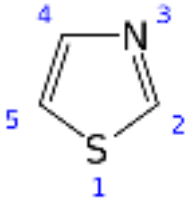
- Act as Diene (4π component)
- O atom is highly electronegative → so conjugated double bonds are readily available as diene in Diels-alder reaction.
- Oxazoles readily undergo Diels – Alder type cycloaddition across the 2,5 – positions
- E.g.

(1) Synthesis of furan

Medicinal compounds

 Use: Anti-inflammatory agent	 Use: Sulphonamide antibacterial agent

THIAZOLE



The five membered heterocyclic ring with 1,3-azole and contain sulphur and nitrogen.

Aromatic cyclic, unsaturated with 6 pi electrons in delocalized pi electron cloud obeys Huckles rule.

Methods of synthesis;

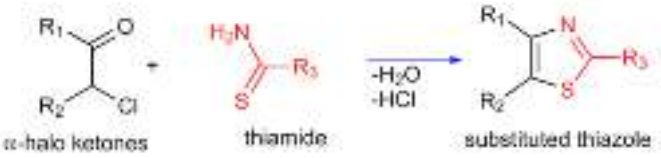
1. Gabriel synthesis

- Condensation of acylaminocarbonyl compound in presence of Phosphorus pentasulfide.

α- acylamino -carbonyl-compound

2. From an α- Hydroxy - Carbonyl Component (Hantzsch Thiazole Synthesis)

- condensation of α-haloketones and thioamides referred to as the Hantzsch thiazole synthesis.



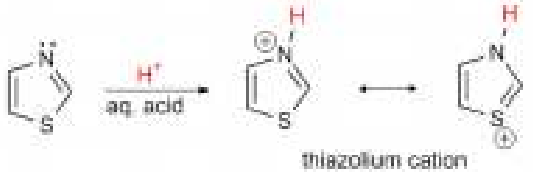
α-halo ketones thiamide substituted thiazole

3. From an thiocyanate salts

chloroacetone thiocyanate salt 2-hydroxy-4-methylthiazole

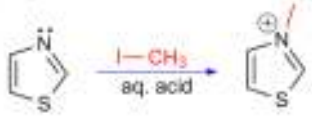
Reactions:

a. Protonation (basic property)



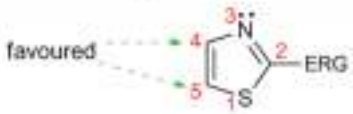
thiazolium cation

b. *N*-alkylation

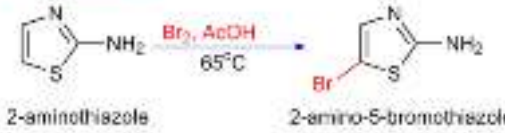


N-methyl-thiazolium salt

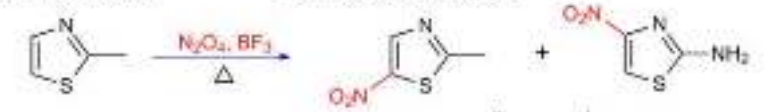
2. Electrophilic substitution to C



a. Nitration

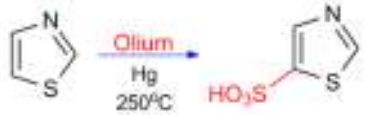


2-aminothiazole — 2-amino-5-bromothiazole



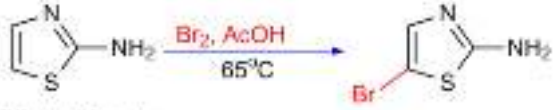
2-Methylthiazole — 2-methyl-5-nitrothiazole : 2-methyl-4-nitrothiazole

b. Sulphonation

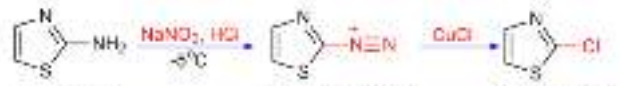


thiazole-5-sulfonic acid

c. Halogenation

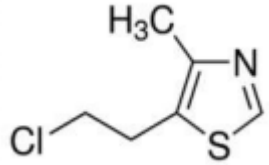
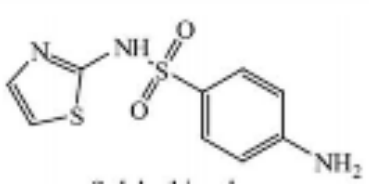


2-Methylthiazole — 2-amino-5-bromothiazole



2-aminothiazole — thiazole-2-diazonium — 2-chlorothiazole

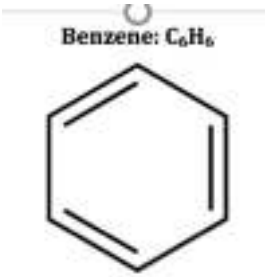
Medicinal Compounds

 Chlormethiazole Use: sedative and Hyptonic	 Sulphathiazole Use: Sulphonamide-antibacterial agent

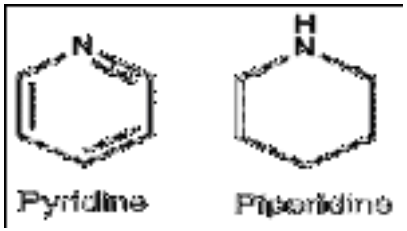
HETEROCYCLIC COMPOUNDS

Heterocyclic compounds are cyclic compounds in which the ring structure is madeup of hetero atoms like N, S, O, Si, P in addition to Carbons

Ex. Benzene is a Carbocyclic compound as the ring conatine only carbon atoms



But the pyridine and piperidine ring contain carbons(5) and one heteroatom i.e. Nitorogen, so these are heterocyclic compound



A large number of synthetic and natural medicinal compounds contain heterocyclic rings in their structure.

Classification of Heterocyclic compounds

There are different basis for the classification of heterocyclic compounds

I. Classification based on ring size

II. Classification based on Mono or Fused poly heterocyclic compounds

The above I and II category of heterocyclic compounds can be further subclassified in to

a. Unsaturated (Aromatic) and Saturated (non-aromatic) heterocyclic compounds.
b. Mono or poly hetero atoms

I. Based on Size of the Ring

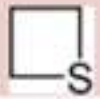
1. 3-membered-heterocyclic (saturated) and unsaturated

Ex.

Saturated	Unsaturated
Aziridine 	Azirine 
Ethylene oxide 	Oxirene 
Thiirane 	Thiirene 

2. Four membered heterocyclic compounds saturated and unsaturated

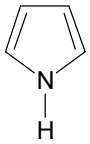
Ex.

Saturated	Unsaturated
Azetidine 	Azete 
Oxetane 	Oxete 
Thietane 	Thiete 

3. Five membered heterocyclic compounds –Saturated (Aroamtic) and unsaturated (Non-aromatic)

Ex.

Aromatic

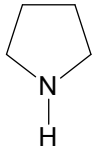


Pyrrole

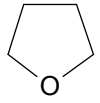
Furan

Thiophene

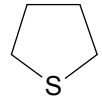
Non-Aromatic



tetrahydropyrrole
(Pyrrolidine)

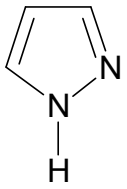


tetrahydrofuran
(THF)

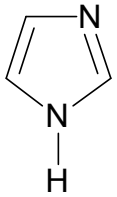


tetrahydrothiophene

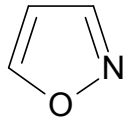
4. Five membered heterocyclic compounds with two hetero atoms
Ex. Azoles-five membered heterocyclic with two hetero atoms one is nitrogen



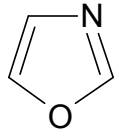
Pyrrazole



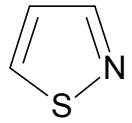
Imidazole



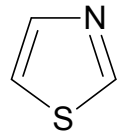
Isooxazole



Oxazole



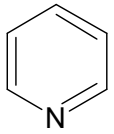
Isothiazole



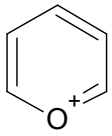
Thiazole

5. Six membered heterocyclic with one hetero atom

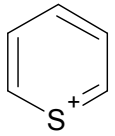
Ex Un saturated



Pyridine

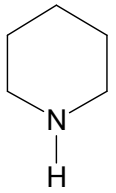


Pyrilium

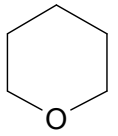


Thiopyran

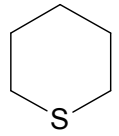
saturated



Piperidine



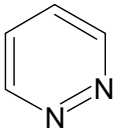
tetrahydropyran



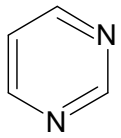
Thiane

6. Six membered heterocyclic with two nitrogen hetero atoms

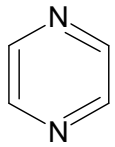
Ex Diazines



Pyridazine



Pyrimidine

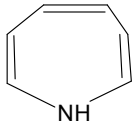


Pyrazine

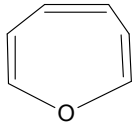
7.Seven membered heterocyclic compounds

saturated

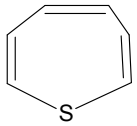
Ex unsaturated



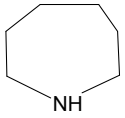
Azepine



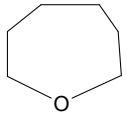
Oxepine



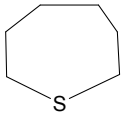
Thiepine



Azepane

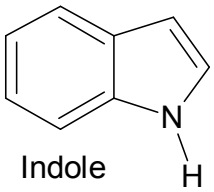


Oxepane

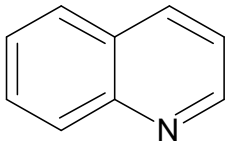


Thiepane

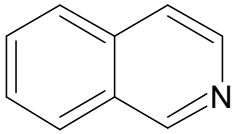
8. Fused heterocyclic compounds



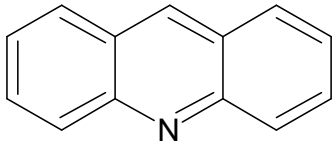
Indole



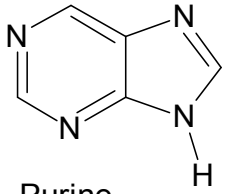
Quinoline



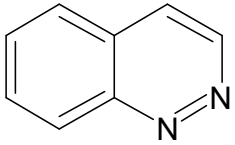
Isoquinoline



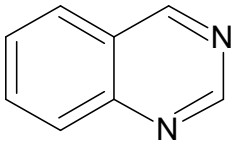
Acridine



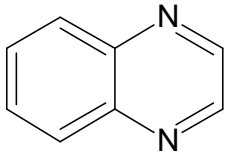
Purine



Cinnoline



Quinazoline



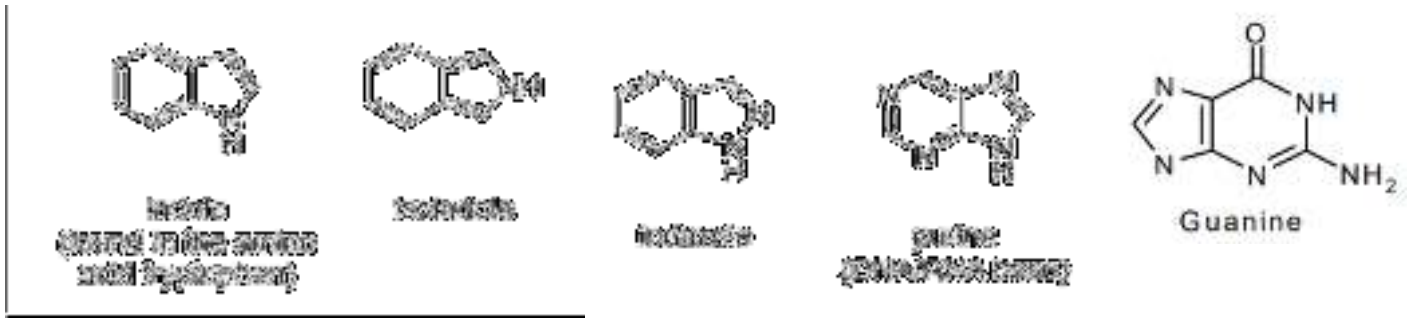
Quinoxaline

Heterocyclic compounds Nomenclature

The cyclic compounds which contain hetero atom like N, S, O, Si, P , S in addition to carbon in their ring structure are called heterocyclic compounds.

In the nomenclature of these cyclic compounds different methods are adopted such as

1. Common names/Trivial names
2. The replacement nomenclature
3. Hantzsch-Widman IUPAC nomenclature
4. depending on the nature of heteroatom, ring size, saturation and unsaturation , fused heterocyclic compounds



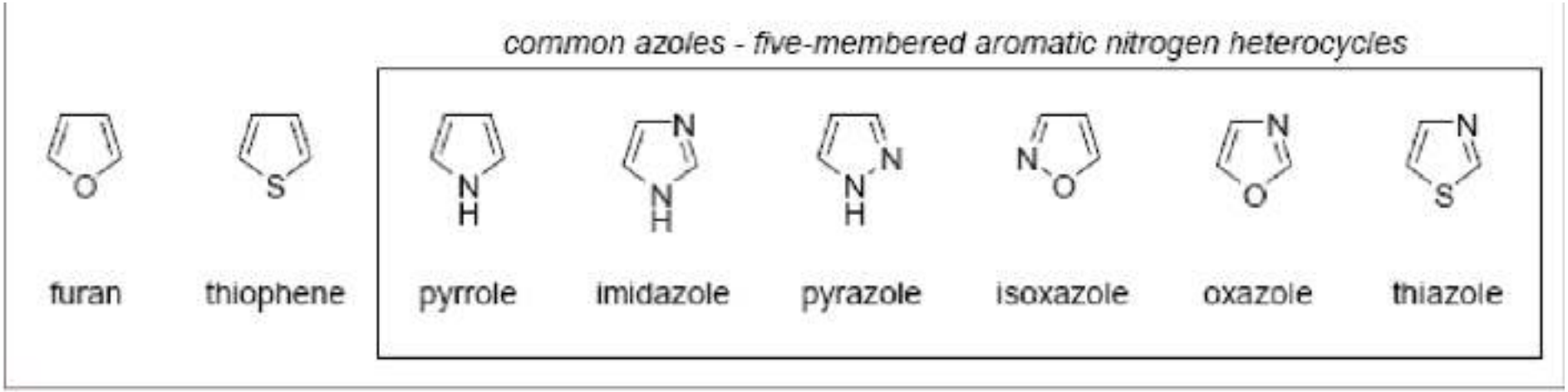
1. COMMON NOMENCLATURE

There are a large number of important ring systems which are named widely known with their non-systematic or common names.

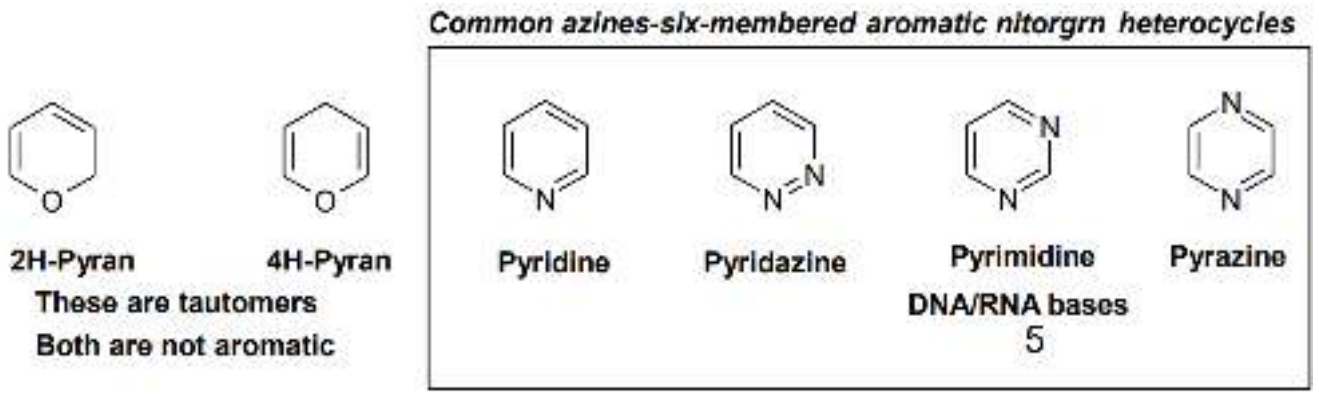
Each compound is given the corresponding trivial name. This usually originates from the compounds occurrence, its first preparation or its special properties.

Trivial names

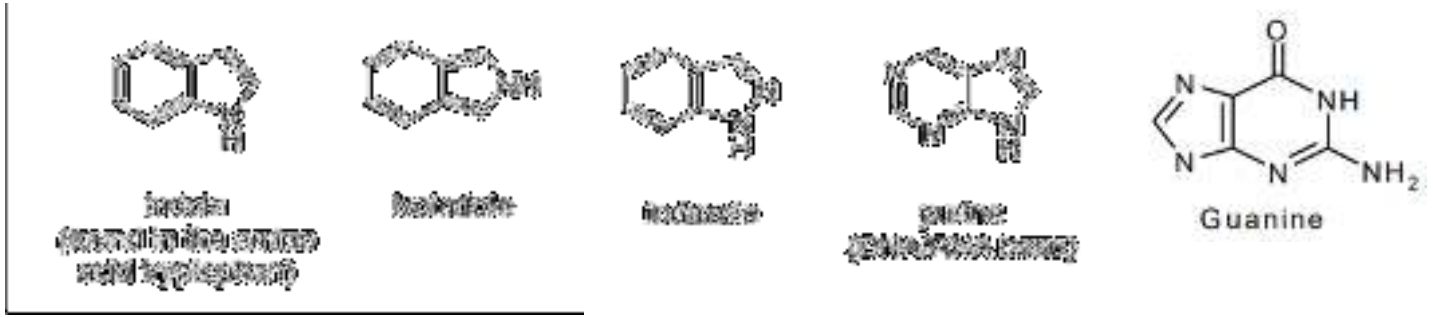
1) 5-membered heterocycles with one or two heteroatoms

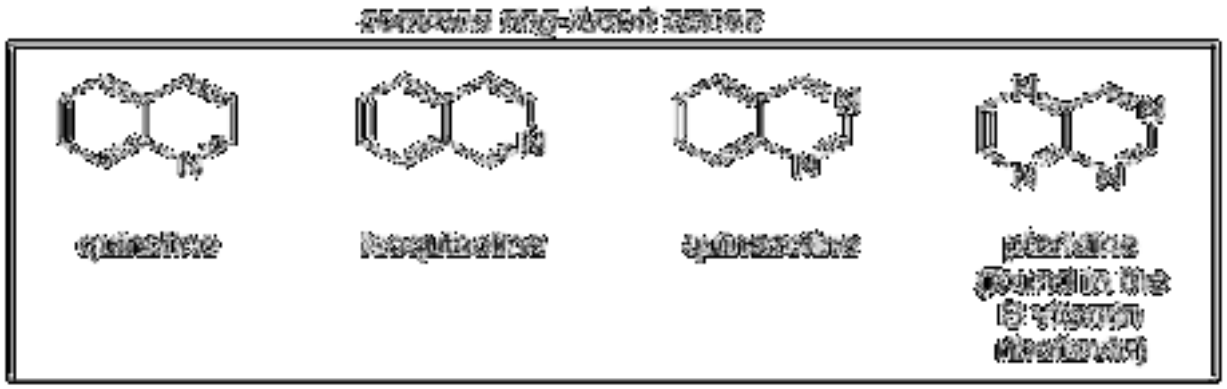


2) 6-membered heterocycles with one or two heteroatoms



3) Fused heterocycles





4) Saturated heterocycles

II- Replacement nomenclature

Heterocycle's name is composed of the corresponding carbocycle's name and an elemental prefix for the heteroatom introduced.

(if more than one heteroatom is present they should be listed according to the priority order shown in (table 1).

ATOM	PREFIX	
O	Oxa	 Priority decreases
S	Thia	
Se	Selena	
N	Aza	
P	Phospha	

Replacement nomenclature

Benzene

1,4-Diazabenzene

Cyclopentadiene

Oxacyclopenta-2,4-diene

Cyclopentadiene

1-Oxa-3-azacyclopenta-2,4-diene

Cyclopropane

Oxacyclopropane

Cyclopropene

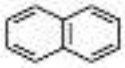
Oxazacyclopropene

Cyclopentadiene

1-Thia-2-azacyclopenta-2,4-diene

Cyclohexane

1-Oxa-4-azacyclohexane



Naphthalene

2-Azanaphthalene

III-Hantzsch-Widman nomenclature (IUPAC)

This systematic nomenclature of heterocyclic compounds was proposed by German chemists Arthur Hantzsch and Oskar Widman, proposed similar systematic naming of heterocyclic compounds in 1887 and 1888 respectively

In this system of nomenclature

IUPAC name = locants+ prefix + suffix

Three to ten-membered rings named by combining the appropriate prefix (or prefixes) that denotes the type and position of the heteroatom present in the ring with suffix that determines both the ring size and the degree of unsaturation.

In addition, the suffixes distinguish between nitrogen containing heterocyclics and heterocyclics that do not contain nitrogen.

Table 1.1 Prefix for Hetero Atoms

Hetero atom	*Valence*	*Prefix*
O	2	Oxa
N	3	Aza
S	2	Thia
Se	2	Selena
Te	2	Tellura
P	3	Phospha
As	3	Arsa
Si	4	Sila
Ge	4	Germa

Table 1.2 Common Name Endings for Heterocyclic Compounds

Ring size	*Suffixes for fully unsaturated compounds*		*Suffixes for fully saturated compounds*	
	With N	*Without N*	*With N*	*Without N*
3	-irine	-irene	-iridine	-irane
4	-ete	-ete	-etidine	-etane
5	-ole	-ole	-olidine	-olane
6	-ine	-in		-ane
7	-epine	-epin		-epane
8	-ocine		-ocin	-ocane

IUPAC nomenclature of heterocyclic compounds adopting the prefixes and suffixes indicated by Hantzsch and Widman method

A. Unsubstituted heterocyclic ring with one hetero atom

1. Identify the heteroatom present in the ring and choose the corresponding prefix .

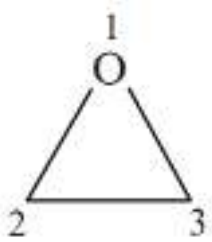
2. Choose the appropriate suffix from (table 2) depending on whether or not nitrogen atom is present in the ring, the size of the ring and presence or absence of any double bonds

3. Combine the prefix(s) and suffix together and drop the first vowel if two vowels came together.

This ring contains (N) Prefix is aza

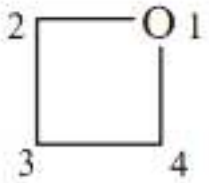
- The ring is 3-membered and fully saturated suffix is iridine
- By combining the prefix and suffix, two vowels

ended up together (azairidine), therefore the vowel on the end of the first part should be dropped. This gives the correct name: **Aziridine**



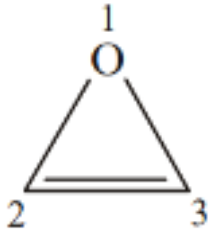
Oxirane

Heteroatom Oxygen so prefix oxa, non nitrogenous three membered saturated ring so suffix –irane. Thus the name Oxirane



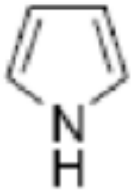
Oxetane

Heteroatom Oxygen so prefix oxa, non nitrogenous Four membered saturated ring so suffix –etane. Thus the name Oxetane

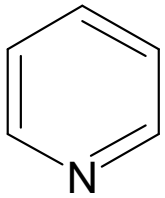


Oxirene

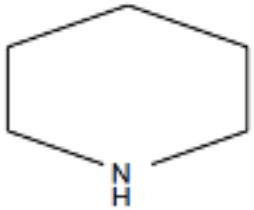
Heteroatom Oxygen so prefix oxa, non nitrogenous three membered unsaturated ring so suffix –irene. Thus the name Oxirene



Heteroatom Nitrogen so prefix Aza, nitrogenous Five membered fully un saturated ring so suffix –Ole. Thus the name **Azole** Common name **pyrrole**



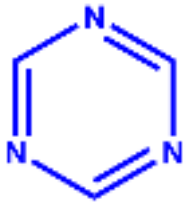
Heteroatom Nitrogen so prefix Aza, nitrogenous SIX membered fully un saturated ring so suffix –ine. Thus the name **Azine** Common name **Pyridine**



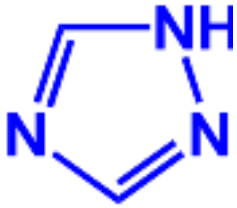
Heteroatom Nitrogen so prefix Aza, nitrogenous SIX membered fully saturated ring so prefix **Perhydro.** Thus the name Perhydro**Azine** Common name **Piperidine**

B. Heterocyclic ring with more than one Hetero atom:

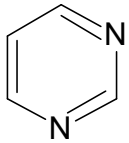
Two or more similar atoms contained in a ring are indicated by the pre- fixes ‘di-’, ‘tri’, etc. placed before the appropriate name



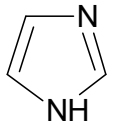
1,3,5-Triazine



1,2,4-Triazole



1,3-diazine
(Common name-Pyrimidine)

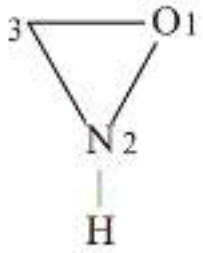


1,3-diazole
(Common name-Imidazole)

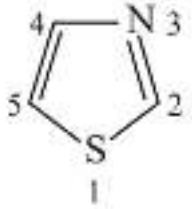
If two or more different hetero atoms occur in the ring, then it is named by combining the prefixes in Table 1.1 with the ending in Table 1.2 in order of their preference, i.e. **O > S > N.**

The ring is numbered from the atom of preference in such a way so as to give the smallest possible number to the other hetero atoms in the ring. As a result the position of the substituent plays no part in determining how the ring is numbered in such compounds.

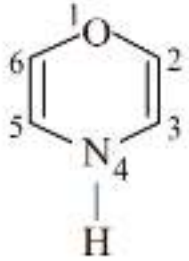
EX.



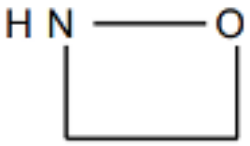
Oxaziridine



Thiazole



1,4-Oxazine



1,2-oxazetidine

1,2,5-Oxadiazole

C. Substituted Heterocyclic ring nomenclature:

Conventionally, the hetero atom is assigned position 1 and the substituents are then counted around the ring in a manner so as to give them the lowest possible numbers.

While writing the name of the compound, the substituents are placed in an alphabetical order.

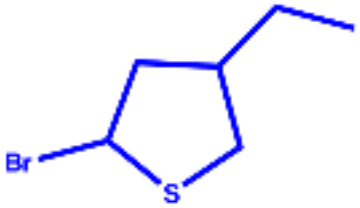
In case the heterocyclic ring contains more than one hetero atom, the order of preference for number- ing is O, S and N.

The ring is numbered from the atom of preference in such a way so as to give the smallest possible number to the other hetero atoms in the ring.

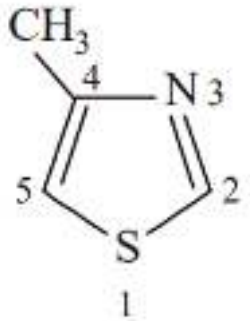
As a result the position of the substituent plays no part in determining how the ring is numbered in such compounds.

Ex.

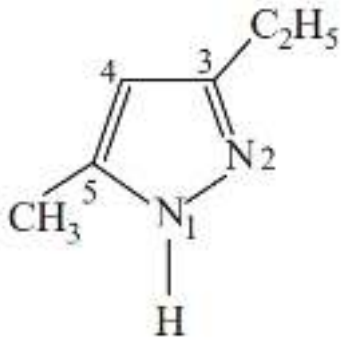
2-Propyloxirane



2-Bromo-4-ethylthiolane



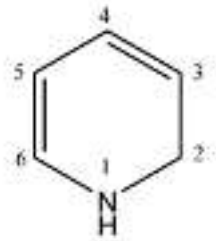
4-Methylthiazole



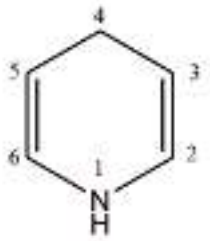
3-Ethyl-5-methylpyrazole

D. Nomenclature of Partially unsaturated or partially saturated Heterocyclic rings.

i. The position of the hydrogen atom in a partially saturated heterocyclic ring can be indicated by writing 1, 2-dihydro, or trihydro, tetrahydro etc. with the name of the compound. Alternatively, the position of the double bond can also be specified as Δ1, Δ2, Δ3.,. etc., which indicates that 1 and 2; 2 and 3; 3 and 4 atoms respectively have a double bond.



1,2-Dihydroazine



1,4-Dihydroazine

2,3,4,5-Tetrahydroazine

2,3-Dihydrooxole

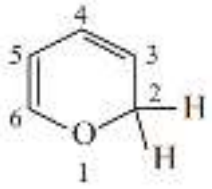
Δ^3-Azoline

Δ^2-Oxolene

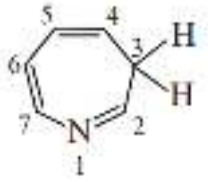
Δ^4-1,3-Thiazoline

Δ^2-1,3-Diazoline

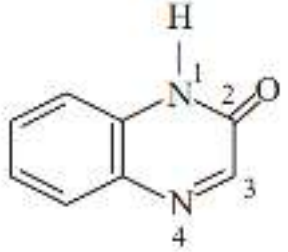
ii. In a heterocyclic ring with maximum unsaturation, if the double bonds can be arranged in more than one way, then their positions are specified by numbering those nitrogen or carbon atoms which are not multiply-bonded, i.e. bear an ‘extra’ hydrogen atom, by italic capital ‘1H’ ‘2H’ ‘3H’, etc. The numerals indicate the position of these atoms having the extra hydrogen atom.



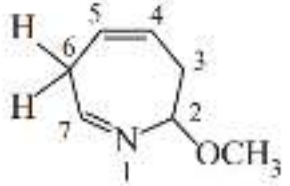
2*H*-Pyran



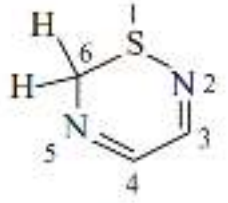
3*H*-Azepine



Quinoxaline-2(1*H*)-one



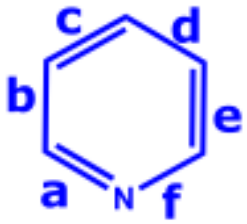
2-Methoxy-6*H*-azepine



6*H*-1,2,5-Thiadiazine

E. Nomenclature of fused heterocyclic rings.

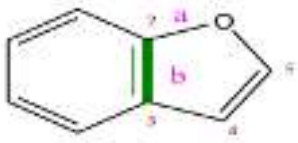
When naming such compounds the side of the heterocyclic ring is labeled by the letters a, b, c, etc., starting from the atom numbered 1. Therefore side ‘a’ being between atoms 1 and 2, side ‘b’ between atoms 2 and 3, and so on. as shown below for pyridine and furan.



The name of the heterocyclic ring is chosen as the parent compound and the name of the fused ring is attached as a prefix. The prefix in such names has the ending ‘o’, i.e., benzo, naphtho and so on.

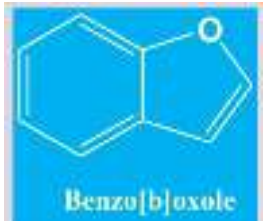
1. prefix: the word benzo
2. letter in square brackets: indicating the position of fusion
3. name of heterocyclic ring: (common or IUPAC name). Name= Benzo[letter]name of heterocyclic ring

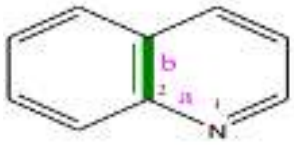
EX.



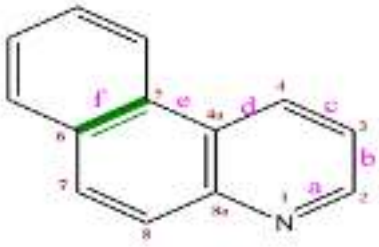
Benzo[b]furan

or

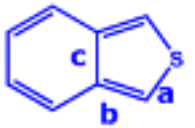




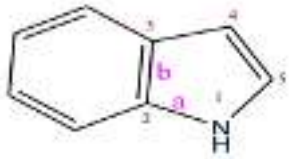
Benzo[b]pyidine
Qunioline



Benzo[f]qunioline



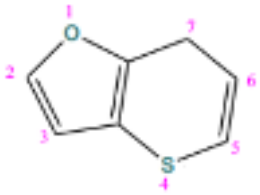
Benzo [c] thiophene



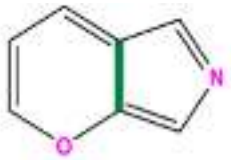
Benzo[b]pyrrole
Indole

The numbering system for the whole fused system is not the same as the numbers in the square brackets (i.e. there are three numbering systems; one for parent ring, one for substituent ring and the third is for the system as a whole)

Naming the fused rings as a single molecule



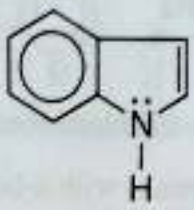
7*H*-Thiopyrano[3,2-*b*]furan



pyrano[2,3-*c*]pyrrole

INDOLE AND ITS DERIVATIVES

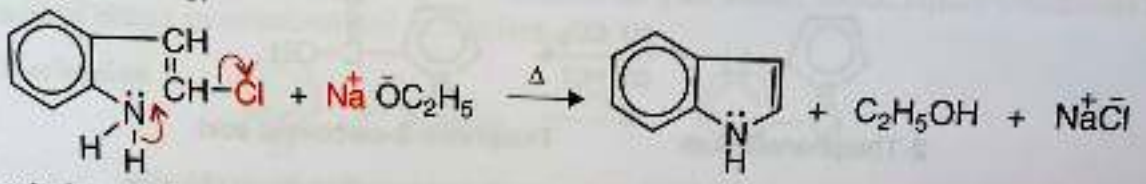
INDOLE, α, β-*Benzopyrrole,*



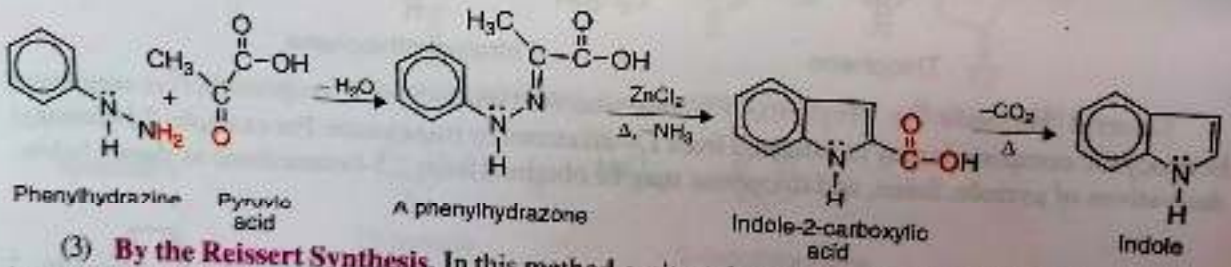
Indole consists of a benzene ring fused to the α, β positions of a pyrrole ring. It derives its name from the fact that it was first obtained by distilling oxindole, a degradation product of indigo, with zinc dust. Indole occurs in coal-tar and in the oils of jasmine and orange blossoms. It is also found as a part of the total structure of a number of alkaloids and amino acids *e.g.*, serotonin, reserpine, and tryptophan. Indole, like pyrrole, produces red color with a pine splint moistened with concentrated hydrochloric acid.

Preparation. Indole may be obtained :

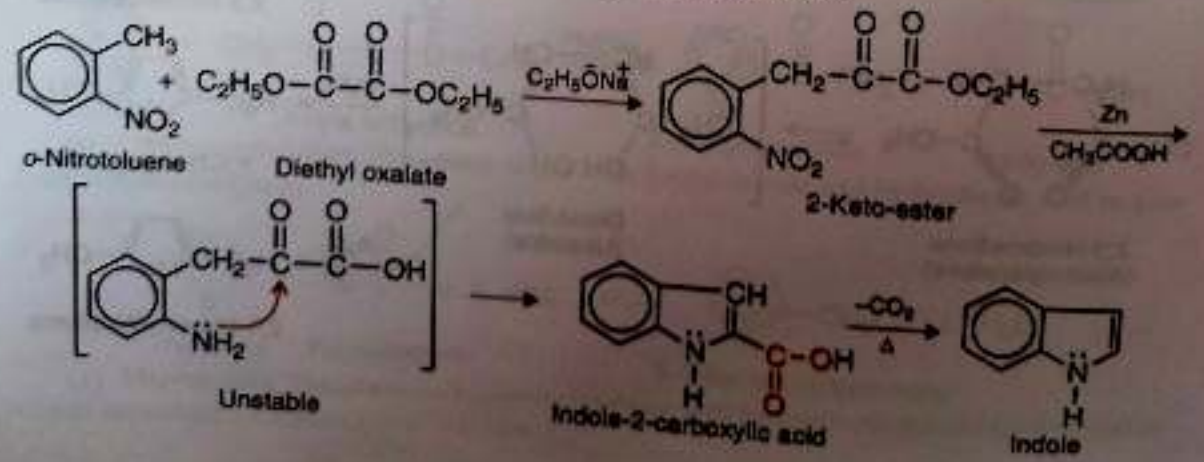
(1) **By the Lipp Synthesis.** In this method *o*-amino-ω-chlorostyrene is heated with sodium ethoxide at 160–170°C.



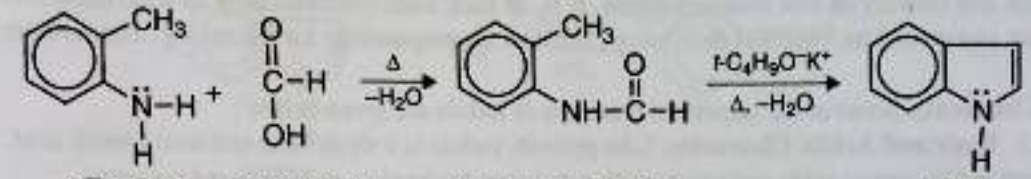
(2) **By the Fischer-Indole Synthesis.** In this method pyruvic acid is first treated with phenylhydrazine to form the corresponding phenylhydrazone. The hydrazone is heated with anhydrous zinc chloride or polyphosphoric acid ($H_3PO_4 + P_2O_5$) to give indole-2-carboxylic acid which on decarboxylation yields indole.



(3) **By the Reissert Synthesis.** In this method *o*-nitrotoluene is condensed with diethyl oxalate in the presence of a base to form a 2-*keto*-ester. This is then reduced with zinc and glacial acetic acid to give indole-2-carboxylic acid which on decarboxylation gives indole.

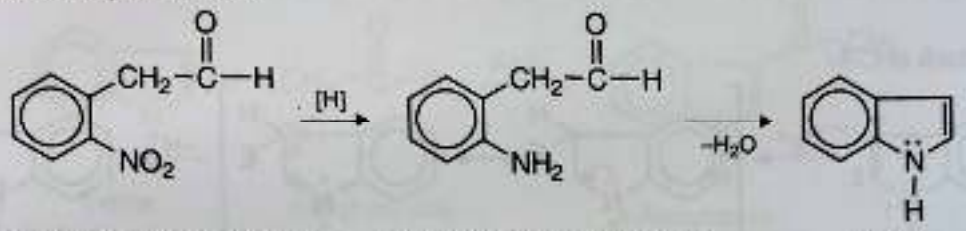


(4) **From o-Toluidine.** This involves treatment of *o*-toluidine with formic acid to form *N*-formyl-*o*-toluidine. This undergoes dehydration on heating with potassium *t*-butoxide to yield indole.



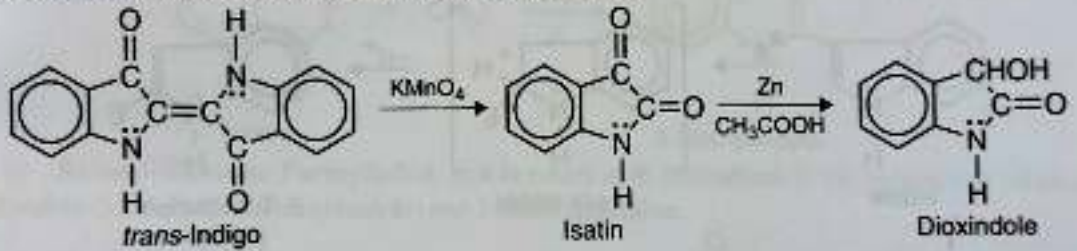
o-Toluidine Formic acid *N*-Formyl-*o*-toluidine Indole

(5) **From o-Nitrophenylacetaldehyde.** This involves reduction of *o*-nitrophenylacetaldehyde with iron powder and sodium bisulfite to give *o*-aminophenylacetaldehyde, which cyclizes spontaneously to yield indole.

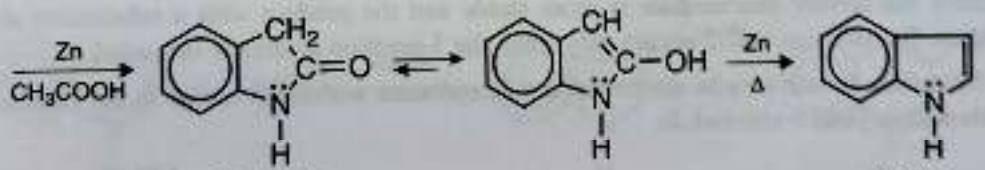


o-Nitrophenylacetaldehyde *o*-Aminophenylacetaldehyde Indole

(6) **From *trans*-Indigo.** This involves oxidation of *trans*-indigo with potassium permanganate to form isatin. Isatin on reduction with zinc and glacial acetic acid first gives dioxindole and finally oxindole. This is next distilled with zinc dust to give indole.



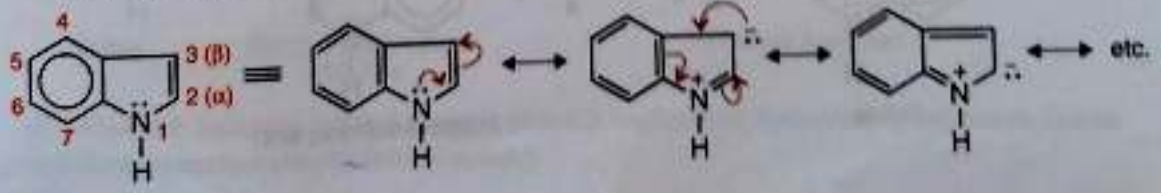
trans-Indigo Isatin Dioxindole



Oxindole Indole

Structure of Indole. Like pyrrole, all ring atoms in indole (*eight* carbons + *one* nitrogen) are sp^2 hybridized. The sp^2 hybrid orbitals overlap with each other and with *s* orbitals of hydrogens to form C—C, C—N, C—H, and N—H σ bonds. Each ring atom also possesses a *p* orbital and these are perpendicular to the plane containing the σ bonds. The *p* orbitals on carbons contain one electron each and the *p* orbital on nitrogen contains two electrons (the lone pair). The lateral overlap of these *p* orbitals produces a π molecular orbital containing *ten* electrons. Indole shows aromatic properties because the resulting π molecular orbital satisfies the Huckel's rule ($n = 2$ in $4n + 2$).

Indole is considered to be hybrid of several canonical forms, some of which are shown below :



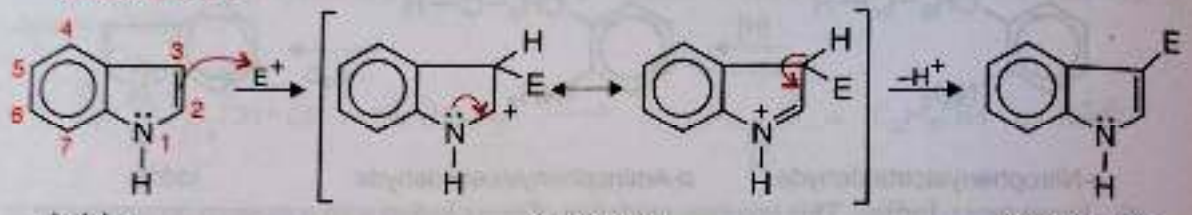
Properties (Physical). Indole is a colorless, volatile solid, mp 52°C. It is sparingly soluble in *cold* water, but dissolves in hot water and most organic solvents. Indole has a powerful odor which is pleasant and flowery in low concentrations. It is, in fact, used commercially as a perfume base. In contrast, indole and its 3-methyl derivative (*Skatole*) are responsible for the strong offensive odor of faces.

(Chemical). Some of the important reactions of indole are given below :

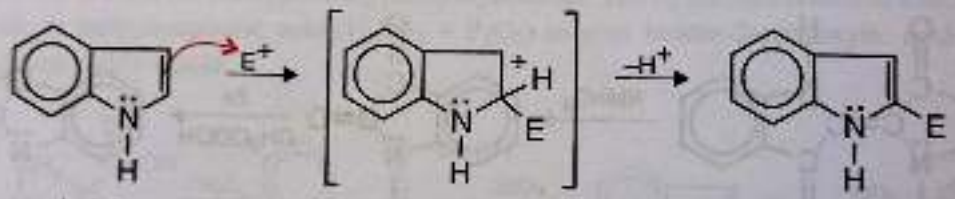
(1) **Basic and Acidic Character.** Like pyrrole, indole is a weak base and also a weak acid. It is polymerized by strong acids and reacts with potassium hydroxide and Grignard reagents.

(2) **Electrophilic Substitutions.** Unlike pyrrole, indole undergoes electrophilic substitution at *C-3*. This is because *two* resonance forms can be written for intermediate cation obtained from attack at *C-3* (without disturbing the benzene ring), whereas only one such form is possible for substitution at *C-2*.

Attack at C-3 :

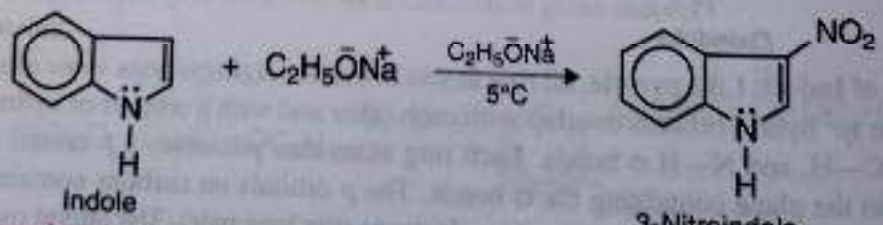


Attack at C-2 :

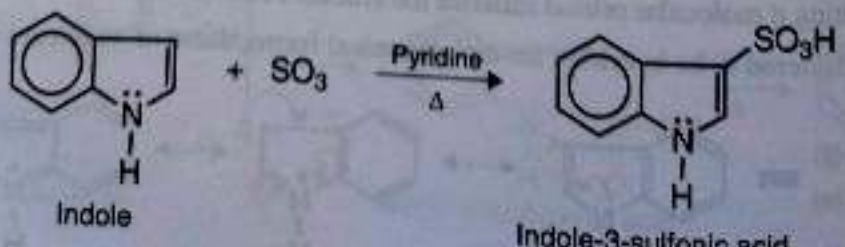


Consequently the former intermediate is more stable and the product with a substituent at *C-3* predominates. Substitution at *C-2* occurs only when the 3-position is already occupied.

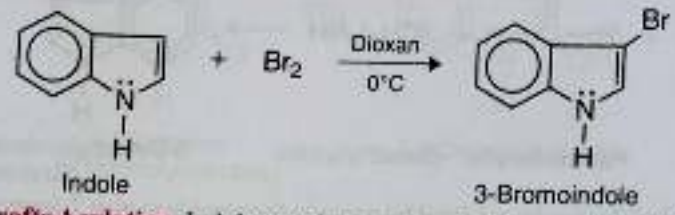
(*a*) **Nitration.** Indole may be nitrated at low temperature with ethyl nitrate in the presence of sodium ethoxide to yield 3-nitroindole.



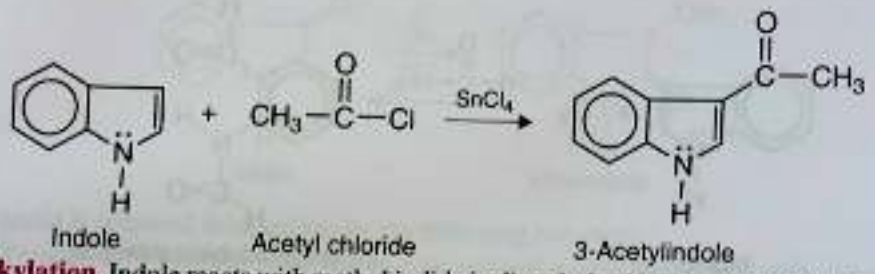
(*b*) **Sulfonation.** Indole undergoes sulfonation with sulfur trioxide in pyridine at 110°C to give indole-3-sulfonic acid.



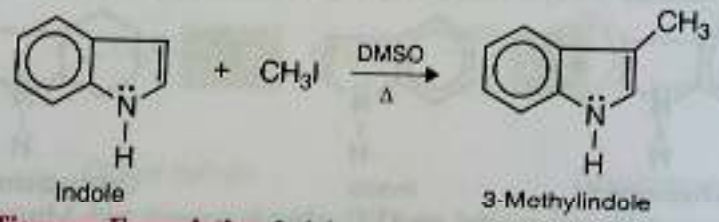
(*c*) **Bromination.** Indole can be brominated with bromine in dioxan at 0°C to form 3-bromoindole.



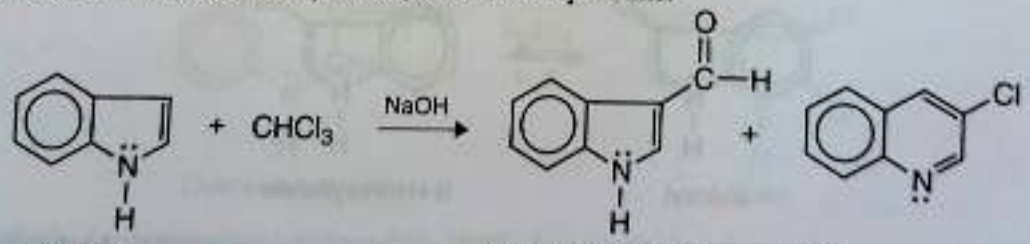
(*d*) **Friedel-Crafts Acylation.** Indole may be acetylated with acetyl chloride in the presence of $SnCl_4$ to yield 3-acetylindole.



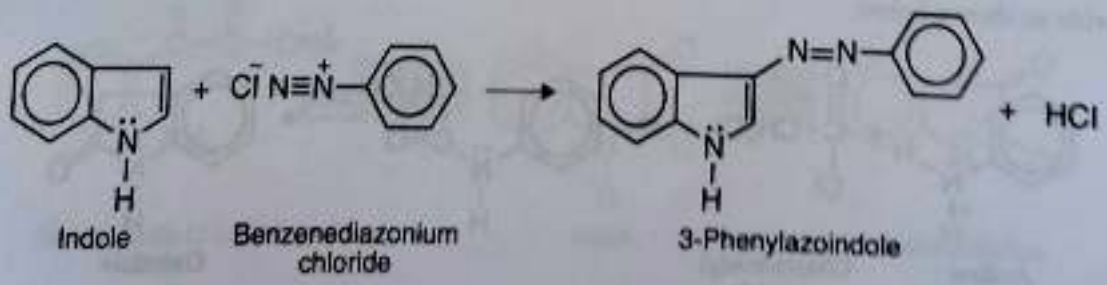
(*e*) **Alkylation.** Indole reacts with methyl iodide in dimethyl sulfoxide (*DMSO*) at about 80°C to give 3-methylindole.



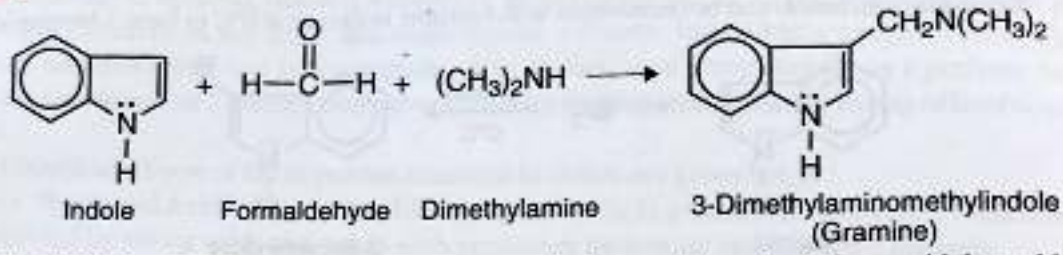
(*f*) **Reimer-Tiemann Formylation.** Indole reacts with chloroform in the presence of alkali to yield indole-3-aldehyde (3-formylindole) and 3-chloroquinoline.



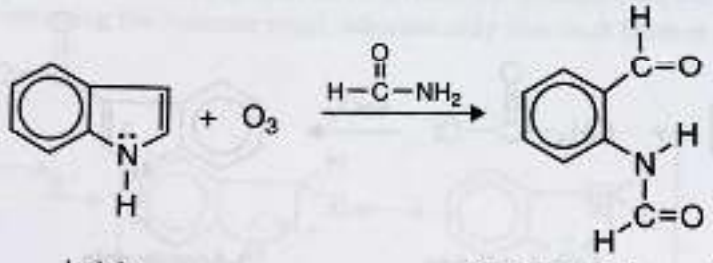
(*g*) **Diazo Coupling.** Indole couples with benzenediazonium chloride in a weakly acidic solution to yield 3-phenylazoindole.



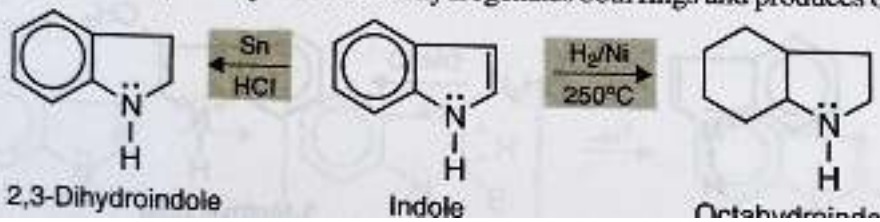
(*h*) **Mannich Reaction.** Indole undergoes Mannich reaction with formaldehyde and dimethylamine to give 3-dimethylaminomethylindole (*Gramine*).



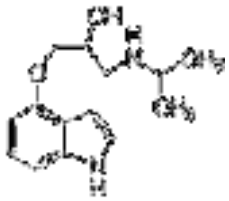
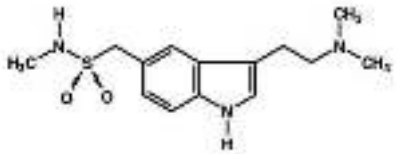
(3) **Oxidation.** Indole may be oxidized by ozone in formamide to give 2-formamidobenzaldehyde. Notice that this product is obtained by cleavage of the 2,3-bond in indole.



(4) **Reduction.** Mild reduction of indole with zinc (or tin) and hydrochloric acid yields 2,3-dihydroindole (*Indoline*). Catalytic reduction hydrogenates both rings and produces octahydroindole.



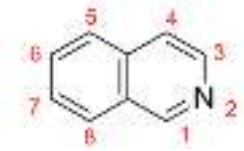
Medicinal compounds with indole nucleus

 Pindolol Use: Antihypertensive agent and antiglaucoma agent	 Sumatripatn Use: antimigraine agent

Other drugs: Reserpine alkaloid – Antihypertensive agent

Vinca alkaloids_ Anti cancer agents

ISOQUINOLINE



This fused bicyclic heterocyclic system of benzopyridine C_9H_7N is an isomer of quinoline, in this the fusion of benzene with pyridine involves the c-phase of pyridine thus it is 2-**azanaphthalene or benzo[c]pyridine.**

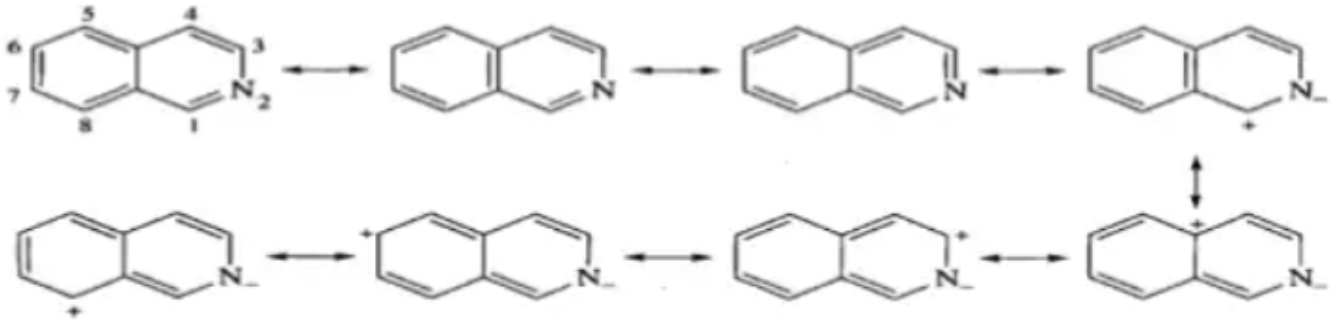
It Occurs in coal-tar and bone oil • Isoquinoline is also found as part of the total structure of a number of alkaloids e.g., papaverine and morphine.

AROMATICITY and STRUCTURE OF ISOQUINOLINE

In isoquinoline all ring atoms (9 carbons and 1 nitrogen) are SP2 hybridized. • Two SP2 orbitals on each atom overlap with each other to form the C-C and C-N σ bonds. The third SP2 orbital on each carbon atom overlaps with an S orbital of hydrogen and forms C-H σ bonds.

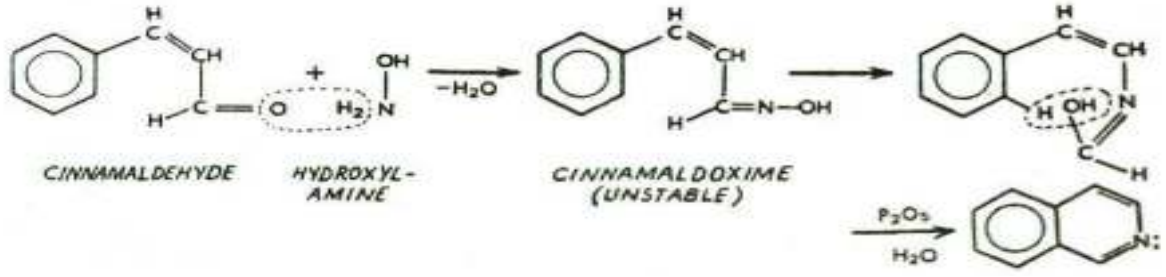
The third SP2 orbital of nitrogen is occupied by the nitrogen lone pair of electrons. • Each ring atom possess one un hybridized p – orbital containing one electron and those are perpendicular to the plane containing the σ bonds.

Overlap of these p – orbitals produces delocalized π – molecular orbital containing 10 electrons. • Isoquinoline shows aromatic properties because the resulting molecular orbital satisfies the Huckle's rule (4n+2 rule). • The nitrogen lone pair is not released into the aromatic system because it is perpendicular to the π system. •The nitrogen withdraws electrons by resonance, resulting in an electron-deficient ring system

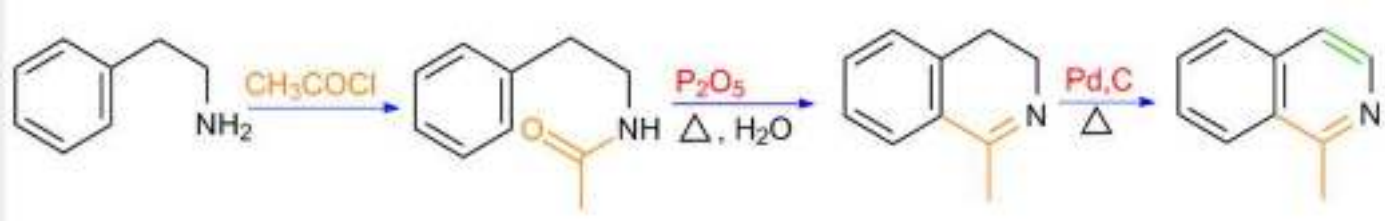


METHODS OF SYNTHESIS

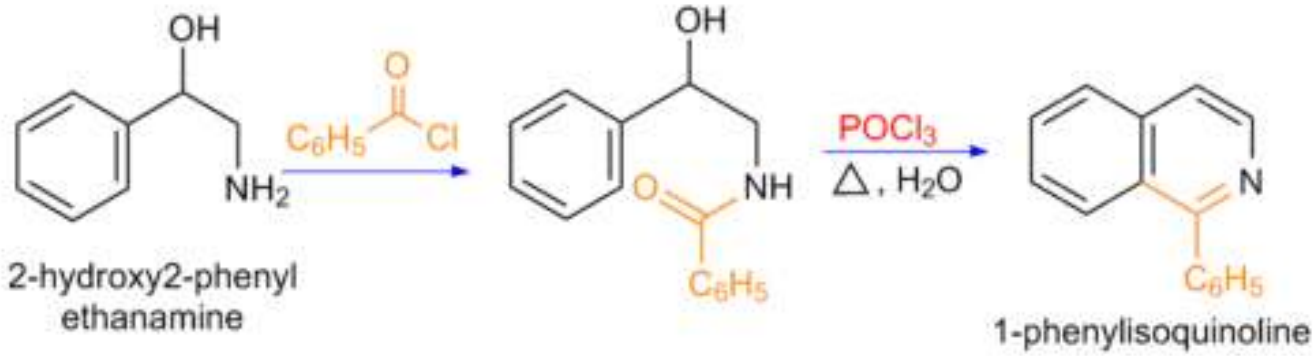
1. **From Cinnamaldehyde:** Cinnamaldehyde with hydroxylamine forms the corresponding oxime which then upon heating with phosphorus pentoxide undergo Beckmann rearrangement and followed by cyclization yields isoquinoline.



2. **Bischler-Napieralski Synthesis;**
   In this method β-phenylethylamine is reacted with an acyl chloride and a base to give the corresponding amide (R1 = H)
   Then this is cyclized to a 3,4-dihydroisoquinoline by treatment with either phosphorus pentoxide or phosphorus oxychloride.
   Finally, aromatization is accomplished by heating the 3,4-dihydroisoquinoline over palladium on charcoal.



3. **Pictet-Gams synthesis:** This reaction is a modification of the Bischler–Napieralski isoquinoline synthesis. The transformation of *N*-acyl 2-hydroxy (or alkoxy) phenylethylamine into isoquinoline derivatives by the treatment with a dehydration agent such as P_2O_5 or PCl_5in toluene or xylene.



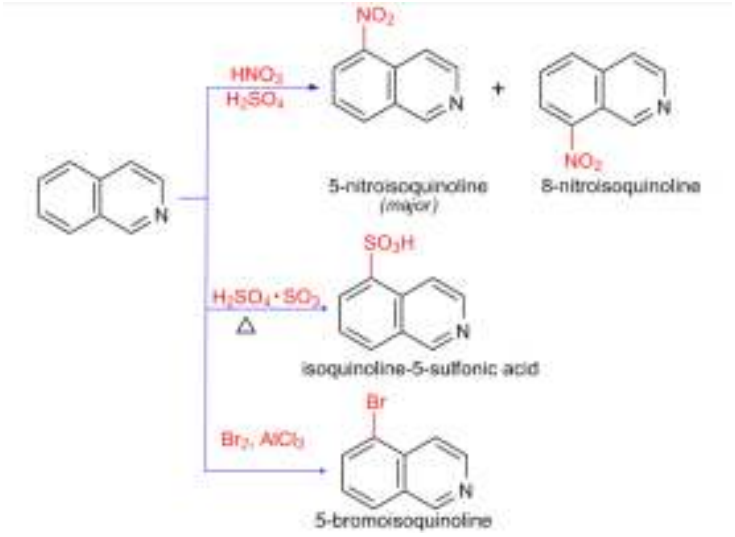
PROPERTIES

Isoquinoline is a colorless solid •(mp 26°C; bp 243°C) • Smell like that of benzaldehyde (Almond like). •It is sparingly soluble in water, and is soluble in many organic solvents. •It turns yellow on normal storage.

Chemical properties of Isoquinoline: Isoquinoline resembles quinoline in most of its chemical properties.

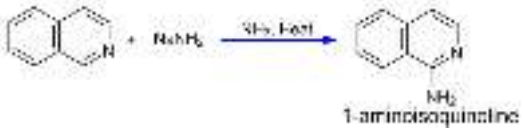
1. **Basic Character**: •Isoquinoline is a stronger base than quinoline (pka 5.14). It forms stable salts with acids

ELECTROPHILIC SUBSTITUTION REACTIONS: This aromatic heterocyclic comound undergo Aromatic electrophilic substitution reactions. The substitution preferably occurs in benzene ring at C5 and C8

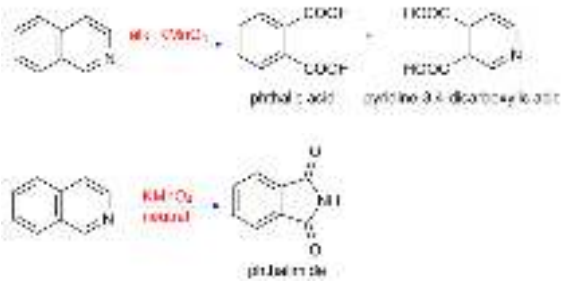


NUCLEOPHILIC SUBSTITUION: occur at C1 or C3 if C1 occupied

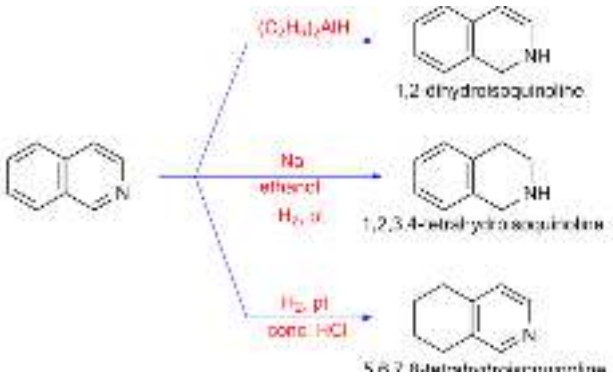
Chichibabin reaction

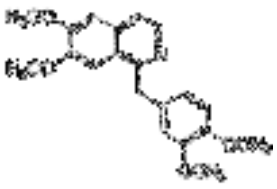
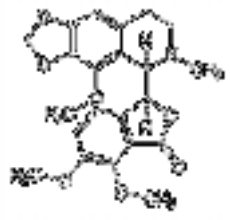


OXIDATION:

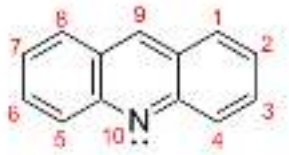


Reduction:



MEDICINAL COMPOUNDS	
 **PAPAVARINE (Use** Antispasmodic agent on smooth muscle)	 **Noscapine (use:Antusussive)**

ACRIDINE



This fused tricyclic heterocyclic compound is with molecular formula $C_{13}H_9N$

2,3-Benzoquinoline or Dibenzo[b,c]pyridine. Different derivatives with this nucleus have found usage as antimalarial agents.

AROMATCIY AND STRUCTURE OF ACRIDINE

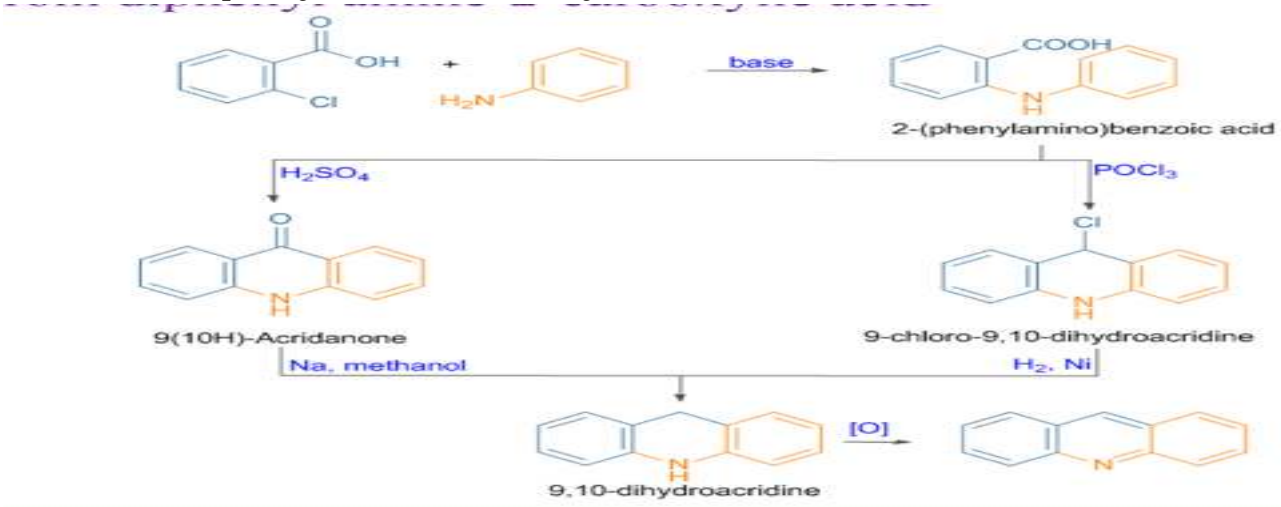
In acridine all ring atoms (13 carbons and 1 nitrogen) are SP2 hybridized. • Two SP2 orbitals on each atom overlap with each other to form the C-C and C-N σ bonds. The third SP2 orbital on each carbon atom overlaps with an S orbital of hydrogen and forms C-H σ bonds.

The third SP2 orbital of nitrogen is occupied by the lone pair of electron of nitrogen. • Each ring atom in ring possess one un hybridized p – orbital containing one electron and those are perpendicular to the plane containing the σ bonds.

Overlap of these p – orbitals produces delocalized π – molecular orbital containing 14 electrons. • Acridine shows aromatic properties because the resulting molecular orbital satisfies the Huckle's rule (4n+2 rule). • The nitrogen lone pair is not released into the aromatic system. • It is a planar molecule that is structurally related to anthracene with one of the central CH group is replaced by nitrogen.

METHODS OF SYNTHESIS OF ACRIDINE

1. From diphenyl amine-2-carboxylic acid:



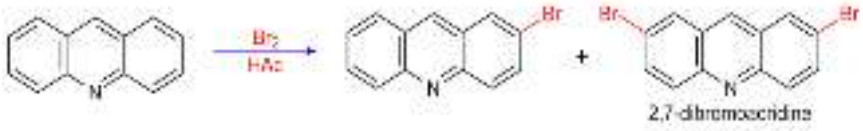
2. Bernthsen acridine synthesis

- diarylamine heated with a carboxylic acid (*or* acid anhydride) and zinc chloride to form a 9-substituted acridine

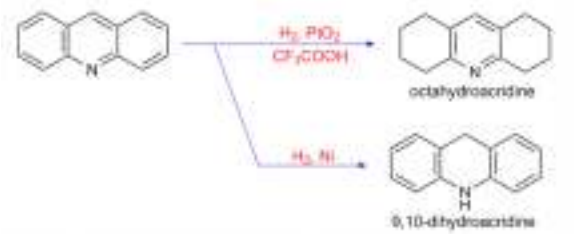
REACTIONS

1. Basic Character: Acridine is a weak base but it forms soluble salts with mineral acids.

2. Electrophilic Substitution reactions:

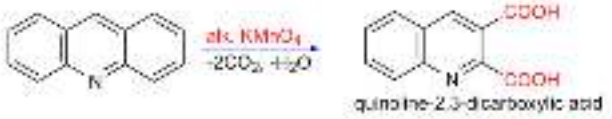


3. Reduction reactions:

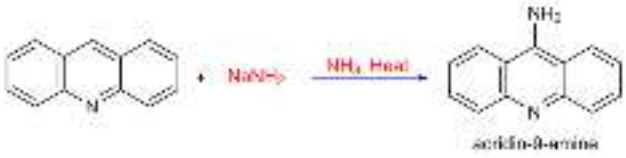


4. Oxidation:

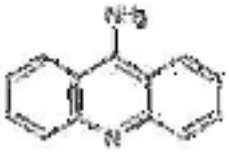
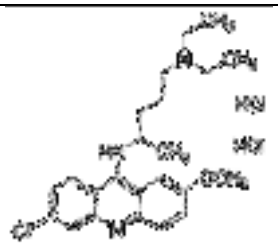
Acridine is degraded by permanganate in an alkaline medium forming quinoline-2,3-dicarboxylic acid.



5. Nucleophilic Substitution reaction



Medicinal Compounds with Acridine nucleus

 **9-aminoacridine** **Use: Antiseptic and disinfectant**	 **Mepacrine(Quinacrin)** **Use: Antimalarial agent**

PURINE

In this fused bicyclic heterocyclic compound pyrimidine ring is fused with imidazole. These are the most widely occurring nitrogen-containing heterocycles in nature. Purine derivatives forms one of the nucleotide nitrogen bases, these include adenine, guanine.

Purine is both a very weak acid (pK_a 8.93) and an even weaker base (pK_a 2.39). It dissolved in pure water.

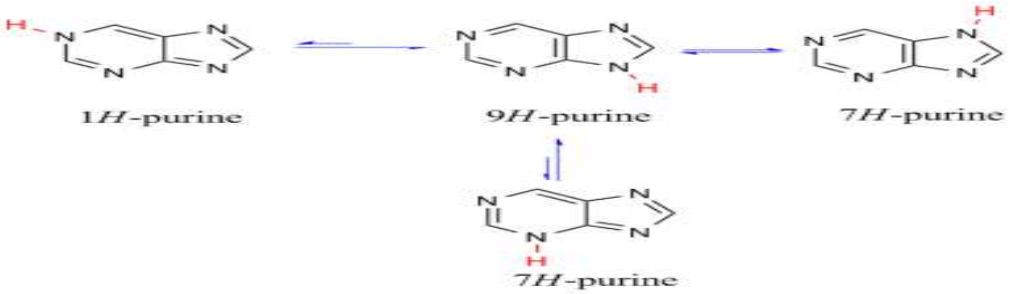
Aromaticity and Structure

Each atom is sp^2 hybridized , planar
the total nu of delocalized e- are 10 (5 of five C, 3 from N_1, N_3, N_7 & 2 from N_9) follows the Hückel's rule

Properties

3. Tautomerism

- 7*H*- and 9*H*- tautomers are more stable



Synthesis

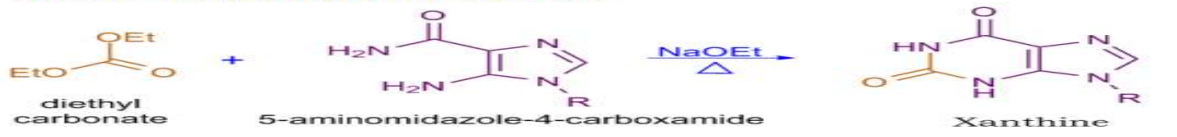
1. Traube Synthesis

- Synthesis of purines by heating 4,5 - diaminopyrimidines with carbonic acid / formamide

2. From formamide

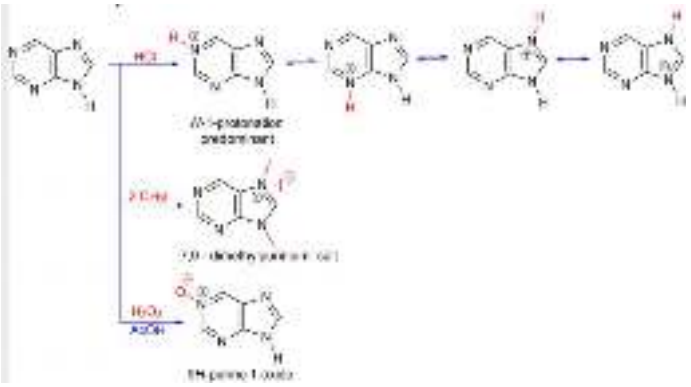
- Laboratory synthesis , formamide is heated in an vessel at 120 °C

3. From substituted imidazole

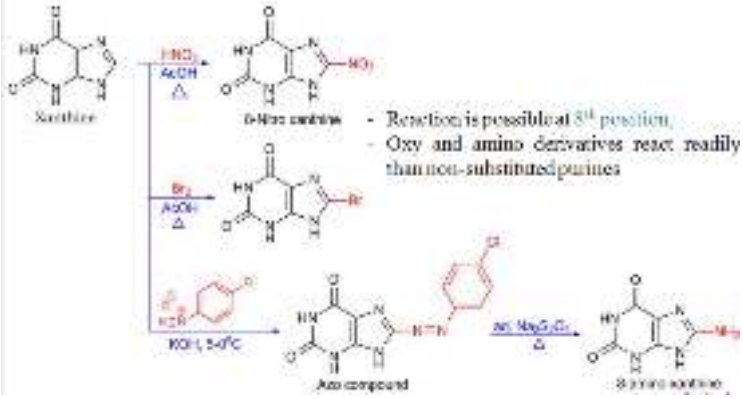


Reactions

Basicity



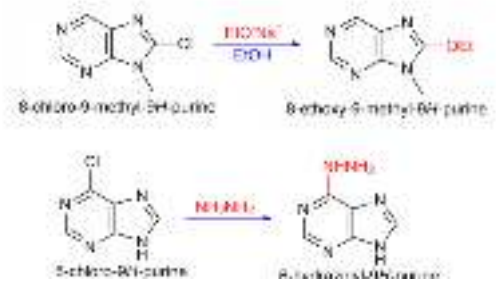
2. Electrophilic aromatic substitution



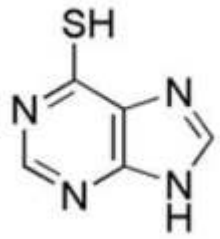
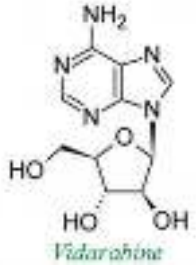
- Reaction is possible at 8th position.
- Oxy and amino derivatives react readily than non-substituted purines

3. Nucleophilic substitution

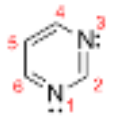
- Nucleophilic *displacement*, where halides are the most popular leaving group



Medicinal Compounds

 6-Mercaptopurine Use -Anticancer	 *Vidarabine* Use: Antiviral

PYRIMIDINE



These six membered heterocyclic rings contain two nitrogen atoms at 1,3 position, it belongs to the category of diazines.

It is aromatic and basic in nature.

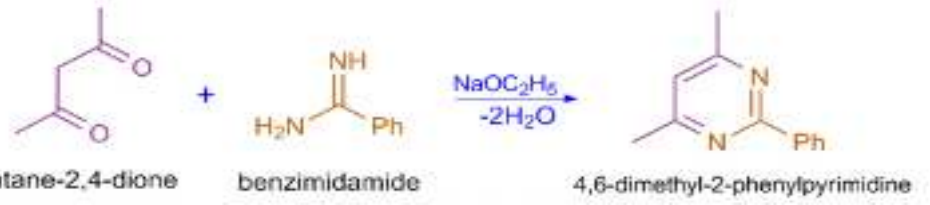
Methods of synthesis:

1. From 1,3 - Dicarbonyl Compound

- Combining 1,3 - dicarbonyl component with an N – C – N fragment such as a urea, an amidine or a guanidine.

1,3 - dicarbonyl compound

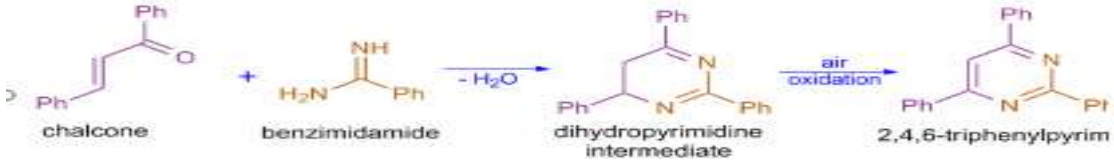
E.g.



pentane-2,4-dione benzimidamide 4,6-dimethyl-2-phenylpyrimidine

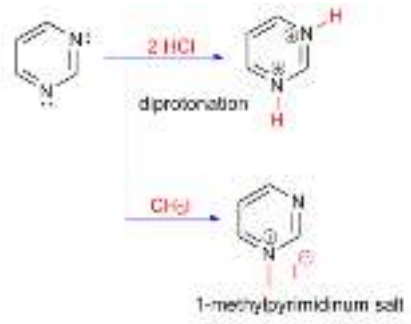
diethyl malonate urea pyrimidine-2,4,6-trione (Barbituric acid) pyrimidine-2,4,6-triol

2. From α, β - Unsaturated Ketones



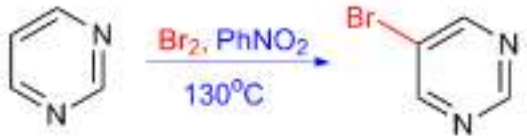
chalcone benzimidamide dihydropyrimidine intermediate 2,4,6-triphenylpyrim

Basicity



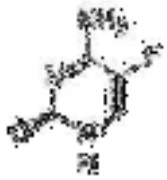
Electrophilic substitution reactions:

- Less reactive due to two N present in hetero skeletal
- Reaction is possible at 5th position, if ring is *activated by EDG.*
- no nitration *or* sulfonation



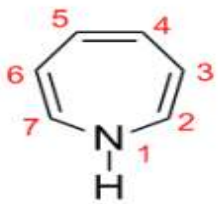
3. Nucleophilic substitution

MEDICINAL COMPOUNDS

 Flucytosine Use: Antifungal agent	 5-Fluorouracil Use: Anticancer agent

AZEPINE

These seven membered heterocyclic compounds with nitrogen have 8 electrons in delocalized pi electron cloud and it also exists as non-planar structure.



boat conformation
(with 22% chair conformation)

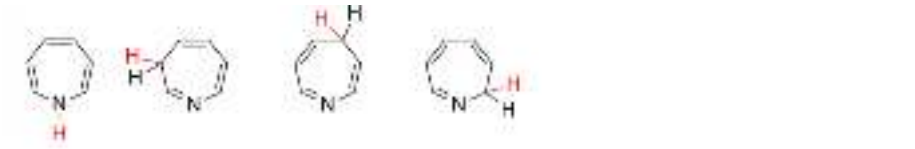
Planar Azepines (N is Sp^2) have potential 8 e- systems → cyclic & planar with 4n π e- is antiaromatic character → least stable.

thus ..azepines and its tautomers exist in non-planar conformation (boat conformation , one atom with Sp^3).

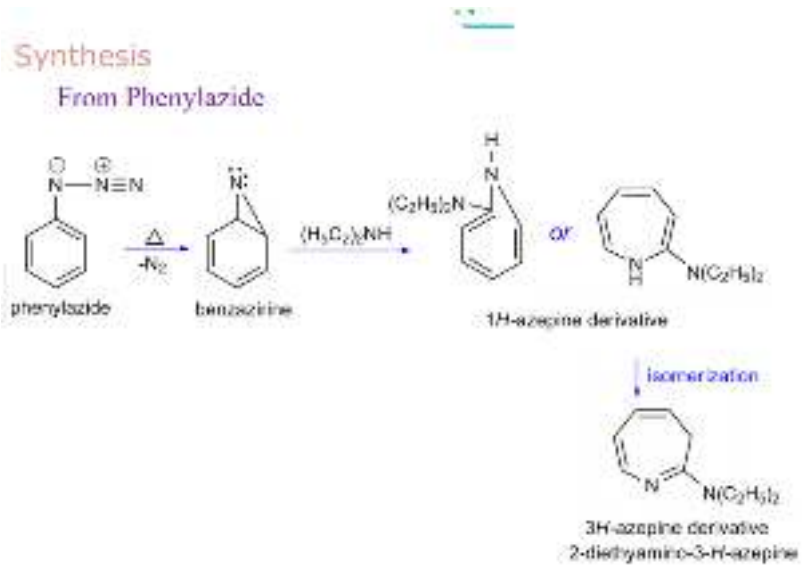
Compound do not comply with Hückel's rule of (4n + 2) π e-
So… azepine is non- aromatic compound

Properties

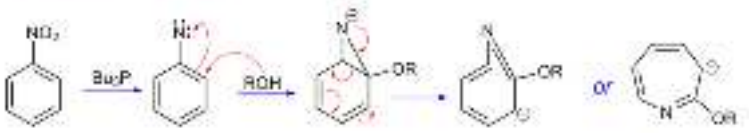
2. Tautomerism



Method of Synthesis



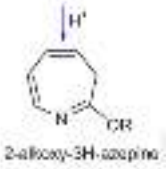
From Nitrobenzene



Deoxygenation of nitro group by tributyl-phosphine

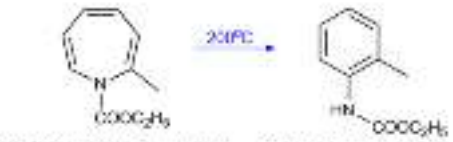
Nucleophilic addition of Alkoxy group to arylnitrine

Rearrangement



Reactions

1. Thermal reaction

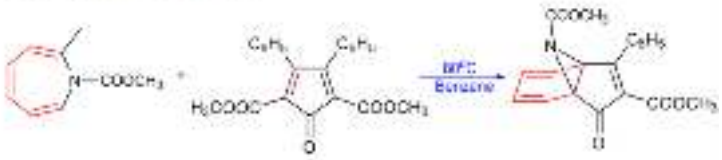


2. Ring contraction

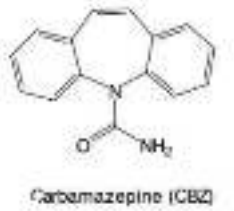
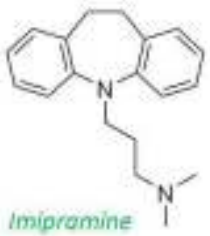
- Orbital symmetry controlled disrotatory electrocyclic process.

3. Diels-Alder reaction

- 6+2 π electron reaction

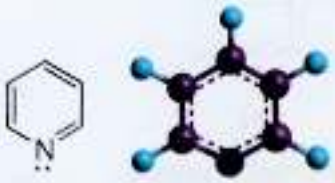


MEDICINAL COMPOUNDS

 Carbamazepine (CBZ) Carbamazepine Use: Anticonvulsant	 Imipramine Use: Antidepressant

SIX-MEMBERED RINGS

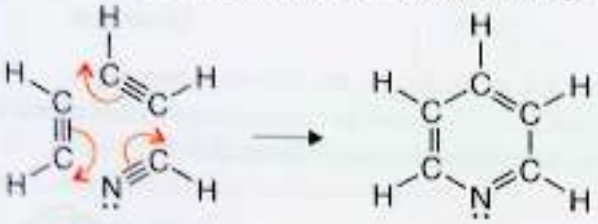
PYRIDINE,



Pyridine is the most important of the heterocyclic ring systems. It occurs along with pyrrole in bone oil and in the light oil fraction (bp up to 170°C) of coal-tar. It can be isolated from the latter by extracting it with dilute sulfuric acid. This removes pyridine and other bases in the acid layer as soluble sulfates. The acid layer is then treated with sodium hydroxide when a dark brown liquid separates. Pyridine is obtained from this oily liquid by fractional distillation.

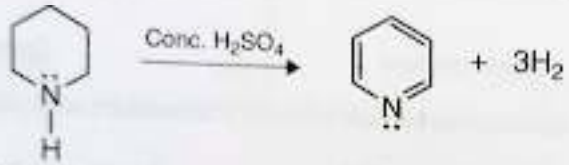
Preparation. Pyridine may be obtained :

(1) By passing a mixture of acetylene and hydrogen cyanide through a red-hot tube.



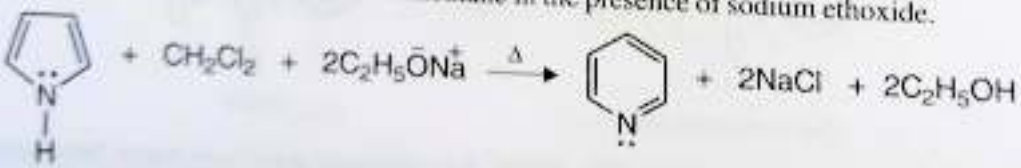
Pyridine

(2) By dehydrogenation of piperidine with concentrated sulfuric acid at 300°C or with nitrobenzene at 260°C.



Piperidine Pyridine

(3) By heating pyrrole with dichloromethane in the presence of sodium ethoxide.

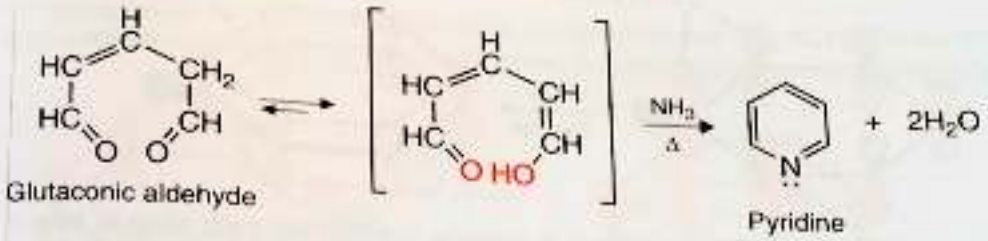


Pyrrole Pyridine

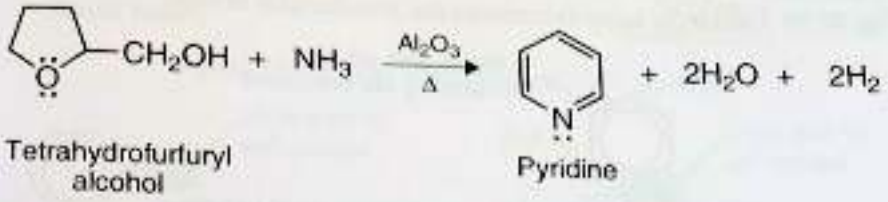
(4) By oxidation of β-picoline with potassium dichromate and sulfuric acid to give nicotinic acid (pyridine-3-carboxylic acid). Nicotinic acid on decarboxylation with calcium oxide yields pyridine.

β-Picoline Nicotinic acid Pyridine

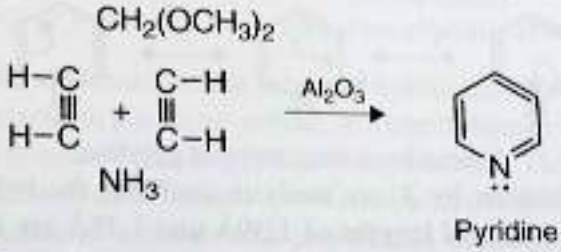
(5) By heating glutaconic aldehyde with ammonia.



(6) By heating tetrahydrofurfuryl alcohol with ammonia in the presence of aluminium oxide at 500°C. (*Commercial Method*)



(7) By reaction of acetylene with ammonia and formaldehyde dimethylacetal in the presence of aluminium oxide at 500°C. (*Commercial Method*)



Structure of Pyridine. In pyridine all ring atoms (*five* carbons + *one* nitrogen), are sp^2 hybridized. Two of the sp^2 orbitals on each atom overlap with each other to form the C—C and C—N σ bonds. The third sp^2 orbital on each carbon atom overlaps with an *s* orbital from hydrogen to form the C—H σ bonds ; the third sp^2 orbital on nitrogen is occupied by the nitrogen lone pair electrons (Fig.40.8). All σ bonds in pyridine lie in one plane and all bond angles are approximately equal to 120°C.

Also each ring atom in pyridine possesses an unhybridized *p* orbital (containing *one* electron) and these are perpendicular to the plane containing the σ bonds. The lateral overlap of the *p* orbitals produces a delocalized π molecular orbital containing six electrons (Aromatic Sextet). One half of this π molecular orbital lies above and the other half below the plane of σ bonds (Fig.40.9). Pyridine shows some aromatic properties because the resulting molecular orbital satisfies the Huckel's rule ($n = 1$ in $4n + 2$).

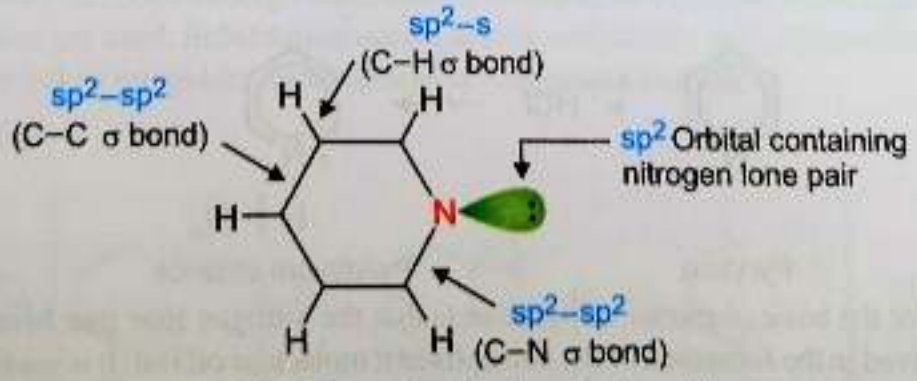


Fig.40.8. Formation of σ bonds in pyridine.

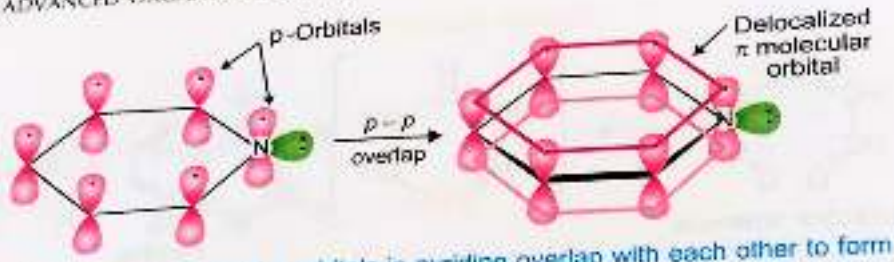


Fig.40.9. The unhybridized *p* orbitals in pyridine overlap with each other to form a delocalized π molecular orbital above and below the plane of σ bonds. The nitrogen lone pair electrons being in sp^2 hybrid orbital do not interact with π molecular orbital.

A common shorthand representation of pyridine is simply hexagon, a six-membered ring, with a circle inside (Fig.40.9). The circle again represents the π molecular orbital.

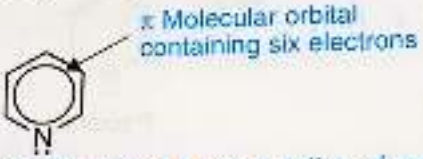
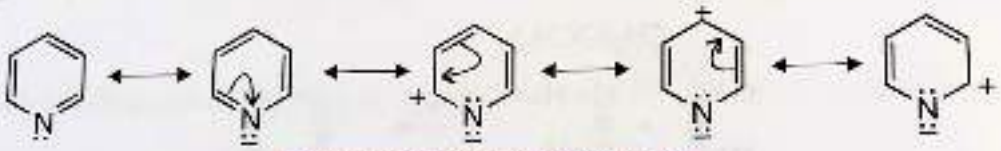


Fig.40.10. Simplified representation of pyridine.

According to the resonance theory, pyridine is considered to be hybrid of the following five resonance structures.



Resonance structures of pyridine.

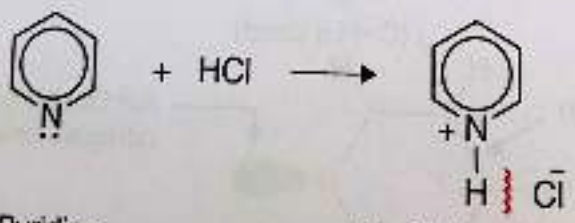
Measurement of bond lengths by X-ray analysis confirms the hybrid nature of the pyridine molecule. The C—C and C—N bond lengths of 1.39Å and 1.37Å are intermediate between those corresponding to a *single* and a *double* bond.

Properties (Physical). Pyridine is a colorless, liquid, bp 115°C. It has a very characteristic pungent and disgusting odor. Pyridine is miscible with water and most organic solvents. It is very hygroscopic. Pyridine reacts with sodium and so should be dried over solid potassium hydroxide or barium oxide. The presence of water in pyridine can be detected easily by adding pure benzoyl chloride. If water is present, a precipitate of benzoic anhydride will be formed immediately.

Almost all classes of organic compounds are soluble in pyridine, even many of the high melting solids which scarcely dissolve in solvents such as ethanol and benzene. It is consequently used as a solvent. Pyridine forms an azeotrope with water, which boils at 92–93°C.

(Chemical). The main chemical reactions of pyridine are described below :

(1) **Basic Character.** Pyridine behaves as a base ($pK_n = 5.2$). It reacts with acid to form fairly stable salts.



Pyridine Pyridinium chloride

The reason for the basic character of pyridine is that the nitrogen lone pair being in sp^2 hybrid orbital is not involved in the formation of the delocalized π molecular orbital. It is readily available for the formation of a new N—H bond with proton. Pyridine is a stronger base than pyrrole (or aniline) in

which the basicity is reduced by delocalization of the nitrogen lone pair (Fig.40.11). On the other hand, pyridine is a considerably weaker base than trimethylamine (a typical aliphatic tertiary amine) (Fig.40.12).

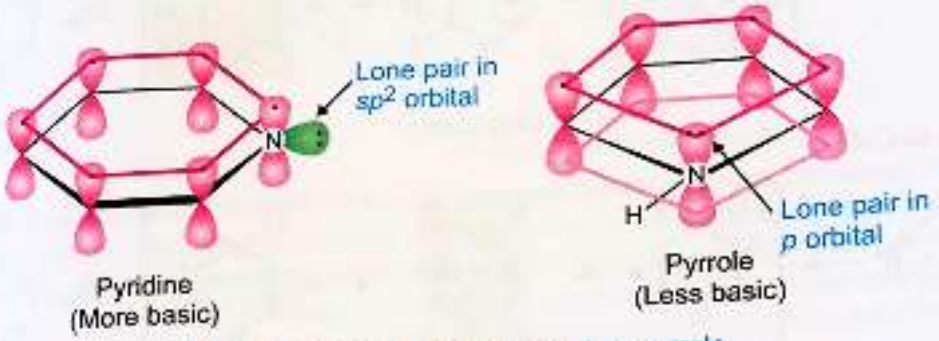


Fig.40.11.Pyrdine is more basic than pyrrole.

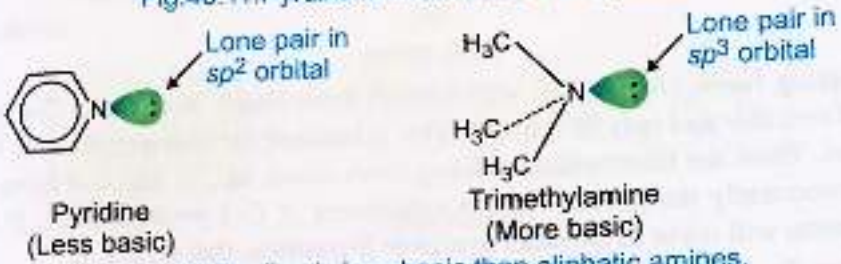


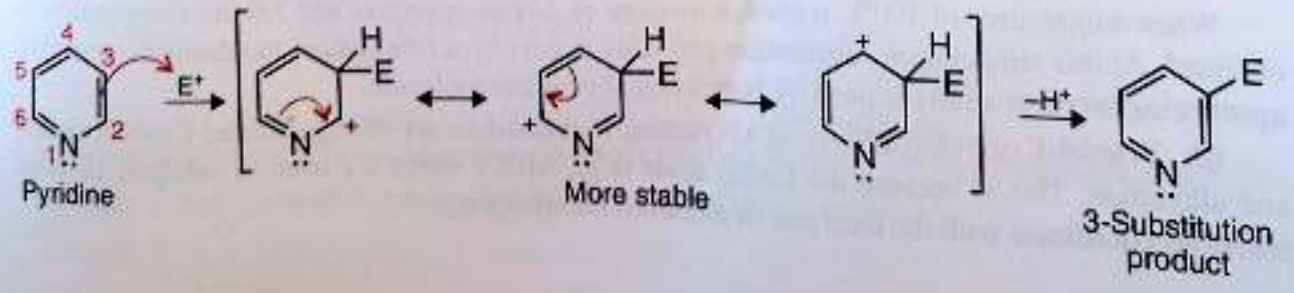
Fig.40.12.Pyrdine is less basic than aliphatic amines.

This is probably due to the difference in the nature of hybrid orbitals containing the nitrogen lone pair in the two molecules. In pyridine it is an sp^2 orbital; in trimethylamine it is an sp^3 orbital. Recall that sp^2 orbitals are smaller (due to more *s* character) than the sp^3 orbital. This means that the lone pair of electrons on nitrogen in pyridine is more closely associated with the nitrogen nucleus. It is, therefore, less available for the formation of a bond with proton and consequently the relative basicity is reduced.

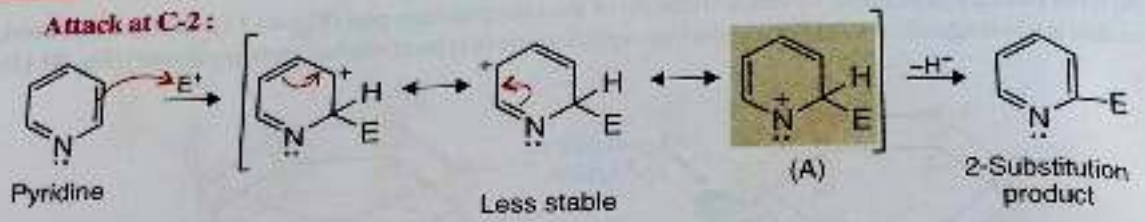
(2) **Electrophilic Substitutions.** Pyridine is considerably less reactive than benzene towards electrophilic substitution. This is so as : (*i*) the nitrogen atom in pyridine, because of its electronegativity lowers the electron density around the ring carbons ; and (*ii*) the usual electrophiles can coordinate with the lone pair of electrons on nitrogen to form resonance stabilized pyridinium salts.

Pyridine, however, does undergo electrophilic substitution reactions when extremely vigorous reaction conditions are used. Substitution occurs almost exclusively at *C-3* (β-position). This can be understood if we follow our guide of examining the intermediate cation.

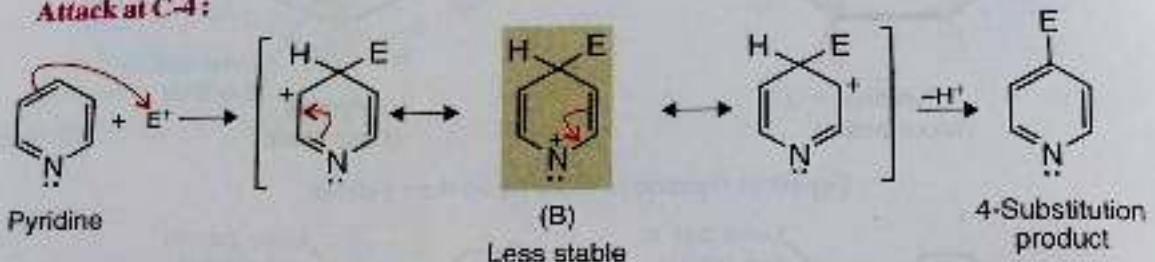
Attack at C-3 :



Attack at C-2 :

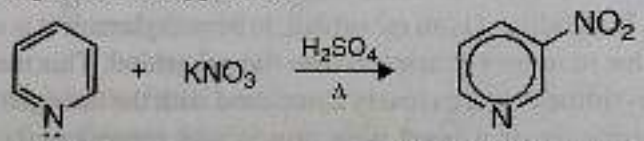


Attack at C-4 :

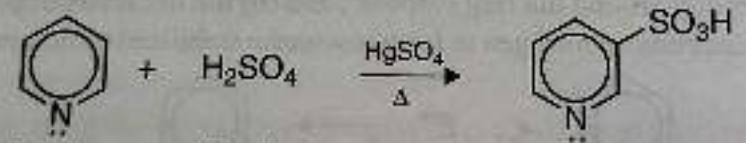


The contributing forms (A) and (B) which result from attack at *C-2* and *C-4* respectively are energetically unfavorable and may be ignored. This is because the nitrogen atom in these forms has only *six* electrons. Thus, the intermediates arising from attack at *C-2* and *C-4* have two resonance forms each. Consequently the product with a substituent at *C-3* predominates. If *C-3* is already blocked, substitution will occur at the other available β-position, that is, at *C-5*.

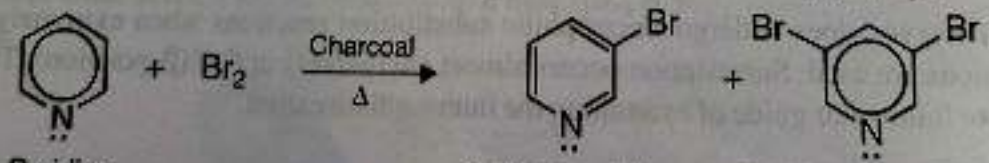
(*a*) **Nitration.** Pyridine undergoes nitration (in poor yield) with potassium nitrate in the presence of sulfuric acid at 300°C to yield 3-nitropyridine.



(*b*) **Sulfonation.** Pyridine undergoes sulfonation with fuming sulfuric acid in the presence of mercuric sulfate at 230°C to give pyridine-3-sulfonic acid.



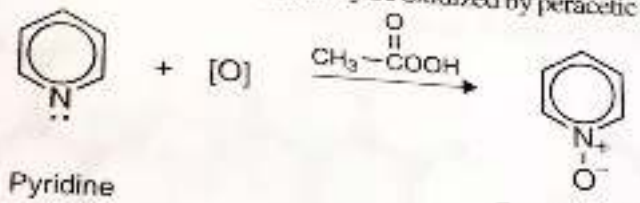
(*c*) **Bromination.** Pyridine may be brominated by passing the vapors of pyridine and bromine over charcoal catalyst at 300°C to yield 3-bromopyridine and 3,5-dibromopyridine.



When temperature of 500°C is used, a mixture of 2-bromopyridine and 2,6-dibromopyridine is obtained. At this temperature substitution probably occurs by a free radical mechanism, the active agent being bromine atom obtained by homolysis of bromine molecule.

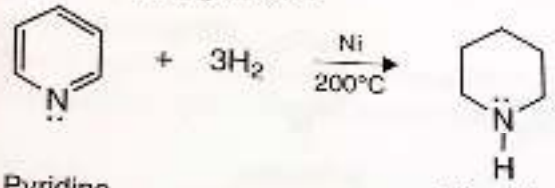
(*d*) **Friedel-Crafts Acylation and Alkylation.** Pyridine does not undergo Friedel-Crafts acylation and alkylation. This is because the Lewis acids (*e.g.*, $AlCl_3$) which are used as catalysts in these reactions coordinate with the lone pair of electrons on nitrogen.

(4) **Oxidation.** Like benzene pyridine is quite stable towards mild oxidizing agents. It does not react with chromic acid or nitric acid. However, it may be oxidized by peracetic acid to give pyridine-*N*-oxide.



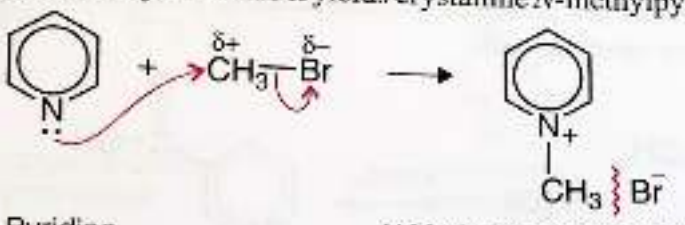
Pyridine — Pyridine-*N*-oxide (Pyridine-1-oxide)

(5) **Reduction.** Pyrrole undergoes reduction with lithium aluminium hydride ($LiAlH_4$), or hydrogen in the presence of nickel catalyst to form piperidine.



Pyridine — Piperidine

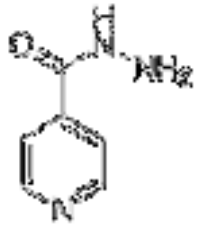
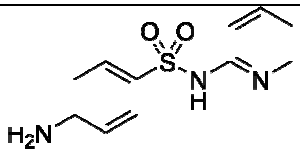
(6) **Reaction with Alkyl Halides.** Pyridine reacts with alkyl halides to form *N*-alkyl-pyridinium halides. For example, with methyl bromide it yields crystalline *N*-methylpyridinium bromide.



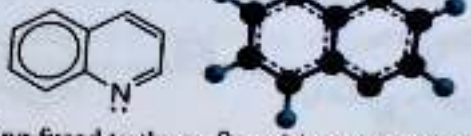
Pyridine — *N*-Methylpyridinium bromide (1-Methylpyridinium bromide)

Uses. Pyridine is used : (1) in organic synthesis as a basic solvent, whereby it not only exerts a catalytic action but also can combine with acids produced in reactions. For example, acylation and benzoylation takes place smoothly in pyridine solution; (2) to *denature* ethyl alcohol; and (3) as a starting material in the preparation of Sulfapyridine, Zclan and Niacin.

Medicinal compounds with Pyridine nucleus

 **Isoniazid (INH)** **Use: Antiutbercular agent**	 **Sulphapyridine** **Use: Antibacterial agent**

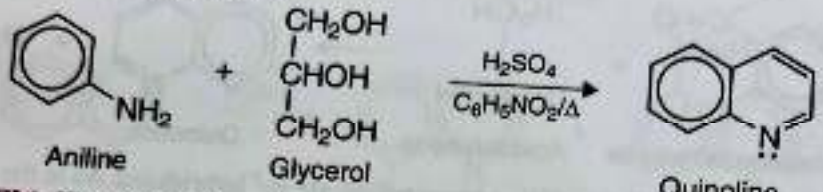
QUINOLINE, α,β-Benzopyridine



Quinoline consists of a benzene ring fused to the α, β positions of a pyridine ring. It derives its name from the fact that it was first obtained by heating the famous antimalarial alkaloid *quinine*, with alkali. Quinoline occurs in coal-tar, bone oil, and in *angostura* bark.

Preparation. Quinoline may be obtained :

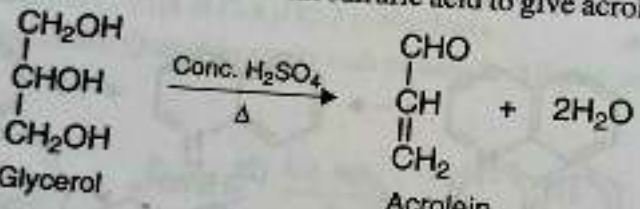
(1) **By Skraup Synthesis.** In this reaction, a mixture of aniline and glycerol is heated in the presence of sulfuric acid and a mild oxidizing agent, usually nitrobenzene or arsenic pentoxide. The reaction is exothermic and tends to become very violent. Ferrous sulphate or boric acid is generally added to make the reaction less violent.



Aniline + Glycerol → Quinoline

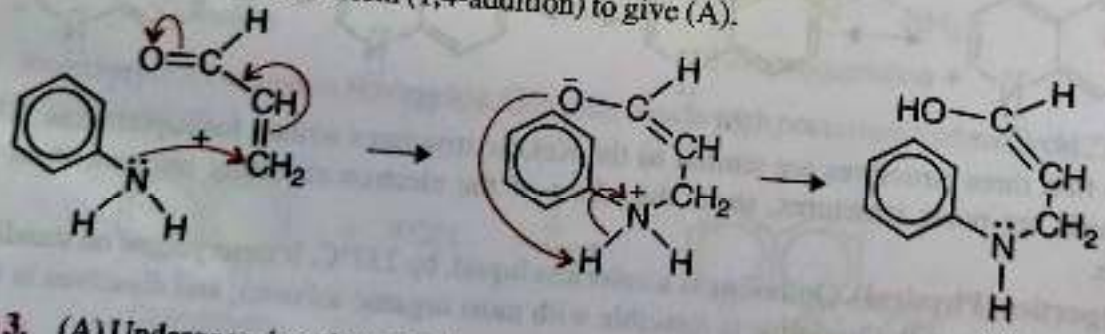
MECHANISM. The mechanism of this reaction is not completely understood. However, it is believed that it proceeds by the following steps.

Step 1. Glycerol undergoes dehydration with sulfuric acid to give acrolein.

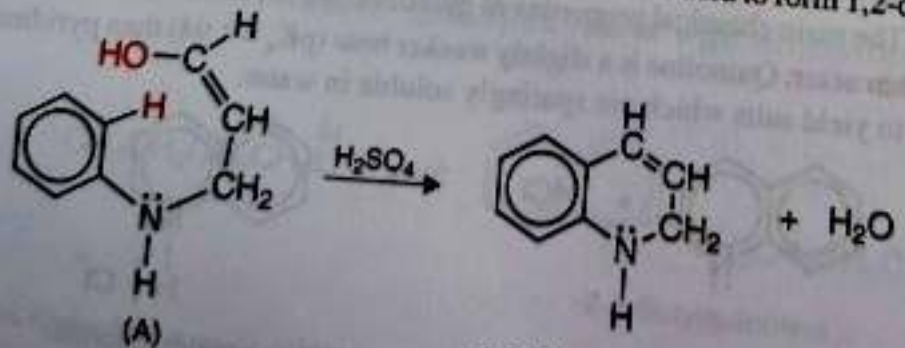


Glycerol → Acrolein

Step 2. Aniline adds to acrolein (1,4-addition) to give (A).

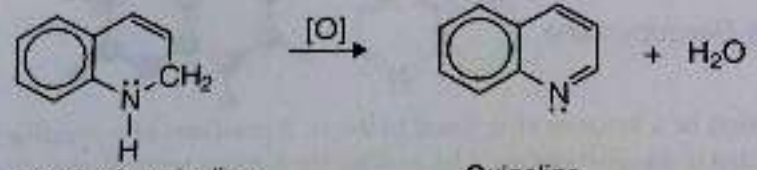


Step 3. *(A)* Undergoes ring closure in the presence of sulfuric acid to form 1,2-dihydroquinoline.



(A) → 1,2-Dihydroquinoline

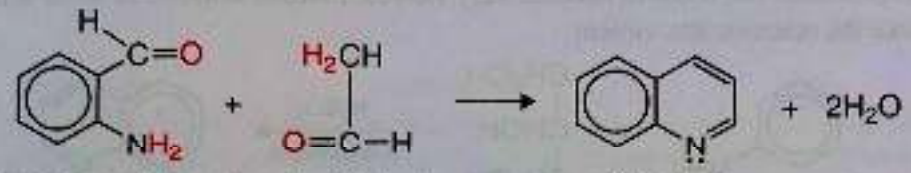
Step 4. 1,2-Dihydroquinoline undergoes oxidation with nitrobenzene to finally yield quinoline. Nitrobenzene itself is reduced to aniline which is reused in step (2)



1,2-Dihydroquinoline Quinoline

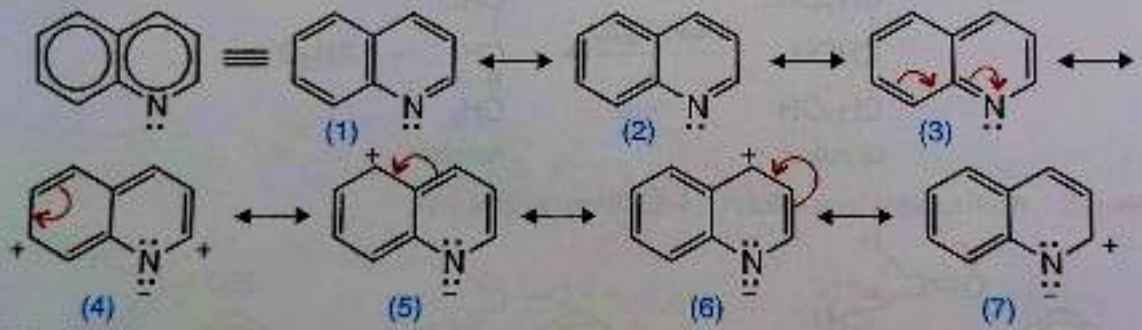
This synthesis is used for the commercial preparation of quinoline. It is also important because by starting with substituted anilines, substituted quinolines can be made.

(2) **By the Friedlander Synthesis.** This involves the condensation of *o*-aminobenzaldehyde with acetaldehyde in the presence of an alkali.



o-Aminobenzaldehyde Acetaldehyde Quinoline

Structure of Quinoline. All ring atoms in quinoline are sp^2 hybridized. As in the case of pyridine, the nitrogen lone pair electrons reside in an sp^2 orbital, and are not involved in the formation of the delocalized π molecular orbital. It shows aromatic properties because its π orbital contains *ten* electrons and satisfies the Huckel's rule ($n = 2$ in $4n + 2$). Quinoline is considered to be the hybrid of the following resonance forms.

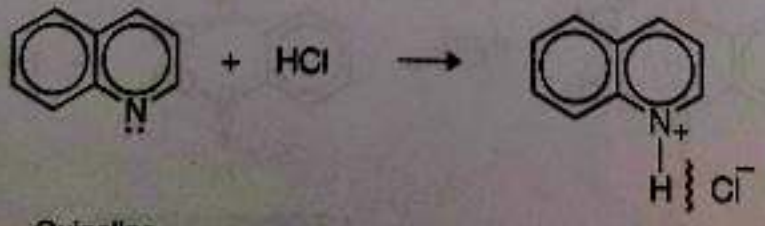


The first three structures are similar to the Kekule structures written for naphthalene. The last four, which are polar structures, show the effect of the electron-attracting nitrogen atom on the molecule.

Properties (Physical). Quinoline is a colorless liquid, bp 237°C. It turns yellow on standing, and has pyridine-like smell. Quinoline is miscible with most organic solvents, and dissolves in water to about 0-7 per cent at room temperature.

(Chemical). The main chemical properties of quinoline are described below :

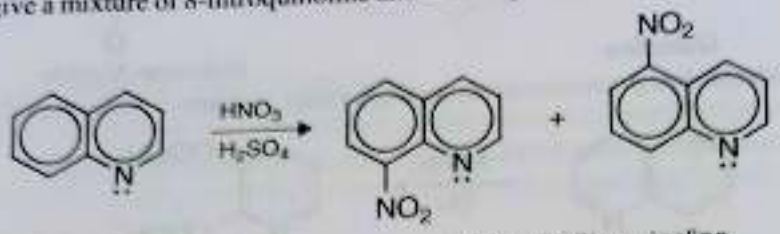
(1) **Basic Character.** Quinoline is a slightly weaker base ($pK_a = 4.94$) than pyridine ($pK_a = 5.2$). It reacts with acids to yield salts which are sparingly soluble in water.



Quinoline Quinolinium chloride

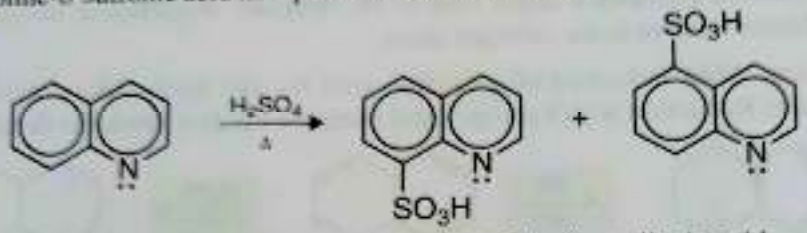
(2) **Electrophilic Substitutions.** Quinoline undergoes electrophilic substitution reactions only under vigorous conditions, as was the case with pyridine. Substitution occurs at C-8 and C-5.

(*a*) **Nitration.** Quinoline undergoes nitration with fuming nitric acid in the presence of fuming sulfuric acid to give a mixture of 8-nitroquinoline and 5-nitroquinoline.



Quinoline 8- and 5-Nitroquinoline

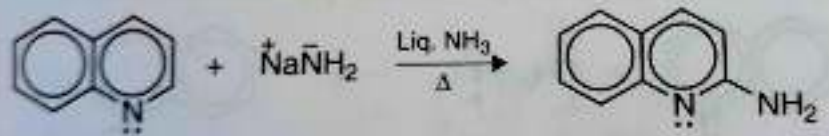
(*b*) **Sulfonation.** Quinoline may be sulfonated with fuming sulfuric acid at 220°C to yield a mixture of quinoline-8-sulfonic acid and quinoline-5-sulfonic acid.



Quinoline 8- and 5-Quinolinesulfonic acid

(3) **Nucleophilic Substitutions.** Like pyridine, quinoline undergoes nucleophilic substitution reactions. Substitution occurs at C-2 (or at C-4 if C-2 is blocked).

(*a*) **Reaction with Sodamide.** Quinoline reacts with sodamide in liquid ammonia at about 100°C to form 2-aminoquinoline.

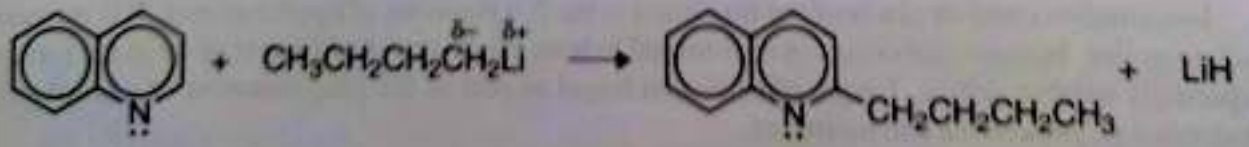


Quinoline 2-Aminoquinoline

(*b*) **Reaction with Potassium Hydroxide.** Quinoline reacts with potassium hydroxide at 220°C to give 2-hydroxyquinoline.

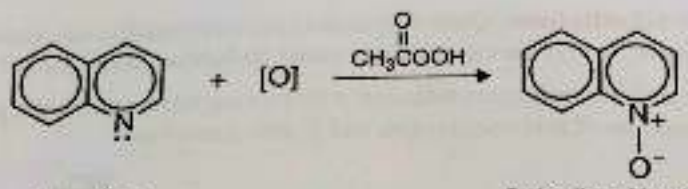
Quinoline 2-Hydroxyquinoline

(*c*) **Reaction with *n*-Butyllithium.** Quinoline reacts with *n*-butyllithium to yield 2-*n*-butylquinoline.



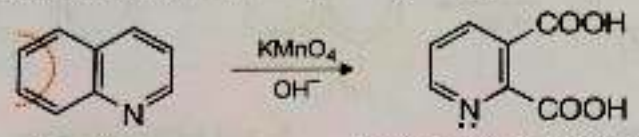
Quinoline 2-*n*-Butylquinoline

(4) **Oxidation.** Quinoline is oxidized by peracetic acid to give quinoline-*N*-oxide.



Quinoline — Quinoline-*N*-oxide

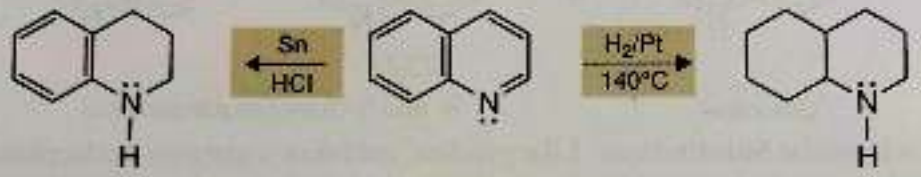
Oxidation with alkaline potassium permanganate yields pyridine-2,3-dicarboxylic acid.



Quinoline — Pyridine-2,3-dicarboxylic acid (Quinolinic acid)

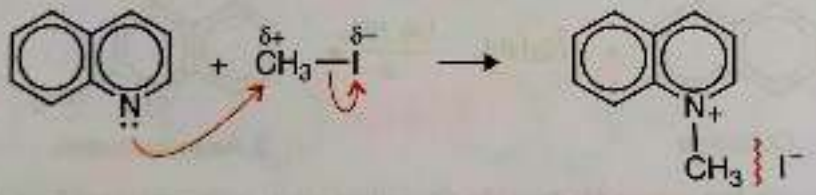
The above reaction provides a major clue to the structure of quinoline because it shows the position of ring fusion relative to the nitrogen atom.

(5) **Reduction.** Mild reduction of quinoline with tin and hydrochloric acid gives 1,2,3,4-tetrahydroquinoline. Reduction with hydrogen and platinum catalyst produces decahydroquinoline.



1,2,3,4-Tetrahydroquinoline — Quinoline — Decahydroquinoline

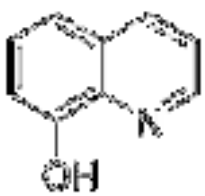
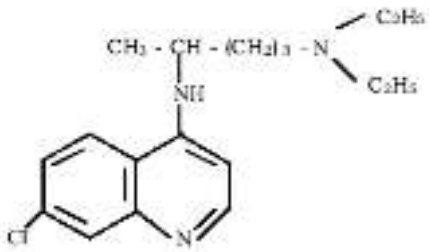
(6) **Reaction with Alkyl Halides.** Quinoline reacts with alkyl halides to give *N*-alkylquinolinium halides. For example, with methyl iodide it yields *N*-methylquinolinium iodide.



Quinoline — N-Methylquinolium iodide (1-Methylquinolium iodide)

Uses. Quinoline is used : (1) in organic synthesis as a high-boiling basic solvent, whereby it not only exerts a catalytic action but also can combine with acids produced in reactions; (2) in the manufacture of pharmaceuticals, dyes and insecticides.

Medicinal Compounds with Quinoline nucleus

 **8-Hydroxyquinoline** **Use: Topical antiseptic**	 **Chloroquine** **Use: Antimalarial**

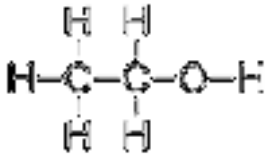
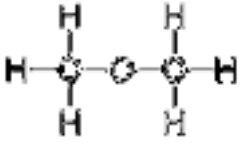
ISOMERISM

The chemical compounds which have similar chemical formula (Molecular formula) but differ in their physical and chemical properties due the differences in the arrangement of atoms i.e. difference in bond connectivity's in their molecules are called **ISOMERS**. The phenomenon exhibited by isomers is called **Isomerism**.

The word "isomer" is derived from the Greek words "isos" and "meros", which mean "equal parts".

Example

Ethanol and **Dimethyl ether** have similar molecular formula **C_2H_6O,** but due to difference in arrangement of atoms in molecule, they differ in their functional groups and thus differ in their properties. Ethanol with OH functional group belongs to alcohols and dimethyl ether with alkoxy functional group belongs to ether class. So, these are Isomers

Ethnaol	**Dimethyl ether**
Molecular formula **C_2H_6O**	Molecular formula **C_2H_6O**
Structural formula	**Structural formula**
	
Functional group: **–OH** (hydroxyl)	Functional group: -**OCH_3 (**alkoxy)
Belongs to **Alcohols** class	Belongs to **Ethers** class

Classification of Isomerism

The isomerism exhibited by different isomers is broadly classified into

I. **Structural Isomerism/** constitutional isomerism
II. **Stereo isomerism**

I. Structural Isomerism

Structural Isomers have similar molecular formula, but differ in their structural formula due to difference in bond connectivity's of different atoms or groups in the molecule. The phenomenon exhibited by structural isomers in known as structural isomerism.
Structural isomerism also known as constitutional isomerism.
Structural Isomerism is further categorized as

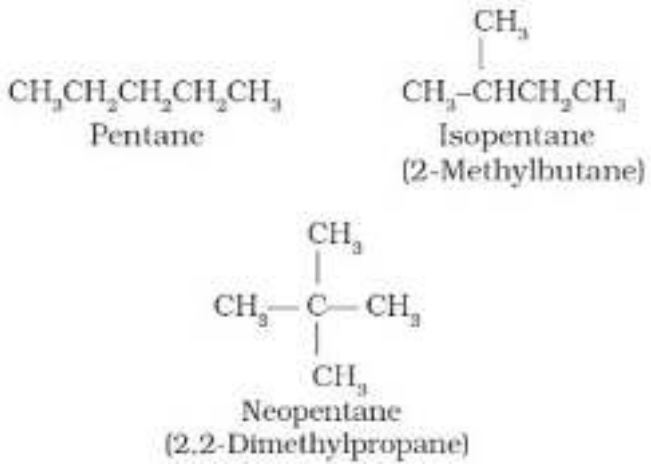
1. Chain isomerism
2. Positional isomerism
3. Functional isomerism
4. Metamerism

5. Tautomerism
6. Ring-chain isomerism

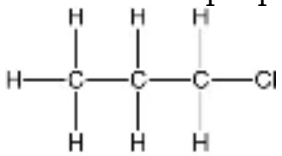
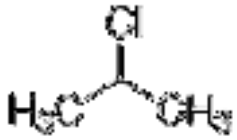
1. **Chain isomerism**: It is also known as skeletal isomerism. It is characterized by the structural isomers which have similar molecular formula but differ in their structural formula due to the difference in the arrangement of carbon atoms in forming carbon chains of the compound.

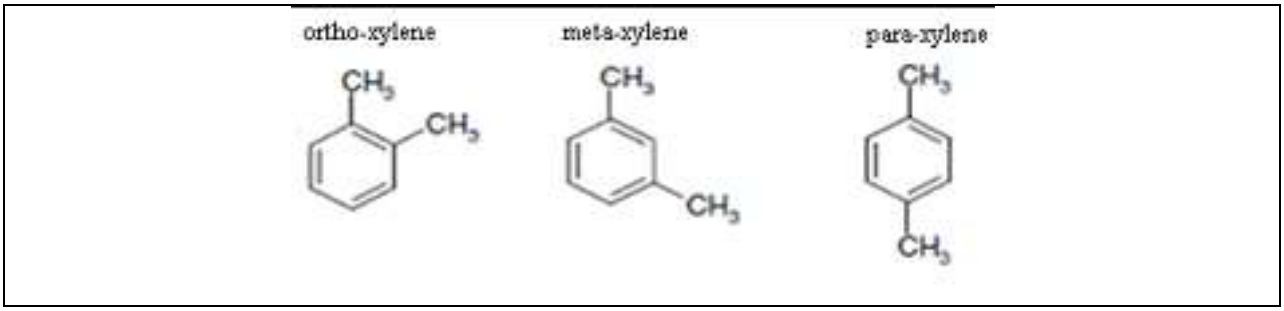
   Ex. **n-pentane, isopentane** and **neopentane** have similar molecular formula **C_5H_{12}**, but they differ in the arrangement of the Five carbon atoms in their structural formula

   In **n-penatane** the five carbons join to form a **linear straight chain**. But in **iso** and **neo pentane** the carbon 5 carbon atoms join to form **branched chains**.

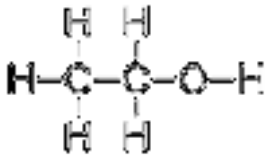
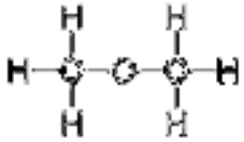
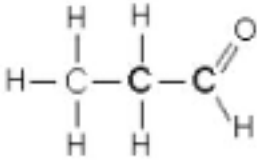


2. **Positional Isomerism**: The positional isomers are structural isomers which have similar molecular formula but differ in their structural formula due to **difference in the position** of a functional group or substituent in the hydrocarbon.
   Examples

1-chloropropane	2-chloropropane
 1-chloropropane and	



3. **Functional Isomerism:**
Functional isomers are structural isomers which have similar molecular formula, but posses' different functional groups due to difference in the connectivity or arrangement of atoms in the molecule.
Examples

Functional isomers	
Ethnaol Molecular formula **C_2H_6O** **Structural formula**  Functional group: **–OH (hydroxyl)** Class**: Alcohols**	**Dimethyl ether** Molecular formula **C_2H_6O** **Structural formula**  Functional group -**OCH_3 (alkoxy)** Class: **Ethers**
Propanal Molecular formula **C_3H_6O** Structural formula  Functional group: -CHO (aldehyde)	**Propanone/Acetone** Molecular formula **C_3H_6O** Structural formula  Functional group**: CO (ketone)**

4. **Metamerism**: This type of isomerism arises due to the presence of different alkyl chains on each side of the functional group. It is a rare type of isomerism and is generally limited to molecules that contain a divalent atom (such as sulfur or oxygen), surrounded by alkyl groups.

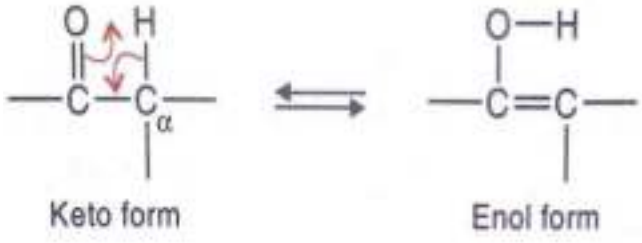
Metamers are structural isomers which have similar molecular formula, but differ in the structural formula due difference in distribution of carbon chains on divalent atoms such as sulfur or oxygen.

Ex. The isomeric ethers such as **diethyl ether** and **methyl propyl ether** have similar molecular formula, but, due to difference in the distribution of alkyl chains on either side of oxygen they differ in their structures and thus are called metamers.

Metamers	
diethyl ether Molecular formula **$C_4H_{10}O$** **Structural formula** 	**methyl propyl ether** Molecular formula **$C_4H_{10}O$** **Structural formula** 

5. **Tautomerism**: Tautomerism is the phenomenon exhibited by **tautomers.** Tautomers are the structural isomers which have similar molecular formula, but contain different inter convertible functional groups due to intra molecular migration of proton, thus the tautomers exist in dynamic equilibrium.

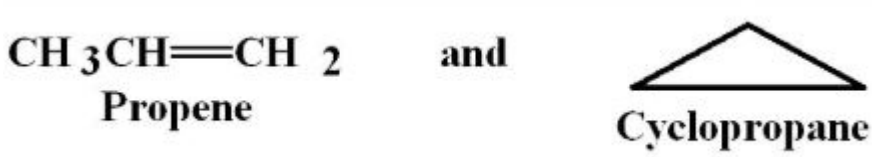
   Ex. Keto-enol tautomerism: Aldehydes, ketones undergo this type of tautomerism, it involves the migration of a proton from α carbon to the carbonyl oxygen



Examples

6. Ring-Chain Isomerism

- In ring-chain isomerism, one of the isomers has an open-chain structure whereas the other has a ring structure.
- They generally contain a different number of pi bonds.
- example of this type of isomerism can be observed in C_3H_6. Propene and cyclopropane are the resulting isomers, as illustrated below.



II. Stereoisomerism

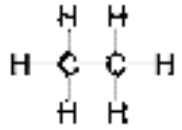
This kind of isomerism is exhibited by **stereo isomers**. Different stereo isomers of a compound have similar molecular formula, similar structural formula but differ in their properties due to **difference in the spatial arrangement of atoms** in their structure.

The stereoisomerism related to spatial arrangement of atoms in molecules is categorized in to

1. Conformational isomerism/ Rotational isomerism
2. Configurational Isomerism -This is further categorized as
    a. Optical isomerism
    b. Geometrical isomerism

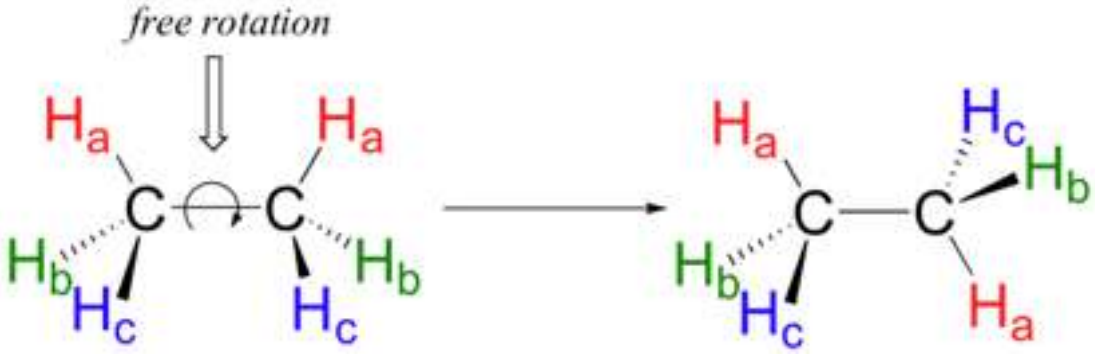
1. **Conformational isomerism or Rotational Isomerism** is characterized by the compounds that have similar molecular formula, similar structural formula but differ in the spatial arrangement of atom or groups on carbon atoms due to free rotation around C-C single bond. So, such stereoisomers are interconvertible by rotation around C-C single bond.
   This kind of isomerism is observed in saturated hydrocarbons such as alkanes and cycloalkanes in which free rotation is possible around C-C single bonds.

   Ex. Ethane
   Molecular formula C_2H_6,
   Structural formula

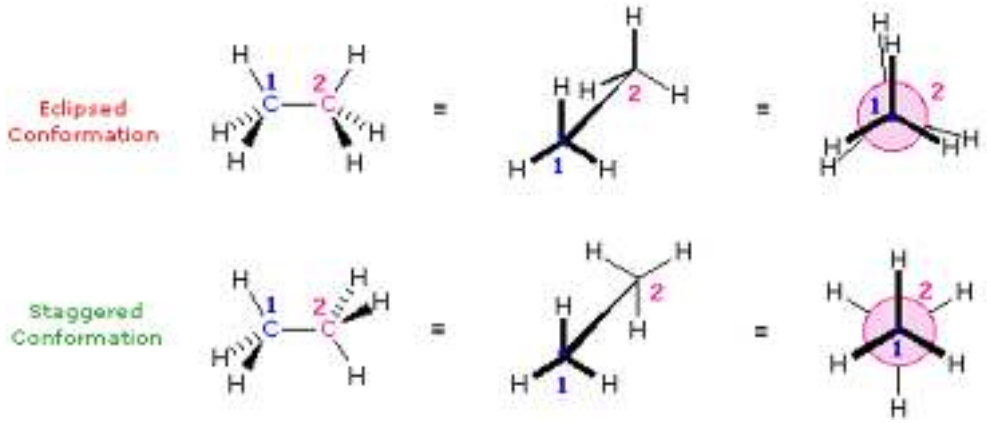


Three-dimensional structure of ethane (Stereoisomeric structures)

In ethane as the carbons are joined by single bond free rotation is possible around this bond and this can result in various spatial arrangement of hydrogen atoms bonded to carbons.



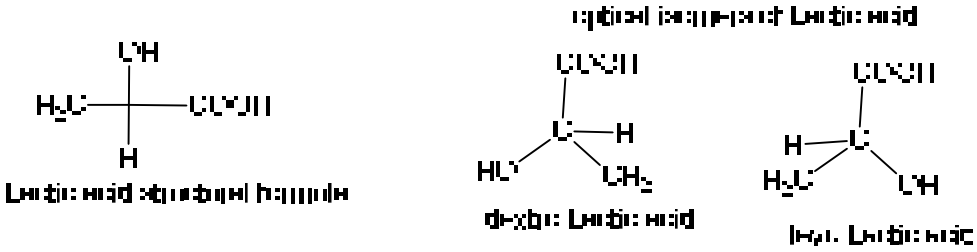
In ethane two conformers are possible i.e Staggered and Eclipsed.



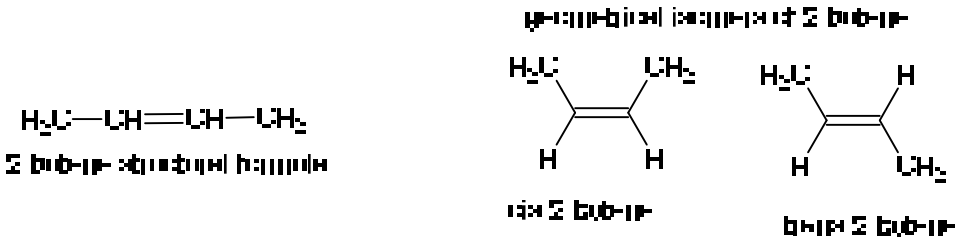
2. **Configurational Isomerism**: In this stereoisomerism the isomers differ in the spatial arrangement of atoms i.e. configurationa and cannot be interconverted by rotation around bonds. Bonds are broken and new bonds are formed in conversion of one isomer to other.
   This is further classified as.
   a. Optical isomerism
   b. Geometrical isomerism

   a. **Optical Iosmerism** : Optical isomers of a compound are optically active and have similar molecular formula, similar structural formula but differ in the spatial arrangement of atoms or groups i.e configuration and because of their molecular asymmetry these compounds differ in their optically active i.e. ability to rotate the plane of plane polarized light.
   One isomer which rotate plane of plane polarized light to right-side is called dextrorotatory and its optical isomer which rotate the plane of plane polarized light to left side is called levorotatory.
   This phenomenon exhibited by optical isomers is called optical isomerism
   Ex. Lactic acid exists in two optically active isomeric forms.

   Dextro rotatory and levorotatory lactic acid



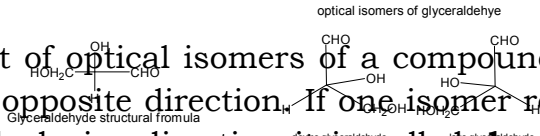
b. **Geometrical isomerism:** Geometrical isomers have similar molecular formula, similar structural formula but differ in the spatial arrangement of atoms i.e. configuration due to restricted rotation around a C-C double bond or ring carbons. Thus geometrical isomerism is observed in unsaturated compounds such as alkenes, oximes or cyclic structures such as cycloalkanes.



OPTICAL ISOMERISM

Optical isomerism is a stereoisomerism exhibited by optical isomers. Optical isomers are stereoisomers of a compound which have similar molecular formula, similar structural formula, but due to difference in spatial arrangement of atoms i.e. Configuration they **differ in their optical activity.**

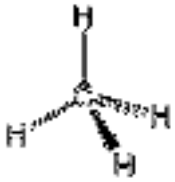
Optical activity refers to the ability of a compound to rotate the plane of plane polarized light.



A set of optical isomers of a compound may rotate plane of plane polarized light by equal and opposite direction. If one isomer rotates the plane of plane polarized light to right side or clockwise direction it is called **dextrorotary isomer** and the mirror image of it which differ in the spatial arrange of atom rotate the plane of plane polarized to left or anticlockwise direction and it is called **levorotatory isomer**.

Ex. Glyceraldehyde can exist in two different optically active isomeric forms which differ in spatial arrangement of atoms and thus differ in their optical activity.

The optical isomerism of carbon compounds can be justified by considering the three-dimensional tetrahedral spatial arrangement of atoms or groups in saturated sp3 hybridized carbon atom. The carbon atom lies at the Centre and the four valency groups at four corners of a tetrahedron.



Example: ***2-hydroxypropanoic acid (***Lactic acid) exists in two optically active stereo isomeric forms which have similar molecular and structural formula but differ in the spatial arrangement of groups on the central tetrahedral carbon, due to the difference in their spatial arrangement of atoms they differ in their optical activity one isomer is dextrorotatory and its mirror image is levorotatory.

Dextro rotatory lactic acid is obtained from meat extract and is known as **sarcolactic acid**.

Leavo rotatory lactic acid may be obtained by the fermentation of sucrose by Bacillus Acidi laevolactiti.

Ordinary lactic acid in sour milk or manufactured by fermentation or by synthetic method is racemic mixture.

The optical activity of optical isomers is indicated by the symbol **d** or (+) if it is a dextrorotatory isomer and its levorotatory isomer is indicated by **l** or (-).

Thus, lactic acid exists as

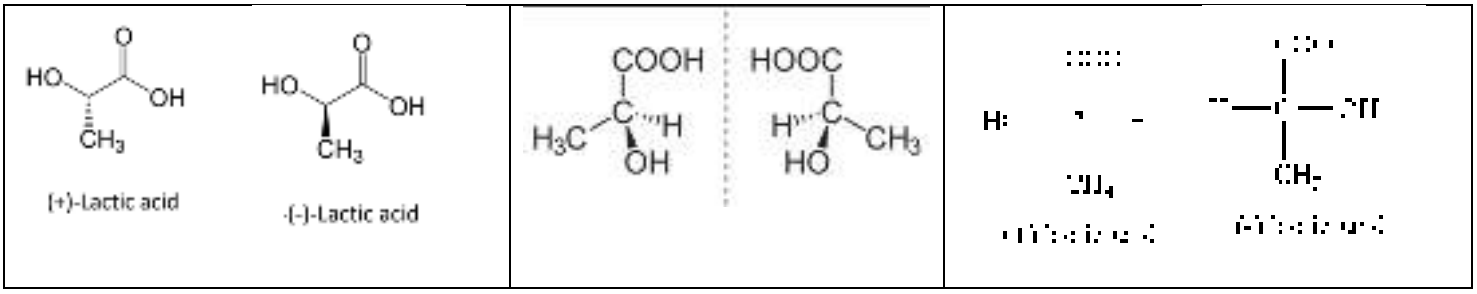
dextrorotatory lactic acid i.e. (+)lactic acid or ***d*** lactic acid

Levorotary lactic acid i.e. (-)lactic acid or ***l*** lactic acid and the third form of lactic acid which contain equal amounts of dextro and levorotatory lactic acid is optically inactive and it is called racemic mixture ***dl*** lactic acid

Molecular formula of Lactic acid $C_3H_6O_3$

Condensed structural formula of lactic acid $CH_3CHOHCO_2H$

Three-dimensional structure of lactic acid leading to optical isomers i.e dextro and levo rotatory lactic acids.



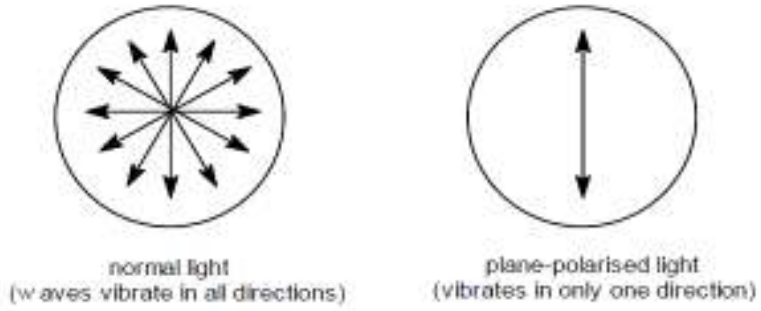
Plane polarized light and OPTICAL ACTIVITY.

The isomers which have the tendency to rotate the plane of plane polarized light are said to be optically active and phenomenon is called optical activity.

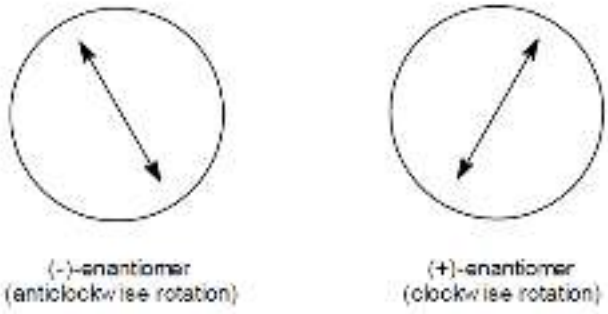
A beam of ordinary light consists of electromagnetic waves that oscillate in an infinite number of planes at right angles to the direction of light travel.

When a beam of ordinary light is passed through a device called a polarizer, or a Nicol prism (made of calcite or CaCO3), the light emerging from the polarizer vibrate in only one plane and is said to be **plane-polarized Light** waves in all other planes are blocked out.

The wave vibrations are perpendicular to the direction of travel of the wave.



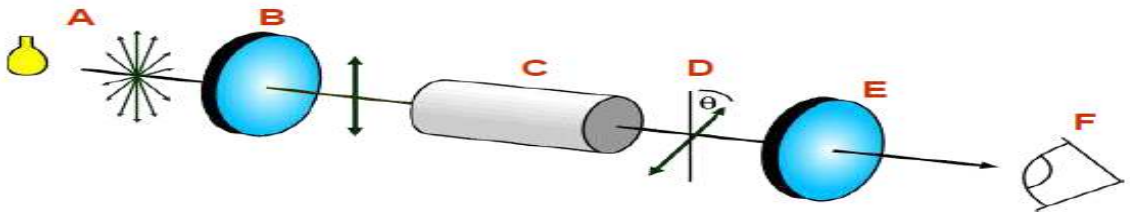
When a beam of plane polarized light passes through a solution of certain organic molecules, such as sugar or camphor, the plane of polarization is rotated through an angle α, and such compound are said to be optically active. Optically active compounds have the ability to rotate plane of plane polarized light to either right (clockwise) or left (anticlockwise)direction.



The angle of rotation can be measured with an instrument called a polarimeter. When a solution of known concentration of an optically active material is placed in the polarimeter, the beam of light is rotated either to the right (clockwise) or to the left (anti-clockwise). So the compounds which rotate the plane polarized light (PPL) to the right (clockwise) is said to be Dextrorotatory, and those which rotate the PPL to the left is said to be Levorotatory. Dextrorotatory is indicated by + sign, while Levorotatory by a minus sign (–)

A **polarimeter** is an instrument that allows polarized light to travel through a sample tube containing an organic compound and permits measurement of the degree to which the light is rotated.

The construction of polarimeter



A Light source produces light vibrating in all directions
B Polarising filter only allows through light vibrating in one direction
C Plane polarised light passes through sample
D If substance is optically active it rotates the plane polarised light
E Analysing filter is turned so that light reaches a maximum
F Direction of rotation is measured coming towards the observer

With optically active compounds solution in sample tube the plane of the polarized light is rotated through an angle α. The angle α is measured in degrees (°) and is called the observed rotation.

Specific Rotation ($[\alpha]_D$) The extent of rotation depends on the number of optically active molecules encountered by the light beam. This number, in turn, depends on sample concentration and sample path length. If the concentration of sample is doubled, the observed rotation doubles. If the concentration is kept constant but the length of the sample tube is doubled, the observed rotation doubles. In addition, the angle of rotation depends on the wavelength of the light used.

To express optical rotations in a meaningful way so that comparisons can be made, we have to choose standard conditions. The **specific rotation**, **$[\alpha]_D$** , of a compound is defined as "the observed rotation when light of 589.6 nanometer (nm; 1 nm = 10^{-9} m) wavelength is used with a sample path length **l** of **1** decimeter (dm; 1 dm = 10 cm) and a sample concentration **c** of **1 g/cm^3**"

$$[\alpha]_D = \frac{\text{Observed rotation (degrees)}}{\text{Pathlength, } l \text{ (dm)} \times \text{ Concentration, } c \text{ (g/cm}^3\text{)}} = \frac{\alpha}{l \times c}$$

Specific rotation, $[\alpha]_D$, is a physical constant characteristic of a given optically active compound. For example, (+)-lactic acid has $[\alpha]_D$ = +3.82, and (—)-lactic acid has $[\alpha]_D$ = —3.82. That is, the two enantiomers rotate plane-polarized light to the same extent but in opposite directions.

CHIRALITY/ CHIRAL AND ACHIRAL MOLECULES (conditions for optical isomerism)

The minimum and necessary condition for an organic compound to be optically active is it should possess chirality, i.e handedness.

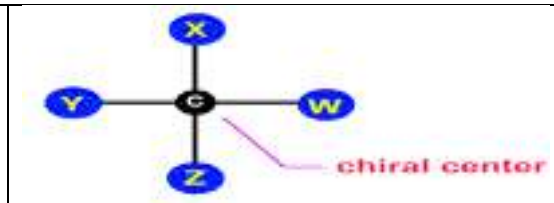
A molecule (or object) which is **not superimposable on its mirror image** is said to possess **chirality** and it **is a chiral molecule**. All chiral compounds are **optically active.**

Structures/molecules which are superimposable on their mirror images are said to be **ACHIRAL.** Achiral compounds are optically inactive**.**

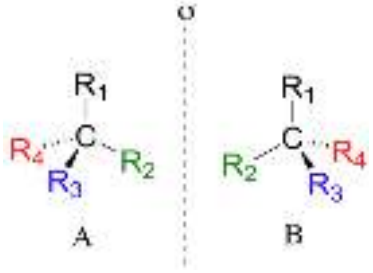
It is generally observed that majority of the chiral molecules possess **chiral center** or **Asymmetric Centre** or **asymmetric carbon.**

Asymmetric carbon: A carbon which is attached/bonded to **four different atoms** or groups is said to be asymmetric carbon.

So, a **C**abde type of molecule in which carbon is bonded to four different groups is asymmetric,

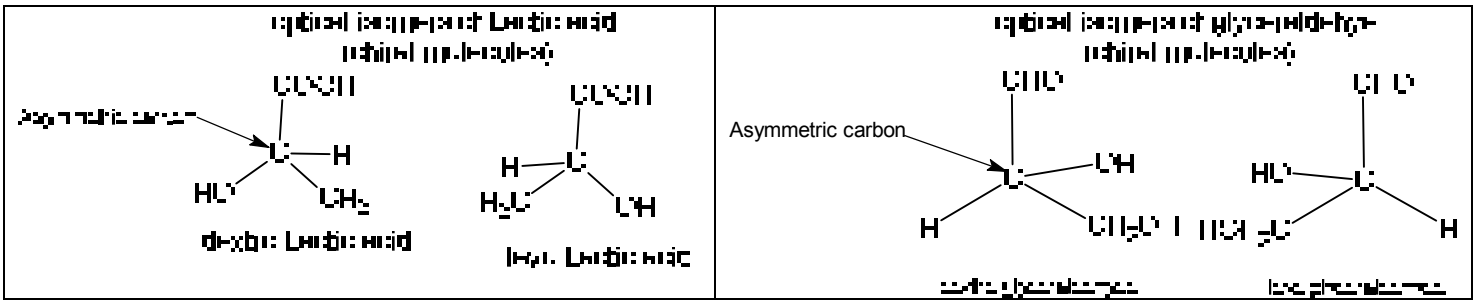


These asymmetric carbon compounds with three-dimensional tetrahedral spatial arrangement of groups are not superimposable on their mirror images, and thus are chiral and possess optical activity.



Ex. Bromochlorofluoroiodomethane in which carbon is bonded to four different atoms is asymmetric and the compound is chiral and exists in two optically active isomeric forms i.e. dextro and levo.

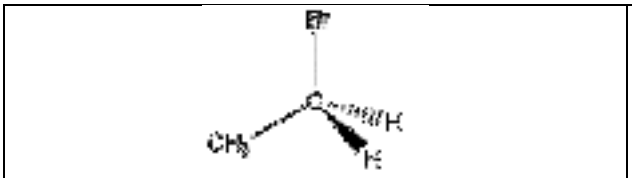
Similarly, Glyceraldehyde, lactic acid compound which contain asymmetric carbons and are not superimposable on their mirror images are chiral compounds and exists in two optically active isomeric forms.



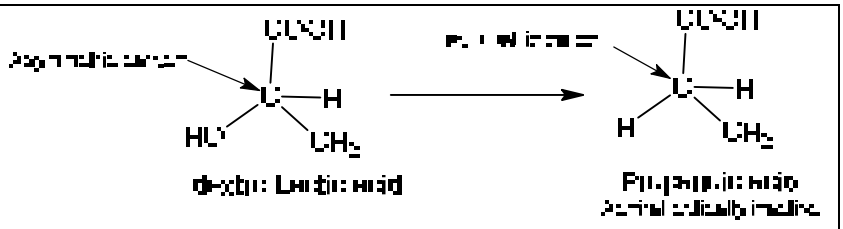
Symmetric carbon/ Achiral molecules: When asymmetric carbon groups are replaced by identical atoms or groups it is called symmetric carbon and it would be super imposable on its mirror image, thus it is achiral, optically inactive and it cannot exist in two isomeric forms. So, a Ca_2b_2 or Ca_2bd type of molecules are achiral and are optically inactive.

Ex. Bromoethane (Ca_2bd) molecule contain symmetric carbons and it is achiral as it would be superimposable on its mirror image and it is optically in active.

Similarly, when lactic acid is converted to propanoic acid it looses its chirality and propanoic acid is achiral and optically inactive.



Bromoethane
(achiral-optically inactive)



But the presence of asymmetric carbon is not a necessary condition for a compound to be chiral.

In general, all the organic compounds which contain one asymmetric carbon are chiral and optically active, exists in two isomeric forms.

Compounds with more than one asymmetric carbon may or may not be chiral.

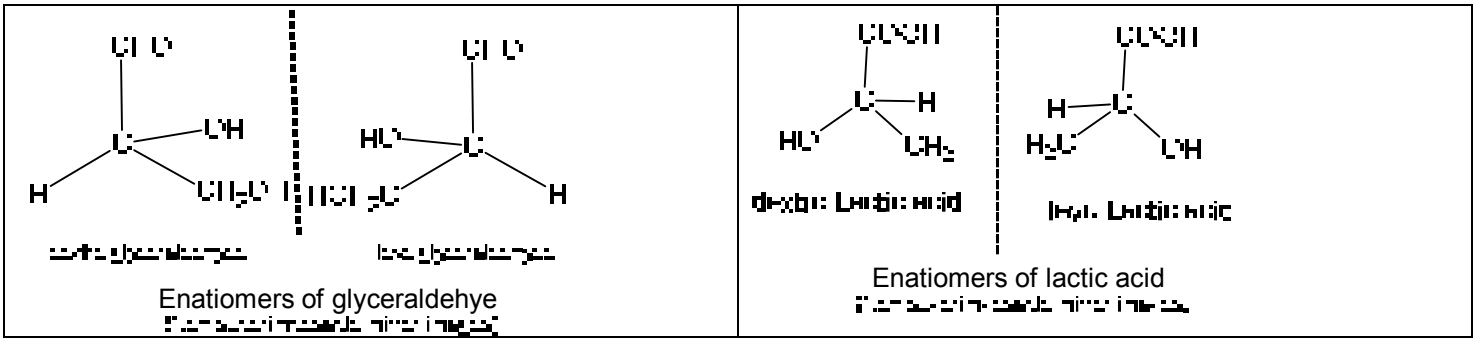
Certain organic compound doesn't contain asymmetric carbons in their structure but as a whole the molecule may be chiral and can exist in two optically active isomeric forms ex. Substituted allenes and Biphenyl compounds (Atropisomerism).

ENANTIOMERS

Enatiomers are a pair of optically active stereoisomers of a compound which are mirror images of each other and are non-superimposable, due to difference the spatial arrangement of atoms they differ in their optical activity and causes an equal and opposite rotation when they are separated from its enantiomer. So, one isomer is dextrorotatory an its enantiomeric mirror image is levorotatory.

All the carbon compound with one asymmetric carbon can exist as a pair of enantiomers with opposite optical activity.

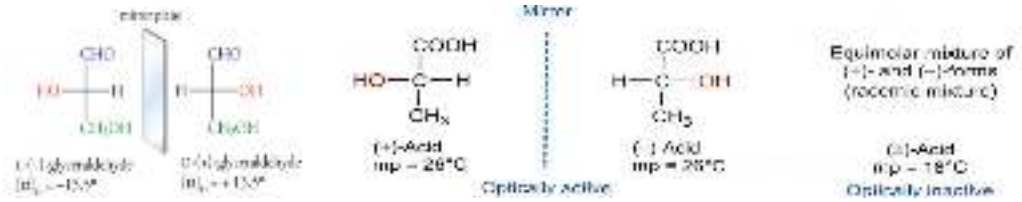
Ex. Glyceraldehyde and lactic acid with one asymmetric carbon in each can exist as a pair of enantiomers. The two optically active isomeric forms, which are mirror images of each other and or non-super imposable and possess equal and opposite optical activity.



Enatiomers of glyceraldehye

Enatiomers of lactic acid

Enantiomers of a compound have similar physical properties except the sign of optical activity.

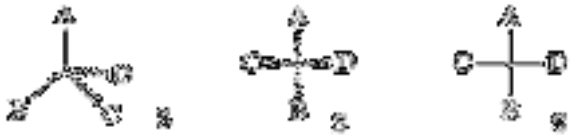


FISCHER PROJECTION OF CHIRAL MOLECULES (Planar representation of Chiral molecules)

It is not always convenient to draw three-dimensional formulas of molecules as the number of chiral center increases. Scientist developed a two dimensional projection formula called Fisher Projection formulas for carbohydrates and amino acids, which is nowadays being used to represent many chiral molecules.

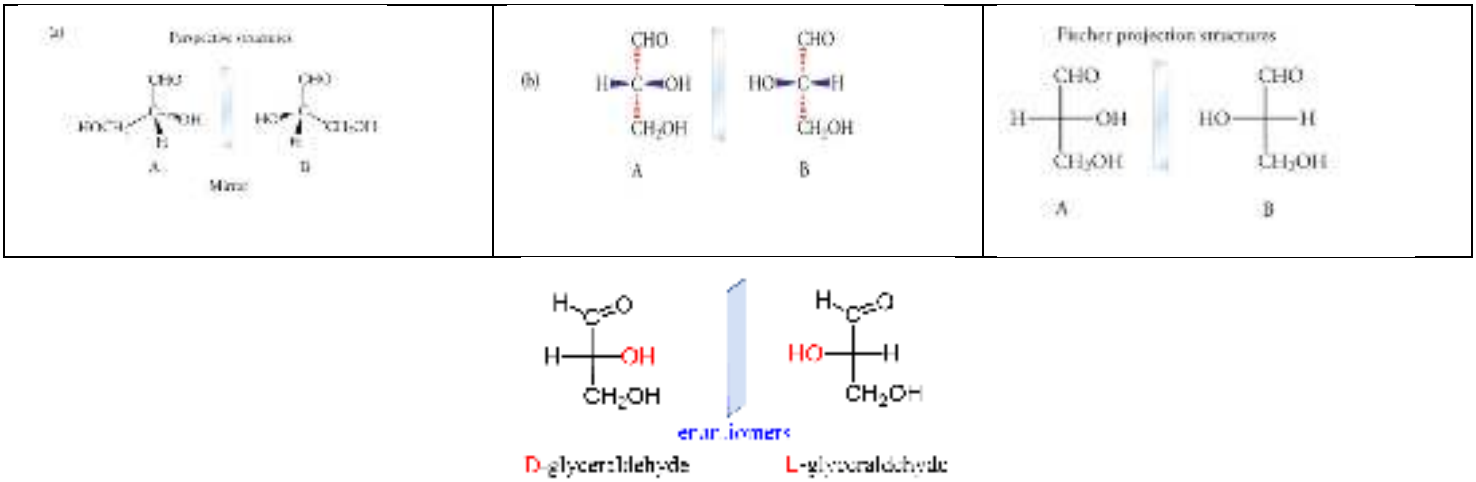
Fischer projection is a convenient 2-D drawing that represents a 3-D molecule.

To depict an asymmetric carbon two lines crossed at right angles to each other are drawn, the chiral or asymmetric carbon is believed to lie at the intersection of these lines. The four atoms or groups are then attached to the four ends of the two crossed lines.



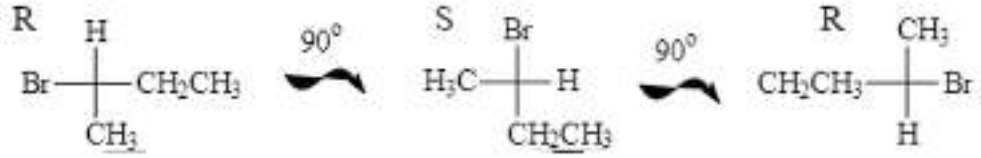
In such projections it is assumed that the horizontal lines represent bond coming toward the observer out of the plane of the paper, whereas the vertical lines represent bonds going away from the observer behind the plane of the paper.

Ex. Glyceraldehyde Fischer representation



As Fischer projections are two dimensional representations of a three-dimensional molecules certain guidelines are followed to test the superimposability of these representations.

1. The carbon chain of the compound is projected vertically, with the most oxidized carbon at the top or place the carbon number one at the top (as defined by nomenclature rule).
2. The enantiomeric pairs of a compound are not drawn randomly. One of the formulae is drawn first and the other is drawn only as its mirror image.
3. The projections can be rotated keeping the on the plane of the paper.
   Rotating Fischer projections may change the stereochemistry.
   i. 90 degree rotation interconvert enantiomers
   ii. 180 degree rotation retains enatiomer



iii. Switching substituents on fischer projections

a. Any single (odd#) exchange of 2 substituents gives the other enantiomer.

b. Any two (even #) of exchanges gives the same enantiomer.

4. To test the superimposability of mirror image of Fischer projections, the structures should not be folded on one other, they can be imagined to lift and placed one above the other or roatated 180^0 on plane of the paper

STEREOCHEMISTRY OF CARBON COMPOUNDS WITH TWO ASYMMETRIC CENTRES

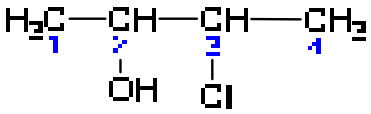
Or

DIASTEREOISOMERISM and DIASTEREOMERS

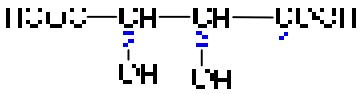
In compound with two asymmetric centers two types of compounds are possible.

1. **Compounds with dissimilar asymmetric centers**: The two asymmetric carbon atoms may be dissimilar when the atoms or groups attached to one asymmetric carbon center are different from those attached to the other.
2. **Compounds with similar asymmetric centers:** The two asymmetric carbon atoms may be similar when the different atoms or groups attached to the two asymmetric carbon atoms are identical.

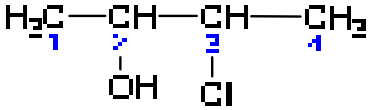
Ex. Compound with two dissimilar asymmetric centers. 3-chloro-2-butanol



Compound with two similar asymmetric centers: Tartaric acid

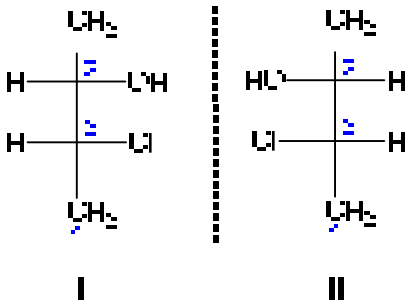


Stereochemistry of 3-chloro-2-butanol:



This compound contain two asymmetric carbons at C_2 and C_3, The two asymmetric center are dissimilar as C_2 asymmetric carbon is substituted by groups such as $-CH_3$, -OH, -H, and $-CH(Cl)CH_3$ and C3 asymmetric carbon is substituted by the groups such as $-CH_3$, Cl, -H, and $-CH(OH)CH_3$.

The various stereoisomers of this compound arising due to the spatial arrangement of groups on these two asymmetric carbon atoms can be represented by the following Fischer projection.

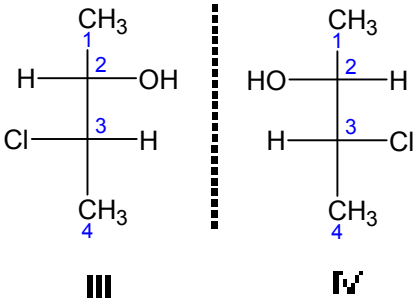


I II

Stereoisomers **I** and **II** are non-superimposable mirror images, thus they are a pair of **Eantiomers**

These isomers **I** and **II** which differ in the arrangement of groups on asymmetric centers are not interconvertible by simple rotation about C-C single bonds. They have independent existence. Moreover, **I** and **II** isomers are mirror images of each other and are not superimposable, and are optically active thus **I** and **II** are a pair of enantiomers.

We can draw another pair of isomers **III** and **IV** if we change arrangement of groups at only one asymmetric center in isomer **I** or **II**



III IV

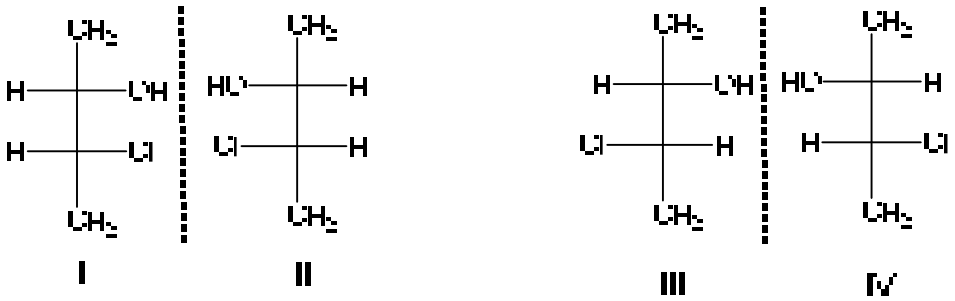
Stereoisomers **III** and **IV** are non-superimposable mirror images, thus they are a pair of **Eantiomers**

Isomers **III** and **IV** differ from I and II in arrangement of groups on asymmetric centers and are not interconvertible by rotation about C-C single bonds thus have independent existence. Isomer III and IV are nonsuperimposable mirror images thus they are a pair of enantiomers and are optically active.

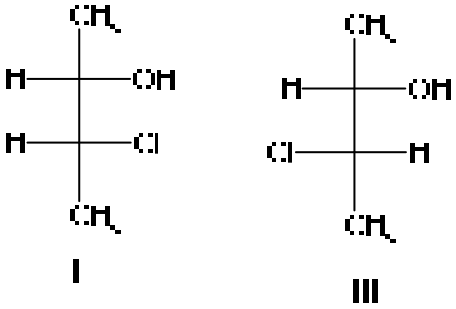
So, the compound with two dissimilar asymmetric carbon atoms can exist in **Four stereoisomeric forms** or **two pairs of enantiomers**.

In general, the compounds with ***n*** number asymmetric carbon atoms can exist in 2^n stereoisomeric forms.

In the above stereoisomers of 3-chloro-2-butanol I-II and III-IV are enantiomers as they are nonsuperimposable mirror images of each other.



If we compare the relationship of isomer **I** or **II** with **III** or **IV** they are neither mirror images of each other nor superimposable, such pair of stereo isomers of a compound are called **diastereoisomers**



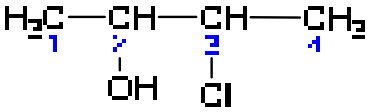
Stereoisomers **I** and **III** are neither mirror images of each other nor superimposable on one other, thus they are a pair of **Diastereomers**

Short notes on
Diastereoisomerism and Diastereomers

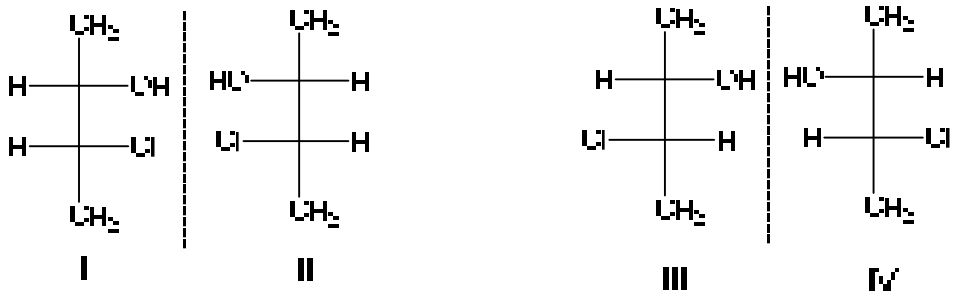
A pair of stereoisomers of a compound which are neither mirror images of each other nor superimposable on one other are called diastereomers.

Diastereoisomerism is possible in compounds containing more than one asymmetric center. In a poly asymmetric center compounds, the diastereomers may differ in configuration i.e. arrangement of groups at one or more asymmetric center.

Ex. 3-chlro-2-butanol

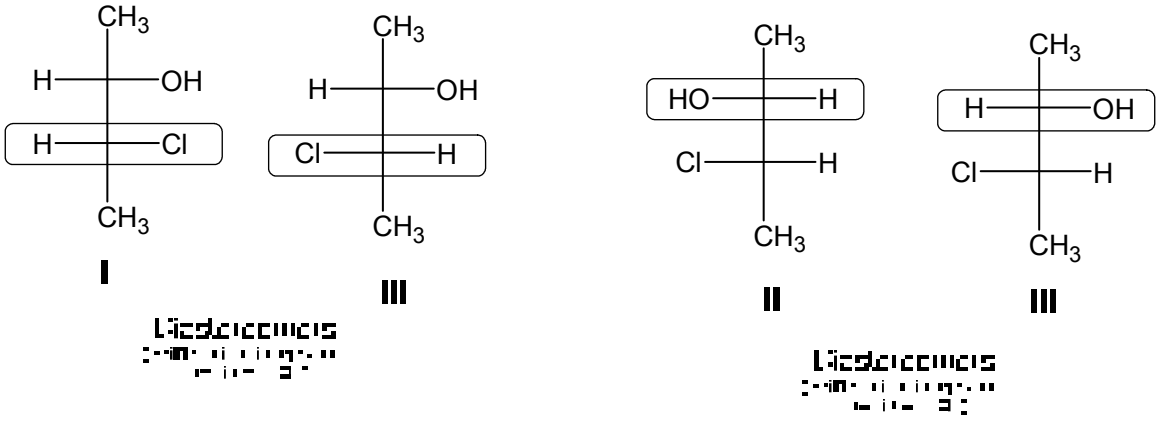


with two asymmetric centers can exist in four stereoisomeric forms,



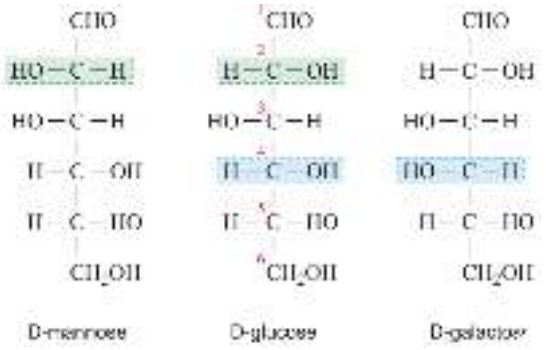
In the above isomers of 3-chloro-2-butanol I and II and III and IV are enantiomers as they are nonsuperimposable mirror images.

If we compare the relationship of isomer **I** or **II** with **III** or **IV** they are neither mirror images of each other nor superimposable, they have identical configuration i.e. Spatial arrangement of atoms at one asymmetric center, so, I-III/I-IV/II-III/II-IV are **diastereomers**



Similarly in carbohydrate chemistry different monosaccharide with poly asymmetric centers can exhibit diastereoisomerism.

Ex. D-Mannose and D-Glactose are diastereoisomers of D-Glucose



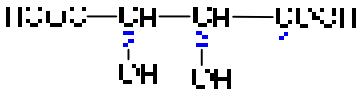
Stereochemistry of tartaric acid/ Short notes on MESO ISOMERS

Meso compounds are **optically inactive** stereoisomers of a compound which are superimposable on their mirror images **despite the presence of asymmetric centers**. Meso compounds contain **plane of symmetry** that cuts the molecule in to two equal halves thus one half is mirror image of other.

So, meso compounds are optically inactive due to **internal compensation**, i.e. due to the presence of mirror images with in the molecule rotation caused by one half of the molecule is cancelled by the equal and opposite rotation caused by the other half of the molecule.

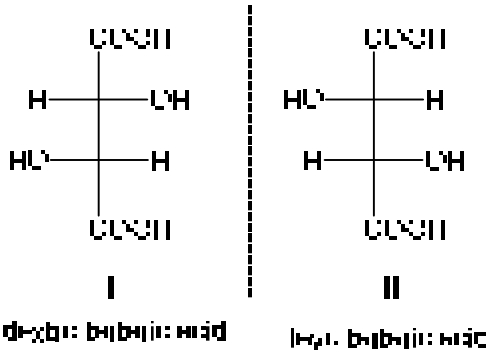
Meso isomers exist in compound which contain one two or more asymmetric carbons substituted by similar atoms or groups.

Tartaric acid (2,3-dihydroxysuccinic acid), with molecular formula $C_4H_6O_6$, is an organic compound that can be found in grape, bananas, and in wine,



The structural formula of tartaric acid indicates the presence of two asymmetric centers at C-2 and C3.Both these asymmetric centers contain similar substituents such as -COOH, OH, -H and -CH(OH)COOH

The various stereoisomers of this compound arising due to the spatial arrangement of groups on these two asymmetric carbon atoms can be represented by the following Fischer projection.



I

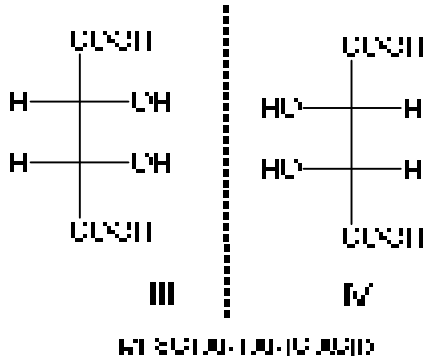
II

Stereoisomers **I** and **II** are non-superimposable mirror images, thus they are a pair of **Eantiomers**

These isomers **I** and **II** which differ in the arrangement of groups on asymmetric centers are not interconvertible by simple rotation about C-C single bonds. They have independent existence. Moreover, **I** and **II** isomers are mirror images of each other and are not superimposable and are optically active thus **I** and **II** are a pair of enantiomers.

I is dextro-tartaric acid and **II** is levo-tartaric acid

We can draw another pair of isomers **III** and **IV** if we change arrangement of groups at only one asymmetric center in isomer **I** or **II**

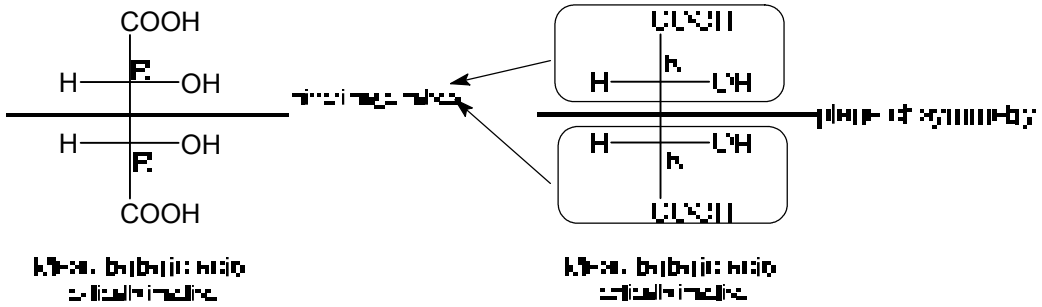


Stereoisomers III and IV are superimposable and, they are identical. So it is only one isomer, which is optically inactive known as **Meso tartaric acid.**

Isomer III and IV are mirror images but are superimposable when the structure is rotated through 180^0 on the plane of paper, thus structure IV has no independent existence and III and IV are identical it is only one isomer.

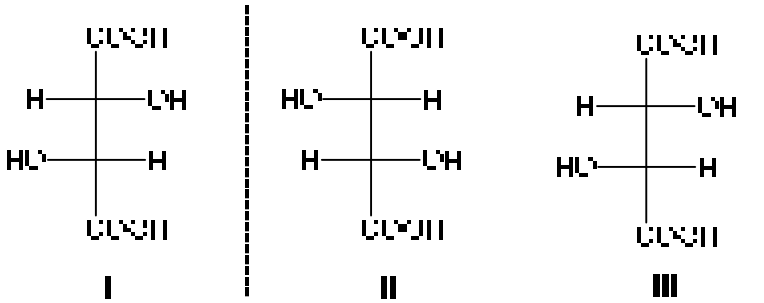
As isomer III is superimposable on its mirror image it is achiral **and optically inactive**, this optically inactive isomer of tartaric acid is known as **meso-tartaric acid.**

This meso-tartaric acid contains plane of symmetry, the imaginary plane that cuts the molecule in two equal halves, which are mirror images of each.



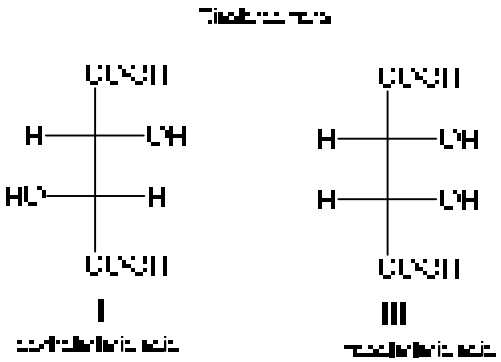
Meso compounds differ in physical properties compare to their optically active enatiomeric iosmers.

Enantiomers



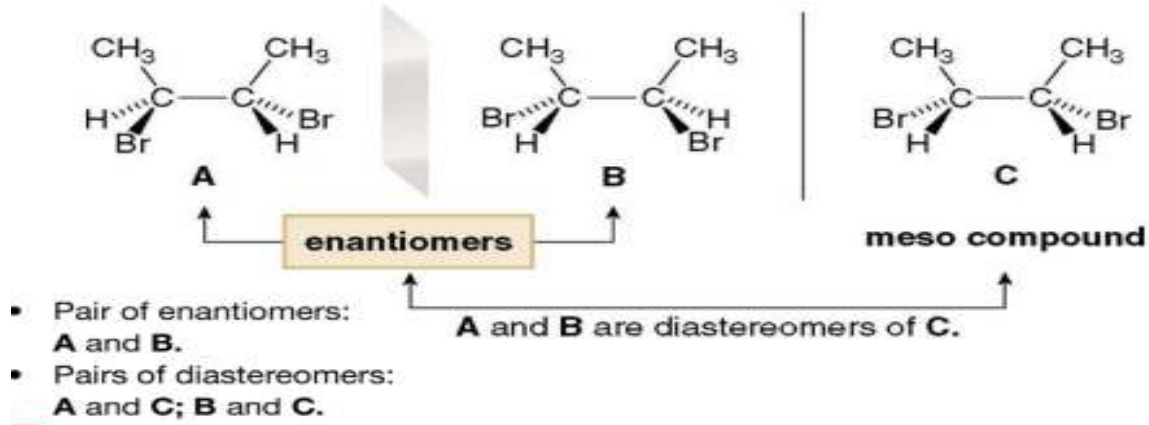
	I	II	III
	dextro tartaric acid	laevo tartaric acid	meso tartaric acid
melting point	170°	170°	146°
specific rotation	+11.1	-11.1	0

III is a diastereoisomer of I and II as they are neither mirror images nor superimposable on one other.



I	III
racemic acid	tartaric acid

Similarly, 2,3-dibromobutane with two asymmetric centers can exist in meso form



ELEMENTS OF SYMMETRY

Chiral molecules are not superimposable on their mirror images thus, they are optically active.

The presence or absence of chirality in different stereoisomeric structures of compounds can be ascertained by performing different symmetry operations.

Symmetry operations are spatial transformations (rotations, reflections, inversions). A molecule is said to possess a symmetry element if the molecule is unchanged in appearance after applying the symmetry operation corresponding to the symmetry element.

Elements of symmetry offer a simple device to decide whether a molecule is chiral or achiral, i.e., whether it is superimposable on its mirror image or not.

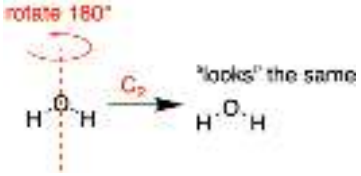
The different elements of symmetry that determine the chirality of a molecule are

1. Proper or simple Axis of Symmetry (Cn)
2. Plane of Symmetry (σ)
3. Centre of Symmetry (*i*)
4. Alternating Axis of symmetry (S_n)

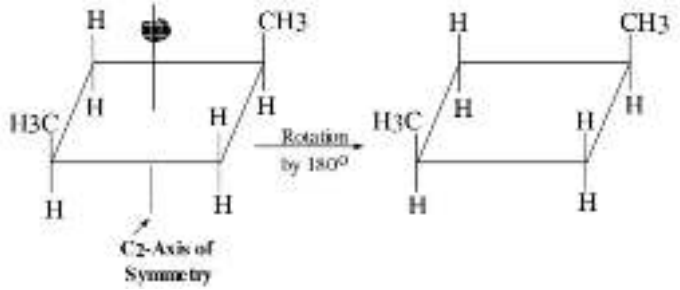
Any molecule or stereoisomer if contain any of these elements of symmetry is achiral and optically inactive.

When a molecule has no plane of symmetry, no centre of symmetry and no alternating axis of symmetry, it is non superimposable on its mirror image and is chiral (optically active).

1. **Simple or Proper axis of Symmetry** (C_n): Simple or n fold axis of symmetry of a molecule is an imaginary line (axis) passing through the molecule such that, if the molecule is rotated an angle of $360^0/n$ around this axis a structure indistinguishable from the original i.e an equivalent structure results. Such an axis is called n-fold axis of symmetry.
   In this symmetry operation performed is rotation.
   This can be applied to three dimensional molecules and planar structures.
   Ex. The H_2O molecule has a C_2 axis

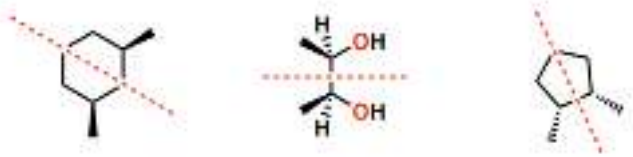


   Cis-1,3-dimethylcyclobutane has a two fold axis of symmetry (C_2) i.e rotation by 180^0 gives indistinguishable from the original form.

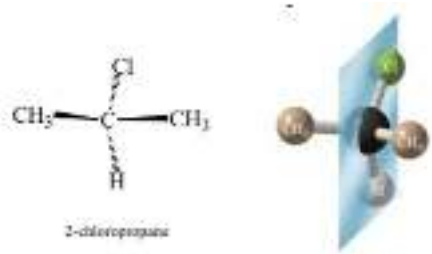


Some molecules have more than one Cn axis, in which case the one with the highest value of n is called the principal axis. Ex. Benzene has six C_2 axis and one C_6 axis. Note that by convention rotations are counter clockwise about the axis.

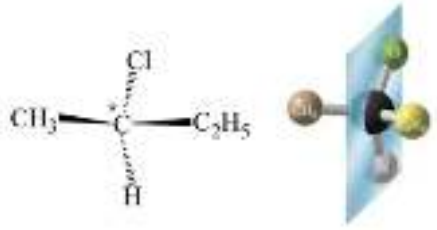
2. **Plane of symmetry** (σ): A plane of symmetry also called mirror plane is an imaginary plane which cuts the molecules into two equal parts, so that each part is the mirror image of the other.
   The compounds containing plane of symmetry are optically inactive.
   In this the symmetry operation performed is reflection
   This can be applied for both solid (tetrahedral) and plane Fischer formulae. i.e. plane of symmetry can cut through both atoms and bonds.



   In general, the carbon atom substituted by identical atoms i.e symmetric carbon possess plane of symmetry and are optically inactive.
   The compounds with one asymmetric carbon do not contain plane of symmetry and are optically active.
   Ex. 2-chloroporpane has plane of symmetry and is optically inactive.



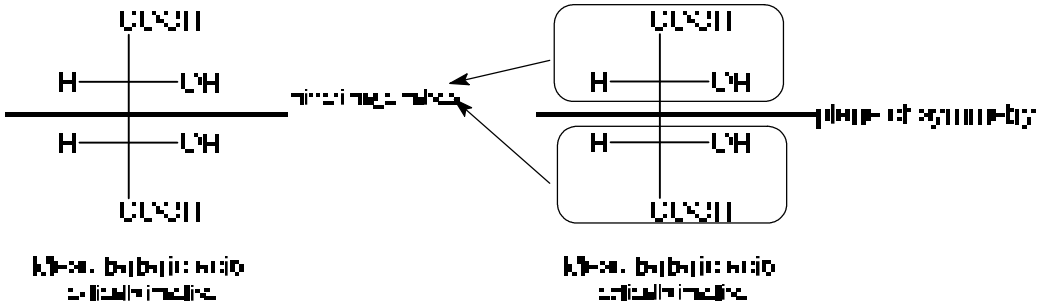
   But, 2-chlorobutane which has no plane of symmetry is optically active



But, compounds with more than one asymmetric centres may be optically inactive if they possess plane of symmetry.

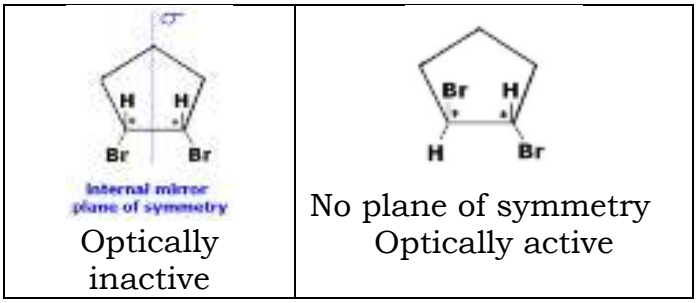
Ex. Meso tartaric acid

The structure of tartaric acid conatin two asymmertic centres it exhists in optically active dextro and levoroatory forms, but the third isomer i.e. **meso tartaric acid** is **optically inactive** as the structure possess **plane of symmetry**, the imaginary line which cuts the molecule in to two equal halfs, thus wih in the molecule each asymertic carbons is a mirror image of another.



So, the rotation caused by one half of the molecule is cancelled by the equal and opposite rotation caused by the other mirro image half of moecule. Thus meso compounds are optical inactive due to internal compensation of rotation/opticalactivity.

Similarly the **cis** isomer of 1,2-dibromocyclopenatane is optically inactive due to plane of symmerty in molecule, while the trans isomers are optically active.

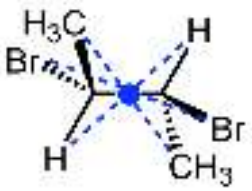


3. Center of Symmetry (*i*) A centre of symmetry is an imaginary point in the in molecule such that if a line is drawn from any group of the molecule to this point and then extended to an equal distance beyond the point, it meets the mirror image of the original group.

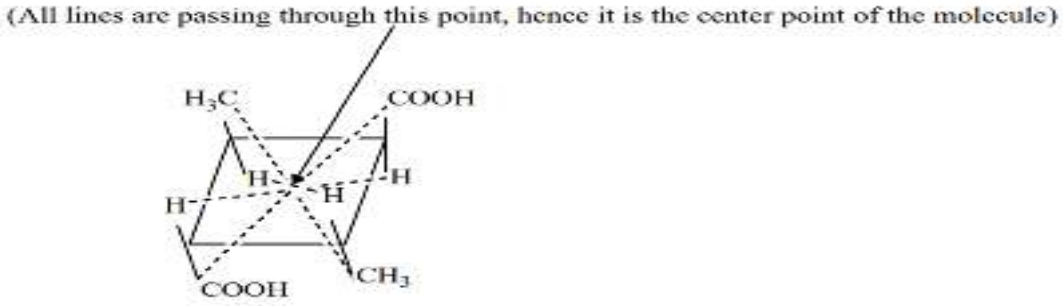
In this the symmetry operation performed is inversion.

This symmetry operation can be applied to 3-dimensional formula anr ring systems

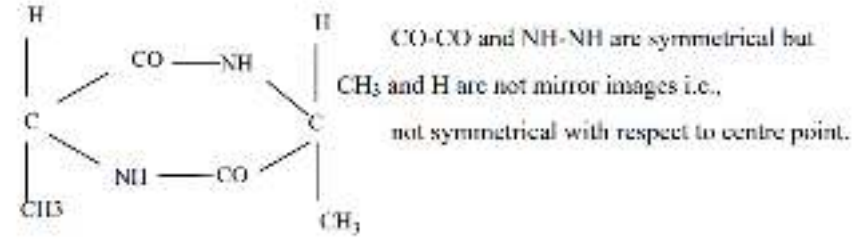
Ex. The following isomeric structure of 2,3-dibromobutane has center of symmetry and is optically inactive

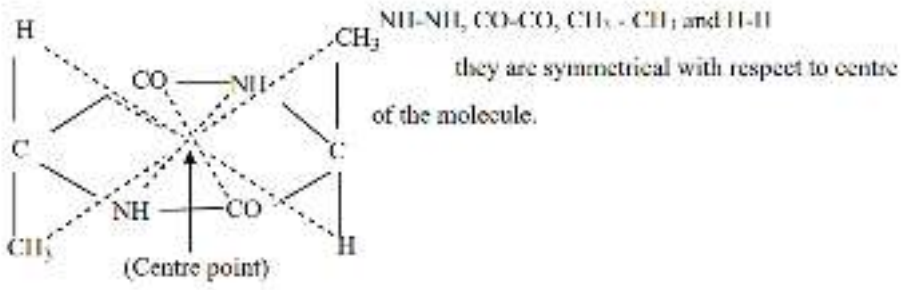


Similarly,the molecule of trans -2,4-dimethyl-cyclobutane –trans-1,3- dicarboxaylic acid has a center of symmetry. A centre of symmetry is equal to twofold alternating axis of symmetry.

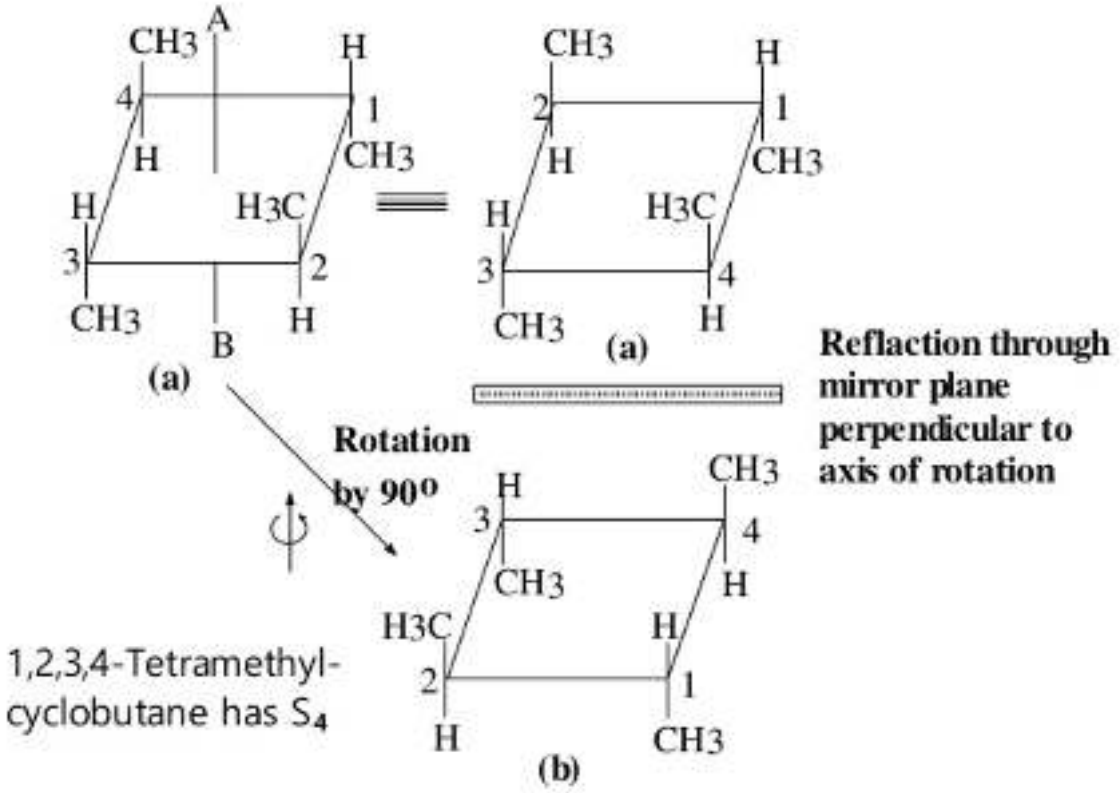


Another example is dimethyl ketopiperizine. This has two isomers, cis and trans. The cis form has no plane of symmetry or centre of symmetry. The trans form on other hand, has a centre of symmetry.





4. **Alternating axis of symmetry** (S_n): It is also known as Rotation-reflection axis of symmetry. It is an axis such that rotation of the molecule about the axis by $360^0/n$ followed by reflection in a plane perpendicular to this axis generates a such identical to the original one. Thus the molecule is optically inactive.
   Ex. Rotation of molecule **a** of 1,2,3,4-tetramethyl cyclobutene through 90^0 (360/4) about the **axis AB** which passes through the centre of the ring perpendicular to its plane gave **b** and reflection of b in the plane of the ring gave **a.** So, this molecule possess four fold alternating axis of symmetry and is optically inactive

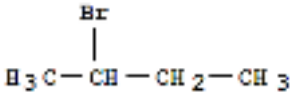


CONFIGURATION

The arrangement of atoms or groups that characterizes a particular stereoisomer is called Configuration.

Ex. The molecular formula of 2-Bromobutane is C_4H_9Br.

The structural formula is



In this structural formula C-2 carbon is asymmetric. So, 2-bromobutane exists as a pair of optically active enantiomers, dextro and levo isomers. The dextro and levo forms differ in spatial arrangement of atoms on asymmetric carbon.

The configuration of optical isomers is indicated by adopting two common conventions known as

1. **D** and **L** system (**relative configuration**)
2. **R** and **S** system (**Absolute configuration**)

1. **D** and **L** system (**relative configuration**): This is one of the oldest and the most commonly used system for assigning configuration to a given enantiomer. The system was developed by Fischer and Rosanoff.
Fischer first developed a method for drawing carbohydrates in two-dimensions, and a convention with respect to orientation, so as to indicate their three-dimensional structures called Fischer projections,

Fischer and Rosanoff then devised a notation for designating the configurations of stereogenic centers, depicted in Fischer projections, as either **D** or **L**.

This assignment of configuration of stereoisomers is relative configuration, because this was based on comparison of configuration with glyceraldehyde isomers.

Fischer has arbitrarily assigned the configuration to the two enantiomers of glyceraldehyde as **D** and **L**.

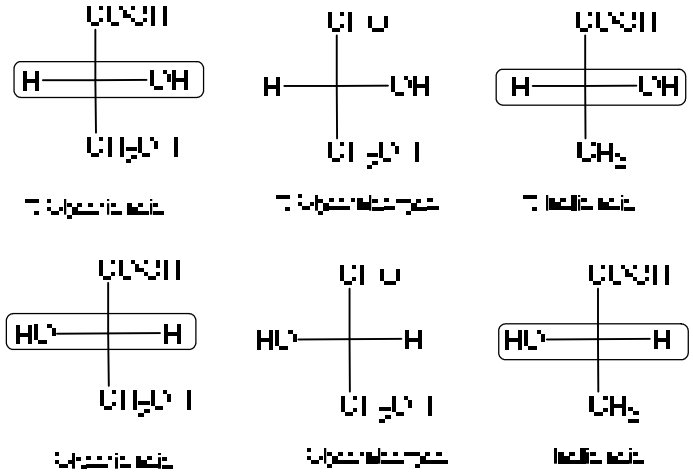
In this accepted convention in D glyceraldehyde in fischer projection the hydroxyl group at asymmetric centre is arranged to right side and

Its mirror image in which hydroxyl group is to the left side is called L isomer

The relative configurations of a large number of compounds were determined by correlating them with D or L-glyceraldehyde.

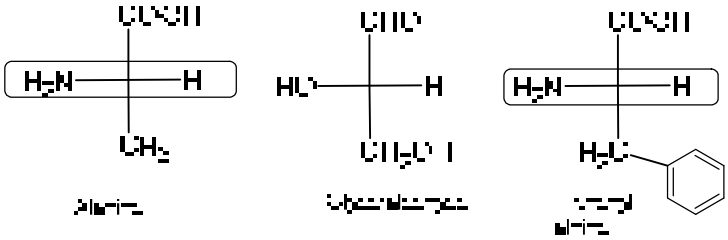
Thus, the stereoisomers were grouped as D-series and L-series.
D-Series: Any optical isomer which can be obtained or converted to D- glyceradehyde belongs to D-series, i.e., if the configuration at asymmetric carbon atom can be related to D-Glyceraldehyde.

L-Series: Any optical isomer which can be obtained or converted to L- glyceradehyde belongs to L-series, i.e., if the configuration at asymmetric carbon atom can be related to L-Glyceraldehyde



AMINO ACIDS: This relative configuration was also extended to amino acids, all naturally occurring α-aminoa cids have a configuration with NH2 group on asymmetric carbon is oriented to left side similar to L-glyceraldehyde belongs to L-series irrespective of their direction in which they rotate the plane polarized light.

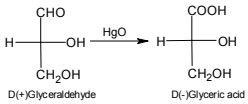
EX.



The symbols D and L have nothing to do with optical activity and sign of rotation of an optically active molecule which is designated (+)- (or d) and (-)- (or l).

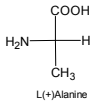
D and L indicate only configuration.

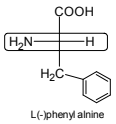
It was a co-incidence that D-glyceraldehyde happens to be dextrorotatory, thus it indicated as D(+) glyceraldehyde and its mirror image is L(-)glyceraldehyde.



As the optical activity is the property of different groups on asymmetric carbons, the stereoisomers of different compounds with similar configuration (D or L) may or may not have similar optical activity.

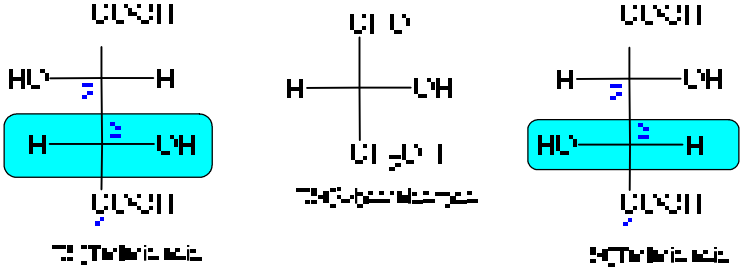
Ex. D-Glyceraldehyde is dextrorotatory, when it is oxidized with mercuric oxide it yielded D(-) glyceric acid. In this conversion there is a change in sign of rotation but not in configuration.

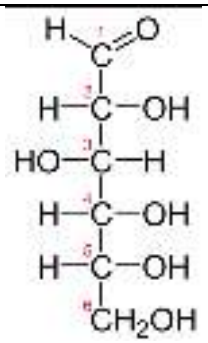




In isomers with more than one asymmetric centre's the configuration at highest asymmetric centre is compared with glyceraldehyde to assign the relative configuration.

Ex.Tartaric acid



 D(+)Glucose	

II. **R and S Configuration** (Absolute configuration):

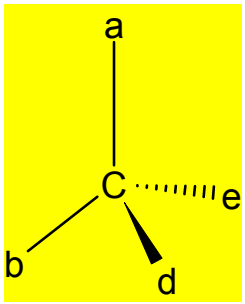
To overcome the problem of D-L system, R.S. Cahn (England), Sir Christopher Ingold (England), and V. Prelog (Zürich) evolved a new and unambiguous system for assigning absolute configuration to chiral molecules.

This system is named as CIP (Cahn, Ingold, Prelog) system after their names.
It is called as R-S system as the prefixes R-and S-are used to designate the configuration at a particular chirality centre. The letter (**R**) comes from the Latin rectus (means right) while (**S**) comes from the Latin sinister (means left).

Any Chiral carbon atoms have either an (R) configuration or a (S) configuration. Therefore, one enantiomer is (R) and the other is (S). A racemic mixture may be designated as (RS), meaning a mixture of the two.

The absolute configuration of stereoisomer is designated as R or S by a two step process involving:

Step-1
In order to specify configuration an asymmetric carbon of $\mathbf{C_{abde}}$ type in step 1 the groups **a, b, d** and **e** attached to the asymmetric carbon are first **assigned priorities** (1,2,3,4) following the **sequence rules** proposed by Cahn-Ingold-Prelog known as **CIP rules**

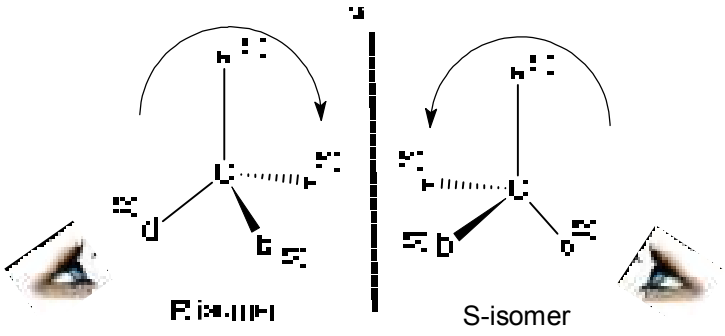


Assign a numerical priority to each group bonded to the asymmetric carbon:

group 1 = highest priority and group 4 = lowest priority

Groups **a** > b > d > e
Priority order (1) (2) (3) (4)

Step-2
After assigning priorities to groups attached tot asymmetric carbon, in step-2 the tetrahedral molecule is viewed, so oriented that the group of lowest priority is directed away from the observer and the arrangement of remaining groups is observed.
If in proceeding from the group of highest priority to the group of second and then to third if movement of eye travels in a clock wise direction (right hand direction) the configuration is termed as **R** and if movement of eye travel in anticlockwise direction the configuration is termed as **S**



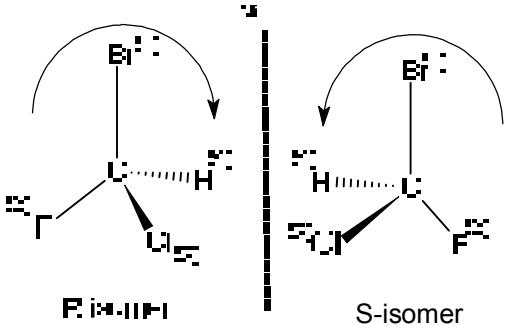
SEQUENCE RULES TO DETERMINE THE ORDER OF PRIORITY OF GROUPS ON ASYMMETRIC CARBON (CIP rules)

Rule 1: When four different atoms directly attached to the chiral carbon are different, priority depends on their atomic number. The atom having highest atomic number gets the highest priority, the group with next higher atomic number is given the next higher priority and so on. The atom with lowest atomic number is given lowest priority.

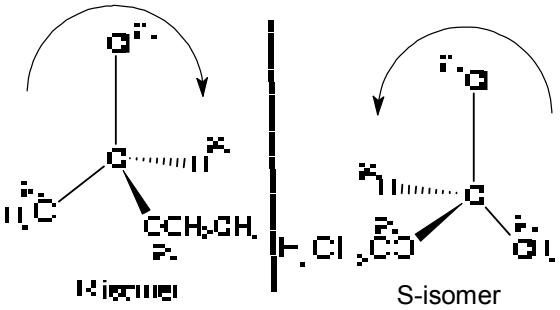
Ex. In bromochlorofluoromethane CHBrClF, the priority order of the substituents on asymmetric carbon are

Br (35) > Cl(17) > F (9) > H (1)

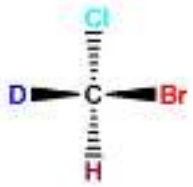
Priority order (1) (2) (3) (4)



Similarly in the following compound the priority order is



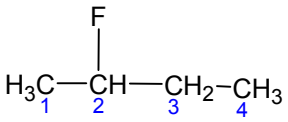
Rule 2: If two atoms are isotopes of same element, the atom of higher mass number has higher priority.



Br (1) > Cl (2) > D(3) > H (4)

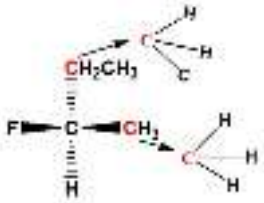
Rule 3: If two or more groups have identical firsta toms attached to asymmetric carbon the priority order is determined by considering the atomic number of the second atoms and if the second atoms are also identical third atoms along the chain are examined.

Ex. Sec-butylfluoride



The groups attached to asymmetric carbon are -F, -H, $-CH_3$ and $-CH_2CH_3$. So, first atoms if the groups are F, H, C, C. according to rule 1 flourine with higher atomic number is assigned priority 1 and hygrogen least priority 4. But the first atoms of methyl and ethyl groups are same i.e. carbon, thus we consider the second atoms of these groups.

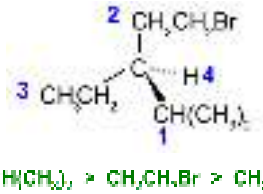
Second atoms of methyl group are three hydrogens (H,H,H), where as second atoms ethyl group are two hydrogens and one carbon (H,H, C), thus ethyl group is accorded higher priority than ethyl. So the order of priority is



- F > $-CH_2CH_3$ > $-CH_3$ > H

Priority order (1) (2) (3) (4)

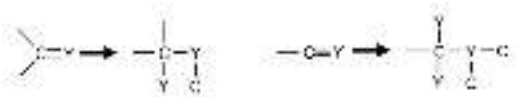
Rule 4: If two carbon chains are attached to the chiral carbon the chain with secondary carbon is of higher priority than one with primary carbon.

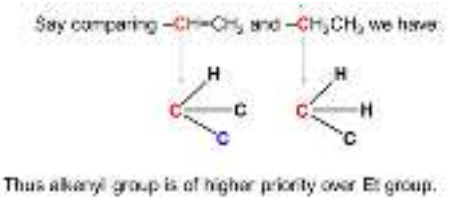


$CH(CH_3)_2$ > CH_2CH_2Br > CH_2CH_3

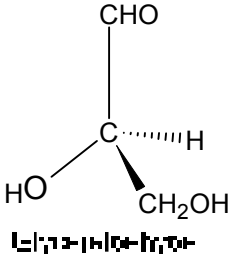
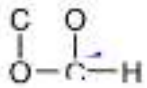
Rule 5:

i. A doubly or triply bonded atom is treated to be bonded to two or three such atoms.

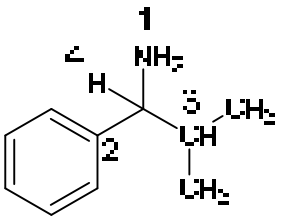




Thus alkenyl group is of higher priority over Et group.

	In glyceraldehyde the groups attached to the asymmetric carbon are -CHO. -OH, $-CH_2OH$ and H. So, the first atoms of these groups directly attached to asymmetric carbon are -C, O, C and H respectively. Thus based on rule I -OH is given highest priority and H least priority. But -CHO and CH_2OH with first atom similarity consider the second atoms, According to rule 5 The -the aldehyde carbon -CHO is equal to  , it is given priority over $-CH_2OH$ in which the second atoms are (H,H,O)

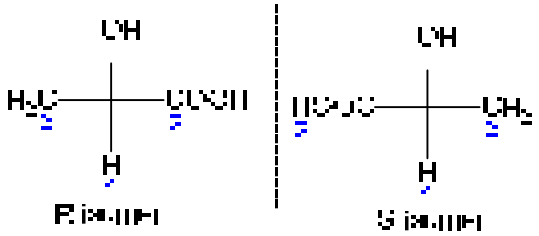
ii. Phenyl group or benzene ring is considered as kekule structure (with fixed double bonds) and carbon of phenyl ring directly bonded to asymmetric carbon is considered to be bonded to three other carbons as secondary atoms.

Ex. In 1-amino-2-methyl-1-phenylpropane 

The priority order is NH_2>-C_6H_5(phenyl)>C_3H_7 (isopropyl)>H

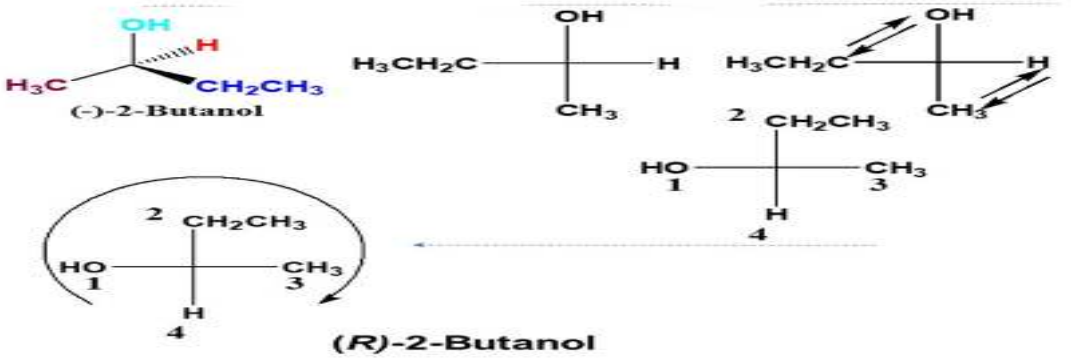
Assignment of R and S configuration with Fischer projections:

In planar Fischer projections of asymmetric carbons, the vertical lines represent the bonds directed away from the observer and the horizontal lines represent the bonds directed toward the observer. So, while assigning the R and S configuration at asymmetric centres of fischer projections the least priority group is placed on vertical plane. Thus it is directed away from the observer and the arrangement of remaining groups is noted to assign R or S configuration.



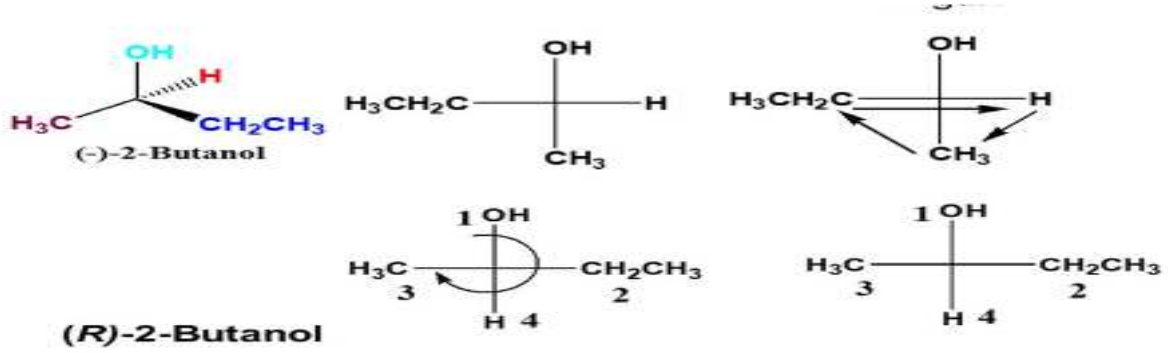
If the least priority group is on horizontal plane of Fischer projection formulae, it is projected towards observer, this leads to wrong assignment of R and S notations, as in R and S the least priority group should be oriented away from the observer.

In Fischer representation of sterioisomers one interchange of groups on asymmetric carbon results in its enantiomer, but two interchanges of groups are permited to retain the original isomer and configuration.



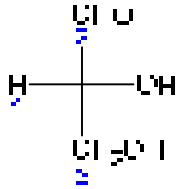
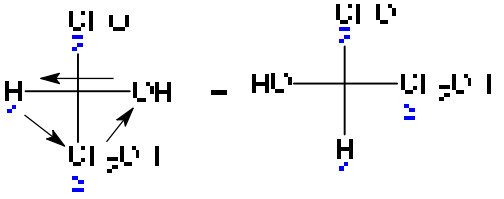
Ex

By trigonal exchange of groups on asymmetric carbon also we can retain original configuration.

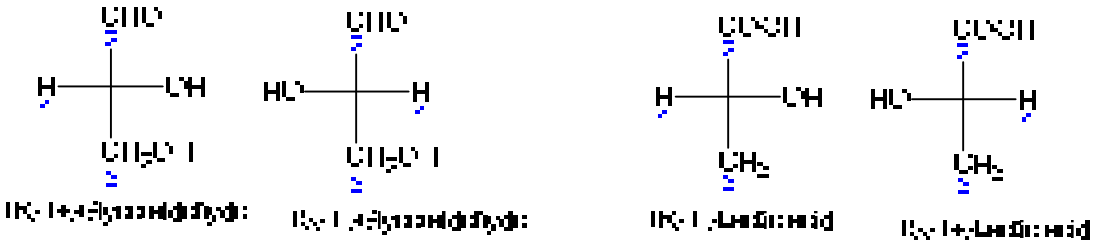


Otherwise in Fischer projection with least priority group on horizontal plane, the observed configuration is opposite to that of original configuration of the isomer. So, in Fischer projection with least priority group projected towards observer if the configuration is observed is R it should be treated as S or vice-verse.

Ex.

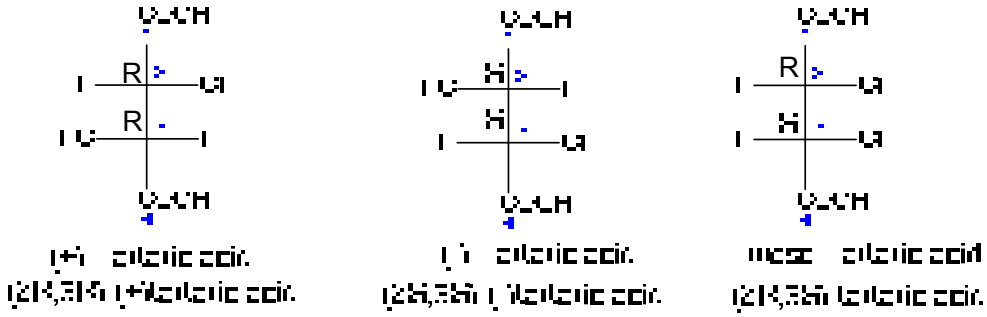
In the following glyceraldehyde isomer as the least priority H atom is on horizontal plane the configuration appears to be **S**  D(+)Glyceraldehyde	But it is originally R, this can be corrected if be bring H on vertical plane by making two interchanges of groups on asymmetric carbon.  R-(+)Glyceraldehyde

While indicating the configuration The letters R and S are written in parenthesis



In stereoisomers containing more than one chiral carbon configuration of R or S is indicated separately at each asymmetric centre.

Ex Tartaric acid

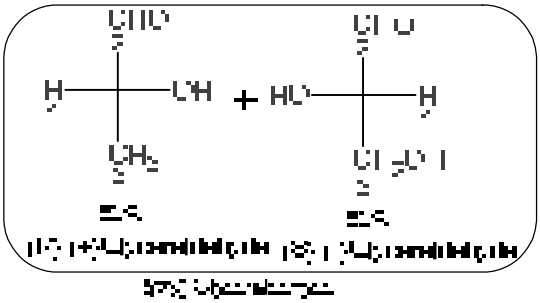


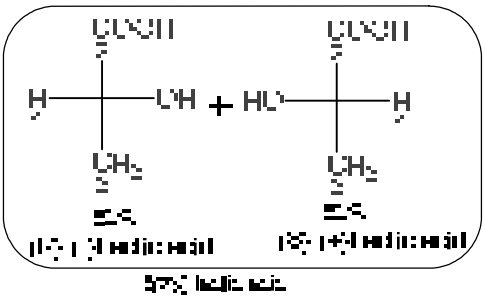
RACEMIC MIXTURE:

"An optically in-active equimolar mixture of a pair of enantiomers is called as racemate or racemic mixture or racemic modification

A racemic mixture is denoted by the prefix (±)- or dl- , indicating an equal (1:1) mixture of dextro and levo isomers. Also the prefix rac- (or racem-) or the symbols RS and SR (all in italic letters) are used.

Ex.

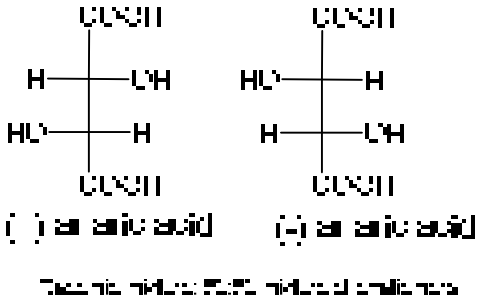




Synthesis of an optically active compound produces a mixture of + and –ve isomers in equal amounts. these isomers are non-superimposable mirror images and are called enantiomers. Such a mixture is called racemic mixture or a racemate.

Properties of Racemate: Racemate may have different physical properties from either of the pure enantiomers because of the differential intermolecular interactions.

The change from a pure enantiomer to a racemate can change its density, melting point, solubility, heat of fusion, refractive index, and its various spectra. Crystallization of a racemate can result in separate (+) and (−) forms, or a single racemic compound.



(+) tartaric acid (-)tartaric acid Racemic mixture

Properties			
Melting point	170^0	170^0	206^0
Specific rotation	$+11.2^0$	-11.2^0	0^0

RESOLUTION OF RACEMIC MIXTURE

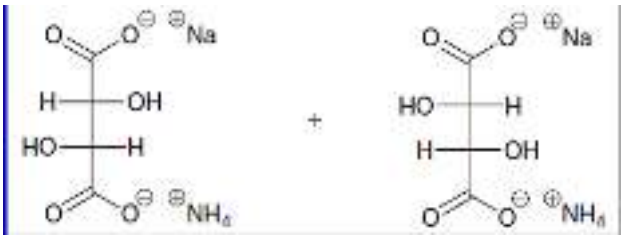
The process of separation of an optically inactive racemic mixture into its two optically active compounds (+ and – isomers) is known as Resolution. If the enantiomers are separated, the mixture is said to have been resolved.

Resolution is necessary to prepare optically pure chiral auxiliaries, to purify products of low enantiomeric excess and it is valid strategy for chiral synthesis.

The different methods of resolution of racemic mixture are

1. Mechanical separation
2. Preferential crystallization
3. Biochemical separation
4. Kinetic method
5. By precipitation
6. Chiral chromatographic technique
7. Chemical method or by conversion to Diastereomers

1. **Mechanical separation:** This is also known as spontaneous resolution by crystallization. This method is developed by L. Pasteur in 1847. It is applicable to only solid substances which form well defined crystals.
   It depends on the crystallization of two forms separately, which are then separated physically by using forceps. This method is applicable only for racemic mixtures where the crystal forms of the enantiomers are themselves enatiomorphous i.e being mirror image of each other, crystal of the two forms have different shapes and are separated physically.
   Ex. L. Pasteur in 1847 separated the racemate of sodium ammonium tartrate into its enantiomers by carrying out the crystallization at 28^0C. At a temperature higher than this, a racemic compound is obtained, at this transition temperature the two enantiomers with distinct crystalline shapes are obtained and are separated by hand picking.

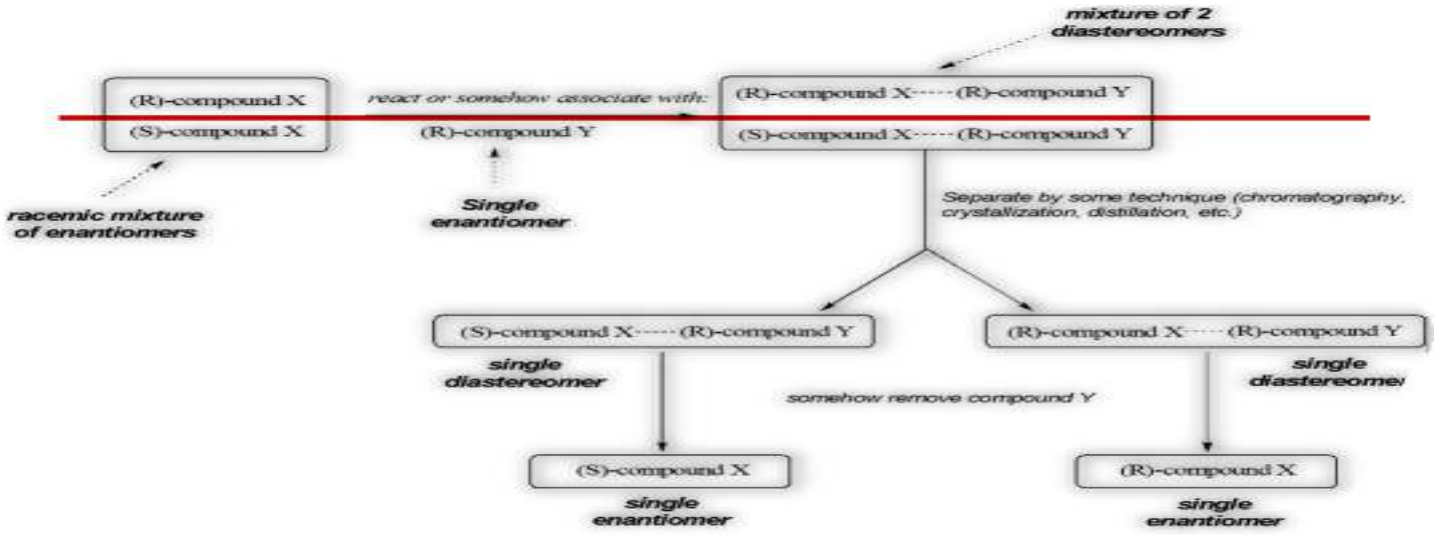


   This method is time consuming and every compound cannot be crystallized at room temperature. This method is too tedious for practical purposes.

2. **PREFERENTIAL CRYSTALIZATION BY INOCULATION (Gernez-1866)**
   When a super saturated solution of the racemate is inoculated with a pure crystal of one of the enantiomers, that enantiomer preferentially crystallizes out.
   Ex. Resolution of glutamic acid by inoculation.
   Preferential crystallization depends on solubility of enantiomer which is less then solubility of racemic form. Copper complex of DL-Aspartic acid resolved by inoculation.
   Sometimes resolution can be carried out with the help of crystals of another optically active compound.

Ex. (-)asparagine helps to crystallize the dextrorotatory (+)sodium ammonium ammonium tartrate from its racemate.

3. **BIOCHEMICAL METHOD:** This method involves the preferential destruction of one of the two enantiomers of a racemate with th help of moulds or by bacteria, by allowing them to grow in a dilute solution of a racemate. As a result one enantiomer is obtained at the end of the process.
   Ex. When penicillium glaucum (mould) is allowed to grow I a dilute solution of ammonium tartarate racemate, it destroys the (+) isomer rapidly than the (-) isomer. Similarly, when yeast is allowed to grow in a dilute solution of glucose racemate it destroys (+) glucose more rapidly than (-) form.
   Disadvantages: i. difficult to geta suitable micro-organism which will destroy only one isomer.
   ii. There is loss of material as one of the isomer is completely destroyed and other one is recovered in less than 50%.
   iii. Very dilute solutions of a racemate has to be used so, the amount obtained will be small.
4. **KINETIC RESOLUTION**: Enantiomer react with chiral compounds at different rates, so it possibly affects a partial separation by stopping the reaction before completion.
   Ex. Enantiomer react with chiral compounds at different rates, so it possibly affects a partial separation by stopping the reaction before completion.
   Thus when mandelic acid racemate is esterified with a limited quantity of (-) menthol the major product will be (+)(-)ester than (-)(-) ester. Which is separated and hydrolyzed to yield (+) mandelic acid.
5. **PRECIPITATION METHOD**: This method is based on formation of precipitate by reaction between any reagent and racemic mixture. Example: (+) & (-) narcotine when dissolved in HCL, precipitates (+) narcotine
6. **CHROMATOGRAPHIC SEPERATION:** The racemic mixture can be separated by chromatography on an optically active support. The diastereomeric adsorbates which are formed have different stabilities. Thus, one enantiomer will be held more tightly than the other and would be eluted first.
   Optically active substances are selectively adsorbed by optically active adsorbent. Wool and casein selectively adsorb (+)-Mandelic acid from aqueous solution of (+-)-Mandelic acid.
   Stereoselective adsorbents prepared in the presence of a suitable reference compound of known configuration.eg: silica gel in the presence of quinine. Silica gel adsorbs quinine more readily then its stereoisomer quinidine.
   •Cinchonidine (configurationally related to quinine) is adsorbed more readily then its stereoisomer cinchonine (configurationally related to quinidine).
7. **CHEMICAL RESOLUTION or by CONVERSION TO DIASTEREOMERS**
   This is the most widely employed method of resolution. This method is based on the principle that enantiomers have similar physical properties thus they cannot be separated. Diastereomers, on the other hand, have different physical properties, and this fact is used to achieve resolution of racemates. Reaction of a racemate with an enantiomerically pure chiral reagent gives a mixture of diastereomers, which can be separated.



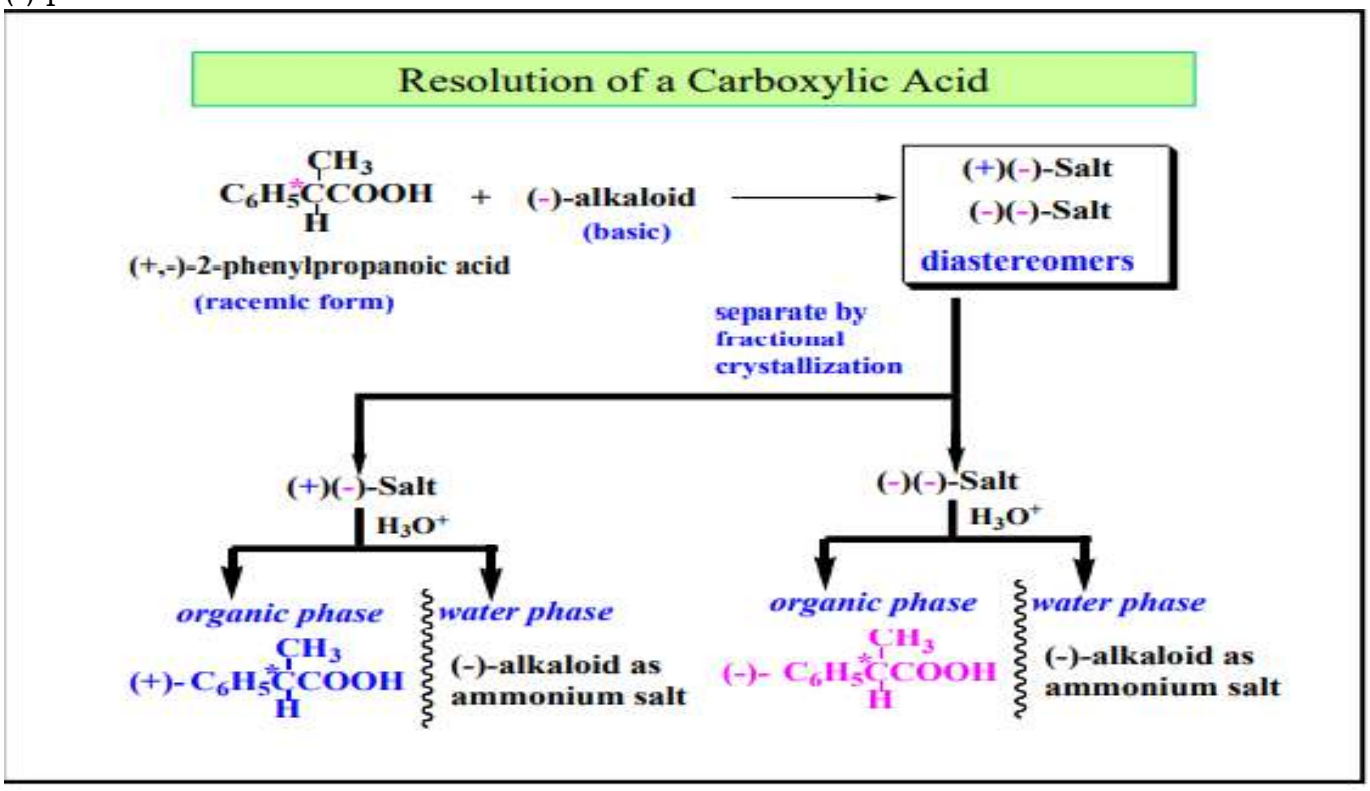
Depending on the nature of functional group in enantiomers, the racemate is treated with a chiral reagent to generate diastereomeric products which are separated and hydrolyzed to yield optically active substrate enantiomers.

Thus, organic bases react with organic acids to yield diastereomeric salts and vice versa.

a. **Resolution of acid racemate**: The racemate of an acid on treatment with an optically active base mostly an alkaloid yields crystals of two different salts. The salts are diastereoisomers as the configuration of asymmetric center obtained from base would identical and the other asymmetric center derived from different enantiomers would be different.

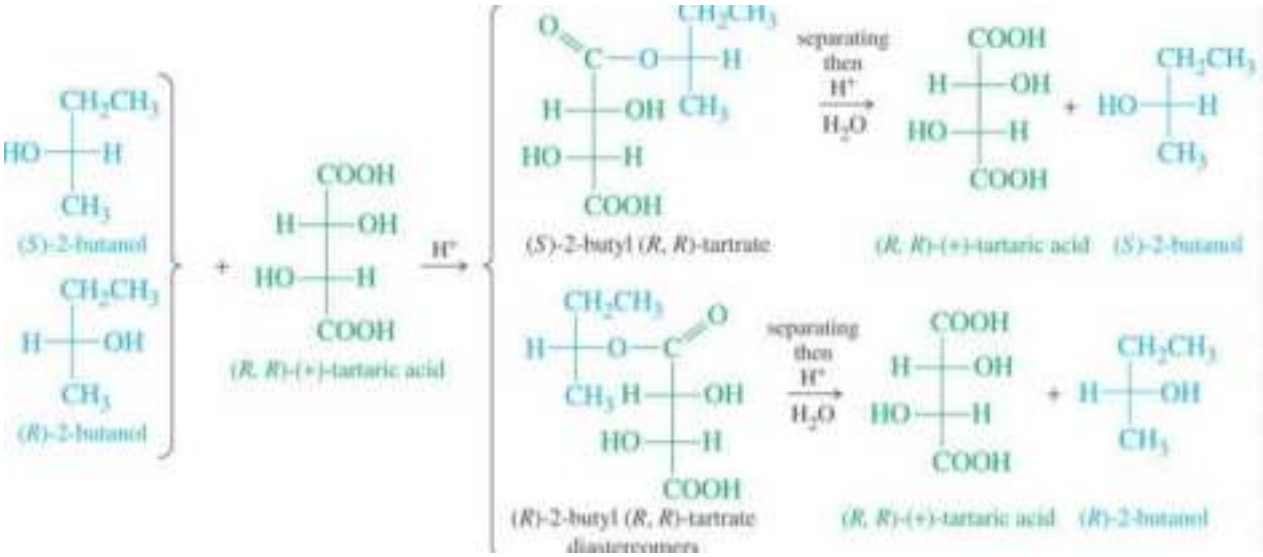
These diastereoisomers have different solubilities they can be separated by fractional crystallization. After separation the optically active enantiomers can be recovered by the hydrolysis of each salt with mineral acid or alkali.

Ex. Resolution of a racemate of a carboxylic acid derivative using alkaloidal base (-)quinine



The commonly used base in resolution of acid racemate are (-)brucine, (-) quinine, (-)strychnine.
For resolution of bases the commonly used acid chiral reagents are (+)tartaric acid, (-)camphor-β-sulphonic acid and (-) malic acid.

b. Resolution of racemate of alcohol enantiomers: The racemate of alcohols is converted into diastereomeric esters by reaction with chiral carboxylic acid, which are then separated and hydrolyzed.



c. Resolution of Racemate of Aldehydes and ketones: Resolved by reaction with optically active hydrazine ex. (-)methylhydrazine.

d. Resolution of Amino acids racemate: Because the amino acids exist as dipolar zwitter ions, they cannot be easily resolved by using optically active acids or base. Thus they are converted to their acyl derivates which no longer exists as zwitter ions and have free carboxylic acid group which then can be converted to diastereomeric salt by reaction with optically active alkaloidal base.

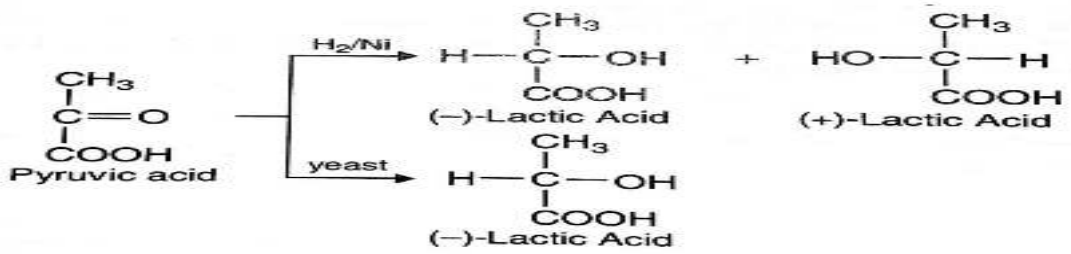
Ex. Alanine racemate is first converted to benzoyl alanine and treated with (-)brucine, the resulting diastereomeric salts are separated and hydrolysed to respective enantiomers of alanine.

ASYMMETRIC SYNTHESIS

Asymmetric synthesis is the process of converting an optically inactive i.e. Achiral molecule into optically active chiral molecule without the process of resolution.

In general, the conversion of a symmetric compound into asymmetric results in optically inactive racemic mixture. But, in asymmetric synthesis one of the enantiomers is formed exclusively or as a major product.

Ex. When pyruvic acid is reduced it forms a racemic mixture of lactic acid, but when this reduction is carried out in chiral environment such as enzymes produced by yeast it resulted in major proportion of (-) lactic acid.

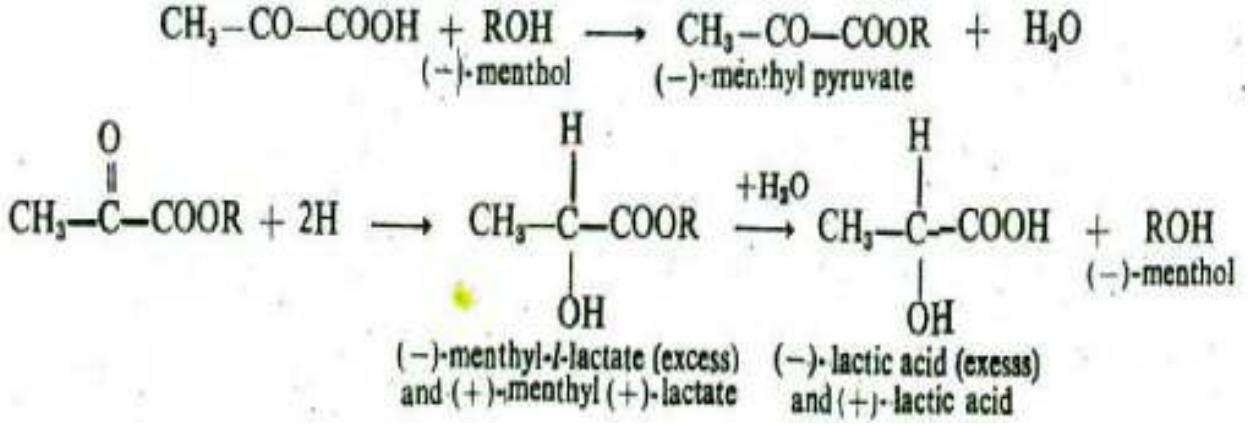


Depending the relative ratio of formation of the enantiomeric chiral molecules from achiral, asymmetric synthesis is broadly classified into

I. Partial asymmetric synthesis
II. Absolute asymmetric synthesis.

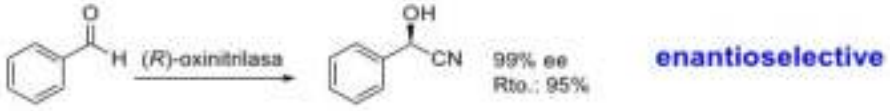
I. **Partial asymmetric synthesis**: This involves the conversion of an optically inactive Achiral molecule in to optically active Chiral molecule using an optically active reagent (Chiral reagent). In this method of asymmetric synthesis when a prochiral or Achiral molecule is converted to Chiral it results in both possible enantiomeric forms in varying proportions and one isomer is formed in excess. Thus it is not a racemic mixture and is optically active.

Ex. When pyruvic acid is reduced as such, it yields (±)- lactic acid. However, when pyruvic acid is first combined with an optically active alcohol, ROH, such as (—)-menthol to form an ester (-) menthylpyruvate which is then reduced and hydrolyzed to yield (-)lactic acid in excess.

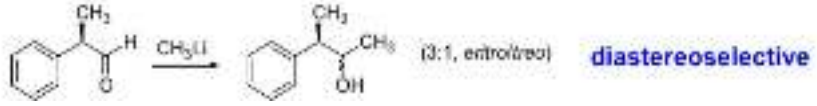


In partial asymmetric synthesis depending on the different ratio of formation of enantiomers or diastereomers it can be enantiomeric excess or diastereomeric excess.

Enantioselective An enantioselective reaction is one in which one enantiomer is formed in preference to the other, in a reaction that creates an optically active product from an achiral starting material, using either a chiral catalyst, an enzyme or a chiral reagent.



Diastereoselective A diastereoselective reaction is one in which one diastereomer is formed in preference to another, establishing a preferred relative stereochemistry. In this case, either two or more chiral centres are formed at once such that one relative stereochemistry is favoured

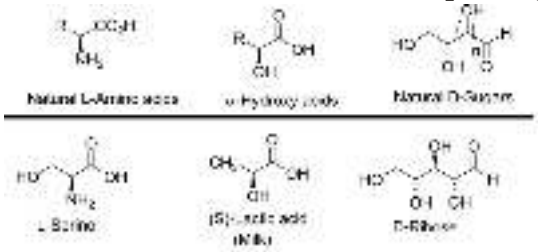


In partial asymmetric synthesis different approaches are employed to achieve enantiomeric excess or diastereomeric excess.
These approaches include

1. Chiral Pool synthesis
2. Chiral Auxiliaries
3. Chiral reagents
4. Chiral Catalysts and Chiral ligands

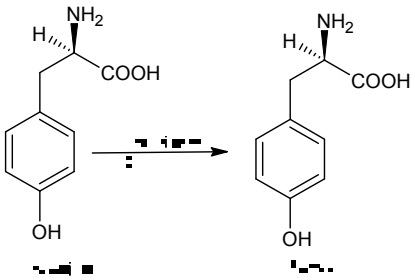
1. **Chiral pool synthesis or Chiron approach**: This is the simplest and oldest approaches for enantioselective synthesis. In this method an enantiomerically pure natural product is employed as starting material to convert it into a new chiral product.

   A set of naturally occurring chiral molecules such as pure natural amino acids, hydroxy acids and sugars form the source of Chiral pool, from which different chiral compound can be synthesized.
   Ex. Natural substrates for chiral pool synthesis

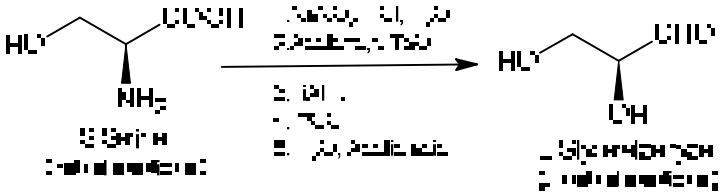


In this method the chiral centre of natural substrate may or may not involve the chemical transformation.

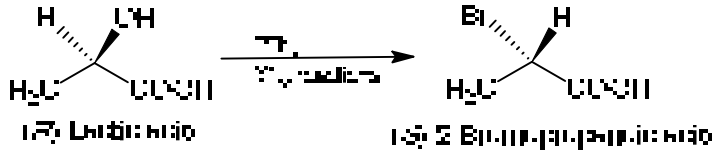
Ex. 1. In the conversion of L-tyrosine to L-Dopa the chiral centre of substrate is nor involved in the reaction.



Ex. 2. In a multistep functional group conversion of a natural enantiomer S-serine to L-glyceraldehyde there is a retention of configuration in the substrate to product.

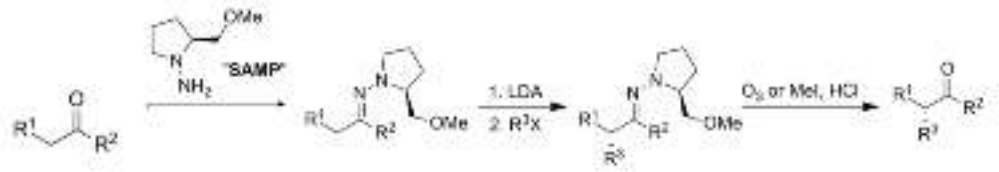


Ex. 3. In the conversion of natural R-lactic acid to S-2-Bromopropanoic acid the reaction involves the chiral centre of substrate.

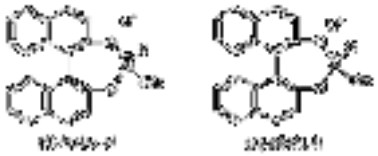


2. **Chiral Auxiliaries** (second generation method): In this approach a prochiral substrate attach with a chiral auxiliary to give a chiral intermediate. During which auxiliary dictates the preferred stereochemistry. Finally, we can remove the auxiliary from product to use it again.
   A chiral auxiliary is a chiral molecule that can be temporarily incorporated in an achiral substrate to guide selective formation of one of a possible pair of enantiomers.
   Some of the chiral Auxiliaries are (4*S*)-4-isopropyl-2-oxazolidinone, (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) or (*R*)-1-amino-2-methoxymethylpyrrolidine (RAMP) are used in the selective asymmetric carbon-carbon bond formation reaction in aldehydes and ketones.

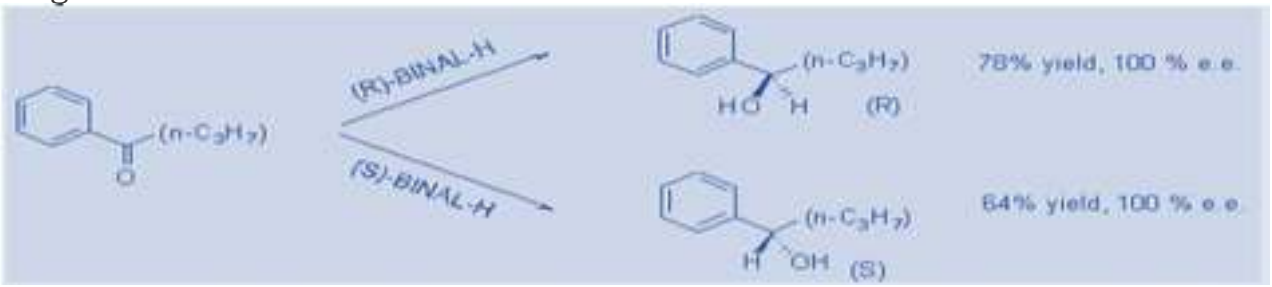
   Ex. The first step is to form the hydrazone between (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) and a ketone or aldehyde.
   Afterwards, the hydrazone is deprotonated by lithium diisopropylamide (LDA) to form an azaenolate, which reacts with alkyl halides or other suitable electrophiles to give alkylated hydrazone species with the simultaneous generation of a new chiral center. Finally, the alkylated ketone or aldehyde can be regenerated by ozonolysis or hydrolysis.



3. **Use of chiral reagents** (third generation methods): In this method an inactive substrate converted selectively into one of the enantiomer(enantiospecific). In this type of synthesis chiral reagent turns achiral by transforming an achiral substrate to chiral. Thus the reagent is "self- immolative".
   Ex. Binaphthol-modified lithium aluminum hydride (**BINAL-H**), affects asymmetric reduction of a variety of phenyl alkyl ketones to produce the alcohols 2 with very high to perfect levels of enantioselectivity when the alkyl groups are methyl or primary.

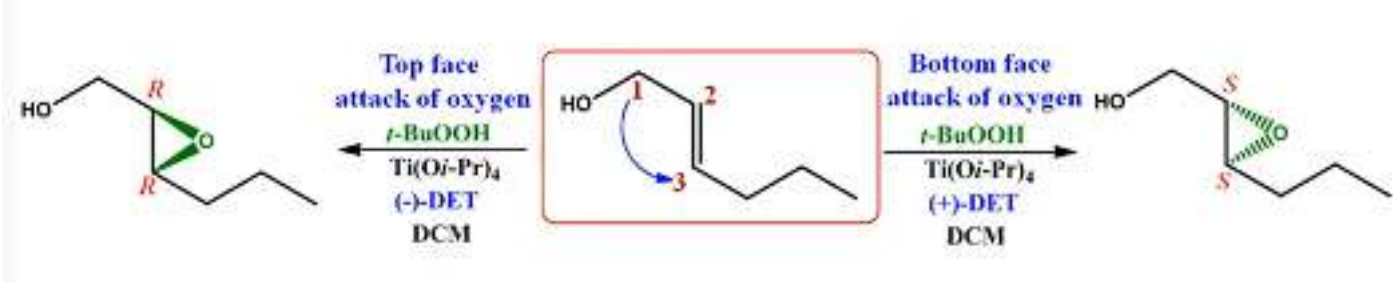


Eg: Reduction of a prochiral carbonyl group enantioselectively by a chiral reducing agent BINAL-H



4. **Use of chiral catalyst** Effective optically pure catalysts are much more promising, because reagents are required in stoichiometric amounts, while catalysts are required only in very small amounts.

Ex. Sharpless asymmetric epoxidation is a very important name reaction. In this reaction an allylic alcohol is epoxidized by ter-butylhydroperoxide in the presence of titaniumtetraisopropoxide as a catalyst and (+) or (-)-dialkyltartrate as a chiral ligand to produce enantioselectively one enantiomer of epoxide



Summary of different approaches in Partial asymmeteic synthesis.

Method	Advantages	Disadvantages	Examples
resolution	both enantiomers available	maximum 50% yield	synthesis of BINAP
chiral pool	100% ee guaranteed	often only 1 enantiomer available	amino acid- and sugar-derived syntheses
chiral auxiliary	often excellent ees; can recrystallize to purify to high ee	extra steps to introduce and remove auxiliary	oxazolidinones
chiral reagent	often excellent ees; can recrystallize to purify to high ee	only a few reagents are successful and often for few substrates	enzymes, CBS reducing agent
chiral catalyst	economical: only small amounts of recyclable material used	only a few reactions are really successful; recrystallization can improve only already high ees	asymmetric hydrogenation, epoxidation, dihydroxylation

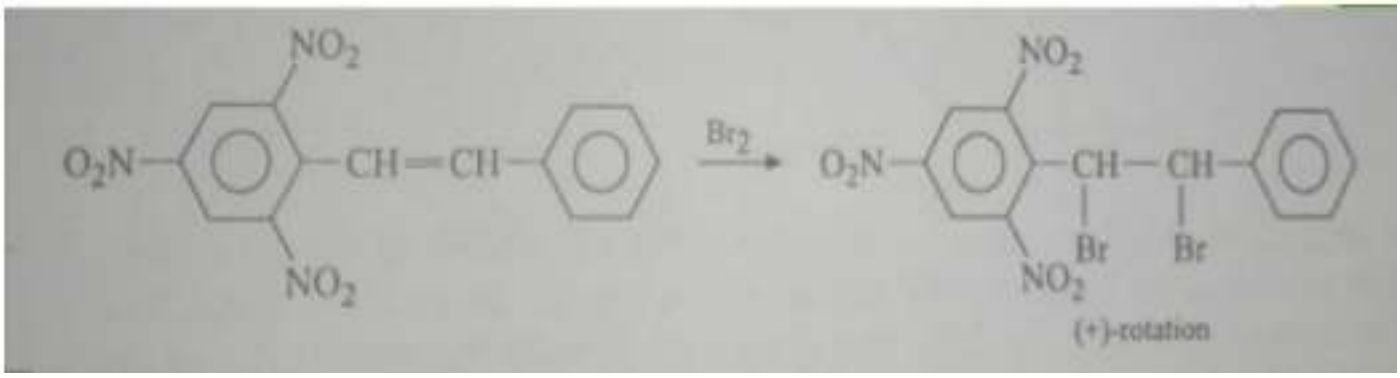
II **ABSOLUTE ASYMMETRIC SYNTHESIS:**

This involves the conversion of an achiral (Symmetric) substrate or racemic precursors in to an optically active chiral product without use of optically active reagents, catalysts or auxiliaries. This method only one of the enantiomeric or diastereomeric isomer is formed exclusively.

Absolute asymmetric synthesis can be achieved by carrying out the achiral compound conversion to Chiral under the influence of Circularly polarized light (CPL), either right or(RCL) or left circularly polarized light (LCL) circular dichroism, i.e. that absorption of CPL may be different for the two enantiomers.so, that one of the enantiomers is selectively destroyed leaving only one chiral compound in pure form.

Absolute asymmetric synthesis can also be achieved by total spontaneous resolution.

Ex. The bromination of 2,4,6-trinitrostilbene when carried out under the influence of right circularly polarized light it resulted in the formation of dextrorotatory Bromo derivative instead of racemic mixture.



APPLICATIONS OF ASYMMETRIC SYNTHESIS

• Many of the building blocks of biological systems, such as sugars and amino acids, nucleocides are produced exclusively as one enantiomer.

• living systems possess a high degree of chemical chirality and will often react differently with the various enantiomers of a given compound.in our living system.

• . Neary 60% of the drugs are chiral.

• Drug substances which exist in more than one isomeric form, the different isomers of the drug may differ in their therapeutic efficacy. The isomer which is more potent is called Eutomer and isomer of it which is more toxic is called distomer. More over the isomers of a single drug may have different therapeutic profile

There is a necessity to synthesize drugs in pure isomeric forms.

Ex. Propoxyphene – • both enantiomers are biologically active. • R-isomer is an analgesic while • S-isomer has antitussive property

UNIT-II (POC III)

PART A

GEOMETRICAL ISOMERISM

Geometrical isomers also known as Cis-Trans isomers are stereoisomers which have similar molecular formula and similar structural formula but differ in spatial arrangement of atoms or groups due to restricted rotation about a C-C or C-N double bond or rigid alicyclic ring structures.

Thus, this kind of isomerism is observed in substituted alkenes, oximes, cycloalkanes and cycloalkenes.

These are configurational isomers because they cannot be interconverted without breaking and making of bonds. They are also diastereoisomers as they are not mirror images of each other.

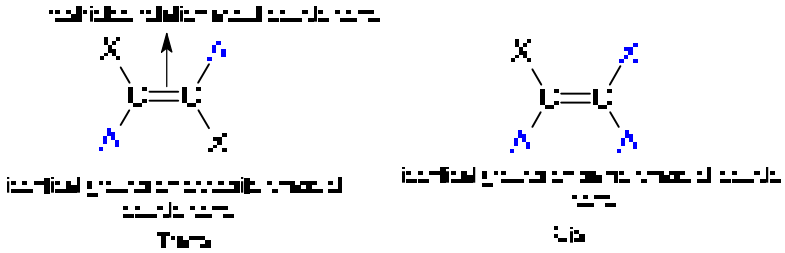
Ex. 1,2-dichloroethene can exist in two stereoisomeric forms which differ in the spatial arrangement of hydrogen and chlorine atoms about the C-C double bond.

cis-1,2-Dichloroethene *trans*-1,2-Dichloroethen

Thus, geometrical isomerism is due to this kind of isomerism is observed in substituted alkenes, oximes, cycloalkanes.

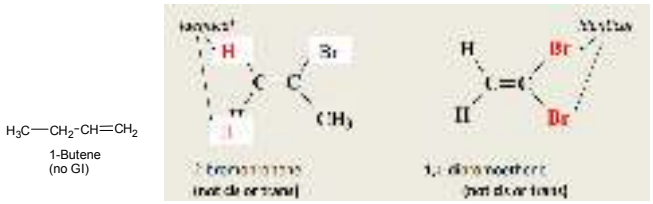
Geometrical Isomerism in Alkenes

Alkenes the unsaturated hydrocarbons are characterized by the presence of C-C double bonds. The sp2 hybrid carbons are bonded by double bond involving sigma and pi bonds. Thus C=C bonds have restricted rotation, so, the spatial position of the groups attached to the double bonded carbons is fixed thus alkenes with different substituents on the double bonded carbons can have two isomeric structures which differ in their spatial arrangement about double bond and cannot be interchanged without breaking and making of a pi bond. These isomers are called geometrical isomers.



All alkenes do not show geometrical isomerism. Geometric isomerism is possible only when each double bonded carbon atom is two different atoms or groups.

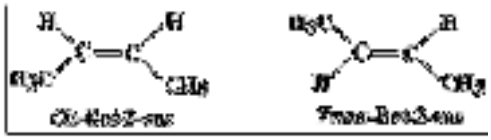
Ex. The following alkenes with identical groups on doble bonded carbon cannot exhibit geometrical isomerism



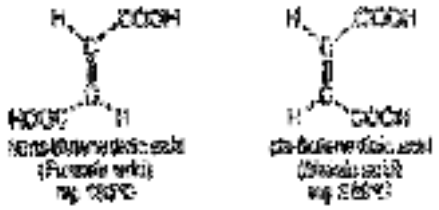
1-Butene cannot exhibit GI but 2-butene can exist in two geometric isomers

But 2-Butene in which both the double bonded carbons having different groups exhibit geometrical isomerism

2-Butene exist in two isomeric forms which have similar molecular and structural formula but due to restricted rotation about C=C double differ in spatial arrangement of CH3 and H atoms of about the two double bonded carbons which are not interconvertible and are known as Cia and Tran 2-butenes.



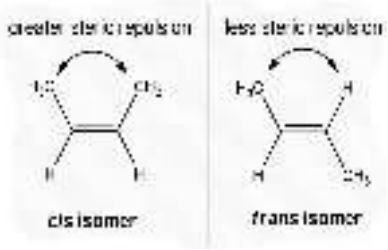
Similarly, Butenedioic acid ( )also exhibit geometrical isomerism.



The isomer is called Maleic acid and the trans isomer is known as Fumeric acid.

Stability

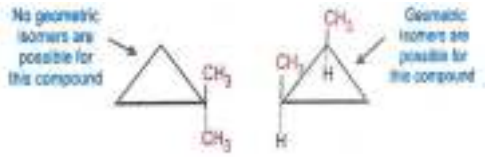
The trans isomers are more stable than the corresponding cis isomer because in cis isomer the bulky groups are on the same side of the double bond. The steric repulsion of the groups make the cis isomer least stable.

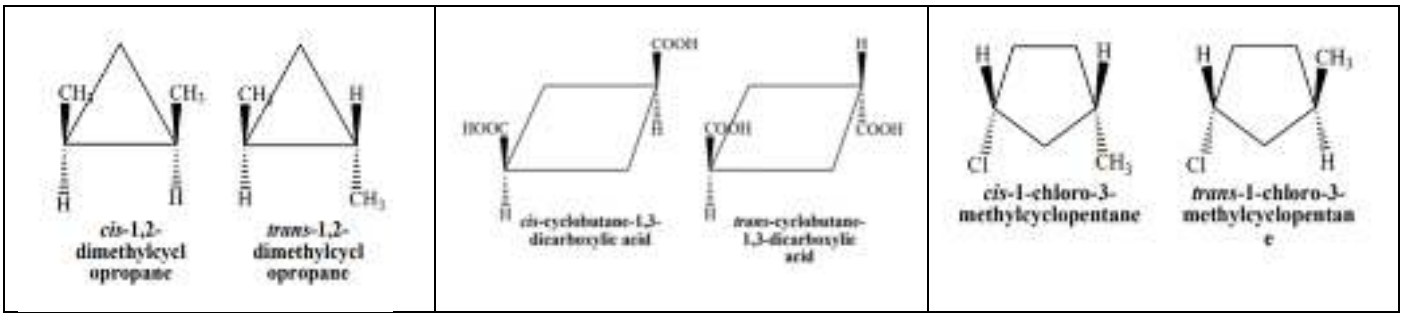


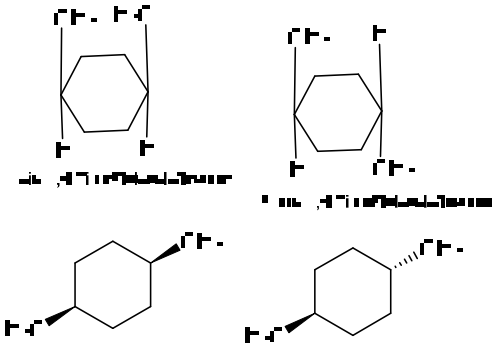
2. **Geometrical Isomerism in Cycloalkanes/Alicyclic compounds**: The cyclic compounds such as disubstituted cyclopropane, cyclobutane, cyclopentane and cyclohexane can exhibit geometrical isomerism due to hindered rotation C-C single bonds

in ring. So, the spatial arrangement of groups above and below the plane of the ring structure is fixed.

A requirement for geometric isomerism in cyclic compounds is that there must be at least two other groups besides hydrogens on the ring and these must be on different ring carbons.

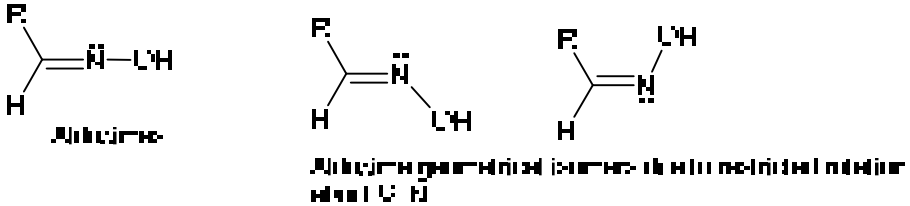






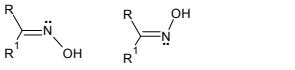
3. Geometrical Isomerism in OXIMES: Geometrical isomerism also possible in compounds containing C=N (oximes) and N=N (Azo) compounds. Like alkenes both double bonded atoms (carbon and nitrogen) are sp2 hybridized. The lone pair of electrons of nitrogen are present in sp2 hybrid orbitals. This fixes the position of all substituents around C=N and N=N double bonds. This results in geometrical isomerism.

In aldoximes geometrical isomers the spatial relationship of hydrogen attached to double bonded carbon and hydroxyl attached to nitrogen can be different and is fixed to due to restricted rotation around C=N double bond.

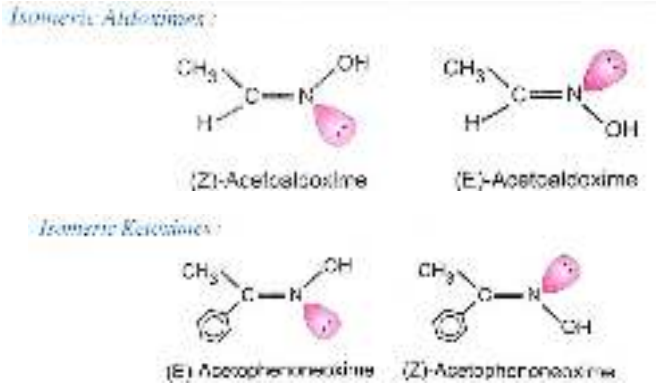


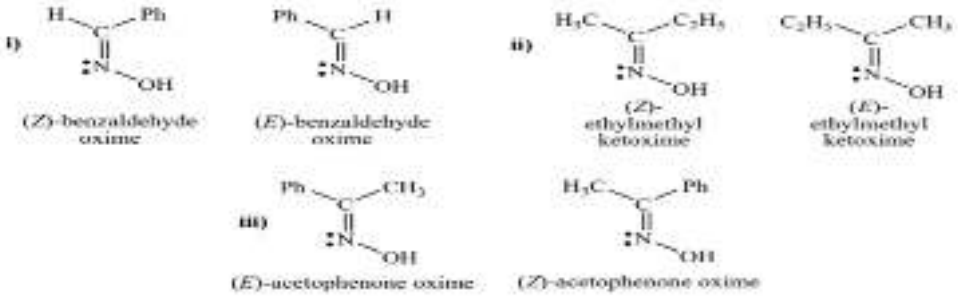
And in ketoximes if the alkyl/aryl groups of double bonded carbons are different their spatial relationship with the sp2 hybrid orbital containing lone pair of electrons of nitrogen can be different thus exhibit geometrical isomerism.


Ketoxime


Ketoxime geometrical isomers due to restricted rotation about C=N

Example





Assignment of configuration in Geometrical Isomerism or Nomenclature of Geometrical isomers

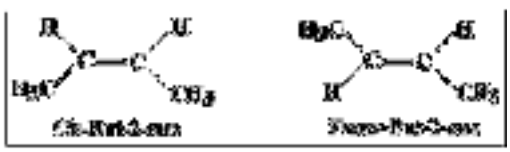
The configuration of isomers in geometrical isomerism is indicated by two systems

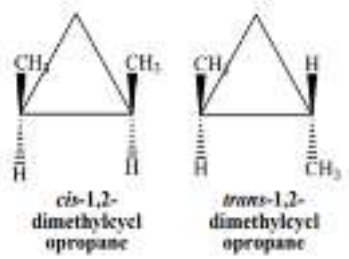
I. **CIS-TRANS System**
II. **E and Z system**

I. **Cis-Trans System:** The most common method for specifying configuration in geometrical isomers of alkenes and cycloalkanes and cycloalkenes uses the prefixes **cis** and **Trans.**

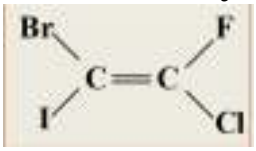
Cis- The identical groups lie on the same side of double bond of alkenes or plane of the ring in cycloalkanes

Trans- The identical groups lie on the opposite side of double bond of alkenes or plane of the ring in cycloalkanes.





II. **E and Z System of assigning configuration**: The simple convention of denoting the geometrical isomers by cis/trans descriptors is not sufficient when there are more than two different substituents on a double bond. To differentiate the stereochemistry in them, a new system of nomenclature known as the E & Z notation method is to be adopted. Ex. The configuration of the following alkene with four different substituents on double bonded carbons can not be indicated by Cis/trans notations.

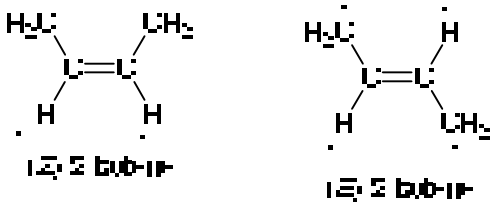


This can be assigned by E and Z notations.

In E and Z system of assignment of configuration a two-step process is adopted

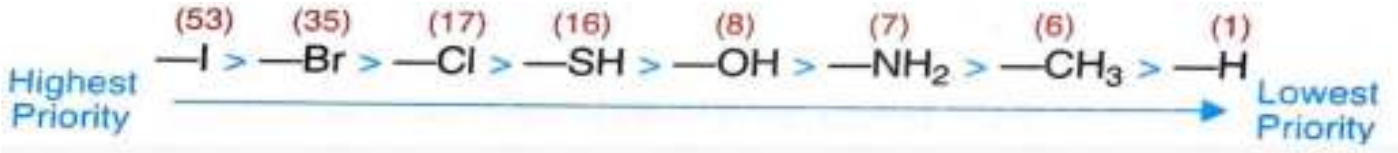
Step-1: Priorities 1 and 2 or A and B are assigned to the atoms/groups attached to the double bonded carbons separately based on **CIP** rules (Cahn-Ingold-Prelog).

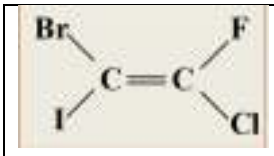
Step-2: The configuration is denoted as **Z (Zusammen-together)** if the identical priority groups on the double bonded carbons lie on the same side of the double bond**.** The prefix **E (Entgegen-opposite)** is used if the identical priority groups on the double bonded carbons lie on the opposite sides of double bond.



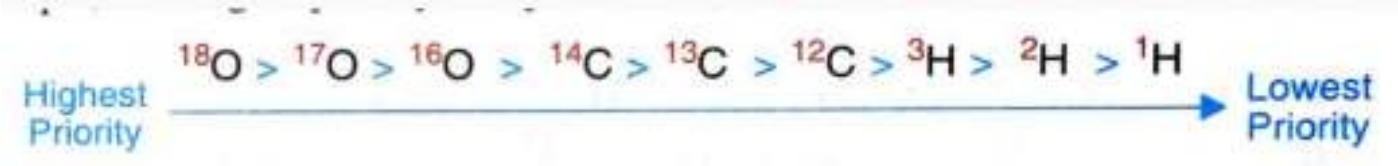
The priorities are assigned by following **Cahn-Ingold-Prelog sequence rules (CAN rules)** described below.

1. Rank the atoms directly attached to the olefinic carbon according to their atomic number. High priority is given to the atom with higher atomic number.

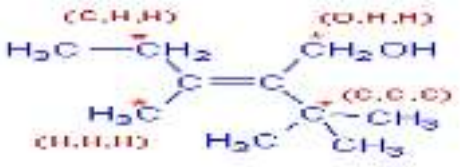


	In this isomer on first carbon the groups are Br and I so highest priority is assigned to I followed by Br On second carbon chlorine has higher priority over Fluorine So, this isomer is Z as identical priority groups i.e. I and Cl are lieing on the same side of double bond

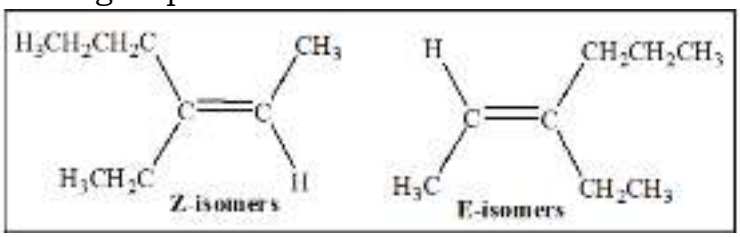
2. If isotopes of same element are present, the higher priority is given to the isotope with higher atomic mass.
   E.g. The Deuterium isotope (H^2 or D) has more priority than protium (H^1 or H).
   The C^{13} isotope has more priority than C^{12}.

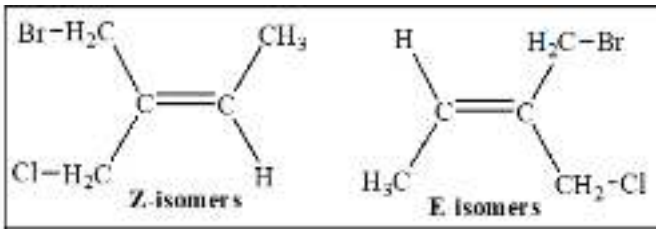


3. If priority cannot be assigned on the basis of atomic number or atomic mass considering the first atom of a group, then look at the next set of atoms and continue until a priority can be assigned. Priority can be assigned at the first point of difference. If the atoms directly linked to the double bond are the same, then the second, third, fourth, etc. atoms (away from the double bond) are ranked until a difference is found.
   Examine the lists of atoms directly linked to the highlighted carbons in the following compound, (2Z)-2-tert-Butyl-3-methylpent-2-en-1-ol.

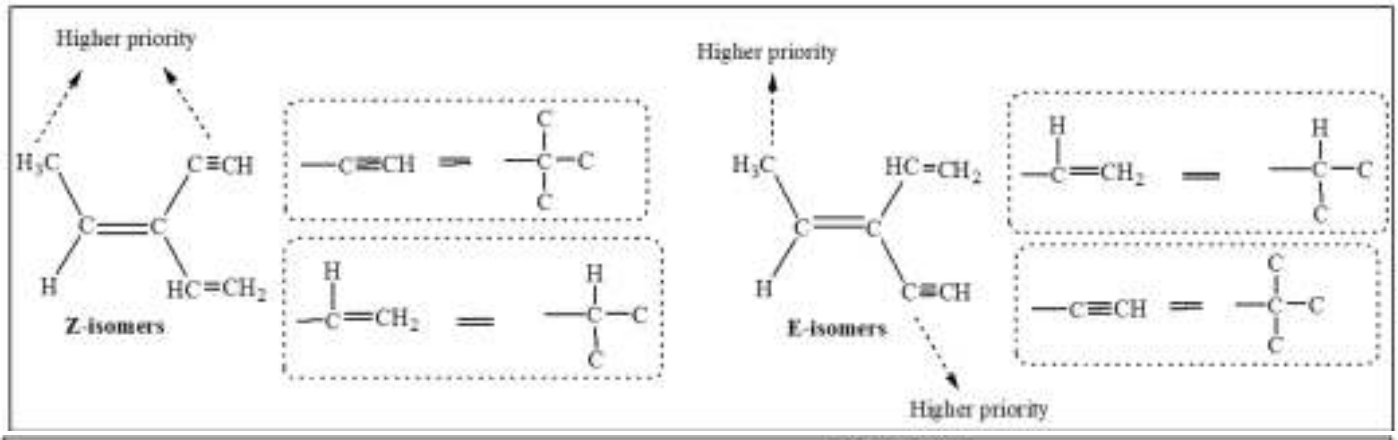


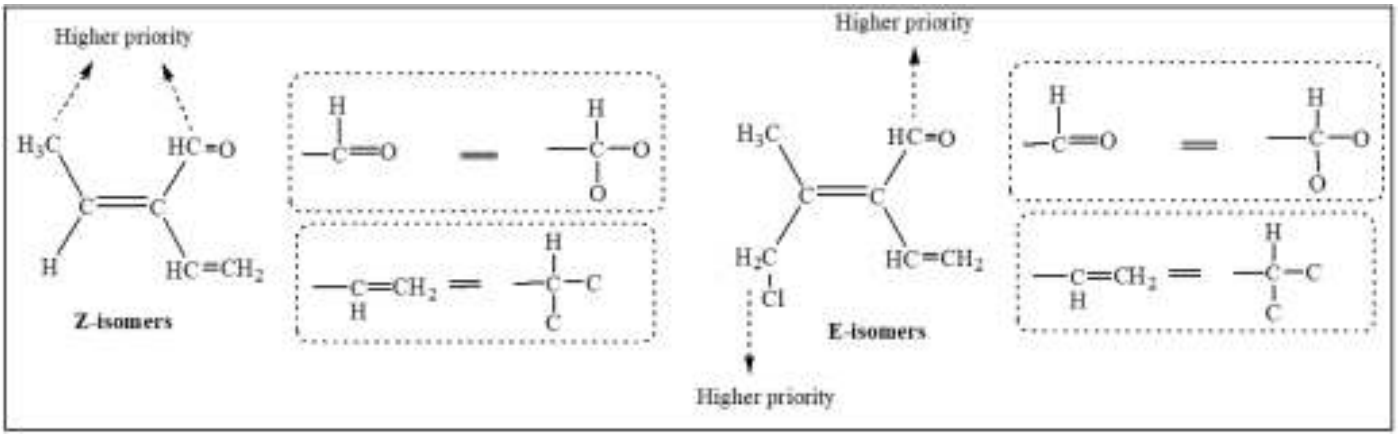
   The (C,H,H) list has more priority over (H,H,H). Whereas, the (O,H,H) has more priority over (C,C,C). Since the groups with highest priorities are on the same side of the double bond, the descriptor, Z is used to represent the stereochemistry of groups at double bond.

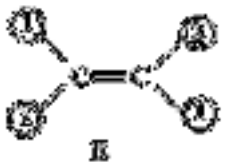




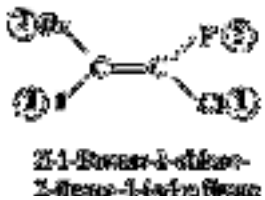
4. The multiple bonds are counted as multiples of that same atom i.e., each π bond is treated as if it were another σ bond to that type of atom.

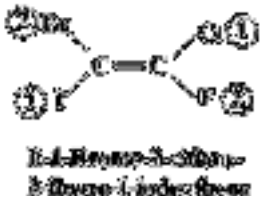

Higher priority
Higher priority
Z-isomers
Higher priority
Higher priority
E-isomers

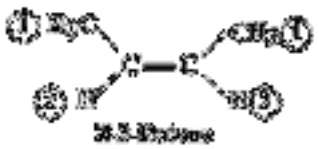

Higher priority
Higher priority
Z-isomers
Higher priority
Higher priority
E-isomers

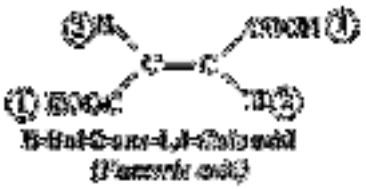

E


Z



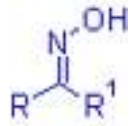






Nomenclature of Geometrical isomers of Oximes or Syn and Anti nomenclature in Oximes geometrical isomers.

The oximes are formed when carbonyl compounds are treated with hydroxyl amine. These are represented as:



oxime

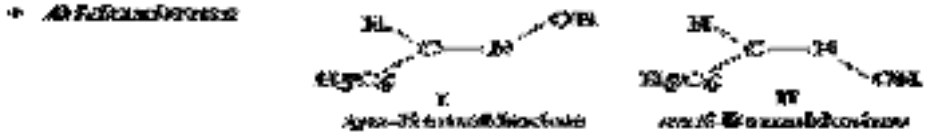
Where R & R^1 are hydrogens; or alkyl or aryl groups.
The oximes are of two types:

1) Aldoximes: These are derived from aldehydes. In this case, at least either R or R^1 is hydrogen.
2) Ketoximes: These are derived from ketones. In this case, both R or $R^1$are alkyl or aryl groups only.

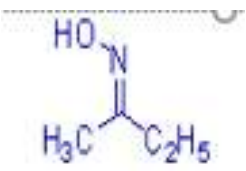
The oximes show geometrical isomerism due to restricted rotation of C=N bond. Two geometrical forms are possible for the oximes as shown below.

The descriptors, ***syn*** and ***anti*** are used to distinguish them.
* In case of aldoximes, the *syn* form is the one in which both the hydrogen and the hydroxyl (-OH) group are on the same side of the C=N. Whereas in the *anti*-form, they are on the opposite side.
E.g. The syn and anti forms of acetaldoxime are shown below.

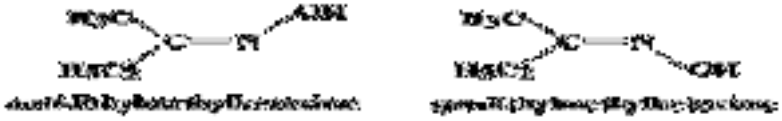
syn oxime anti oxime



However with ketoximes, the *syn* and *anti* descriptors indicate the spatial relationship between the first group cited in the name and the hydroxyl group. For example, the following ketoxime of butanone can be named as either syn methyl ethyl ketoxime or anti ethyl methyl ketoxime.



- **Ketoximes**



IUPAC SYSTEM OF NOMENCLATURE OF OXIMES:

* In the IUPAC system of nomenclature, the oximes are named as: N-hydroxyalkanimines, where the C=N group is represented by the suffix, imine and the -OH group on nitrogen is represented by the prefix, N-hydroxy.

E.g. The *syn* and *anti* forms of acetaldoxime are named as follows:

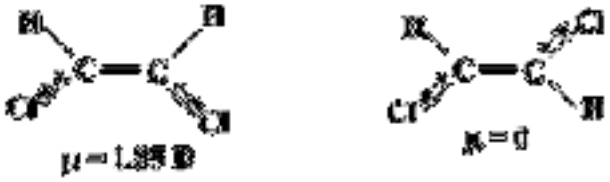
PART B

Determination of Configuration in Geometrical isomers

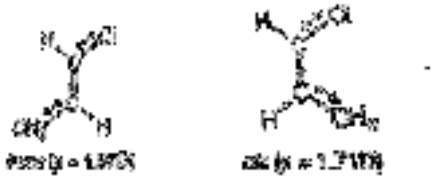
There is no absolute method for the determination of the configuration of cis-trans isomers. Several elementary relationships are helpful to relate the configuration of geometrical isomers. These methods are

I. Physical methods
II. Chemical methods

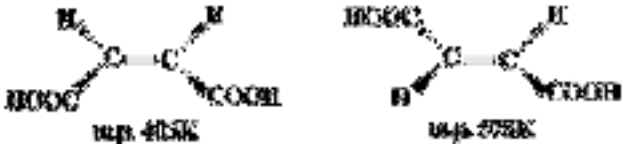
I. **Physical methods**: As the geometrical isomers differ in the spatial arrangement of atoms or groups about a double bond or alicyclic ring the isomers may differ in some of their physical properties.
   a. **Dipole moment**: In general, the trans isomers have less dipole moment than their corresponding cis isomers. As in geometrical isomers of 1,2-dichloroethylene, in trans isomer the two polar bond moments of C-Cl bonds are opposed because of symmetry of the molecules, but in cis isomer being non symmetrical has a dipole moment because the bond moments are not opposed.



But, if one substituent is electron donating and other electron-withdrawing , the bond moments are fully additive in trans isomer. Thus trans isomer has a higher dipole moment than its cis isomer. Ex. 1-chloropropene



2. **Melting points** and related phenomena: In genral trans isomer has greater symmetry than the corresponding cis isomer. Thus it packs more easily in the crystal lattice and hence has a higher melting point. Cis compound on the other hand have low melting point as they being less symmetrical do not have closed packing in crystal lattice.

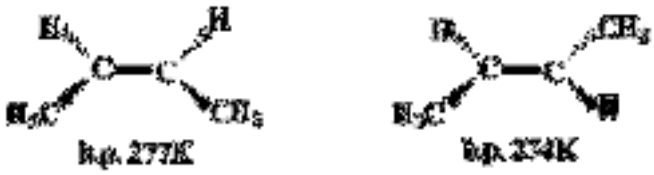


Solubility: More over the weaker forces of attraction can be easily broken by the dielectric constant of solvents and hence the cis isomer have greater solubility than trans.

Ex. Maleic acid (cis isomer) solubility is 79.0g/100ml

Fumeric acid (Trans isomer) solubility is 0.7g/100ml

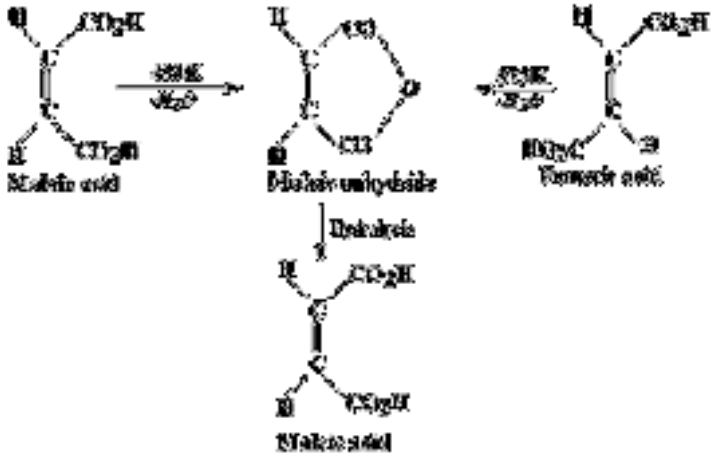
Boiling Points: Cis isomers have higher boiling points as they have higher dipole moment and form stronger attractive forces.



II. CHEMICAL METHODS

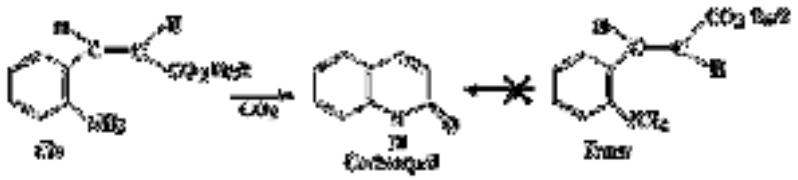
a. **Method of formation of cyclic compounds**: The cyclization of open chain compound to ring structure would be faster if the reacting group are close to each other. Similarly in conversion of alkene to cyclic structure would be faster if the reacting groups are on the same side of double bond, so, cis isomer can be cyclized mor readily than trans.

Ex. The cyclization of 2,3-diene-but-1,4-dioic acid to its cyclic anhydrideis faster in its cis isomer maleic acid as the reacting carboxylic groups are closer compare to trans Fumeric acid.



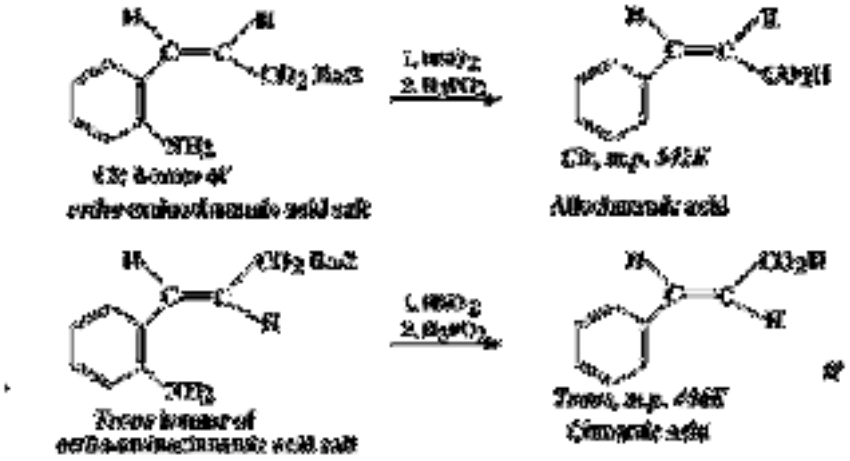
Similarly, Ortho-cinnamic acids: The Ba-salt of an isomer of ortho-cinnamic acid on treatment with CO2 at room temperature gives carbostyril. This shows that the substituted phenyl group must be cis in this isomer. On the other hand, the Ba-salt of the

other isomer of ortho-cinnamic acid does not give carbostyril under the same condition and therefore it must have the trans configuration



b. **Method of chemical correlation**: In this method the configuration of a geometrical isomer is deduced based on its conversion into a compound of know configuration. Ex.

Ex.1



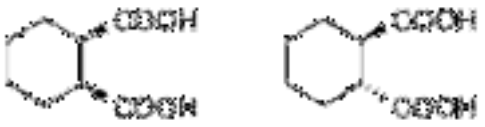
Ex.2 The conversion of one form of the trichlorocrotionic acid into fumaric acid on hydrolysis, so the substrate trichlorocrotonic acid must be the trans-isomer moreover the same trichlorocrotonic acid gives crotonic acid (m.p=72 degree Celsius) on reduction. The other isomer of trichlorocrotonic acid does not give fumaric acid on hydrolysis and from isocrotonic acid (m.p 15.5 degree Celsius) on reduction.

Hence the isocrotonic acid and the corresponding trichlorocrotonic acid are cis-isomers

C. **Method of optical activity**: Among the two member of geometrical isomers only one form is optically active whereas the other is optically inactive due to presence of an element of symmetry is optically active form can be resolved and may be used to establish its configuration

• Ex. Hexahydropthalic acid the trans-form of which has been resolved

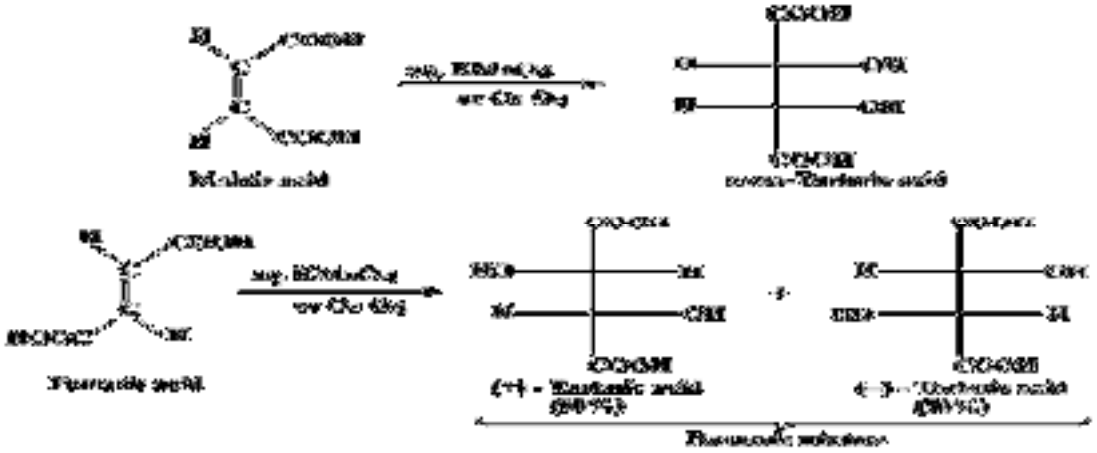
Cis = Optically inactive due to plane of symmetry Trans= Optically active and hence resolved



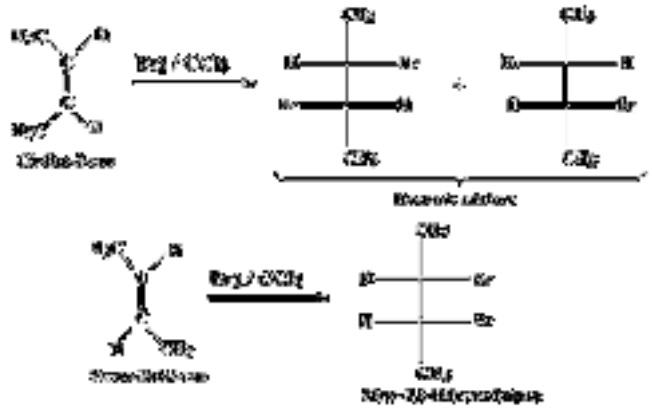
Cis Trans

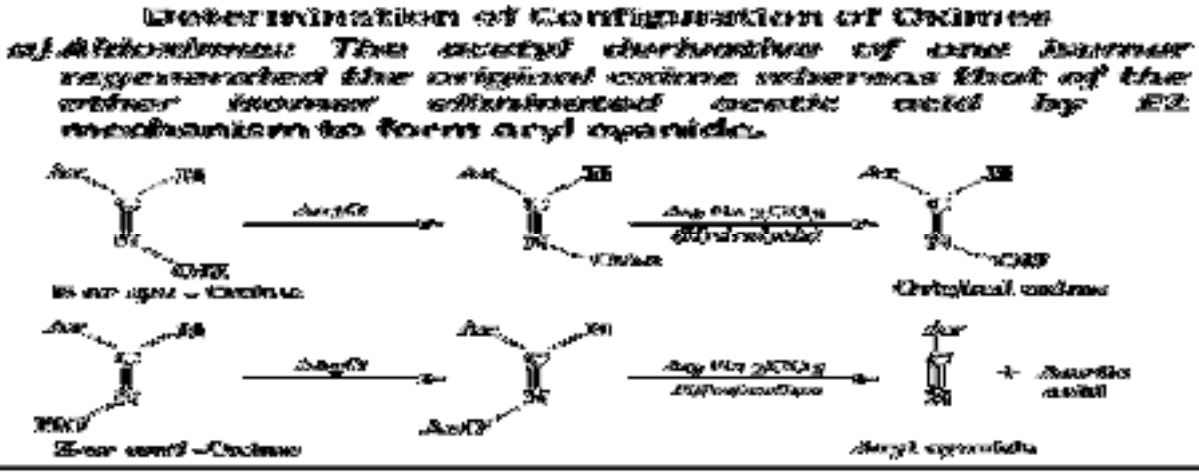
D. **Method of stereoselective addition** Reaction:

i. Hydroxylation of double bond is stereo specifically *cis*



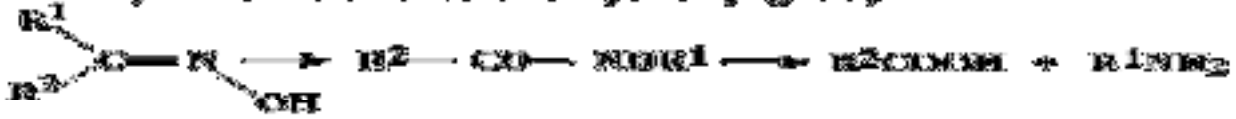
ii. Addition of bromine to double bond is stereo specifically *Trans.* Therefore, addition of bromine to trans isomer gives meso and cis gives racemic mixture.





b) *Ketoximes*

- The configuration of the geometric isomers of the unsymmetrical ketoximes are determined by *Beckmann rearrangement* which consists in treating ketoxime with acidic reagents such as PCl_5, H_3PO_4, P_2O_5 etc. when the oxime isomerizes to a substituted amide by migration of the group (R^1 or R^2) which is anti to the hydroxyl group.



Determination of structure of amine formed in the above sequence of reactions plays a key role in deciding which group has migrated during Beckmann rearrangement.

CONFORMATIONAL ANALYSIS

Conformers or Rotational isomers stereoisomers of a compound which have similar molecular and structural formula but differ in the spatial arrangement of atoms or groups due to rotation about a C-C single bond and conformers are interconvertible by rotation about the bond unlike configuration isomers which are not interconvertible by simple rotation about a bond.

Alkanes and cycloalkanes (Alicyclic compounds) which are characterized by the presence of C-C single bond can exhibit conformational isomerism as free rotation is possible about C-C single bond and results various spatial arrangements of atoms or groups.

Ex. Ethane can exist in different interconvertible rotational isomers arise due to free rotation about C-C single bond

The spatial arrangement of these interconvertible stereoisomers can be represented by

a. Saw-Horse arrangement
b. Newmans projections.

Ex. 1. **Conformers of Ethane**

The molecular formula of ethane is C_2H_6 and the structural formula is

In this structural formula of ethane both carbons are sp3 hybridized and the carbos are joined by C-C single bond. Each carbon is attached to three hydrogens, as free rotation is possible about C-C single bond. So, if we allow one of the carbons to rotate about C-C keeping other carbon fixed, various spatial arrangement of hydrogen atoms are possible depending on the angle through which we rotate CH_3 group.

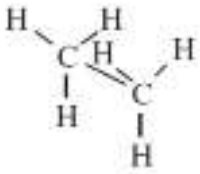
This angle of rotation is called **Diheral angle** and the resulting spatial arrangements are called **rotational isomers** or **Conformers**.

In ethane two conformers are possible known as

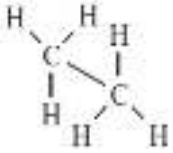
1. Staggered
2. Elcipsed

1. **Staggered** : In this conformer the hydrogen atoms of both singly boned carbon atoms are ass part apart as possible.
2. **Eclipsed**: In this conformer the hydrogen atoms of one carbon crowded or eclipsed over the hydrogens of the second carbon

Saw-horse representation of conformers of ethane



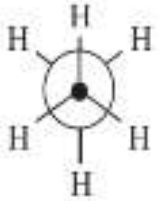
Eclipsed conformer



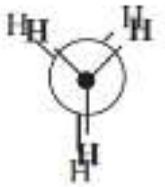
Staggered conformer

Newmans representation of Staggered and eclipsed conformers

In this representation the front carbon is represented as dot and the three bonds radiating from the center of the dot, and the back carbon connected to front carbon is represented as circle and the three bonds radiating from the edges of circle.



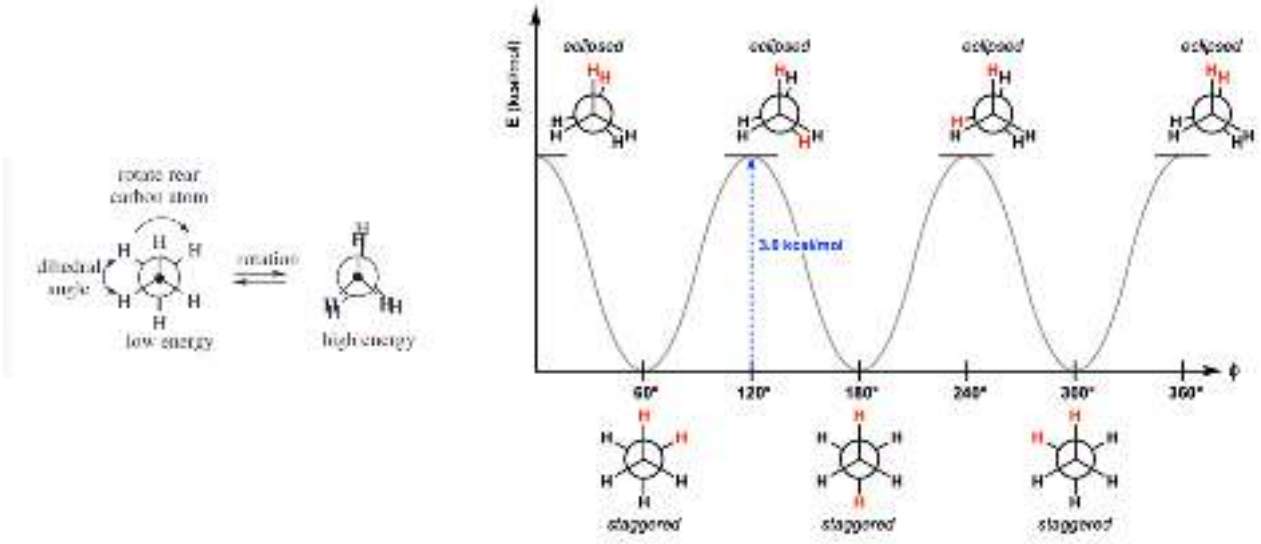
Staggered conformer



Eclipsed conformer

These projections shows that the rotation of front CH_3 group by 60^0 about C-C single bond converts staggered into eclipsed conformers. Similarly, if rotation is continued, we get different staggered and eclipsed forms for one complete rotation of 360^0.

But, staggered and eclipsed conformers differ in their stabilities due to difference in their potential energy. If we plot the graph of potential energy v/s conformers (dihedral angle) it appears as



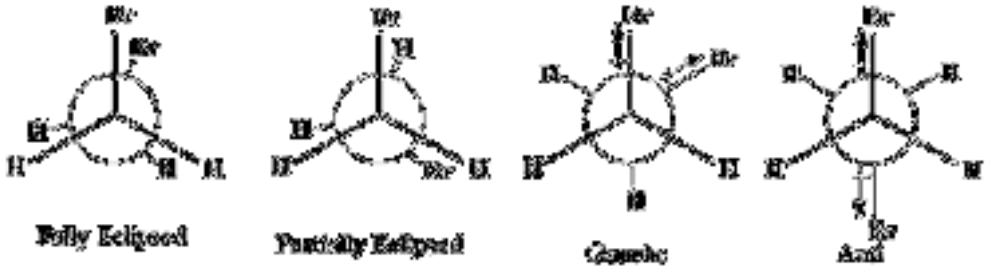
The above potential energy diagram indicates that the eclipse has greater energy and less stability, in the conversion of one staggered form to another it has to overcome an energy barrier of **3 kcal/mole**. So, staggered is more stable than eclipse.

This energy difference is attributed to the

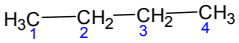
1. **Torsional strain**: In eclipsed conformer, the electron cloud of C-H bond of one carbon atom is crowded over the C-H bond of second carbon atom, thus there would be repulsion between these bonded electron clouds of different bonds, which is known as **Torsional strain** and this results increased potential energy and decreased stability of molecule. But in staggered form as the C-H bond electrons of different carbons are as far apart as possible. So, repulsive interactions are less and stability is more.

The amount of energy that need to be supplied to overcome this torsional strain and permit free rotation from one conformer to another is called Torsional energy.
The angle between front and back hydrogen is dihedral (or torsional) angle.
In ethane the energy differnce between staggered and eclipsed is only 3kcla/ mole and thus permit a free roation about C-C in ethane thus, thay can not be separated easily.

In 1,2-disubstituted ethane there is intermediate satble conformer between satggered and eclipsed which is known as Skew or Gauch conformer in which identical groups are sepated by dihedral angle of 60^0.
Ex. In 1,2dibromoethane the possible conformers are



Staggered (Anti) from is most stable followed by Gauche.
So, the order of stability is
Staggered (Anti from)>Gauche>partially eclipsed>Fully eclipsed

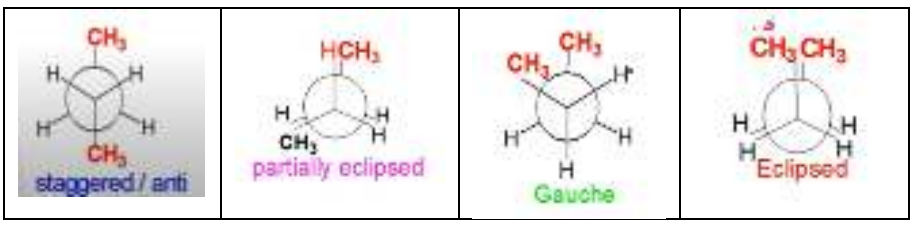


CONFORMATIONS OF n-BUTANE

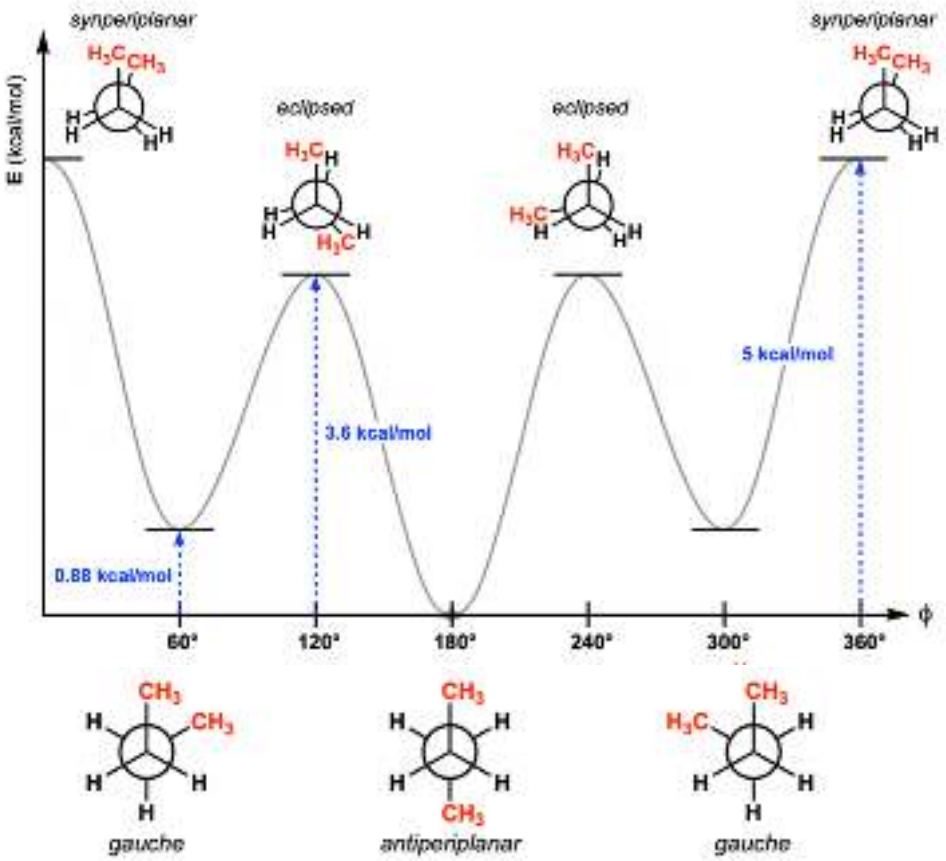
The molecular formula of butane is C_4H_{10}
The structural formula of n-butane is

When we consider the conformations of n-butane, since it has four carbon atoms and its dihedral angle could vary across three C-C carbons.

But when we consider the rotations about central C2-C3 single bond and treat end carbons as methyl groups, different rotational isomers that differ in the spatial disposition of the two hydrogens and one methyl attached to the C2 and C3 carbons would arise. In butane four conformations of two different eclipsed and two different staggered conformers would be possible and the conformers differ by the relative positions of the two methyl substituents.



The potential energy of different conformers of n-butane that arises for each rotation of 60^0 about C2-C3 carbons was found to be



From the above potential energy diagram it observed that the order of stability of different conformers of butane is

Antiperiplanar > Gauche conformer>partially eclipsed>synperiplanr(fullyeclipsed)

In fully eclipsed conformer (synperiplanar) as the identical groups are crowded and there are greater steric repulsions between the bulky methyl groups which have 0^0 dihedral angle and as a result the torsional strain increases and stability decreases.

In Gauche staggered form the torsional strain is less compared to synperiplanar, but it has steric repulsions between the bulky methyl groups as they have dihedral angle of 60^0

In antiperiplanar there are no steric repulsions and torsional strain as all hydrogens and methyl groups are as far apart as possible and the bulky methyl groups separated by dihedral angle of 180^0 therefore it is most stable conformer of n-butane

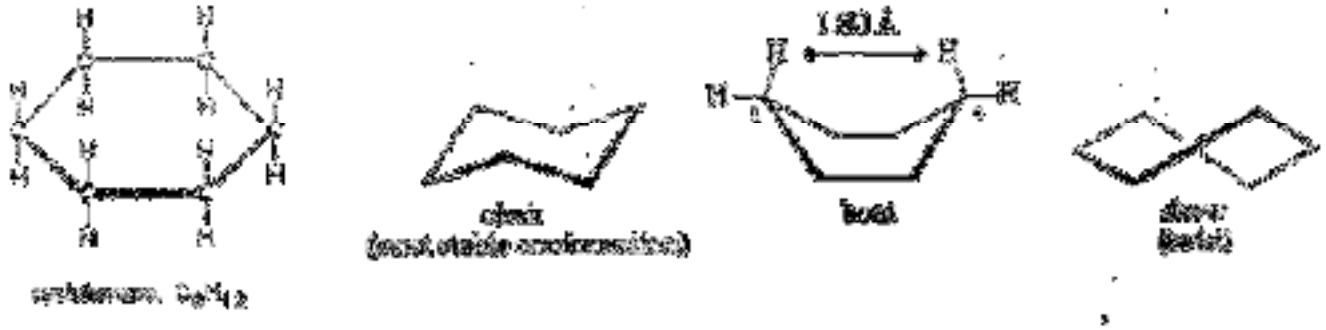
CONFORMATIONS OF CYCLOHEXANE

The concept of ring twisting in higher cyclokanes that contribute for their strain less forms, and increased stability was proposed by Sache-Mohr could be explained in cyciohexane molecule.

In cyclohexane planar representation the bond angle of C-C-C bond was assumed to be 120^0 by Baeyer. But cyclohexane undergoes ring twisting and can assume strain less conformations in which the C-C-C bond angles is restored to normal tetrahedral angle of 109.5^0

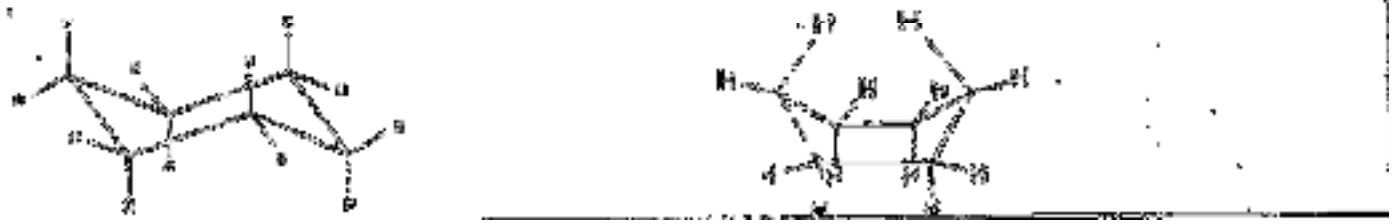
Cyclohexane can exist in two strain less forms such as chair and Boat forms.

In cyclohexane the two strain less forms are **Chair** form and **Boat** form.

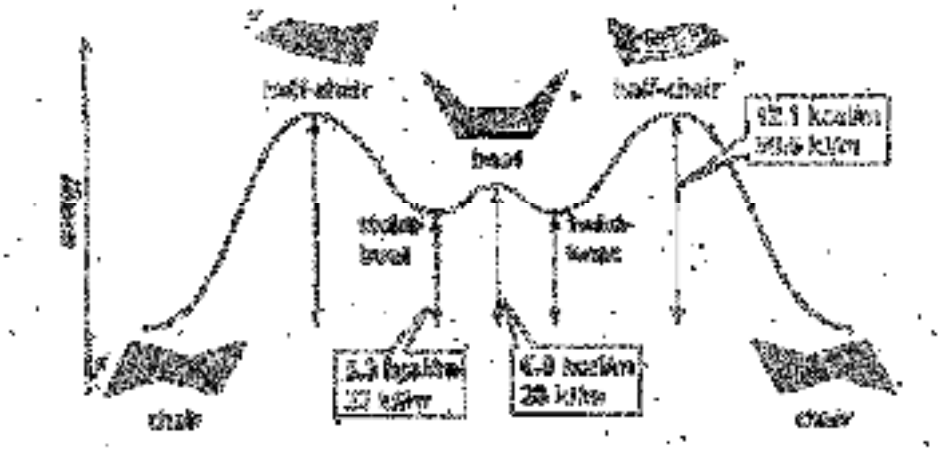


Conformational analysis of Cyclohexane

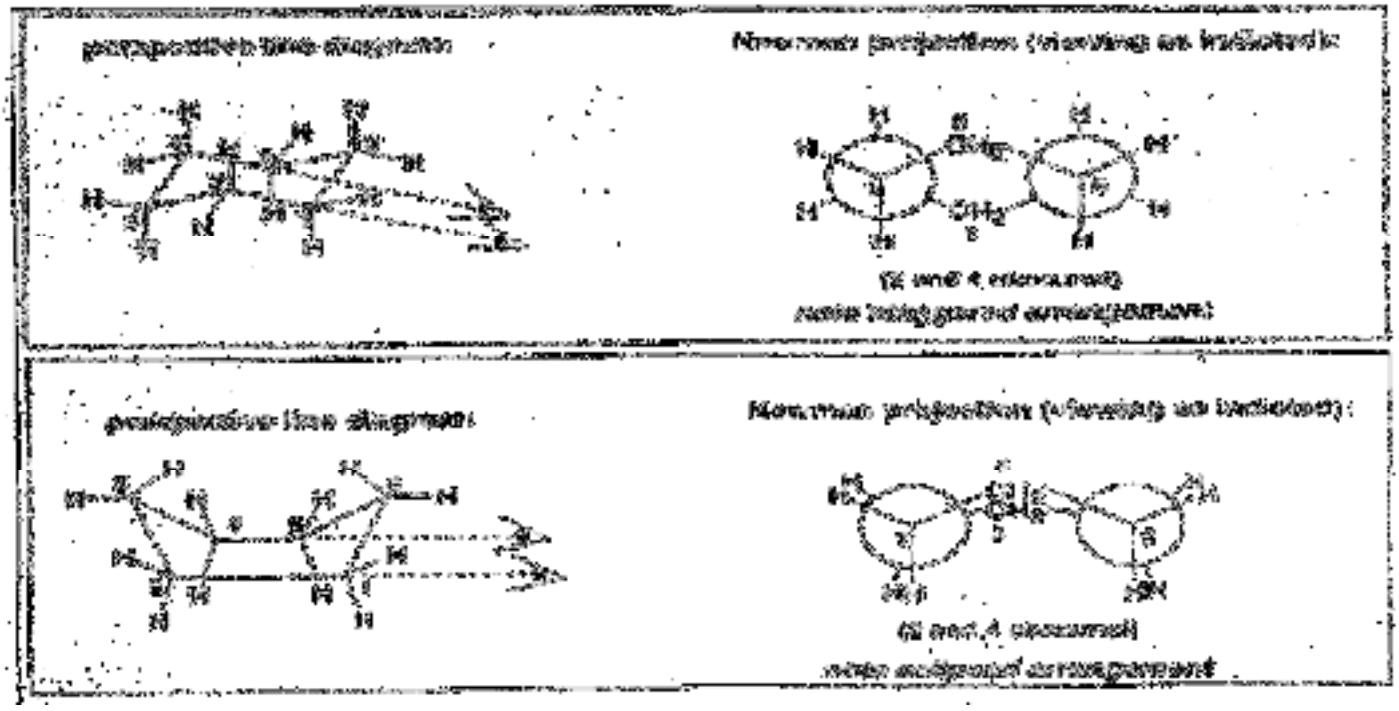
The two strainless forms of cyclohexane: Chair and Boat form are interconvertable by rotation of the bonds. So, these are known as conformers of cyclohexane



Both the Chair form and boat form are free from angle strain but they differ in their stability due to difference in their torsional strain. When chair form is converted into boat form the molecule undergo distortion and several bonds need to be rotated, this increases the potential energy and the molecule has to overcome high energy barrier. The representation of potential energy vs conformer in the transfer of a chair form to boat form appears as follows



The above potential energy diagram of conformers of cyclohexane reveal that, chair form has less potential energy and it is the most stable conformer. In the conversion of a chair form into boat form the molecule has to overcome an energy barrier of about 12 kcal/mole. It also indicates that the P.E of boat form is about 7 KCal more than that of the chair form. This high energy state of boat form is due to torsional strain in the molecule. The newmann projections of chair form and boat form explain the greater stability of chair form and the high energy state and lower stability of boat form.

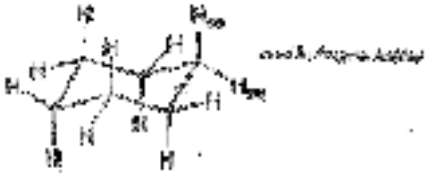


In the chair form all the C-H bonds on the adjacent carbon atoms are in staggered conformation. So, it is stable. But in boat form 1&6 and 3& 4 are in staggered. Similarly 1&2 and 3&4. But there are eclipsed interations between C2-C3 and C5-C6. These eclipsed interations increase the energy of the system. In addition to this it also experiences flag pole interactions between the hydrogens of C-1 and C-4 which are about 1.83 A° apart

which is less than their vanderwalls radius. This causes repulsion between them. As a result the energy of boat form is relatively high and it is less stable.

HYDROGENS IN CYCLOHEXANE CONFORMERS

In cyclohexane chair form the hydrogens exist in different spatial arrangement. One set of 6 H atoms are arranged in such way that they are parallel to the axis of the molecule or perpendicular to the plane of the molecule. These hydrogens arranged Axial hydrogens/axial bonds. The other set of 6 H-atoms are arranged in such a way that they are deflected away from the axis or make an angle with the plane of the molecule, these are known as Equatorial hydrogens/bonds. At each carbon atom one hydrogen would be axially oriented and other is equatorial.

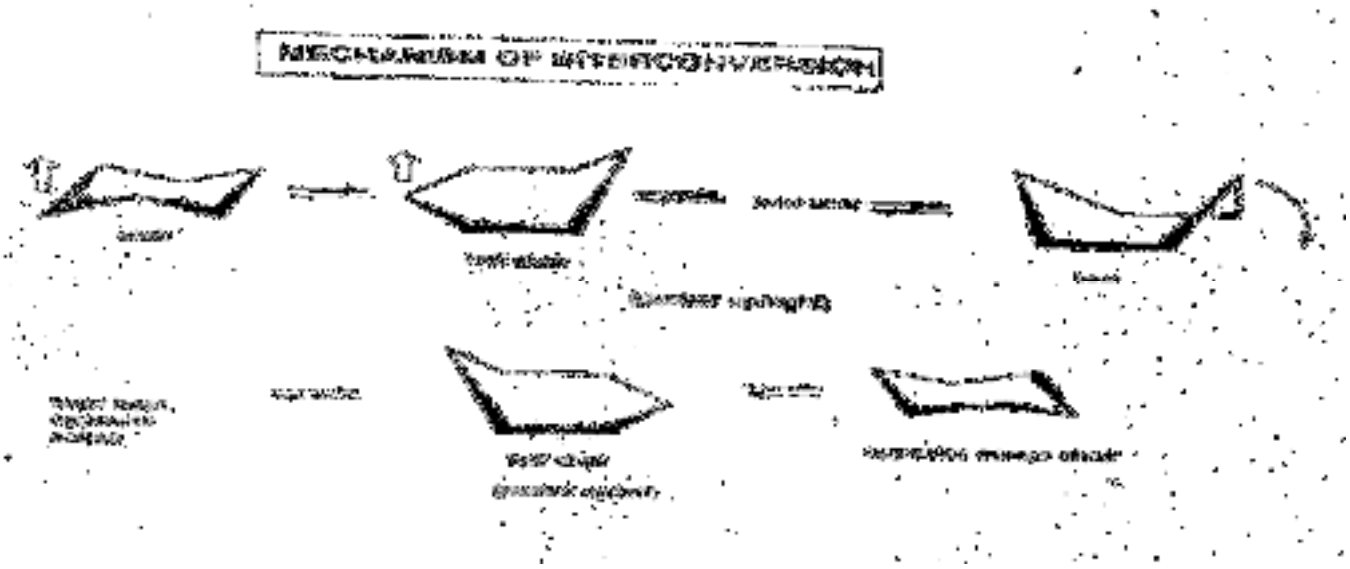


Conformational interconversion of Cyclohexane chair form:

Due to the mobility of chair form, one chair form is converted into another chair form. This conversion is known as ring flipping or Conformational inter conversion. In ring flipping the chair form is converted to twisted boat form then to boat form and again twisted boat form and finally a new chair form.

CHAIR-CHAIR INTERCONVERSIONS OR RING FLIP IN CYCLOHEXANE

(Hydrogens are removed, only C-H bonds are shown)



In ring flipping the orientation of axial and equatorial bonds change i.e all axial bonds are converted into equatorial and all equatorial bonds are converted to axial.

When substituted cyclohexane undergo conformational inter change the relative existence of two chair conformers which differ in the spatial orientation of the substituent depend on the nature of the substituents.

When we replace one of the hydrogen substituents with something larger, such as a methyl group, two chair conformations are possible which are different: in one, the methyl group is equatorial and in the other it is

axial.

methyl group axial

methyl group equatorial (more stable)

When the methyl group is in the axial position, it is brought close enough to the hydrogens on carbons #3 and #5 to cause steric repulsion.

When in the equatorial position, the methyl group is pointing out away from the rest of the ring, eliminating this unfavourable interaction. As a consequence, the conformation in which the methyl group is in the equatorial position is more stable, by approximately 1.7 kcal/mol. At room temperature, methylcyclohexane exists as a rapid equilibrium between the two chair forms, but the equilibrium constant (K_{eq}) favors the conformation where the methyl group is equatorial.

The importance of the steric repulsion factor increases with the increasing size of a substituent. Tert-butyl cyclohexane, for example, is much more stable (by approximately 5.6 kcal/mol) in the chair conformation in which the bulky tert-butyl group is in the equatorial position.

As a general rule, the most stable chair conformation of a disubstituted ring will be that in which the bulkier groups are in the equatorial position.

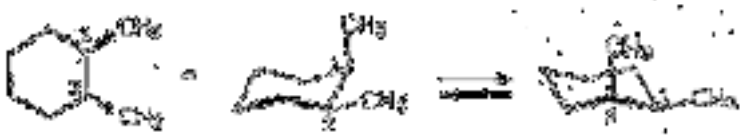
Geometrical Isomerism in Cyclohexane

The existence of geometrical isomerism in cycloalkane due to the spatial arrangement of groups above and below the plane of the ring structure could be explained by considering the chair conformers of cyclohexane.

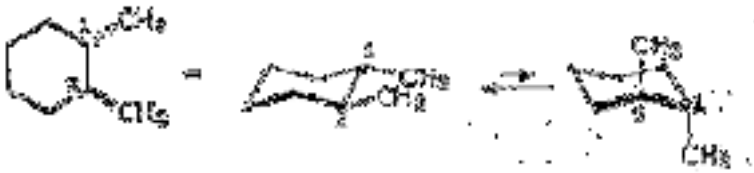
Ex: In a disubstituted cyclohexane geometrical isomerism is possible due to the arrangement of substituents as axial or equatorial orientations on different carbons of ring.

There are two geometrical isomers (cis & trans) possible in case of dimethylcyclohexane based on the position of substituents as shown below

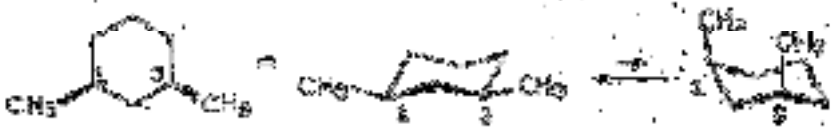
cis-1,2-dimethylcyclohexane



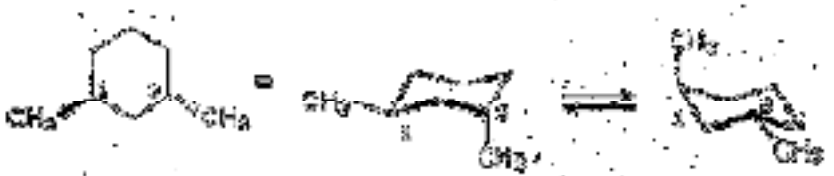
trans-1,2-dimethylcyclohexane



cis-1,3-dimethylcyclohexane

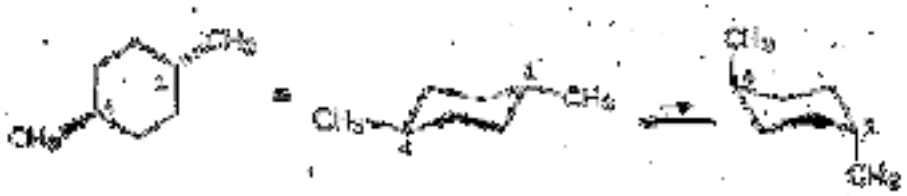


trans-1,3-dimethylcyclohexane



cis-1,4-dimethylcyclohexane

trans-1,4-dimethylcyclohexane



Therefore, for cis-1,2-disubstitution, one of the substituents must be equatorial and the other axial; in the trans-isomer both may be equatorial. Because of the alternating nature of equatorial and axial bonds, the opposite relationship is true for 1,3-disubstitution (cis is all equatorial, trans is equatorial/axial). Finally, 1,4-disubstitution reverts to the 1,2-pattern.

ATROPISOMERISM

Atropisomers are stereoisomers or conformers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers (from Greek, a = not and tropos = turn).

The name was introduced by Kuhn in 1933, but atropisomerism was first detected in 6,6'dinitro-2,2'-diphenic acid by Cristie in 1922.

The concept of atropisomerism can be explained based on substituted biphenyl compounds.

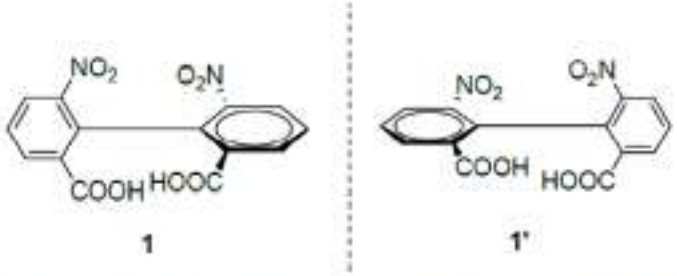
Biphenyls are compounds whereby a phenyl ring is connected to another through a central σ bond.

In unsubstituted biphenyl, there is sufficient amount of freedom of rotation around the central single bond to allow for free interconversion between the various conformers or rotamers so that the various rotamers cannot exist independently.

However, biphenyls with large substituents at the ortho positions on either side of the central σ bond experience restricted rotation along this bond due to steric hindrance. If the substituents are different, a chiral molecule existing as a pair of enantiomers called atropisomers is obtained.

Ex. In substituted biphenyl compounds such as 6,6'dinitro-2,2'-diphenic acid, due the bulky groups at ortho positions of single bonded phenyl rings, there would be greater steric repulsions between the non bonded groups and prevent free rotation about C-C single bond, as a result the phenyl rings will be no longer planar and they would be perpendicular to each other. Thus, the whole molecule would be asymmetric and is not superimposable on its mirror image.

So, 6,6'dinitro-2,2'-diphenic acid exists in a set of enantiomers (non-superimposable mirror images) atropisomers. In these isomers the molecule has no asymmetric /chiral center but due to restricted rotation about C-C single bond the whole molecule has be become asymmetric.



Enantiomers of the 6,6'-dinitrobiphenyl-2,2'-dicarboxylic acid

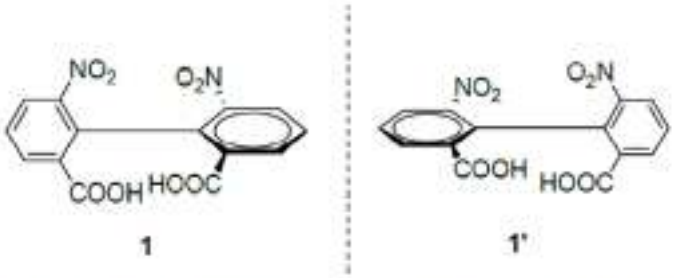
Atropisomerism is also called axial chirality and the chirality is not simply a center or a plane but an axis.

CONDITIONS NECESSARY FOR ATROPISOMERISM IN BIPPHENYL COMPOUNDS

1. A rotationally stable axis
2. Presence of different substituents on both sides of the axis

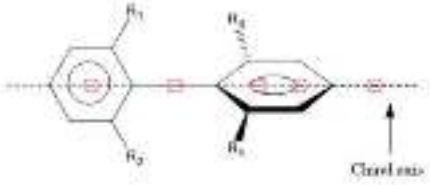
The configurational stability of axially chiral biaryl compounds is mainly determined by three following factors:

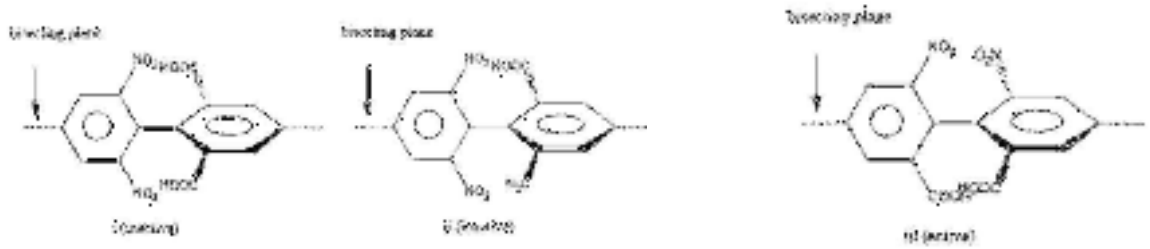
1 The combined steric demand of the substituent in the proximity of the axis.: The substituents in the ortho-position must have a large size. If three bulky groups present on ortho position they cause restriction. The groups are large enough to interfere mechanically i.e., to behave as obstacles then free rotation about the single bond is restricted. Thus, the two benzene rings cannot be co-planar.



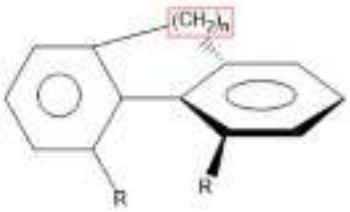
Enantiomers of the 6,6'-dinitrobiphenyl-2,2'-dicarboxylic acid

3. Resolvable biphenyls must contain different ortho substituted on each ring, if one or both rings contain two identical substitutions the molecule is not chiral, in other words plane of symmetry must be absent in biphenyls.



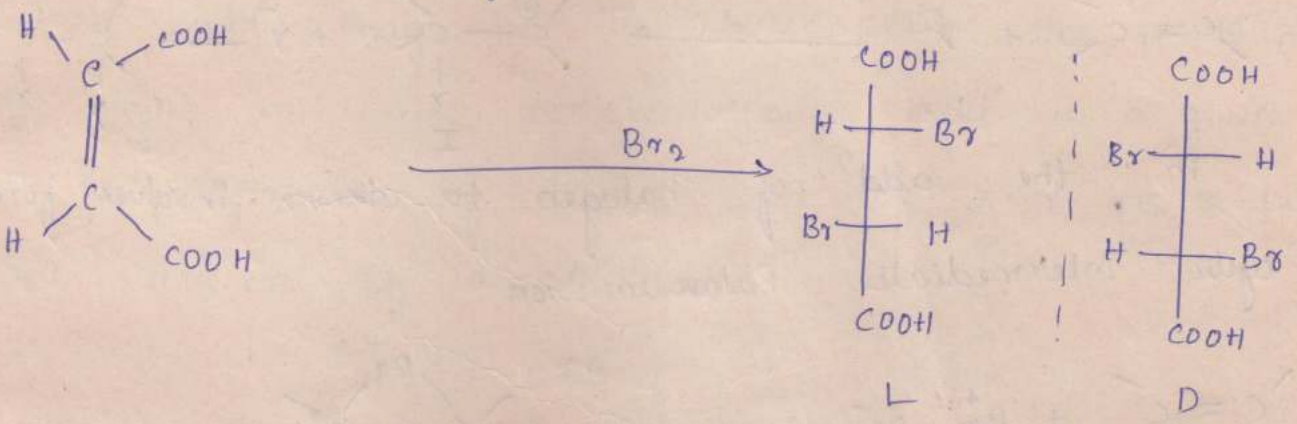


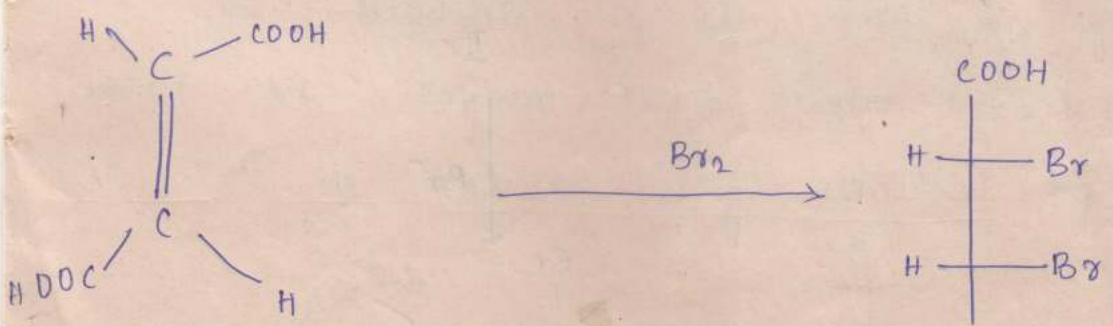
ii. The existence, length and rigidity of bridges: Biphenyls with 2 and 2' positions bridged with rings of various sizes can also exhibit atropisomerism. Biphenyls of this type, where n>2 are always optically active.



Any reac^n in which only one of a set of stereoisomers is formed exclusively or predominantly is called a stereo selective reac^n. The terminology can also be applied when a mixture of two or more stereoisomers are formed predominantly at the expense of other stereoisomers. In a stereospecific reac^n the given isomer leads to one product & other stereoisomer of it forms opposite product. All stereospecific reac^n are necessarily stereoselective.

Eg:- When Maleic acid is brominated it forms D & L pair of 2,3-dibromosuccinic acid but not its meso form. The fumaric acid which is stereoisomer of maleic acid on bromination forms meso 2,3-dibromosuccinic acid but not D & L isomers. So this reac^n is stereospecific & stereoselective because two opp isomers give two opposite products



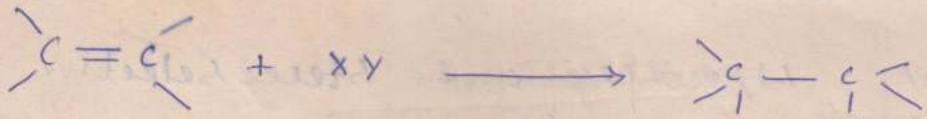


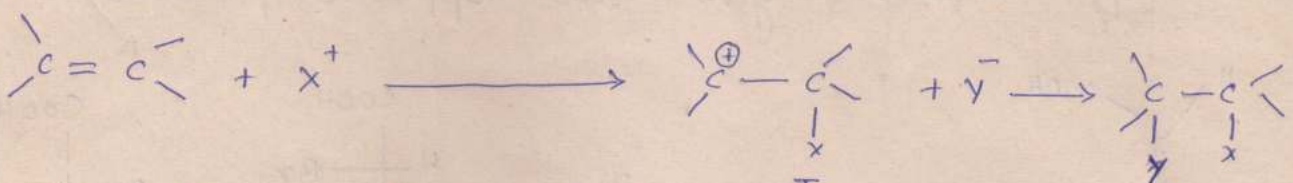
formed D & L pair & a mixture in which D & L pair predominated the reaⁿ would be stereoselective but not stereospecific. If in both reaⁿ D, L & meso forms are formed. the reaⁿ would have been non stereoselective. if a reaⁿ is carried out on a comp that has no stereoisomers it cannot be stereospecific It can be only stereoselective.

Eg:- Addⁿ of Br_2 to methylacetyline results preferentially the formⁿ of trans 1,2-dibromopropane. It is stereoselective but not stereospecific reaⁿ

Stereochemistry of electrophilic addition to alkenes: (Addition of halogen to alkene:)

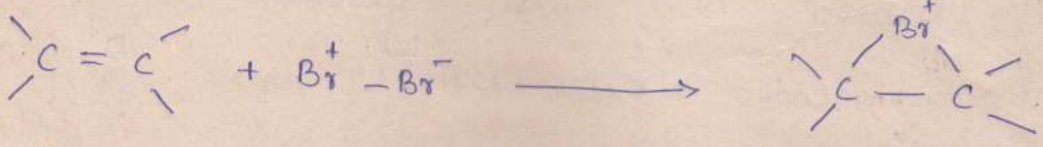
Alkenes undergo E^+ addⁿ reaⁿ. The general mechⁿ of E^+ addⁿ to alkene involves two steps.



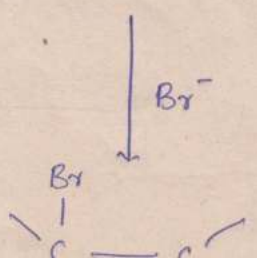


I

But in the addⁿ of halogen to alkene involves formⁿ of cyclic intermediate halonium ion



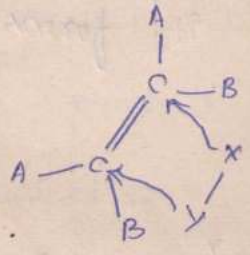
II



& 4 atoms attached are all in a plane. So they are three possibilities of add^n of reagent x-y to an alkene.

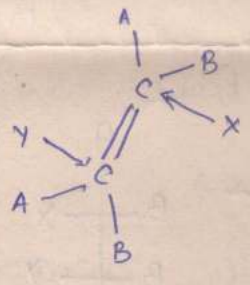
ABC = CAB

1) The groups x-y may enter from same side of plane in which case the add^n is stereospecific and it is known as Syn add^n.



Syn addition

2) The groups x-y may enter from opposite side of the plane in which case add^n is stereospecific which is known as Anti add^n.

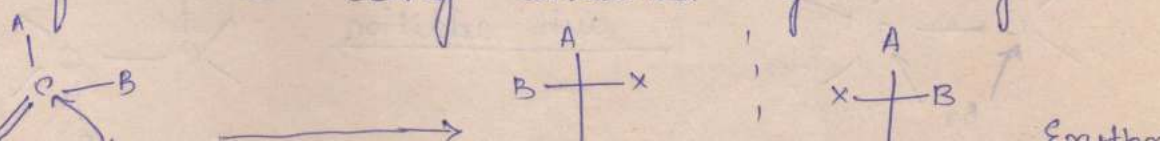


Anti addition.

3) The add^n may be non stereospecific. The possibilities of syn, anti are non stereospecific add^n in a given reac^n can be explained by taken add^n of x-y to a cis & trans isomers of a substrate.

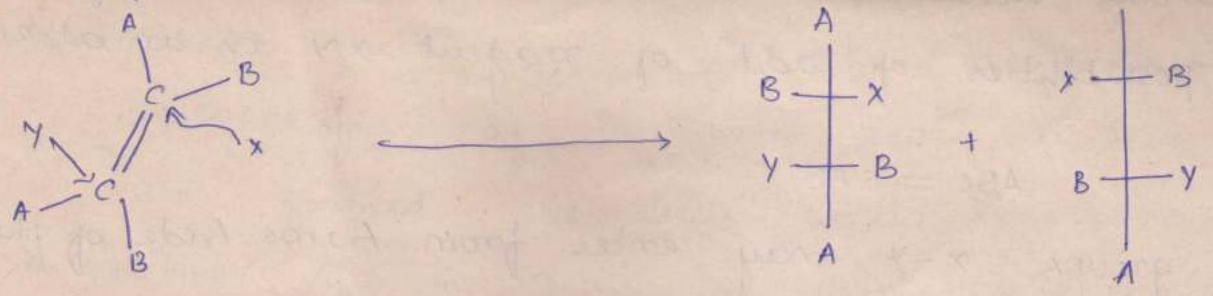
ABC = CAB

1) If the substrate is cis, add^n is syn, products would be erythro D & L pair because each carbon has 50% of chance being attacked by x or y.

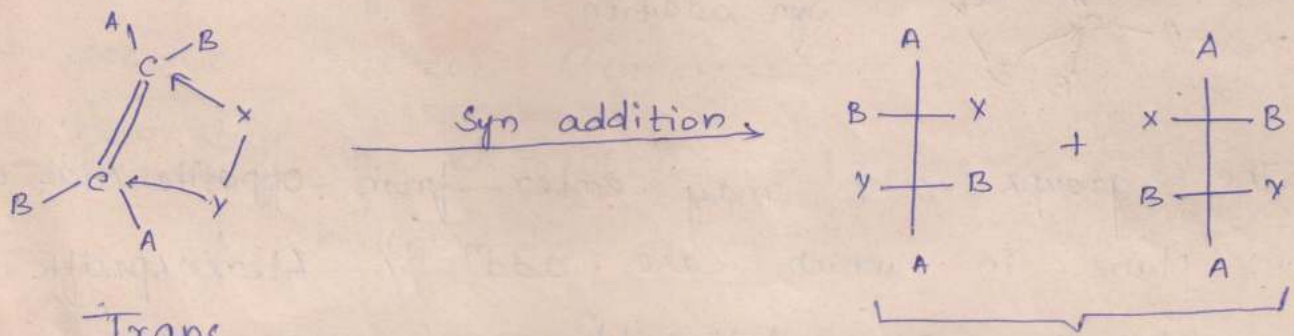


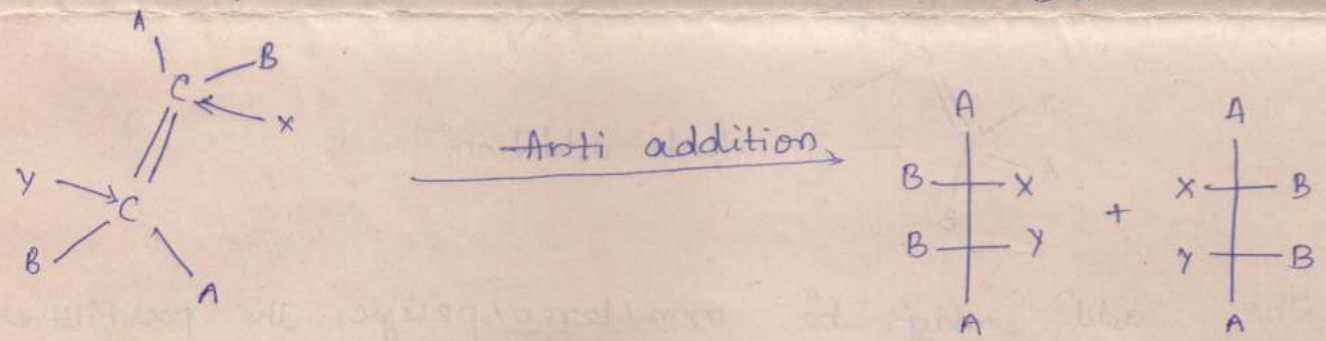
Erythro

D & L pairs.

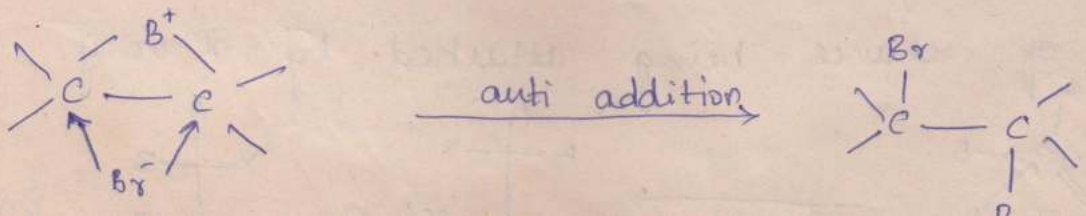


3) If the substrate is trans, add^n is syn. It forms Threo D & L pairs, if add^n is anti it forms erythro D & L pairs.

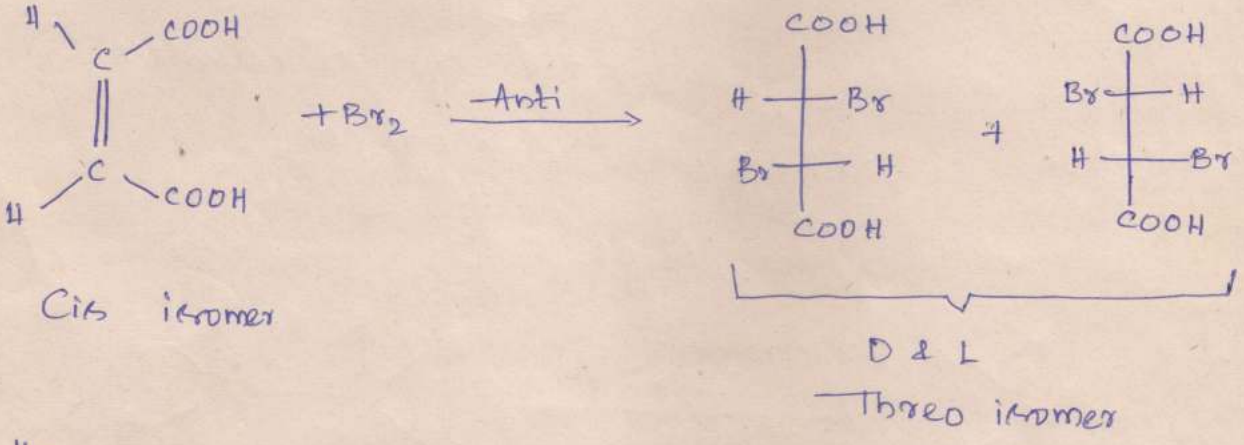




The add^n of halogen to alkene is stereospecific & it is always anti add^n because it involves form^n of cyclic intermediate halonium ion. So the second carbon attacks from opposite end.



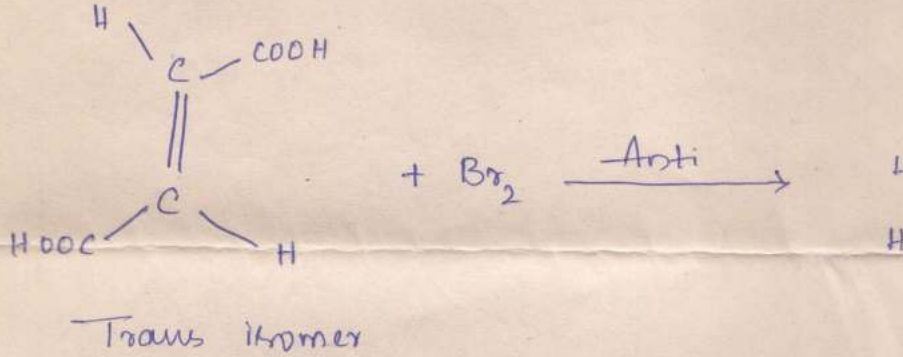
& trans isomers form diff products. The syn maleic acid upon anti add^n of Br_2 yields threo D & L pair of 2,3-dibromo succinic acid. The trans isomers upon anti add^n of Br_2 yields the erythro 2,3-dibromo succinic acid which is a meso compound.



Cis isomer

D & L

Threo isomer



Trans isomer

meso compound

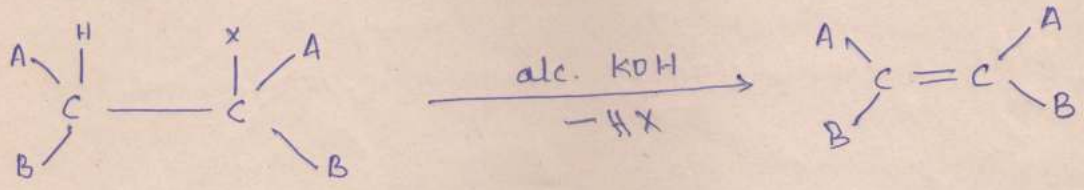
erythro isomer

The add^n reac^n involving form^n of Carbocation. If Carbocation has relatively ~~have~~ long life the add^n would be non stereospecific since there will be free rotation above the single bond.

Stereochemistry of Nucleophilic Substitution Reaction

Stereochemistry of Elimination Reaction:

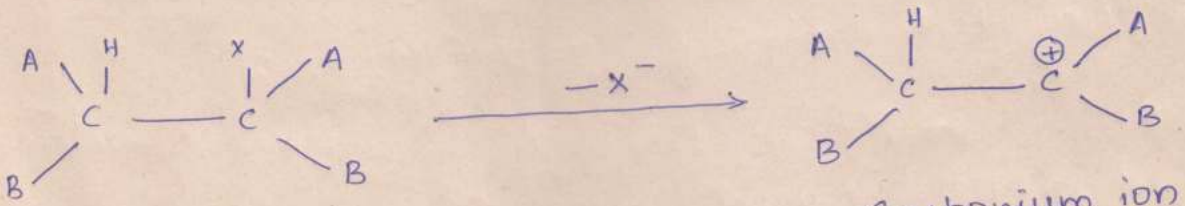
When two atoms or groups are removed from adjacent Carbon atoms without being replaced by other atoms. it forms double bond b/n the two Carbons.



Elimination involves two types of mechanisms.

1) E_1 elimination or unimolecular elimination:

It involves two steps.



Carbonium ion

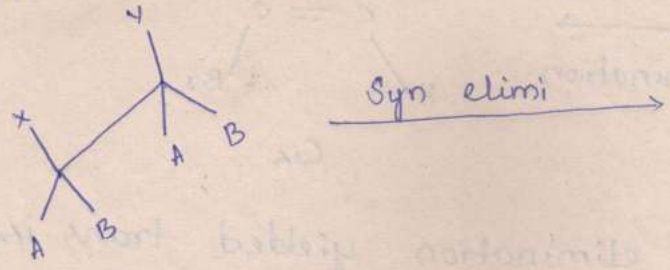
Since this involves form^n of carbonium ion. if Carbonium ion has relatively long life the eliminat^n would be non stereospecific since there is will be free rotation about the single bond in Carbonium ion.

2) E_2 elimination:

In this elim^n bimolecular reac^n the clevage of the two bonds occurs simultaneously.

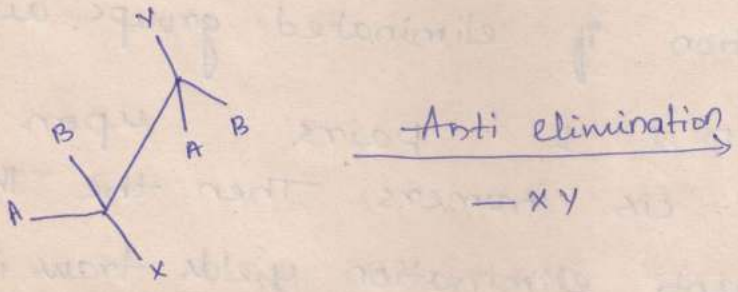
Eg:- In the dehydrohalogenation of alkylhalides in presence of

groups are eliminated from same side.

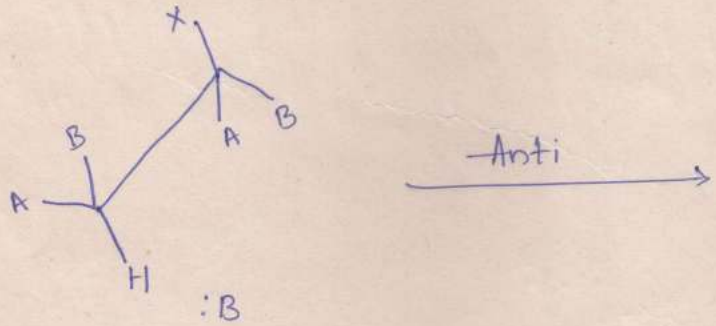


In this the dihedral angle b/n eliminated groups is zero.

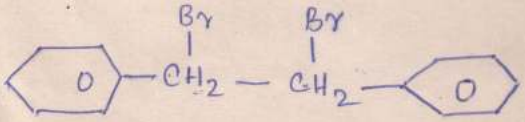
Anti elimination: In this the two groups are eliminated from opposite side which have a dihedral angle of 180°

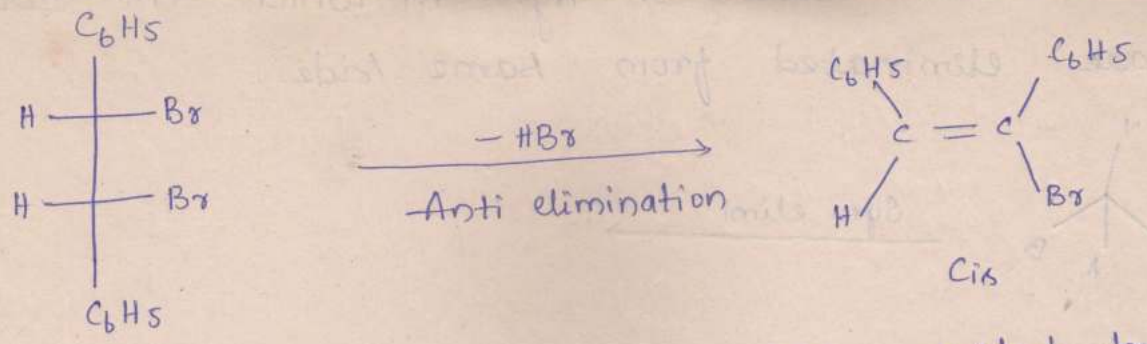


In the E_2 elimination of dehydrohalogenation of alkylhalides, the substrate and abstracting of H^+ are in one plane so anti elimination is prefered.

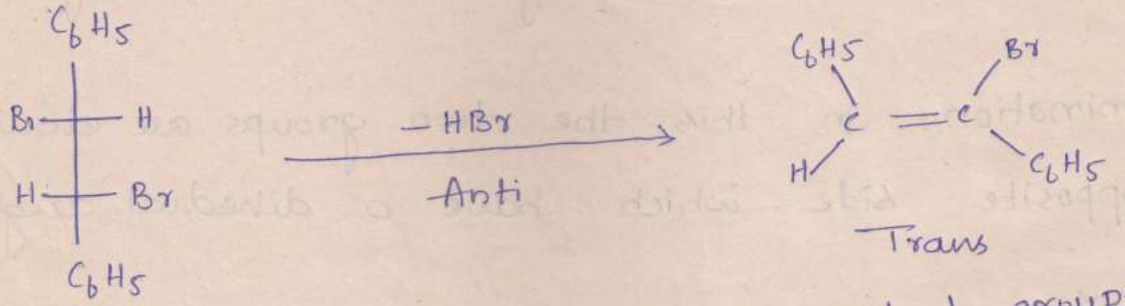


This is proved in the elimination reaⁿ of meso 1, 2 - dibromo - 1, 2 - diphenyl ethane ~~2, 3 - dibromo - 2, 3 - diphenyl - 2 - methyl ethane~~ to form an alkene The erythro isomer upon elimination yielded cis isomer



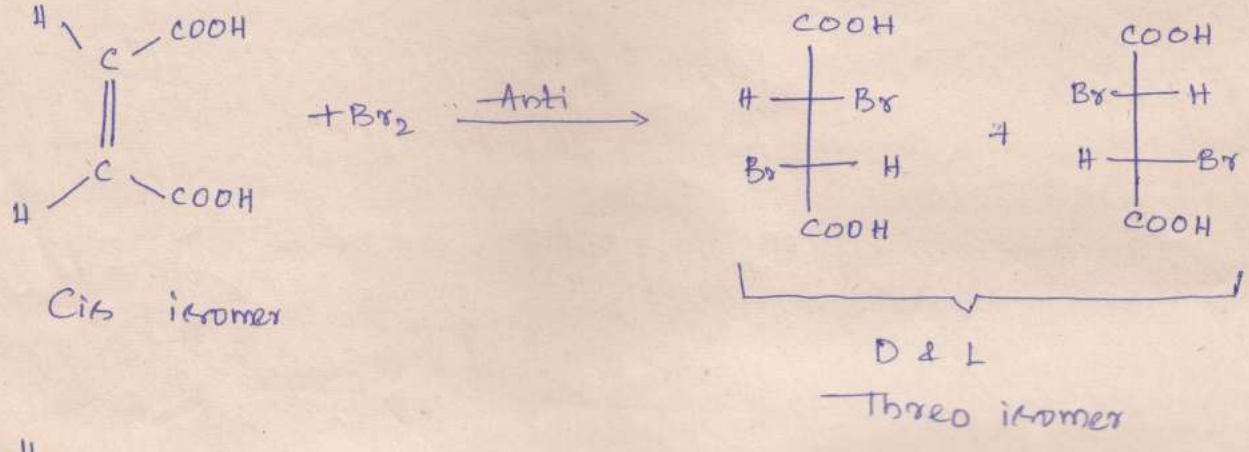


The Threo isomer upon elimination yielded trans isomer.



So in E_2 elimination if eliminated groups are dissimilar. Erythro D & L - pairs upon anti elimination yields cis isomers. Then the Threo D & L pair upon anti elimination yields trans isomer.

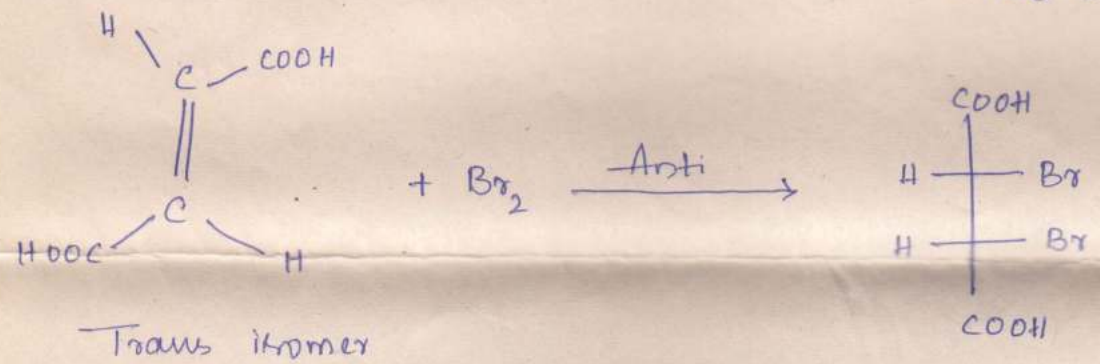
In the add^n to Maleic acid & fumaric acid the cis & trans isomers form diff products. The syn maleic acid upon anti add^n of Br_2 yields threo D & L pair of 2,3-dibromo succinic acid. The trans isomers upon anti add^n of Br_2 yields the erythro 2,3-dibromo succinic acid which is a meso compound.



Cis isomer

D & L

Threo isomer



Trans isomer

meso compound

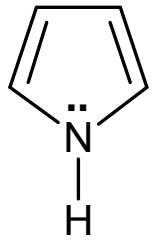
erythro isomer

The add^n reac^n involving form^n of Carbocation. If Carbocation has relatively have long life the add^n would be nonstereospecific since there will be free rotation above the single bond.

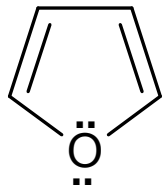
Stereochemistry of Nucleophilic Substitution Reaction

CHEMISTRY OF FIVE MEMBERED HETEROCYCLIC COMPOUNDS

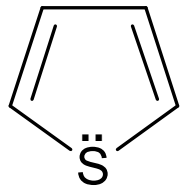
The three important five membered heterocyclic compounds (Fully unsaturated) containing Nitrogen, Oxygen and Sulphur hetero atom are PYRROLE FURAN , THIOPHENE



Pyrrole

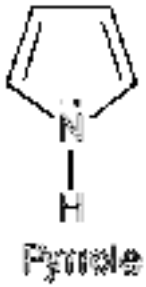


Furan



Thiophene

PYRROLE



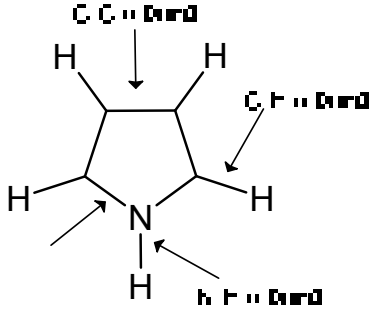
Pyrrole is an important five membered heterocyclic compound possessing a nitrogen atom as hetero atom.Many naturally occurring substances contain pyrrole ring e.g. Chlorophyll, hemoglobin and some alkaloids.

It occurs in coal-tar and in bone oil.

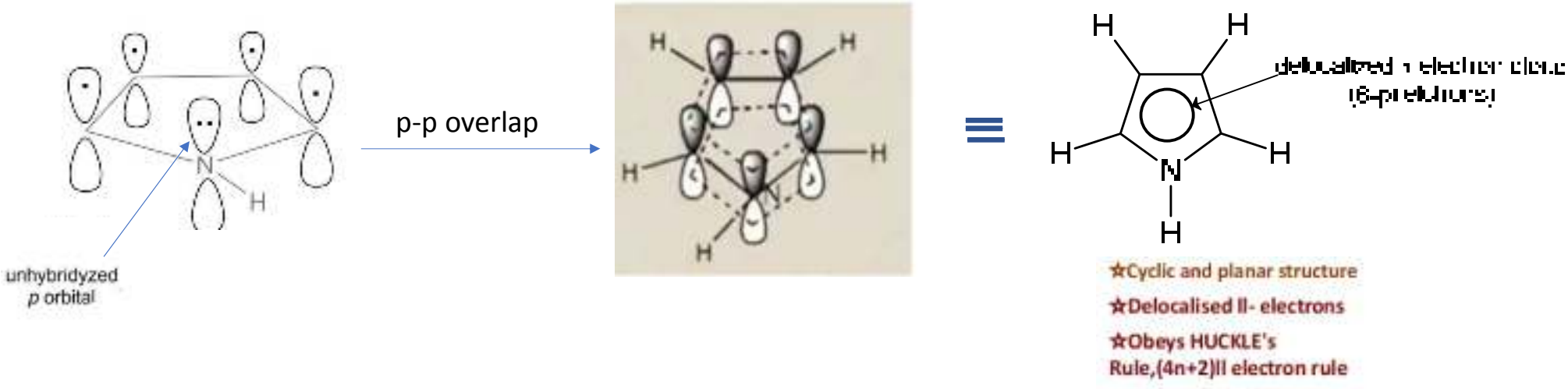
Structure-Aromaticity in Pyrrole

The molecular formula of pyrrole is C_4H_5N

The cyclic structure of pyrrole is Aza-cyclopenta-2,4-diene. In pyrrole the nitrogen atom and the four carbon atoms are sp2 hybridized. The sp2 hybrid orbitals overlap with each other and with s orbitals of five hydrogens atoms forming C-C, C-N, C-H and N-H sigma bonds. All these σ bonds lie in one plane.



In this sigma skeletal structure all the four carbons and Nitrogen have one unhybridized p atomic orbital arranged perpendicularly to the plane of the sigma bonds. The p orbitals of carbons contain one unpaired electron and the p orbital of nitrogen contain two electrons (the lone pair). The lateral overlap of the p orbitals of carbons form two pi bonds. But, as the p orbitals of heteroatom i.e nitrogen with lone pair of electron also merge with the p orbitals of carbon and it results in a delocalized pi electron cloud above and below the plane of the molecule and the pi electron cloud contain six pi electrons.



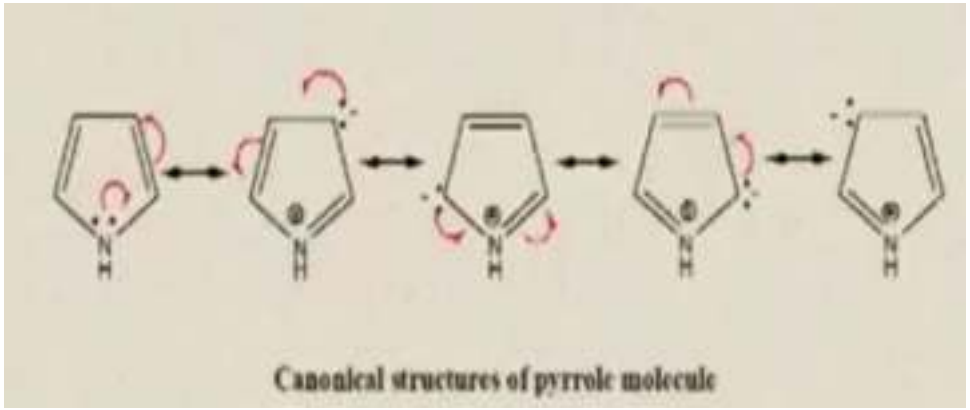
This structure of pyrrole is aromatic as it satisfies all the requirements of aromatic compounds i.e. i. cyclic and Planar

ii. Unsaturated and conjugated and contain delocalized pi electron cloud due to merger of unhybrid p orbitals of four carbons and nitrogen

iii. Obeys Huckles 4n+2 rule of pi electrons, the number of pi electrons in the delocalized pi electron cloud are 6 (4 p electrons one each from 4 carbons and one lone pair of electrons of nitrogen. So, 4n+2 = 6 and n=1

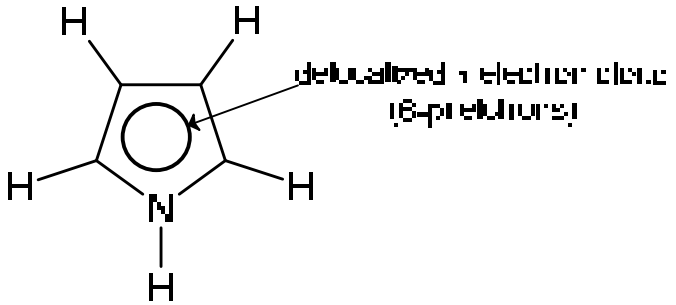
Resonance hybrid structure of Pyrrole

According to resonance theory, pyrrole is considered as a hybrid of the following resonance structure and the position of double bond is not fixed as it forms delocalized pi electron cloud



Canonical structures of pyrrole molecule

≡



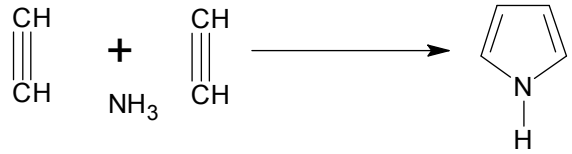
Resonance hybrid structure of Pyrrole

As in canonical structures the donation of electrons by nitrogen atom, the electron density on ring carbons increase as they carry negative charge, thus pyrrole carbons undergo electrophilic substitution reactions

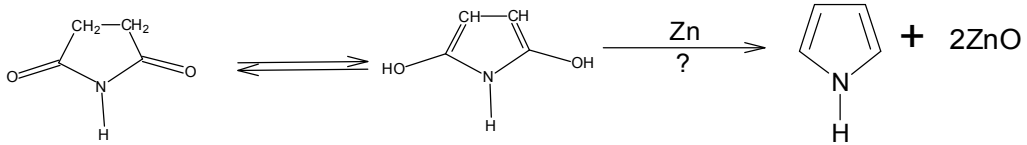
Measurement of bond lengths by X-ray analysis confirms the hybrid character of the pyrrole molecule. The C-N bond length of 1.38A^0 is shorter than the normal C-N single bond length of 1.48 A^0

METHODS OF PREPARATION OF PYRROLE

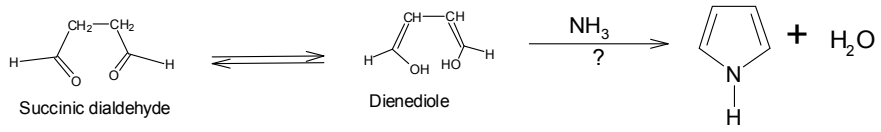
1. By passing mixture of acetylene and ammonia through a red hot tube



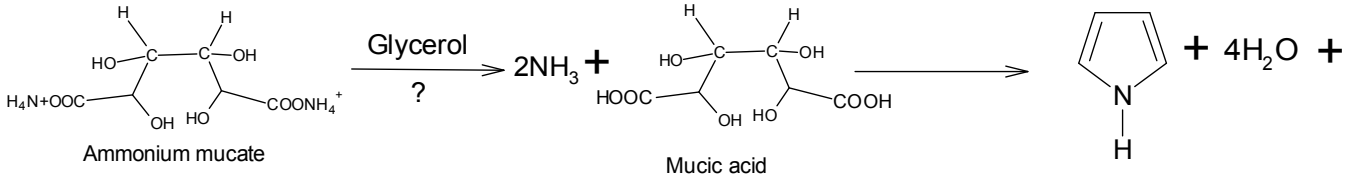
2. By heating succinimide with zinc dust



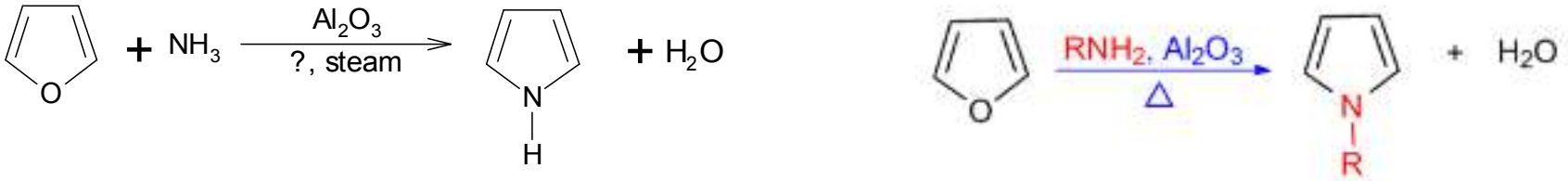
3. By warming succinic dialdehyde with ammonia



4. By heating ammonium mucate with glycerol at 200^0C. This results in mucic acid and ammonia. The acid then undergo dehydration , decarboxylation and ring closure by reaction with ammonia



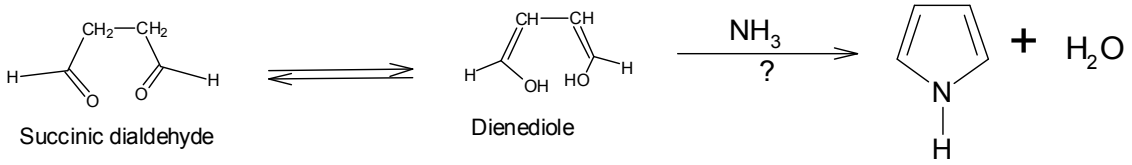
5. By passing a mixture of furan, ammonia and stem over aluminium oxide catalyst at 480^0-490^0C



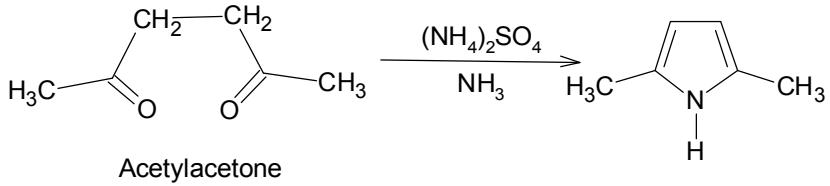
6.Different substituted Pyrroles are prepared by various cyclization/ring closure reactions

6a. **Paal-Knorr synthesis**: This is a general method of synthesis of pyrrole, furan, thiophene derivatives using 1,4-dicarbonyl compounds as substrates.

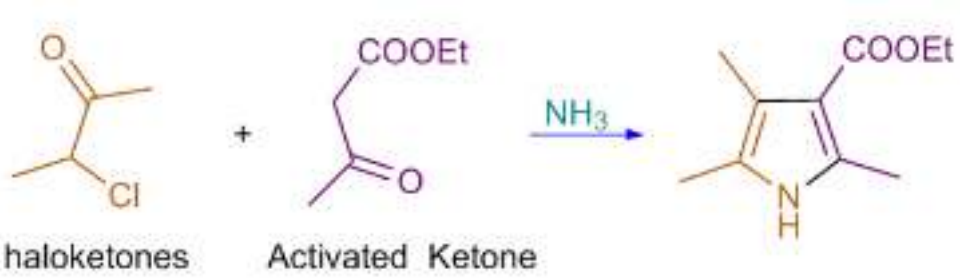
For pyrrole 1,4-diketone is condensed with ammonia or primary amine.
Simple pyrrole is prepared by the reaction of succinaldehyde and ammonia



The reaction of acetylacetone (a 1,4-dicarbonyl compound) with ammonia (used as ammonium sulphate) yields 2,5-dimethylpyrrole



6b. **Hantzsch Pyrrole synthesis**: Involves the cyclization of α-haloketone or aldehyde with β ketoester in the presence of nitrogen containing bases such as ammonia or amine

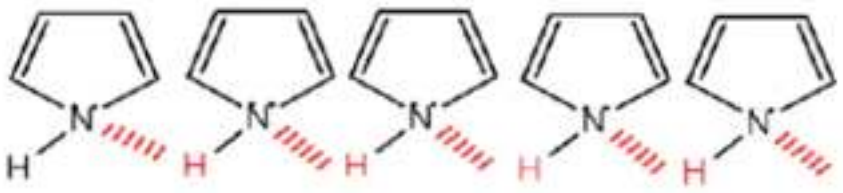


3-chloro-2-butanone Ethyl acetoacetate

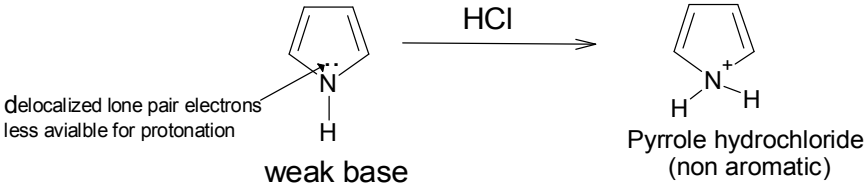
PROPERTIES OF PYRROLE It is colorless volatile liquid, It is sparingly soluble in water but readily soluble in alcohol and ether.

Tautomerism: due to migration of hydrogen from nitrogen to carbon it can exist in

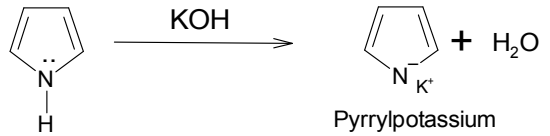
Pyrrole has a relatively high boiling point as compared to furan and thiophene, this is due to the presence of intermolecular hydrogen bonding in pyrrole.

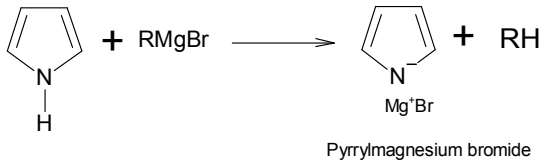


BASIC CHARACTER: Pyrrole is weak base with its conjugate acid pKa 3.4. The weak basic character of pyrrole is attributed to the non availability of lone pair of electrons of nitrogen as they are involved in delocalized pi electron cloud. When the lone pair of electrons accept a proton pyrrole loses its aromatic character and resonance stability.
It reacts with dilute hydrochloric acid to give crystalline pyrrole hydrochloride salt. This salt rapidly undergo polymerization in presence of oxygen to form a brown resin



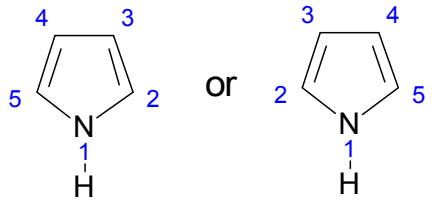
ACIDIC CHARACTER: Pyrrole with free hydrogen on nitrogen (imino hydrogen) posses weak acid character (pKa 17.5). It form salts with strong bases such as solid KOH and Grignard reagents. Pyrrole looses proton as the resulting Pyrril anion is resonance stabilized





ELECTROPHILIC SUBSTITUTION REACTIONS: Due to its aromatic character pyrrole undergo aromatic electrophilic substitution reactions like benzene. But its less aromatic and more reactive than benzene, thus it also undergo addition reactions readily.

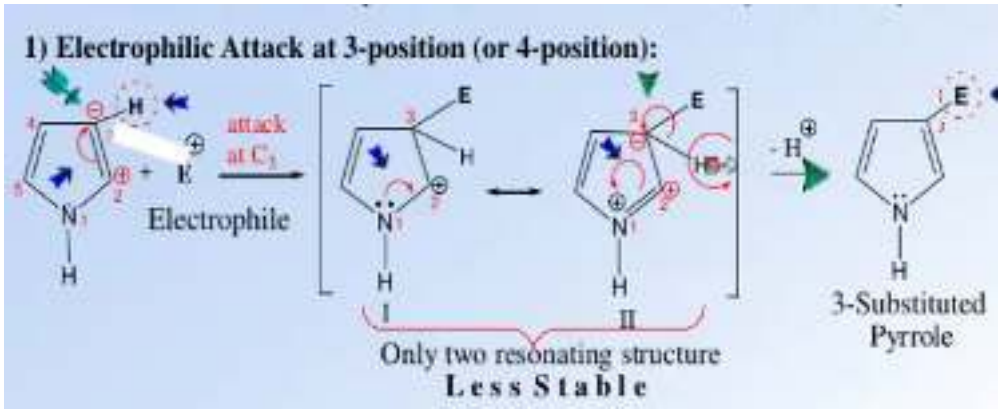
In pyrrole mono susbstituion can occur at two places on the ring i.e, C-2(C-5) or C-3(C-4).

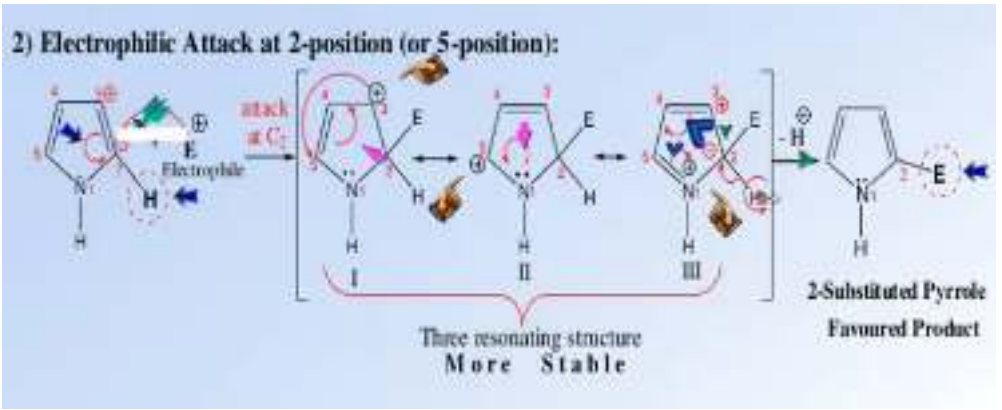


Position 2 and 5 are identical
and so are 3 and 4

ELECTROPHILIC SUBSTITUTION REACTIONS in pyrrole preferably occur at C-2. This can justified by comparing the resonance stability of intermediates carbocations formed in the rate determining step of Aromatic electrophilic substitution reactions at C-2 and C-3 in pyrrole.

Resonating structures of an intermediate carbonium ion (σ- complex) formed by the attack of electrophile (E+) at 2-position and 3-position are given below





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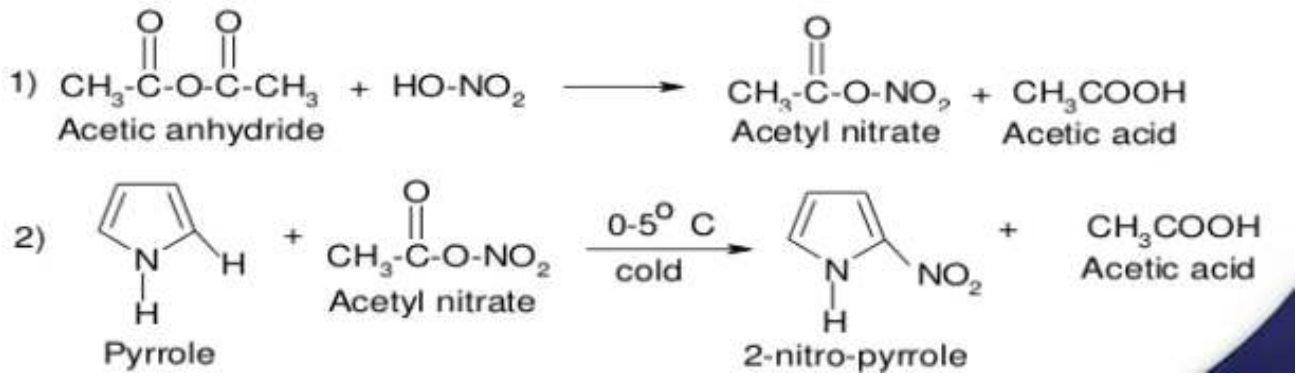
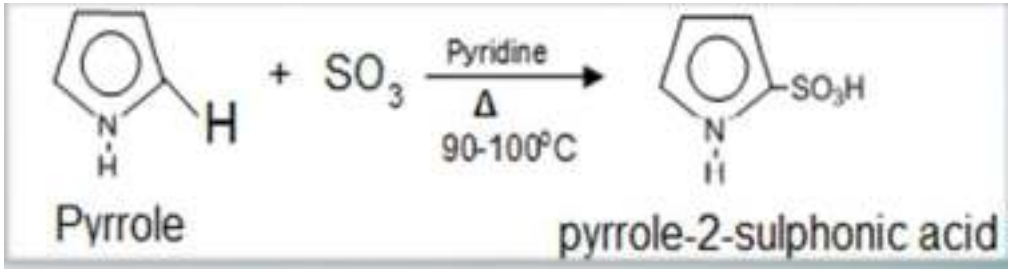
Pyrrole electrophilic substitution reactions are not carried out in presence of strong acids are reagents that give rise to strong acids, because under such conditions the pi bonds of ring undergo protonation and the resulting carbocation can attack another pyrrole ring, this leads to polymerization and resinification.

The different electrophilic substitution reactions and reaction conditions in Pyrrole are

1. **Nitration of Pyrrole:** Nitration of pyrrole is carried out using mild nitrating mixture such as cold solution of nitric acid and acetic anhydride, which forms acetyl nitrate as source of nitronium ion. The nitration occur at C-2 and from 2-nitropyrrole

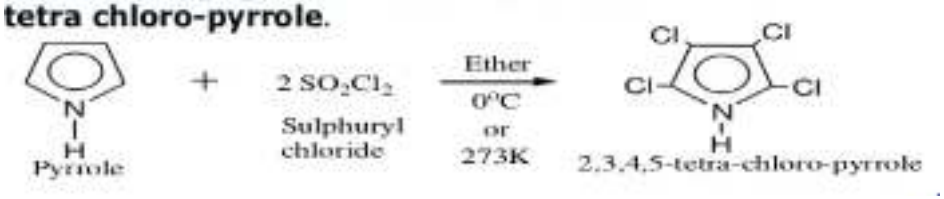


2.**Sulphonation of Pyrrole:** When pyrrole is heated with sulphur trioxide (SO_3) in pyridine, as a solvent, at about 90-100°C it forms pyrrole – 2-sulphonic acid (or 2-pyrrole- sulphonic acid).

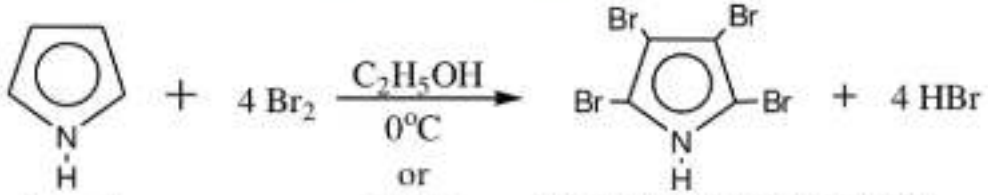


3.**Halogenation of Pyrrole:** Halogenation reactions of pyrrole proceeds with greater vigor an dfrom poly halogenated compounds.

a. **Chlorination**- When **pyrrole** is reacted or treated or heated with **sulphuryl chloride** (SO_2Cl_2) in ether at 0°C (273 K) ; to form **2, 3, 4, 5 – tetra chloro-pyrrole**.

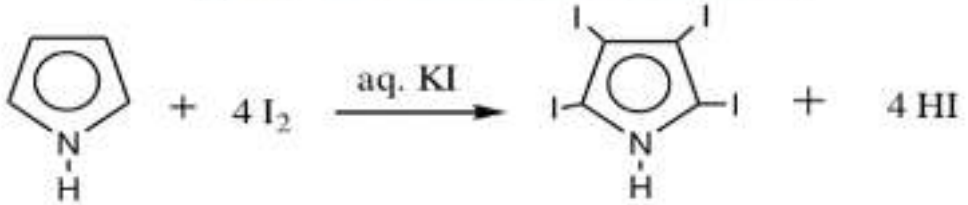


Bromination When **pyrrole** is reacted or treated with **bromine** (4 equivalents) in presence of **ethanol** at 0°C (or 273K); to form **2,3,4,5 –tetra bromo-pyrrole**.



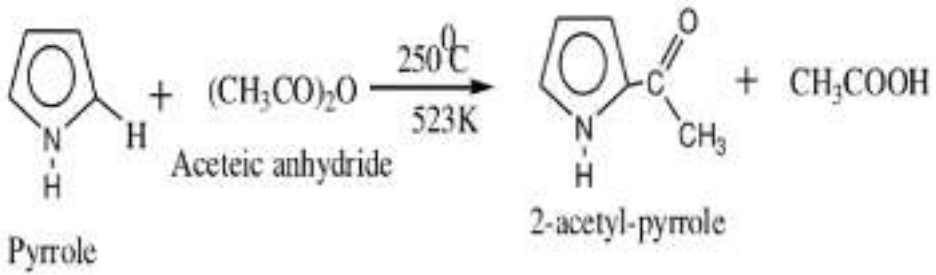
Pyrrole — 2,3,4,5-tetra-bromo-pyrrole

Iodination When **pyrrole** is reacted or treated with **iodine** (4 moles) in presence of in **aqueous potassium iodide** (KI) solution; to form **2,3,4,5 – tetra-iodo-pyrrole (or iodole)**.



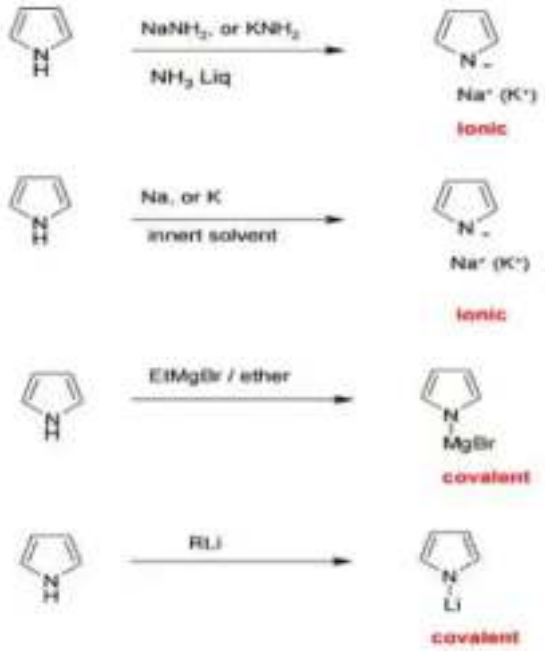
Pyrrole — 2,3,4,5-tetra-iodo-pyrrole

FRIEDEL-CRAFTS ACYLATION When pyrrole is heated with acetic anhydride at 250°C, pyrrole undergoes acylation and form 2-acetyl pyrrole. No catalyst is required in this reaction.

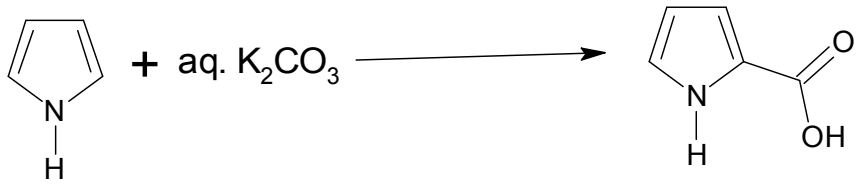


Substitution at nitrogen:

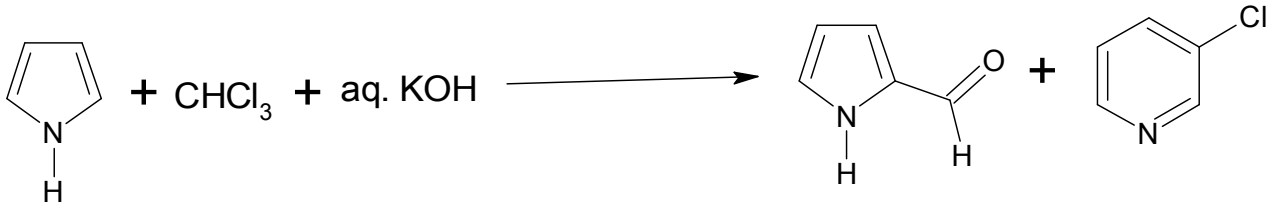
A) Metallation of Pyrrole



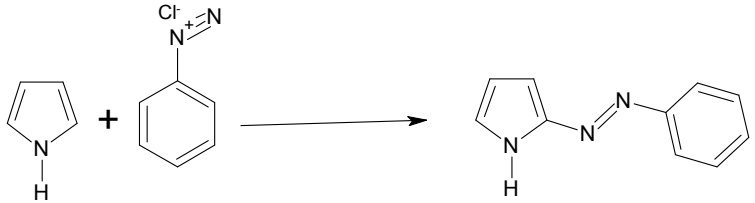
KOLBE_SCHMIDT Carboxylation: Pyrrole reacts with aqueous potassium carbonate at 100^0C to form pyrrole 2-carboxylic acid



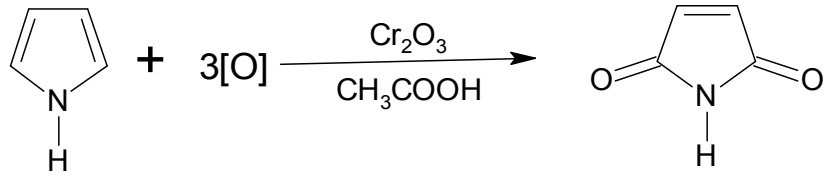
Reimer-Tiemann Formylation: Pyrrole reacts with chloroform in presence of alkali to yield pyrrole-2-aldehyde (2-formylpyrrole) and 3-chloropyridine as by product



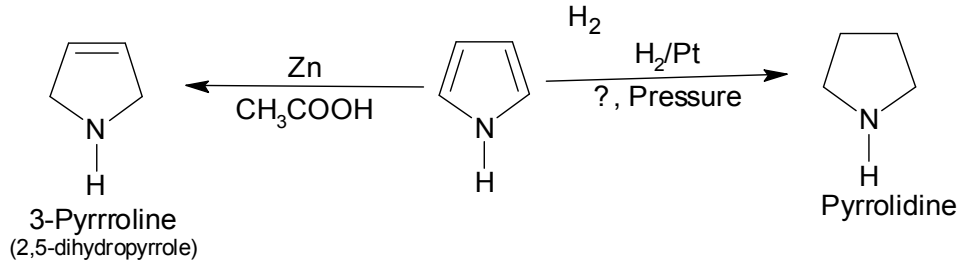
Diazocoupling: Pyrrole couples with benzenediazonium chloride in a weakly acidic solution to give 2-phenylazopyrrole



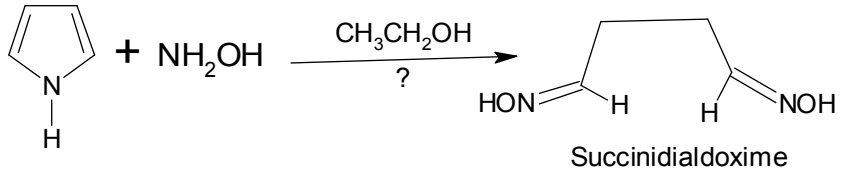
Oxidation: Pyrrole is oxidized by chromium trioxide in acetic acid to give the imide of maleic acid.



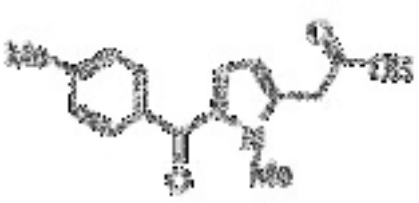
Reduction: Mild reduction of pyrrole with Zinc and acetic acid yields 3-pyrroline (2,5-dihydro pyrrole. Catalytic reduction completely hydrogenates the ring and produces pyrrolidine.



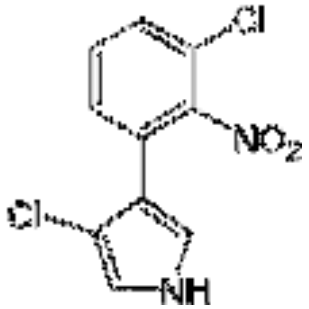
Ring opening reactions: Due decreased aromatic character and presence of electronegative nitrogen pyrrole is susceptible to ring cleavage by the attack of nucleophiles. Eg. When treated with hot ethanolic hydroxylamine, pyrrole undergoes ring opening and form dioxime of succindialdehyde



MEDICINAL COMPOUNDS WITH PYRROLE NUCLEUS



Tolmetin
Uses: Antiarthritic agent



Pyrrolnitrin
Uses: Antifungal antibiotic

FURAN

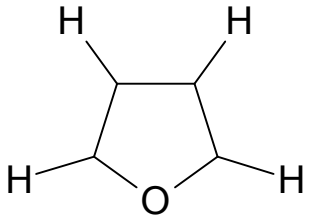
Furan is a heterocyclic organic compound, consisting of a five-membered aromatic ring with four carbon atoms and one oxygen atom.

.Furan is found in heat-treated commercial foods and is produced through thermal degradation of natural food constituents.[15][16] It can be found in roasted coffee, instant coffee, and processed baby foods

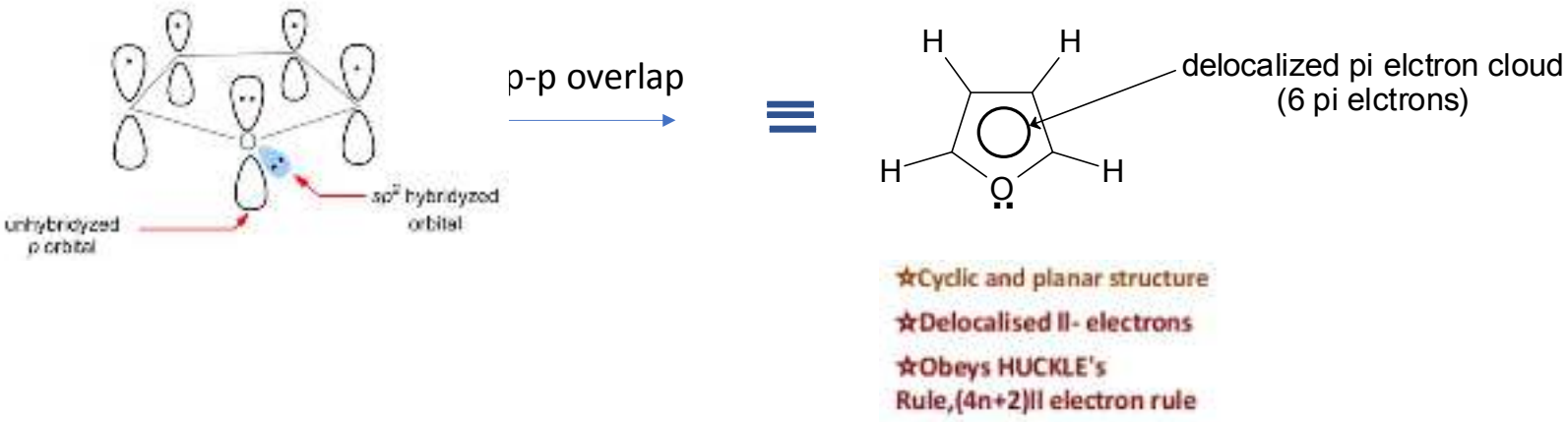
Structure-Aromaticity in Pyrrole

The molecular formula of Furan is C_4H_4O

The cyclic structure of Furan is Oxa-cyclopenta-2,4-diene. In Furan the oxygen atom and the four carbon atoms are sp2 hybridized. The sp2 hybrid orbitals overlap with each other and with s orbitals of four hydrogens atoms forming C-C, C-O, C-H sigma bonds. All these σ bonds lie in one plane.



In this sigma skeletal structure all the four carbons and Oxygen have one unhybridized p atomic orbital arranged perpendicularly to the plane of the sigma bonds. The p orbitals of carbons contain one unpaired electron and the p orbital of oxygen contain two electrons (the lone pair). The lateral overlap of the p orbitals of carbons form two pi bonds. But, as the p orbitals of heteroatom i.e oxygen with lone pair of electron also merge with the p orbitals of carbon and it results in a delocalized pi electron cloud above and below the plane of the molecule and the pi electron cloud contain six pi electrons.



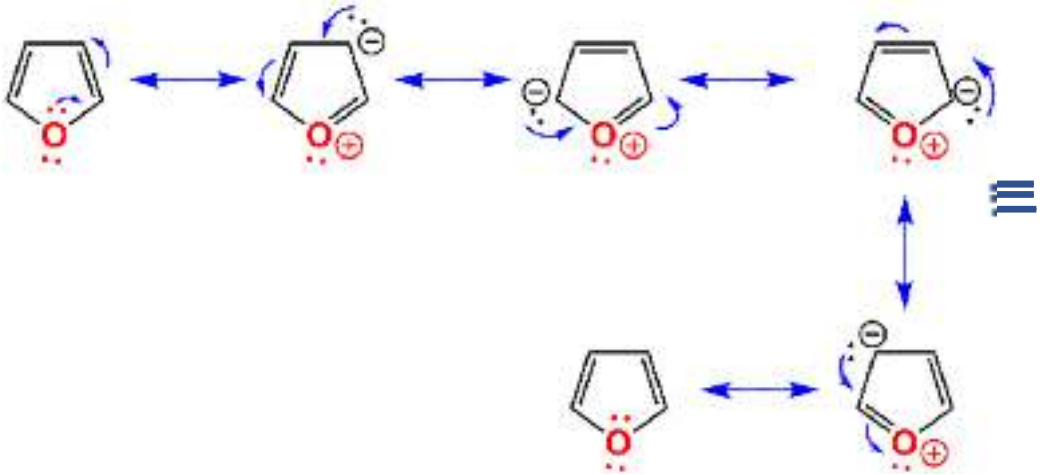
This structure of Furan is aromatic as it satisfies all the requirements of aromatic compounds i.e. i. cyclic and Planar

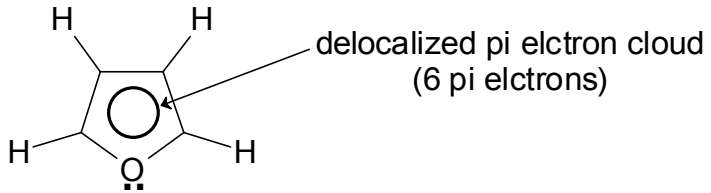
ii. Unsaturated and conjugated and contain delocalized pi electron cloud due to merger of unhybrid p orbitals of four carbons and nitrogen

iii. Obeys Huckles 4n+2 rule of pi electrons, the number of pi electrons in the delocalized pi electron cloud are 6 (4 p electrons one each from 4 carbons and one lone pair of electrons of oxygen. So, 4n+2 = 6 and n=1

Resonance hybrid structure of Furan

According to resonance theory, Furan is considered as a hybrid of the following resonance structure and the position of double bond is not fixed as it forms delocalized pi electron cloud





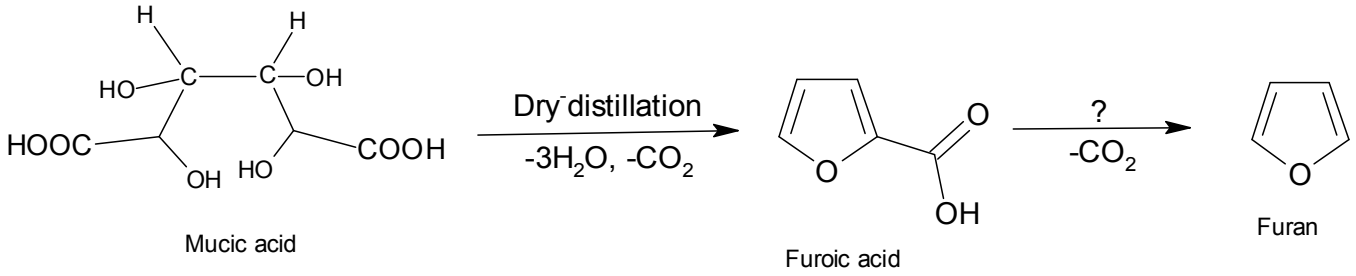
Resonance hybrid structure of Furan

As in canonical structures the donation of electrons by oxygen atom, the electron density on ring carbons increase as they carry negative charge, thus furan carbons undergo electrophilic substitution reactions

Measurement of bond lengths by X-ray analysis confirms the hybrid character of the pyrrole molecule. The C-O bond length of 1.37A^0 is shorter than the normal C-O single bond length of 1.43 A^0

METHODS OF PREPARATION OF FURAN

1. By distillation of Mucic acid and heating the resulting productfuroic acid at 200-300^{0}C

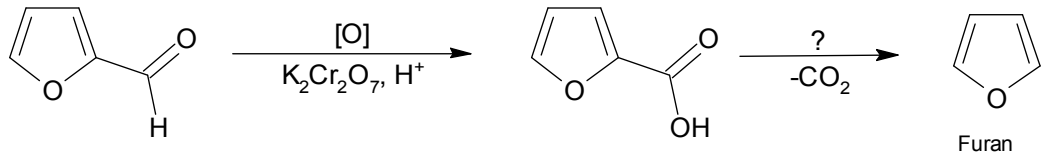


Mucic acid

Furoic acid

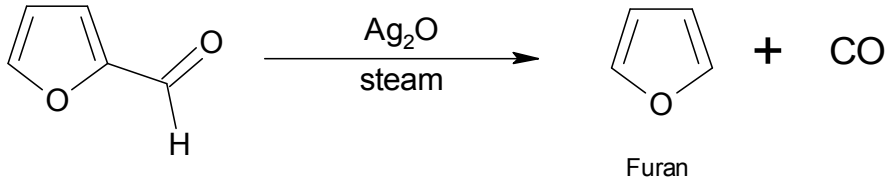
Furan

2 By oxidation of furfural with potassium dichromate to give furoic acid and subsequent decarboxylation at 200-300^{0}C



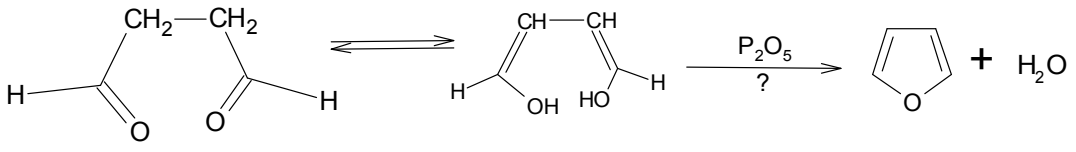
Furfural Furoic acid Furan

3. By decarboxylation of furfural in stem in the presence of silveroxide catalyst (commercial method of synthesis)



Furfural Furan

4. By dehydration of succinic dialdehyde upon heating with P_2O_5 or $ZnCl_2$



Succinic dialdehyde Dienediole

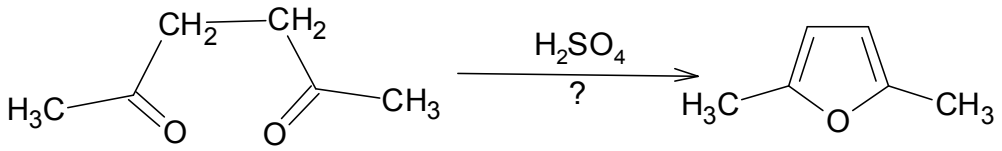
5. FROM PENTOSE SUGARS: By distillation of carbohydrate with sulfuric acid results in furfural, which is then subjected to catalytic decomposition.

6.Different substituted Furans are prepared by various cyclization/ring closure reactions

6a. **Paal-Knorr synthesis**: This is a general method of synthesis of pyrrole, furan, thiophene derivatives using 1,4-dicarbonyl compounds as substrates.

For furan 1,4-diketone is heated in acidic medium thus undergo cyclization, by intramolecular nucleophilic addition.

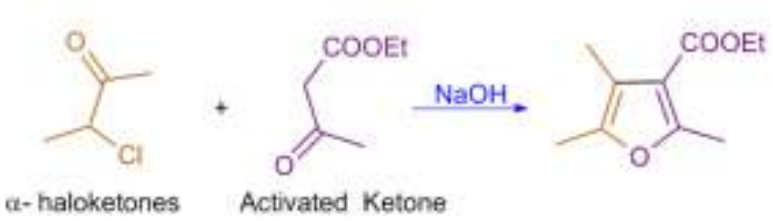
The reaction of acetylacetone (a 1,4-dicarbonyl compound) with acid yields 2,5-dimethylfuran



Acetylacetone

6b. Feist – Benary Synthesis

Reaction of α- haloketones with β-ketoesters in the presence of a base (not ammonia) to give furans.



3-chloro-2-butanone Ethyl acetoacetate

PROPERTIES OF Furan

Furan is a colorless, flammable, highly volatile liquid with a boiling point close to room temperature. It is soluble in common organic solvents, including alcohol, ether, and acetone, and is slightly soluble in water

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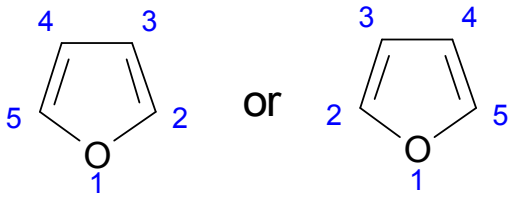

Position 2 and 5 are identical (α) and so are 3 and 4 (β)

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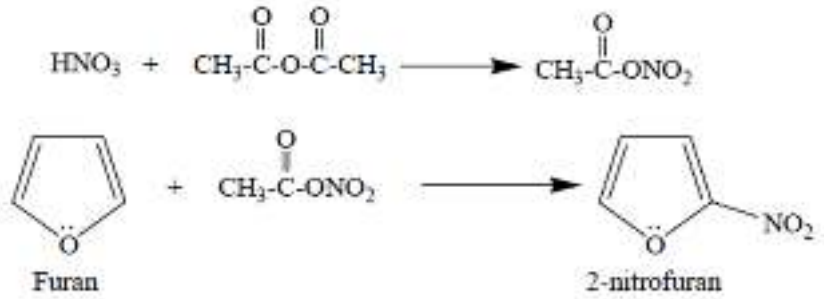
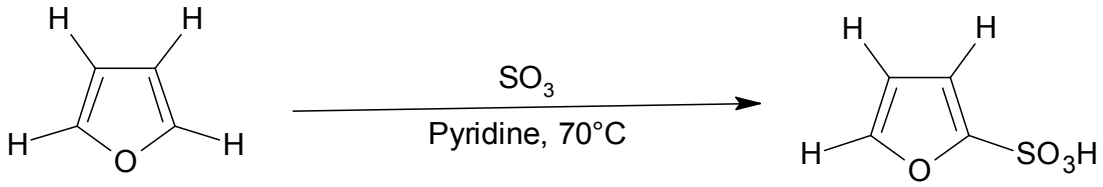
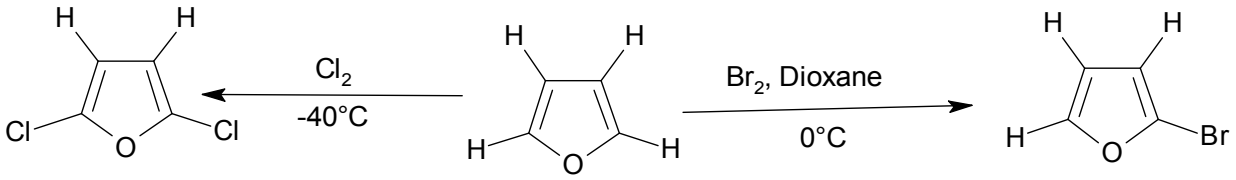


2.**Sulphonation of Furan:** When Furan is heated with sulphur trioxide (SO_3) in pyridine, as a solvent, at about 70°C it forms Furan– 2-sulphonic acid.

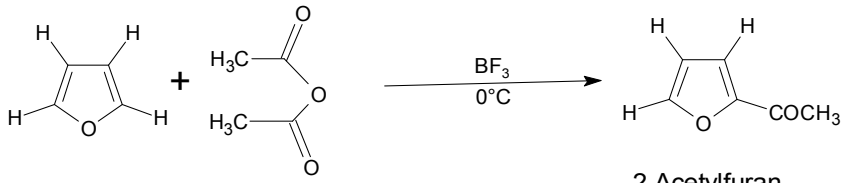


3.**Halogenation of Furan:** Halogenation reactions of Furan proceeds vigorously with chlorine and bromine to give polyhalogenated products. Milder condition are used to obtain monohalo derivativeswith greater vigor an dfrom poly halogenated compounds.



2-Bromofuran

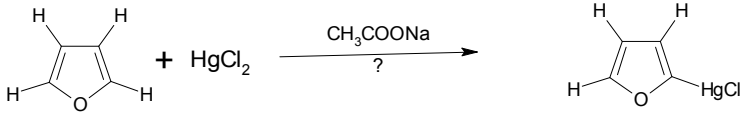
4. Friedel-Crafts acylation: Acylated with acetic anhydride in presence of BF_3 or $SnCl_4$ at 0^0C to yield 2-acetylfuran



aceticanhydride

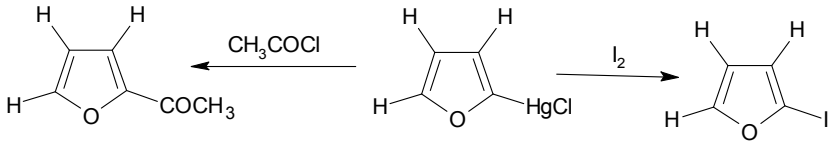
2-Acetylfuran

5. Mercuration: Furan on heating with mercuric chloride in aqueous sodium acetate yields 2-chloromercurifuran



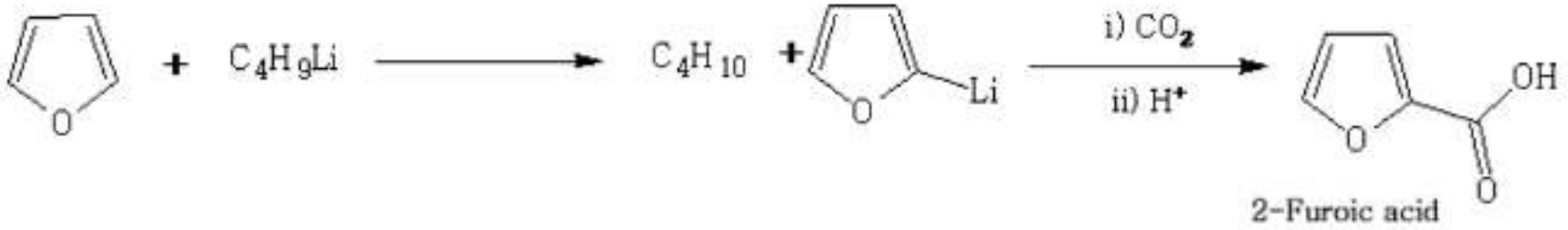
2-chloromercurifuran

2-chloromercurifuran has synthetic applications as mercury group can be replaced by iodine or bromine or acyl groups.



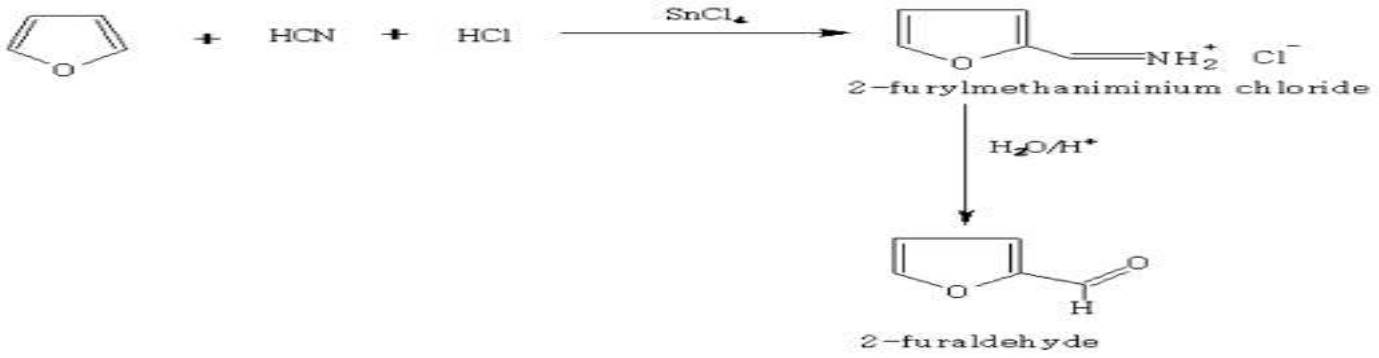
2-Acetylfuran 2-chloromercurifuran 2-Iodofuran

6. Reaction with n-butyllithium: Furan form organometallic compounds with n-butyl lithium which can be used as intermediates in the synthesis of furan derivatives. E.g.

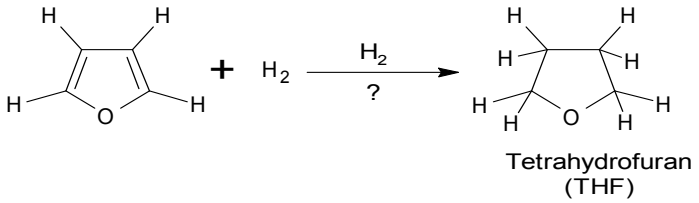


2-Furoic acid

7. Gatterman formylation: Furan undergoes the *Gattermann formylation reaction*[1] to form furfural.

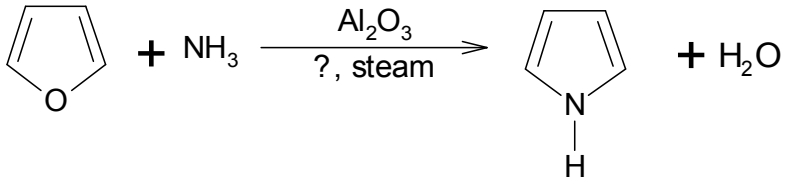


8. Reduction: Furan upon catalytic hydrogenation yield tetrahydrofuran

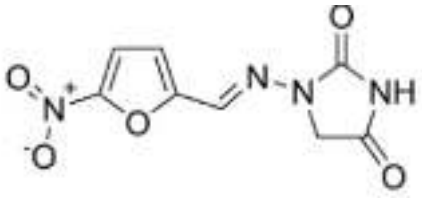


9. Diels-Alder reaction (Reaction with maleic anhydride): **Furan is less aromatic due to greater electronegativity of oxygen thus the lone pair of electrons of oxygen are less delocalized, so, furan acts as conjugated diene (4 π electron system) and can react undergo Diels-Alder reaction thus react with dienophile (2 π electron system) and form cyclic adduct. Ex. Furan upon reaction with maleic anhydride undergo 4π + 2π cycloaddition across C-2 and C-5 carbons.**

10. Ring opening reactions: By passing a mixture of furan, ammonia and stem over aluminium oxide catalyst at 480^0-490^0C yields pyrrole

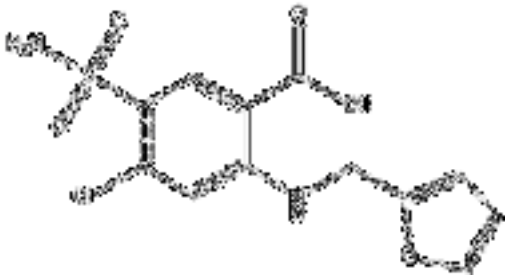


MEDICINAL COMPOUNDS WITH FURAN RING



nitrofurantoin

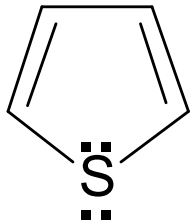
Use: Antiinfective and antiprotozoal agent



FUROSIMIDE

USE: DIuretic

THIOPHENE



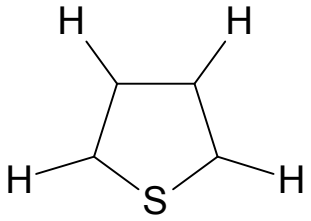
Thiphene is a heterocyclic organic compound, consisting of a five-membered aromatic ring with four carbon atoms and one Sulphur atom.

Thiophene occurs in light oil fraction of coal-tar an is usually present as an impurity in commercial benzene.

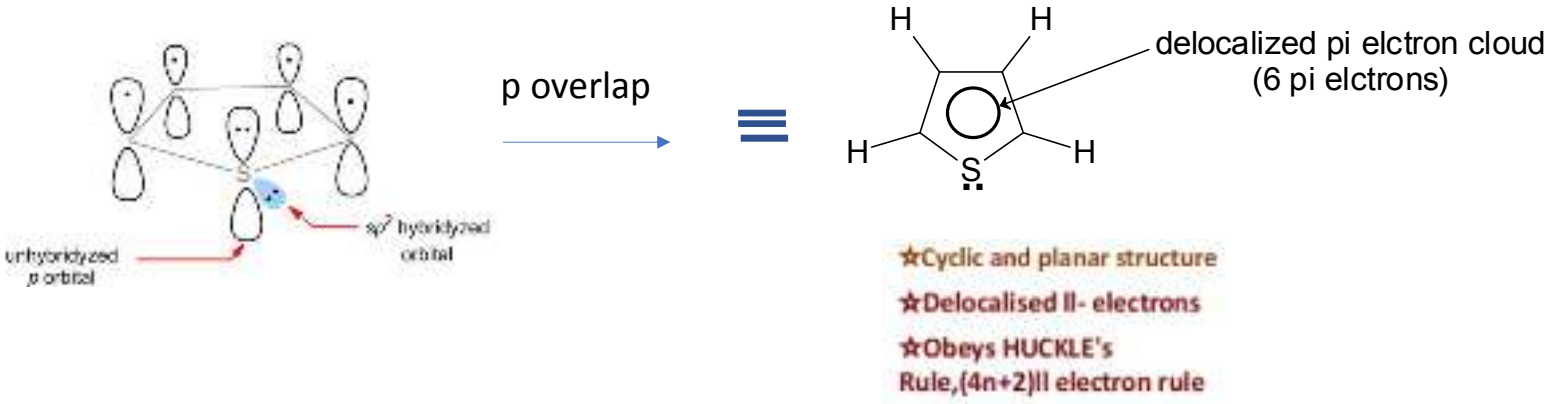
Structure-Aromaticity in Pyrrole

The molecular formula of Thiophene is C_4H_4S

The cyclic structure of Thiophene is Thia-cyclopenta-2,4-diene. In thiophene the sulphur atom and the four carbon atoms are sp2 hybridized. The sp2 hybrid orbitals overlap with each other and with s orbitals of four hydrogens atoms forming C-C, C-S C-H sigma bonds. All these σ bonds lie in one plane.



In this sigma skeletal structure all the four carbons and Sulphur have one unhybridized p atomic orbital arranged perpendicularly to the plane of the sigma bonds. The p orbitals of carbons contain one unpaired electron and the p orbital of Sulphur contain two electrons (the lone pair). The lateral overlap of the p orbitals of carbons form two pi bonds. But, as the p orbitals of heteroatom i.e sulphur with lone pair of electron also merge with the p orbitals of carbon and it results in a delocalized pi electron cloud above and below the plane of the molecule and the pi electron cloud contain six pi electrons.



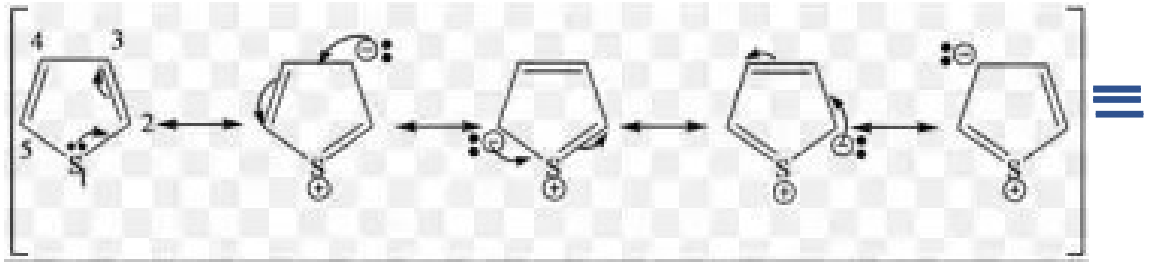
This structure of Thiophene is aromatic as it satisfies all the requirements of aromatic compounds i.e. i. cyclic and Planar

ii. Unsaturated and conjugated and contain delocalized pi electron cloud due to merger of unhybrid p orbitals of four carbons and nitrogen

iii. Obeys Huckles 4n+2 rule of pi electrons, the number of pi electrons in the delocalized pi electron cloud are 6 (4 p electrons one each from 4 carbons and one lone pair of electrons of sulphur. So, 4n+2 = 6 and n=1

Resonance hybrid structure of Thiophene

According to resonance theory, Thiophene is considered as a hybrid of the following resonance structure and the position of double bond is not fixed as it forms delocalized pi electron cloud



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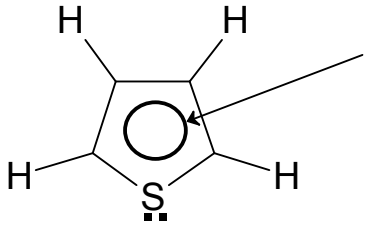


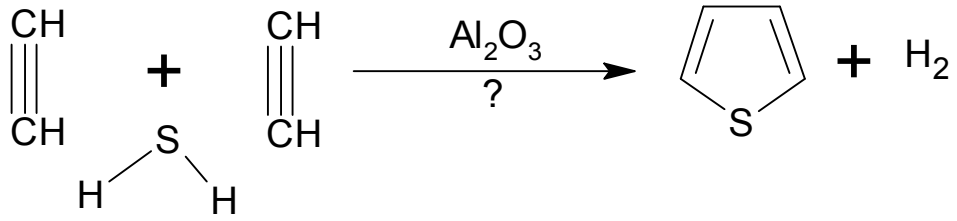
delocalized pi elctron cloud
(6 pi elctrons)

Resonance hybrid structure of Thiophene

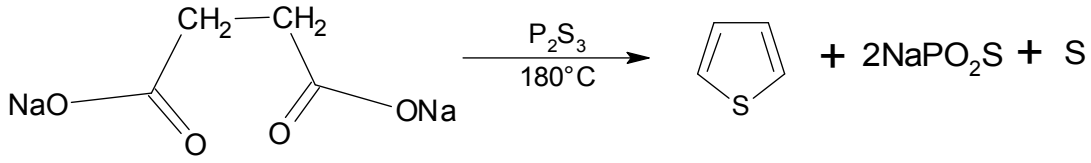
As in canonical structures the donation of electrons by sulphur atom, the electron density on ring carbons increase as they carry negative charge, thus furan carbons undergo electrophilic substitution reactions

METHODS OF PREPARATION OF THIOPHENE

1. By passing a mixture of acetylene and hydrogen sulfide through a tube containing aluminiumoxide at 400^0C



2. By heating sodium succinate with phosphorous trisulfide

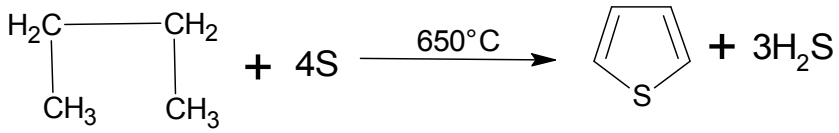


Sodium succinate

3. By distillation of furoic acid with barium sulfide

Furoic acid

4. By reaction of sulfur with n-butane in the gas phase at 650^0C

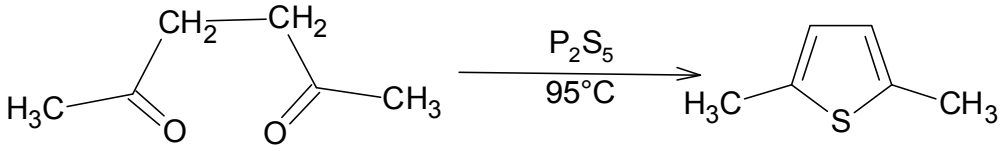


n-butane

5.Different substituted Thiophenes are prepared by various cyclization/ring closure reactions

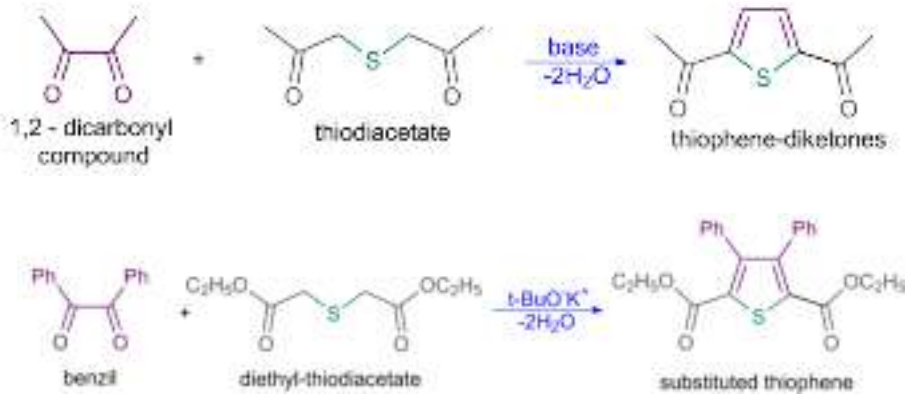
5a. **Paal-Knorr synthesis**: This is a general method of synthesis of pyrrole, furan, thiophene derivatives using 1,4-dicarbonyl compounds as substrates.

For thiophen 1,4-diketone is heated in phosphorus pentasulfide to give 2,5-disubstituted thiophenes



Acetylacetone

5b.**Hinsberg method**: Involves the reaction between 1,2-dicarbonyl compound and diethylthiodiacetate in presence of a strong base.

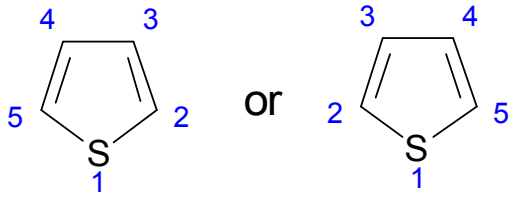


PROPERTIES OF THIOPHENE : Thiophen is a colorless liquid with a boiling point 84^0C. It is insoluble in water and miscible with most organic solvents

Thiophen is is more satble than Pyrrole and furan, it does not undergo Diels-Alder reaction.

ELECTROPHILIC SUBSTITUTION REACTIONS: Due to its aromatic character Thiophene undergo aromatic electrophilic substitution reactions like benzene. But its less aromatic and more reactive than benzene.

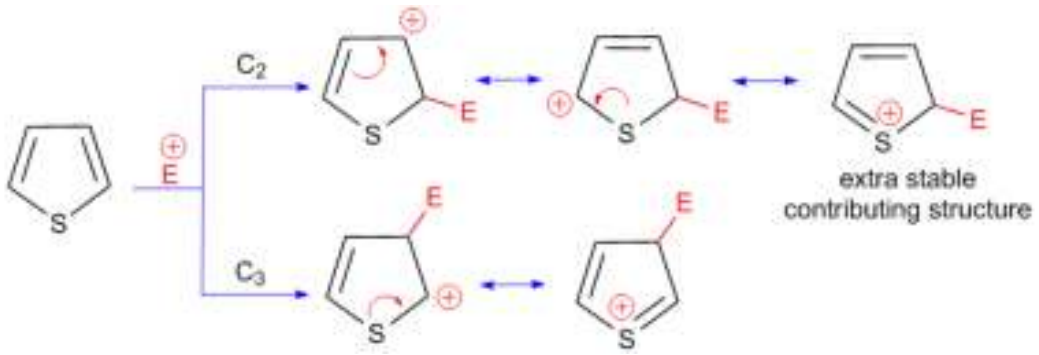
In Thiophen mono substitution can occur at two places on the ring i.e, C-2(C-5) or C-3(C-4).



or

Position 2 and 5 are identical (α) and so are 3 and 4 (β)

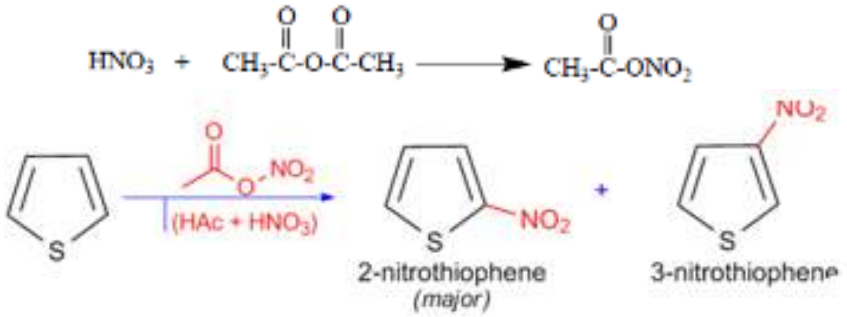
ELECTROPHILIC SUBSTITUTION REACTIONS in Thiophen preferably occur at C-2.



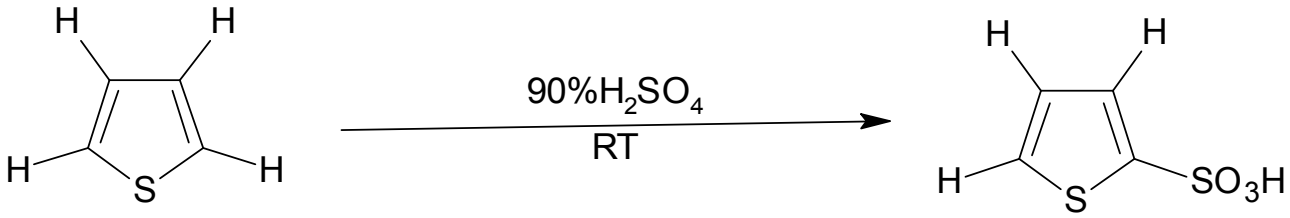
C2 attack gives more resonance contributing structures than C3.
Extra stable contributing structure generates upon C2 attack

The different electrophilic substitution reactions and reaction conditions in thiophene are

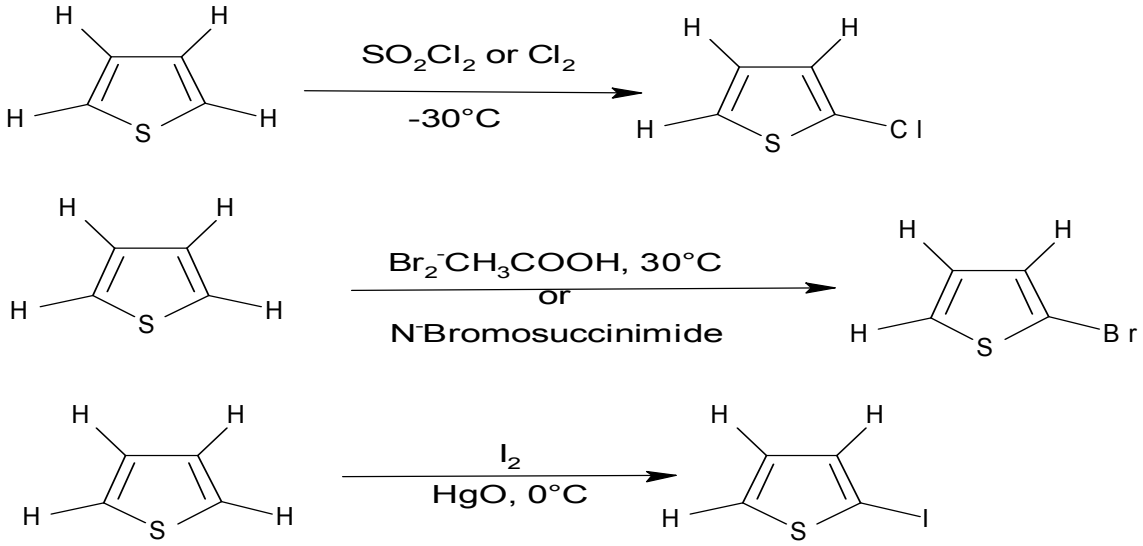
1. **Nitration of Thiophen:** Nitration of Thiophen is carried out using mild nitrating mixture such as cold solution of nitric acid and acetic anhydride, which forms acetyl nitrate as source of nitronium ion. The nitration occur at C-2 and from 2-nitrothiophen



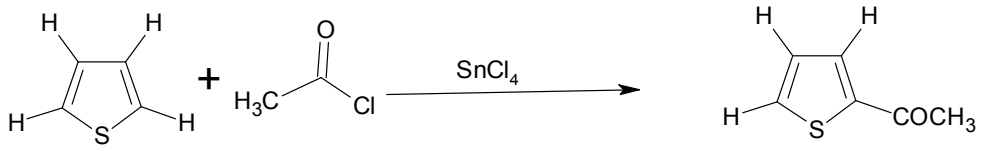
2.**Sulphonation of Thiophene:** When Thiophene is heated with concentrated sulphuric acid it forms thiophen-2-sulfonic acid.



3.**Halogenation of Thiophene: Thiophen reacts with chlorine to yield a mixture of substituted and addition products. Bromination occurs rapidly even in dark at-300C. Iodination results in mono and diiodothiophen**

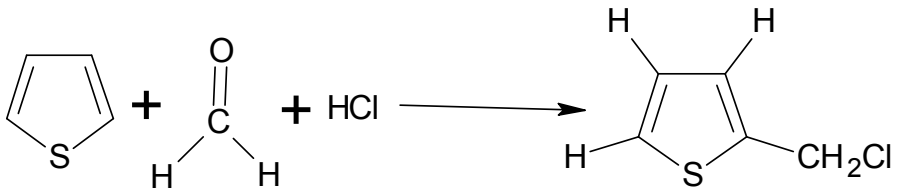


4. Friedel-Crafts acylation: Acylated with acetyl chloride in presence of stannic chloride



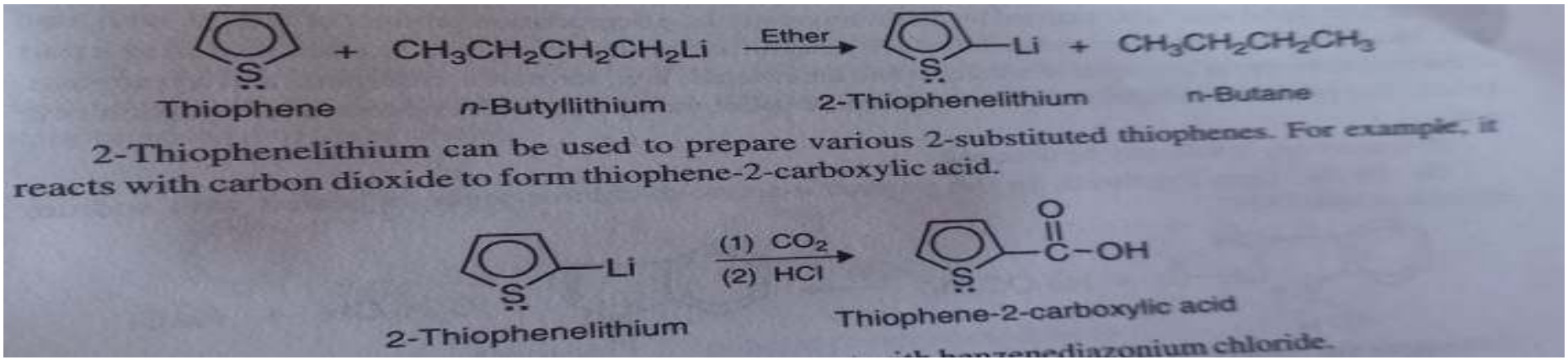
2-Acetylthiophene

4. Chloromethylation: Thiophene react with formaldehyde and HCl to give 2-chloromethyl thiophene

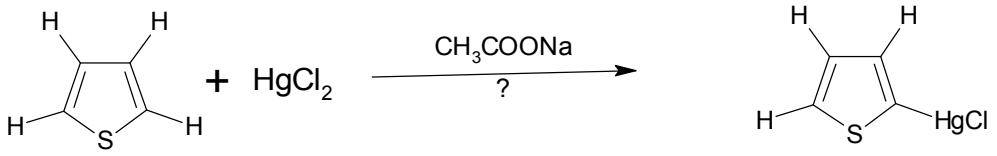


2-Chloromethylthiophene

6. Reaction with n-butyllithium: Thiophene form organometallic compounds with n-butyl lithium which can be used as intermediates in the synthesis of thiophen derivatives. E.g.

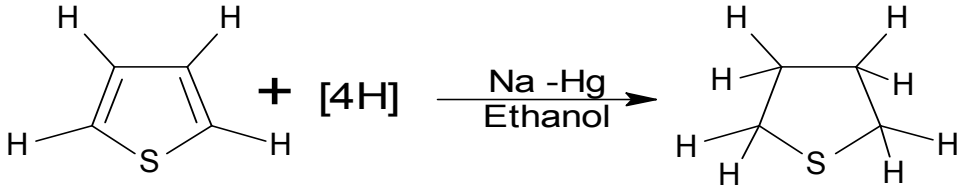


7. Mercuration: Thiophne undergo mercuration with mercuric chloride in aqueous sodium acetate and from 2-chloromercurithiophen

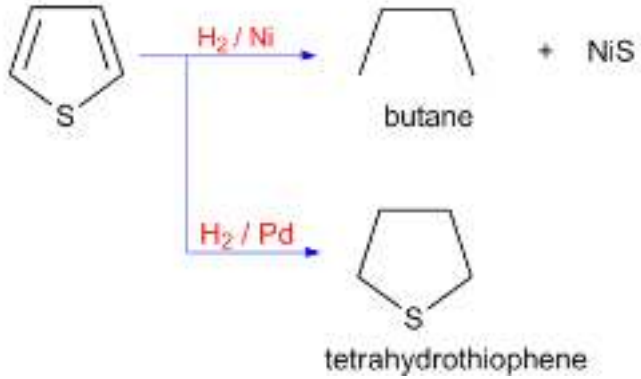


2-chloromercurithiophen

8. Reduction: Thiophen upon hydrogenation with sodium amalgam and ethanol yield tetrahydrothiophenecatalytic hydrogenation yield tetrahydrofuran



Tetrahydrothiophene

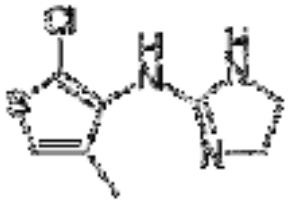


tetrahydrothiophene

MEDICINAL COMPOUNDS WITH Thiophene RING

Pyrantel

Use: anthelmintic



Tiamenidine

USE: antihypertensive

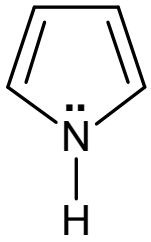
WRITE A NOTE ON AROMATICIYT OF FIVE MEMBERED HETEROCYCLIC COMPOUNDS FURAN, PYRROLE, THIOPHENE

OR

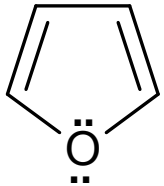
COMPARE THE AROMATICIYT OF PYRROLE, FURAN, THIOPHENE

ANSWER:

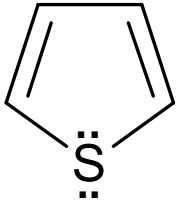
The three major five membered heterocyclic compounds are Pyrrole, Furan, Thiophene



Pyrrole



Furan



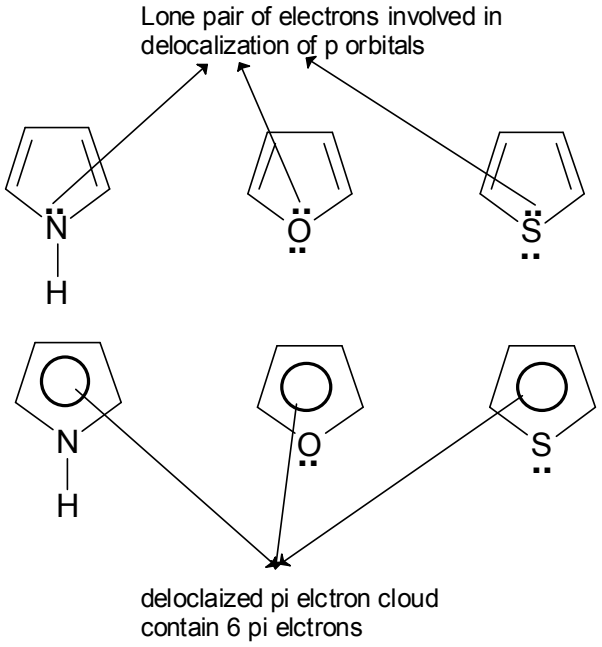
Thiophene

These cyclopentadiene derivatives in which the carbon is substituted by heteroatom such as Oxygen(OXA), Nitrogen(AZA) and Sulphur(THIA), in ring structures all the carbons and heteroatoms are in sp2 hybridized state and the diene system is formed by the overlapping of un-hybrid p orbitals of carbons. But, as the un-hybrid p orbitals of hetero atom which contain lone pair of electrons are also involved in delocalization with p orbitals of carbon, the delocalized pi electron system in these heterocyclic structures contain 6 pi electrons (4 electrons of carbons and 2 lone pair electrons of hetero atom).

Thus these five membered heterocyclic ring structures satisfy the requirements of aromatic compounds
i.e. They are planar ring structures
Unsaturated and conjugated with delocalized pi electron cloud and obey Huckles rule of 4n+2 Pi electorns

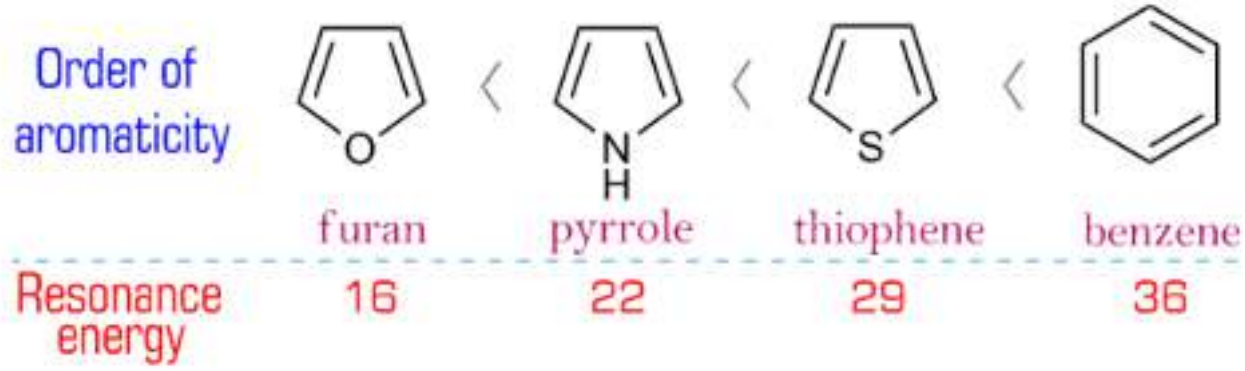
As the lone pair of electrons of hetero atom are involved in delocalization
4n+2=6 (4 p electrons of carbons and 2 lone pair electrons of hetero atom)
N=1

Thus Pyrrole, Furan and thiophene are aromatic.



☆Cyclic and planar structure
☆Delocalised Π- electrons
☆Obeys HUCKLE's Rule,(4n+2)Π electron rule

But, these 5 membered heterocyclic compounds are less aromatic than benzene and also among them the order of aromaticity differs.



The above resonance energy values indicates that furan is less aromatic and thiophene possess greater aromaticity. This is because in five membered heterocyclic compounds the aromatic character depends on the delocalization of lone pair of electrons of hetero atom. This in turn depends on the electronegativity of heteroatom. The more the electronegativity of hetero atom lesser would be the delocalization and lower the aromaticity.

As in Furan, Pyrrole and Thiophene the hetero atoms of the rings are Oxygen, Nitrogen and Sulphur . The order of electronegativity these atoms is O>N>S

So, in furan the more electronegative oxygen has greater hold on its lone pair of electrons and are less involved in delocalization compare to the N and S . Therefore Furan is less aromatic. It behaves like conjugated diene and undergo Diels-Alder reaction.

As Pyrrole , Furan, Thiophene are less aromatic than Benzene, they are more reactive than benzene and undergo addition and ring opening reaction more readily than benzene.

The order of reactivity of these compounds is Pyrrole> Furan> Thiophene

UNIT-V

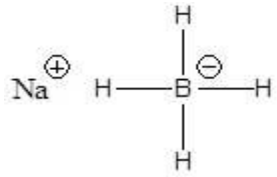
REACTIONS OF SYNTHETIC IMPORTANCE

I. Different types of Reduction reactions
    a. Metalhydrides-$LiAlH_4$ and $NaBH_4$
    b. Metal reduction- Clemmensen reduction, Wolf-Kishner reduction
    c. Dissolving metal reduction- Birch reduction
    d. Mervin-Pondorff-Verley reduction(Oppenauer oxidation)

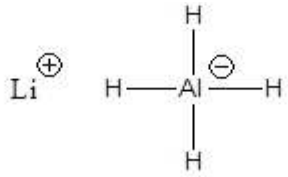
II. Dakin reaction
III. Beckman rearrangement
IV. Schmidt reaction
V. Claisen-Schmidt condensation

METAL HYDRIDES AS REDUCING AGENTS

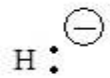
The most common metal hydrides which serves as source of nucleophile Hydride and act as reducing agents are **Lithium aluminium hydride ($LiAlH_4$)** and **sodium borohydride ($NaBH_4$).** The hydride anion is not present during this reaction; rather, these reagents serve as a source of hydride due to the presence of a polar metal-hydrogen bond.



Sodium Borohydride



Lithium Aluminum Hydride

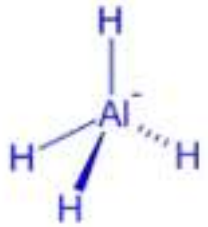


Hydride Nucleophile

Lithium aluminium hydride (**LiAlH4**):

Lithium aluminium hydride, $LiAlH_4$, also abbreviated as **LAH**,

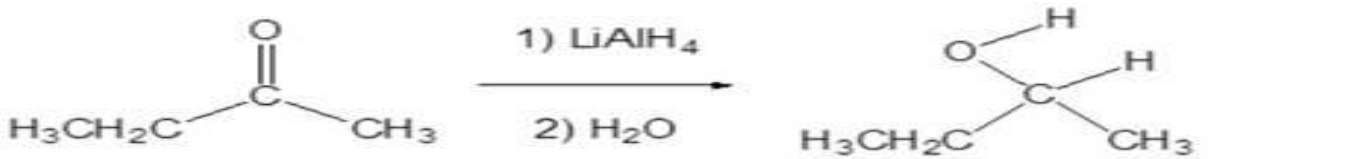
There is a tetrahedral arrangement of hydrogens around Al^{3+} in aluminium hydride, AlH_4^- ion. It is formed by coordination of hydride, H^- ions to Al^{3+} ion. The hybridization in central Al is sp^3.



$LiAlH_4$ is prepared by the reaction between lithium hydride and aluminium chloride.

It is widely used in organic chemistry as a reducing agent. It is a nucleophilic reducing agent, best used to reduce polar multiple bonds like carbonyl compounds (C=O).

Ex.



Butanone
(methyl ethyl ketone) or MEK

2-Butanol, or *sec*-butanol

The reduction reaction employing $LiAlH_4$ as reducing agent must be carried out in anhydrous non protic solvents like diethyl ether, THF.

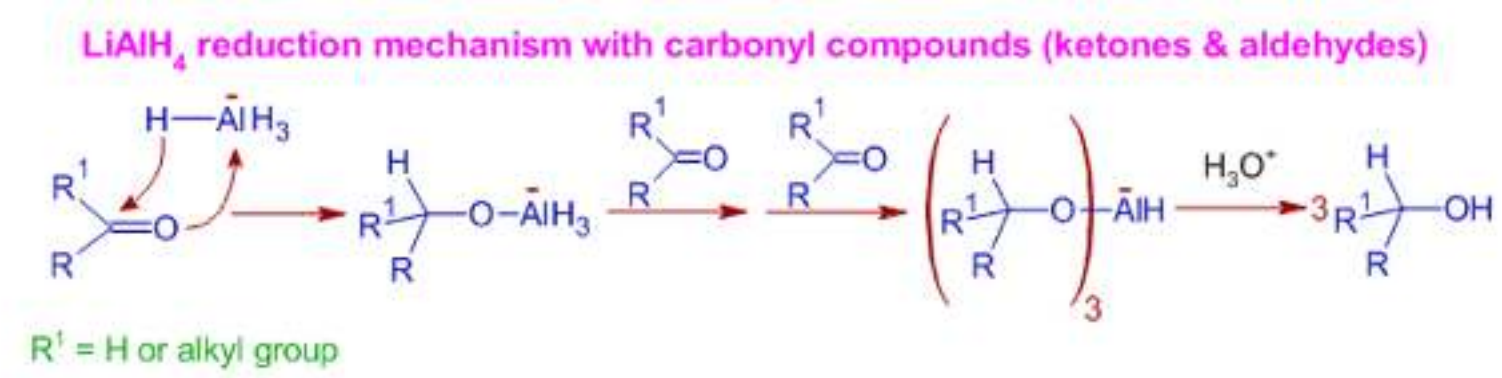
LiAlH4 is a strong, unselective reducing agent for polar double bonds. It will reduce aldehydes, ketones, esters, carboxylic acid chlorides, carboxylic acids to alcohols. Amides and nitriles are reduced to amines.

Mechanism of reduction using $LiAlH_4$

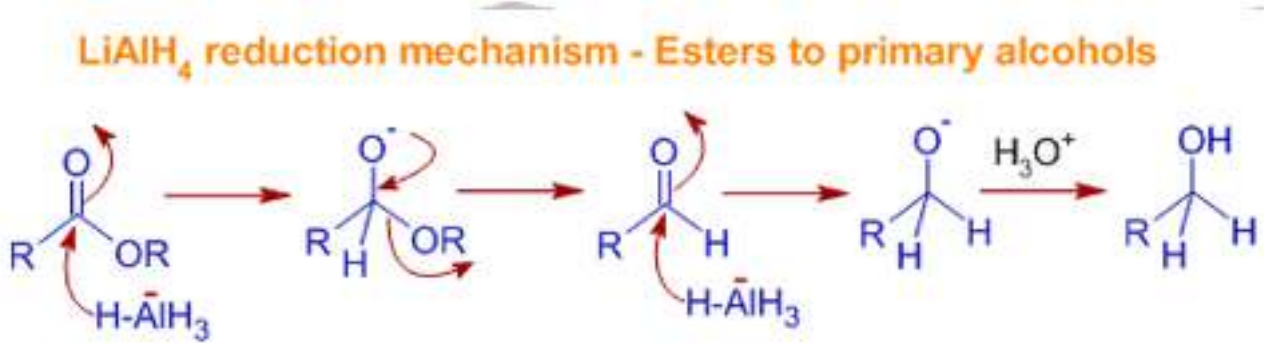
$LiAlH_4$ is a nucleophilic reducing agent since the hydride transfer to the carbonyl carbon occurs prior to the coordination to the carbonyl oxygen. It reacts faster with electron deficient carbonyl groups. The reactivity of carbonyl compounds with this reagent follows the order:

Aldehydes > Ketones > ester > amide > carboxylic acid

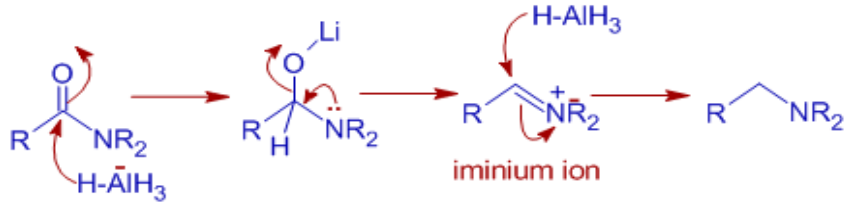
A. Mechanism of Reduction of Aldehydes or Ketones to 1^0 or 2^0 alcohols: Initially, a hydride ion is transferred onto the carbonyl carbon and the oxygen atom coordinates to the remaining aluminium hydride species to furnish an alkoxytrihydroaluminate ion, which can reduce the next carbonyl molecule. Thus three of the hydride ions are used up in reduction



B. Mechanism of Reduction of Esters to 1^0 alcohols by $LiAlH_4$: The ester is first converted to aldehyde which is further reduced to primary alcohol.



C. Mechanism of Reduction of Amides to amines: Amides are converted to amines. The LAH reduction mechanism is slightly different from that depicted for esters. In iminium ion is formed during the reaction since nitrogen atom is relatively a good donor than oxygen atom.

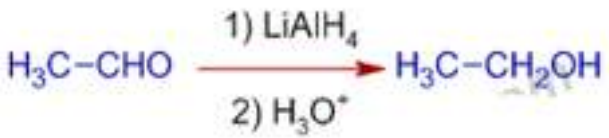


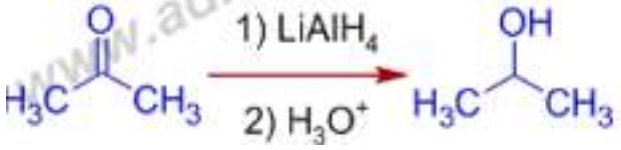
Applications of $LiAlH_4$

Functional group conversion	equivalents of $LiAlH_4$
Aldehydes, ketones -------> Alcohols	1
Carboxylic acids -------> Alcohols	3
Esters, acid halides -------> Alcohols	2
Amides -------> amines	2
Nitriles -------> amines	2
oxiranes (epoxides) -------> alcohols	1
lactones -------> diols	2
haloalkanes, haloarenes -------> alkanes, arenes	1

1) **Reduction of carbonyl compounds using $LiAlH_4$**: The **aldehydes or ketones** are reduced by $LiAlH_4$ to the corresponding primary or secondary alcohols respectively.

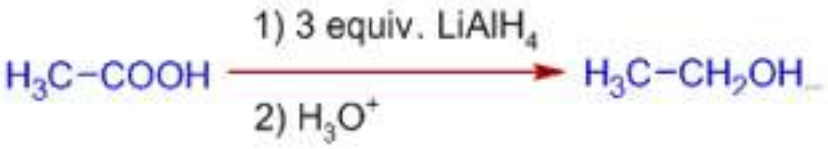
E.g. Acetaldehyde is reduced to ethyl alcohol and acetone is reduced to isopropyl alcohol.

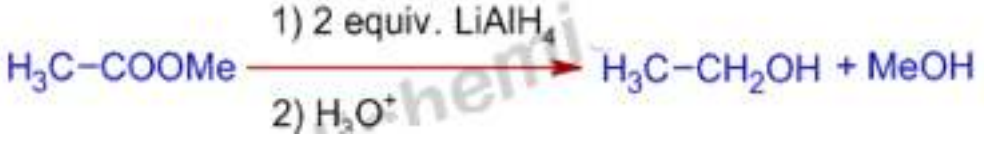


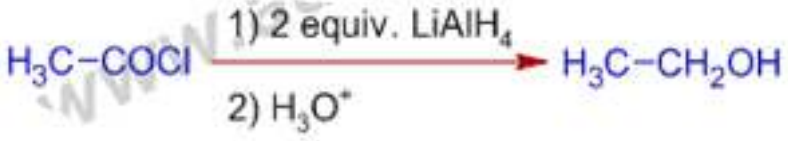


2) The **carboxylic acids, esters and acid halides** are reduced to corresponding primary alcohols by Lithium aluminium hydride.

E.g. The reduction of Acetic acid, methyl acetate and acetyl chloride by $LiAlH_4$ furnish the same ethyl alcohol.

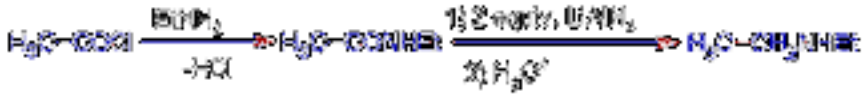






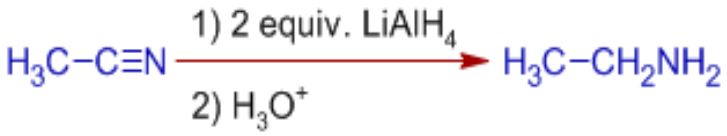
3) The **amides** are reduced to amines by Lithium aluminium hydride, $LiAlH_4$. Especially this method is used to get secondary amines.

E.g. Diethyl amine can be prepared starting from acetyl chloride as follows:



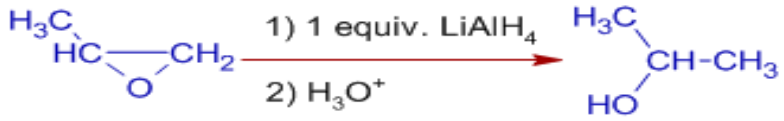
4) The **nitriles** are reduced to primary amines by $LiAlH_4$.

E.g. Acetonitrile is reduced to ethyl amine by $LiAlH_4$.



5) Lithium aluminium hydride reduces the **oxiranes (epoxides)** to alcohols. The mechanism involves hydride attack occurs at less hindered side of the epoxide.

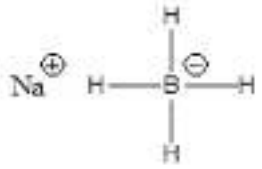
E.g. 2-methyloxirane gives 2-propanol predominantly.



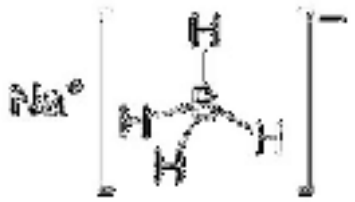
Reduction of epoxides by $LiAlH_4$

Sodium borohydride ($NaBH_4$). : is also known as sodium tetrahydroborate and sodium tetrahydridoborate.This is also one of the most widely employed metal hydride as reducing agent.

Sodium borohydride is a salt formed by cation Na^+ and anion BH_4^-. This anion has a tetrahedral structure, with the Boron atom being sp3 h



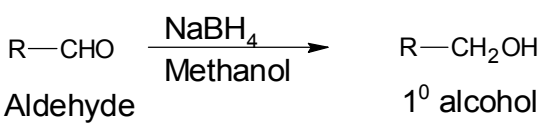
Sodium Borohydride

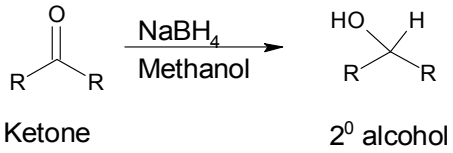


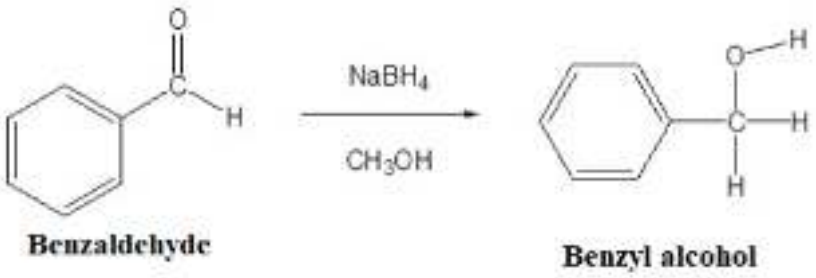
sodium borohydride is industrially **prepared** from **sodium** hydride (produced by reacting Na and H_2) and trimethyl borate at 250–270 °C:

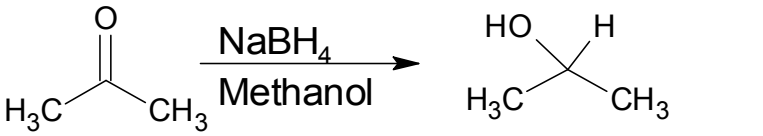
$$B(OCH_3)_3 + 4\ NaH \rightarrow NaBH_4 + 3\ NaOCH_3$$

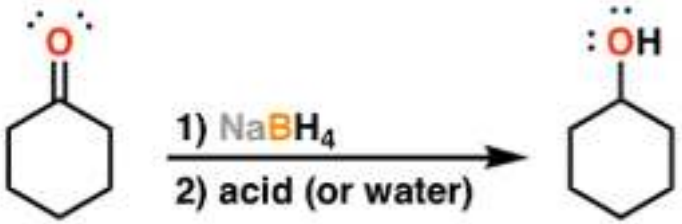
Sodium borohydride is mainly used to reduce aldehydes or ketones to primary or secondary alcohols.







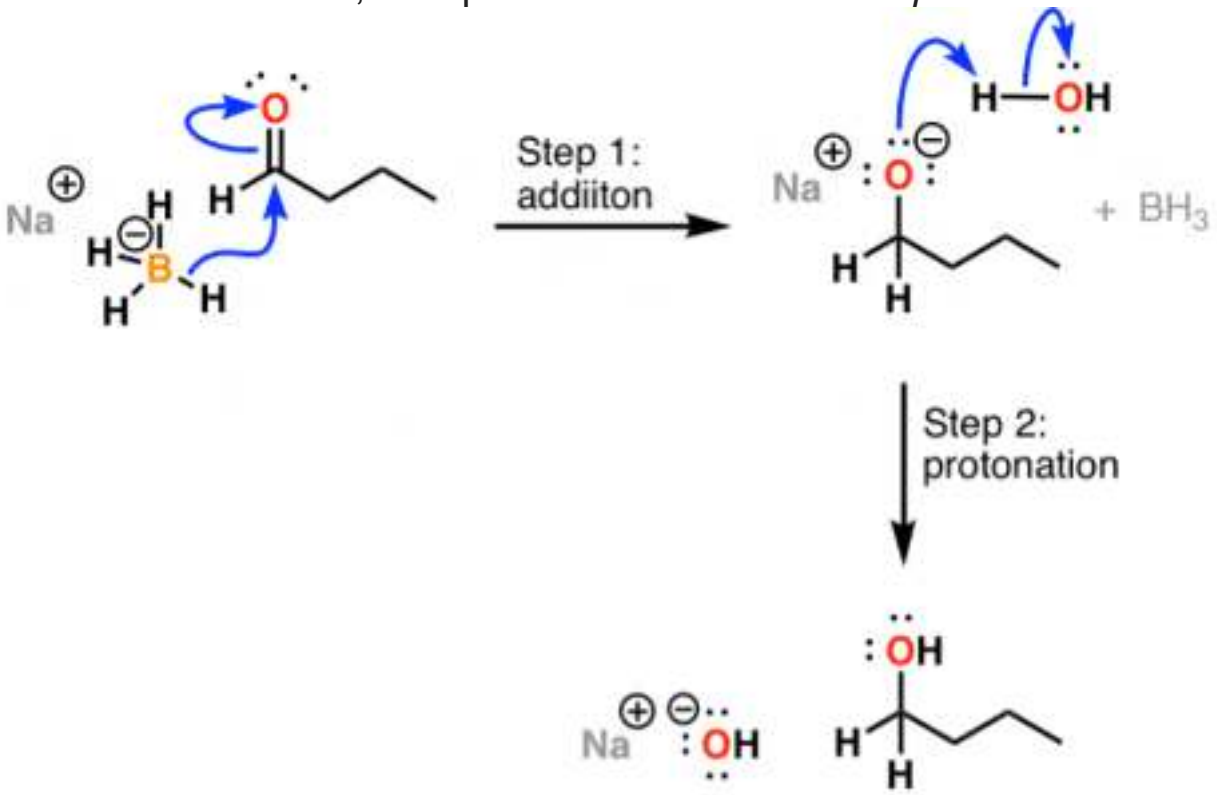




MECHANISM OF REDUCTION USING SODIUM BOROHYDRIDE

The mechanism of the reaction of sodium borohydride with aldehydes and ketones proceeds in two steps.

In the first step, H(–) detaches from the BH_4(–) and adds to the carbonyl carbon and forms alkoxide ion; In the second step, a proton from water (or an acid) is added to the alkoxide to make the alcohol. This is performed at the end of the reaction, a step referred to as the *workup*.



As Sodium borohydride is mild reducing agent in comparison with $LiAlH_4$ under normal conditions it can not reduce carboxylic acids and esters. So, it can be used to selectively reduce aldehydes and ketones in compounds which contain aldehyde or ketone functionality along with carboxylic acid or esters. But, it can reduce acyl halides to alcohols.

The low reactivity of $NaBH_4$ compare to $LiAlH_4$ is because, the hydrogen in $NaBH_4$ is bonded to more electronegative Boron compared to Lithium in $LiAlH_4$ so it can not be donated as hydride easily.

Sodium borohydride	***Lithium aluminium hydride***
Boron being part of second period makes shorter and stronger bond with hydrogen	Aluminium being part of third period makes longer and weaker bond with hydrogen.
The **B-H** bond of **$NaBH_4$** has more ***covalent character***	The **Al-H bond** has more ***ionic character*** in **$LiAlH_4$**
It is less reactive	It is more reactive
It is a weak base	It is a stronger base

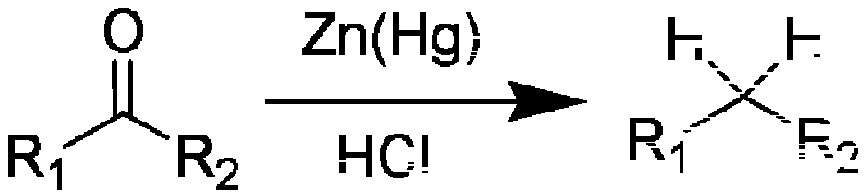
- Reduction of Carbonyl compounds to Hydrocarbons

1. Clemmensen reduction
2. Wolf –Kishner reduction

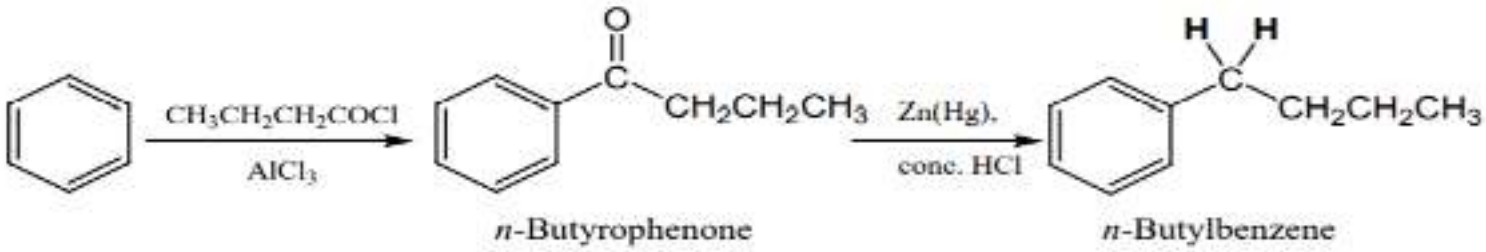
CLEMMENSEN REDUCTION

1. This reaction was first reported by Clemmensen of Park Davis in 1913.
2. It is the reduction of carbonyl groups (in aldehyde and ketone) to methylene group.
3. This reaction done with zinc amalgam and hydrochloric acid and it is generally known as Clemmensen reduction.
4. The Clemmensen reduction is particularly effective at reducing aryl- alkyl ketones, such as those formed in a Friedel-Crafts acylation.
5. The Clemmensen reduction is most commonly used to convert acylbenzenes (from Friedel-Crafts acylation) to alkylbenzenes, but it also works with other ketones or aldehydes that are not sensitive to acid.

The carbonyl compound is heated with an excess of amalgamated zinc (zinc treated with mercury; Zn (Hg), and concentrated hydrochloric acid (HCl). The actual reduction occurs by a complex mechanism on the surface of the zinc.



Clemmensen Reduction



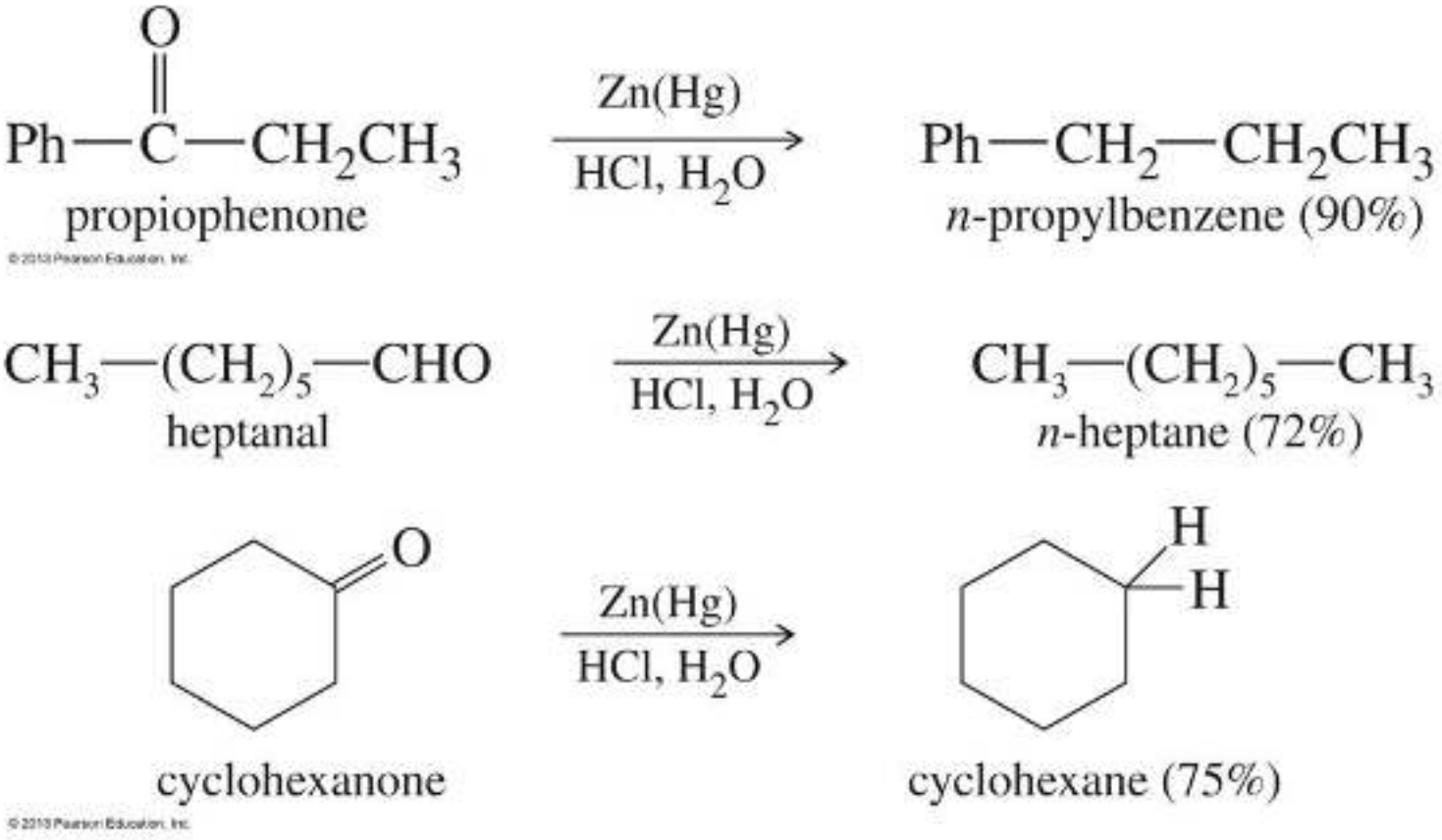
n-Butyrophenone

n-Butylbenzene

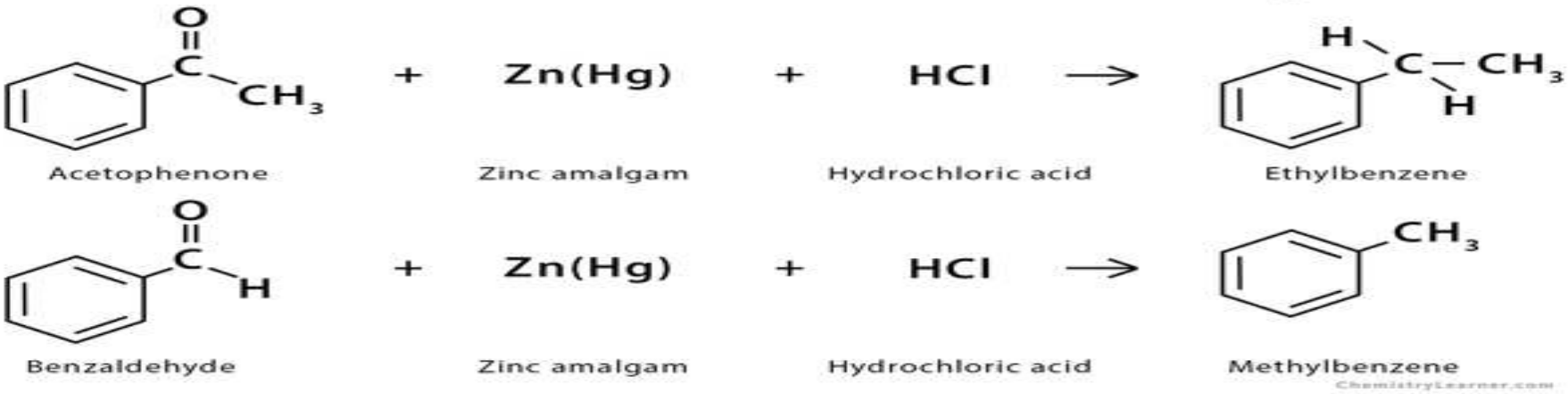
Applications:

1. This reaction has widely used to convert a carbonyl group into a methylene group.
2. It's important application in the preparation of polycyclic aromatics and aromatics containing unbranched side hydrocarbon chains.
3. This reaction helps to reduce the aliphatic and mixed aliphatic-aromatic carbonyl compounds.

Clemmensen Reduction



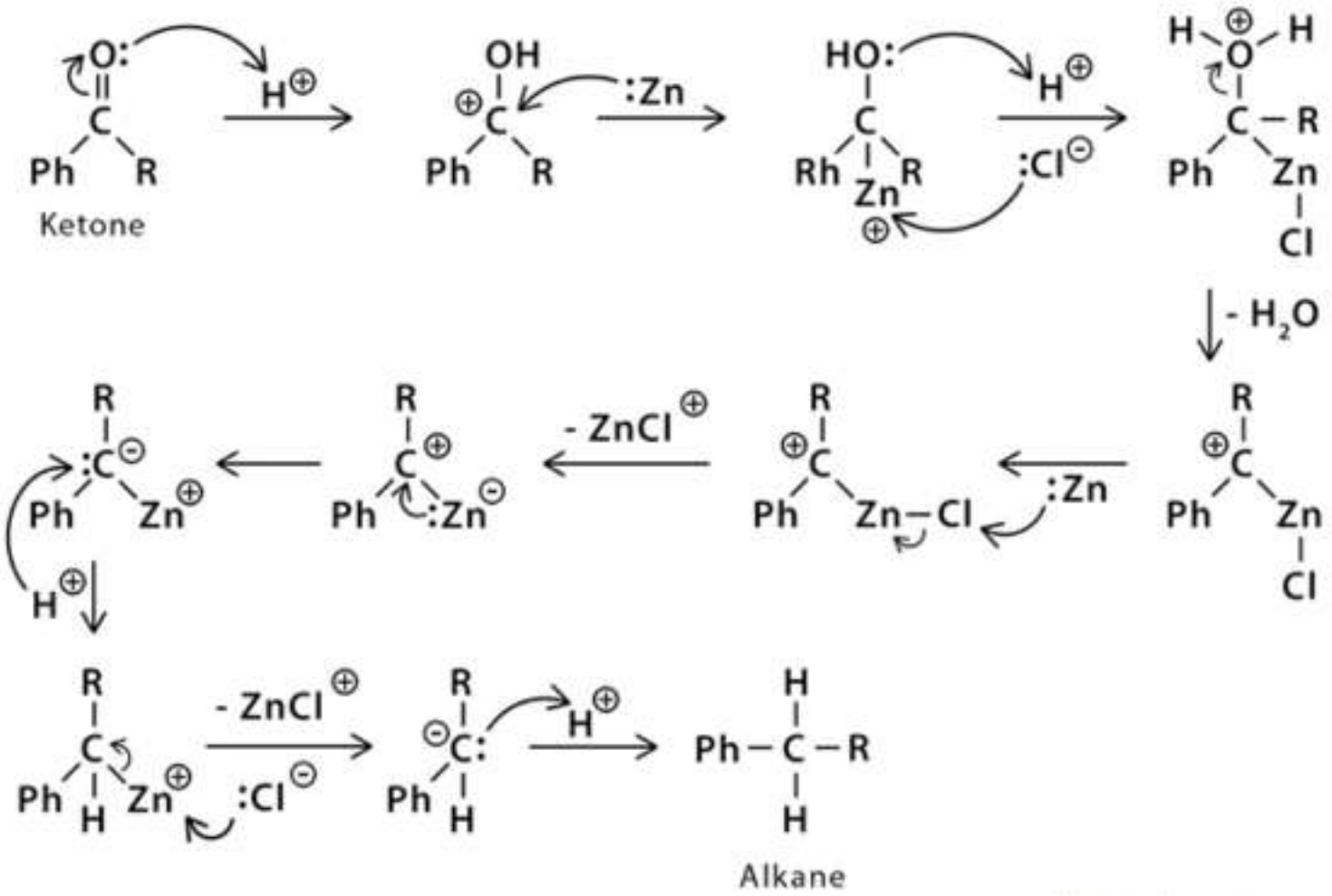
Clemmensen Reduction Examples



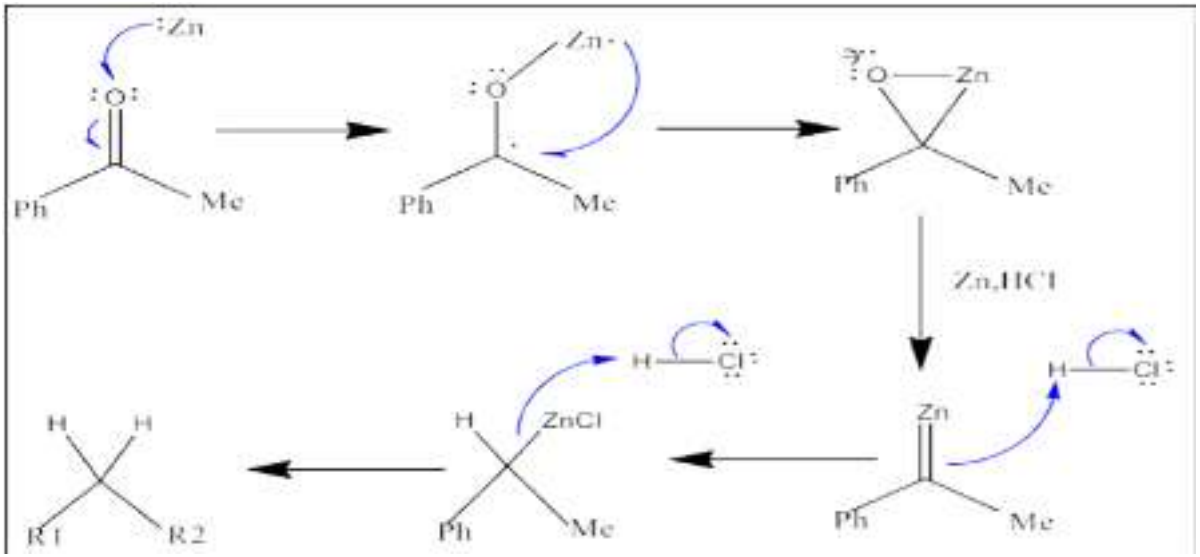
This process works best for aromatic ketones; non-aromatic ketones, not so much. The mechanism has not been thoroughly worked out; it's thought to occur through a series of one-electron transfers from zinc amalgam.

MECHANISM OF CLEMENSEN REDUCTION

The reduction may take place through two possible mechanisms.
The first one is called the **carbanionic mechanism**, where the zinc attacks the protonated carbonyl directly.
The second one is called the **carbenoid mechanism, which is a radical process**. The reduction happens on the surface of the zinc metal.


Ketone
Alkane

The second one is called the **carbenoid mechanism, which is a radical process**. The reduction happens on the surface of the zinc metal.

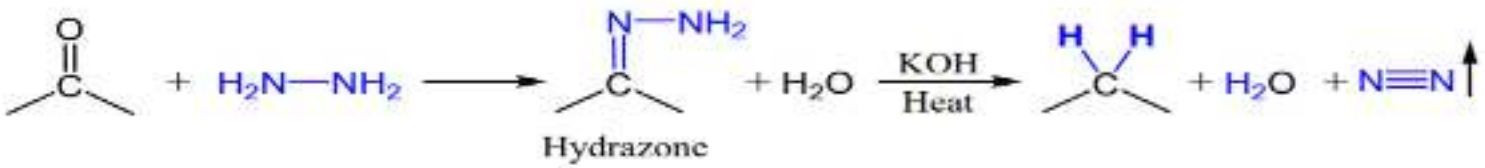


WOLFF–KISHNER REACTION

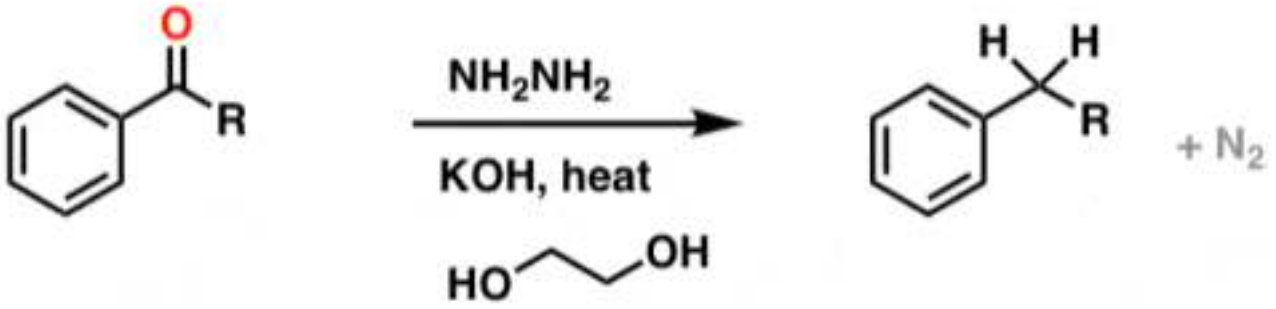
1. The Wolff– Kishner reduction was discovered independently by N. Kishner in 1911 and L. Wolff in 1912.
2. The Wolff– Kishner reduction is a reaction used in organic chemistry to convert carbonyl functionalities into methylene groups.
3. The Wolff-Kishner reduction is an organic reaction used to convert an aldehyde or ketone to an alkane using hydrazine, base, and thermal conditions.
4. Because of the Wolff–Kishner reduction requires highly basic conditions, it is unsuitable for base-sensitive substrates.

Compounds that cannot survive treatment with hot acid can be deoxygenated using the Wolff–Kishner reduction. The ketone or aldehyde is converted to hyrazone by treating with Hydrazine (NH_2NH_2), and this is heated with strong base such as KOH. Ethylene glycol, diethylene glycol, or another high-boiling solvent is used to facilitate the high temperature (140-200°C) needed in the second step.

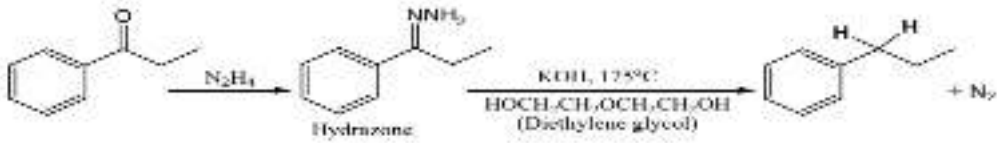
WOLF-KISHNER General reaction

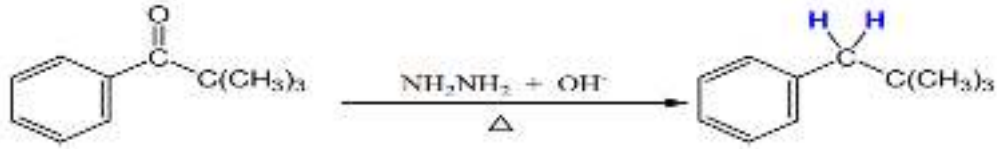


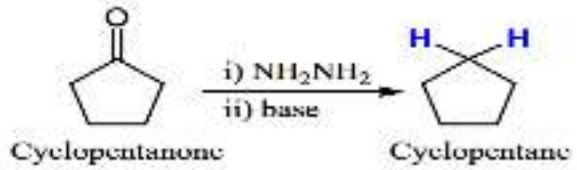
The Wolff-Kishner Reduction



Examples:


O
N_2H_4
NNH$_2$
Hydrazone
KOH, 175°C
HOCH$_2$CH$_2$OCH$_2$CH$_2$OH
(Diethylene glycol)
H
H
+ N_2

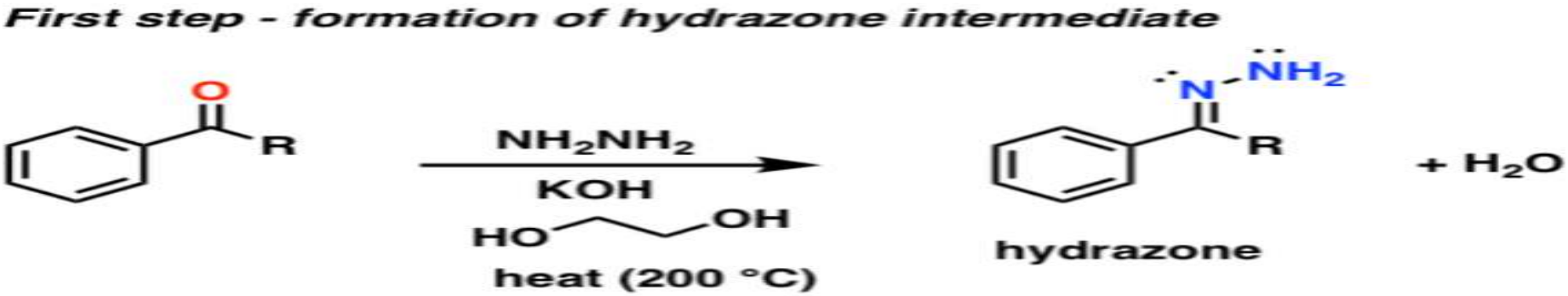

O
C
$C(CH_3)_3$
NH_2NH_2 + OH^-
△
H
H
C
$C(CH_3)_3$


O
i) NH_2NH_2
ii) base
H
H
Cyclopentanone
Cyclopentane

MECHANISM OF WOLF –KISHNER REDUCTION

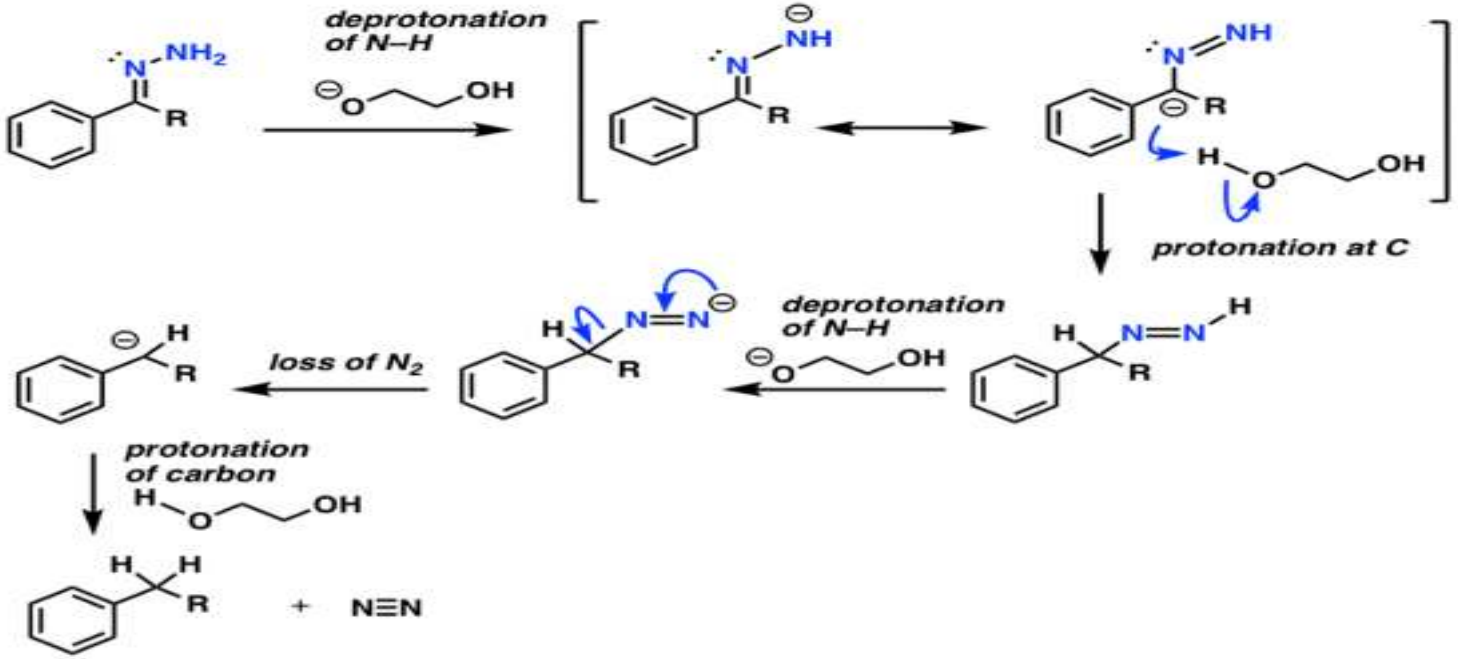
This involves a two step process

The first step is formation of a hydrazone from Alehyde or the ketone:
Hydrazine (NH_2NH_2) adds to the carbonyl, and following a series of proton transfer steps, water is expelled.



STEP-II Hydrazone to Hydrocarbon: Invovel the following steps

- The NH_2 of the hydrazone is acidic and deprotonated by strong base at a high temperature (the base is conjugate base of ethylene glycol). This deprotonation is the rate-limiting step. This results in carboanion,
- The carboanion undergo protonation on the *carbon*. This gives a species with a nitrogen-nitrogen double bond, which, further undergo deprotonation by base, and decomposes irreversibly to give nitrogen gas and a carbanion.
- Protonation of the carboanion results in hydrocarbon.



Applications:

1. This reaction has widely used to convert a carbonyl group into a methylene group.
2. It's important application in the preparation of polycyclic aromatics and aromatics containing unbranched side hydrocarbon chains.
3. This reaction helps to reduce the aliphatic and mixed aliphatic-aromatic carbonyl compounds.
4. The Wolff–Kishner reduction has also been used on kilogram scale for the synthesis of a functionalized imidazole substrate.
5. This reaction has very broad application in organic synthesis, especially for the multiwalled carbon nanotubes.

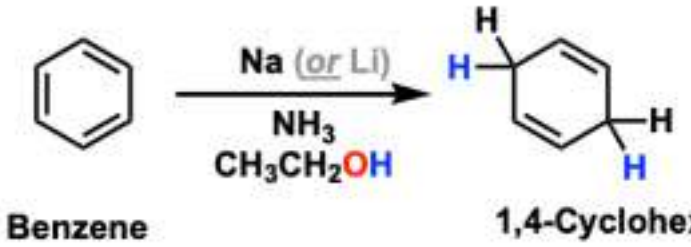
BIRCH REDUCTION

The Birch reduction is an organic reaction that is used to convert arenes to cyclohexadienes. The reaction is named after the Australian chemist Arthur Birch and involves the organic reduction of aromatic rings in liquid ammonia with sodium, or lithium, or potassium and an alcohol, such as ethanol and tert-butanol

Ex. Converting benzene (and its aromatic relatives) to 1,4-cyclohexadiene using sodium (or lithium) as a **reducing** agent in liquid ammonia as solvent in the presence of an alcohol such as ethanol, methanol or t-butanol.

When benzene is treated with metallic sodium (or lithium) in liquid ammonia as a solvent, in the presence of a proton source (e.g. ethanol, methanol, or *t*-butanol) the result is the *net* reduction of one of the double bonds of the benzene ring to give 1,4-cyclohexadiene.

The Birch Reduction: Reduction of Benzene To 1,4 Cyclohexadiene



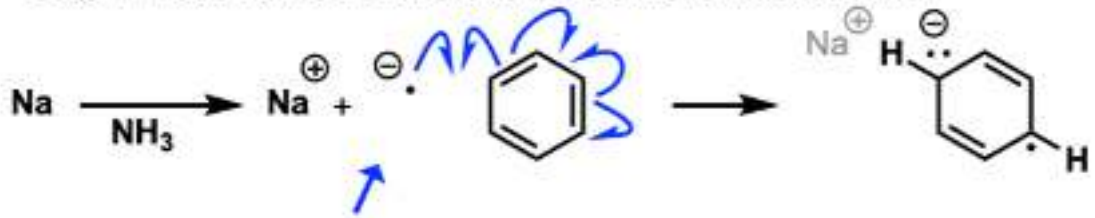
Benzene **1,4-Cyclohexadiene**

- **NH_3 is the solvent**
- **The alcohol is the source of H**
- **Conducted at temperatures from –80°C to –33°C**

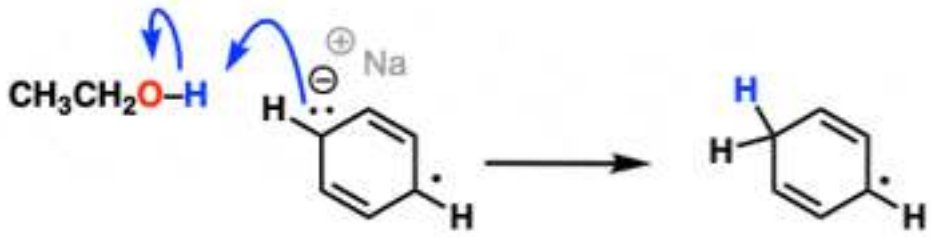
Ammonia (NH_3) is a gas at room temperature, boiling at a balmy –33 °C. Gaseous ammonia can be condensed to a liquid using a dry ice/acetone (–78°C) cold-finger, where it can serve as a solvent for alkali metals (e.g. Li, Na, and K). Although these metals are only sparingly soluble in liquid ammonia.

Birch Reduction Mechanism:

Step 1: Reduction of Benzene to the benzene "radical anion"



Step 2: Protonation of the benzene "radical anion"



pentadienyl radical
(only one resonance form shown)

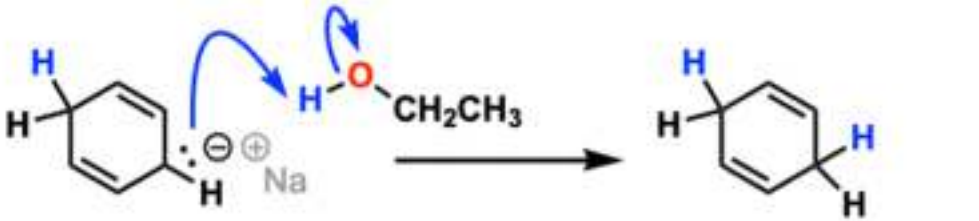
The resulting pentadienyl radical can then accept an electron from the "electron pool", resulting in a new anion (a "pentadienyl anion").

Step 3: Reduction of the radical to an anion by the electron

Radical
Pentadienyl radical

Anion
Pentadienyl anion

Step 4: Protonation of the anion by alcohol



Anion
Pentadienyl anion

+ $NaOCH_2CH_3$

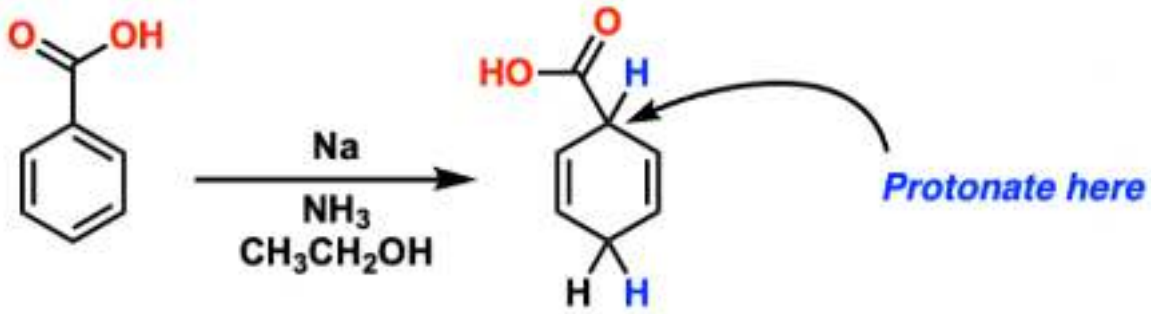
Substituent Effects In The Birch Reduction/ Regioselectivity in Birch reduction

In birch reduction the rate determining step is intermediate carbonation, the substituted benzene differ in the rate of reaction

the reaction is **faster** on aromatic rings with electron-withdrawing substituents (e.g. CO_2H) and **slower** on aromatic rings with electron-donating substituents (OCH_3).

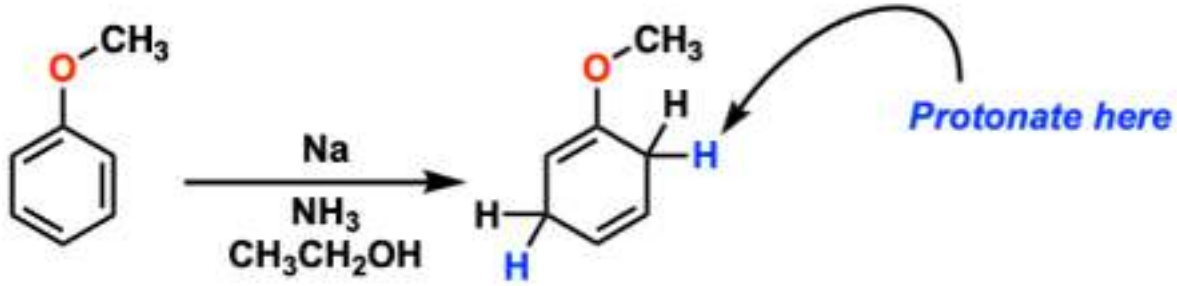
More over when the aromatic ring is substituted, the nature of the substitute (Electron donating or Electron withdrawing) affects the regioselectivity of the reduction and production substituted benzenes the nature of substituent also has influence on the regioselectivity of the reduction and nature of reduced product.

Birch reduction on aromatic rings with electron-withdrawing groups results in protonation on the carbon bearing the EWG



followed by acidic workup
to protonate the carboxylic acid

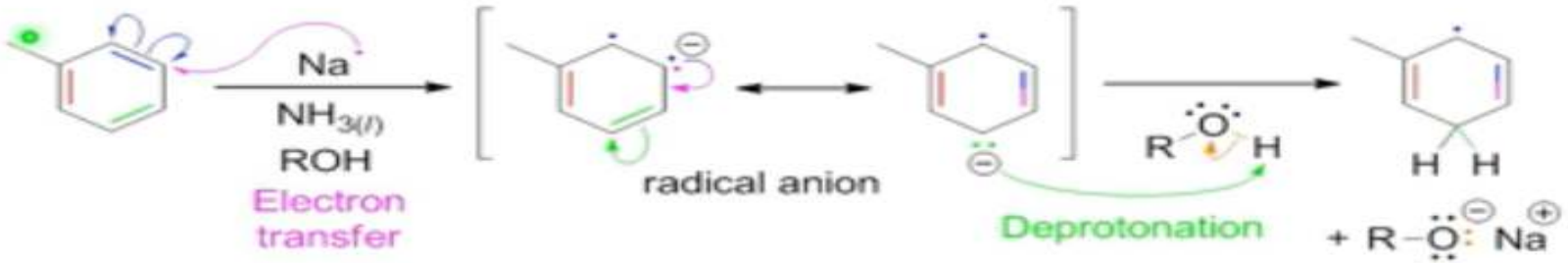
Birch Reduction on aromatic rings with electron-donating groups results in protonation "ortho" to the electron donating group



This is because of the stabilization or destabilization of the intermediate carboanion in the rate determining step of birch reduction.

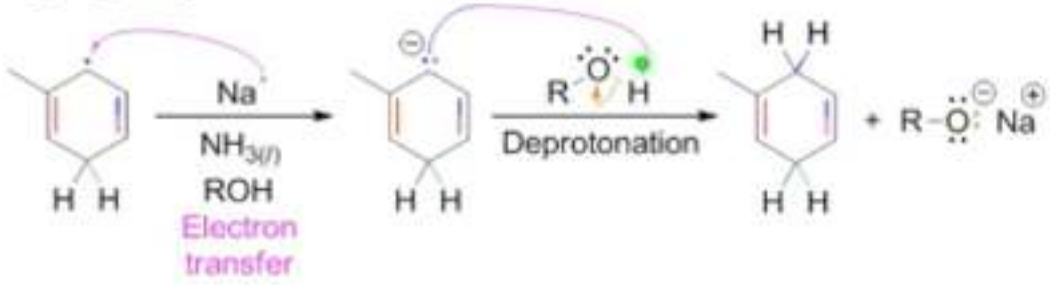
Specific examples with regiochemistry:

- Toluene bears an electron-donating methyl group on the ring that would destabilize an anion if it appeared on the neighboring carbon
- Therefore, the reaction proceeds so as to avoid the placement of negative charge adjacent to the electron-donating methyl group



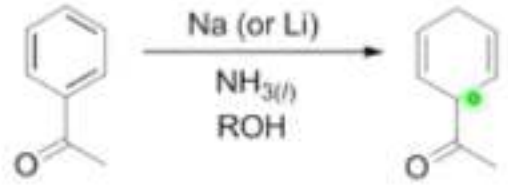
Specific examples with regiochemistry:

- The radical then accepts a second electron, forming an anion that deprotonates another alcohol to yield the 1,4-cyclohexadiene product
- Notice that at no point in the mechanism did the negative charge appear on the carbon next to the electron-donating methyl group



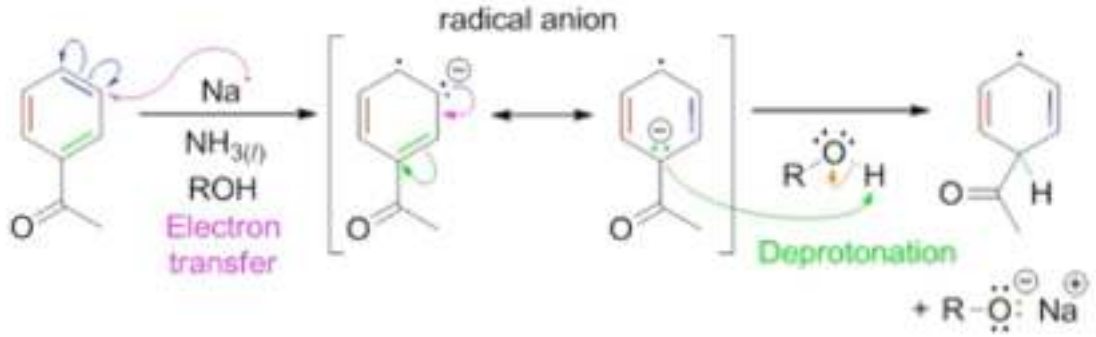
Specific examples with regiochemistry:

- In the next example, acetophenone is reduced
- In this case, the substrate has an electron-withdrawing ketone on the aromatic ring
- Notice that the substituent is not on a double bond in the product of this reaction



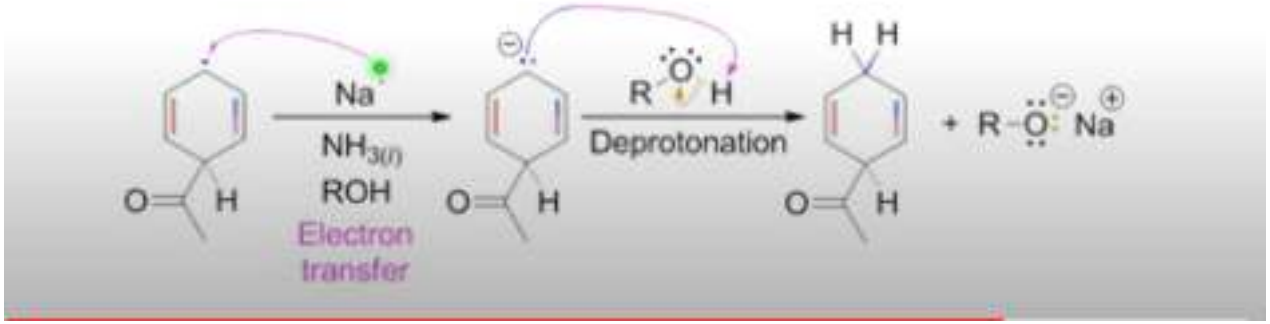
Specific examples with regiochemistry:

- Since the ketone is electron withdrawing, it will stabilize an anion on the adjacent carbon
- Consequently, the reaction progresses so as to place the negative charge at that location



Specific examples with regiochemistry:

• The radical intermediate subsequently accepts a second electron, and the anion thus formed deprotonates an alcohol to afford the final 1,4-cyclohexadiene product



Summary:

- The Birch reduction converts an aromatic ring into a 1,4-cyclohexadiene.

- The reaction requires sodium or lithium as the electron source, an alcohol as the proton source, and liquid ammonia as the solvent.

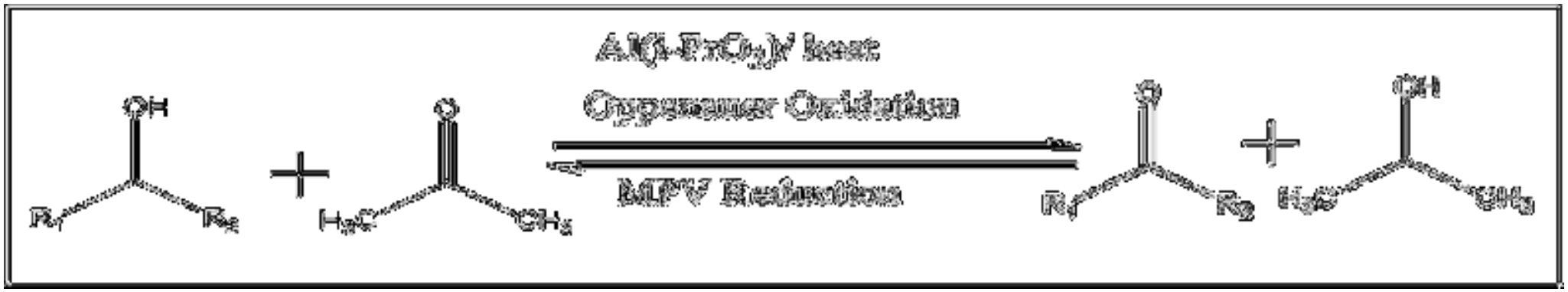
- The regiochemistry of the reduction is affected by the nature of substituents on the ring.

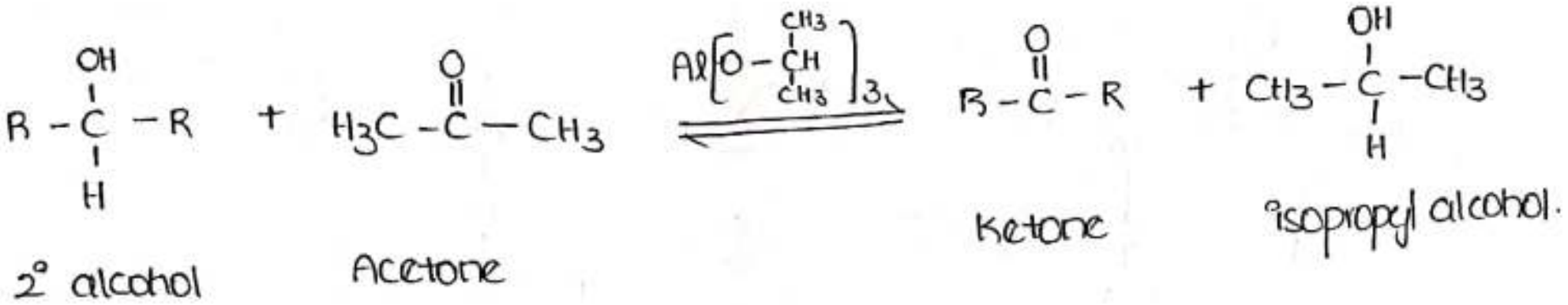
- Electron-donating substituents appear on a double bond of the product, while electron-withdrawing groups do not

Oppenauer oxidation

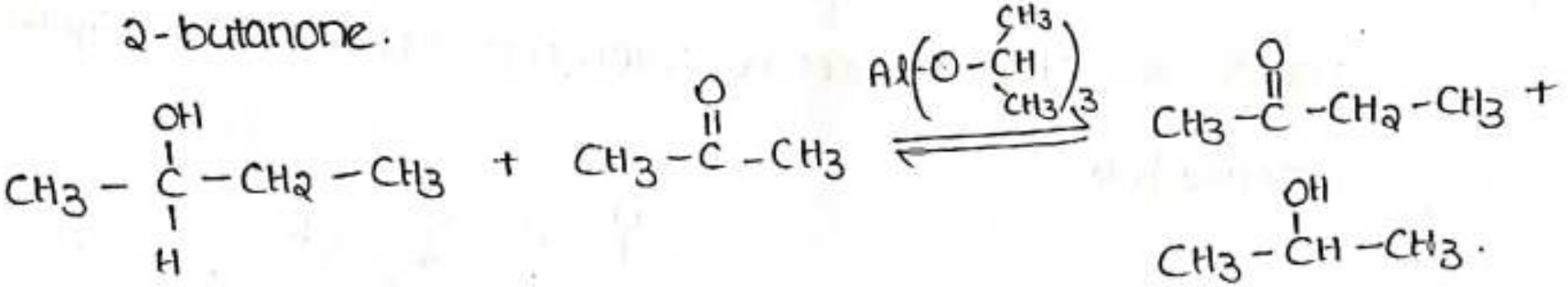
Named after Rupert Viktor Oppenauer.
1. It is a gentle method for selectively oxidizing secondary alcohols to ketones.
2. This is a reversible process the back ward reduction process is known as Meerwein–Ponndorf –Verley reduction.
3. The alcohol is oxidized with aluminium isopropoxide in excess acetone or benzophenone which act as hydride acceptor.
4. This shifts the equilibrium toward the product side. During the process acetone is reduced to isopropyl alcohol

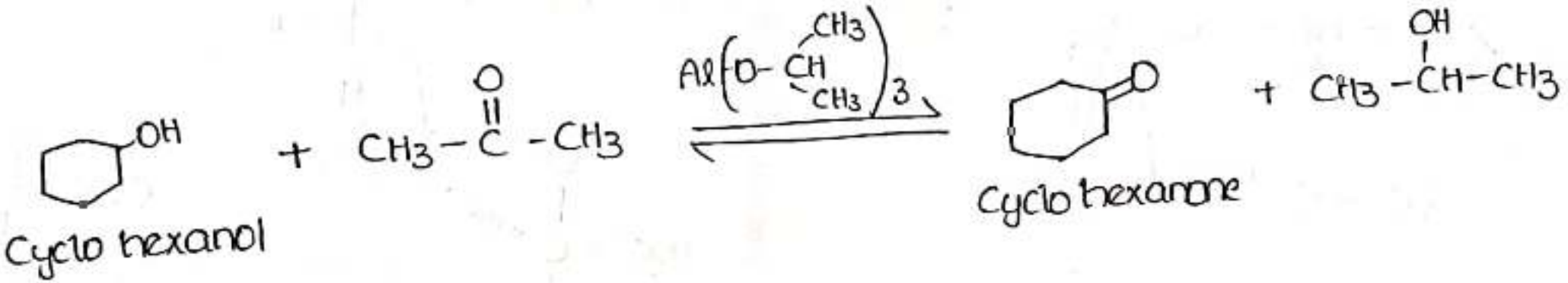
This oxidation is highly selective for secondary alcohols and does not oxidize other sensitive functional groups such as amines and sulfides,
Though primary alcohols can also be oxidized under Oppenauer conditions, primary alcohols are seldom oxidized by this method due to the competing aldol condensation of aldehyde products.
The Oppenauer oxidation is still used for the oxidation of acid labile substrates.


Al(i-PrO)3/ Toluene
Oppenauer Oxidation
MPV Reduction


Al[O-CH(CH3)2]3
2° alcohol
Acetone
Ketone
isopropyl alcohol.

Eg:- 2-butanol upon Oppenaur oxidation with Aluminium isopropoxide yields 2-butanone.





Cyclo hexanol

Cyclo hexanone

Oppenaur oxidation is a reversible process. In backward reaction, ketones are reduced to 2° alcohols. This reversible reduction is known as Meerwein - Pondorf - Verley reduction (MPV reduction).

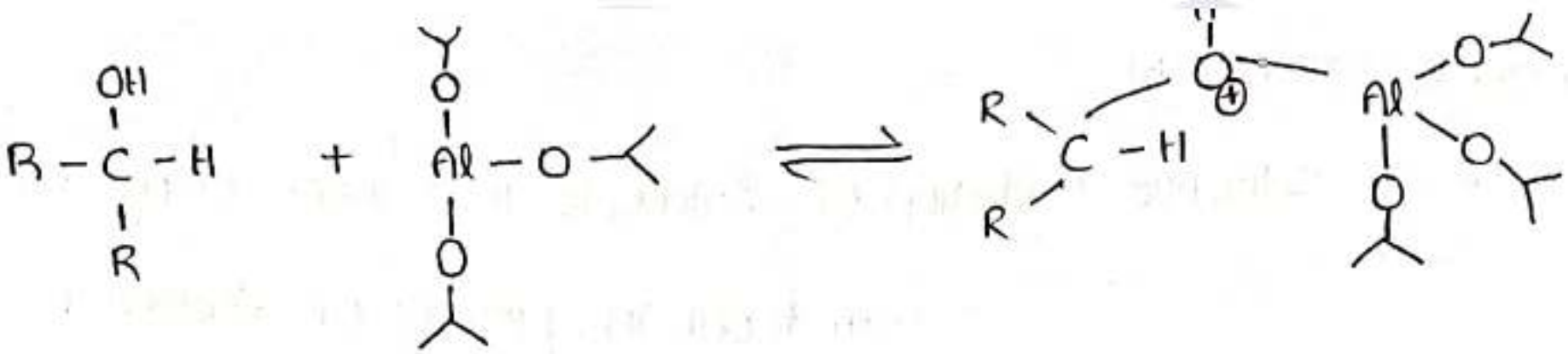
In oppenaur oxidation, the equilibrium can be shifted to the desired RIGHT hand direction i.e, the formation of ketones by using excess of acetone.

MECHANISM :-

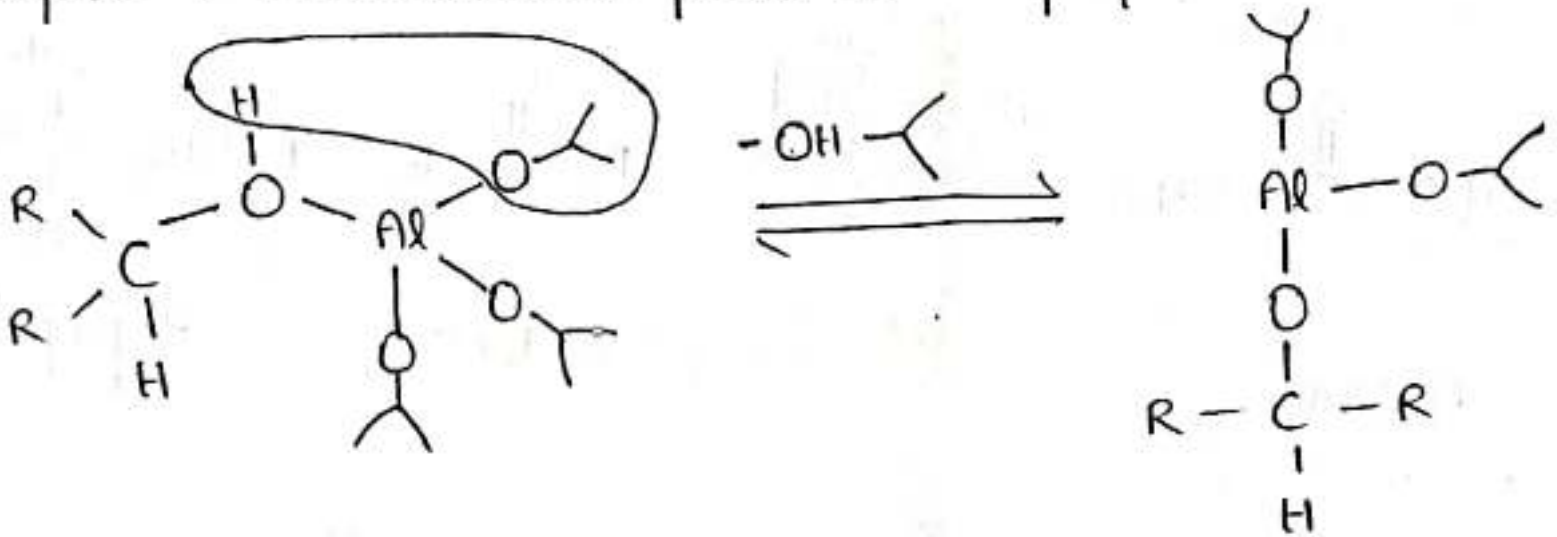
Step I :- The hydroxyl oxygen of 2° alcohol acts as neutral nucleophile.

-Aluminium of Aluminium isopropoxide acts as neutral electrophile.

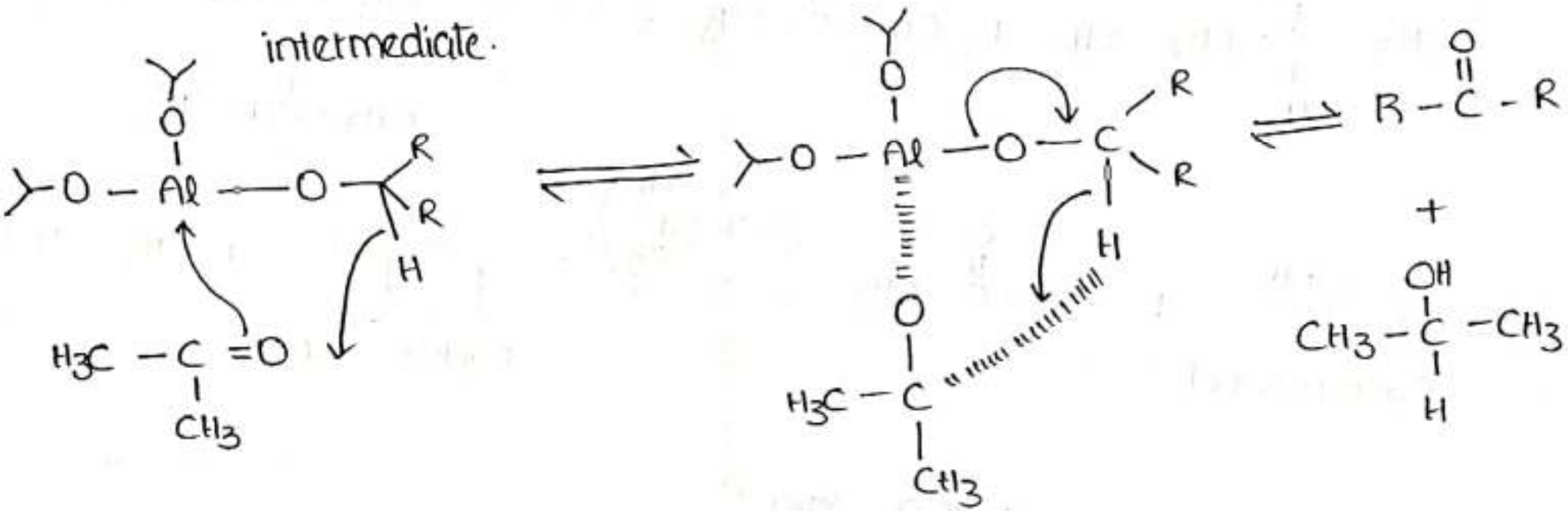
Thus the hydroxyl oxygen co ordinates with aluminium.



Step II :- Elimination of proton and isopropoxide as isopropyl alcohol.



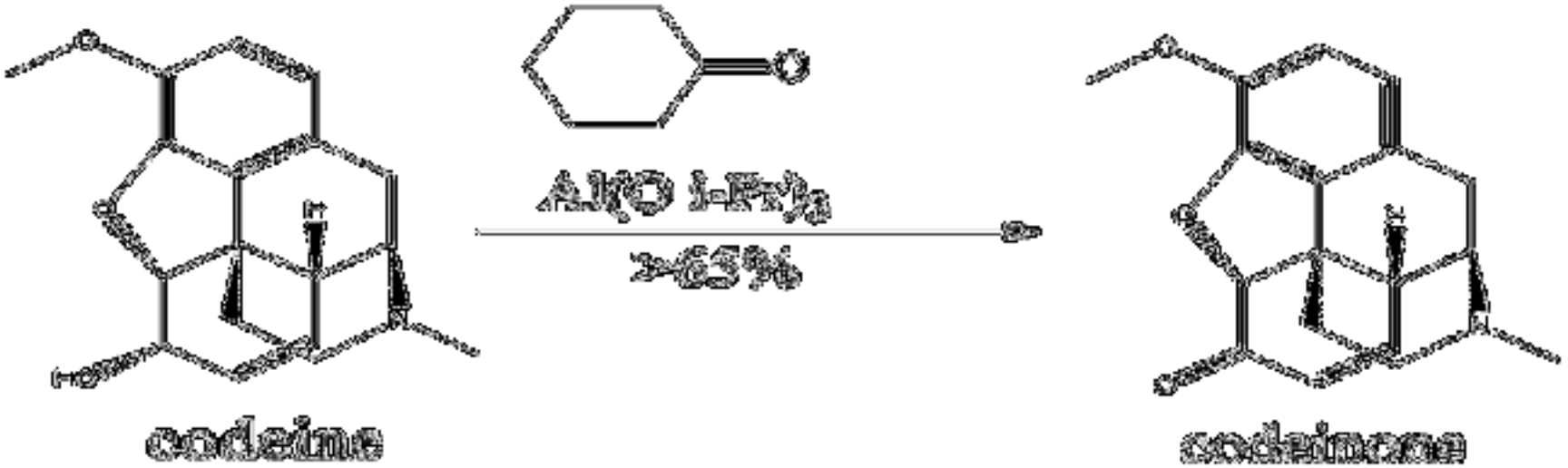
Step III :- Oxidation of 2° alcohol by the transfer of hydride ion and simultaneous reduction of acetone through a six membered cyclic intermediate.

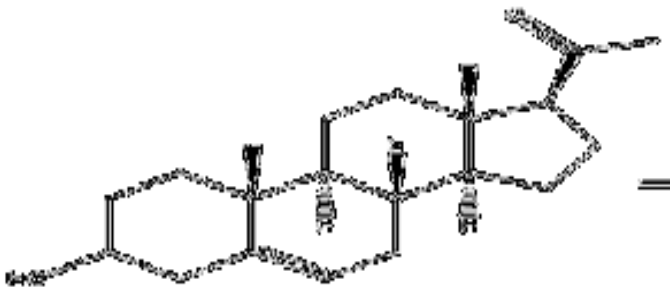


Oppenauer oxidation is more specific and substrate which contain other oxidisable functionalities such as amides and sulphides in addition to 2° alcohols can be subjected to selective 2° alcohol oxidation to ketones without affecting the other functionalities.

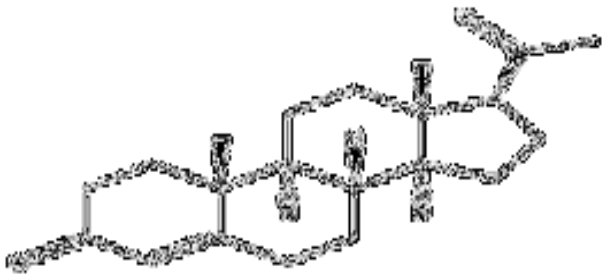
Applications:

1. The Oppenauer oxidation is used to prepare analgesics in the pharmaceutical industry such as morphine and codeine. For instance, codeinone is prepared by the Oppenauer oxidation of codeine.
2. The Oppenauer oxidation is also used to synthesize hormones.
3. Progesterone is prepared by the Oppenauer oxidation of pregnenolone.
4. The Oppenauer oxidation is also used in the synthesis of lactones from 1,4 and 1,5 diols.

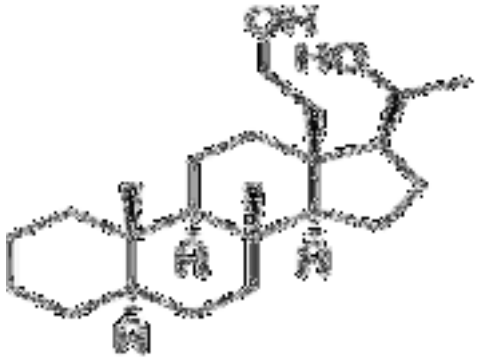




pyrancoumarin



Pyranocoumarin

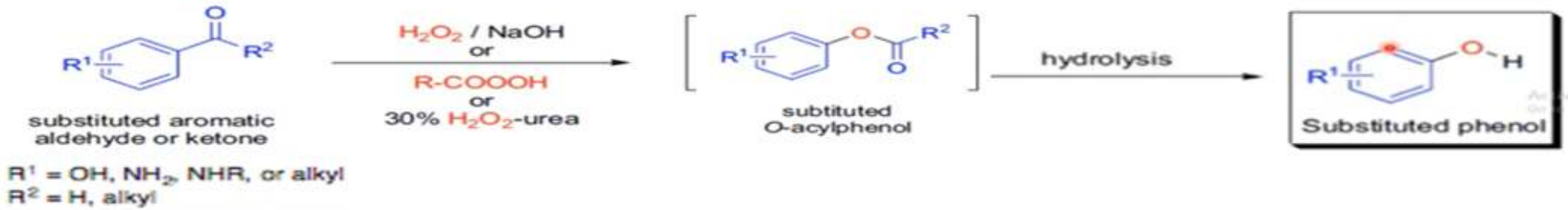


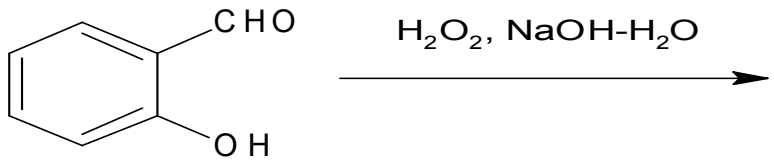
DAKIN REACTION

The **Dakin oxidation** (or **Dakin reaction**) is an organic redox reaction in which an aryl aldehyde or aryl ketone containing ring activating groups such as hydroxyl or amino or alkyl at ortho or para to carbonyl group is oxidized with hydrogenperoxide in alkaline medium or by using Peroxybenzoic acid or peroxyaceticacd to form a benzenediol and a carboxylate.

Overall, the carbonyl group is oxidized, and the hydrogen peroxide is reduced.

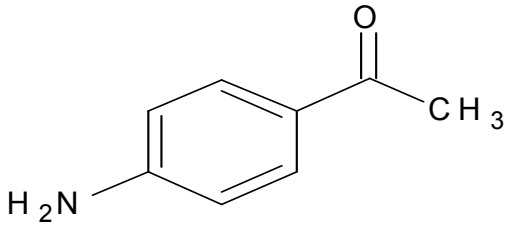
Reaction Steps:-

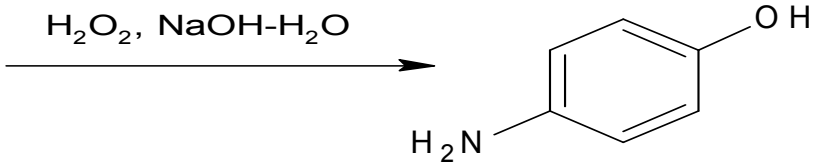




O-hydroxybenzaldehyde

Catechol





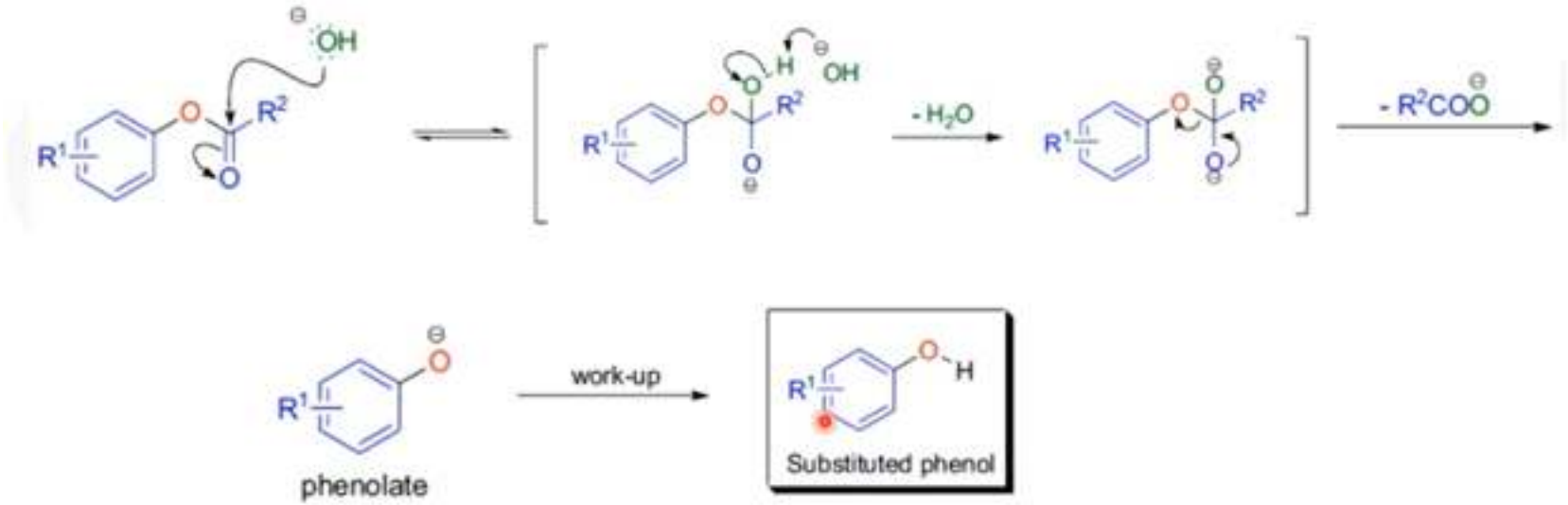
p-aminoacetophenone

p-aminophenol

DAKIN REACTION MECHANISM

Step1 and 2 The hydroperoxide anion generated from hydrogen peroxide in alkaline medium act as nucleophile and attack the carbonyl carbon and from a tetrahedral intermediate.
The intermediate undergo [1,2]-aryl migration of phenyl ring to electron deficient oxygen with the simultaneous elimination of hydroxide ion and results in the formation of phenyl ester.

Step-3 and 4 The phenyl ester is undergo hydrolysis by the nucleophilic addition of hydroxide from solution to the ester carbonyl carbon forms a second tetrahedral intermediate which then breaks down into phenoxide ion and carboxylic acid, the phenoxide ion undergo protonation to yield substituted phenol



APPLICATIONS OF DAKIN REACTION

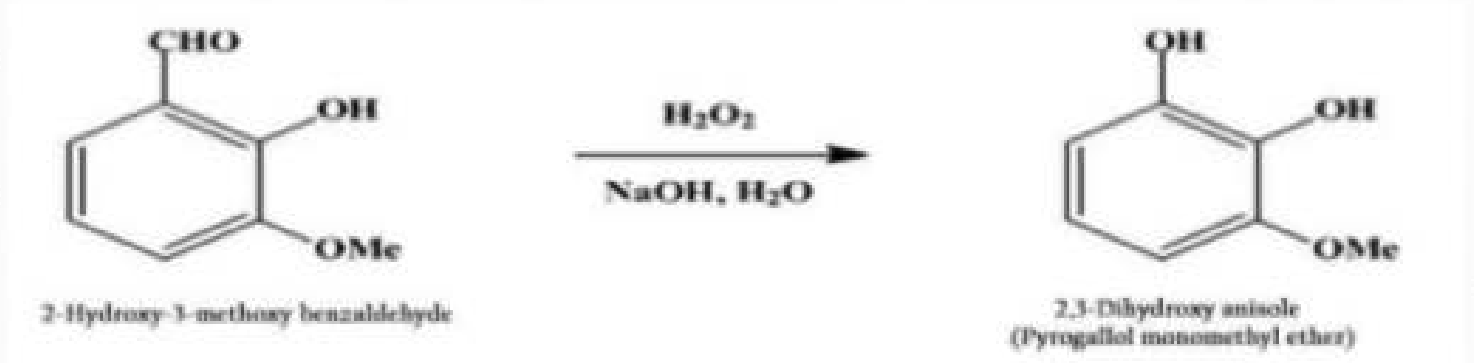
The Dakin oxidation is most commonly used to synthesize benzenediols and alkoxyphenols.

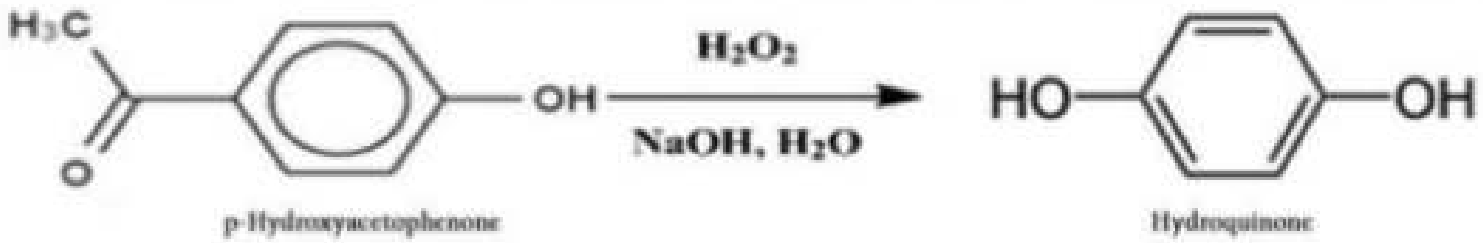
Catechol, for example, is synthesized from o-hydroxy and o-alkoxy phenyl aldehydes and ketones and is used as the starting material for synthesis of several compounds, including the catecholamines, catecholamine derivatives and 1,4-tertbutlycatechol a common antioxidant and polymerization inhibitor

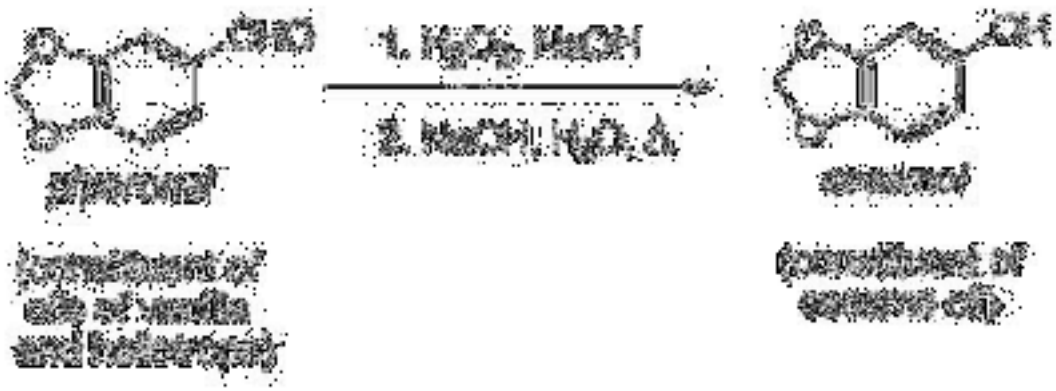
Other synthetically useful products of the Dakin reaction include guaiacol, a precursor of several flavoring agents

Hydroquinone, a common photograph-developing agent; and 2-tertbutyl-4-hydrooxyanisole and 3-tertbutyl-4- hydrooxyanisole, two antioxidants commonly used to preserve packaged food

- Dakin reaction has many useful synthetic application.



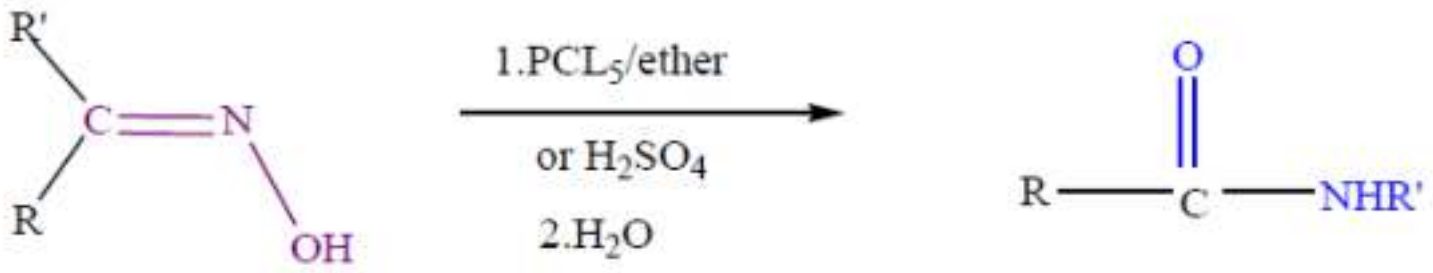




BECKMAN -REARRANGEMNT

1.The Beckmann rearrangement, named after the German chemist Ernst Otto Beckman (1853–1923).

2. It is an acid catalyzed conversion of keto oximes to N-substituted amides usually called the Bechmann rearrangement. This rearrangement is occurs in both cyclic and acyclic compounds . Aldoximes are less reactive.

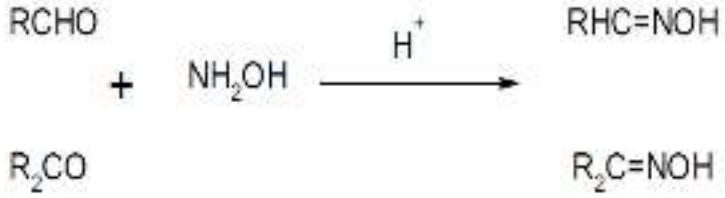


The acid catalyst can be Conc.H2SO4, HCl, PCl5, PCl3, SOCl2, ZnO SiO2 P P A (Poly phosphoric acid).

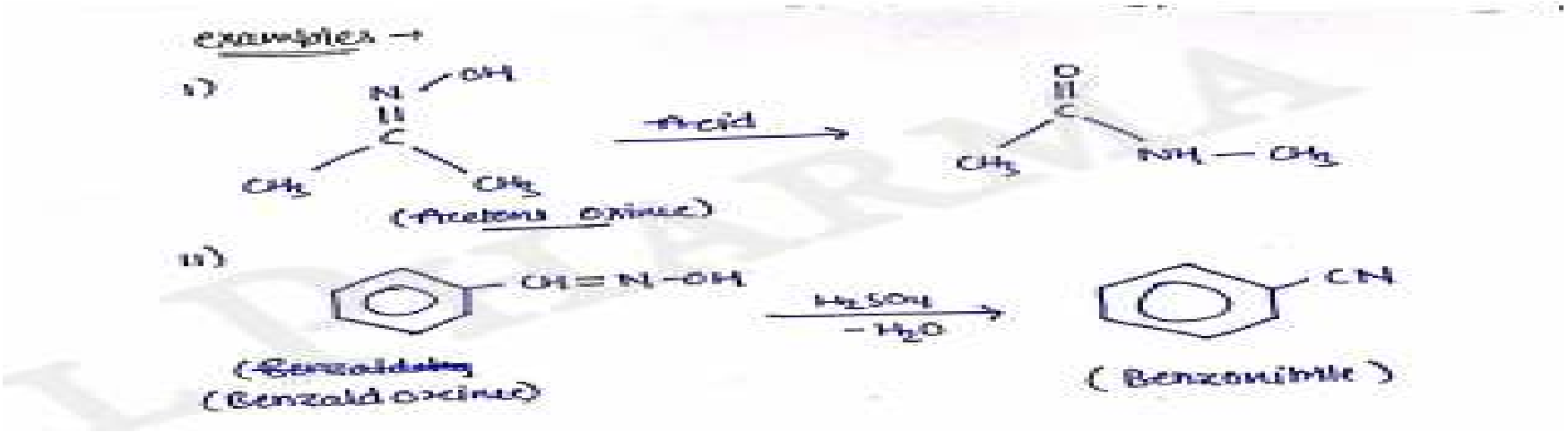
OXIMES

Oximes are the condensation products of aldehydes and ketones with hydroxyl amine containing the grouping C = N-OH, Two types of oximes are known:

Aldoxime: combination of aldehyde with hydroxylamine.
Ketoxime: Combination of Ketones with hydroxylamine.

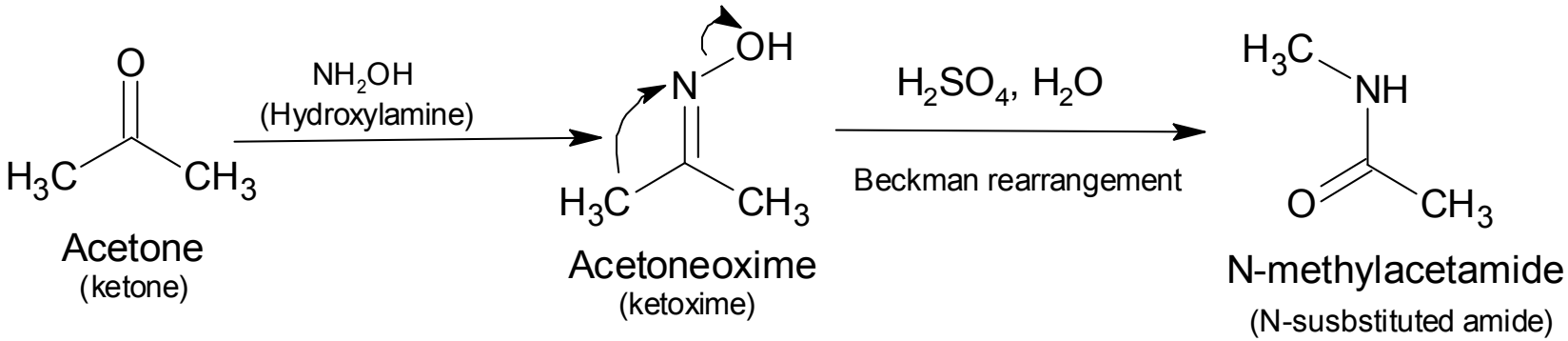


Open chain ketoxime upon Beckman rearrangement yield N-substituted amides. Cyclic ketoximes yields cyclic amides with ring expansion. Aldoximes yield nitriles.



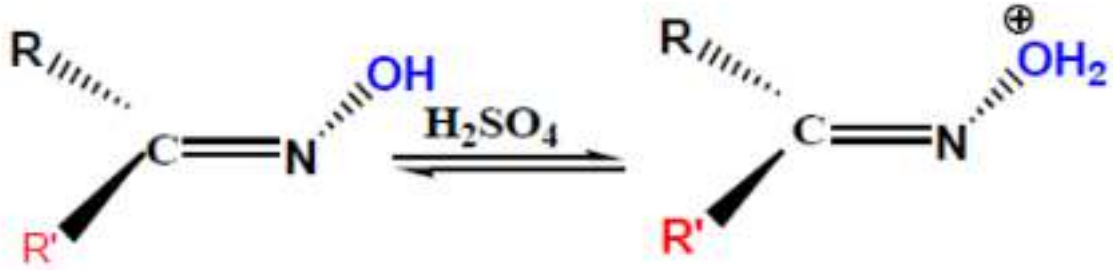
In Beckman rearrangement first the ketone upon reaction with hydroxyl amine forms ketoxime which then upon reaction with acidic reagent undergo Beckman rearrangement and forms N-substituted amide.

Ex.

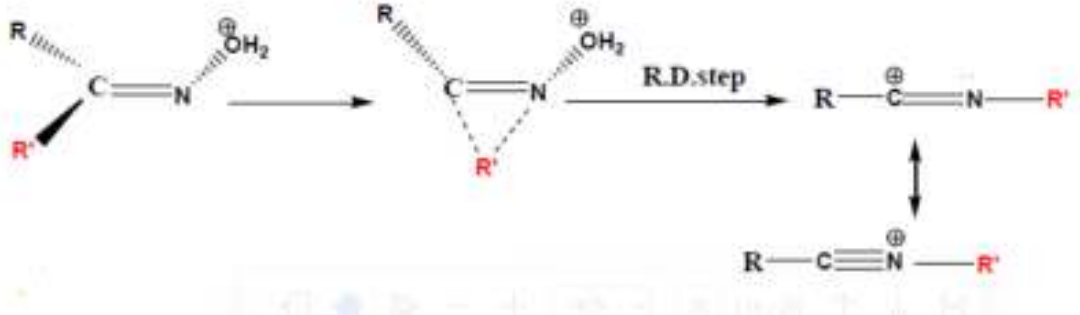


MECHANISM OF BECKMAN REARRANGEMNT This molecular rearrangement reaction which involves the elimination of hydroxyl (leaving group) and alkyl migration to electron deficient nitrogen involves the following steps

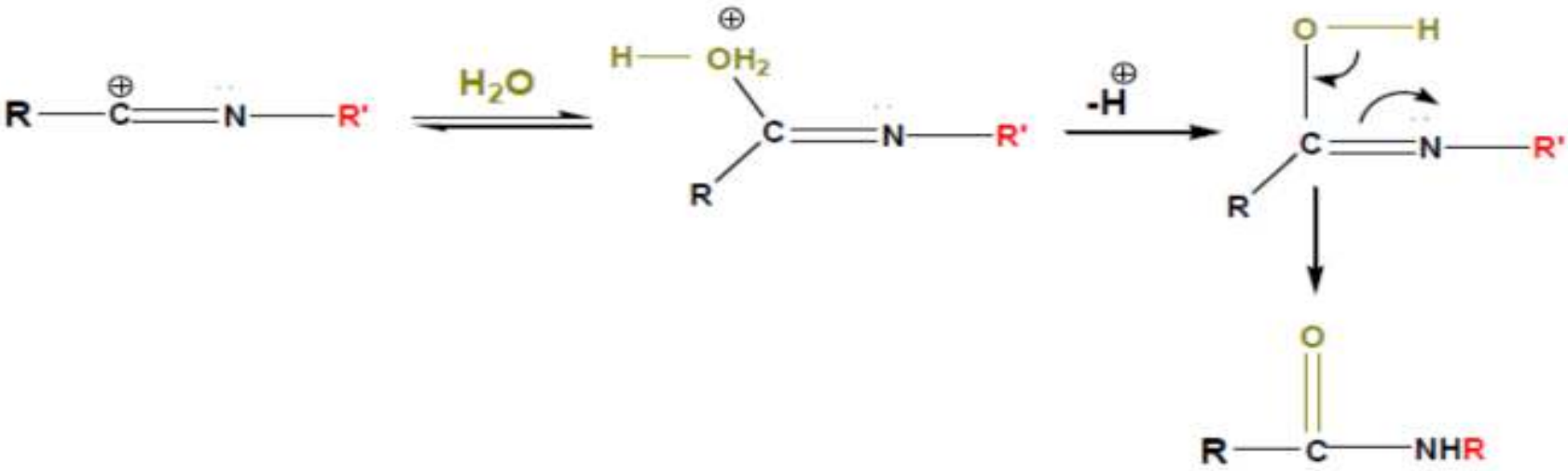
Step-1- Protonation of hydroxyl of oxime converts it into a better leaving group Oxonium ion



Step-2- Elimination of leaving group (H_2O^+) and simultaneous migration of alkyl group which is antiperiplanar to the leaving group to electron deficient nitrogen results in nitrilium ion

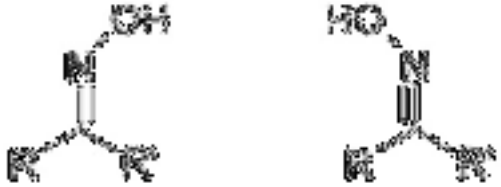


Step-3-Solvolysis of nitrilium ion to an imidate which then tautomerizes to AMIDE

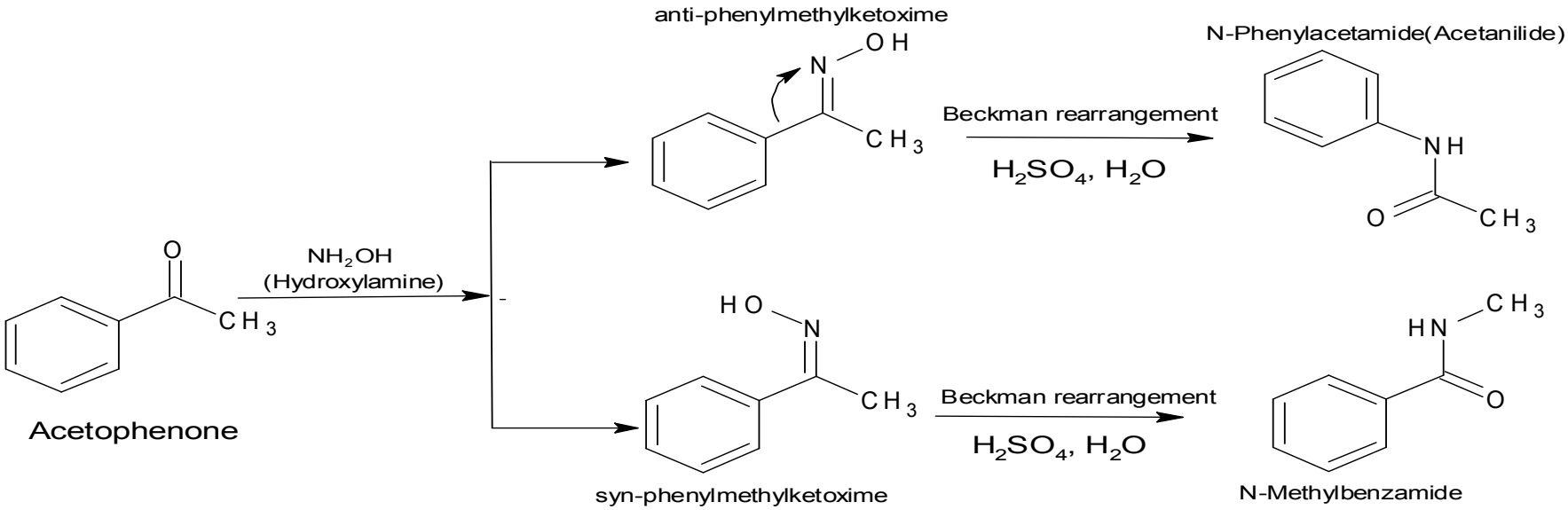


Beckman rearrangement occurs stereospecifically for ketoximes, with the migrating group being always anti (i.e. trans) to the leaving group (hydroxyl group) on the nitrogen.

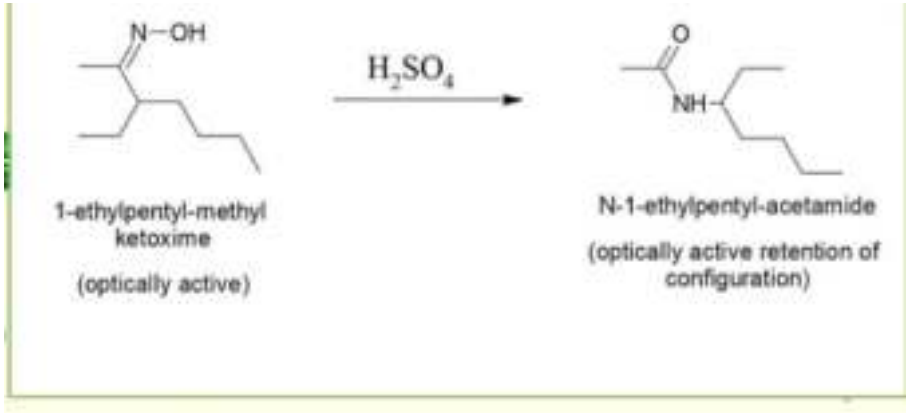
Ex. A ketone with different alkyl groups can form two isomeric (Geometric isomers) ketoximes, which differ in the spatial arrangement of hydroxyl group of nitrogen with respect to alkyl groups. Each this geometrical oximes can yield different N-substituted amides upon Beckman rearrangement depending on the alkyl group which is trans to hydroxyl



Ex. Acetophenone upon reaction with hydroxyl amine could yield isomeric oximes anti-phenylmethylketoxime or syn-phenylmethylketoxime. Each of this yield different amides upon Beckman rearrangement

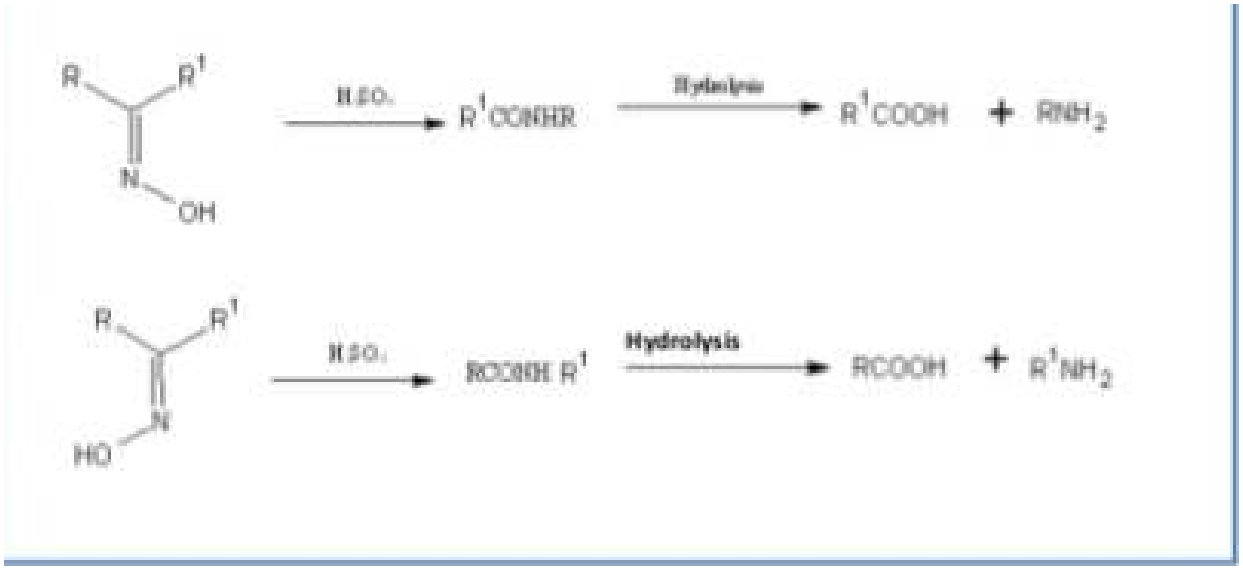

anti-phenylmethylketoxime
N-Phenylacetamide(Acetanilide)
Beckman rearrangement
H_2SO_4, H_2O
NH_2OH
(Hydroxylamine)
Acetophenone
syn-phenylmethylketoxime
Beckman rearrangement
H_2SO_4, H_2O
N-Methylbenzamide

More over in Beckman rearrangement the electron rich group undergo migration preferably and stereochemistry of migrating group is retained.
Ex.

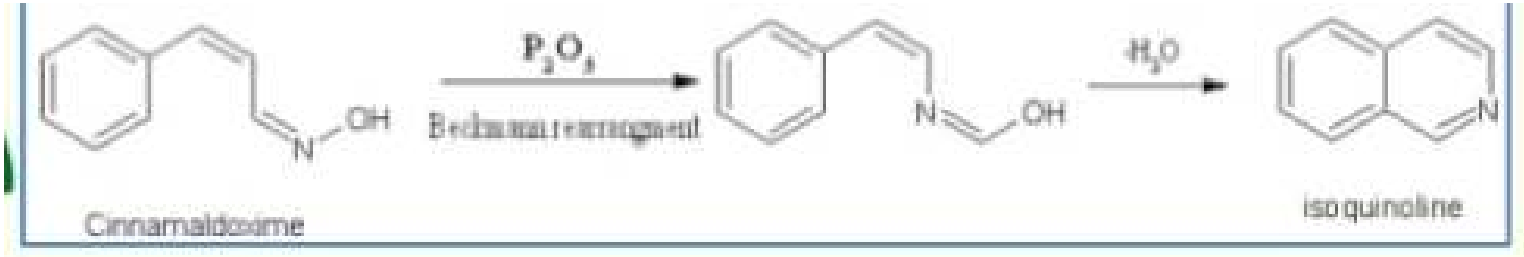


Applications of Beckman rearrangement

1. Determination of configuration of ketoxime:

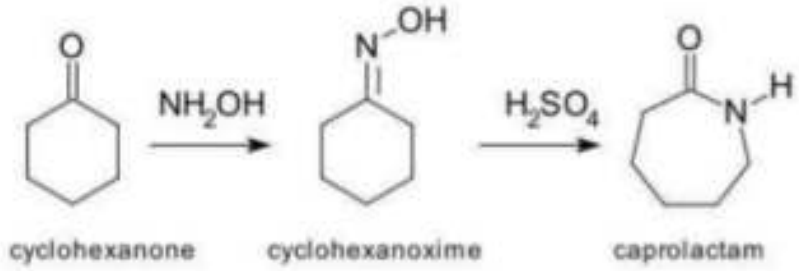


2. Synthesis of Isoquinoline

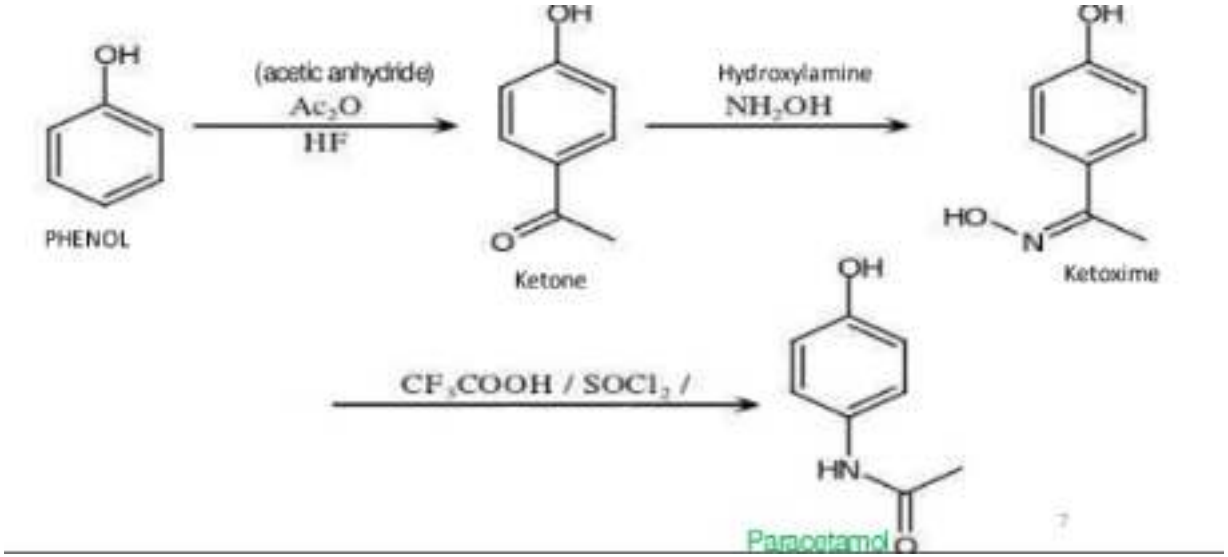


3. Acyclic oximes yield amides

4. Cyclic oximes yield lactams



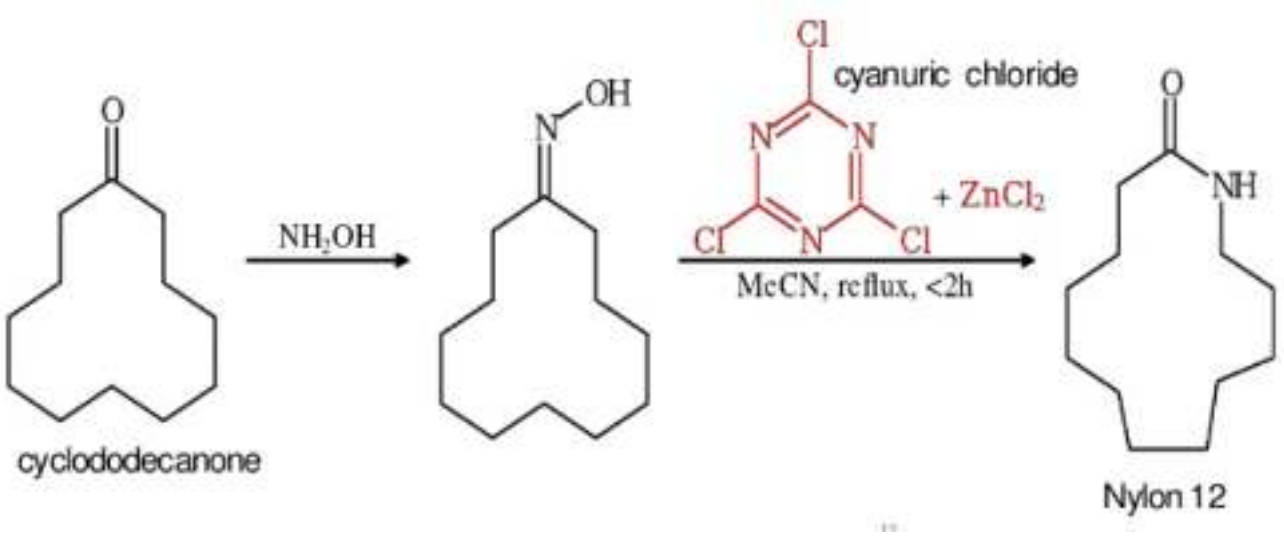
5. In drugs production ex. Alternate method of synthesis of Paracetamol



TheBeckmann rearrangement is also usedin the synthesis of •DHEA •Benazepril •Etazepine etc

6. In polymer synthesis

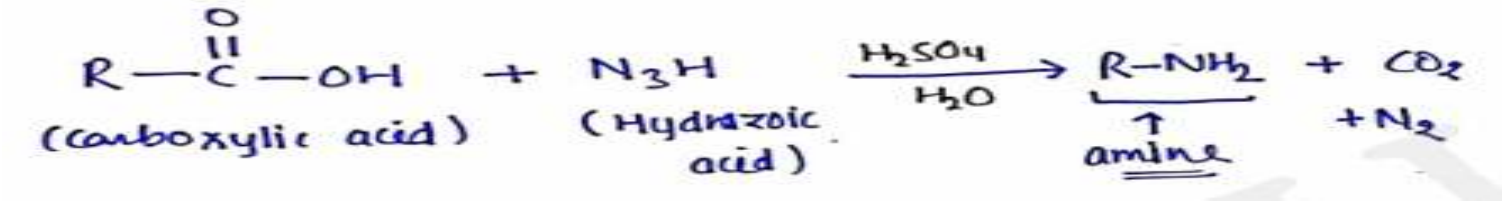
Beckmann rearrangement can be rendered catalytic using cyanuric chloride and zinc chloride as a co-catalyst. For example, cyclododecanone can be converted to the corresponding lactam, the monomer used in the production of Nylon 12

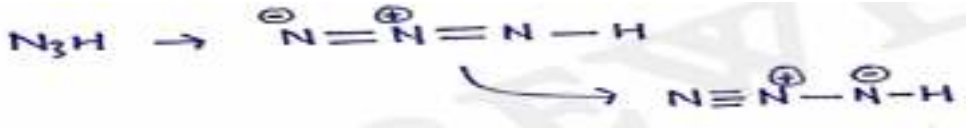


SCHMIDT REACTION In this molecular rearrangement reaction azide (conjugate base of Hydrazoic acid)reacts with a carbonyl derivative such as carboxylic acid, ketones, aldehydes under acidic conditions to give amine or amide with liberation of nitrogen. This involves a molecular rearrangement in which an alkyl or aryl group with its bonding electrons migrate from carbon to adjacent electron deficient nitrogen.

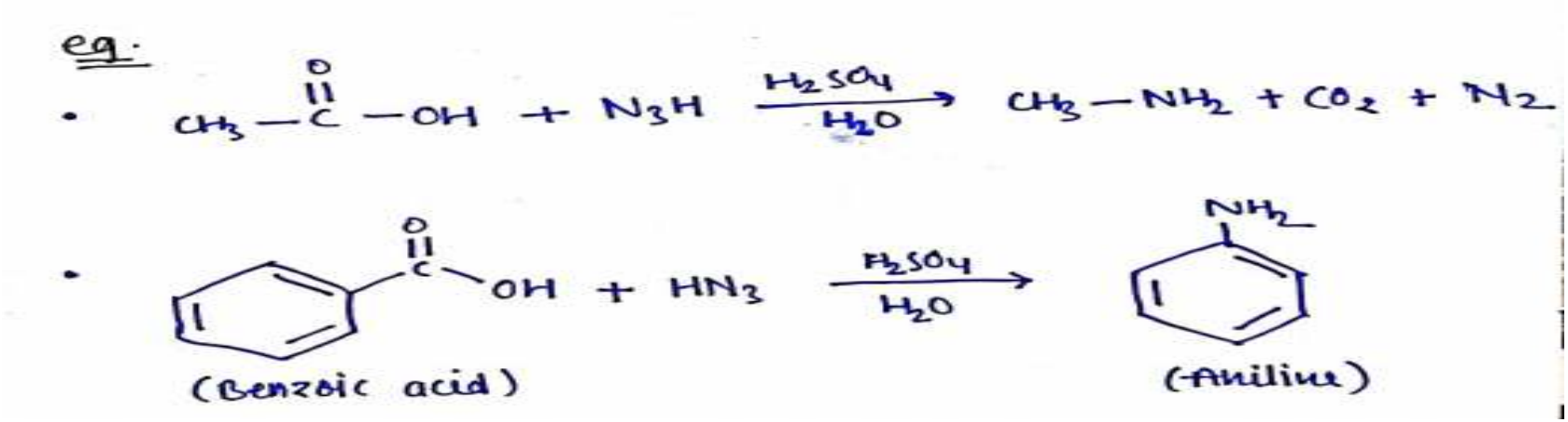
It is also known as Schmidt rearrangement reaction. It is closely related to Curtius rearrangement

In this process carboxylic acids can be converted to amines and ketones to N-substituted amides by reaction with hydrazoic acid in acidic medium

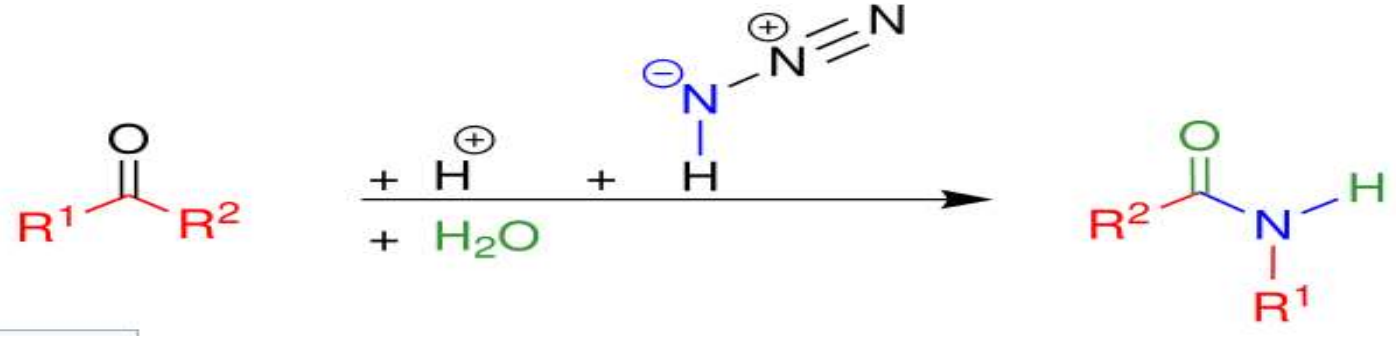


Hydrazoic acid 

Ex. Acetic acid is converted to Methyl amine and Benzoic acid is converted to Aniline



Ketones yield amides



•SCHMIDT REARRANGEMENT MECAHNISM

•1. CONVERSION OF CARBOXYLIC ACID IN TO AMINE: involved the following sequence of steps

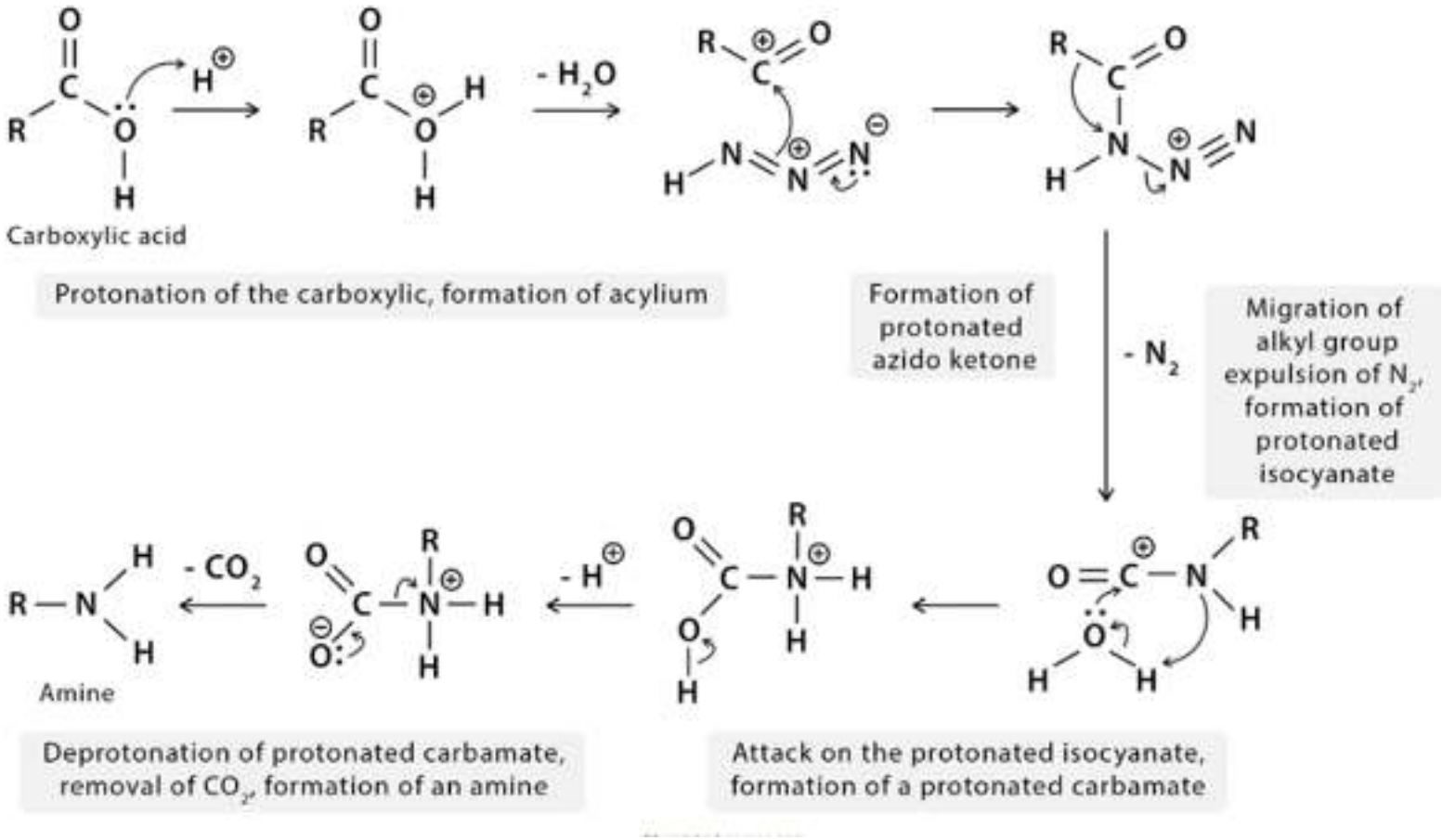
•Step1: Protonation of Carboxylic acid followed by elimination of water results in formation of reactive acylium ion.

•Step-2 This acylium ion attack hydrazoic acid and form a protonated azido ketone.

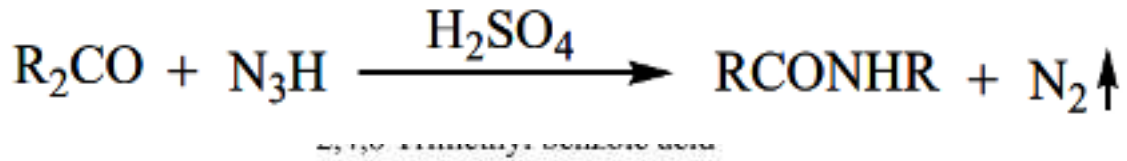
•Step-3 The protonated azido ketone undergo molecular rearrangement in which the alkyl group (R group) migrates to electron deficient nitrogen with the elimination of N_2 this leads to the formation of a protonated isocyanate.

•Step-4 and 5 The protonated isocyanate upon attack by water forms carbamate, which is then deprotonated and removal of CO_2 yields the required amine.

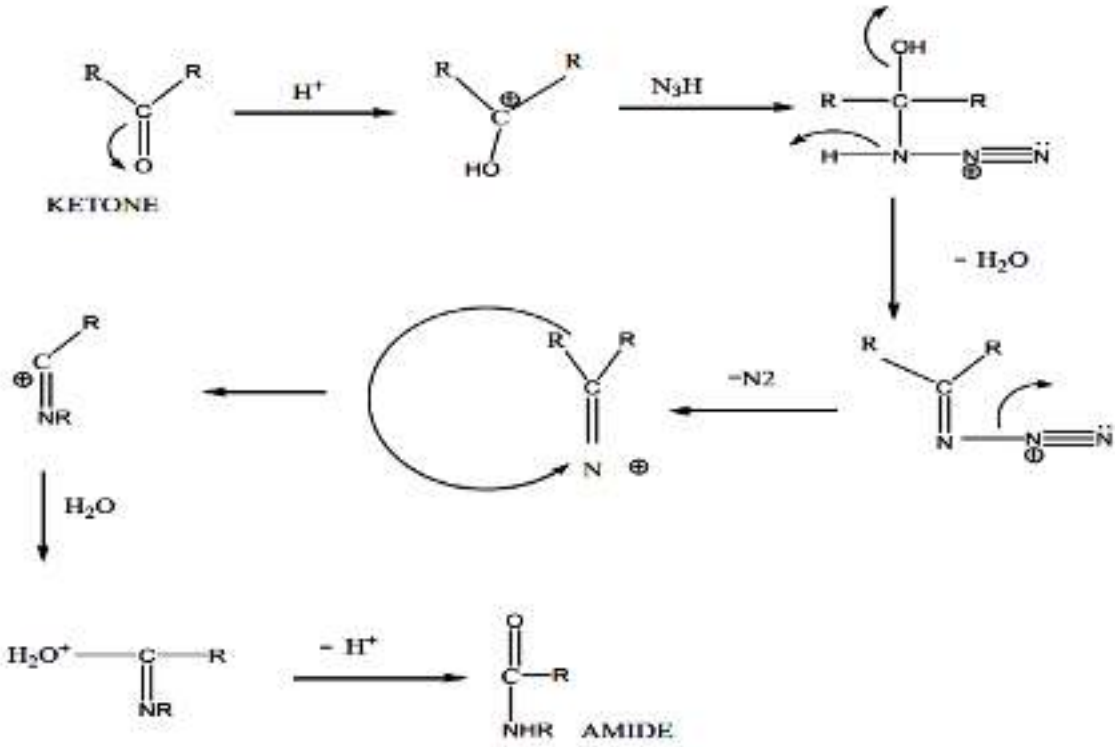
SCHMIDT MECAHNISM Carboxylic acid to Amine



Schmidt reaction also occurs in ketones which are converted to N-alkyl amide analogues to Beckman rearrangement



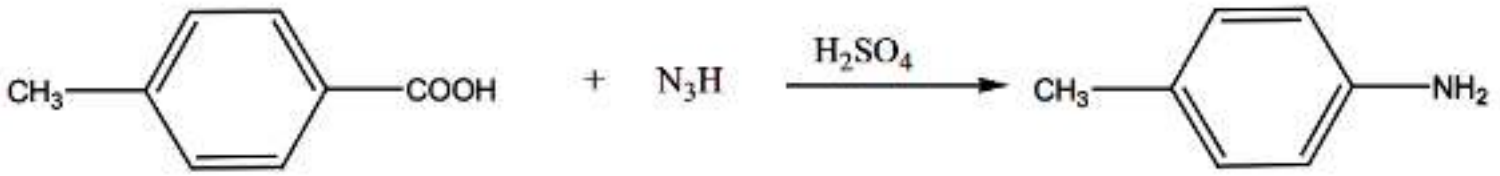
Reaction with **Ketone**:



APPLICATIONS OF SCHMIDT REACTION

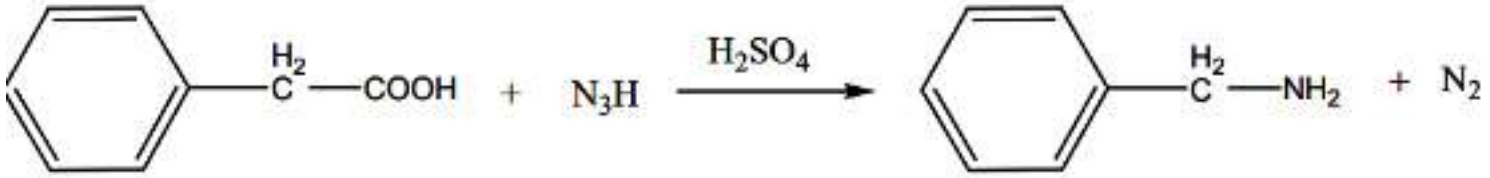
The Schmidt reaction can be applied to prepare amino acids, diamines, cyclic amides, lactams, and tetrazole. Each one of these compounds has a unique application.

Preparation of **Primary Amines**- (It is a direct method for the preparation of primary amines from carboxylic acid and give usually better yield than the hofmann or curtius reaction)



para toluic acid

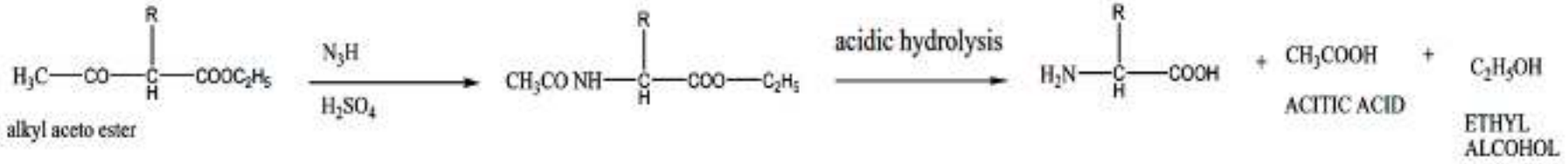
para toluidine



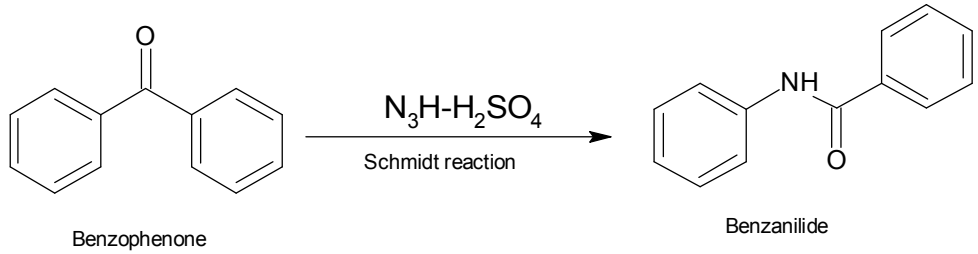
Phenyl acitic acid

benzyl amine

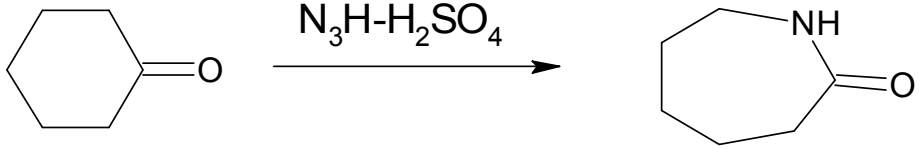
Preparation of alpha amino acids from active methylene compounds



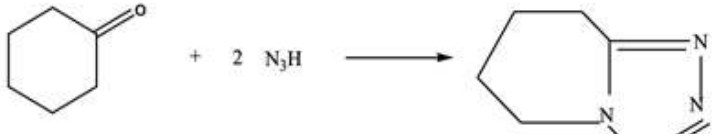
The Schmidt reaction can be used to prepare benzanilide from benzophenone and hydrogen azide.



Preparation of lactams- cyclic ketones to lactams



In the above reaction excess of acid azide can result in tetrazole

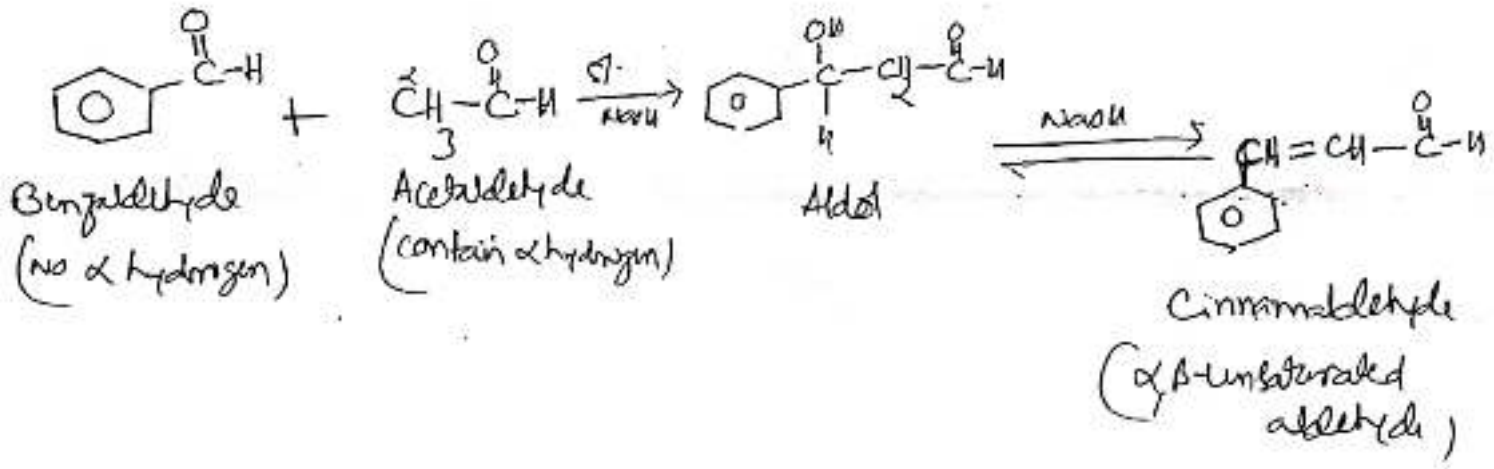


CLAISEN –SCHMIDT CONDENSATION

This is also known as Crossed aldol condensation, involves the formation of C-C bond. In this reaction an aldehyde or ketone which do not possess alpha hydrogens react with aldehydes or ketones which posses alpha hydrogen in presence of a base such as NaOH or KOH (10%) and form β-hydroxy carbonyl compound which undergo base catalyzed dehydration and yieldα,β-unsaturated carbonyl compounds

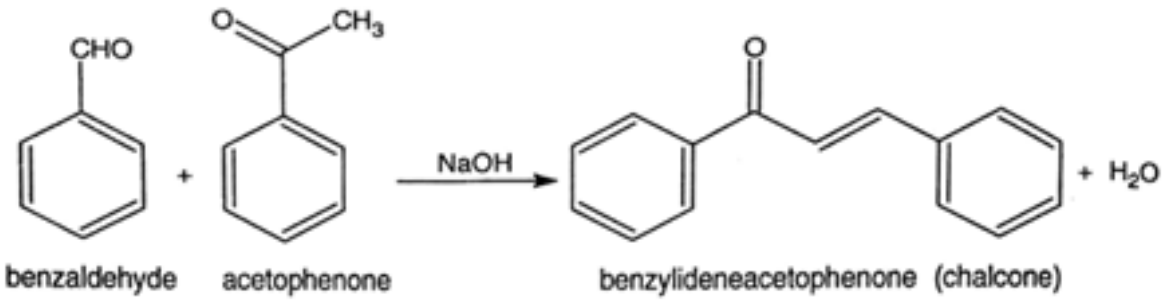
Example:

The aldol condensation involving Benzaldehyde (which donot possess alpha hydrogen) and acetaldehyde (which possess alpha hydrogens) undergo claisen-schmidt condensati



In Claisen-Schmidt reaction when an aromatic aldehyde without α hydrogen is reacted with aromatic ketone which possess α hydrogen in alkaline medium yields 1,3-diphenylpropenes commonly known as Chalcones.

Ex. Benzaldehyde which do not possess alpha hydrogen upon reaction with acetophenone which contain alpha hydrogen from benzylideneacetophenone i.e. Chalcone



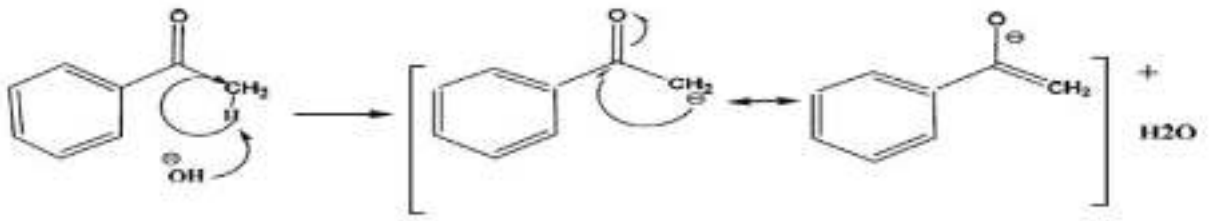
In Claisen-Schmidt condensation the aromatic aldehyde with electron donating group at ortho or para position is less reactive, where as the presence of electron withdrawing groups increases the activity.

Mechanism of Claisen Schmidt reaction:

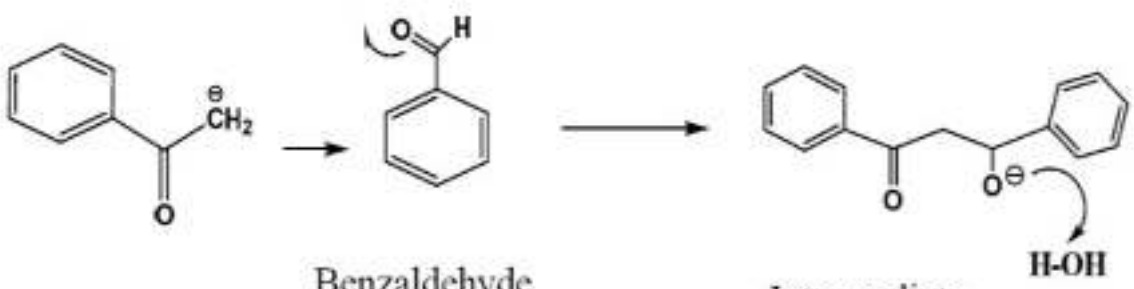
Step1 The carbonyl compound which possess alpha hydrogen losses proton in alkaline medium and form the carboanion (enolate ion).

Step2 The enolate (carboanion) attack the carbonyl carbon of aldehyde or ketone which do not possess alpha hydrogen and followed by protonation yield β-hydroxy carbonyl carbonyl compound.

step 3. The β-hydroxy carbonyl compound undergo base catalyzed dehydration and form α,β-unsaturated carbonyl compound

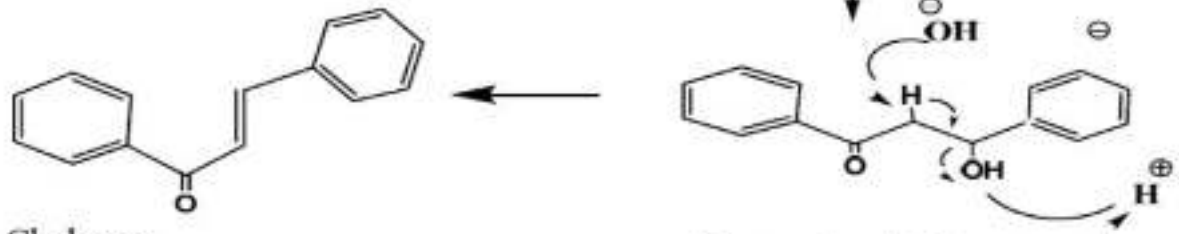


Acetophenone



Benzaldehyde

Intermediate

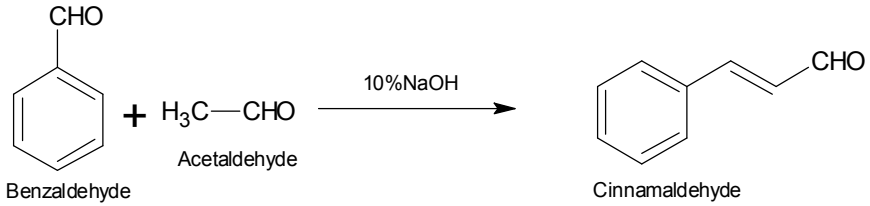


Chalcone

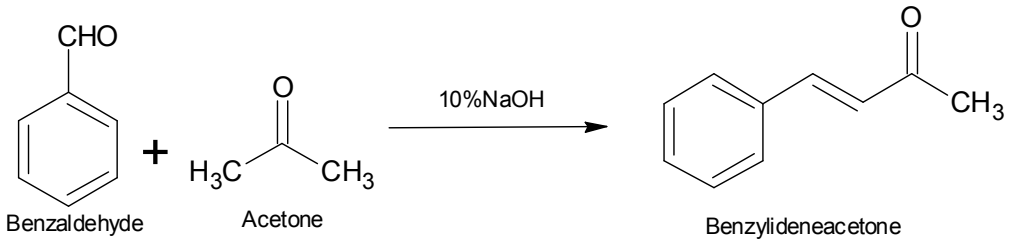
Protonation & Deprotonation

Synthetic Applications of Claisen-Schmidt Reaction

1. Synthesis of cinnamaldehyde: Cinnamaldehyde is used is used in perfume industry



2. Synthesis of Benzylideneacetone: Cinnamaldehyde is used is used in perfume industry



3 Synthesis of Chalcones: Chalcones are the scaffold for the synthesis of different natural products such as flavones, coumarins, and different heterocyclic compounds.