

# **Engineering Chemistry**

## **BCHY101L**



## Module-3

### Organic intermediates and reaction transformations

#### Contents.... (6 h)

**Organic intermediates** - stability and structure of carbocations, carbanions and radicals; (2 h)

**Aromatics** (aromaticity) and heterocycles (3, 4, 5, 6 membered and fused systems); (2 h)

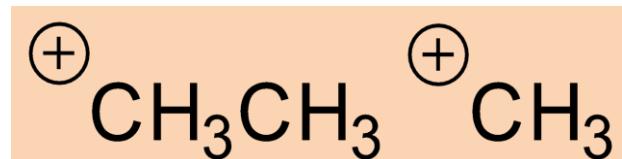
Organic transformations for making useful **drugs** for specific disease targets (two examples) and **dyes**. (2 h)

# Organic Reaction Intermediates

- ❖ Most of the organic reactions occur via a specific chemical species (intermediate) which is extremely reactive and short – lived ( $10^{-6}$  second to a few seconds). Isolation of such species seemed to have difficult task.
- ❖ These reactive intermediates can have the valency of carbon atoms either 2 or 3.
- ❖ Examples of such reaction intermediates are carbocations, carbanions, free radicals, carbenes and nitrenes – and they are quickly converted into more stable molecules.
- ❖ However, fairly stable organic intermediates have been prepared such as carbenes and carbocations.
- ❖ Among all the intermediates, only carbanions have a complete octet around the carbon.
- ❖ There are many other organic ions and radicals with charges and unpaired electrons on atoms other than carbon, they are nitrenes- the nitrogen analogs of carbenes.

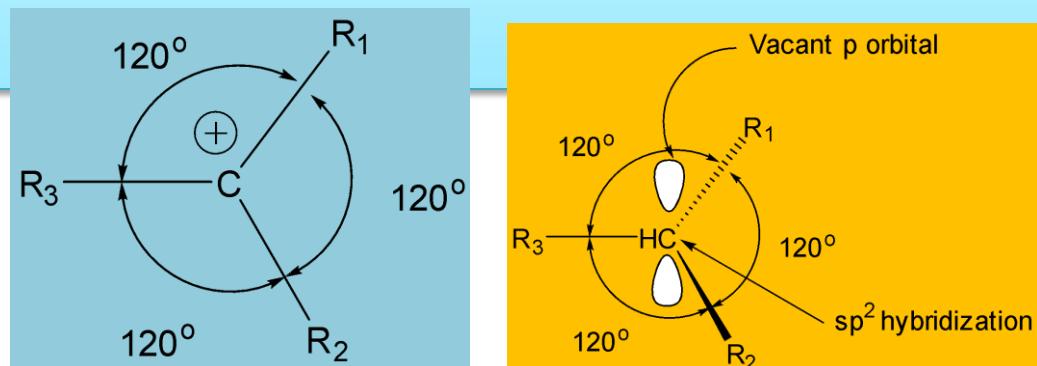
# Carbocations

Organic species having a positively charged carbon atom bearing only six bonded electrons are called carbocations. For example:



## Structure:

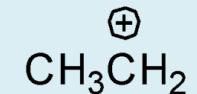
- ❖ The carbon atom with a positive charge is referred as carbocation (or carbonium ion) and it belongs to  $sp^2$  hybridization.
- ❖ The three  $sp^2$  hybridized orbitals are utilized in making bonds to three substituents.
- ❖ In order to minimize repulsion between the bonding electron pairs (i.e. to afford maximum separation of these electron pairs) a carbocation possesses a planar configuration with bond angles of  $120^\circ$ . The empty  $p$  orbital is perpendicular to the plane.



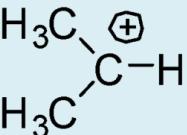
- ❖ Carbocations are extremely reactive species due to their ability to complete the octet of the electron-deficient carbon.

# Classification of Carbocations

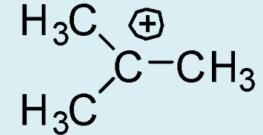
Carbocations are classified as primary ( $1^\circ$ ), secondary ( $2^\circ$ ), and tertiary ( $3^\circ$ ) on the basis of number of carbon atoms (one, two, or three) directly attached to positively charged carbon. For example:



ethyl cation is a primary carbocation



isopropyl cation is a secondary carbocation



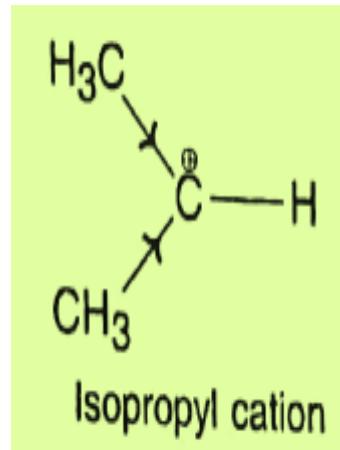
t-butyl cation is a tertiary carbocation

The factors responsible for carbocation stability are –

- (i) Inductive effect, (ii) Hyperconjugative effect, (iii) Resonance effect, (iv) Steric effect and (v) Constituting an aromatic system.

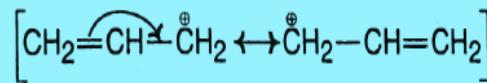
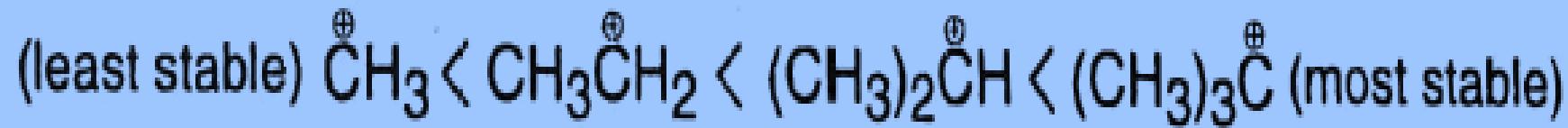
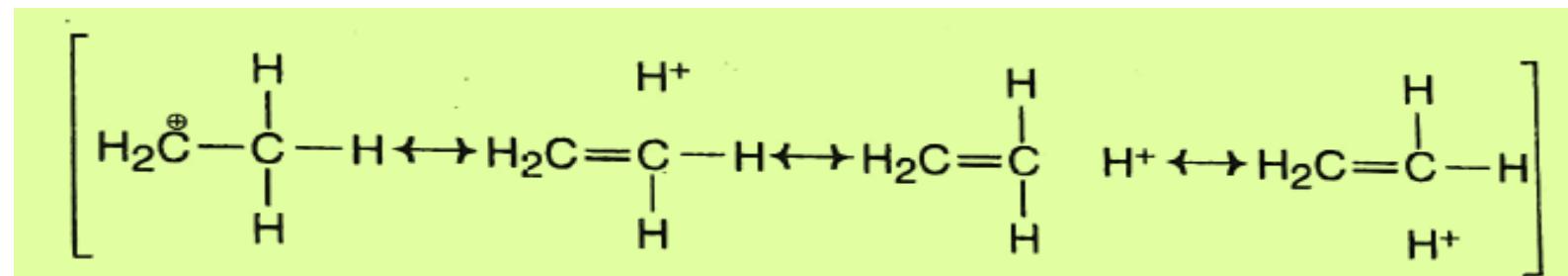
## (i) Inductive effect

- ❖ A charge-dispersing factor stabilizes an ion.
- ❖ The electron-releasing inductive effect (+I) exerted by an alkyl group attached to the positive carbon of a carbocation neutralizes the charge partially.
- ❖ As a consequence, the charge becomes dispersed over the alkyl groups and the system becomes stabilized.
- ❖ For example, the methyl groups in isopropyl cation stabilize the system through their +I effects.
- ❖ The stability of carbocations increases with increasing the number of alkyl groups attached to the positive carbon.

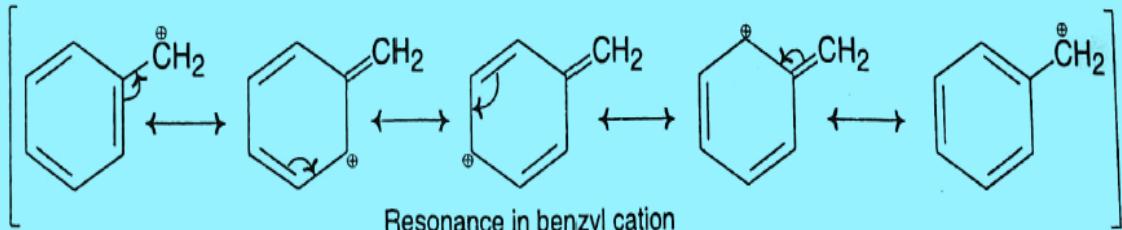


## (ii) Hyperconjugative effect

- An alkyl group may reduce the positive charge of a carbocation by hyperconjugative electron- release.
- The charge becomes dispersed over the  $\alpha$ -hydrogens and consequently, the system becomes stabilized. Hyperconjugation in ethyl cation, for example, occurs as follows
- As the number of  $\alpha$ -hydrogens, i.e., the number of hyperconjugative forms increases, the stability of carbocations increases. Hence, the order of stabilities of methyl substituted carbocations is ::



Effective resonance in allyl cation



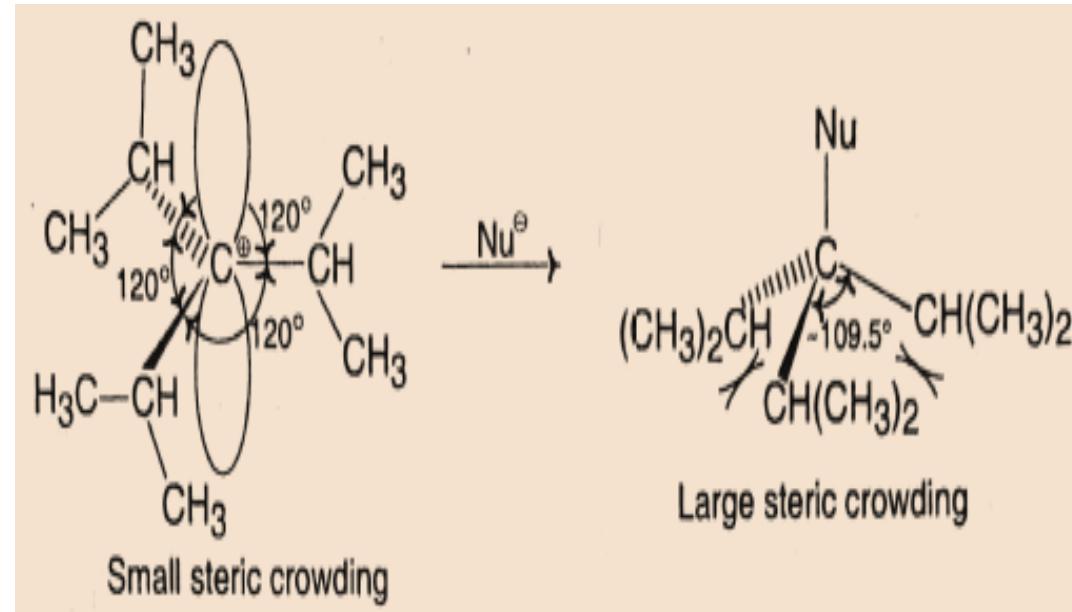
Resonance in benzyl cation

## (iii) Resonance effect

- Resonance is a major factor influencing the stability of carbocations.
- When the positive carbon of a carbocation is next to a double bond, effective charge delocalization with consequent stabilization occurs.
- Allyl and benzyl cations, for examples, are found to be highly stabilized by resonance.

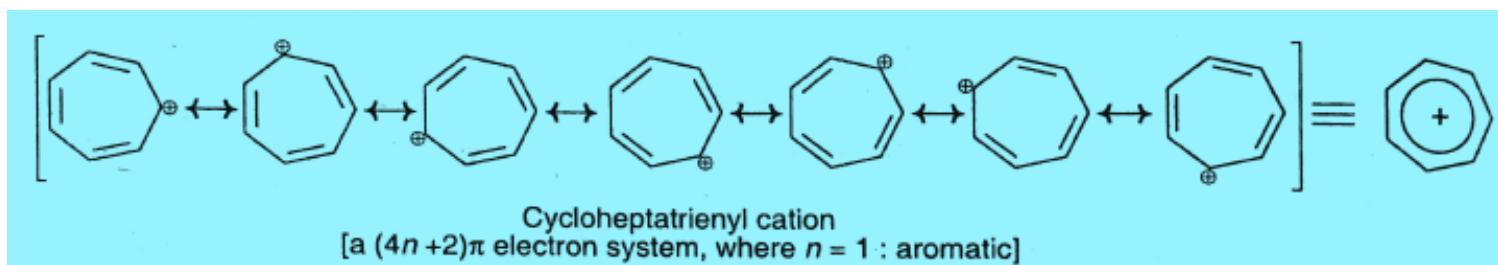
#### (iv) Steric effect

- ❖ Steric effect causes an increase in stability of tertiary carbocations having bulky alkyl groups.
- ❖ For example, the substituents in tri-isopropyl cation (having planar arrangement with  $120^\circ$  angles) are far apart from each other and so there is no steric interference among them.
- ❖ However, if this carbocation is added to a nucleophile, i.e., if a change of hybridization of the central carbon atom from  $sp^2$  (trigonal) to  $sp^3$  (tetrahedral) takes place, the bulky isopropyl groups will be pushed together.
- ❖ This will result in a steric strain (B strain) in the product molecule. Because of this, the carbocation is much reluctant to react with a nucleophile, that is, its stability is enhanced due to steric reason.



#### (v) Constituting an aromatic system

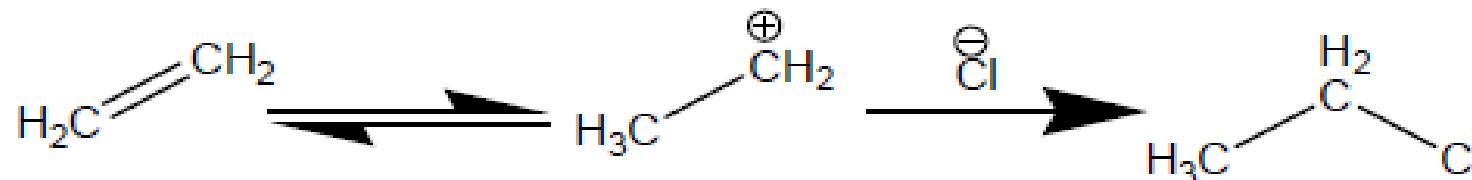
- ❖ The vacant  $p$  orbital of a carbocation may be involved in constituting a planar  $(4n + 2)\pi$  electron system. where  $n = 0, 1, 2, \dots$  etc., i.e., a carbocation may be stabilized by constituting an aromatic system.
- ❖ Cycloheptatrienyl cation, for example, is unusually stable because it is a planar  $6\pi$  electron system and aromatic.



# Reaction of Carbocations

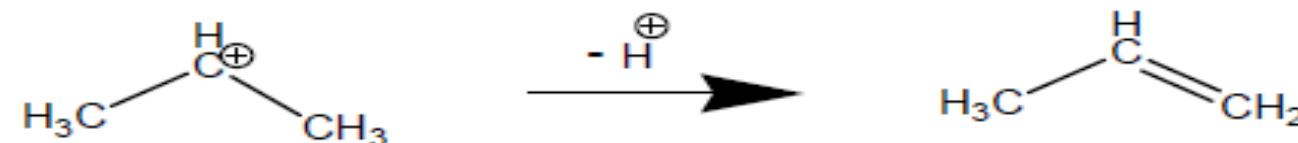
## 1. Combination with an anion:

The carbocation reacts with a negatively charged species to give a stable product. Example - Addition of hydrochloric acid to ethylene to yield ethyl chloride.<sup>2</sup>

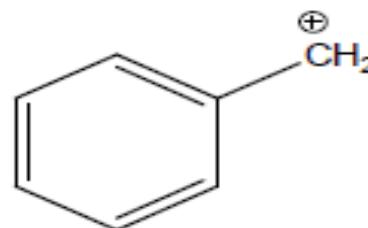


## 2. Elimination of proton:

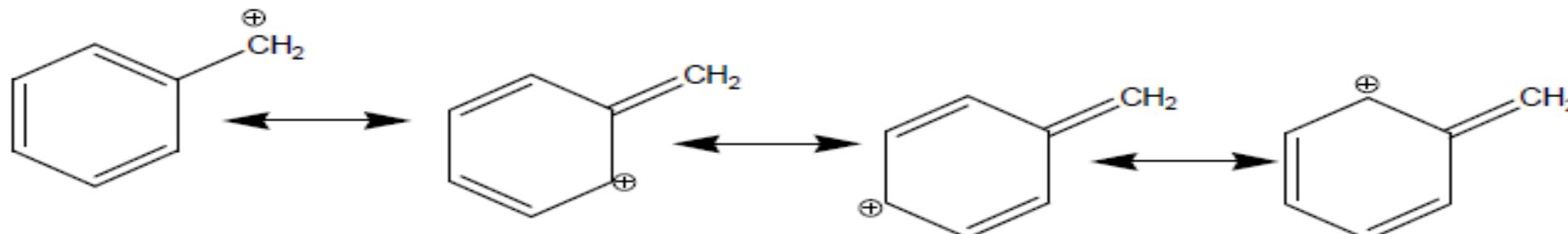
Carbocation may donate the proton to yield unsaturated compound.



Another stability aspect of carbocation is structural stability. The decrease in energy of transition state forms carbocation. The generated carbocation by unimolecular dissociation of leaving group is resonance stabilised.<sup>14</sup>

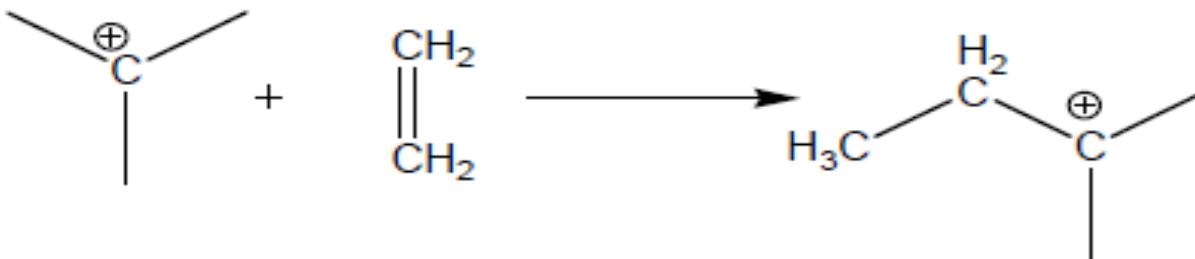


Benzyl carbocation

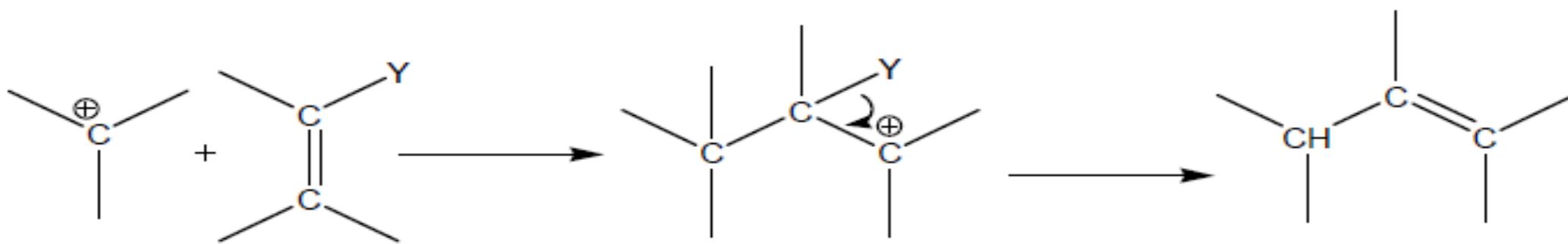


## REARRANGEMENTS

### Intermolecular alkylation by carbocation



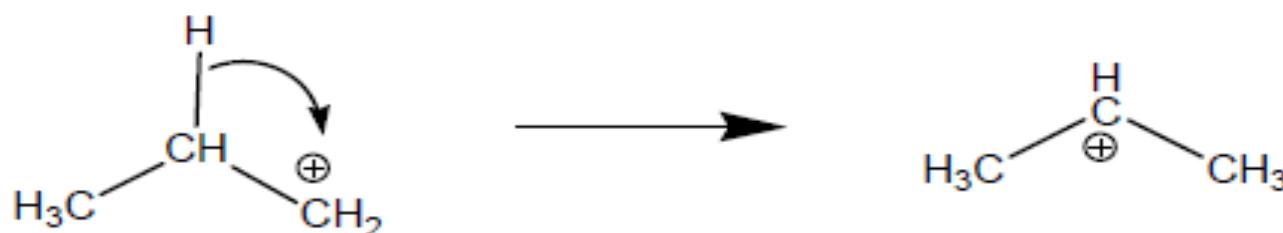
The problem occurs as the second generated carbocation reacts with another doubly bonded species to form another product. This leads to generation of polymerization reaction.



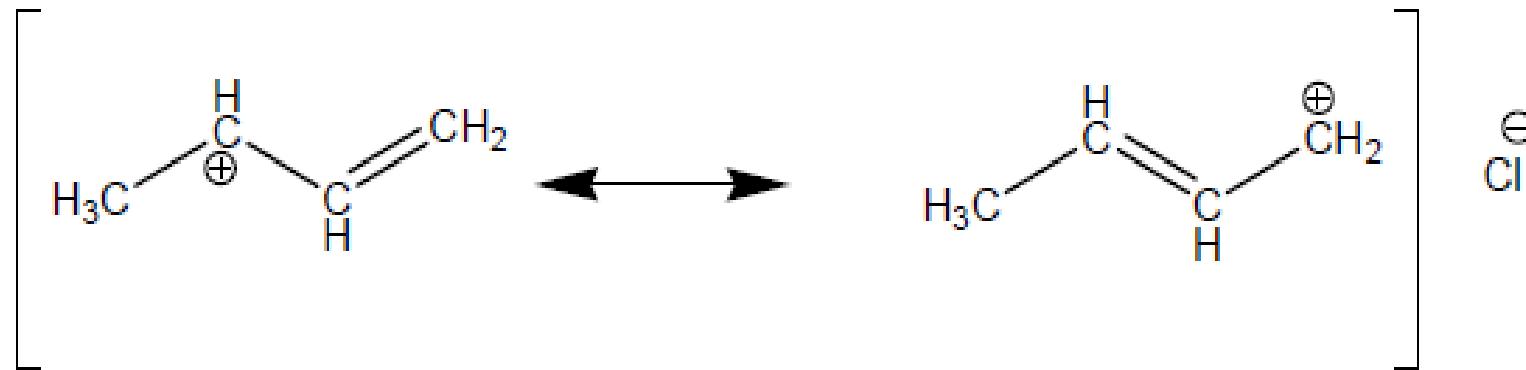
Example-In this the stannyll or silyl substituent is eliminated to form a stable alkene.<sup>16</sup>

#### 1, 2 hydride shift

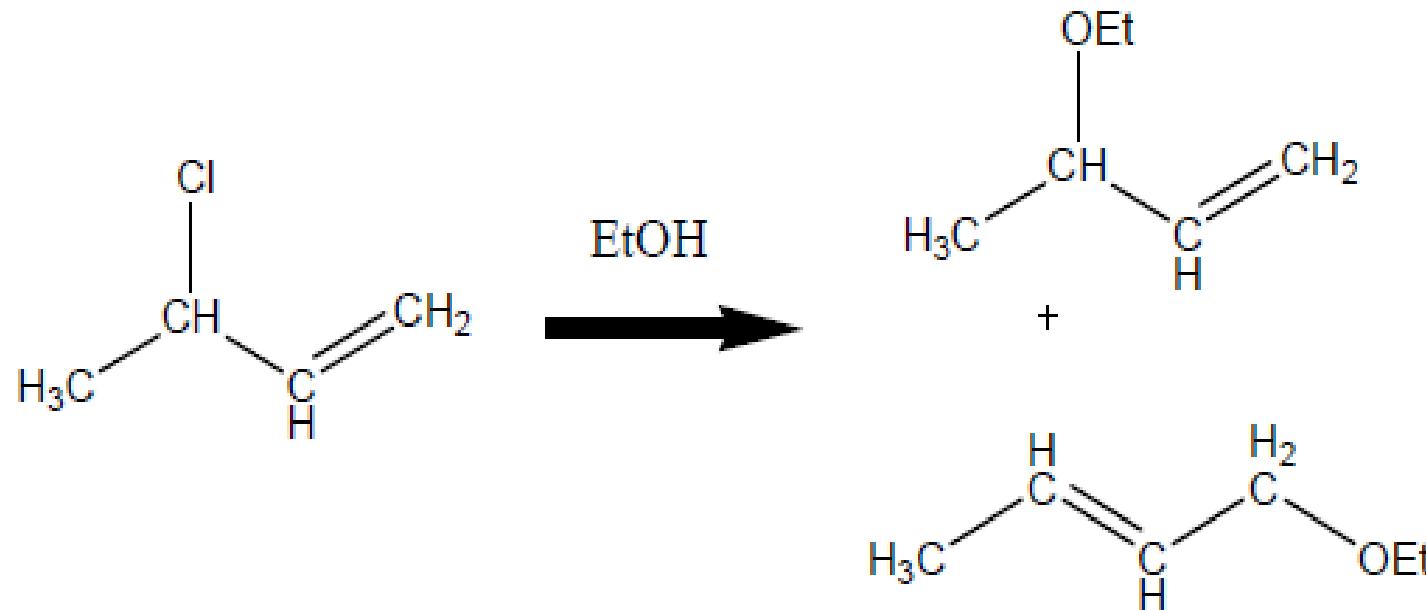
1-propyl cation rearranges to form 2-propyl cation this is because the secondary cation is more stable than the primary



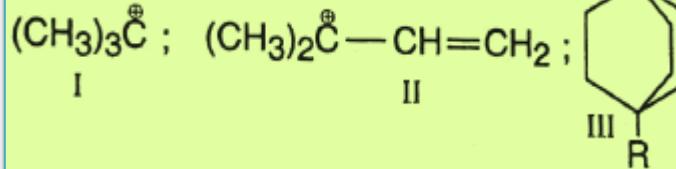
## Allylic rearrangements



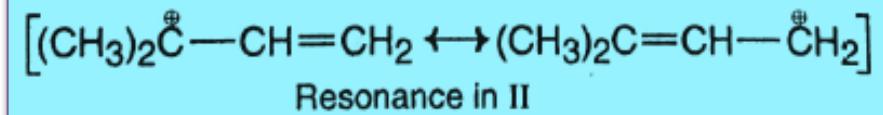
Example is SN1 solvolysis if 3-chlorobut-1-ene. Here rapid nucleophilic attack takes on C1 or C3.



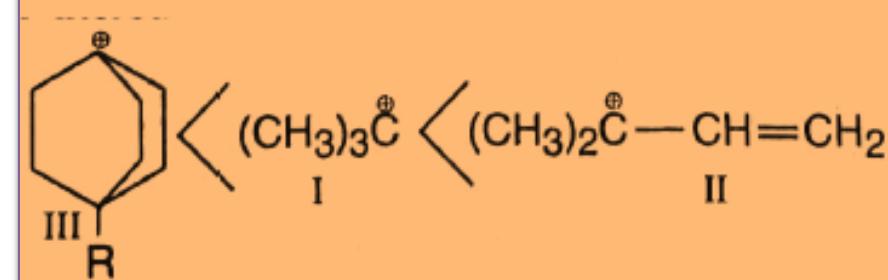
**Question:** Arrange the following carbocations in order of their increasing stability and provide reason.



- ❖ The carbocation I is stabilized by the +I effects of three -CH<sub>3</sub> groups and hyperconjugative effect involving nine C-H bonds.
- ❖ The carbocation III is similarly stabilized by +I effect of three ring bonds.
- ❖ However, it is not stabilized by hyperconjugation because formation of a double bond at the bridgehead position is not possible (Bredt's rule).
- ❖ Again, the carbocation suffers from angle strain because the angle between bonds is somewhat less than the sp<sup>2</sup> bond angle, i.e., 120°.
- ❖ So, the carbocation III, although a 3° one, is less stable than the 3° carbocation I.
- ❖ The carbocation II is the most stable one because it is highly stabilized by resonance and also by both inductive and hyperconjugative effects of two methyl groups.

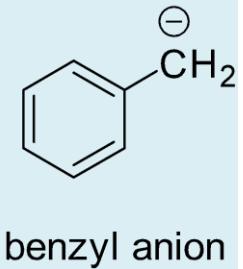
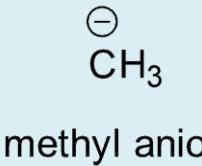


Hence, the order of their increasing stability is:



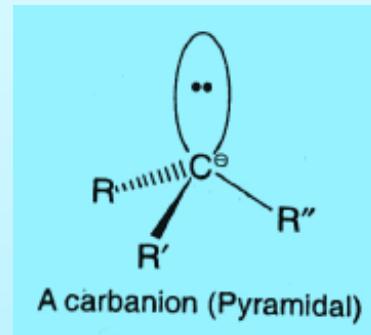
# Carbanions

The species containing negatively charged carbon atom is known as carbanion. For example:



## Structure:

- ❖ The central carbon atom of a carbanion is  $\text{sp}^3$  hybridized.
- ❖ It is surrounded by three bonding pairs and one unshared pair of electrons which occupies an  $\text{sp}^3$  orbital. Thus, a carbanion is expected to have the tetrahedral shape.



- ❖ However, the shape is not exactly that of a tetrahedron. It is found to have the pyramidal shape.
- ❖ Since the repulsion between the unshared pair and any bonding pair is greater than the repulsion between any two bonding pairs, the angle between two bonding pairs (i.e., two  $\text{sp}^3$ -  $\sigma$  bonds) is slightly less than the normal tetrahedral value of  $109.5^\circ$  and because of this, a carbanion appears to be shaped like a pyramid with the negative carbon at the apex and the three groups at the corners of a triangular base.
- ❖ However, the resonance-stabilized carbanions, such as allylic and benzylic carbanions are  $\text{sp}^2$  hybridized and they assume trigonal planar structure.

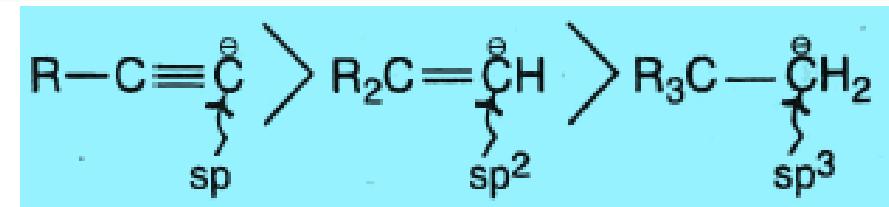
## The factors responsible for carbanion stability are -

The structural features responsible mainly for the increased stability of carbanions are :

- (i) the amount of 's' character of the carbanion carbon atom,
- (ii) inductive electron withdrawal,
- (iii) conjugation of the non-bonding electron pair with an unsaturated system, and
- (iv) constituting an aromatic system.

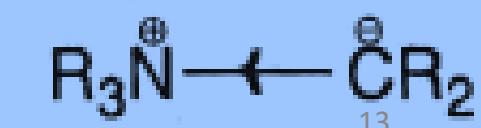
### (i) The amount of 's' character of the carbanion carbon atom

- ❖ An s orbital is closer to the nucleus than the p orbital in a given main quantum level and it possesses lower energy.
- ❖ An electron pair in an orbital having large s character is, therefore, more tightly held by the nucleus and hence of lower energy than an electron pair in an orbital having small s character.
- ❖ Hence, a carbanion at an sp hybridized (50% s character) carbon atom is more stable than a carbanion at a sp<sup>2</sup> hybridized (33.33% s character) carbon atom, which in turn is more stable than a carbanion at an sp<sup>3</sup> hybridized (25% s character) carbon atom. Thus, the order of carbanion stability is:



### (ii) Inductive electron withdrawal

- ❖ Groups having electron-withdrawing inductive effects (H) stabilize a carbanion by dispersing the negative charge.
- ❖ In a nitrogen ylide, for example, the carbanion is stabilized by the -I effect of the adjacent positive nitrogen.

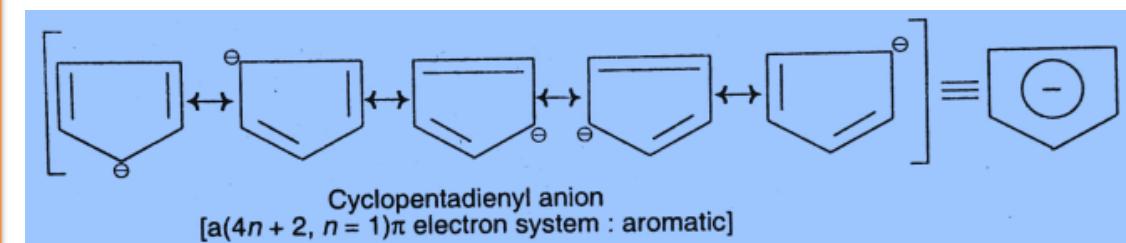
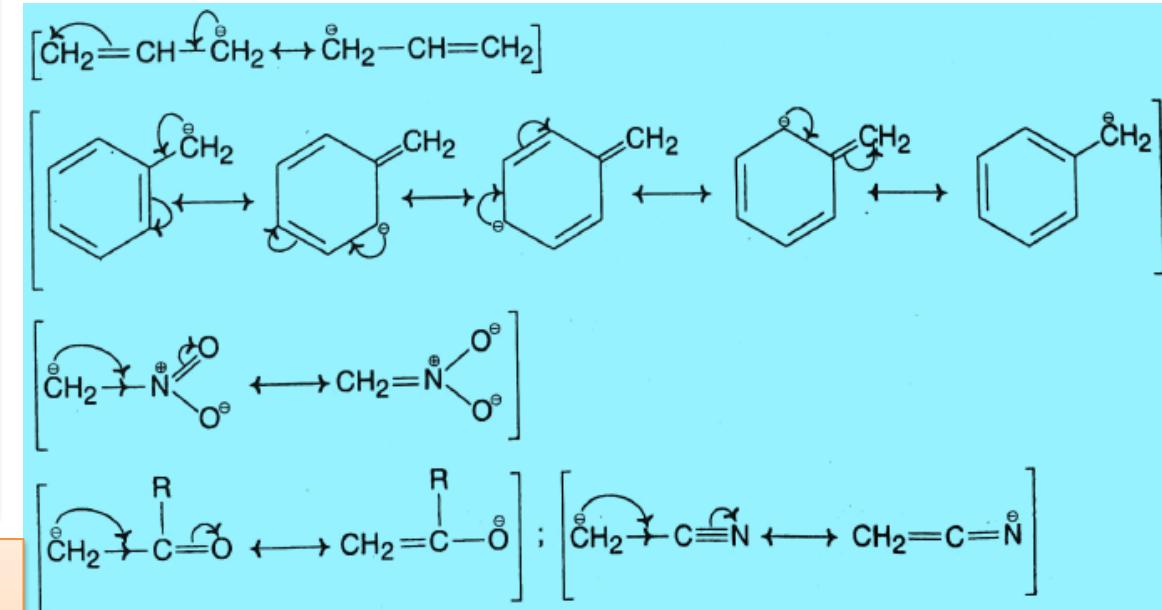


### (iii) Conjugation of a non-bonding electron pair with an unsaturated system

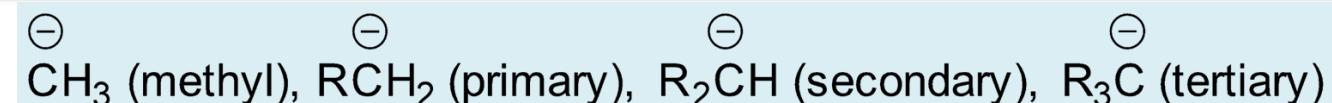
- ❖ Where there is a double or triple bond  $\alpha$  to the carbanion carbon atom, the anion is stabilized by delocalization of its negative charge with the orbitals of the multiple bond.
- ❖ Thus, allylic and benzylic carbanions and the carbanions attached to the functional groups such as  $-\text{NO}_2$ ,  $-\text{C}\equiv\text{N}$ ,  $>\text{C}=\text{O}$ , etc. are stabilized by resonance.

### (iv) Constituting an aromatic system

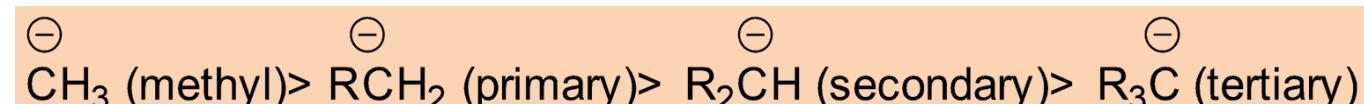
- ❖ The unshared pair of a carbanion may be involved in constituting a planar  $(4n + 2)\pi$  electron system where  $n = 0, 1, 2\dots$  etc., i.e., a carbanion may be stabilized by constituting an aromatic system
- ❖ Cyclopentadienyl anion, for example. is unusually stable because it is a  $6\pi$  electron system and aromatic.



**Question:** Predict the decreasing order of stability of the following simple carbanions.



Because of the destabilizing influence of electron-donating effect of alkyl groups, the order of stability of these simple carbanions is as follows:

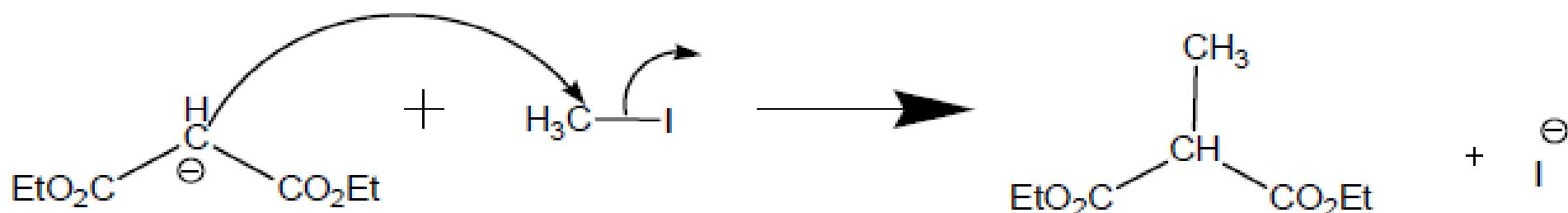


# Reaction of Carbanions

They undergo various types of reactions, like

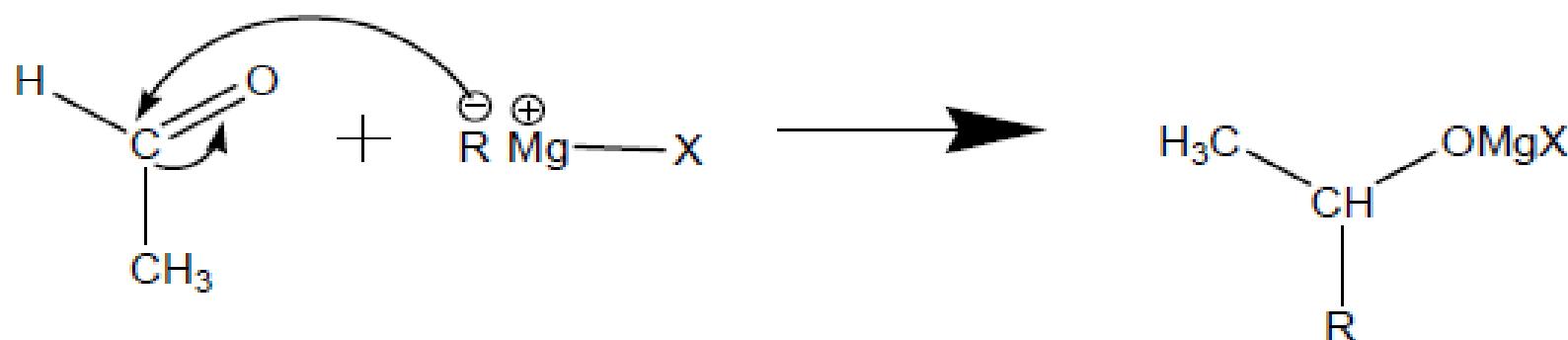
## 1. Displacement reaction:

The alkylated product is formed by displacement halogen from an alkyl halide



## 2. Addition to multiple bonds

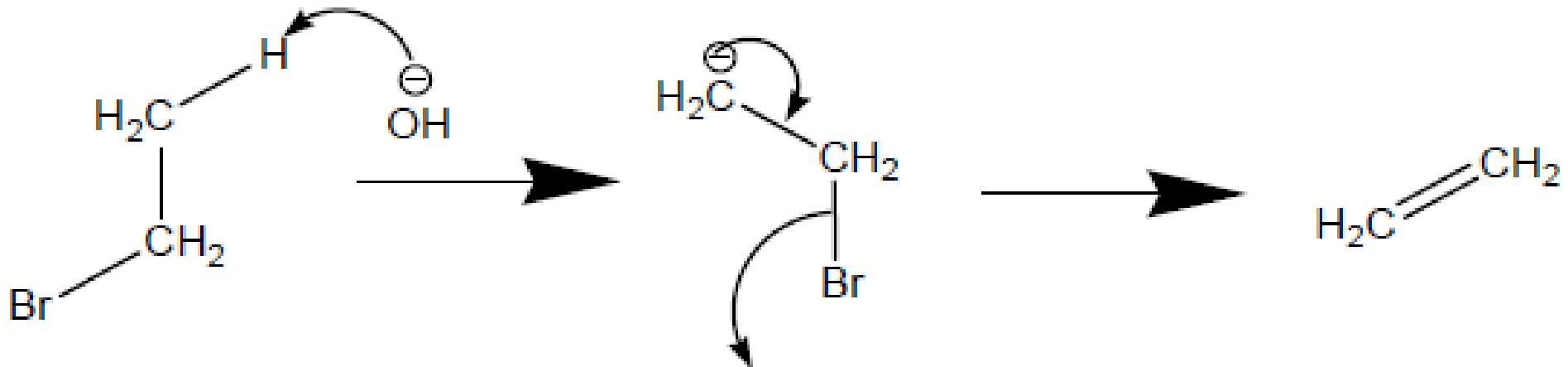
This involves addition of Grignard's reagent to carbonyl group.



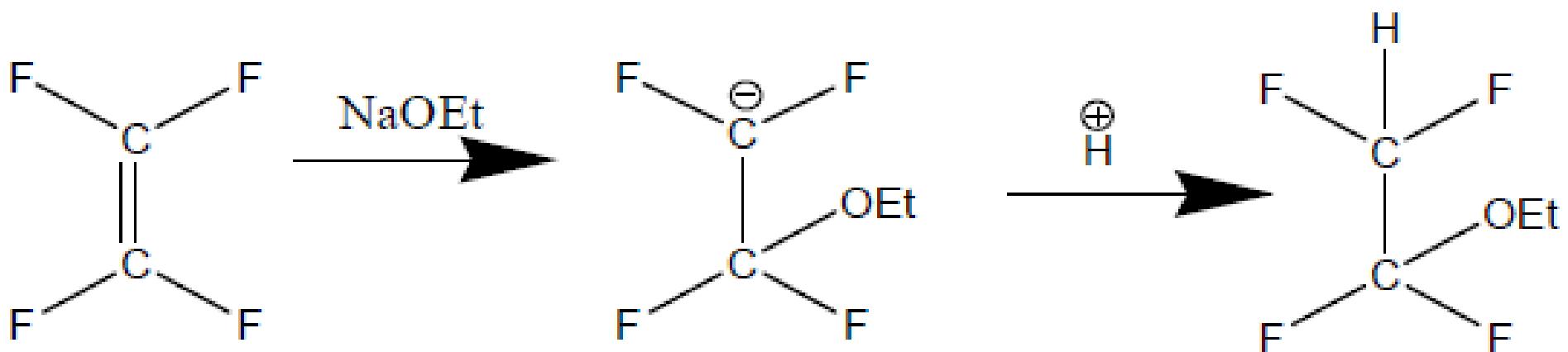
# Reactions of Carbanions

## 3. Elimination reaction

Formation of alkene by alkyl halide in presence of alcoholic alkali



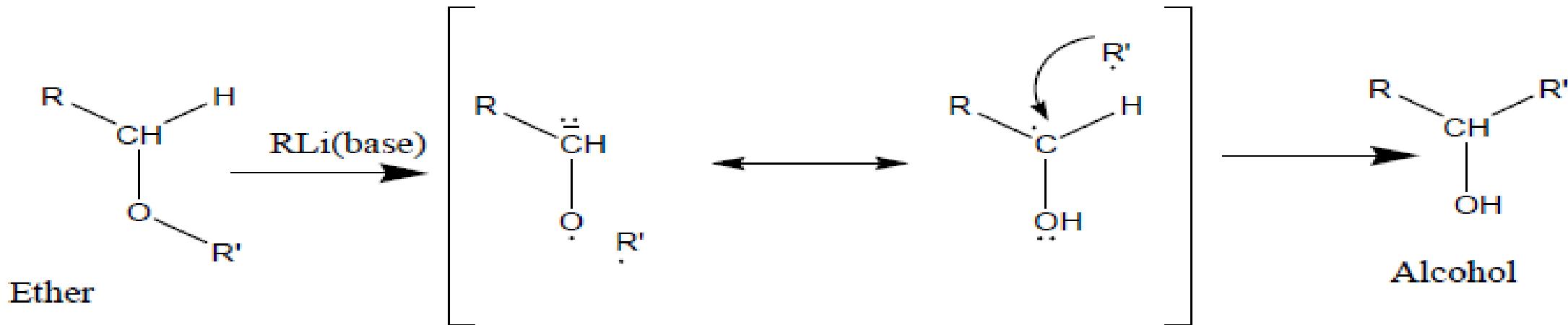
## 4. Combination with cation



## REARRANGEMENTS

### Wittig rearrangement

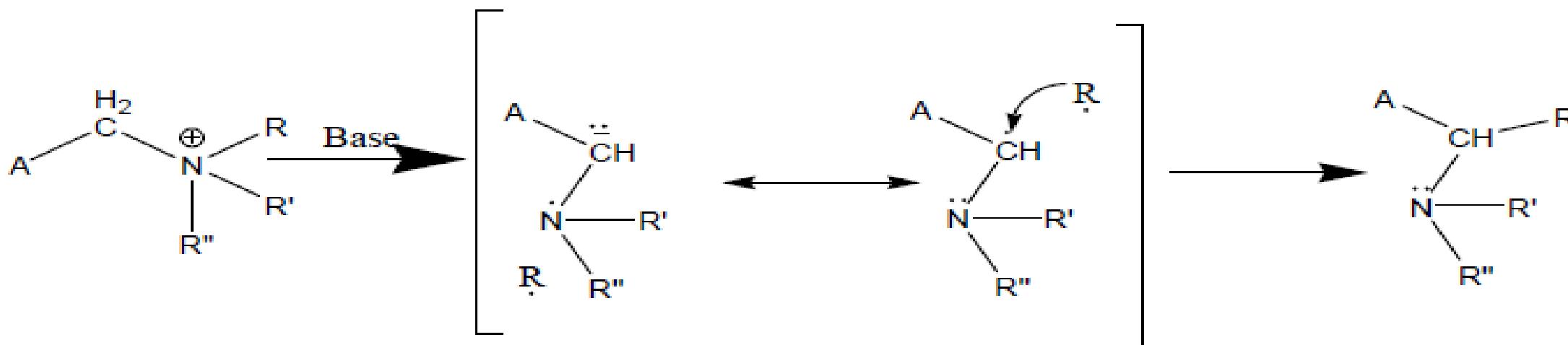
This rearrangement involves the formation of carbanion which is stabilized by substitution group R or R'.



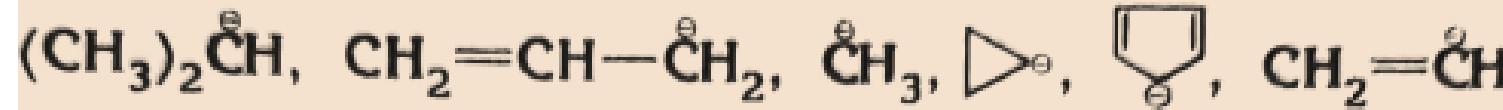
### Stevens Rearrangement

This has quaternary ammonium salt as starting material.

The stability of carbanion depends on the group attached. The A represents electron withdrawing group.<sup>19</sup>



**Question:** Arrange the following carbanions in the order of increasing stability.



I

II

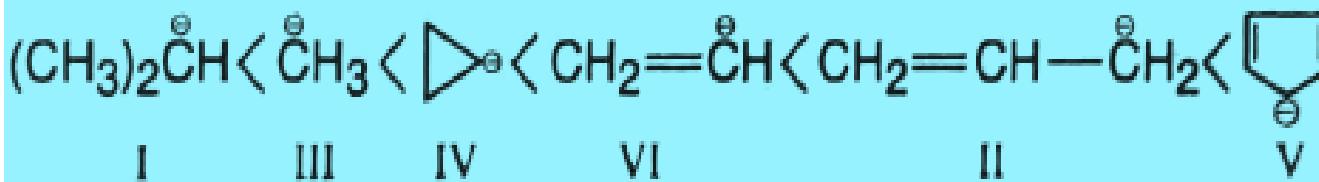
III

IV

V

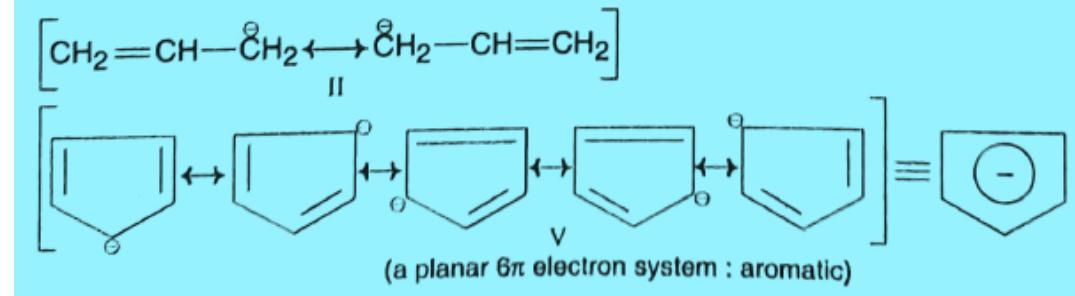
VI

The order of increasing stability of these carbanions is:



I      III      IV      VI

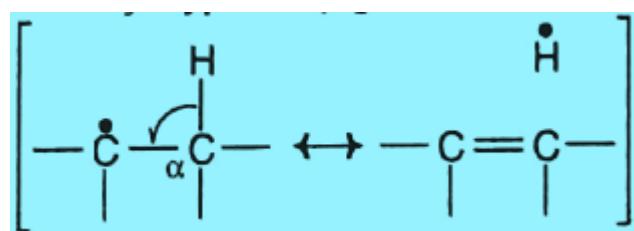
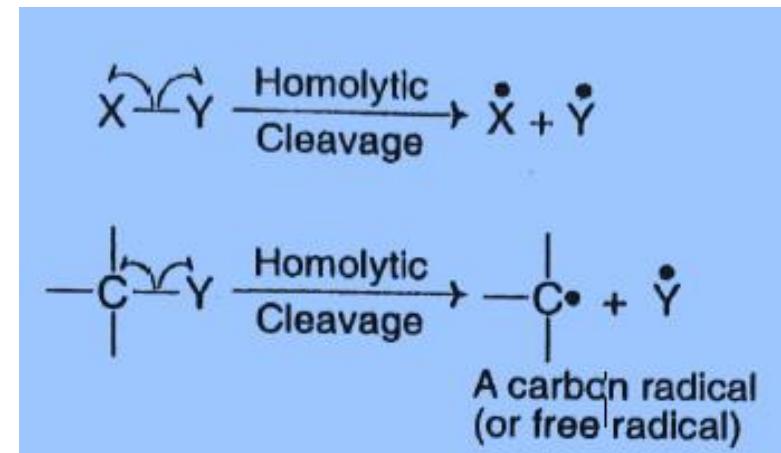
II



- ❖ The electron-releasing methyl groups of isopropyl anion (I) intensify the negative charge on carbon and make it less stable than methyl anion (III) where there is no possibility of charge intensification.
- ❖ The external orbitals (orbitals directed to the outside bonds) in cyclopropane have larger (33%) s character i.e., they are approximately  $\text{sp}^2$  orbitals. Because of this, the unshared pair in cyclopropyl anion (IV) is more tightly held with the carbon nucleus than the electrons in methyl anion (III) that occupies an  $\text{sp}^3$  orbital (25% s character). Consequently, the former anion is more stable than the latter.
- ❖ In vinyl anion (VI), the unshared pair occupies an sp orbital (33.33% s character) and so this anion is somewhat more stable than cyclopropyl anion (IV).
- ❖ The charge in allyl anion (II) is delocalized by resonance with the adjacent double bond and so it is more stable than vinyl anion (VI) in which the charge is localized.
- ❖ Since the unshared pair in cyclopentadienyl anion (V) is involved in forming an aromatic system, charge delocalization and consequent stabilization is far greater for this anion than for allyl anion.

# Free Radicals

- ❖ Homolytic cleavage of covalent bonds leads to the formation of neutral species possessing an unpaired electron. These are known as free radicals.
- ❖ Free radicals containing odd electrons on carbon atoms are collectively called carbon radicals or simply free radicals. For example, methyl radical ( $\dot{\text{C}}\text{H}_3$ ), phenyl radical ( $\text{Ph}\cdot$ ), etc.
- ❖ They are classified as primary, secondary, and tertiary free radicals according to the number of carbon atoms (one, two or three) directly attached to the carbon atom bearing the unpaired electron.
- ❖ For example, ethyl radical ( $\text{CH}_3\dot{\text{C}}\text{H}_2$ ) is a primary, isopropyl radical ( $\text{Me}_2\dot{\text{C}}\text{H}$ ) is a secondary and tertbutyl radical ( $\text{Me}_3\dot{\text{C}}$ ) is a tertiary radical.



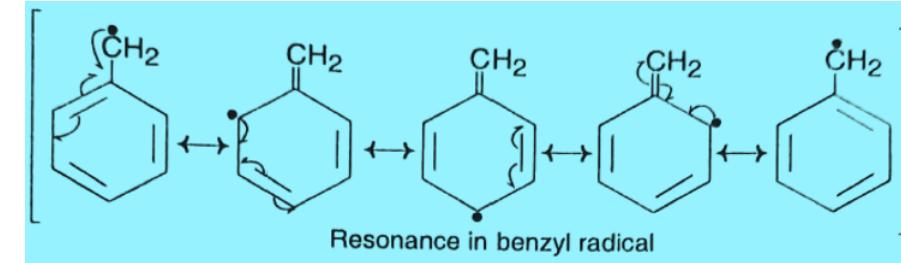
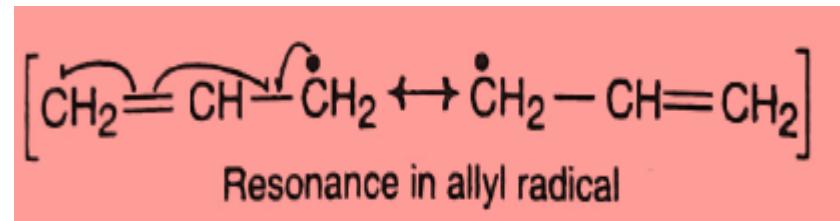
## Stability:

### (i) Hyperconjugation: Free radicals become stabilized by hyperconjugation involving $\alpha$ -H atoms

- ❖ As the number of  $\alpha$ -H atoms increases, hyperconjugation becomes more effective and consequently, the radical becomes more stabilized.
- ❖ The relative stability of simple alkyl radicals is found to follow the sequence  
(most stable)  $\text{R}_3\dot{\text{C}}$  (tertiary)  $>$   $\text{R}_2\dot{\text{C}}\text{H}$  (secondary)  $>$   $\text{R}\dot{\text{C}}\text{H}_2$  (primary)  $>$   $\dot{\text{C}}\text{H}_3$  (methyl) (least stable).
- ❖ For example, tert-butyl radical,  $\text{Me}_3\dot{\text{C}}$  (with nine hyperconjugable  $\alpha$ -H atom) is more stable than isopropyl radical,  $\text{Me}_2\dot{\text{C}}\text{H}$  (with six hyperconjugable  $\alpha$ -H atom) which in turn is more stable than ethyl radical,  $\text{Me}\dot{\text{C}}\text{H}_2$  (with only three hyperconjugable  $\alpha$ -H atom). The methyl radical,  $\dot{\text{C}}\text{H}_3$ , is least stable because the unpaired electron is not at all delocalized.

### (ii) Resonance:

- ❖ Resonance is a major factor influencing the stability of free radicals.
- ❖ When the carbon bearing the odd electron is  $\alpha$ - to a double bond, effective delocalization of the unpaired electron with the  $\pi$  orbital system with consequent stabilization occurs.
- ❖ Allyl and benzyl radicals, for example, are found to be particularly stable because of resonance.



### (iii) Steric Strain:

- ❖ Another factor responsible for the increased stability of tertiary radicals is steric.
- ❖ There occurs considerable relief of steric strain when a  $\text{sp}^2$  hybridized tertiary radical is formed from an  $\text{sp}^3$  hybridized precursor and this is because repulsion between the bulky alkyl groups is relieved to a certain extent by an increase in bond angles from  $109.5^\circ$  to about  $120^\circ$ .
- ❖ Thus, the radical is much reluctant to react further, i.e., its stability is enhanced due to steric reason.

# Reactions of Free Radicals

Reactions of free radicals either give stable products (termination reactions) or lead to other radicals, which themselves must usually react further (propagation reactions). The most common termination reactions are simple combinations of similar or different radicals:



Another termination process is disproportionation:<sup>304</sup>

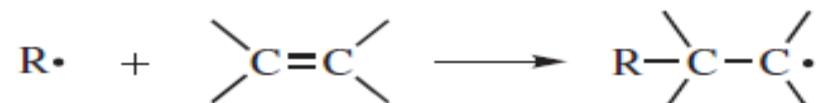
There are four principal propagation reactions, of which the first two are most common:



**1.** *Abstraction of Another Atom or Group, Usually a Hydrogen Atom* (see Chapter 14):



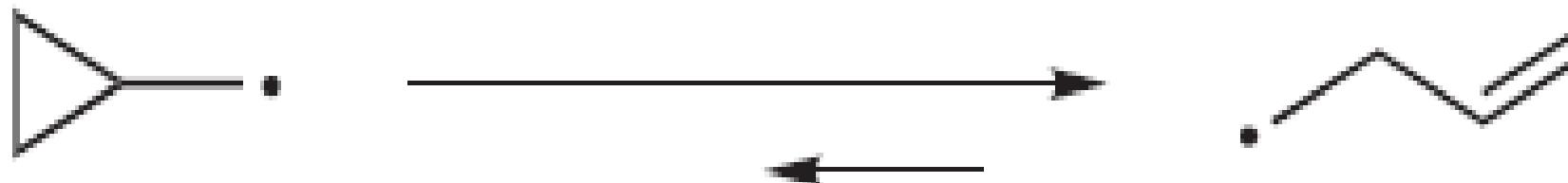
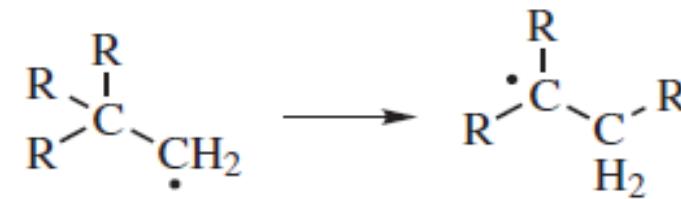
**2.** *Addition to a Multiple Bond* (see Chapter 15):



The radical formed here may add to another double bond and so on. This is one of the chief mechanisms for vinyl polymerization.

**3. Decomposition.** This can be illustrated by the decomposition of the benzoxy radical (above).

**4. Rearrangement:**



# AROMATICITY

## Features of aromatic compounds

Aromatic compounds are conjugated planar ring systems having delocalized pi-electron with alternating double and single bonds.

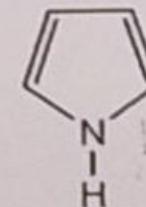
- ❖ They have high degree of stability due to filled bonding molecular orbital.
- ❖ The high degree of stability is associated with greater resonance energy.
- ❖ An aromatic compound with high potential energy is least stable.

Aromaticity  $\propto$  Resonance energy (RE)  $\propto$  Stability  $\propto$

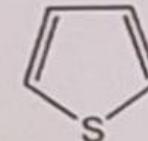
1

Potential Energy (P.E)

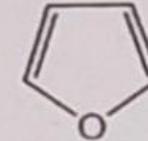
Resonance energy  
of some of the  
aromatic systems



21 kcal/mol



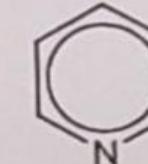
29 kcal/mol



16 kcal/mol



36 kcal/mol



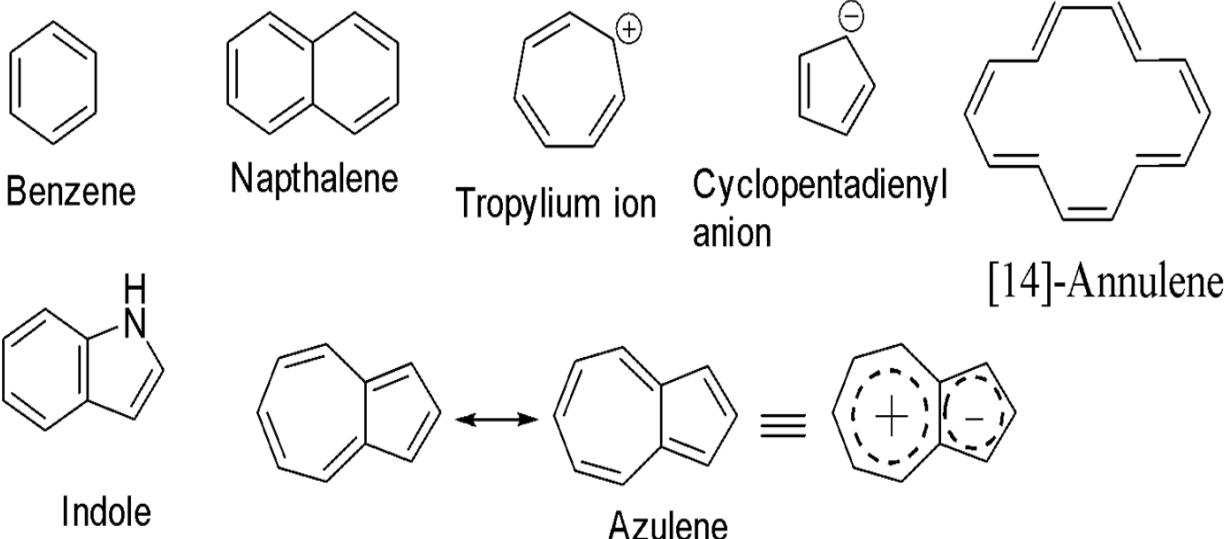
32 kcal/mol



Ignition test for Aromatic Compounds: Place a small amount of compound on the end of a spatula or on a porcelain lid and apply the flame from a Bunsen burner. Aromatic compounds burn with a yellow sooty flame.

- ❖ It shows **electrophilic substitution reaction** rather than **electrophilic addition reaction** (means doesn't decolorize bromine water solution).
- ❖ Aromatic compound follows **Hückel's rule**, a cyclic planar conjugated species having  $(4n+2\pi)$  electrons (where  $n=0, 1, 2, 3, \dots$ ) is aromatic in nature.
- ❖ Each carbon must be  **$sp^2$ - hybridized or  $sp$ -hybridized**.
- ❖ Each atom in the ring must have an unhybridized p orbital. (The ring atoms are usually  $sp^2$  hybridized or occasionally  $sp$  hybridized.)
- ❖ Delocalization of the pi electrons over the ring must lower the electronic energy and increases the stability.
- ❖ There is **diamagnetic ring current** which causes protons outside of the ring to be shifted **downfield** while any **inner protons** are shifted **upfield**, observed in **Nuclear Magnetic Resonance spectra**.
- ❖ Compounds that sustain a diamagnetic ring current are called **diatropic**; and are prevalent in **2, 6, 10, 14, 18...** electron systems.

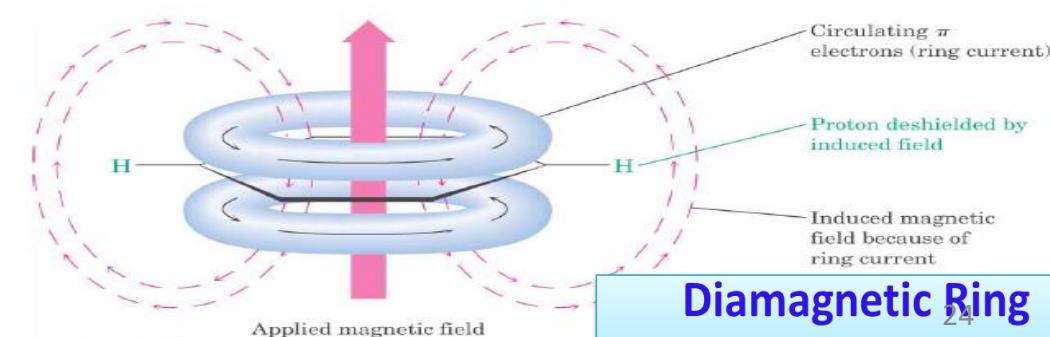
### Examples:



Aromatic ring oriented perpendicular to a strong magnetic field, delocalized  $\pi$  electrons producing a small local magnetic field

Opposes applied field in middle of ring but *reinforces* applied field outside of ring

Results in outside H's resonance at lower field



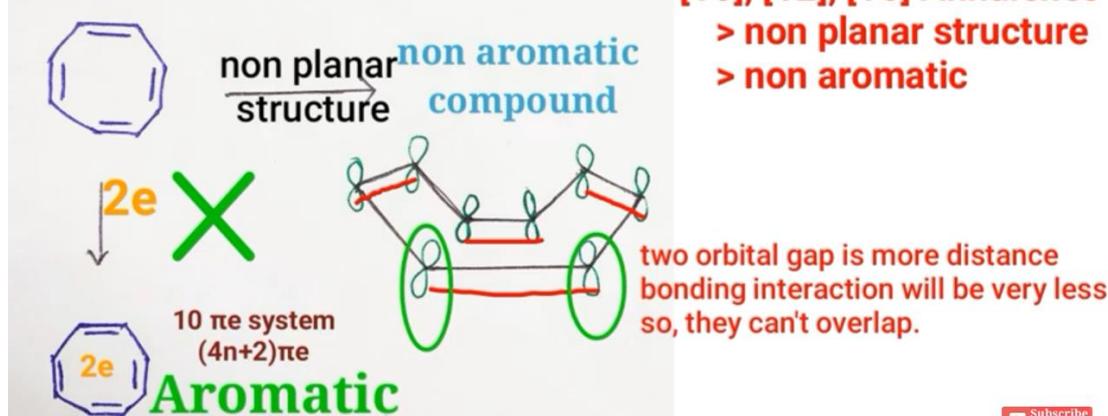
Diamagnetic Ring  
current effects

# Features of non-aromatic compounds

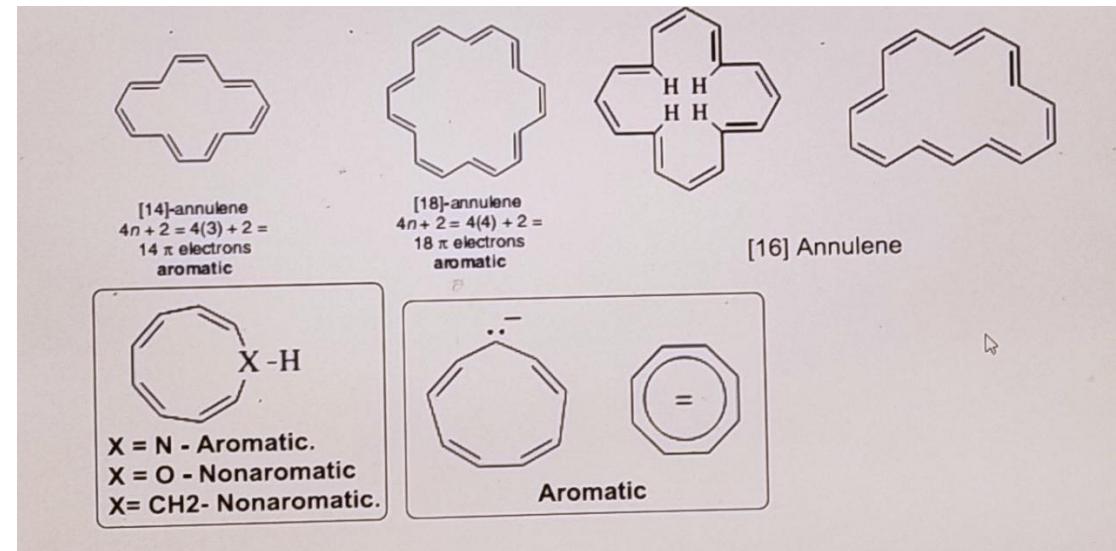
- For a molecule to be non-aromatic it must be:

- Cyclic or acyclic
- Do not have a continuous and overlapping  $p$ -orbitals, i.e. on every atom in ring
- Non-planar
- Posses  $4n$   $p$ -electrons ( $n = \text{any integer}$ )

## Cyclooctatetraene (COT)



[10], [12], [16] Annulenes  
→ non planar structure  
→ non aromatic



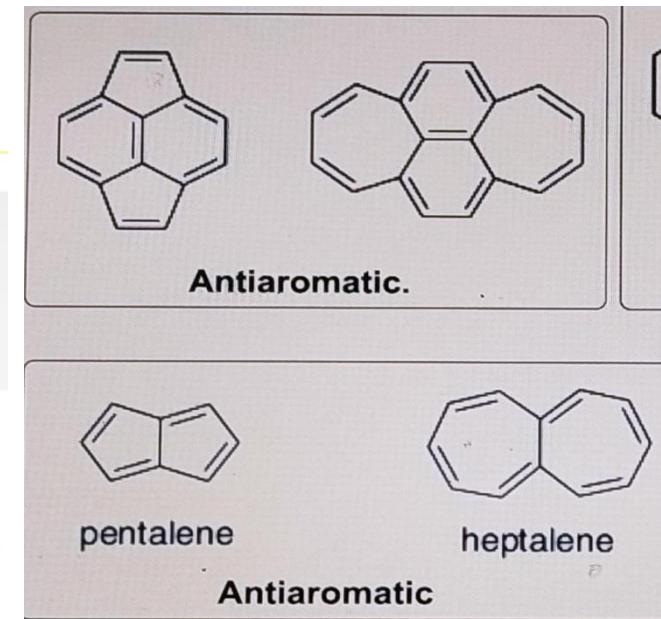
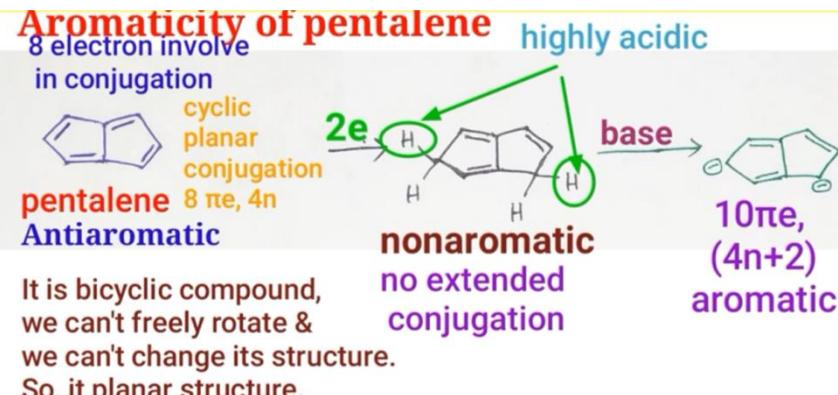
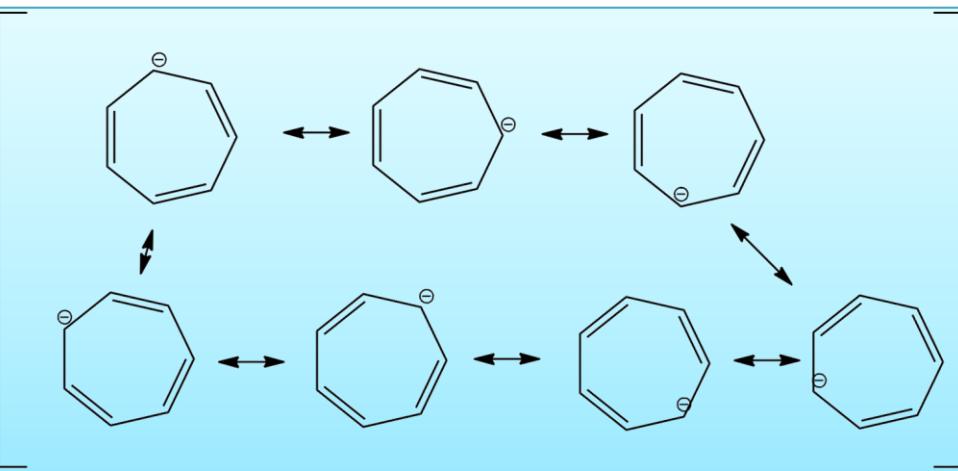
- Cyclooctatetraene would be an anti-aromatic compound if Huckel's rule is applied, so the conjugation of its double bonds is energetically unfavorable.
- Huckel's rule applies to a compound only if there is a continuous ring of overlapping  $p$  orbitals, usually in a planar system.
- Cyclooctatetraene is more flexible than cyclobutadiene and it assumes a non-planar 'tub shaped' conformation that avoids most of the overlap between  $\pi$  bonds.
- Huckel's rule is simply not applicable for non planar structures.

# Features of anti-aromatic compounds

- For a molecule to be anti-aromatic it must:

- Be cyclic and planar
- Have a continuous, overlapping ring of p orbitals, i.e. on every atom in ring
- Delocalization of the  $\pi$ -electrons over the ring increases the electronic energy and decreases the stability.
- Posses  $4n \pi$ -electrons ( 2, 4, 6, 8 ) as (  $n = 1, 2, 3$  etc. )

## Tropylium ion



- . Anti-aromatic systems exhibit a paramagnetic ring current, which causes protons on the outside of the ring to be shifted upfield while any inner protons are shifted downfield (eg-12-annulene), in sharp contrast to a diamagnetic ring current, which causes shifts in the opposite directions.
- Compounds that sustain a paramagnetic ring current are called paratropic; and are prevalent in 4, 8, 12, 16, 20... electron system

# Types of aromatic compounds

•  $2\pi$ - electron system.

Examples:

I. It follows  $(4n+2)\pi$ - electron system.

II. If electrons are delocalized, then compound is aromatic.

III. If electrons are not delocalized, then compound is non-aromatic.

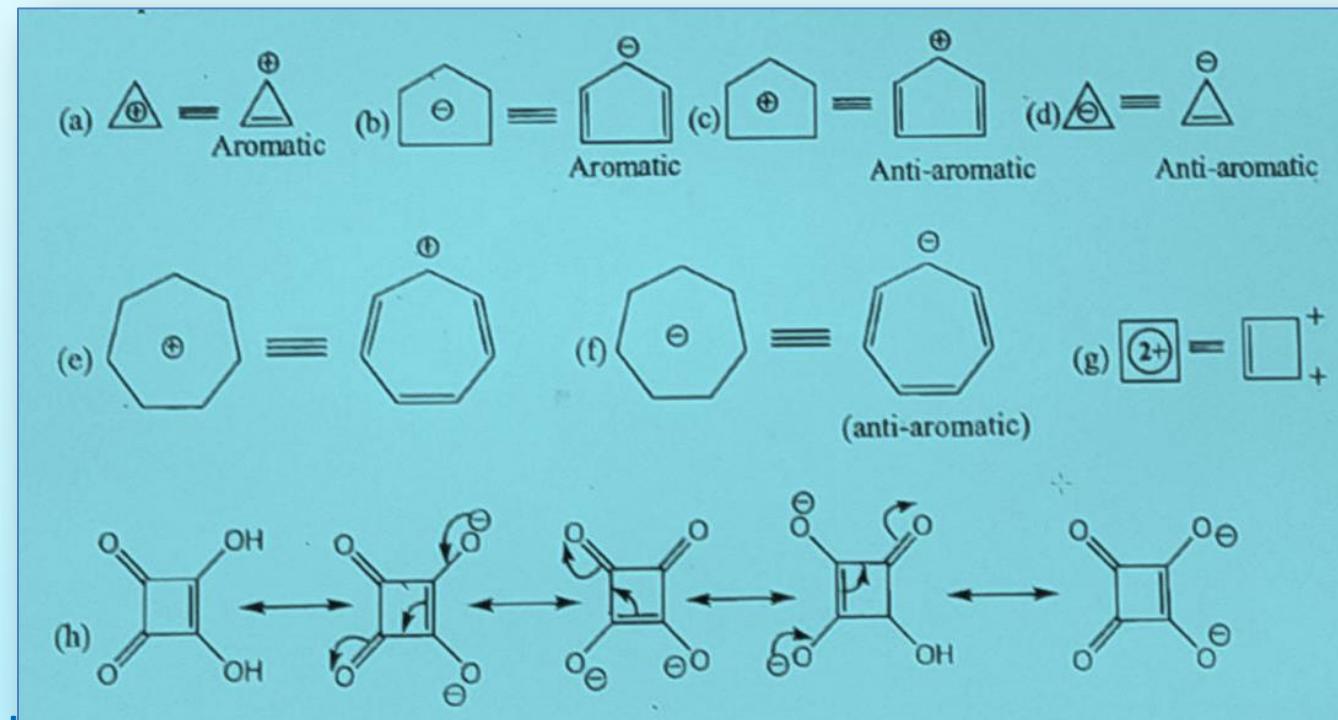
IV. Compound will never be anti-aromatic.

•  $4\pi$ - electron system.

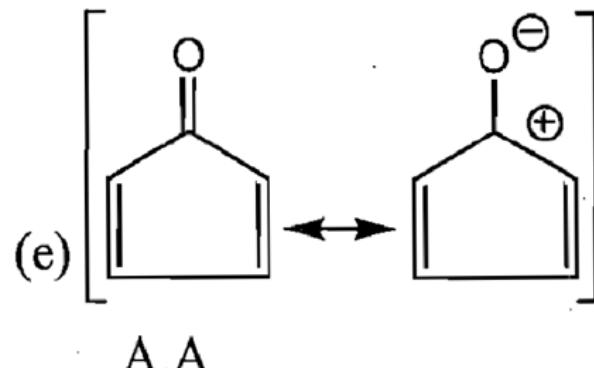
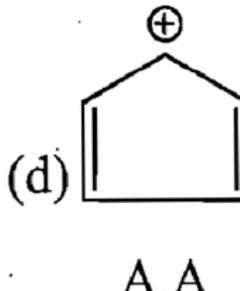
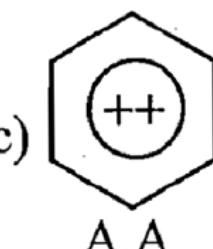
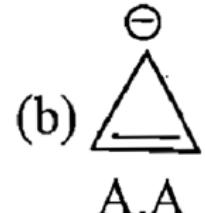
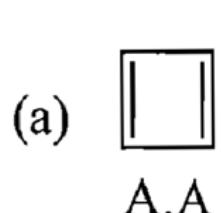
I. Belongs to  $4n\pi$ - electron system doesn't follow Huckel's rule.

II. If electron is delocalized then compound is Anti-aromatic.

III. If electron does not delocalized then compound is never aromatic then compound is non-aromatic.



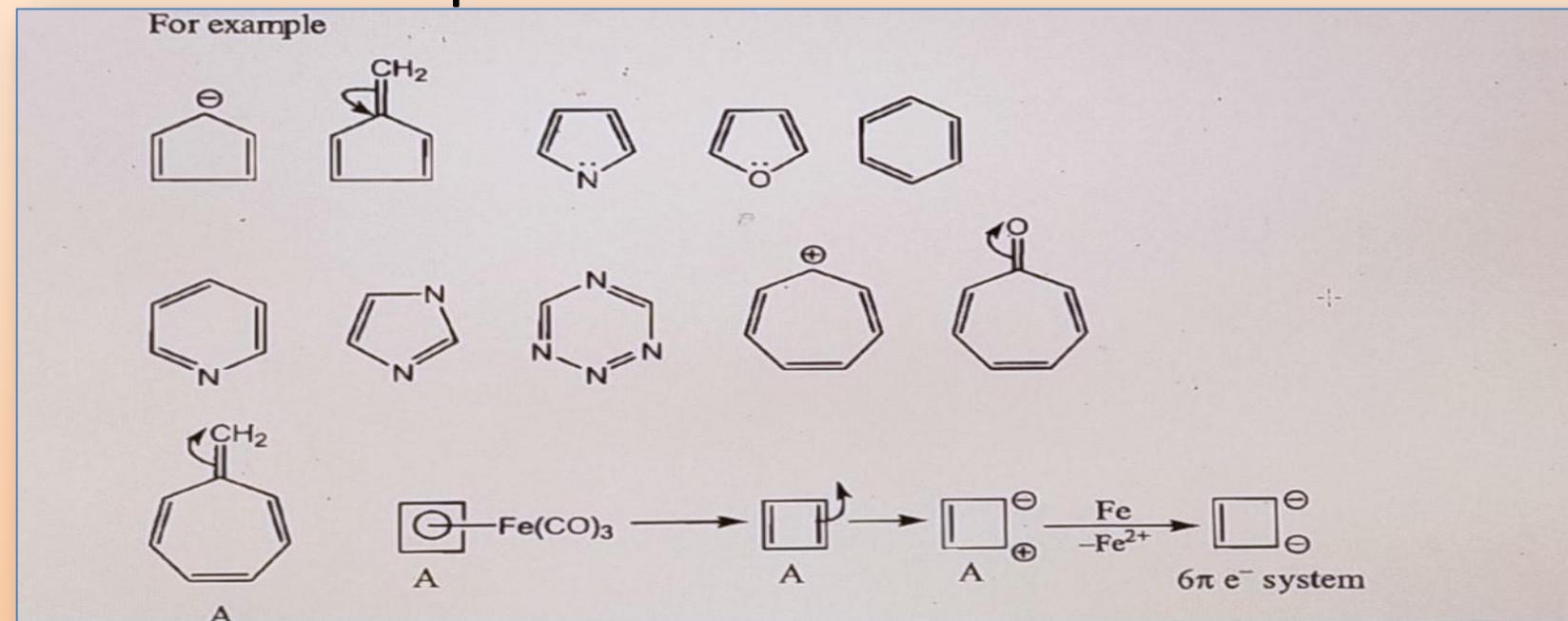
Examples:



A.A. = Anti-aromatic

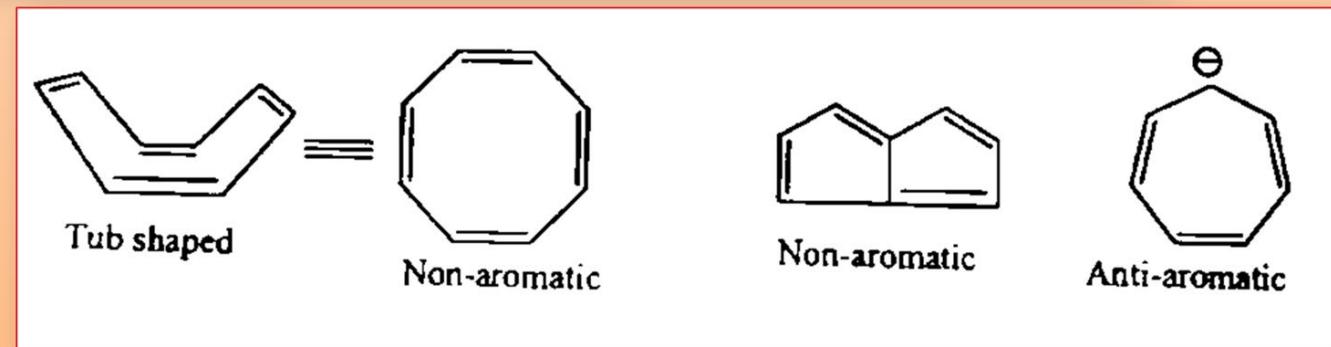
## (A) $6\pi$ - electron system

- I. Belongs to  $(4n+2)\pi$ - electron system.
  - II. If electron is delocalized then compound is aromatic.
  - III. If electron does not delocalized then compound must be non-aromatic



- **8 $\pi$ - electron system**

- I. Belongs to  $(4n)\pi$ - electron system.
  - II. If electron is delocalized then compound must be Anti-aromatic.
  - III. If electron does not delocalized then compound is non-aromatic.



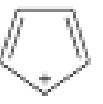
# Cyclopentadienyl anion



cyclopentadienyl anion

- $6 \pi$  electrons
- contains  $4n + 2 \pi$  electrons

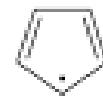
aromatic



cyclopentadienyl cation

- $4 \pi$  electrons
- contains  $4n \pi$  electrons

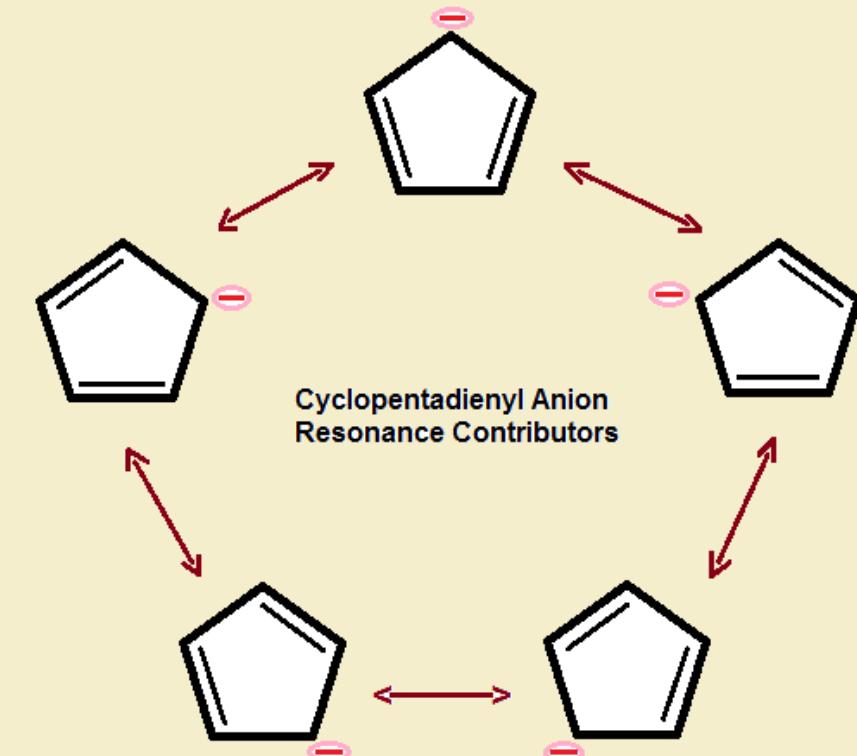
antiaromatic



cyclopentadienyl radical

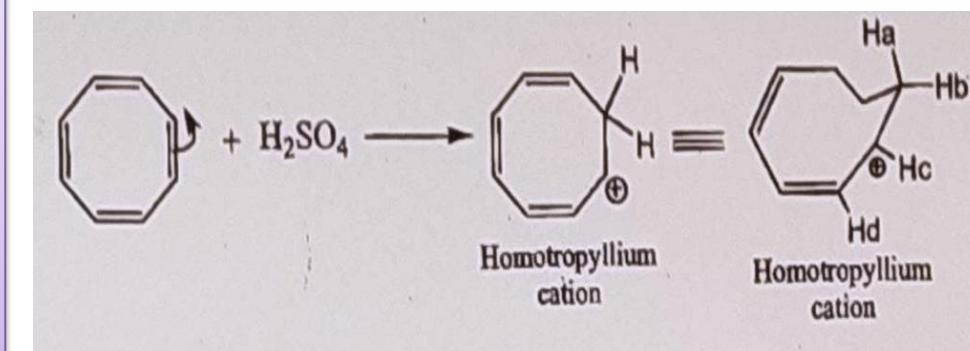
- $5 \pi$  electrons
- does not contain either  $4n$  or  $4n + 2 \pi$  electrons

nonaromatic



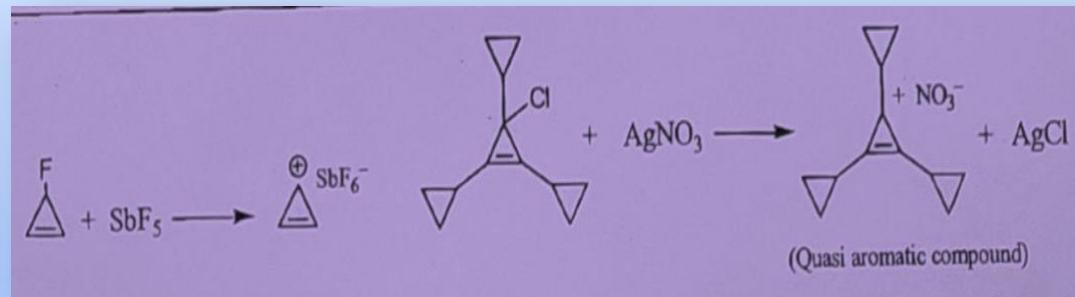
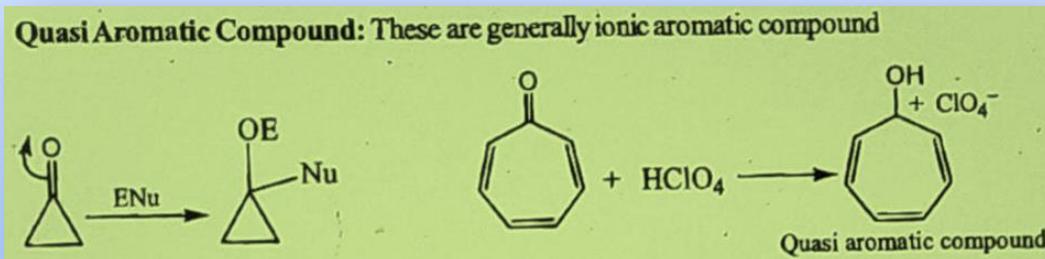
## Homoaromatic compound

- ❖ Compound that contains one or more  $sp^3$ -hybridized C-atom in a conjugate cyclic ring but  $sp^3$ -hybridized carbon atoms are forced to lie almost vertically above the plane (out of the plane) of the aromatic system for effective orbital overlapping in a closed loop known as homoaromatic compounds. Homoaromatic compound involves delocalization of  $\pi$ -electron cloud bypassing  $sp^3$  hybridized atom.
- ❖ When cyclooctatetraene is dissolved in concentrated  $H_2SO_4$ , a proton adds to one of the double bonds to form the homotropylium ion. In this species, an aromatic sextet is spread over seven carbons, as in the tropylium ion. The eighth carbon is a  $sp^3$  carbon and so cannot take part in the aromaticity.



# Quasi aromatic

- Aromatic compounds in which +ve or -ve charge is part of Hückel's rule of aromaticity, i.e., the charge is present in the ring, are called quasi aromatic compounds or most preferably quasi aromatic ions.
- Thus, all quasi-aromatic ions are aromatic compounds but the reverse is not true. Quasi-aromatic compounds are highly stable.



- **Stability Order:**

Aromatic > Homoaromatic > Non-aromatic > Anti-aromatic.

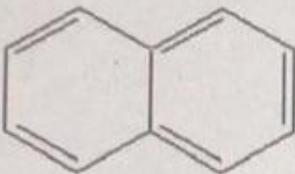
- **Energy Order:**

Anti-aromatic > Non-aromatic > Homoaromatic > Aromatic

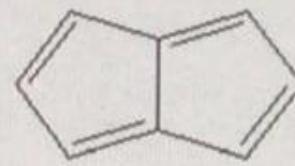
1. Determine if the following compounds are AROMATIC, ANTIAROMATIC, or NOT AROMATIC



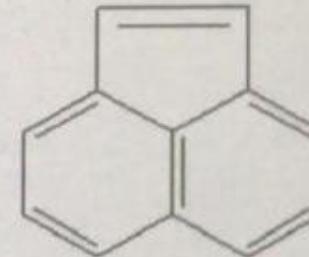
Cyclobuta-1,3-diene



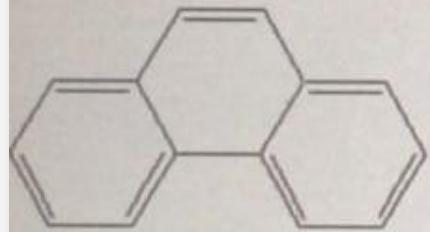
Naphthalene



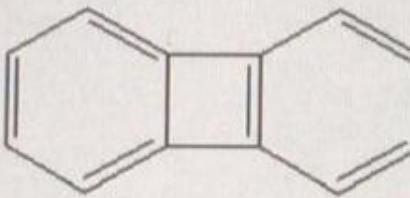
Pentalene



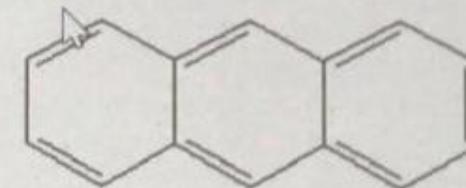
Acenaphthylene



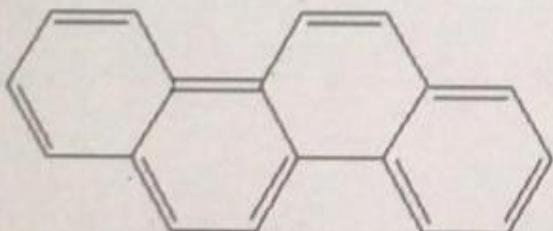
Phenanthrene



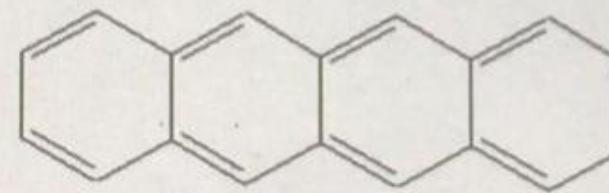
Biphenylene



Anthracene



Chrysene



Tetracene

## Characteristics of 3-Membered Ring Heterocyclic Compounds

### Some Elusive Three-Membered Rings



Oxirene

(never observed)



1H-Azirene

(never observed)



Thiirene

(never observed)

**Anti-aromatic  
Cyclic,  
Conjugated  $sp^2$  hybridised carbons  
 $4\pi$  electrons (  $4n$  rule)**



AZIRINE

(2H-AZIRINE)



OXIRANE

(ETHYLENE  
OXIDE)



THIIRANE

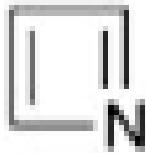
(ETHYLENE  
SULFIDE)



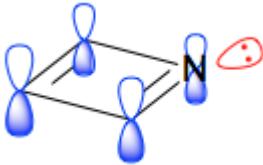
AZIRIDINE

(ETHYLENE  
IMINE)

- Non-aromatic
- Cyclic
- no conjugated  $sp^2$  hybridised carbons



azete



Anti-aromatic  
Cyclic  
Conjugated  $sp^2$   
hybridised carbons  
 $4\pi$  elections (4n rule)

## Characteristics of 4-Membered Ring Heterocyclic Compounds

- The Azete is an anti-aromatic.
- While counting the number of  $\pi$ -electrons, you count the electrons which are delocalized over the ring.
- In this case the nitrogen lone pair is localised and does not participate in resonance.
- The nitrogen lone pair is in an  $sp^2$  orbital (red) which is orthogonal to the  $\pi$  system (blue):
- So, the total number of  $\pi$ -electrons is only four: two from each double bond.



AZITIDINE



2H-OXETE



OXETANE



2H-THIETE

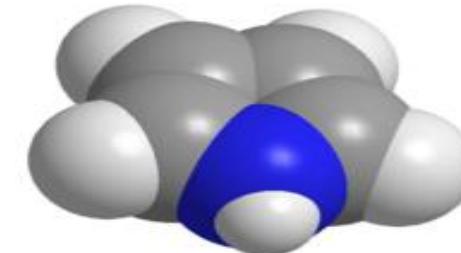
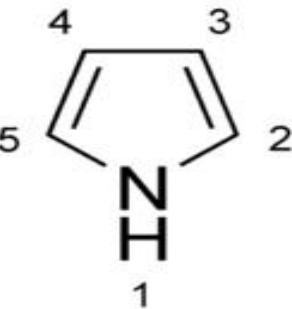
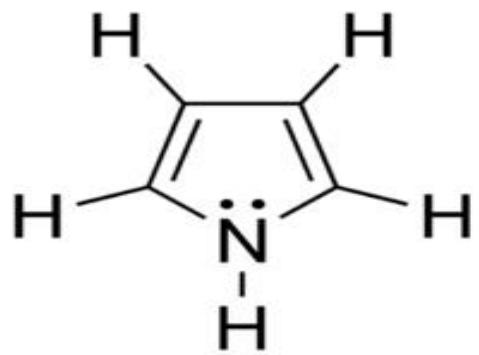


THIETANE

## NON-AROMATIC HETECYCLES

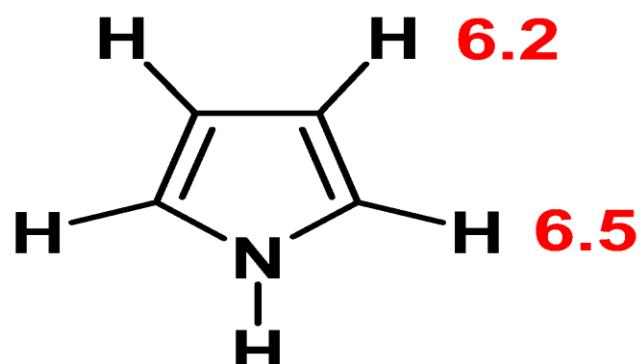
- Non-aromatic
- Cyclic
- no conjugated  $sp^2$  hybridised carbons

# Five Membered Heterocycle: Pyrrole



**$^1\text{H}$  NMR:**

$\delta$



**Pyrrole**

Aromatic:  $6\pi$  electrons

Sp<sup>2</sup> hybridised and planar

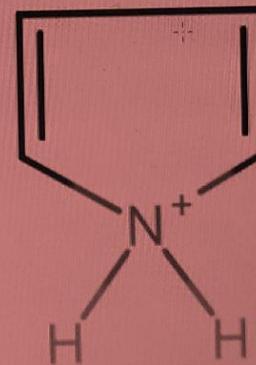
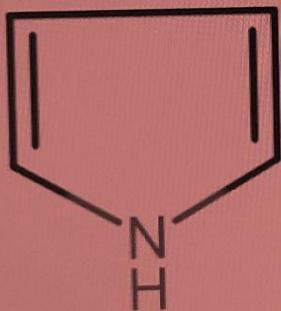
Lone pair tied up in aromatic ring

**Pyrrole is  $\pi$ -electron excessive**

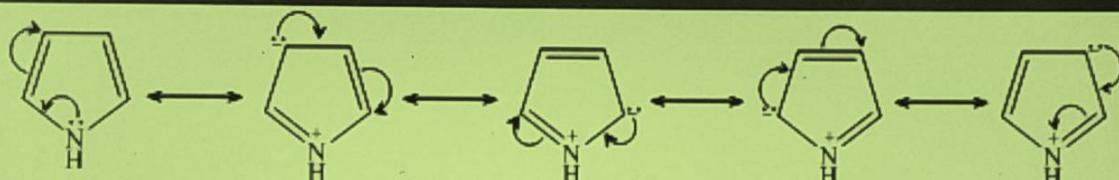
Thus, Electrophilic Aromatic Substitution is Easy

Nucleophilic Substitution is Difficult

The nitrogen lone pair electrons are not part of the aromatic system. Pyrrole is aromatic but when nitrogen atom of pyrrole is protonated, it becomes non-aromatic.



## Resonance structures of Pyrrole

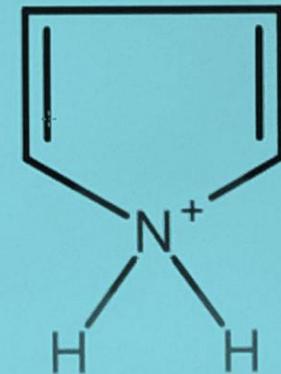


- Lone pair of electrons present on the nitrogen atom take part in resonance.
- Planar
- Cyclic
- Follows Huckel Rule
- $(4n+2)\pi = 6$
- $n=1$
- It is Aromatic.

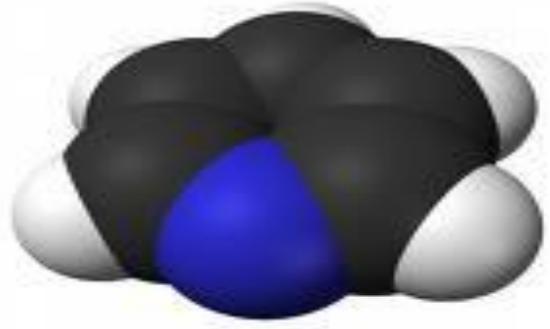


## Protonated Pyrrole

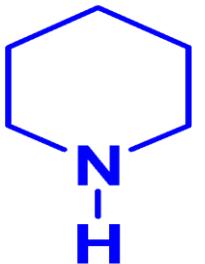
- Lone pair present on the nitrogen atom is lost due to protonation of nitrogen atom
- No Conjugation
- Doesn't obey Huckel Rule  
 $(4n+2)=4$
- It is non-aromatic.



# Six Membered Heterocycle: Pyridine



pyridine



piperidine

Heterocycle: any cyclic compound that contains ring atom(s) other than carbon (N, O, S, P). Cyclic compounds that contain only carbon are called carbocycles.

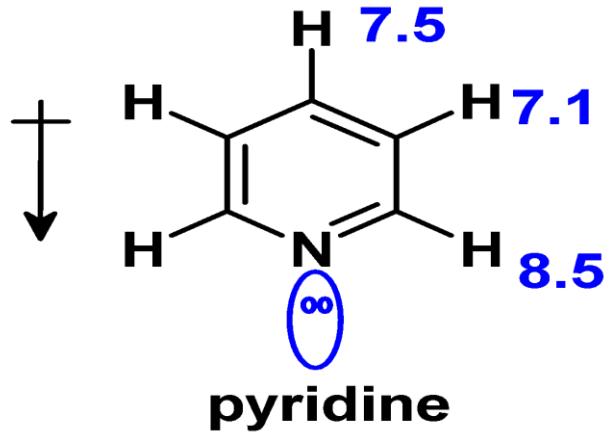
Pyridine: pi-electron structure resembles benzene (6 pi-electrons)

Pyridine replaces the CH of benzene by a N atom (and a pair of electrons)

Hybridization =  $sp^2$  with similar resonance stabilization energy

Lone pair of electrons not involved in aromaticity

## $^1\text{H}$ NMR: $\delta$



Pyridinium ion:  $pK_a = 5.5$

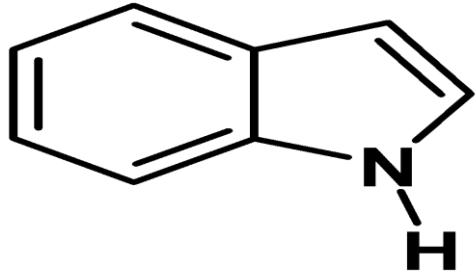
Piperidine:  $pK_a = 11.29$

diethylamine :  $pK_a = 10.28$

Pyridine is a weak base.  
Pyridine is  $\pi$ -electron deficient.  
Electrophilic aromatic substitution is difficult.  
Nucleophilic aromatic substitution is easy.

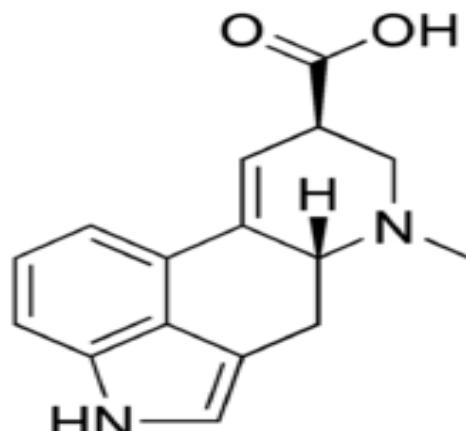
# Fused Heterocyclic Compounds

## Indole



**Indole**

### Indole Alkaloids

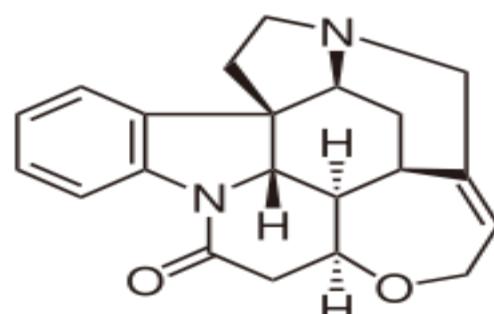
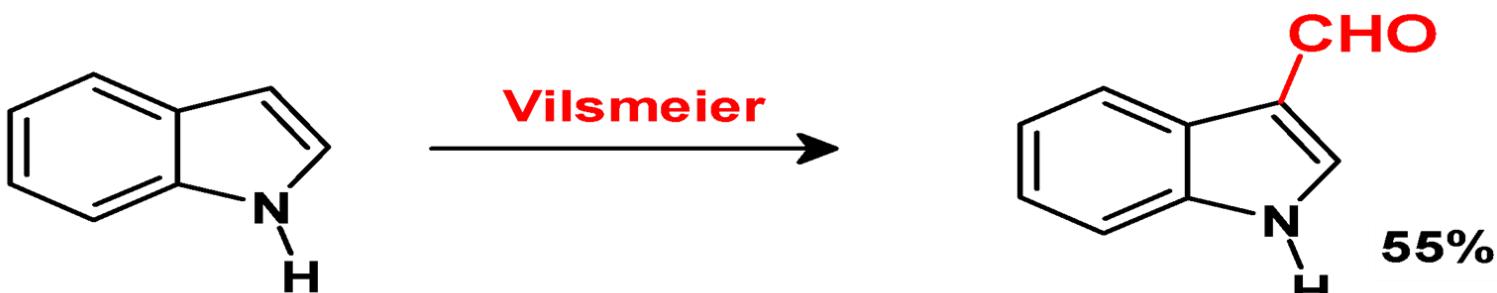


**Lysergic acid (LSD)**

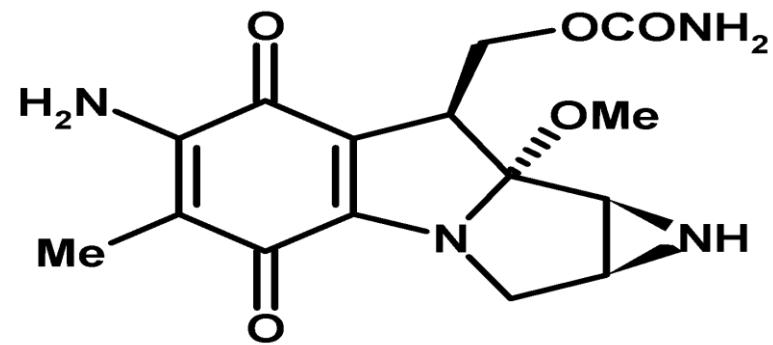
Aromatic due to 10  $\pi$ -electrons

Benzene part is non-reactive

*Electrophilic aromatic substitution occurs at the 3-position*



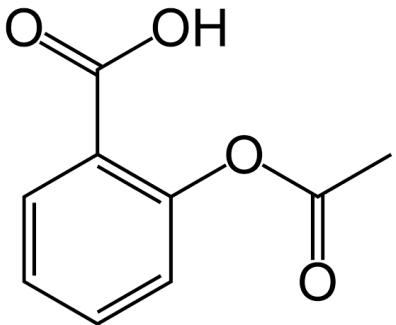
**Strychnine**



**Mitomycin C**

# Aspirin

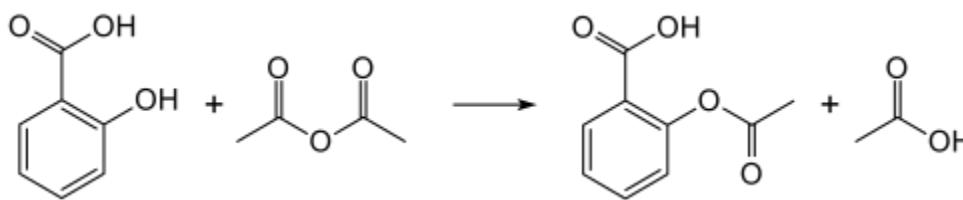
(Acetyl Salicylic Acid)



## PROPERTIES

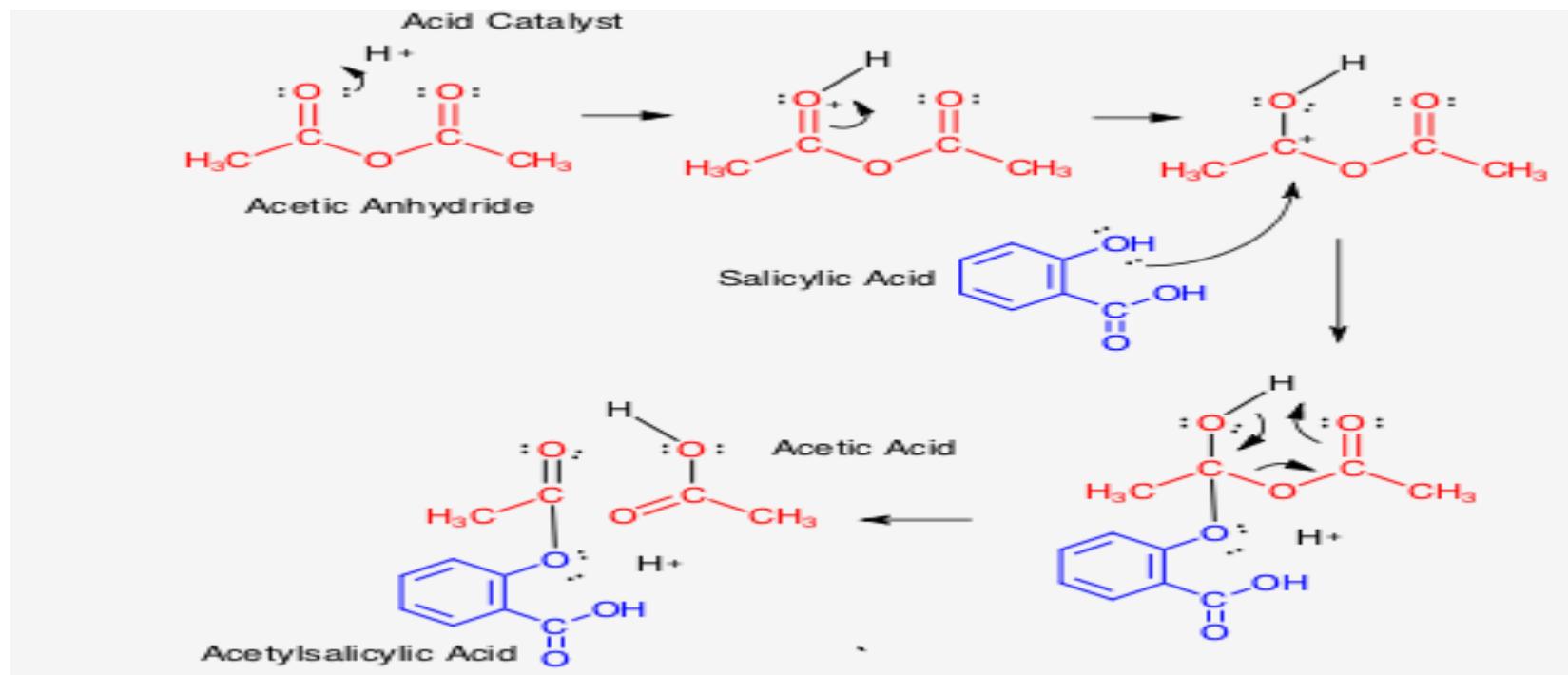
- Acetylsalicylic Acid is a colourless / white crystalline solid.
- It has a smell similar to that of vinegar, because of the hydrolysis yielding salicylic and acetic acid of Acetylsalicylic Acid
- It is bitter in taste, and density is 1.4 g/cc
- The melting point of aspirin is 135 deg C, & decomposes at higher temperature
- soluble in water, ethyl ether, ethanol, and chloroform.

## Synthetic Route of Aspirin



The synthesis of aspirin is an esterification reaction. Salicylic acid is treated with acetic anhydride, an acid derivative, causing a chemical reaction that turns OH group of salicylic acid into an ester group ( $\text{R-OH} \rightarrow \text{R-OCOCH}_3$ ). This process yields aspirin and acetic acid. The catalyst used in this reaction is sulphuric acid or phosphoric acid.

## Mechanism of Aspirin Synthesis



# **Applications of Aspirin**

In the year of 1897, Bayer laboratory gave Acetyl salicylic Acid the name of Aspirin.

It is a very popular medicine and is available all over the world in large quantities. Ever since the naming, the commercialization of it began.

This medicine is most commonly used as an anti-inflammatory and antipyretic.

However, considering its use in recent decades, it has also gained a reputation for treating cardiovascular diseases.

The other uses also include rheumatic fever and Kawasaki disease.

Similarly, we also use it as an intermediate and raw material in producing other medicines or chemical compounds like 4-hydroxycoumarin.

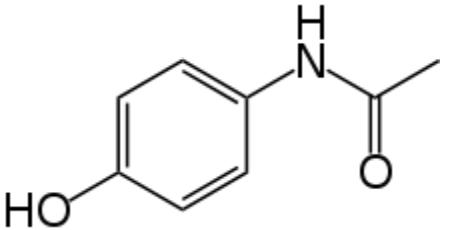
## **Safety Hazards**

When kept at room temperature. Aspirin will remain stable.

However, try to keep it dry so as to avoid its hydrolysis.

If you continue using it for a long period of time, it can result in causing gastritis and ulceration.

Similarly, it is also incompatible with tough oxidizing agents and strong acids and bases.



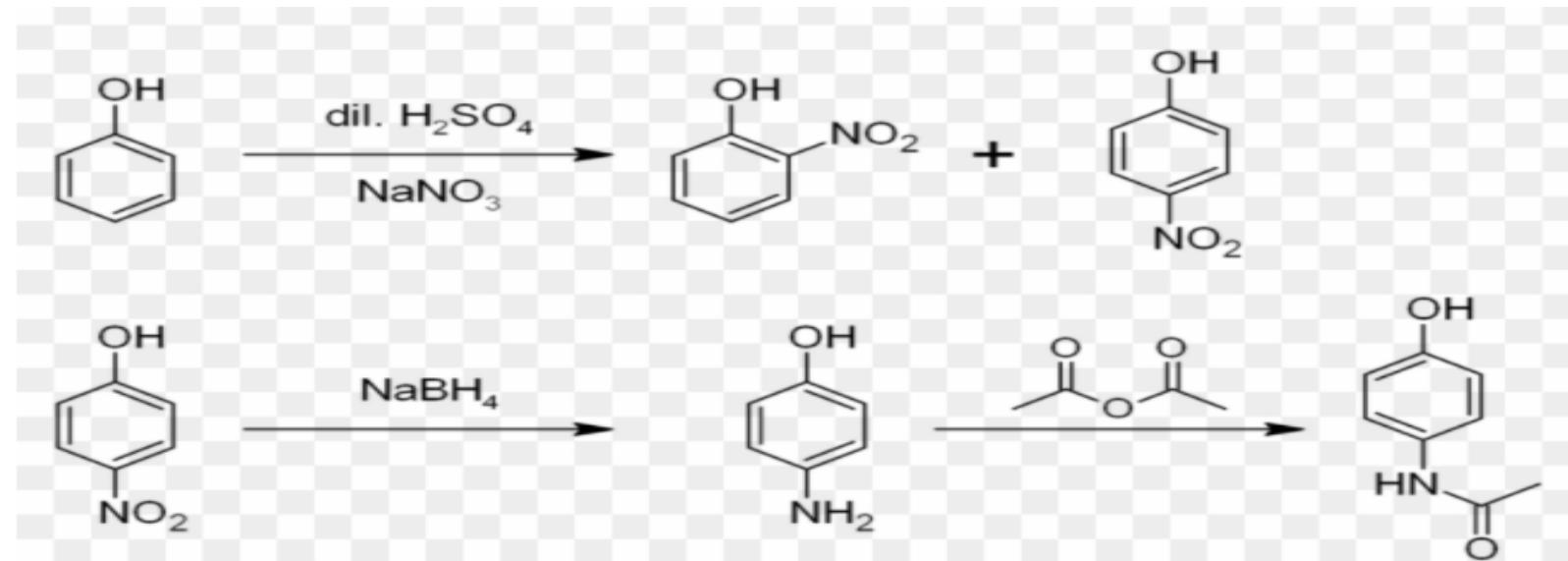
# PARACETAMOL



## PROPERTIES

Density	1.263 g/cm <sup>3</sup>
Melting point	169 °C (336 °F)
Solubility in water	12.78 g/kg (20 °C) ~14 mg/ml (20 °C)

## Synthetic Route of Paracetamol



# Application of Paracetamol

Paracetamol is a common painkiller (analgesic) used to treat aches and pain.

It can also be used to reduce a high temperature (antipyretic).

but it has no useful anti-inflammatory properties.

It's available combined with other painkillers and anti-sickness medicines.

It's also an ingredient in a wide range of cold and flu remedies.

Paracetamol's effects are thought to be related to inhibition of prostaglandin synthesis.

Paracetamol is readily absorbed from the gastrointestinal tract.

## Safety Hazards

Adverse effects of Paracetamol are rare but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia, neutropenia, pancytopenia, leukopenia and agranulocytosis but these were not necessarily causality related to Paracetamol

Very rare cases of serious skin reactions have been reported.

## **Dyes- Definition , Classification of Dyes, Disadvantages of Natural**

**Dyes and Synthetic Dyes, Chemistry of Dyeing,**

❖ Example for dyes: Methyl Orange, Malachite Green Dye,  
Rosaniline Dye, Phenolphthalein Dye, Indigo

- ❖ Dyes are colored organic compounds and they are used to impart the color to various substances/ materials like fabrics, paper, food, hair and drugs etc.
- ❖ With regard to their solubility, organic colorants fall into two classes, viz. dyes and pigments.
- ❖ The key distinction is that dyes are soluble in water and/or an organic solvent, while pigments are insoluble in both types of liquid media.
- ❖ Dyes are used to color substrates to which they have affinity.
- ❖ Pigments can be used to color any polymeric substrate
- ❖ Mechanistically in dyes, the surface coloration only is involved while the pigment is mixed with the polymer before fiber or molded article formation.

To be used, dye must possess these four properties:

- (i) Color
- (ii) Solubility in water and/or an organic solvent
- (iii) Ability to be absorbed and retained by fiber (substantively) or to be chemically combined with it (reactivity)
- (iv) Ability to withstand washing, dry cleaning and exposure to light

# Classification of Dyes

## 1. ON THE BASIS OF SOURCE:

### (a) Natural dyes:

- ❖ Natural dyes are dyes or colorants derived from plants, invertebrates, or minerals. The majority of natural dyes are vegetable dyes from plant sources—roots, berries, bark, leaves, and wood—and other biological sources such as fungi and lichens.
- ❖ There are two types of natural dyes. Additive dyes (non-substantive) such as madder must use a mordant (a chemical that fixes a dye) to bond with fibers. These are the most common type and have been used for at least 2,000 years.

Substantive dyes require no pretreatment to the fabric (e.g., indigo, orchil and turmeric) and there are three types: direct dye (for cotton, e.g., turmeric, safflower); acid dye (for silk and wool, e.g., saffron, lac) or basic dye (for silk and wool, e.g., berberine).

Mordants are chemical compounds that combine with the fiber and the dye forming a chemical bridge between the two. Common mordants are weak organic acids, such as acetic or tannic acid, and metal salts including aluminum ammonium or potassium sulfate, ferrous sulfate, and copper sulfate. Usually, the textile to be dyed is simmered in a mordant solution before dyeing (pre-mordanting). Other options include adding the mordant to the dye bath or treating with another mordant after dyeing to shift the color.

Natural mordant dyes are either monogenetic or polygenetic; monogenetic dyes produce only one colour irrespective of mordant, whereas polygenetic dyes produce different colours according to the mordant employed (e.g., logwood, alizarin, fustic and cochineal).

## Disadvantages of Natural Dyes

Before the advent of synthetic dyes, natural dyes were widely used, often together with mordants such as alum, to dye natural fibres including wool, linen, cotton and silk, but their use declined after the discovery of synthetic dyes. However, interest in natural dyes has been revived owing to increasing demands on manufacturers to produce more environmentally friendly alternatives to petrochemical-derived dyes. One main issue associated with the use of natural dyes in the coloring of textiles is their poor to moderate light-fastness, and despite their long tradition, not all natural dyes are especially environmentally friendly. Some natural dyes have no or little affinity for the textile materials and they require heavy-metal salts as mordants for fixation and color-fastness. Natural dyes may be sustainable but they need water and land to produce and there is insufficient dye yield per acre of plant material to sustain industrial-scale production.

## (b) Synthetic Dyes

Synthetic dyes are manufactured from organic molecules. Before synthetic dyes were discovered in 1856, dyestuffs were manufactured from natural products but batches of natural dye were never exactly alike in hue and intensity, whereas synthetic dyestuffs can be manufactured consistently. The use of computers and computer color matching (CCM) produces color that is identical from batch to batch.

### Discovery of first synthetic dye

William Henry Perkin, an eighteen-year-old English chemist, was searching for a cure for malaria, a synthetic quinine, and accidentally discovered the first synthetic dye. He found that the oxidation of aniline could color silk. From a coal tar derivative he made a reddish purple dye. The brilliant purple was called mauve.

The dye was not stable to sunlight or water and faded easily to the color presently named mauve, a pale purple. This discovery resulted in additional research with coal tar derivatives and other organic compounds and an entire new industry of synthetic dyes was born. In the twenty-first century, synthetic dyes are less expensive, have better colorfastness, and completely dominate the industry as compared with natural dyes. Thousands of distinctly different synthetic dyes are manufactured in the world.

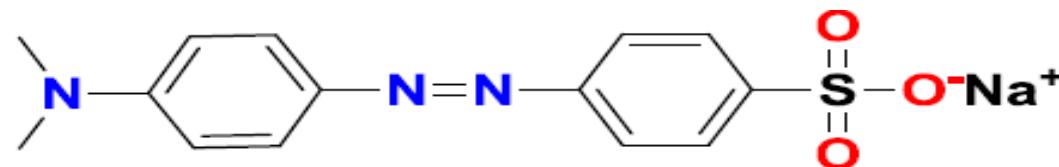
**2. ON THE BASIS OF CHROMOPHORE:** Dyes may be classified according to chromophore present in their structures.

**(a) Azo dyes:** Azo dyes are characterised by presence in the molecule of one or more azo groups —N=N—, which form bridges between organic residues, of which at least one is usually an aromatic nucleus. Many methods are available for preparing azo compounds, but manufacture of azo dyes is always based on the coupling of diazonium compounds with phenols, naphthols, arylamines, pyrazolones or other suitable components to give hydroxyazo or aminoazo compounds or their tautomeric equivalents. In the resulting dyes the azo group is the chromophore and the hydroxyl or amino group is an auxochrome.

The importance of azo dyes is shown by the fact that they account for over 60% of the total number of dye structures known to be manufactured.

A full range of shades is available, but on hydrophilic fibres the blues and greens lack fastness to light unless they are metallised; the metallised derivatives have dull shades.

The chemistry of these dyes ranges from simple monoazo compounds to complex polyazo structures with a molecular weight of 1800 or more, and their properties vary accordingly.



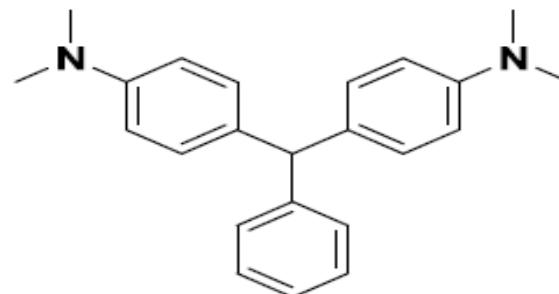
**Methyl Orange Dye**

## (b) Triphenylmethane Dyes:

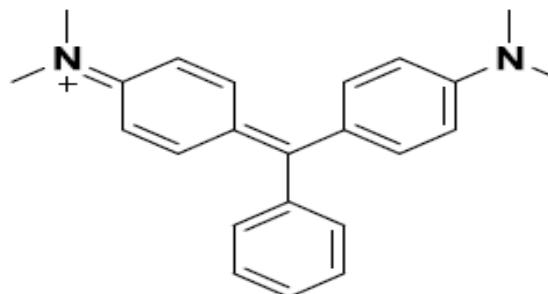
Synthetic organic dyes having molecular structures based upon that of the hydrocarbon triphenylmethane. They have poor resistance to light and to chemical bleaches and are used chiefly in copying papers, in hectograph and printing inks, and in textile applications for which lightfastness is not an important requirement.

The triphenylmethane derivatives are among the oldest man-made dyes, a practical process for the manufacture of fuchsine having been developed in 1859. Several other members of the class were discovered before their chemical constitutions were fully understood. Crystal violet, the most important of the group, was introduced in 1883.

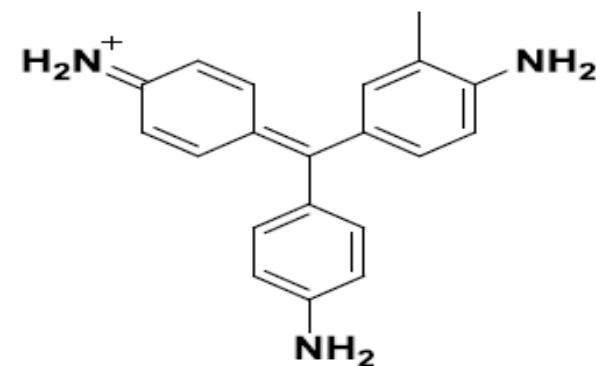
The range of colours is not complete but includes reds, violets, blues, and greens. They are applied by various techniques, but most belong to the basic class, which are adsorbed from solution by silk or wool, but have little affinity for cotton unless it has been treated with a mordant such as tannin.



**Leucomalachite Green**



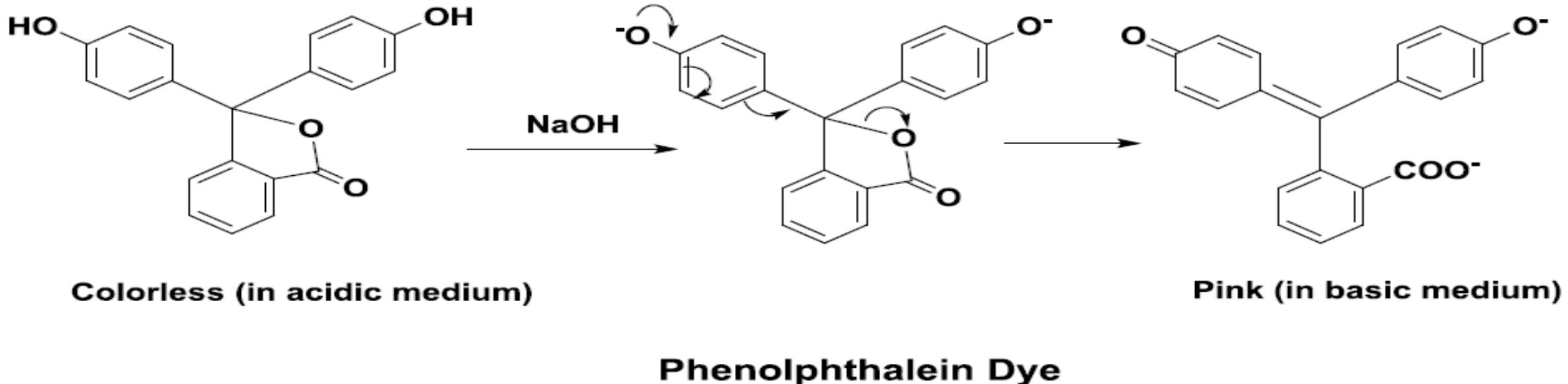
**Malachite Green Dye**



**Rosaniline Dye  
(Fuchsine Dye)**

(c) Phthalein dyes are a class of dyes mainly used as pH indicators, due to their ability to change colors depending on pH. They are formed by the reaction of phthalic anhydride with various phenols. They are a subclass of triarylmethane dyes.

- Common phthalein dyes include: Phenolphthalein, o-Cresolphthalein, Dixylenolphthalein, Guaiacolphthalein,  $\alpha$ -Naphtholphthalein,



# Chemistry of Dyeing

The process of applying color to fiber stock, yarn or fabric is called dyeing. There may or may not be thorough penetration of the colorant into the fibers or yarns.

The dyeing of a textile fibre is carried out in a solution, generally aqueous, known as the dye liquor or dye bath.

For true dyeing to have taken place, coloration of fabric and absorption are important determinants.

**Coloration:** The coloration must be relatively permanent: that is not readily removed by rinsing in water or by normal washing procedures. Moreover, the dyeing must not fade rapidly on exposure to light.

**Absorption:** The process of attachment of the dye molecule to the fiber is one of absorption: that is the dye molecules concentrate on the fibre surface.

There are four kinds of forces by which dye molecules are bound to the fiber:

1) Ionic forces 2) Hydrogen bonding 3) Vander Wals' forces and 4) Covalent chemical linkages.

**Exhaustion:** In any dyeing process, whatever the chemical class of dye being used, heat must be supplied to the dye bath; energy is used in transferring dye molecules from the solution to the fiber as well as in swelling the fiber to render it more receptive. The technical term for this process is exhaustion.

**Levelness:** An Important Quality, evenness of dyeing, known as levelness is an important quality in the dyeing of all forms of natural and synthetic fibers. It may be attained by the control of dyeing conditions.

## Conditions to attain Levelness

By agitation to ensure proper contact between dye liquor and substance being dyed and by use of restraining agents to control rate of dyeing or strike.

**Solvent Dyeing** Serious consideration has recently been given to the methods of dyeing in which water as the medium is replaced by solvents such as the chlorinated hydrocarbons used in dry cleaning.

The technological advantages in solvent dyeing are: 1. Rapid wetting of textiles 2. Less swelling 3. Increased speed of dyeing per given amount of material 4. Savings in energy, as less heat is required to heat or evaporate per-chloro-ethylene.

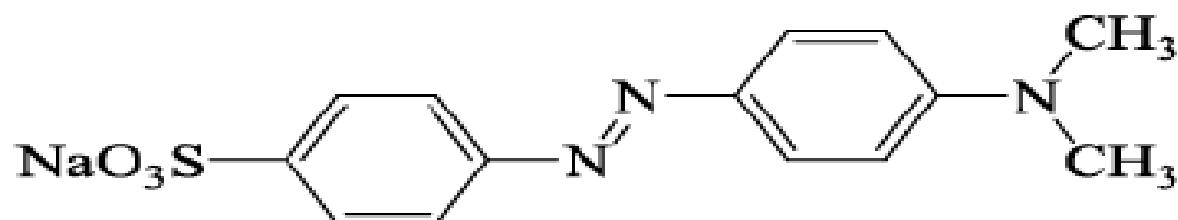
Thus it eliminates the effluent (pollution) problems associated with the conventional methods of dyeing and finishing.

# Methyl Orange

## Diazo Coupling

### A Synthesis of Methyl Orange

In this experiment the azo dye **methyl orange** is prepared by a electrophilic substitution with arenediazonium salts (diazo coupling).



***p*-Dimethylamino-Azobenzenesulfonic Acid (Methyl Orange)**

**Methyl orange** is a pH indicator and due to its clear color change it is very often used in titrations. Methyl orange changes color at the pH of a mid-strength acid and is usually used in titrations for acids. Unlike a so called universal indicator, methyl orange does not have a full spectrum of color change, but has a sharper end point.

Methyl orange is prepared from sulfanilic acid and *N,N*-dimethylaniline. The first product obtained from the coupling is the bright red acid form of methyl orange, called **helianthin**. In base, helanthin is converted to the orange sodium salt, called methyl orange.

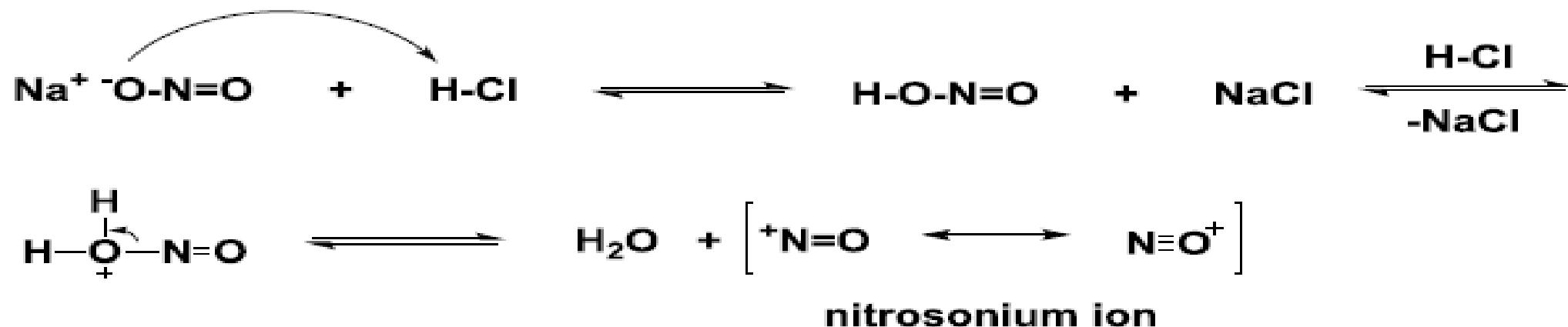
### Preparation:

Step-1. The first step is to dissolve sulfanilic acid in basic solution.

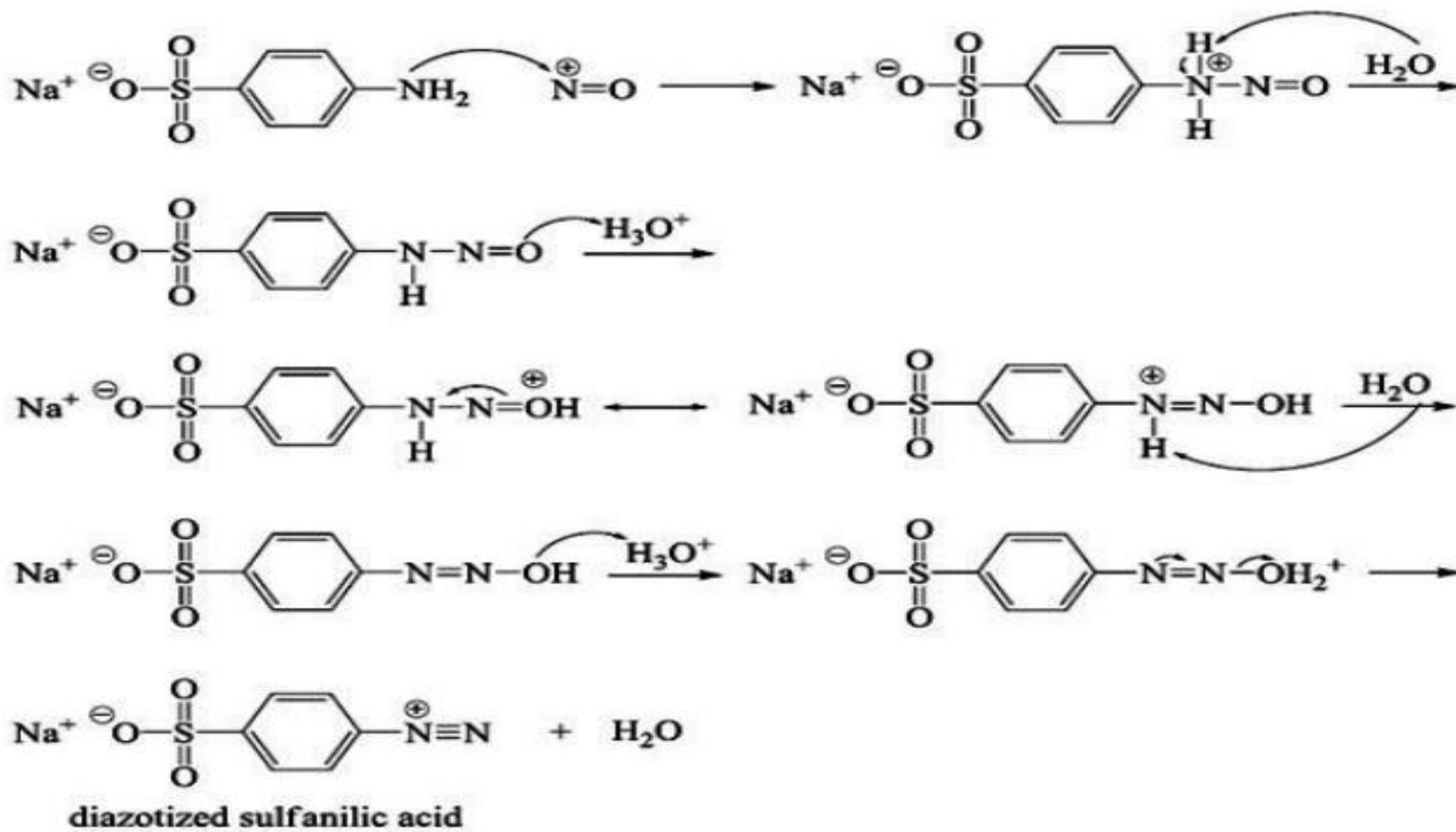


Step-2. Formation of Nitrosonium Ion

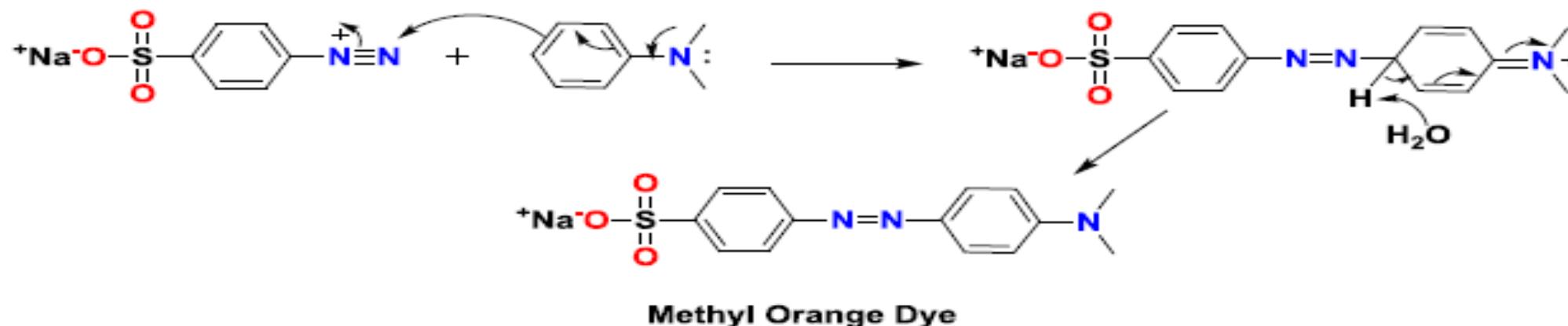
Step-2. Formation of Nitrosonium Ion



### Step-3. Formation of Diazotized Sulphanilic Acid

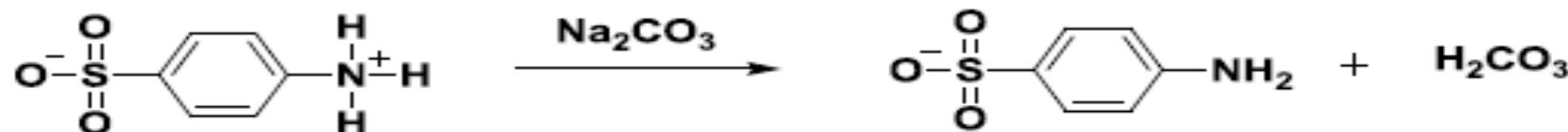


## Step-4. Addition to N,N-Dimethylaniline

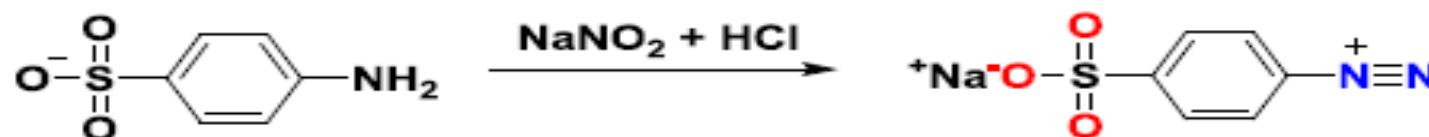


## Overall preparation of methyl orange

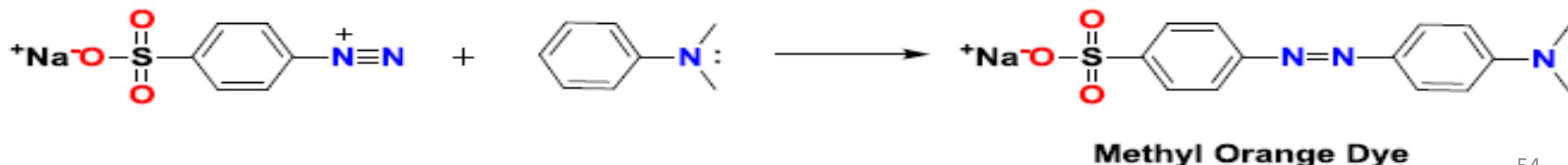
**Step-1**



**Step-2**



**Step-3**



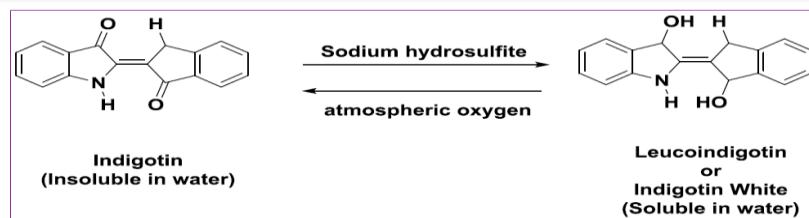
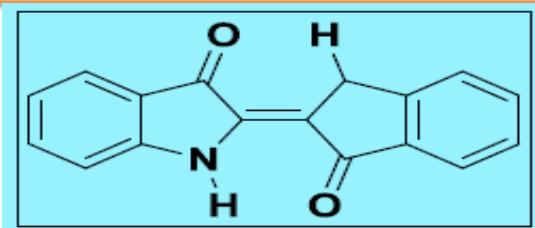
# INDIGOTIN DYE

- ❖ Indigo is an ancient compound, and has been known and used as a distinctive blue dye since prehistoric times.
- ❖ The earliest users were from India, and the country gained its English name from the ancient Greek word for *indigo*.
- ❖ Historically, indigo played an important role in the economies of many countries because natural blue dyes are rare. Today it will be most familiar to you as the dye used to color blue jeans.

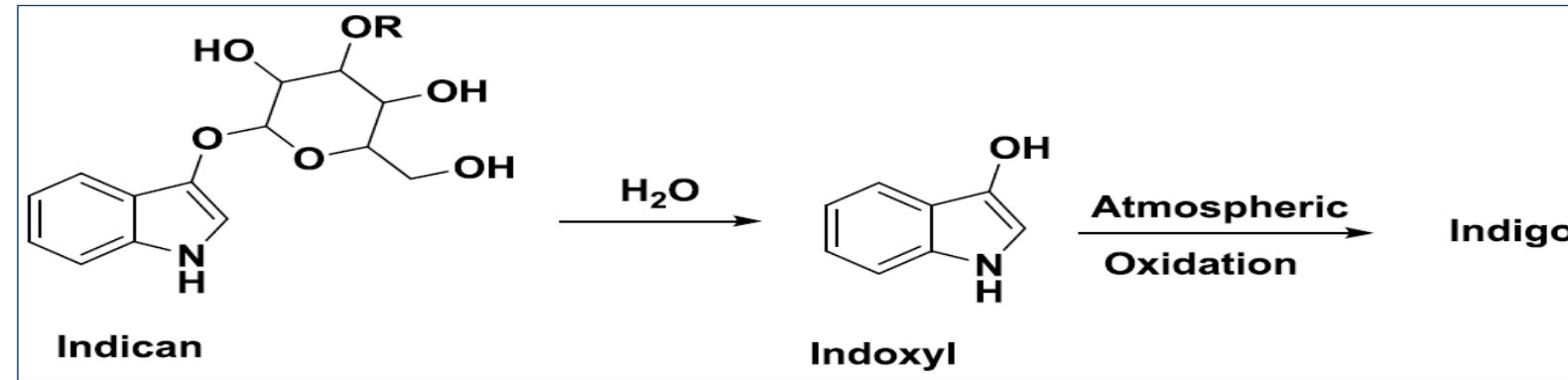
The chemical in indigo which is responsible for the blue colour is indigotin, which is a dark blue powder at room temperature and is insoluble in water and ethanol. It is most soluble in chloroform, nitrobenzene and sulphuric acid. It has a fused nitrogen heterocyclic structure.

Indigo in its synthesised or purified form is insoluble in water and other polar solvents. To overcome this problem, the dye is reduced to soluble leucoindigo (known as 'white indigo'), and applied to clothes in this form. When exposed to atmospheric oxygen it re-oxidises to the insoluble form and regains its colour. Originally this reduction was done with urine, although synthetic urea replaced it in the 19th century and later sodium hydrosulfite was employed as a much more effective reducing agent.

Once the problem of applying the dye to the clothing had been overcome the insolubility of the dye is of course beneficial - it will not wash out of the fabric in water.

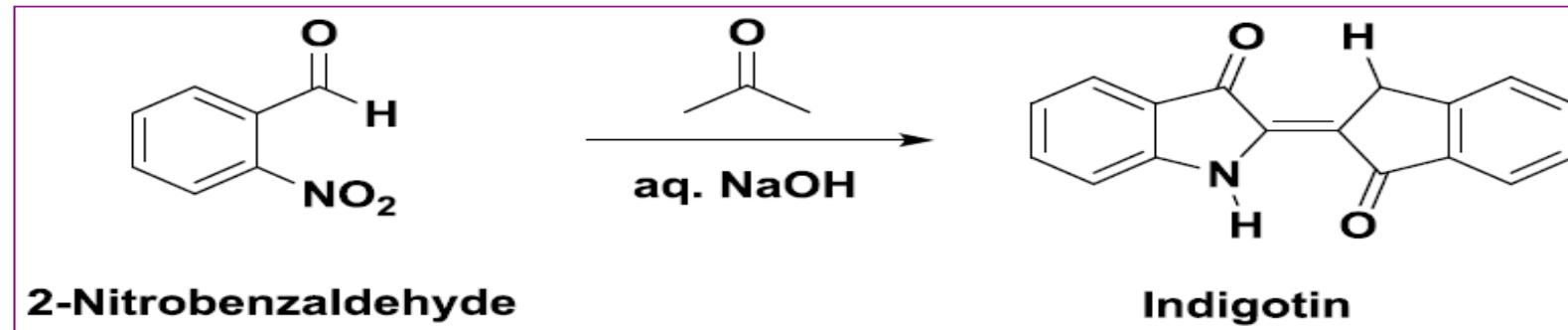


**Extraction:** Indigo has been known since ancient times and originally came from a plant extract. Plants of the *Indigofera* genus contain a glycoside called *indican* in their leaves and stems, which is extracted, and acid-hydrolyzed into indoxyl. Mild oxidation in atmospheric oxygen will then produce indigo.

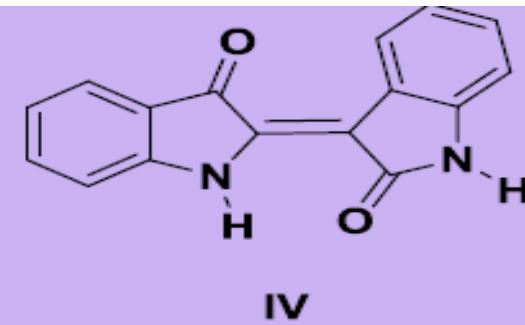
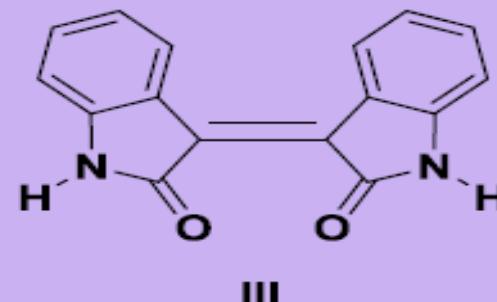
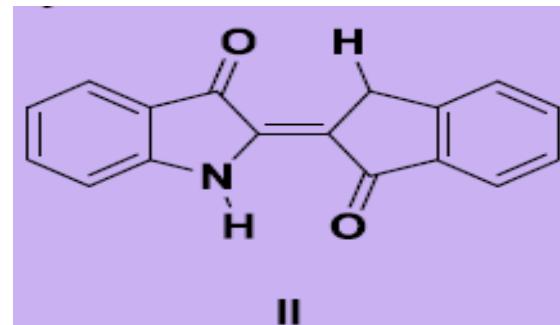


**Synthesis:** Dissolve 1 g. of o-nitrobenzaldehyde in 3 ml of pure acetone, add about an equal volume of water, which leaves a clear solution, and then, drop by drop, sodium hydroxide solution. Heat is developed and the solution becomes dark brown.

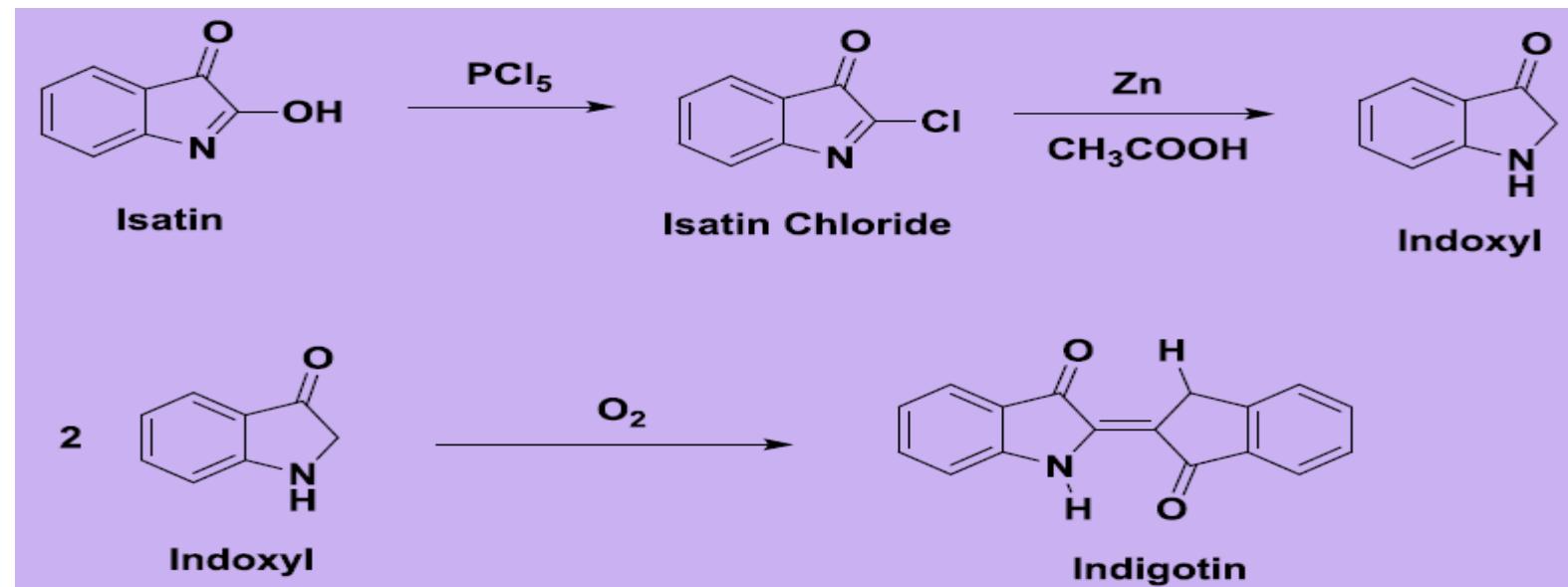
After a short time the dye separates in crystalline flakes. Collect the precipitate at the pump after five minutes and wash, first with alcohol then with ether. Indigo so prepared is specially pure and has a beautiful violet lustre.



**Structure of Indigo:** On the basis of structure of Isatin, Indigo may possess either of the following structure (II, III and IV). All of them when oxidized yield two molecules of Isatin.



**Synthesis:** The structure of indigo has been further confirmed by the various synthesis of indigo.



# **End of Module 3**