Module-3

Organic intermediates and reaction transformations

Contents.... (6 h)

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

Aromatics - **(aromaticity including heterocycles)** (2 h)

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

An intermediate is a molecular species that is formed from two or more reactants and then reacts further to give the products.
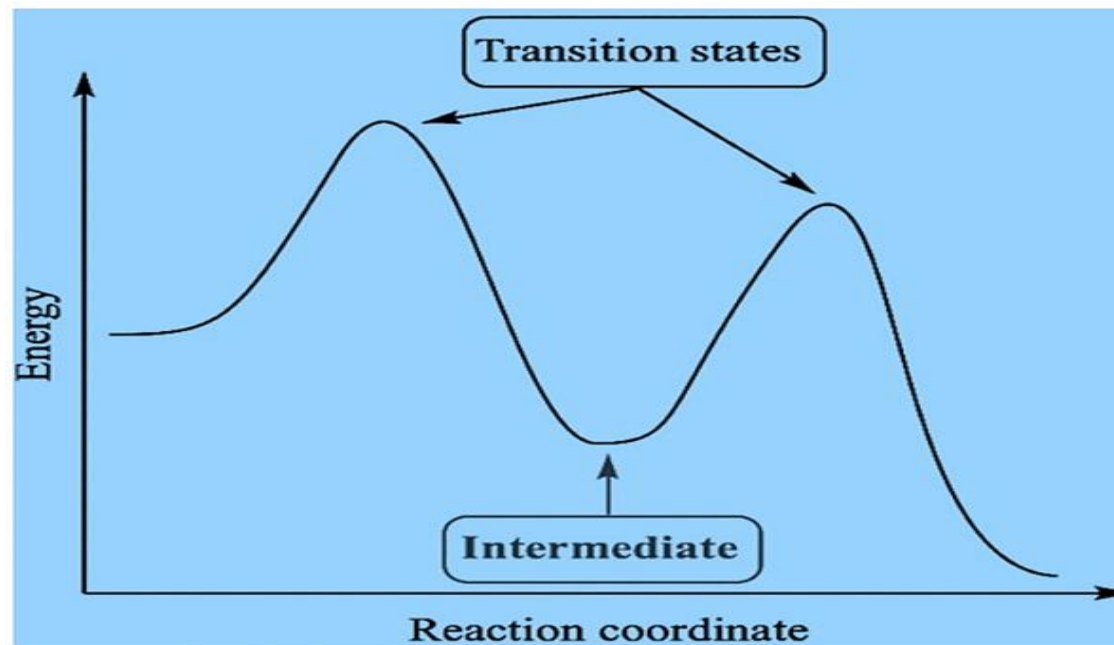
Organic Intermediates

- Carbocations
- Carbanions
- Free radicals
- Carbenes
- Nitrenes
- Benzyne

- **These specific organic intermediates are short-lived (10^{-6} second to a few seconds only).**
- **They are ready to convert into more stable molecules.**
- Among all, carbenes and carbocations are relatively stable.
- **Only carbanions have a complete octet around the carbon.**

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Carbocations

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

$$\overset{\oplus}{C}H_2CH_3 \quad \overset{\oplus}{C}H_3$$
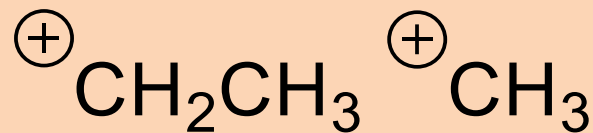
Structure:

❖ The **carbon atom with a positive charge is referred as carbocation** and it belongs to *sp²* **hybridization.**

❖ The three *sp²* 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°.** The empty *p* orbital is perpendicular to the plane.
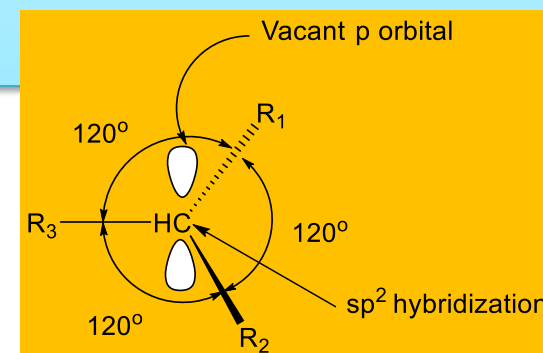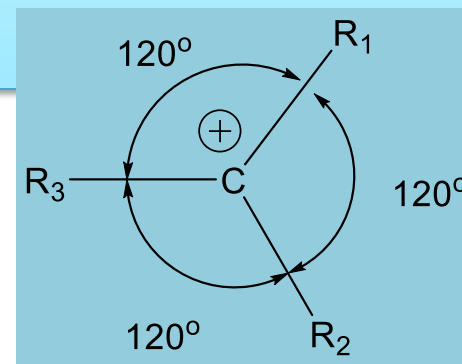
❖**Carbocations are extremely reactive species due to their ability to complete the octet of the electron-deficient carbon.**
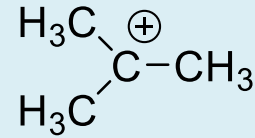
Classification of Carbocations

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

$$\overset{\oplus}{CH_3CH_2}$$
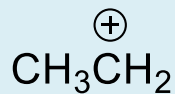
ethyl cation is a primary carbocation
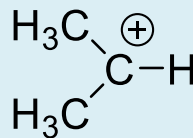
isopropyl cation is a secondary carbocation

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.
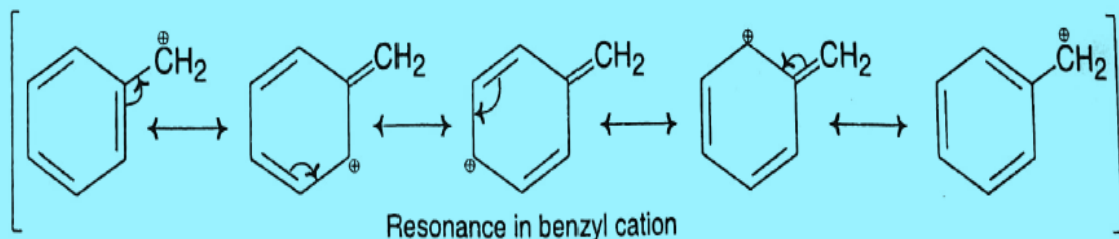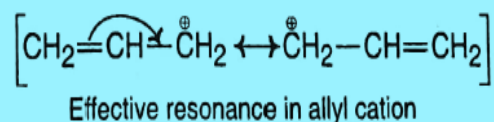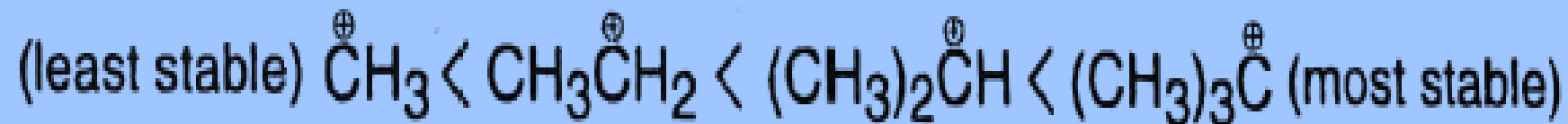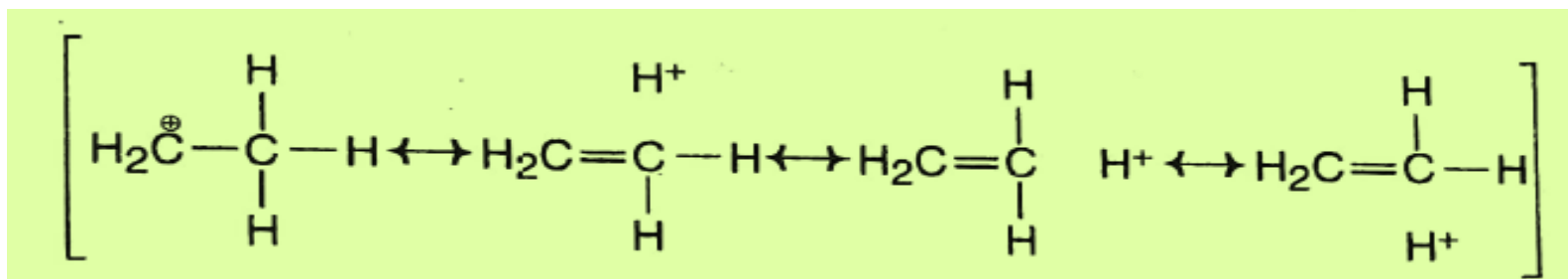
(i) Inductive effect

❖ 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.

Isopropyl cation
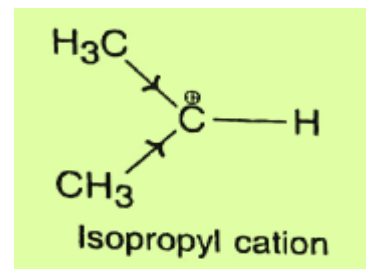
(ii) Hyperconjugative effect

❖ **An alkyl group may reduce the positive charge of a carbocation by hyperconjugative electron- release.**

❖ **The charge becomes dispersed over the α-hydrogens and consequently, the system becomes stabilized. Hyperconjugation in ethyl cation, for example, occurs as follows**

❖ **As the number of α-hydrogens, i.e., the number of hyperconjugative forms increases, the stability of carbocations increases. Hence, the order of stabilities of methyl substituted carbocations is ::**


$$(\text{least stable}) \ \overset{\oplus}{C}H_3 < CH_3\overset{\oplus}{C}H_2 < (CH_3)_2\overset{\oplus}{C}H < (CH_3)_3\overset{\oplus}{C} \ (\text{most stable})$$

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° 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.

Small steric crowding

Large steric crowding
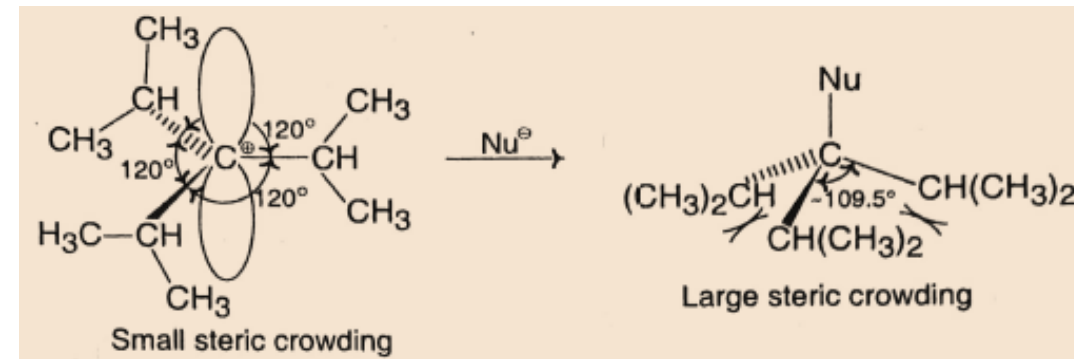
(v) Constituting an aromatic system

❖ The vacant *p* orbital of a carbocation may be involved in constituting a planar $(4n +2)\pi$ electron system. where n = 0,1,2.... 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 6π electron system and aromatic.

Cycloheptatrienyl cation
[a $(4n +2)\pi$ electron system, where $n = 1$: aromatic]
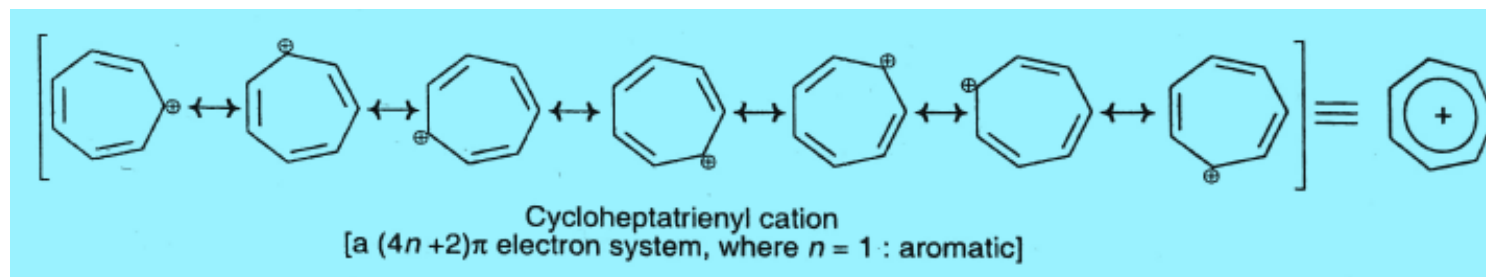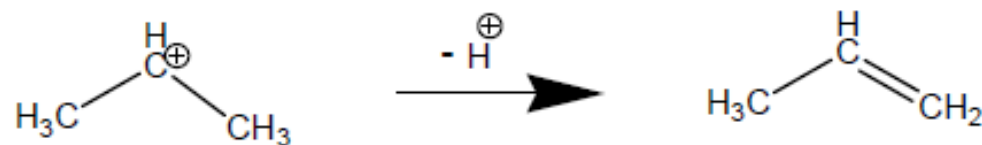
Reaction of Carbocations

1. Combination with an anion:

The carbocation reacts with a negatively charge species to give a stable product. Example - Addition of hydrochloric acid to ethylene to yield ethyl chloride. [2]
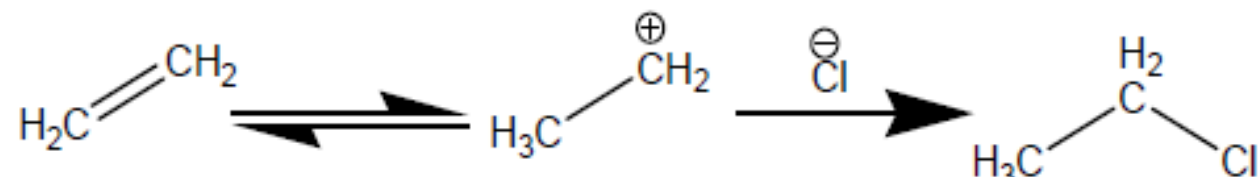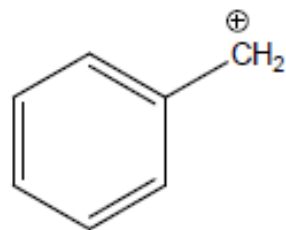

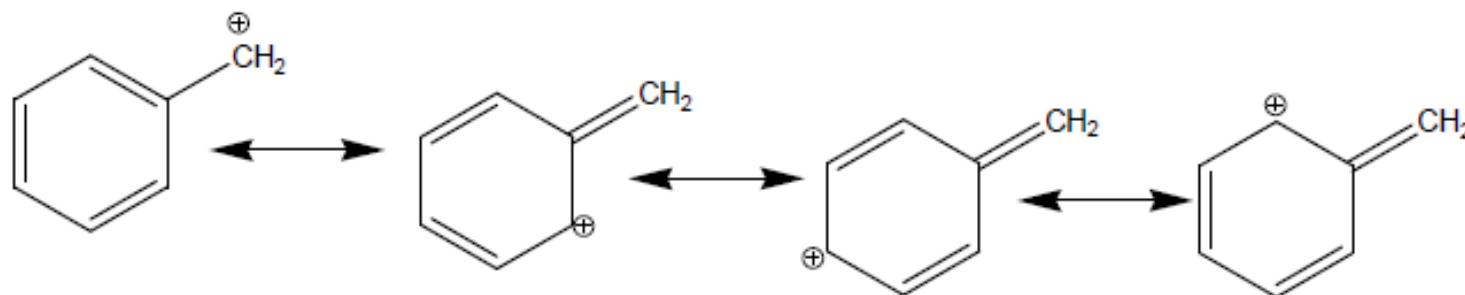
2. Elimination of proton:

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. [14]
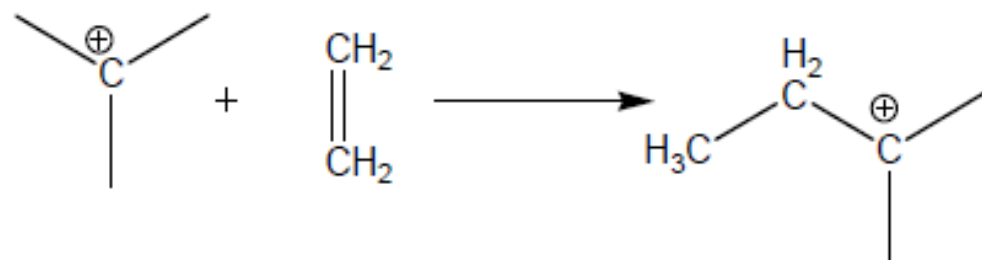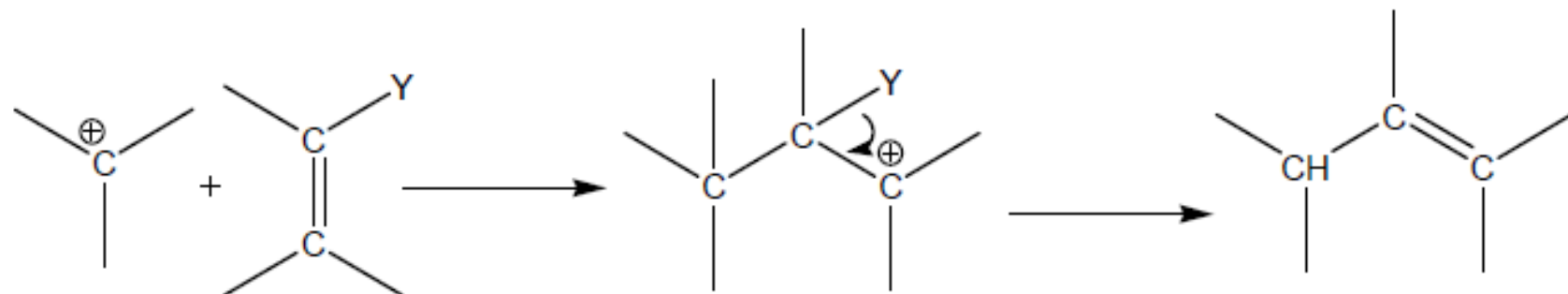

Benzyl carbocation

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 stannyl or silyl substituent is eliminated to form a stable alkene.
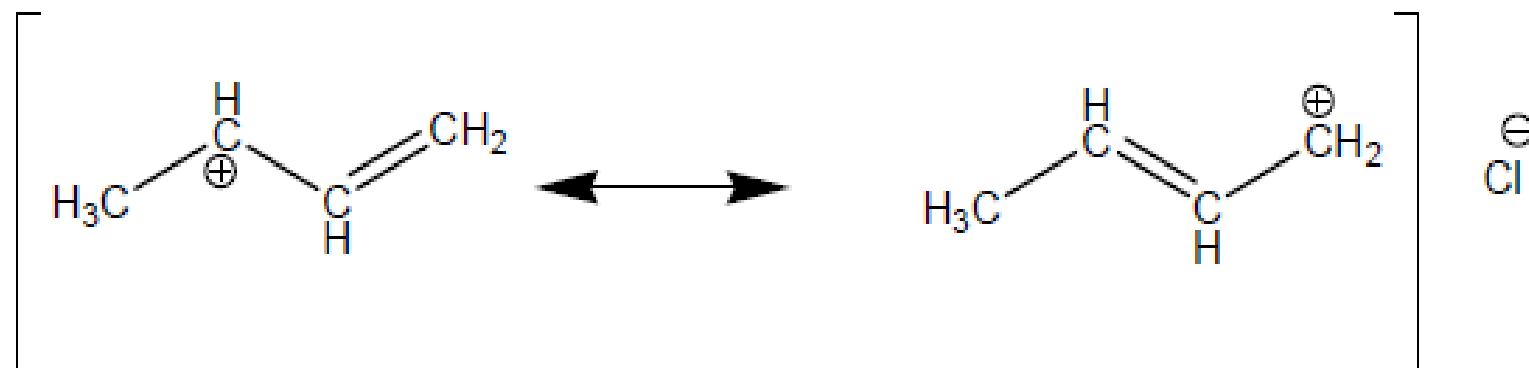
1, 2 hydride shift

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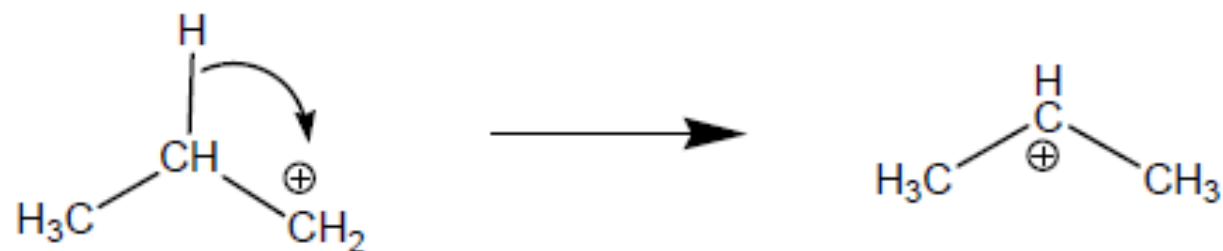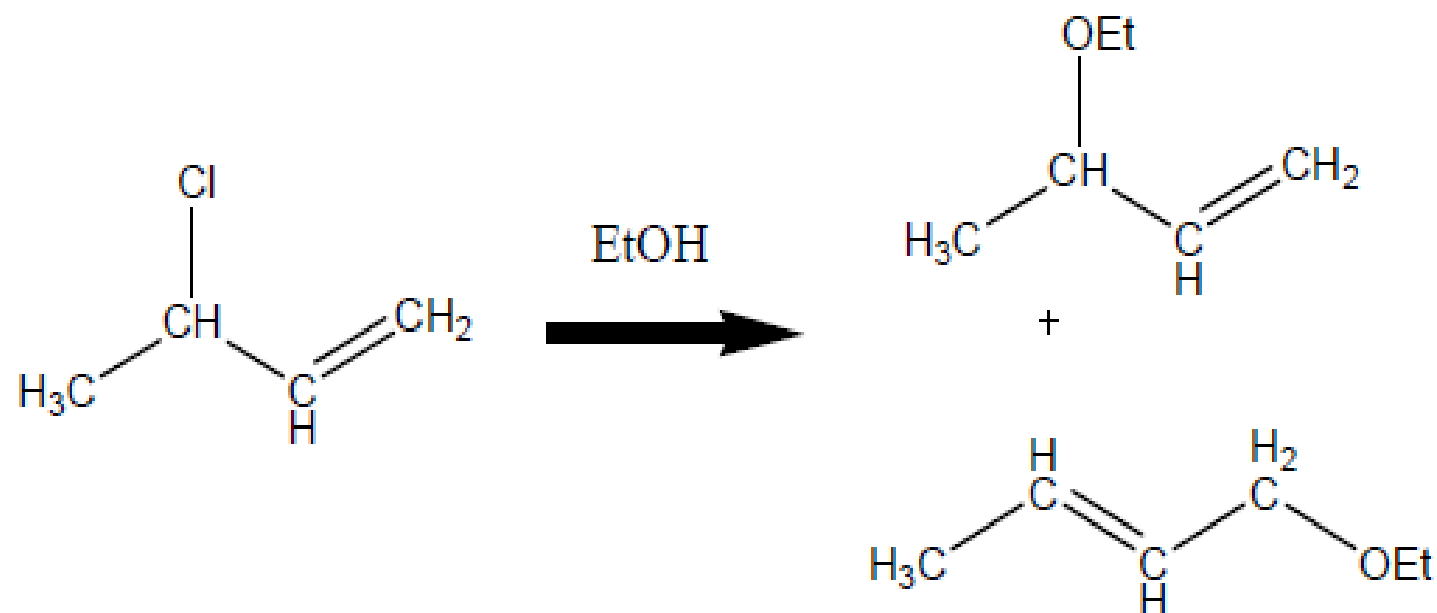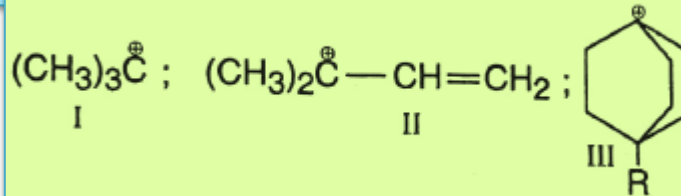
Allylic rearrangements

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

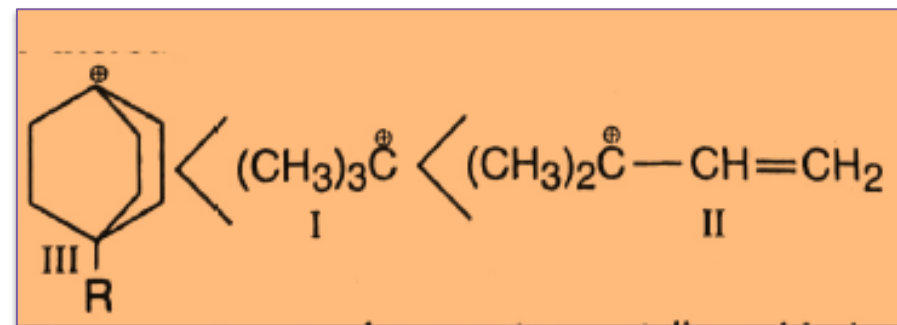**Question:** Arrange the following carbocations in order of their increasing stability and provide reason.

$(CH_3)_3\overset{\oplus}{C}$; $(CH_3)_2\overset{\oplus}{C}-CH=CH_2$;

I

II

III R

- ❖ The carbocation I is stabilized by the +I effects of three -CH$_3$ 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 sp2 bond angle, i.e., 120".

- ❖ 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.
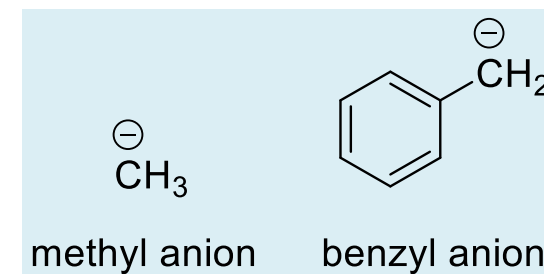
$\left[(CH_3)_2\overset{\oplus}{C}-CH=CH_2 \longleftrightarrow (CH_3)_2C=CH-\overset{\oplus}{C}H_2\right]$

Resonance in II
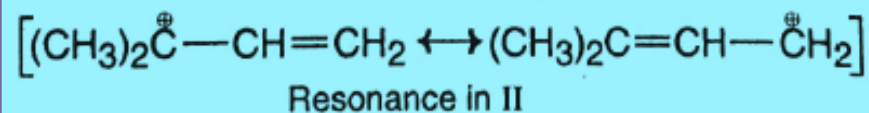
Hence, the order of their increasing stability is:

III R $<$ $(CH_3)_3\overset{\oplus}{C}$ $<$ $(CH_3)_2\overset{\oplus}{C}-CH=CH_2$

I

II

Carbanions

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

methyl anion   benzyl anion

Structure:

❖ The central carbon atom of a carbanion is sp^3 hybridized.

❖ It is surrounded by three bonding pairs and one unshared pair of electrons which occupies an sp^3 orbital. Thus, a carbanion is expected to have the tetrahedral shape.

A carbanion (Pyramidal)
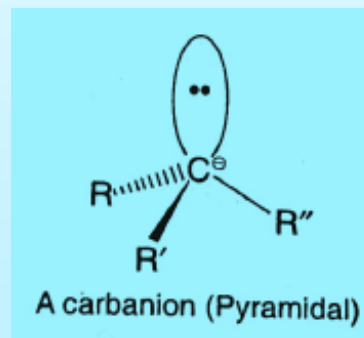
❖ However, the shape is not exactly that of a tetrahedron. It is found to have the pyramidal shape.

❖ 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 sp^3- σ bonds) is slightly less than the normal tetrahedral value of 109.5° 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 sp^2 hybridized and they assume trigonal planar structure.

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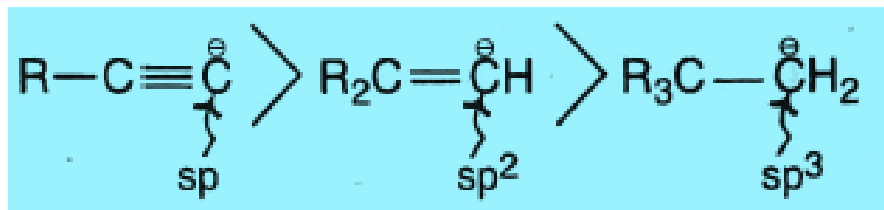## The factors responsible for carbanion stability are -

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^2 hybridized (33.33% s character) carbon atom, which in turn is more stable than a carbanion at an sp^3 hybridized (25% s character) carbon atom. Thus, the order of carbanion stability is:

$$R-C\equiv\overset{\ominus}{\underset{sp}{C}} \quad > \quad R_2C=\overset{\ominus}{\underset{sp^2}{C}H} \quad > \quad R_3C-\overset{\ominus}{\underset{sp^3}{C}H_2}$$

(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.

$$R_3\overset{\oplus}{N}\longleftarrow\overset{\ominus}{C}R_2$$
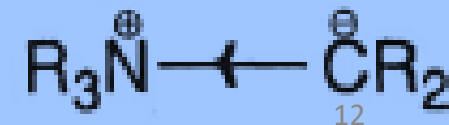
(iii) Conjugation of a non-bonding electron pair with an unsaturated system

❖ **Where there is a double or triple bond α to the carbanion carbon atom, the anion is stabilized by delocalization of its negative charge with the t orbitals of the multiple bond.**

❖ **Thus, allylic and benzylic carbanions and the carbanions attached to the functional groups such as -NO$_2$, -C≡N, >C=O, etc. are stabilized by resonance.**
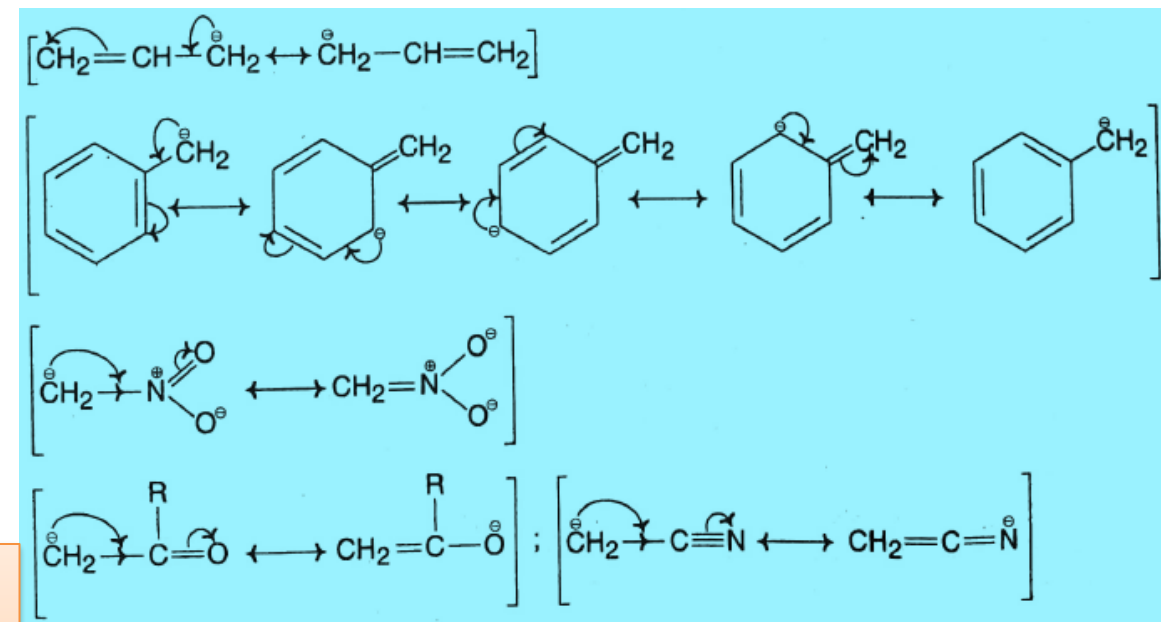
(iv) Constituting an aromatic system

❖ **The unshared pair of a carbanion may be involved in constituting a planar (4n + 2)π electron system where n = 0, 1, 2... etc., i.e., a carbanion may be stabilized by constituting an aromatic system**

❖ **Cyclopentadienyl anion, for example. is unusually stable because it is a 6π electron system and aromatic.**

Cyclopentadienyl anion
[a(4n + 2, n = 1)π electron system : aromatic]
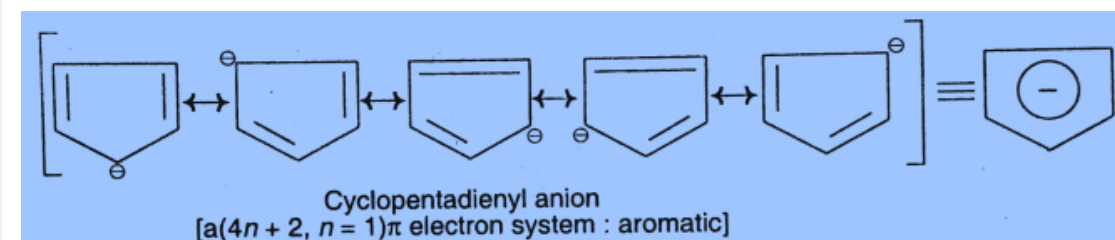
Question: Give the order of stability of the following simple carbanions :

$\overset{\ominus}{CH_3}$ (methyl), $R\overset{\ominus}{CH_2}$ (primary), $R_2\overset{\ominus}{CH}$ (secondary), $R_3\overset{\ominus}{C}$ (tertiary)
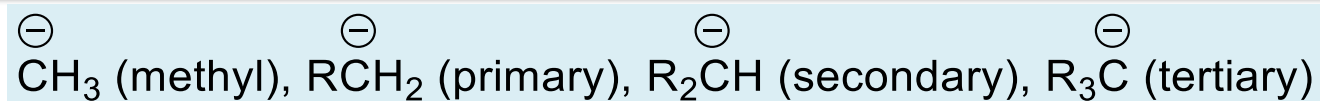
Because of the destabilizing influence of the electron-donating inductive effect of alkyl groups, the order of stability of these simple carbanions is as follows:
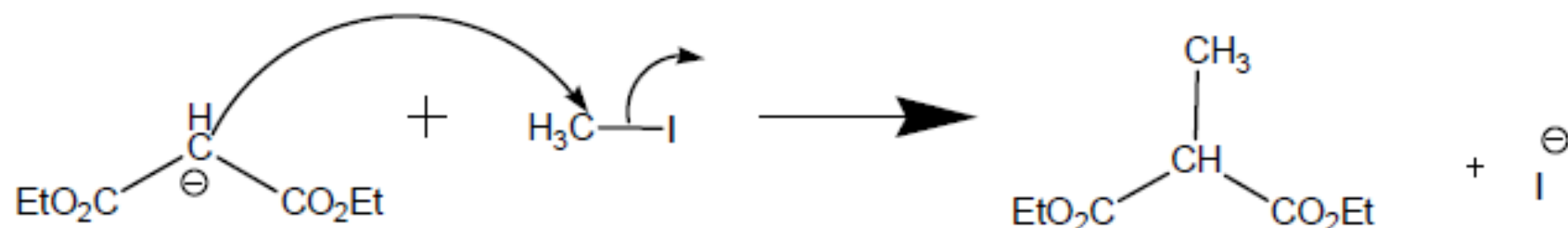
$\overset{\ominus}{CH_3}$ (methyl)> $R\overset{\ominus}{CH_2}$ (primary)> $R_2\overset{\ominus}{CH}$ (secondary)> $R_3\overset{\ominus}{C}$ (tertiary)

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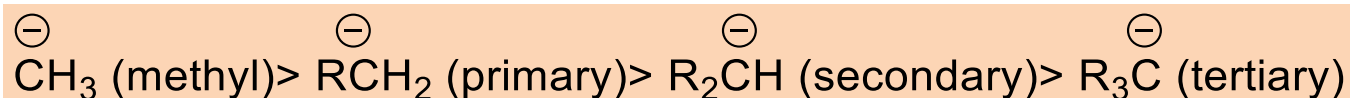
Reaction of Carbanions

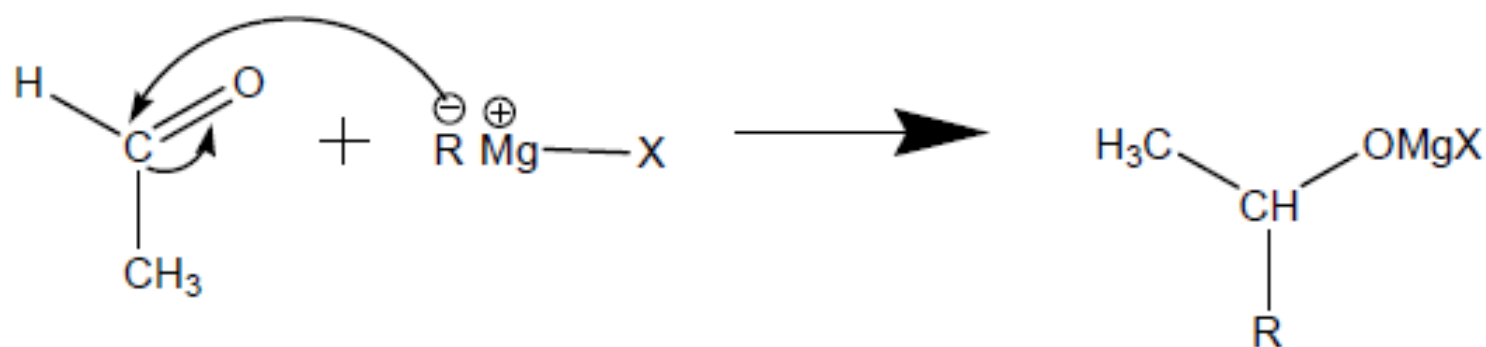They undergo various types of reactions, like

1. Displacement reaction:

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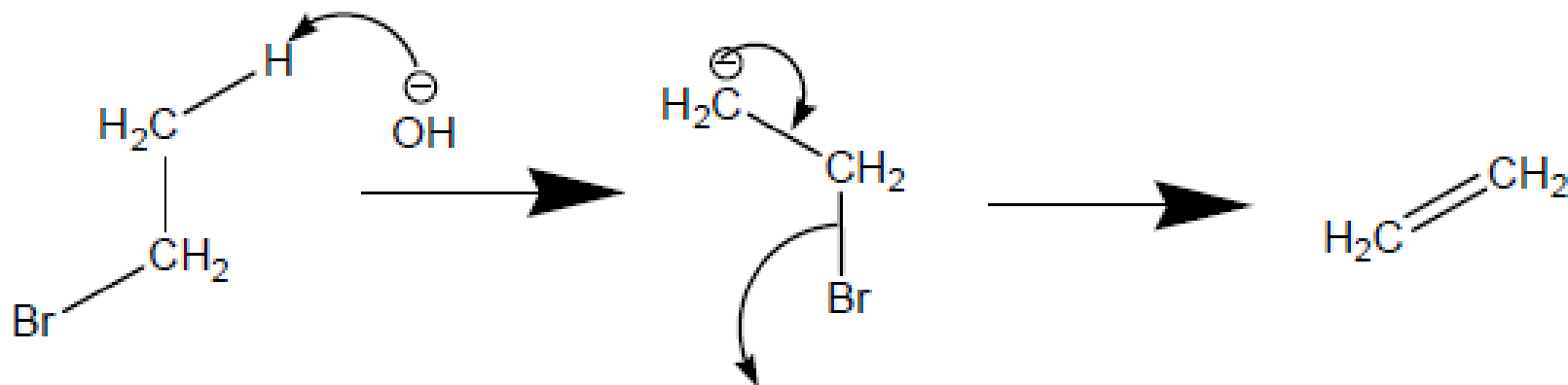

2. Addition to multiple bonds

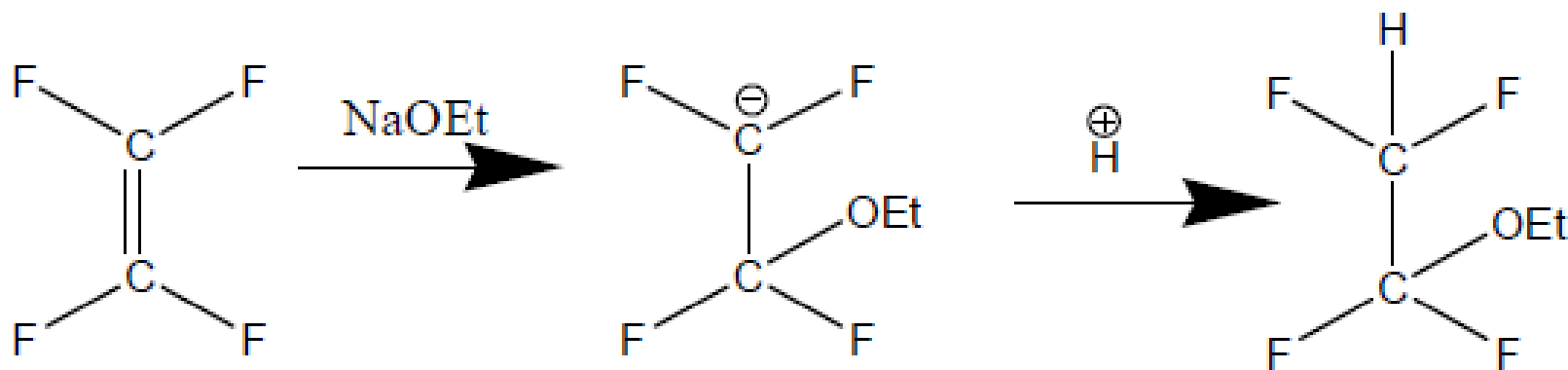This involves addition of Grignard's reagent to carbonyl group.

Reactions of Carbanions

3. Elimination reaction

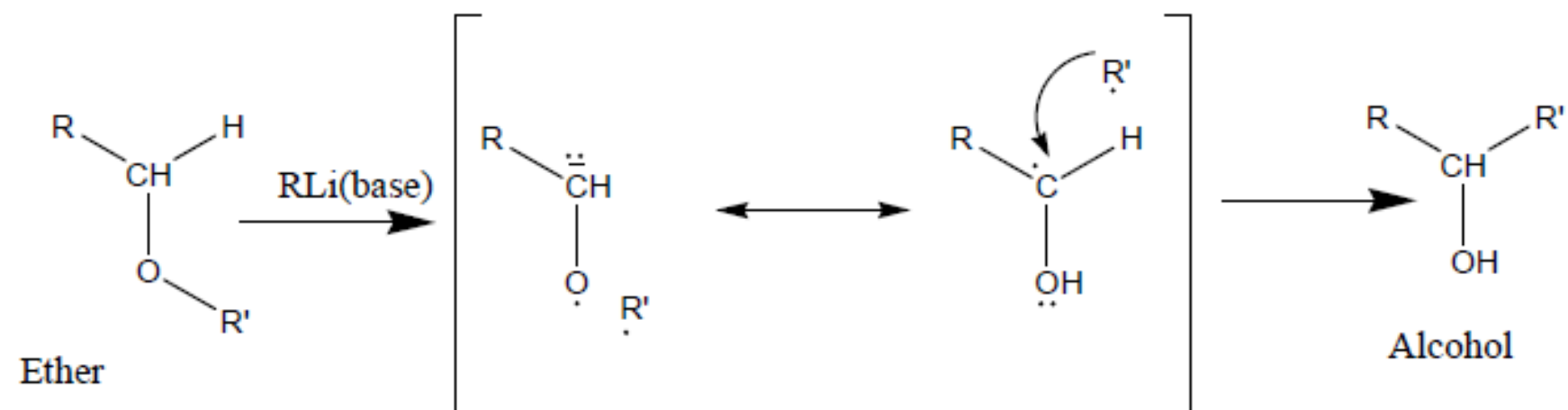Formation of alkene by alkyl halide in presence of alcoholic alkali
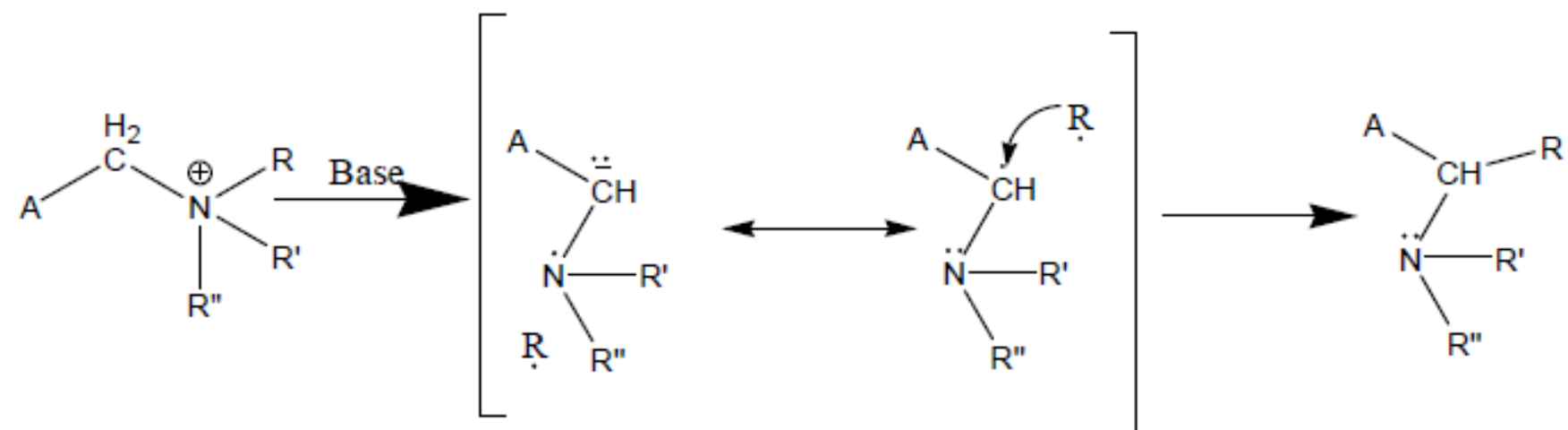

4. Combination with cation

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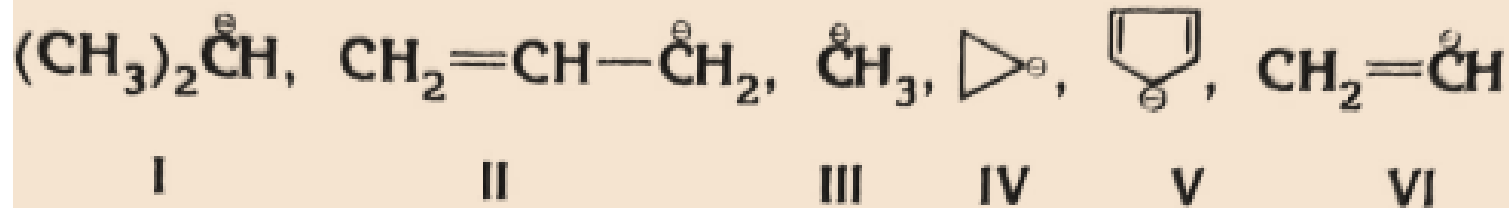This rearrangement involves the formation of carbanion which is stabilized by substitution group R or R'.

Ether → (via RLi(base)) → Alcohol

Stevens Rearrangement
This has quaternary ammonium salt as starting material.

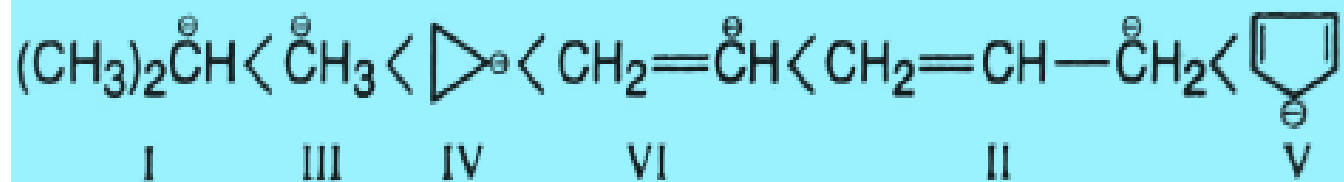The stability of carbanion depends on the group attached. The A represents electron withdrawing group.

$$(CH_3)_2\overset{\ominus}{C}H, \quad CH_2=CH-\overset{\ominus}{C}H_2, \quad \overset{\ominus}{C}H_3, \quad \triangleright^{\ominus}, \quad \underset{\ominus}{\bigcirc\!\!\!\bigtriangledown}, \quad CH_2=\overset{\ominus}{C}H$$

$$\quad\text{I} \qquad\qquad \text{II} \qquad\qquad \text{III} \quad \text{IV} \quad \text{V} \qquad \text{VI}$$

The order of increasing stability of these carbanions is:

$$(CH_3)_2\overset{\ominus}{C}H < \overset{\ominus}{C}H_3 < \triangleright^{\ominus} < CH_2=\overset{\ominus}{C}H < CH_2=CH-\overset{\ominus}{C}H_2 < \underset{\ominus}{\bigcirc\!\!\!\bigtriangledown}$$

$$\quad\text{I} \qquad \text{III} \qquad \text{IV} \qquad \text{VI} \qquad\qquad \text{II} \qquad\qquad \text{V}$$

$$\left[CH_2=CH-\overset{\ominus}{C}H_2 \longleftrightarrow \overset{\ominus}{C}H_2-CH=CH_2 \right]$$
$$\text{II}$$

$$\left[\text{resonance structures} \right] = \underset{\ominus}{\bigcirc}$$
$$\text{V}$$

(a planar 6π electron system : aromatic)
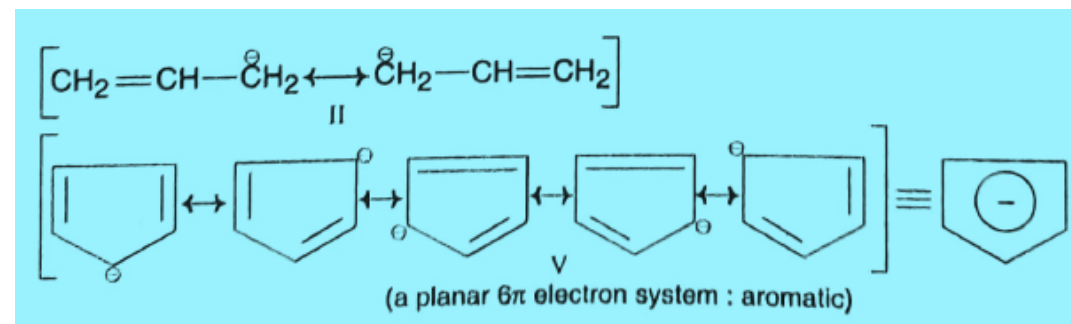
❖ The electron-releasing methyl groups of isopropyl anion (I) intensify the negative charge on carbon and make it less stable than methyl anion (III) where there is no possibility of charge intensification.

❖ The external orbitals (orbitals directed to the outside bonds) in cyclopropane have larger (33%) s character i.e., they are approximately 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 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.

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 ($\dot{C}H_3$), phenyl radical (Ph·), 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 ($CH_3\dot{C}H_2$) is a primary, isopropyl radical ($Me_2\dot{C}H$) is a secondary and tertbutyl radical ($Me_3\dot{C}$) is a tertiary radical.
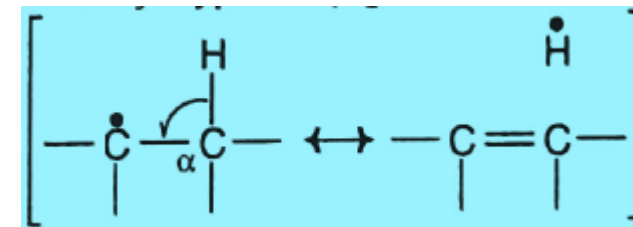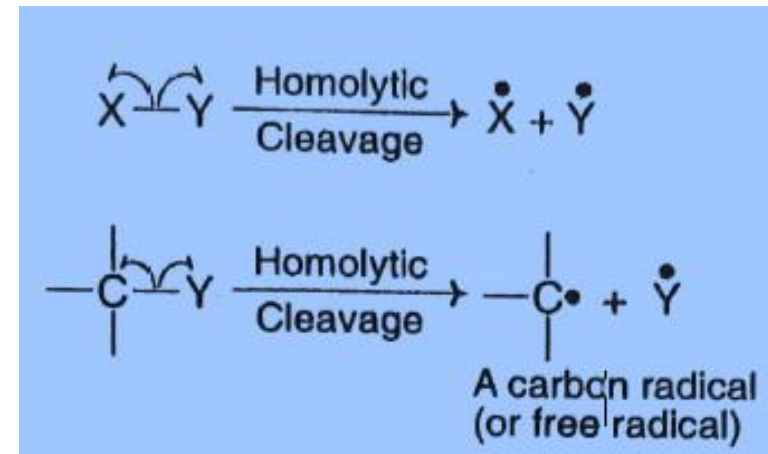
Stability:

(i) Hyperconjugation: Free radicals become stabilized by hyperconjugation involving α-H atoms

❖ As the number of α-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) $R_3\dot{C}$ (tertiary) > $R_2\dot{C}H$ (secondary) > $R\dot{C}H_2$ (primary) > $\dot{C}H_3$ (methyl) (least stable).

❖ For example, tert-butyl radical, $Me_3\dot{C}$ (with nine hyperconjugable α-H atom) is more stable than isopropyl radical, $Me_2\dot{C}H$ (with six hyperconjugable α-H atom) which in turn is more stable than ethyl radical, $Me\dot{C}H_2$ (with only three hyperconjugable α-H atom). The methyl radical, $\dot{C}H_3$ 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 α- to a double bond, effective delocalization of the unpaired electron with the π orbital system with consequent stabilization occurs.**

❖ **Allyl and benzyl radicals, for example, are found to be particularly stable because of resonance.**

Resonance in allyl radical

Resonance in benzyl radical
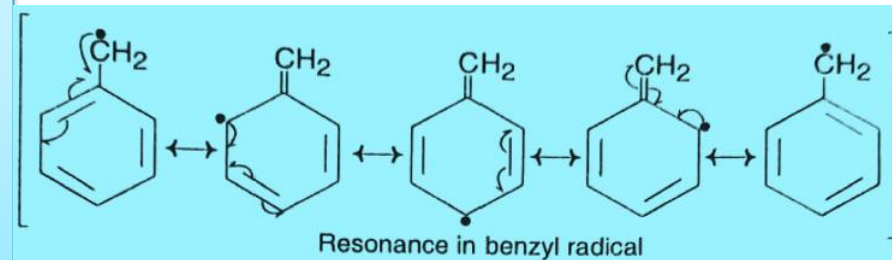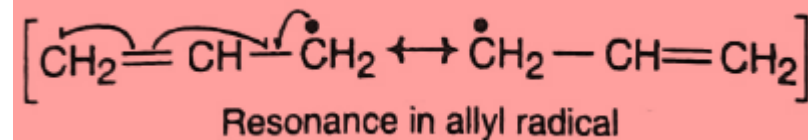
(iii) Steric Strain:

❖ **Another factor responsible for the increased stability of tertiary radicals is steric.**

❖ **There occurs considerable relief of steric strain when a sp^2 hybridized tertiary radical is formed from an 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° to about 120°.**

❖ **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:

$$R\cdot \;+\; R'\cdot \longrightarrow R-R'$$
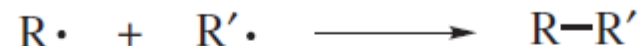
Another termination process is disproportionation:[304]

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

$$2\,CH_3-CH_2^{\cdot} \longrightarrow CH_3-CH_3 \;+\; CH_2{=}CH_2$$

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

$$R\cdot \;+\; R'-H \longrightarrow R-H \;+\; R'\cdot$$

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

$$R\cdot \;+\; \;{\textstyle\diagdown}\!C{=}C\!{\textstyle\diagup} \longrightarrow R-\overset{\textstyle|}{\underset{\textstyle|}{C}}-\overset{\textstyle|}{\underset{\textstyle|}{C}}\cdot$$
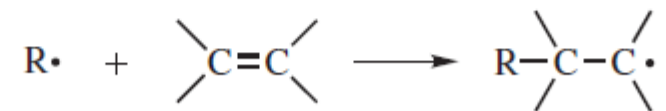
The radical formed here may add to another double bond and so on. This is one of the chief mechanisms for vinyl polymerization.

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

4. *Rearrangement*:
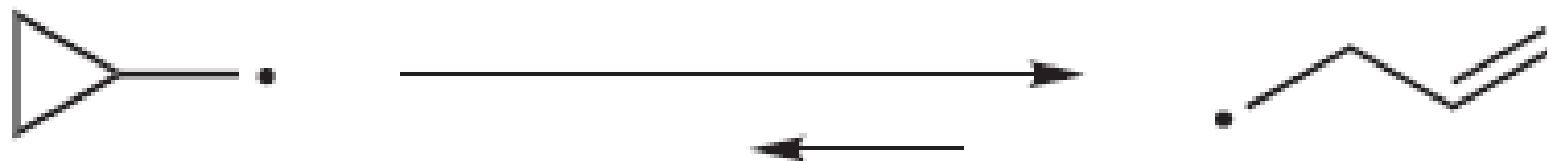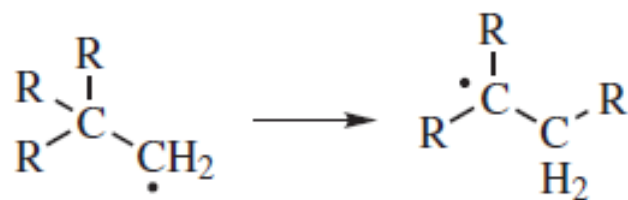
Aromaticity

- Aromaticity was associated with a specific chemical reactivity (substitution reactions in preference to addition).

- Aromaticity is now generally associated with the property of special stability of certain completely conjugated cyclic and planar molecules.

- A major contribution to the stability of aromatic systems comes from the delocalization of electrons (which also imparts diamagnetic ring current).

- Hückel molecular orbital (HMO) theory states that planar monocyclic completely conjugated hydrocarbons will be aromatic when the ring contains $4n+2$ π electrons (Huckel's Rule).

Criteria of Aromaticity

Aromatic compounds are

- **Rule 1: Always cyclic structures**

- **Rule 2: Each element of the ring should have overlapping p-orbitals which are perpendicular to the ring and imparts planarity to the molecule.**
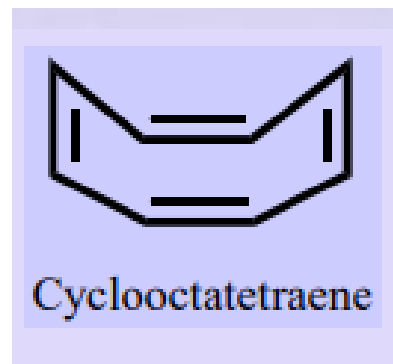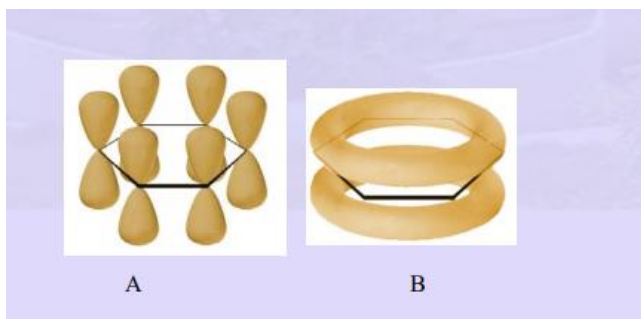
Aromatic ring oriented perpendicular to a strong magnetic field, delocalized π electrons producing a small local magnetic field

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

Results in outside H's resonance at lower field

A   B

Cyclooctatetraene

Circulating π electrons (ring current)

Proton deshielded by induced field

Induced magnetic field because of ring current

Applied magnetic field

© 2004 Thomson/Brooks Cole
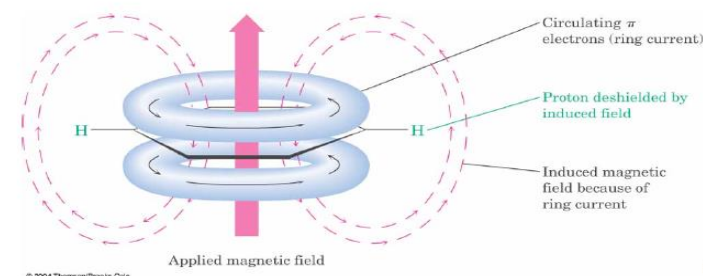
31

- **Rule 3 : Delocalization is possible only if p orbitals can overlap efficiently** which provides additional stability to the system. (delocalization energy or resonance energy). *For example,* cyclooctatetraene despite having alternate single and double bonds, do not show the extended overlap of p-orbitals and delocalization as it is a tub shaped.

- **Rule 4: All the aromatic compounds obey the Huckel's rule of (4n+2) π electrons**.

Aromaticity α Resonance energy (R.E) α Stability α $\dfrac{1}{\text{Potential Energy (P.E)}}$

Aromatic compounds: Molecules which obey all the 4 rules.

Non-aromatic compounds: Molecules which follow these 4 rules partially i.e. non-cyclic, non-planar, or do not hold a comprehensive conjugated π system inside the ring.

Anti-aromatic compounds: Exclusively do not follow Huckel's rule.

$$4n+2 \ (n = 0)= 2 \ \pi \ \text{electrons}$$
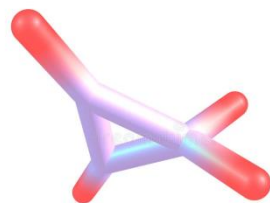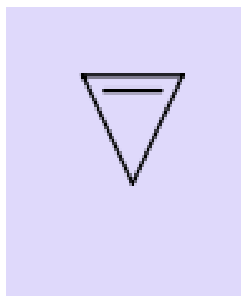
Cyclic
Non Planar
Not Conjugated
Follow Huckel's rule
Non Aromatic

Cyclopropenyl cation
2 electrons (4n+2; n = 0); the delocalization of 2 electrons is possible through the empty p orbital;
Aromatic

Cyclic
Planar
Conjugated
Follow Huckel's rule
Aromatic
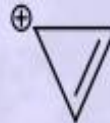
Resonance contributors in cyclopropenyl cation
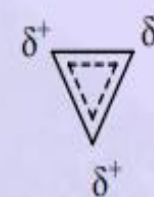
Resonance Hybrid

Stability Order: **Aromatic > Nonaromatic > Antiaromatic**

*4n+2 (n = 1)= 6 π electrons
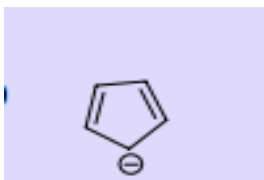
Cyclopentadienyl anion
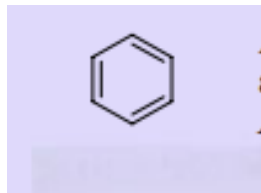
Benzene [6]-Annulene.

Cyclic
Planar
Conjugated
Follow Huckel's rule
Aromatic

Cyclopentadienyl Anion Resonance Contributors

6 pi electrons

sp²

Tropylium ion
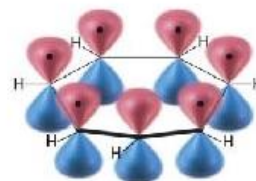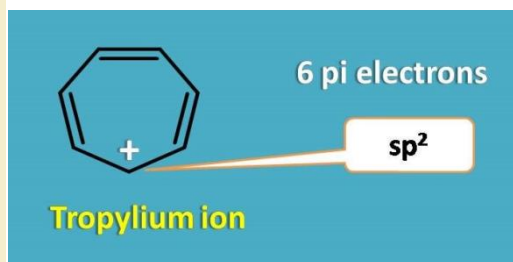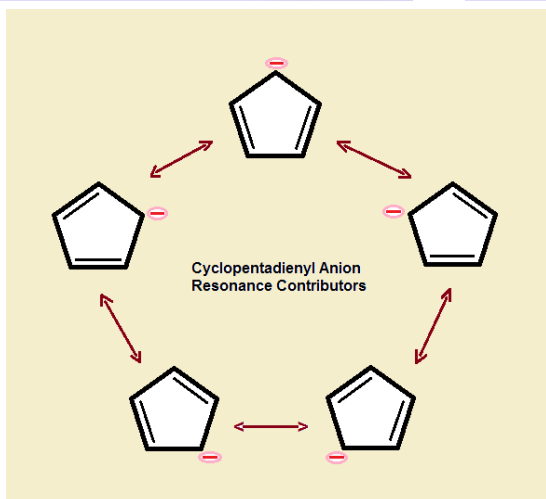
Cycloheptatrienyl cation
six π electrons
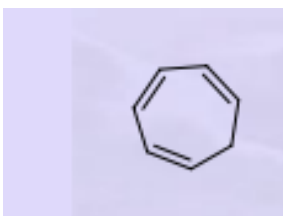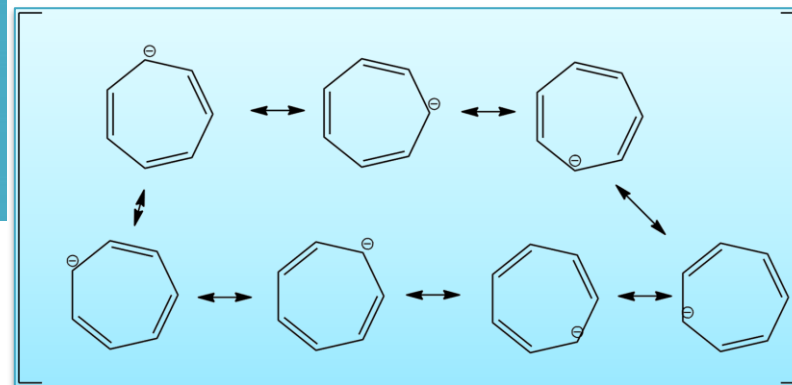
Cycloheptatriene

Cyclic
Non Planar
Non Conjugated
Follow Huckel's rule
Non Aromatic
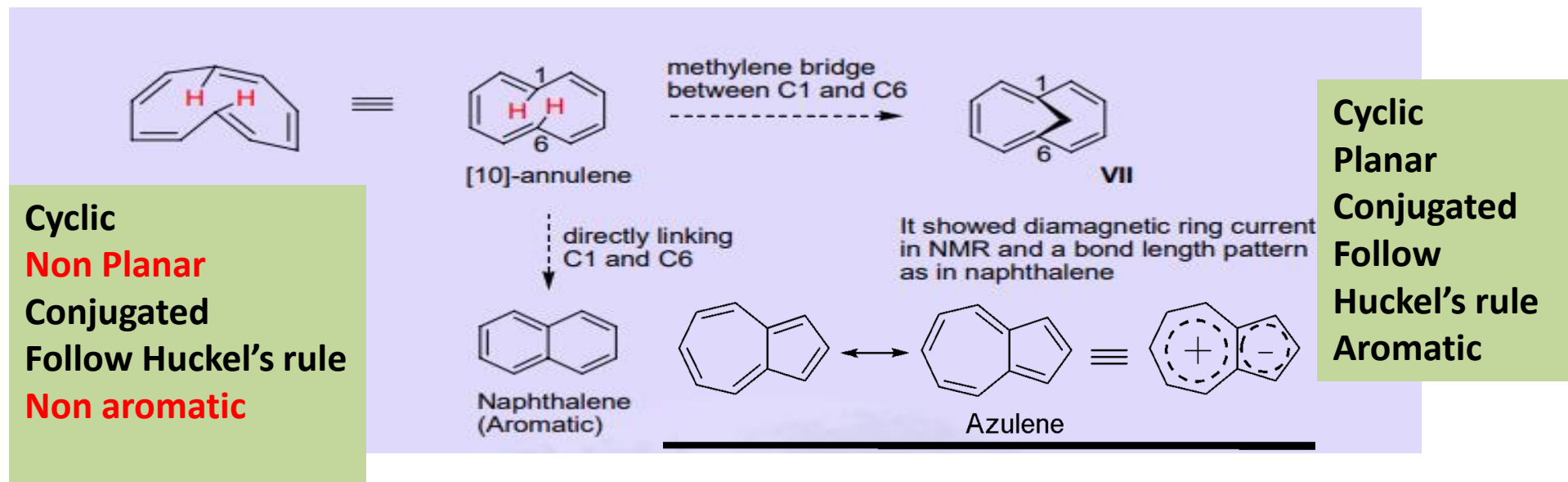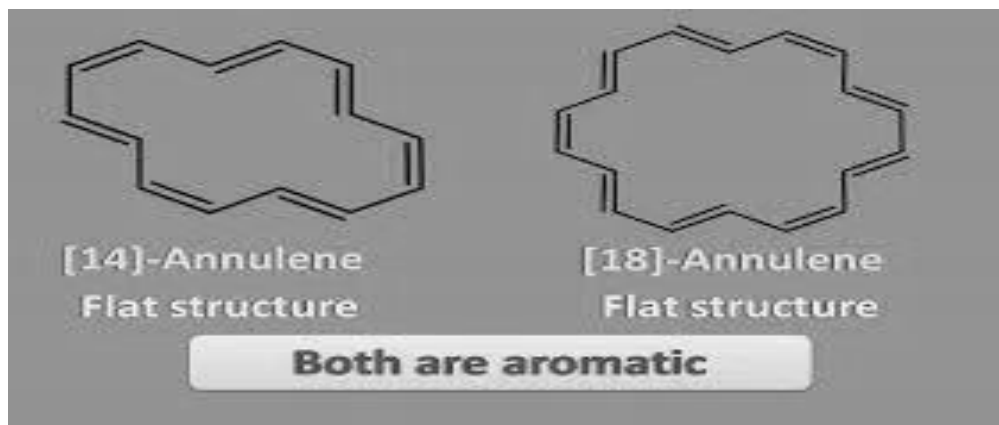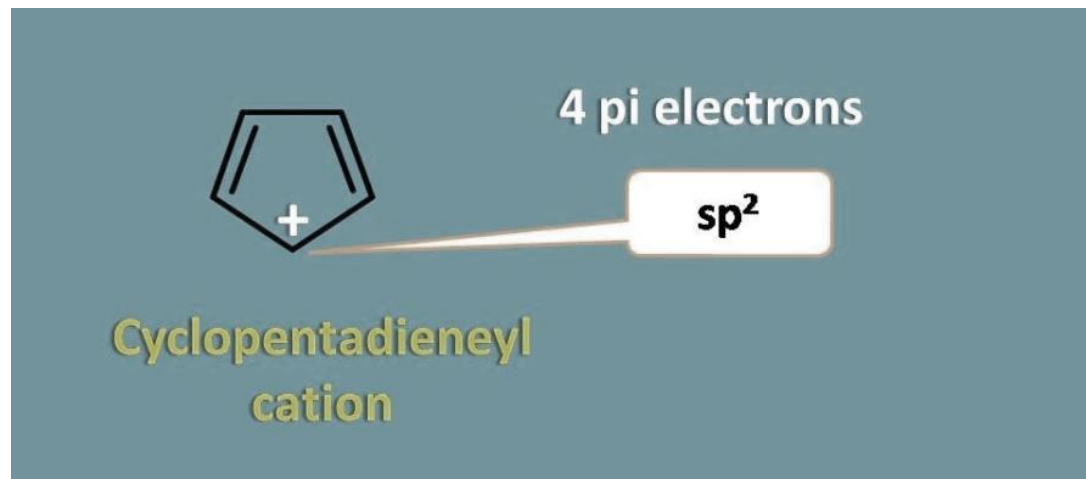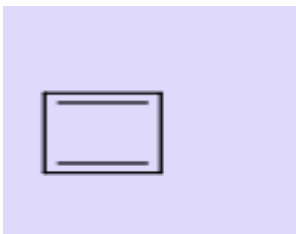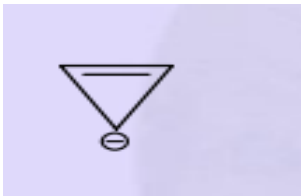
Cyclic
Non Planar
Conjugated
Follow Huckel's rule
Non aromatic

[10]-annulene

methylene bridge
between C1 and C6

VII

It showed diamagnetic ring current
in NMR and a bond length pattern
as in naphthalene

directly linking
C1 and C6

Naphthalene
(Aromatic)

Azulene

Cyclic
Planar
Conjugated
Follow
Huckel's rule
Aromatic

[14]-Annulene
Flat structure

[18]-Annulene
Flat structure

Both are aromatic

Cyclic
Planar
Conjugated
Follow Huckel's rule
Aromatic

4n (n=1) = 4 π electrons

4 pi electrons

sp²

Cyclopentadieneyl cation

-Cyclic
-Planar
-Conjugated
- Do not Follow Huckel's rule
➡ **Antiaromatic**

4 pi electrons

sp³

Cyclopentadiene
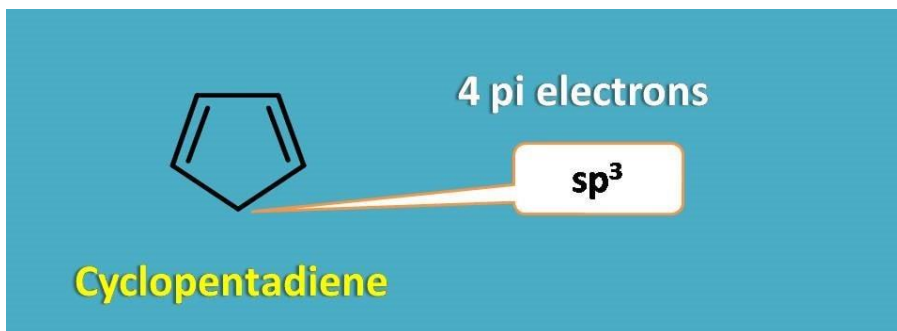
Cyclic
Non Planar
Non Conjugated
Do not Follow Huckel's rule
Non aromatic

Cyclooctatetraene
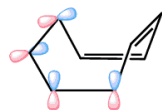
p orbitals of adjacent double bonds **cannot overlap.**
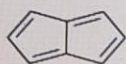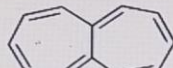
pentalene   heptalene

Antiaromatic

Cyclooctatetraene is more flexible than cyclobutadiene and it assumes a non-planar 'tub shaped' conformation that avoids most of the overlapping between p-orbitals.

Cyclic
Non Planar
Conjugated
Do not Follow Huckel's rule nonaromatic due to non planarity

*4n (n = 3,4)= 12 and16 π electrons

[12]-annulene

[12]-annulene (4n, n = 3) is antiaromatic and hence is not stable above -50°C. Its dianion (4n+2, n = 3) is however stable up to 30°C and is aromatic (Figure 10).

Antiaromatic
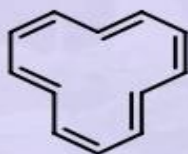
[12]-annulene
Not stable above -50°C

Cyclic
Planar
Conjugated
Do not Follow Huckel's rule
Antiaromatic

H H
H H
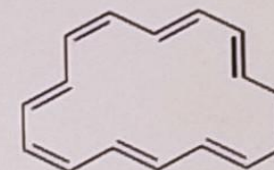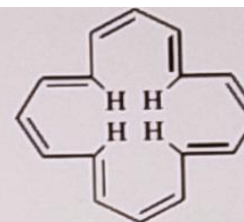
[16] Annulene

Cyclic
Non Planar
Conjugated
Do not Follow Huckel's rule
non aromatic
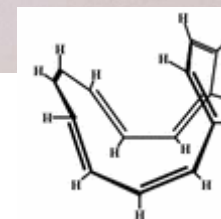
Aromatic	**Anti-aromatic**	**Non-aromatic**
Aromatic compounds are organic compounds composed of carbon and hydrogen atoms arranged in ring structures with delocalized pi electrons	Antiaromatic compounds are molecules that are cyclic, planar and completely conjugated but are consist of 4n pi electrons	Nonaromatic compounds are molecules that lack one or more of the requirements to be aromatic: being planar and cyclic structure, completely conjugated system
Stable	Highly unstable	Unstable
Have delocalized pi electron system and $4n + 2$ pi electrons	Have delocalized pi electron system and $4n$ pi electrons	May or may not have delocalized pi electron system
Have $4n + 2$ pi electrons	Have $4n$ pi electrons	Number of pi electrons is not applicable
Less reactive	Highly reactive	Less reactive

Characteristics of 3-Membered Ring Heterocyclic Compounds

Some Elusive Three-Membered Rings

Oxirene
(never observed)

1H-Azirene
(never observed)

Thiirene
(never observed)

Cyclic,
Conjugated sp^2 hybridised carbons
4 π elections (4n rule)
Anti-aromatic

AZIRINE
(2H-AZIRINE)

OXIRANE
(ETHYLENE OXIDE)

THIIRANE
(ETHYLENE SULFIDE)

AZIRIDINE
(ETHYLENE IMINE)

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

Aromaticity of 4-Membered Ring Heterocyclic Compounds
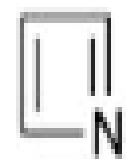
azete
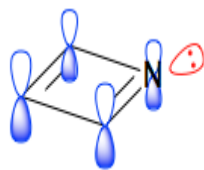
Cyclic
Conjugated sp² hybridised carbons
4 π elections (4n rule)
Anti-aromatic

- While counting the number of π-electrons, first count the electrons which are delocalized over the ring.
- In this case, nitrogen lone pair is localised in an sp² orbital (red) which is orthogonal to the π system (blue) and does not participate in resonance.
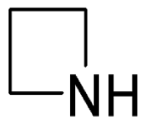
AZITIDINE   2H-OXETEN   OXETANE   2H-THIETEN   THIETANE
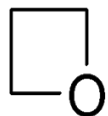
- **Non-aromatic**
- **Cyclic**
- **no conjugated sp² hybridised carbons**

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Structure and Aromaticity of Pyrrole
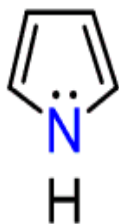
6 e⁻ - **Aromatic**

4π e⁻ - double bonds

2 e⁻ - lone pair

p orbital

sp^2 orbital

OH
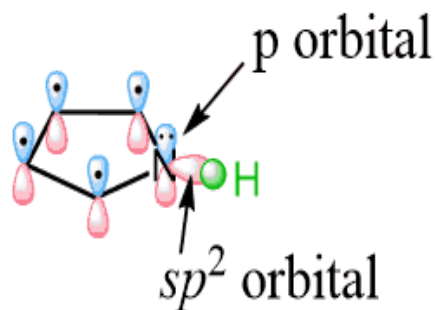
Protonated Pyrrole

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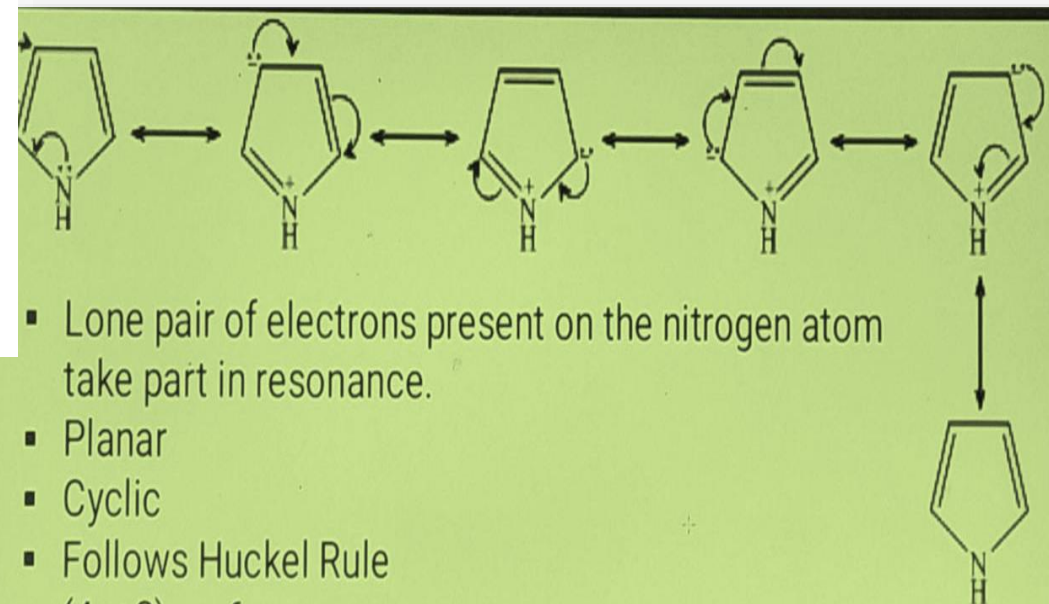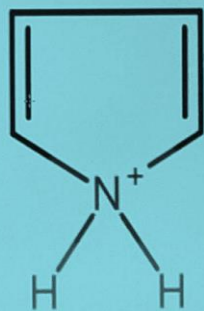
- Lone pair of electrons present on the nitrogen atom take part in resonance.
- Planar
- Cyclic
- Follows Huckel Rule
- $(4n+2)\pi = 6$
- n=1
- It is Aromatic.

Six Membered Heterocycle: Pyridine

pyridine

H 7.5
H 7.1
H 8.5

sp^2 orbital
not part of π e$^-$
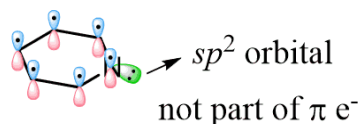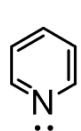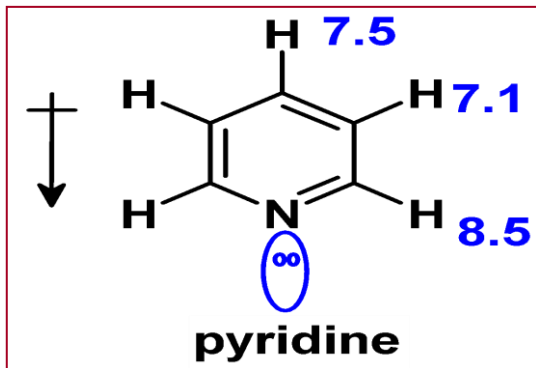
- Pyridine replaces the CH of benzene by an N atom with a lone pair of electrons and hybridization is sp^2 with similar resonance stabilization energy.
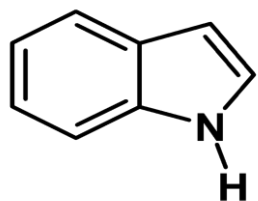- Lone pair of electrons does not involve in aromaticity.

- Pyridine is a weak base.
- Pyridine is π-electron deficient.
- Electrophilic aromatic substitution is difficult.
- Nucleophilic aromatic substitution is easy.

Resonance energy of some of the aromatic systems

21 kcal/mol   29 kcal/mol   16 kcal/mol   36 kcal/mol   32 kcal/mol

Fused Heterocyclic Compounds

Indole

- Aromatic due to 10 π-electrons
- Benzene part is non-reactive
- *Electrophilic aromatic substitution occurs at the 3-position.*
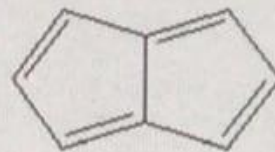
Model Questions

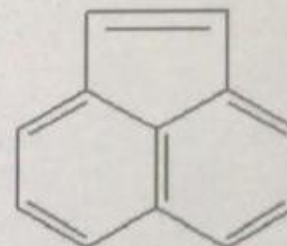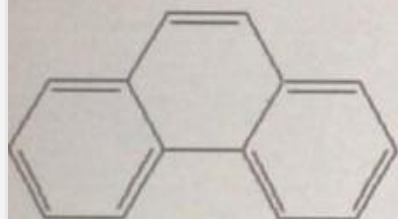1. Determine if the following compounds are AROMATIC, ANTIAROMATIC, or NOT AROMATIC

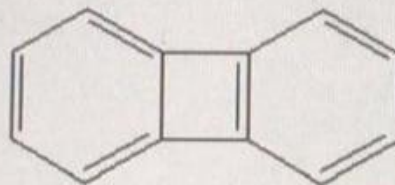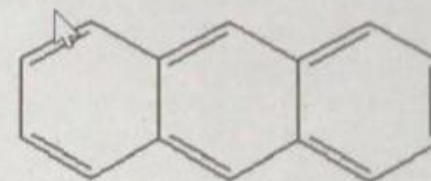

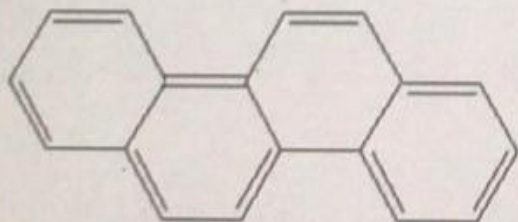Cyclobuta-1,3-diene
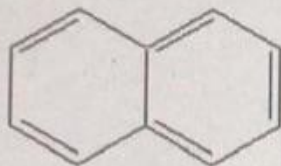
Naphthalene

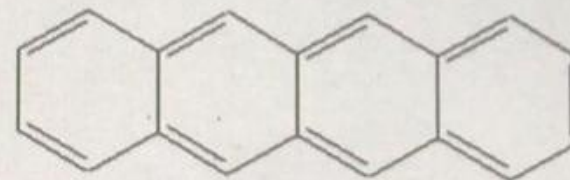Pentalene

Acenaphthylene

Phenanthrene

Biphenylene
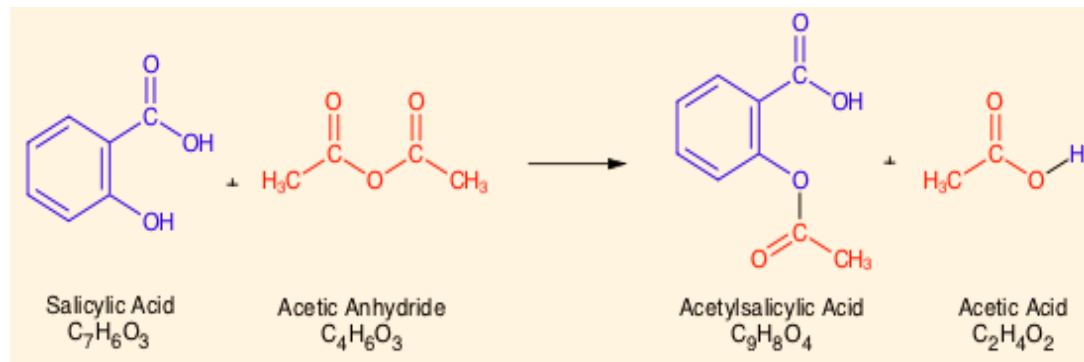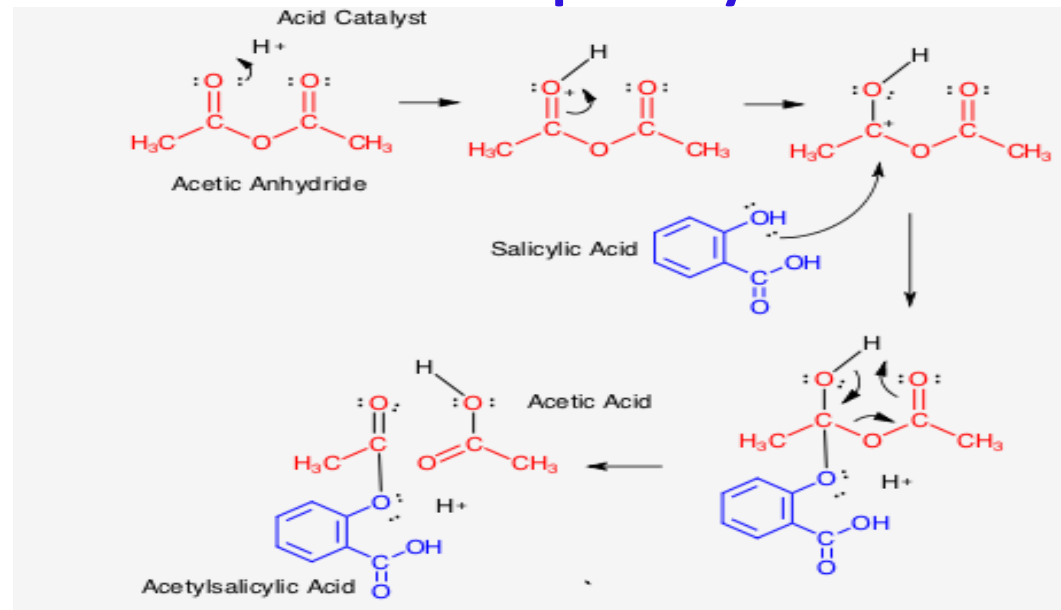
Anthracene

Chrysene

Tetracene

Synthetic Route of Aspirin

In the year of 1897, Bayer laboratory gave acetyl salicylic acid the name of Aspirin. Aspirin is one of the safest and most effective medicines and is extensively used medications globally, which is displayed on the WHO's List of Essential Medicines.

Mechanism of Aspirin Synthesis

- Synthesis of aspirin is an esterification reaction of salicylic acid and acetic anhydride with an acid catalyst (sulfuric or phosphoric acid).


Salicylic Acid
$C_7H_6O_3$

Acetic Anhydride
$C_4H_6O_3$

Acetylsalicylic Acid
$C_9H_8O_4$

Acetic Acid
$C_2H_4O_2$

Acid Catalyst

Acetic Anhydride

Salicylic Acid

Acetic Acid

Acetylsalicylic Acid

Uses of Aspirin/Acetylsalicylic acid-($C_9H_8O_4$)

❖ **Used as an inhibitor of cyclooxygenase, in the treatment of different types of headaches and to prevent venous and arterial thrombosis.**

❖ **Useful as an anti-inflammatory agent for long-term as well as acute inflammation; gained a reputation for treating cardiovascular and cancer.**

❖ **It is a first-line treatment for the fever and joint-pain symptoms of acute rheumatic fever and Kawasaki disease.**

❖ **Similarly, used as an intermediate and raw material in producing other medicines or chemical compounds like 4-hydroxycoumarin.**

Synthetic Route of Paracetamol
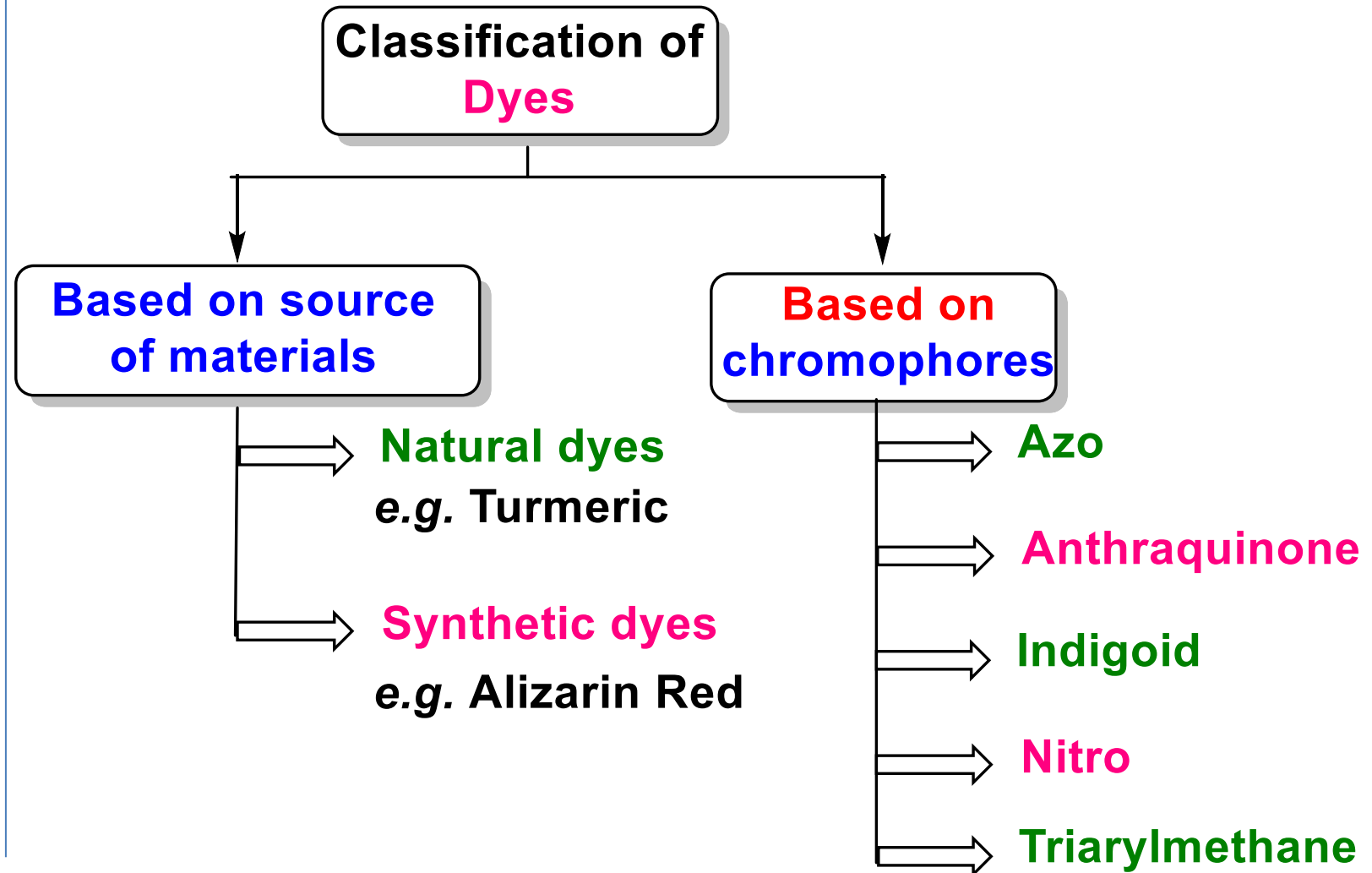

Reaction Mechanism
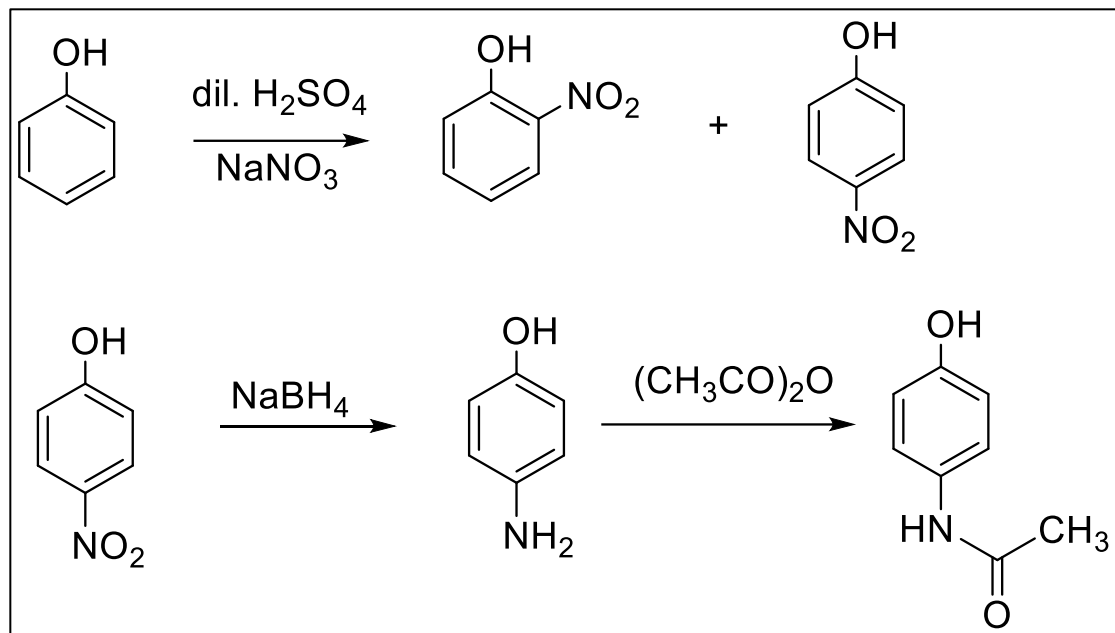
Uses of Paracetamol

❖ **Antipyretic drugs** are used to reduce fever. Paracetamol is a safest antipyretic drug for children and pregnant women.

❖ An **analgesic** is a pain-reducing or relieving remedy. Paracetamol is an analgesic drug without any significant anti-inflammatory effects.

❖ It is available combined with other painkillers and anti-sickness medicines.

❖ It is 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.

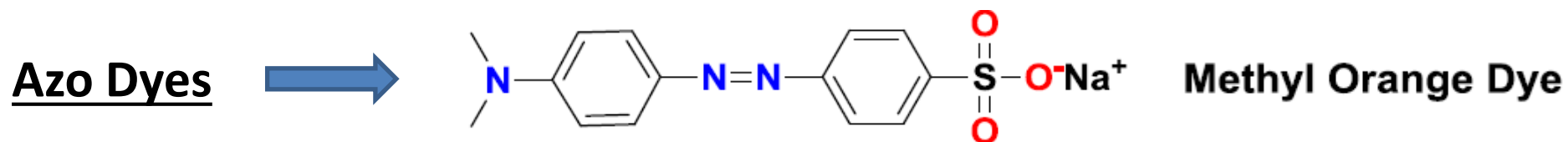❖ **Paracetamol** is readily absorbed from the gastrointestinal tract.
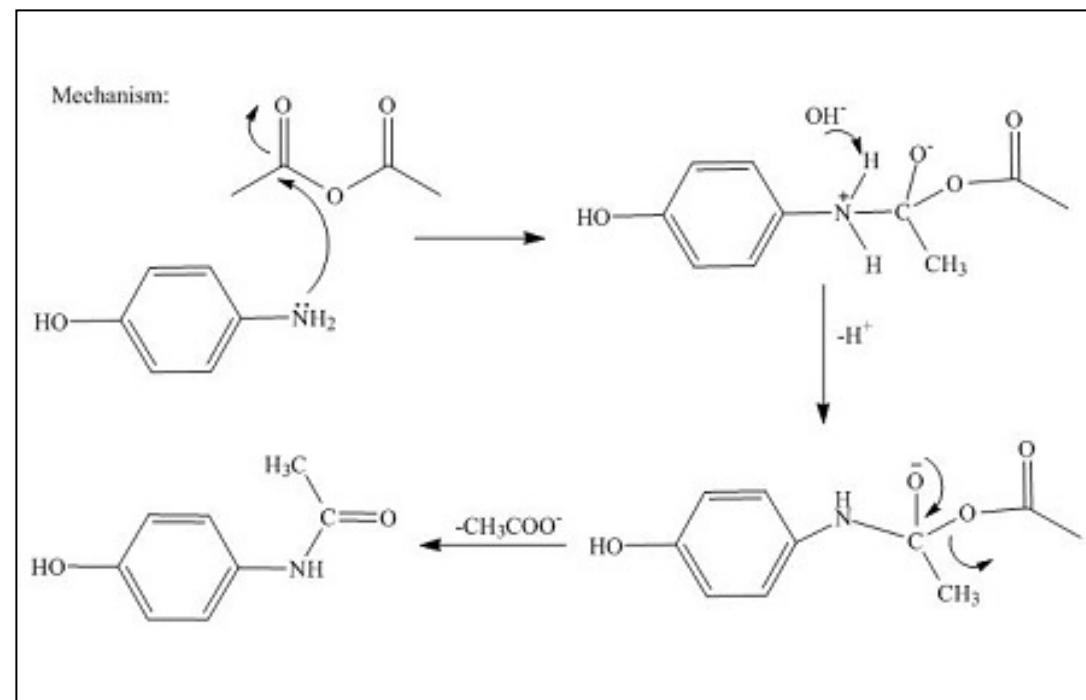
Dyes

❖ **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.**

❖ **Based on the solubility in water and/or an solvent, organic colorants fall into two classes, viz. dyes and pigments.**
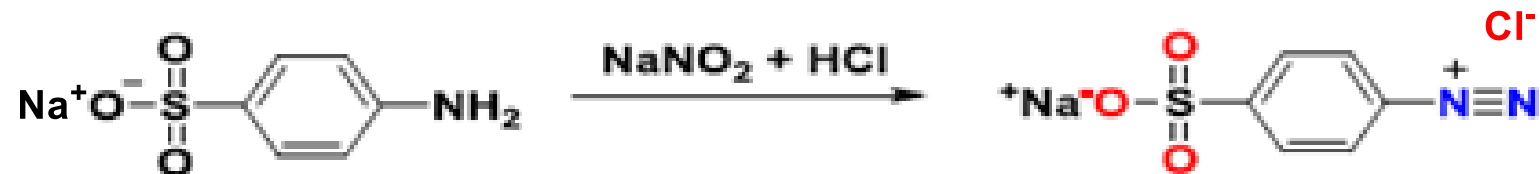
Classification of Dyes

Based on source of materials

⟹ Natural dyes
e.g. Turmeric

⟹ Synthetic dyes
e.g. Alizarin Red

Based on chromophores

⟹ Azo

⟹ Anthraquinone

⟹ Indigoid

⟹ Nitro

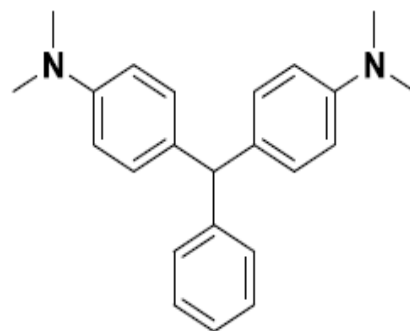⟹ Triarylmethane

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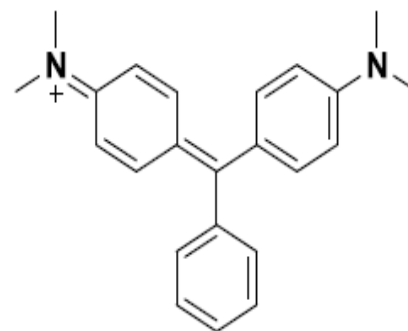# Preparation of Methyl Orange

Azo Dyes ⟹ **Methyl Orange Dye**

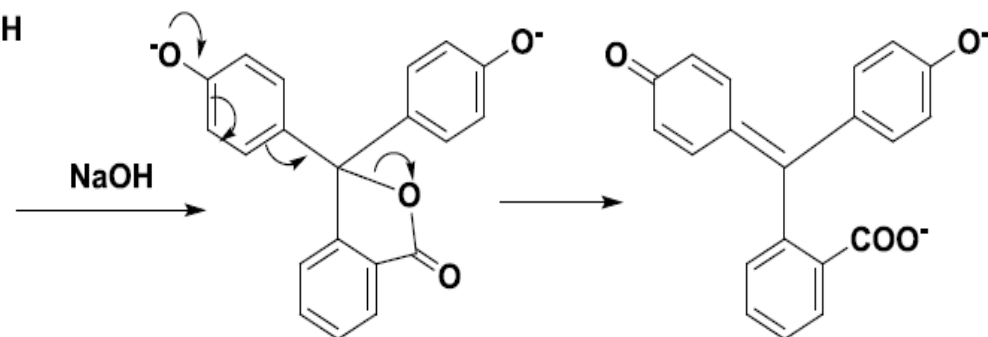**Triphenylmethane Dyes** → Leucomalachite Green, Malachite Green Dye, Rosaniline Dye (Fuchsine Dye)
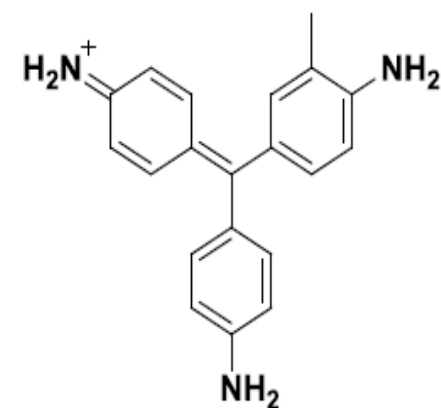
**Phthalein dyes** → Phenolphthalein Dye
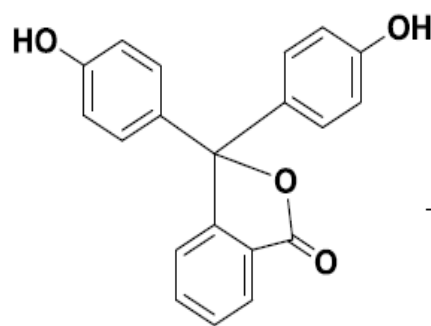
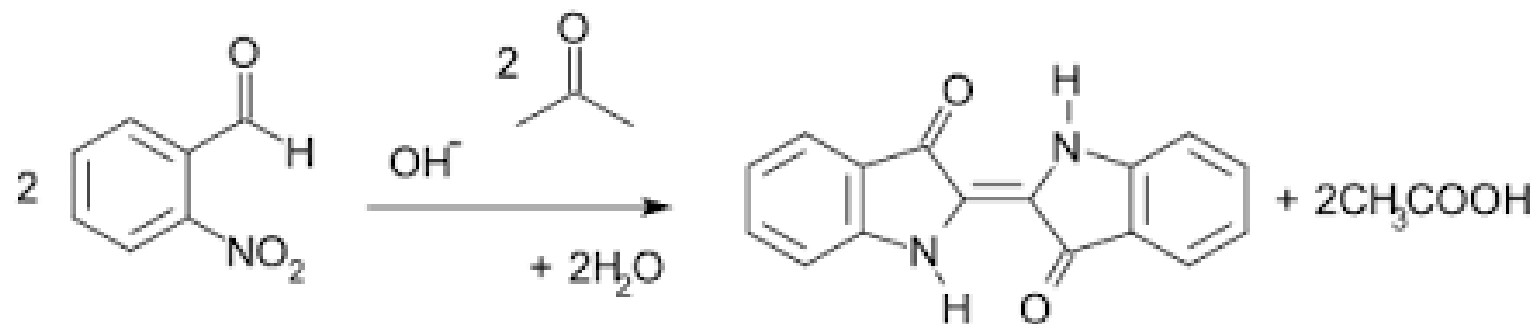Colorless (in acidic medium) —NaOH→ Pink (in basic medium)

INDIGOTIN DYE

❖ Indigo dye is widely 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.

❖ To overcome the solubility 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..

❖ Once the dye is applied to the fabrics, the dye will not be leached out even after several washings due to its insolubility in water.

indigo   leucoindigo (indigo white)
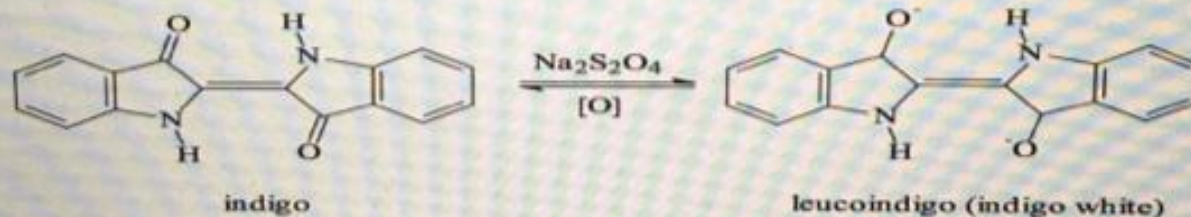
Figure 2: The reaction showing the conversion of the insoluble blue indigo dye to the clear yellow, water soluble leucoindigo or indigo white.

Synthesis:

Mechanism: