

Module-3

Organic Intermediates and Reaction Transformations

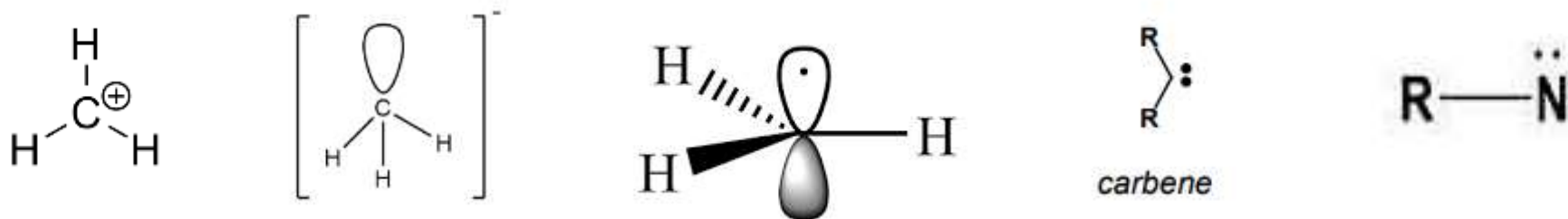
Organic intermediates - stability and structure of carbocations, carbanions and radicals; (2 h)

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

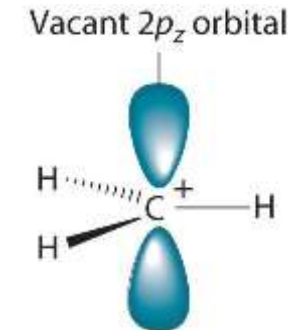
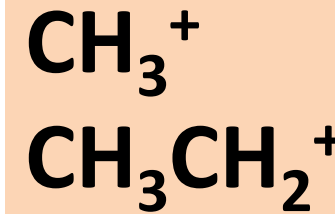
- Most of the organic reactions occur via a specific chemical species (intermediate) which is extremely reactive and short – lived (10^{-6} second to a few seconds). Isolation of such species is a difficult task.
- These reactive intermediates can have the valency of carbon atoms either 2 or 3.
- Examples 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.

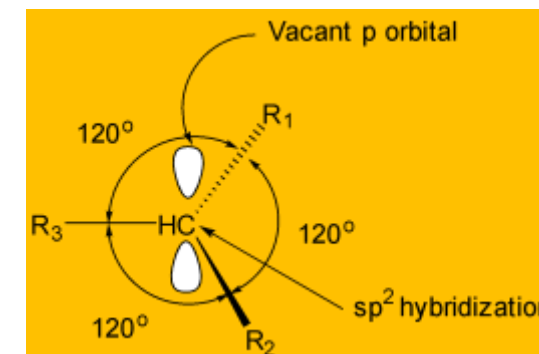
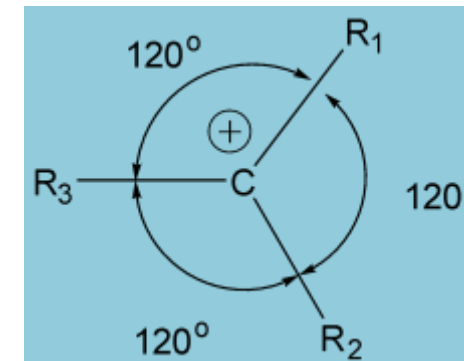
Carbocations

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



Structure:

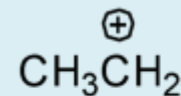
- ❖ The **carbon atom with a positive charge** is referred as **carbocation** (or carbonium ion) and it belongs to **sp^2 hybridization**.
- ❖ The three **sp^2 hybridized orbitals** are utilized in making bonds to three substituents.
- ❖ In order to minimize repulsion between the bonding electron pairs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



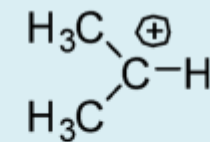
- ❖ Carbocations are extremely reactive species due to their ability to complete the octet of the electron-deficient carbon.

Classification of Carbocations

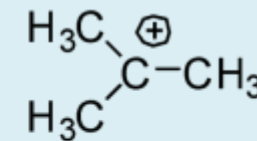
Carbocations are classified as primary (1°), secondary (2°), and tertiary (3°) on the basis of **number of carbon atoms (one, two, or three) directly attached to positively charged carbon**. For example:



ethyl cation is a primary carbocation



isopropyl cation is a secondary carbocation



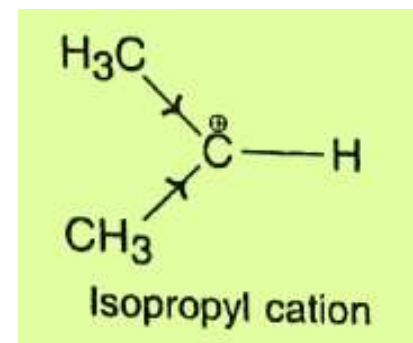
t-butyl cation is a tertiary carbocation

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.

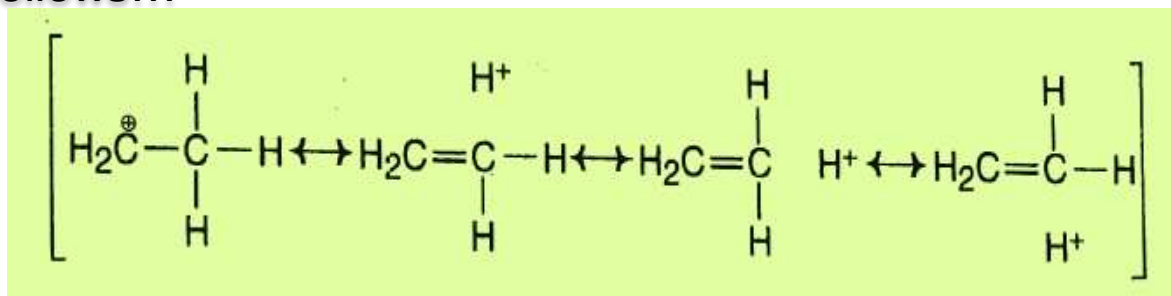
(i) Inductive effect

- ❖ 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.**

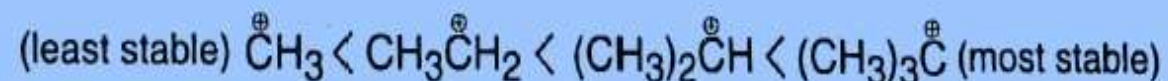


(ii) Hyperconjugative effect

- ❖ An alkyl group may reduce the positive charge of a carbocation by hyperconjugative electron-release (no bond resonance).
- ❖ The charge becomes dispersed over the α -hydrogens and consequently, the system becomes stabilized.
- ❖ Hyperconjugation in ethyl cation, for example, occurs as follows...

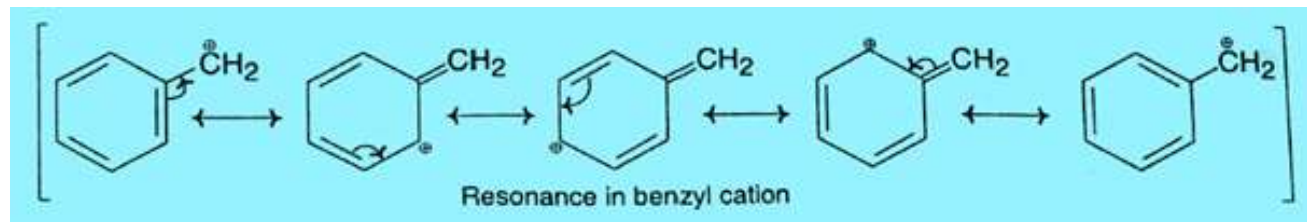
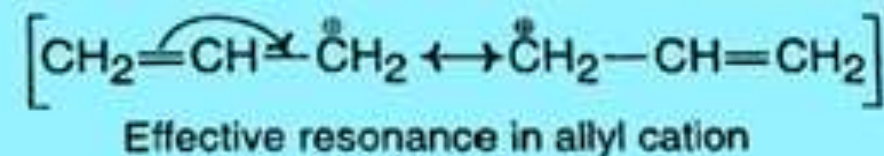


❖ As the number of α -hydrogens increases, i.e., the number of hyperconjugative forms increases, the stability of carbocations increases. Hence, the order of stabilities of methyl substituted carbocations is ...



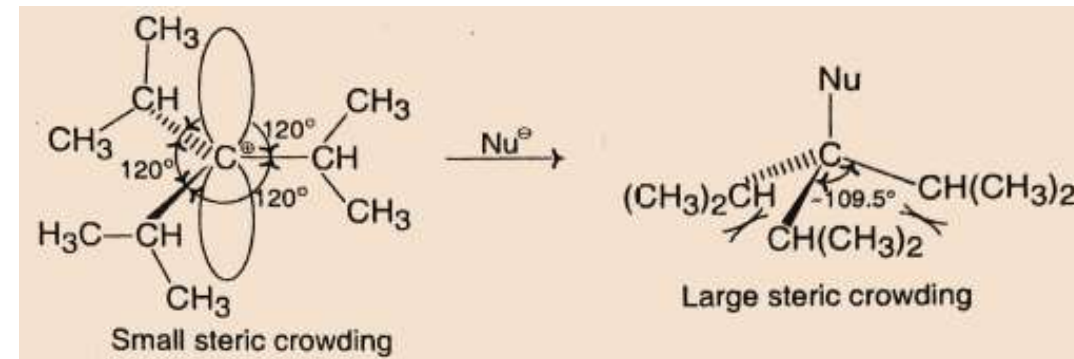
(iii) Resonance effect

- ❖ 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**.



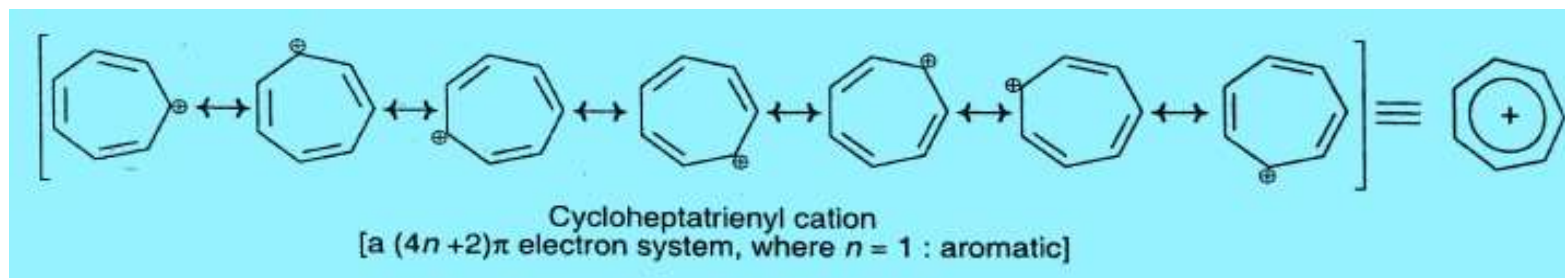
(iv) Steric effect

- ❖ 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.



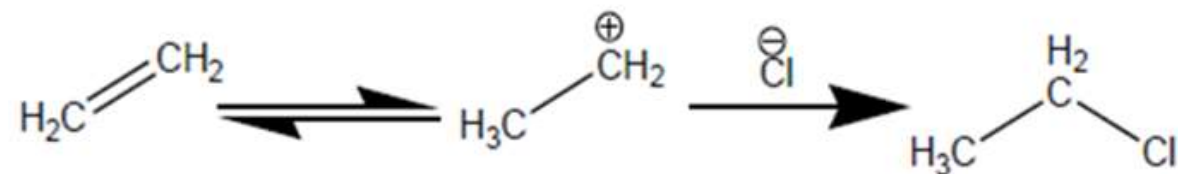
(v) Constituting an aromatic system

- ❖ 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 6π electron system and aromatic.

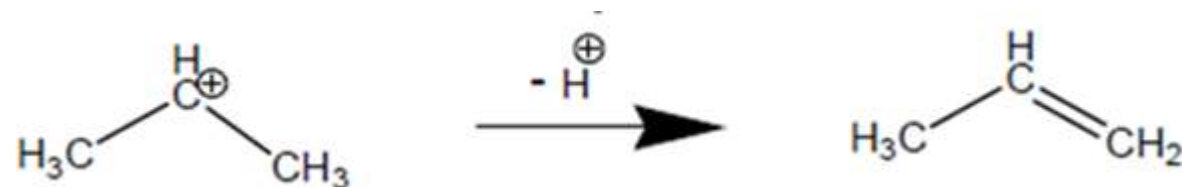


Reaction of Carbocations

- 1. Combination with an anion:** The carbocation reacts with a negatively charged species to give a stable product. Ex. Addition of HCl to ethylene to yield ethyl chloride.



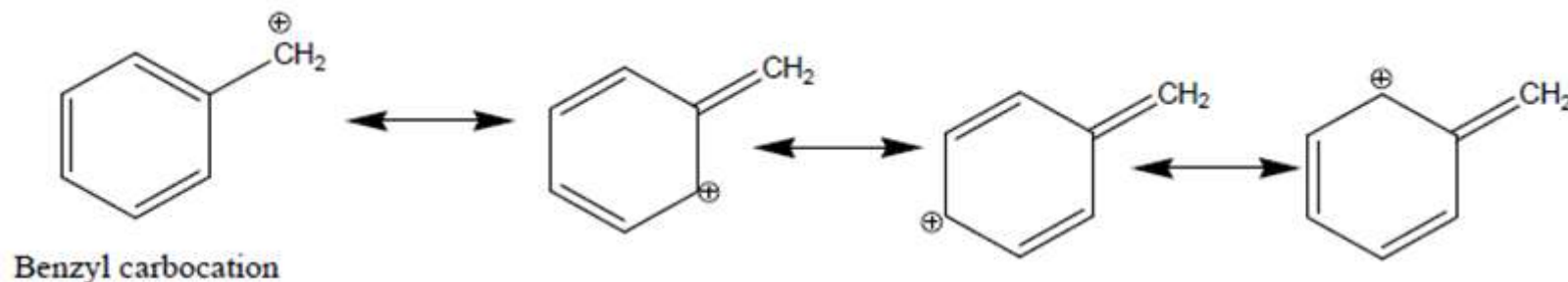
- 2. Elimination of proton:** Carbocation may donate the proton to yield unsaturated compound



Another stability aspect of carbocation is structural stability.

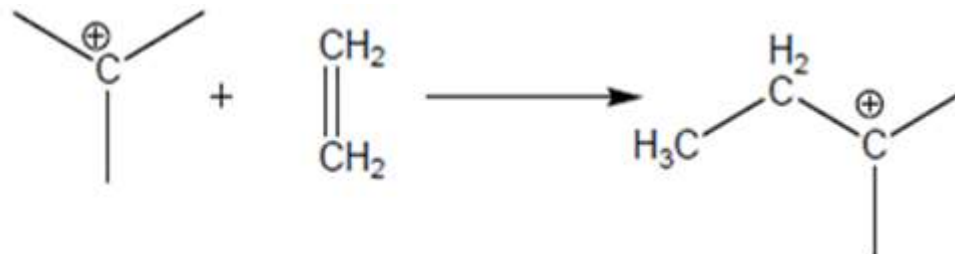
The decrease in energy of transition state forms carbocation.

The generated carbocation by unimolecular dissociation of leaving group is resonance stabilised.

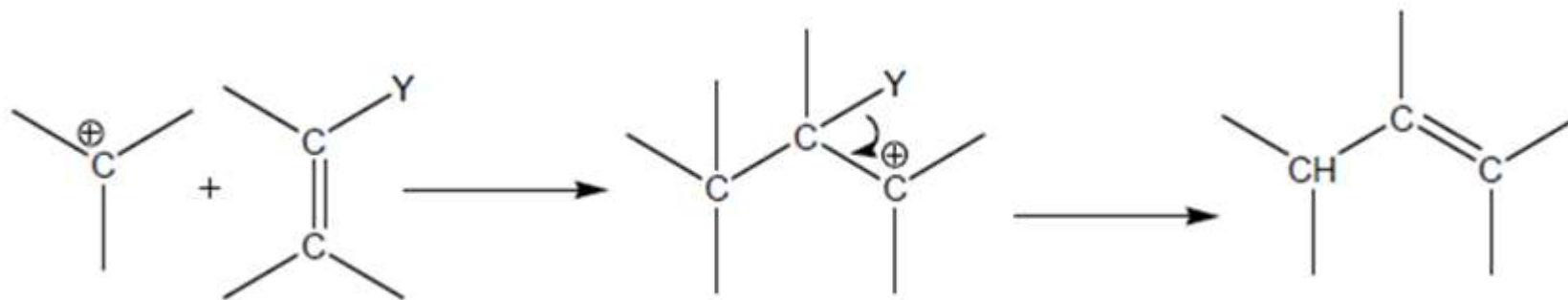


REARRANGEMENTS

Intermolecular alkylation by carbocation



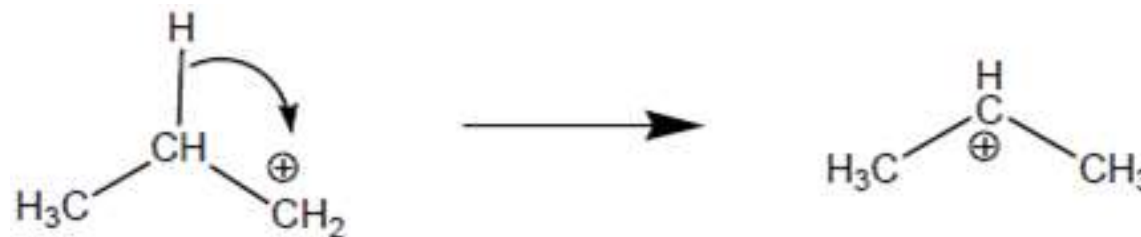
The problem occurs as the **second generated carbocation reacts with another doubly bonded species to form another product. This leads to generation of polymerization reaction.**



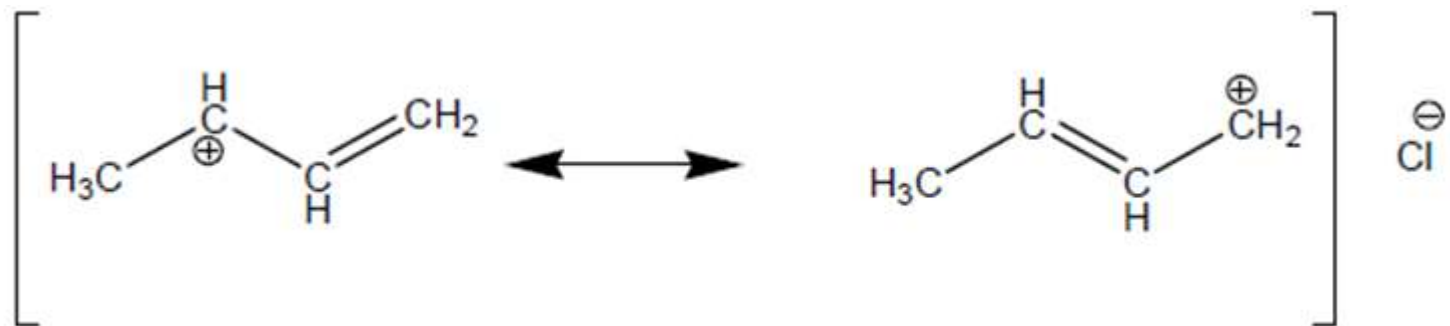
Ex. In this the stannyl or silyl substituent is eliminated to form a stable alkene

1, 2 Hydride Shift:

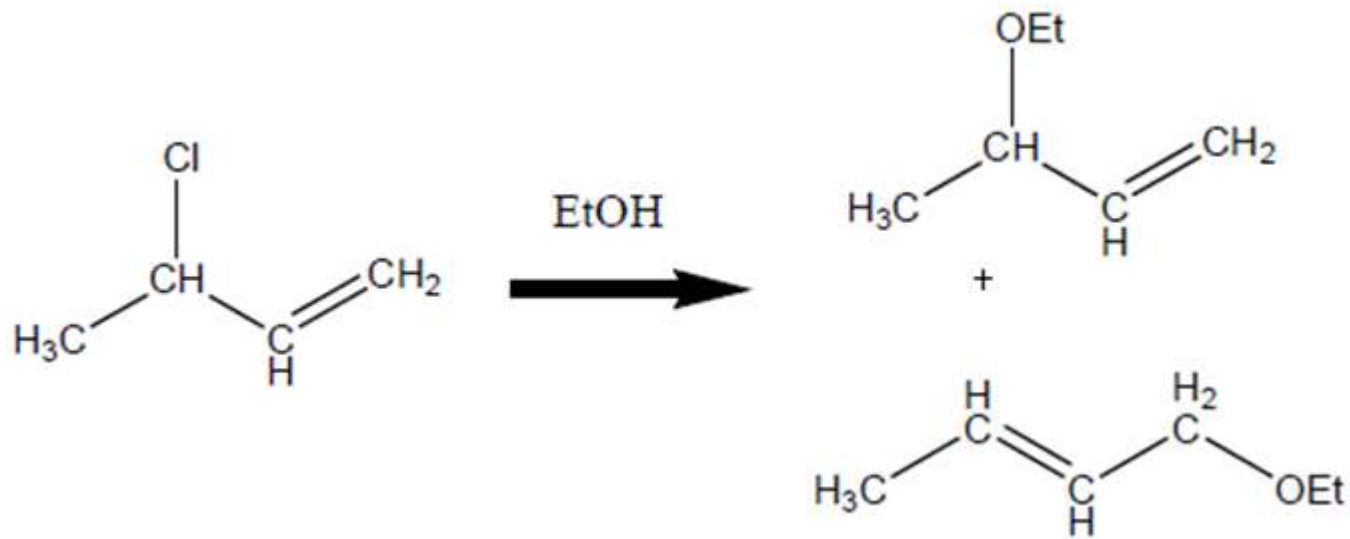
1-propyl cation rearranges to form 2-propyl cation, this is because the secondary cation is more stable than the primary



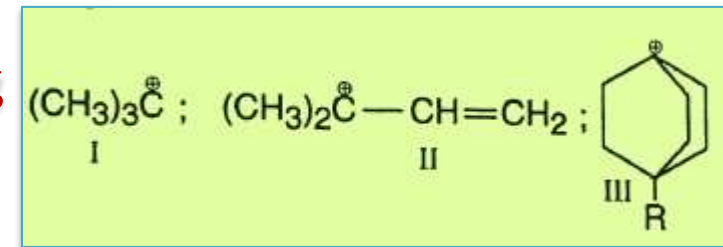
Allylic rearrangements



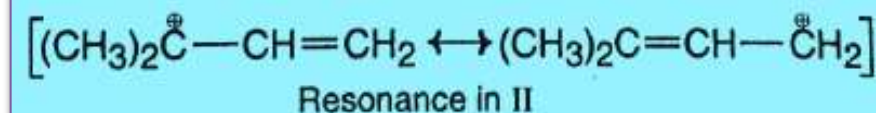
Ex: $\text{S}_{\text{N}}1$ Solvolysis of 3-chlorobut-1-ene. Here rapid nucleophilic attack takes on C1 or C3



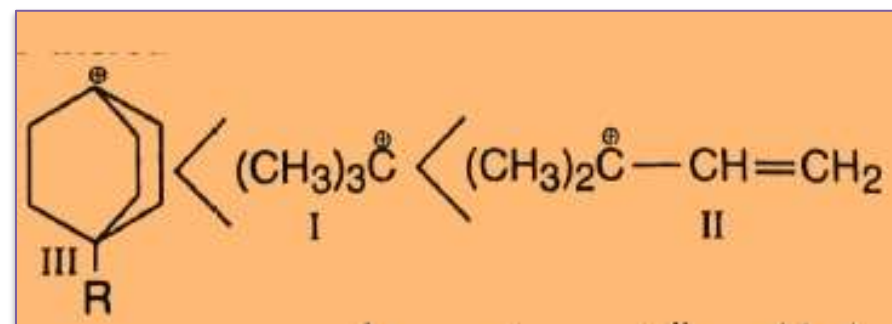
Question: Arrange the following carbocations in order of their increasing stability and provide reason.



- ❖ The **carbocation-I** is stabilized by the +I effects of three $-\text{CH}_3$ 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 sp^2 bond angle, i.e., 120° .
- ❖ So, the **carbocation-II**, although a 3° one, **is more 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.**

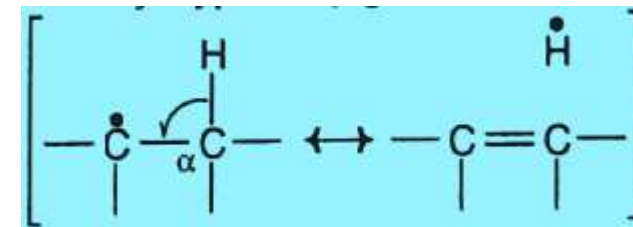
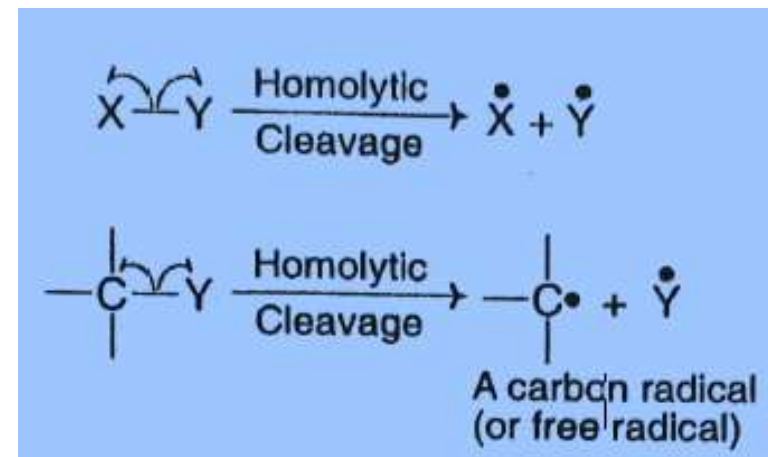


Hence, the order of their increasing stability is:



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.



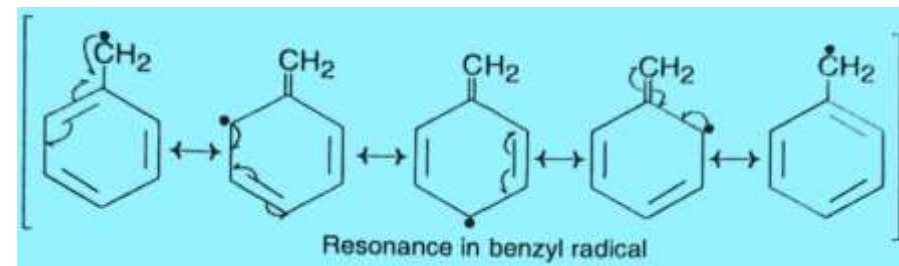
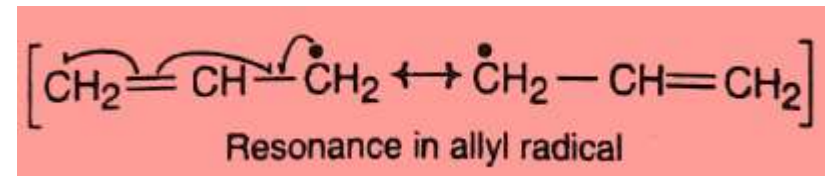
Stability:

(i) Hyperconjugation: Free radicals become stabilized by hyperconjugation involving 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) $\text{R}_3\dot{\text{C}}$ (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 α -H atom) is more stable than isopropyl radical, $\text{Me}_2\dot{\text{C}}\text{H}$ (with six hyperconjugable α -H atom) which in turn is more stable than ethyl radical, $\text{Me}\dot{\text{C}}\text{H}_2$ (with only three hyperconjugable α -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 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.

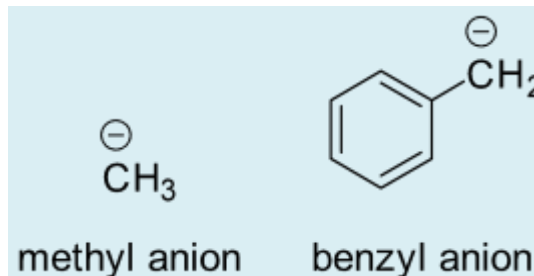


(iii) Steric Strain:

- ❖ 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.

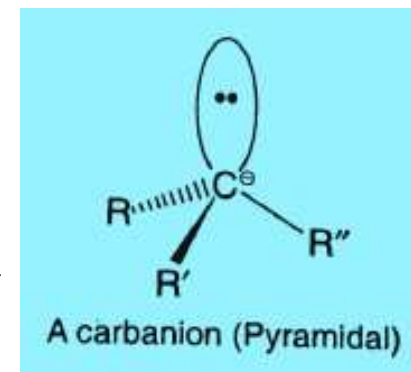
Carbanions

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



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.
- ❖ 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*.



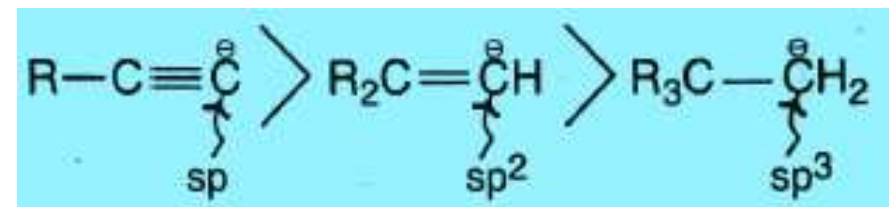
The factors responsible for carbanion stability are -

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.

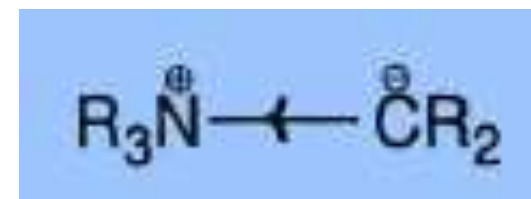
(i) The amount of 's' character of the carbanion carbon atom

- ❖ 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 **sp² hybridized (33.33% s character)** carbon atom, which in turn is more stable than a carbanion at an **sp³ hybridized (25% s character)** carbon atom. Thus, the order of carbanion stability is:



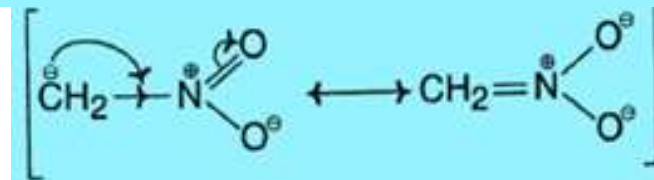
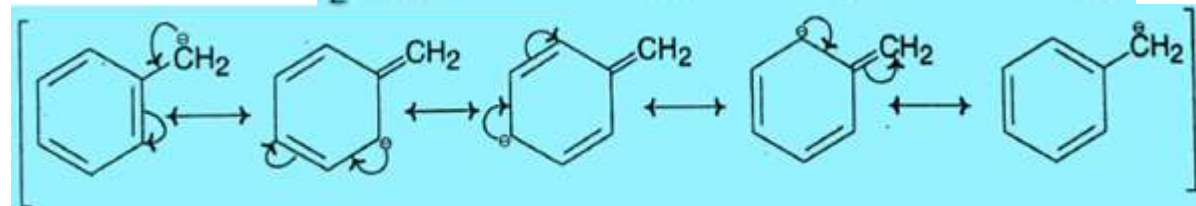
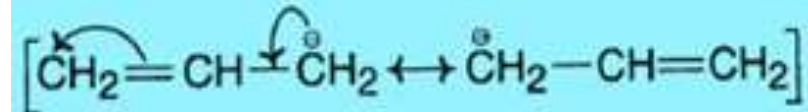
(ii) Inductive electron withdrawal

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



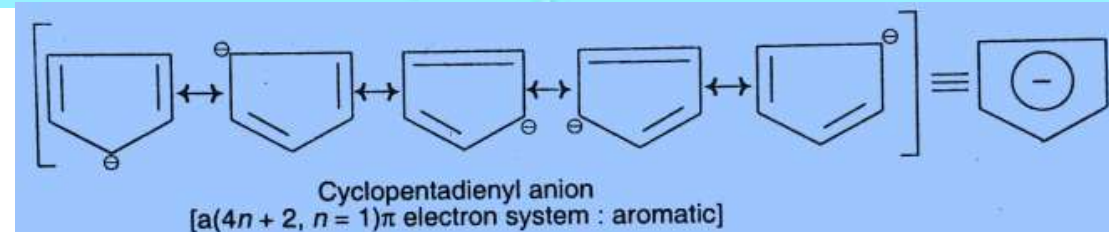
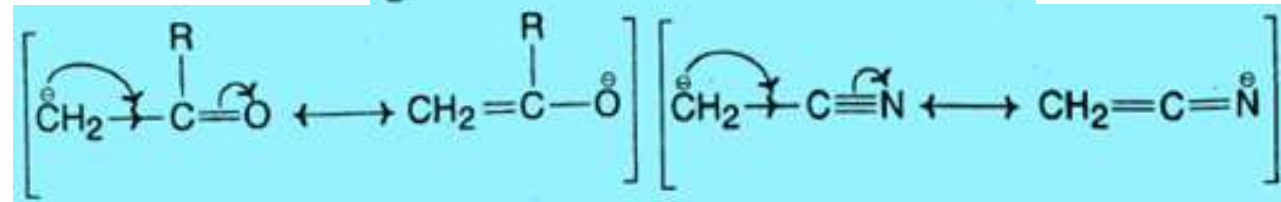
(iii) Conjugation of a non-bonding electron pair with an unsaturated system

- ❖ Where there is a **double or triple bond** is ' α ' 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.

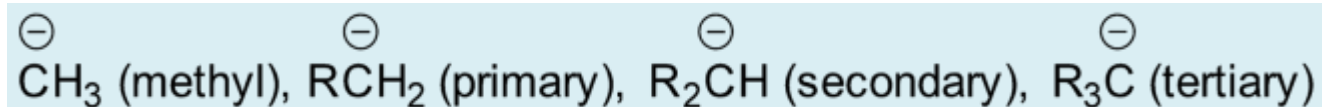


(iv) Constituting an aromatic system

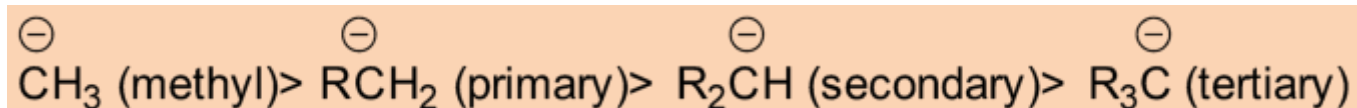
- ❖ The unshared pair of a carbanion may be involved in constituting a planar $(4n+2)\pi$ electron system where $n = 0, 1, 2, \dots$ etc., i.e., a carbanion may be stabilized by constituting an aromatic system
- ❖ **Cyclopentadienyl anion**, for example, is unusually stable because it is a 6π electron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

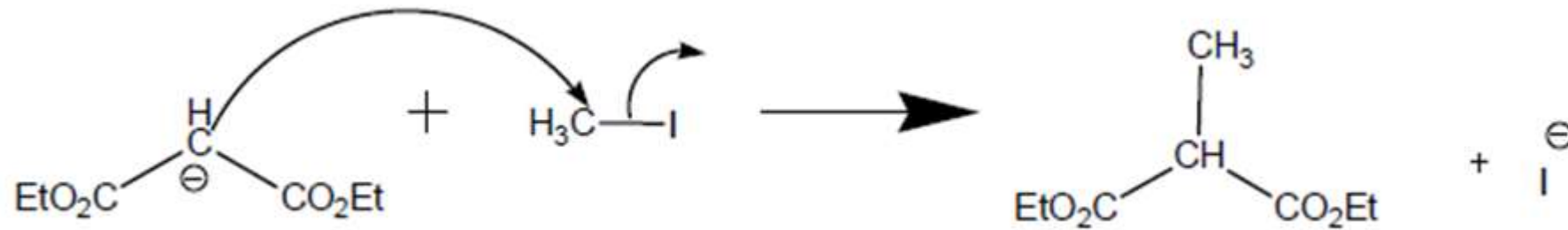


Reaction of Carbanions

They undergo various types of reactions like...

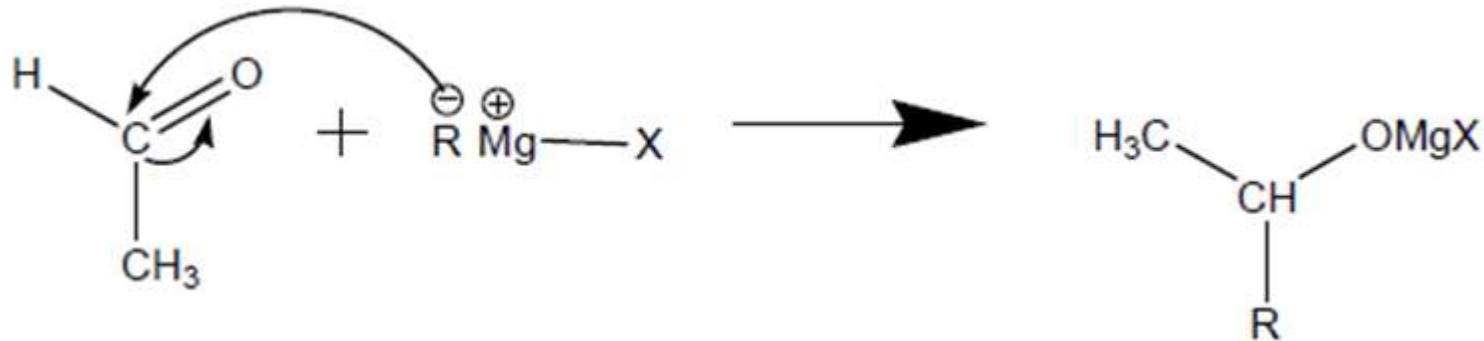
1. Displacement reaction:

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



2. Addition to multiple bonds:

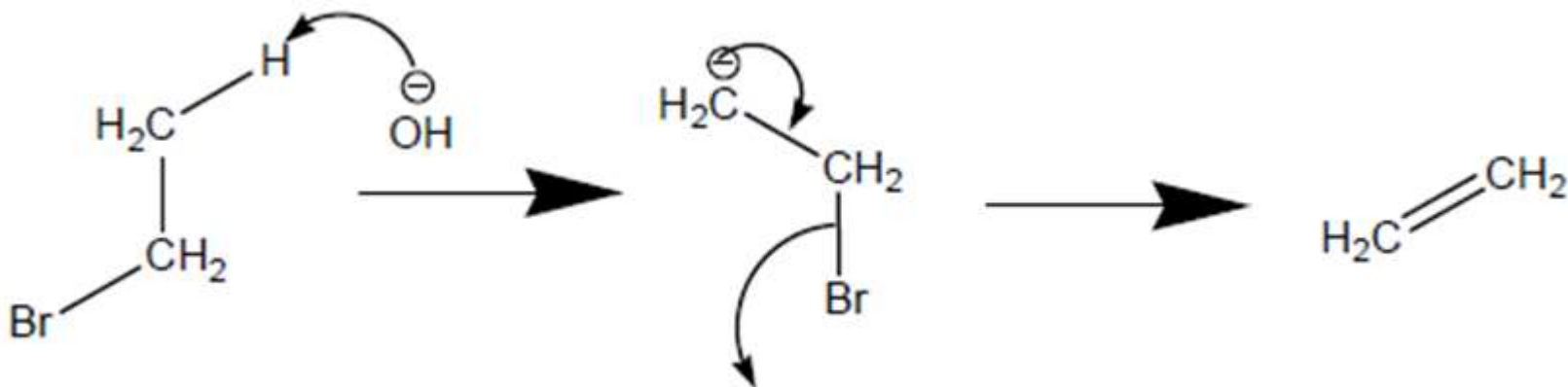
This involves addition of Grignard's reagent to carbonyl group.



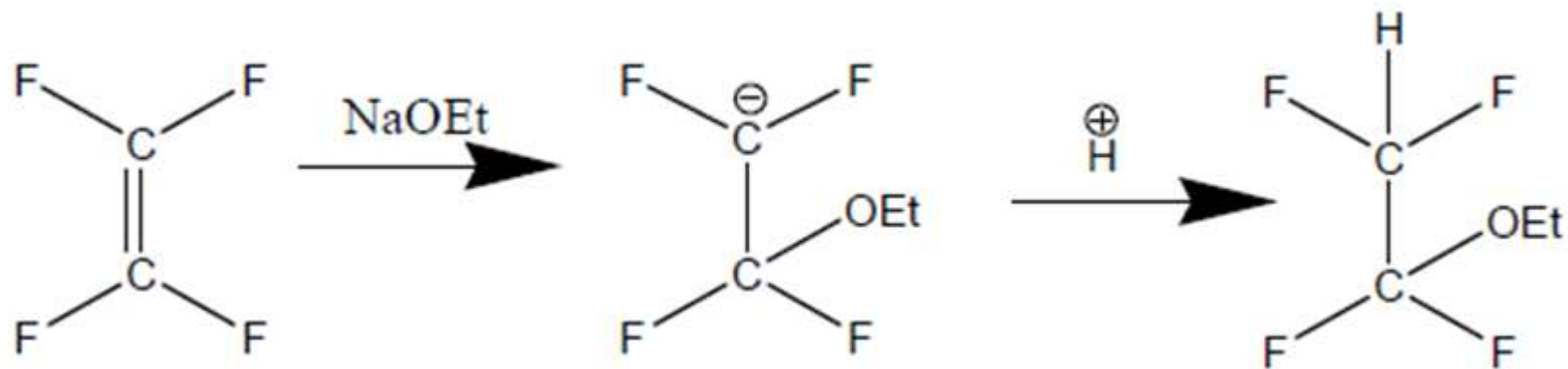
Reactions of Carbanions...

3. Elimination reaction:

Formation of alkene by alkyl halide in presence of alcoholic alkali

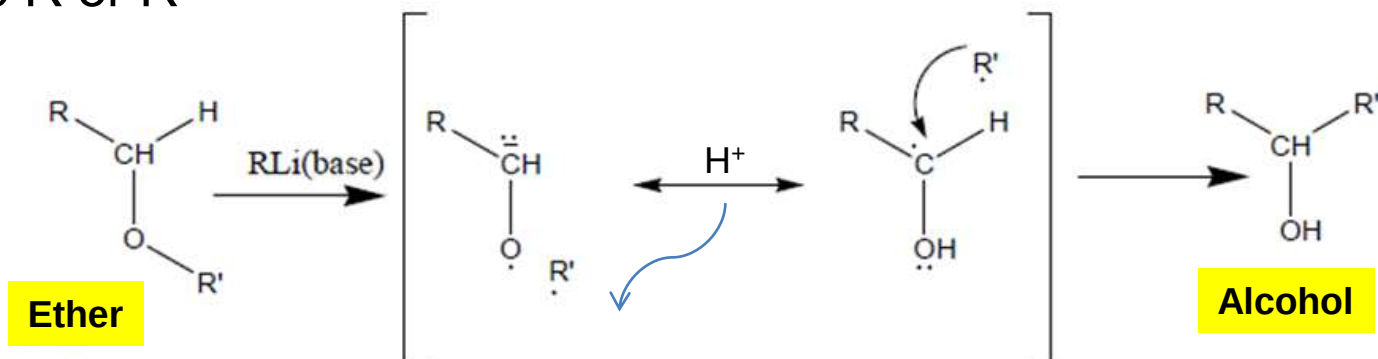


4. Combination with cation:

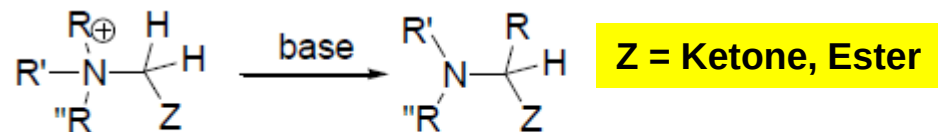


5. Rearrangements...

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

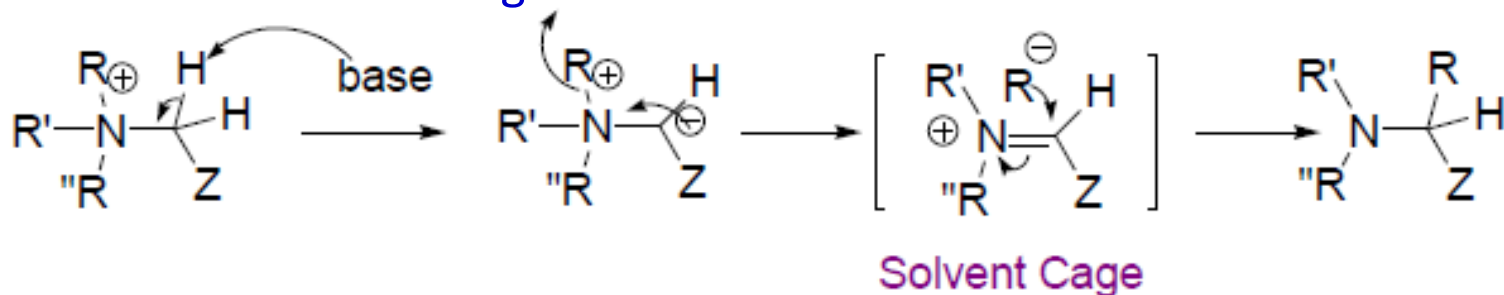


Stevens Rearrangement: This has quaternary ammonium salt as starting material. The stability of carbanion depends on the group attached. The **Z** represents electron withdrawing group.

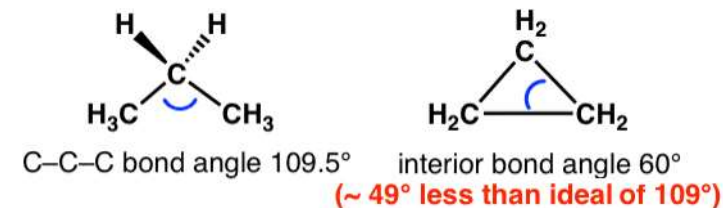
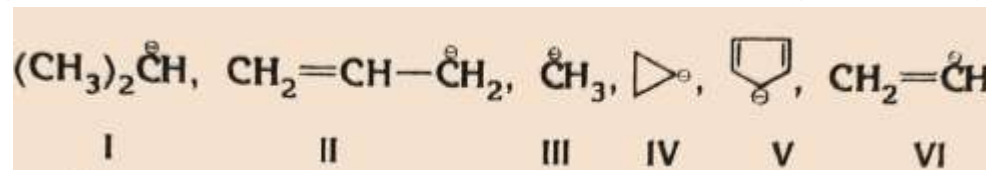


Migratory Aptitude R = propargyl > allyl > benzyl > alkyl

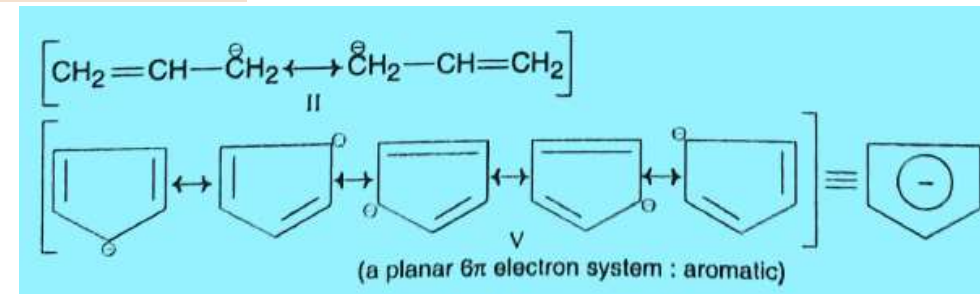
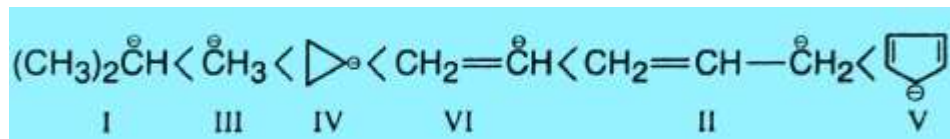
Quaternary ammonium salts containing β-ketone or ester or aryl group, an α-hydrogen is removed by base to give an ylide and then the rearrangement occurs.



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



The order of increasing stability of these carbanions is:



- ❖ 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 (50% 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.**

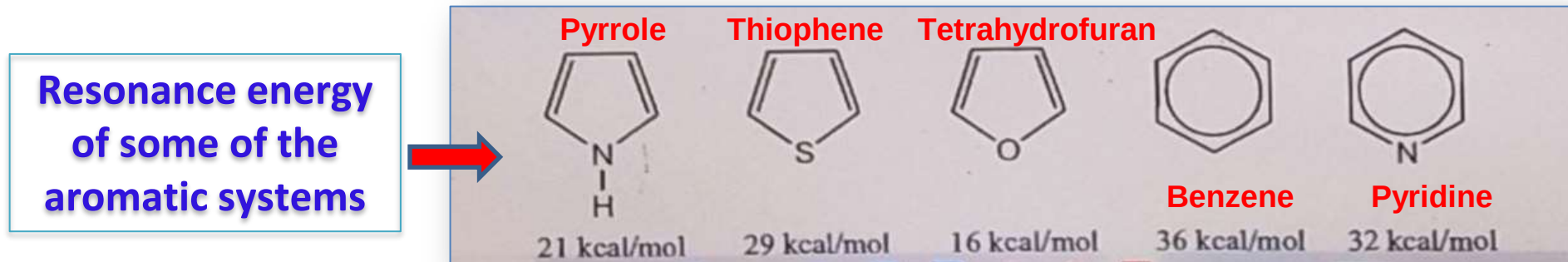
AROMATICITY

Features of aromatic compounds

Aromatic compounds are conjugated planar ring systems having delocalized π -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**.

$$\text{Aromaticity} \propto \text{Resonance Energy (RE)} \propto \text{Stability} \propto \frac{1}{\text{Potential energy}}$$

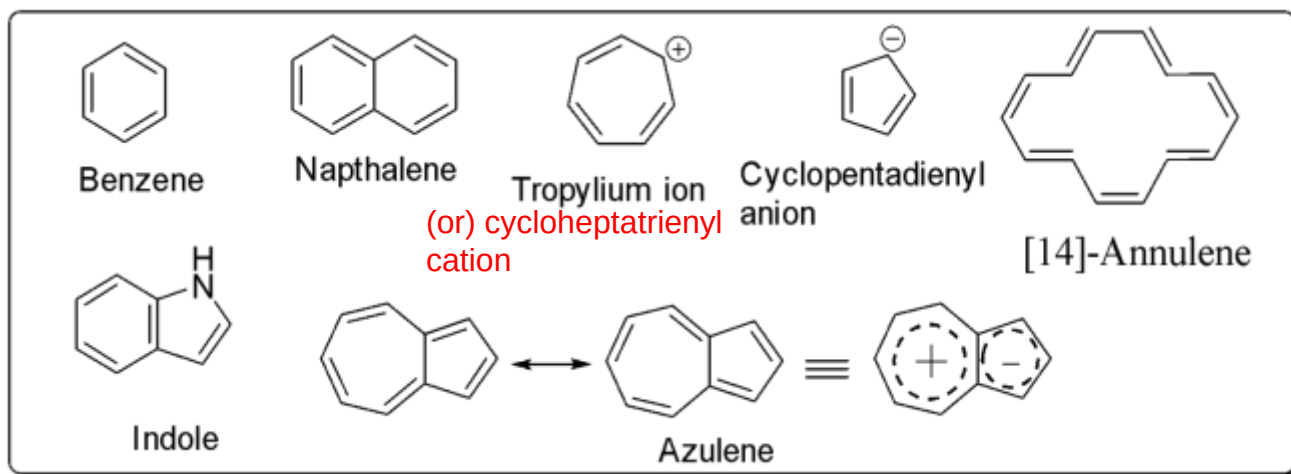


Ignition test for Aromatic Compounds: Place a small amount of compound on the end of a spatula or on a porcelain lid and apply the flame from a Bunsen burner. Aromatic compounds burn with a yellow sooty flame.

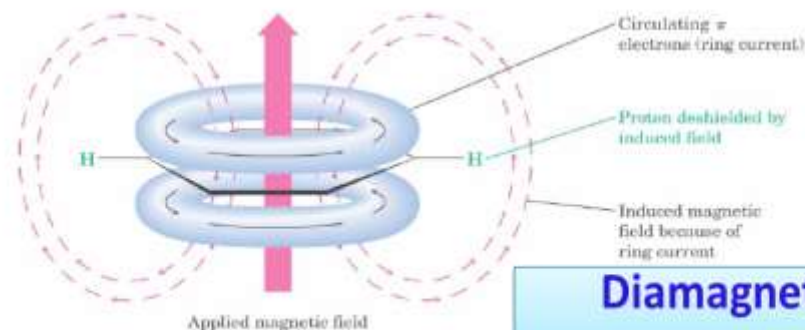


- ❖ It shows **electrophilic substitution reaction** rather than electrophilic addition reaction (means doesn't decolourize bromine water solution).
- ❖ Aromatic compound **follows Huckel 's rule**, a cyclic planar conjugated species having **$(4n+2\pi)$ electrons** (where $n=0,1,2,3,\dots$) is aromatic 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 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



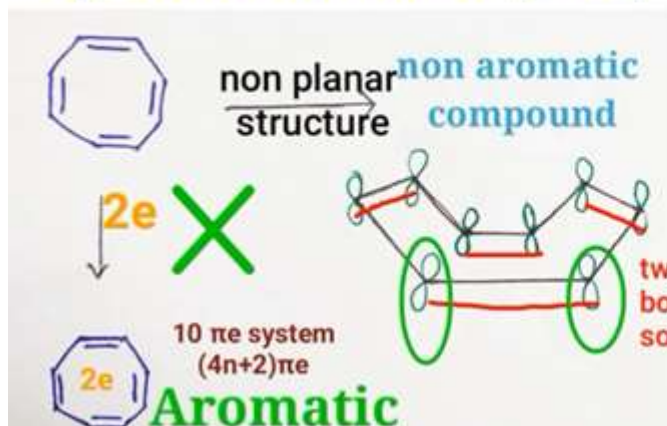
Diamagnetic Ring current effects

Features of non-aromatic compounds

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

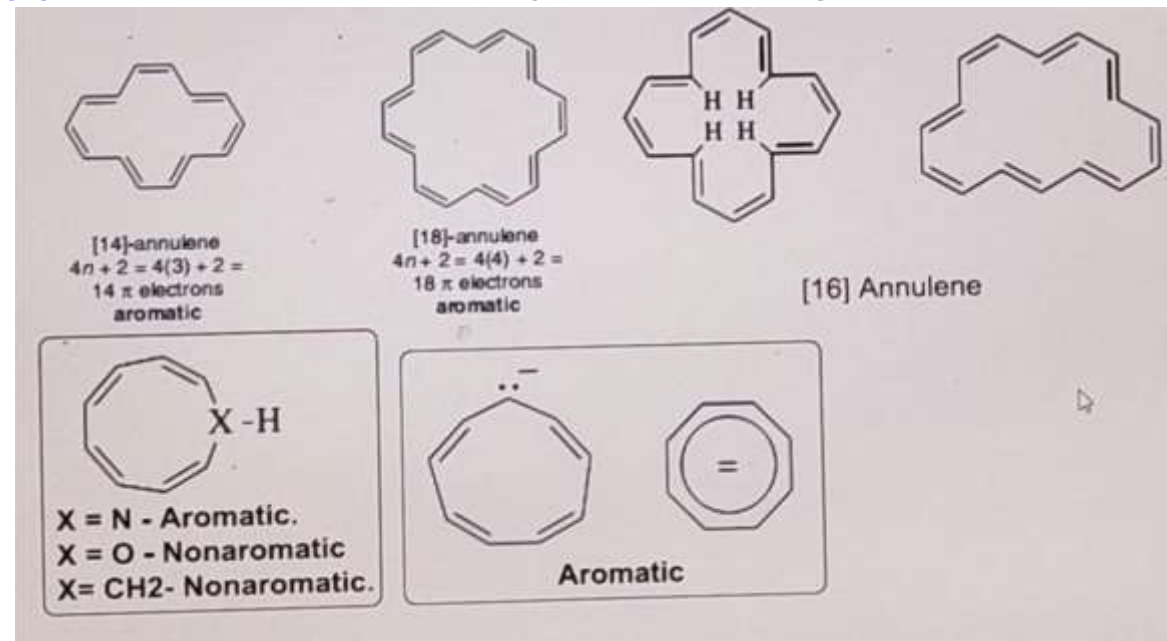
- Cyclic or acyclic
- Do not have a continuous and overlapping p -orbitals, i.e. on every atom in ring
- Non-planar
- Posses $4n \pi$ - electrons (n = any integer)

Cyclooctatetraene (COT)



[12], [16] Annulenes
> non planar structure
> non aromatic

two orbital gap is more distance
bonding interaction will be very less
so, they can't overlap.

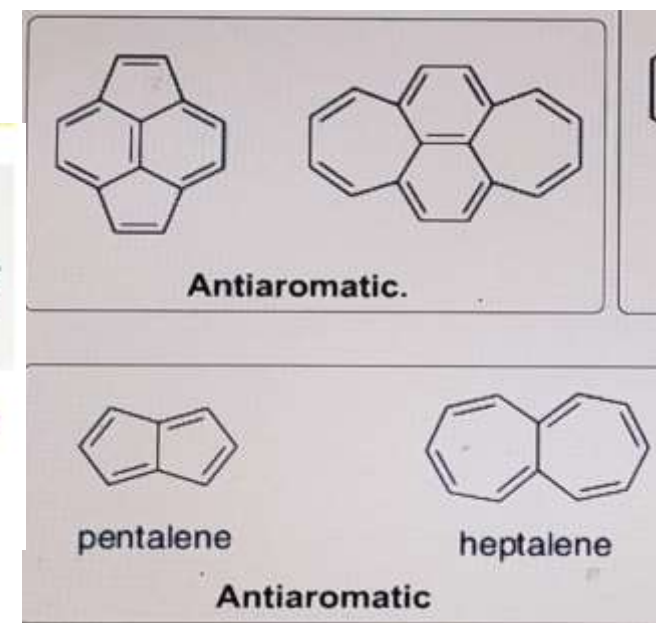
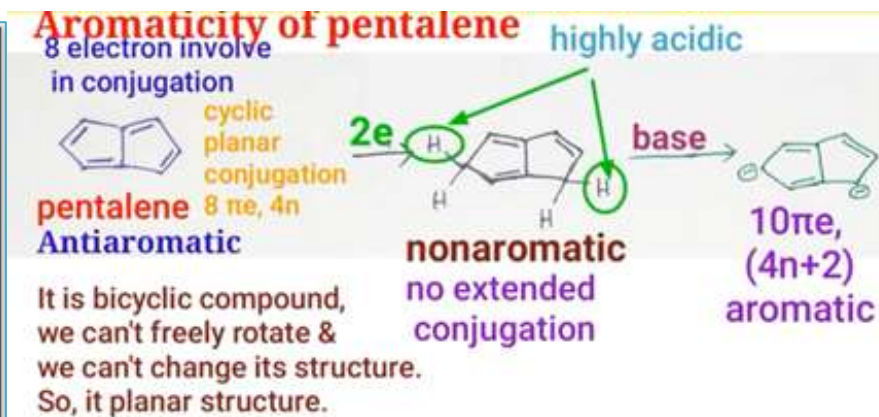
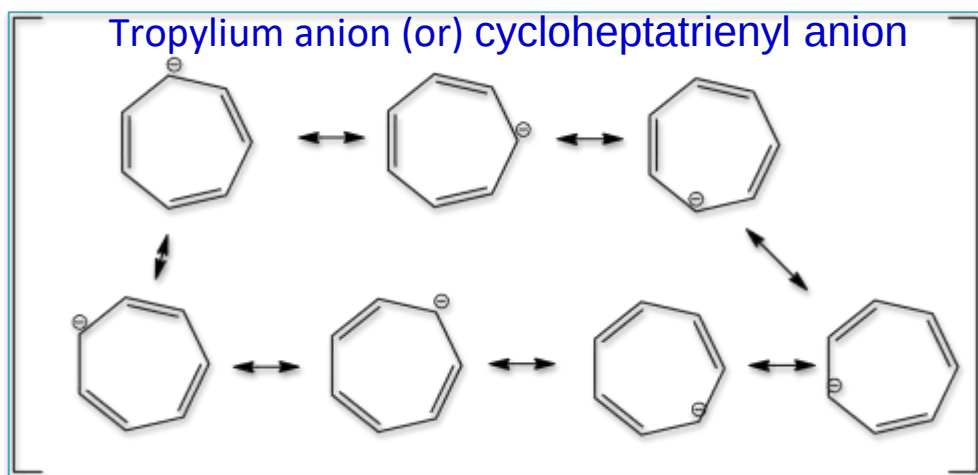


- ❖ Cyclooctatetraene would be an anti-aromatic compound if Huckel 's rule is applied, so the conjugation of its double bonds is energetically unfavorable.
- ❖ Huckel's rule applies to a compound only if there is a continuous ring of overlapping p orbitals, usually in a planar system.
- ❖ Cyclooctatetraene is more flexible than cyclobutadiene and it assumes a non-planar 'tub shaped' conformation that avoids most of the overlap between π -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 π -electrons over the ring increases the electronic energy and decreases the stability.
- Posses $4n$ π -electrons (2, 4, 6, 8) as ($n = 1, 2, 3$ etc.)



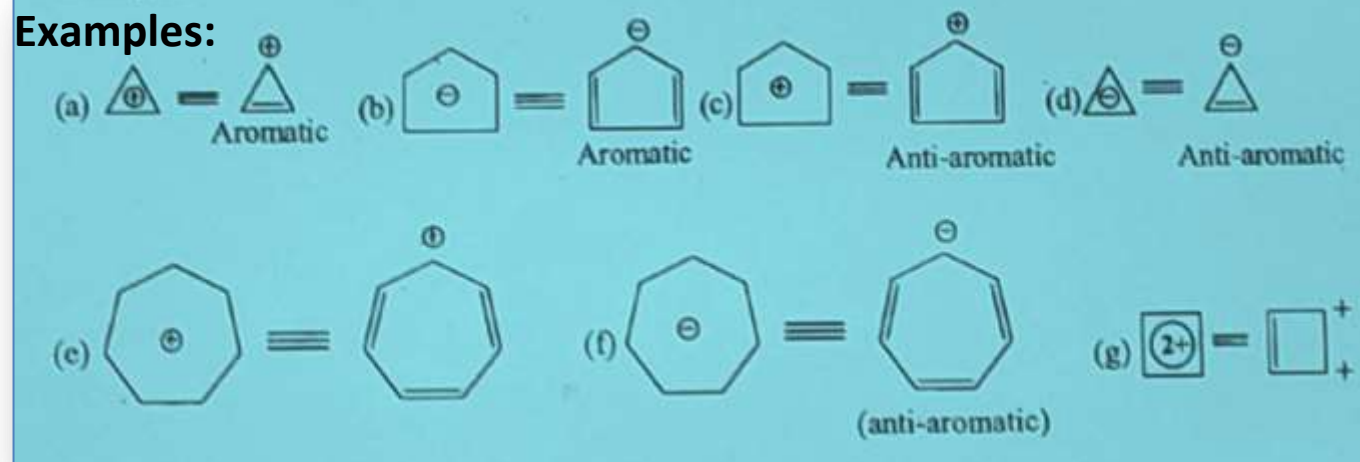
- ❖ **Anti-aromatic systems** exhibit a **paramagnetic ring current**, which causes protons on the outside of the ring to be shifted upfield while any inner protons are shifted downfield (eg-12-annulene), in sharp contrast to a diamagnetic ring current, which causes shifts in the opposite directions.
- ❖ 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 π - electron system.

- It follows $(4n+2)\pi$ - electron system.
- If electrons are delocalized, then compound is aromatic.
- If electrons are not delocalized, then compound is non-aromatic
- compound will never be anti-aromatic.

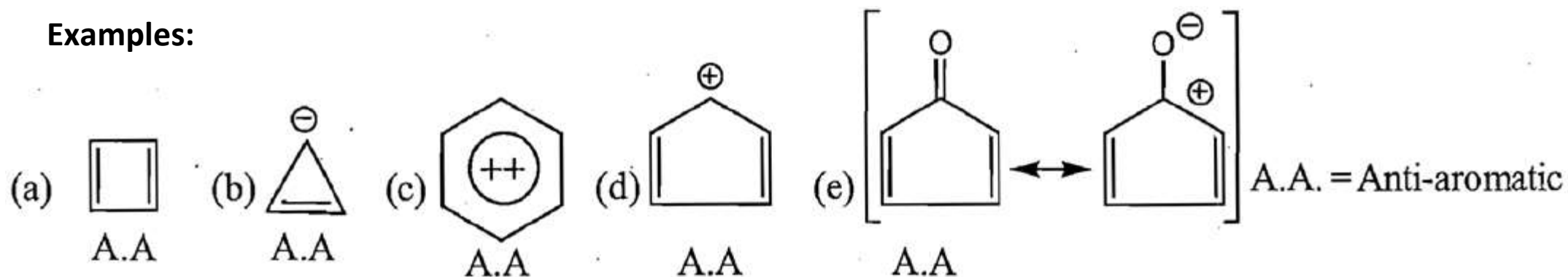
Examples:



4 π - electron system

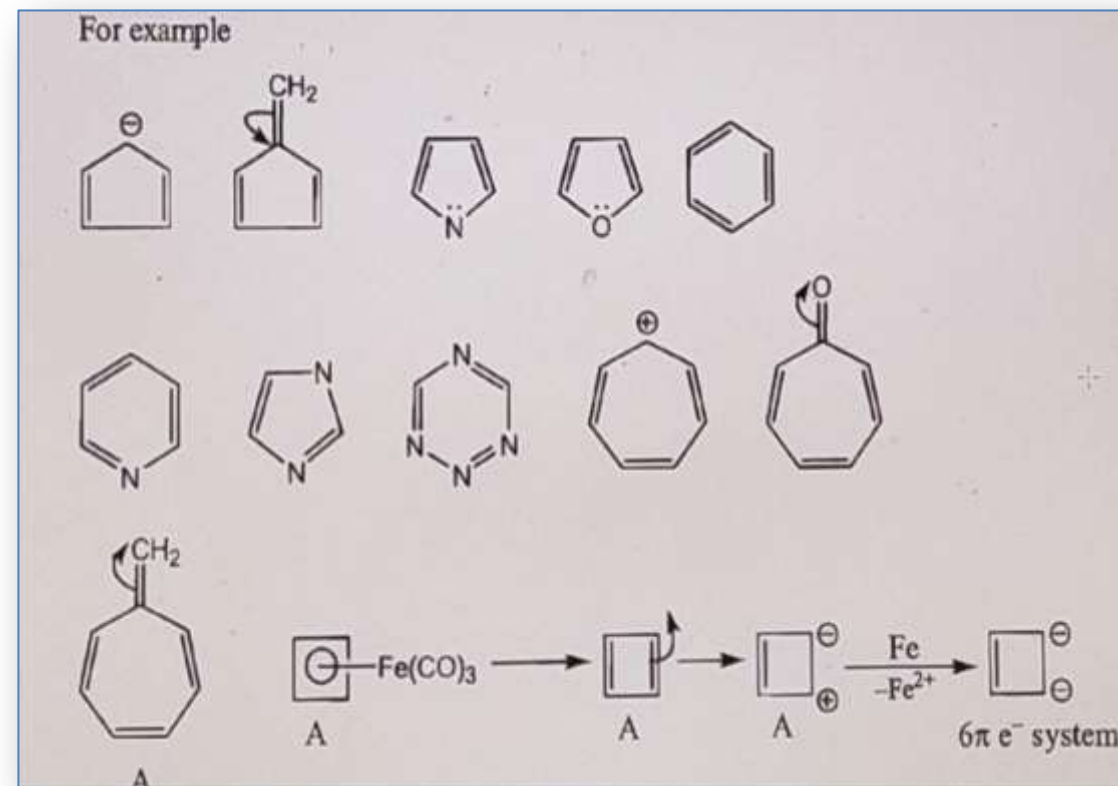
- I. Belongs to $4n\pi$ - electron system doesn't follow Huckel's rule.
- II. If electron is delocalized then compound is Anti-aromatic.
- III. If electron does not delocalized then compound is never aromatic then compound is non-aromatic.

Examples:



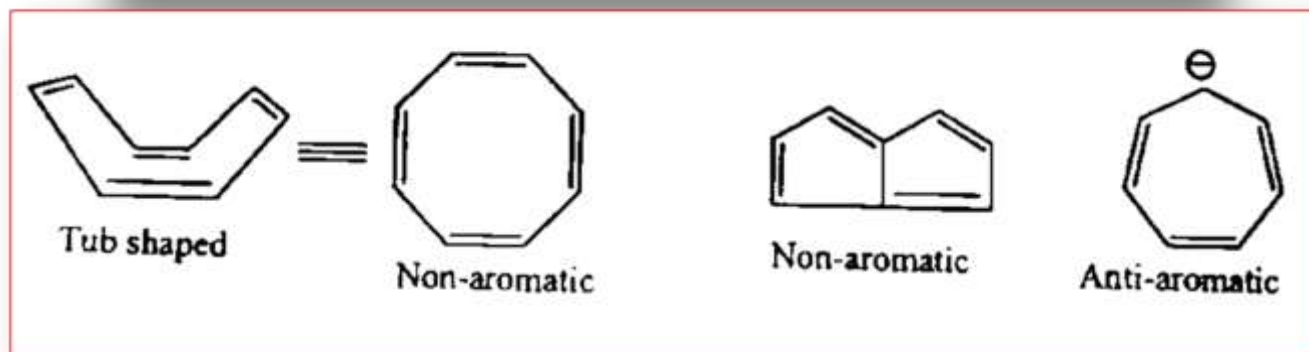
(A) 6π - electron system

- 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.



(B) 8π - 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 π electrons
- contains $4n + 2$ π electrons

aromatic



cyclopentadienyl cation

- 4 π electrons
- contains $4n$ π electrons

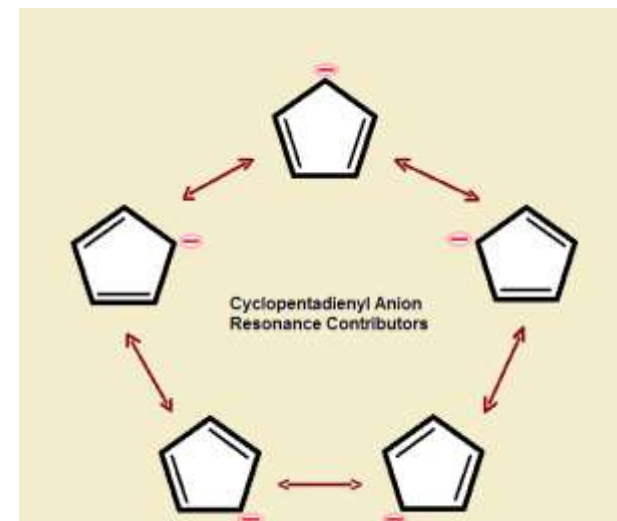
antiaromatic



cyclopentadienyl radical

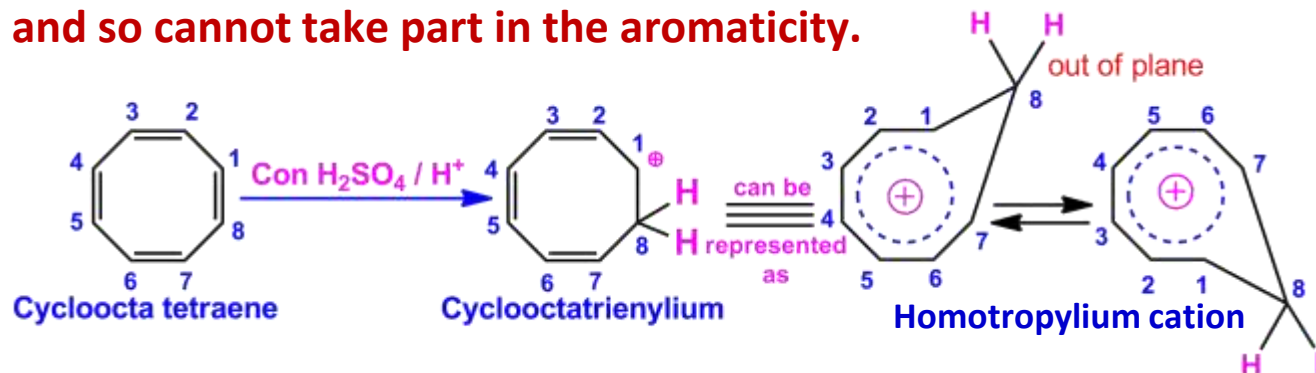
- 5 π electrons
- does not contain either $4n$ or $4n + 2$ π electrons

nonaromatic



Homoaromatic compound

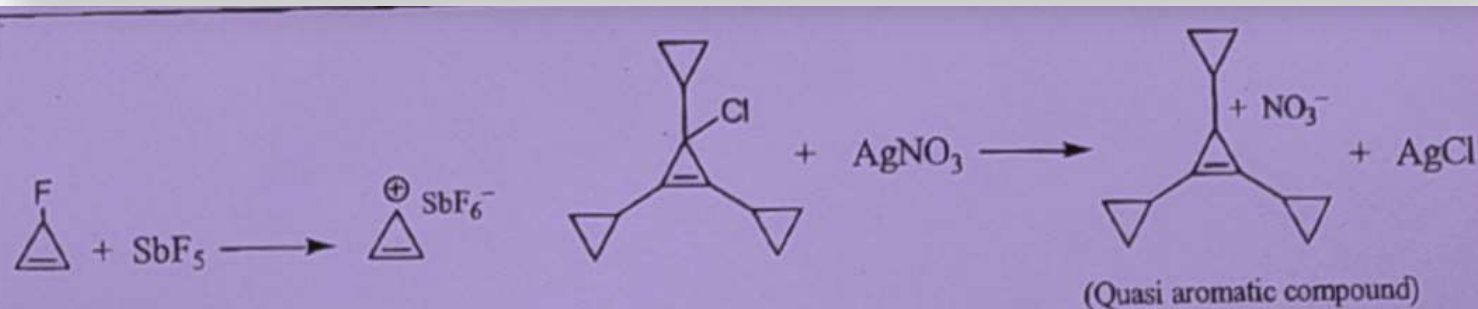
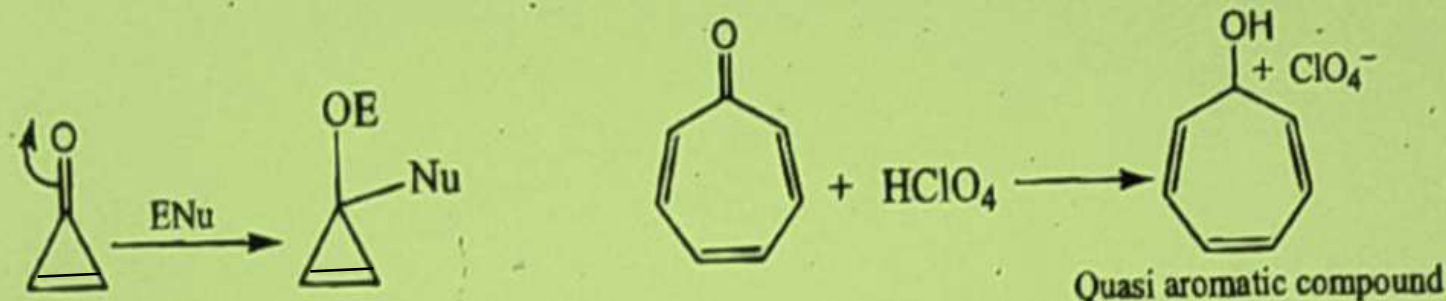
- ❖ Compound that contains one or more sp^3 -hybridized C-atom in a conjugate cyclic ring but sp^3 -hybridized carbon atoms are forced to lie almost vertically above the plane (out of the plane) of the aromatic system for effective orbital overlapping in a closed loop known as homoaromatic compounds.
- ❖ Homoaromatic compound involves delocalization of π -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 Huckle's rule or 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.

Quasi Aromatic Compound: These are generally ionic aromatic compound



- **Stability Order:**

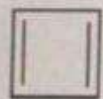
→ **Aromatic > Homoaromatic > Non-aromatic > Anti-aromatic.**

- **Energy Order:**

→ **Anti-aromatic > Non-aromatic > Homoaromatic > Aromatic**

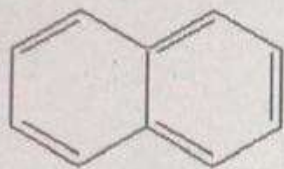
Questions ?

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



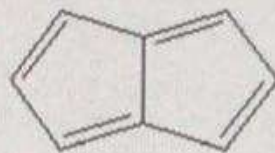
A.A

Cyclobuta-1,3-diene



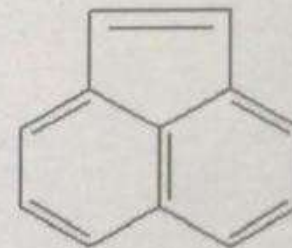
A

Naphthalene



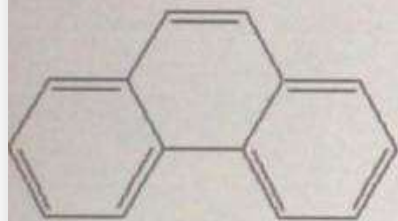
A.A

Pentalene



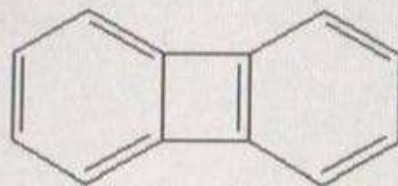
A

Acenaphthylene



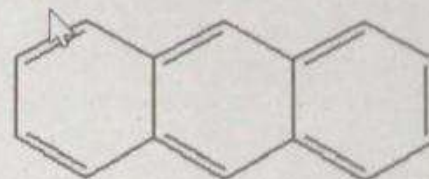
A

Phenanthrene



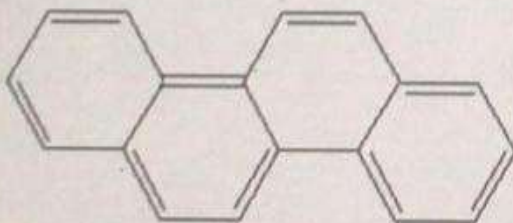
A.A

Biphenylene



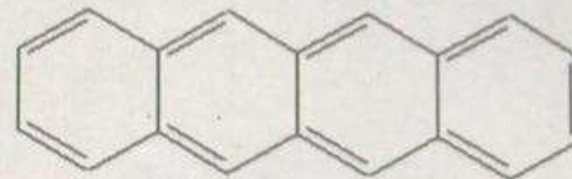
A

Anthracene



A

Chrysene

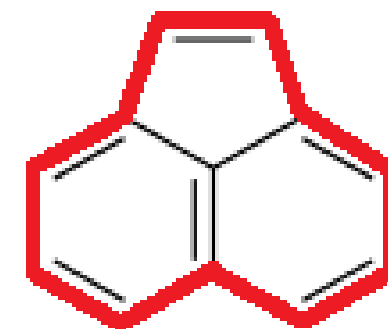
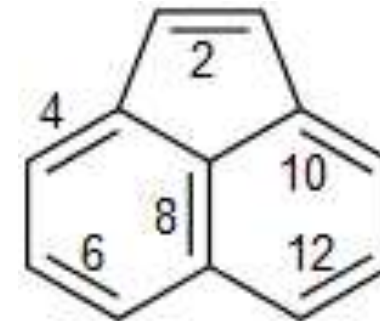


A

Tetracene

Acenaphthylene

- There appear to be 12π electrons. This does not fit the $(4n+2)$.
- **So according to this rule it would appear to not be aromatic!**
- Yet experimentally we have seen that it is aromatic. How is this possible? Why is Huckel's rule being broken?
- Huckel's rule is a bit of an oversimplification, which becomes clear when we have 3 or more fused rings. **People have developed several hypotheses to explain the fact that Huckel's rule may not apply to these molecules.**
- **One is that the center π bond isn't actually part of the aromatic ring. The aromatic ring is just the outside ring. That would mean there are only 10π electrons, which does fit Huckel's rule: $4(2)+2 = 10$.**



- **Experimental Aromaticity**

- Molecules with multiple aromatic rings fused together are called **polycyclic aromatic hydrocarbons (PAHs)**.
- Some of these molecules follow the typical 4 rules of aromaticity. Others need to be tested experimentally.
- **Since aromatics are much more stable than similar non-aromatic molecules, aromaticity can be tested experimentally by comparing the stability of the compound in question with a similar, known, aromatic compound.**

Heterocycle: any cyclic compound that contains ring atom(s) other than carbon (N, O, S, P).

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 π electrons (4n rule)



AZIRINE

(2H-AZIRINE)



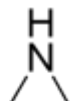
OXIRANE

(ETHYLENE
OXIDE)



THIIRANE

(ETHYLENE
SULFIDE)



AZIRIDINE

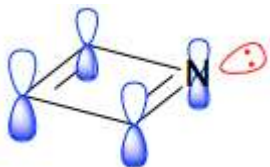
(ETHYLENE
IMINE)

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

Characteristics of 4-Membered Ring Heterocyclic Compounds

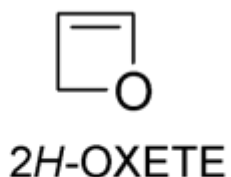
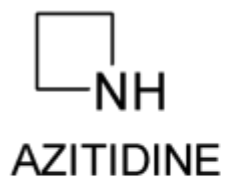


Azete



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

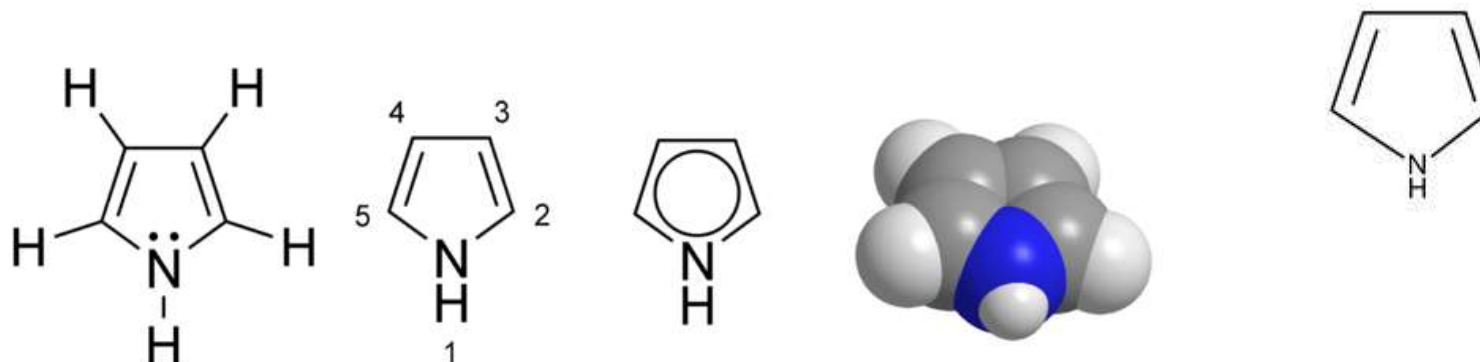
- The Azete is an anti-aromatic.
- While counting the number of π -electrons, you count the electrons which are delocalized over the ring.
- In this case **the nitrogen lone pair is localised and does not participate in resonance.**
- The **nitrogen lone pair is in an sp^2 orbital (red)** which is **orthogonal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



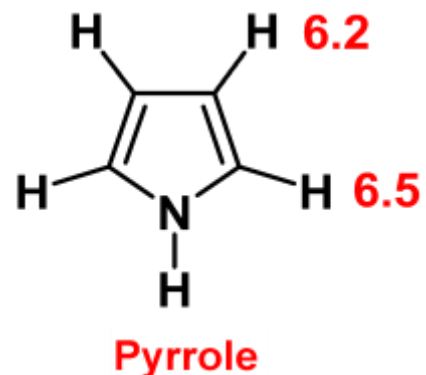
- Non-aromatic
- Cyclic
- no conjugated sp^2 hybridised carbons

NON-AROMATIC HETECYCLES

Five Membered Heterocycle: Pyrrole



^1H NMR: δ



Aromatic: Thus, 6π electrons

sp^2 hybridised and planar

Lone pair tied up in aromatic ring

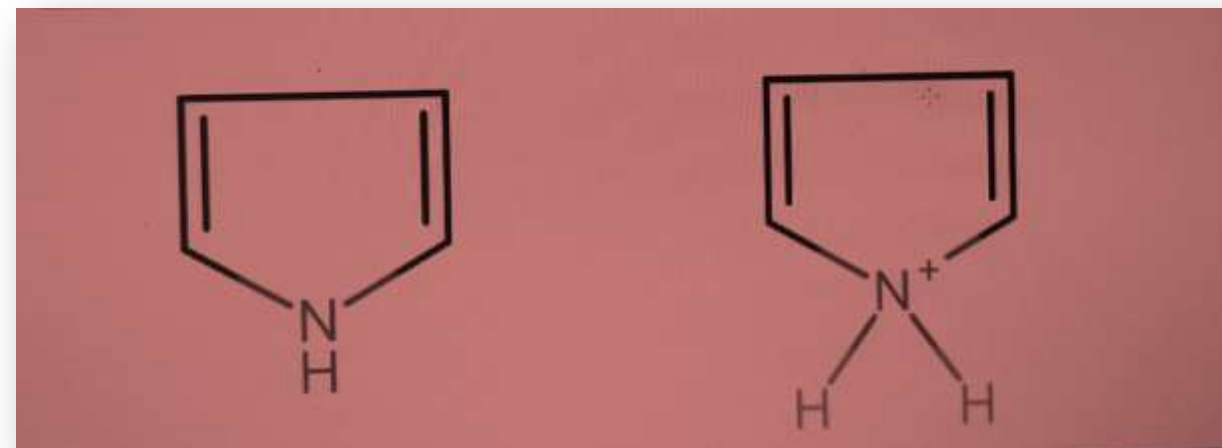
Pyrrole is π -electron excessive

Thus, Electrophilic Aromatic Substitution is Easy

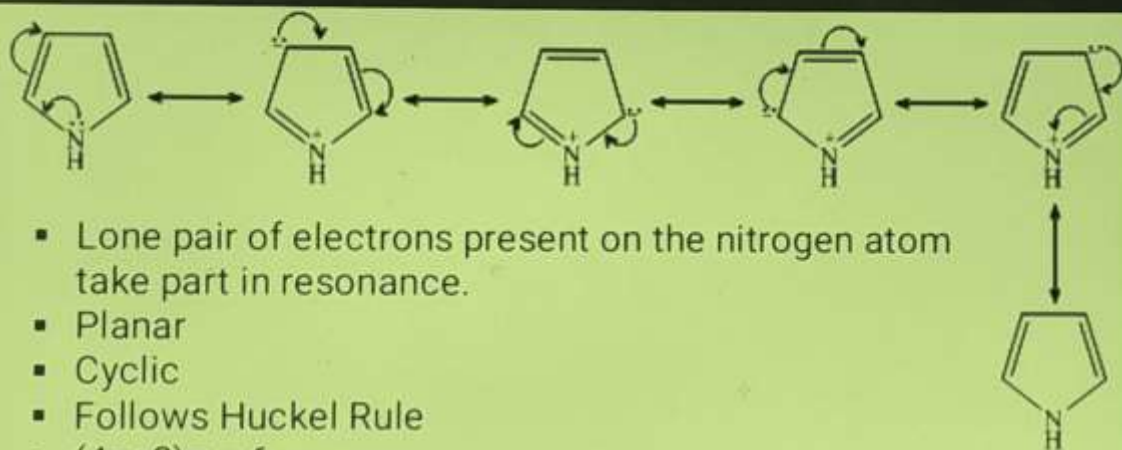
Nucleophilic Substitution is Difficult

Heterocyclic ring
which has 5 p
orbitals and six
 π electrons

- Pyrrole is aromatic but when **nitrogen atom of pyrrole is protonated**, it becomes **non-aromatic**.



Resonance structures of Pyrrole



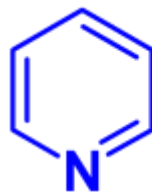
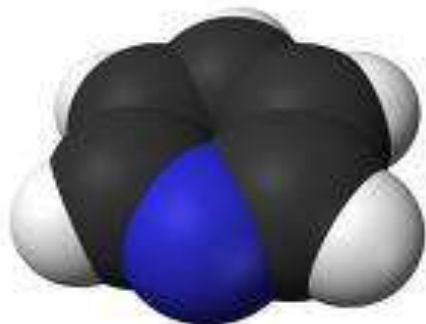
- Lone pair of electrons present on the nitrogen atom take part in resonance.
- Planar
- Cyclic
- Follows Huckel Rule
- $(4n+2)\pi = 6$
- $n=1$
- It is Aromatic.

Protonated Pyrrole

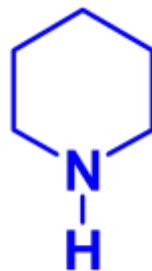
- Lone pair present on the nitrogen atom is lost due to protonation of nitrogen atom
- No Conjugation
- Doesn't obey Huckel Rule
 $(4n+2)=4$
- It is non-aromatic.



Six Membered Heterocycle: Pyridine



pyridine



piperidine

Heterocycle: any cyclic compound that contains ring atom(s) other than carbon (N, O, S, P).

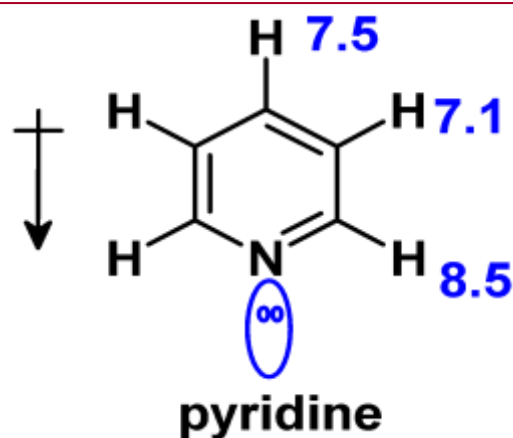
Cyclic compounds that contain only carbon are called carbocycles.
Pyridine: π -electron structure resembles benzene (6 π -electrons)

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

^1H NMR: δ



Pyridine is a weak base.

Pyridine is π -electron deficient.

Electrophilic aromatic substitution is difficult.

Nucleophilic aromatic substitution is easy.

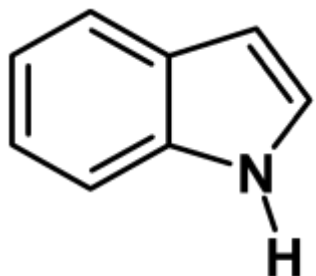
Pyridinium ion: $pK_a = 5.5$

Piperidine: $pK_a = 11.29$

diethylamine : $pK_a = 10.28$

Electron-deficient nature of these heterocycle is due to electron-withdrawing, inductive (I), and mesomeric (M) effects of the nitrogen atom

Fused Heterocyclic Compounds: Indole



Indole

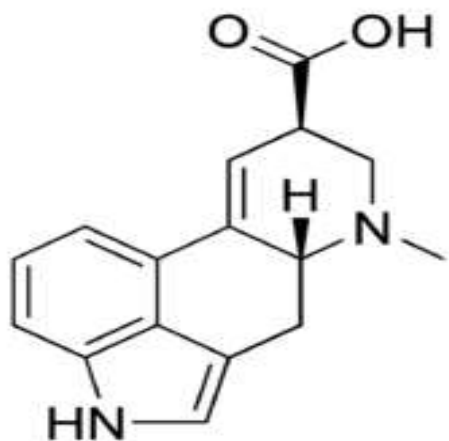
Aromatic due to 10 π -electrons

Benzene part is non-reactive

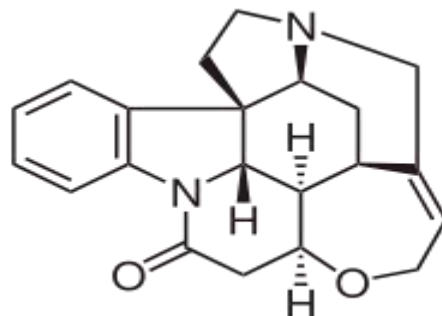
Electrophilic aromatic substitution occurs at the 3-position



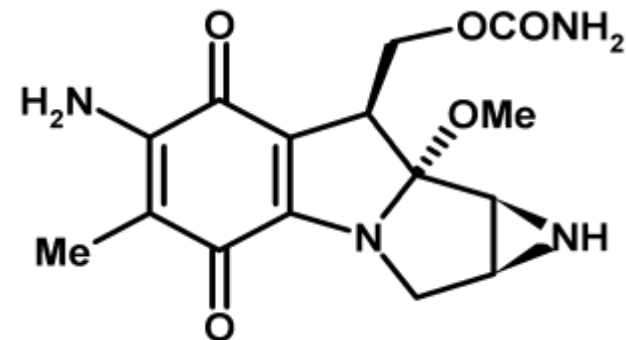
Indole Alkaloids



Lysergic acid (LSD)



Strychnine



Mitomycin C