St Peter’s Institute of Pharmaceutical Sciences

Course : Bachelor of Pharmacy

Subject : Pharmaceutical Organic Chemistry II

Subject Code:BP301T

Benzene and its Derivatives

Chemists have found it useful to divide all organic compounds into two broad classes: aliphatic compounds and aromatic compounds. The original meanings of the words "aliphatic" (fatty) and "aromatic" (fragrant/ pleasant smell).

Aromatic compounds are benzene and compounds that resemble benzene in chemical behavior. Aromatic properties are those properties of benzene that distinguish it from aliphatic hydrocarbons.

Benzene:

- A liquid that smells like gasoline
- Boils at 80°C & Freezes at 5.5°C
- It was formerly used to decaffeinate coffee and component of many consumer products, such as paint strippers, rubber cements, and home dry-cleaning spot removers.
- A precursor in the production of plastics (such as Styrofoam and nylon), drugs, detergents, synthetic rubber, pesticides, and dyes.
- It is used as a solvent in cleaning and maintaining printing equipment and for adhesives such as those used to attach soles to shoes.
- Benzene is a natural constituent of petroleum products, but because it is a known carcinogen, its use as an additive in gasoline is now limited.
- In 1970s it was associated with leukemia deaths.

Structure of benzene

History, Analytical, Synthetic and other evidences in the derivation of structure of benzene:

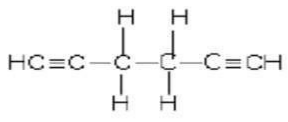
(a) History of benzene:

- Isolated in 1825 by Michael Faraday who determined C:H ratio to be 1:1.
- Synthesized in 1834 by Eilhard Mitscherlich who determined molecular formula to be C6H6. He named it benzin later known as benzene.

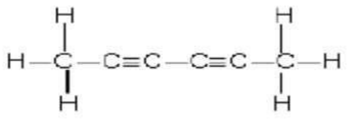
(b) Benzene has the molecular formula C_6H_6. The question was: how are these atoms arranged?
The molecular formula of benzene has been found from analytical data, to be $\mathbf{C_6H_6}$. Relatively higher proportion of carbon and addition of chlorine to benzene molecule indicate it to be an unsaturated compound. Depending on the various facts available to scientists from time to time, many structures for benzene had been proposed. Some are described below.

Open Chain Structure

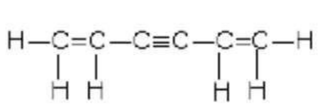
Based upon observable facts given above and the tetravalency of carbon, the following open chain structures were proposed for benzene.



(i)



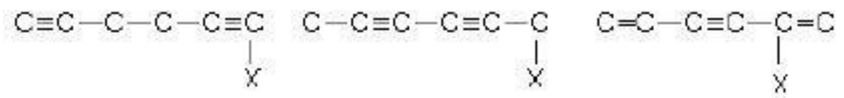
(ii)



(iii)

Drawbacks of open chain structure: The open chain structure for benzene was rejected due to the following reasons:

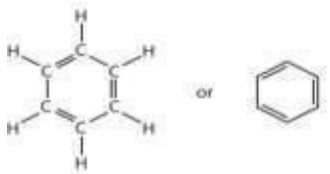
- Addition reactions usually given by alkenes and alkynes are not given by benzene.
- Benzene forms only one kind of mono-substituted product.
- An open chain structure however, can form more than one kind of monosubstituted product as shown below:



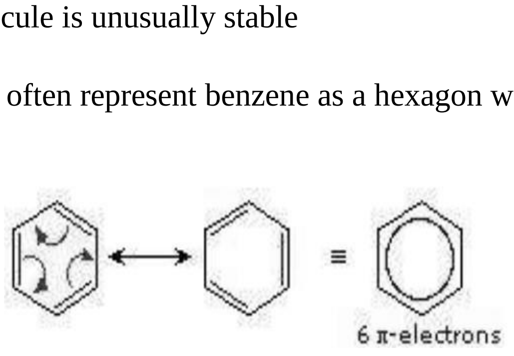
- The open chain compounds do, not give reactions such as FriedelCraft reaction, nitration, sulphonation.
- On reduction with hydrogen in the presence of Ni at 200°C, actually a cyclic compound cyclohexane is obtained.

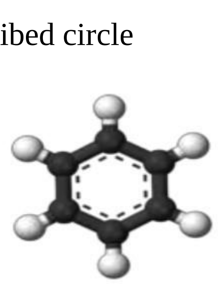
In 1858, August Kekule (of the University of Bonn) had proposed that carbon atoms can join to one another to form chains. Then, in 1865, he offered an answer to the question of benzene: these carbon chains can. Sometimes be closed, to form rings.

Kekule's structure of benzene was one that we would represent today as



- All the carbon-to-carbon bonds in benzene are equivalent
- The molecule is unusually stable
- Chemists often represent benzene as a hexagon with an inscribed circle



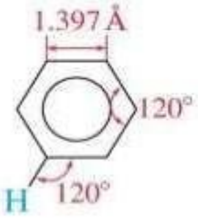


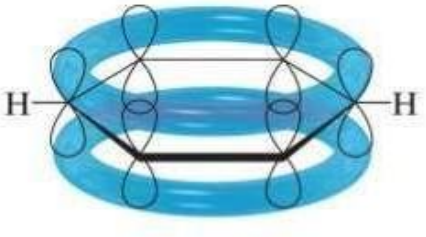
- The inner circle indicates that the valence electrons are shared equally by all six carbon atoms (that is, the electrons are delocalized, or spread out, over all the carbon atoms).

- Each corner of the hexagon is occupied by one carbon atom, and each carbon atom has one hydrogen atom attached to it.

- Any other atom or groups of atoms substituted for a hydrogen atom must be shown bonded to a particular corner of the hexagon.

- The six bond lengths are identical and they are one-and-a half bonds and their length, 1.39 A or 139 picometer (pm), is intermediate between the lengths of single and double bonds (is shorter than typical single-bond lengths, yet longer than typical double-bond lengths).





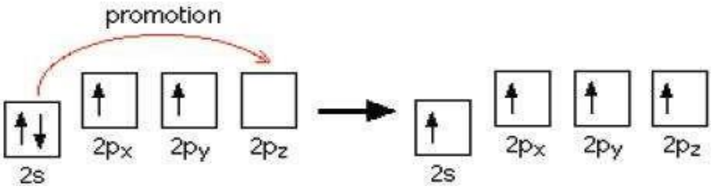
An orbital model for the benzene structure

Building the orbital model

Benzene is built from hydrogen atoms (**$1s^1$**) and carbon atoms (**$1s^2 2s^2 2px^1 2py^1$**).

Each carbon atom has to join to three other atoms (one hydrogen and two carbons) and doesn't have enough unpaired electrons to form the required number of bonds, so it needs to promote one of the **2s2** pair into the empty **2pz** orbital.

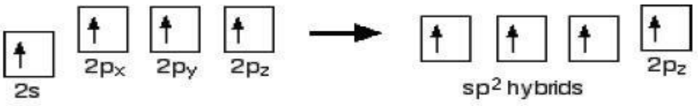
☐ ***Promotion of an electron***



There is only a small energy gap between the **2s** and **2p** orbitals, and an electron is promoted from the **2s** to the empty **2p** to give 4 unpaired electrons. The extra energy released when these electrons are used for bonding more than compensates for the initial input. The carbon atom is now said to be in an excited state.

Hybridisation

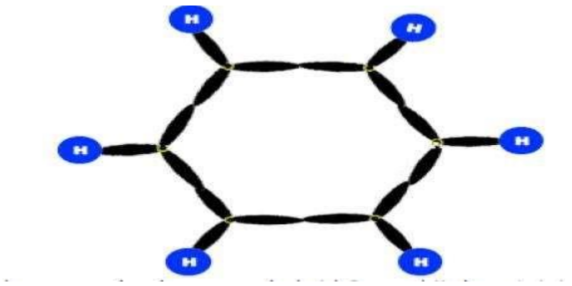
Because each carbon is only joining to three other atoms, when the carbon atoms hybridise their outer orbitals before forming bonds, they only need to hybridise *three* of the orbitals rather than all four. They use the **2s** electron and two of the 2p electrons, but leave the other **2p** electron unchanged.



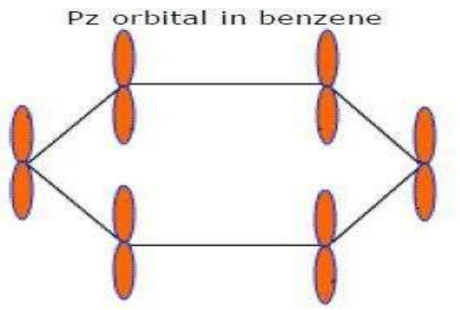
☐ The new orbitals formed are called **sp2** *hybrids*, because they are made by an **s** orbital and two **p** orbitals reorganizing themselves.

- The three **sp2** hybrid orbitals arrange themselves as far apart as possible which is at 120° to each other in a plane. The remaining **p** orbital is at right angles to them.
- Each carbon atom now looks like the diagram on the right. This is all exactly the same as happens in ethene.
- The difference in benzene is that each carbon atom is joined to two other similar carbon atoms instead of just one. Each carbon atom uses the **sp2** hybrids to form sigma bonds with two other carbons and one hydrogen atom.

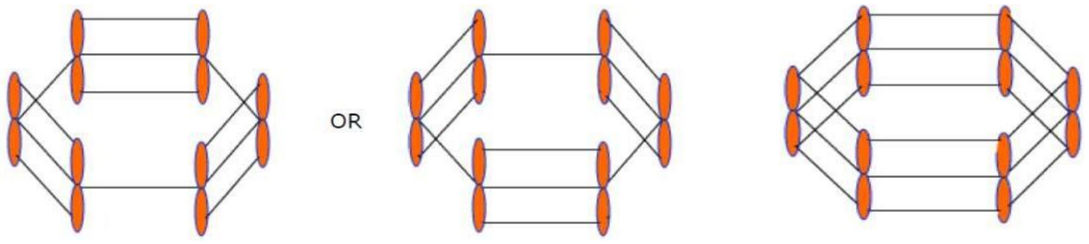
- The next diagram shows the sigma bonds formed, but for the moment leaves the **p** orbitals alone.



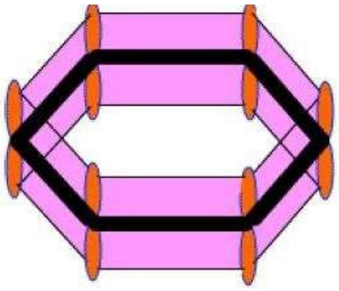
Since sigma bond results from the overlap of above said planar orbital, all **H** and **C** atoms are in the same plane and their generate a hexagonal ring of **C** atoms.



Each **C** atom in benzene also has an unhybrid **2pz** orbital containing one electron. These **2pz** orbital are perpendicular to the plane of sigma bonds.



Actually these **2pz** orbital produce a **π (pi)** molecular orbital containing six electrons. One half of this **π (pi)** molecular orbital lies above the plane of hexagonal ring and remaining half below the ring like a sandwich.

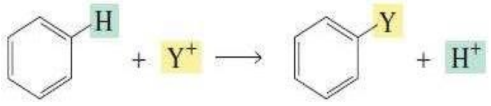


The overlap of these **2pz** orbital results in the formation of a fully delocalized **π (pi)** bond, which extends all over the six **C** atoms of benzene nucleus. The molecular orbital approach clearly indicates that these six electrons could be found anywhere in highly delocalized manner. As a result of delocalization, a stronger **π (pi)** bond and a more stable benzene molecule is obtained which undergo substitution reactions more frequently than addition reactions.

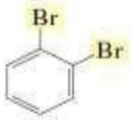
- Benzene is a flat molecule, with every carbon and hydrogen lying in the same plane these bonds are designated as a sigma (σ) bonds.

- Each sp^2 hybridized C in the ring has an unhybridized *p* orbital perpendicular to the ring which overlaps around the ring.
- The six pi (π) electrons are delocalized over the six carbons.

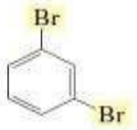
(c) Benzene yields only one monosubstitution product, C_6H_5Y. Only one bromobenzene, C_6H_5Br, is obtained when one hydrogen atom is replaced by bromine; similarly, only one chlorobenzene, C_6H_5C1, or one nitrobenzene, $C_6H_5NO_2$, etc., has ever been made. This fact places a severe limitation on the structure of benzene: each hydrogen must be exactly equivalent to every other hydrogen, since the replacement of any one of them yields the same product.



(d) Benzene yields three isomeric disubstitution products, $C_6H_4Y_2$ or C_6H_4YZ. e.g. like only three isomeric dibromobenzenes, $C_6H_4Br_2$, three chloronitrobenzenes, $C_6H_4ClNO_2$, etc. This fact further limits our choice of a structure to Kekule's structure of benzene compare to any other structures with the molecular formula C_6H_6.



1,2-dibromobenzene
ortho-dibromobenzene
o-dibromobenzene

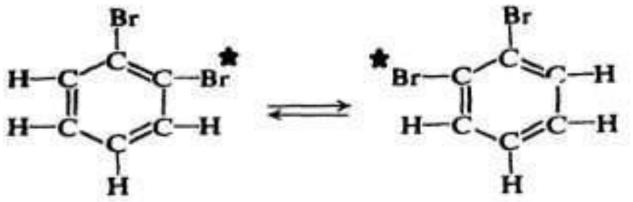


1,3-dibromobenzene
meta-dibromobenzene
m-dibromobenzene

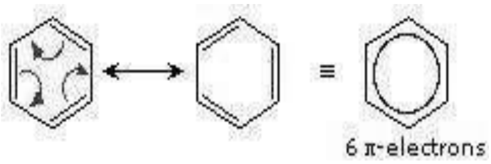
1,4-dibromobenzene
para-dibromobenzene
p-dibromobenzene

The relative positions of two substituents on a benzene ring can be indicated either by numbers or by the prefixes ortho, meta, and para. Adjacent substituents are called ortho, substituents separated by one carbon are called meta, and substituents located opposite one another are designated para. Often, only their abbreviations (o, m, p) are used in naming compounds.

However, that two 1,2-dibromo isomers differing in the positions of bromine relative to the double bonds, should be possible:



On the other hand, it is believed by some that Kekule had unthinkingly anticipated our present concept of *delocalized electrons*, and drew two pictures (as shown above). The currently accepted structure did not arise from the discovery of new facts about benzene, but is the result of an extension or modification of the structural theory; this extension is the concept of resonance.



OR

I

II

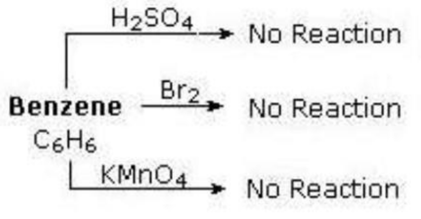
Resonance: structures that differ only in the arrangement of electrons. Benzene is a hybrid of I and II. Since; I and II are exactly equivalent, and hence of exactly the same stability, they make equal contributions to the hybrid.

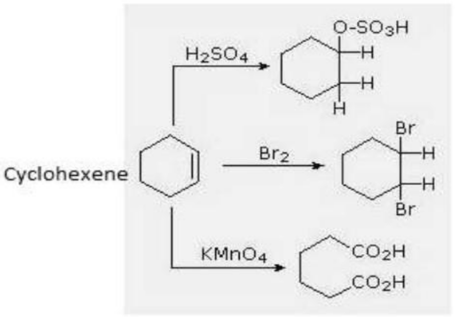
Stability:

The most striking evidence to unusual stability of benzene ring is found in the chemical reactions of benzene & the heat released in a hydrogenation reaction of one mole of an unsaturated compound.

☐ **Benzene undergoes substitution rather than addition.**

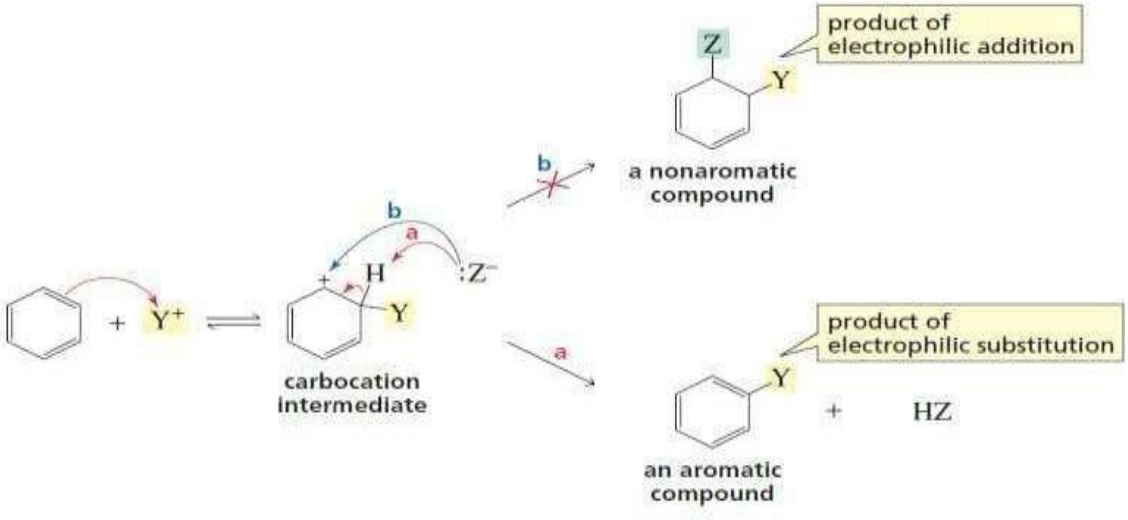
- Kekule's structure of benzene is one that we would call "cyclohexatriene." We would expect this cyclohexatriene, like the very similar compounds, cyclohexadiene and cyclohexene, to undergo readily the addition reactions characteristic of the alkene structure.
- Example: cyclohexene an alkene undergoes rapid addition reaction, under same conditions were benzene reacts either not at all or very slowly and this exhibited a high degree of unusual chemical stability of benzene compared with known alkenes and cycloalkenes (aliphatic compounds).





- Example: In addition reaction an alkene reacts with an electrophile, thereby forming a carbocation intermediate. In the second step of an electrophilic addition reaction, the carbocation reacts with a nucleophile to form an addition product.

If the carbocation intermediate formed from the reaction of benzene with an electrophile were to react similarly with a nucleophile (depicted as event b in Figure below), the addition product would not be aromatic. If, however, the carbocation loses a proton from the site of electrophilic attack (depicted as event a in Figure below), the aromaticity of the benzene ring is restored. Because the aromatic product is much more stable than the nonaromatic addition product, the overall reaction is an electrophilic substitution reaction rather than an electrophilic addition reaction. In the substitution reaction, an electrophile substitutes for one of the hydrogens attached to the benzene ring.



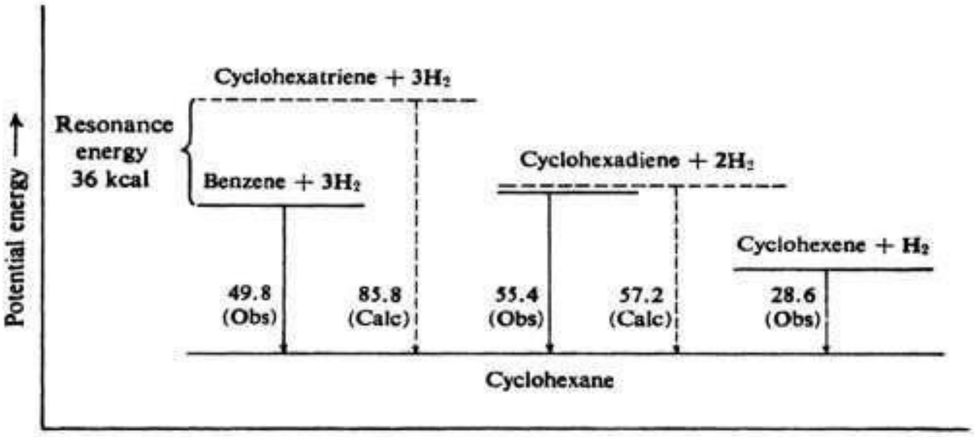
In place of addition reactions, benzene readily undergoes a new set of reactions, all involving substitution. The most important are **Halogenation, Nitration, Sulfonation, Friedel–Crafts acylation & Friedel–Crafts alkylation.**

In an electrophilic aromatic substitution reaction, an electrophile is put on a ring carbon, and the H^+ comes off the same ring carbon.

Heat of hydrogenation (resonance energy) and combustion.

- The heat released in a hydrogenation reaction of one mole of an unsaturated (double bonded) compound is called the **heat of hydrogenation**.
- A quantitative data which show how much more stable is benzene.
- Cyclohexene has a heat of hydrogenation of 28.6 kcal and cyclohexadiene has one about twice that (55.4 kcal.)

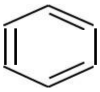
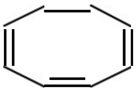
- We expected cyclohexatriene (i.e. in imagine that benzene contains three double bonds in it) to have a heat of hydrogenation about three times as large as cyclohexene, that is, about 85.8 kcal. Actually the value for benzene (49.8 kcal) is 36 kcal less than this expected amount.
- The fact that benzene evolves 36 kcal less energy than predicted can only mean that benzene contains 36 kcal less energy than predicted; in other words, *benzene is more stable* by 36 kcal than we would have expected cyclohexatriene to be.



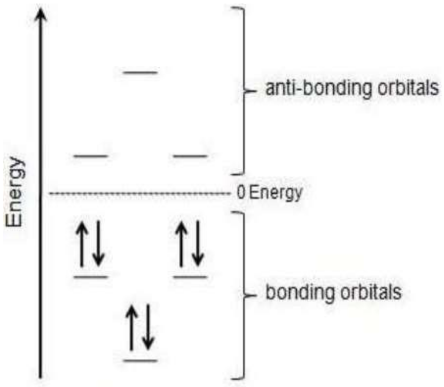
Aromatic character: The Huckel 4n + 2 rule

In 1931, German chemist and physicist Erich Hückel proposed a theory to help determine if a planar ring molecule would have aromatic properties. His rule states that if a cyclic, planar molecule has 4n+2 π (*Pi*) electrons, it is considered aromatic. This rule would come to be known as Hückel's Rule.

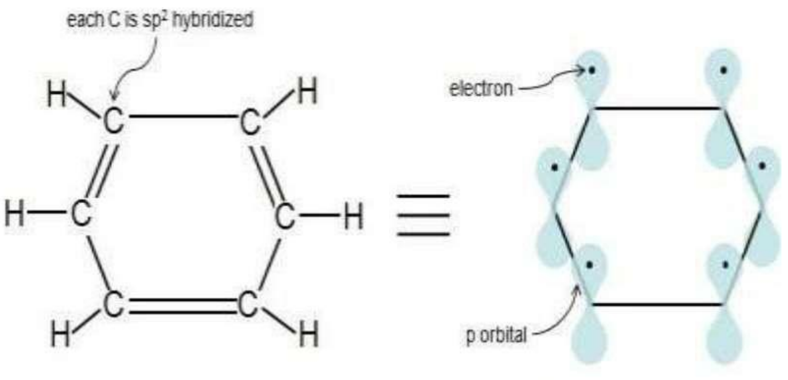
Criteria for Aromaticity & Anti-Aromaticity:

Aromatic	Anti-aromatic	Non-aromatic
The molecule is cyclic (a ring of atoms)	The molecule is cyclic (a ring of atoms)	Fails any one of the criteria on the left OR everything else
The molecule is planar or flat (all atoms in the molecule lie in the same plane)	The molecule is planar or flat (all atoms in the molecule lie in the same plane)	
The molecule is fully conjugated (p orbitals at every atom in the ring)	The molecule is fully conjugated (p orbitals at every atom in the ring)	
The molecule has 4n+2 π electrons (n=0 or any positive integer)	The molecule has 4n π Electrons	
Unusually stable	Unusually stable	
 Benzene	 Cyclobutadiene	 Cyclooctatetraene
Resonance energy (heat of hydrogenation energy) 36 kcal/mol	Only stable below -100°C	

- According to Hückel's Molecular Orbital Theory, a compound is particularly stable if all of its bonding molecular orbitals are filled with paired electrons.
- With aromatic compounds, 2 electrons fill the lowest energy molecular orbital, and 4 electrons fill each subsequent energy level (the number of subsequent energy levels is denoted by n) leaving all bonding orbitals filled and no anti-bonding orbitals occupied.
- This gives a total of 4n+2 π electrons.
- In benzene, each double bond (π bond) always contributes 2 π electrons. Benzene has 3 double bonds, so it has 6 π electrons.
- Its first 2 π electrons fill the lowest energy orbital, and 4 π electrons remaining fill in the orbitals of the succeeding energy level.
- Notice how all of its bonding orbitals are filled, but none of the anti-bonding orbitals have any electrons.



molecular orbital diagram for benzene



benzene has 6 π electrons

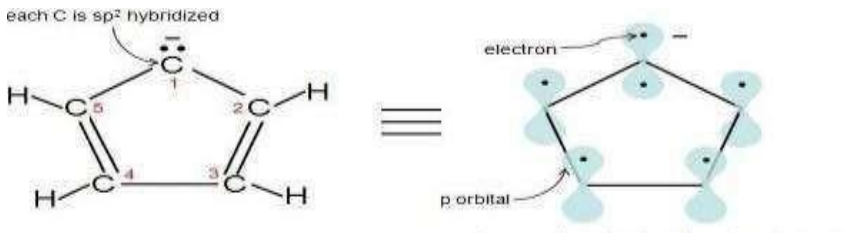
- To apply the 4n+2 rule, first count the number of π electrons in the molecule. Then, set this number equal to 4n+2 and solve for n. If is 0 or any positive integer (1, 2, 3,...), the rule has been met. For example, benzene has six π electrons:

$$4n+2=6$$
$$4n=4$$
$$n=1$$

For benzene, we find that n=1, which is a positive integer, so the rule is met. Benzene is aromatic compound.

Aromatic Ions

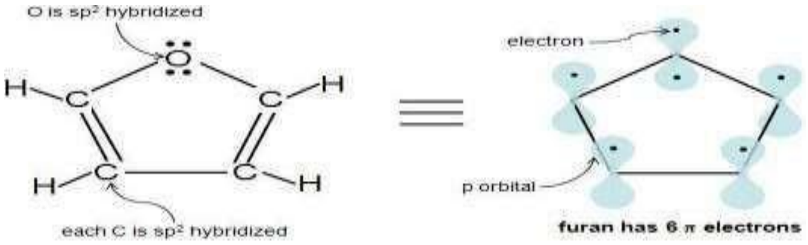
- Hückel's Rule also applies to ions especially aromatic ions. As long as a compound has 4n+2 π electrons, it does not matter if the molecule is neutral or has a charge.
- For example, cyclopentadienyl anion is an aromatic ion.
- Carbons 2-5 are sp2 hybridized because they have 3 attached atoms and have no lone electron pairs.
- If an atom has 1 or more lone pairs and is attached to an sp2 hybridized atom, then that atom is sp2 hybridized also.
- Therefore, carbon 1 also sp2 hybridized, it has a p orbital. Cyclopentadienyl anion has 6 π electrons and fulfills the 4n+2 rule.



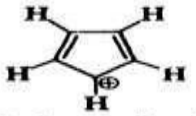
cyclopentadienyl anion has 6 π electrons

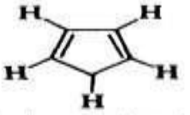
Heterocyclic Aromatic Compounds

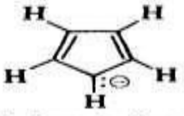
- Heterocyclic compounds contain 1 or more different atoms other than carbon in the ring. A common example is furan, which contains an oxygen atom.
- All carbons in furan are sp^2 hybridized.
- The oxygen has at least 1 lone electron pair and is attached to an sp2 hybridized atom, so it is sp^2 hybridized as well.
- Notice how oxygen has 2 lone pairs of electrons. How many of those electrons are π electrons?
- A sp^2 hybridized atom only has 1 p orbital, which can only hold 2 electrons, so we know that 1 electron pair is in the p orbital, while the other pair is in an sp^2 orbital. So, only 1 of oxygen's 2 lone electron pairs are π electrons.
- So, Furan has 6 π electrons and fulfills the 4n+2 rule

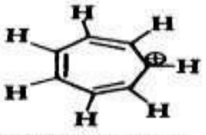


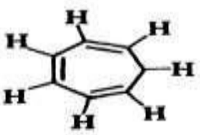
Working example I: Using the criteria for aromaticity, determine if the following molecules are aromatic:

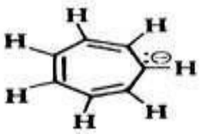

Cyclopentadienyl cation


Cyclopentadienyl radical

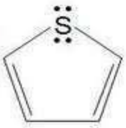

Cyclopentadienyl anion

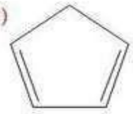

Cycloheptatrienyl cation (Tropylium ion)


Cycloheptatrienyl radical


Cycloheptatrienyl anion

Working example II: Using the criteria for aromaticity, determine if the following molecules are aromatic:

1)


2)


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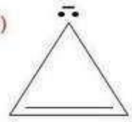

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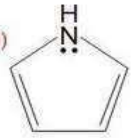

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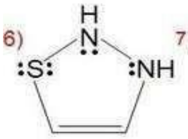

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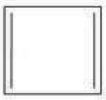

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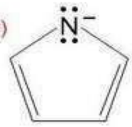

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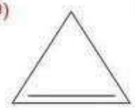

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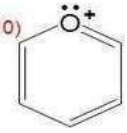

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