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Research Article

## SURVEY IN AROMATIC COMPOUNDS

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### Abstract

In this survey, aromatic compounds, methods of preparations, reactions, stability, active position (ortho, meta, para)-substitution on benzene ring or other aromatic rings, some of applications, comparison of stability, nomenclature, hetero cycles containing more than one hetero atom.

**Keywords:** benzene, electrophyl, substitution, aromatic compound, nucleophile.

### Introduction

#### Aromatic Substitution Reactions

#### Electrophilic Substitution of Disubstituted Benzene Rings

When a benzene ring has two substituent groups, each exerts an influence on subsequent substitution reactions. The activation or deactivation of the ring can be predicted more or less by the sum of the individual effects of these substituents. The site at which a new substituent is introduced depends on the orientation of the existing groups and their individual directing effects. We can identify two general behavior categories, as shown in the following table. Thus, the groups may be oriented in such a manner that their directing influences act in concert, reinforcing the outcome; or are opposed (antagonistic) to each other. Note that the orientations in each category change depending on whether the groups have similar or opposite individual directing effects.

The products from substitution reactions<sup>(1-4)</sup> of compounds having a reinforcing orientation of substituents are easier to predict than those having antagonistic substituents. For example, the six equations shown below are all examples of reinforcing or cooperative directing effects operating in the expected manner. Symmetry, as in the first two cases,

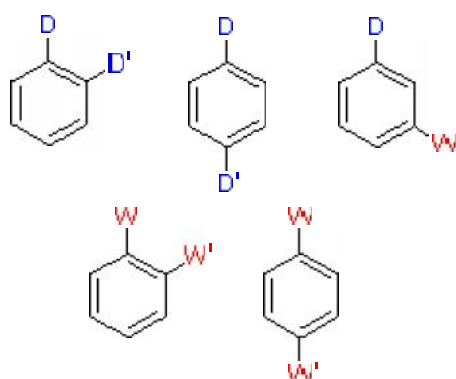
makes it easy to predict the site at which substitution is likely to occur. Note that if two different sites are favored, substitution will usually occur at the one that is least hindered by ortho groups.

The first three examples have two similar directing groups in a meta-relationship to each other. In examples 4 through 6, oppositely directing groups have an ortho or para-relationship. The major products of electrophilic substitution, as shown, are the sum of the individual group effects. The strongly activating hydroxyl (–OH) and amino (–NH<sub>2</sub>) substituents favor dihalogenation in examples 5 and six.

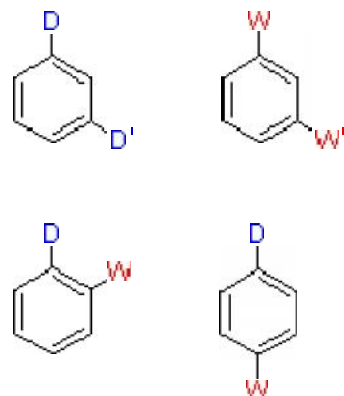
Substitution reactions of compounds having an antagonistic orientation of substituents require a more careful analysis. If the substituents are identical, as in example 1 below, the symmetry of the molecule will again simplify the decision. When one substituent has a pair of non-bonding electrons available for adjacent charge stabilization, it will normally exert the product determining influence, examples 2, 4 & 5, even though it may be overall deactivating (case 2). Case 3 reflects a combination of steric hindrance and the superior innate stabilizing ability of methyl groups relative to other alkyl substituents. Example 6 is interesting in that it demonstrates the conversion of an activating ortho/para-directing group into a deactivating meta-directing "onium" cation [–NH(CH<sub>3</sub>)<sub>2</sub><sup>(+)</sup>] in a strong acid environment.

### Oriental Interaction of Substituents

#### Antagonistic or Non-Cooperative



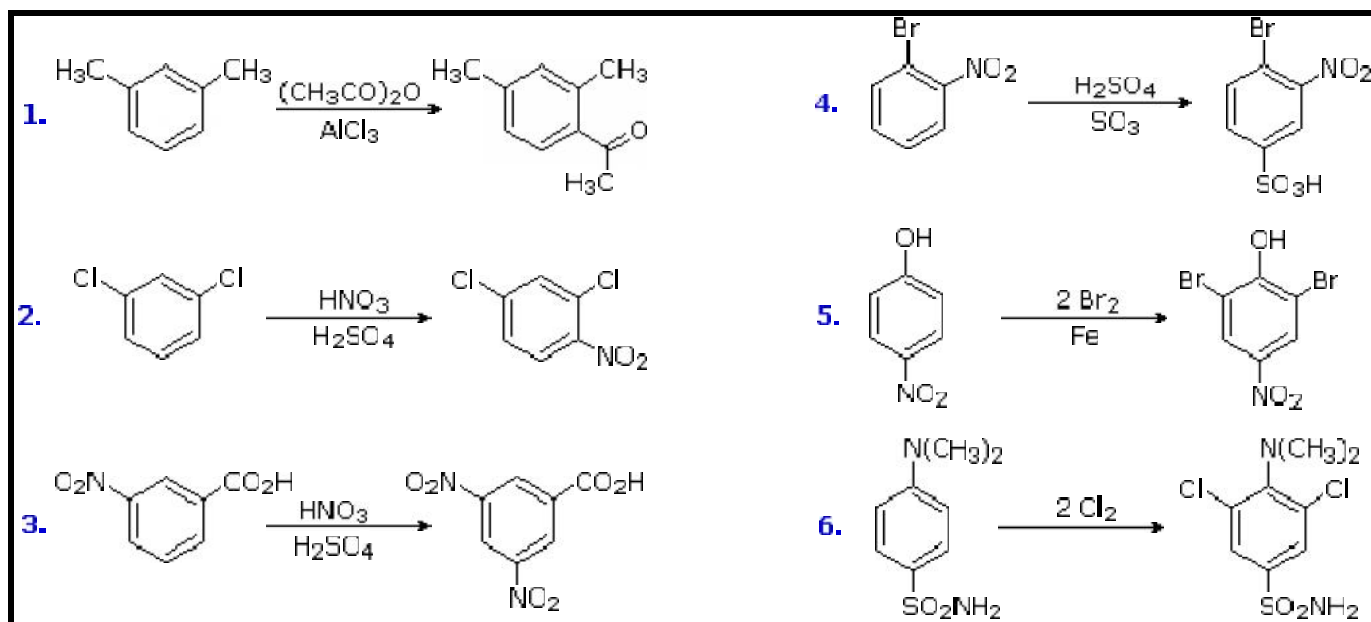
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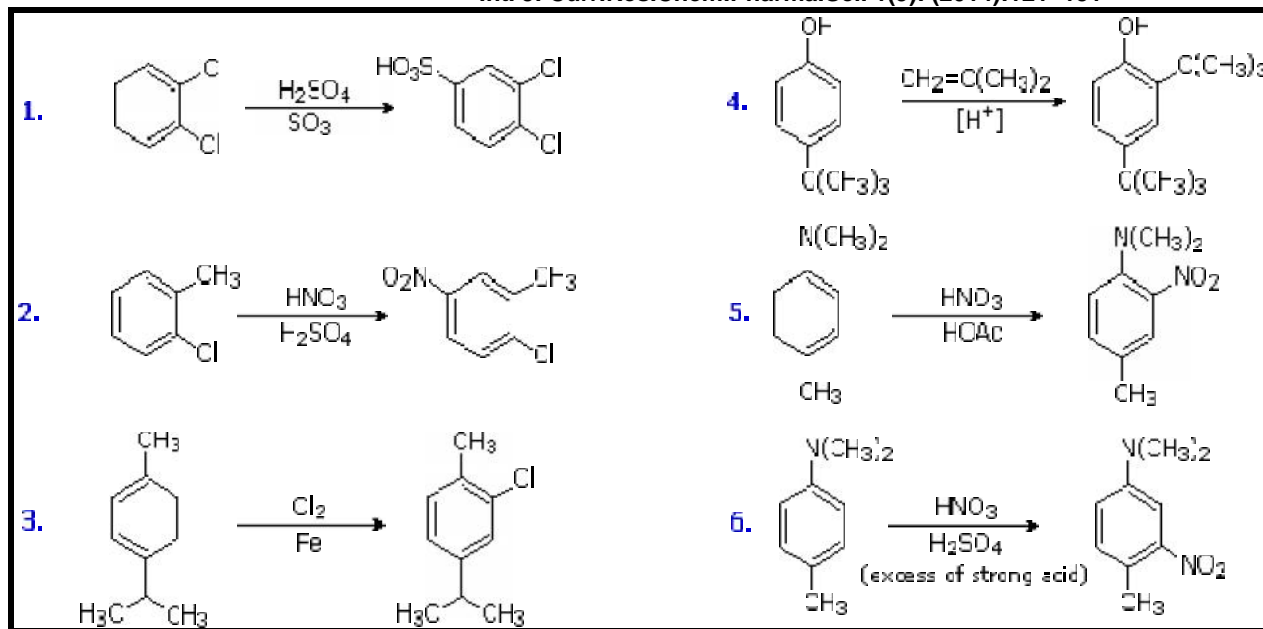


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D = Electron Donating Group (ortho/para-directing)

W = Electron Withdrawing Group (meta-directing)

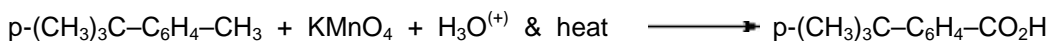
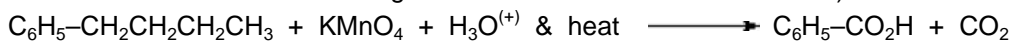




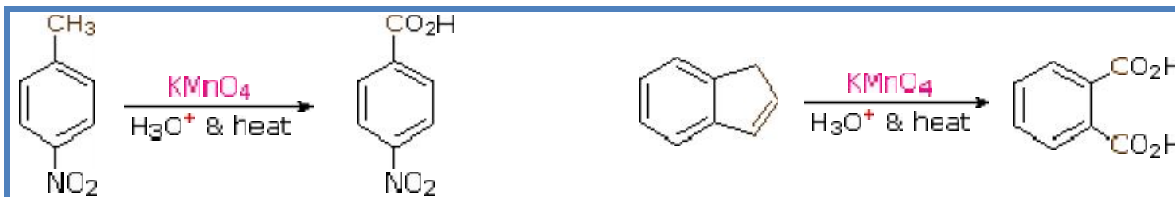
## Reactions of Substituent Groups

### A. Oxidation of Alkyl Side-Chains

The benzylic hydrogens of alkyl substituents on a benzene ring are activated toward free radical attack, as noted earlier. Furthermore,  $S_N1$ ,  $S_N2$  and  $E1$  reactions of benzylic halides, show enhanced reactivity, due to the adjacent aromatic ring. The possibility that these observations reflect a general



These equations are not balanced. The permanganate oxidant is reduced, usually to Mn(IV) or Mn(II). Two other examples of this reaction are given below, and



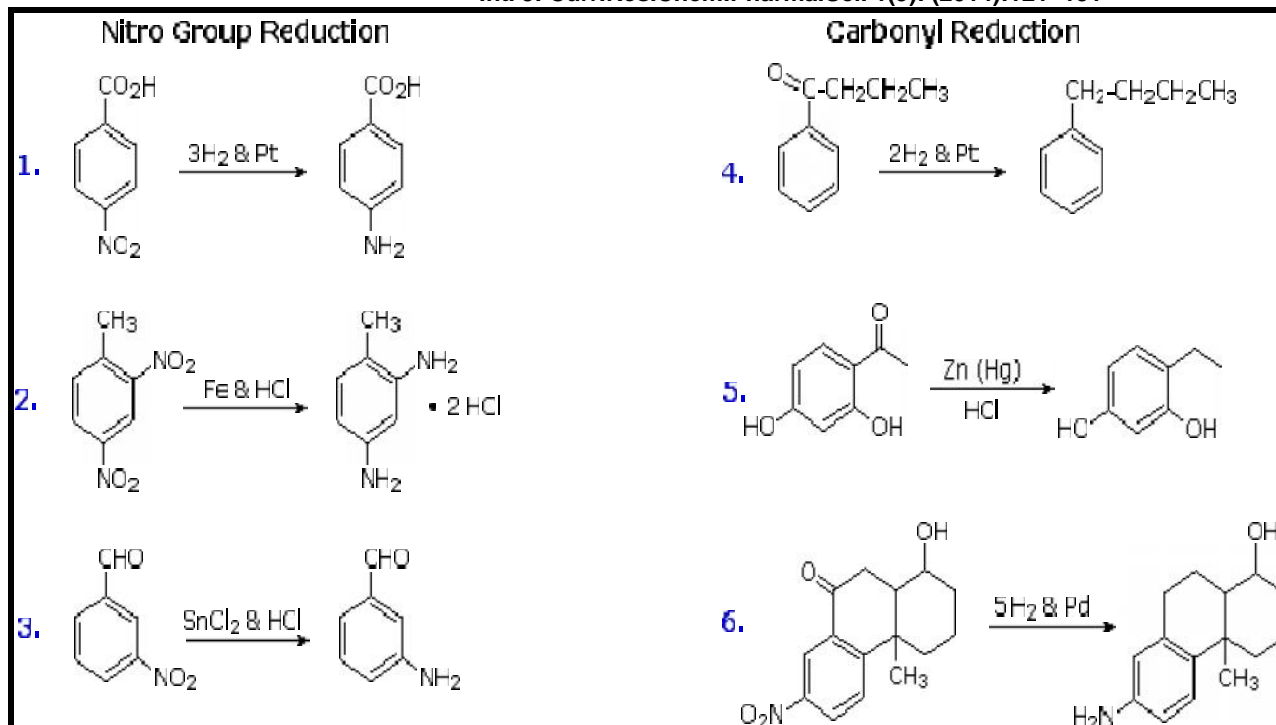
### B. Reduction of Nitro Groups and Aryl Ketones

Electrophilic nitration<sup>(5-8)</sup> and Friedel-Crafts acylation reactions introduce deactivating, meta-directing substituents on an aromatic ring. The attached atoms are in a high oxidation state, and their reduction converts these electron withdrawing functions into electron donating amino and alkyl groups. Reduction is easily achieved either by catalytic hydrogenation ( $H_2$  + catalyst), or with reducing metals in acid. Examples

benzylic activation is supported by the susceptibility of alkyl side-chains to oxidative degradation, as shown in the following examples (the oxidized side chain is colored). Such oxidations are normally effected by hot acidic permanganate solutions, but for large scale industrial operations catalyzed air-oxidations are preferred. Interestingly, if the benzylic position is completely substituted this oxidative degradation does not occur (second equation, the substituted benzylic carbon is colored blue).

illustrate its usefulness in preparing substituted benzoic acids.

of these reductions are shown here, equation 6 demonstrating the simultaneous reduction of both functions. Note that the butylbenzene product in equation 4 cannot be generated by direct Friedel-Crafts alkylation due to carbocation rearrangement. The zinc used in ketone reductions, such as 5, is usually activated by alloying with mercury (a process known as amalgamation).

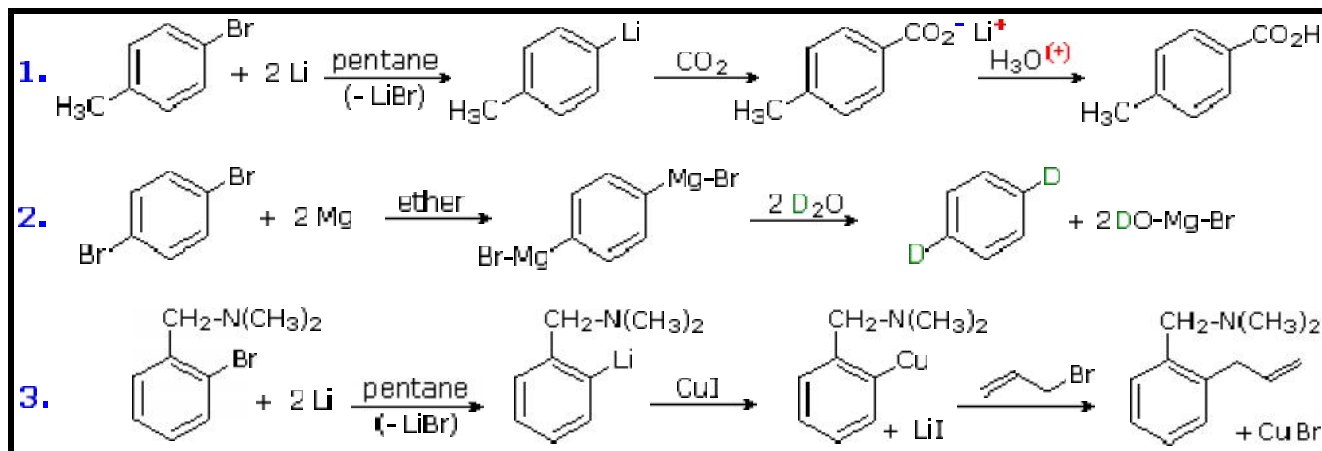


Several alternative methods for reducing nitro groups to amines are known. These include zinc or tin in dilute mineral acid, and sodium sulfide in ammonium hydroxide solution. The procedures described above are sufficient for most cases.

### C. Conversion of Halogens to Organometallic Reagents

The reaction of alkyl and aryl halides with reactive metals (usually Li & Mg) to give nucleophilic reagents has been noted. This provides a powerful tool for the conversion of chloro, bromo or iodo substituents into a variety of other groups. Many reactions of these aryl lithium and Grignard reagents will be discussed in later sections, and the following equations provide typical examples of carboxylation, protonation and Gilman

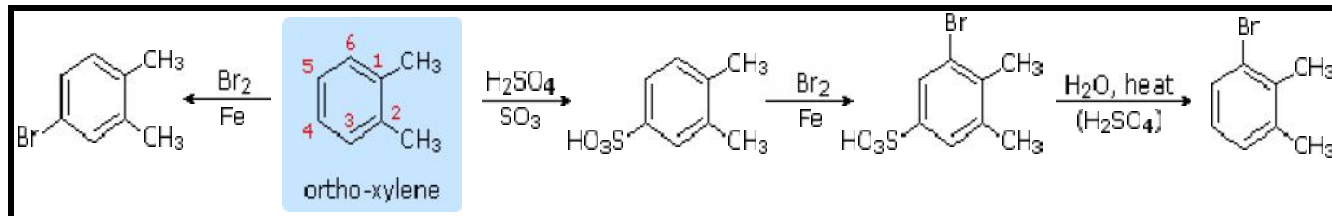
coupling. Metal halogen exchange reactions take place at low temperature, and may be used to introduce iodine at designated locations. An example of this method will be displayed below by clicking on the diagram. In this example care must be taken to maintain a low temperature, because elimination to an arylene intermediate takes place on warming.



### D. Hydrolysis of Sulfonic Acids

The potential reversibility of the aromatic sulfonation reaction was noted earlier. The following equation illustrates how this characteristic of the sulfonic acids

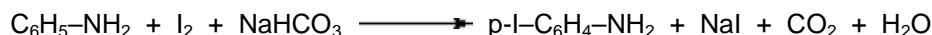
may be used to prepare the 3-bromo derivative of ortho-xylene. Direct bromination would give the 4-bromo derivative.



### E. Modifying the Influence of Strong Activating Groups

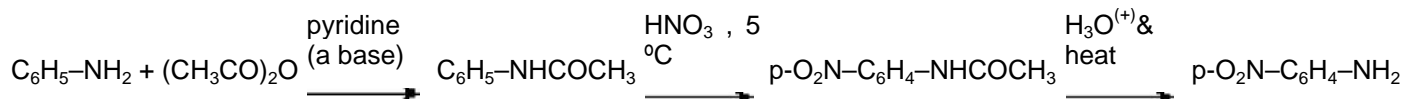
The strongest activating and ortho/para-directing substituents are the amino (-NH<sub>2</sub>) and hydroxyl (-OH) groups. Direct nitration of phenol (hydroxybenzene) by dilute nitric acid gives modest yields of nitrated phenols and considerable oxidative decomposition to tarry materials; aniline (aminobenzene) is largely destroyed. Bromination of both phenol and aniline is difficult to control, with di- and tri-bromo products

forming readily. Because of their high nucleophilic reactivity, aniline and phenol undergo substitution reactions with iodine, a halogen that is normally unreactive with benzene derivatives. The mixed halogen iodine chloride (ICl) provides a more electrophilic iodine moiety, and is effective in iodinating aromatic rings having less powerful activating substituents.



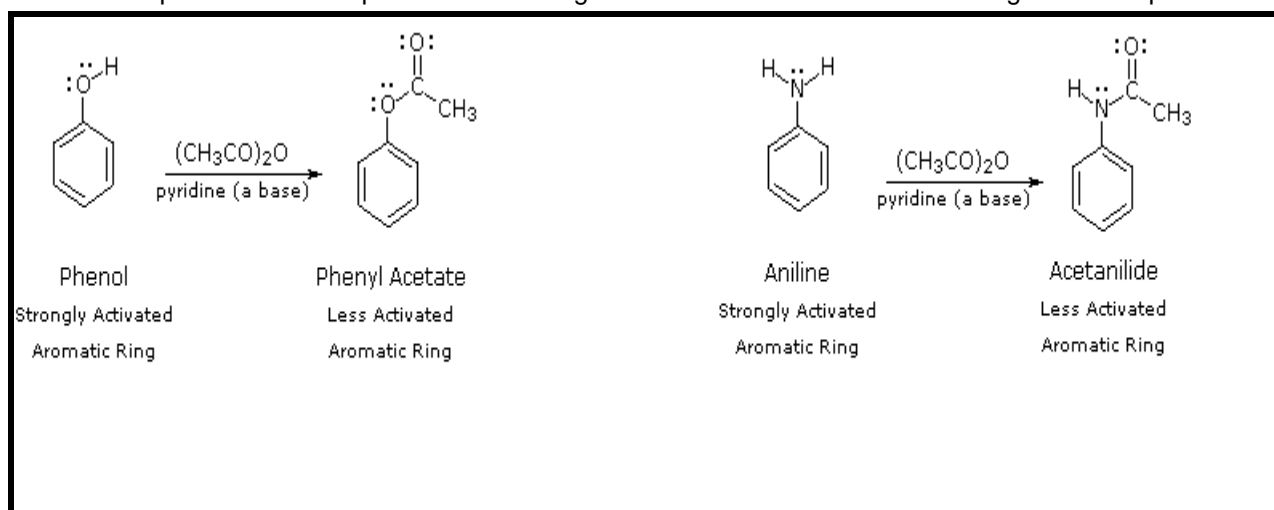
By acetylating the heteroatom substituent on phenol and aniline, its activating influence can be substantially attenuated. For example, acetylation of aniline gives acetanilide (first step in the following equation), which undergoes nitration at low temperature, yielding the para-nitro product in high yield. The modifying acetyl

group can then be removed by acid-catalyzed hydrolysis (last step), to yield para-nitroaniline. Although the activating influence of the amino group has been reduced by this procedure, the acetyl derivative remains an ortho/para-directing and activating substituent.

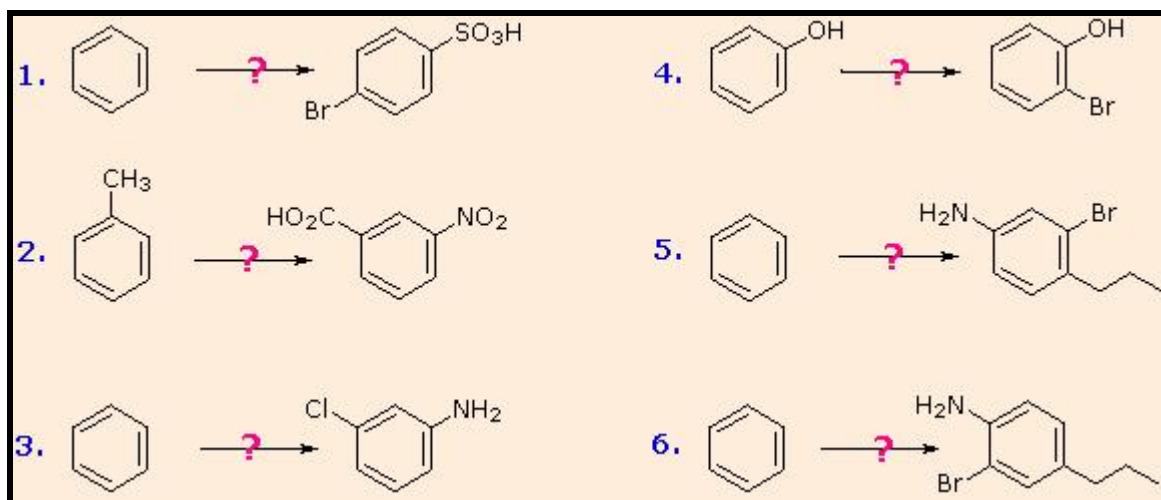


The following diagram illustrates how the acetyl group acts to attenuate the overall electron donating character of oxygen and nitrogen. The non-bonding valence electron pairs that are responsible for the high

reactivity of these compounds (blue arrows) are diverted to the adjacent carbonyl group (green arrows). However, the overall influence of the modified substituent is still activating and ortho/para-directing.



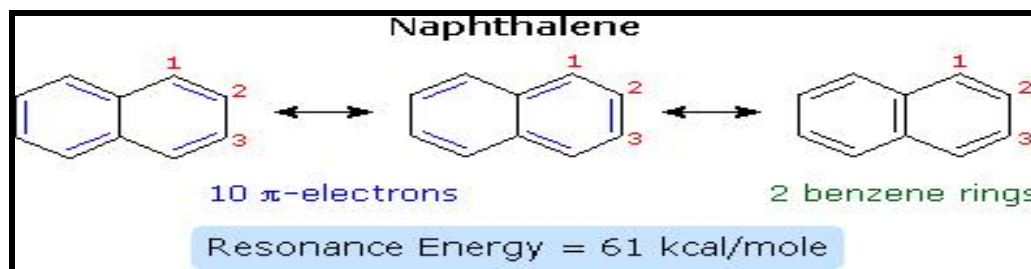
It should now be apparent that an extensive "toolchest" of reactions are available to us for the synthesis of substituted benzenes. Just as an expert carpenter must understand the characteristics and limitations of his/her tools, chemists must appreciate the nature of their "tools" when applying them to a specific synthesis. Six proposed syntheses are listed in the following diagram in rough order of increasing complexity. You should try to conceive a plausible reaction sequence for each. Once you have done so, you may check suggested answers by clicking on the question mark for each.



### Reactions of Fused Benzene Rings

Compounds in which two or more benzene rings are fused together were described in an earlier section, and they present interesting insights into aromaticity

and reactivity. The smallest such hydrocarbon is naphthalene. Naphthalene is stabilized by resonance. Three canonical resonance contributors may be drawn, and are displayed in the following diagram.

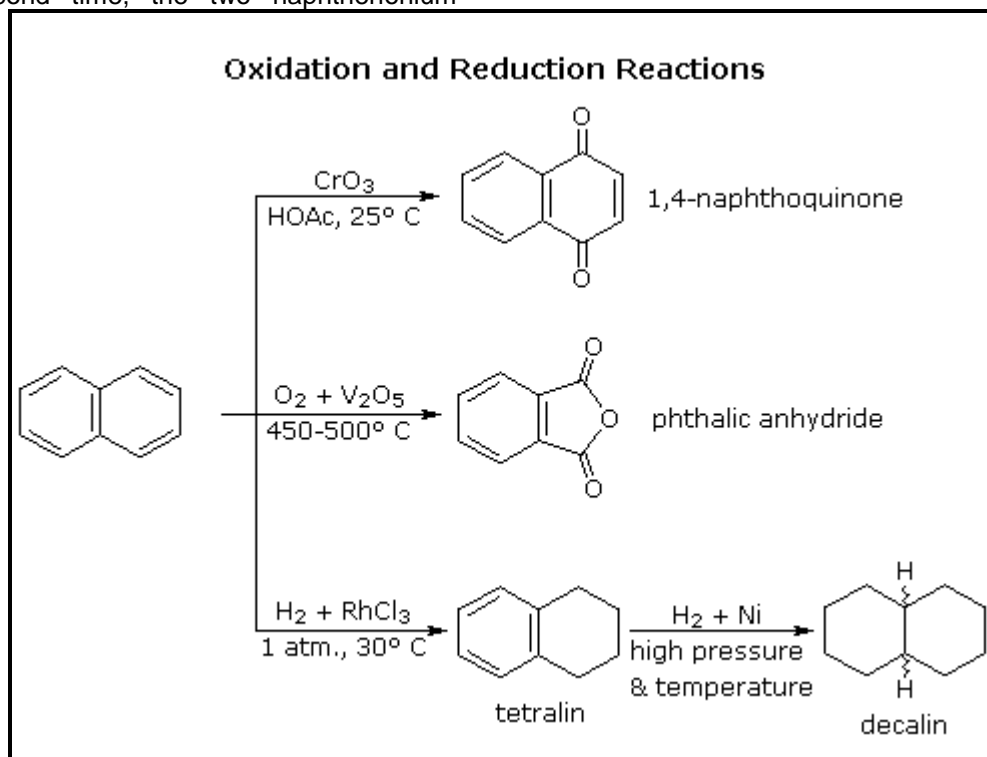


The two structures on the left have one discrete benzene ring each, but may also be viewed as 10- $\pi$ -electron annulenes having a bridging single bond. The structure on the right has two benzene rings which share a common double bond. From heats of hydrogenation or combustion, the resonance energy of naphthalene is calculated to be 61 kcal/mole, 11 kcal/mole less than that of two benzene rings ( $2 \times 36$ ). As expected from an average of the three resonance contributors, the carbon-carbon bonds in naphthalene show variation in length, suggesting some localization of the double bonds. The C1–C2 bond is 1.36 Å long, whereas the C2–C3 bond length is 1.42 Å. This contrasts with the structure of benzene, in which all the C–C bonds have a common length, 1.39 Å.

Naphthalene is more reactive than benzene, both in substitution and addition reactions, and these reactions tend to proceed in a manner that maintains one intact benzene ring. The following diagram shows three oxidation and reduction reactions that illustrate this feature. In the last example, catalytic hydrogenation of one ring takes place under milder conditions than those required for complete saturation (the decalin product exists as cis/trans isomers). Electrophilic substitution reactions take place more rapidly at C1, although the C2 product is more stable and predominates at equilibrium. Examples of these reactions will be displayed by clicking on the diagram. The kinetically favored C1 orientation reflects a

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intermediates created by attack at C1 and C2 will be displayed.



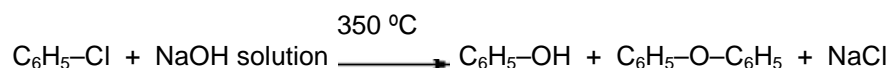
The structure and chemistry of more highly fused benzene ring compounds, such as anthracene and

phenanthrene show many of the same characteristics described above.

### Nucleophilic Substitution, Elimination & Addition Reactions

### Nucleophilic Substitution, Elimination & Addition Reactions of Benzene Derivatives Substitution<sup>(9-12)</sup>:

An early method of preparing phenol (the Dow process) involved the reaction of chlorobenzene with a

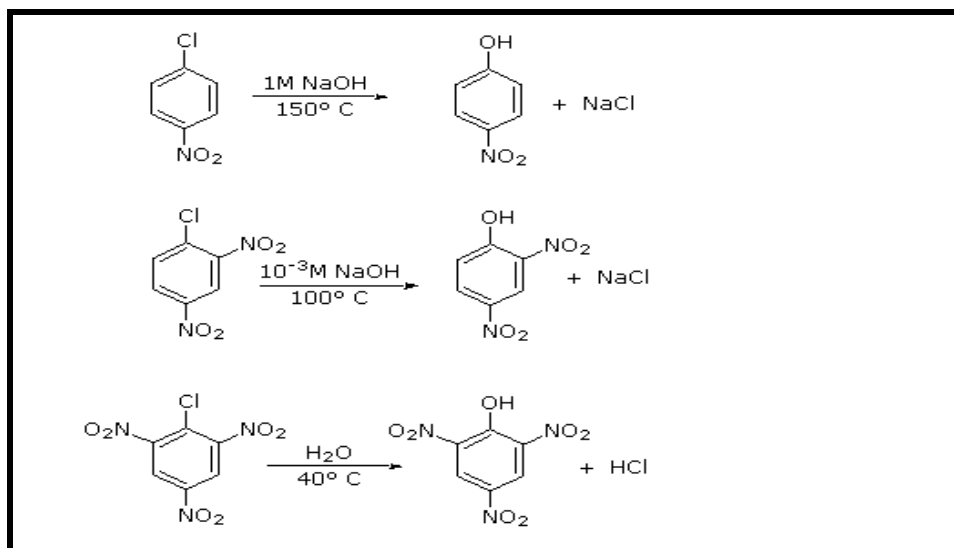


The presence of electron-withdrawing groups (such as nitro) ortho and para to the chlorine substantially enhance the rate of substitution, as shown in the set of equations presented on the left below. To explain this, a third mechanism for nucleophilic substitution has been proposed. This two-step mechanism is characterized by initial addition of the nucleophile (hydroxide ion or water) to the aromatic ring, followed by loss of a halide anion from the negatively charged intermediate. This is illustrated by clicking the "Show Mechanism" button next to the diagram. The sites over which the negative charge is delocalized are colored blue, and the ability of nitro, and other electron withdrawing, groups to stabilize adjacent negative

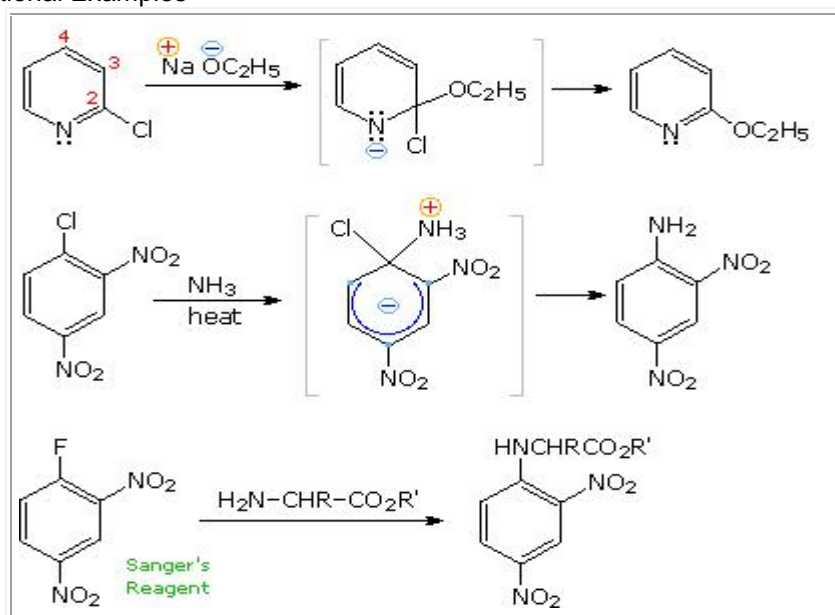
concentrated sodium hydroxide solution at temperatures above 350 °C. The chief products are phenol and diphenyl ether (see below). This apparent nucleophilic substitution reaction is surprising, since aryl halides are generally incapable of reacting by either an S<sub>N</sub>1 or S<sub>N</sub>2 pathway.

charge accounts for their rate enhancing influence at the ortho and para locations.

Three additional examples of aryl halide nucleophilic substitution are presented on the right. Only the 2- and 4-chloropyridine isomers undergo rapid substitution, the 3-chloro isomer is relatively unreactive. Nitrogen nucleophiles will also react, as evidenced by the use of Sanger's reagent for the derivatization of amino acids. The resulting N-2,4-dinitrophenyl derivatives are bright yellow crystalline compounds that facilitated analysis of peptides and proteins, a subject for which Frederick Sanger received one of his two Nobel Prizes in chemistry.



## Additional Examples



Such addition-elimination processes generally occur at  $sp^2$  or  $sp$  hybridized carbon atoms, in contrast to  $S_N1$  and  $S_N2$  reactions. When applied to aromatic halides, as in the present discussion, this mechanism is called

$S_NAr$ . Some distinguishing features of the three common nucleophilic substitution mechanisms are summarized in the following table.

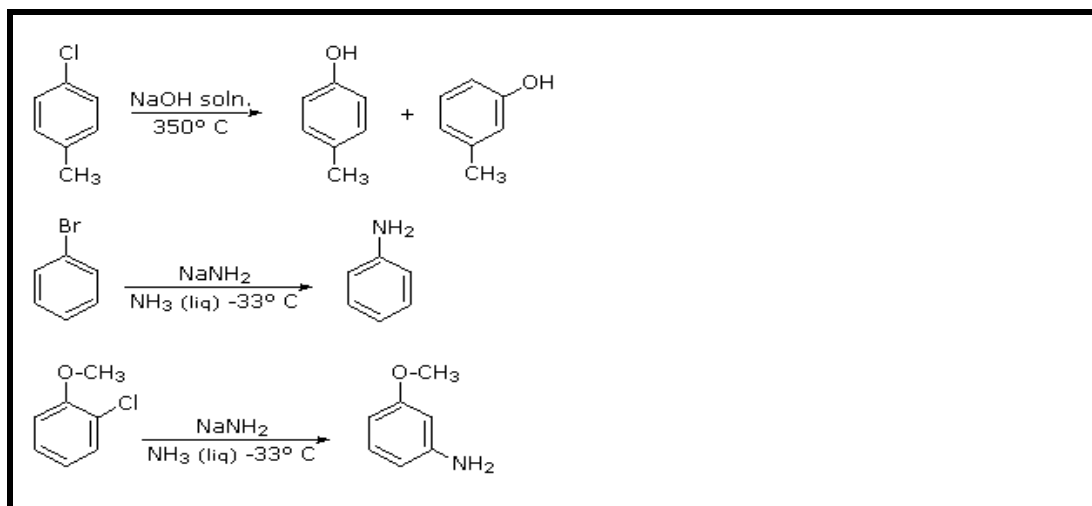
Mechanism	Number of Steps	Bond Formation Timing	Carbon Hybridization
$S_N1$	Two	After Bond Breaking	Usually $sp^3$
$S_N2$	One	Simultaneous with Bond Breaking	Usually $sp^3$
$S_NAr$	Two	Prior to Bond Breaking	Usually $sp^2$



**Elimination:**

There is good evidence that the synthesis of phenol from chlorobenzene does not proceed by the addition-elimination mechanism ( $S_NAr$ ) described above. For example, treatment of para-chlorotoluene with sodium hydroxide solution at temperatures above 350 °C gave an equimolar mixture of meta- and para-cresols

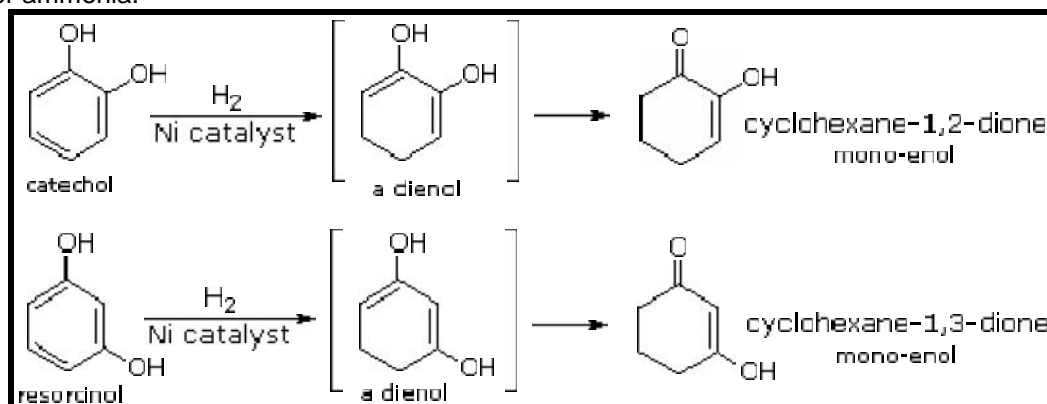
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The explanation for this curious repositioning of the substituent group lies in a different two-step mechanism we can refer to as an elimination-addition process. The intermediate in this mechanism is an unstable benzyne species, as displayed in the above illustration by clicking the "Show Mechanism" button. In contrast to the parallel overlap of p-orbitals in a stable alkyne triple bond, the p-orbitals of a benzyne are tilted *ca.*120° apart, so the reactivity of this incipient triple bond to addition reactions is greatly enhanced. In the absence of steric hindrance (top example) equal amounts of meta- and para-cresols are obtained. The steric bulk of the methoxy group and the ability of its ether oxygen to stabilize an adjacent anion result in a substantial bias in the addition of amide anion or ammonia.

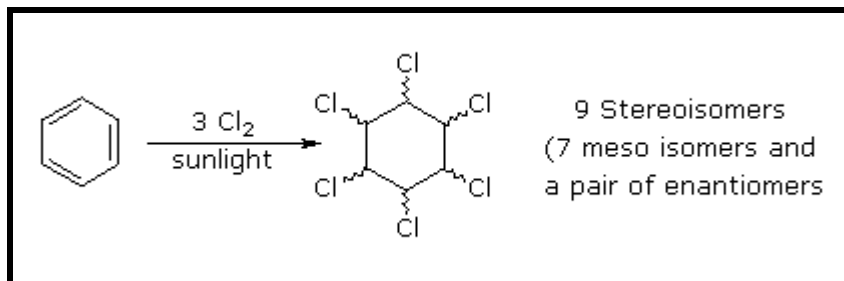
**Addition<sup>(13-17)</sup> :**

Although it does so less readily than simple alkenes or dienes, benzene adds hydrogen at high pressure in the presence of Pt, Pd or Ni catalysts. The product is cyclohexane and the heat of reaction provides evidence of benzene's thermodynamic stability. Substituted benzene rings may also be reduced in this fashion, and hydroxy-substituted compounds, such as phenol, catechol and resorcinol, give carbonyl products resulting from the fast ketonization of intermediate enols. Nickel catalysts are often used for this purpose, as noted in the following equations.



Benzene is more susceptible to radical addition reactions than to electrophilic addition. We have already noted that benzene does not react with chlorine or bromine in the absence of a catalyst and heat. In strong sunlight or with radical initiators benzene adds these halogens to give hexahalocyclohexanes. It is worth noting that these

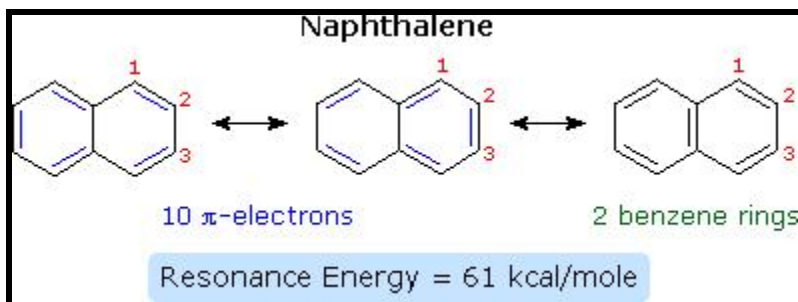
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### Reactions of Fused Benzene Rings<sup>(17-25)</sup> :

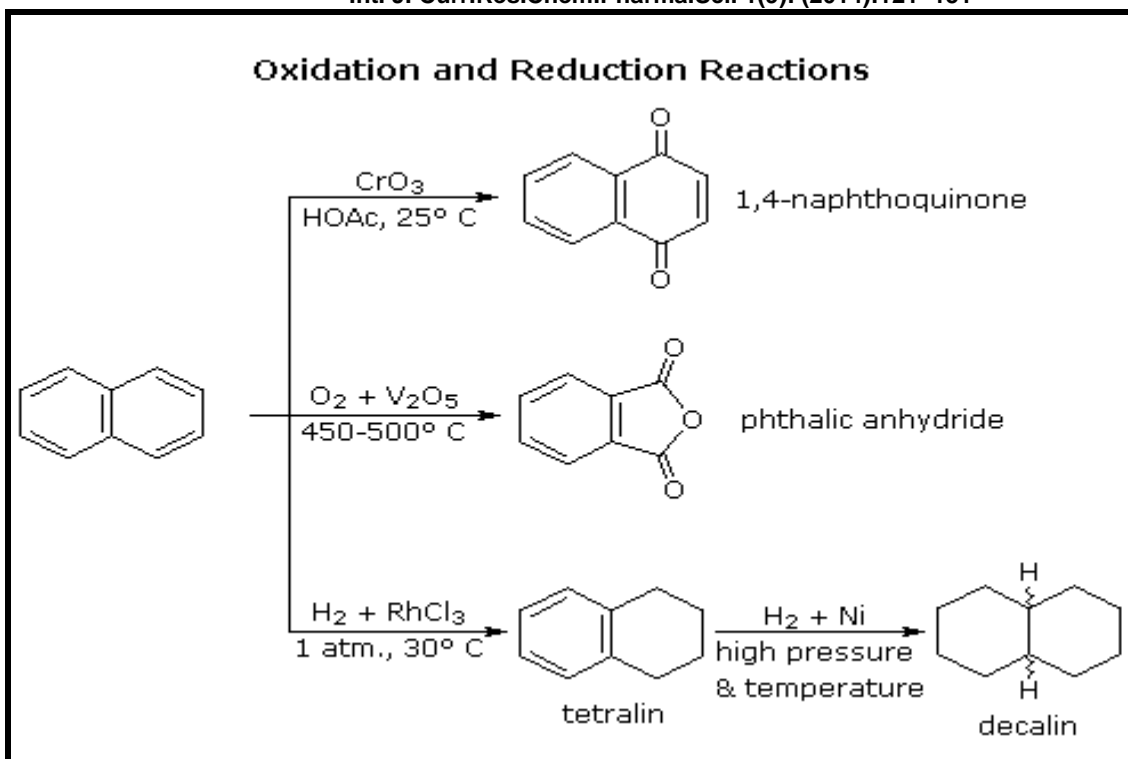
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The two structures on the left have one discrete benzene ring each, but may also be viewed as 10-pi-electron annulenes having a bridging single bond. The structure on the right has two benzene rings which share a common double bond. From heats of hydrogenation or combustion, the resonance energy of naphthalene is calculated to be 61 kcal/mole, 11 kcal/mole less than that of two benzene rings ( $2 \times 36$ ). As expected from an average of the three resonance contributors, the carbon-carbon bonds in naphthalene show variation in length, suggesting some localization of the double bonds. The C1–C2 bond is 1.36 Å long, whereas the C2–C3 bond length is 1.42 Å. This contrasts with the structure of benzene, in which all the C–C bonds have a common length, 1.39 Å. Naphthalene is more reactive than benzene, both in substitution and addition reactions, and these

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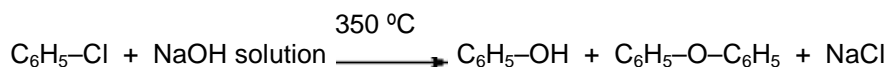
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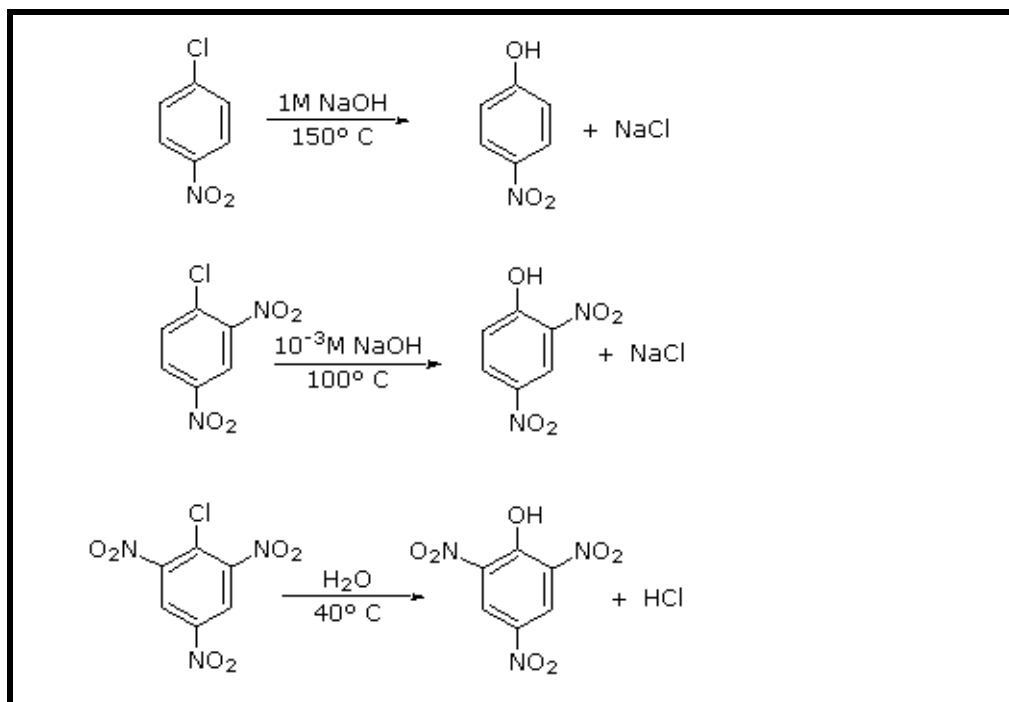


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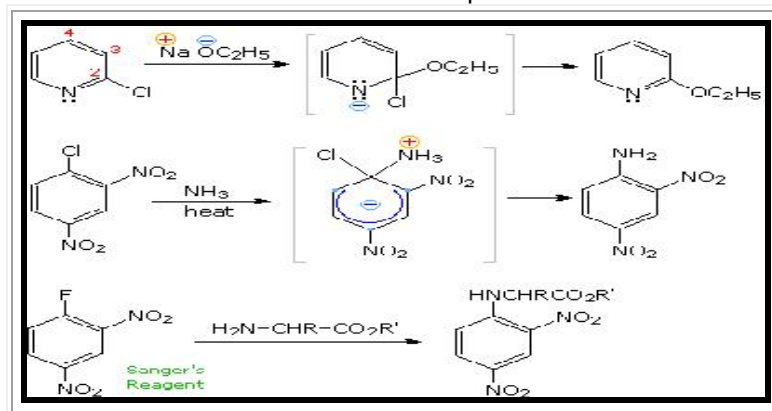
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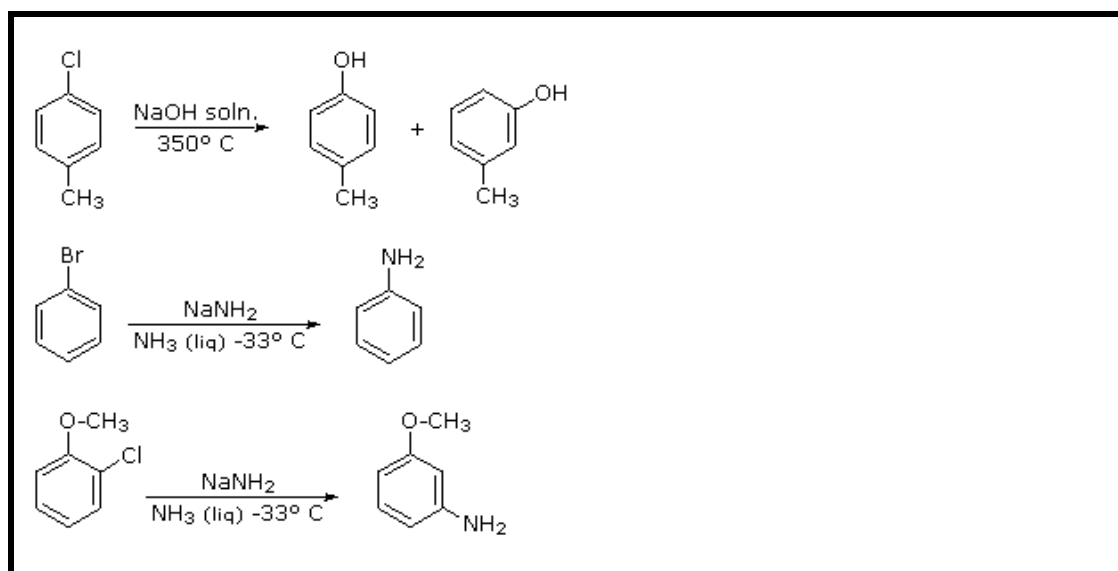
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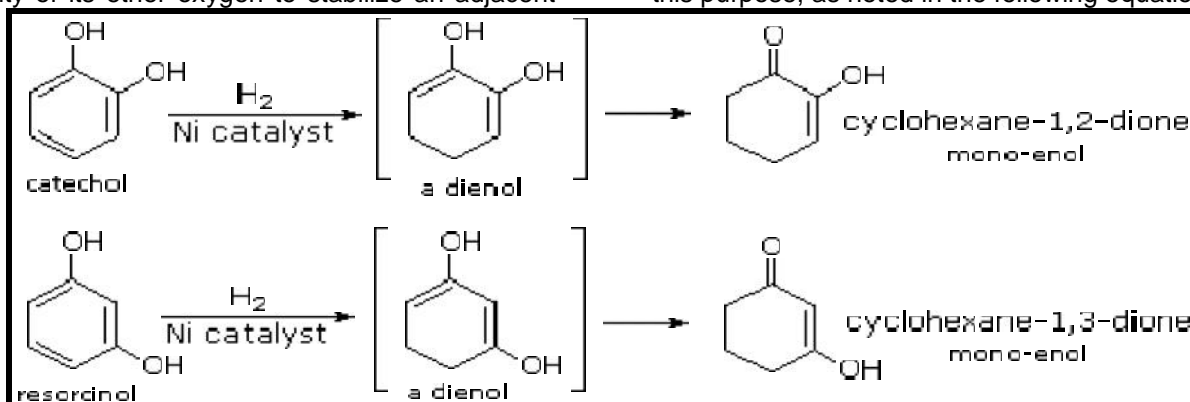
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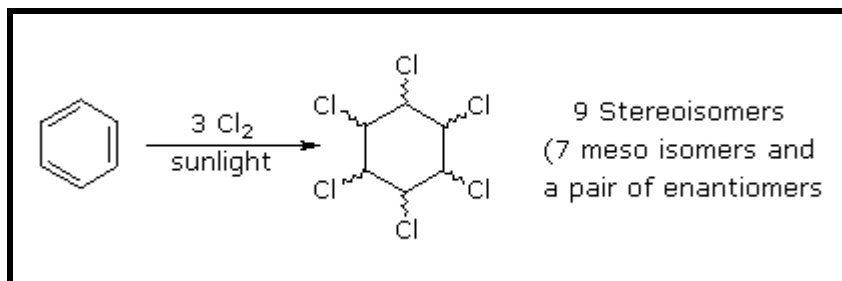
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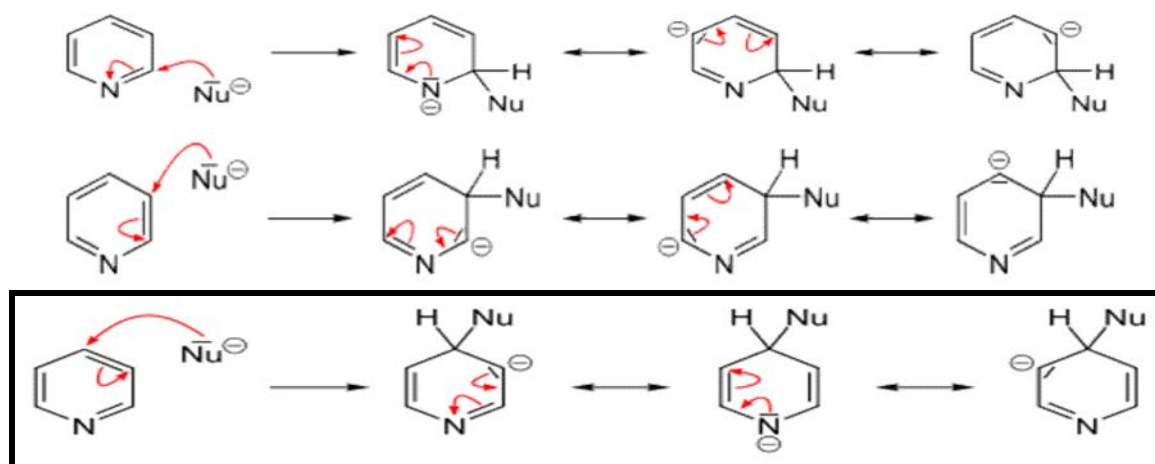
same conditions effect radical substitution of cyclohexane, the key factors in this change of behavior are the pi-bonds array in benzene, which permit addition, and the weaker C-H bonds in cyclohexane. The addition of chlorine is shown below; two of the seven meso-stereoisomers will appear if the "Show Isomer" button is clicked.



### Nucleophilic substitutions in Aromatic Systems:

In contrast to benzene, pyridine efficiently supports several nucleophilic substitutions, and is regarded as a good nucleophile (donor number 33.1). The reason for this is relatively lower electron density of the carbon

atoms of the ring. These reactions include substitutions with elimination of a hydride ion and elimination-additions with formation of an intermediate aryne configuration, and usually proceed at 2- or 4-position.<sup>[24][25]</sup>



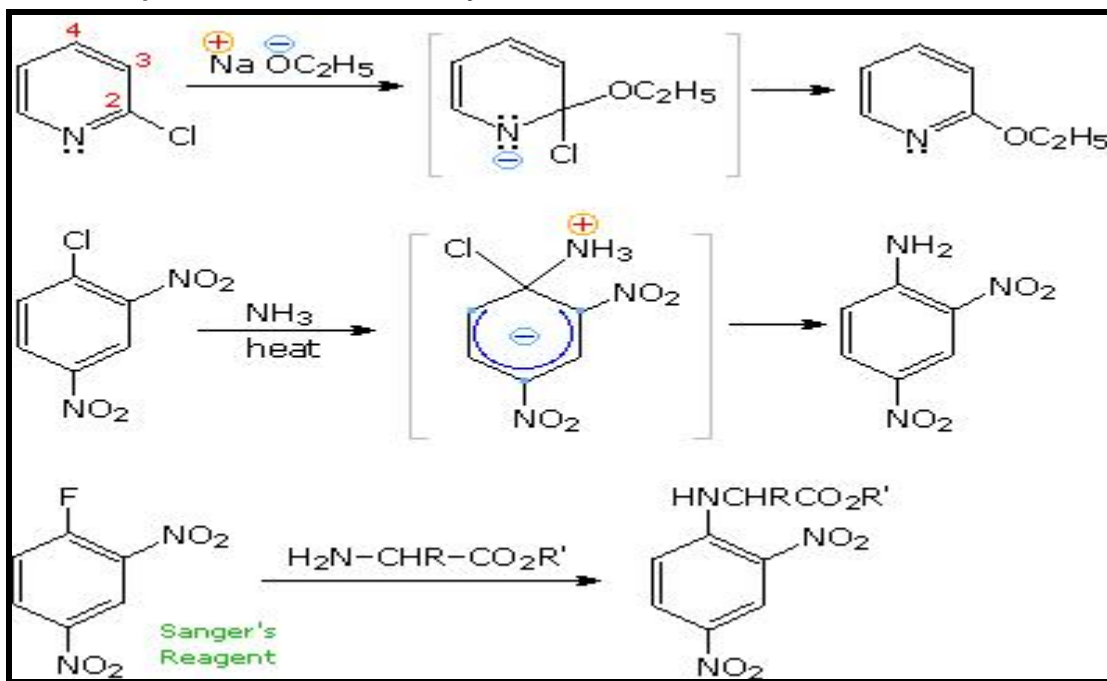
Many nucleophilic substitutions occur easier not with bare pyridine, but with pyridine modified with bromine, chlorine, fluorine or sulfonic acid fragments which then become a leaving group. So fluorine is the best leaving group for the substitution with organolithium compounds. The nucleophilic attack compounds may be alkoxides, thiolates, amines, and ammonia (at elevated pressures).

The hydride ion is generally a poor leaving group and occurs only in a few heterocyclic reactions. They include the Chichibabin reaction which yields pyridine derivatives aminated at the 2-position. Here sodium

amide is used as the nucleophile yielding 2-aminopyridine. The hydride ion released in this reaction combines with a proton of an available amino group forming a hydrogen molecule.

Analogous to benzene, nucleophilic substitutions to pyridine can result in the formation of pyridyne intermediates as heteroaryne. For this purpose, pyridine derivatives can be eliminated with good leaving groups using strong bases such as sodium and potassium tert-butoxide. The subsequent addition of a nucleophile to the triple bond has low selectivity and the result is a mixture of the two possible adducts.

## Addition - Elimination processes OF Aromatic Systems :



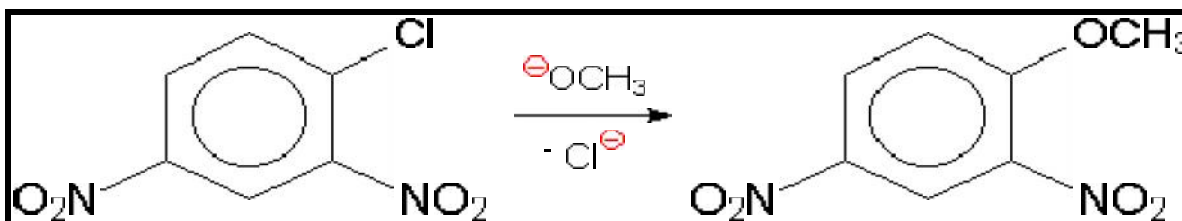
Such addition-elimination processes generally occur at  $sp^2$  or  $sp$  hybridized carbon atoms, in contrast to  $S_N1$  and  $S_N2$  reactions. When applied to aromatic halides

### Nucleophilic Substitution in Aromatic System ( $Ar-S_N$ )

Electrophilic aromatic substitution (nucleophilic attack): is considerably promoted by electron-donating first substituents. That is, the electron density of the electron system is increased. Thus, the

electron cloud's nucleophilic attack on the electrophile is easily made possible. On the other hand, the question is, whether or not strong electron-withdrawing first substituents may enable a nucleophilic attack on a carbon of the aromatic ring.

In fact, the halogen atom (Cl, Br, or I) of substituted halobenzenes that carry two nitro groups in *ortho* and *para* position, for instance, is actually substituted by a nucleophilic attack of a good nucleophile, such as  $OCH_3^-$

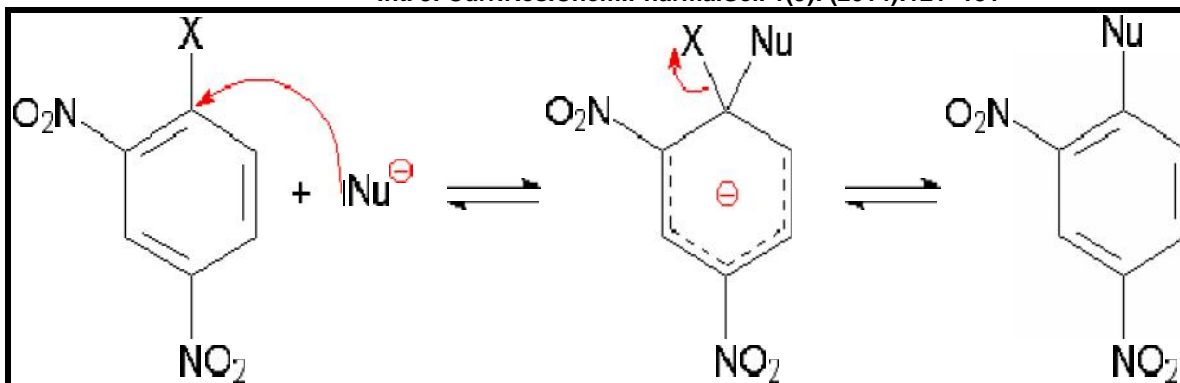


Nucleophilic substitution of chloride for methoxide in chloro-2,4-dinitrobenzene.

Comparison of the electrostatic potential surfaces illustrates the considerably stronger chlorine-carrying carbon's positive polarization by the electron-withdrawing nitro groups, which enables a nucleophilic attack on this carbon (red means a more negative potential, blue means a more positive potential).

The reaction proceeds more easily according to the number of electron-withdrawing substituents the

aromatic compound possesses. However, substituents in *ortho* and *para* position, above all, promote a nucleophilic attack, while substituents in *meta* position almost never do. These observations may be explained by a mechanism that resembles the electrophilic aromatic substitution's mechanism and that represents, so to speak, its "nucleophilic counterpart".

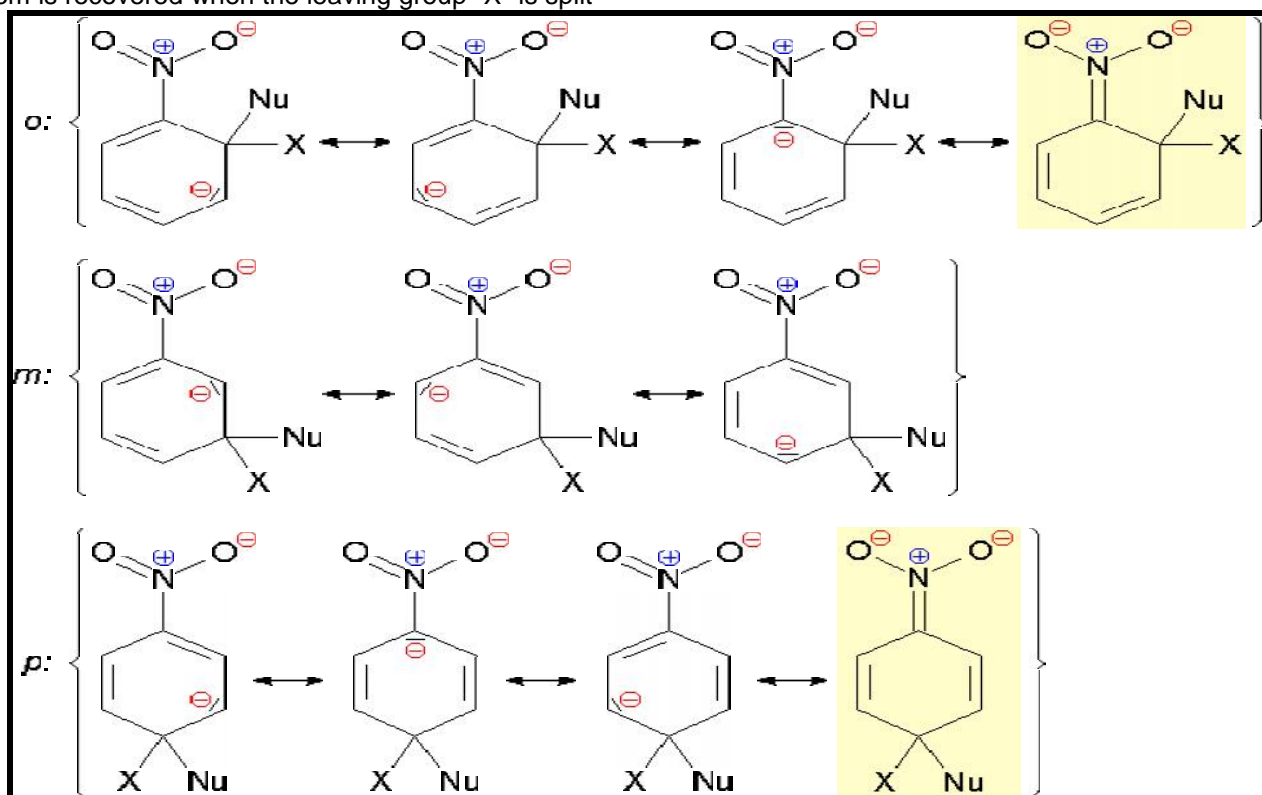


### Mechanism of the nucleophilic aromatic substitution.

Analogous to electrophilic aromatic substitution, the mechanism of nucleophilic aromatic substitution is an addition-elimination mechanism. However, in the first, rate-determining step, the aromatic system is broken by the attack of a nucleophile (Nu) on the aromatic ring and not by a nucleophilic attack of the aromatic compound's electron cloud on an electrophile. Consequently, it is not a carbocation but an intermediate carbanion that is formed. The negative charge of the carbanion is delocalized. It is distributed among the five remaining, formerly aromatic,  $sp^2$ -hybridized ring carbons. Finally, the aromatic system is recovered when the leaving group "X" is split

off. The conceivable elimination of the nucleophile, which would lead back to the starting products, hardly ever occurs, as a good nucleophile is usually also a poor leaving group.

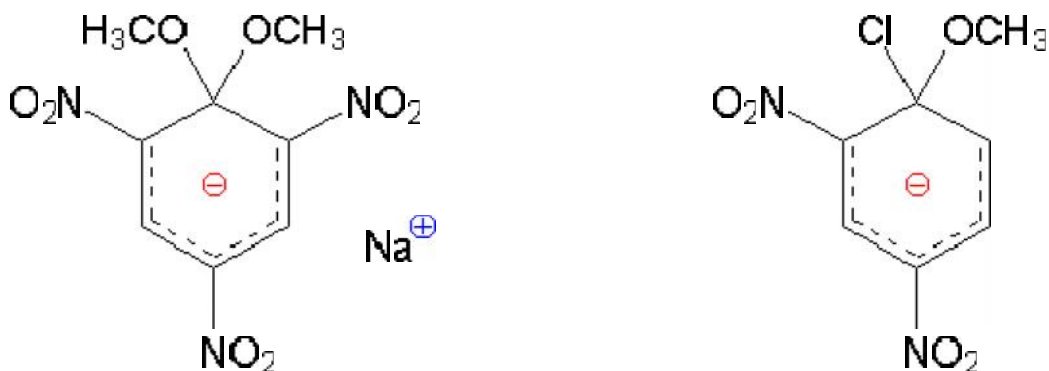
An additional delocalization and, thus, stabilization of the intermediate carbanion's negative charge through conjugation with  $-M$  and  $-I$  substituents is possible when these substituents are in *ortho* or *para* position regarding the  $sp^3$  ring carbon. Stabilization by a  $-I$  substituent is at its highest when the substituent is bound to the center that possesses the largest negative charge density, that is, if it is in *para* position. However, stabilization by a  $-I$  substituent in *ortho* position is merely a bit smaller.





Resonance structures of intermediate carbanions with a -M substituent in nucleophilic aromatic substitution. If the nucleophile (Nu) as well as the desired nucleofuge (X) are poor leaving groups and the aromatic compound possesses three nitro groups in *ortho* and *para* positions, the intermediate carbanion of

a nucleophilic aromatic substitution is stable enough to be isolated. These stable carbanions are known as Meisenheimer complexes, while nonisolable intermediate carbanions of nucleophilic aromatic substitutions are termed Meisenheimer complex-analogous intermediates.



Meisenheimer complex and Meisenheimer complex-analogous intermediate.

The electrostatic potential surface of the Meisenheimer complex illustrates the stabilization by the strong delocalization (no position with considerable charge localization, that is, no intensively red or blue coloured areas, which would indicate strongly negative or positive electrostatic potentials).

The reactivity of nucleophilic anions may be noticeably increased when the reaction is carried out in a polar, aprotic solvent. In such solvents, the anion is soluble, though it cannot be stabilized by hydrogen bridge bonds. Under these conditions, nucleophilic aromatic substitution may also occur with halobenzenes that

are not further activated through additional substituents.

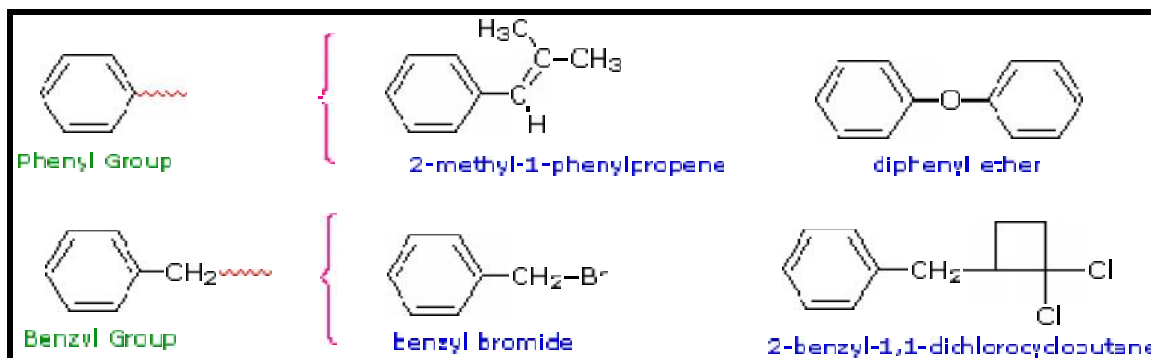
### Benzene Derivatives

The nomenclature of substituted benzene ring compounds is less systematic than that of the alkanes, alkenes and alkynes. A few mono-substituted compounds are named by using a group name as a prefix to "benzene", as shown by the combined names listed below. A majority of these compounds, however, are referred to by singular names that are unique. There is no simple alternative to memorization in mastering these names.

				<b>Combined Names</b>	
chlorobenzene	bromobenzene	ethylbenzene	nitrobenzene		
 toluene	 styrene	 benzoic acid	 benzaldehyde	 acetophenone	<b>Singular Names</b>
 benzonitrile	 phenol	 anisole	 aniline	 benzenesulfonic acid	

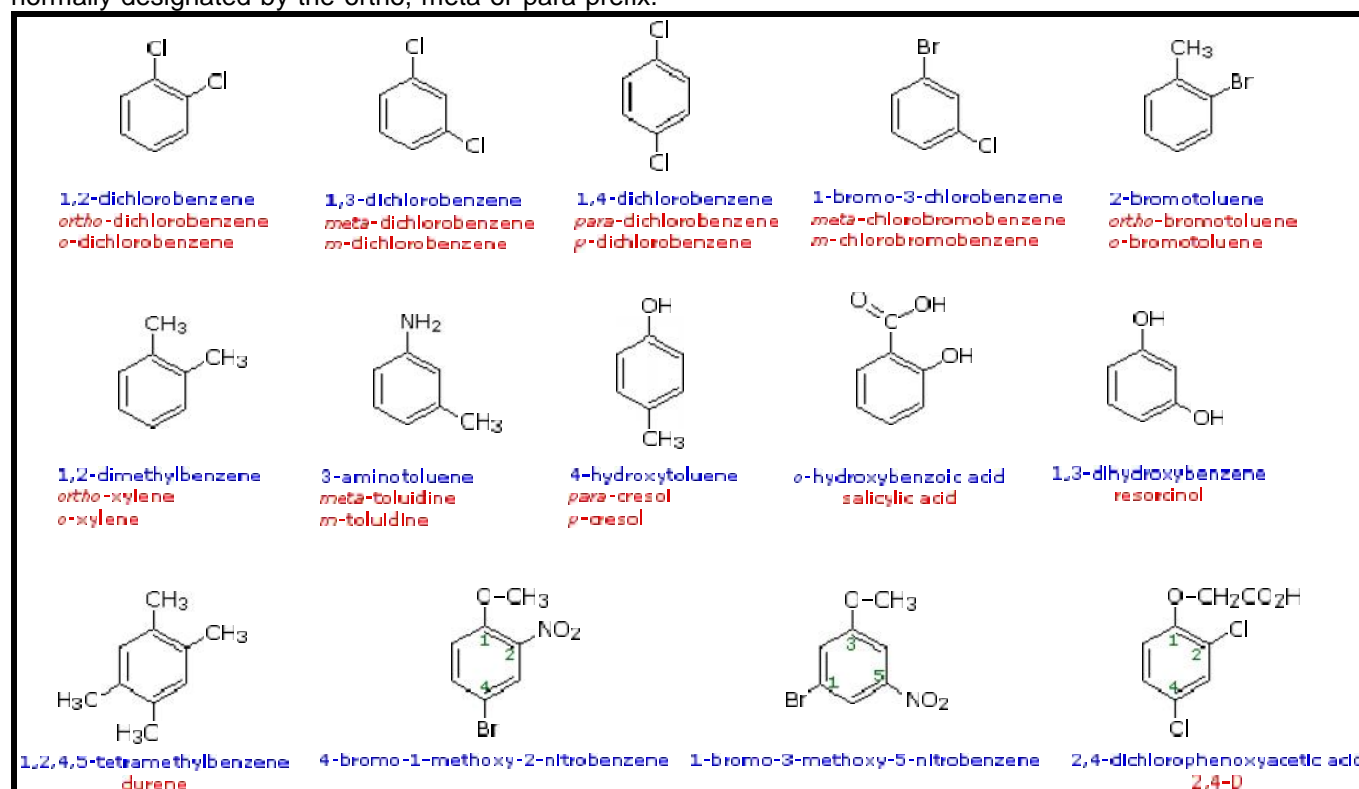
Two commonly encountered substituent groups that incorporate a benzene ring are phenyl, abbreviated Ph-, and benzyl, abbreviated Bn-. These are shown here with examples of their use. Be careful not to confuse a phenyl (pronounced *fenyl*) group with the

compound phenol (pronounced *feenol*). A general and useful generic notation that complements the use of R- for an alkyl group is Ar- for an aryl group (any aromatic ring).




When more than one substituent is present on a benzene ring, the relative locations of the substituents must be designated by numbering the ring carbons or by some other notation. In the case of disubstituted benzenes, the prefixes *ortho*, *meta* & *para* are commonly used to indicate a 1,2- or 1,3- or 1,4-relationship respectively. In the following examples, the first row of compounds show this usage in red. Some disubstituted toluenes have singular names (e.g. xylene, cresol & toluidine) and their isomers are normally designated by the *ortho*, *meta* or *para* prefix.

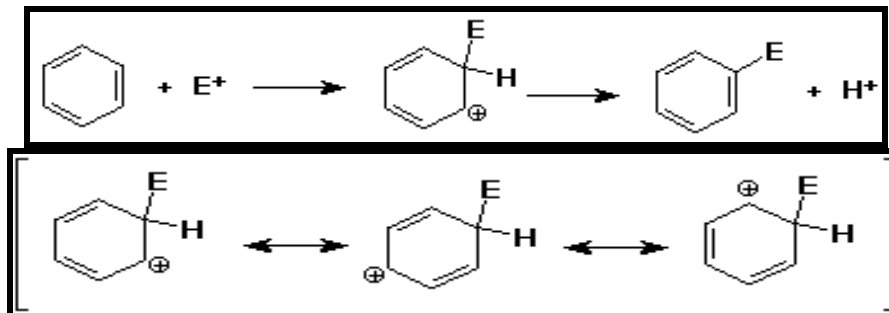
A few disubstituted benzenes have singular names given to specific isomers (e.g. salicylic acid & resorcinol). Finally, if there are three or more substituent groups, the ring is numbered in such a way as to assign the substituents the lowest possible numbers, as illustrated by the last row of examples. The substituents are listed alphabetically in the final name. If the substitution is symmetrical (third example from the left) the numbering corresponds to the alphabetical order.



The following table shows the effect substituent's have on both the rate and orientation of electrophilic aromatic substitution reactions.

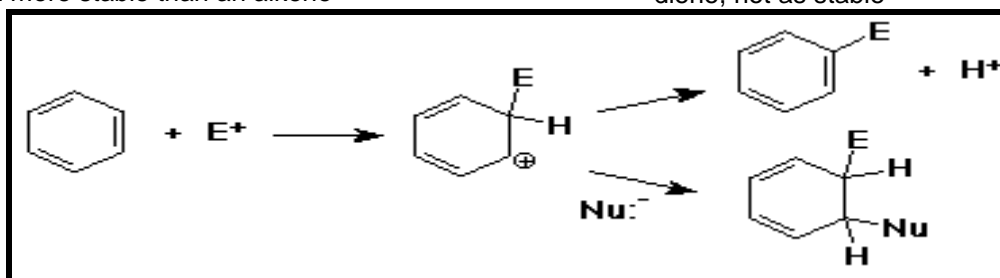
		<i>Most Activating</i>							
Activating <b>EDG</b>	Reference	$-\ddot{\text{O}}^-$	Strongly Activating	ortho / para directing					
		$-\ddot{\text{N}}\text{R}_2$							
		$-\text{NH}_2$							
		$-\ddot{\text{O}}\text{H}$							
		$-\ddot{\text{O}}\text{R}$							
		$-\ddot{\text{N}}\text{H}\text{C}(\text{R})=\text{O}$	Moderately Activating						
		$-\ddot{\text{O}}\text{C}(\text{R})=\text{O}$							
		$-\text{R}$	Weakly Activating						
									
						$-\text{C}(\text{H})=\text{CR}_2$			
Deactivating <b>EWG</b>	Reference	$-\text{H}$	Weakly Deactivating	meta directing					
		$-\text{X}$							
		$-\text{C}(\text{H})=\text{O}$	Moderately Deactivating						
		$-\text{C}(\text{R})=\text{O}$							
		$-\text{C}(\text{O})\text{R}$							
		$-\text{C}(\text{O})\text{OH}$							
		$-\text{C}(\text{O})\text{Cl}$							
		$-\text{CF}_3$	Strongly Deactivating						
		$-\text{C}\equiv\text{N}$							
		$-\text{S}(\text{O})_2\text{OH}$							
		$-\text{NH}_3^+$							
		$-\text{NR}_3^+$							
		$-\text{N}^+(\text{O}^-)$							
						<i>Most Deactivating</i>			

- benzene can be made to react with very strong electrophiles (E<sup>+</sup>)
- intermediate is a carbocation (like addition to one of the pi bonds)
- nucleophiles don't add to the cation (H<sup>+</sup> leaves, regenerates benzene ring)
- reaction is substitution (E<sup>+</sup> for H<sup>+</sup>)
- Mechanism of Aromatic Substitution



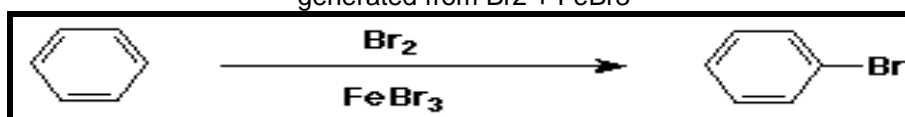
Mechanism - why slower than alkenes ?

- E<sub>a</sub> for electrophilic attack on benzene is greater than E<sub>a</sub> for electrophilic attack on an alkene
- although the cation intermediate is delocalized and more stable than an alkyl cation, benzene is much more stable than an alkene
- Mechanism - why substitution ?
- the substitution product regains the aromatic stability
- an addition product would be a conjugated diene, not as stable

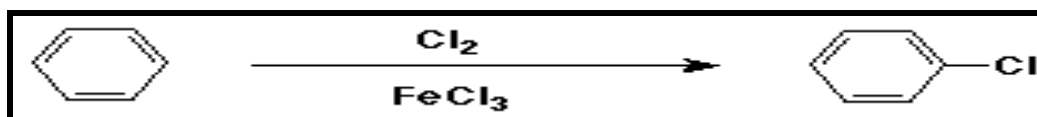


Bromination of Benzene

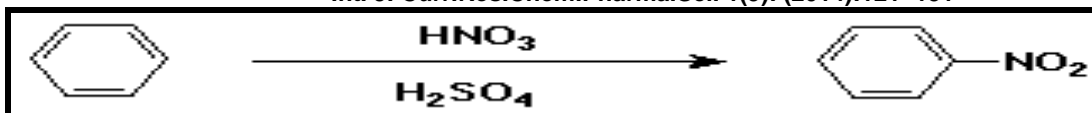
electrophile is Br<sup>+</sup>  
generated from Br<sub>2</sub> + FeBr<sub>3</sub>



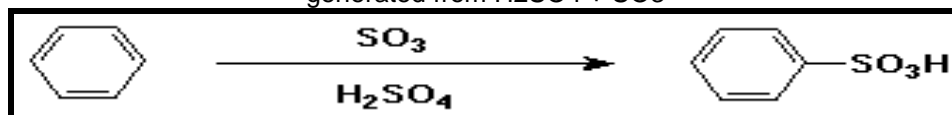
Chlorination of Benzene  
electrophile is Cl<sup>+</sup>  
generated from Cl<sub>2</sub> + FeCl<sub>3</sub>



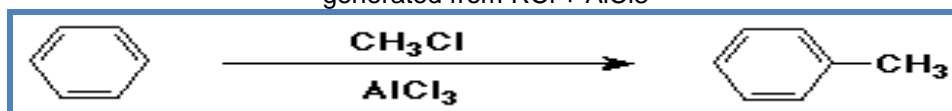
Nitration of Benzene  
electrophile is NO<sub>2</sub><sup>+</sup>  
generated from H<sub>2</sub>SO<sub>4</sub> + HNO<sub>3</sub>



Sulfonation of Benzene  
electrophile is  $\text{HSO}_3^+$   
generated from  $\text{H}_2\text{SO}_4 + \text{SO}_3$



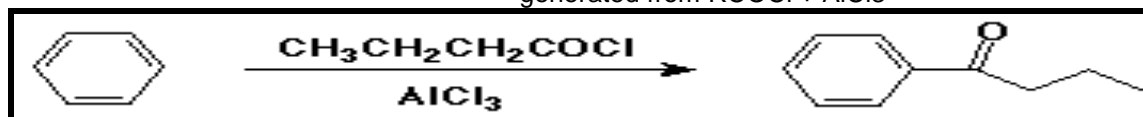
Friedel-Crafts Alkylation  
electrophile is an alkyl cation ( $\text{R}^+$ )  
generated from  $\text{RCl} + \text{AlCl}_3$



limitations of the Friedel-Crafts reaction  
cation rearrangements may occur  
doesn't work with deactivated aromatic rings  
extensions of the Friedel-Crafts reaction  
other sources of cations, e.g., alkene +  $\text{H}^+$

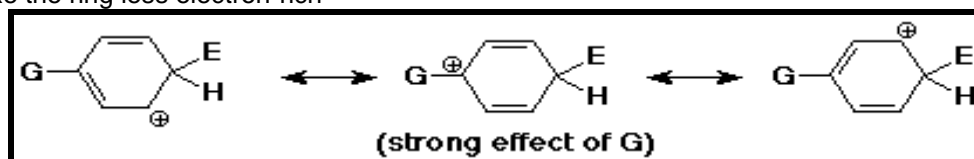
Friedel-Crafts Acylation

electrophile is an acyl cation ( $\text{RCO}^+$ )  
generated from  $\text{RCOCl} + \text{AlCl}_3$

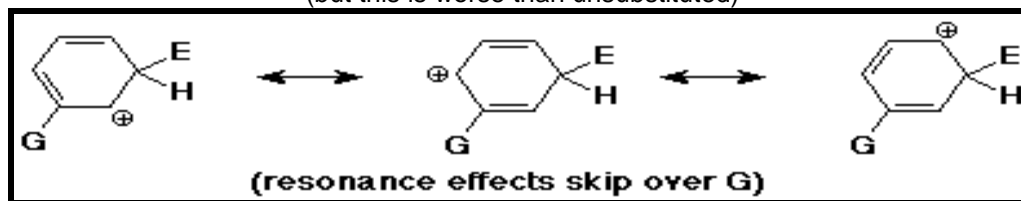


### Substituent Effects

- substituents on the benzene ring can affect the reaction in two ways:
  - reactivity - substituted benzene may react faster or slower than benzene itself reacts
  - orientation - the new group may be oriented ortho, meta, or para with respect to the original substituent
- Reactivity Effects
- activating - reaction is faster  
observed with electron-donating groups that make the ring more electron-rich
- deactivating - reaction is slower  
observed with electron-withdrawing groups that make the ring less electron-rich
- Orientation Effects
- substituent already present on the benzene ring determines the location of the new group
- ortho,para-directors: electron-donating groups direct the new group mainly to ortho&para
- meta-directors: electron-withdrawing groups direct new group mainly meta
- Ortho, Para Directors
- the best cation is formed when the electrophile adds either ortho or para (better than unsubstituted)



Meta Directors



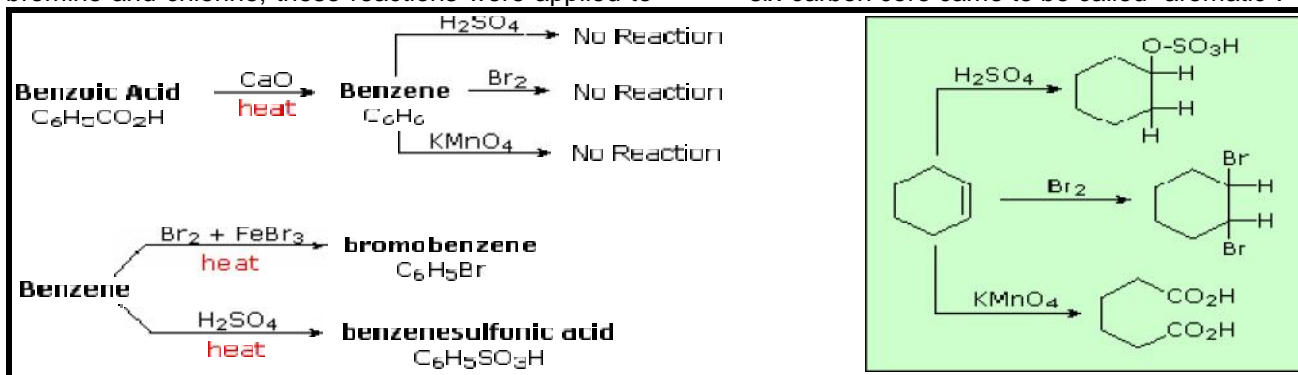
Classifying Substituents  
 activating and o,p-directing:  
 alkyl, aryl, O and N groups  
 deactivating and m-directing:  
 N+ groups, polar multiple bonds  
 deactivating but o,p-directing:  
 the halogens (F, Cl, Br, I)

(electron-withdrawing atoms, but lone pairs can stabilize the cation when it is ortho or para).

### Benzene and Other Aromatic Compounds

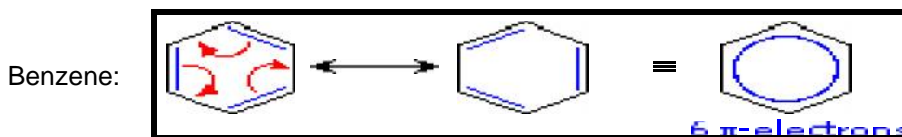
The adjective "aromatic" is used by organic chemists in a rather different way than it is normally applied. It has its origin in the observation that certain natural substances, such as cinnamon bark, wintergreen leaves, vanilla beans and anise seeds, contained fragrant compounds having common but unexpected properties. Cinnamon bark, for example, yielded a pleasant smelling compound, formula  $C_9H_8O$ , named cinnamaldehyde. Because of the low hydrogen to carbon ratio in this and other aromatic compounds (note that the H:C ratio in an alkane is  $>2$ ), chemists expected their structural formulas would contain a large number of double or triple bonds. Since double bonds are easily cleaved by oxidative reagents such as potassium permanganate or ozone, and rapidly add bromine and chlorine, these reactions were applied to

these aromatic compounds. Surprisingly, products that appeared to retain many of the double bonds were obtained, and these compounds exhibited a high degree of chemical stability compared with known alkenes and cycloalkenes (aliphatic compounds). On treatment with hot permanganate solution, cinnamaldehyde gave a stable, crystalline  $C_7H_6O_2$  compound, now called benzoic acid. The H:C ratio in benzoic acid is  $<1$ , again suggesting the presence of several double bonds. Benzoic acid was eventually converted to the stable hydrocarbon benzene,  $C_6H_6$ , which also proved unreactive to common double bond transformations, as shown below. For comparison, reactions of cyclohexene, a typical alkene, with these reagents are also shown (green box). As experimental evidence for a wide assortment of compounds was acquired, those incorporating this exceptionally stable six-carbon core came to be called "aromatic".



If benzene is forced to react by increasing the temperature and/or by addition of a catalyst, it undergoes substitution reactions rather than the addition reactions that are typical of alkenes. This further confirms the previous indication that the six-carbon benzene core is unusually stable to chemical modification. The conceptual contradiction presented by a high degree of unsaturation (low H:C ratio) and

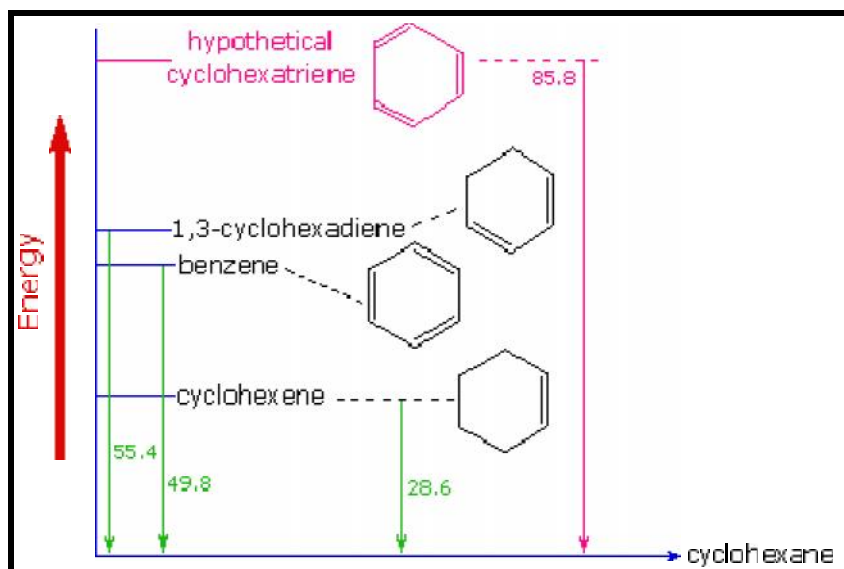
high chemical stability for benzene and related compounds remained an unsolved puzzle for many years. Eventually, the presently accepted structure of a regular-hexagonal, planar ring of carbons was adopted, and the exceptional thermodynamic and chemical stability of this system was attributed to resonance stabilization of a conjugated cyclic triene.



Here, two structurally and energetically equivalent electronic structures for a stable compound are written, but no single structure provides an accurate or even an adequate representation of the true molecule. The six-membered ring in benzene is a perfect hexagon (all carbon-carbon bonds have an identical length of 1.40 Å). The cyclohexatriene contributors would be expected to show alternating bond lengths, the double bonds being shorter (1.34 Å) than the single bonds (1.54 Å). An alternative representation for benzene (circle within a hexagon) emphasizes the pi-electron delocalization in this molecule, and has the advantage of being a single diagram. In cases such as these, the electron delocalization described by resonance enhances the stability of the molecules, and compounds composed of such molecules often show exceptional stability and related properties.

Evidence for the enhanced thermodynamic stability of benzene was obtained from measurements of the heat

released when double bonds in a six-carbon ring are hydrogenated (hydrogen is added catalytically) to give cyclohexane as a common product. In the following diagram cyclohexane represents a low-energy reference point. Addition of hydrogen to cyclohexene produces cyclohexane and releases heat amounting to 28.6 kcal per mole. If we take this value to represent the energy cost of introducing one double bond into a six-carbon ring, we would expect a cyclohexadiene to release 57.2 kcal per mole on complete hydrogenation, and 1,3,5-cyclohexatriene to release 85.8 kcal per mole. These heats of hydrogenation would reflect the relative thermodynamic stability of the compounds. In practice, 1,3-cyclohexadiene is slightly more stable than expected, by about 2 kcal, presumably due to conjugation of the double bonds. Benzene, however, is an extraordinary 36 kcal/mole more stable than expected. This sort of stability enhancement is now accepted as a characteristic of all aromatic compounds.

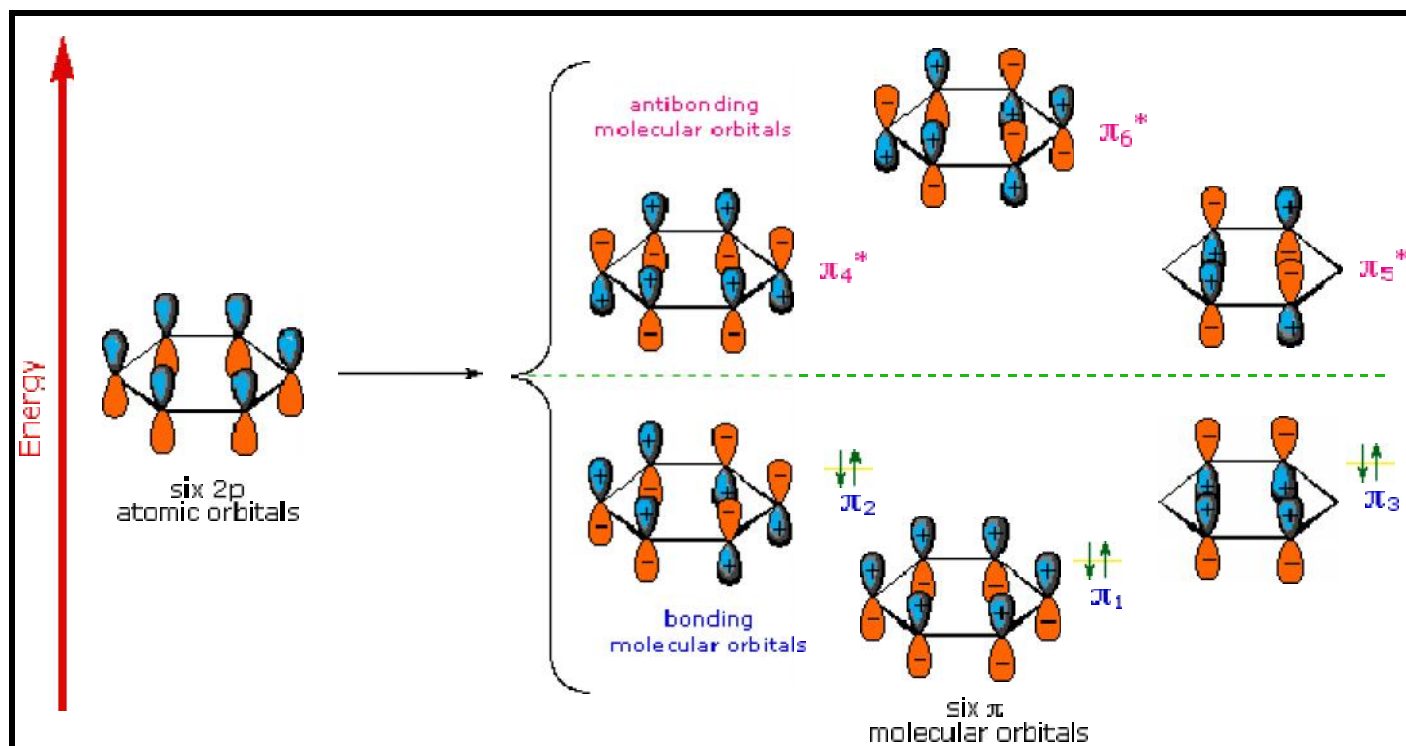


A molecular orbital description of benzene provides a more satisfying and more general treatment of "aromaticity". We know that benzene has a planar hexagonal structure in which all the carbon atoms are  $sp^2$  hybridized, and all the carbon-carbon bonds are equal in length. As shown below, the remaining cyclic array of six p-orbitals (one on each carbon) overlap to generate six molecular orbitals, three bonding and three antibonding. The plus and minus signs shown in

the diagram do not represent electrostatic charge, but refer to phase signs in the equations that describe these orbitals (in the diagram the phases are also color coded). When the phases correspond, the orbitals overlap to generate a common region of like phase, with those orbitals having the greatest overlap (e.g.  $\sigma$ ) being lowest in energy. The remaining carbon valence electrons then occupy these molecular orbitals in pairs, resulting in a fully occupied (6

electrons) set of bonding molecular orbitals. It is this completely filled set of bonding orbitals, or closed shell, that gives the benzene ring its thermodynamic

and chemical stability, just as a filled valence shell octet confers stability on the inert gases.



### The Molecular Orbitals of Benzene

To examine a model of the p-orbital components of these benzene orbitals.

To examine the benzene pi-molecular orbitals

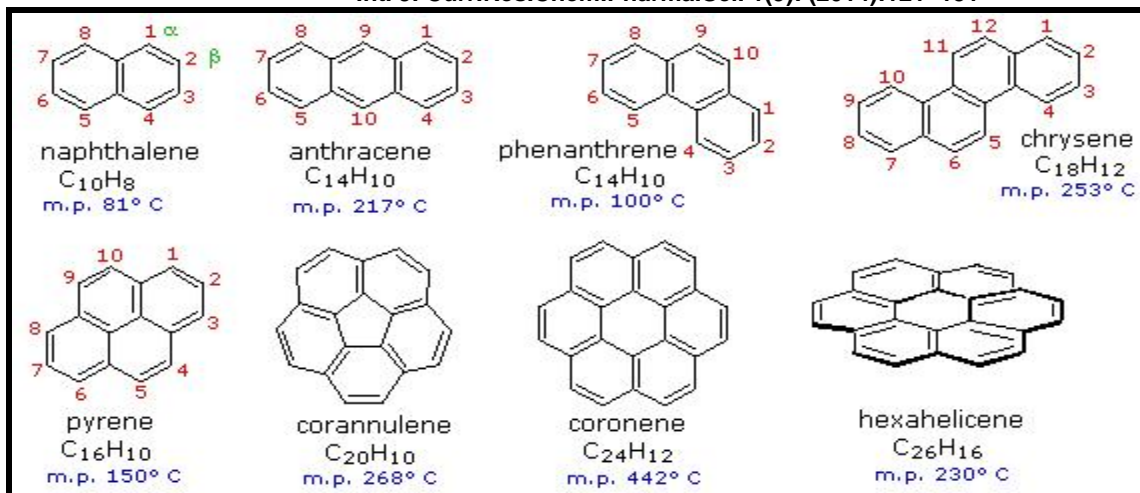
### Fused Benzene Ring Compounds<sup>(19-25)</sup>

Benzene rings may be joined together (fused) to give larger polycyclic aromatic compounds. A few examples are drawn below, together with the approved numbering scheme for substituted derivatives. The peripheral carbon atoms (numbered in all but the last three examples) are all bonded to hydrogen atoms. Unlike benzene, all the C-C bond

lengths in these fused ring aromatics are not the same, and there is some localization of the pi-electrons. For a discussion of this characteristic in cases of naphthalene and phenanthrene click on their formulas.

The six benzene rings in coronene are fused in a planar ring; whereas the six rings in hexahelicene are not joined in a larger ring, but assume a helical turn, due to the crowding together of the terminal ring atoms. This helical configuration renders the hexahelicene molecule chiral, and it has been resolved into stable enantiomers having specific rotations of 3700°. Models of coronene, coronene and hexahelicene may be examined by clicking on the appropriate structure in the diagram.

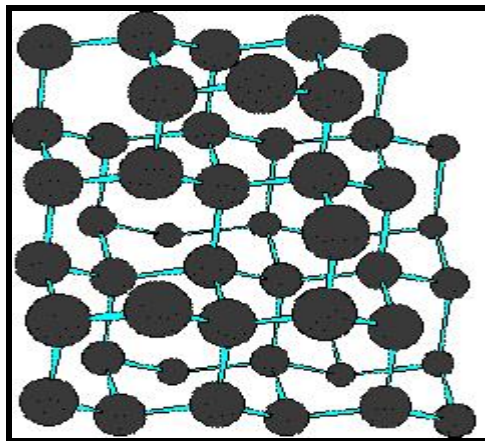




As these extended aromatic compounds become larger, the ratio of hydrogen to carbon decreases. For example, the symmetrical hexacyclic compound coronene has a H/C ratio = 1/2, compared with 1 for benzene. If we were to imagine fused ring systems of this kind to be further extended in space, the H/C ratio would approach zero, and the resulting compound would be a form of carbon. Such a carbon allotrope exists and is called graphite. Another well-

characterized carbon allotrope is diamond. The structures for these two forms of carbon are very different, and are displayed below. Diamond is an extended array of sp<sup>3</sup> hybridized carbon atoms; whereas, graphite consists of overlapping sheets of sp<sup>2</sup> hybridized carbon atoms arranged in a hexagonal pattern. You may examine models of partial diamond and graphite structures by clicking on the appropriate structure below.

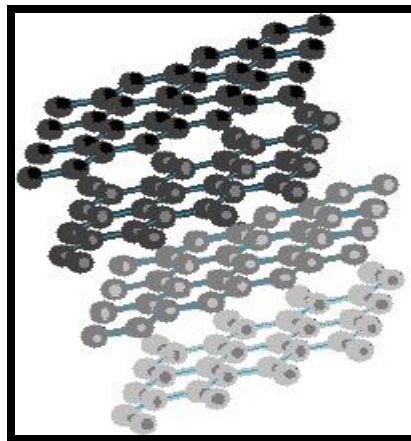
Diamond



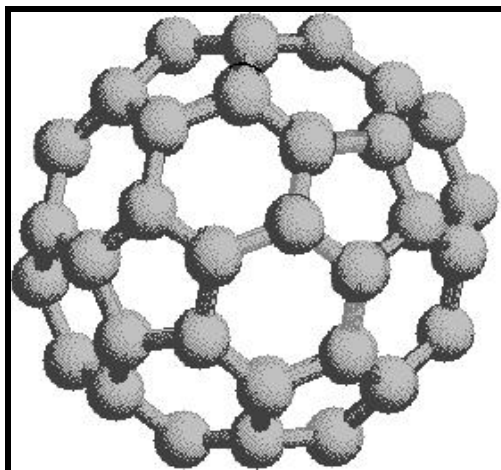
A comparison of the coronene and corannulene models discloses an interesting difference in their shapes. Coronene is absolutely flat and, aside from the peripheral hydrogens, resembles a layer of graphite. Its very high melting point reflects this resemblance. Corannulene, on the other hand, is slightly curved, resulting in a bowl-like shape.

If we extend the structure of corannulene by adding similar cycles of five benzene rings, the curvature of the resulting molecule should increase, and eventually close into a sphere of carbon atoms. The archetypical compound of this kind (C<sub>60</sub>) has been named buckminsterfullerene because of its resemblance to

Graphite



the geodesic structures created by Buckminster Fuller. It is a member of a family of similar carbon structures that are called fullerenes. These materials represent a third class of carbon allotropes. Alternating views of the C<sub>60</sub> fullerene structure are shown on the right, together with a soccer ball-like representation of the 12 five and 20 six-membered rings composing its surface. Precise measurement by Atomic Force Microscopy (AFM) has shown that the C-C bond lengths of the six-membered rings are not all equal, and depend on whether the ring is fused to a five or six-membered neighbor. By clicking on this graphic, a model of C<sub>60</sub> will be displayed.

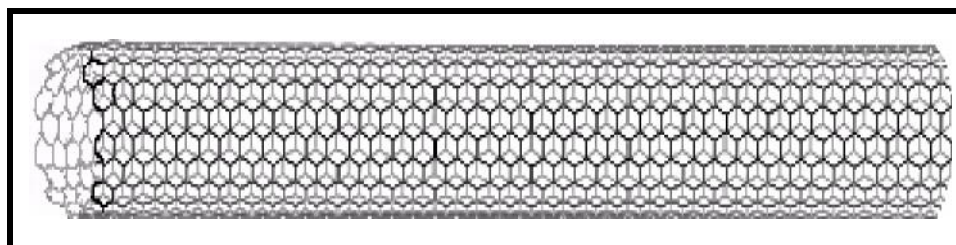


Although  $C_{60}$  is composed of fused benzene rings its chemical reactivity resembles that of the cycloalkenes more than benzene. Indeed, exposure to light and oxygen slowly degrade fullerenes to cage opened products. Most of the reactions thus far reported for  $C_{60}$  involve addition to, rather than substitution of, the core structure. These reactions include hydrogenation, bromination and hydroxylation. Strain introduced by the curvature of the surface may be responsible for the enhanced reactivity of  $C_{60}$ .

Larger fullerenes, such as  $C_{70}$ ,  $C_{76}$ ,  $C_{82}$  &  $C_{84}$  have ellipsoidal or distorted spherical structures, and fullerene-like assemblies up to  $C_{240}$  have been detected. A model of the  $C_{70}$  fullerene may be examined by [clicking here](#). A fascinating aspect of these structures is that the space within the carbon cage may hold atoms, ions or small molecules. Such

species are called endohedral fullerenes. The cavity of  $C_{60}$  is relatively small, but encapsulated helium, lithium and atomic nitrogen compounds have been observed. Larger fullerenes are found to encapsulate lanthanide metal atoms.








Interest in the fullerenes has led to the discovery of a related group of carbon structures referred to as nanotubes. As shown in the following illustration, nanotubes may be viewed as rolled up segments of graphite. The chief structural components are six-membered rings, but changes in tube diameter, branching into side tubes and the capping of tube ends is accomplished by fusion with five and seven-membered rings. Many interesting applications of these unusual structures have been proposed. A model of a nanotube will be displayed by clicking on the diagram



### Other Aromatic Systems

Many unsaturated cyclic compounds have exceptional properties that we now consider characteristic of

"aromatic" systems. The following cases are illustrative:

Compound	Structural Formula	Reaction with Br <sub>2</sub>	Thermodynamic Stabilization
1,3-Cyclopentadiene		Addition ( 0 °C )	Slight
1,3,5-Cycloheptatriene		Addition ( 0 °C )	Slight
1,3,5,7-Cyclooctatetraene		Addition ( 0 °C )	Slight
Benzene		Substitution	Large
Pyridine		Substitution	Large
Furan		Substitution ( 0 °C )	Moderate
Pyrrole		Substitution	Moderate

The first three compounds (cyclic polyenes) have properties associated with alkenes in general. Each reacts readily with bromine to give addition products, as do most alkenes. The thermodynamic change on introducing double bonds into the carbon atom ring is also typical of alkenes (a destabilization of ca. 26 kcal/mol for each double bond). Conjugation offsets this increase in energy by a small amount (4-6 kcal/mol).

The remaining four compounds exhibit very different properties, and are considered aromatic. Benzene and pyridine are relatively unreactive with bromine, requiring heat and/or catalysts to force reaction, the result of which is substitution rather than addition. Furan and pyrrole react more rapidly with bromine, but they also give substitution products. This tendency to favor substitution rather than addition suggests that the parent unsaturated ring system has exceptional stability. Thermodynamic measurements support this conclusion. The enhanced stability, often referred to as aromatic stabilization, ranges (in the above cases)

from a low of 16 kcal/mol for furan to 36 kcal/mol for benzene.

#### Factors Required for Aromaticity

A planar (or near planar) cycle of sp<sup>2</sup> hybridized atoms, the p-orbitals of which are oriented parallel to each other. These overlapping p-orbitals generate an array of π-molecular orbitals.

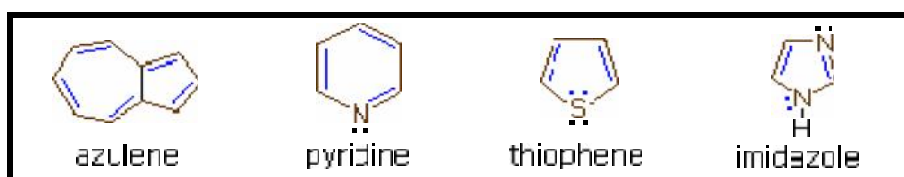
These π-orbitals are occupied by 4n+2 electrons (where n is an integer or zero). This requirement is known as The Hückel Rule. All the aromatic compounds discussed above have 6 π-electrons (n=1).

1,3-Cyclopentadiene and 1,3,5-cycloheptatriene both fail to meet the first requirement, since one carbon atom of each ring is sp<sup>3</sup> hybridized and has no p-orbital. Cyclooctatetraene fails both requirements, although it has a ring of sp<sup>2</sup> hybridized atoms. This molecule is not planar ( a geometry that would have 135° bond angles ). Angle strain is

relieved by adopting a tub-shaped conformation; consequently, the p-orbitals can only overlap as isolated pairs, not over the entire ring. Furthermore, cyclooctatetraene has 8  $\pi$ -electrons, a number not consistent with the Hückel Rule.

Benzene is the archetypical aromatic compound. It is planar, bond angles=120°, all carbon atoms in the ring are  $sp^2$  hybridized, and the pi-orbitals are occupied by 6 electrons. The aromatic heterocycle pyridine is similar to benzene, and is often used as a weak base for scavenging protons. Furan and pyrrole have

heterocyclic five-membered rings, in which the heteroatom has at least one pair of non-bonding valence shell electrons. By hybridizing this heteroatom to a  $sp^2$  state, a p-orbital occupied by a pair of electrons and oriented parallel to the carbon p-orbitals is created. The resulting planar ring meets the first requirement for aromaticity, and the  $\pi$ -system is occupied by 6 electrons, 4 from the two double bonds and 2 from the heteroatom, thus satisfying the Hückel Rule.



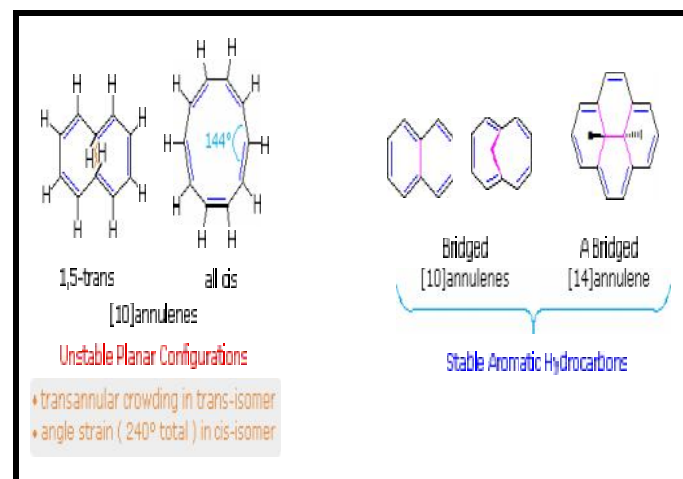
Four illustrative examples of aromatic compounds are shown above. The  $sp^2$  hybridized ring atoms are connected by brown bonds, the  $\pi$ -electron pairs and bonds that constitute the aromatic ring are colored blue. Electron pairs that are not part of the aromatic  $\pi$ -electron system are black. The first example is azulene, a blue-colored 10  $\pi$ -electron aromatic hydrocarbon isomeric with naphthalene. The second and third compounds are heterocycles having aromatic properties. Pyridine has a benzene-like six-membered ring incorporating one nitrogen atom. The non-bonding electron pair on the nitrogen is not part of the aromatic  $\pi$ -electron sextet, and may bond to a proton or other electrophile without disrupting the aromatic system. In the case of thiophene, a sulfur analog of furan, one of the sulfur electron pairs (colored blue) participates in the aromatic ring  $\pi$ -electron conjugation. The last compound is imidazole, a heterocycle having two nitrogen atoms. Note that only one of the nitrogen non-bonding electron pairs is used for the aromatic  $\pi$ -electron sextet. The other electron pair (colored black) behaves similarly to the electron pair in pyridine.

## Annulenes

Monocyclic compounds made up of alternating conjugated double bonds are called annulenes. Benzene and 1,3,5,7-cyclooctatetraene are examples of annulenes; they are named [6]annulene and [8]annulene respectively, according to a general nomenclature system in which the number in brackets designates the number of pi-electrons in an annulene is designated by a number in brackets. Some annulenes are aromatic (e.g. benzene), but many are not due to non-planarity or a failure to satisfy the Hückel Rule. Compounds classified as [10]annulenes (a Hückel Rule system) Barrelene

serve to illustrate these factors.

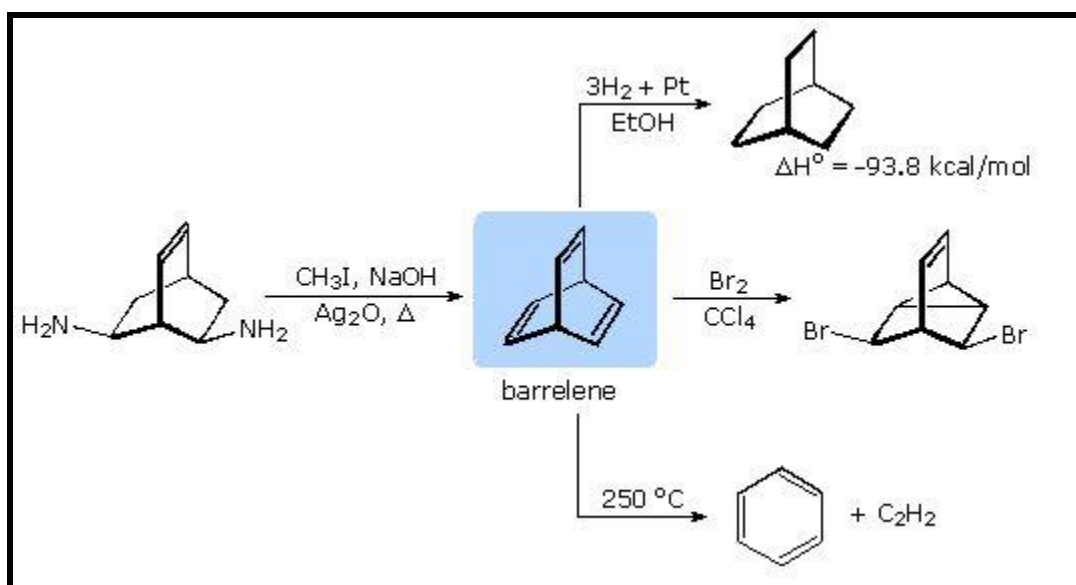
As shown in the following diagram, 1,3,5,7,9-cyclodecapentaene fails to adopt a planar conformation, either in the all cis-configuration or in its 1,5-trans-isomeric form. The transannular hydrogen crowding that destabilizes the latter may be eliminated by replacing the interior hydrogens with a bond or a short bridge (colored magenta in the diagram). As expected, the resulting 10  $\pi$ -electron annulene derivatives exhibit aromatic stability and reactivity as well as characteristic ring current anisotropy in the nmr. Naphthalene and azulene are [10]annulene analogs stabilized by a transannular bond. Although the  $CH_2$  bridged structure to the right of naphthalene in the diagram is not exactly planar, the conjugated 10  $\pi$ -electron ring is sufficiently close to planarity to achieve aromatic stabilization. The bridged [14]annulene compound on the far right, also has aromatic properties.



Formulation of the Hückel rule prompted organic chemists to consider the possible aromaticity of many unusual unsaturated hydrocarbons. One such compound was the 6  $\pi$ -electron bicyclic structure, now known as barrelene. Although the  $\pi$ -bonds in barrelene are not coplanar, it was believed that transannular overlap might still lead to aromatic stabilization.

A synthesis of barrelene (bicyclo[2.2.2]-2,5,7-

octatriene) was accomplished nearly fifty years ago by H. Zimmerman (Wisconsin), using a double Hofmann elimination. As shown in the following diagram, the chemical behavior of this triene confirmed it was not aromatic in the accepted sense of this term. Bromine addition took place rapidly with transannular bond formation, in the same fashion as with norbornadiene (bicyclo[2.2.1]-2,5-heptadiene). Pyrolysis of barrelene gave the expected cycloreversion products benzene and acetylene.

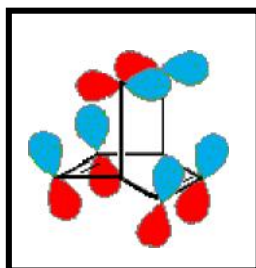


The heat of hydrogenation of barrelene reflects its thermodynamic stability. The value for cyclohexene is -28 kcal/mol, significantly less than one third of the barrelene number. Furthermore, the first double bond of barrelene is reduced with the release of 36.7 kcal/mol heat, indicating destabilization rather than stabilization.

The electronic spectrum of barrelene shows a  $\pi$ - $\pi^*$  electron interaction similar to that in related homoconjugated dienes. ( $\lambda_{\text{max}} \approx 220\text{-}230\text{ nm}$ ).

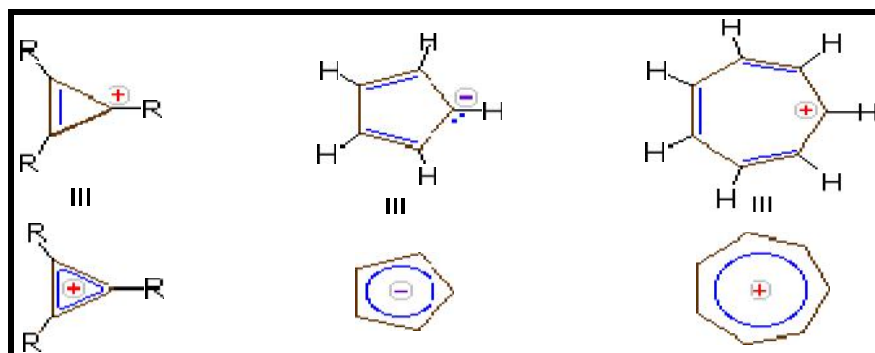
[javascript:barrel\(\);](#) An explanation for the lack of aromatic behavior in the case of barrelene may be

found by comparing the orbital symmetry of the six component p-orbitals with those of benzene. Benzene is an annulene in which all six p-orbitals may be oriented with congruent overlapping phases. The cylindrical array of p-orbitals in barrelene cannot be so arranged, as shown in the diagram on the right. There will always be one region (a nodal plane) in which the transannular overlap is incongruent. By clicking on this diagram, a Jmol model of barrelene will be displayed in a separate window. This model may be moved about for viewing. The p-orbitals of the double bonds may also be displayed.



**Aromatic Ions**<sup>(20-25)</sup>

Carbanions and carbocations may also show aromatic stabilization. Some examples are:

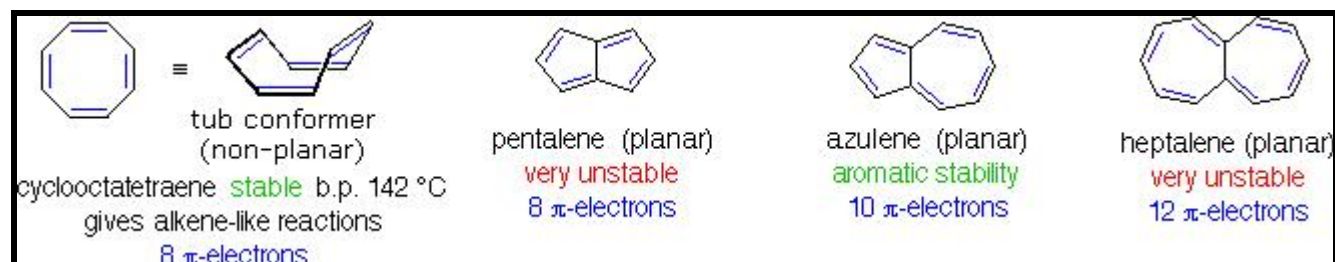


The three-membered ring cation has 2  $\pi$ -electrons and is surprisingly stable, considering its ring strain. Cyclopentadiene is as acidic as ethanol, reflecting the stability of its 6  $\pi$ -electron conjugate base. Salts of cycloheptatrienylcation (tropylium ion) are stable in water solution, again reflecting the stability of this 6  $\pi$ -electron cation.

**Antiaromaticity**

Conjugated ring systems having  $4n$   $\pi$ -electrons (e.g. 4, 8, 12 etc. electrons) not only fail to show any

aromatic properties, but appear to be less stable and more reactive than expected. As noted above, 1,3,5,7-cyclooctatetraene is non-planar and adopts a tub-shaped conformation. The compound is readily prepared, and undergoes addition reactions typical of alkenes. Catalytic hydrogenation of this tetraene produces cyclooctane. Planar bridged annulenes having  $4n$   $\pi$ -electrons have proven to be relatively unstable. Examples of 8 and 12- $\pi$ -electron systems are shown below, together with a similar 10  $\pi$ -electron aromatic compound.



The simple  $C_8H_6$  hydrocarbon pentalene does not exist as a stable compound, and its hexaphenyl derivative is air sensitive. The 12- $\pi$ -electron analog heptalene has been prepared, but is also extremely reactive (more so than cyclooctatetraene). On the other hand, azulene is a stable 10- $\pi$ -electron hydrocarbon that incorporates structural features of both pentalene and heptalene. Azulene is a stable blue crystalline solid that undergoes a number of

typical aromatic substitution reactions. The unexpected instability of  $4n$   $\pi$ -electron annulenes has been termed "antiaromaticity".

Other examples may be cited. Thus, all attempts to isolate 1,3-cyclobutadiene have yielded its dimer, or products from reactions with other compounds introduced

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