

# Chapter 15

## Reactions of Aromatic Compounds

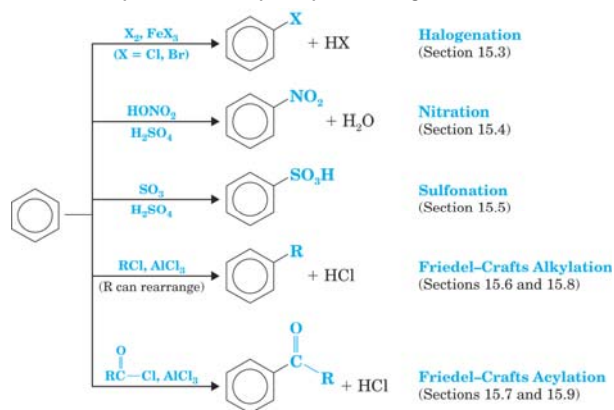
### ◆ Electrophilic Aromatic Substitution

→ Arene (Ar-H) is the generic term for an aromatic hydrocarbon

↳ The aryl group (Ar) is derived by removal of a hydrogen atom from an arene

→ Aromatic compounds undergo electrophilic aromatic substitution (EAS)

↳ The electrophile has a full or partial positive charge



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## ◆ A General Mechanism for Electrophilic Aromatic Substitution: Arenium Ion Intermediates

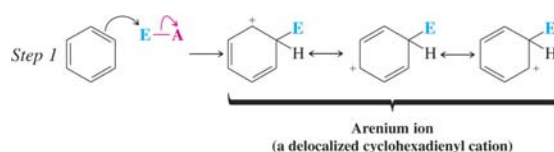
→ Benzene reacts with an electrophile using two of its  $\pi$  electrons

⌘ This first step is like an addition to an ordinary double bond

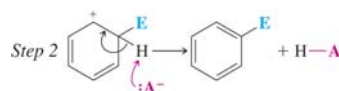
→ Unlike an addition reaction, the benzene ring reacts further so that it may regenerate the very stable aromatic system

→ In step 1 of the mechanism, the electrophile reacts with two  $\pi$  electrons from the aromatic ring to form an arenium ion

⌘ The arenium ion is stabilized by resonance which delocalizes the charge



→ In step 2, a proton is removed and the aromatic system is regenerated



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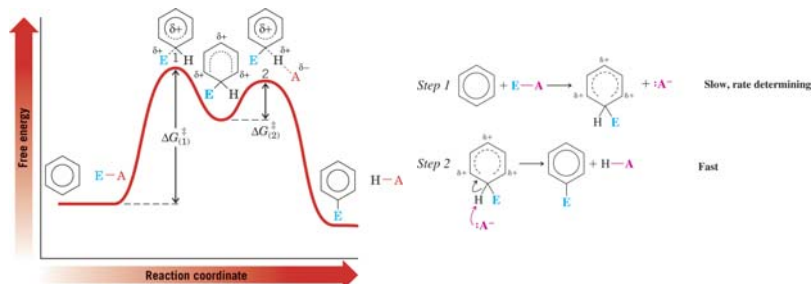
→ The energy diagram of this reaction shows that the first step is highly endothermic and has a large  $\Delta G^\ddagger$  (1)

⌘ The first step requires the loss of aromaticity of the very stable benzene ring, which is highly unfavorable

⌘ The first step is rate-determining

→ The second step is highly exothermic and has a small  $\Delta G^\ddagger$  (2)

⌘ The ring regains its aromatic stabilization, which is a highly favorable process

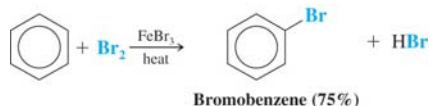
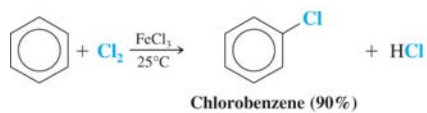


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## ◆ Halogenation of Benzene

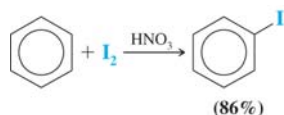
→ Halogenation of benzene requires the presence of a Lewis acid



→ Fluorination occurs so rapidly it is hard to stop at monofluorination of the ring

⌘ A special apparatus is used to perform this reaction

→ Iodine is so unreactive that an alternative method must be used



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→ In the step 1 of the mechanism, bromine reacts with ferric bromide to generate an electrophilic bromine species

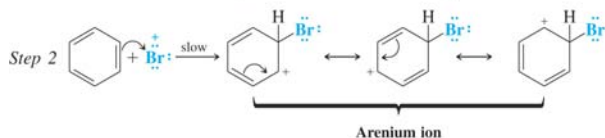
→ In step 2, the highly electrophilic bromine reacts with  $\pi$  electrons of the benzene ring, forming an arenium ion

→ In step 3, a proton is removed from the arenium ion and aromaticity is regenerated

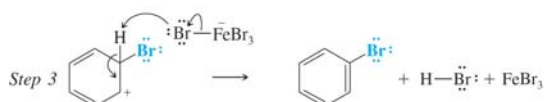
⌘ The  $\text{FeBr}_3$  catalyst is regenerated



Bromine combines with  $\text{FeBr}_3$  to form a complex that dissociates to form a positive bromine ion and  $\text{FeBr}_4^-$ .



The positive bromine ion attacks benzene to form an arenium ion.



A proton is removed from the arenium ion to become bromobenzene.

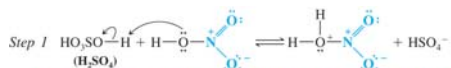
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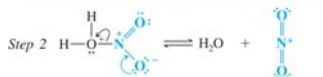
## ◆ Nitration of Benzene

→ Nitration of benzene occurs with a mixture of concentrated nitric and sulfuric acids

¶ The electrophile for the reaction is the nitronium ion ( $\text{NO}_2^+$ )

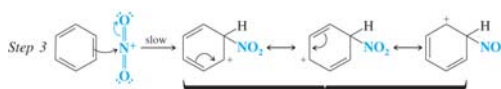


In this step nitric acid accepts a proton from the stronger acid, sulfuric acid.



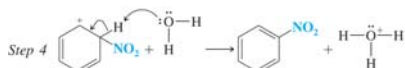
Nitronium ion

Now that it is protonated, nitric acid can dissociate to form a nitronium ion.



Arenium ion

The nitronium ion is the actual electrophile in nitration; it reacts with benzene to form a resonance-stabilized arenium ion.



The arenium ion then loses a proton to a Lewis base and becomes nitrobenzene.

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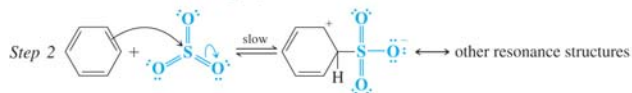
## ◆ Sulfonation of Benzene

→ Sulfonation occurs most rapidly using fuming sulfuric acid (concentrated sulfuric acid that contains  $\text{SO}_3$ )

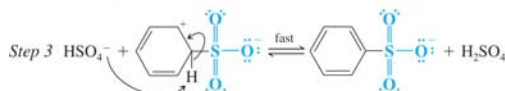
¶ The reaction also occurs in conc. sulfuric acid, which generates small quantities of  $\text{SO}_3$ , as shown in step 1 below



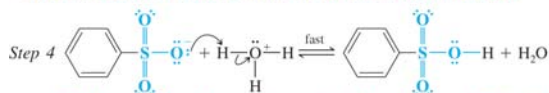
This equilibrium produces  $\text{SO}_3$  in concentrated  $\text{H}_2\text{SO}_4$ .



$\text{SO}_3$  is the actual electrophile that reacts with benzene to form an arenium ion.



A proton is removed from the arenium ion to form the benzenesulfonate ion.



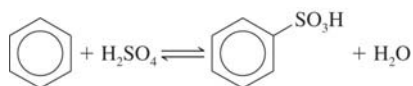
The benzenesulfonate ion accepts a proton to become benzenesulfonic acid.

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→ Sulfonation is an equilibrium reaction; all steps involved are equilibria

- ⌘ The sulfonation product is favored by use of concentrated or fuming sulfuric acid
- ⌘ Desulfonation can be accomplished using dilute sulfuric acid (i.e. with a high concentration of water), or by passing steam through the reaction and collecting the volatile desulfonated compound as it distills with the steam



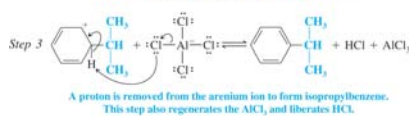
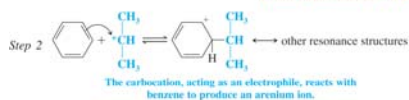
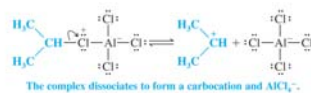
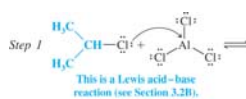
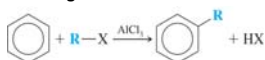
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## ◆ Friedel-Crafts Alkylation

→ An aromatic ring can be alkylated by an alkyl halide in the presence of a Lewis acid

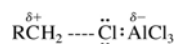
- ⌘ The Lewis acid serves to generate a carbocation electrophile



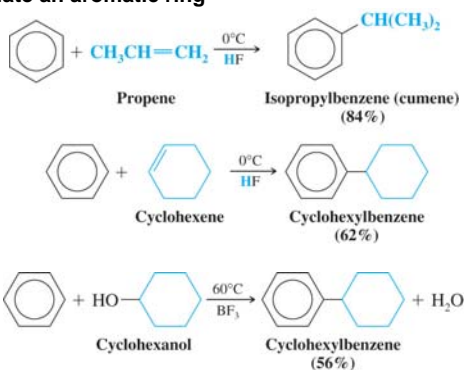
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→ Primary alkyl halides probably do not form discrete carbocations but the primary carbon in the complex develops considerable positive charge



→ Any compound that can form a carbocation can be used to alkylate an aromatic ring

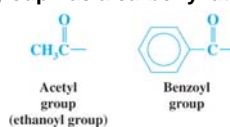


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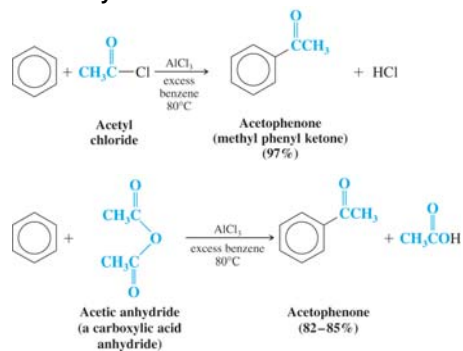
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## ◆ Friedel-Crafts Acylation

→ An acyl group has a carbonyl attached to some R group



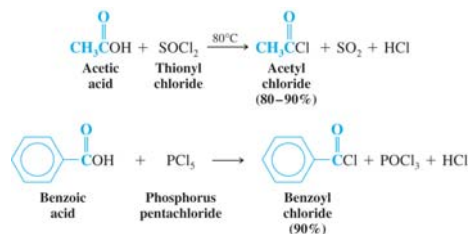
→ Friedel-Crafts acylation requires reaction of an acid chloride or acid anhydride with a Lewis acid such as aluminium chloride



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→ Acid chlorides are made from carboxylic acids

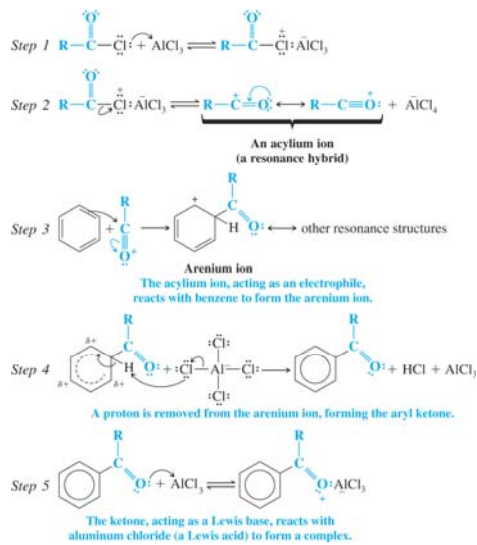


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→ The electrophile in Friedel-Crafts acylation is an acylium ion

⚡ The acylium ion is stabilized by resonance



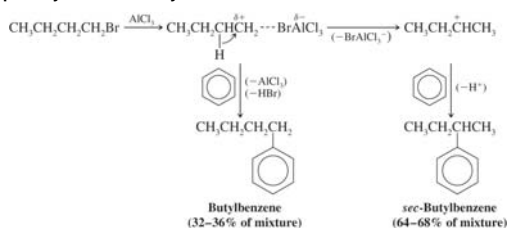
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## ◆ Limitations of Friedel-Crafts Reactions

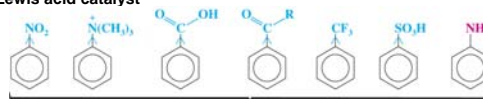
→ In Friedel-Crafts alkylation, the alkyl carbocation intermediate may rearrange to a more stable carbocation prior to alkylation

⌘ The reaction of *n*-butyl bromide leads to a mixture of products derived from primary and secondary carbocations



→ Powerful electron-withdrawing groups make an aromatic ring much less reactive toward Friedel-Crafts alkylation or acylation

⌘ Amino groups also make the ring less reactive to Friedel-Crafts reaction because they become electron-withdrawing groups upon Lewis acid-base reaction with the Lewis acid catalyst



These usually give poor yields in Friedel-Crafts reactions.

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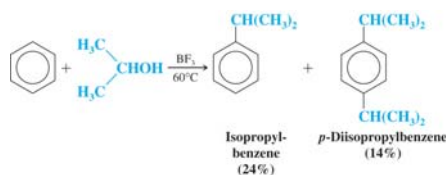
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→ Aryl and vinyl halides cannot be used in Friedel-Crafts reactions because they do not form carbocations readily



→ Polyalkylation occurs frequently with Friedel-Crafts alkylation because the first alkyl group introduced activates the ring toward further substitution

⌘ Polyacylation does not occur because the acyl group deactivates the aromatic ring to further substitution



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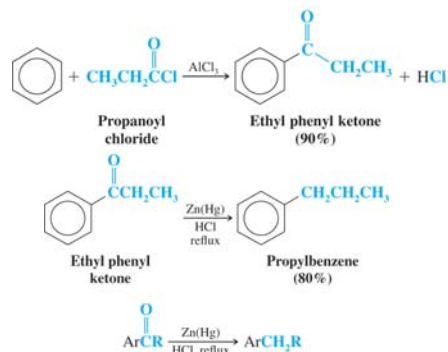


## ◆ Synthetic Applications of Friedel-Crafts Acylations: The Clemmensen Reduction

→ Primary alkyl halides often yield rearranged products in Friedel-Crafts alkylation which is a major limitation of this reaction

→ Unbranched alkylbenzenes can be obtained in good yield by acylation followed by Clemmensen reduction

⚡ Clemmensen reduction reduces phenyl ketones to the methylene (CH<sub>2</sub>) group

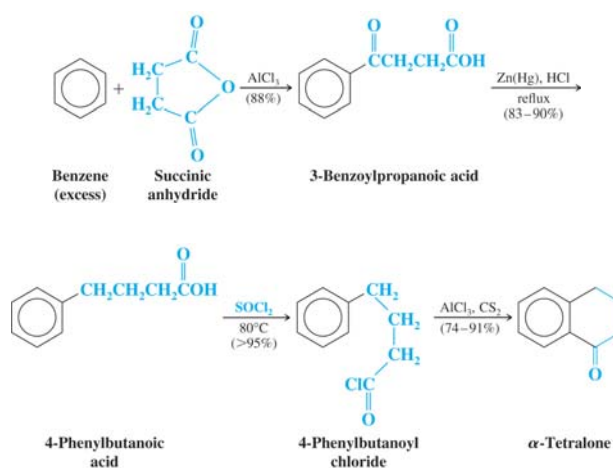


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→ This method can be used to add a ring to an aromatic ring starting with a cyclic anhydride

⚡ Note that the Clemmensen reagents do not reduce the carboxylic acid



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## ◆ Effects of Substituents on Reactivity and Orientation

→ The nature of groups already on an aromatic ring affect both the reactivity and orientation of future substitution

- ⌘ Activating groups cause the aromatic ring to be more reactive than benzene
- ⌘ Deactivating groups cause the aromatic ring to be less reactive than benzene
- ⌘ Ortho-para directors direct future substitution to the ortho and para positions
- ⌘ Meta directors direct future substitution to the meta position

### ● Activating Groups: Ortho-Para Directors

→ All activating groups are also ortho-para directors

- ⌘ The halides are also ortho-para directors but are mildly deactivating

→ The methyl group of toluene is an ortho-para director

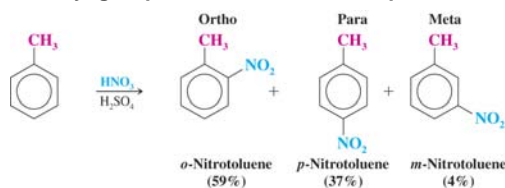
- ⌘ Toluene reacts more readily than benzene, e.g. at a lower temperatures than benzene



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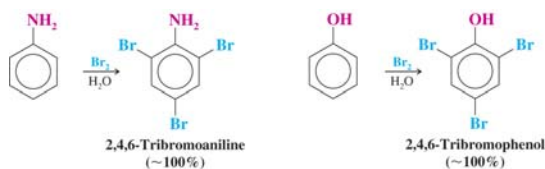
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→ The methyl group of toluene is an ortho-para director



→ Amino and hydroxyl groups are also activating and ortho-para directors

- ⌘ These groups are so activating that catalysts are often not necessary



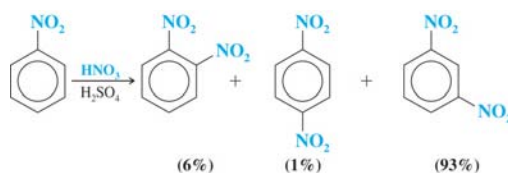
→ Alkyl groups and heteroatoms with one or more unshared electron pairs directly bonded to the aromatic ring will be ortho-para directors (see chart on slide 22)

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- **Deactivating Groups: Meta Directors**

→ Strong electron-withdrawing groups such as nitro, carboxyl, and sulfonate are deactivators and meta directors



- **Halo Substituents: Deactivating Ortho-Para Directors**

→ Chloro and bromo groups are weakly deactivating but are also ortho, para directors

¶ In electrophilic substitution of chlorobenzene, the ortho and para products are major:

Reaction	Ortho Product (%)	Para Product (%)	Total Ortho and Para (%)	Meta Product (%)
Chlorination	39	55	94	6
Bromination	11	87	98	2
Nitration	30	70	100	
Sulfonation		100	100	

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## ◆ Classification of Substituents

Ortho-Para Directors	Meta Directors
<b>Strongly Activating</b> $-\ddot{\text{N}}\text{H}_2, -\ddot{\text{N}}\text{HR}, -\ddot{\text{N}}\text{R}_2$ $-\ddot{\text{O}}\text{H}, -\ddot{\text{O}}:^-$	<b>Moderately Deactivating</b> $-\text{C}\equiv\text{N}$ $-\text{SO}_3\text{H}$ $-\text{CO}_2\text{H}, -\text{CO}_2\text{R}$ $-\text{CHO}, -\text{COR}$
<b>Moderately Activating</b> $-\ddot{\text{N}}\text{HCOCH}_3, -\ddot{\text{N}}\text{HCOR}$ $-\ddot{\text{O}}\text{CH}_3, -\ddot{\text{O}}\text{R}$	<b>Strongly Deactivating</b> $-\text{NO}_2$ $-\text{NR}_3^+$ $-\text{CF}_3, -\text{CCl}_3$
<b>Weakly Activating</b> $-\text{CH}_3, -\text{C}_2\text{H}_5, -\text{R}$ $-\text{C}_6\text{H}_5$	
<b>Weakly Deactivating</b> $-\ddot{\text{F}}:, -\ddot{\text{Cl}}:, -\ddot{\text{Br}}:, -\ddot{\text{I}}:$	

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## ◆ Theory of Substituent Effects on Electrophilic Substitution

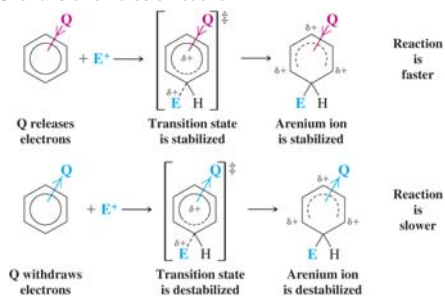
### ● Reactivity: The Effect of Electron-Releasing and Electron-Withdrawing Groups

→ Electron-releasing groups activate the ring toward further reaction

⌞ Electron-releasing groups stabilize the transition state of the first step of substitution and lead to lower  $\Delta G^\ddagger$  and faster rates of reaction

→ Electron-withdrawing groups deactivate the ring toward further reaction

⌞ Electron-withdrawing groups destabilize the transition state and lead to higher  $\Delta G^\ddagger$  and slower rates of reaction

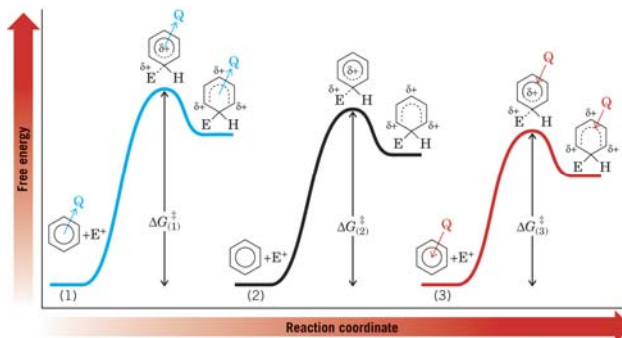


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→ The following free-energy profiles compare the stability of the first transition state in electrophilic substitution when various types of substituents are already on the ring

⌞ These substituents are electron-withdrawing, neutral (e.g., H), and electron-donating



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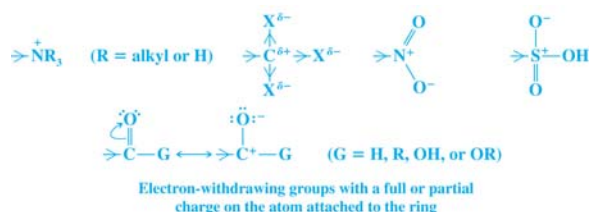
● **Inductive and Resonance Effects: Theory of Orientation**

→ The inductive effect of some substituent Q arises from the interaction of the polarized bond to Q with the developing positive charge in the ring as an electrophile reacts with it

⌘ If Q is an electron-withdrawing group then attack on the ring is slowed because this leads to additional positive charge on the ring



→ The following are some other groups that have an electron-withdrawing effect because the atom directly attached to the ring has a partial or full positive charge

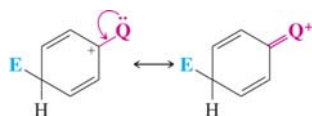


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→ The resonance effect of Q refers to its ability to increase or decrease the resonance stabilization of the arenium ion

⌘ When Q has a lone pair on the atom directly attached to the ring it can stabilize the arenium by contributing a fourth resonance form



→ Electron-donating resonance ability is summarized below



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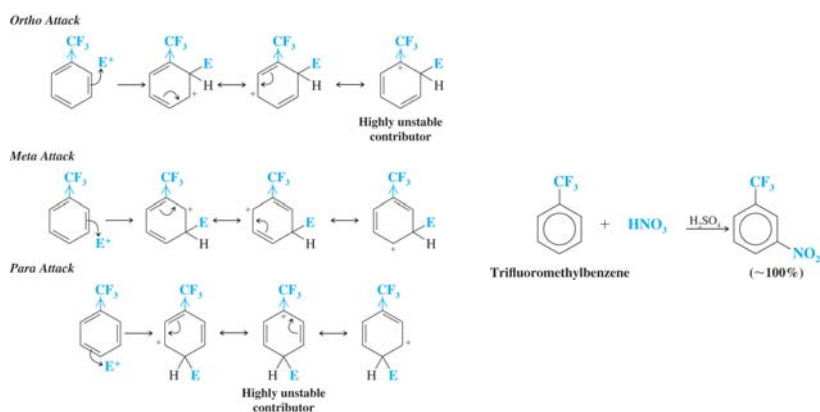
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- **Meta-directing Groups**

- All meta-directing groups have either a partial or full positive charge on the atom directly attached to the aromatic ring

- The trifluoromethyl group destabilizes the arenium ion intermediate in ortho and para substitution pathways

- ⚡ The arenium ion resulting from meta substitution is not so destabilized and therefore meta substitution is favored

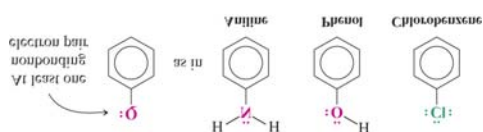


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- **Ortho-Para Directing Groups**

- Many ortho-para directors are groups that have a lone pair of electrons on the atom directly attached to the ring

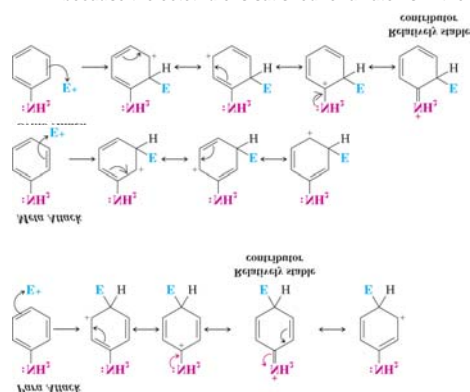


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→ **Activating groups having unshared electrons on the atom bonded to the ring exert primarily a resonance effect**

- ⌘ The aromatic ring is activated because of the resonance effect of these groups
- ⌘ They are ortho-para directors because they contribute a fourth important resonance form which stabilizes the arenium ion in the cases of ortho and para substitution only
- ⌘ The fourth resonance form that involves the heteroatom is particularly important because the octet rule is satisfied for all atoms in the arenium ion

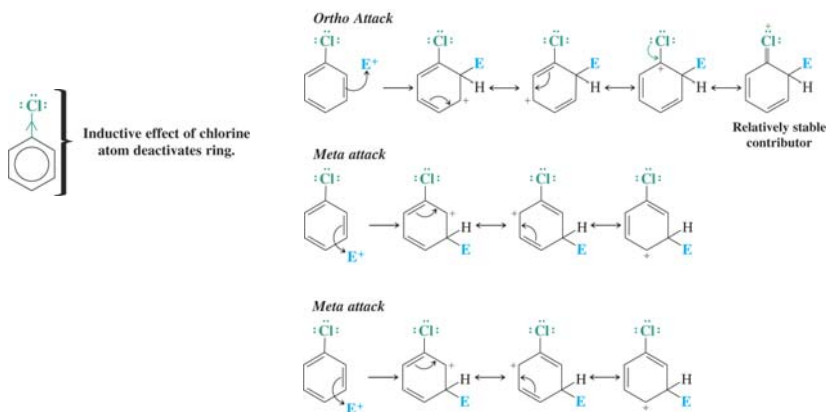


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→ **Halo groups are ortho-para directors but are also deactivating**

- ⌘ The electron-withdrawing inductive effect of the halide is the primary influence that deactivates haloaromatic compounds toward electrophilic aromatic substitution
- ⌘ The electron-donating resonance effect of the halogen's unshared electron pairs is the primary ortho-para directing influence



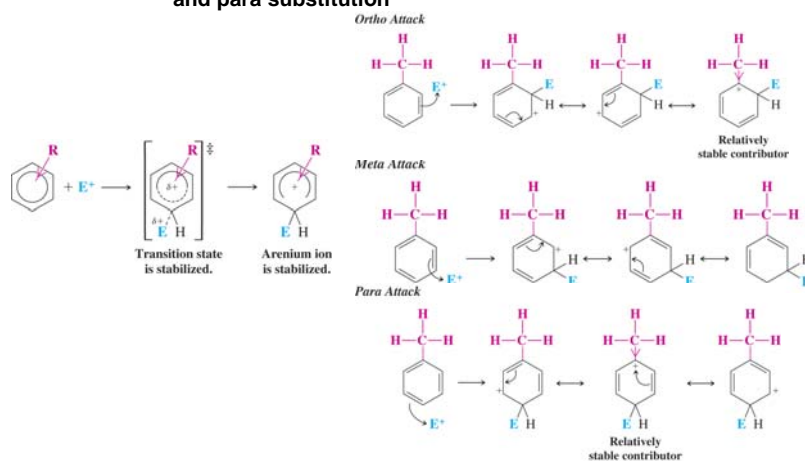
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- **Ortho-Para Direction and Reactivity of Alkylbenzenes**

- Alkyl groups activate aromatic rings by inductively stabilizing the transition state leading to the arenium ion

- Alkyl groups are ortho-para directors because they inductively stabilize one of the resonance forms of the arenium ion in ortho and para substitution



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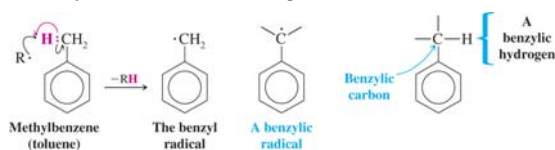
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- ◆ **Reactions of the Side Chain of Alkylbenzenes**

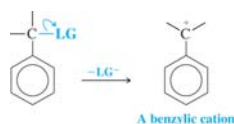
- **Benzylic Radicals and Cations**

- When toluene undergoes hydrogen abstraction from its methyl group it produces a benzyl radical

- ⚡ A benzylic radical is a radical in which the carbon bearing the unpaired electron is directly bonded to an aromatic ring



- Departure of a leaving group by an  $S_N1$  process from a benzylic position leads to formation of a benzylic cation

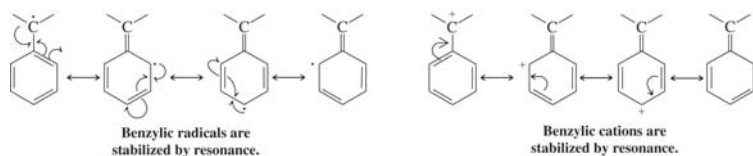


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→ Benzylic radicals and cations are stabilized by resonance delocalization of the radical and positive charge, respectively



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### ● Halogenation of the Side Chain: Benzylic Radicals

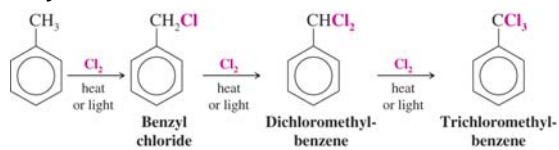
→ Benzylic halogenation takes place under conditions which favor radical reactions

→ Reaction of *N*-bromosuccinamide with toluene in the presence of light leads to allylic bromination

⚡ Recall *N*-bromosuccinamide produces a low concentration of bromine which favors radical reaction



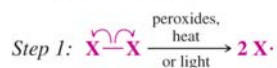
→ Reaction of toluene with excess chlorine can produce multiple benzylic chlorinations



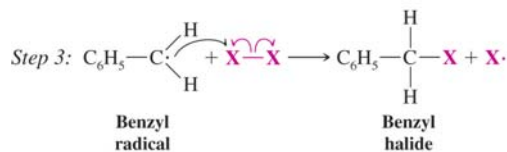
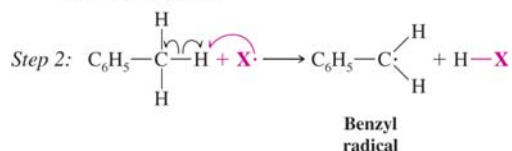
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### Chain Initiation



### Chain Propagation



→ When ethylbenzene or propylbenzene react under radical conditions, halogenation occurs primarily at the benzylic position

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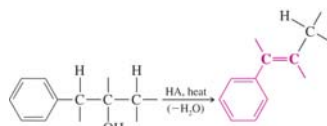
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## ◆ Alkenylbenzenes

### ● Stability of Conjugated Alkenylbenzenes

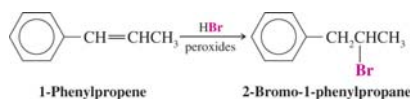
→ Conjugated alkenyl benzenes are more stable than nonconjugated alkenylbenzenes

‡ Dehydration of the alcohol below yields only the more stable conjugated alkenyl benzene



### ● Additions to the Double Bond of Alkenylbenzenes

→ Additions proceed through the most stable benzylic radical or benzylic cation intermediates

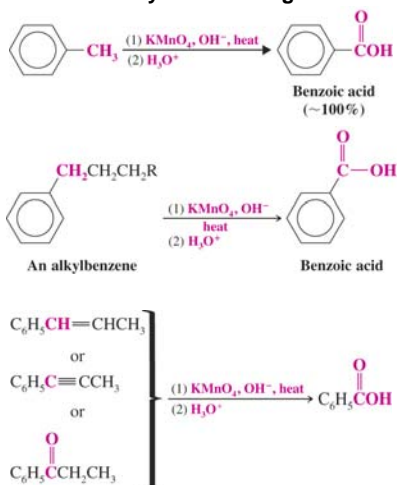


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- Oxidation of the Side Chain

→ Alkyl and unsaturated side chains of aromatic rings can be oxidized to the carboxylic acid using hot  $\text{KMnO}_4$



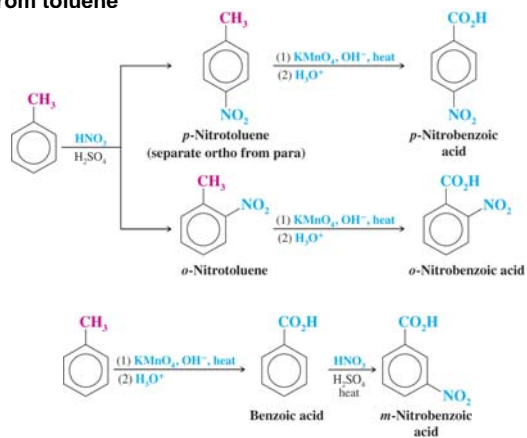
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- ◆ Synthetic Applications

→ When designing a synthesis of substituted benzenes, the order in which the substituents are introduced is crucial

→ Example: Synthesize ortho-, meta-, and para-nitrobenzoic acid from toluene



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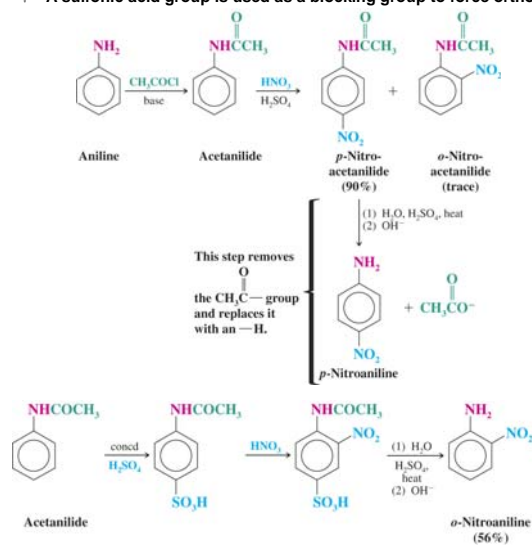
- Use of Protecting and Blocking Groups

→ Strong activating groups such as amino and hydroxyl cause the aromatic ring to be so reactive that unwanted reactions can take place

- ⌘ These groups activate aromatic rings to oxidation by nitric acid when nitration is attempted; the ring is destroyed
- ⌘ An amino group can be protected (and turned into a moderately activating group) by acetylation

→ Example: The synthesis of *p*- and *o*-nitroaniline from aniline

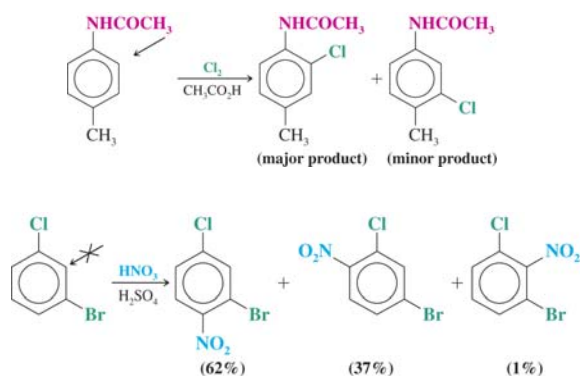
⌘ A sulfonic acid group is used as a blocking group to force ortho substitution



### ● Orientation in Disubstituted Benzenes

→ When two substituents are present on the ring initially, the more powerful activating group generally determines the orientation of subsequent substitution

- ⌘ Ortho-para directors determine orientation over meta directors
- ⌘ Substitution does not occur between meta substituents due to steric hindrance

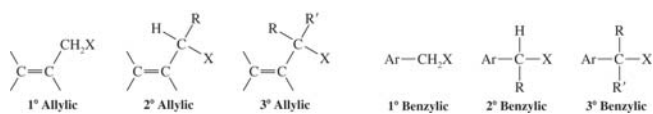


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### ◆ Allylic and Benzylic Halides in Nucleophilic Substitution Reactions

→ Allylic and benzylic halides are classified in similar fashion to other halides



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→ Both primary and secondary allylic and benzylic halides can undergo  $S_N1$  or  $S_N2$  reaction

¶ These primary halides are able to undergo  $S_N1$  reaction because of the added stability of the allylic and benzylic carbocation

→ Tertiary allylic and benzylic halides can only undergo  $S_N1$  reaction

