

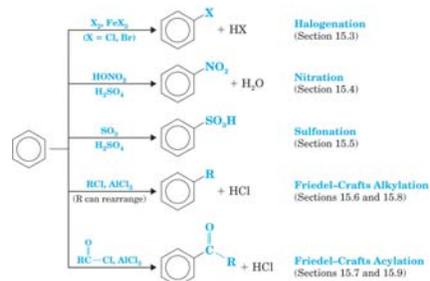
Chapter 15 Reactions of Aromatic Compounds

♦ 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

VERY IMPORTANT SLIDE

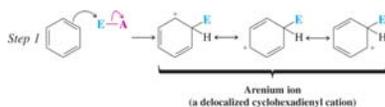
→ Benzene reacts with an electrophile using two of its π electrons

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

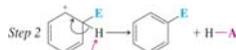
→ Unlike an addition reaction, the benzene ring reacts further so that it may regenerate the very stable aromatic system

→ In **step 1** of the mechanism, the electrophile reacts with two π 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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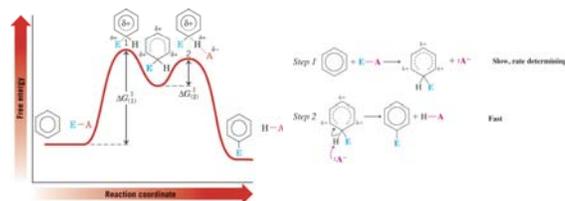
→ The energy diagram of this reaction shows that the first step is highly endothermic and has a large $\Delta G^\ddagger_{(1)}$

↳ 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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◆ 1st reaction: Halogenation of Benzene

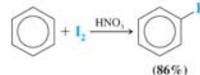
→ Halogenation of benzene requires the presence of a Lewis acid



→ 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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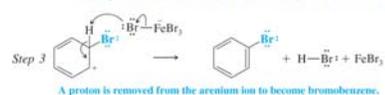
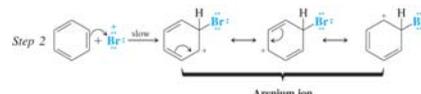
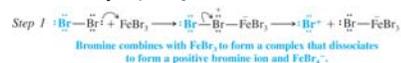
MECHANISM: IMPORTANT

→ 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 π 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 FeBr_3 catalyst is regenerated

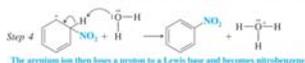
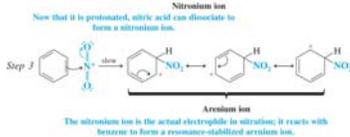
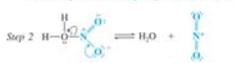
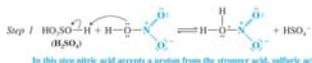


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◆ 2nd reaction: Nitration of Benzene

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

∴ The electrophile for the reaction is the nitronium ion (NO_2^+)

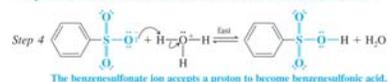
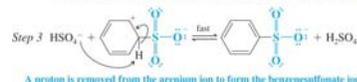
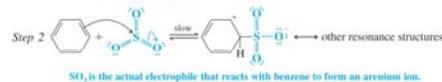
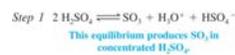


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◆ 3rd reaction: Sulfonation of Benzene

→ Sulfonation occurs most rapidly using fuming sulfuric acid (concentrated sulfuric acid that contains SO_3)

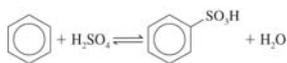
∴ The reaction also occurs in conc. sulfuric acid, which generates small quantities of SO_3 , as shown in step 1 below



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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

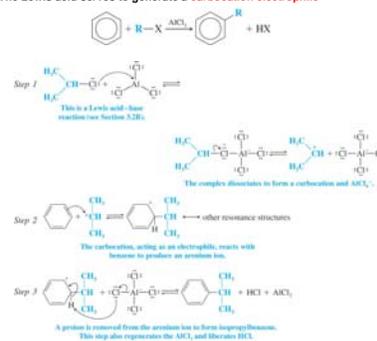


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◆ 4th reaction: Friedel-Crafts Alkylation

→ 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

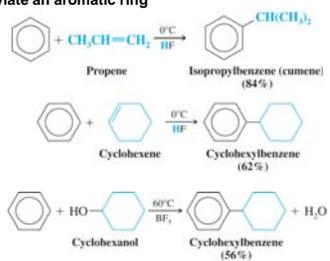


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→ Primary alkyl halides probably do not form discrete carbocations but the primary carbon in the complex develops considerable positive charge



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

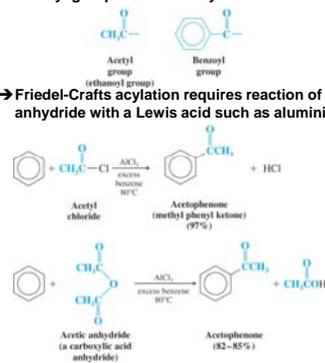


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◆ 5th reaction: Friedel-Crafts Acylation

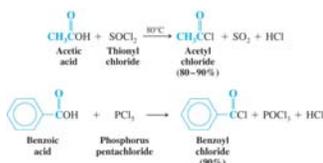
→ An acyl group has a carbonyl attached to some R group

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



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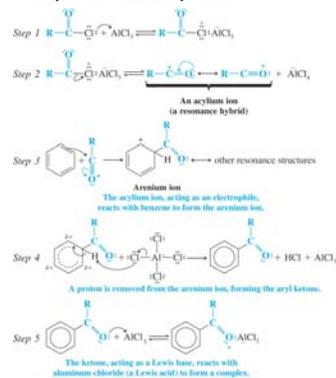
→ Acid chlorides are made from carboxylic acids
(Will be studied in Chapter 17)



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

• The acylium ion is stabilized by resonance

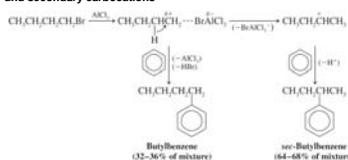


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♦ Limitations of Friedel-Crafts Reactions

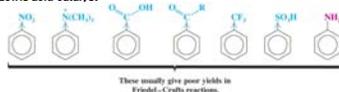
→ In Friedel-Crafts alkylation, the alkyl carbocation intermediate may rearrange to a more stable carbocation prior to alkylation

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



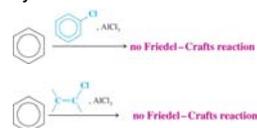
→ Powerful electron-withdrawing groups make an aromatic ring much less reactive toward Friedel-Crafts alkylation or acylation

• 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



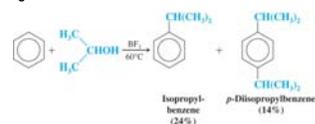
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→ Aryl and vinyl halides cannot be used in Friedel-Crafts reactions because they do not form carbocations readily



→ Polyacylation 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

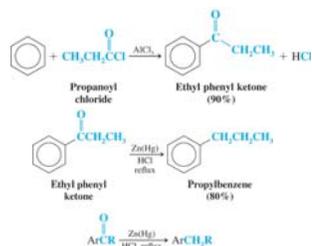


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◆ Synthetic Applications of Friedel-Crafts Acylations: The Clemmensen Reduction

- 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

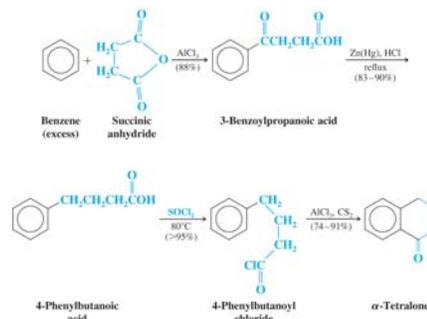
☞ Clemmensen reduction reduces phenyl ketones to the methylene (CH₂) group



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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

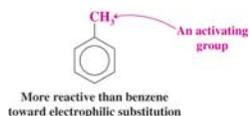
● Activating Groups: Ortho-Para Directors

→ 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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→ 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

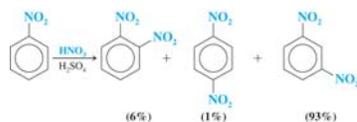


→ Alkyl groups and heteroatoms with one or more unshared electron pairs directly bonded to the aromatic ring will be ortho-para directors (see chart later)

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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	0
Sulfonation		100	100	0

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Classification of Substituents

Ortho-Para Directors	Meta Directors
Strongly Activating	Moderately Deactivating
-NH ₂ , -NHR, -NR ₂	-C≡N
-OH, -O ⁻	-SO ₃ H
Moderately Activating	-CO ₂ H, -CO ₂ R
-NHCOCH ₃ , -NHCOR	-CHO, -COR
-OCH ₃ , -OR	Strongly Deactivating
Weakly Activating	-NO ₂
-CH ₃ , -C ₂ H ₅ , -R	-NR ₃ ⁺
-C ₆ H ₅	-CF ₃ , -CCl ₃
Weakly Deactivating	
-F, -Cl, -Br, -I	

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Theory of Substituent Effects on Electrophilic Substitution

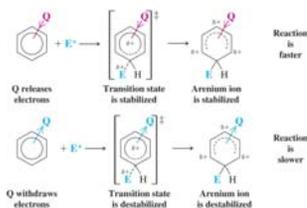
Reactivity: The Effect of Electron-Releasing and Electron-Withdrawing Groups

→ Electron-releasing groups Q activate the ring toward further reaction

↳ Electron-releasing groups stabilize the transition state of the first step of substitution and lead to lower ΔG^\ddagger and faster rates of reaction

→ Electron-withdrawing groups Q deactivate the ring toward further reaction

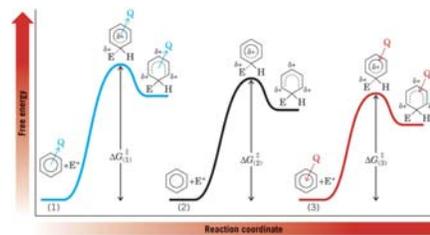
↳ Electron-withdrawing groups destabilize the transition state and lead to higher ΔG^\ddagger and slower rates of reaction



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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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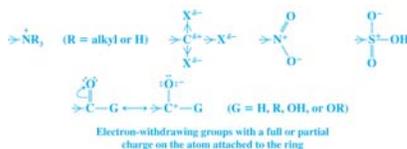
Inductive and Resonance Effects: Theory of Orientation

→ 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



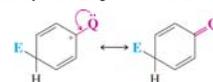
→ The following are some other groups that have an electron-withdrawing effect because the atom directly attached to the ring has a partial or full positive charge



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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



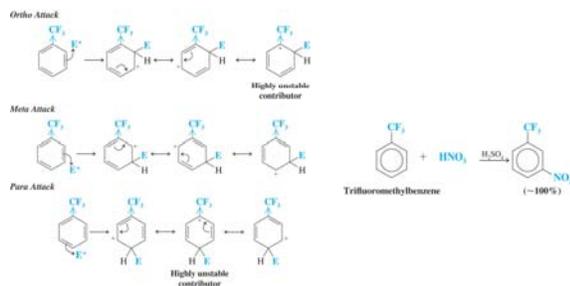
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Meta-directing Groups: Mechanism of EAS

→ 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

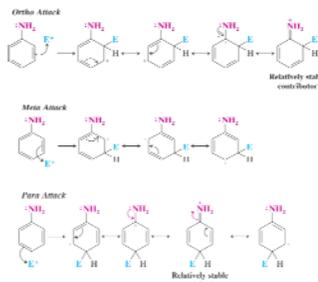
→ Many ortho-para directors are groups that have a lone pair of electrons on the atom directly attached to the ring



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

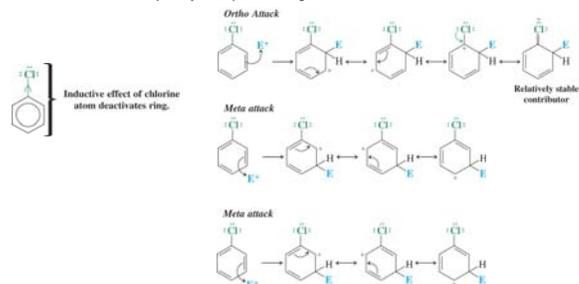
- ¶ The aromatic ring is activated because of the resonance effect of these groups
- ¶ They are ortho-para directors because they contribute a fourth important resonance form which stabilizes the arenium ion in the cases of ortho and para substitution only
- ¶ The fourth resonance form that involves 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 (!)

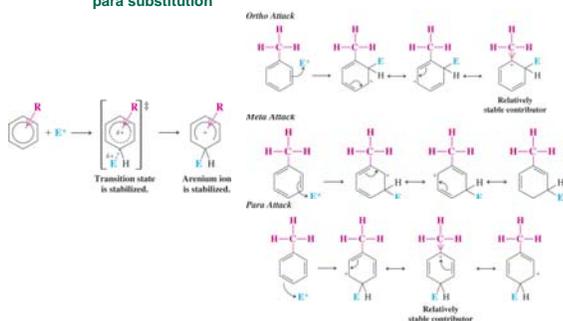
- ¶ The electron-withdrawing inductive effect of the halide is the primary influence that deactivates haloaromatic compounds toward electrophilic aromatic substitution
- ¶ The electron-donating resonance effect of the halogen's unshared electron pairs is the primary ortho-para directing influence



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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



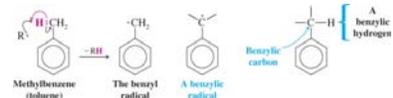
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◆ Reactions of the Side Chain of Alkylbenzenes

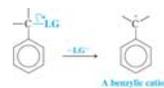
• Benzylic Radicals and Cations

- 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

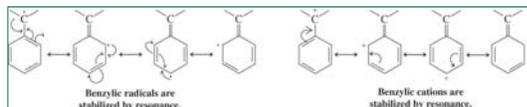


- Departure of a leaving group by an S_N1 process from a benzylic position leads to formation of a benzylic cation



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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*-bromosuccinimide with toluene in the presence of light leads to allylic bromination

† Recall *N*-bromosuccinimide produces a low concentration of bromine which favors radical reaction



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



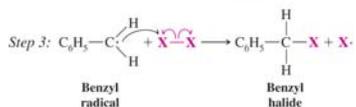
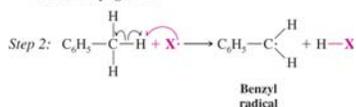
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Step by step mechanism of benzylic halogenation

Chain Initiation



Chain Propagation



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

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Alkenylbenzenes (Arenes conjugated with double bonds)

• Stability of Conjugated Alkenylbenzenes

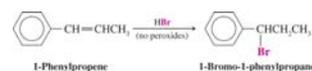
→ Conjugated alkenyl benzenes are more stable than nonconjugated alkenylbenzenes

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



• Additions to the Double Bond of Alkenylbenzenes

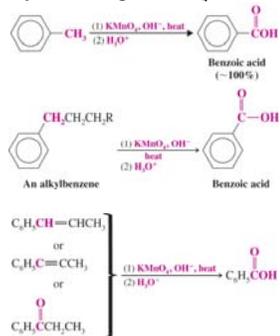
→ Additions proceed through the most stable benzylic radical or benzylic cation intermediates



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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 KMnO_4

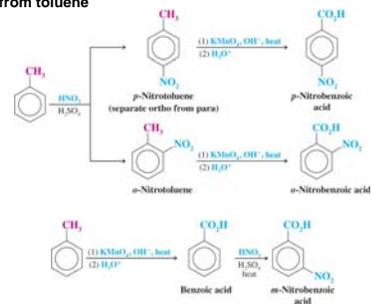


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◆ Synthetic Applications

→ 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

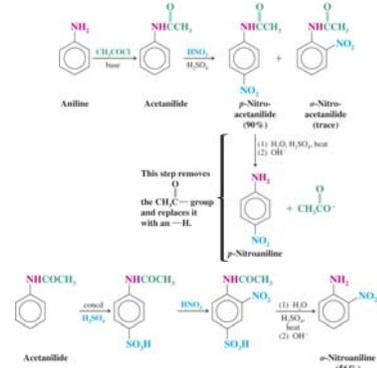
- ? These groups activate aromatic rings to oxidation by nitric acid when nitration is attempted; the ring is destroyed
- ? An amino group can be protected (and turned into a moderately activating group) by acetylation

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

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

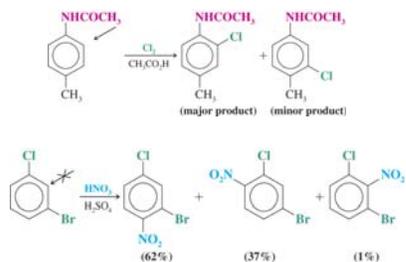


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● Orientation in Disubstituted Benzenes

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

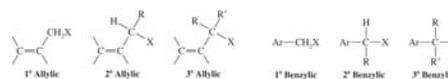
- ⤴ Ortho-para directors determine orientation over meta directors
- ⤴ Substitution does not occur between meta substituents due to steric hindrance



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◆ Allylic and Benzylic Halides in Nucleophilic Substitution Reactions

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

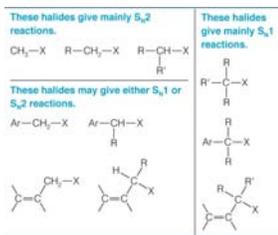


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→ Both primary and secondary allylic and benzylic halides can undergo S_N1 or S_N2 reaction

- ⤴ These primary halides are able to undergo S_N2 reaction because of the added stability of the allylic and benzylic carbocation

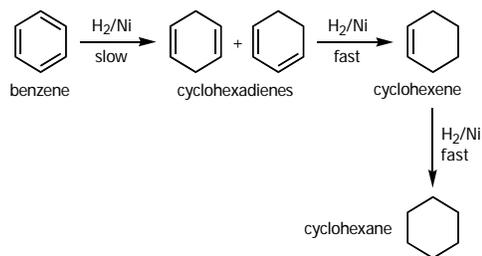
→ Tertiary allylic and benzylic halides can only undergo S_N1 reaction



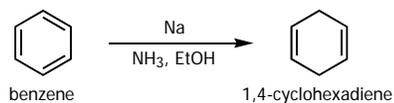
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Reduction of the Aromatic compounds



The Birch reduction



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