

Organic Chemistry, *Fourth Edition*

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Chapter 18 Lecture Outline

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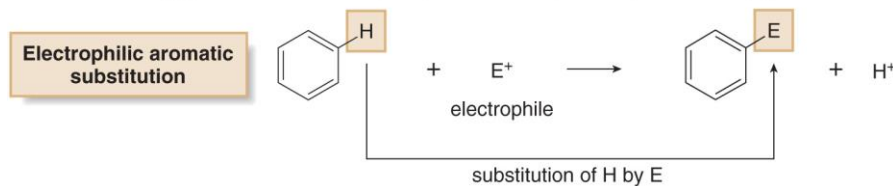
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1

Electrophilic Aromatic Substitution

- The characteristic reaction of benzene is **electrophilic aromatic substitution**—a hydrogen atom is replaced by an electrophile.
- Since benzene is especially stable, reactions that keep the aromatic ring intact are favored.

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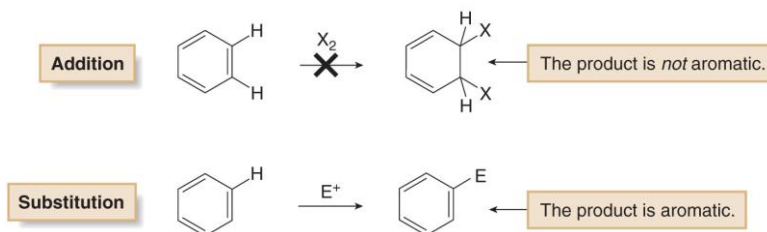


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Substitution Instead of Addition

- Benzene does not undergo addition reactions like other unsaturated hydrocarbons, because addition would yield a product that is not aromatic.
- Substitution of a hydrogen keeps the aromatic ring intact.
- There are several common examples of electrophilic aromatic substitution.

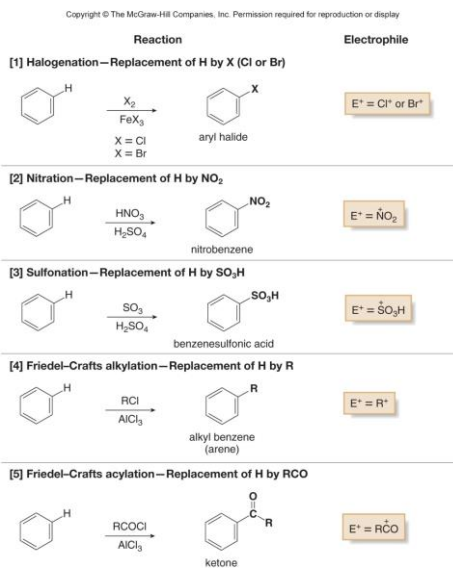
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Examples of Electrophilic Aromatic Substitution

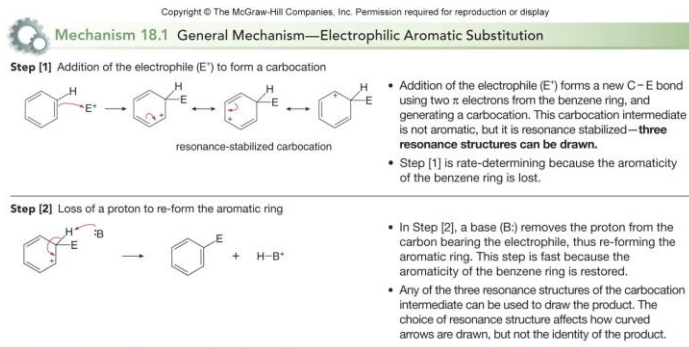
Figure 18.1



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Mechanism of Substitution

- Regardless of the electrophile used, all electrophilic aromatic substitution reactions occur by the same two-step mechanism:
 - addition of the electrophile E^+ to form a resonance-stabilized carbocation,
 - followed by deprotonation with base.

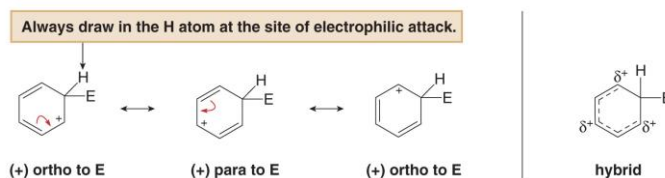


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Resonance-Stabilized Aromatic Carbocation

- The first step in electrophilic aromatic substitution forms a carbocation, for which three resonance structures can be drawn.
- To help keep track of the location of the positive charge:

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- Always draw in the H atom on the carbon bonded to E. This serves as a reminder that it is the only sp^3 hybridized carbon in the carbocation intermediate.
 - Notice that the positive charge in a given resonance structure is always located ortho or para to the new C–E bond. In the hybrid, therefore, the charge is delocalized over three atoms of the ring.

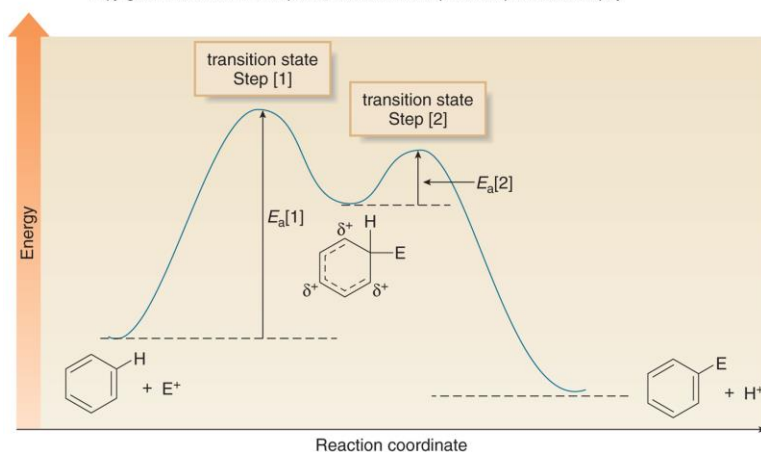


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Energy Diagram for Electrophilic Aromatic Substitution

Figure 18.2

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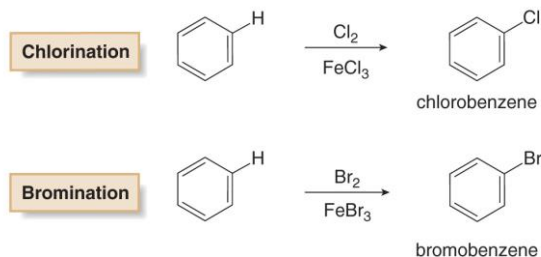


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Halogenation

- In **halogenation**, benzene reacts with Cl_2 or Br_2 in the presence of a Lewis acid catalyst, such as $FeCl_3$ or $FeBr_3$, to give the aryl halides chlorobenzene or bromobenzene, respectively.
- Analogous reactions with I_2 and F_2 are not synthetically useful because I_2 is too unreactive and F_2 reacts too violently.

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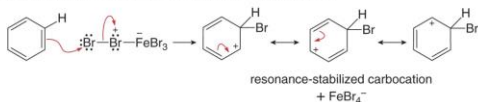
Mechanism 18.2 Bromination of Benzene

Step [1] Generation of the electrophile



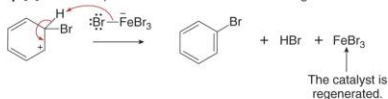
- Lewis acid-base reaction of Br₂ with FeBr₃ forms a species with a weakened and polarized Br-Br bond. This adduct serves as a source of Br⁺ in the next step.

Step [2] Addition of the electrophile to form a carbocation



- Addition of the electrophile forms a new C-Br bond and generates a carbocation. This carbocation intermediate is resonance stabilized—**three resonance structures can be drawn**.
- The FeBr₄⁻ also formed in this reaction is the base used in Step [3].

Step [3] Loss of a proton to re-form the aromatic ring



- FeBr₄⁻ removes the proton from the carbon bearing the Br, thus re-forming the aromatic ring.
- FeBr₃, a catalyst, is also regenerated for another reaction cycle.

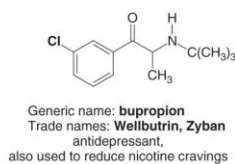
- Chlorination proceeds by a similar mechanism.

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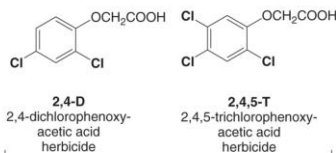
Biologically Active Alkyl Chlorides

Figure 18.3

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Herbicides were used extensively during the Vietnam War to defoliate dense jungle areas. The concentration of certain herbicide by-products in the soil remains high today.

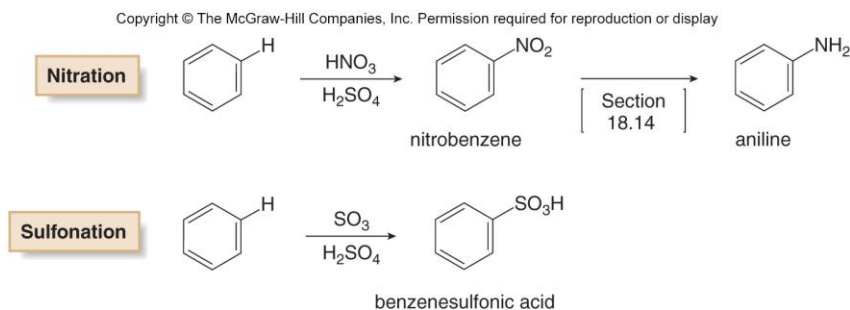


the active components in **Agent Orange**,
a defoliant used in the Vietnam War

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Nitration and Sulfonation

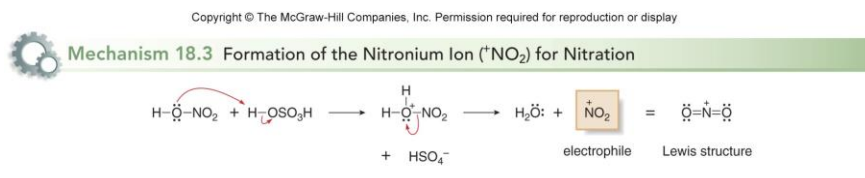
- **Nitration** and **sulfonation** introduce two different functional groups into the aromatic ring.
- Nitration is especially useful because the nitro group can be reduced to an NH_2 group.



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Nitration Mechanism

- Generation of the electrophile in nitration requires strong acid.



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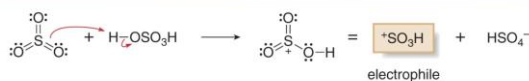
Sulfonation Mechanism

- Generation of the electrophile in sulfonation requires strong acid.

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Mechanism 18.4 Formation of the Electrophile $^+\text{SO}_3\text{H}$ for Sulfonation

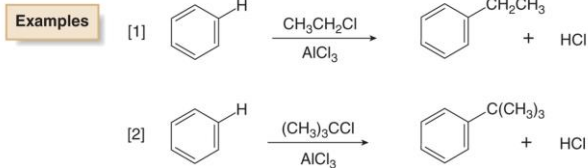
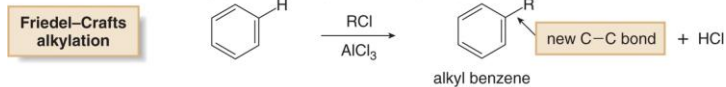


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Friedel–Crafts Alkylation

- In **Friedel–Crafts alkylation**, treatment of benzene with an alkyl halide and a Lewis acid (AlCl_3) forms an alkyl benzene.

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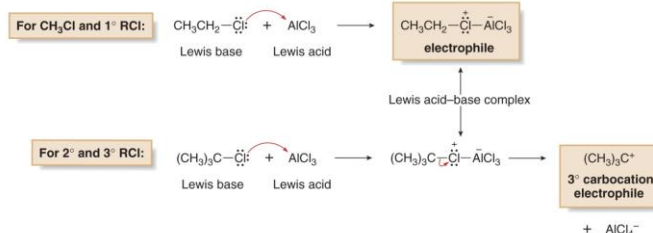
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Electrophiles in Friedel–Crafts Alkylation

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Mechanism 18.5 Formation of the Electrophile in Friedel–Crafts Alkylation—Two Possibilities



- For CH_3Cl and 1°RCl , the Lewis acid–base complex itself serves as the electrophile for electrophilic aromatic substitution.
- With 2° and 3°RCl , the Lewis acid–base complex reacts further to give a 2° or 3° carbocation, which serves as the electrophile. Carbocation formation occurs only with 2° and 3° alkyl chlorides, because they afford more stable carbocations.

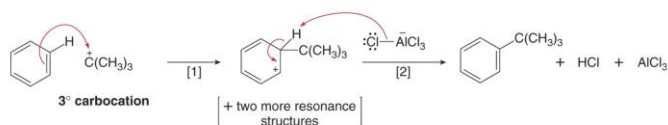
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Friedel–Crafts Alkylation with 3° Carbocation

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Mechanism 18.6 Friedel–Crafts Alkylation Using a 3° Carbocation



- Addition of the electrophile (a 3° carbocation) forms a new carbon–carbon bond in Step [1].
- AlCl_4^- removes a proton on the carbon bearing the new substituent, thus re-forming the aromatic ring in Step [2].

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Other Facts About Friedel–Crafts Alkylation

[1] Vinyl halides and aryl halides do not react in Friedel–Crafts alkylation.

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Unreactive halides in the Friedel–Crafts alkylation



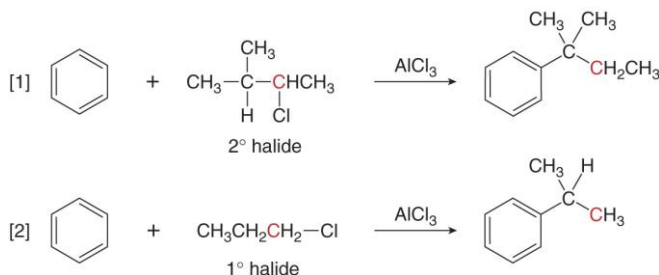
vinyl halide



aryl halide

[2] Rearrangements can occur.

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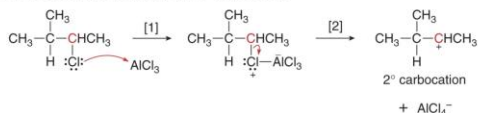
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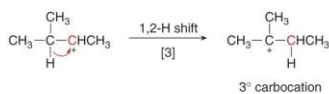
Mechanism 18.8 Friedel–Crafts Alkylation Involving Carbocation Rearrangement

Steps [1] and [2] Formation of a 2° carbocation



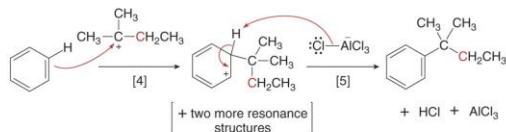
- Reaction of the alkyl chloride with AlCl_3 forms a complex that decomposes in Step [2] to form a 2° carbocation.

Step [3] Carbocation rearrangement



- 1,2-Hydride shift converts the less stable 2° carbocation to a more stable 3° carbocation.

Steps [4] and [5] Addition of the carbocation and loss of a proton



- Friedel–Crafts alkylation occurs by the usual two-step process: **addition of the carbocation** followed by **loss of a proton** to form the alkylated product.

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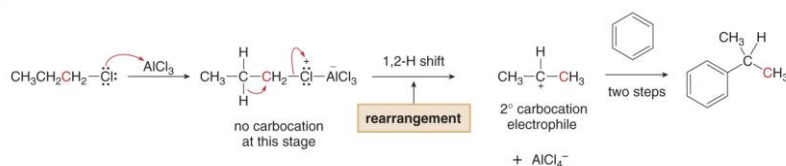
Rearrangements of 1° Alkyl Halides

- Rearrangements can occur even when no free carbocation is formed initially.

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Mechanism 18.9 A Rearrangement Reaction Beginning with a 1° Alkyl Chloride



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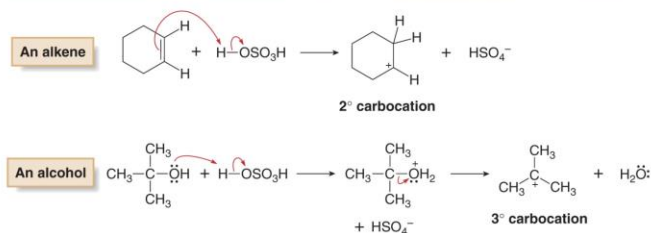
Other Carbocations in Friedel–Crafts Alkylation

- [3] Other functional groups that form carbocations can also be used as starting materials.

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- Protonation of an alkene forms a carbocation, which can then serve as an electrophile in a Friedel–Crafts alkylation.

- Protonation of an alcohol, followed by loss of water, likewise forms a carbocation.

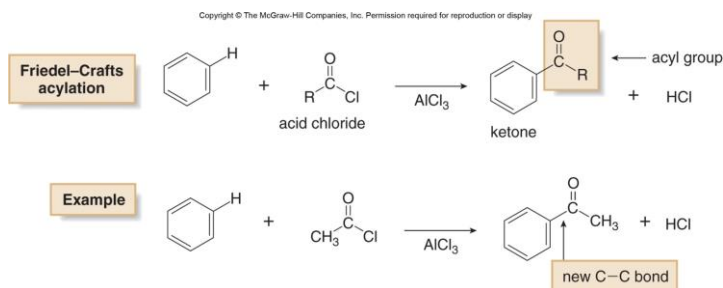


- Carbocations formed in the presence of benzene can then substitute onto the ring by the usual mechanism.

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Friedel–Crafts Acylation

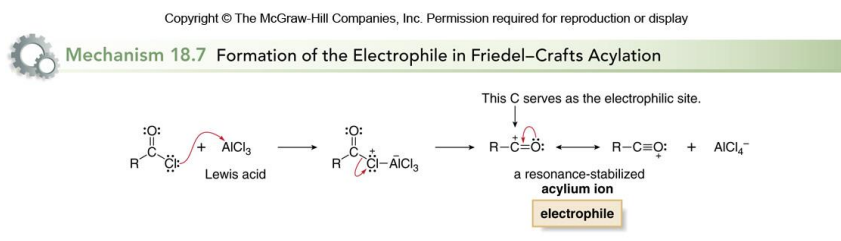
- In **Friedel–Crafts acylation**, a benzene ring is treated with an acid chloride (**RCOCl**) and AlCl_3 to form a ketone.
- Because the new group bonded to the benzene ring is called an **acyl group**, the transfer of an acyl group from one atom to another is an acylation.



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Friedel–Crafts Acylation

- In Friedel–Crafts acylation, the Lewis acid AlCl_3 ionizes the carbon–halogen bond of the acid chloride, thus forming a positively charged carbon electrophile called an **acylium ion**, which is resonance stabilized.
- The positively charged carbon atom of the acylium ion then goes on to react with benzene in the two-step mechanism of electrophilic aromatic substitution.

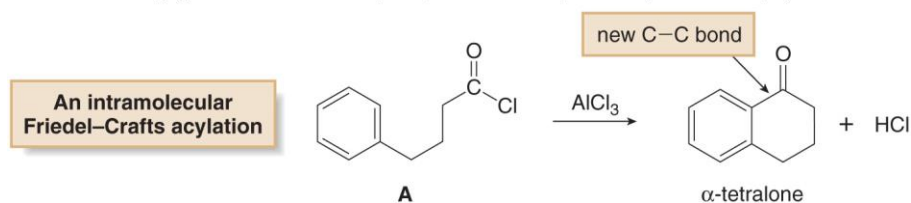


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Intramolecular Friedel–Crafts Reactions

- Starting materials that contain both a benzene ring and an electrophile are capable of intramolecular Friedel–Crafts reactions.

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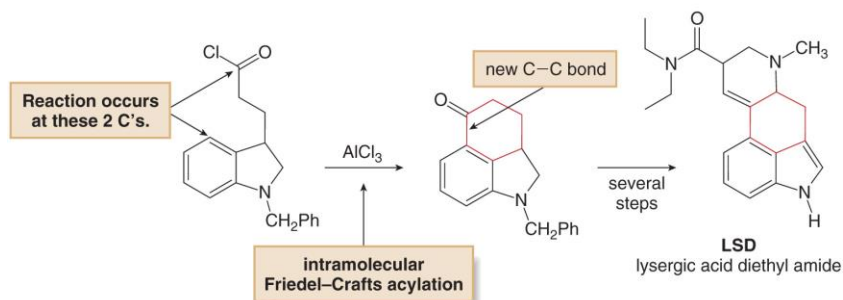


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Intramolecular Friedel–Crafts Reactions

Figure 18.4
Synthesis of LSD

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Substituent Effects of Substituted Benzenes

- Many substituted benzene rings undergo electrophilic aromatic substitution.
- Each substituent either increases or decreases the electron density in the benzene ring, and this affects the course of electrophilic aromatic substitution.
 - Donation of electron density to the ring makes benzene more electron rich.
 - Withdrawal of electron density from the ring makes benzene less electron rich.
- Electrophilic substitution on an already substituted benzene produces isomers, some of which are favored over others.

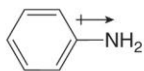
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Inductive Effects

- Considering inductive effects only, the NH_2 group withdraws electron density and CH_3 donates electron density.

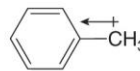
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Electron-withdrawing inductive effect



- N is **more electronegative** than C.
- N inductively withdraws electron density.

Electron-donating inductive effect



- Alkyl groups are **polarizable**, making them electron-donating groups.

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Resonance Effects

- Resonance effects are only observed with substituents containing lone pairs or π bonds.

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- A resonance effect is electron donating when resonance structures place a negative charge on carbons of the benzene ring.
- A resonance effect is electron withdrawing when resonance structures place a positive charge on carbons of the benzene ring.

- An electron-donating resonance effect is observed whenever an atom Z having a lone pair of electrons is directly bonded to a benzene ring.

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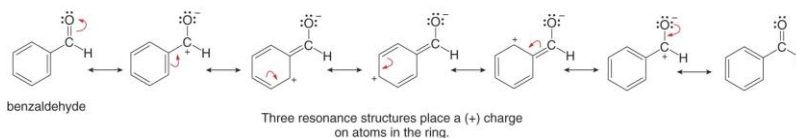


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Electron-Withdrawing Resonance Effects

- An electron-withdrawing resonance effect is observed in substituted benzenes having the general structure $\text{C}_6\text{H}_5\text{-Y=Z}$, where Z is more electronegative than Y.
- Seven resonance structures can be drawn for benzaldehyde ($\text{C}_6\text{H}_5\text{CHO}$).
- Because three of them place a positive charge on a carbon atom of the benzene ring, the CHO group withdraws electrons from the benzene ring by a resonance effect.

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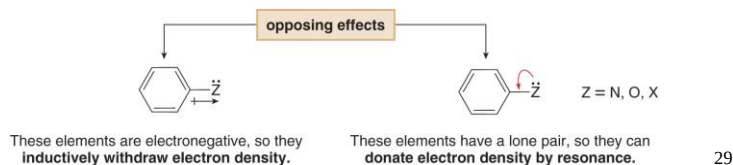


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Inductive and Resonance Effects

- To predict whether a substituted benzene is more or less electron rich than benzene itself, we must consider the net balance of both the inductive and resonance effects.
- Alkyl groups donate electrons by an inductive effect, but they have no resonance effect because they lack nonbonded electron pairs or π bonds.
- Thus, any alkyl-substituted benzene is more electron rich than benzene itself.
- The same analysis can be done with groups other than alkyl.

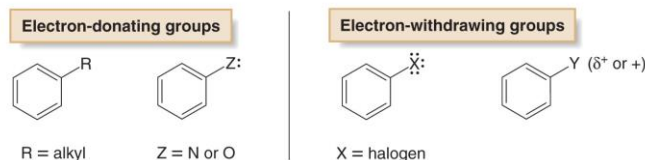
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Electron-Donating and Electron-Withdrawing Groups

- These compounds represent examples of the general structural features in electron-donating and electron-withdrawing substituents.

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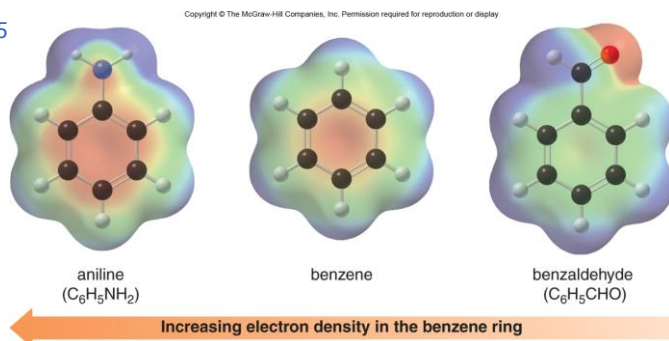
- Common electron-donating groups are alkyl groups or groups with an N or O atom (with a lone pair) bonded to the benzene ring.
- Common electron-withdrawing groups are halogens or groups with an atom Y bearing a full or partial positive charge (δ^+ or +) bonded to the benzene ring.

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Electron-Donating and Electron-Withdrawing Groups

- The NH_2 group donates electron density making the benzene ring more electron rich.
- The CHO group withdraws electron density, making the benzene ring less electron rich.

Figure 18.5



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Substituent Effects on Electrophilic Aromatic Substitution

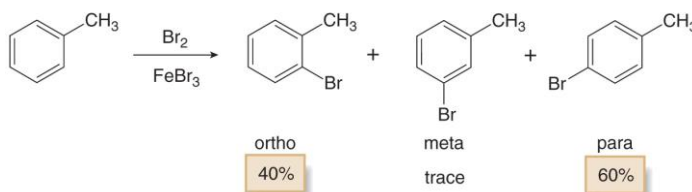
- Electrophilic aromatic substitution is a general reaction of all aromatic compounds, including polycyclic aromatic hydrocarbons, heterocycles, and substituted benzene derivatives.
- A substituent affects two aspects of the electrophilic aromatic substitution reaction:
 1. The rate of the reaction: A substituted benzene reacts faster or slower than benzene itself.
 2. The orientation: The new group is located either ortho, meta, or para to the existing substituent.
 - The identity of the first substituent determines the position of the second incoming substituent.

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Ortho, Para Directors—Activators

- Toluene reacts faster than benzene in all substitution reactions.
- The electron-donating CH_3 group activates the benzene ring to electrophilic attack.
- **Ortho** and **para** products predominate.
- The CH_3 group is called an **ortho, para director**.

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Meta Directors—Deactivators

- Nitrobenzene reacts more slowly than benzene in all substitution reactions.
- The electron-withdrawing NO_2 group deactivates the benzene ring to electrophilic attack.
- The meta product predominates.
- The NO_2 group is called a **meta director**.

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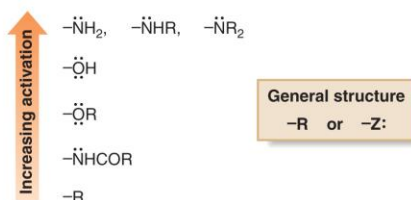
Categorizing Directors and Activators

- All substituents can be divided into three general types:

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[1] Ortho, para directors and activators

- Substituents that *activate* a benzene ring and direct substitution ortho and para.



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Categorizing Directors and Activators

- Halogens are in a class by themselves.

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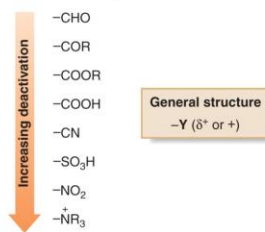
[2] Ortho, para deactivators

- Substituents that *deactivate* a benzene ring and direct substitution ortho and para.



[3] Meta directors

- Substituents that direct substitution meta.
- All meta directors *deactivate* the ring.



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Characteristics of Ortho and Para Directors and Meta Directors

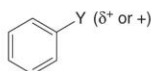
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- All ortho, para directors are R groups or have a nonbonded electron pair on the atom bonded to the benzene ring.



Z = N or O $\rightarrow$ The ring is **activated**.
Z = halogen $\rightarrow$ The ring is **deactivated**.

- All meta directors have a full or partial positive charge on the atom bonded to the benzene ring.



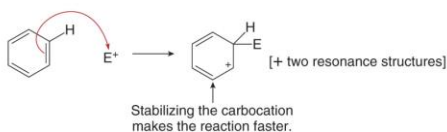
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Mechanism of Activation/Deactivation

- To understand how substituents activate or deactivate the ring, we must consider the first step in electrophilic aromatic substitution.
- The first step involves addition of the electrophile (E^+) to form a resonance-stabilized carbocation.
- The Hammond postulate makes it possible to predict the relative rate of the reaction by looking at the stability of the carbocation intermediate.

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- The more stable the carbocation, the lower in energy the transition state that forms it, and the faster the reaction.

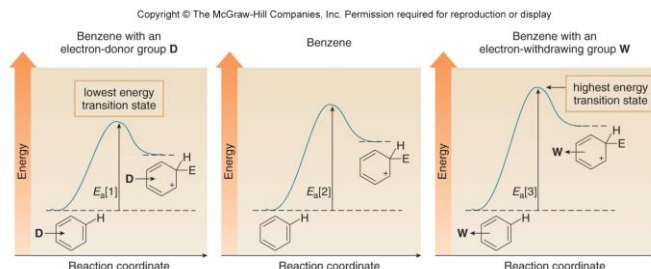


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Energy Diagrams Comparing Substitution Rates

- The energy diagrams below illustrate the effect of electron-withdrawing and electron-donating groups on the transition state energy of the rate-determining step.

Figure 18.6 Energy diagrams comparing the rate of electrophilic substitution of substituted benzenes

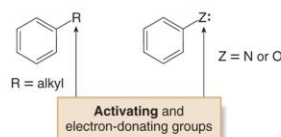


- Electron-donor groups **D** stabilize the carbocation intermediate, lower the energy of the transition state, and increase the rate of reaction.
- Electron-withdrawing groups **W** destabilize the carbocation intermediate, raise the energy of the transition state, and decrease the rate of reaction.

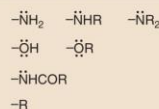
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Summary: Activators and Deactivators

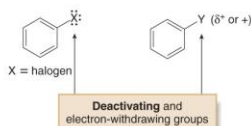
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- All activators are either R groups or they have an N or O atom with a lone pair bonded directly to the benzene ring. These are the electron-donor groups of Section 18.6.



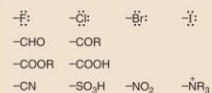
Activating groups:



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- All deactivators are either halogens or they have an atom with a partial or full positive charge bonded directly to the benzene ring. These are the electron-withdrawing groups of Section 18.6.



Deactivating groups:



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Orientation Effects in Substituted Benzenes

- There are two general types of ortho, para directors and one general type of meta director.
- All ortho, para directors are R groups or have a nonbonded electron pair on the atom bonded to the benzene ring.
- All meta directors have a full or partial positive charge on the atom bonded to the benzene ring.

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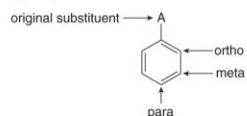
Determining Directing Effects

- To evaluate the effects of a given substituent, we can use the following stepwise procedure:

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How To Determine the Directing Effects of a Particular Substituent

Step [1] Draw all resonance structures for the carbocation formed from attack of an electrophile E^+ at the ortho, meta, and para positions of a substituted benzene (C_6H_5-A).



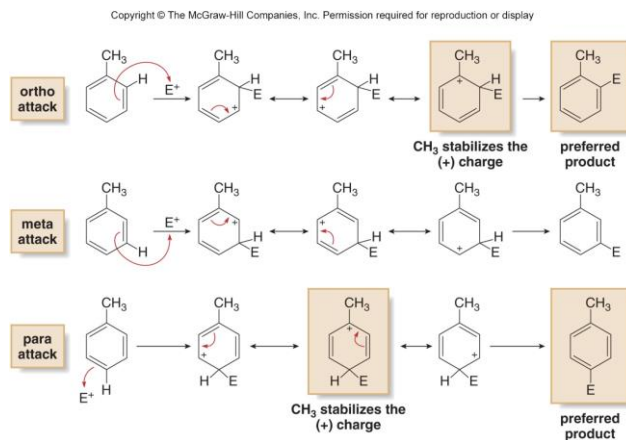
- There are at least three resonance structures for each site of reaction.
- Each resonance structure places a positive charge ortho or para to the new C-E bond.

Step [2] Evaluate the stability of the intermediate resonance structures. The electrophile attacks at those positions that give the most stable carbocation.

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Methyl Carbocation Stabilization

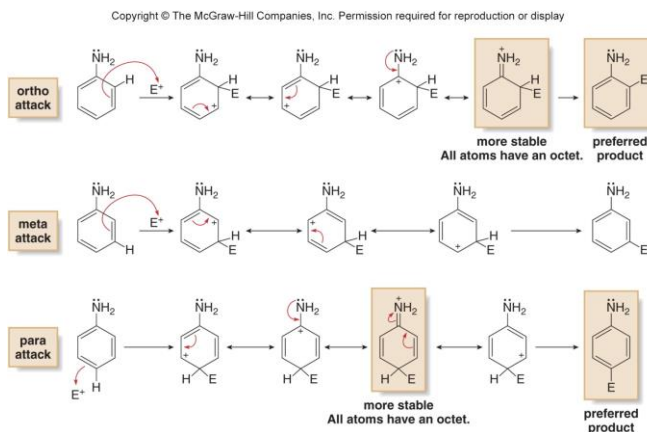
- A CH_3 group directs electrophilic attack ortho and para to itself because an electron-donating inductive effect stabilizes the carbocation intermediate.



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Amine Carbocation Stabilization

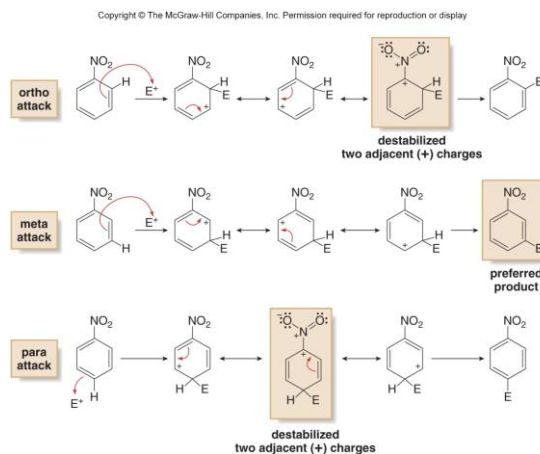
- An NH_2 group directs electrophilic attack ortho and para to itself because the carbocation intermediate has additional resonance stabilization.



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Nitro Carbocation Stabilization

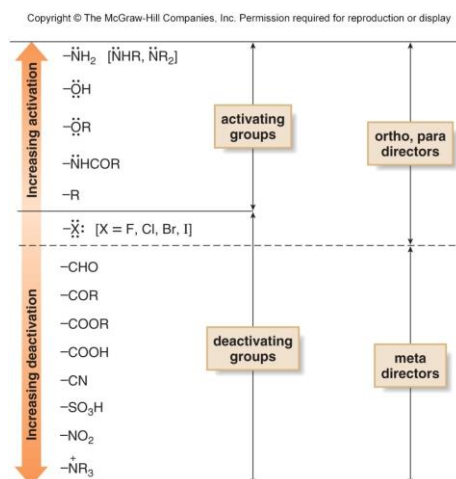
- With the NO_2 group (and all meta directors) meta attack occurs because attack at the ortho and para position gives a destabilized carbocation intermediate.



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Summary of Reactivity and Directing Effects

Figure 18.7

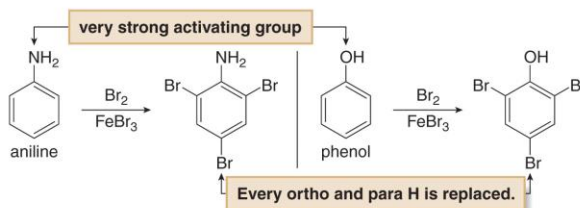


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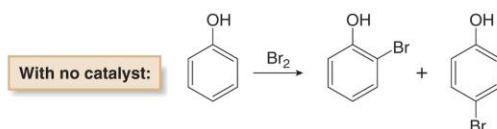
Reactions of Activated Rings

- Benzene rings activated by strong electron-donating groups—OH, NH₂, and their derivatives (OR, NHR, and NR₂)—undergo polyhalogenation when treated with X₂ and FeX₃.

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Monosubstitution of H by Br occurs with Br₂ alone without added catalyst to form a mixture of ortho and para products.

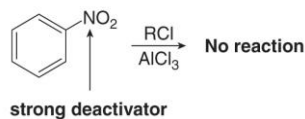


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Reactions of Deactivated Rings

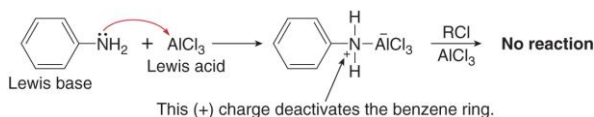
- A benzene ring deactivated by strong electron-withdrawing groups (i.e., any of the meta directors) is not electron rich enough to undergo Friedel–Crafts reactions.

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- Friedel–Crafts reactions also do not occur with NH₂ groups because the complex that forms between the NH₂ group and the AlCl₃ catalyst deactivates the ring towards Friedel–Crafts reactions.

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Friedel–Crafts Reactions and Ring Activation

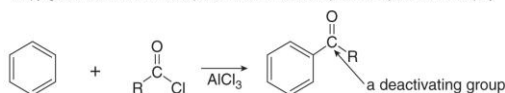
- Treatment of benzene with an alkyl halide and AlCl_3 places an electron-donor R group on the ring.
- Since R groups activate the ring, the alkylated product ($\text{C}_6\text{H}_5\text{R}$) is now more reactive than benzene itself towards further substitution, and it reacts again with RCl to give products of polyalkylation.

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- Polysubstitution does not occur with Friedel–Crafts acylation.

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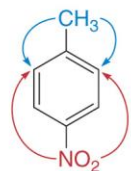
49

Reinforcing Directing Effects

1. When the directing effects of two groups reinforce, the new substituent is located on the position directed by both groups.

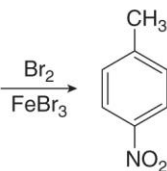
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ortho, para director



meta director

p-nitrotoluene

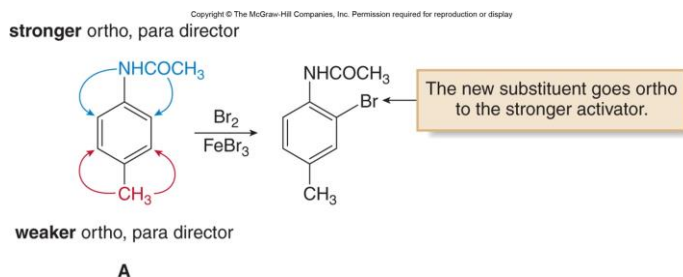


The new group is ortho to the CH_3 group and meta to the NO_2 group.

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Opposing Directing Effects

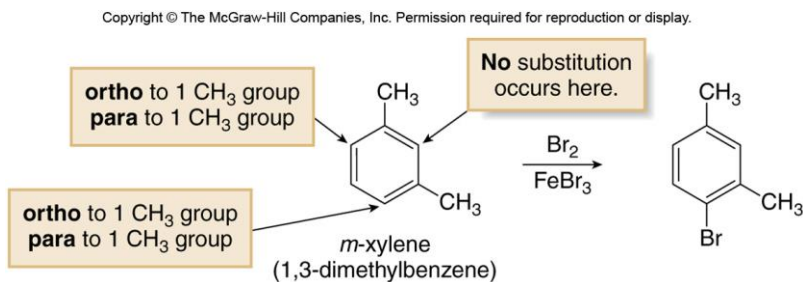
2. If the directing effects of two groups oppose each other, the more powerful activator "wins out."



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Steric Limitations to Directing Effects

3. No substitution occurs between two meta substituents because of crowding.

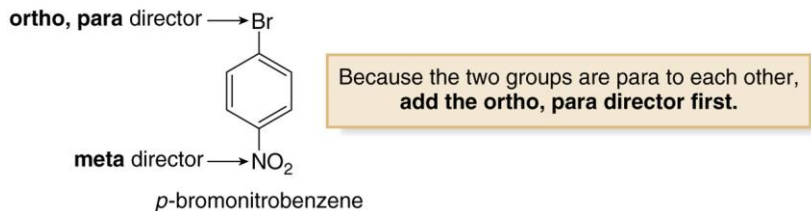


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Synthesis of Benzene Derivatives

- In a disubstituted benzene, the directing effects indicate which substituent must be added to the ring first.

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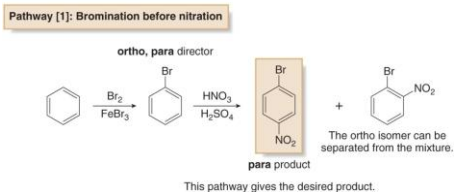


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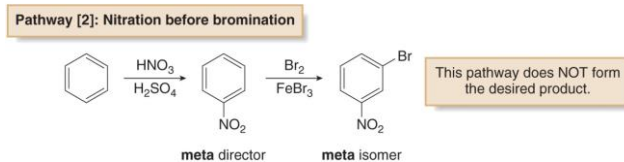
Synthesis of Benzene Derivatives

- Pathway 1, in which bromination precedes nitration, yields the desired product.
- Pathway 2 yields the undesired meta isomer.

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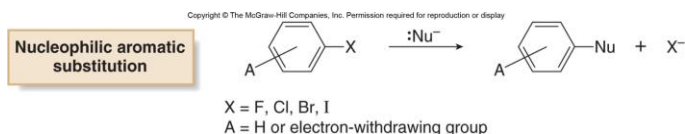
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Nucleophilic Aromatic Substitution

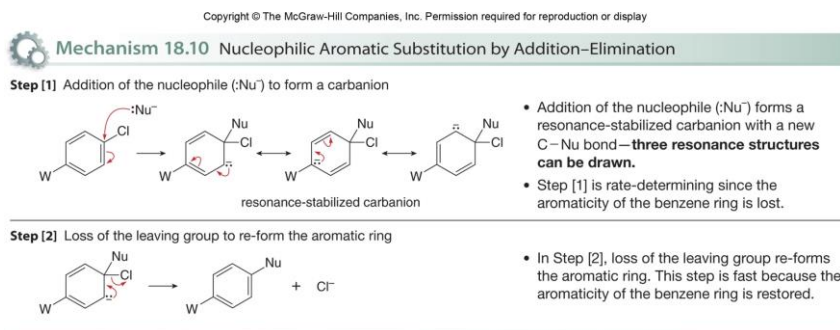
- Nucleophilic aromatic substitution results in the substitution of a halogen on a benzene ring by a nucleophile.



- Two different mechanisms are proposed to explain the result of the reaction.
 - Addition-elimination
 - Elimination-addition

55

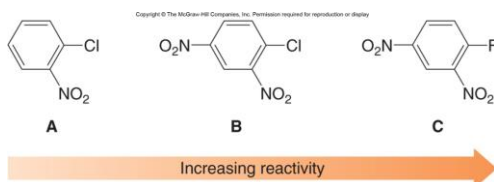
Nucleophilic Aromatic Substitution by Addition-Elimination



56

Reactivity Trends in Nucleophilic Aromatic Substitution

- Increasing the number of electron-withdrawing groups increases the reactivity of the aryl halide.
 - Electron-withdrawing groups stabilize the intermediate carbanion.
- Increasing the electronegativity of the halogen increases the reactivity of the aryl halide.
 - A more electronegative halogen stabilizes the intermediate carbanion by an inductive effect.



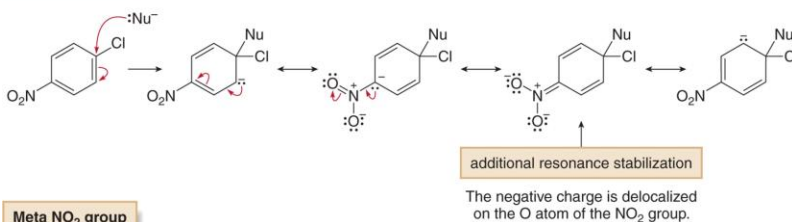
57

Orientation for Addition-Elimination

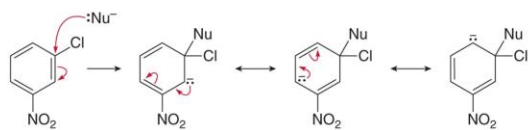
- Nucleophilic aromatic substitution only occurs by an addition-elimination mechanism with aryl halides that contain ortho or para electron-withdrawing substituents.

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Para NO₂ group



Meta NO₂ group



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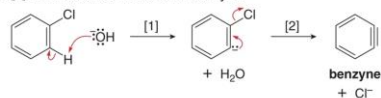
Nucleophilic Aromatic Substitution by Elimination-Addition

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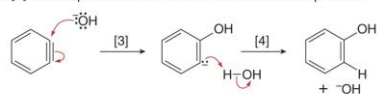
Mechanism 18.11 Nucleophilic Aromatic Substitution by Elimination-Addition: Benzyne

Part [1] Elimination of HX to form benzyne



- Elimination of H and X from two adjacent carbons forms a reactive benzyne intermediate (Steps [1] and [2]).

Part [2] Nucleophilic addition to form the substitution product



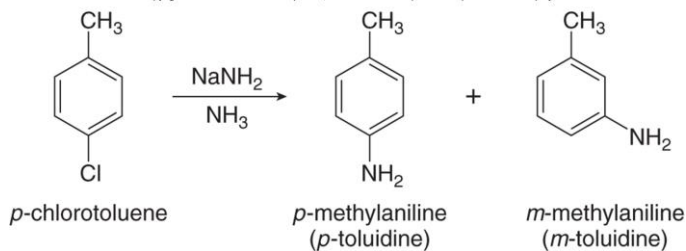
- Addition of the nucleophile (OH⁻ in this case) and protonation form the substitution product (Steps [3] and [4]).

59

Products of Elimination-Addition

- Formation of a benzyne intermediate explains why substituted aryl halides form mixtures of products.
- Nucleophilic aromatic substitution by an elimination-addition mechanism affords substitution on the carbon directly bonded to the leaving group and the carbon adjacent to it.

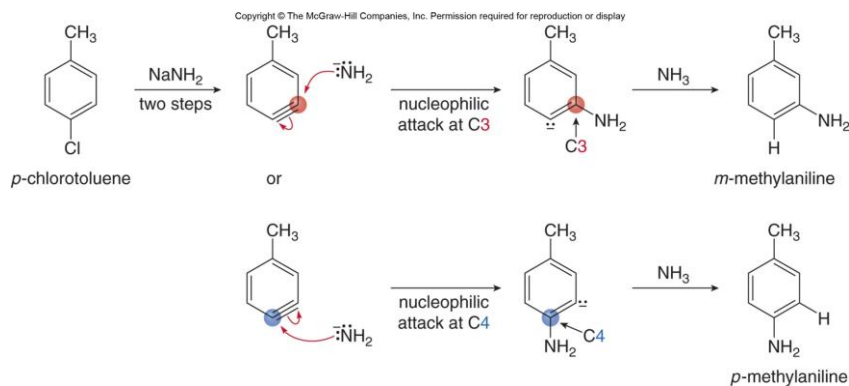
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60

Products of Elimination-Addition

- Nucleophilic attack on the benzyne intermediate may occur at C3 to form *m*-methylaniline, or C4 to form *p*-methylaniline.



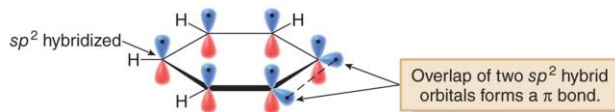
61

Products of Elimination-Addition

- The second π bond of benzyne is different from all other π bonds seen thus far:
 - It is formed by the side-by-side overlap of sp^2 hybrid orbitals, not p orbitals.
 - Therefore, it is extremely weak.

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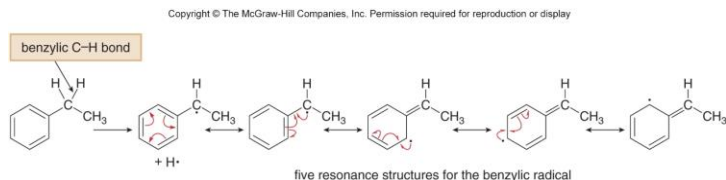
- The σ bond is formed by overlap of two sp^2 hybrid orbitals.
- One π bond is formed by overlap of two p orbitals perpendicular to the plane of the molecule.
- The second π bond is formed by overlap of two sp^2 hybrid orbitals.



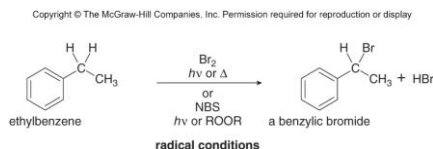
62

Halogenation of Alkyl Benzenes

- Benzylic C–H bonds are weaker than most other sp^3 hybridized C–H bonds, because homolysis forms a resonance-stabilized benzylic radical.



- As a result, alkyl benzenes undergo selective bromination at the weak benzylic C–H bond under radical conditions to form the benzylic halide.



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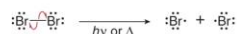
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Mechanism 18.12 Benzylic Bromination

Initiation

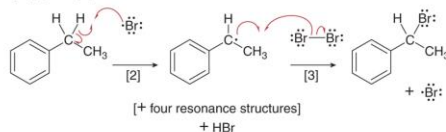
Step [1] Bond cleavage forms two radicals.



- The reaction begins with homolysis of the Br–Br bond using energy from light or heat to form two Br· radicals.

Propagation

Steps [2] and [3] One radical reacts and a new radical is formed.

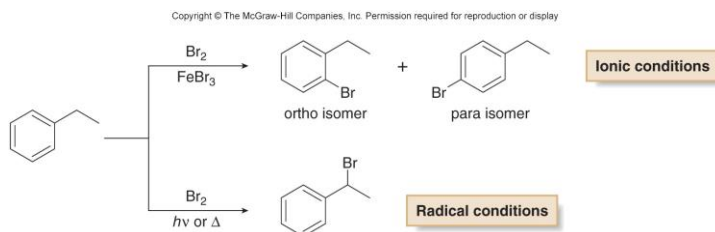


- Abstraction of a benzylic hydrogen by a Br· radical forms the resonance-stabilized benzylic radical in Step [2], which reacts with Br₂ in Step [3] to form the bromination product.
- Because the Br· radical formed in Step [3] is a reactant in Step [2], Steps [2] and [3] can occur repeatedly without additional initiation.

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Ionic and Radical Halogenation

- Alkyl benzenes undergo two different reactions depending on the reaction conditions:

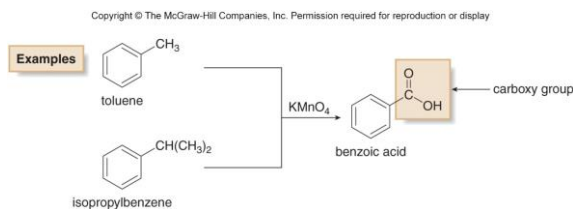


- With Br_2 and FeBr_3 (ionic conditions), electrophilic aromatic substitution occurs, resulting in replacement of H by Br on the aromatic ring to form ortho and para isomers.
- With Br_2 and light or heat (radical conditions), substitution of H by Br occurs at the benzylic carbon of the alkyl group.

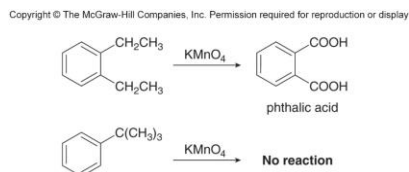
65

Oxidation of Alkyl Benzenes

- Arenes containing at least one benzylic C–H bond are oxidized with KMnO_4 to benzoic acid.



- Substrates with more than one alkyl group are oxidized to dicarboxylic acids.
- Compounds without a benzylic hydrogen are inert to oxidation.

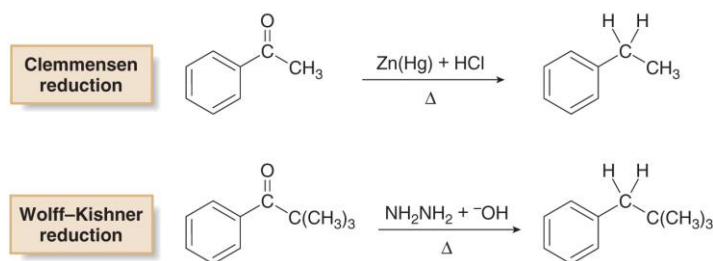


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Reduction of Acyl Benzenes

- Ketones formed as products of Friedel–Crafts acylation can be reduced to alkyl benzenes by two different methods:
1. The **Clemmensen reduction**—uses zinc and mercury in the presence of strong acid.
 2. The **Wolff–Kishner reduction**—uses hydrazine (NH_2NH_2) and strong base (KOH).

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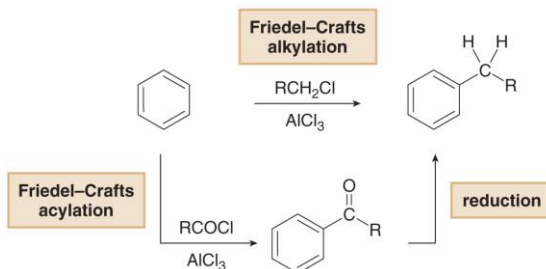
67

Synthesis of Alkyl Benzenes

- We now know two different ways to introduce an alkyl group on a benzene ring:
1. A one-step method using Friedel–Crafts alkylation.
 2. A two-step method using Friedel–Crafts acylation to form a ketone, followed by reduction.

Figure 18.8

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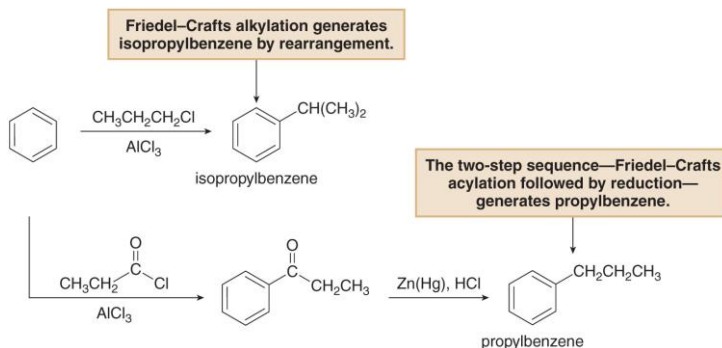


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Synthesis of Alkyl Benzenes

- Although the two-step method seems more roundabout, it must be used to synthesize certain alkyl benzenes that cannot be prepared by the one-step Friedel–Crafts alkylation because of rearrangements.

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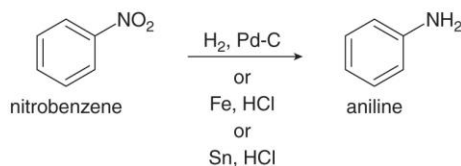


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Reduction of Nitro Benzenes

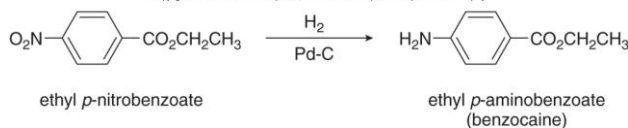
- A nitro group (NO_2) that has been introduced on a benzene ring by nitration with strong acid can readily be reduced to an amino group (NH_2) under a variety of conditions.

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- Reduction of ethyl *p*-nitrobenzoate with H_2 and a palladium catalyst forms ethyl *p*-aminobenzoate, a local anesthetic commonly called benzocaine.

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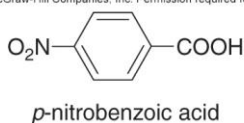


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Multistep Synthesis

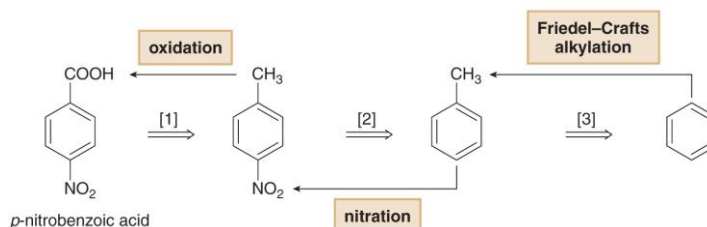
- Write out a synthesis of *p*-nitrobenzoic acid from benzene.

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- First, perform retrosynthetic analysis.

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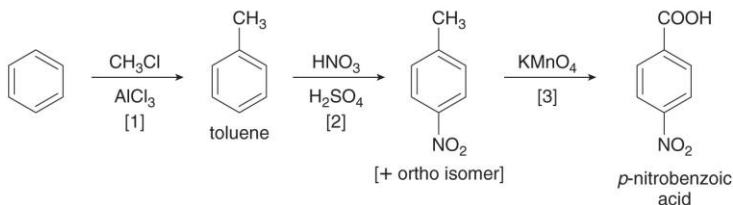


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Multistep Synthesis

- Then, write out the synthesis from starting material to product.

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- Make sure you put the methyl group on first as nitro is a meta director and deactivator.
- Do not oxidize the methyl group until after adding the nitro as a carboxylic acid is a meta director and deactivator.

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