LSD, commonly referred to as “acid,” is a powerful hallucinogen prepared from lysergic acid, the principal organic compound derived from one of the ergot fungi. Immortalized in the 1967 Beatles’ song, “Lucy in the Sky with Diamonds,” LSD produces sensory illusions, making it difficult for the user to distinguish between reality and fantasy. Given its potent biological properties, LSD has been the target of several different laboratory syntheses. A key step in one of them involves carbon–carbon bond formation using electrophilic aromatic substitution, the most common reaction of aromatic compounds and the subject of Chapter 18.
Chapter 18 discusses the chemical reactions of benzene and other aromatic compounds. Although aromatic rings are unusually stable, making benzene unreactive in most of the reactions discussed so far, benzene acts as a nucleophile with certain electrophiles, yielding substitution products with an intact aromatic ring.

We begin with the basic features and mechanism of electrophilic aromatic substitution (Sections 18.1–18.5), the basic reaction of benzene. Next, we discuss the electrophilic aromatic substitution of substituted benzenes (Sections 18.6–18.12), and conclude with other useful reactions of benzene derivatives (Sections 18.13–18.14). The ability to interconvert resonance structures and evaluate their relative stabilities is crucial to understanding this material.

18.1 Electrophilic Aromatic Substitution

Based on its structure and properties, what kinds of reactions should benzene undergo? Are any of its bonds particularly weak? Does it have electron-rich or electron-deficient atoms?

• Benzene has six π electrons delocalized in six p orbitals that overlap above and below the plane of the ring. These loosely held π electrons make the benzene ring electron rich, and so it reacts with electrophiles.
• Because benzene’s six π electrons satisfy Hückel’s rule, benzene is especially stable. Reactions that keep the aromatic ring intact are therefore favored.

As a result, the characteristic reaction of benzene is electrophilic aromatic substitution—a hydrogen atom is replaced by an electrophile.

Electrophilic aromatic substitution

Benzene does not undergo addition reactions like other unsaturated hydrocarbons, because addition would yield a product that is not aromatic. Substitution of a hydrogen, on the other hand, keeps the aromatic ring intact.

Addition

Substitution

Five specific examples of electrophilic aromatic substitution are shown in Figure 18.1. The basic mechanism, discussed in Section 18.2, is the same in all five cases. The reactions differ only in the identity of the electrophile, E⁺.

Problem 18.1 Why is benzene less reactive towards electrophiles than an alkene, even though it has more π electrons than an alkene (six versus two)?

18.2 The General Mechanism

No matter what electrophile is used, all electrophilic aromatic substitution reactions occur via a two-step mechanism: addition of the electrophile E⁺ to form a resonance-stabilized carbocation, followed by deprotonation with base, as shown in Mechanism 18.1.
Mechanism 18.1  General Mechanism—Electrophilic Aromatic Substitution

Step [1] Addition of the electrophile \( (E^+) \) to form a carbocation

- Addition of the electrophile \( (E^+) \) forms a new \( C-E \) bond using two \( \pi \) electrons from the benzene ring, and generating a carbocation. This carbocation intermediate is not aromatic, but it is resonance stabilized—three resonance structures can be drawn.
- Step [1] is rate-determining because the aromaticity of the benzene ring is lost.

Step [2] Loss of a proton to re-form the aromatic ring

- In Step [2], a base \( (B^-) \) removes the proton from the carbon bearing the electrophile, thus re-forming the aromatic ring. This step is fast because the aromaticity of the benzene ring is restored.
- Any of the three resonance structures of the carbocation intermediate can be used to draw the product. The choice of resonance structure affects how curved arrows are drawn, but not the identity of the product.
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:

- 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.

Always draw in the H atom at the site of electrophilic attack.

This two-step mechanism for electrophilic aromatic substitution applies to all of the electrophiles in Figure 18.1. The net result of addition of an electrophile ($E^+$) followed by elimination of a proton ($H^+$) is substitution of E for H.

The energy changes in electrophilic aromatic substitution are shown in Figure 18.2. The mechanism consists of two steps, so the energy diagram has two energy barriers. Because the first step is rate-determining, its transition state is higher in energy.

**Problem 18.2**

In Step [2] of Mechanism 18.1, loss of a proton to form the substitution product was drawn using one resonance structure only. Use curved arrows to show how the other two resonance structures can be converted to the substitution product (PhE) by removal of a proton with :B.

### 18.3 Halogenation

The general mechanism outlined in Mechanism 18.1 can now be applied to each of the five specific examples of electrophilic aromatic substitution shown in Figure 18.1. For each mechanism we must learn how to generate a specific electrophile. This step is different with each electrophile.
phile. Then, the electrophile reacts with benzene by the two-step process of Mechanism 18.1. These two steps are the same for all five reactions.

In halogenation, benzene reacts with Cl₂ or Br₂ in the presence of a Lewis acid catalyst, such as FeCl₃ or FeBr₃, to give the aryl halides chlorobenzene or bromobenzene, respectively. Analogous reactions with I₂ and F₂ are not synthetically useful because I₂ is too unreactive and F₂ reacts too violently.

In bromination (Mechanism 18.2), the Lewis acid FeBr₃ reacts with Br₂ to form a Lewis acid–base complex that weakens and polarizes the Br–Br bond, making it more electrophilic. This reaction is Step [1] of the mechanism for the bromination of benzene. The remaining two steps follow directly from the general mechanism for electrophilic aromatic substitution: addition of the electrophile (Br⁺ in this case) forms a resonance-stabilized carbocation, and loss of a proton regenerates the aromatic ring.

Chlorination proceeds by a similar mechanism. Reactions that introduce a halogen substituent on a benzene ring are widely used, and many halogenated aromatic compounds with a range of biological activity have been synthesized, as shown in Figure 18.3.

Problem 18.3  Draw a detailed mechanism for the chlorination of benzene using Cl₂ and FeCl₃.
Nitration and Sulfonation

Nitration and sulfonation of benzene introduce two different functional groups on an aromatic ring. Nitration is an especially useful reaction because a nitro group can then be reduced to an NH$_2$ group, a common benzene substituent, in a reaction discussed in Section 18.14.

In nitration, the electrophile is $^+$NO$_2$ (the nitronium ion), formed by protonation of HNO$_3$ followed by loss of water (Mechanism 18.3).

In sulfonation, protonation of sulfur trioxide, SO$_3$, forms a positively charged sulfur species ($^+$SO$_3$H) that acts as an electrophile (Mechanism 18.4).
These steps illustrate how to generate the electrophile $E^+$ for nitration and sulfonation, the process that begins any mechanism for electrophilic aromatic substitution. To complete either of these mechanisms, you must replace the electrophile $E^+$ by either $^\circ\text{NO}_2$ or $^\circ\text{SO}_3\text{H}$ in the general mechanism (Mechanism 18.1). Thus, the two-step sequence that replaces $H$ by $E$ is the same regardless of $E^+$. This is shown in Sample Problem 18.1 using the reaction of benzene with the nitronium ion.

**Sample Problem 18.1** Draw a stepwise mechanism for the nitration of a benzene ring.

![Mechanism 18.4 Formation of the Electrophile $^\circ\text{SO}_3\text{H}$ for Sulfonation](image)

These steps illustrate how to generate the electrophile $E^+$ for nitration and sulfonation, the process that begins any mechanism for electrophilic aromatic substitution. To complete either of these mechanisms, you must replace the electrophile $E^+$ by either $^\circ\text{NO}_2$ or $^\circ\text{SO}_3\text{H}$ in the general mechanism (Mechanism 18.1). Thus, the two-step sequence that replaces $H$ by $E$ is the same regardless of $E^+$. This is shown in Sample Problem 18.1 using the reaction of benzene with the nitronium ion.

**Solution** We must first generate the electrophile and then write the two-step mechanism for electrophilic aromatic substitution using it.

**Problem 18.4** Draw a stepwise mechanism for the sulfonation of an alkyl benzene such as A to form a substituted benzenesulfonic acid B. Treatment of B with base forms a sodium salt C that can be used as a synthetic detergent to clean away dirt (see Problem 3.15).

**18.5 Friedel–Crafts Alkylation and Friedel–Crafts Acylation**

**Friedel–Crafts alkylation** and **Friedel–Crafts acylation** form new carbon–carbon bonds.

**18.5A General Features**

In **Friedel–Crafts alkylation**, treatment of benzene with an alkyl halide and a Lewis acid (AlCl$_3$) forms an alkyl benzene. This reaction is an **alkylation** because it results in transfer of an alkyl group from one atom to another (from Cl to benzene).
In **Friedel–Crafts acylation**, a benzene ring is treated with an **acid chloride** (RCOCl) and AlCl₃ 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**.

**Examples**

- **[1]**
  \[ \text{CH}_3\text{CH}_2\text{Cl} \quad \xrightarrow{\text{AlCl}_3} \quad \text{CH}_3\text{CCH}_3 \quad + \quad \text{HCl} \]

- **[2]**
  \[ \text{(CH}_3\text{)}_3\text{CCl} \quad \xrightarrow{\text{AlCl}_3} \quad \text{C(CH}_3)_3 \quad + \quad \text{HCl} \]

**Problem 18.5**
What product is formed when benzene is treated with each organic halide in the presence of AlCl₃?

- a. (CH₃)₂CHCl
- b. \[ \text{CH}_3\text{CH}_2\text{Cl} \]
- c. (CH₃)₂C\(\text{CH}_2\text{Cl} \]

**Problem 18.6**
What acid chloride would be needed to prepare each of the following ketones from benzene using a Friedel–Crafts acylation?

- a. \[ \text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2 \]
- b. \[ \text{CH}_3\text{CCH}_3 \]
- c. \[ \text{C}_5\text{H}_9\text{C} \]

**18.5B Mechanism**

The mechanisms of alkylation and acylation proceed in a manner analogous to those for halogenation, nitration, and sulfonation. The unique feature in each reaction is how the electrophile is generated.

In **Friedel–Crafts alkylation**, the Lewis acid AlCl₃ reacts with the alkyl chloride to form a Lewis acid–base complex, illustrated with CH₃CH₂Cl and (CH₃)₂CCl as alkyl chlorides. The identity of the alkyl chloride determines the exact course of the reaction as shown in Mechanism 18.5.
Mechanism 18.5  Formation of the Electrophile in Friedel–Crafts Alkylation—Two Possibilities

For CH₃Cl and 1° RCl:

- CH₃Cl + AlCl₃ → CH₃–Cl + AlCl₃
- Lewis base + Lewis acid

For 2° and 3° RCl:

- (CH₃)₂C–Cl + AlCl₃ → (CH₃)₃C + AlCl₃
- Lewis base + Lewis acid

- For CH₃Cl 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.

In either case, the electrophile goes on to react with benzene in the two-step mechanism characteristic of electrophilic aromatic substitution, illustrated in Mechanism 18.6 using the 3° carbocation, (CH₃)₃C⁺.

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].
- AlCl₄⁻ removes a proton on the carbon bearing the new substituent, thus re-forming the aromatic ring in Step [2].

In Friedel–Crafts acylation, the Lewis acid AlCl₃ ionizes the carbon–halogen bond of the acid chloride, thus forming a positively charged carbon electrophile called an acylium ion, which is resonance stabilized (Mechanism 18.7). 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.

Mechanism 18.7  Formation of the Electrophile in Friedel–Crafts Acylation

- This C serves as the electrophilic site.
- A resonance-stabilized acylium ion as the electrophile.
To complete the mechanism for acylation, insert the electrophile into the general mechanism and draw the last two steps, as illustrated in Sample Problem 18.2.

**Sample Problem 18.2** Draw a stepwise mechanism for the following Friedel–Crafts acylation.

\[
\text{Ar} + \text{CH}_3\text{COCl} \rightarrow \text{ArCH}_3\text{CO} + \text{HCl}
\]

**Solution**
First generate the acylium ion, and then write the two-step mechanism for electrophilic aromatic substitution using it for the electrophile.

**Problem 18.7** Draw a stepwise mechanism for the Friedel–Crafts alkylation of benzene with \( \text{CH}_3\text{CH}_2\text{Cl} \) and AlCl₃.

### 18.5C Other Facts About Friedel–Crafts Alkylation

Three additional facts about Friedel–Crafts alkylations must be kept in mind.

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

Most Friedel–Crafts reactions involve carbocation electrophiles. Because the carbocations derived from vinyl halides and aryl halides are highly unstable and do not readily form, these organic halides do not undergo Friedel–Crafts alkylation.

2. **Rearrangements can occur.**

The Friedel–Crafts reaction can yield products having rearranged carbon skeletons when \( 1^\circ \) and \( 2^\circ \) alkyl halides are used as starting materials, as shown in Equations [1] and [2]. In both reactions, the carbon atom bonded to the halogen in the starting material (labeled in red) is not bonded to the benzene ring in the product, thus indicating that a rearrangement has occurred.
Recall from Section 9.9 that a 1,2-shift converts a less stable carbocation to a more stable carbocation by shift of a hydrogen atom or an alkyl group.

The result in Equation [1] is explained by a carbocation rearrangement involving a 1,2-hydride shift: the less stable 2° carbocation (formed from the 2° halide) rearranges to a more stable 3° carbocation, as illustrated in Mechanism 18.8.

**Mechanism 18.8 Friedel–Crafts Alkylation Involving Carbocation Rearrangement**

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

Reaction of the alkyl chloride with AlCl₃ 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.

Rearrangements can occur even when no free carbocation is formed initially. For example, the 1° alkyl chloride in Equation [2] forms a complex with AlCl₃, which does not decompose to an unstable 1° carbocation, as shown in Mechanism 18.9. Instead, a 1,2-hydride shift forms a 2° carbocation, which then serves as the electrophile in the two-step mechanism for electrophilic aromatic substitution.

**Mechanism 18.9 A Rearrangement Reaction Beginning with a 1° Alkyl Chloride**
Problem 18.9  Draw a stepwise mechanism for the following reaction.

\[
\text{AlCl}_3 + (\text{CH}_3)_2\text{CHCH}_2\text{Cl} \xrightarrow{\text{HCl}} \text{HCl} + \text{C(CH}_3)_3
\]

Problem 18.10  Offer an explanation as to why rearrangements do not occur with the acylium ion formed in a Friedel–Crafts acylation reaction.

Other functional groups that form carbocations can also be used as starting materials.

Although Friedel–Crafts alkylation works well with alkyl halides, any compound that readily forms a carbocation can be used instead. The two most common alternatives are alkenes and alcohols, both of which afford carbocations in the presence of strong acid.

- 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.

Each carbocation can then go on to react with benzene to form a product of electrophilic aromatic substitution. For example:

\[
\text{(CH}_3)_3\text{C-OH} + \text{H}_2\text{SO}_4 \xrightarrow{\text{HCl}} \text{C(CH}_3)_3 + \text{H}_2\text{O}, \quad \text{new C-C bond}
\]

Problem 18.11  Draw the product of each reaction.

a. \(\text{H}_2\text{SO}_4\)

b. \(\text{H}_2\text{SO}_4\)

c. \(\text{H}_2\text{SO}_4\)

d. \(\text{H}_2\text{SO}_4\)

18.5D  Intramolecular Friedel–Crafts Reactions

All of the Friedel–Crafts reactions discussed thus far have resulted from intermolecular reaction of a benzene ring with an electrophile. Starting materials that contain both units are capable of **intramolecular reaction**, and this forms a new ring. For example, treatment of compound A,
Friedel–Crafts Alkylation and Friedel–Crafts Acylation

which contains both a benzene ring and an acid chloride, with AlCl₃, forms α-tetralone by an intramolecular Friedel–Crafts acylation reaction.

An intramolecular Friedel–Crafts acylation

Such an intramolecular Friedel–Crafts acylation was a key step in the synthesis of LSD, the molecule that introduced Chapter 18, as shown in Figure 18.4.

Problem 18.12

Draw a stepwise mechanism for the intramolecular Friedel–Crafts acylation of compound A to form B. B can be converted in one step to the antidepressant sertraline (trade name Zoloft).

Problem 18.13

Intramolecular reactions are also observed in Friedel–Crafts alkylation. Draw the intramolecular alkylation product formed from each of the following reactants. (Watch out for rearrangements!)

- a.
- b.
- c.
18.6 Substituted Benzenes

Many substituted benzene rings undergo electrophilic aromatic substitution. Common substituents include halogens, OH, NH₂, alkyl, and many functional groups that contain a carbonyl. Each substituent either increases or decreases the electron density in the benzene ring, and this affects the course of electrophilic aromatic substitution, as we will learn in Section 18.7.

What makes a substituent on a benzene ring electron donating or electron withdrawing? The answer is inductive effects and resonance effects, both of which can add or remove electron density.

Inductive Effects

Inductive effects stem from the electronegativity of the atoms in the substituent and the polarizability of the substituent group.

- Atoms more electronegative than carbon—including N, O, and X—pull electron density away from carbon and thus exhibit an electron-withdrawing inductive effect.
- Polarizable alkyl groups donate electron density, and thus exhibit an electron-donating inductive effect.

Considering inductive effects only, an NH₂ group withdraws electron density and CH₃ donates electron density.

Resonance Effects

Resonance effects can either donate or withdraw electron density, depending on whether they place a positive or negative charge on the benzene ring.

- 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 (general structure—C₆H₅−Z:). Common examples of Z include N, O, and halogen. For example, five resonance structures can be drawn for aniline (C₆H₅NH₂). Because three of them place a negative charge on a carbon atom of the benzene ring, an NH₂ group donates electron density to a benzene ring by a resonance effect.

In contrast, an electron-withdrawing resonance effect is observed in substituted benzenes having the general structure C₆H₅−Y = Z, where Z is more electronegative than Y. For exam-
ple, 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, a CHO group withdraws electron density from a benzene ring by a resonance effect.

Three resonance structures place a (+) charge on atoms in the ring.

**Problem 18.15**

Draw all resonance structures for each compound and use the resonance structures to determine if the substituent has an electron-donating or electron-withdrawing resonance effect.

- a. \(\text{OCH}_3\)
- b. \(\text{CH}_3\)

**Considering Both 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 the resonance effects. Alkyl groups, for instance, donate electrons by an inductive effect, but they have no resonance effect because they lack nonbonded electron pairs or \(\pi\) bonds. As a result,

- An alkyl group is an electron-donating group and an alkyl benzene is more electron rich than benzene.

When electronegative atoms, such as N, O, or halogen, are bonded to the benzene ring, they inductively withdraw electron density from the ring. All of these groups also have a nonbonded pair of electrons, so they donate electron density to the ring by resonance. The identity of the element determines the net balance of these opposing effects.

[Diagram showing opposing effects]

These elements are electronegative, so they inductively withdraw electron density.

These elements have a lone pair, so they can donate electron density by resonance.

- When a neutral O or N atom is bonded directly to a benzene ring, the resonance effect dominates and the net effect is electron donation.
- When a halogen X is bonded to a benzene ring, the inductive effect dominates and the net effect is electron withdrawal.

Thus, \(\text{NH}_2\) and \(\text{OH}\) are electron-donating groups because the resonance effect predominates, whereas \(\text{Cl}\) and \(\text{Br}\) are electron-withdrawing groups because the inductive effect predominates.

Finally, the inductive and resonance effects in compounds having the general structure \(\text{C}_6\text{H}_5\sim \text{Y}\sim \text{Z}\) (with \(Z\) more electronegative than \(Y\)) are both electron withdrawing; in other words, the two effects reinforce each other. This is true for benzaldehyde (\(\text{C}_6\text{H}_5\text{CHO}\)) and all other compounds that contain a carbonyl group bonded directly to the benzene ring.

Thus, on balance, an \(\text{NH}_2\) group is electron donating, so the benzene ring of aniline (\(\text{C}_6\text{H}_5\text{NH}_2\)) has more electron density than benzene. An aldehyde group (CHO), on the other hand, is
Electrophilic Aromatic Substitution

electron withdrawing, so the benzene ring of benzaldehyde \((C_6H_5CHO)\) has less electron density than benzene. These effects are illustrated in the electrostatic potential maps in Figure 18.5. These compounds represent examples of the general structural features in electron-donating and electron-withdrawing substituents:

- 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 (+ or \(\delta^+\)) bonded to the benzene ring.

The net effect of electron donation and withdrawal on the reactions of substituted aromatics is discussed in Sections 18.7–18.9.

Sample Problem 18.3

Classify each substituent as electron donating or electron withdrawing.

a. \(\text{OCOCH}_3\)  
b. \(\text{CN}\)

**Solution**

Draw out the atoms and bonds of the substituent to clearly see lone pairs and multiple bonds. Always look at the atom bonded directly to the benzene ring to determine electron-donating or electron-withdrawing effects. An O atom with a lone pair of electrons makes a substituent electron donating. A halogen or an atom with a partial positive charge makes a substituent electron withdrawing.

a. \(\text{OCOCH}_3\)  
- An O atom with a lone pair bonded directly to the benzene ring
  - an electron-donating group

b. \(\text{CN}\)  
- An atom with a partial (+) charge bonded directly to the benzene ring
  - an electron-withdrawing group
Problem 18.16 Classify each substituent as electron donating or electron withdrawing.

a. \[ \text{OCH}_3 \]  
b. \[ \text{I} \]  
c. \[ \text{C(CH}_3\text{)}_3 \]  

18.7 Electrophilic Aromatic Substitution of Substituted Benzenes

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 electrophilic aromatic substitution:

- **The rate of reaction:** A substituted benzene reacts faster or slower than benzene itself.
- **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 substituent.

Toluene (C₆H₅CH₃) and nitrobenzene (C₆H₅NO₂) illustrate two possible outcomes.

[1] **Toluene**

Toluene reacts faster than benzene in all substitution reactions. Thus, its **electron-donating CH₃ group activates the benzene ring** to electrophilic attack. Although three products are possible, compounds with the new group ortho or para to the CH₃ group predominate. The CH₃ group is therefore called an ortho, para director.

\[
\begin{align*}
\text{CH}_3 & \quad \text{Br}_2 & \quad \text{Br} \\
\text{FeBr}_3 & \quad \text{CH}_3 & \quad \text{Br} & \quad \text{Br} \\
\text{ortho} & \quad 40\% & \quad \text{meta} & \quad \text{trace} & \quad \text{para} & \quad 60\%
\end{align*}
\]

[2] **Nitrobenzene**

Nitrobenzene reacts more slowly than benzene in all substitution reactions. Thus, its **electron-withdrawing NO₂ group deactivates the benzene ring** to electrophilic attack. Although three products are possible, the compound with the new group meta to the NO₂ group predominates. The NO₂ group is called a meta director.

\[
\begin{align*}
\text{NO}_2 & \quad \text{HNO}_3 & \quad \text{NO}_2 \\
\text{H}_2\text{SO}_4 & \quad \text{NO}_2 & \quad \text{NO}_2 & \quad \text{NO}_2 \\
\text{ortho} & \quad 7\% & \quad \text{meta} & \quad 93\% & \quad \text{para} & \quad \text{trace}
\end{align*}
\]

Substituents either activate or deactivate a benzene ring towards electrophiles, and direct selective substitution at specific sites on the ring. **All substituents can be divided into three general types.**
Ortho, para directors and activators

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

- $\text{-NH}_2$, $\text{-NHR}$, $\text{-NR}_2$
- $\text{-OH}$
- $\text{-OR}$
- $\text{-NHCOR}$
- $\text{-R}$

**General structure**

$\text{-R or -Z}$

Ortho, para deactivators

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

- $\text{F}$
- $\text{Cl}$
- $\text{Br}$

Meta directors

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

- $\text{-CHO}$
- $\text{-COR}$
- $\text{-COOR}$
- $\text{-COOH}$
- $\text{-CN}$
- $\text{-SO}_3\text{H}$
- $\text{-NO}_2$
- $\text{-NR}_3$

**General structure**

$\text{Y} (\delta^+ \text{ or } +)$

To learn these lists: **Keep in mind that the halogens are in a class by themselves.** Then learn the general structures for each type of substituent.

- 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.

Sample Problem 18.4 shows how this information can be used to predict the products of electrophilic aromatic substitution reactions.
Sample Problem 18.4

Draw the products of each reaction and state whether the reaction is faster or slower than a similar reaction with benzene.

a. \[
\text{NHCOCH}_3 + \text{HNO}_3 \rightarrow \text{COOCH}_3
\]

b. \[
\text{Br}_2 + \text{FeBr}_3 \rightarrow \text{Br} - \text{C} - \text{Br}
\]

Solution

To draw the products:

- Draw the Lewis structure for the substituent to see if it has a lone pair or partial positive charge on the atom bonded to the benzene ring.
- Classify the substituent—ortho, para activating, ortho, para deactivating, or meta deactivating—and draw the products.

a. The lone pair on N makes this group an ortho, para activator. This compound reacts faster than benzene.

b. The δ⁺ on this C makes the group a meta deactivator. This compound reacts more slowly than benzene.

Problem 18.17

Draw the products of each reaction.

a. \[
\text{OCH}_3 + \text{CH}_3\text{CH}_2\text{Cl} + \text{AlCl}_3 \rightarrow \text{OCH}_3
\]

b. \[
\text{Br} + \text{HNO}_3 \rightarrow \text{H}_2\text{SO}_4 \rightarrow \text{Br} - \text{O} - \text{NO}_2
\]

c. \[
\text{NO}_2 + \text{Cl}_2 \rightarrow \text{FeCl}_3
\]

Problem 18.18

Draw the products formed when each compound is treated with HNO₃ and H₂SO₄. State whether the reaction occurs faster or slower than a similar reaction with benzene.

a. \[
\text{COCH}_3
\]

b. \[
\text{CN}
\]

c. \[
\text{OH}
\]

d. \[
\text{Cl}
\]

e. \[
\text{CH}_2\text{CH}_3
\]

18.8 Why Substituents Activate or Deactivate a Benzene Ring

- Why do substituents activate or deactivate a benzene ring?
- Why are particular orientation effects observed? Why are some groups ortho, para directors and some groups meta directors?

To understand why some substituents make a benzene ring react faster than benzene itself (activators), whereas others make it react slower (deactivators), we must evaluate the rate-determining step (the first step) of the mechanism. Recall from Section 18.2 that the first step in electrophilic aromatic substitution is the addition of an electrophile (E⁺) to form a resonance-stabilized carbocation. The Hammond postulate (Section 7.15) makes it possible to predict the relative rate of the reaction by looking at the stability of the carbocation intermediate.
• The more stable the carbocation, the lower in energy the transition state that forms it, and the faster the reaction.

\[
\text{[Two resonance structures]}
\]

Stabilizing the carbocation makes the reaction faster.

The principles of inductive effects and resonance effects, first introduced in Section 18.6, can now be used to predict carbocation stability.

• Electron-donating groups stabilize the carbocation and activate a benzene ring towards electrophilic attack.
• Electron-withdrawing groups destabilize the carbocation and deactivate a benzene ring towards electrophilic attack.

The energy diagrams in Figure 18.6 illustrate the effect of electron-donating and electron-withdrawing groups on the energy of the transition state of the rate-determining step in electrophilic aromatic substitution. From Section 18.6, we now know which groups increase or decrease the rate of reaction of substituted benzenes with electrophiles.

• 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.

\[
\begin{align*}
\text{Activating groups:} & \quad \text{Activating and electron-donating groups} \\
& \quad -\text{NH}_2, -\text{NH}_n, -\text{NHR}, -\text{NR}_2, -\text{OH}, -\text{OR}, -\text{NHCOR}, -\text{R}
\end{align*}
\]

**Figure 18.6** Energy diagrams comparing the rate of electrophilic aromatic 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.
• 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.

\[
\text{Deactivating groups:} \quad \begin{align*}
\text{–F} & \quad \text{–CHO} & \quad \text{–COOR} & \quad \text{–CN} \\
\text{–Cl} & \quad \text{–COR} & \quad \text{–COOH} & \quad \text{–CN} \\
\text{–Br} & \quad \text{–SO}_3\text{H} & \quad \text{–NO}_2 & \quad \text{+NR}_3
\end{align*}
\]

Problem 18.19 Label each compound as more or less reactive than benzene in electrophilic aromatic substitution.

a. \[
\begin{array}{c}
\text{C(CH}_3\text{)}_3
\end{array}
\]
b. \[
\begin{array}{c}
\text{C}_6\text{H}_5\text{OH}
\end{array}
\]
c. \[
\begin{array}{c}
\text{C}_6\text{H}_5\text{COOCH}_2\text{CH}_3
\end{array}
\]
d. \[
\begin{array}{c}
\text{C}_6\text{H}_5\text{+N(CH}_3\text{)}_3
\end{array}
\]

Problem 18.20 Rank the compounds in each group in order of increasing reactivity in electrophilic aromatic substitution.

a. \[
\begin{array}{c}
\text{Cl} & \quad \text{OCH}_3
\end{array}
\]
b. \[
\begin{array}{c}
\text{NO}_2 & \quad \text{CH}_3
\end{array}
\]

18.9 Orientation Effects in Substituted Benzenes

To understand why particular orientation effects arise, you must keep in mind the general structures for ortho, para directors and for meta directors already given in Section 18.7. 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.

To evaluate the directing effects of a given substituent, we can follow a stepwise procedure.

### 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 \((C_6H_5 \equiv A)\).

- 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 \(C \equiv E\) bond.

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

Sections 18.9A–C show how this two-step procedure can be used to determine the directing effects of the \(\text{CH}_3\) group in toluene, the \(\text{NH}_2\) group in aniline, and the \(\text{NO}_2\) group in nitrobenzene, respectively.
18.9A The CH₃ Group—An ortho, para Director

To determine why a CH₃ group directs electrophilic aromatic substitution to the ortho and para positions, first draw all resonance structures that result from electrophilic attack at the ortho, meta, and para positions to the CH₃ group.

Note that the positive charge in all resonance structures is always ortho or para to the new C=E bond. It is not necessarily ortho or para to the CH₃ group.

To evaluate the stability of the resonance structures, determine whether any are especially stable or unstable. In this example, attack ortho or para to CH₃ generates a resonance structure that places a positive charge on a carbon atom with the CH₃ group. The electron-donating CH₃ group stabilizes the adjacent positive charge. In contrast, attack meta to the CH₃ group does not generate any resonance structure stabilized by electron donation. Other alkyl groups are ortho, para directors for the same reason.

- Conclusion: The CH₃ group directs electrophilic attack ortho and para to itself because an electron-donating inductive effect stabilizes the carbocation intermediate.

18.9B The NH₂ Group—An ortho, para Director

To determine why an amino group (NH₂) directs electrophilic aromatic substitution to the ortho and para positions, follow the same procedure.
Attack at the meta position generates the usual three resonance structures. Because of the lone pair on the N atom, attack at the ortho and para positions generates a fourth resonance structure, which is stabilized because every atom has an octet of electrons. This additional resonance structure can be drawn for all substituents that have an N, O, or halogen atom bonded directly to the benzene ring.

• Conclusion: The NH$_2$ group directs electrophilic attack ortho and para to itself because the carbocation intermediate has additional resonance stabilization.

18.9C The NO$_2$ Group—A meta Director

To determine why a nitro group (NO$_2$) directs electrophilic aromatic substitution to the meta position, follow the same procedure.
Attack at each position generates three resonance structures. One resonance structure resulting from attack at the ortho and para positions is especially destabilized, because it contains a positive charge on two adjacent atoms. Attack at the meta position does not generate any particularly unstable resonance structures.

- Conclusion: With the NO₂ group (and all meta directors), meta attack occurs because attack at the ortho or para position gives a destabilized carbocation intermediate.

Problem 18.21
Draw all resonance structures for the carbocation formed by ortho attack of the electrophile +NO₂ on each starting material. Label any resonance structures that are especially stable or unstable.

    a. C(CH₃)₃  b. OH  c. CHO

Problem 18.22
Use the procedure illustrated in Sections 18.9A–C to show why chlorine is an ortho, para director.

Figure 18.7 summarizes the reactivity and directing effects of the common substituents on benzene rings. You do not need to memorize this list. Instead, follow the general procedure outlined in Sections 18.9A–C to predict particular substituent effects.

In summary:
[1] All ortho, para directors except the halogens activate the benzene ring.
[2] All meta directors deactivate the benzene ring.
18.10 Limitations on Electrophilic Substitution Reactions with Substituted Benzenes

Although electrophilic aromatic substitution works well with most substituted benzenes, halogenation and the Friedel–Crafts reactions have some additional limitations that must be kept in mind.

18.10A Halogenation of Activated Benzenes

Considering all electrophilic aromatic substitution reactions, halogenation occurs the most readily. As a result, benzene rings activated by strong electron-donating groups—OH, NH₂, and their alkyl derivatives (OR, NHR, and NR₂)—undergo polyhalogenation when treated with X₂ and FeX₃. For example, aniline (C₆H₅NH₂) and phenol (C₆H₅OH) both give a tribromo derivative when treated with Br₂ and FeBr₃. Substitution occurs at all hydrogen atoms ortho and para to the NH₂ and OH groups.

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

Problem 18.23 Draw the products of each reaction.

a. Cl₂ OH FeCl₃
b. Cl₂ OH

c. Cl₂ CH₃ FeCl₃

18.10B Limitations in Friedel–Crafts Reactions

Friedel–Crafts reactions are the most difficult electrophilic aromatic substitution reactions to carry out in the laboratory. For example, they do not occur when the benzene ring is substituted with NO₂ (a strong deactivator) or with NH₂, NHR, or NR₂ (strong activators).

A benzene ring deactivated by a strong electron-withdrawing group—that is, any of the meta directors—is not electron rich enough to undergo Friedel–Crafts reactions.

Friedel–Crafts reactions also do not occur with NH₂ groups, which are strong activating groups. NH₂ groups are strong Lewis bases (due to the nonbonded electron pair on N), so they react with
AlCl₃, the Lewis acid needed for alkylation or acylation. The resulting product contains a positive charge adjacent to the benzene ring, so the ring is now strongly deactivated and therefore unreactive in Friedel–Crafts reactions.

\[
\text{Lewis base} + \text{AlCl}_3 \rightarrow \text{Lewis acid} + \text{NH}_2^+ \text{Cl}^- \\
\text{This (+) charge deactivates the benzene ring.}
\]

**Problem 18.24** Which of the following compounds undergo Friedel–Crafts alkylation with CH₃Cl and AlCl₃? Draw the products formed when a reaction occurs.

a. \(\text{SO}_3\text{H}\)  

b. \(\text{Cl}\) 

c. \(\text{N(CH}_3\text{)}_2\) 

d. \(\text{NHCOCH}_3\)

Another limitation of the Friedel–Crafts alkylation arises because of **polyalkylation**. Treatment of benzene with an alkyl halide and AlCl₃ places an electron-donor R group on the ring. Because R groups activate a ring, the alkylated product (C₆H₅R) is now more reactive than benzene itself towards further substitution, and it reacts again with RCl to give products of polyalkylation.

Polysubstitution does not occur with Friedel–Crafts acylation, because the product now has an electron-withdrawing group that deactivates the ring towards another electrophilic substitution.

**18.11 Disubstituted Benzenes**

What happens in electrophilic aromatic substitution when a disubstituted benzene ring is used as starting material? To predict the products, look at the directing effects of both substituents and then determine the net result, using the following three guidelines.

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

For example, the CH₃ group in \(p\)-nitrotoluene is an ortho, para director and the NO₂ group is a meta director. These two effects reinforce each other so that one product is formed on treatment with Br₂ and FeBr₃. Notice that the position para to the CH₃ group is “blocked” by a nitro group so no substitution can occur on that carbon.
Rule [2] If the directing effects of two groups oppose each other, the more powerful activator “wins out.”

In compound A, the \( \text{NHCOCH}_3 \) group activates its two ortho positions, and the \( \text{CH}_3 \) group activates its two ortho positions to reaction with electrophiles. Because the \( \text{NHCOCH}_3 \) is a stronger activator, substitution occurs ortho to it.

\[
\begin{align*}
\text{NHCOCH}_3 & \quad \text{CH}_3 \\
\text{Br} & \quad \text{FeBr}_3 \\
\end{align*}
\]

The new substituent goes ortho to the stronger activator.

\[
\begin{align*}
\text{A}
\end{align*}
\]

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

For example, no substitution occurs at the carbon atom between the two \( \text{CH}_3 \) groups in \( m \)-xylene, even though two \( \text{CH}_3 \) groups activate that position.

Sample Problem 18.5 Draw the products formed from nitration of each compound.

a. 
\[
\begin{align*}
\text{OH} \\
\text{CH}_3
\end{align*}
\]

b. 
\[
\begin{align*}
\text{OH} \\
\text{CH}_3
\end{align*}
\]

Solution

a. Both the \( \text{OH} \) and \( \text{CH}_3 \) groups are ortho, para directors. Because the \( \text{OH} \) group is a stronger activator, substitution occurs ortho to it.

\[
\begin{align*}
\text{OH} & \quad \text{CH}_3 \\
\text{HNO}_3 & \quad \text{H}_2\text{SO}_4 \\
\end{align*}
\]

The new substituent goes ortho to the stronger activator.
b. Both the OH and CH₃ groups are ortho, para directors whose directing effects reinforce each other in this case. No substitution occurs between the two meta substituents, however, so two products result.

![No substitution occurs here.]

Three positions are activated by both substituents.

**Problem 18.25** Draw the products formed when each compound is treated with HNO₃ and H₂SO₄.

![Draw the products formed when each compound is treated with HNO₃ and H₂SO₄.]

**18.12 Synthesis of Benzene Derivatives**

To synthesize benzene derivatives with more than one substituent, we must always take into account the directing effects of each substituent. In a disubstituted benzene, for example, **the directing effects indicate which substituent must be added to the ring first.**

For example, the Br group in p-bromonitrobenzene is an ortho, para director and the NO₂ group is a meta director. Because the two substituents are para to each other, the ortho, para director must be introduced *first* when synthesizing this compound from benzene.

**Ortho, para director**

**Meta director**

p-bromonitrobenzene

Thus, Pathway [1], in which bromination precedes nitration, yields the desired para product, whereas Pathway [2], in which nitration precedes bromination, yields the undesired meta isomer.

**Pathway [1]: Bromination before nitration**

<table>
<thead>
<tr>
<th>Ortho, para director</th>
<th>Br</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta director</td>
<td>NO₂</td>
</tr>
</tbody>
</table>

The ortho isomer can be separated from the mixture.

This pathway gives the desired product.
Pathway [2]: Nitration before bromination

\[
\text{Pathway [2]: Nitration before bromination}
\]

\[
\text{meta director} \quad \text{meta isomer}
\]

Pathway [1] yields both the desired para product as well as the undesired ortho isomer. Because these compounds are constitutional isomers, they are separable. Obtaining such a mixture of ortho and para isomers is often unavoidable.

Sample Problem 18.6
Devise a synthesis of o-nitrotoluene from benzene.

\[
\begin{align*}
\text{o-nitrotoluene} & \quad \text{CH}_3 \\
\end{align*}
\]

**Solution**

The CH₃ group in o-nitrotoluene is an ortho, para director and the NO₂ group is a meta director. Because the two substituents are ortho to each other, the ortho, para director must be introduced first. The synthesis thus involves two steps: Friedel–Crafts alkylation followed by nitration.

\[
\begin{align*}
\text{Friedel–Crafts alkylation first} & \quad \text{CH}_3 \quad \text{CH}_3\text{Cl} \quad \text{AlCl}_3 \\
\end{align*}
\]

Problem 18.26
Devise a synthesis of each compound from the indicated starting material.

\[
\begin{align*}
a. & \quad \text{Cl} \quad \text{SO}_3\text{H} \\
b. & \quad \text{O}_2\text{N} \quad \text{CH}_3 \\
c. & \quad \text{OH} \quad \text{OH} \\
\end{align*}
\]

18.13 Halogenation of Alkyl Benzenes

We finish Chapter 18 by learning some additional reactions of substituted benzenes that greatly expand the ability to synthesize benzene derivatives. These reactions do not involve the benzene ring itself, so they are not further examples of electrophilic aromatic substitution. In Section 18.13 we return to radical halogenation, and in Section 18.14 we examine useful oxidation and reduction reactions.

Benzylic C–H bonds are weaker than most other sp³ hybridized C–H bonds, because homolysis forms a resonance-stabilized benzylic radical.
As a result, an alkyl benzene undergoes selective bromination at the weak benzylic C–H bond under radical conditions to form a **benzylic halide**. For example, radical bromination of ethylbenzene using either Br₂ (in the presence of light or heat) or N-bromosuccinimide (NBS, in the presence of light or peroxides) forms a benzylic bromide as the sole product.

![Chemical structure of ethylbenzene and its radical bromination product](image)

The bond dissociation energy for a benzylic C–H bond (356 kJ/mol) is even less than the bond dissociation energy for a 3° C–H bond (381 kJ/mol).

The mechanism for halogenation at the benzylic position resembles other radical halogenation reactions, and so it involves initiation, propagation, and termination. Mechanism 18.10 illustrates the radical bromination of ethylbenzene using Br₂ (hv or Δ).

**Mechanism 18.10 Benzylic Bromination**

**Initiation**

*Step [1]* Bond cleavage forms two radicals.

\[
\text{Br}_2 \xrightarrow{hv \text{ or } \Delta} \cdot \text{Br} + \cdot \text{Br}
\]

- 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.

**Termination**

*Step [4]* Two radicals react to form a bond.

\[
\cdot \text{Br} + \cdot \text{Br} \rightarrow \cdot \text{Br} - \cdot \text{Br}
\]

- To terminate the reaction, two radicals, for example two Br· radicals, react with each other to form a stable bond.

Thus, an alkyl benzene undergoes two different reactions with Br₂, depending on the reaction conditions.

- With Br₂ and FeBr₃ (ionic conditions), electrophilic aromatic substitution occurs, resulting in replacement of H by Br on the aromatic ring to form ortho and para isomers.
- With Br₂ and light or heat (radical conditions), substitution of H by Br occurs at the benzylic carbon of the alkyl group.
Problem 18.27  Explain why C₆H₅CH₂CH₂Br is not formed during the radical bromination of C₆H₅CH₂CH₃.

Problem 18.28  Draw the products formed when isopropylbenzene [C₆H₅CH(CH₃)₂] is treated with each reagent: (a) Br₂, FeBr₃; (b) Br₂, hv; (c) Cl₂, FeCl₃.

The radical bromination of alkyl benzenes is a useful reaction because the resulting benzylic halide can serve as starting material for a variety of substitution and elimination reactions, thus making it possible to form many new substituted benzenes. Sample Problem 18.7 illustrates one possibility.

Sample Problem 18.7  Design a synthesis of styrene from ethylbenzene.

**Solution**
The double bond can be introduced by a two-step reaction sequence: bromination at the benzylic position under radical conditions, followed by elimination of HBr with strong base to form the π bond.

**Problem 18.29**  How could you use ethylbenzene to prepare each compound? More than one step is required.

a.  

b.  

c.  

d.  

18.14  Oxidation and Reduction of Substituted Benzenes

Oxidation and reduction reactions are valuable tools for preparing many other benzene derivatives. Because the mechanisms are complex and do not have general applicability, reagents and reactions are presented only, without reference to the detailed mechanism.

18.14A  Oxidation of Alkyl Benzenes

Arenes containing at least one benzylic C–H bond are oxidized with KMnO₄ to benzoic acid, a carboxylic acid with the carboxy group (COOH) bonded directly to the benzene ring. With some alkyl benzenes, this also results in the cleavage of carbon–carbon bonds, so the product has fewer carbon atoms than the starting material.
Substrates with more than one alkyl group are oxidized to dicarboxylic acids. Compounds without a benzylic C–H bond are inert to oxidation.

Substrates with more than one alkyl group are oxidized to dicarboxylic acids. Compounds without a benzylic C–H bond are inert to oxidation.

18.14B Reduction of Aryl Ketones to Alkyl Benzenes

Ketones formed as products in Friedel–Crafts acylation can be reduced to alkyl benzenes by two different methods.

- The **Clemmensen reduction** uses zinc and mercury in the presence of strong acid.
- The **Wolff–Kishner reduction** uses hydrazine (NH₂NH₂) and strong base (KOH).

Because both C–O bonds in the starting material are converted to C–H bonds in the product, the reduction is difficult and the reaction conditions must be harsh.

We now know two different ways to introduce an alkyl group on a benzene ring (Figure 18.8):

- A one-step method using Friedel–Crafts alkylation
- A two-step method using Friedel–Crafts acylation to form a ketone, followed by reduction
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. Recall from Section 18.5C that propylbenzene cannot be prepared by a Friedel–Crafts alkylation. Instead, when benzene is treated with 1-chloropropane and AlCl$_3$, isopropylbenzene is formed by a rearrangement reaction. Propylbenzene can be made, however, by a two-step procedure using Friedel–Crafts acylation followed by reduction.

\[ \text{CH}_3\text{CH}_2\text{CH}_2\text{Cl} \xrightarrow{\text{AlCl}_3} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3 \]

Friedel–Crafts alkylation generates isopropylbenzene by rearrangement.

\[ \text{CH}_3\text{CH}_2\text{CH}_2\text{Cl} \xrightarrow{\text{AlCl}_3} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3 \]

The two-step sequence—Friedel–Crafts acylation followed by reduction—generates propylbenzene.

**Problem 18.30** Write out the two-step sequence that converts benzene to each compound:
(a) C$_6$H$_5$CH$_2$CH$_2$CH$_2$CH$_3$; (b) C$_6$H$_5$CH$_2$C(CH$_3$)$_3$.

**Problem 18.31** What steps are needed to convert benzene into $p$-isobutylacetophenone, a synthetic intermediate used in the synthesis of the anti-inflammatory agent ibuprofen.

\[ \text{p-isobutylacetophenone} \xrightarrow{\text{several steps}} \text{ibuprofen} \]

**Problem 18.32** Only one alkyl benzene with the general structure C$_6$H$_5$CH$_2$R can be made by both Friedel–Crafts alkylation and Friedel–Crafts acylation followed by reduction. What is the identity of R in this compound?

### 18.14C Reduction of Nitro Groups

A nitro group (NO$_2$) is easily introduced on a benzene ring by nitration with strong acid (Section 18.4). This process is useful because the nitro group is readily reduced to an amino group (NH$_2$) under a variety of conditions. The most common methods use H$_2$ and a catalyst, or a metal (such as Fe or Sn) and a strong acid like HCl.

\[ \text{nitrobenzene} \xrightarrow{\text{H}_2, \text{Pd-C or Fe, HCl or Sn, HCl}} \text{aniline} \]

For example, reduction of ethyl $p$-nitrobenzoate with H$_2$ and a palladium catalyst forms ethyl $p$-aminobenzoate, a local anesthetic commonly called benzocaine.

\[ \text{ethyl } p\text{-nitrobenzoate} \xrightarrow{\text{H}_2, \text{Pd-C}} \text{ethyl } p\text{-aminobenzoate (benzocaine)} \]
Sample Problem 18.8 illustrates the utility of this process in a short synthesis.

**Sample Problem 18.8** Design a synthesis of m-bromoaniline from benzene.

![Chemical structure of m-bromoaniline]

**Solution**
To devise a retrosynthetic plan, keep in mind:
- The NH₂ group cannot be introduced directly on the ring by electrophilic aromatic substitution. It must be added by a two-step process: nitration followed by reduction.
- Both the Br and NH₂ groups are ortho, para directors, but they are located meta to each other on the ring. However, an NO₂ group (from which an NH₂ group is made) is a meta director, and we can use this fact to our advantage.

**Retrosynthetic Analysis**
Working backwards gives the following three-step retrosynthetic analysis:

1. Form the NH₂ group by reduction of NO₂.
2. Introduce the Br group meta to the NO₂ group by halogenation.
3. Add the NO₂ group by nitration.

**Synthesis**
The synthesis then involves three steps, and the order is crucial for success. Halogenation (Step [2] of the synthesis) must occur before reduction (Step [3]) in order to form the meta substitution product.

![Synthesis steps diagram]

**Problem 18.33** Synthesize each compound from benzene.

a. ![Chemical structure of benzoic acid]

b. ![Chemical structure of aniline]

c. ![Chemical structure of 4-bromo benzoic acid]
18.15 Multistep Synthesis

The reactions learned in Chapter 18 make it possible to synthesize a wide variety of substituted benzenes, as shown in Sample Problems 18.9–18.11.

Sample Problem 18.9

Synthesize \( p \)-nitrobenzoic acid from benzene.

\[
\begin{align*}
\text{O}_2\text{N} & \hspace{1cm} \text{COOH} \\
p\text{-nitrobenzoic acid}
\end{align*}
\]

Solution

Both groups on the ring (NO\(_2\) and COOH) are meta directors. To place these two groups para to each other, remember that the COOH group is prepared by oxidizing an alkyl group, which is an ortho, para director.

Retrosynthetic Analysis

Working backwards:
- [1] Form the COOH group by oxidation of an alkyl group.
- [2] Introduce the NO\(_2\) group para to the CH\(_3\) group (an ortho, para director) by nitration.
- [3] Add the CH\(_3\) group by Friedel–Crafts alkylation.

Synthesis

- Friedel–Crafts alkylation with CH\(_3\)Cl and AlCl\(_3\) forms toluene in Step [1]. Because CH\(_3\) is an ortho, para director, nitration yields the desired para product, which can be separated from its ortho isomer (Step [2]).
- Oxidation with KMnO\(_4\) converts the CH\(_3\) group into a COOH group, giving the desired product in Step [3].

Sample Problem 18.10

Synthesize \( p \)-chlorostyrene from benzene.

\[
\begin{align*}
\text{Cl} & \hspace{1cm} \text{CH} = \text{CH} \quad \text{Cl} \\
p\text{-chlorostyrene}
\end{align*}
\]

Solution

Both groups on the ring are ortho, para directors located para to each other. To introduce the double bond in the side chain, we must follow the two-step sequence in Sample Problem 18.7.
Retrosynthetic Analysis

Working backwards:
1. Form the double bond by two steps: benzylic halogenation followed by elimination.
2. Introduce the CH₂CH₂ group by Friedel–Crafts alkylation.
3. Add the Cl atom by chlorination.

Synthesis

- Benzylic bromination followed by elimination with strong base [KOC(CH₃)₃] (Steps [3] and [4]) forms the double bond of the target compound, p-chlorostyrene.

Sample Problem 18.11

Synthesize the trisubstituted benzene A from benzene.

Solution
Two groups (CH₃CO and NO₂) in A are meta directors located meta to each other, and the third substituent, an alkyl group, is an ortho, para director.

Retrosynthetic Analysis
With three groups on the benzene ring, begin by determining the possible disubstituted benzenes that are immediate precursors of the target compound, and then eliminate any that cannot be converted to the desired product. For example, three different disubstituted benzenes (B–D) can theoretically be precursors to A. However, conversion of compounds B or D to A would require a Friedel–Crafts reaction on a deactivated benzene ring, a reaction that does not occur. Thus, only C is a feasible precursor of A.
To complete the retrosynthetic analysis, prepare \( \text{C} \) from benzene:

- \([1]\) Add the ketone by Friedel–Crafts acylation.
- \([2]\) Add the alkyl group by the two-step process—Friedel–Crafts acylation followed by reduction. It is not possible to prepare butylbenzene by a one-step Friedel–Crafts alkylation because of a rearrangement reaction (Section 18.14B).

**Synthesis**

- Friedel–Crafts acylation followed by reduction with Zn(Hg), HCl yields butylbenzene (Steps \([1]\)–\([2]\)).
- Friedel–Crafts acylation gives the para product \( \text{C} \), which can be separated from its ortho isomer (Step \([3]\)).
- Nitration in Step \([4]\) introduces the \( \text{NO}_2 \) group ortho to the alkyl group (an ortho, para director) and meta to the \( \text{CH}_3\text{CO} \) group (a meta director).

**Problem 18.34** Synthesize each compound from benzene.

a. \( \text{CH}_3\text{SO}_3\text{H} \)
b. \( \text{Br} \)
c. \( \text{CHO} \)
KEY CONCEPTS

Electrophilic Aromatic Substitution

Mechanism of Electrophilic Aromatic Substitution (18.2)

- Electrophilic aromatic substitution follows a two-step mechanism. Reaction of the aromatic ring with an electrophile forms a carbocation, and loss of a proton regenerates the aromatic ring.
- The first step is rate-determining.
- The intermediate carbocation is stabilized by resonance; a minimum of three resonance structures can be drawn. The positive charge is always located ortho or para to the new C-E bond.

Three Rules Describing the Reactivity and Directing Effects of Common Substituents (18.7–18.9)

[1] All ortho, para directors except the halogens activate the benzene ring.
[2] All meta directors deactivate the benzene ring.
[3] The halogens deactivate the benzene ring and direct ortho, para.

Summary of Substituent Effects in Electrophilic Aromatic Substitution (18.6–18.9)

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Inductive effect</th>
<th>Resonance effect</th>
<th>Reactivity</th>
<th>Directing effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>[1] R = alkyl</td>
<td>donating</td>
<td>none</td>
<td>activating</td>
<td>ortho, para</td>
</tr>
<tr>
<td>[2] Z = N or O</td>
<td>withdrawing</td>
<td>donating</td>
<td>activating</td>
<td>ortho, para</td>
</tr>
<tr>
<td>[3] X = halogen</td>
<td>withdrawing</td>
<td>donating</td>
<td>deactivating</td>
<td>ortho, para</td>
</tr>
<tr>
<td>[4] Y (δ+ or +)</td>
<td>withdrawing</td>
<td>withdrawing</td>
<td>deactivating</td>
<td>meta</td>
</tr>
</tbody>
</table>

Five Examples of Electrophilic Aromatic Substitution

[1] Halogenation—Replacement of H by Cl or Br (18.3)

- Polyhalogenation occurs on benzene rings substituted by OH and NH₂ (and related substituents) (18.10A).

[2] Nitration—Replacement of H by NO₂ (18.4)
Key Concepts

[3] Sulfonation—Replacement of H by SO$_3$H (18.4)

\[
\begin{align*}
\text{H} & \quad \text{SO}_3 \quad \text{H}_2\text{SO}_4 \\
\text{benzenesulfonic acid}
\end{align*}
\]


\[
\begin{align*}
\text{H} & \quad \text{RCl} \quad \text{AlCl}_3 \\
\text{alkyl benzene}
\end{align*}
\]

- Rearrangements can occur.
- Vinyl halides and aryl halides are unreactive.
- The reaction does not occur on benzene rings substituted by meta deactivating groups or NH$_2$ groups (18.10B).
- Polyalkylation can occur.

Variations:

[1] with alcohols

\[
\begin{align*}
\text{H} & \quad \text{ROH} \quad \text{H}_2\text{SO}_4 \\
\text{R}
\end{align*}
\]

[2] with alkenes

\[
\begin{align*}
\text{H} & \quad \text{CH} = \text{CHR} \quad \text{H}_2\text{SO}_4 \\
\text{R}
\end{align*}
\]

[5] Friedel–Crafts acylation—Replacement of H by RCO (18.5)

\[
\begin{align*}
\text{H} & \quad \text{RCOCl} \quad \text{AlCl}_3 \\
\text{ketone}
\end{align*}
\]

- The reaction does not occur on benzene rings substituted by meta deactivating groups or NH$_2$ groups (18.10B).

Other Reactions of Benzene Derivatives

[1] Benzyllic halogenation (18.13)

\[
\begin{align*}
\text{Br}_2 \quad \text{hv or } \Delta \\
\text{or NBS} \quad \text{hv or ROOR}
\end{align*}
\]


\[
\begin{align*}
\text{KmnO}_4
\end{align*}
\]

- A benzylic C-H bond is needed for reaction.

[3] Reduction of ketones to alkyl benzenes (18.14B)

\[
\begin{align*}
\text{Zn(Hg), HCl} \quad \text{or NH}_2\text{NH}_2, \text{OH}
\end{align*}
\]

alkyl benzene
[4] Reduction of nitro groups to amino groups (18.14C)

\[ \text{Ph-NO}_2 + \text{H}_2 \xrightarrow{\text{Pd-C or Fe, HCl or Sn, HCl}} \text{Ph-NH}_2 \]

PROBLEMS

Reactions

18.35 Draw the products formed when phenol (C₆H₅OH) is treated with each reagent.

- a. HNO₃, H₂SO₄
- b. SO₃, H₂SO₄
- c. CH₃CH₂Cl, AlCl₃
- d. (CH₃CH₂)₂CHCOCl, AlCl₃
- e. Br₂, FeBr₃
- f. Br₂
- g. Cl₂, FeCl₃
- h. product in (a), then Sn, HCl
- i. product in (d), then Zn(Hg), HCl
- j. product in (d), then NH₂NH₂, H₂O
- k. product in (c), then Br₂, hv
- l. product in (c), then KMnO₄

18.36 Draw the products formed when benzonitrile (C₆H₅CN) is treated with each reagent.

- a. Br₂, FeBr₃
- b. HNO₃, H₂SO₄
- c. SO₃, H₂SO₄
- d. CH₃CH₂CH₂Cl, AlCl₃
- e. CH₃COCl, AlCl₃

18.37 Draw the products formed when each compound is treated with CH₃CH₂COCl, AlCl₃.

- a. \( \text{CH(CH₃)₂} \)
- b. \( \text{C} \)
- c. \( \text{N(CH₃)₂} \)
- d. \( \text{Br} \)
- e. \( \text{NCH₃C} \)

18.38 Draw the products of each reaction.

- a. \( \text{HO} \xrightarrow{\text{HNO₃, H₂SO₄}} \text{NO}_2 \)
- b. \( \text{CH₃} \xrightarrow{\text{SO₃, H₂SO₄}} \)
- c. \( \text{Cl} \xrightarrow{\text{CH₃CH₂Cl, AlCl₃}} \text{OCHOCH₃} \)
- d. \( \text{CHO} \xrightarrow{\text{Br₂, FeBr₃}} \)
- e. \( \text{CH₂O} \xrightarrow{\text{CH₃COCl, AlCl₃}} \)
- f. \( \text{NO₂} \xrightarrow{\text{HNO₃, H₂SO₄}} \)
- g. \( \text{CH₃O} \xrightarrow{\text{Cl₂, FeCl₃}} \text{OCH₃} \)
- h. \( \text{Br} \xrightarrow{\text{SO₃, H₂SO₄}} \text{OCH₃} \)

18.39 What products are formed when benzene is treated with each alkyl chloride and AlCl₃?

- a. \( \text{CH} \)
- b. \( \text{CH} \)
- c. \( \text{CH} \)
- d. \( \text{CH} \)

18.40 Write out two different routes to ketone A using a Friedel–Crafts acylation.

\( \text{OCH₃} \)

\( \text{A} \)
18.41  Draw the products of each reaction.

a. \(\text{CH}_3\text{C(CH}_3\text{)_3}\) \(\text{KMnO}_4\)

b. \(\text{Br}_2\)

c. \(\text{Zn(Hg), HCl}\)

d. \(\text{Br}_2\)

e. \(\text{NH}_2\text{NH}_2\)

18.42  You have learned two ways to make an alkyl benzene: Friedel–Crafts alkylation, and Friedel–Crafts acylation followed by reduction. Although some alkyl benzenes can be prepared by both methods, it is often true that only one method can be used to prepare a given alkyl benzene. Which method(s) can be used to prepare each of the following compounds from benzene? Show the steps that would be used.

a. \(\text{CH}_2\text{CH}_3\)

b. \(\text{C(CH}_3\text{)_3}\)

c. \(\text{CH}_3\text{CCH}_2\text{CH}_3\)

d. \(\text{C(CH}_3\text{)_3}\)

18.43  Explain why each of the following reactions will not form the given product. Then, design a synthesis of \(\text{A}\) from benzene and \(\text{B}\) from phenol (\(\text{C}_6\text{H}_5\text{OH}\)).

a. \(\text{SO}_3\text{H}\) \(\text{SO}_3\text{H}\) \(\text{CH}_3\text{COCl, AlCl}_3\) \(\text{Cl}_2, \text{FeCl}_3\) = \(\text{A}\)

b. \(\text{OCH}_3\) \(\text{OCH}_3\) \(\text{CH}_3\text{CH}_2\text{CH}_2\text{Cl, AlCl}_3\) \(\text{HNO}_3, \text{H}_2\text{SO}_4\) = \(\text{B}\)

18.44  Rank the compounds in each group in order of increasing reactivity in electrophilic aromatic substitution.

a. \(\text{C}_6\text{H}_5\text{NO}_2, \text{C}_6\text{H}_6, \text{C}_6\text{H}_5\text{OH}\)

d. \(\text{C}_6\text{H}_6, \text{C}_6\text{H}_5\text{CH}_2\text{Cl, C}_6\text{H}_5\text{CHCl}_2\)

b. \(\text{C}_6\text{H}_6, \text{C}_6\text{H}_5\text{Cl, C}_6\text{H}_5\text{CHO}\)

e. \(\text{C}_6\text{H}_5\text{CH}_3, \text{C}_6\text{H}_5\text{NH}_2, \text{C}_6\text{H}_5\text{CH}_2\text{NH}_2\)

c. \(\text{C}_6\text{H}_6, \text{C}_6\text{H}_5\text{NO}_2, \text{C}_6\text{H}_5\text{NH}_2\)

18.45  Draw all resonance structures for each compound, and explain why a particular substituent has an electron-donating or electron-withdrawing resonance effect:

a. \(\text{C}_6\text{H}_5\text{NO}_2\)

b. \(\text{C}_6\text{H}_5\text{F}\)

18.46  For each of the following substituted benzenes: [1] \(\text{C}_6\text{H}_5\text{Br}; [2] \text{C}_6\text{H}_5\text{CN}; [3] \text{C}_6\text{H}_5\text{OCOCH}_3;\)

a. Does the substituent donate or withdraw electron density by an inductive effect?

b. Does the substituent donate or withdraw electron density by a resonance effect?

c. On balance, does the substituent make a benzene ring more or less electron rich than benzene itself?

d. Does the substituent activate or deactivate the benzene ring in electrophilic aromatic substitution?

18.47  Which benzene ring in each compound is more reactive in electrophilic aromatic substitution?

a. \(\text{O}\)

b. \(\text{CH}_3\)

c. \(\text{O}\)
18.48 For each N-substituted benzene, predict whether the compound reacts faster than, slower than, or at a similar rate to benzene in electrophilic aromatic substitution. Then draw the major product(s) formed when each compound reacts with a general electrophile $E^+$. 

- a. 
- b. 
- c. 
- d. 

18.49 Explain each statement in detail using resonance structures.

- a. A phenyl group ($\text{C}_6\text{H}_5^-$) is an ortho, para director that activates a benzene ring towards electrophilic attack.
- b. A nitroso group ($-\text{NO}$) is an ortho, para director that deactivates a benzene ring towards electrophilic attack.

18.50 Explain the following observation. Ethyl 3-phenylpropanoate ($\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_2\text{CH}_3$) reacts with electrophiles to afford ortho- and para-disubstituted arenes, but ethyl 3-phenyl-2-propenoate ($\text{C}_6\text{H}_5\text{CH}=-\text{CHCO}_2\text{CH}_2\text{CH}_3$) reacts with electrophiles to afford meta-disubstituted arenes.

18.51 Explain why the meta product is formed in the following reaction despite the fact that $-\text{N(CH}_3\text{)}_2$ is usually an ortho, para director.

18.52 Draw a stepwise mechanism for each reaction.

- a. 
- b. 

18.53 Draw a stepwise, detailed mechanism for the following intramolecular reaction.

18.54 Draw a stepwise, detailed mechanism for the following reaction.

18.55 Friedel–Crafts alkylation of benzene with (2$\text{R}$)-2-chlorobutane and $\text{AlCl}_3$ affords sec-butylbenzene.

- a. How many stereogenic centers are present in the product?
- b. Would you expect the product to exhibit optical activity? Explain, with reference to the mechanism.
Although two products (A and B) are possible when naphthalene undergoes electrophilic aromatic substitution, only A is formed. Draw resonance structures for the intermediate carbocation to explain why this is observed.

\[
\text{naphthalene} \xrightarrow{E^+} \begin{array}{c} \text{A} \\ \text{This product is formed.} \end{array} + \begin{array}{c} \text{B} \\ \text{This product is not formed.} \end{array}
\]

Draw a stepwise mechanism for the following reaction, which is used to prepare the pesticide DDT.

\[
2 \begin{array}{c} \text{Cl} \\ \text{Cl} \end{array} \xrightarrow{2 \ \text{H}_2\text{SO}_4} \begin{array}{c} \text{Cl} \\ \text{Cl} \end{array} \xrightarrow{\text{H}_2\text{O}^+} \text{DDT}
\]

Benzene undergoes electrophilic aromatic substitution with anhydrides, compounds having the general structure (RCO)\(_2\)O, in a reaction that resembles Friedel–Crafts acylation. Draw a stepwise mechanism for the reaction of benzene with glutaric anhydride in the presence of AlCl\(_3\).

\[
\text{benzene} \xrightarrow{[1] \text{AlCl}_3} \text{glutaric anhydride} \xrightarrow{[2] \text{H}_2\text{O}^+} \text{product}
\]

Benzyl bromide (C\(_6\)H\(_5\)CH\(_2\)Br) reacts rapidly with CH\(_3\)OH to afford benzyl methyl ether (C\(_6\)H\(_5\)CH\(_2\)OCH\(_3\)). Draw a stepwise mechanism for the reaction, and explain why this 1° alkyl halide reacts rapidly with a weak nucleophile under conditions that favor an Sn1 mechanism. Would you expect the para-substituted benzyl halides CH\(_3\)OC\(_6\)H\(_4\)CH\(_2\)Br and O\(_2\)NC\(_6\)H\(_4\)CH\(_2\)Br to each be more or less reactive than benzyl bromide in this reaction? Explain your reasoning.

Explain why HBr addition to C\(_6\)H\(_5\)CH=CHCH\(_3\) forms only one alkyl halide, C\(_6\)H\(_5\)(Br)CH\(_2\)CH\(_3\).

Draw a stepwise mechanism for the following reaction, which is used to prepare bisphenol A (BPA), a widely used monomer in polymer synthesis. Although BPA is not acutely toxic, safety concerns over low-dose exposure, especially in infants, have led to a re-examination of its use in baby bottles and infant formula cans.

Synthesis

Synthesize each compound from benzene and any other organic or inorganic reagents.

- isopropylbenzene
- butylbenzene
- o-butylchlorobenzene
- m-bromonitrobenzene
- o-bromonitrobenzene
- f. COOH
- g. COOH
- h. Br
- i. Br
- j. COOH
- k. Cl
- l. Cl
- m. NO\(_2\)
18.63 Synthesize each compound from benzene and any other organic or inorganic reagents.

18.64 Synthesize each compound from toluene (C₆H₅CH₃) and any other organic or inorganic reagents.

18.65 Devise a synthesis of each compound from phenol (C₆H₅OH) and any other organic or inorganic reagents.

18.66 Use the reactions in this chapter along with those learned in Chapters 11 and 12 to synthesize each compound. You may use benzene, acetylene (HC≡CH), two-carbon alcohols, ethylene oxide, and any inorganic reagents.

18.67 Devise a synthesis of 1-phenyl-1-propyne (C₆H₅C≡CCH₃) from benzene and organic compounds having ≤ 3 C’s. You may use any required inorganic or organic reagents.

18.68 Ibufenac, a para-disubstituted arene with the structure HO₂CCH₂C₆H₄CH₂CH(CH₃)₂, is a much more potent analgesic than aspirin, but it was never sold commercially because it caused liver toxicity in some clinical trials. Devise a synthesis of ibufenac from benzene and organic halides having fewer than five carbons.

18.69 Carboxylic acid X is an intermediate in the multistep synthesis of proparacaine, a local anesthetic. Devise a synthesis of X from phenol and any needed organic or inorganic reagents.
18.70 Identify the structures of isomers A and B (molecular formula C₈H₉Br).

18.71 Propose a structure of compound C (molecular formula C₁₀H₁₂O) consistent with the following data. C is partly responsible for the odor and flavor of raspberries.

Compound C: IR absorption at 1717 cm⁻¹
18.72 Compound $X$ (molecular formula $C_{10}H_{12}O$) was treated with $\text{NH}_2\text{NH}_2, \text{OH}$ to yield compound $Y$ (molecular formula $C_{10}H_{14}$). Based on the $^1\text{H}$ NMR spectra of $X$ and $Y$ given below, what are the structures of $X$ and $Y$?

![1H NMR of X](image1)

![1H NMR of Y](image2)

18.73 Reaction of $p$-cresol with two equivalents of 2-methyl-1-propene affords BHT, a preservative with molecular formula $C_{15}H_{24}O$. BHT gives the following $^1\text{H}$ NMR spectral data: 1.4 (singlet, 18 H), 2.27 (singlet, 3 H), 5.0 (singlet, 1 H), and 7.0 (singlet, 2 H) ppm. What is the structure of BHT? Draw a stepwise mechanism illustrating how it is formed.

$$\text{CH}_3$$

$\text{CH}_3$

$p$-cresol

CH$_3$

CH$_3$

2-methyl-1-propene

(2 equiv)

$$\xrightarrow{\text{H}_2\text{SO}_4}$$

BHT ($C_{15}H_{24}O$)

18.74 Compound $Z$ (molecular formula $C_{9}H_{9}ClO$) can be converted to the antidepressant bupropion (Figure 18.3) by a series of reactions. $Z$ shows a strong peak in its IR spectrum at 1683 cm$^{-1}$. The $^1\text{H}$ NMR spectrum of $Z$ shows peaks at 1.2 (triplet, 3 H), 2.9 (quartet, 2 H), and 7.2–8.0 (multiplet, 4 H) ppm. Propose a structure for $Z$.

$$\xrightarrow{\text{several steps}}$$

bupropion

$Z$
Challenge Problems

18.75 The $^1$H NMR spectrum of phenol (C$_6$H$_5$OH) shows three absorptions in the aromatic region: 6.70 (2 ortho H’s), 7.14 (2 meta H’s), and 6.80 (1 para H) ppm. Explain why the ortho and para absorptions occur at lower chemical shift than the meta absorption.

18.76 Explain the reactivity and orientation effects observed in each heterocycle.

\[
\text{pyridine} \rightarrow \text{E}^+ \rightarrow \text{pyridine} \quad \text{C3} \\
\text{pyrrole} \rightarrow \text{E}^+ \rightarrow \text{pyrrole} \quad \text{C2}
\]

a. Pyridine is less reactive than benzene in electrophilic aromatic substitution and yields 3-substituted products.

b. Pyrrole is more reactive than benzene in electrophilic aromatic substitution and yields 2-substituted products.

18.77 Draw a stepwise, detailed mechanism for the dienone–phenol rearrangement, a reaction that forms alkyl-substituted phenols from cyclohexadienes.

\[
\text{O} \quad \text{H}_2\text{SO}_4 \quad \text{OH}
\]

18.78 Draw a stepwise mechanism for the following intramolecular reaction, which is used in the synthesis of the female sex hormone estrone.

\[
\text{RO} \quad \text{OH} \quad \text{RO} \quad \text{HO}
\]

18.79 Although aryl halides are generally inert to nucleophilic substitution, aryl halides that also contain a nitro group ortho or para to the halogen undergo nucleophilic aromatic substitution, as shown in the following example.

\[
O_2N-\text{Cl} + \text{CH}_3\text{O}^- \rightarrow O_2N-\text{OCH}_3 + \text{Cl}^-
\]

a. Keeping in mind that the reaction cannot follow an S$_{N}$1 or S$_{N}$2 mechanism, suggest a mechanism for this process.

b. Explain why an electron-withdrawing NO$_2$ group is needed for this nucleophilic substitution to occur.

c. Explain why $m$-chloronitrobenzene does not undergo this reaction.