CHAPTER

15

Reactions of Aromatic Compounds

Although aromatic molecules have special electronic properties that render them inert to many standard reaction conditions, there are a number of ways to change the atoms that are attached to such systems by a process called electrophilic aromatic substitution. For instance, the six hydrogen atoms on benzene can all be replaced with different groups—for example, with halogens, carbonyl groups, or aliphatic chains. Such processes can convert benzene, a material that is a liquid at room temperature and serves as a solvent, into thousands of different molecules, including drugs like aspirin and explosives like trinitrotoluene (TNT). In biosynthesis, similar reactions produce biological molecules like thyroxine, a key hormone involved in metabolism, and pallidol, a compound produced by grapes. We will learn about these processes later in the chapter. The synthetic possibilities are nearly endless, but key to unlocking that potential is an understanding of the concepts, logic, and rules that determine how these reactions can be achieved.

IN THIS CHAPTER WE WILL CONSIDER:

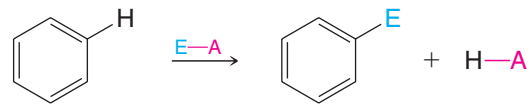
- the general parameters that allow for substitution reactions of benzene
- how substituents on a benzene ring can impact reactivity and the ability to undergo additional substitutions
- reactions that can convert a given substituent into new functional groups

[WHY DO THESE TOPICS MATTER?] At the end of the chapter, we will explore a special group of molecules that undergo different versions of the same reactions, both in nature and in the laboratory, to produce a diverse array of structures from similar starting materials.

PHOTO CREDIT: Image Source

15.1 ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS

Some of the most important reactions of aromatic compounds are those in which an electrophile replaces one of the hydrogen atoms of the ring.



(E—A is an electrophilic reactant)

These reactions, called **electrophilic aromatic substitutions (EAS)**, allow the direct introduction of groups onto aromatic rings such as benzene, and they provide synthetic routes to many important compounds. Figure 15.1 outlines five different types of electrophilic aromatic substitutions that we will study in this chapter, including carbon–carbon bond-forming reactions and halogenations.

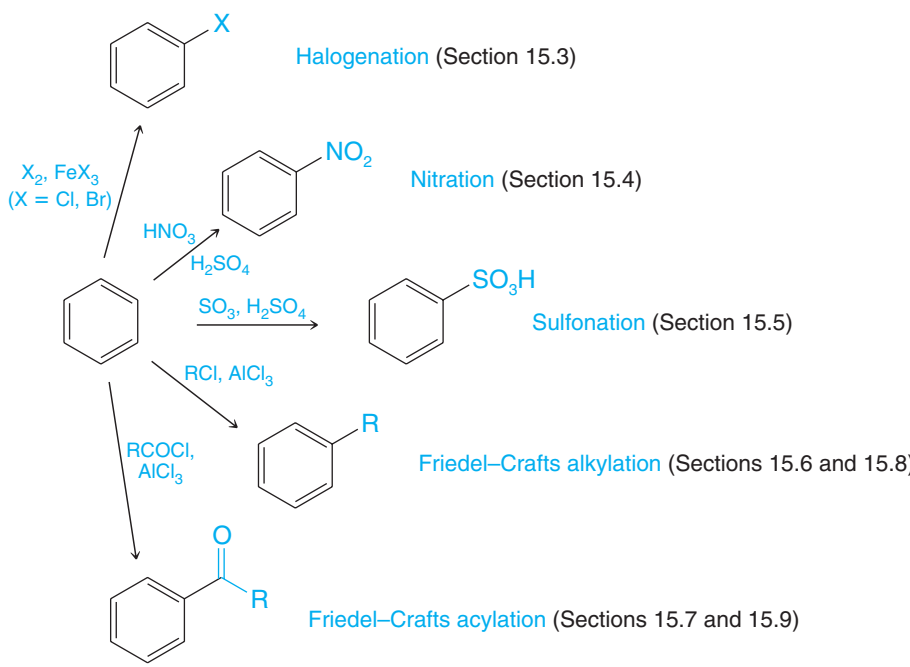
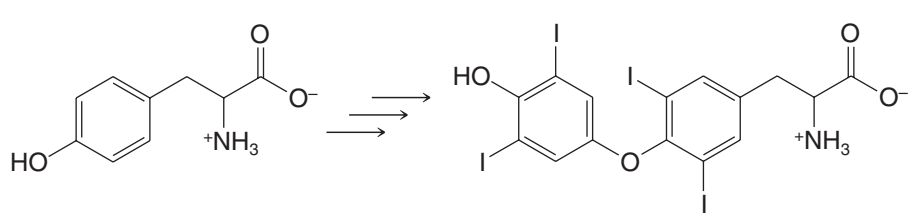


FIGURE 15.1 Electrophilic aromatic substitution reactions.

A noteworthy example of electrophilic aromatic substitution in nature, as mentioned in the introduction, is biosynthesis of the thyroid hormone thyroxine, where iodine is incorporated into benzene rings that are derived from tyrosine.



Tyrosine
(a dietary amino acid)

Thyroxine
(a thyroid hormone)

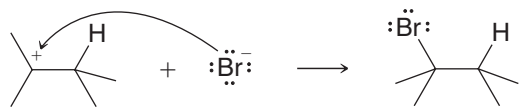
In the next section we shall learn the general mechanism for the way an electrophile reacts with a benzene ring. Then, in Sections 15.3–15.7, we shall see specific examples of electrophiles and how each is formed in a reaction mixture.

15.2 A GENERAL MECHANISM FOR ELECTROPHILIC AROMATIC SUBSTITUTION

The π electrons of benzene react with strong electrophiles. In this respect, benzene has something in common with alkenes. When an alkene reacts with an electrophile, as in the addition of HBr (Section 8.2), electrons from the alkene π bond react with the electrophile, leading to a carbocation intermediate.

Alkene **Electrophile** **Carbocation**

The carbocation formed from the alkene then reacts with the nucleophilic bromide ion to form the addition product.



Carbocation **Addition product**

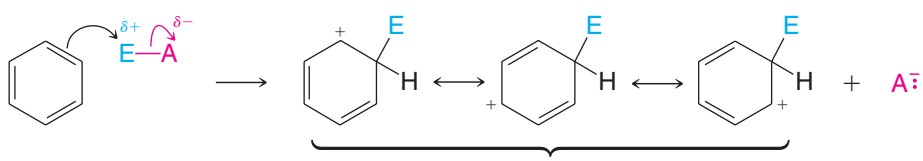
The similarity of benzene reactivity with that of an alkene ends, however, at the carbocation stage, prior to nucleophilic attack. As we saw in Chapter 14, benzene's closed shell of six π electrons give it special stability.

- Although benzene is susceptible to electrophilic attack, it undergoes *substitution reactions* rather than *addition reactions*.

Substitution reactions allow the aromatic sextet of π electrons in benzene to be regenerated after attack by the electrophile. We can see how this happens if we examine a general mechanism for **electrophilic aromatic substitution**.

Experimental evidence indicates that electrophiles attack the π system of benzene to form a ***nonaromatic cyclohexadienyl carbocation*** known as an **arenium ion**. In showing this step, it is convenient to use Kekulé structures, because these make it much easier to keep track of the π electrons:

Step 1



Arenium ion
(a delocalized cyclohexadienyl cation)

- In step 1 the electrophile takes two electrons of the six-electron π system to form a σ bond to one carbon atom of the benzene ring.

Formation of this bond interrupts the cyclic system of π electrons, because in the formation of the arenium ion the carbon that forms a bond to the electrophile becomes sp^3 hybridized and, therefore, no longer has an available p orbital. Now only five carbon atoms of the ring are sp^2 hybridized and still have p orbitals. The four π electrons of the arenium ion are delocalized through these five p orbitals. A calculated electrostatic potential map for the arenium ion formed by electrophilic addition of bromine to benzene indicates that positive charge is distributed in the arenium ion ring (Fig. 15.2), just as was shown in the contributing resonance structures.

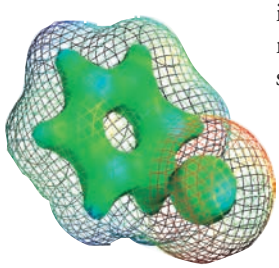


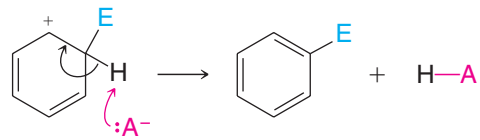
FIGURE 15.2 A calculated structure for the arenium ion intermediate formed by electrophilic addition of bromine to benzene (Section 15.3). The electrostatic potential map for the principal location of bonding electrons (indicated by the solid surface) shows that positive charge (blue) resides primarily at the ortho and para carbons relative to the carbon where the electrophile has bonded. This distribution of charge is consistent with the resonance model for an arenium ion. (The van der Waals surface is indicated by the wire mesh.)

Helpful Hint

Resonance structures (like those used here for the arenium ion) will be important for our study of electrophilic aromatic substitution.

- In step 2 a proton is removed from the carbon atom of the arenium ion that bears the electrophile, restoring aromaticity to the ring.

Step 2



The two electrons that bonded the proton to the ring become a part of the π system. The carbon atom that bears the electrophile becomes sp^2 hybridized again, and a benzene derivative with six fully delocalized π electrons is formed. The proton is removed by any of the bases present, for example, by the anion derived from the electrophile.

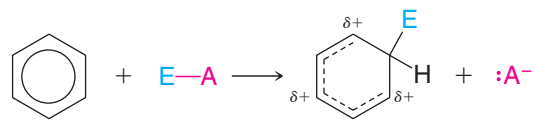
PRACTICE PROBLEM 15.1 Show how loss of a proton can be represented using each of the three resonance structures for the arenium ion and show how each representation leads to the formation of a benzene ring with three alternating double bonds (i.e., six fully delocalized π electrons).

Kekulé structures are more appropriate for writing mechanisms such as electrophilic aromatic substitution because they permit the use of resonance theory, which, as we shall soon see, is invaluable as an aid to our understanding. If, for brevity, however, we wish to show the mechanism using the hybrid formula for benzene we can do it in the following way. We draw the arenium ion as a delocalized cyclohexadienyl cation:

Helpful Hint

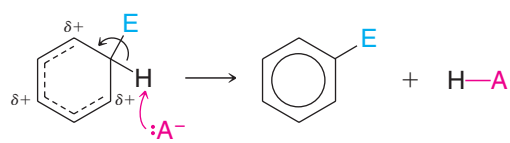
In our color scheme for chemical formulas, blue generally indicates groups that are electrophilic or have electron-withdrawing character. Red indicates groups that are or become Lewis bases, or have electron-donating character.

Step 1



Arenium ion

Step 2



There is firm experimental evidence that the arenium ion is a true *intermediate* in electrophilic substitution reactions. It is not a transition state. This means that in a free-energy diagram (Fig. 15.3) the arenium ion lies in an energy valley between two transition states.

The free energy of activation for step 1, $\Delta G^{\ddagger}_{(1)}$, has been shown to be much greater than the free energy of activation for step 2, $\Delta G^{\ddagger}_{(2)}$, as depicted in Figure 15.3. This is

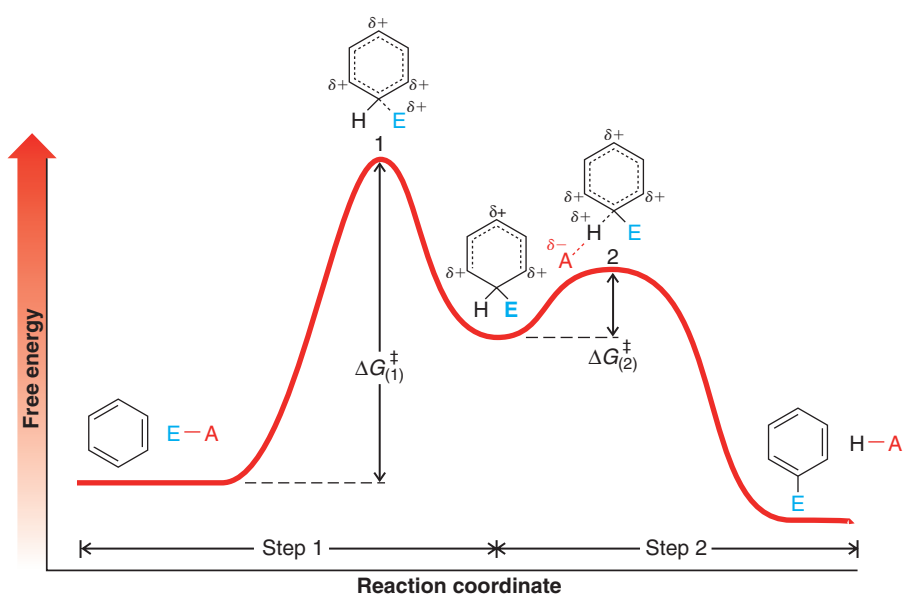
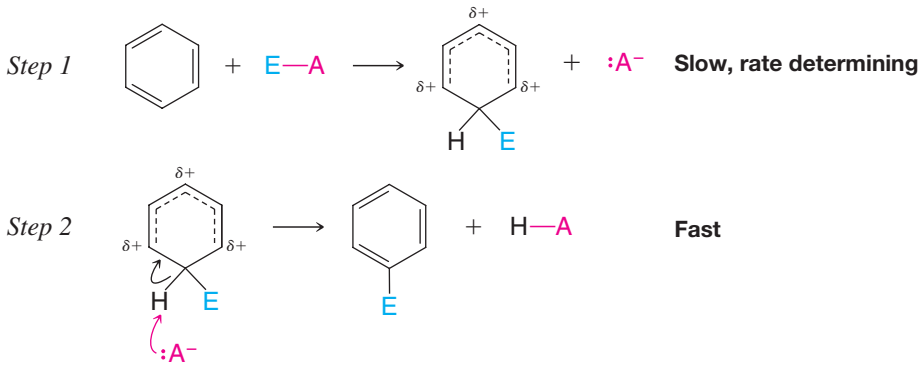


FIGURE 15.3 The free-energy diagram for an electrophilic aromatic substitution reaction. The arenium ion is a true intermediate lying between transition states 1 and 2. In transition state 1 the bond between the electrophile and one carbon atom of the benzene ring is only partially formed. In transition state 2 the bond between the same benzene carbon atom and its hydrogen atom is partially broken. The bond between the hydrogen atom and the conjugate base is partially formed.

consistent with what we would expect. The reaction leading from benzene and an electrophile to the arenium ion is highly endothermic, because the aromatic stability of the benzene ring is lost. The reaction leading from the arenium ion to the substituted benzene, by contrast, is highly exothermic because it restores aromaticity to the system.

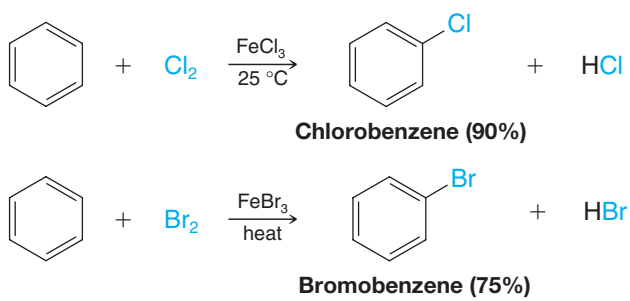
Of the following two steps, step 1 (the formation of the arenium ion) is usually the rate-determining step in electrophilic aromatic substitution because of its higher free energy of activation:



Step 2, the removal of a proton, occurs rapidly relative to step 1 and has no effect on the overall rate of reaction.

15.3 HALOGENATION OF BENZENE

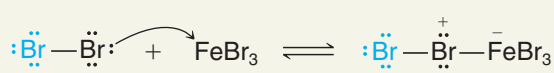
Benzene reacts with bromine and chlorine in the presence of Lewis acids to give halogenated substitution products in good yield.



The Lewis acids typically used are aluminum chloride ($AlCl_3$) and iron chloride ($FeCl_3$) for chlorination, and iron bromide ($FeBr_3$) for bromination. The purpose of the Lewis acid is to make the halogen a stronger electrophile. A mechanism for electrophilic aromatic bromination is shown here.

A MECHANISM FOR THE REACTION — Electrophilic Aromatic Bromination

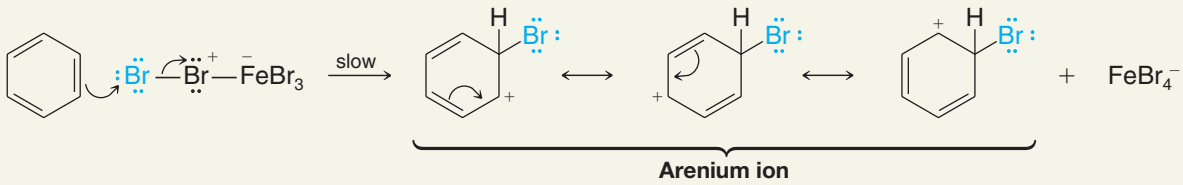
Step 1



Bromine combines with $FeBr_3$ to form a complex.

(mechanism continues on the next page)

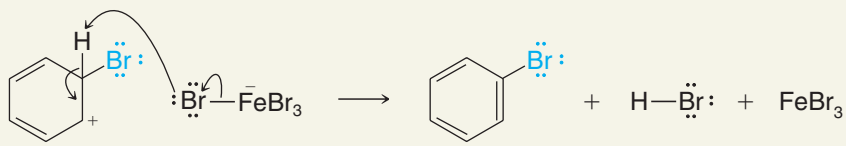
Step 2



Helpful Hint
An electrostatic potential map for this arenium ion is shown in Fig. 15.2.

The benzene ring donates an electron pair to the terminal bromine, forming the arenium ion and neutralizing the formal positive charge on the other bromine.

Step 3

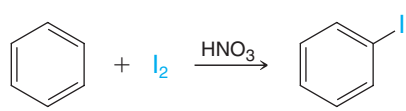


A proton is removed from the arenium ion to form bromobenzene and regenerate the catalyst.

The mechanism of the chlorination of benzene in the presence of ferric chloride is analogous to the one for bromination.

Fluorine reacts so rapidly with benzene that aromatic fluorination requires special conditions and special types of apparatus. Even then, it is difficult to limit the reaction to monofluorination. Fluorobenzene can be made, however, by an indirect method that we shall see in Section 20.7D.

Iodine, on the other hand, is so unreactive that a special technique has to be used to effect direct iodination; the reaction has to be carried out in the presence of an oxidizing agent such as nitric acid:

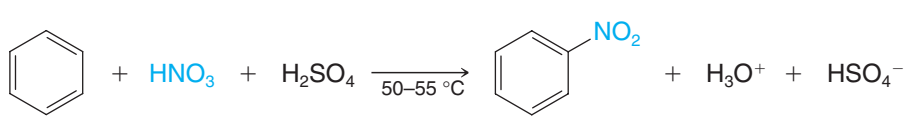


86%

Biochemical iodination, as in the biosynthesis of thyroxine, occurs with enzymatic catalysis.

15.4 NITRATION OF BENZENE

Benzene undergoes nitration on reaction with a mixture of concentrated nitric acid and concentrated sulfuric acid.

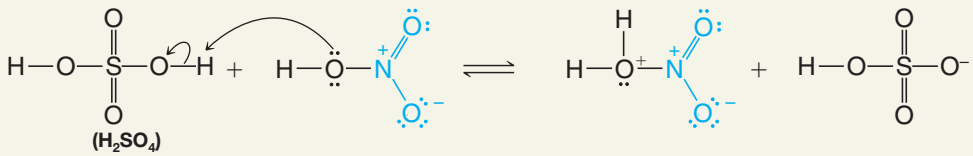


85%

Concentrated sulfuric acid increases the rate of the reaction by increasing the concentration of the electrophile, the nitronium ion (NO_2^+), as shown in the first two steps of the following mechanism.

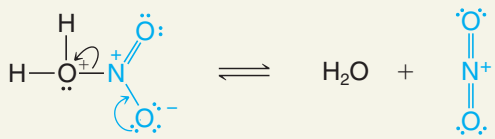
A MECHANISM FOR THE REACTION — Nitration of Benzene

Step 1



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

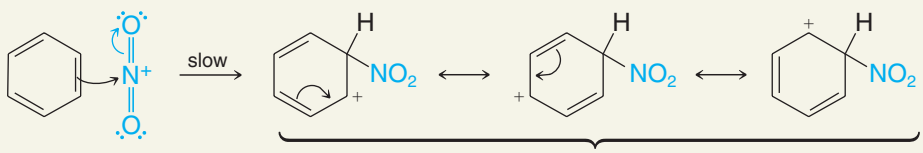
Step 2



Nitronium ion

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

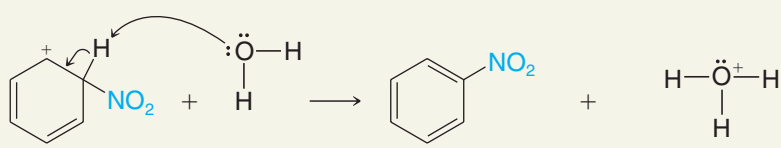
Step 3



Arenium ion

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

Step 4



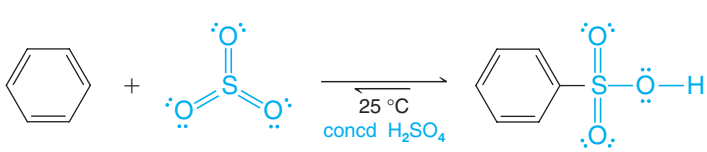
The arenium ion then loses a proton to a Lewis base and becomes nitrobenzene.

PRACTICE PROBLEM 15.2

Given that the pK_a of H_2SO_4 is −9 and that of HNO_3 is −1.4, explain why nitration occurs more rapidly in a mixture of concentrated nitric and sulfuric acids than in concentrated nitric acid alone.

15.5 SULFONATION OF BENZENE

Benzene reacts with fuming sulfuric acid at room temperature to produce benzenesulfonic acid. Fuming sulfuric acid is sulfuric acid that contains added sulfur trioxide (SO_3). Sulfonation also takes place in concentrated sulfuric acid alone, but more slowly. Under either condition, the electrophile appears to be sulfur trioxide.

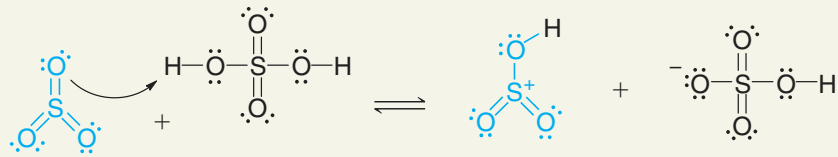


Sulfur trioxide — **Benzenesulfonic acid (56%)**

In concentrated sulfuric acid, sulfur trioxide is produced in an equilibrium in which H_2SO_4 acts as both an acid and a base (see step 1 of the following mechanism).

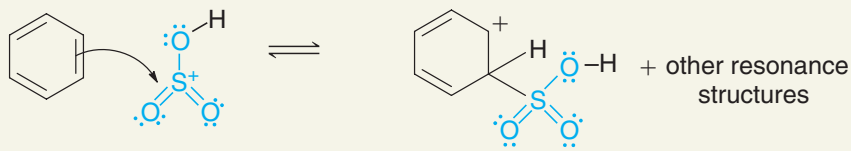
A MECHANISM FOR THE REACTION — Sulfonation of Benzene

Step 1



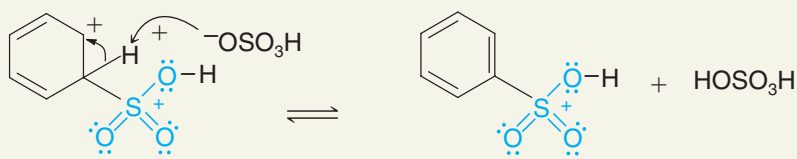
SO_3 is protonated to form SO_3H^+

Step 2



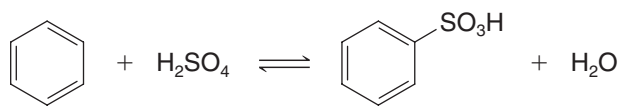
SO_3H^+ reacts as an electrophile with the benzene ring to form an arenium ion.

Step 3



Loss of a proton from the arenium ion restores aromaticity to the ring and regenerates the acid catalyst.

All of the steps in sulfonation are equilibria, which means that the overall reaction is reversible. The position of equilibrium can be influenced by the conditions we employ.



- If we want to sulfonate the ring (install a sulfonic acid group), we use concentrated sulfuric acid or—better yet—fuming sulfuric acid. Under these conditions the position of equilibrium lies appreciably to the right, and we obtain benzenesulfonic acid in good yield.
- If we want to desulfonate the ring (**remove** a sulfonic acid group), we employ dilute sulfuric acid and usually pass steam through the mixture. Under these conditions—with a high concentration of water—the equilibrium lies appreciably to the left and desulfonation occurs.

We shall see later that sulfonation and desulfonation reactions are often used in synthetic work.

Helpful Hint
Sulfonation–desulfonation is a useful tool in syntheses involving electrophilic aromatic substitution.

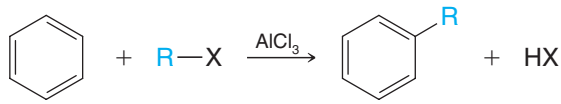
- We sometimes install a sulfonate group **as a protecting group**, to temporarily block its position from electrophilic aromatic substitution, or **as a directing group, to influence the position** of another substitution relative to it (Section 15.10). When it is no longer needed we remove the sulfonate group.

15.6 FRIEDEL–CRAFTS ALKYLATION

Charles Friedel, a French chemist, and his American collaborator, James M. Crafts, discovered new methods for the preparation of alkylbenzenes (ArR) and acylbenzenes (ArCOR) in 1877. These reactions are now called the Friedel–Crafts **alkylation** and

acylation reactions. We shall study the Friedel–Crafts alkylation reaction here and take up the **Friedel–Crafts acylation** reaction in Section 15.7.

- The following is a general equation for a **Friedel–Crafts alkylation** reaction:

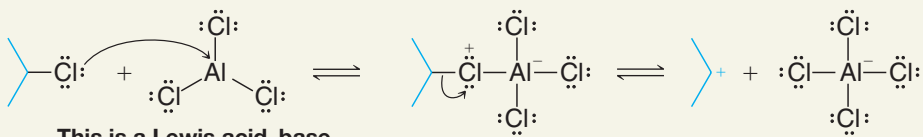


- The mechanism for the reaction starts with the formation of a carbocation.
- The carbocation then acts as an electrophile and attacks the benzene ring to form an arenium ion.
- The arenium ion then loses a proton.

This mechanism is illustrated below using 2-chloropropane and benzene.

A MECHANISM FOR THE REACTION — Friedel–Crafts Alkylation

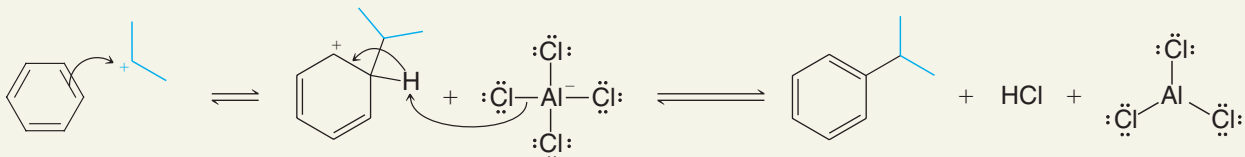
Step 1



This is a Lewis acid–base reaction (see Section 15.3).

The complex dissociates to form a carbocation and $AlCl_4^-$.

Step 2

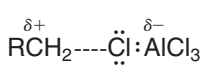


The carbocation, acting as an electrophile, reacts with benzene to produce an arenium ion.

A proton is removed from the arenium ion to form isopropylbenzene. This step also regenerates the $AlCl_3$ and liberates HCl.

- When R—X is a primary halide, a simple carbocation probably does not form. Instead, the aluminum chloride forms a complex with the alkyl halide, and this complex acts as the electrophile.

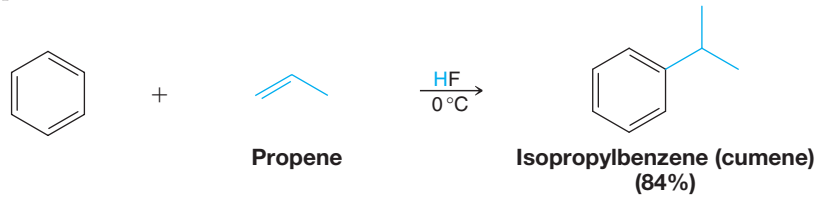
The complex is one in which the carbon–halogen bond is nearly broken—and one in which the carbon atom has a considerable positive charge:



Even though this complex is not a simple carbocation, it acts as if it were and it transfers a positive alkyl group to the aromatic ring.

- These complexes react so much like carbocations that they also undergo typical carbocation rearrangements (Section 15.8).
- Friedel–Crafts alkylations are not restricted to the use of alkyl halides and aluminum chloride. Other pairs of reagents that form carbocations (or species like carbocations) may be used in Friedel–Crafts alkylations as well.

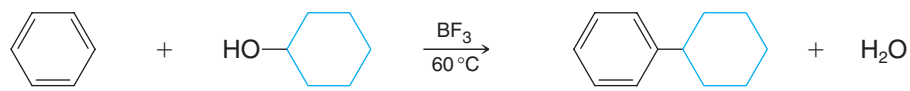
These possibilities include the use of a mixture of an alkene and an acid:



Propene — Isopropylbenzene (cumene) (84%)

Cyclohexene — Cyclohexylbenzene (62%)

A mixture of an alcohol and an acid may also be used:

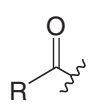


Cyclohexanol — Cyclohexylbenzene (56%)

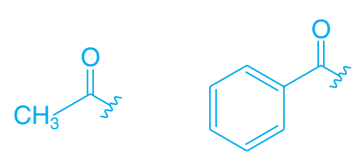
There are several important limitations of the Friedel–Crafts reaction. These are discussed in Section 15.8.

PRACTICE PROBLEM 15.3 Outline all steps in a reasonable mechanism for the formation of isopropylbenzene from propene and benzene in liquid HF (just shown). Your mechanism must account for the product being isopropylbenzene, not propylbenzene.

15.7 FRIEDEL–CRAFTS ACYLATION

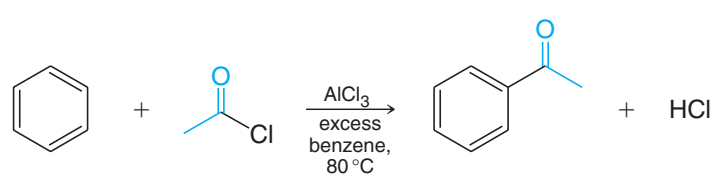


The group is called an **acyl group**, and a reaction whereby an acyl group is introduced into a compound is called an **acylation** reaction. Two common acyl groups are the acetyl group and the benzoyl group. (The benzoyl group should not be confused with the benzyl group, $-CH_2C_6H_5$; see Section 14.2.)



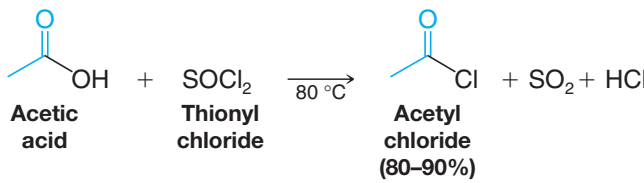
Acetyl group (ethanoyl group) — Benzoyl group

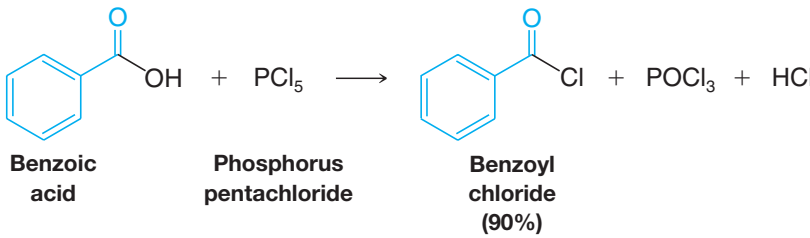
The **Friedel–Crafts acylation** reaction is often carried out by treating the aromatic compound with an **acyl halide** (often an acyl chloride). Unless the aromatic compound is one that is highly reactive, the reaction requires the addition of at least one equivalent of a Lewis acid (such as $AlCl_3$) as well. The product of the reaction is an aryl ketone:



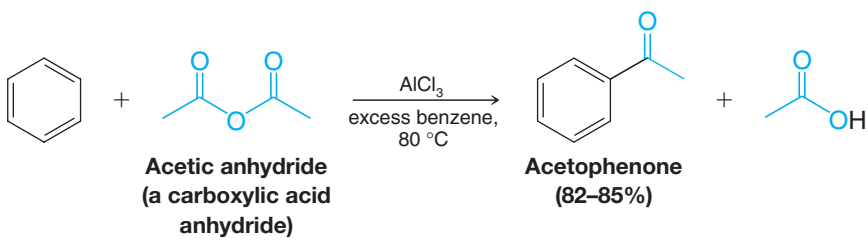
Acetyl chloride — Acetophenone (methyl phenyl ketone) (97%)

Acyl chlorides, also called **acid chlorides**, are easily prepared (Section 18.5) by treating carboxylic acids with thionyl chloride ($SOCl_2$) or phosphorus pentachloride (PCl_5):



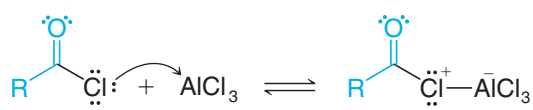


Friedel–Crafts acylations can also be carried out using carboxylic acid anhydrides. For example,

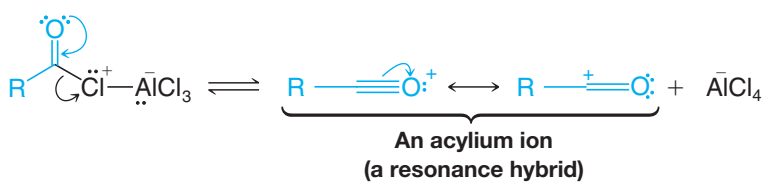


In most Friedel–Crafts acylations the electrophile appears to be an **acylium ion** formed from an acyl halide in the following way:

Step 1



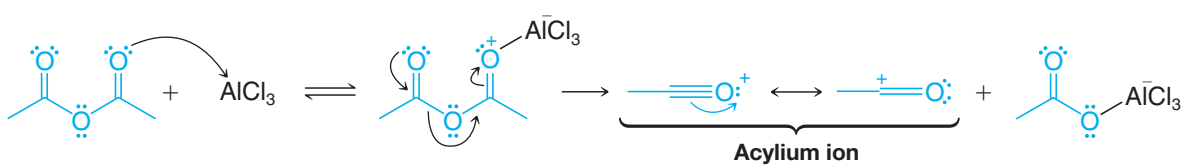
Step 2



SOLVED PROBLEM 15.1

Show how an acylium ion could be formed from acetic anhydride in the presence of $AlCl_3$.

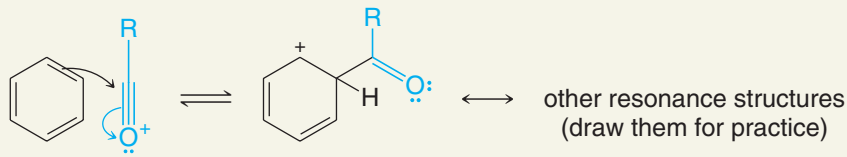
STRATEGY AND ANSWER: We recognize that $AlCl_3$ is a Lewis acid and that an acid anhydride, because it has multiple unshared electron pairs, is a Lewis base. A reasonable mechanism starts with a Lewis acid–base reaction and proceeds to form an acylium ion in the following way.



The remaining steps in the Friedel–Crafts acylation of benzene are the following:

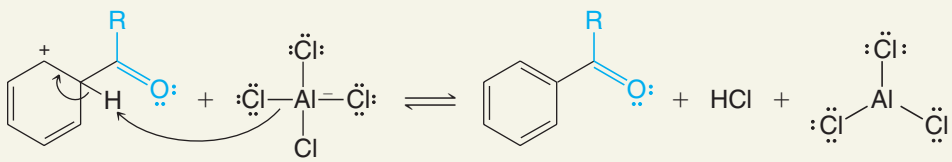
A MECHANISM FOR THE REACTION — Friedel–Crafts Acylation

Step 3



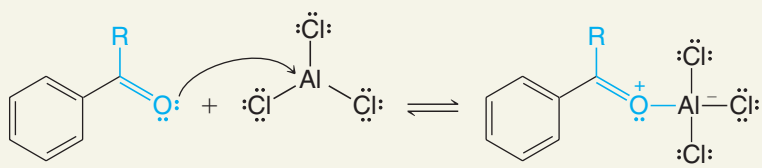
The acylium ion, acting as an electrophile, reacts with benzene to form the arenium ion.

Step 4



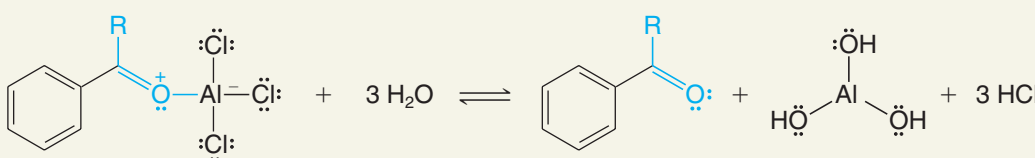
A proton is removed from the arenium ion, forming the aryl ketone.

Step 5



The ketone, acting as a Lewis base, reacts with aluminum chloride (a Lewis acid) to form a complex.

Step 6



Treating the complex with water liberates the ketone and hydrolyzes the Lewis acid.

Several important synthetic applications of the Friedel–Crafts reaction are given in Section 15.9.

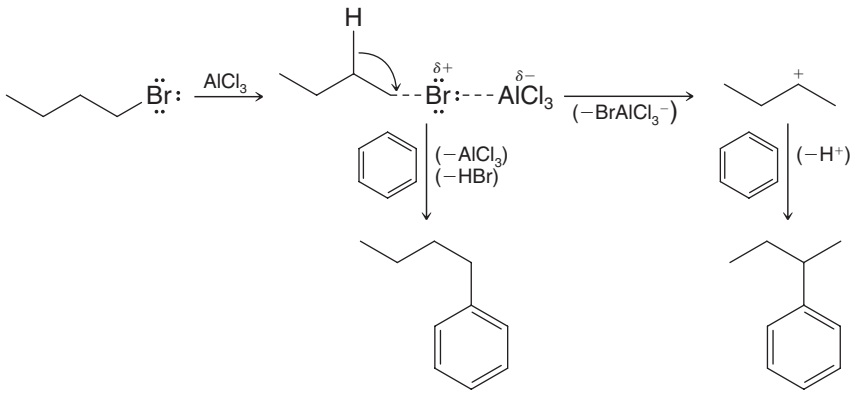
15.8 LIMITATIONS OF FRIEDEL–CRAFTS REACTIONS

Several restrictions limit the usefulness of Friedel–Crafts reactions:

1. **When the carbocation formed from an alkyl halide, alkene, or alcohol can rearrange to one or more carbocations that are more stable, it usually does so, and the major products obtained from the reaction are usually those from the more stable carbocations.**

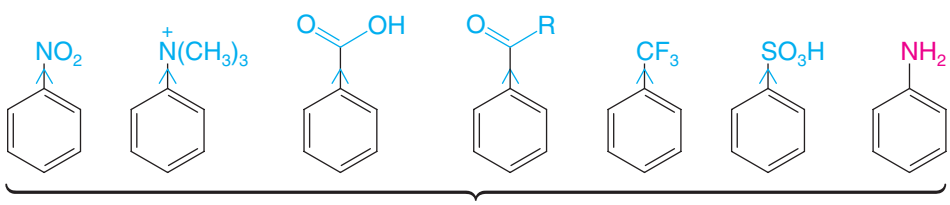
   When benzene is alkylated with butyl bromide, for example, some of the developing butyl cations rearrange by a hydride shift. Some of the developing 1° carbocations (see following reactions) become more stable 2° carbocations. Then

benzene reacts with both kinds of carbocations to form both butylbenzene and *sec*-butylbenzene:



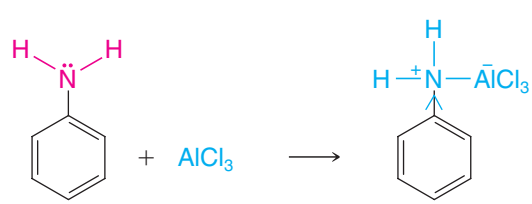
Butylbenzene (32–36% of mixture) **sec-Butylbenzene (64–68% of mixture)**

2. **Friedel–Crafts reactions usually give poor yields when powerful electron-withdrawing groups** (Section 15.11) **are present on the aromatic ring or when the ring bears an** —NH_2, —NHR, **or** —NR_2 **group**. This applies to both alkylations and acylations.



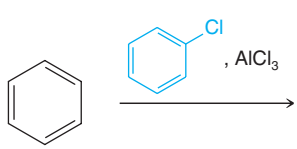
These usually give poor yields in Friedel-Crafts reactions.

We shall learn in Section 15.10 that groups present on an aromatic ring can have a large effect on the reactivity of the ring toward electrophilic aromatic substitution. **Electron-withdrawing groups make the ring less reactive by making it electron deficient**. Any substituent more electron withdrawing (or deactivating) than a halogen, that is, **any meta-directing group** (Section 15.11C), **makes an aromatic ring too electron deficient to undergo a Friedel–Crafts reaction**. The amino groups, —NH_2, —NHR, and —NR_2, are changed into powerful electron-withdrawing groups by the Lewis acids used to catalyze Friedel–Crafts reactions. For example,

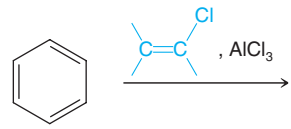


Does not undergo a Friedel–Crafts reaction

3. **Aryl and vinylic halides cannot be used as the halide component because they do not form carbocations readily** (see Section 6.14A):

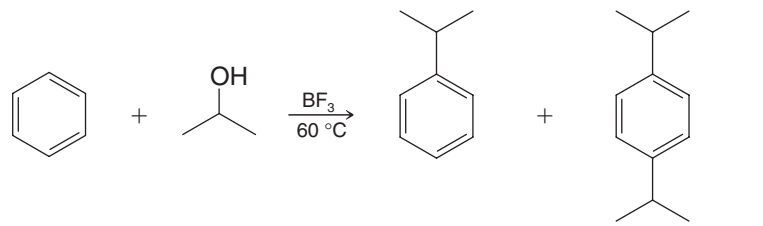


No Friedel–Crafts reaction because the halide is aryl



No Friedel–Crafts reaction because the halide is vinylic

4. **Polyalkylations often occur.** Alkyl groups are inductive electron-releasing groups, and once one is introduced into the benzene ring, it activates the ring toward further substitution (see Section 15.10):



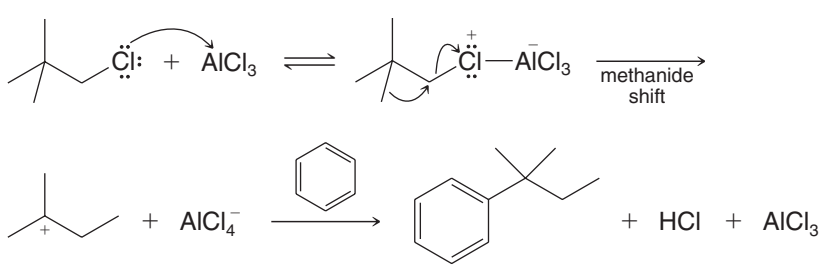
Isopropylbenzene (24%) **p-Diisopropylbenzene (14%)**

Polyacylations are not a problem in Friedel–Crafts acylations. The acyl group (RCO—) by itself is an electron-withdrawing group, and when it forms a complex with $AlCl_3$ in the last step of the reaction (Section 15.7), it is made even more electron withdrawing. This strongly inhibits further substitution and makes monoacylation easy.

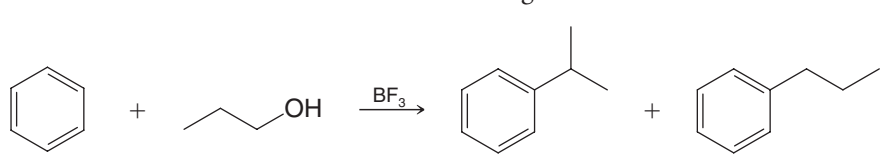
SOLVED PROBLEM 15.2

When benzene reacts with 1-chloro-2,2-dimethylpropane (neopentyl chloride) in the presence of aluminum chloride, the major product is 2-methyl-2-phenylbutane, not 2,2-dimethyl-1-phenylpropane (neopentylbenzene). Explain this result.

STRATEGY AND ANSWER: The carbocation formed by direct reaction of $AlCl_3$ with 1-chloro-2,2-dimethylpropane would be a primary carbocation; however, it rearranges to the more stable tertiary carbocation before it can react with the benzene ring.



PRACTICE PROBLEM 15.4 Provide a mechanism that accounts for the following result.

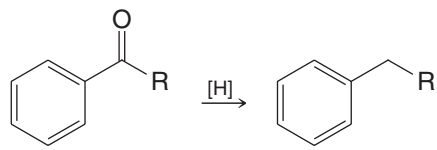


15.9 SYNTHETIC APPLICATIONS OF FRIEDEL–CRAFTS ACYLATIONS: THE CLEMMENSEN AND WOLFF–KISHNER REDUCTIONS

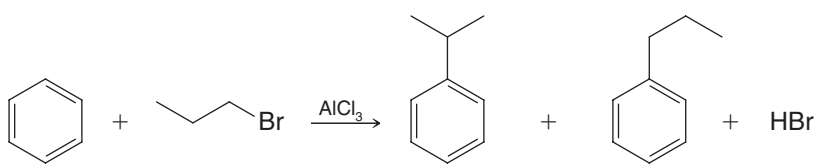
- Rearrangements of the carbon chain do not occur in Friedel–Crafts acylations.

The acylium ion, because it is stabilized by resonance, is more stable than most other carbocations. Thus, there is no driving force for a rearrangement. Because rearrangements do not occur, Friedel–Crafts acylations followed by reduction of the carbonyl group to a CH_2 group often give us much better routes to unbranched alkylbenzenes than do Friedel–Crafts alkylations.

- The carbonyl group of an aryl ketone can be reduced to a CH_2 group.

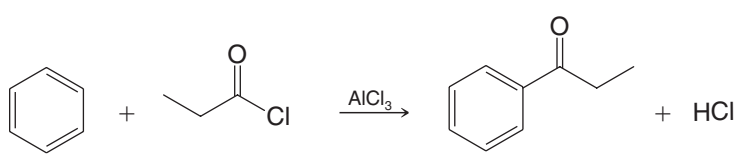


As an example, let us consider the problem of synthesizing propylbenzene. If we attempt this synthesis through a Friedel–Crafts alkylation, a rearrangement occurs and the major product is isopropylbenzene (see also Practice Problem 15.4):



Isopropylbenzene (major product) **Propylbenzene (minor product)**

By contrast, the Friedel–Crafts acylation of benzene with propanoyl chloride produces a ketone with an unrearranged carbon chain in excellent yield:



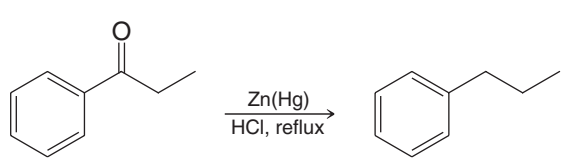
Propanoyl chloride **Ethyl phenyl ketone (90%)**

This ketone can then be reduced to propylbenzene by several methods.

15.9A The Clemmensen Reduction

One general method for reducing a ketone to a methylene group—called the **Clemmensen reduction**—consists of refluxing the ketone with hydrochloric acid containing amalgamated zinc. [*Caution*: As we shall discuss later (Section 20.4B), zinc and hydrochloric acid will also reduce nitro groups to amino groups.]

A Clemmensen Reduction

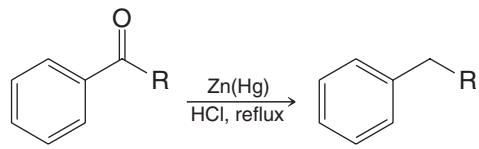


Ethyl phenyl ketone **Propylbenzene (80%)**

Helpful Hint

Friedel–Crafts acylation followed by ketone reduction is the synthetic equivalent of Friedel–Crafts alkylation.

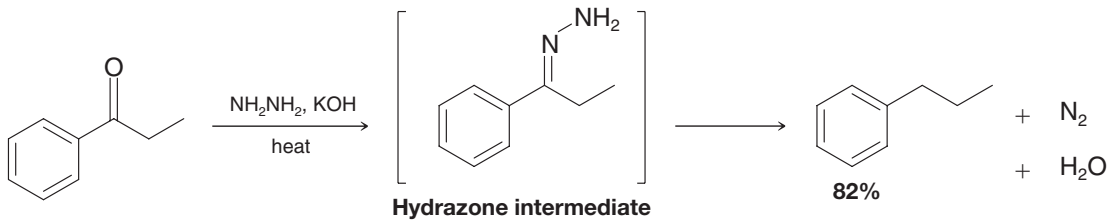
In general,



15.9B The Wolff–Kishner Reduction

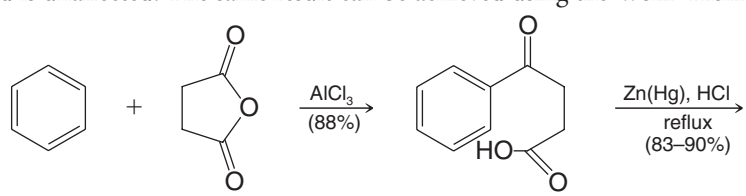
Another method for reducing a ketone to a methylene group is the Wolff–Kishner reduction, which involves heating the ketone with hydrazine and base. The Wolff–Kishner reduction complements the Clemmensen reduction in that it is conducted under basic conditions, whereas the Clemmensen reduction involves acidic conditions. The Wolff–Kishner reduction proceeds via a hydrazone intermediate (Section 16.8B) that is not isolated during the reaction. Ethyl phenyl ketone can be reduced to propylbenzene by the Wolff–Kishner reduction as follows, for example.

A Wolff–Kishner Reduction

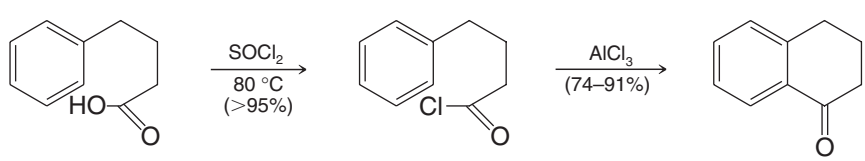


Hydrazone intermediate (see Section 16.8B)

When cyclic anhydrides are used as one component, the Friedel–Crafts acylation provides a means of adding a new ring to an aromatic compound. One illustration is shown here. Note that only the ketone is reduced in the Clemmensen reduction step. The carboxylic acid is unaffected. The same result can be achieved using the Wolff–Kishner reduction.



Benzene (excess) **Succinic anhydride** **3-Benzoylpropanoic acid**

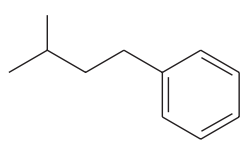


4-Phenylbutanoic acid **4-Phenylbutanoyl chloride** **α-Tetralone**

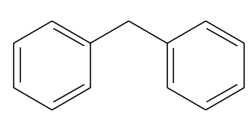
PRACTICE PROBLEM 15.5 Starting with benzene and the appropriate acyl chloride or acid anhydride, outline a synthesis of each of the following:

(a) Butylbenzene

(b)

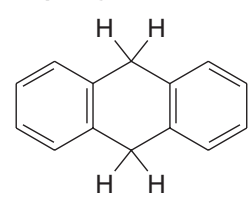


(c)



Diphenylmethane

(d)



9,10-Dihydroanthracene

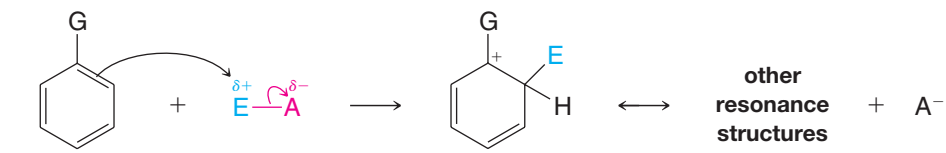
15.10 SUBSTITUENTS CAN AFFECT BOTH THE REACTIVITY OF THE RING AND THE ORIENTATION OF THE INCOMING GROUP

A **substituent group** already present on a benzene ring can affect both the **reactivity** of the ring toward electrophilic substitution and the **orientation** that the incoming group takes on the ring.

- A substituent can make the ring **more reactive** than benzene (i.e., it can make the compound react faster than benzene reacts). Such a group is called an **activating group**.
- A substituent can make the ring **less reactive** than benzene (i.e., it can make the compound react more slowly than benzene reacts). Such groups are called **deactivating groups**.

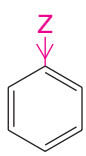
15.10A How Do Substituents Affect Reactivity?

Recall from Fig. 15.3 and Section 15.2 that the slow step in electrophilic aromatic substitution, the step that determines the overall rate of reaction, is the first step. In this step an electron-seeking reagent reacts by accepting an electron pair from the benzene ring.



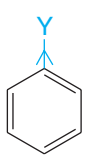
A substituted benzene | **Electrophilic reagent** | **Arenium ion**

If a substituent that is already present on the ring makes the ring more electron rich by donating electrons to it, then the ring will be more nucleophilic, more reactive toward the electrophile, and the reaction will take place faster.



If Z donates electrons the ring is more electron rich and it reacts faster with an electrophile.

On the other hand, if the substituent on the ring withdraws electrons, the ring will be electron poor and an electrophile will react with the ring more slowly.

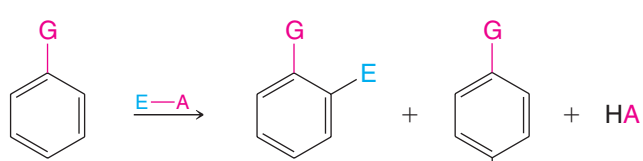


If Y withdraws electrons the ring is electron poor and it reacts more slowly with an electrophile.

15.10B Ortho–Para-Directing Groups and Meta-Directing Groups

A substituent on the ring can also affect the **orientation** that the incoming group takes when it replaces a hydrogen atom on the ring. Substituents fall into two general classes:

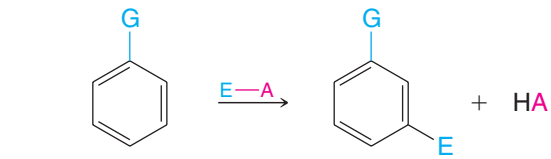
- **Ortho–para directors** predominantly direct the incoming group to a position ortho or para to itself.



G is an ortho–para director.

Ortho product | **Para product**

- **Meta directors** predominantly direct the incoming group to a position meta to itself.

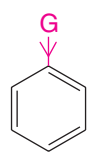


G is a meta director. **Meta product**

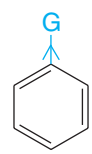
15.10C Electron-Donating and Electron-Withdrawing Substituents

Whether a substituent is an activating group or a deactivating group, and whether it is an ortho–para director or a meta director, depends largely on whether the substituent donates electrons to the ring or whether it withdraws electrons.

- All electron-donating groups are activating groups and all are ortho–para directors.
- With the exception of halogen substituents, all electron-withdrawing groups are deactivating groups and all are meta directors.
- Halogen substituents are weakly deactivating groups and are ortho–para directors.



If G donates electrons the ring is activated; it reacts faster, and at an ortho or para position.



If G withdraws electrons the ring is deactivated; it reacts more slowly, and at a meta position (except when G is a halogen).

15.10D Groups: Ortho–Para Directors

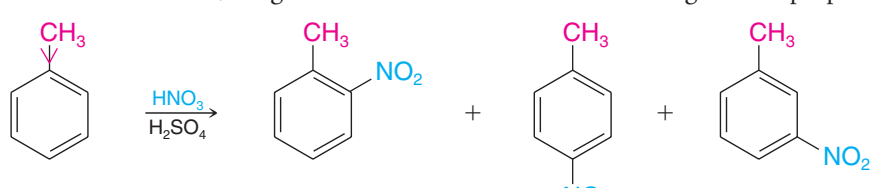
- Alkyl substituents are electron-donating groups and they are **activating groups**. They are also **ortho–para directors**.

Toluene, for example, reacts considerably faster than benzene in all electrophilic substitutions:

Toluene is more reactive than benzene toward electrophilic substitution.

We observe the greater reactivity of toluene in several ways. We find, for example, that with toluene, milder conditions—lower temperatures and lower concentrations of the electrophile—can be used in electrophilic substitutions than with benzene. We also find that under the same conditions toluene reacts faster than benzene. In nitration, for example, toluene reacts 25 times as fast as benzene.

We find, moreover, that when toluene undergoes electrophilic substitution, most of the substitution takes place at its ortho and para positions. When we nitrate toluene with nitric and sulfuric acids, we get mononitrotoluenes in the following relative proportions:



***o*-Nitrotoluene (59%)** ***p*-Nitrotoluene (37%)** ***m*-Nitrotoluene (4%)**

Of the mononitrotoluenes obtained from the reaction, 96% (59% + 37%) have the nitro group in an ortho or para position. Only 4% have the nitro group in a meta position.

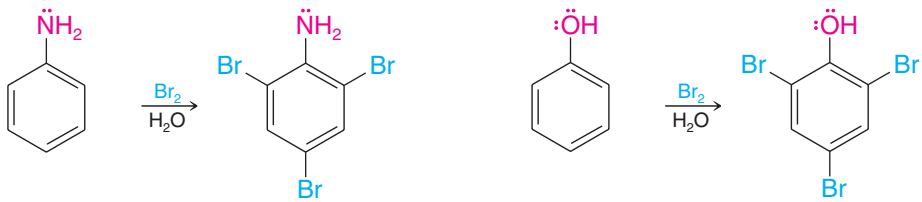
PRACTICE PROBLEM 15.6

Explain how the percentages just given show that the methyl group exerts an ortho–para directive effect by considering the percentages that would be obtained if the methyl group had no effect on the orientation of the incoming electrophile.

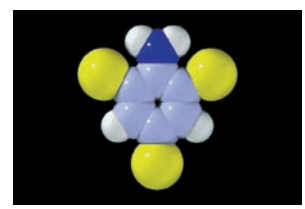
Predominant substitution of toluene at the ortho and para positions is not restricted to nitration reactions. The same behavior is observed in halogenation, sulfonation, and so forth.

- Groups that have an unshared electron pair on the atom attached to the aromatic ring, such as amino, hydroxyl, alkoxyl, and amides or esters with the oxygen or nitrogen directly bonded to the ring, are powerful activating groups and are strong ortho–para directors.

Phenol and aniline react with bromine in water (no catalyst is required) at room temperature to produce compounds in which both of the ortho positions and the para position become substituted.



2,4,6-Tribromoaniline (~100%) **2,4,6-Tribromophenol (~100%)**

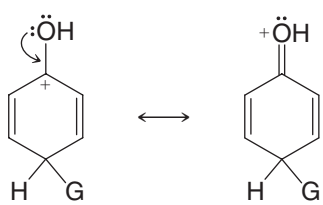


2,4,6-Tribromoaniline

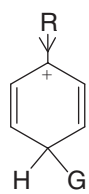
- In general, substituent groups with unshared electron pairs on the atom adjacent to the benzene ring (e.g., hydroxyl, amino) are stronger activating groups than groups without unshared electron pairs (i.e., alkyl groups).
- Contribution of electron density to the benzene ring through resonance is generally stronger than through an inductive effect.

As a corollary, even though amides and esters have an unshared electron pair on the atom adjacent to the ring, their activating effect is diminished because the carbonyl group provides a resonance structure where electron density is directed away from the benzene ring. This makes amides and esters less activating than groups where the only resonance possibilities involve donation of electron density toward the benzene ring.

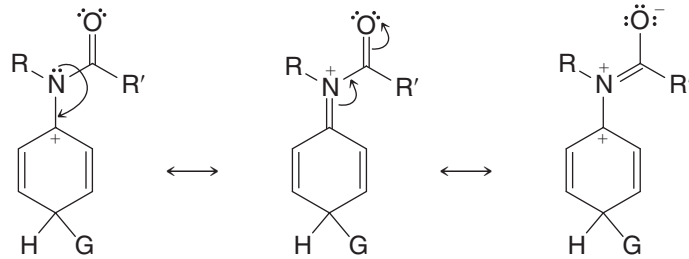
Examples of stabilization of an arenium ion by resonance and inductive effects



Electron donation through resonance



Electron donation through the inductive effect

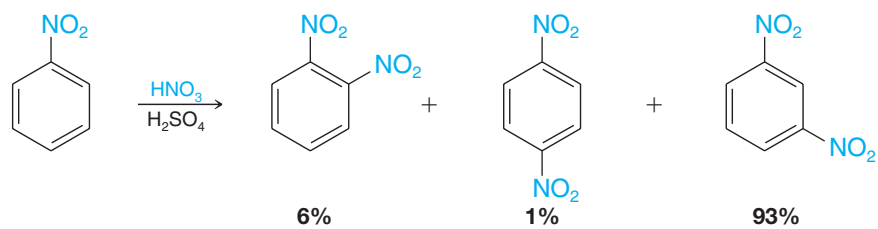


Electron donation to the ring by resonance is reduced when there is an alternative resonance pathway away from the ring.

15.10E Deactivating Groups: Meta Directors

- The nitro group is a very strong **deactivating group** and, because of the combined electronegativities of the nitrogen and oxygen atoms, it is a powerful electron-withdrawing group.

Nitrobenzene undergoes nitration at a rate only 10^{-4} times that of benzene. The nitro group is a **meta director**. When nitrobenzene is nitrated with nitric and sulfuric acids, 93% of the substitution occurs at the meta position:



- The carboxyl group (—CO_2H), the sulfonic acid group (—SO_3H), and the trifluoromethyl group (—CF_3) are also deactivating groups; they are also meta directors.

15.10F Halo Substituents: Deactivating Ortho–Para Directors

- The chloro, bromo, and iodo groups are ortho–para directors. However, even though they contain unshared electron pairs, they are deactivating toward electrophilic aromatic substitution because of the electronegative effect of the halogens.

Chlorobenzene and bromobenzene, for example, undergo nitration at a rate approximately 30 times slower than benzene. The relative percentages of monosubstituted products that are obtained when chlorobenzene is chlorinated, brominated, nitrated, or sulfonated are shown in Table 15.1.

TABLE 15.1 ELECTROPHILIC SUBSTITUTIONS OF CHLOROBENZENE

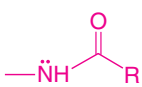
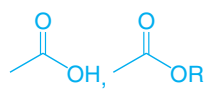
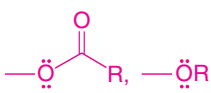
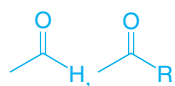
Reaction	Ortho Product (%)	Para Product (%)	Total Ortho and Para (%)	Meta Product (%)
Chlorination	39	55	94	6
Bromination	11	87	98	2
Nitration	30	70	100	
Sulfonation		100	100	

Similar results are obtained from electrophilic substitutions of bromobenzene.

15.10G Classification of Substituents

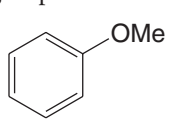
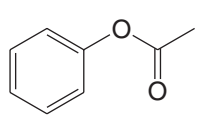
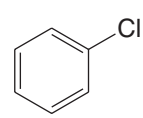
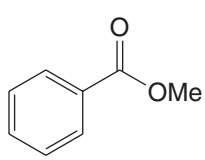
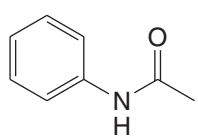
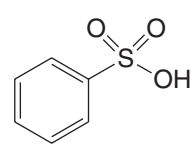
A summary of the effects of some substituents on reactivity and orientation is provided in Table 15.2.

TABLE 15.2 EFFECT OF SUBSTITUENTS ON ELECTROPHILIC AROMATIC SUBSTITUTION

Ortho–Para Directors	Meta Directors
Strongly Activating	**Moderately Deactivating**
—$\ddot{N}H_2$, —$\ddot{N}HR$, —$\ddot{N}R_2$	—C≡N
—$\ddot{O}H$, —$\ddot{O}:^-$	—SO_3H
Moderately Activating	
	
	
Weakly Activating	**Strongly Deactivating**
—R (alkyl)	—NO_2
—C_6H_5 (phenyl)	—NR_3^+
Weakly Deactivating	—CF_3, CCl_3
—$\ddot{F}:$, —$\ddot{C}l:$, —$\ddot{B}r:$, —$\ddot{I}:$	

SOLVED PROBLEM 15.3

Label each of the following aromatic rings as activated or deactivated based on the substituent attached, and state whether the group is an ortho–para or meta director.

(a) 
(c) 
(e) 
(b) 
(d) 
(f) 

STRATEGY AND ANSWER: If a substituent donates electron density it will activate the ring and cause ortho and para substitution. If a substituent withdraws electron density it will deactivate the ring and cause meta substitution (except for halogens, which are electron withdrawing but cause ortho–para substitution). **(a)** Activated; an ether is an ortho–para director; **(b)** deactivated; the ester carbonyl is a meta director; **(c)** activated; the single-bonded oxygen of the ester is directly bonded to the ring, and therefore it is an ortho–para director; **(d)** activated; the amide nitrogen is an ortho–para director; **(e)** deactivated; however, the halogen is ortho–para director through resonance; **(f)** deactivated; the sulfonate group is a meta director.

PRACTICE PROBLEM 15.7

Predict the major products formed when:

(a) Toluene is sulfonated. **(c)** Nitrobenzene is brominated.

(b) Benzoic acid is nitrated. **(d)** Isopropylbenzene reacts with acetyl chloride and $AlCl_3$.

If the major products would be a mixture of ortho and para isomers, you should so state.

15.11 HOW SUBSTITUENTS AFFECT ELECTROPHILIC AROMATIC SUBSTITUTION: A CLOSER LOOK

15.11A Reactivity: The Effect of Electron-Releasing and Electron-Withdrawing Groups

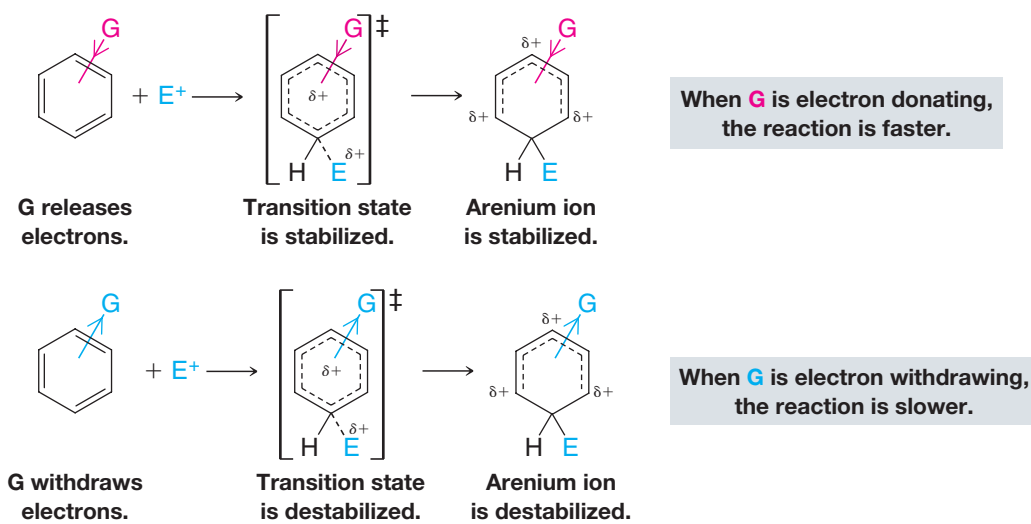
We can account for relative reaction rates by examining the transition state for the rate-determining steps.

- Any factor that reduces the energy of the transition state relative to that of the reactants lowers the free energy of activation and increases the relative rate of the reaction.
- Any factor that raises the energy of the transition state relative to that of the reactants increases the free energy of activation and decreases the relative rate of the reaction.

The rate-determining step in electrophilic substitutions of substituted benzenes is the step that results in the formation of the arenium ion. We can write the formula for a substituted benzene in a generalized way if we use the letter G to represent any ring substituent, including hydrogen.

When we examine this step for a large number of reactions, we find that the relative rates of the reactions depend on whether G **releases** or **withdraws** electrons.

- If G is an electron-releasing group (relative to hydrogen), the reaction occurs faster than the corresponding reaction of benzene.
- If G is an electron-withdrawing group, the reaction is slower than that of benzene:



It appears, then, that the substituent (G) must affect the stability of the transition state relative to that of the reactants.

- Electron-releasing groups make the transition state more stable, whereas electron-withdrawing groups make it less stable.

That this is so is entirely reasonable, because the transition state resembles the arenium ion, and the arenium ion is a delocalized *carbocation*.

This effect illustrates another application of the Hammond–Leffler postulate (Section 6.13A). The arenium ion is a high-energy intermediate, and the step that leads to it is a *highly endothermic step*. Thus, according to the Hammond–Leffler postulate, there should be a strong resemblance between the arenium ion itself and the transition state leading to it.

Since the arenium ion is positively charged, we would expect an electron-releasing group to stabilize the arenium ion *and the transition state leading to it*, for the transition state is a developing delocalized carbocation. We can make the same kind of arguments about the effect of electron-withdrawing groups. An electron-withdrawing group should

make the arenium ion *less stable*, and in a corresponding way it should make the transition state leading to the arenium ion *less stable*.

Figure 15.4 shows how the electron-withdrawing and electron-releasing abilities of substituents affect the relative free energies of activation of electrophilic aromatic substitution reactions.

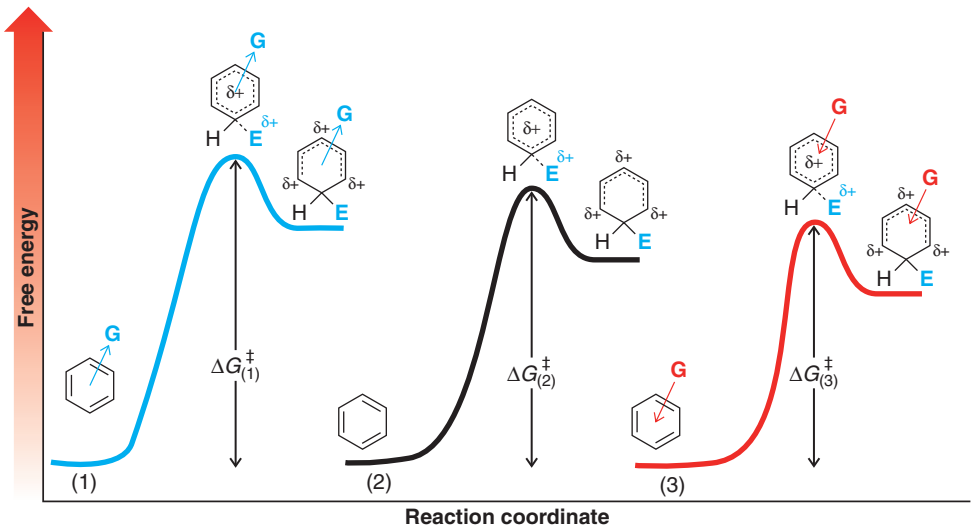


FIGURE 15.4 A comparison of free-energy profiles for arenium ion formation in a ring with an electron-withdrawing substituent (≻ G), no substituent, and an electron-donating substituent (≺ G). In (1) (blue energy profile), the electron-withdrawing group G raises the transition state energy. The energy of activation barrier is the highest, and therefore the reaction is the slowest. Reaction (2), with no substituent, serves as a reference for comparison. In (3) (red energy profile), an electron-donating group G stabilizes the transition state. The energy of activation barrier is the lowest, and therefore the reaction is the fastest.

Calculated electrostatic potential maps for two arenium ions comparing the charge-stabilizing effect of an electron-donating methyl group with the charge-destabilizing effect of an electron-withdrawing trifluoromethyl group are shown in Fig. 15.5. The arenium ion at the left (Fig. 15.5*a*) is that from electrophilic addition of bromine to methylbenzene (toluene) at the para position. The arenium ion at the right (Fig. 15.5*b*) is that from electrophilic addition of bromine to trifluoromethylbenzene at the meta position. Notice that the atoms of the ring in Fig. 15.5*a* have much less blue color associated with them, showing that they are much less positive and that the ring is stabilized.

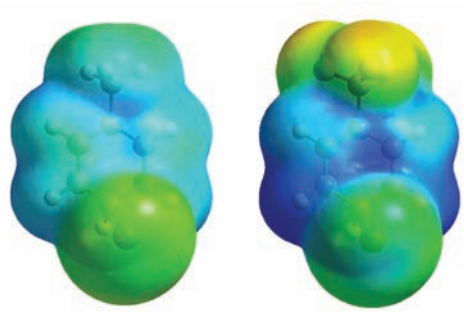
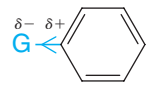


FIGURE 15.5 Calculated electrostatic potential maps for the arenium ions from electrophilic addition of bromine to (*a*) methylbenzene (toluene) and (*b*) trifluoromethylbenzene. The positive charge in the arenium ion ring of methylbenzene (*a*) is delocalized by the electron-releasing ability of the methyl group, whereas the positive charge in the arenium ion of trifluoromethylbenzene (*b*) is enhanced by the electron-withdrawing effect of the trifluoromethyl group. (The electrostatic potential maps for the two structures use the same color scale with respect to potential so that they can be directly compared.)

15.11B Inductive and Resonance Effects: Theory of Orientation

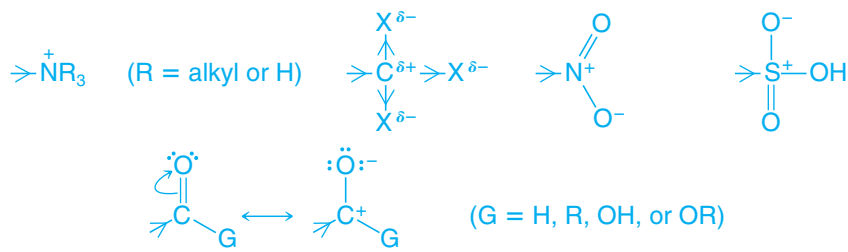
We can account for the electron-withdrawing and electron-releasing properties of groups on the basis of two factors: *inductive effects* and *resonance effects*. We shall also see that these two factors determine orientation in aromatic substitution reactions.

Inductive Effects The **inductive effect** of a substituent G arises from the electrostatic interaction of the polarized bond to G with the developing positive charge in the ring as it is attacked by an electrophile. If, for example, G is a more electronegative atom (or group) than carbon, then the ring will be at the positive end of the dipole:



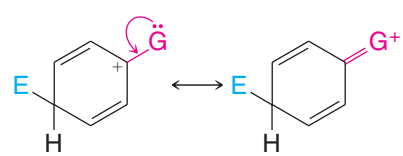
(e.g., G = F, Cl, or Br)

Attack by an electrophile will be slowed because this will lead to an additional full positive charge on the ring. The halogens are all more electronegative than carbon and exert an electron-withdrawing inductive effect. Other groups have an electron-withdrawing inductive effect because the atom directly attached to the ring bears a full or partial positive charge. Examples are the following:



Electron-withdrawing groups with a full or partial charge on the atom attached to the ring

Resonance Effects The **resonance** effect of a substituent G refers to the possibility that the presence of G may increase or decrease the resonance stabilization of the intermediate arenium ion. The G substituent may, for example, cause one of the three contributors to the resonance hybrid for the arenium ion to be better or worse than the case when G is hydrogen. Moreover, when G is an atom bearing one or more nonbonding electron pairs, it may lend extra stability to the arenium ion by providing a *fourth* resonance contributor in which the positive charge resides on G:



This electron-donating resonance effect applies with decreasing strength in the following order:

Most electron donating $-\ddot{N}H_2$, $-\ddot{N}R_2$ > $-\ddot{O}H$, $-\ddot{O}R$ > $-\ddot{X}:$ **Least electron donating**

This order also indicates the relative activating ability of these groups.

- Amino groups are highly activating, hydroxyl and alkoxyl groups are somewhat less activating, and halogen substituents are weakly deactivating.

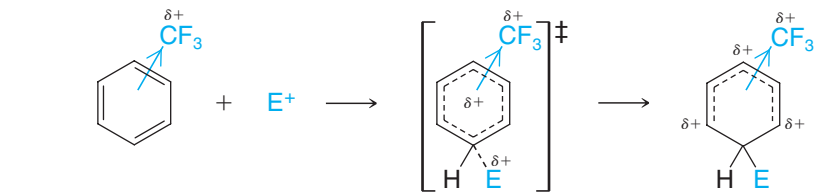
When X = F, this order can be related to the electronegativity of the atoms with the nonbonding pair. The more electronegative the atom is, the less able it is to accept the positive charge (fluorine is the most electronegative, nitrogen the least). When X = Cl, Br, or I, the relatively poor electron-donating ability of the halogens by resonance is understandable on a different basis. These atoms (Cl, Br, and I) are all larger than carbon, and, therefore, the orbitals that contain the nonbonding pairs are further from the nucleus and do not overlap well with the 2*p* orbital of carbon. this is a general phenomenon: resonance effects are not transmitted well between atoms of different rows in the periodic table.

15.11C Meta-Directing Groups

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

As a typical example let us consider the trifluoromethyl group. The trifluoromethyl group, because of the three highly electronegative fluorine atoms, is strongly electron withdrawing. It is a strong deactivating group and a powerful meta director in electrophilic aromatic substitution reactions. We can account for both of these characteristics of the trifluoromethyl group in the following way.

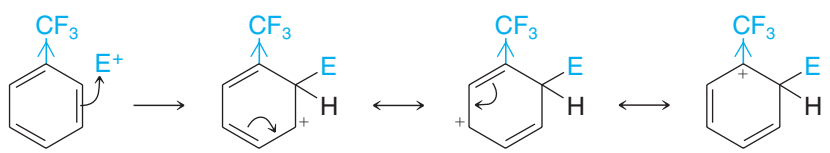
The trifluoromethyl group affects the rate of reaction by causing the transition state leading to the arenium ion to be highly unstable. It does this by withdrawing electrons from the developing carbocation, thus increasing the positive charge on the ring:



Trifluoromethylbenzene **Transition state** **Arenium ion**

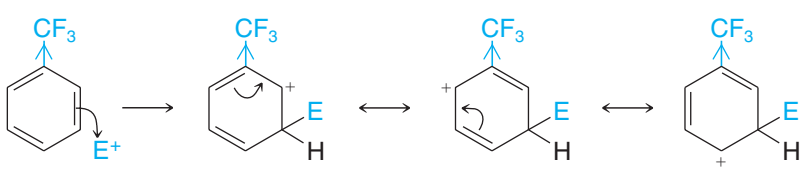
We can understand how the trifluoromethyl group affects *orientation* in electrophilic aromatic substitution if we examine the resonance structures for the arenium ion that would be formed when an electrophile attacks the ortho, meta, and para positions of trifluoromethylbenzene.

Ortho Attack

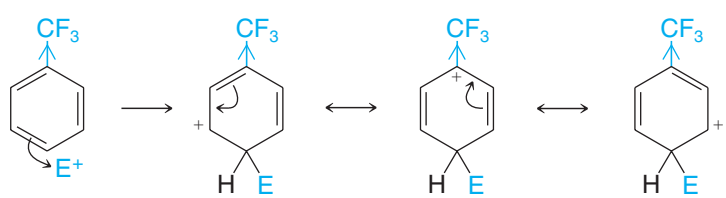


Highly unstable contributor

Meta Attack



Para Attack

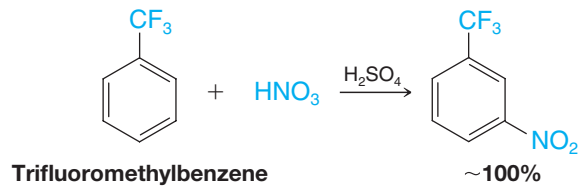


Highly unstable contributor

- The arenium ion arising from ortho and para attack each has *one contributing structure that is highly unstable relative to all the others because the positive charge is located on the ring carbon that bears the electron-withdrawing group.*

- The arenium ion arising from meta attack has *no* such highly unstable resonance structure.
- By the usual reasoning we would also expect the transition state leading to the meta-substituted arenium ion to be the least unstable and, therefore, that meta attack would be favored.

This is exactly what we find experimentally. The trifluoromethyl group is a powerful meta director:



Trifluoromethylbenzene **~100%**

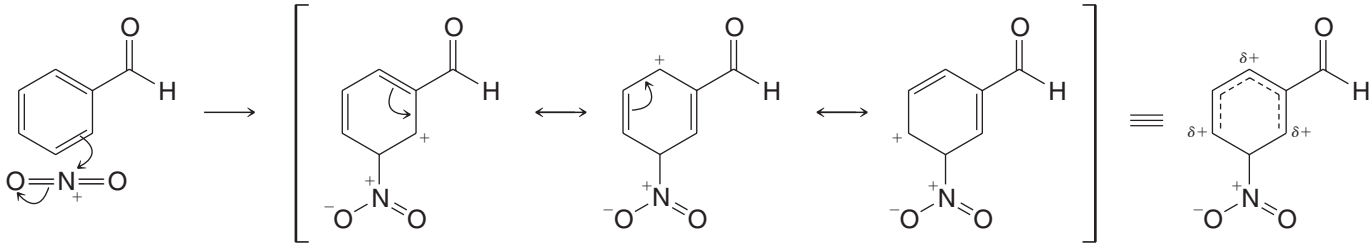
Bear in mind, however, that meta substitution is favored only in the sense that *it is the least unfavorable of three unfavorable pathways*. The free energy of activation for substitution at the meta position of trifluoromethylbenzene is less than that for attack at an ortho or para position, but it is still far greater than that for an attack on benzene. Substitution occurs at the meta position of trifluoromethylbenzene faster than substitution takes place at the ortho and para positions, but it occurs much more slowly than it does with benzene.

- The nitro group, the carboxyl group, and other meta-directing groups (see Table 15.2) are all powerful electron-withdrawing groups and act in a similar way.

SOLVED PROBLEM 15.4

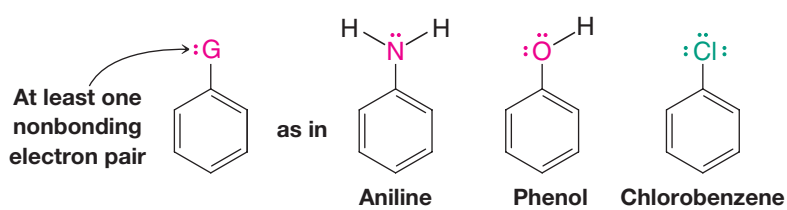
Write contributing resonance structures and the resonance hybrid for the arenium ion formed when benzaldehyde undergoes nitration at the meta position.

STRATEGY AND ANSWER:



15.11D Ortho–Para-Directing Groups

Except for the alkyl and phenyl substituents, all of the ortho–para-directing groups in Table 15.2 are of the following general type:



Aniline **Phenol** **Chlorobenzene**

This structural feature—an unshared electron pair on the atom adjacent to the ring—determines the orientation and influences reactivity in electrophilic substitution reactions.

The *directive effect* of groups with an unshared pair is predominantly caused by an electron-releasing resonance effect. The resonance effect, moreover, operates primarily in the arenium ion and, consequently, in the transition state leading to it.

Except for the halogens, the primary effect of these groups on relative reactivity of the benzene ring is also caused by an electron-releasing resonance effect. And, again, this effect operates primarily in the transition state leading to the arenium ion.

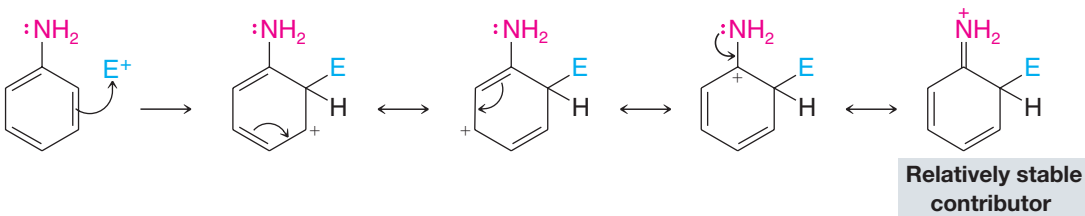
In order to understand these resonance effects, let us begin by recalling the effect of the amino group on electrophilic aromatic substitution reactions. The amino group is not only a powerful activating group, it is also a powerful ortho–para director. We saw earlier (Section 15.10D) that aniline reacts with bromine in aqueous solution at room temperature and in the absence of a catalyst to yield a product in which both ortho positions and the para position are substituted.

The inductive effect of the amino group makes it slightly electron withdrawing. Nitrogen, as we know, is more electronegative than carbon. The difference between the electronegativities of nitrogen and carbon in aniline is not large, however, because the carbon of the benzene ring is sp^2 hybridized and so it is somewhat more electronegative than it would be if it were sp^3 hybridized.

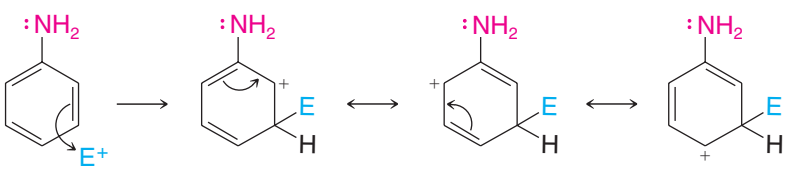
- The resonance effect of the amino group is far more important than its inductive effect in electrophilic aromatic substitution, and this resonance effect makes the amino group electron releasing.

We can understand this effect if we write the resonance structures for the arenium ions that would arise from ortho, meta, and para attack on aniline:

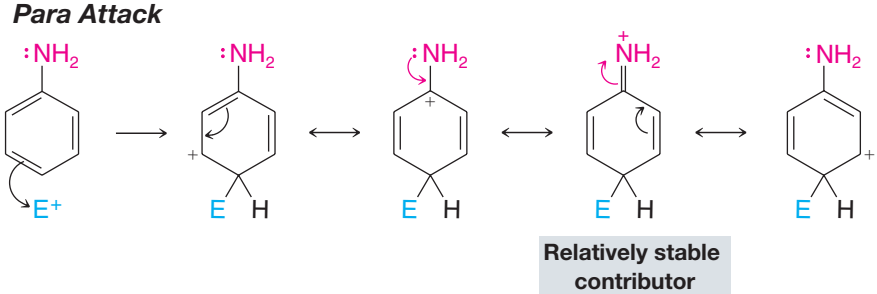
Ortho Attack



Meta Attack



Para Attack

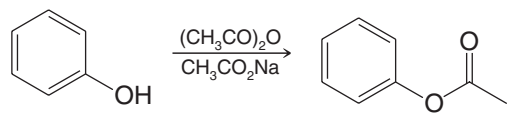


Four reasonable resonance structures can be written for the arenium ions resulting from ortho and para attack, whereas only three can be written for the arenium ion that results from meta attack. This observation, in itself, suggests that the ortho- and para-substituted arenium ions should be more stable. Of greater importance, however, are the relatively stable structures that contribute to the hybrid for the ortho- and para-substituted arenium ions. In these structures, nonbonding pairs of electrons from nitrogen form an additional covalent bond to the carbon of the ring. This extra bond—and the fact that every atom in each of these structures has a complete outer octet of electrons—makes these structures the most stable of all of the contributors. Because these structures are unusually stable,

they make a large—*and stabilizing*—contribution to the hybrid. This means, of course, that the ortho- and para-substituted arenium ions themselves are considerably more stable than the arenium ion that results from the meta attack. The transition states leading to the ortho- and para-substituted arenium ions occur at unusually low free energies. As a result, electrophiles react at the ortho and para positions very rapidly.

PRACTICE PROBLEM 15.8 Use resonance theory to explain why the hydroxyl group of phenol is an activating group and an ortho–para director. Illustrate your explanation by showing the arenium ions formed when phenol reacts with a Br^+ ion at the ortho, meta, and para positions.

PRACTICE PROBLEM 15.9 Phenol reacts with acetic anhydride in the presence of sodium acetate to produce the ester phenyl acetate:



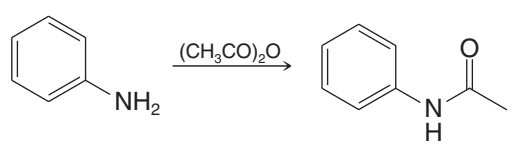
Phenol **Phenyl acetate**

The CH_3COO- group of phenyl acetate, like the $-OH$ group of phenol (Practice Problem 15.8), is an ortho–para director.

(a) What structural feature of the CH_3COO- group explains this?

(b) Phenyl acetate, although undergoing reaction at the ortho and para positions, is less reactive toward electrophilic aromatic substitution than phenol. Use resonance theory to explain why this is so.

(c) Aniline is often so highly reactive toward electrophilic substitution that undesirable reactions take place (see Section 15.14A). One way to avoid these undesirable reactions is to convert aniline to acetanilide (below) by treating aniline with acetyl chloride or acetic anhydride:



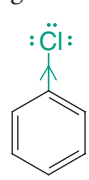
Aniline **Acetanilide**

What kind of directive effect would you expect the acetamido group (CH_3CONH-) to have?

(d) Explain why it is much less activating than the amino group, $-NH_2$.

The directive and reactivity effects of halo substituents may, at first, seem to be contradictory. *The halo groups are the only ortho–para directors* (in Table 15.2) *that are deactivating groups*. [Because of this behavior we have color coded halogen substituents green rather than red (electron donating) or blue (electron withdrawing).] All other deactivating groups are meta directors. We can readily account for the behavior of halo substituents, however, if we assume that their electron-withdrawing inductive effect influences *reactivity* and their electron-donating resonance effect governs *orientation*.

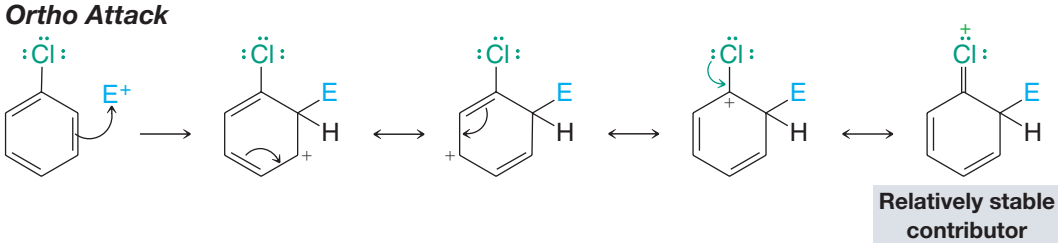
Let us apply these assumptions specifically to chlorobenzene. The chlorine atom is highly electronegative. Thus, we would expect a chlorine atom to withdraw electrons from the benzene ring and thereby deactivate it:



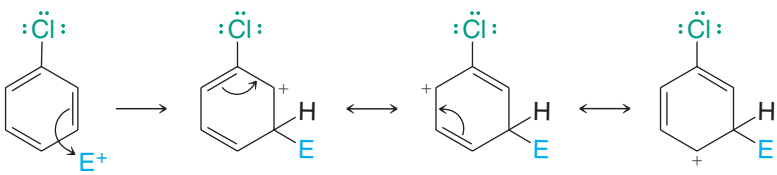
The inductive effect of the chlorine atom deactivates the ring.

On the other hand, when electrophilic attack does take place, the chlorine atom stabilizes the arenium ions resulting from ortho and para attack relative to that from meta attack. The chlorine atom does this in the same way as amino groups and hydroxyl groups do—***by donating an unshared pair of electrons***. These electrons give rise to relatively stable resonance structures contributing to the hybrids for the ortho- and para-substituted arenium ions.

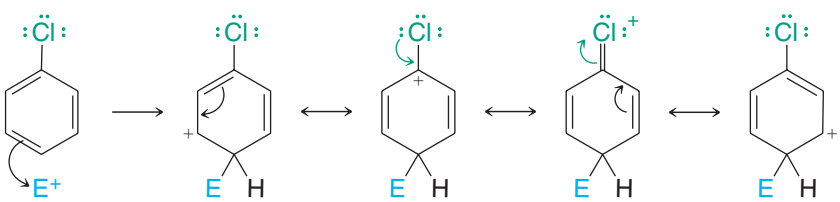
Ortho Attack



Meta Attack



Para Attack



What we have said about chlorobenzene is also true of bromobenzene.

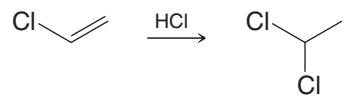
We can summarize the inductive and resonance effects of halo substituents in the following way.

- Through their electron-withdrawing inductive effect, halo groups make the ring more electron deficient than that of benzene. This causes the free energy of activation for any electrophilic aromatic substitution reaction to be greater than that for benzene, and, therefore, halo groups are deactivating.
- Through their electron-donating resonance effect, however, halo substituents cause the free energies of activation leading to ortho and para substitution to be lower than the free energy of activation leading to meta substitution. This makes halo substituents ortho–para directors.

You may have noticed an apparent contradiction between the rationale offered for the unusual effects of the halogens and that offered earlier for amino or hydroxyl groups. That is, oxygen is *more* electronegative than chlorine or bromine (and especially iodine). Yet the hydroxyl group is an activating group, whereas halogens are deactivating groups. An explanation for this can be obtained if we consider the relative stabilizing contributions made to the transition state leading to the arenium ion by resonance structures involving a group $-\ddot{G}(-\ddot{G} = -\ddot{N}H_2, -\ddot{O}-H, -\ddot{F}:, -\ddot{Cl}:, -\ddot{Br}:, -\ddot{I}:)$ that is directly attached to the benzene ring in which G donates an electron pair. If $-\ddot{G}$ is $-\ddot{O}H$, or $-\ddot{N}H_2$ these resonance structures arise because of the overlap of a $2p$ orbital of carbon with that of oxygen or nitrogen. Such overlap is favorable because the atoms are almost the same size. With chlorine, however, donation of an electron pair to the benzene ring

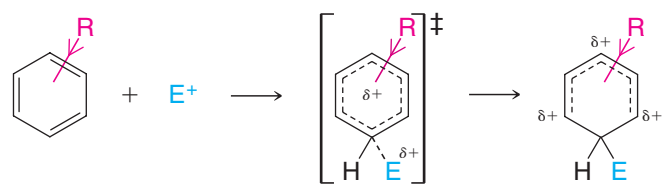
requires overlap of a carbon 2*p* orbital with a chlorine 3*p* orbital. Such overlap is less effective; the chlorine atom is much larger and its 3*p* orbital is much further from its nucleus. With bromine and iodine, overlap is even less effective. Justification for this explanation can be found in the observation that fluorobenzene (G = —F:) is the most reactive halobenzene in spite of the high electronegativity of fluorine and the fact that —F: is the most powerful ortho–para director of the halogens. With fluorine, donation of an electron pair arises from overlap of a 2*p* orbital of fluorine with a 2*p* orbital of carbon (as with —NH_2 and —OH). This overlap is effective because the orbitals of =C< and —F: are of the same relative size.

PRACTICE PROBLEM 15.10 Chloroethene adds hydrogen chloride more slowly than ethene, and the product is 1,1-dichloroethane. How can you explain this using resonance and inductive effects?



15.11E Ortho–Para Direction and Reactivity of Alkylbenzenes

Alkyl groups are better electron-releasing groups than hydrogen. Because of this, they can activate a benzene ring toward electrophilic substitution by stabilizing the transition state leading to the arenium ion:



Transition state is stabilized. **Arenium ion is stabilized.**

For an alkylbenzene the free energy of activation of the step leading to the arenium ion (just shown) is lower than that for benzene, and alkylbenzenes react faster.

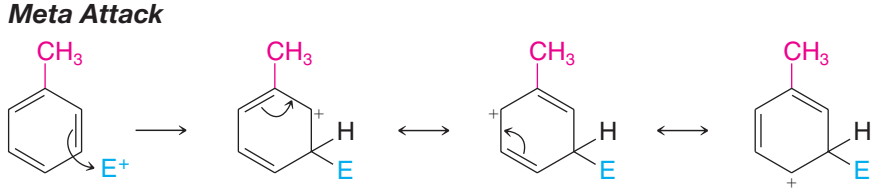
Alkyl groups are ortho–para directors. We can also account for this property of alkyl groups on the basis of their ability to release electrons—an effect that is particularly important when the alkyl group is attached directly to a carbon that bears a positive charge. (Recall the ability of alkyl groups to stabilize carbocations that we discussed in Section 6.11 and in Fig. 6.8.)

If, for example, we write resonance structures for the arenium ions formed when toluene undergoes electrophilic substitution, we get the results shown below:

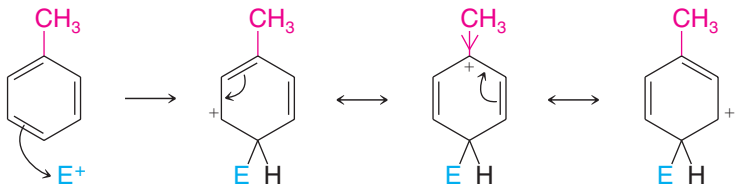
Ortho Attack

Relatively stable contributor

Meta Attack



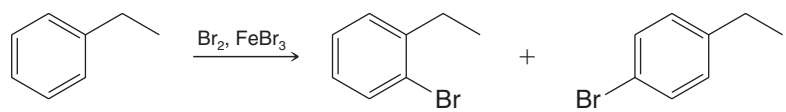
Para Attack



In ortho attack and para attack we find that we can write resonance structures in which the methyl group is directly attached to a positively charged carbon of the ring. These structures are more *stable* relative to any of the others because in them the stabilizing influence of the methyl group (by inductive electron release) is most effective. These structures, therefore, make a large (stabilizing) contribution to the overall hybrid for ortho- and para-substituted arenium ions. No such relatively stable structure contributes to the hybrid for the meta-substituted arenium ion, and as a result it is less stable than the ortho- or para-substituted arenium ions. Since the ortho- and para-substituted arenium ions are more stable, the transition states leading to them occur at lower energy and ortho and para substitutions take place most rapidly.

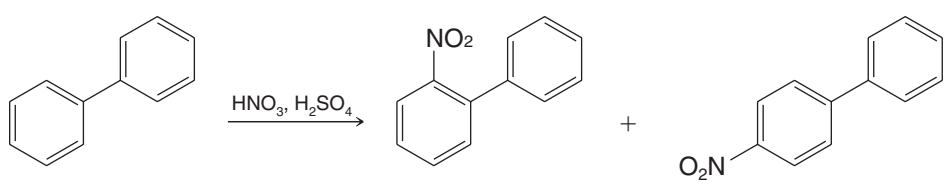
PRACTICE PROBLEM 15.11

Write resonance structures for the arenium ions formed when ethylbenzene reacts with a Br^+ ion (as formed from $Br_2/FeBr_3$) to produce the following ortho and para products.



PRACTICE PROBLEM 15.12

Provide a mechanism for the following reaction and explain why it occurs faster than nitration of benzene.

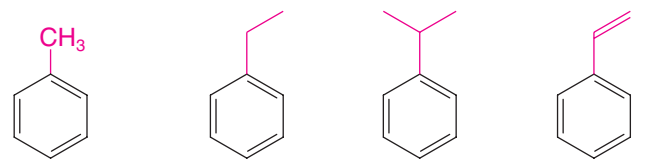


15.11F Summary of Substituent Effects on Orientation and Reactivity

With a theoretical understanding now in hand of **substituent effects** on orientation and reactivity, we refer you back to Table 15.2 for a summary of specific groups and their effects.

15.12 REACTIONS OF THE SIDE CHAIN OF ALKYLBENZENES

Hydrocarbons that consist of both aliphatic and aromatic groups are also known as **arenes**. Toluene, ethylbenzene, and isopropylbenzene are **alkylbenzenes**:

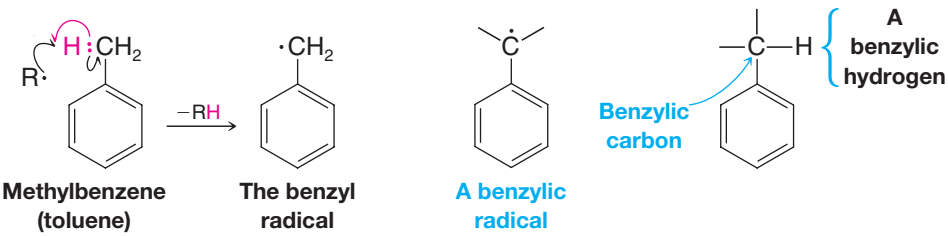


Methylbenzene (toluene) **Ethylbenzene** **Isopropylbenzene (cumene)** **Phenylethene (styrene or vinylbenzene)**

Phenylethene, usually called styrene, is an example of an **alkenylbenzene**. The aliphatic portion of these compounds is commonly called the **side chain**.

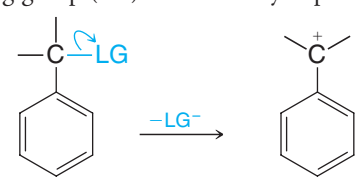
15.12A Benzylic Radicals and Cations

Hydrogen abstraction from the methyl group of methylbenzene (toluene) produces a radical called the **benzyl radical**:

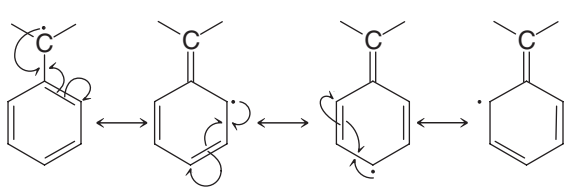


The name benzyl radical is used as a specific name for the radical produced in this reaction. The general name **benzylic radical** applies to all radicals that have an unpaired electron on the side-chain carbon atom that is directly attached to the benzene ring (Section 10.9). The hydrogen atoms of the carbon atom directly attached to the benzene ring are called **benzylic hydrogen atoms**. A group bonded at a benzylic position is called a **benzylic substituent**.

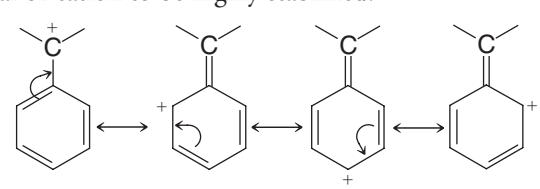
Departure of a leaving group (LG) from a benzylic position produces a **benzylic cation**:



Benzylic radicals and benzylic cations are *conjugated unsaturated systems* and *both are unusually stable*. They have approximately the same stabilities as allylic radicals (Section 10.8) and allylic cations (Section 13.4). This exceptional stability of benzylic radicals and cations can be explained by resonance theory. In the case of each entity, resonance structures can be written that place either the unpaired electron (in the case of the radical) or the positive charge (in the case of the cation) on an ortho or para carbon of the ring (see the following structures). Thus resonance delocalizes the unpaired electron or the charge, and this delocalization causes the radical or cation to be highly stabilized.



Benzylic radicals are stabilized by resonance.



Benzylic cations are stabilized by resonance.

Calculated structures for the benzyl radical and benzyl cation are presented in Fig. 15.6. These structures show the presence at their ortho and para carbons of unpaired electron density in the radical and positive charge in the cation, consistent with the resonance structures above.

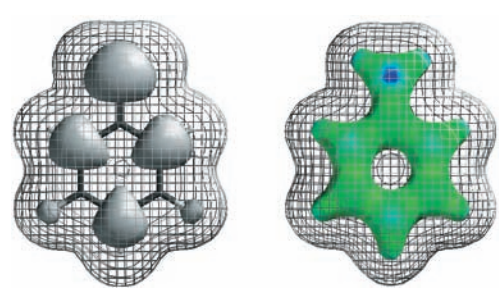
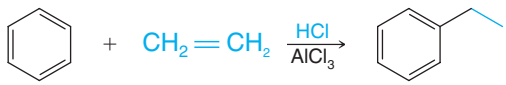


FIGURE 15.6 The gray lobes in the calculated structure for the benzyl radical (left) show the location of density from the unpaired electron. This model indicates that the unpaired electron resides primarily at the benzylic, ortho, and para carbons, which is consistent with the resonance model for the benzylic radical discussed earlier. The calculated electrostatic potential map for the bonding electrons in the benzyl cation (right) indicates that positive charge (blue regions) resides primarily at the benzylic, ortho, and para carbons, which is consistent with the resonance model for the benzylic cation. The van der Waals surface of both structures is represented by the wire mesh.

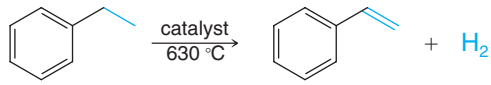
THE CHEMISTRY OF... Industrial Styrene Synthesis

Styrene is one of the most important industrial chemicals—more than 11 billion pounds is produced each year. The starting material for a major commercial synthesis of styrene is ethylbenzene, produced by Friedel–Crafts alkylation of benzene:



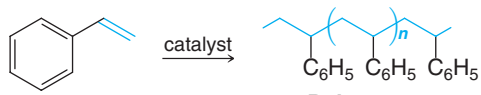
Ethylbenzene

Ethylbenzene is then dehydrogenated in the presence of a catalyst (zinc oxide or chromium oxide) to produce styrene.



Styrene
(90–92% yield)

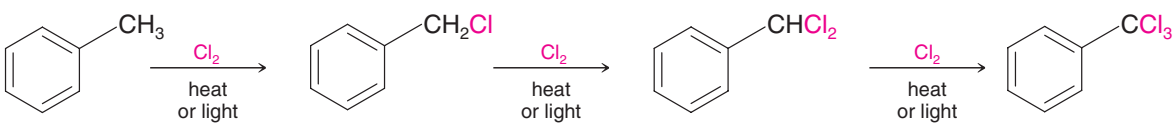
Most styrene is polymerized (Special Topic A) to the familiar plastic, polystyrene:



Polystyrene

15.12B Benzylic Halogenation of the Side Chain

We have already seen in this chapter that we can substitute bromine and chlorine for hydrogen atoms on the benzene ring of toluene and other alkylaromatic compounds using electrophilic aromatic substitution reactions. We can also substitute bromine and chlorine for hydrogen atoms on the **benzylic** carbons of alkyl side chains by radical reactions in the presence of heat, light, or a radical initiator like a peroxide, as we first saw in Chapter 10, (Section 10.9). This is made possible by the special stability of the benzylic radical intermediate (Section 15.12A). For example, benzylic chlorination of toluene takes place in the gas phase at 400–600 °C or in the presence of UV light, as shown here. Multiple substitutions occur with an excess of chlorine.

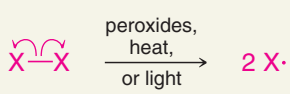


Benzyl chloride | **Dichloromethyl-benzene** | **Trichloromethyl-benzene**

A MECHANISM FOR THE REACTION — Benzylic Halogenation

Chain Initiation

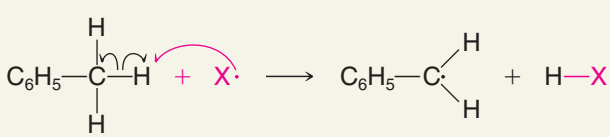
Step 1



Peroxides, heat, or light cause halogen molecules to cleave into redicals.

Chain Propagation

Step 2

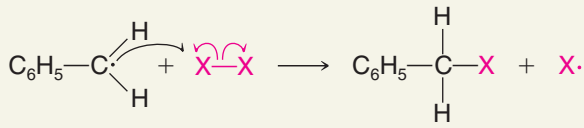


Benzyl radical

A halogen radical abstracts a benzylic hydrogen atom, forming a benzylic radical and a molecule of the hydrogen halide.

(mechanism continues on the next page)

Step 3

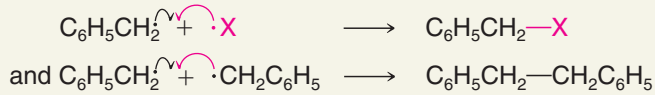


Benzyl radical **Benzyl halide**

The benzylic radical reacts with a halogen molecule to form the benzylic halide product and a halogen radical that propagates the chain.

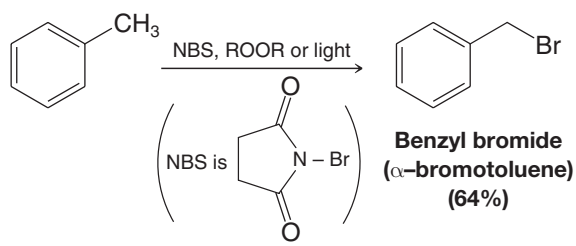
Chain Termination

Step 4



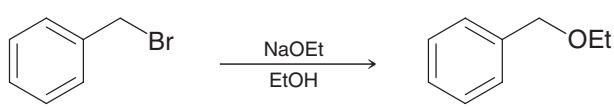
Various radical coupling reactions terminate the chain.

NBS (*N*-bromosuccinimide, Section 10.9) is often used in benzylic brominations because it provides a stoichiometric amount of bromine in low concentration.



Benzyl bromide (α–bromotoluene) (64%)

Benzylic halogenation provides a useful way to introduce a leaving group when a leaving group may be needed for subsequent nucleophilic substitution or elimination reactions. For example, if we wished to synthesize benzyl ethyl ether from toluene, benzyl bromide could be prepared from toluene as above, and then benzyl bromide could be allowed to react with sodium ethoxide as follows.

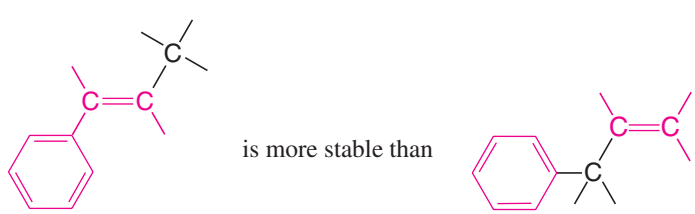


Benzyl ethyl ether

15.13 ALKENYLBENZENES

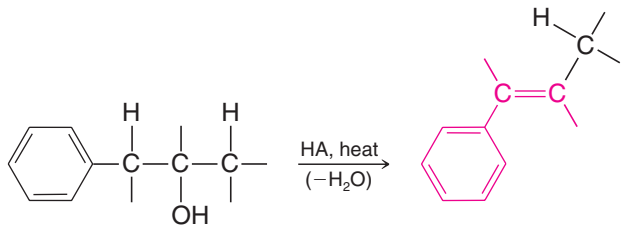
15.13A Stability of Conjugated Alkenylbenzenes

- Alkenylbenzenes that have their side-chain double bond conjugated with the benzene ring are more stable than those that do not:



Conjugated system **Nonconjugated system**

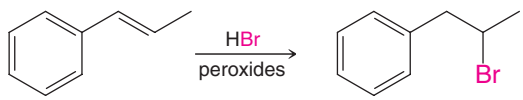
Part of the evidence for this comes from acid-catalyzed alcohol dehydrations, which are known to yield the most stable alkene (Section 7.8A). For example, dehydration of an alcohol such as the one that follows yields exclusively the conjugated system:



Because conjugation always lowers the energy of an unsaturated system by allowing the π electrons to be delocalized, this behavior is just what we would expect.

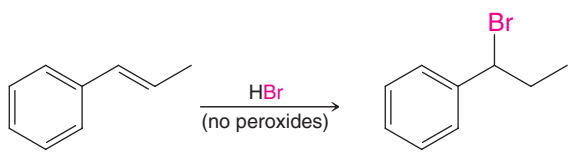
15.13B Additions to the Double Bond of Alkenylbenzenes

In the presence of peroxides, HBr adds to the double bond of 1-phenylpropene to give 2-bromo-1-phenylpropane as the major product:



1-Phenylpropene **2-Bromo-1-phenylpropane**

In the absence of peroxides, HBr adds in just the opposite way:



1-Phenylpropene **1-Bromo-1-phenylpropane**

The addition of hydrogen bromide to 1-phenylpropene proceeds through a benzylic radical in the presence of peroxides and through a benzylic cation in their absence (see Practice Problem 15.15 and Section 10.9).

PRACTICE PROBLEM 15.13

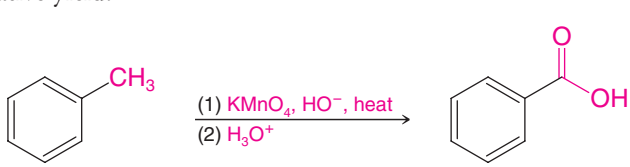
Write mechanisms for the reactions whereby HBr adds to 1-phenylpropene **(a)** in the presence of peroxides and **(b)** in the absence of peroxides. In each case account for the regiochemistry of the addition (i.e., explain why the major product is 2-bromo-1-phenylpropane when peroxides are present and why it is 1-bromo-1-phenylpropane when peroxides are absent).

PRACTICE PROBLEM 15.14

(a) What would you expect to be the major product when 1-phenylpropene reacts with HCl?
(b) What product would you expect when it is subjected to oxymercuration–demercuration?

15.13C Oxidation of the Side Chain

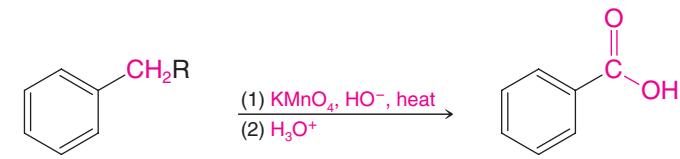
Strong oxidizing agents oxidize toluene to benzoic acid. The oxidation can be carried out by the action of hot alkaline potassium permanganate. This method gives benzoic acid in almost quantitative yield:



Benzoic acid
(~100%)

An important characteristic of side-chain oxidations is that oxidation takes place initially at the benzylic carbon.

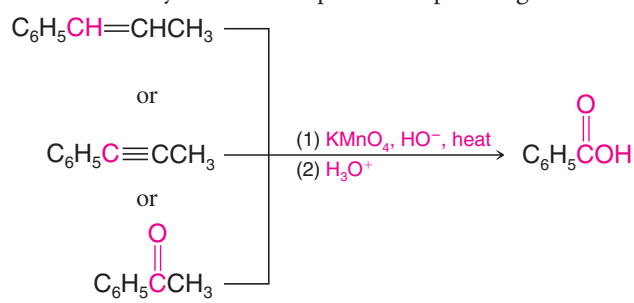
- Alkylbenzenes with alkyl groups longer than methyl are ultimately degraded to benzoic acids:



An alkylbenzene **Benzoic acid**

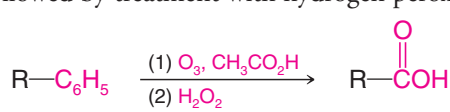
Side-chain oxidations are similar to benzylic halogenations, because in the first step the oxidizing agent abstracts a benzylic hydrogen. Once oxidation is begun at the benzylic carbon, it continues at that site. Ultimately, the oxidizing agent oxidizes the benzylic carbon to a carboxyl group, and, in the process, it cleaves off the remaining carbon atoms of the side chain. (*tert*-Butylbenzene is resistant to side-chain oxidation. Why?)

- Side-chain oxidation is not restricted to alkyl groups. Alkenyl, alkynyl, and acyl groups are also oxidized by hot alkaline potassium permanganate.



15.13D Oxidation of the Benzene Ring

The benzene ring carbon where an alkyl group is bonded can be converted to a carboxyl group by ozonolysis, followed by treatment with hydrogen peroxide.

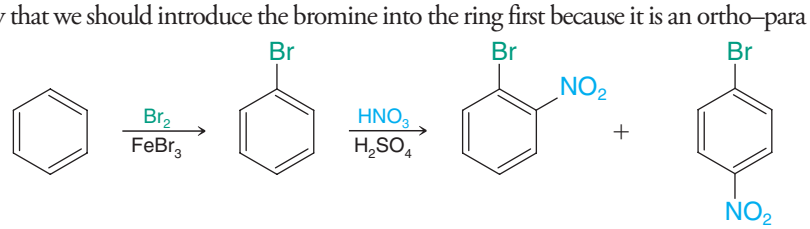


15.14 SYNTHETIC APPLICATIONS

The substitution reactions of aromatic rings and the reactions of the side chains of alkyl- and alkenylbenzenes, when taken together, offer us a powerful set of reactions for organic synthesis. By using these reactions skillfully, we shall be able to synthesize a large number of benzene derivatives.

- Part of the skill in planning a synthesis is deciding in what order to carry out the reactions.

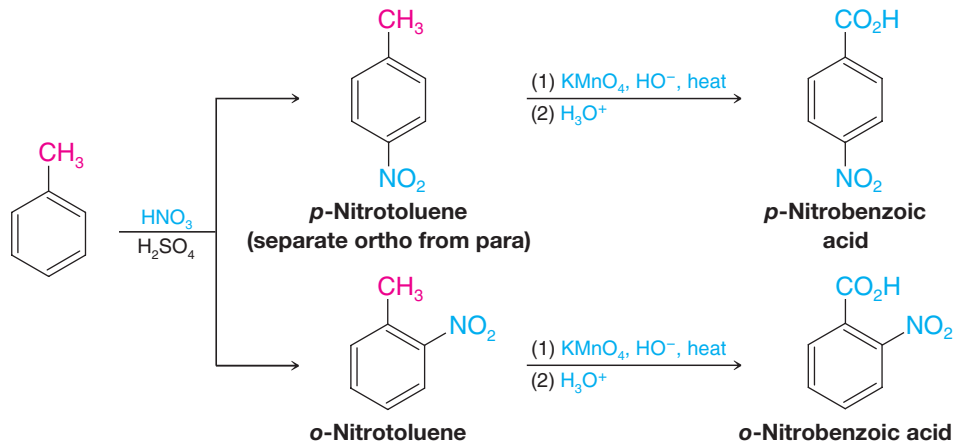
Let us suppose, for example, that we want to synthesize *o*-bromonitrobenzene. We can see very quickly that we should introduce the bromine into the ring first because it is an ortho–para director:



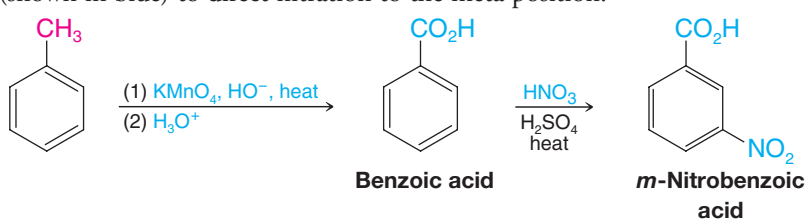
***o*-Bromonitrobenzene** ***p*-Bromonitrobenzene**

The ortho and para products can be separated by various methods because they have different physical properties. However, had we introduced the nitro group first, we would have obtained *m*-bromonitrobenzene as the major product.

Other examples in which choosing the proper order for the reactions is important are the syntheses of the *ortho*-, *meta*-, and *para*-nitrobenzoic acids. Because the methyl group of toluene is an electron-donating group (shown in red below), we can synthesize the *ortho*- and *para*-nitrobenzoic acids from toluene by nitrating it, separating the *ortho*- and *para*-nitrotoluenes, and then oxidizing the methyl groups to carboxyl groups:



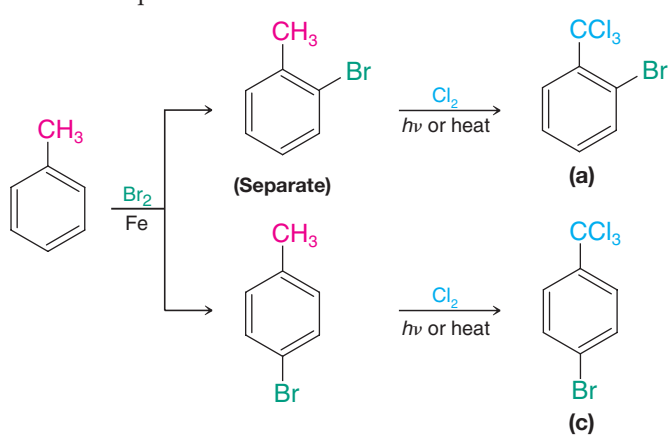
We can synthesize *m*-nitrobenzoic acid by reversing the order of the reactions. We oxidize the methyl group to a carboxylic acid, then use the carboxyl as an electron-withdrawing group (shown in blue) to direct nitration to the meta position.



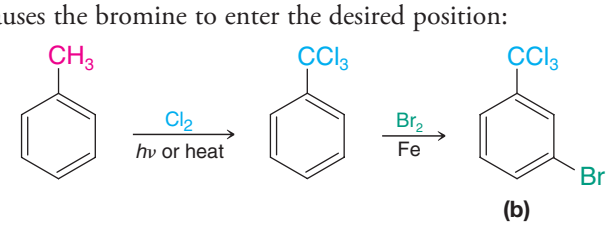
SOLVED PROBLEM 15.5

Starting with toluene, outline a synthesis of **(a)** 1-bromo-2-trichloromethylbenzene, **(b)** 1-bromo-3-trichloromethylbenzene, and **(c)** 1-bromo-4-trichloromethylbenzene.

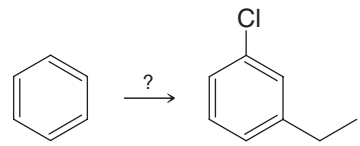
ANSWER: Compounds **(a)** and **(c)** can be obtained by ring bromination of toluene followed by benzylic radical chlorination of the side chain using three molar equivalents of chlorine:



To make compound **(b)**, we reverse the order of the reactions. By converting the side chain to a $-CCl_3$ group first, we create a meta director, which causes the bromine to enter the desired position:



PRACTICE PROBLEM 15.15 Suppose you needed to synthesize *m*-chloroethylbenzene from benzene.



You could begin by chlorinating benzene and then follow with a Friedel–Crafts alkylation using chloroethane and $AlCl_3$, or you could begin with a Friedel–Crafts alkylation followed by chlorination. Neither method will give the desired product, however.

(a) Why will neither method give the desired product?

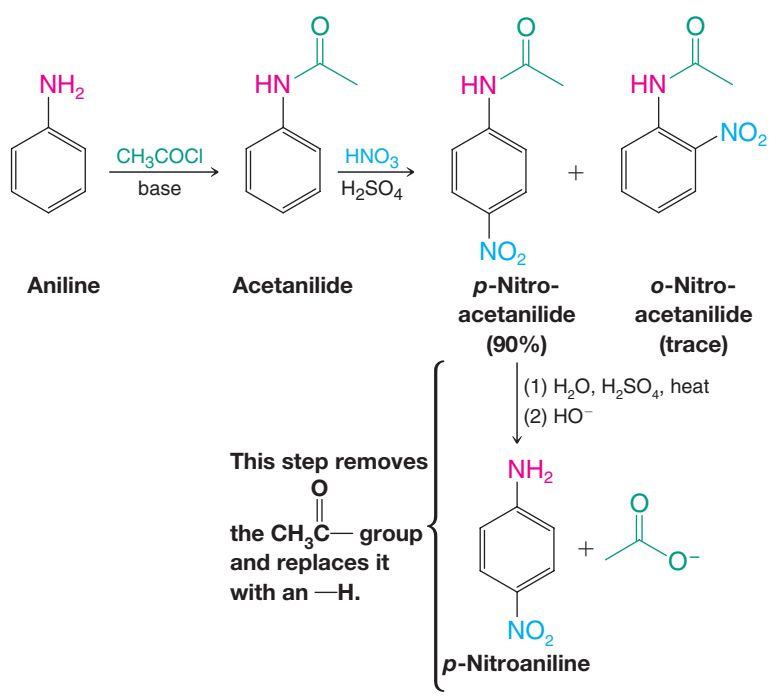
(b) There is a three-step method that will work if the steps are done in the right order. What is this method?

15.14A Use of Protecting and Blocking Groups

- Very powerful activating groups such as amino groups and hydroxyl groups cause the benzene ring to be so reactive that undesirable reactions may take place.

Some reagents used for electrophilic substitution reactions, such as nitric acid, are also strong *oxidizing agents*. Both electrophiles and oxidizing agents seek electrons. Thus, amino groups and hydroxyl groups not only activate the ring toward electrophilic substitution but also activate it toward oxidation. Nitration of aniline, for example, results in considerable destruction of the benzene ring because it is oxidized by the nitric acid. Direct nitration of aniline, consequently, is not a satisfactory method for the preparation of *o*- and *p*-nitroaniline.

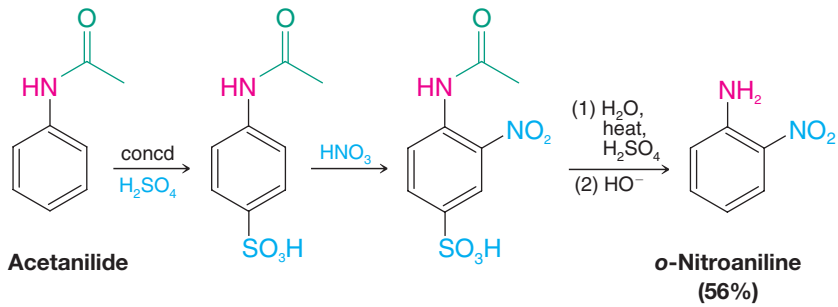
Treating aniline with acetyl chloride, CH_3COCl, or acetic anhydride, $(CH_3CO)_2O$, converts the amino group of aniline to an amide (specifically an acetamido group, $—NHCOCH_3$), forming acetanilide. An amide group is only moderately activating, and it does not make the ring highly susceptible to oxidation during nitration (see Practice Problem 15.9). Thus, with the amino group of aniline blocked in acetanilide, direct nitration becomes possible:



Nitration of acetanilide gives *p*-nitroacetanilide in excellent yield with only a trace of the ortho isomer. Acidic hydrolysis of *p*-nitroacetanilide (Section 18.8F) removes the acetyl group and gives *p*-nitroaniline, also in good yield.

Suppose, however, that we need *o*-nitroaniline. The synthesis that we just outlined would obviously not be a satisfactory method, for only a trace of *o*-nitroacetanilide is obtained in the nitration reaction. (The acetamido group is purely a para director in many reactions. Bromination of acetanilide, for example, gives *p*-bromoacetanilide almost exclusively.)

We can synthesize *o*-nitroaniline, however, through the reactions that follow:



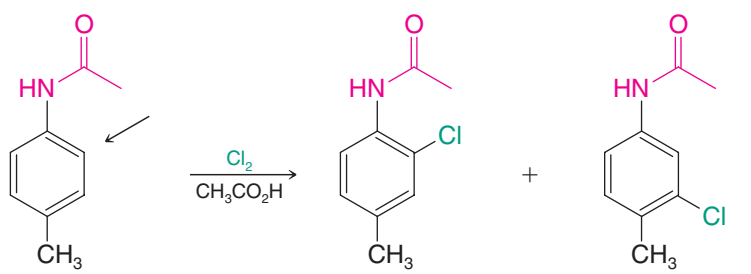
Acetanilide **o-Nitroaniline (56%)**

Here we see how a sulfonic acid group can be used as a "blocking group." We can remove the sulfonic acid group by desulfonation at a later stage. In this example, the reagent used for desulfonation (dilute H_2SO_4) also conveniently removes the acetyl group that we employed to "protect" the benzene ring from oxidation by nitric acid.

15.14B Orientation in Disubstituted Benzenes

- When two different groups are present on a benzene ring, the more powerful activating group (Table 15.2) generally determines the outcome of the reaction.

Let us consider, as an example, the orientation of electrophilic substitution of *p*-methylacetanilide. The amide group is a much stronger activating group than the methyl group. The following example shows that the amide group determines the outcome of the reaction. Substitution occurs primarily at the position ortho to the amide group:



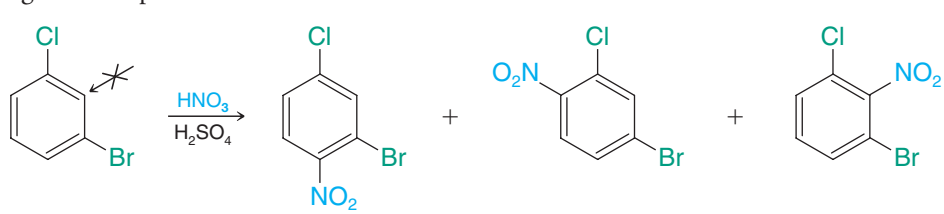
Major product **Minor product**

- An ortho–para director takes precedence over a meta director in determining the position of substitution because all ortho–para-directing groups are more activating than meta directors.

Steric effects are also important in aromatic substitutions.

- Substitution does not occur to an appreciable extent between meta substituents if another position is open.

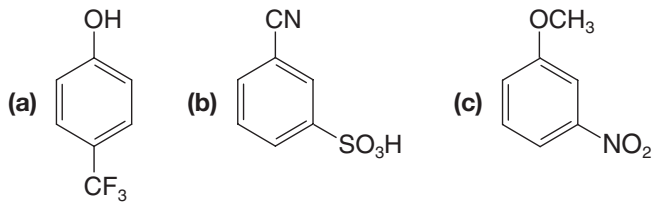
A good example of this effect can be seen in the nitration of *m*-bromochlorobenzene:



62% **37%** **1%**

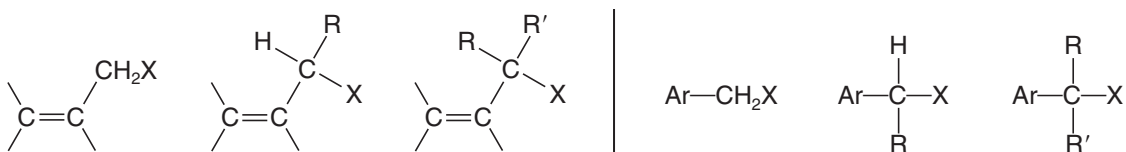
Only 1% of the mononitro product has the nitro group between the bromine and chlorine.

PRACTICE PROBLEM 15.16 Predict the major product (or products) that would be obtained when each of the following compounds is nitrated:



15.15 ALLYLIC AND BENZYLIC HALIDES IN NUCLEOPHILIC SUBSTITUTION REACTIONS

Allylic and benzylic halides can be classified in the same way that we have classified other organic halides:



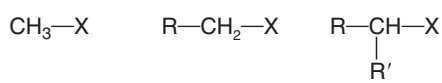
All of these compounds undergo nucleophilic substitution reactions. As with other tertiary halides (Section 6.13A), the steric hindrance associated with having three bulky groups on the carbon bearing the halogen prevents tertiary allylic and tertiary benzylic halides from reacting by an S_N2 mechanism. They react with nucleophiles only by an S_N1 mechanism.

Primary and secondary allylic and benzylic halides can react either by an S_N2 mechanism or by an S_N1 mechanism in ordinary nonacidic solvents. We would expect these halides to react by an S_N2 mechanism because they are structurally similar to primary and secondary alkyl halides. (Having only one or two groups attached to the carbon bearing the halogen does not prevent S_N2 attack.) But primary and secondary allylic and benzylic halides can also react by an S_N1 mechanism because they can form relatively stable **allylic carbocations** and **benzylic carbocations**, and in this regard they differ from primary and secondary alkyl halides.*

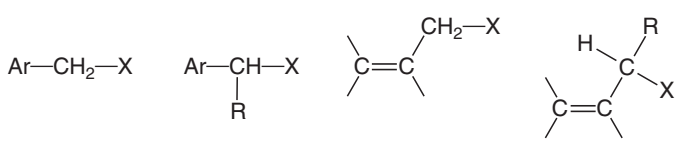
- Overall we can summarize the effect of structure on the reactivity of alkyl, allylic, and benzylic halides in the ways shown in Table 15.3.

TABLE 15.3 A SUMMARY OF ALKYL, ALLYLIC, AND BENZYLIC HALIDES IN S_N REACTIONS

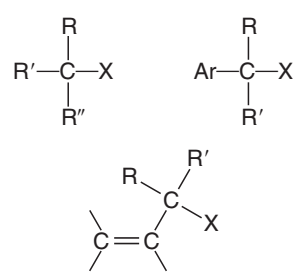
These halides give mainly S_N2 reactions.



These halides may give either S_N1 or S_N2 reactions.



These halides give mainly S_N1 reactions.

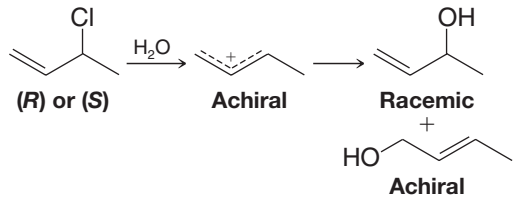


*There is some dispute as to whether 2° alkyl halides react by an S_N1 mechanism to any appreciable extent in ordinary nonacidic solvents such as mixtures of water and alcohol or acetone, but it is clear that reaction by an S_N2 mechanism is, for all practical purposes, the more important pathway.

SOLVED PROBLEM 15.6

When either enantiomer of 3-chloro-1-butene [(*R*) or (*S*)] is subjected to hydrolysis, the products of the reaction are optically inactive. Explain these results.

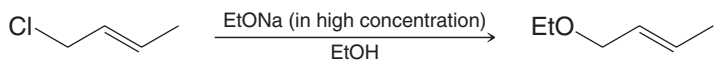
ANSWER: The solvolysis reaction is S_N1. The intermediate allylic cation is achiral and therefore reacts with water to give the enantiomeric 3-buten-2-ols in equal amounts and to give some of the achiral 2-buten-1-ol:



PRACTICE PROBLEM 15.17

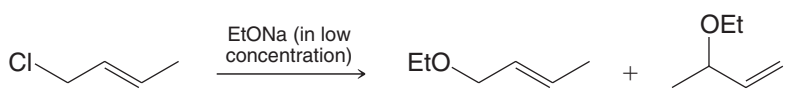
Account for the following observations with mechanistic explanations.

(a)



At high concentration of ethoxide, the rate depends on both the allylic halide and ethoxide concentrations.

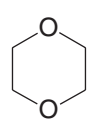
(b)



At low concentration of ethoxide, the rate depends only on the allylic halide concentration.

PRACTICE PROBLEM 15.18

1-Chloro-3-methyl-2-butene undergoes hydrolysis in a mixture of water and dioxane at a rate that is more than a thousand times that of 1-chloro-2-butene. **(a)** What factor accounts for the difference in reactivity? **(b)** What products would you expect to obtain? [Dioxane is a cyclic ether (below) that is miscible with water in all proportions and is a useful cosolvent for conducting reactions like these. Dioxane is carcinogenic (i.e., cancer causing), however, and like most ethers, it tends to form peroxides.]



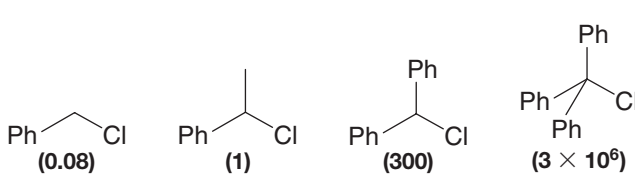
Dioxane

PRACTICE PROBLEM 15.19

Primary halides of the type $ROCH_2X$ apparently undergo S_N1-type reactions, whereas most primary halides do not. Can you propose a resonance explanation for the ability of halides of the type $ROCH_2X$ to undergo S_N1 reactions?

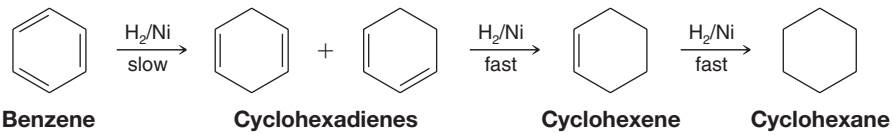
PRACTICE PROBLEM 15.20

The following chlorides (Ph = phenyl) undergo solvolysis in ethanol at the relative rates given in parentheses. How can you explain these results?



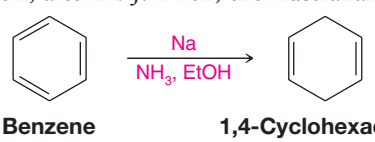
15.16 REDUCTION OF AROMATIC COMPOUNDS

Hydrogenation of benzene under pressure using a metal catalyst such as nickel results in the addition of three molar equivalents of hydrogen and the formation of cyclohexane (Section 14.3). The intermediate cyclohexadienes and cyclohexene cannot be isolated because these undergo catalytic hydrogenation faster than benzene does.



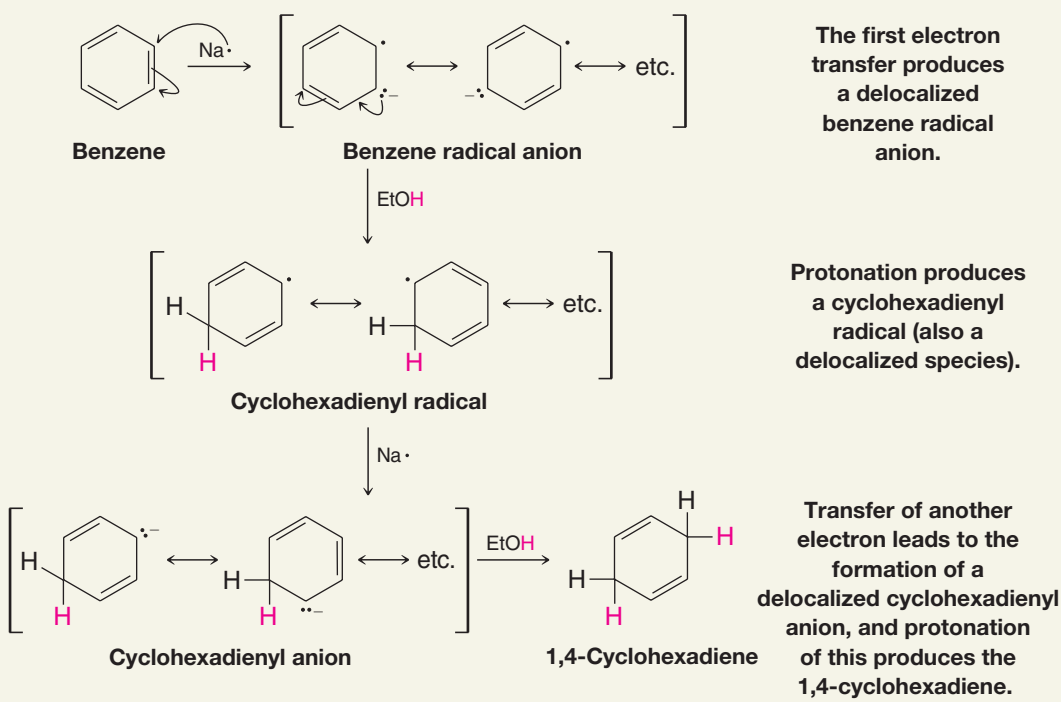
15.16A The Birch Reduction

Benzene can be reduced to 1,4-cyclohexadiene by treating it with an alkali metal (sodium, lithium, or potassium) in a mixture of liquid ammonia and an alcohol. This reaction is called the **Birch reduction**, after A. J. Birch, the Australian chemist who developed it.

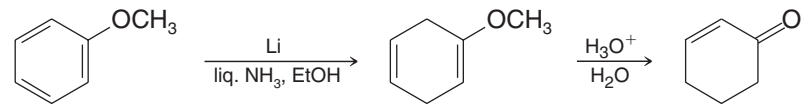


The Birch reduction is a dissolving metal reduction, and the mechanism for it resembles the mechanism for the reduction of alkynes that we studied in Section 7.15B. A sequence of electron transfers from the alkali metal and proton transfers from the alcohol takes place, leading to a 1,4-cyclohexadiene. The reason for formation of a 1,4-cyclohexadiene in preference to the more stable conjugated 1,3-cyclohexadiene is not understood.

A MECHANISM FOR THE REACTION — Birch Reduction

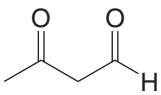
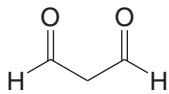


Substituent groups on the benzene ring influence the course of the reaction. Birch reduction of methoxybenzene (anisole) leads to the formation of 1-methoxy-1,4-cyclohexadiene, a compound that can be hydrolyzed by dilute acid to 2-cyclohexenone. This method provides a useful synthesis of 2-cyclohexenones:



Methoxybenzene (anisole) → **1-Methoxy-1,4-cyclohexadiene (84%)** → **2-Cyclohexenone**

PRACTICE PROBLEM 15.21

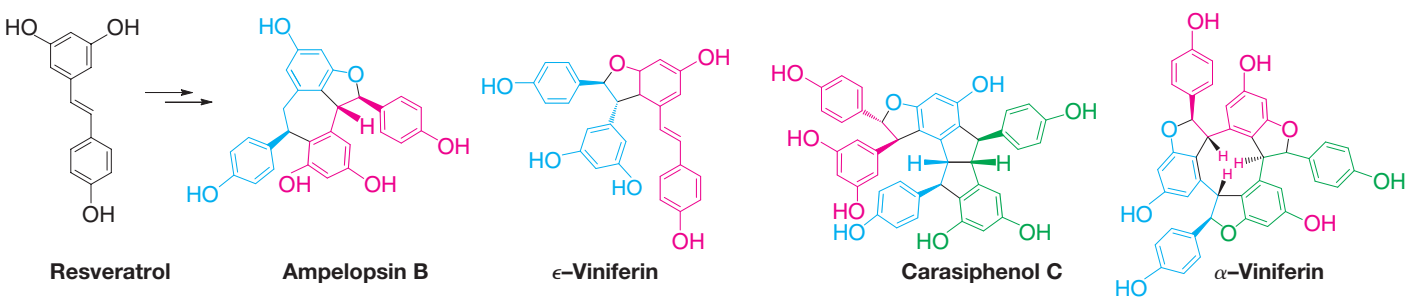
Birch reduction of toluene leads to a product with the molecular formula C_7H_{10}. On ozonolysis followed by reduction with dimethyl sulfide, the product is transformed into  and  . What is the structure of the Birch reduction product?

[WHY Do These Topics Matter?

SYNTHESIZING ARCHITECTURALLY UNIQUE NATURAL PRODUCTS

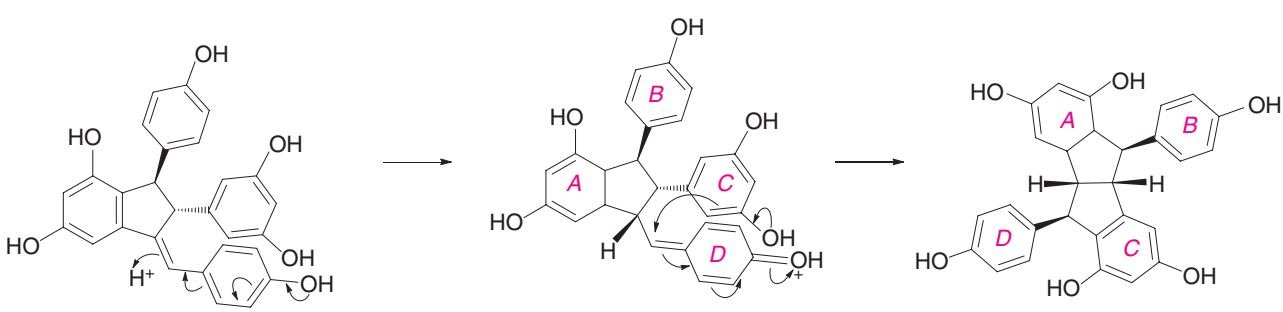
When certain plants like grapevines are attacked by foreign pathogens, such as bacteria and fungi, they use a compound called resveratrol and like Lego building blocks combine it with other resveratrol molecules in different ways to create dozens of new, and larger, molecules. The goal is to synthesize at least one compound with the biological activity required to eradicate, or at least slow, the pathogen so the plant has a chance to survive. A few examples of these compounds are shown below, illustrating just a small portion of the architectural diversity that the family possesses. What is particularly fascinating is that the synthesis of these molecules likely involves two major types of bond formation—radical chemistry and electrophilic aromatic substitutions. Here we focus on the latter.

© Konstantin Suryagin/iStockphoto



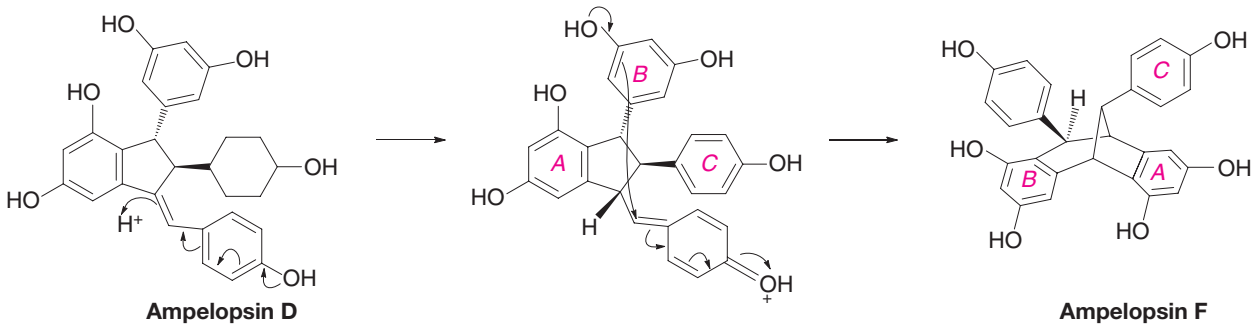
Resveratrol **Ampelopsin B** **ϵ–Viniferin** **Carasiphenol C** **α–Viniferin**

If the resveratrol dimers quadrangularin A and ampelopsin D are exposed to an appropriate acid, it is reasonable to believe that proton activation of their alkenes would create new carbocations, shown here in their resonance-stabilized forms by shifting electrons from the neighboring *para*-phenoxy ring system. Attack by the neighboring electron-rich 3,5-diphenoxy ring system through Friedel–Crafts reactions, as shown, would then forge new C—C bonds (highlighted in red), leading to completely different structures in the form of pallidol and ampelopsin F. All of the benzene rings are labeled in each case so that you can see where they end up. Not only are new structures formed, but new and different biological properties are gained as well. Quadrangularin A is a good radical scavenger, while pallidol possesses potential cancer-fighting properties.



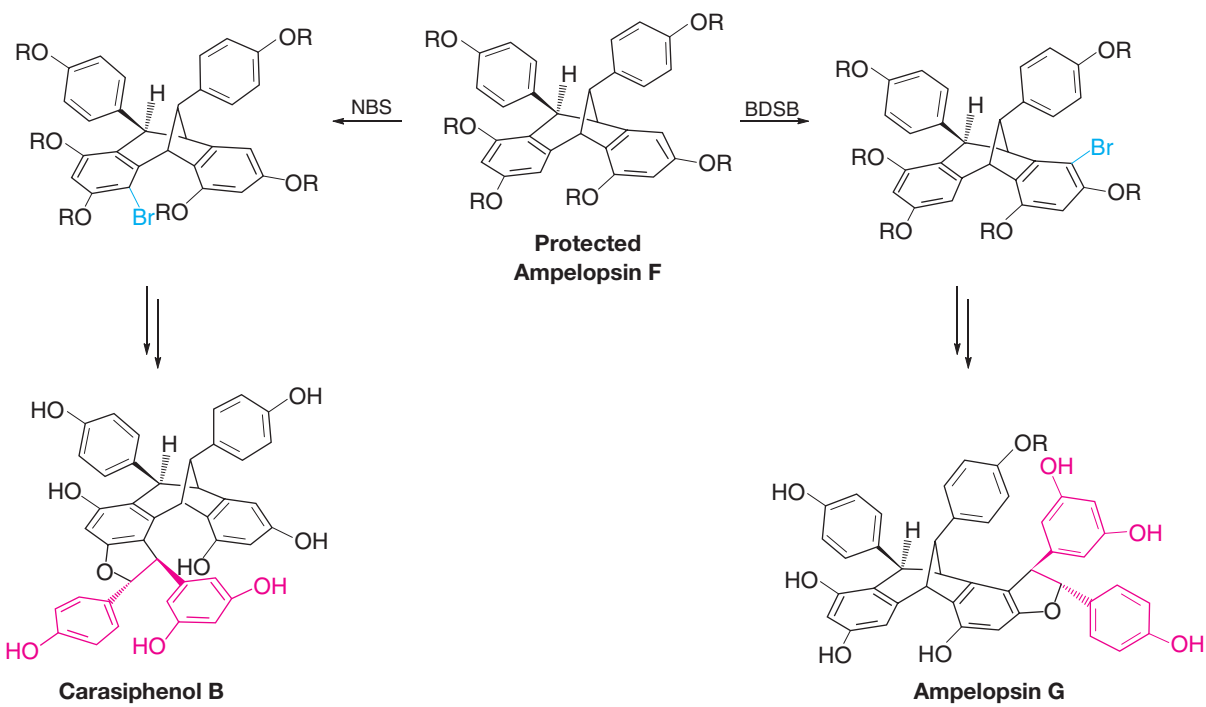
Quadrangularin A **Pallidol**

(continues on next page)



Ampelopsin D **Ampelopsin F**

Chemists have also found creative ways to make these compounds in the laboratory using electrophilic aromatic substitutions. One of the key tools has been substituting aryl hydrogen atoms with bromine. As shown below, if a protected form of ampelopsin F is exposed to an electrophilic bromine source, such as *N*-bromosuccinimide (NBS), an electrophilic aromatic substitution reaction can happen directly without a Lewis acid due to the electron-rich nature of some of the aromatic rings. What is surprising, however, is that while there are many places where that addition can occur, the indicated monobrominated compound is formed selectively. Most other bromonium sources behave in the same way. However, there is one that substitutes a different site first, and that is $Et_2SBr{\bullet}SbCl_5Br$ (BDSB). Because of the ability to achieve this different and specific tailoring, the atoms needed to complete syntheses of the resveratrol trimers carasiphenol B and ampelopsin G could then be added in some additional operations.



Carasiphenol B **Ampelopsin G**

To learn more about these topics, see:

1. Snyder, S. A.; Zografos, A. L.; Lin, Y. "Total Synthesis of Resveratrol-based Natural Products: A Chemoselective Solution" in *Angew. Chem. Int. Ed.* **2007**, *46*, 8186–8191.

2. Snyder, S. A.; Breazzano, S. P.; Ross, A. G.; Lin, Y.; Zografos, A. L. "Total Synthesis of Diverse Carbogenic Complexity within the Resveratrol Class from a Common Building Block" in *J. Am. Chem. Soc.* **2009**, *131*, 1753–1765.

3. Snyder, S. A.; Gollner, A.; Chiriac, M. I. "Regioselective Reactions for Programmable Resveratrol Oligomer Synthesis" in *Nature* **2011**, *474*, 461–466 and references therein.

SUMMARY AND REVIEW TOOLS

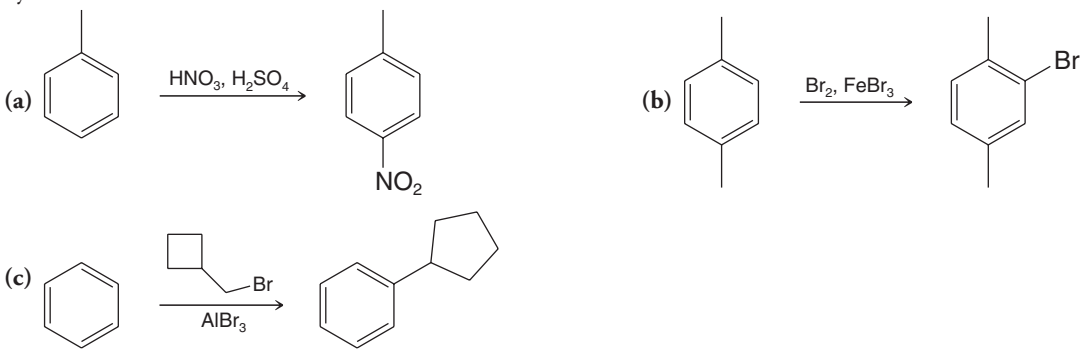
The study aids for this chapter include key terms and concepts (which are hyperlinked to the Glossary from the bold, blue terms in the *WileyPLUS* version of the book at wileyplus.com), a Concept Map regarding electrophilic aromatic substitution, and a Synthetic Connections scheme for reactions that link benzene and a variety of aryl derivatives.

PROBLEMS

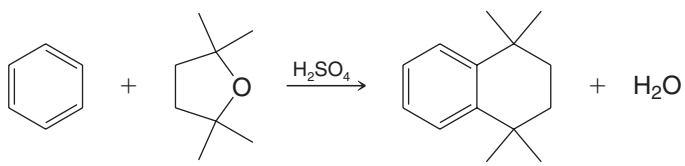
Note to Instructors: Many of the homework problems are available for assignment via *WileyPLUS*, an online teaching and learning solution.

MECHANISMS

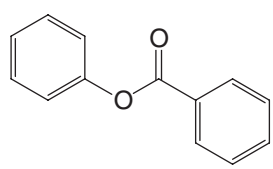
15.22 Provide a detailed mechanism for each of the following reactions. Include contributing resonance structures and the resonance hybrid for the arenium ion intermediates.



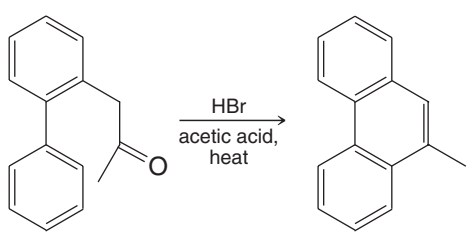
15.23 Provide a detailed mechanism for the following reaction.



15.24 One ring of phenyl benzoate undergoes electrophilic aromatic substitution much more readily than the other. **(a)** Which one is it? **(b)** Explain your answer.



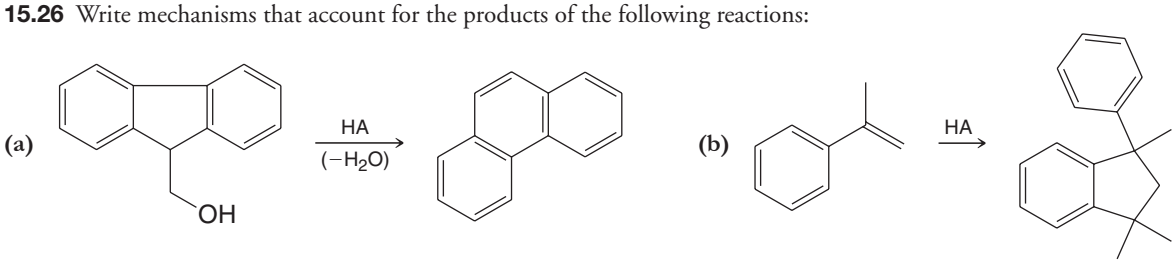
15.25 Many polycyclic aromatic compounds have been synthesized by a cyclization reaction known as the **Bradsher reaction** or **aromatic cyclodehydration**. This method can be illustrated by the following synthesis of 9-methylphenanthrene:



9-Methylphenanthrene

An arenium ion is an intermediate in this reaction, and the last step involves the dehydration of an alcohol. Propose a plausible mechanism for this example of the Bradsher reaction.

15.26 Write mechanisms that account for the products of the following reactions:



15.27 The addition of a hydrogen halide (hydrogen bromide or hydrogen chloride) to 1-phenyl-1,3-butadiene produces (only) 1-phenyl-3-halo-1-butene. **(a)** Write a mechanism that accounts for the formation of this product. **(b)** Is this 1,4 addition or 1,2 addition to the butadiene system? **(c)** Is the product of the reaction consistent with the formation of the most stable intermediate carbocation? **(d)** Does the reaction appear to be under kinetic control or equilibrium control? Explain.

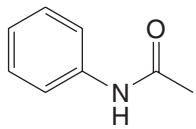
REACTIONS AND SYNTHESIS

15.28 Predict the major product (or products) formed when each of the following reacts with Cl_2 and $FeCl_3$:

(a) Ethylbenzene
(b) Anisole (methoxybenzene)
(c) Fluorobenzene
(d) Benzoic acid
(e) Nitrobenzene
(f) Chlorobenzene
(g) Biphenyl ($C_6H_5—C_6H_5$)
(h) Ethyl phenyl ether

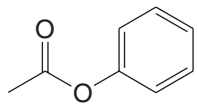
15.29 Predict the major product (or products) formed when each of the following reacts with a mixture of concentrated HNO_3 and H_2SO_4.

(a)



Acetanilide

(b)

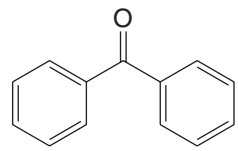


Phenyl acetate

(c) 4-Chlorobenzoic acid

(d) 3-Chlorobenzoic acid

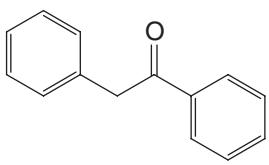
(e)



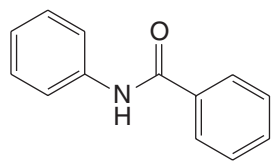
Benzophenone

15.30 What monobromination product (or products) would you expect to obtain when the following compounds undergo ring bromination with Br_2 and $FeBr_3$?

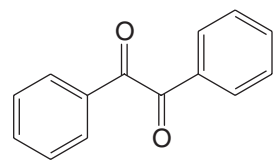
(a)



(b)

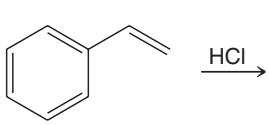


(c)



15.31 Predict the major products of the following reactions:

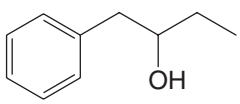
(a)



Styrene

(b) 2-Bromo-1-phenylpropane $\xrightarrow{EtONa}$

(c)



$\xrightarrow{HA,\ heat}$

(d) Product of (c) + HBr $\xrightarrow{peroxides}$

(e) Product of (c) + H_2O $\xrightarrow[heat]{HA}$

(f) Product of (c) + H_2 (1 molar equivalent) $\xrightarrow[25\ °C]{Pt}$

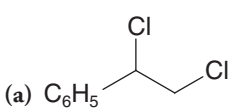
(g) Product of (f) $\xrightarrow[(2)\ H_3O^+]{(1)\ KMnO_4,\ HO^-,\ heat}$

15.32 Starting with benzene, outline a synthesis of each of the following:

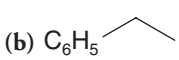
(a) Isopropylbenzene
(b) *tert*-Butylbenzene
(c) Propylbenzene
(d) Butylbenzene
(e) 1-*tert*-Butyl-4-chlorobenzene
(f) 1-Phenylcyclopentene
(g) *trans*-2-Phenylcyclopentanol
(h) *m*-Dinitrobenzene
(i) *m*-Bromonitrobenzene
(j) *p*-Bromonitrobenzene
(k) *p*-Chlorobenzenesulfonic acid
(l) *o*-Chloronitrobenzene
(m) *m*-Nitrobenzenesulfonic acid

15.33 Starting with styrene, outline a synthesis of each of the following:

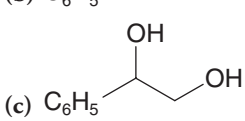
(a)



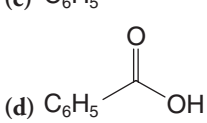
(b)



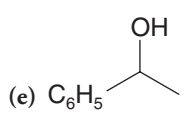
(c)



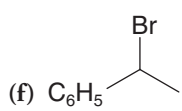
(d)



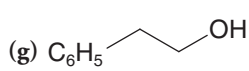
(e)



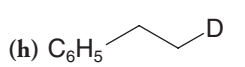
(f)



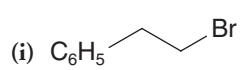
(g)



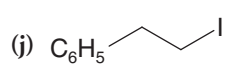
(h)



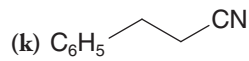
(i)



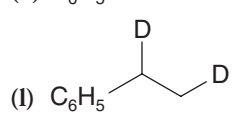
(j)



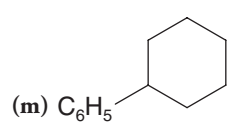
(k)



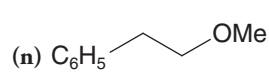
(l)



(m)



(n)



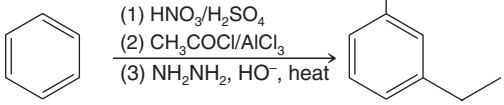
15.34 Starting with toluene, outline a synthesis of each of the following:

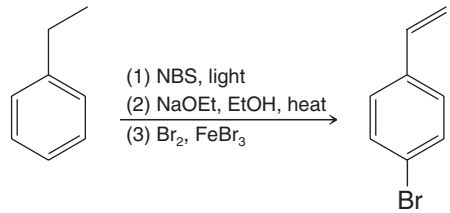
(a) *m*-Chlorobenzoic acid
(b) *p*-Methylacetophenone
(c) 2-Bromo-4-nitrotoluene
(d) *p*-Bromobenzoic acid
(e) 1-Chloro-3-trichloromethylbenzene
(f) *p*-Isopropyltoluene (*p*-cymene)
(g) 1-Cyclohexyl-4-methylbenzene
(h) 2,4,6-Trinitrotoluene (TNT)
(i) 4-Chloro-2-nitrobenzoic acid
(j) 1-Butyl-4-methylbenzene

15.35 Starting with aniline, outline a synthesis of each of the following:

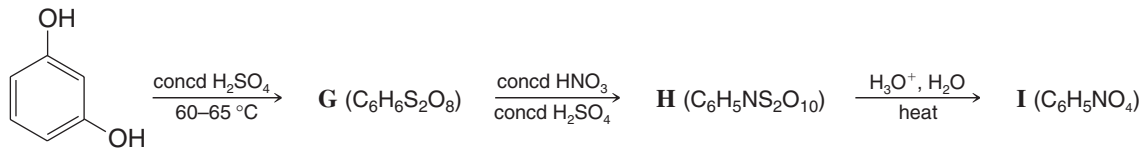
(a) *p*-Bromoaniline
(b) *o*-Bromoaniline
(c) 2-Bromo-4-nitroaniline
(d) 4-Bromo-2-nitroaniline
(e) 2,4,6-Tribromoaniline

15.36 Both of the following syntheses will fail. Explain what is wrong with each one.

(a) 

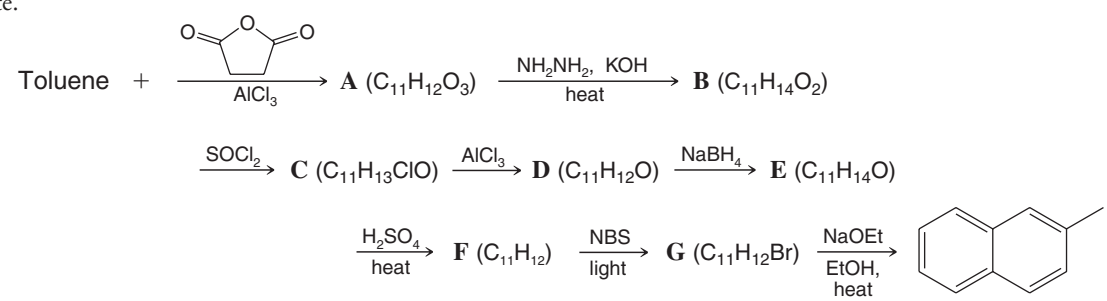
(b) 

15.37 Propose structures for compounds **G–I:**

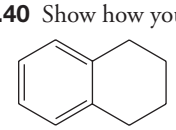


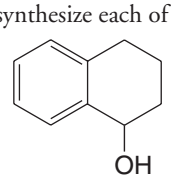
15.38 2,6-Dichlorophenol has been isolated from the females of two species of ticks (*Amblyomma americanum* and *A. maculatum*), where it apparently serves as a sex attractant. Each female tick yields about 5 ng of 2,6-dichlorophenol. Assume that you need larger quantities than this and outline a synthesis of 2,6-dichlorophenol from phenol. (*Hint*: When phenol is sulfonated at 100 °C, the product is chiefly *p*-hydroxybenzenesulfonic acid.)

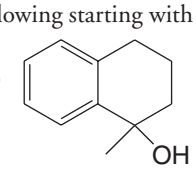
15.39 2-Methylnaphthalene can be synthesized from toluene through the following sequence of reactions. Write the structure of each intermediate.

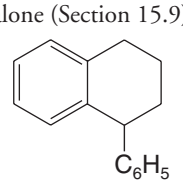


15.40 Show how you might synthesize each of the following starting with α-tetralone (Section 15.9):

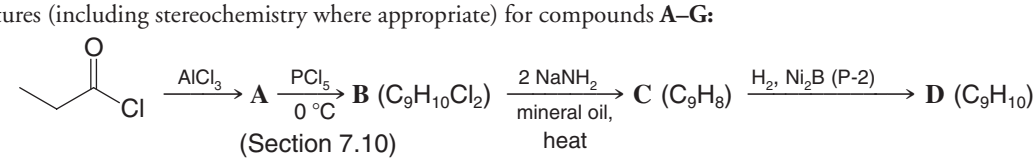
(a) 

(b) 

(c) 

(d) 

15.41 Give structures (including stereochemistry where appropriate) for compounds **A–G:**

(a) 

(Section 7.10)

(*Hint*: The ^{1}H NMR spectrum of compound **C** consists of a multiplet at δ 7.20 (5H) and a singlet at δ 2.0 (3H).)

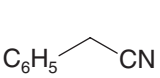
(b) **C** $\xrightarrow[\text{(2) } NH_4Cl \text{ (Section 7.15B)}]{\text{(1) Li, } EtNH_2}$ **E** (C_9H_{10})

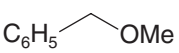
(c) **D** $\xrightarrow[\text{2-5 °C}]{Br_2}$ **F** + enantiomer (major products)

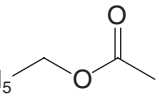
(d) **E** $\xrightarrow[\text{2-5 °C}]{Br_2}$ **G** + enantiomer (major products)

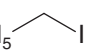
GENERAL PROBLEMS

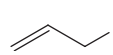
15.42 Show how you might synthesize each of the following compounds starting with either benzyl bromide or allyl bromide:

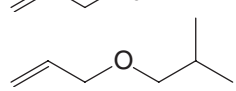
(a) 

(b) 

(c) 

(d) 

(e) 

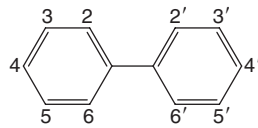
(f) 

15.43 Provide structures for compounds **A** and **B**:

$$\text{Benzene} \xrightarrow[\text{liq. } NH_3,\ EtOH]{Na} \mathbf{A}\ (C_6H_8) \xrightarrow{NBS} \mathbf{B}\ (C_6H_7Br)$$

15.44 Ring nitration of a dimethylbenzene (a xylene) results in the formation of only one dimethylnitrobenzene. Which dimethylbenzene isomer was the reactant?

15.45 The compound phenylbenzene ($C_6H_5—C_6H_5$) is called *biphenyl*, and the ring carbons are numbered in the following manner:



Use models to answer the following questions about substituted biphenyls. **(a)** When certain large groups occupy three or four of the *ortho* positions (e.g., 2, 6, 2′, and 6′), the substituted biphenyl may exist in enantiomeric forms. An example of a biphenyl that exists in enantiomeric forms is the compound in which the following substituents are present: 2-NO_2, 6-CO_2H, 2′-NO_2, 6′-CO_2H. What factors account for this? **(b)** Would you expect a biphenyl with 2-Br, 6-CO_2H, 2′-CO_2H, 6′-H to exist in enantiomeric forms? **(c)** The biphenyl with 2-NO_2, 6-NO_2, 2′-CO_2H, 6′-Br cannot be resolved into enantiomeric forms. Explain.

15.46 Treating cyclohexene with acetyl chloride and $AlCl_3$ leads to the formation of a product with the molecular formula $C_8H_{13}ClO$. Treating this product with a base leads to the formation of 1-acetylcyclohexene. Propose mechanisms for both steps of this sequence of reactions.

15.47 The *tert*-butyl group can be used as a blocking group in certain syntheses of aromatic compounds. **(a)** How would you introduce a *tert*-butyl group? **(b)** How would you remove it? **(c)** What advantage might a *tert*-butyl group have over a $—SO_3H$ group as a blocking group?

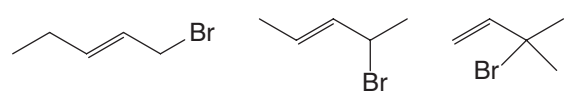
15.48 When toluene is sulfonated (concentrated H_2SO_4) at room temperature, predominantly (about 95% of the total) ortho and para substitution occurs. If elevated temperatures (150–200 °C) and longer reaction times are employed, meta (chiefly) and para substitution account for some 95% of the products. Account for these differences in terms of kinetic and thermodynamic pathways. (*Hint: m*-Toluenesulfonic acid is the most stable isomer.)

15.49 A C—D bond is harder to break than a C—H bond, and, consequently, reactions in which C—D bonds are broken proceed more slowly than reactions in which C—H bonds are broken. What mechanistic information comes from the observation that perdeuterated benzene, C_6D_6, is nitrated at the same rate as normal benzene, C_6H_6?

15.50 Heating 1,1,1-triphenylmethanol with ethanol containing a trace of a strong acid causes the formation of 1-ethoxy-1,1,1-triphenylmethane. Write a plausible mechanism that accounts for the formation of this product.

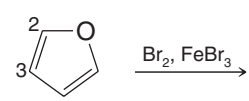
15.51

(a) Which of the following halides would you expect to be most reactive in an S_N2 reaction? **(b)** In an S_N1 reaction? Explain your answers.



CHALLENGE PROBLEMS

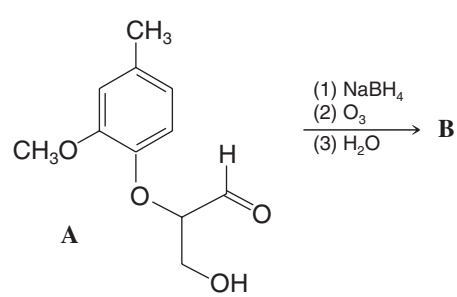
15.52 Furan undergoes electrophilic aromatic substitution. Use resonance structures for possible arenium ion intermediates to predict whether furan is likely to undergo bromination more rapidly at C2 or at C3.



Furan

15.53 Acetanilide was subjected to the following sequence of reactions: (1) concd H_2SO_4; (2) HNO_3, heat; (3) H_2O, H_2SO_4, heat, then HO^-. The ^{13}C NMR spectrum of the final product gives six signals. Write the structure of the final product.

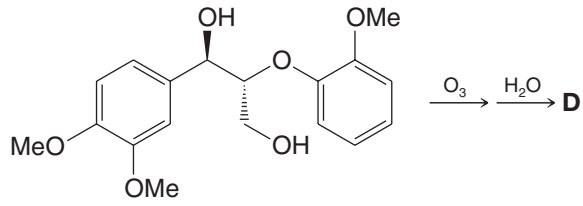
15.54 The lignins are macromolecules that are major components of the many types of wood, where they bind cellulose fibers together in these natural composites. The lignins are built up out of a variety of small molecules (most having phenylpropane skeletons). These precursor molecules are covalently connected in varying ways, and this gives the lignins great complexity. To explain the formation of compound **B** below as one of many products obtained when lignins are ozonized, lignin model compound **A** was treated as shown. Use the following information to determine the structure of **B**.



A

To make **B** volatile enough for GC/MS (gas chromatography–mass spectrometry, Section 9.19), it was first converted to its tris(*O*-trimethylsilyl) derivative, which had M^+ 308 *m/z*. ["Tris" means that three of the indicated complex groups named (e.g., trimethylsilyl groups here) are present. The capital, italicized *O* means these are attached to oxygen atoms of the parent compound, taking the place of hydrogen atoms. Similarly, the prefix "bis" indicates the presence of two complex groups subsequently named, and "tetrakis" (used in the problem below), means four.] The IR spectrum of **B** had a broad absorption at 3400 cm^{-1}, and its ^1H NMR spectrum showed a single multiplet at δ 3.6. What is the structure of **B**?

15.55 When compound **C**, which is often used to model a more frequently occurring unit in lignins, was ozonized, product **D** was obtained. In a variety of ways it has been established that the stereochemistry of the three-carbon side chain of such lignin units remains largely if not completely unchanged during oxidations like this.

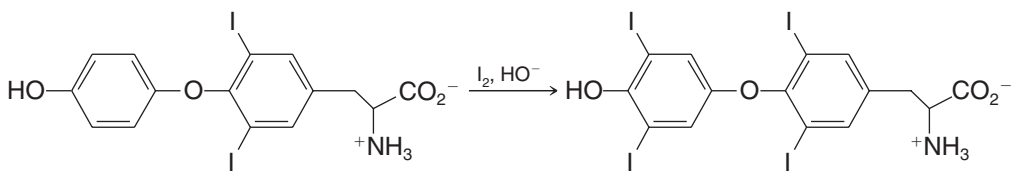


C

For GC/MS, **D** was converted to its tetrakis(*O*-trimethylsilyl) derivative, which had $M^{+\cdot}$ 424 *m/z*. The IR spectrum of **D** had bands at 3000 cm^{-1} (broad, strong) and 1710 cm^{-1} (strong). Its ^1H NMR spectrum had peaks at δ 3.7 (multiplet, 3H) and δ 4.2 (doublet, 1H) after treatment with D_2O. Its DEPT ^{13}C NMR spectra had peaks at δ 64 (CH_2), δ 75 (CH), δ 82 (CH), and δ 177 (C). What is the structure of **D**, including its stereochemistry?

LEARNING GROUP PROBLEMS

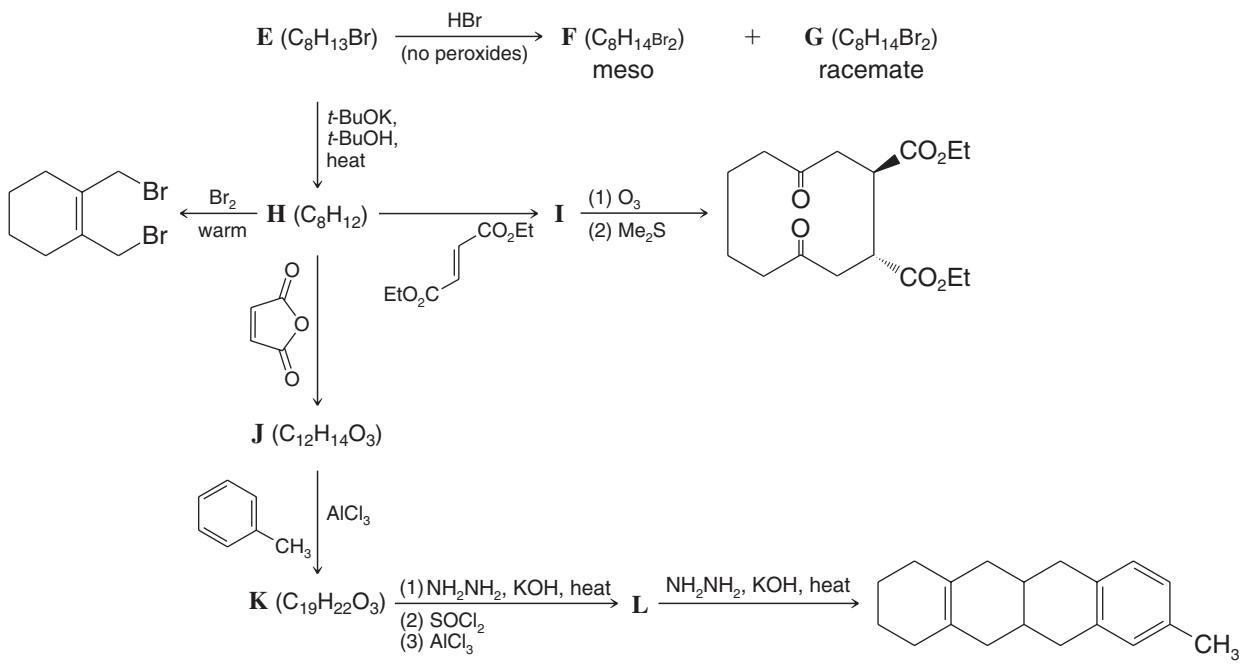
1. The structure of thyroxine, a thyroid hormone that helps to regulate metabolic rate, was determined in part by comparison with a synthetic compound believed to have the same structure as natural thyroxine. The final step in the laboratory synthesis of thyroxine by Harington and Barger, shown below, involves an electrophilic aromatic substitution. Draw a detailed mechanism for this step and explain why the iodine substitutions occur ortho to the phenolic hydroxyl and not ortho to the oxygen of the aryl ether. [One reason iodine is required in our diet (e.g., in iodized salt) is for the biosynthesis of thyroxine.]



Thyroxine

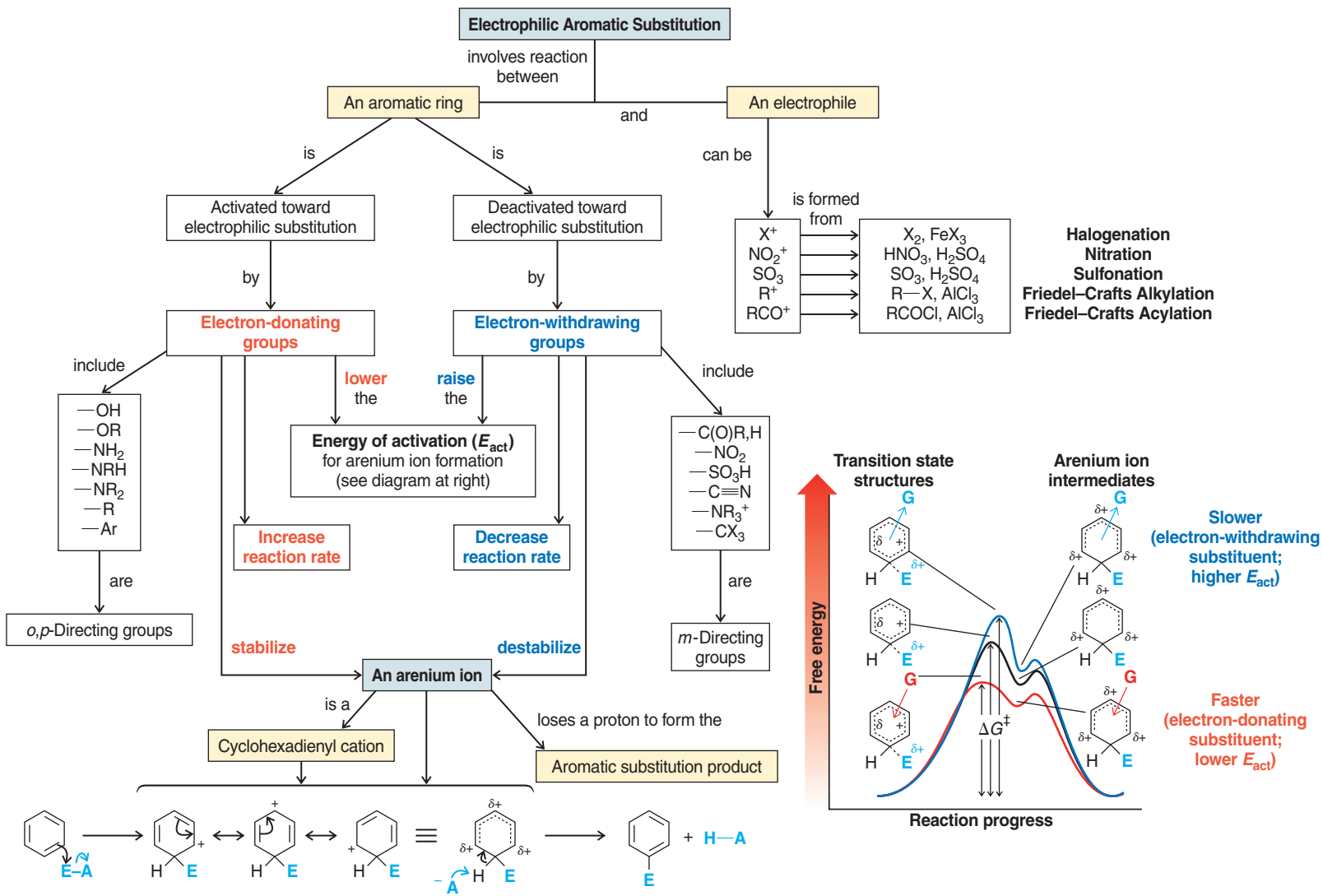
2. Synthesize 2-chloro-4-nitrobenzoic acid from toluene and any other reagents necessary. Begin by writing a retrosynthetic analysis.

3. Deduce the structures of compounds **E–L** in the roadmap below.



[CONCEPT MAP]

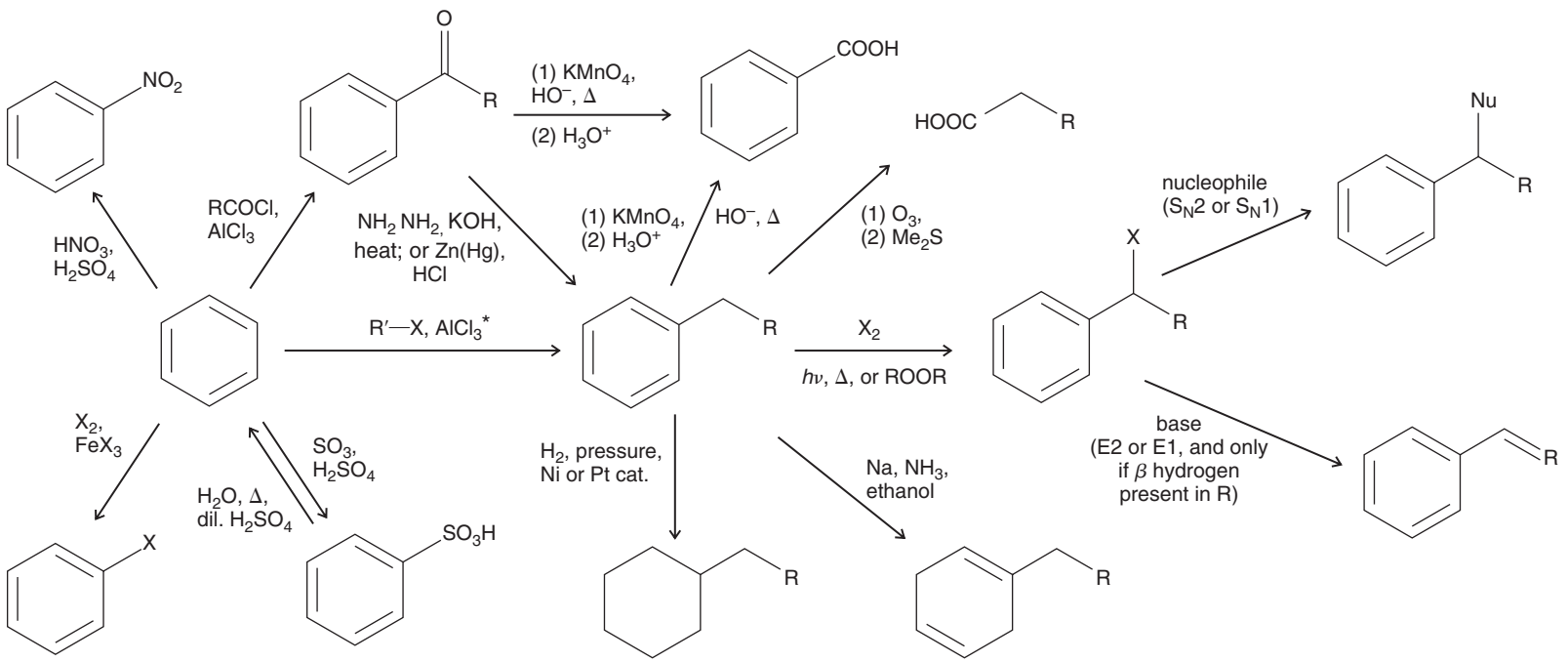
Summary of Mechanisms



[CONCEPT MAP]

Some Synthetic Connections of Benzene and Aryl Derivatives

- Nitration
- Halogenation
- Sulfonation/desulfonation
- Friedel–Crafts alkylation
- Friedel–Crafts acylation
- Wolff–Kishner or Clemmensen reduction
- Side-chain oxidation
- Ring oxidation
- Catalytic hydrogenation of ring
- Birch reduction
- Benzylic radical halogenation
- Benzylic substitution/elimination



*In the Friedel–Crafts alkylation example shown here, R' is a primary alkyl halide. If carbocation rearrangements are likely, then Friedel–Crafts acylation followed by Wolff–Kishner or Clemmensen reduction should be used to incorporate a primary alkyl group.