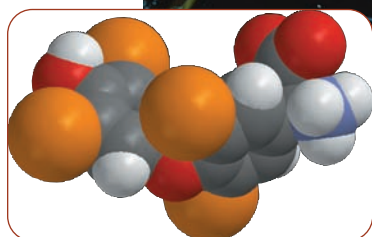


Reactions of Aromatic Compounds



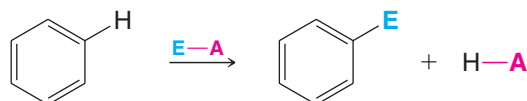
Thyroxine

Thyroxine (see the model above) is an aromatic compound and a key hormone that raises metabolic rate. Low levels of thyroxine (hypothyroidism) can lead to obesity, lethargy, and an enlarged thyroid gland (goiter). The thyroid gland makes thyroxine from iodine and tyrosine, which are two essential components of our diet. Most of us obtain iodine from iodized salt, but iodine is also found in products derived from seaweed, like the kelp shown above. An abnormal level of thyroxine is a relatively common malady, however. Fortunately, low levels of thyroxine are easily corrected by hormone supplements. After we study a new class of reaction in this chapter called electrophilic aromatic substitution, we shall return to see how that reaction is related to thyroxine in "The Chemistry of . . . Iodine Incorporation in Thyroxine Biosynthesis."



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.

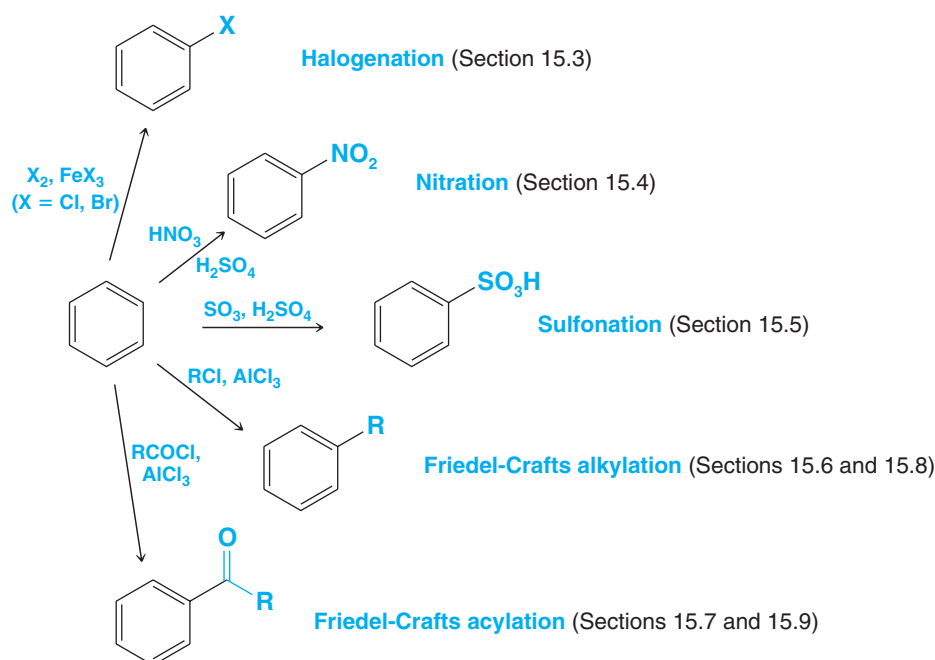
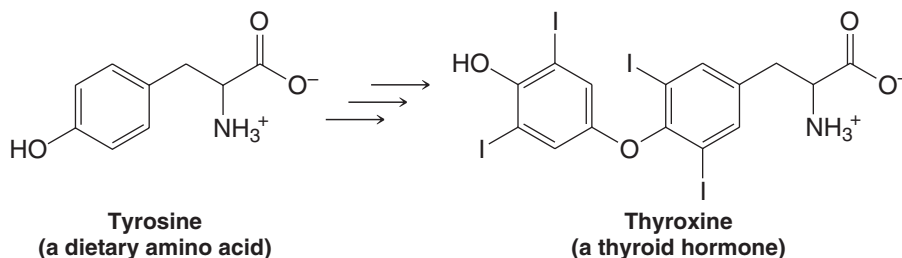


Figure 15.1 Electrophilic aromatic substitution reactions.

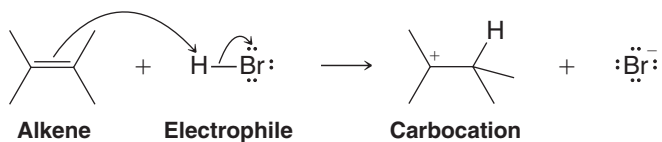
A noteworthy example of electrophilic aromatic substitution in nature, as mentioned above, is biosynthesis of the thyroid hormone thyroxine, where iodine is incorporated into benzene rings that are derived from tyrosine.



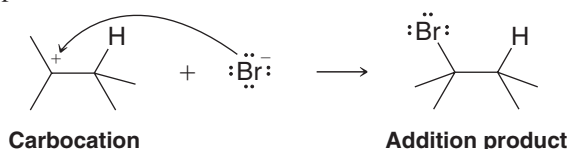
In the next section we shall learn the general mechanism for the way an electrophile reacts with a benzene ring. Then in Sections 15.3–15.7 we shall see specific examples of electrophiles and how each is formed in a reaction mixture.

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.



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



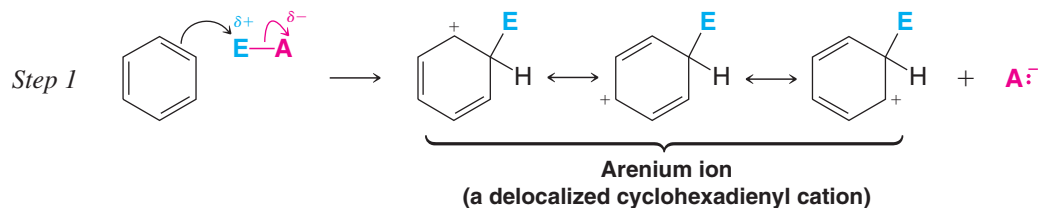
The similarity of benzene reactivity with that of an alkene ends, however, at the carbocation stage, prior to nucleophilic attack. As we saw in Chapter 14, benzene's closed shell of six π electrons give it special stability.

- 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:

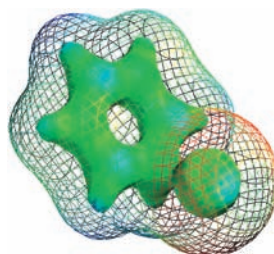
Helpful Hint
Resonance structures (like those used here for the arenium ion) will be important for our study of electrophilic aromatic substitution.



- 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.

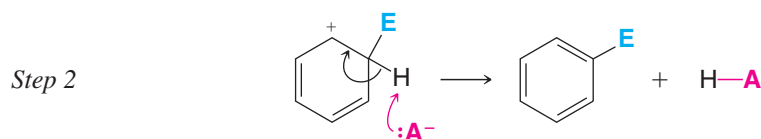
Formation of this bond interrupts the cyclic system of π electrons, because in the formation of the arenium ion the carbon that forms a bond to the electrophile becomes sp^3 hybridized and, therefore, no longer has an available p orbital. Now only five carbon atoms of the ring are sp^2 hybridized and 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.)





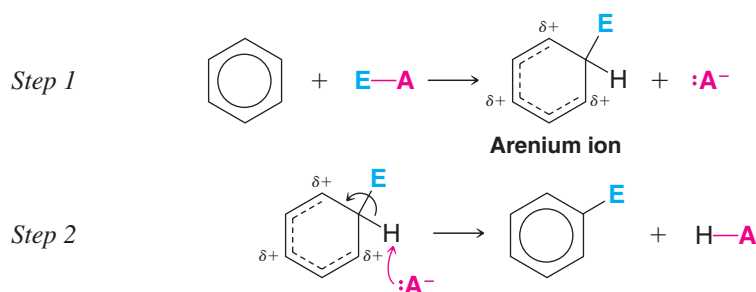
- In step 2 a proton is removed from the carbon atom of the arenium ion that bears the electrophile, restoring aromaticity to the ring.



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.)

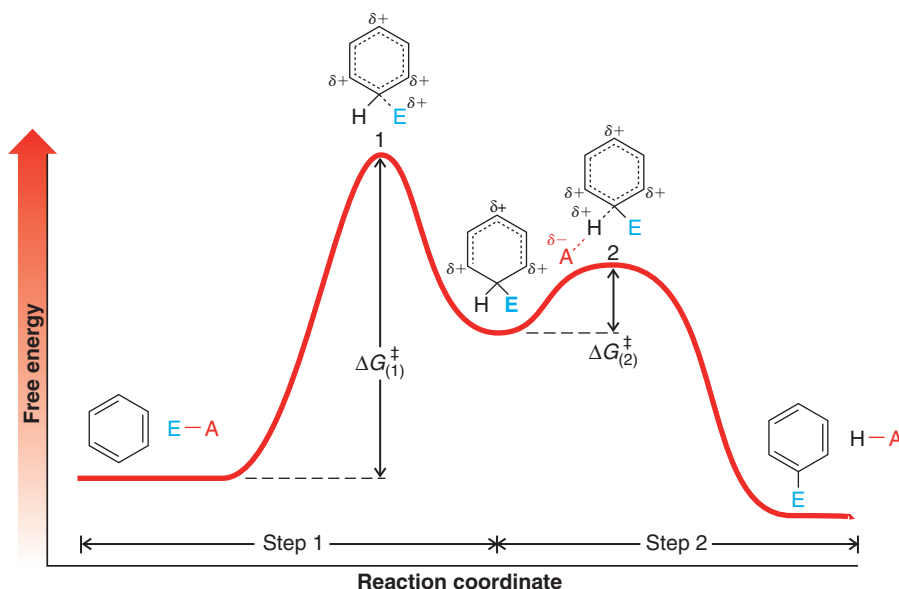
Show how loss of a proton can be represented using each of the three resonance structures for the arenium ion and show how each representation leads to the formation of a benzene ring with three alternating double bonds (i.e., six fully delocalized π electrons).

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:



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, $\Delta G_{(1)}^\ddagger$, has been shown to be much greater than the free energy of activation for step 2, $\Delta G_{(2)}^\ddagger$. This is consistent with what we would expect.



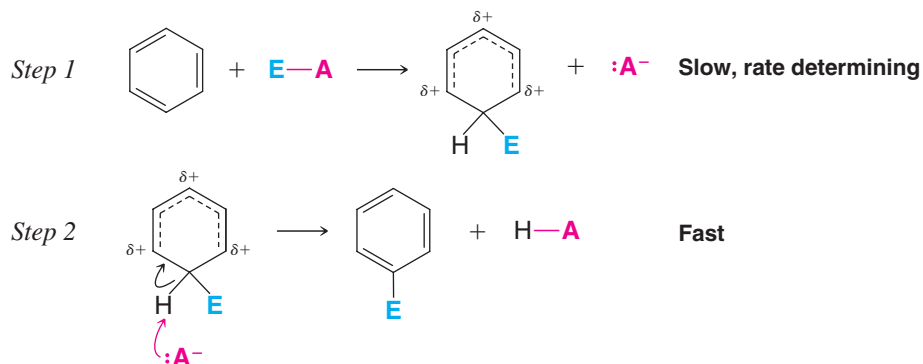
Helpful Hint

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.

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.

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.

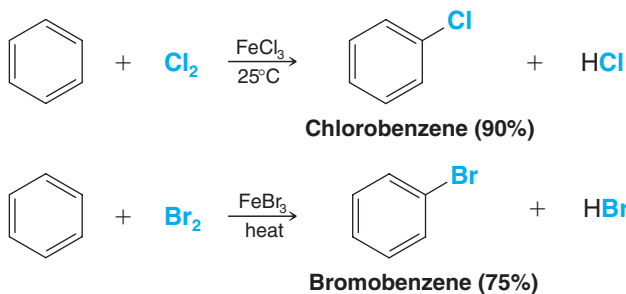
Of the following two steps, step 1 (the formation of the arenium ion) is usually the rate-determining step in electrophilic aromatic substitution because of its higher free energy of activation:



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.



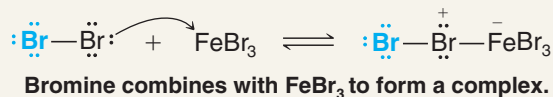
The Lewis acids typically used are aluminum chloride (AlCl₃) and iron chloride (FeCl₃) for chlorination, and iron bromide (FeBr₃) for bromination. The purpose of the Lewis acid is to make the halogen a stronger electrophile. A mechanism for electrophilic aromatic bromination is shown here.

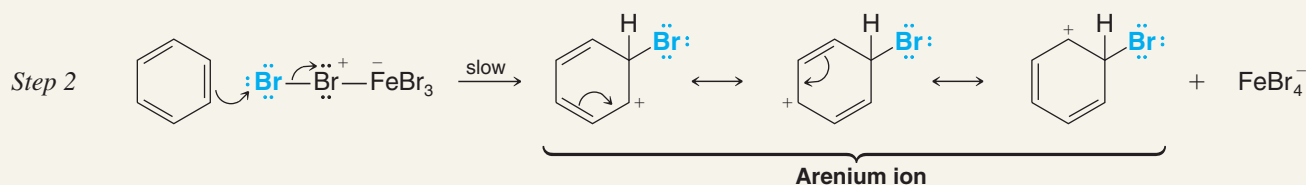


A MECHANISM FOR THE REACTION

Electrophilic Aromatic Bromination

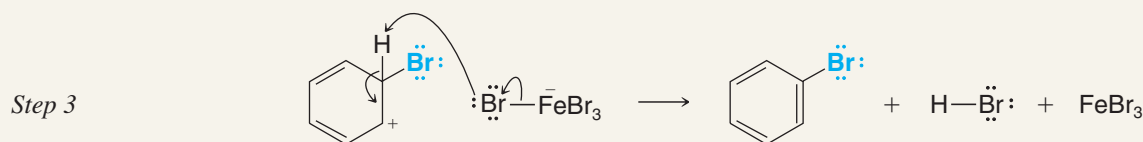
Step 1



**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.

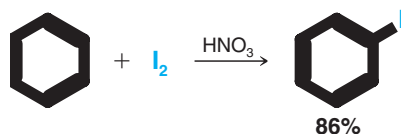


A proton is removed from the arenium ion to form bromobenzene and regenerate the catalyst.

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.

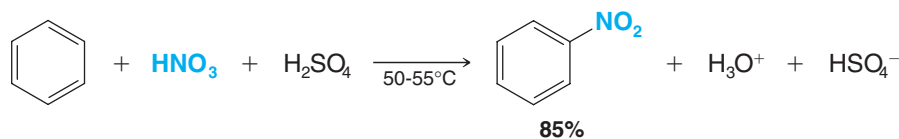
Iodine, on the other hand, is so unreactive that a special technique has to be used to effect direct iodination; the reaction has to be carried out in the presence of an oxidizing agent such as nitric acid:



Biochemical iodination, as in the biosynthesis of thyroxine, occurs with enzymatic catalysis. Thyroxine biosynthesis is discussed further in “The Chemistry of ... Iodine Incorporation in Thyroxine Biosynthesis” box in Section 15.11E.

15.4 Nitration of Benzene

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

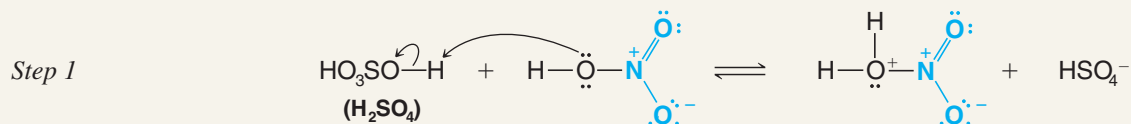


Concentrated sulfuric acid increases the rate of the reaction by increasing the concentration of the electrophile, the nitronium ion (NO_2^+), as shown in the first two steps of the following mechanism.

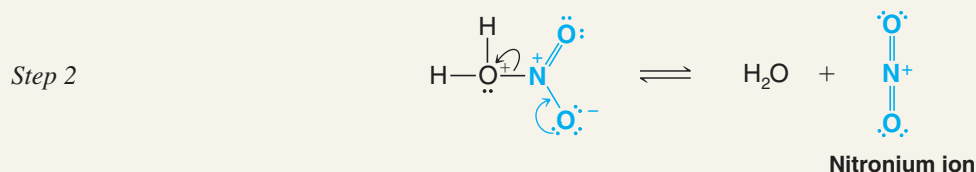


A MECHANISM FOR THE REACTION

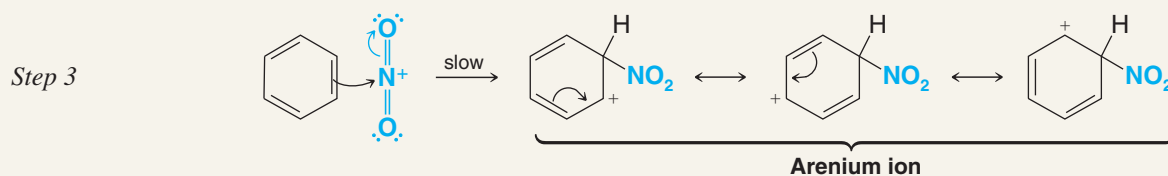
Nitration of Benzene



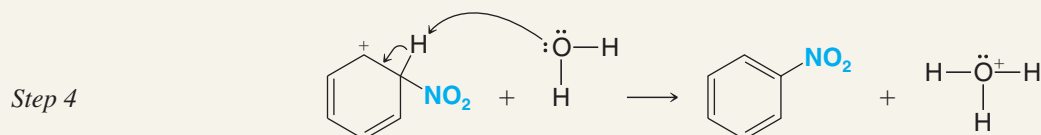
In this step nitric acid accepts a proton from the stronger acid, sulfuric acid.



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



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



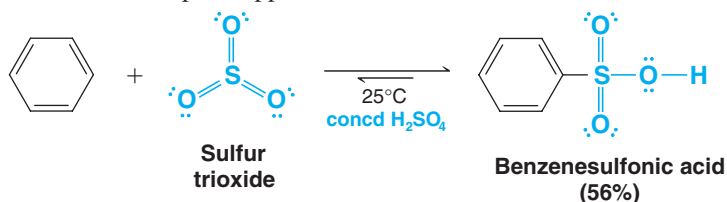
The arenium ion then loses a proton to a Lewis base and becomes nitrobenzene.

Review Problem 15.2

Given that the $\text{p}K_a$ 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.



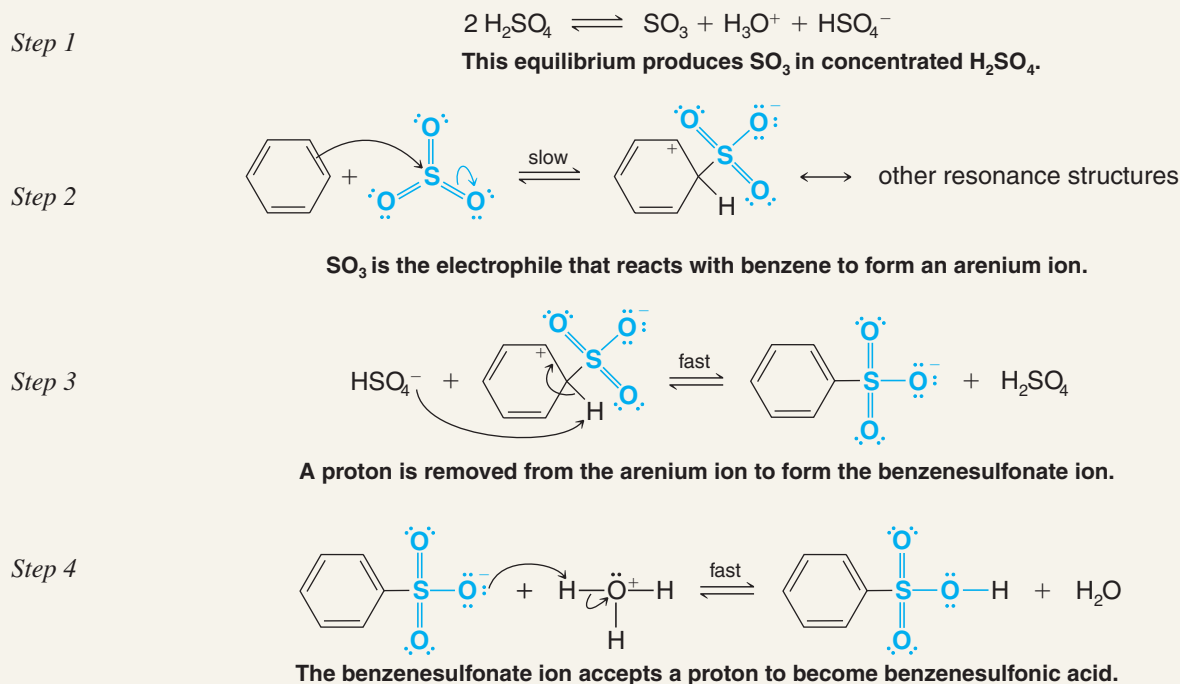


In concentrated sulfuric acid, sulfur trioxide is produced in an equilibrium in which H_2SO_4 acts as both an acid and a base (see step 1 of the following mechanism).

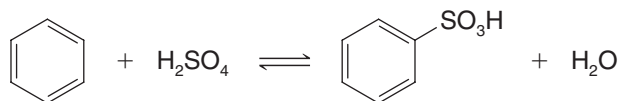


A MECHANISM FOR THE REACTION

Sulfonation of Benzene



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.

- 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.

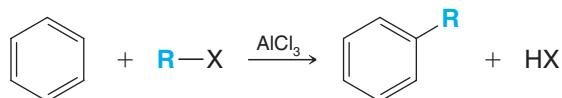
Helpful Hint

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

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:



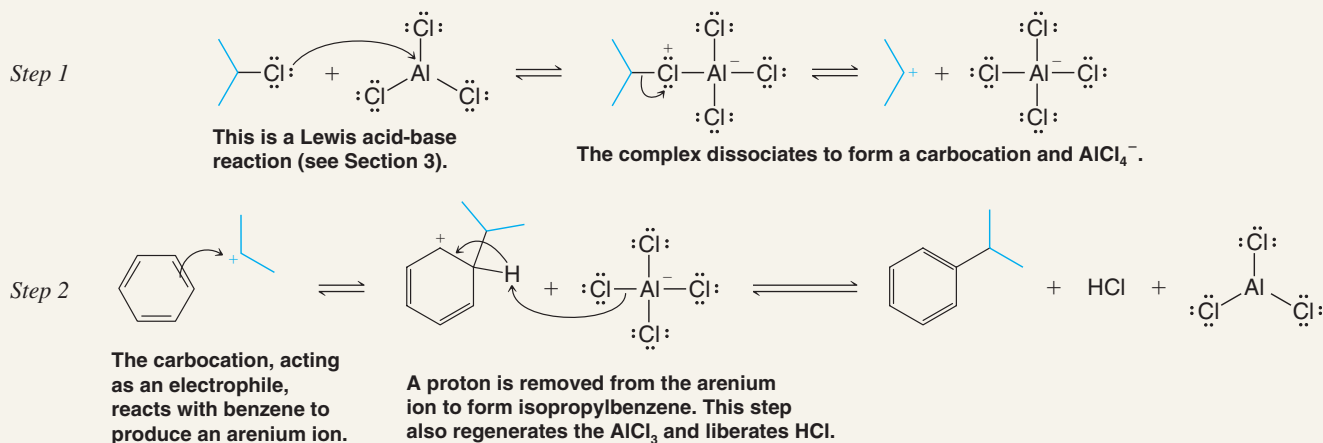
- The mechanism for the reaction starts with the formation of a carbocation.
- The carbocation then acts as an electrophile and attacks the benzene ring to form an arenium ion.
- The arenium ion then loses a proton.

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



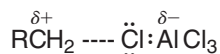
A MECHANISM FOR THE REACTION

Friedel–Crafts Alkylation



- When $\text{R}-\text{X}$ 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:

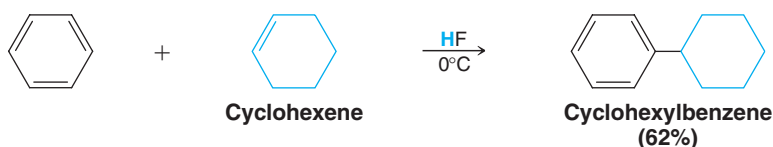
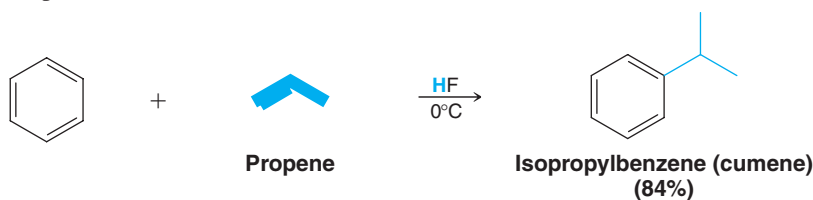


Even though this complex is not a simple carbocation, it acts as if it were and it transfers a positive alkyl group to the aromatic ring.

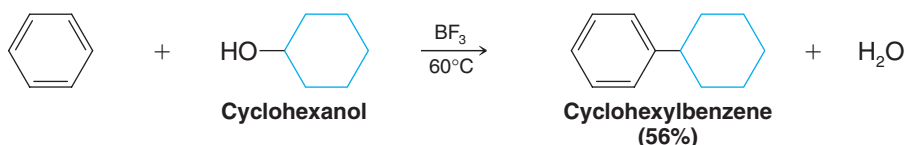
- These complexes react so much like carbocations that they also undergo typical carbocation rearrangements (Section 15.8).
- Friedel–Crafts alkylations are not restricted to the use of alkyl halides and aluminum chloride. Other pairs of reagents that form carbocations (or species like carbocations)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



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



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



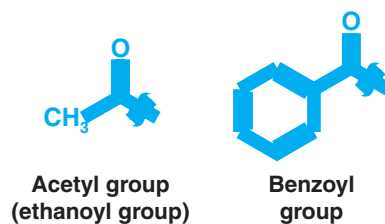
There are several important limitations of the Friedel–Crafts reaction. These are discussed in Section 15.8.

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.

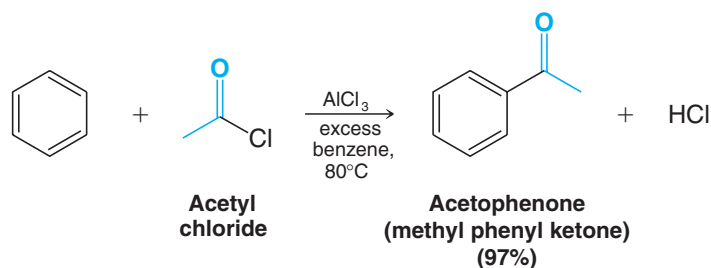
Review Problem 15.3

15.7 Friedel–Crafts Acylation

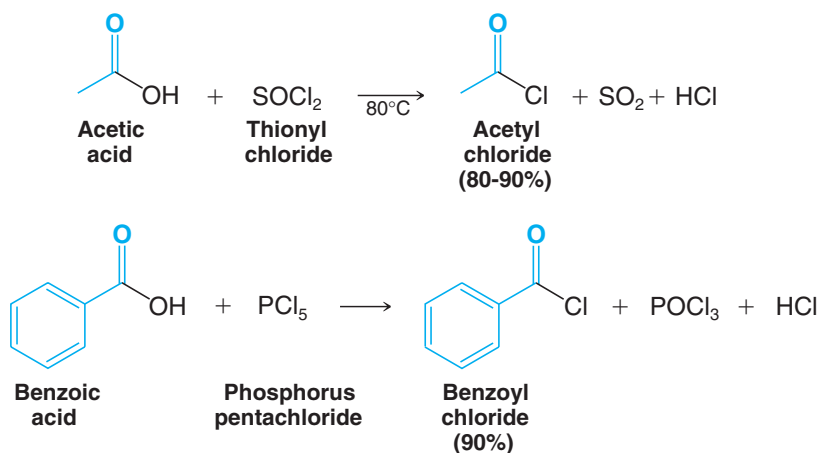
The $\text{R}-\text{C}(=\text{O})-$ group is called an **acyl group**, and a reaction whereby an acyl group is introduced into a compound is called an **acylation** reaction. Two common acyl groups are the acetyl group and the benzoyl group. (The benzoyl group should not be confused with the benzyl group, $-\text{CH}_2\text{C}_6\text{H}_5$; see Section 14.2.)



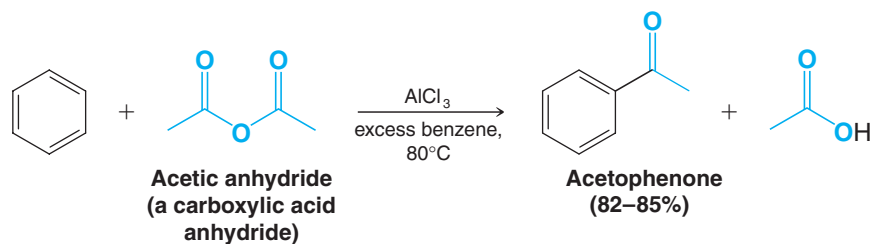
The **Friedel–Crafts acylation** reaction is often carried out by treating the aromatic compound with an **acyl halide** (often an acyl chloride). Unless the aromatic compound is one that is highly reactive, the reaction requires the addition of at least one equivalent of a Lewis acid (such as AlCl_3)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



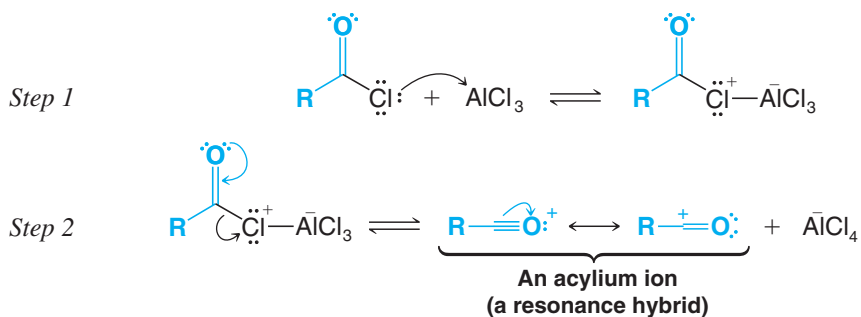
Acyl chlorides, also called **acid chlorides**, are easily prepared (Section 18.5) by treating carboxylic acids with thionyl chloride (SOCl_2) or phosphorus pentachloride (PCl_5):



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



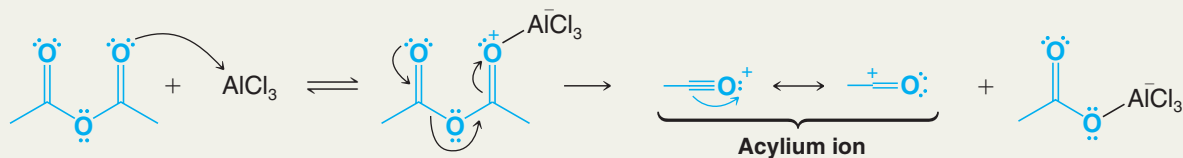
In most Friedel–Crafts acylations the electrophile appears to be an **acylium ion** formed from an acyl halide in the following way:



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.





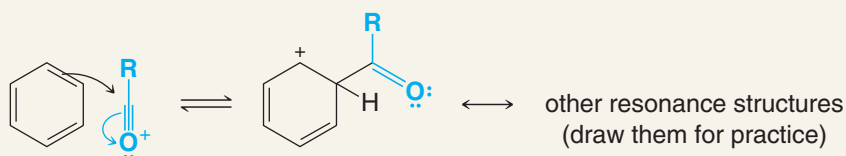
The remaining steps in the Friedel–Crafts acylation of benzene are the following:



A MECHANISM FOR THE REACTION

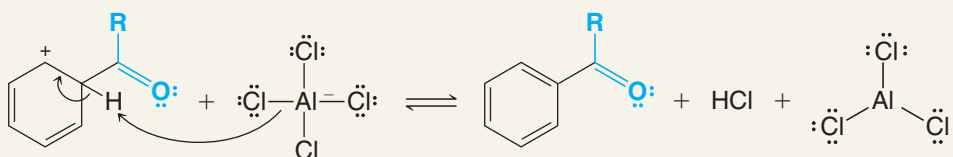
Friedel–Crafts Acylation

Step 3



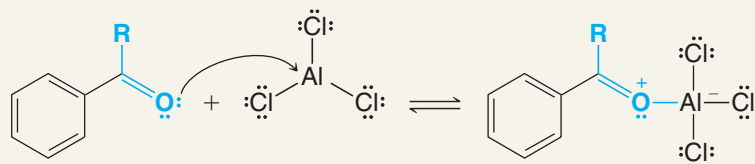
The acylium ion, acting as an electrophile, reacts with benzene to form the arenium ion.

Step 4



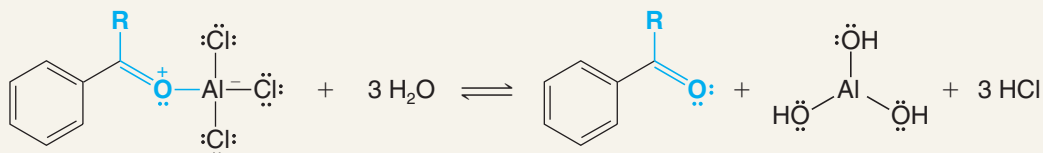
A proton is removed from the arenium ion, forming the aryl ketone.

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.

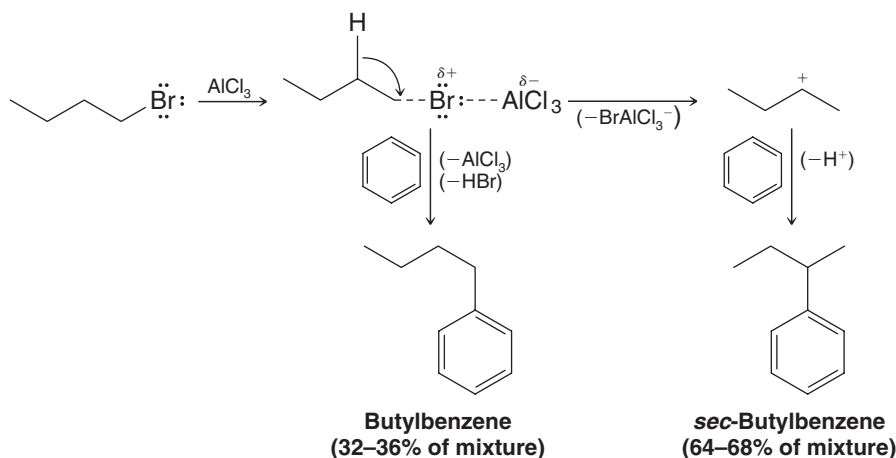
15.8 Limitations of Friedel–Crafts Reactions

Several restrictions limit the usefulness of Friedel–Crafts reactions:

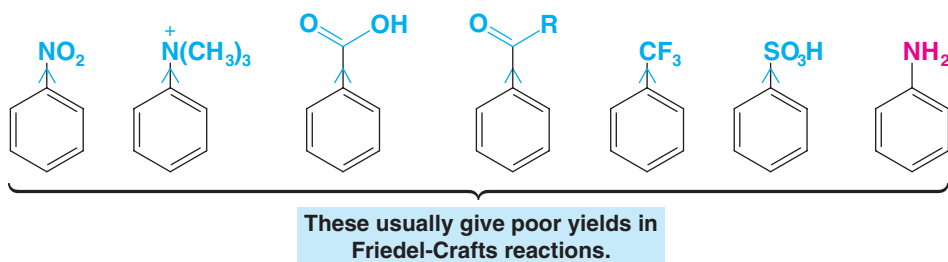
1. When the carbocation formed from an alkyl halide, alkene, or alcohol can rearrange to one or more carbocations that are more stable, it usually does so, and the major products obtained from the reaction are usually those from the more stable carbocations.

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.

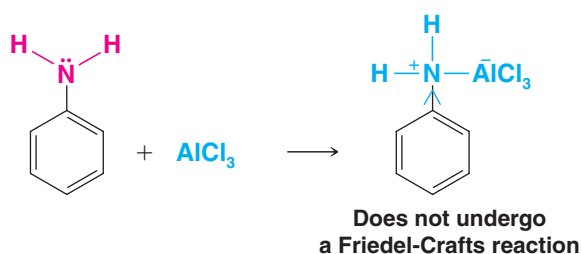
Then benzene reacts with both kinds of carbocations to form both butylbenzene and *sec*-butylbenzene:



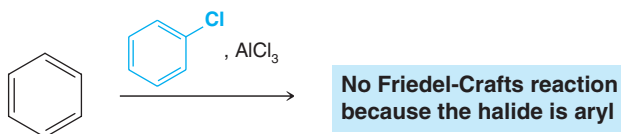
2. Friedel–Crafts reactions usually give poor yields when powerful electron-withdrawing groups (Section 15.11) are present on the aromatic ring or when the ring bears an —NH_2 , —NHR , or —NR_2 group. This applies to both alkylations and acylations.

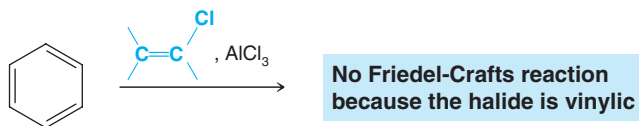


We shall learn in Section 15.10 that groups present on an aromatic ring can have a large effect on the reactivity of the ring toward electrophilic aromatic substitution. **Electron-withdrawing groups make the ring less reactive by making it electron deficient.** Any substituent more electron withdrawing (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,

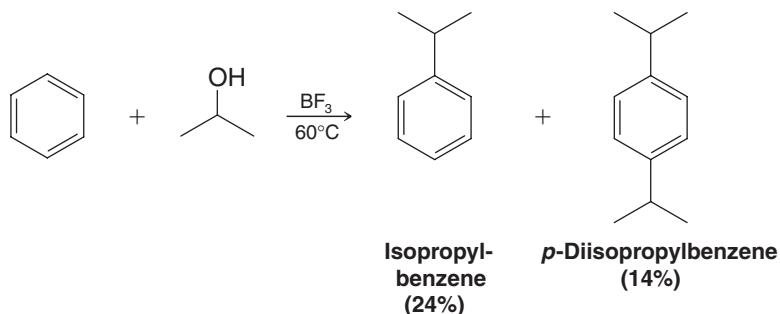


3. Aryl and vinylic halides cannot be used as the halide component because they do not form carbocations readily (see Section 6.14A):





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

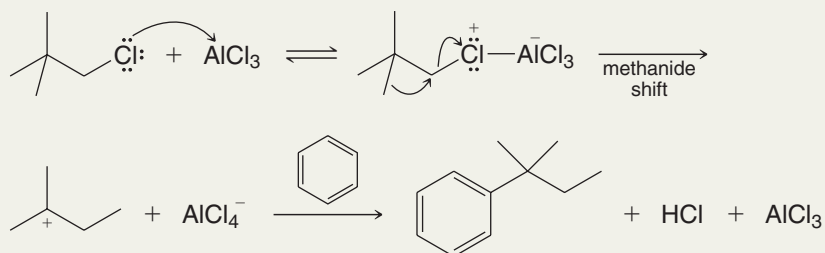


Polyacylations are not a problem in Friedel–Crafts acylations, however. The acyl group (RCO—) by itself is an electron-withdrawing group, and when it forms a complex with AlCl_3 in the last step of the reaction (Section 15.7), it is made even more electron withdrawing. This strongly inhibits further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

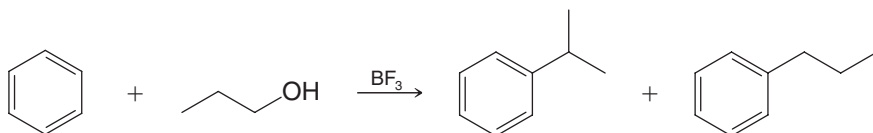
Solved Problem 15.2

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.



Provide a mechanism that accounts for the following result.



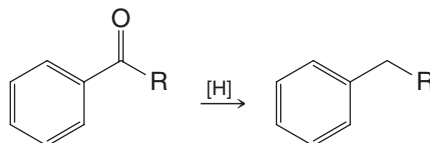
Review Problem 15.4

15.9 Synthetic Applications of Friedel–Crafts Acylations: The Clemmensen Reduction

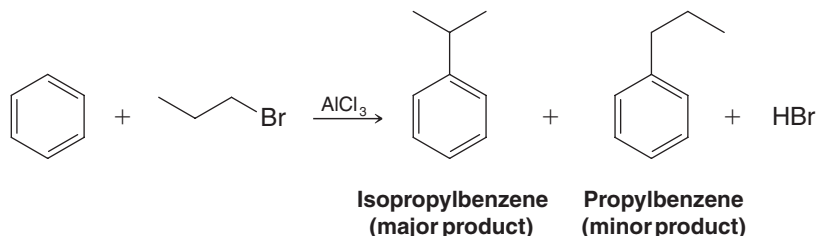
- Rearrangements of the carbon chain do not occur in Friedel–Crafts acylations.

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.

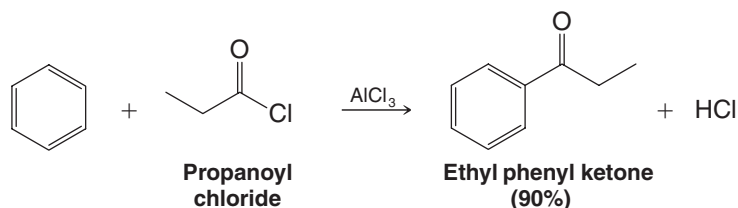
- The carbonyl group of an aryl ketone can be reduced to a CH_2 group.



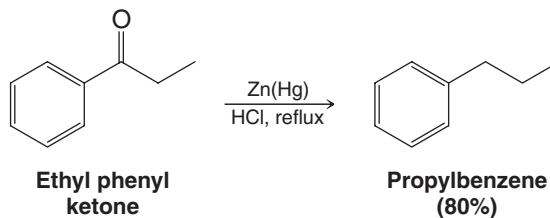
As an example, let us consider the problem of synthesizing propylbenzene. If we attempt this synthesis through a Friedel–Crafts alkylation, a rearrangement occurs and the major product is isopropylbenzene (see also Review Problem 15.4):



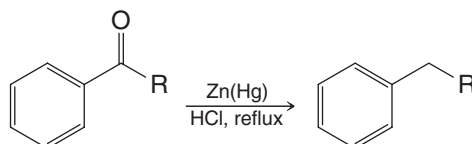
By contrast, the Friedel–Crafts acylation of benzene with propanoyl chloride produces a ketone with an unrearranged carbon chain in excellent yield:



This ketone can then be reduced to propylbenzene by several methods. One general method—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.]

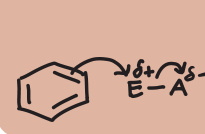


In general,

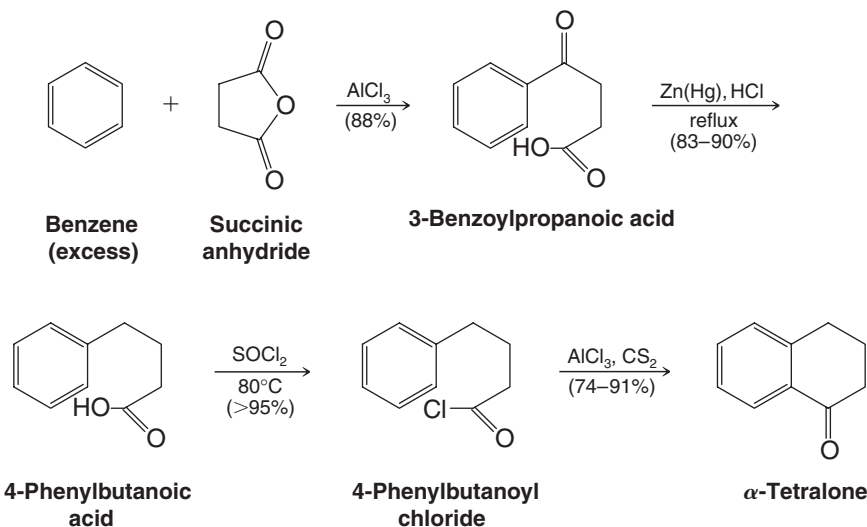


Helpful Hint

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



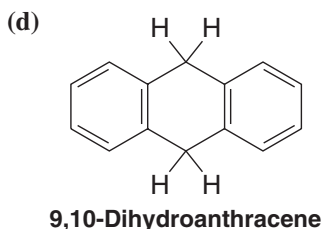
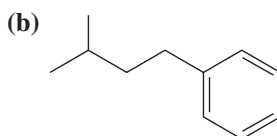
When cyclic anhydrides are used as one component, the Friedel–Crafts acylation provides a means of adding a new ring to an aromatic compound. One illustration is shown here. Note that only the ketone is reduced in the Clemmensen reduction step. The carboxylic acid is unaffected:



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

Review Problem 15.5

(a) Butylbenzene



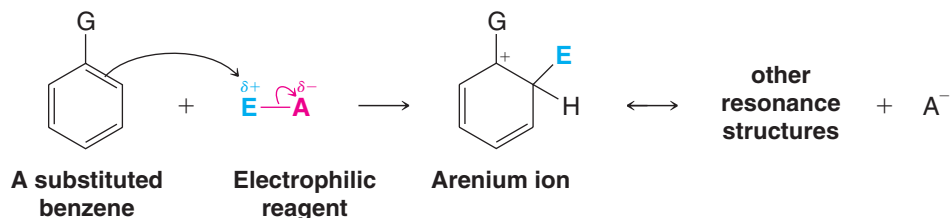
15.10 Substituents Can Affect Both the Reactivity of the Ring and the Orientation of the Incoming Group

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.

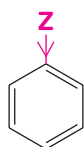
- A substituent can make the ring **more reactive** than benzene (i.e., it can make the compound react faster than benzene reacts). Such a group is called an **activating group**.
- A substituent can make the ring **less reactive** than benzene (i.e., it can make the compound react more slowly than benzene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

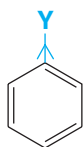


If a substituent that is already present on the ring makes the ring more electron rich by donating electrons to it, then the ring will be more reactive toward the electrophile and the reaction will take place faster.



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.

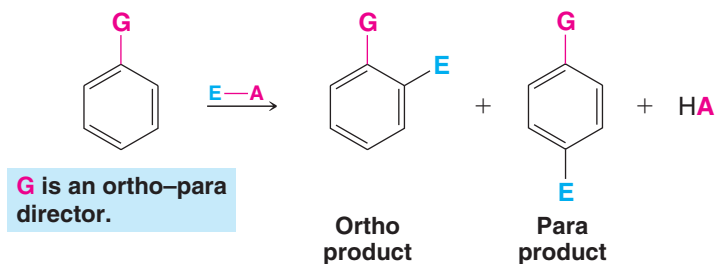


If **Y** withdraws electrons the ring is electron poor and it reacts more slowly with an electrophile.

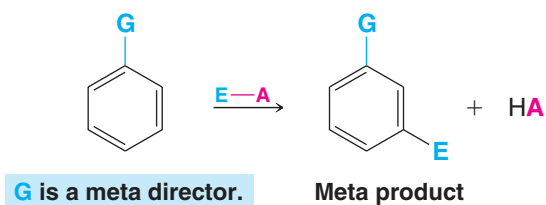
15.10B Ortho-Para-Directing Groups and Meta-Directing Groups

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.



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

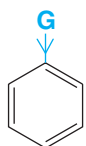




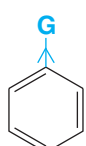
15.10C Electron-Donating and Electron-Withdrawing Substituents

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**.

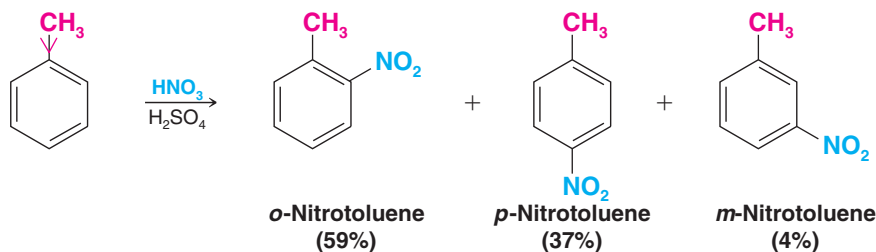
Toluene, for example, reacts considerably faster than benzene in all electrophilic substitutions:



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:



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.

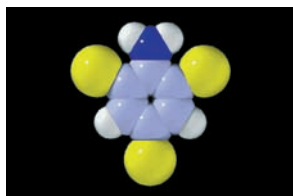
Explain how the percentages just given show that the methyl group exerts an ortho–para directive effect by considering the percentages that would be obtained if the methyl group had no effect on the orientation of the incoming electrophile.

Review Problem 15.6

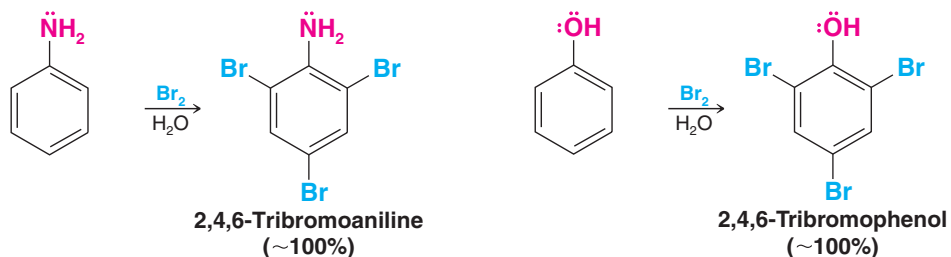
Predominant substitution of toluene at the ortho and para positions is not restricted to nitration reactions. The same behavior is observed in halogenation, sulfonation, and so forth.

- Groups that have an unshared electron pair on the atom attached to the aromatic ring, such as amino, hydroxyl, alkoxy, 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.



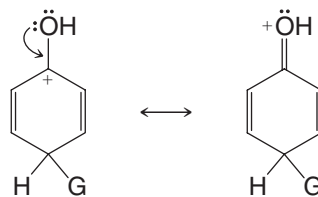
2,4,6-Tribromoaniline



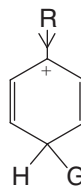
- In general, substituent groups with unshared electron pairs on the atom adjacent to the benzene ring (e.g., hydroxyl, amino) are stronger activating groups than groups without unshared electron pairs (i.e., alkyl groups).
- Contribution of electron density to the benzene ring through resonance is generally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

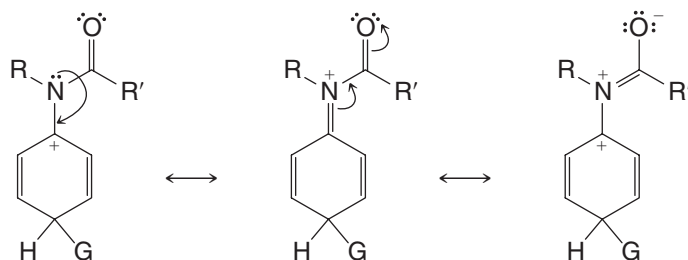
Examples of arenium ion stabilization by resonance and inductive effects



Electron donation through resonance



Electron donation through the inductive effect

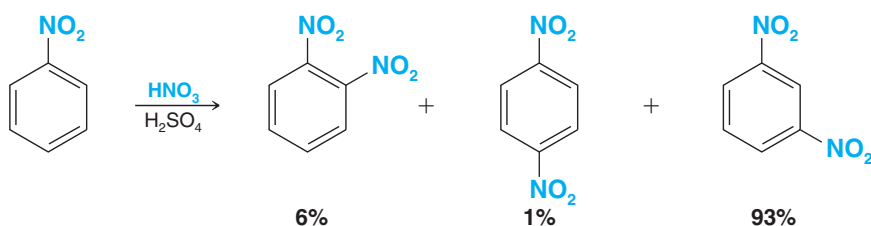


Electron donation to the ring by resonance is reduced when there is an alternative resonance pathway away from the ring.

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 ($-\text{CO}_2\text{H}$), the sulfonic acid group ($-\text{SO}_3\text{H}$), and the trifluoromethyl group ($-\text{CF}_3$) are also deactivating groups; they are also meta directors.

15.10F Halo Substituents: Deactivating Ortho-Para Directors

- The chloro and bromo 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

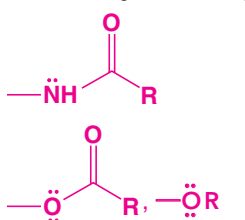
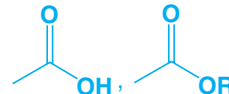
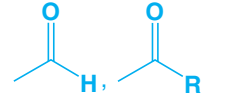
Reaction	Ortho Product (%)	Para Product (%)	Total Ortho and Para (%)	Meta Product (%)
Chlorination	39	55	94	6
Bromination	11	87	98	2
Nitration	30	70	100	
Sulfonation		100	100	

Similar results are obtained from electrophilic substitutions of bromobenzene.

15.10G Classification of Substituents

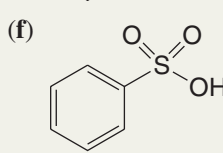
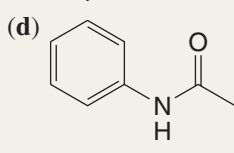
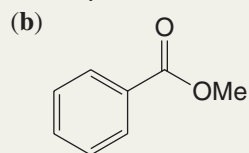
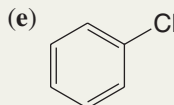
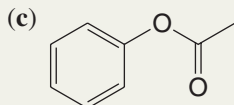
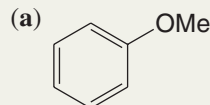
A summary of the effects of some substituents on reactivity and orientation is provided in Table 15.2.

TABLE 15.2 Effect of Substituents on Electrophilic Aromatic Substitution

Ortho-Para Directors	Meta Directors
Strongly Activating $-\ddot{\text{N}}\text{H}_2, -\ddot{\text{N}}\text{HR}, -\text{NR}_2$ $-\ddot{\text{O}}\text{H}, -\ddot{\text{O}}:^-$	Moderately Deactivating $-\text{C}\equiv\text{N}$ $-\text{SO}_3\text{H}$
Moderately Activating 	 
Weakly Activating $-\text{R}$ (alkyl) $-\text{C}_6\text{H}_5$ (phenyl)	Strongly Deactivating $-\text{NO}_2$ $-\text{NR}_3^+$ $-\text{CF}_3, -\text{CCl}_3$
Weakly Deactivating $-\ddot{\text{F}}:, -\ddot{\text{Cl}}:, -\ddot{\text{Br}}:, -\ddot{\text{I}}:$	

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.



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.

Review 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

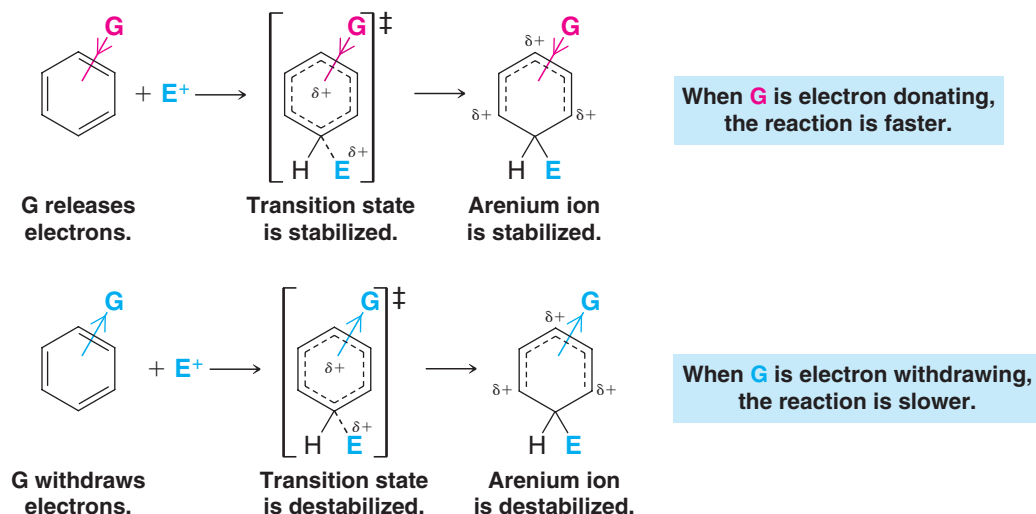
- We can account for relative reaction rates by examining the transition state for the rate-determining steps.

We know that any factor that increases the energy of the transition state relative to that of the reactants decreases the relative rate of the reaction. It does this because it increases the free energy of activation of the reaction. In the same way, any factor that decreases 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.

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** **withdraws** or **releases** 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 apparently 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.

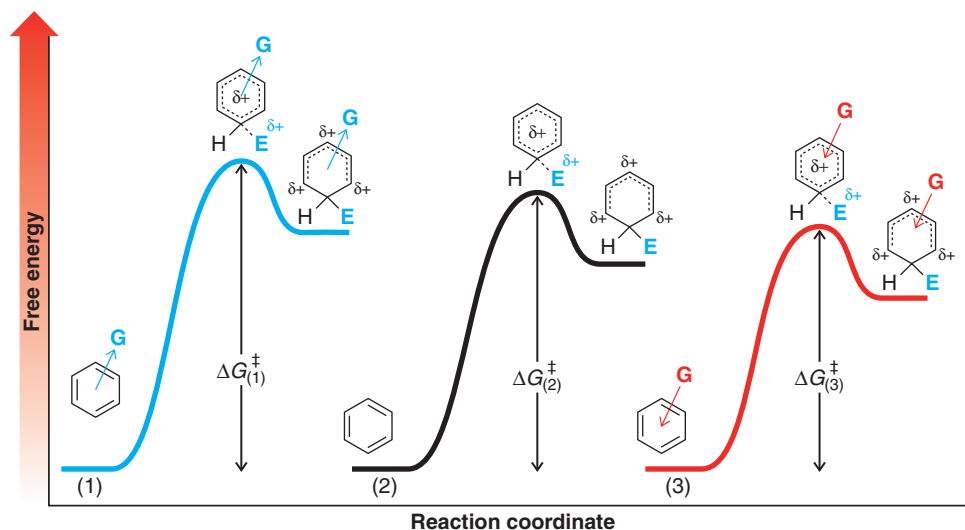
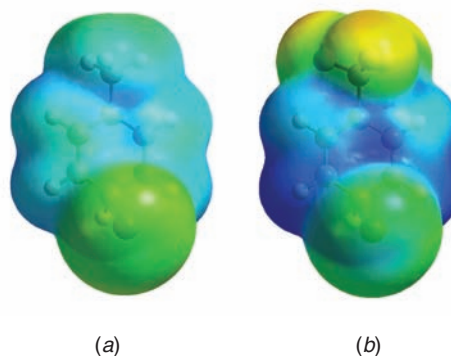


Figure 15.4 A comparison of free-energy profiles for arenium ion formation in a ring with an electron-withdrawing substituent ($\rightarrow G$), no substituent, and an electron-donating substituent ($\leftarrow G$). In (1) (blue energy profile), the electron-withdrawing group G raises the transition 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 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. 15.5a) is that from electrophilic addition of bromine to methylbenzene (toluene) at the para position. The arenium ion at the right (Fig. 15.5b) is that from electrophilic addition of bromine to trifluoromethylbenzene at the meta position. Notice that the atoms of the ring in Fig. 15.5a 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

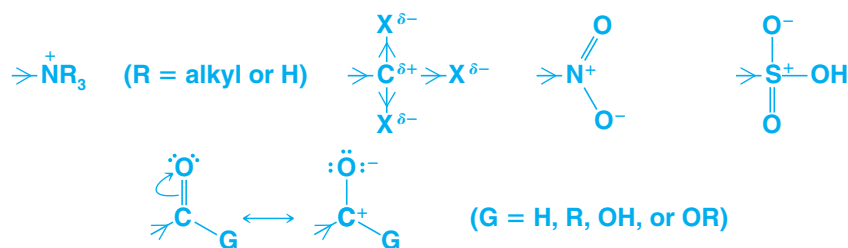
We can account for the electron-withdrawing and electron-releasing properties of groups on the basis of two factors: *inductive effects* and *resonance effects*. We shall also see that these two factors determine orientation in aromatic substitution reactions.



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:



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:



This is also the order of the activating ability of these groups.

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

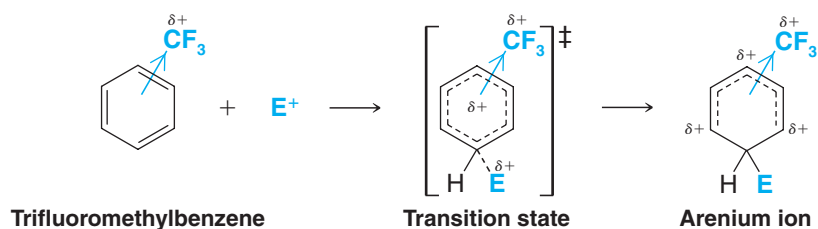
When X = F, this order can be related to the electronegativity of the atoms with the nonbonding pair. The more electronegative the atom is, the less able it is to accept the positive charge (fluorine is the most electronegative, nitrogen the least). When X = Cl, Br, or I, the relatively poor electron-donating 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 $2p$ 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

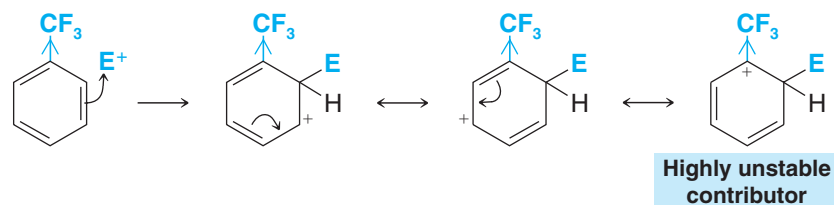
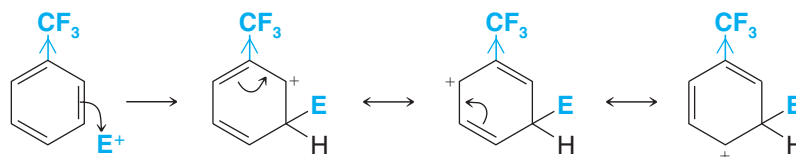
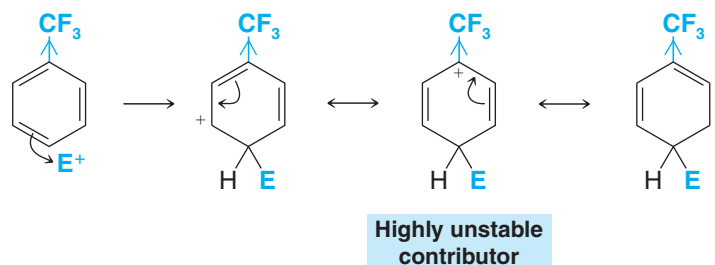
- All meta-directing groups have either a partial positive charge or a full positive charge on the atom directly attached to the ring.

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:



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.

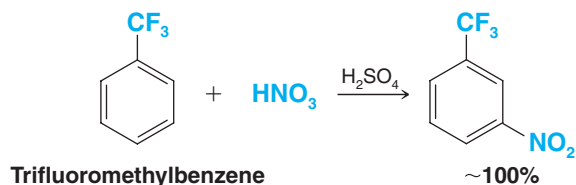
Ortho Attack**Meta Attack****Para Attack**

- 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:



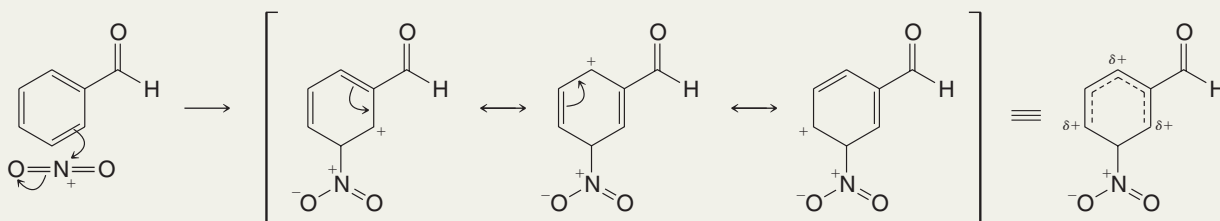
Bear in mind, however, that meta substitution is favored only in the sense that *it is the least unfavorable of three unfavorable pathways*. The free energy of activation for substitution at the meta position of trifluoromethylbenzene is less than that for attack at an ortho or para position, but it 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

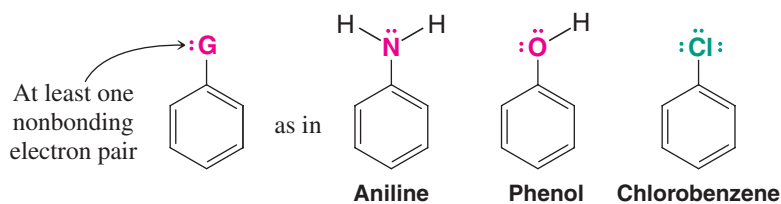
Write contributing resonance structures and the resonance hybrid for the arenium ion formed when benzaldehyde undergoes nitration at the meta position.

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:



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.

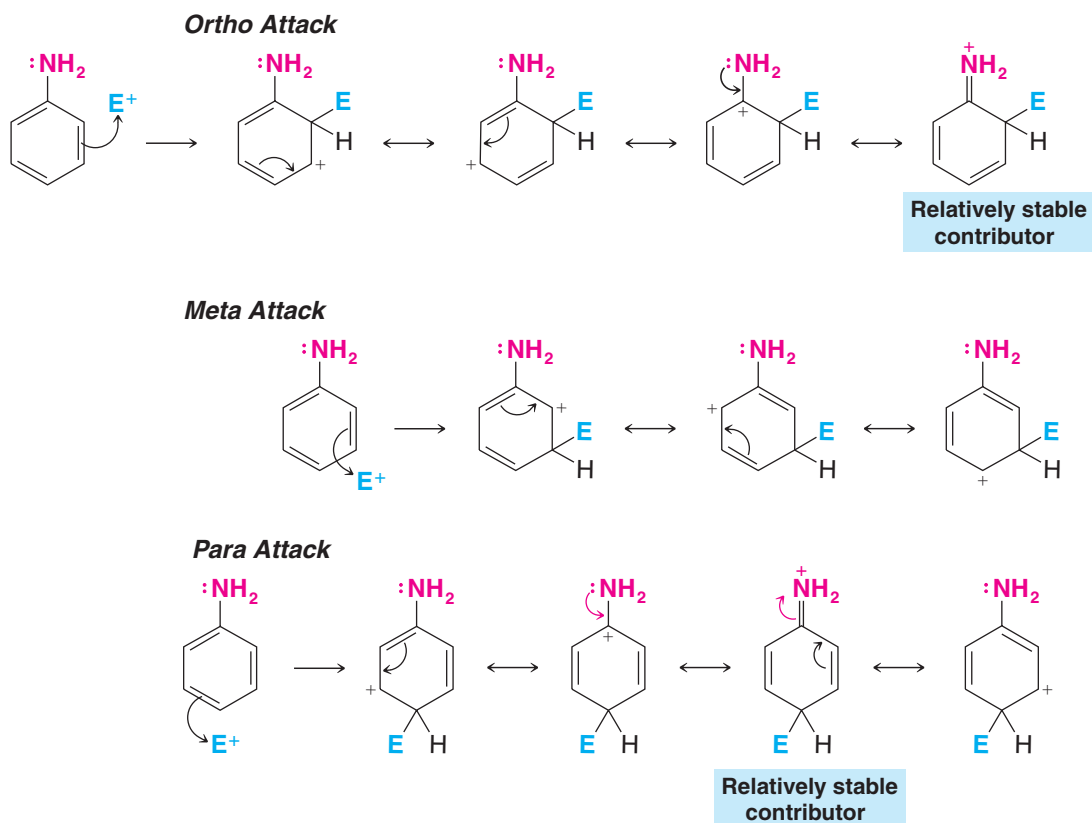
Except for the halogens, the primary effect of these groups on relative reactivity of the benzene ring is also caused by an electron-releasing resonance effect. And, again, this effect operates primarily in the transition state leading to the arenium ion.

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:



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, 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



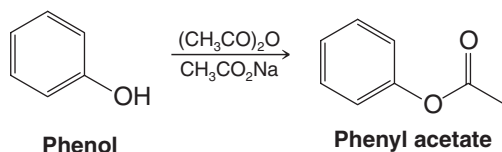
these structures are unusually stable, they make a large—and *stabilizing*—contribution to the hybrid. This means, of course, that the ortho- and para-substituted arenium ions themselves are considerably more stable than the arenium ion that results from the meta attack. The transition states leading 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.

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.

Review Problem 15.8

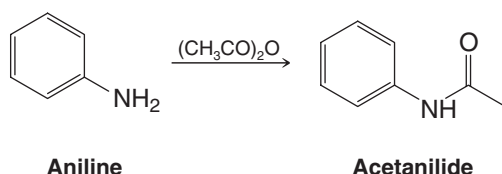
Phenol reacts with acetic anhydride in the presence of sodium acetate to produce the ester phenyl acetate:

Review Problem 15.9



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

- What structural feature of the CH_3COO — group explains this?
- 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.
- 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:

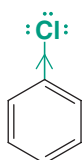


What kind of directive effect would you expect the acetamido group (CH_3CONH —) to have?

- Explain why it is much less activating than the amino group, — NH_2 .

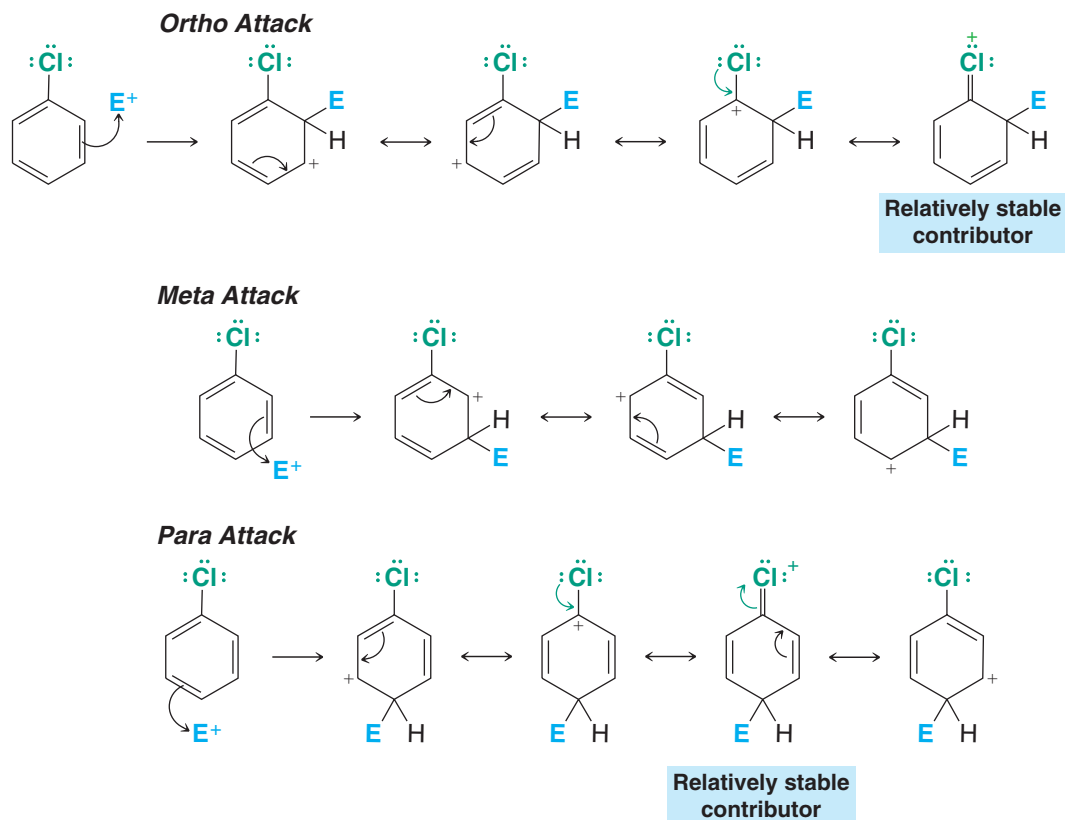
The directive and reactivity effects of halo substituents may, at first, seem to be contradictory. *The halo groups are the only ortho–para directors (in Table 15.2) that are deactivating groups.* [Because of this behavior we have color coded halogen substituents green rather than red (electron donating) 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.



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.

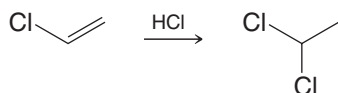
- Through their electron-withdrawing inductive effect, halo groups make the ring more electron deficient than that of benzene. This causes the free energy of activation for any electrophilic aromatic substitution reaction to be greater than that for benzene, and, therefore, halo groups are deactivating.
- 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 \ddot{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 $2p$ orbital with a chlorine $3p$ orbital. Such overlap is less effective; the chlorine atom is much larger and its $3p$ 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 ($G = -\ddot{F}:$) is the most reactive halobenzene in spite of the high electronegativity of fluorine and the fact that $-\ddot{F}:$ is the most powerful ortho-para director of the halogens. With fluorine, donation of an electron pair arises from overlap of a $2p$ orbital of fluorine with a $2p$ orbital of carbon (as with $-\ddot{N}H_2$ and $-\ddot{O}H$). This overlap is effective because the orbitals of $=C$ and $-\ddot{F}:$ are of the same relative size.

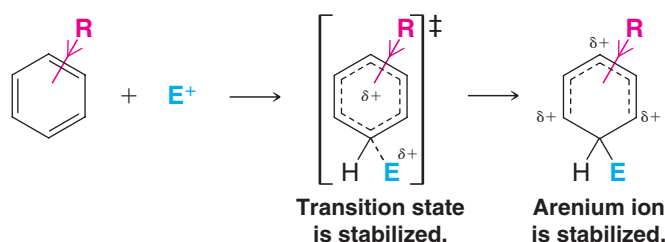
Chloroethene adds hydrogen chloride more slowly than ethene, and the product is 1,1-dichloroethane. How can you explain this using resonance and inductive effects?



Review Problem 15.10

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:

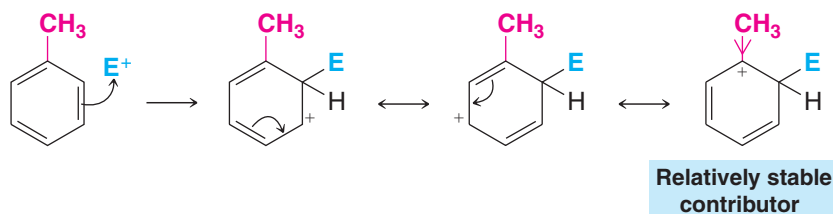


For an alkylbenzene the free energy of activation of the step leading to the arenium ion (just shown) is lower than that for benzene, and alkylbenzenes react faster.

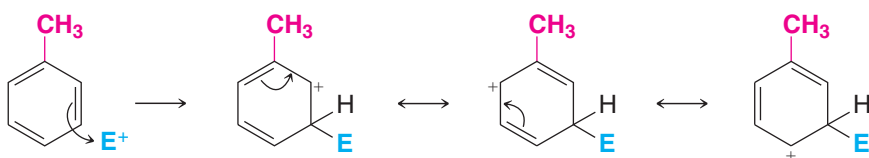
Alkyl groups are ortho-para directors. We can also account for this property of alkyl groups on the basis of their ability to release electrons—an effect that is particularly important when the alkyl group is attached directly to a carbon that bears a positive charge. (Recall the ability of alkyl groups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

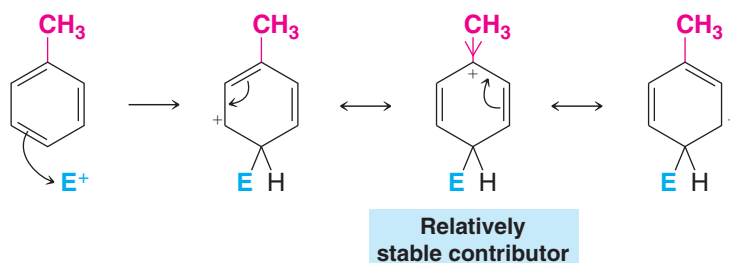
If, for example, we write resonance structures for the arenium ions formed when toluene undergoes electrophilic substitution, we get the results shown below:

Ortho Attack



Meta Attack

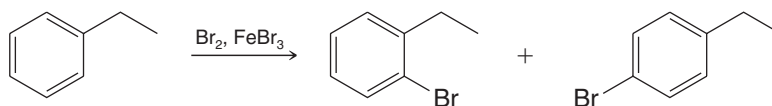


Para Attack

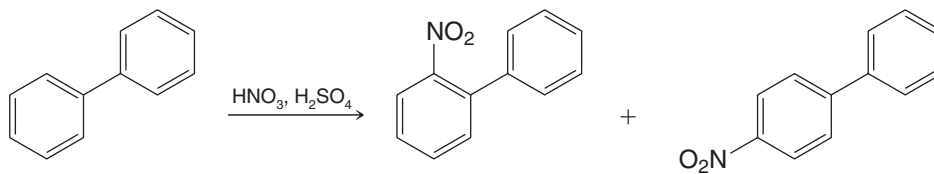
In ortho attack and para attack we find that we can write resonance structures in which the methyl group is directly attached to a positively charged carbon of the ring. These structures are more *stable* relative to any of the others because in them the stabilizing influence of the methyl group (by 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.

Review Problem 15.11

Write resonance structures for the arenium ions formed when ethylbenzene reacts with a Br^+ ion (as formed from $\text{Br}_2/\text{FeBr}_3$) to produce the following ortho and para products.

**Review Problem 15.12**

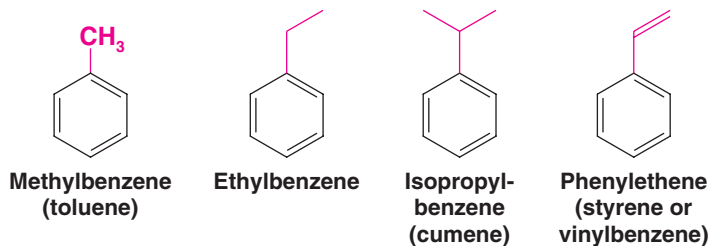
Provide a mechanism for the following reaction and explain why it occurs faster than nitration of benzene.

**15.11F Summary of Substituent Effects on Orientation and Reactivity**

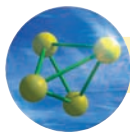
With a theoretical understanding now in hand of substituent effects on orientation and reactivity, we refer you back to Table 15.2 for a summary of specific groups and their effects.

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**:



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



THE CHEMISTRY OF ...

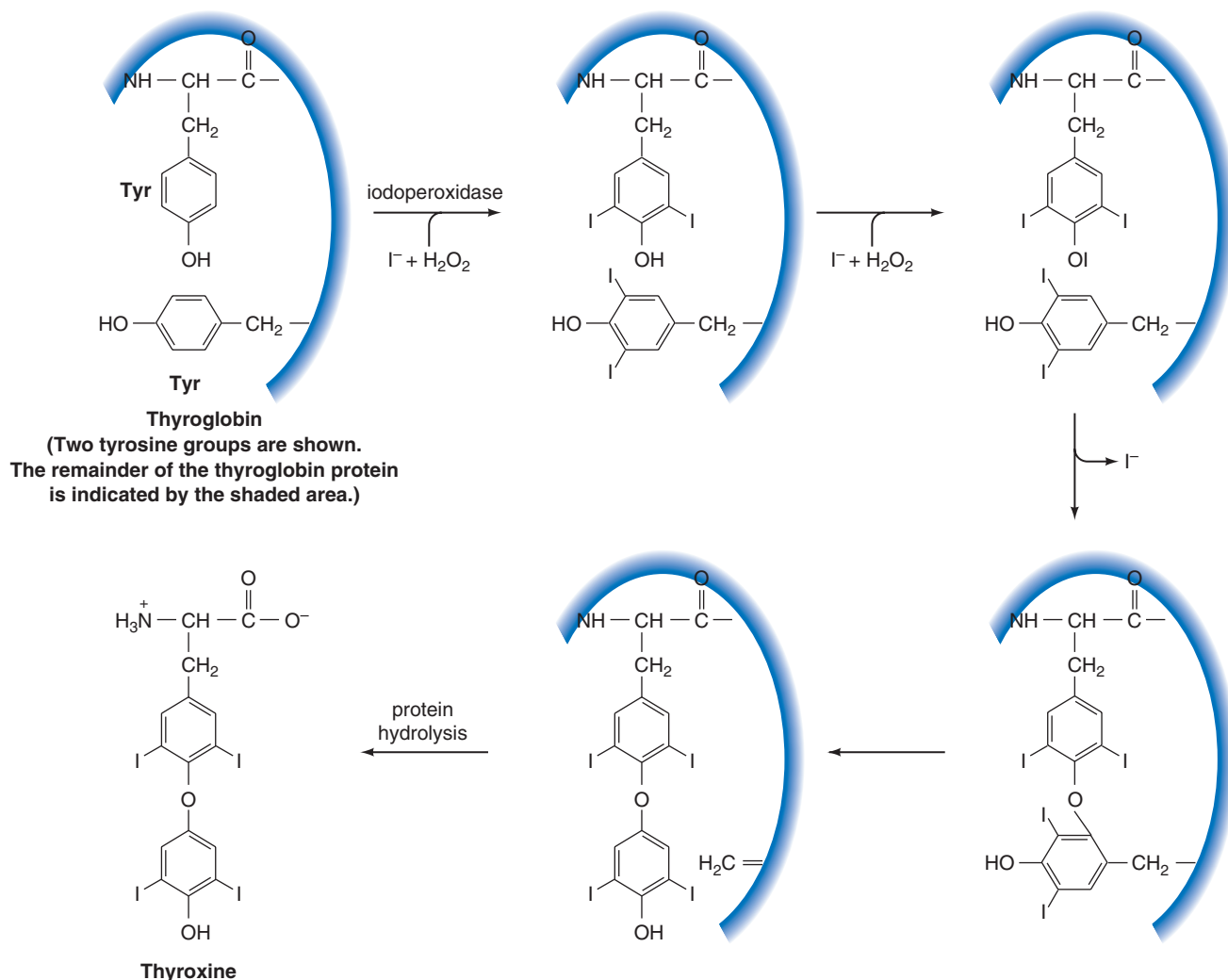
Iodine Incorporation in Thyroxine Biosynthesis

The biosynthesis of thyroxine involves introduction of iodine atoms into tyrosine units of thyroglobin. This process occurs by a biochemical version of electrophilic aromatic substitution. An iodoperoxidase enzyme catalyzes the reaction between iodide anions and hydrogen peroxide to generate an electrophilic form of iodine (presumably a species like $I-OH$). Nucleophilic attack by the aromatic ring of tyrosine on the electrophilic iodine leads to incorporation of iodine at the 3 and 5 positions of the tyrosine rings in thyroglobulin. These are the positions ortho to the phenol hydroxyl group, precisely where we would expect electrophilic aromatic substitution to occur in tyrosine. (Substitution para to the hydroxyl cannot occur in tyrosine because that position is blocked, and substitution ortho to the alkyl group is less favored than ortho to the hydroxyl.) Electrophilic iodine is

also involved in the coupling of two tyrosine units necessary to complete biosynthesis of thyroxine.

Electrophilic aromatic substitution also plays a role in the 1927 laboratory synthesis of thyroxine by C. Harington and G. Barger. Their synthesis helped prove the structure of this important hormone by comparison of the synthetic material with natural thyroxine. Harington and Barger used electrophilic aromatic substitution to introduce the iodine atoms at the ortho positions in the phenol ring of thyroxine. They used a different reaction, however, to introduce the iodine atoms in the other ring of thyroxine (*nucleophilic* aromatic substitution—a reaction we shall study in Chapter 21.)

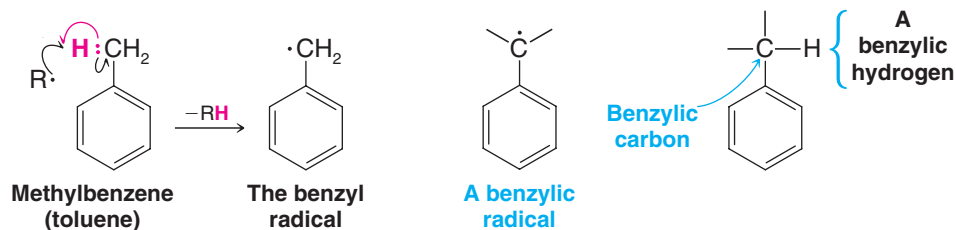
(Figure below adapted with permission of John Wiley & Sons, Inc. from Voet, D. and Voet, J. G., *Biochemistry*, 2nd edition. © 1995 Voet D. and Voet, J. G.)



The biosynthesis of thyroxine in the thyroid gland through the iodination, rearrangement, and hydrolysis (proteolysis) of thyroglobin Tyr residues. The relatively scarce I^- is actively sequestered by the thyroid gland.

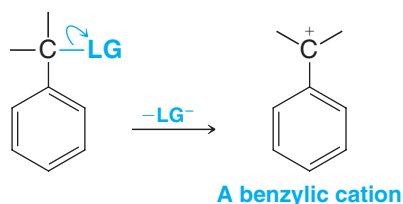
15.12A Benzylic Radicals and Cations

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

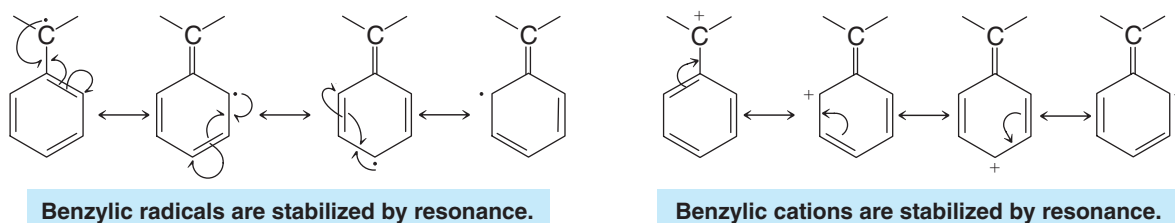


The name benzyl radical is used as a specific name for the radical produced in this reaction. The general name **benzylic radical** applies to all radicals that have an unpaired electron on the side-chain carbon atom that is directly attached to the benzene ring. The hydrogen atoms of the carbon atom 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**:

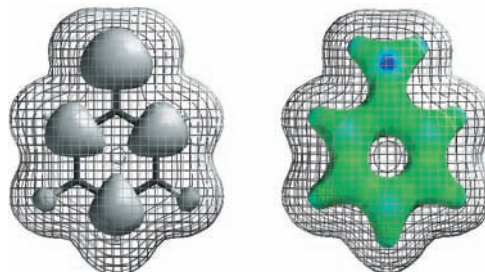


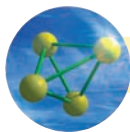
Benzylic radicals and benzylic cations are *conjugated unsaturated systems* and *both are unusually stable*. They have approximately the same stabilities as allylic radicals and cations. This exceptional stability of benzylic radicals and cations can be explained by resonance theory. In the case of each 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.



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.

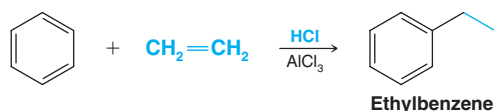




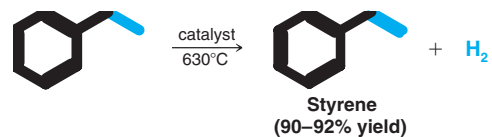
THE CHEMISTRY OF ...

Industrial Styrene Synthesis

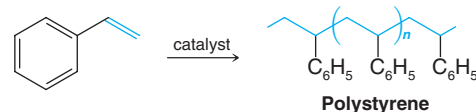
Styrene is one of the most important industrial chemicals—more than 11 billion pounds is produced each year. The starting material for a major commercial synthesis of styrene is ethylbenzene, produced by Friedel–Crafts alkylation of benzene:



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



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

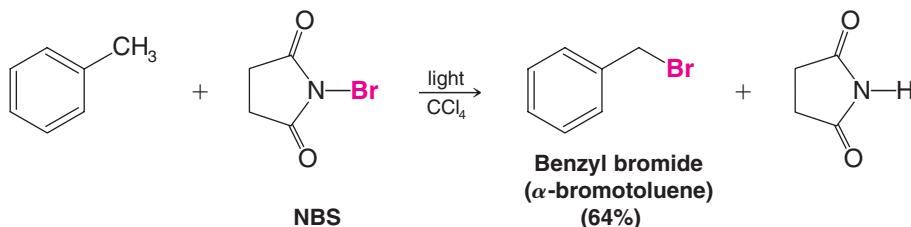


15.12B Halogenation of the Side Chain: Benzylic Radicals

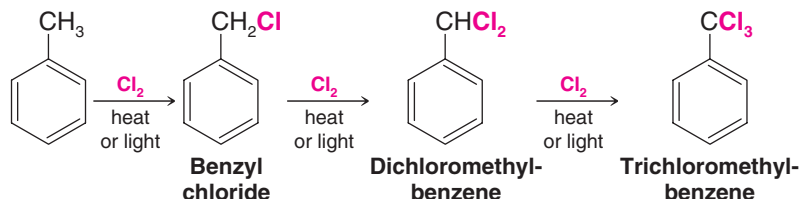
We have already seen that we can substitute bromine and chlorine for hydrogen atoms on the *ring* of toluene and other alkylaromatic compounds using electrophilic aromatic substitution reactions. Chlorine and bromine can also be made to replace hydrogen atoms that are on a *benzylic* carbon, such as the methyl group of toluene.

- Benzylic halogenation is carried out *in the absence of Lewis acids and under conditions that favor the formation of radicals*.

When toluene reacts with *N*-bromosuccinimide (NBS) in the presence of light, for example, the major product is benzyl bromide. *N*-Bromosuccinimide furnishes a low concentration of Br_2 , and the reaction is analogous to that for allylic bromination that we studied in Section 13.2B.



Side-chain chlorination of toluene takes place in the gas phase at 400–600°C or in the presence of UV light. When an excess of chlorine is used, multiple chlorinations of the side chain occur:



These halogenations take place through the same radical mechanism we saw for alkanes in Section 10.4. The halogens dissociate to produce halogen atoms and then the halogen atoms initiate chain reactions by abstracting hydrogens of the methyl group.

Benzylic halogenations are similar to allylic halogenations (Section 13.2) in that they involve the formation of *unusually stable radicals* (Section 15.12A).

- Benzylic and allylic radicals are even more stable than tertiary radicals.

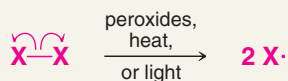


A MECHANISM FOR THE REACTION

Benzylic Halogenation

Chain Initiation

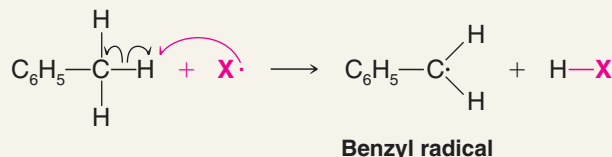
Step 1



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

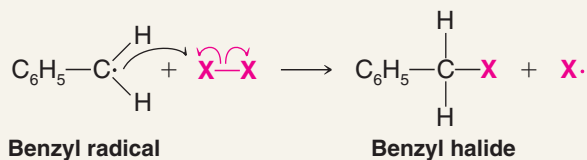
Chain Propagation

Step 2



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

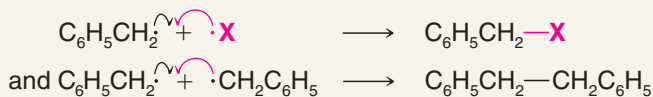
Step 3



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

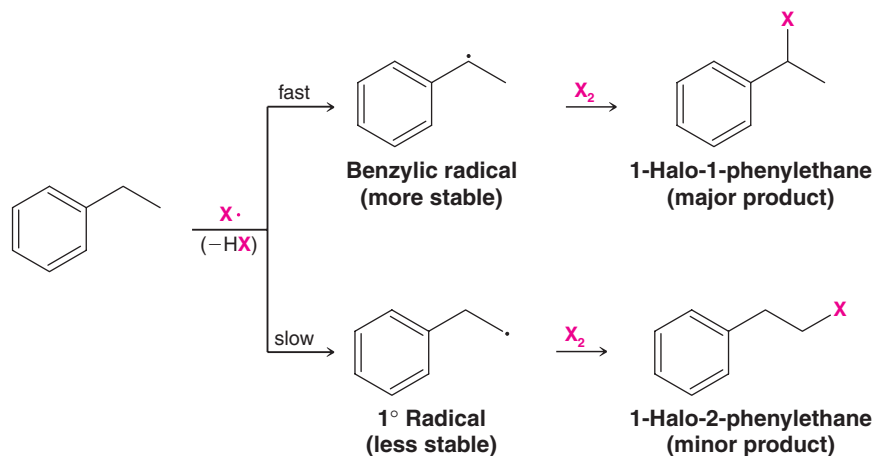
Chain Termination

Step 4



Various radical coupling reactions terminate the chain.

The greater stability of benzylic radicals accounts for the fact that when ethylbenzene is halogenated, the major product is the 1-halo-1-phenylethane. The benzylic radical is formed much faster than the 1° radical:





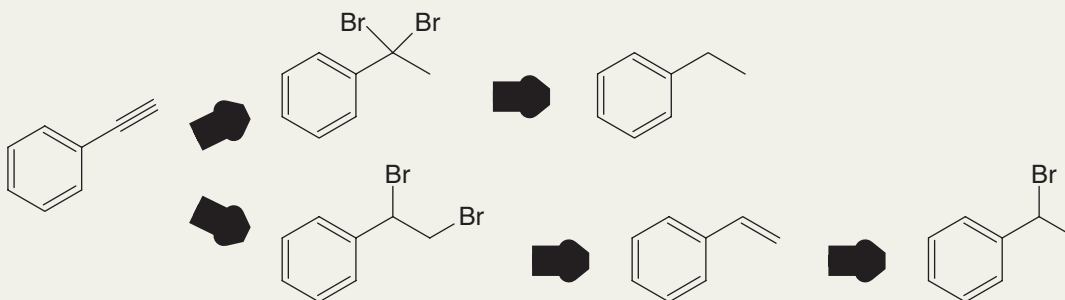
When propylbenzene reacts with chlorine in the presence of UV radiation, the major product is 1-chloro-1-phenylpropane. Both 2-chloro-1-phenylpropane and 3-chloro-1-phenylpropane are minor products. Write the structure of the radical leading to each product and account for the fact that 1-chloro-1-phenylpropane is the major product.

Review Problem 15.13

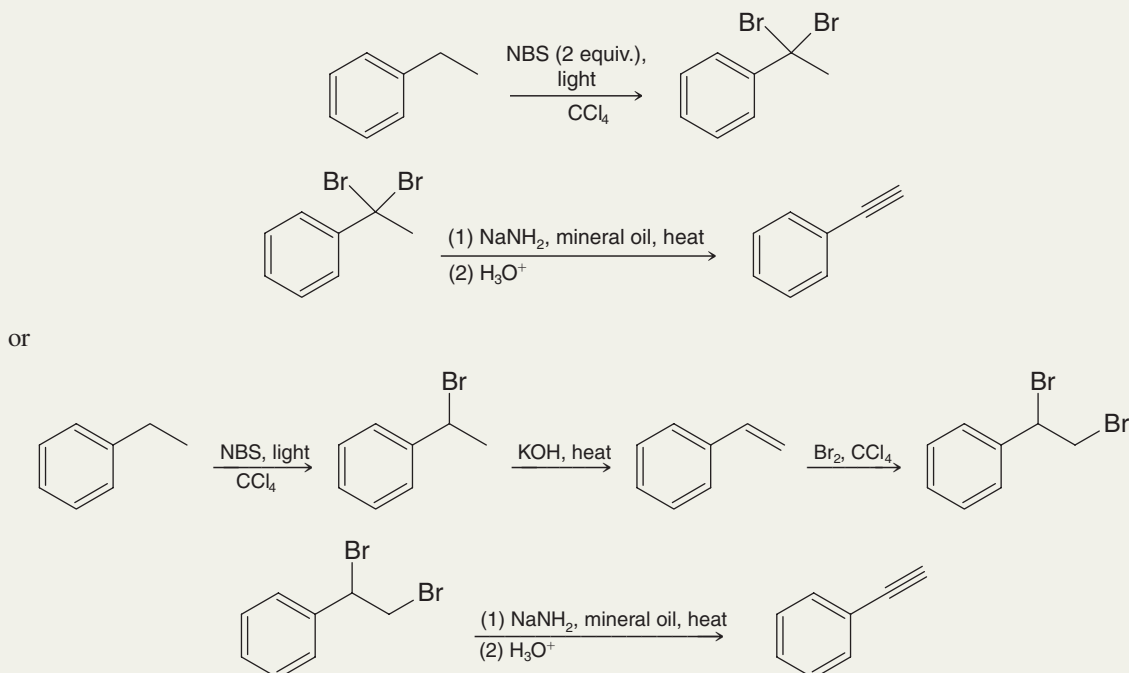
Solved Problem 15.5

ILLUSTRATING A MULTISTEP SYNTHESIS Show how phenylacetylene ($\text{C}_6\text{H}_5\text{C}\equiv\text{CH}$) could be synthesized from ethylbenzene (phenylethane). Begin by writing a retrosynthetic analysis, and then write reactions needed for the synthesis.

ANSWER Working backward, that is, using *retrosynthetic analysis*, we find that we can easily envision two syntheses of phenylacetylene. We can make phenylacetylene by dehydrohalogenation of 1,1-dibromo-1-phenylethane, which could have been prepared by allowing ethylbenzene (phenylethane) to react with 2 mol of NBS. Alternatively, we can prepare phenylacetylene from 1,2-dibromo-1-phenylethane, which could be prepared from styrene (phenylethene). Styrene can be made from 1-bromo-1-phenylethane, which can be made from ethylbenzene.



Following are the synthetic reactions we need for the two retrosynthetic analyses above:



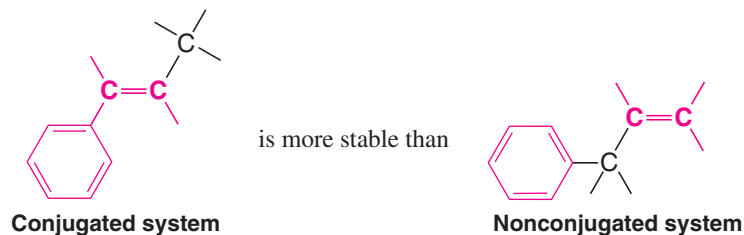
Show how the following compounds could be synthesized from phenylacetylene ($\text{C}_6\text{H}_5\text{C}\equiv\text{CH}$): (a) 1-phenylpropyne, (b) 1-phenyl-1-butyne, (c) (*Z*)-1-phenylpropene, and (d) (*E*)-1-phenylpropene. Begin each synthesis by writing a retrosynthetic analysis.

Review Problem 15.14

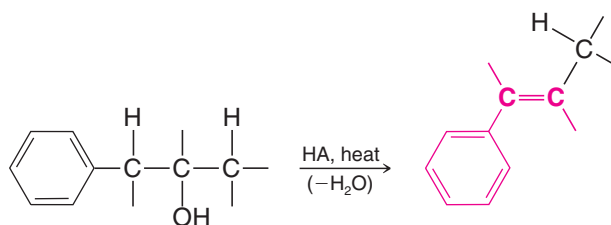
15.13 Alkenylbenzenes

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:



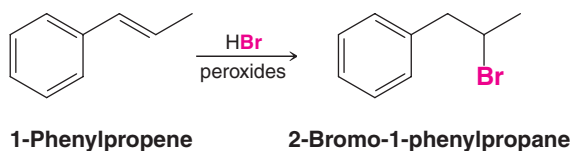
Part of the evidence for this comes from acid-catalyzed alcohol dehydrations, which are known to yield the most stable alkene (Section 7.8A). For example, dehydration of an alcohol such as the one that follows yields exclusively the conjugated system:



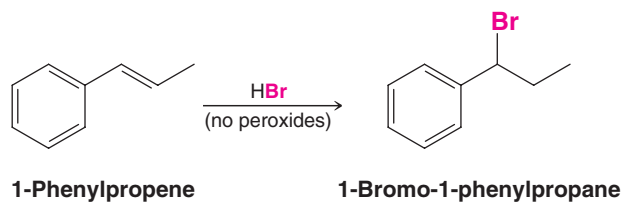
Because conjugation always lowers the energy of an unsaturated system by allowing the π electrons to be delocalized, this behavior is just what we would expect.

15.13B Additions to the Double Bond of Alkenylbenzenes

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



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



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 Review Problem 15.15 and Section 10.9).

Review Problem 15.15

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).

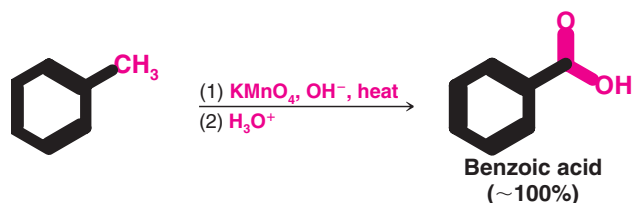


- (a) What would you expect to be the major product when 1-phenylpropene reacts with HCl?
 (b) What product would you expect when it is subjected to oxymercuration–demercuration?

Review Problem 15.16

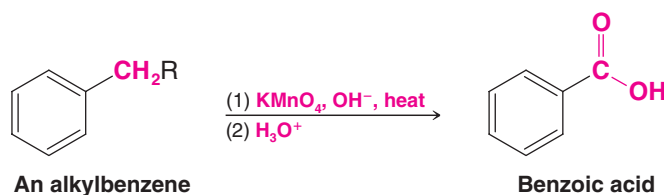
15.13C Oxidation of the Side Chain

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:



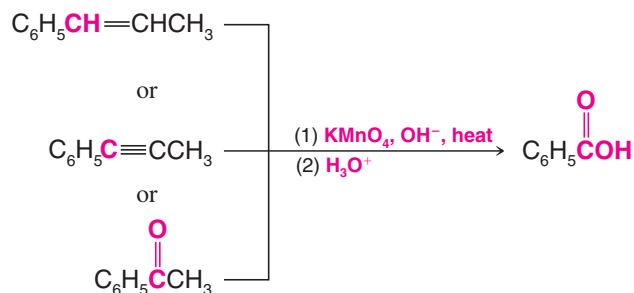
An important characteristic of side-chain oxidations is that oxidation takes place initially at the benzylic carbon.

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



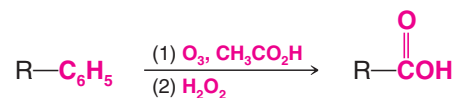
Side-chain oxidations are similar to benzylic halogenations, because in the first step the oxidizing agent abstracts a benzylic hydrogen. Once oxidation is begun at the benzylic carbon, it continues at that site. Ultimately, the oxidizing agent oxidizes the benzylic carbon to a carboxyl group, and, in 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.

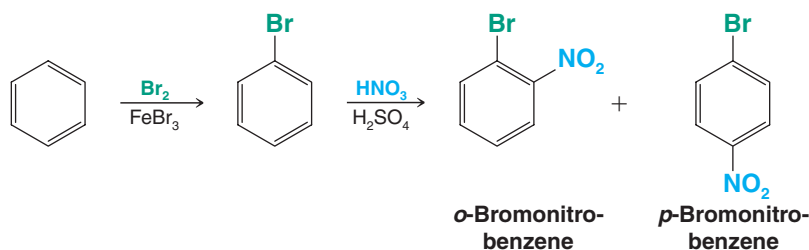


15.14 Synthetic Applications

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.

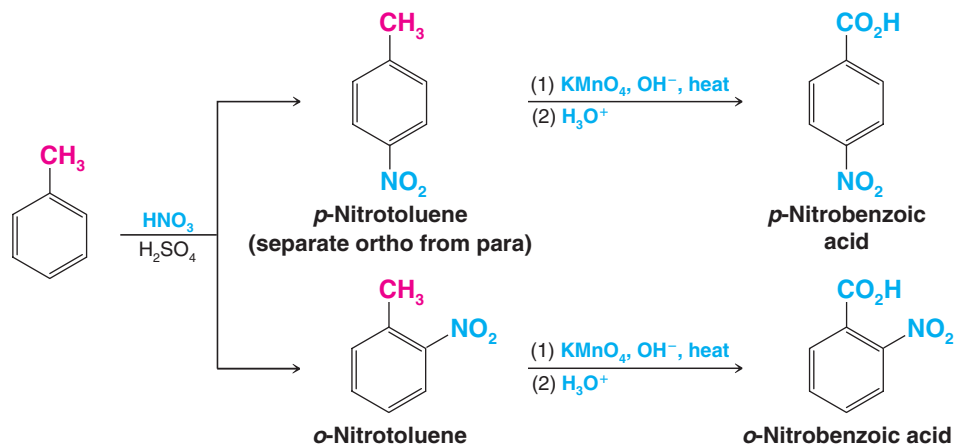
- Part of the skill in planning a synthesis is deciding in what order to carry out the reactions.

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:

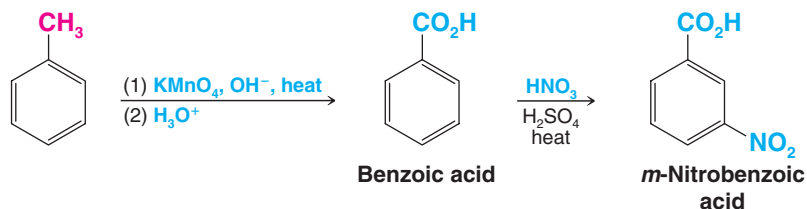


The ortho and para products can be separated by various methods because they have different physical properties. However, had we introduced the nitro group first, we would have obtained *m*-bromonitrobenzene as the major product.

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.

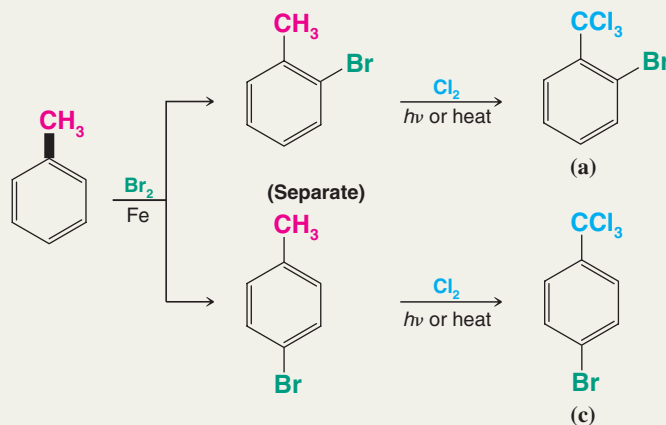




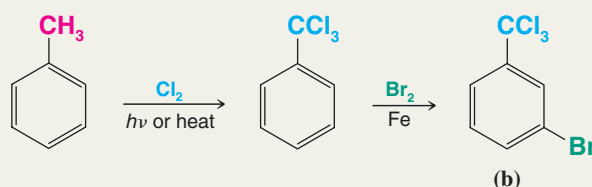
Solved Problem 15.6

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 chlorination of the side chain using three molar equivalents of chlorine:

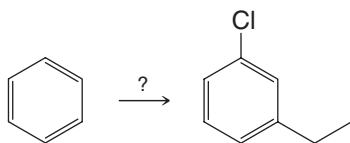


To make compound (b), we reverse the order of the reactions. By converting the side chain to a $-\text{CCl}_3$ group first, we create a meta director, which causes the bromine to enter the desired position:



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

Review Problem 15.17



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.

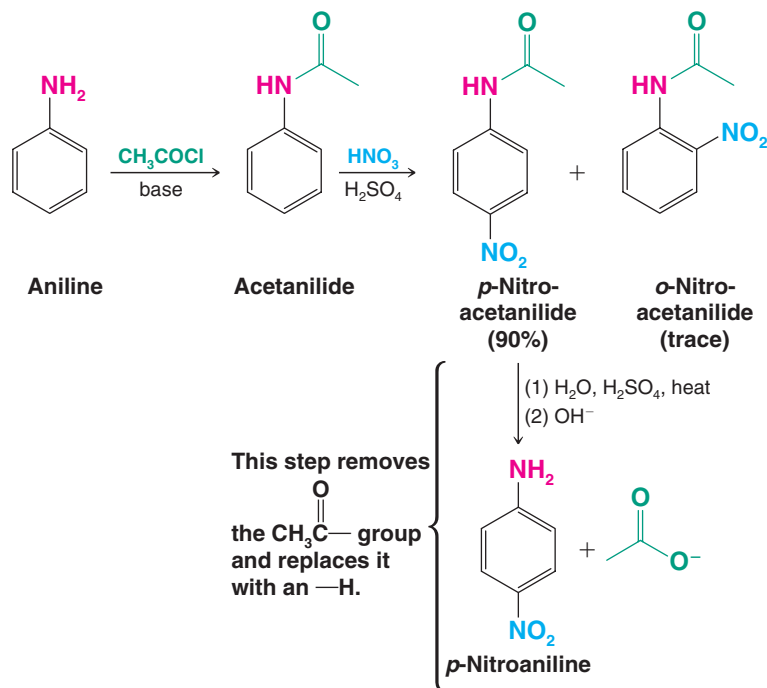
- (a) Why will neither method give the desired product?
 (b) There is a three-step method that will work if the steps are done in the right order. What is this method?

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.

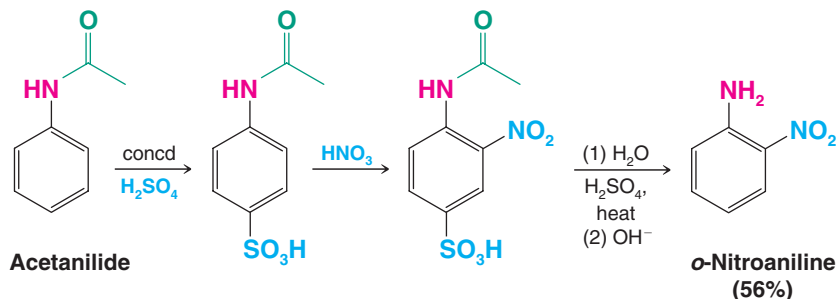
Treating aniline with acetyl chloride, CH_3COCl , or acetic anhydride, $(\text{CH}_3\text{CO})_2\text{O}$, converts the amino group of aniline to an amide, (specifically an acetamido group, $-\text{NHCOCH}_3$), forming acetanilide. An amide group is only moderately activating, and it does not make the ring highly susceptible to oxidation during nitration (see Review 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:



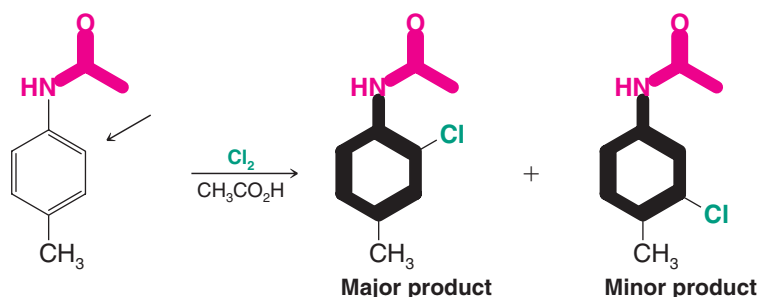
Here we see how a sulfonic acid group can be used as a “blocking group.” We can remove the sulfonic acid group by desulfonation at a later stage. In this example, the reagent used for desulfonation (dilute H_2SO_4) also conveniently removes the acetyl group that we employed to “protect” the benzene ring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

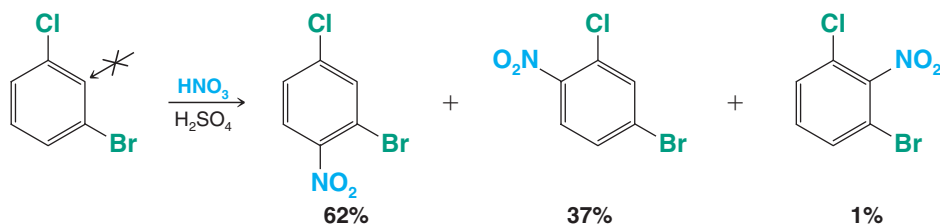


- An ortho–para director takes precedence over a meta director in determining the position of substitution because all ortho–para-directing groups are more activating than meta directors.

Steric effects are also important in aromatic substitutions.

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

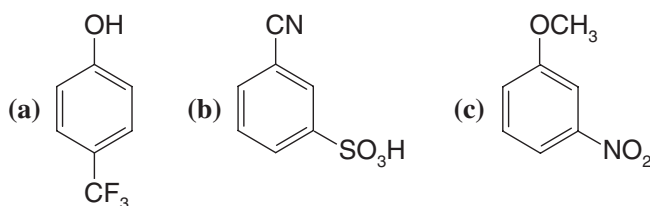
A good example of this effect can be seen in the nitration of *m*-bromochlorobenzene:



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

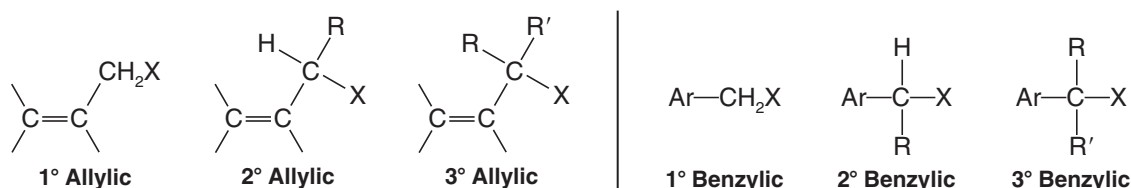
Predict the major product (or products) that would be obtained when each of the following compounds is nitrated:

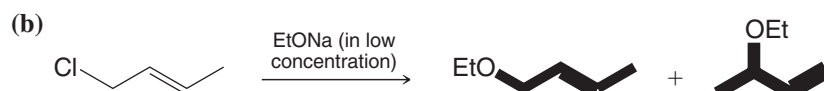
Review Problem 15.18



15.15 Allylic and Benzylic Halides in Nucleophilic Substitution Reactions

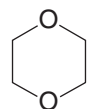
Allylic and benzylic halides can be classified in the same way that we have classified other organic halides:





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

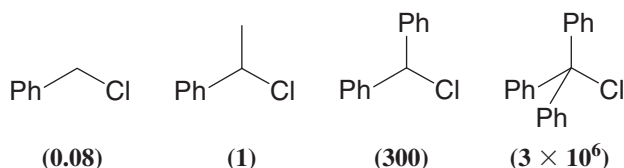
1-Chloro-3-methyl-2-butene undergoes hydrolysis in a mixture of water and dioxane at a rate that is more than a thousand times that of 1-chloro-2-butene. (a) What factor accounts for the difference in reactivity? (b) What products would you expect to obtain? [Dioxane is a cyclic ether (below) that is 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

Primary halides of the type ROCH_2X apparently undergo $\text{S}_{\text{N}}1$ -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 $\text{S}_{\text{N}}1$ reactions?

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



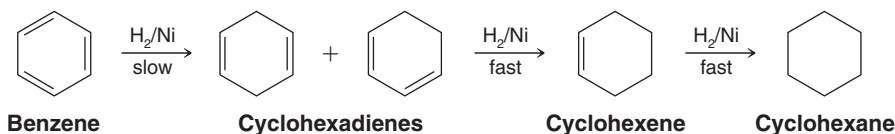
Review Problem 15.20

Review Problem 15.21

Review Problem 15.22

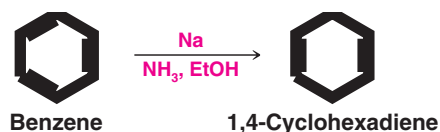
15.16 Reduction of Aromatic Compounds

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.

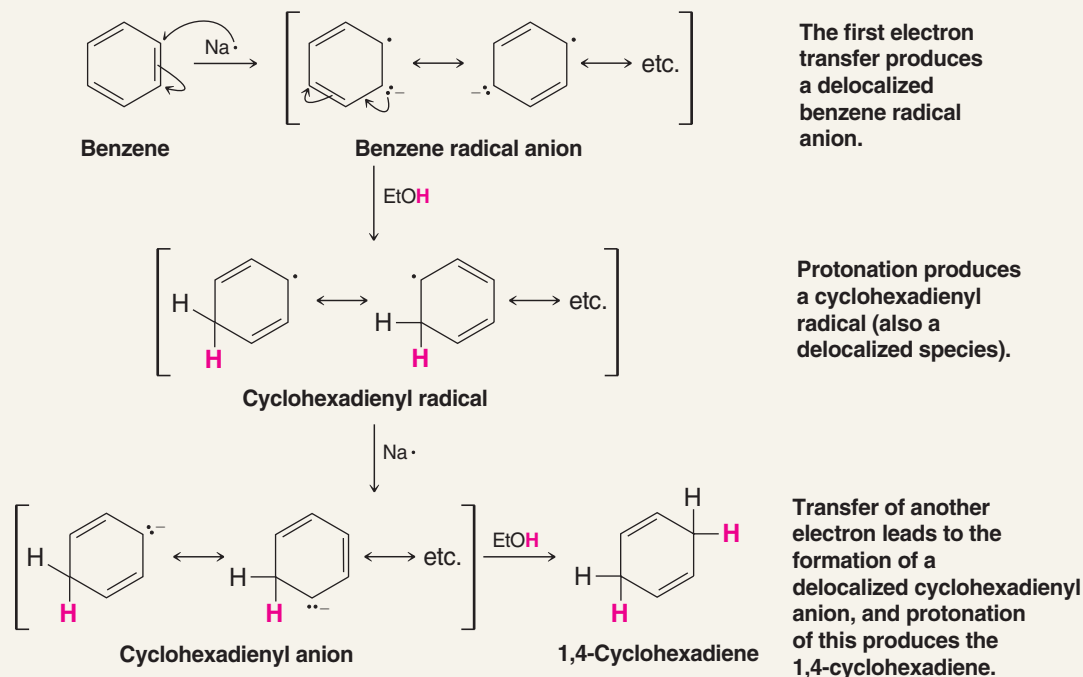


The Birch reduction is a dissolving metal reduction, and the mechanism for it resembles the mechanism for the reduction of alkynes that we studied in Section 7.15B. A sequence of electron transfers from the alkali metal and proton transfers from the alcohol takes place, leading to a 1,4-cyclohexadiene.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

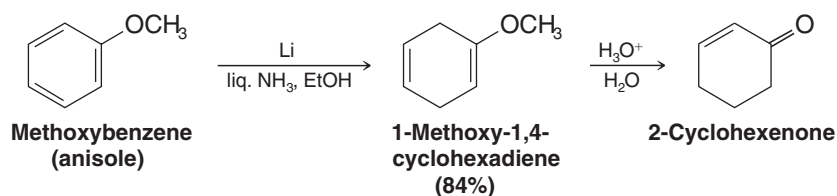


A MECHANISM FOR THE REACTION

Birch Reduction

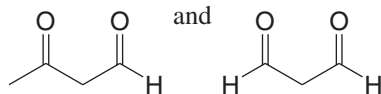


Substituent groups on the benzene ring influence the course of the reaction. Birch reduction of methoxybenzene (anisole) leads to the formation of 1-methoxy-1,4-cyclohexadiene, a compound that can be hydrolyzed by dilute acid to 2-cyclohexenone. This method provides a useful synthesis of 2-cyclohexenones:



Review Problem 15.23

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



Key Terms and Concepts



The key terms and concepts that are highlighted in **bold, blue text** within the chapter are defined in the glossary (at the back of the book) and have hyperlinked definitions in the accompanying **WileyPLUS** course (www.wileyplus.com).



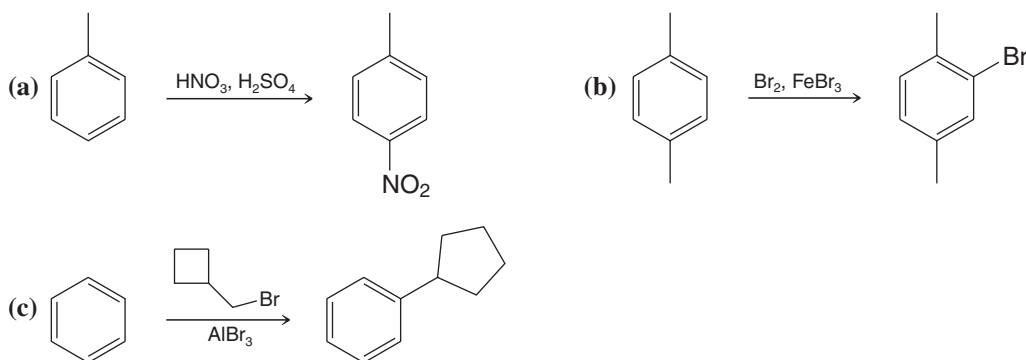
Problems



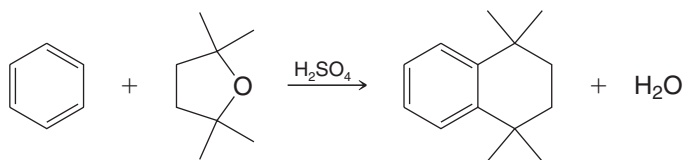
Note to Instructors: Many of the homework problems are available for assignment via Wiley PLUS, an online teaching and learning solution.

MECHANISMS

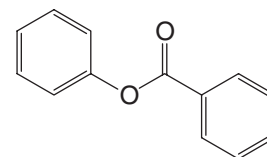
- 15.24** Provide a detailed mechanism for each of the following reactions. Include contributing resonance structures and the resonance hybrid for the arenium ion intermediates.



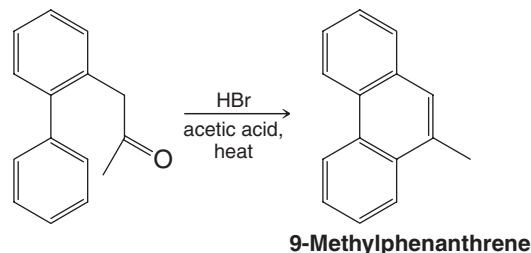
- 15.25** Provide a detailed mechanism for the following reaction.



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

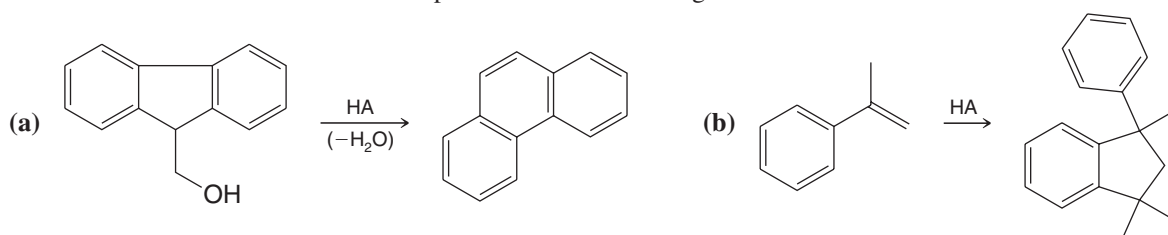


- 15.27** Many polycyclic aromatic compounds have been synthesized by a cyclization reaction known as the **Bradsher reaction** or **aromatic cyclodehydration**. This method can be illustrated by the following synthesis of 9-methylphenanthrene:



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.

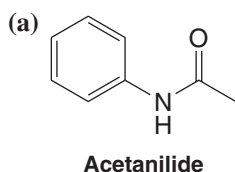
- 15.28** Write mechanisms that account for the products of the following reactions:



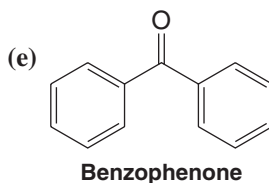
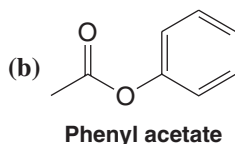
- 15.29** The addition of a hydrogen halide (hydrogen bromide or hydrogen chloride) to 1-phenyl-1,3-butadiene produces (only) 1-phenyl-3-halo-1-butene. **(a)** Write a mechanism that accounts for the formation of this product. **(b)** Is this 1,4 addition or 1,2 addition to the butadiene system? **(c)** 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

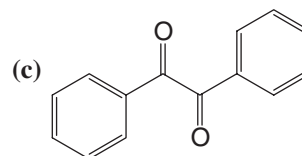
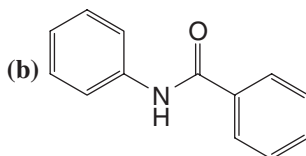
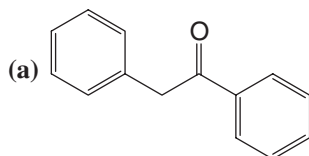
- 15.30** Predict the major product (or products) formed when each of the following reacts with Cl_2 and FeCl_3 :
- (a) Ethylbenzene
 (b) Anisole (methoxybenzene)
 (c) Fluorobenzene
 (d) Benzoic acid
 (e) Nitrobenzene
 (f) Chlorobenzene
 (g) Biphenyl ($\text{C}_6\text{H}_5\text{—C}_6\text{H}_5$)
 (h) Ethyl phenyl ether
- 15.31** Predict the major product (or products) formed when each of the following reacts with a mixture of concentrated HNO_3 and H_2SO_4 .



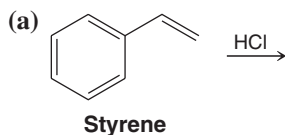
- (c) 4-Chlorobenzoic acid
 (d) 3-Chlorobenzoic acid



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



- 15.33** Predict the major products of the following reactions:

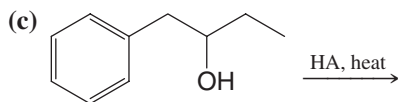


- (d) Product of (c) + $\text{HBr} \xrightarrow{\text{peroxides}}$

- (e) Product of (c) + $\text{H}_2\text{O} \xrightarrow[\text{heat}]{\text{HA}}$



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



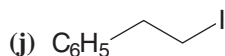
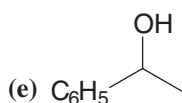
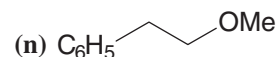
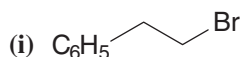
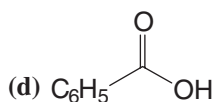
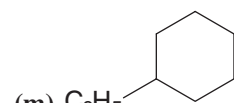
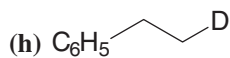
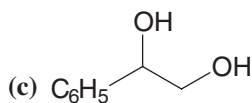
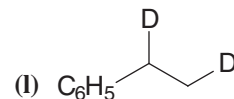
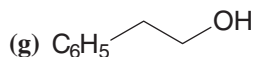
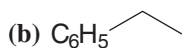
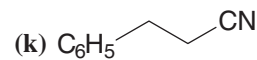
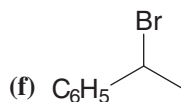
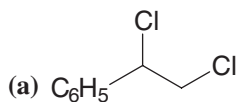
- (g) Product of (f) $\xrightarrow[(2) \text{H}_3\text{O}^+]{(1) \text{KMnO}_4, \text{OH}^-, \text{heat}}$

- 15.34** 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



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



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

(a) *m*-Chlorobenzoic acid

(f) *p*-Isopropyltoluene (*p*-cymene)

(b) *p*-Methylacetophenone

(g) 1-Cyclohexyl-4-methylbenzene

(c) 2-Bromo-4-nitrotoluene

(h) 2,4,6-Trinitrotoluene (TNT)

(d) *p*-Bromobenzoic acid

(i) 4-Chloro-2-nitrobenzoic acid

(e) 1-Chloro-3-trichloromethylbenzene

(j) 1-Butyl-4-methylbenzene

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

(a) *p*-Bromoaniline

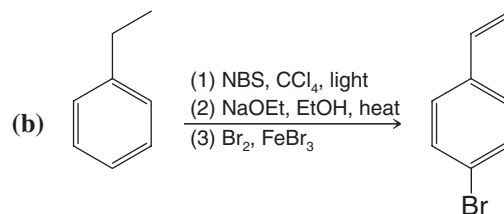
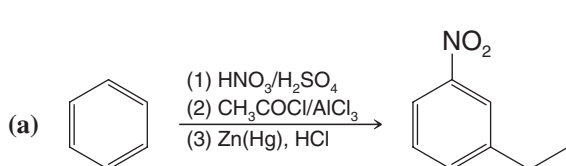
(d) 4-Bromo-2-nitroaniline

(b) *o*-Bromoaniline

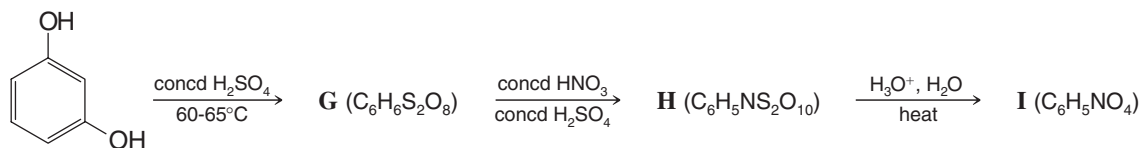
(e) 2,4,6-Tribromoaniline

(c) 2-Bromo-4-nitroaniline

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

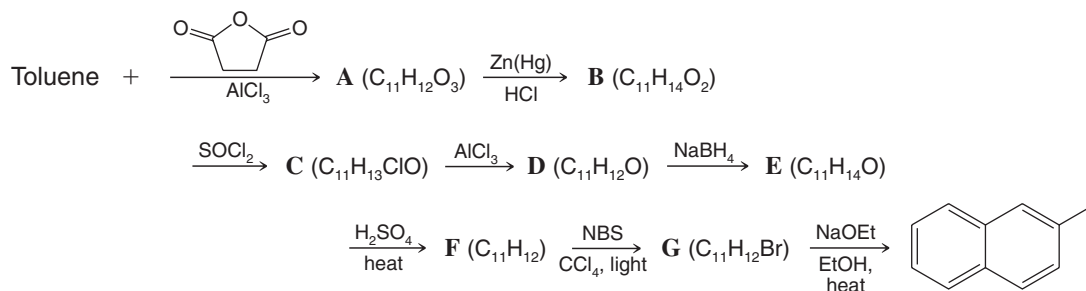


15.39 Propose structures for compounds G–I:

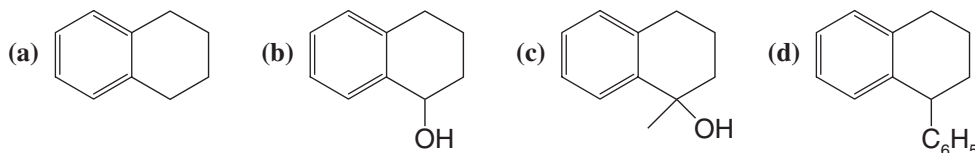


15.40 2,6-Dichlorophenol has been isolated from the females of two species of ticks (*Amblyomma americanum* and *A. maculatum*), where it apparently serves as a sex attractant. Each female tick yields about 5 ng of 2,6-dichlorophenol. Assume that you need larger quantities than this and outline a synthesis of 2,6-dichlorophenol from phenol. [Hint: When phenol is sulfonated at 100°C, the product is chiefly *p*-hydroxybenzenesulfonic acid.]

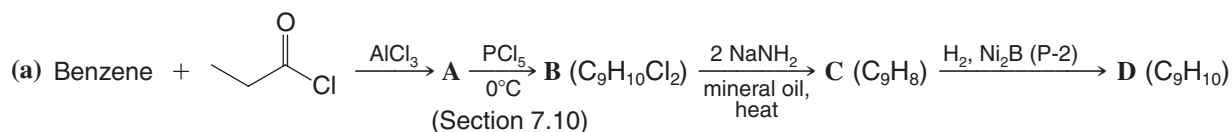
- 15.41** 2-Methylnaphthalene can be synthesized from toluene through the following sequence of reactions. Write the structure of each intermediate.



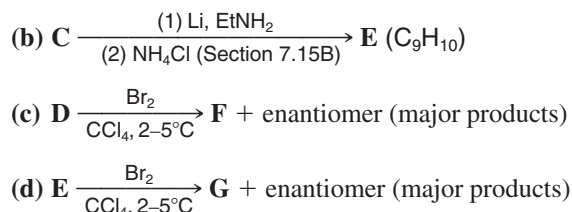
- 15.42** Show how you might synthesize each of the following starting with α -tetralone (Section 15.9):



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

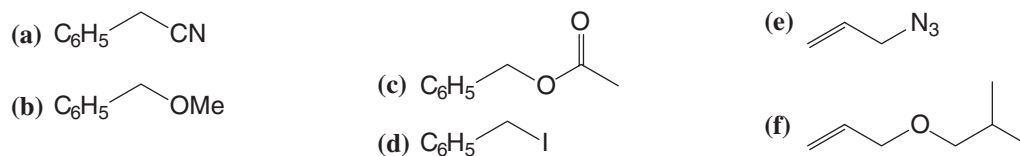


[Hint: The ¹H NMR spectrum of compound C consists of a multiplet at δ 7.20 (5H) and a singlet at δ 2.0 (3H).]

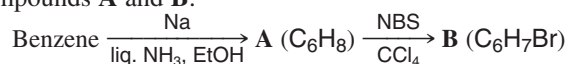


GENERAL PROBLEMS

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

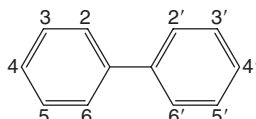


- 15.45** Provide structures for compounds A and B:



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

- 15.47** The compound phenylbenzene (C₆H₅—C₆H₅) is called *biphenyl*, and the ring carbons are numbered in the following manner:



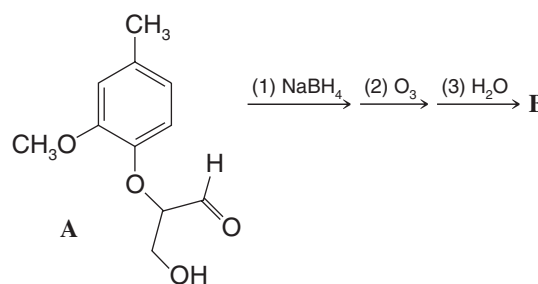
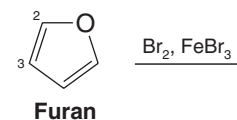


- Use models to answer the following questions about substituted biphenyls. (a) When certain large groups occupy three or four of the *ortho* positions (e.g., 2, 6, 2', and 6'), the substituted biphenyl may exist in enantiomeric forms. An example of a biphenyl that exists in enantiomeric forms is the compound in which the following substituents are present: 2-NO₂, 6-CO₂H, 2'-NO₂, 6'-CO₂H. What factors account for this? (b) Would you expect a biphenyl with 2-Br, 6-CO₂H, 2'-CO₂H, 6'-H to exist in enantiomeric forms? (c) The biphenyl with 2-NO₂, 6-NO₂, 2'-CO₂H, 6'-Br cannot be resolved into enantiomeric forms. Explain.
- 15.48** Treating cyclohexene with acetyl chloride and AlCl₃ leads to the formation of a product with the molecular formula C₈H₁₃ClO. Treating this product with a base leads to the formation of 1-acetylcyclohexene. Propose mechanisms for both steps of this sequence of reactions.
- 15.49** 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 —SO₃H group as a blocking group?
- 15.50** When toluene is sulfonated (concentrated H₂SO₄) 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.]
- 15.51** 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, C₆D₆, is nitrated at the same rate as normal benzene, C₆H₆?
- 15.52** 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.
- 15.53** (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.



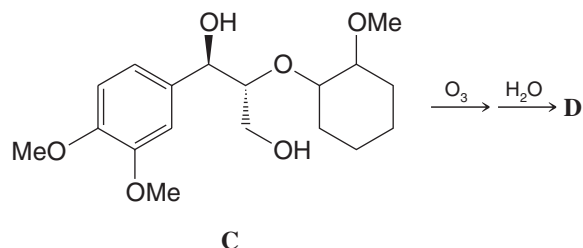
Challenge Problems

- 15.54** 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.
- 15.55** Acetanilide was subjected to the following sequence of reactions: (1) concd H₂SO₄; (2) HNO₃, heat; (3) H₂O, H₂SO₄, heat, then OH[−]. The ¹³C NMR spectrum of the final product gives six signals. Write the structure of the final product.
- 15.56** 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**.



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^{\dagger} 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**?

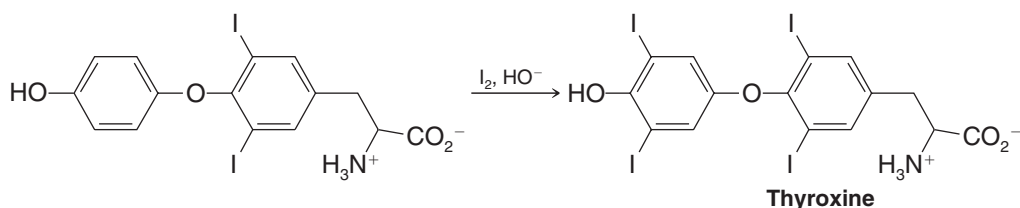
- 15.57 When compound **C**, which is often used to model a more frequently occurring unit in lignins, was ozonized, product **D** was obtained. In a variety of ways it has been established that the stereochemistry of the three-carbon side chain of such lignin units remains largely if not completely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



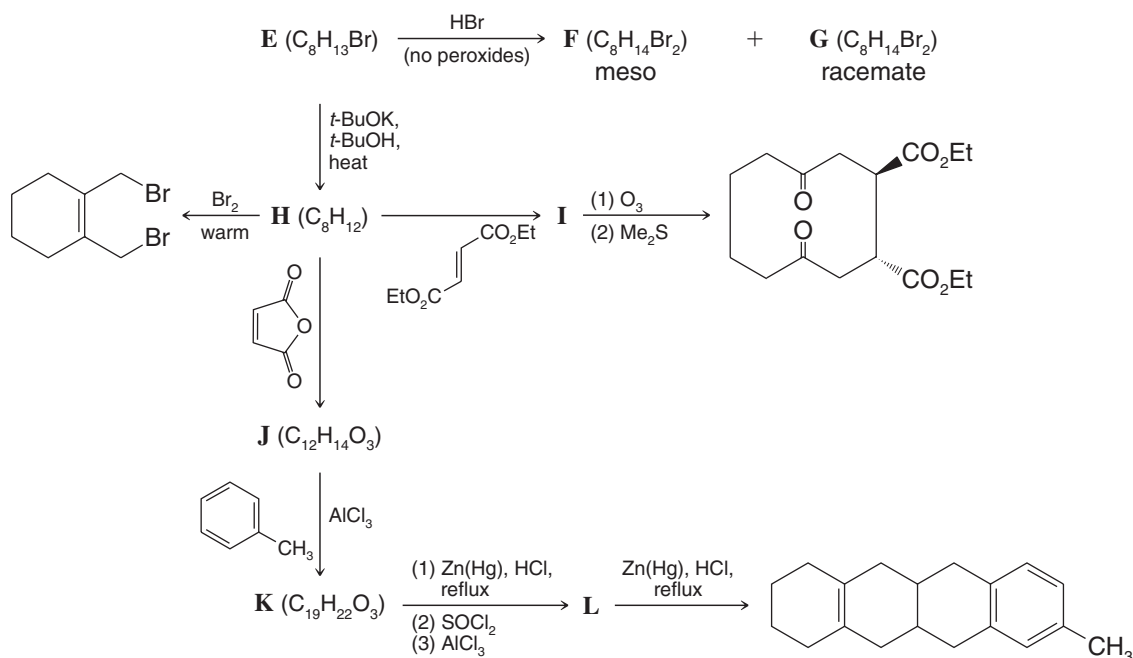
For GC/MS, **D** was converted to its tetrakis(*O*-trimethylsilyl) derivative, which had M^+ 424 *m/z*. The IR spectrum of **D** had bands at 3000 cm^{-1} (broad, strong) and 1710 cm^{-1} (strong). Its $^1\text{H NMR}$ spectrum had peaks at δ 3.7 (multiplet, 3H) and δ 4.2 (doublet, 1H) after treatment with D_2O . Its DEPT $^{13}\text{C NMR}$ spectra had peaks at δ 6.4 (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), of course, is for the biosynthesis of thyroxine.]



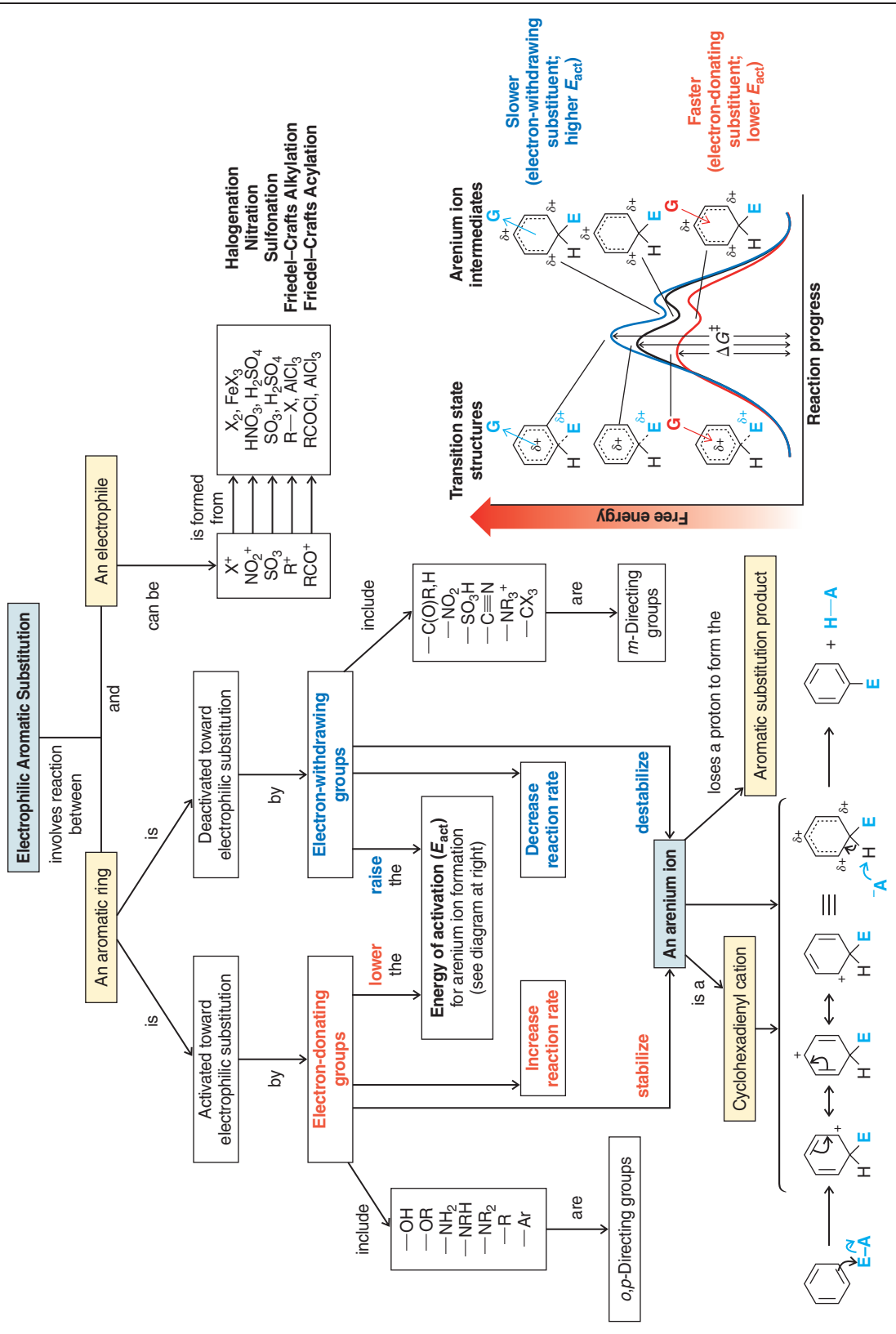
2. Synthesize 2-chloro-4-nitrobenzoic acid from toluene and any other reagents necessary. Begin by writing a retrosynthetic analysis.
3. Deduce the structures of compounds **E–L** in the roadmap below.





CONCEPT MAP

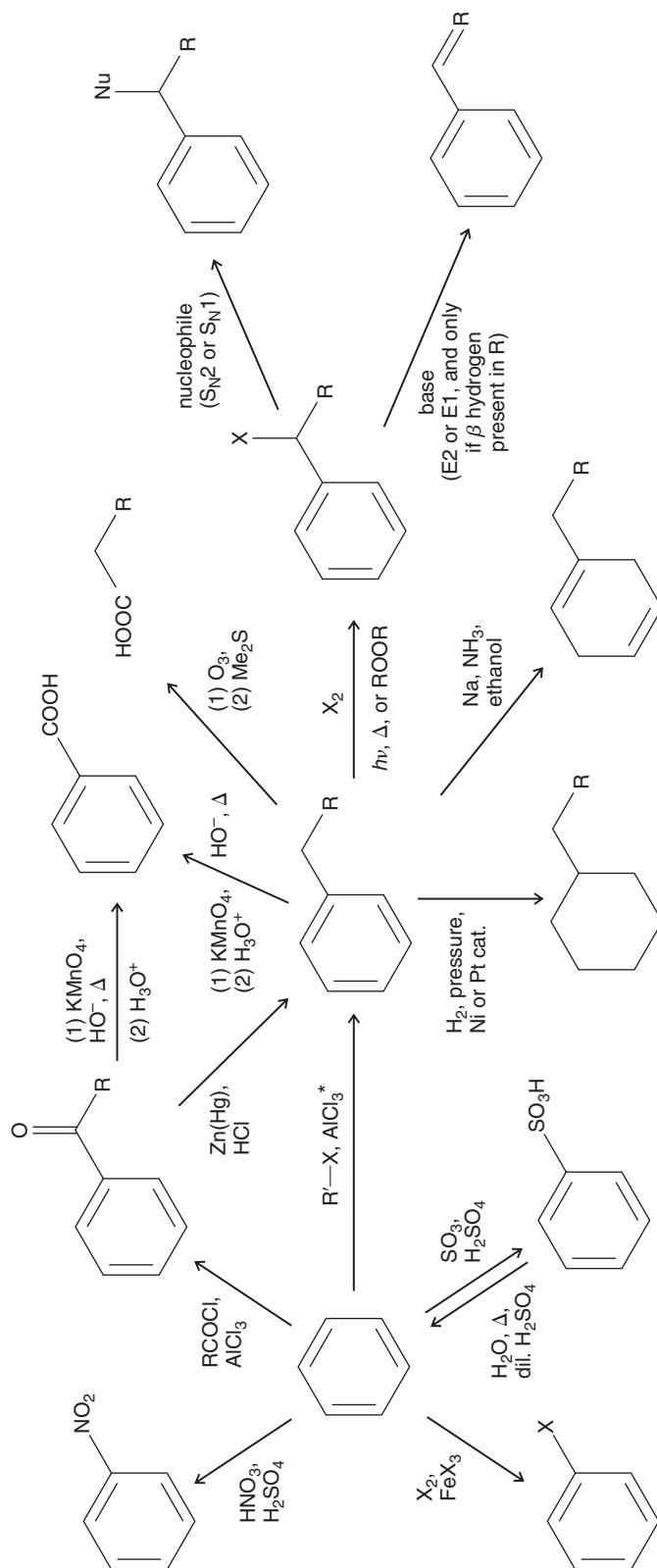
Summary of Mechanisms



CONCEPT MAP

Some Synthetic Connections of Benzene and Aryl Derivatives

- Nitration
- Halogenation
- Sulfonation/desulfonation
- Friedel-Crafts alkylation
- Friedel-Crafts acylation
- 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 Clemmensen reduction should be used to incorporate a primary alkyl group.