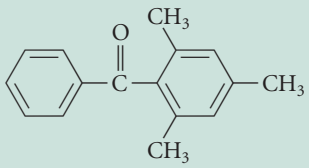
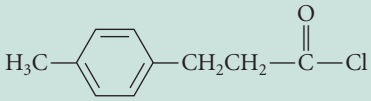
16.19 Show two different Friedel–Crafts acylation reactions that can be used to prepare the following compound.



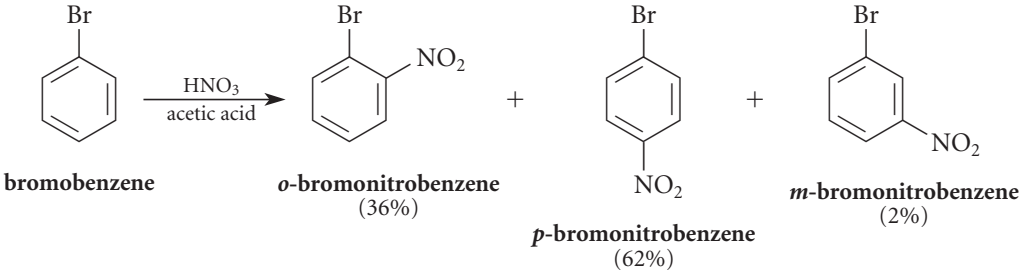
16.20 The following compound reacts with $AlCl_3$ followed by water to give a ketone *A* with the formula $C_{10}H_{10}O$. Give the structure of *A* and a curved-arrow mechanism for its formation.



16.5 ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS OF SUBSTITUTED BENZENES

A. Directing Effects of Substituents

When a monosubstituted benzene undergoes an electrophilic aromatic substitution reaction, three possible disubstitution products might be obtained. For example, nitration of bromobenzene could in principle give *ortho-*, *meta-*, or *para*-bromonitrobenzene. If substitution were totally random, an ortho : meta : para product ratio of 2 : 2 : 1 would be expected. (Why?) It is found experimentally that this substitution is *not* random, but is *regioselective*.



(16.27)

bromobenzene

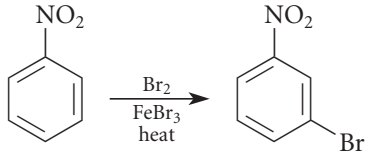
***o*-bromonitrobenzene** (36%)

***p*-bromonitrobenzene** (62%)

***m*-bromonitrobenzene** (2%)

Other electrophilic substitution reactions of bromobenzene also give mostly ortho and para isomers. If a substituted benzene undergoes further substitution mostly at the ortho and para positions, the original substituent is called an **ortho, para-directing group.** Thus, bromine is an ortho, para-directing group, because all electrophilic substitution reactions of bromobenzene occur at the ortho and para positions.

In contrast, some substituted benzenes react in electrophilic aromatic substitution to give mostly the meta disubstitution product. For example, the bromination of nitrobenzene gives only the meta isomer.



(16.28)

nitrobenzene

***m*-bromonitrobenzene** (only product observed)

Other electrophilic substitution reactions of nitrobenzene also give mostly the meta isomers. If a substituted benzene undergoes further substitution mainly at the meta position, the origi-

nal substituent group is called a **meta-directing group.** Thus, the nitro group is a meta-directing group because all electrophilic substitution reactions of nitrobenzene occur at the meta position.

A substituent group is either an ortho, para-directing group or a meta-directing group in all electrophilic aromatic substitution reactions; that is, no substituent is ortho, para directing in one reaction and meta directing in another. A summary of the directing effects of common substituent groups is given in the third column of Table 16.2.

PROBLEM

16.21 Using the information in Table 16.2, predict the product(s) of
(a) Friedel–Crafts acylation of anisole (methoxybenzene) with acetyl chloride (structure in Eq. 16.23) in the presence of one equivalent of $AlCl_3$ followed by H_2O.
(b) Friedel–Crafts alkylation of a large excess of ethylbenzene with chloromethane in the presence of $AlCl_3$.

TABLE 16.2 Summary of Directing and Activating or Deactivating Effects of Some Common Functional Groups

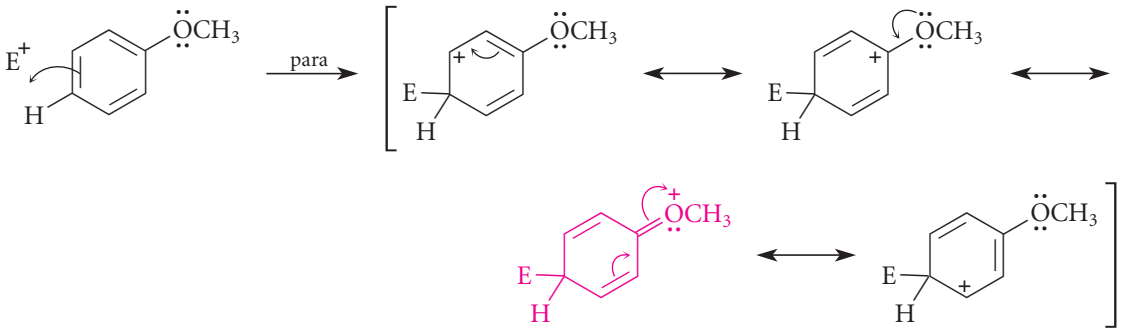
(Groups are listed in decreasing order of activation.)

Substituent group	Name of group	Directing effect	Activating or deactivating
—$\ddot{N}H_2$, —$\ddot{N}R_2$	amino	ortho, para directors	activating substituents
—$\ddot{O}$H	hydroxy		
—$\ddot{O}$R	alkoxy		
—$\ddot{N}$H—C(=O)—R	acylamino		
—R	alkyl		
—$\ddot{O}$—C(=O)—R	acyloxy		
	phenyl		
—$\ddot{F}$:, —$\ddot{B}$r:, —$\ddot{C}$l:, —$\ddot{I}$:	halogens		
—C(=O)—OH, —C(=O)—NH_2, —C(=O)—OR	carboxy, carboxamido, carboalkoxy	meta directors	deactivating substituents
—C(=O)—R	acyl		
—SO_3H	sulfonic acid		
—CN	cyano		
—NO_2	nitro		

These directing effects occur because *electrophilic substitution reactions at one position of a benzene derivative are much faster than the same reactions at another position*. That is, the substitution reactions at the different ring positions are *in competition*. For example, in Eq. 16.27, *o*- and *p*-bromonitrobenzenes are the major products because the rate of nitration is greater at the ortho and para positions of bromobenzene than it is at the meta position. Understanding these effects thus requires an understanding of the factors that control the *rates* of aromatic substitution at each position.

Ortho, Para-Directing Groups All of the ortho, para-directing substituents in Table 16.2 are either *alkyl groups* or *groups that have unshared electron pairs on atoms directly attached to the benzene ring.* Although other types of ortho, para-directing groups are known, the principles on which ortho, para-directing effects are based can be understood by considering electrophilic substitution reactions of benzene derivatives containing these types of substituents.

First imagine the reaction of a general electrophile E^+ with anisole (methoxybenzene). Notice that the atom directly attached to the benzene ring (the oxygen of the methoxy group) has unshared electron pairs. Reaction of E^+ at the para position of anisole gives a carbocation intermediate with the following four important resonance structures:



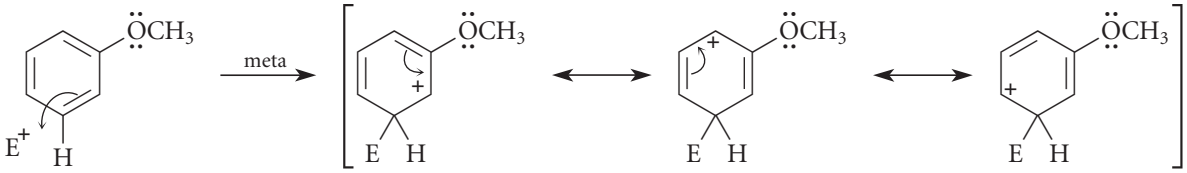
(16.29)

The colored structure shows that the unshared electron pair of the methoxy group can delocalize the positive charge on the carbocation. This is an especially important structure because it contains more bonds than the others, and every atom has an octet.

PROBLEM

16.22 Draw the carbocation that results from the reaction of the electrophile at the ortho position of anisole; show that this ion also has four resonance structures.

If the electrophile reacts with anisole at the meta position, the carbocation intermediate that is formed has fewer resonance structures than the ion in Eq. 16.29. *In particular, the charge cannot be delocalized onto the —OCH_3 group when reaction occurs at the meta position.* There is no structure that corresponds to the colored structure in Eq. 16.29.



(16.30)

For the oxygen to delocalize the charge, it must be adjacent to an electron-deficient carbon, as in Eq. 16.29. The resonance structures show that the positive charge is shared on *alternate* car-

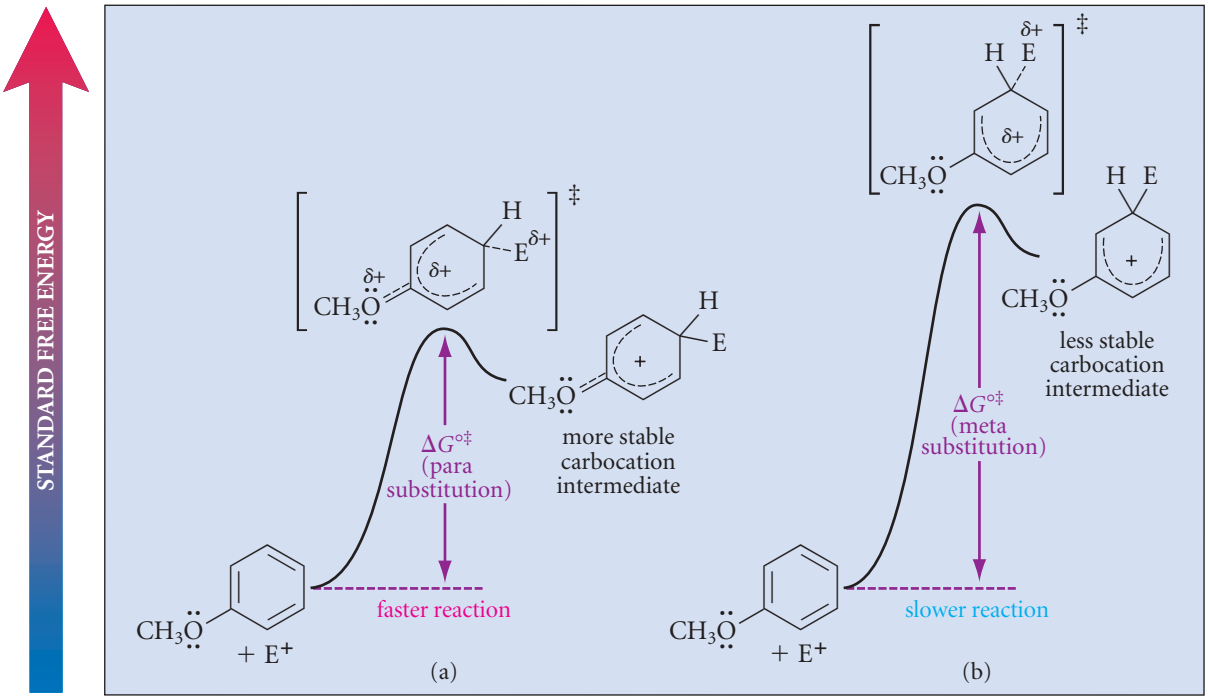


Figure 16.5 Basis of the directing effect of the methoxy group in the electrophilic aromatic substitution reactions of anisole. Substitution of anisole by an electrophile E^+ occurs more rapidly at (a) the para position than at (b) the meta position because a more stable carbocation intermediate is involved in para substitution. The dashed lines within the structures symbolize the delocalization of electrons.

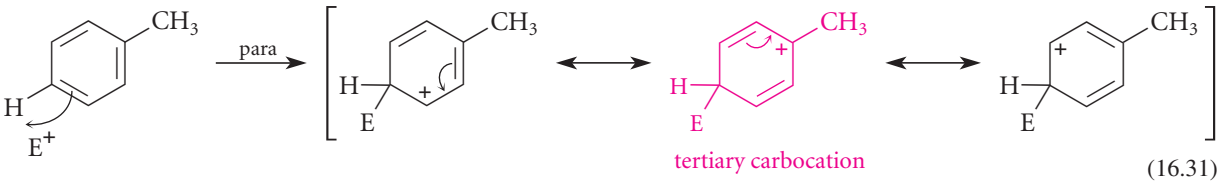
bons of the ring. When meta substitution occurs, the positive charge is not shared by the carbon adjacent to the oxygen.

We now use the resonance structures in Eqs. 16.29 and 16.30 (as well as those you drew in Problem 16.22) to assess relative rates. The logic to be used follows the general outline given in Study Problem 15.3, page 715. A comparison of Eq. 16.29 and the structures you drew for Problem 16.22 with Eq. 16.30 shows that the reaction of an electrophile at either the ortho or para positions of anisole gives a carbocation with more resonance structures—that is, a more stable carbocation. The rate-limiting step in many electrophilic aromatic substitution reactions is *formation of the carbocation intermediate.* Hammond's postulate (Sec. 4.8D) suggests that the more stable carbocation should be formed more rapidly. Hence, the products derived from the more rapidly formed carbocation—the more stable carbocation—are the ones observed. Because the reaction of the electrophile at an ortho or para position of anisole gives a more stable carbocation than the reaction at a meta position, the products of ortho, para substitution are formed more rapidly, and are thus the products observed (see Fig. 16.5). This is why the —OCH_3 group is an ortho, para-directing group.

To summarize: Substituents containing atoms with unshared electron pairs adjacent to the benzene ring are ortho, para directors in electrophilic aromatic substitution reactions because their electron pairs can be involved in the resonance stabilization of the carbocation intermediates.

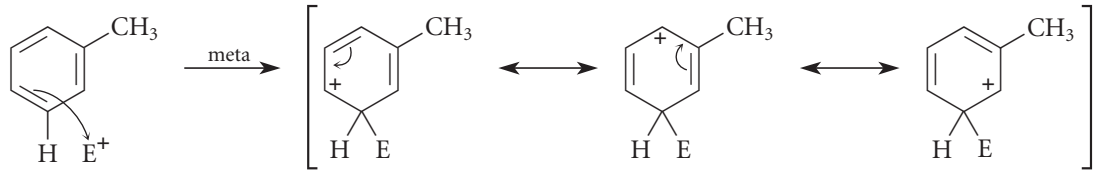
Now imagine the reaction of an electrophile E^+ with an alkyl-substituted benzene such as toluene. Alkyl groups such as a methyl group have no unshared electrons, but the explanation

for the directing effects of these groups is similar. Reaction of E^+ at a position that is ortho or para to an alkyl group gives an ion that has one tertiary carbocation resonance structure (colored structure in the following equation).



(16.31)

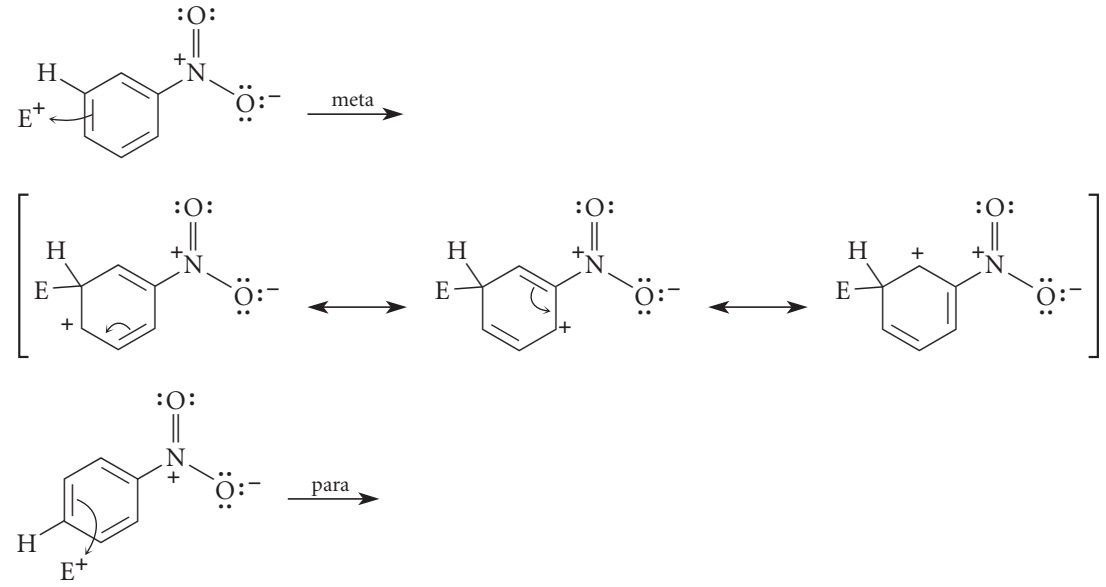
Reaction of the electrophile meta to the alkyl group also gives an ion with three resonance structures, but all resonance forms are secondary carbocations.



(16.32)

Because reaction at the ortho or para position gives the more stable carbocation, alkyl groups are ortho, para-directing groups.

Meta-Directing Groups The meta-directing groups in Table 16.2 are all *polar groups that do not have an unshared electron pair on an atom adjacent to the benzene ring.* The directing effect of these groups can be understood by considering as an example the reactions of a general electrophile E^+ with nitrobenzene at the meta and para positions.

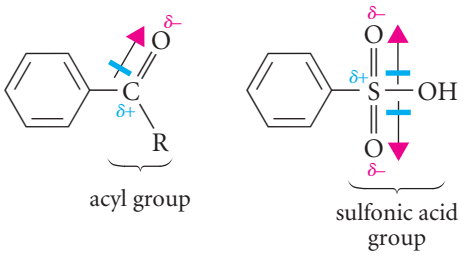


(16.33)

(16.34)

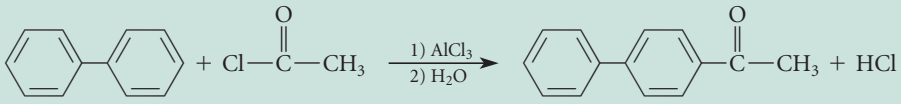
Both reactions give carbocations that have three resonance structures, but reaction at the para position gives an ion with one particularly unfavorable structure (*red*). In this structure, positive charges are situated on adjacent atoms. Because repulsion between two like charges, and consequently their energy of interaction, increases with decreasing separation, the red resonance structure in Eq. 16.34 is less important than the others. Thus, the carbocation in Eq. 16.33, with the greater separation of like charges, is more stable than the carbocation in Eq. 16.34. By Hammond's postulate (Sec. 4.8D), the more stable carbocation intermediate should be formed more rapidly. Consequently, the nitro group is a meta director because the ion that results from meta substitution (Eq. 16.33) is more stable than the one that results from para substitution (Eq. 16.34).

In summary, substituents that have positive charges adjacent to the aromatic ring are meta directors because meta substitution gives the carbocation intermediate in which like charges are farther apart. Notice that not all meta-directing groups have full positive charges like the nitro group, but all of them have bond dipoles that place a substantial amount of positive charge next to the benzene ring.



PROBLEMS

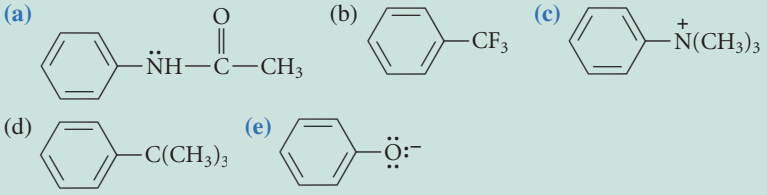
16.23 Biphenyl (phenylbenzene) undergoes the Friedel–Crafts acylation reaction, as shown by the following example.



biphenyl ***p*-phenylacetophenone**

(a) On the basis of this result, what is the directing effect of the phenyl group?
(b) Using resonance arguments, explain the directing effect of the phenyl group.

16.24 Predict the predominant products that would result from bromination of each of the following compounds. Classify each substituent group as an ortho, para director or a meta director, and explain your reasoning.



The Ortho, Para Ratio An aromatic substitution reaction of a benzene derivative bearing an ortho, para-directing group would give twice as much ortho as para product if substitution were completely random, because there are two ortho positions and only one para position available for substitution. However, this situation is rarely observed in practice: it is often

found that the para substitution product is the major one in the reaction mixture. In some cases this result can be explained by the spatial demands of the electrophile. For example, Friedel–Crafts acylation of toluene gives essentially all para substitution product and almost no ortho product. The electrophile cannot react at the ortho position without developing van der Waals repulsions with the methyl group that is already on the ring. Consequently, reaction occurs at the para position, where such repulsions cannot occur.

Typically, para substitution predominates over ortho substitution, but not always. For example, nitration of toluene gives twice as much *o*-nitrotoluene as *p*-nitrotoluene. This result occurs because the nitration of toluene at either the ortho or para position is so fast that it occurs on *every encounter* of the reagents; that is, the energy barrier for the reaction is insignificant. Hence, the product distribution corresponds simply to the relative probability of the reactions. Because the ratio of ortho and para positions is 2 : 1, the product distribution is 2 : 1. In fact, the ready availability of *o*-nitrotoluene makes it is a good starting material for certain other ortho-substituted benzene derivatives.

In summary, the reasons for the ortho, para ratio vary from case to case, and in some cases these reasons are not well understood.

Whatever the reasons for the ortho, para ratio, if an electrophilic aromatic substitution reaction yields a mixture of *ortho* and *para* isomers, a problem of isomer separation arises that must be solved if the reaction is to be useful. Usually, syntheses that give mixtures of isomers are avoided because, in many cases, isomers are difficult to separate. However, the ortho and para isomers obtained in many electrophilic aromatic substitution reactions have sufficiently different physical properties that they are readily separated (Sec. 16.2). For example, the boiling points of *o*- and *p*-nitrotoluene, 220 °C and 238 °C, respectively, are sufficiently different that these isomers can be separated by careful fractional distillation. Thus, either isomer can be obtained relatively pure from the nitration of toluene. The melting points of *o*- and *p*-chloronitrobenzene, 34 °C and 84 °C, respectively, are so different that the para isomer can be selectively crystallized. As you learned in Sec. 16.2, the para isomer of an ortho, para pair typically has the higher melting point, often *considerably* higher. Most aromatic substitution reactions are so simple and inexpensive to run that when the separation of isomeric products is not difficult, these reactions are useful for organic synthesis despite the product mixtures obtained. Thus, you may assume in working problems involving electrophilic aromatic substitution on compounds containing ortho, para-directing groups that the para isomer can be isolated in useful amounts. For the reasons pointed out in the previous paragraph, *o*-nitrotoluene is a relatively rare example of a readily obtained ortho-substituted benzene derivative.

B. Activating and Deactivating Effects of Substituents

Different benzene derivatives have greatly different reactivities in electrophilic aromatic substitution reactions. If a substituted benzene derivative reacts more rapidly than benzene itself, then the substituent group is said to be an **activating group.** The Friedel–Crafts acylation of anisole (methoxybenzene), for example, is 300,000 times faster than the same reaction of benzene under comparable conditions. Furthermore, anisole shows a similar enhanced reactivity relative to benzene in all other electrophilic substitution reactions. Thus, the methoxy group is an *activating group*.

On the other hand, if a substituted benzene derivative reacts more slowly than benzene itself, then the substituent is called a **deactivating group.** For example, the rate for the bromination of nitrobenzene is less than 10^{-5} times the rate for the bromination of benzene; furthermore, nitrobenzene reacts much more slowly than benzene in all other electrophilic aromatic substitution reactions. Thus, the nitro group is a *deactivating group*.

A given substituent group is either activating in all electrophilic aromatic substitution reactions or deactivating in all such reactions. Whether a substituent is activating or deactivat-

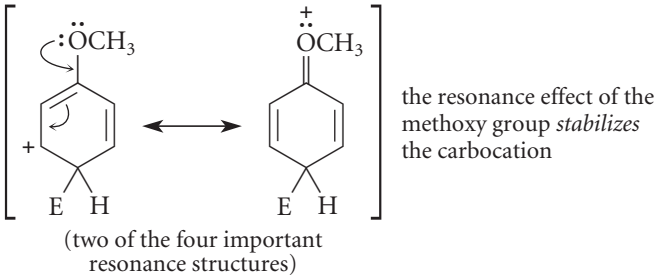
ing is shown in the last column of Table 16.2, p. 763. In this table the most activating substituent groups are near the top of the table. Three generalizations emerge from examining this table.

1. All meta-directing groups are deactivating groups.
2. All ortho, para-directing groups except for the halogens are activating groups.
3. The halogens are deactivating groups.

Thus, except for the halogens, there appears to be a correlation between the activating and directing effects of substituents.

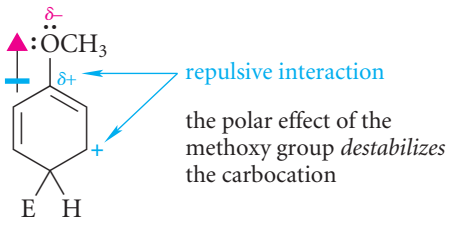
In view of this correlation, it is not surprising that the explanation of activating and deactivating effects is closely related to the explanation for directing effects. A key to understanding these effects is the realization that directing effects are concerned with the relative rates of substitution at different positions of the *same* compound, whereas activating or deactivating effects are concerned with the relative rates of substitution of *different* compounds—a substituted benzene compared with benzene itself. As in the discussion of directing effects, we consider the effect of the substituent on the stability of the intermediate carbocation, and we then apply Hammond's postulate by assuming that the stability of this carbocation is related to the stability of the transition state for its formation.

Two properties of substituents must be considered to understand activating and deactivating effects. First is the *resonance effect* of the substituent. The **resonance effect** of a substituent group is the ability of the substituent to stabilize the carbocation intermediate in electrophilic substitution by delocalization of electrons from the substituent into the ring. The resonance effect is the same effect responsible for the ortho, para-directing effects of substituents with unshared electron pairs, such as —OCH_3 and halogen (colored structure in Eq. 16.29, p. 764). We can summarize this effect with the following two of the four resonance structures for the carbocation intermediate in Eq. 16.29.



(two of the four important resonance structures)

The second property is the *polar effect* of the substituent. The **polar effect** is the tendency of the substituent group, by virtue of its electronegativity, to pull electrons away from the ring. This is the same effect discussed in connection with substituent effects on acidity (Sec. 3.6C). When a ring substituent is electronegative, it pulls the electrons of the ring toward itself and creates an electron deficiency, or positive charge, in the ring. In the carbocation intermediate of an electrophilic substitution reaction, the positive end of the bond dipole interacts repulsively with the positive charge in the ring, thus raising the energy of the ion:



Thus, the electron-donating resonance effect of a substituent group with unshared electron pairs, if it were dominant, would *stabilize* positive charge and would *activate* further substitution. If such a group is electronegative, its electron-withdrawing polar effect, if dominant, would *destabilize* positive charge and would *deactivate* further substitution. These two effects operate simultaneously and in opposite directions. *Whether a substituted derivative of benzene is activated or deactivated toward further substitution depends on the balance of the resonance and polar effects of the substituent group.*

Anisole (methoxybenzene) undergoes electrophilic substitution much more rapidly than benzene because the resonance effect of the methoxy group far outweighs its polar effect. The benzene molecule, in contrast, has no substituent to help stabilize the carbocation intermediate by resonance. Hence, the carbocation intermediate (and the transition state) derived from the electrophilic substitution of anisole is more stable relative to starting materials than the carbocation (and transition state) derived from the electrophilic substitution of benzene. Thus, in a given reaction, the ortho and para substitution of anisole are faster than the substitution of benzene. In other words, the methoxy group activates the benzene ring toward ortho and para substitution.

There is also an important subtlety here. Although the ortho and para positions of anisole are highly activated toward substitution, the meta position is deactivated. When substitution occurs in the meta position, the methoxy group cannot exert its resonance effect (Eq. 16.30), and only its rate-retarding polar effect is operative. Thus, whether a group activates or deactivates further substitution really depends on the *position* on the ring being considered. Thus, the methoxy group activates ortho, para substitution and deactivates meta substitution. But this is just another way of saying that the methoxy group is an ortho, para director. Because ortho, para substitution is the *observed* mode of substitution, the methoxy group is considered to be an activating group. These ideas are summarized in the reaction free-energy diagrams shown in Fig. 16.6.

The deactivating effects of halogen substituents reflect a different balance of resonance and polar effects. Consider the chloro group, for example. Because chlorine and oxygen have similar electronegativities, the polar effects of the chloro and methoxy groups are similar. However, the resonance interaction of chlorine electron pairs with the ring is much less effective than the interaction of oxygen electron pairs because the chlorine valence electrons reside in orbitals with higher quantum numbers. Because these orbitals and the carbon 2*p* orbitals of the benzene ring have *different sizes* and *different numbers of nodes,* they do not overlap so effectively (Fig. 16.7). Because this overlap is the basis of the resonance effect, the resonance effect of chlorine is weak. With a weak rate-enhancing resonance effect and a strong rate-retarding polar effect, chlorine is a deactivating group. Bromine and iodine exert weaker polar effects than chlorine, but their resonance effects are also weaker. (Why?) Hence, these groups, too, are deactivating groups. Fluorine, as a second-period element, has a stronger resonance effect than the other halogens, but, as the most electronegative element, it has a stronger polar effect as well. Fluorine is also a deactivating group.

The deactivating, rate-retarding polar effects of the halogens are similar at all ring positions, but are offset somewhat by their resonance effects when substitution occurs para to the halogen. However, the resonance effect of a halogen cannot come into play at all when substitution occurs at the meta position of a halobenzene. (Why?) Hence, meta substitution in halobenzenes is deactivated even more than para substitution is. This is another way of saying that halogens are ortho, para-directing groups.

Alkyl substituents such as the methyl group have no resonance effect, but the polar effect of any alkyl group toward electron-deficient carbons is an electropositive, stabilizing effect (Sec. 4.7C). It follows that alkyl substituents on a benzene ring stabilize carbocation intermediates in electrophilic substitution, and for this reason, they are activating groups. It turns out

(text continues on p. 772)

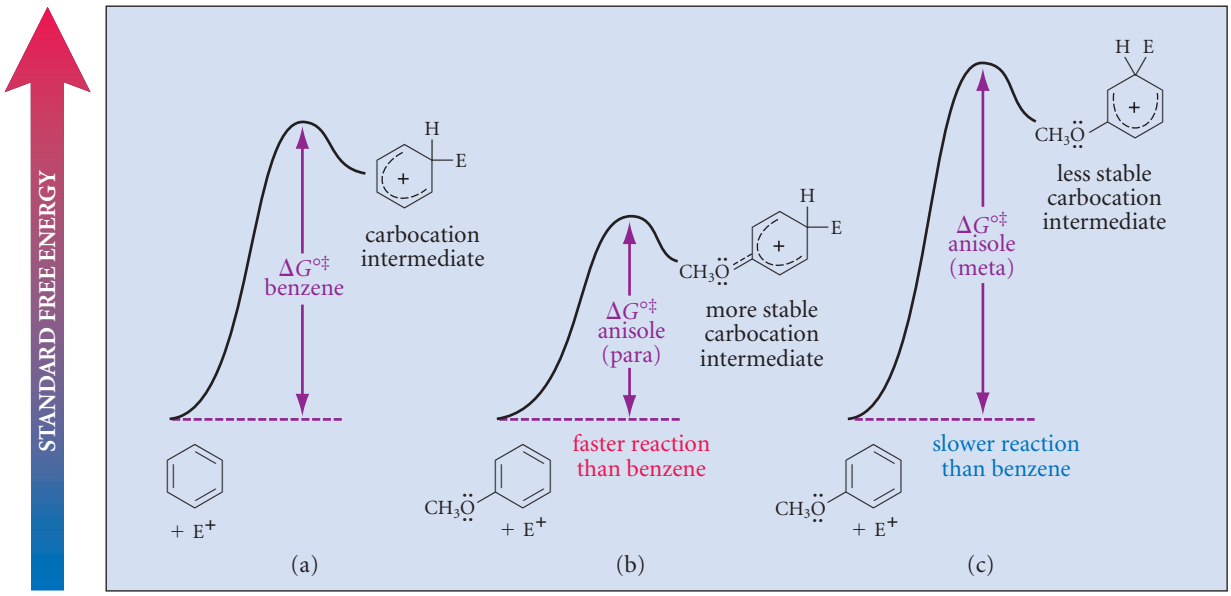
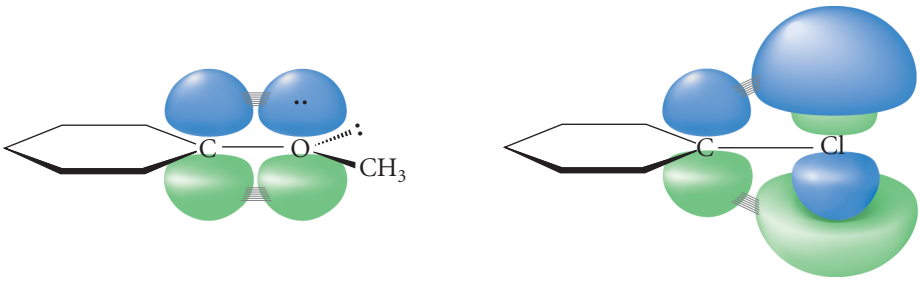


Figure 16.6 Basis of the activating effect of the methoxy group on electrophilic aromatic substitution in anisole. (a) The energy barrier for substitution of benzene by an electrophile E^+. (b) The energy barrier for substitution of anisole by E^+ at the para position. (c) The energy barrier for substitution of anisole by E^+ at the meta position. (Notice that the diagrams for parts (b) and (c) are the same as parts (a) and (b) of Fig. 16.5, p. 765.) The substitution of anisole at the para position is faster than the substitution of benzene; the substitution of anisole at the meta position is slower than the substitution of benzene. The methoxy group is an activating group because the observed reaction of anisole—substitution at the para position—is faster than the substitution of benzene.



overlap of carbon and oxygen 2*p* orbitals
(a)

overlap of carbon 2*p*
and chlorine 3*p* orbitals
(b)

Figure 16.7 The overlap of carbon and oxygen 2*p* orbitals, which is shown in part (a), is more effective than the overlap of carbon 2*p* and chlorine 3*p* orbitals, shown in part (b), because orbitals with different quantum numbers have different sizes and different numbers of nodes. The blue and green parts of the orbitals represent wave peaks and wave troughs, respectively. Bonding overlap occurs only when peaks overlap with peaks and troughs overlap with troughs.

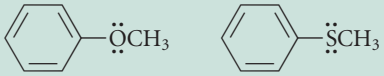
that alkyl groups activate substitution at all ring positions, but they are ortho, para directors because they activate ortho, para substitution more than they activate meta substitution (Eqs. 16.31 and 16.32, p. 766).

Finally, consider the deactivating effects of meta-directing groups such as the nitro group. Because a nitro group has no electron-donating resonance effect, the polar effect of this electronegative group destabilizes the carbocation intermediate and retards electrophilic substitution at *all* positions of the ring. The nitro group is a meta-directing group because substitution is retarded more at the ortho and para positions than at the meta positions (Eqs. 16.33 and 16.34, p. 766). In other words, the meta-directing effect of the nitro group is not due to selective activation of the meta positions, but rather to greater *deactivation* of the ortho and para positions. For this reason, the nitro group and the other meta-directing groups might be called *meta-allowing groups*.

PROBLEMS

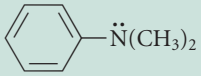
16.25 Draw reaction-free energy profiles analogous to that in Fig. 16.6 in which substitution on benzene by a general electrophile E^+ is compared with substitution at the para and meta positions of **(a)** chlorobenzene; (b) nitrobenzene.

16.26 Explain why the nitration of anisole is much faster than the nitration of thioanisole under the same conditions.



anisole **thioanisole**

16.27 Which should be faster: bromination of benzene or bromination of *N*,*N*-dimethylaniline? Explain your answer carefully.



***N*,*N*-dimethylaniline**

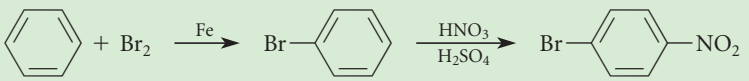
C. Use of Electrophilic Aromatic Substitution in Organic Synthesis

Both activating/deactivating and directing effects of substituents can come into play in planning an organic synthesis that involves electrophilic substitution reactions. The importance of directing effects is illustrated in Study Problem 16.2.

Study Problem 16.2

Outline a synthesis of *p*-bromonitrobenzene from benzene.

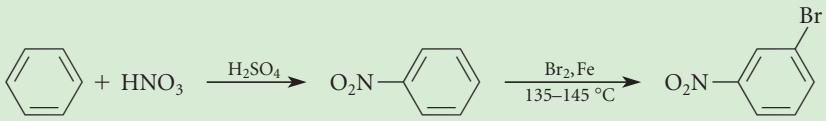
Solution The key to this problem is whether the bromine or the nitro group should be the first ring substituent introduced. Introduction of the bromine first takes advantage of its directing effect in the subsequent nitration reaction:



(16.35)

benzene **bromobenzene** ***p*-bromonitrobenzene**

Introduction of the nitro group first followed by bromination would give instead *m*-bromonitrobenzene, because the nitro group is a meta-directing group.

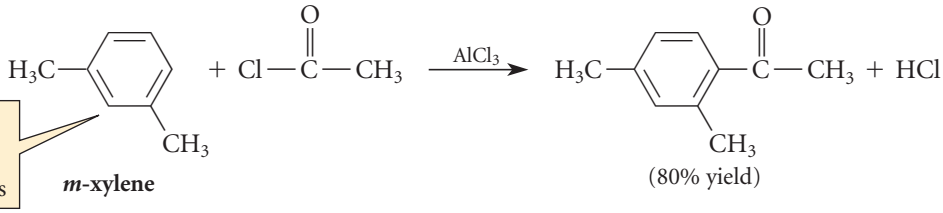


(16.36)

benzene **nitrobenzene** ***m*-bromonitrobenzene**

Hence, to prepare the desired compound, brominate first and *then* nitrate the resulting bromobenzene, as shown in Eq. 16.35.

When an electrophilic substitution reaction is carried out on a benzene derivative with more than one substituent, the activating and directing effects are roughly the sum of the effects of the separate substituents. First, let's consider directing effects. In the Friedel–Crafts acylation of *m*-xylene, for example, both methyl groups direct the substitution to the same positions.



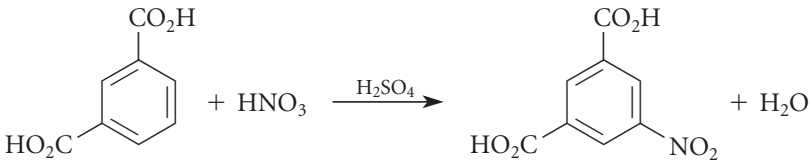
(16.37)

substitution at this position is hindered by two ortho methyl groups

***m*-xylene**

Methyl groups are ortho, para directors. Substitution at the position ortho to both methyl groups is difficult because van der Waals repulsions between both methyls and the electrophile would be present in the transition state. Consequently, substitution occurs at a ring position that is para to one methyl and, of necessity, ortho to the other, as shown in Eq. 16.37.

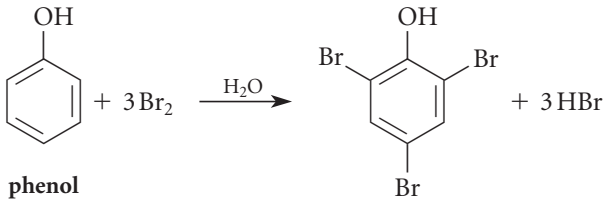
Two meta-directing groups on a ring, such as the carboxylic acid (—CO_2H) groups in the following example, direct further substitution to the remaining open meta position:



(16.38)

1,3-benzenedicarboxylic acid **5-nitro-1,3-benzenedicarboxylic acid** (96% of product)

In each of the previous two examples, both substituents direct the incoming group to the same position. What happens when the directing effects of the two groups are in conflict? If one group is much more strongly activating than the other, the directing effect of the more powerful activating group generally predominates. For example, the —OH group is such a powerful activating group that phenol can be brominated three times, even without a Lewis acid catalyst. (Notice that the —OH group is near the top of Table 16.2, p. 763.)



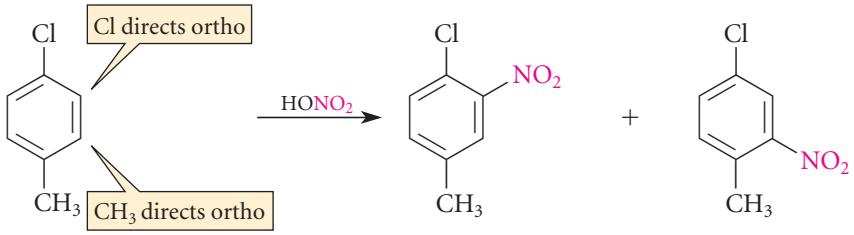
phenol

2,4,6-tribromophenol
quantitative;
virtually instantaneous

(16.39)

After the first bromination, the —OH and —Br groups direct subsequent brominations to different positions. The strong activating and directing effect of the —OH group at the ortho and para positions overrides the weaker directing effect of the —Br group.

In other cases, mixtures of isomers are typically obtained.



4-chlorotoluene

4-chloro-3-nitrotoluene
(42%)

4-chloro-2-nitrotoluene
(58%)

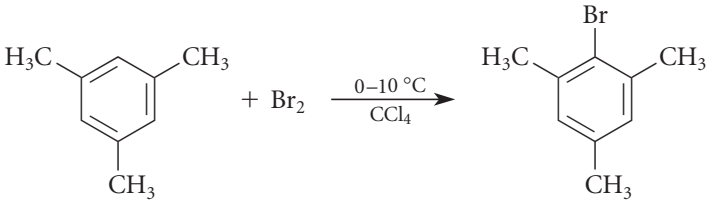
(16.40)

PROBLEM

16.28 Predict the predominant product(s) from:
(a) monosulfonation of *m*-bromotoluene (b) mononitration of *m*-bromoiodobenzene

STUDY GUIDE LINK 16.3
Reaction Conditions and Reaction Rate

You've just learned that the activating and directing effects of substituents must be taken into account in developing the strategy for an organic synthesis that involves a substitution reaction on an already-substituted benzene ring. The activating or deactivating effects of substituents in an aromatic compound also determine the *conditions* that must be used in an electrophilic substitution reaction. The bromination of nitrobenzene, for example (Eq. 16.28, p. 762), requires relatively harsh conditions of heat and a Lewis acid catalyst because the nitro group deactivates the ring toward electrophilic substitution. The conditions in Eq. 16.28 are more severe than the conditions required for the bromination of benzene itself, because benzene is the more reactive compound. An even more dramatic example in the other direction is provided by the bromination of mesitylene (1,3,5-trimethylbenzene), Mesitylene can be brominated under *very* mild conditions, because the ring is activated by three methyl groups; a Lewis acid catalyst is not even necessary.

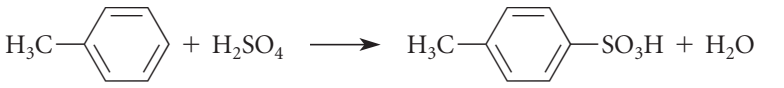


mesitylene

(80% yield)

(16.41)

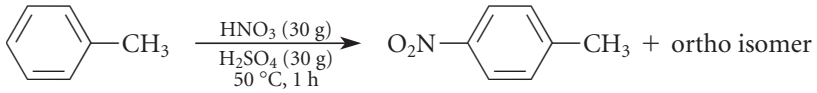
A similar contrast is apparent in the conditions required to sulfonate benzene and toluene. Sulfonation of benzene requires fuming sulfuric acid (Eq. 16.12, p. 755). However, because toluene is more reactive than benzene, toluene can be sulfonated with concentrated sulfuric acid, a milder reagent than fuming sulfuric acid.



(16.42)

toluene — ***p*-toluenesulfonic acid**

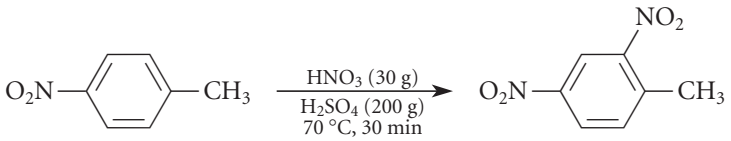
Another very important consequence of activating and deactivating effects is that when a deactivating group—for example, a nitro group—is being introduced by an electrophilic substitution reaction, it is easy to introduce one group at a time, because the products are *less reactive* than the reactants. Thus, toluene can be nitrated only once because the nitro group that is introduced retards a second nitration on the same ring. The following three equations show the conditions required for successive nitrations. Notice that each additional nitration requires harsher conditions.



(16.43a)

toluene
50 g

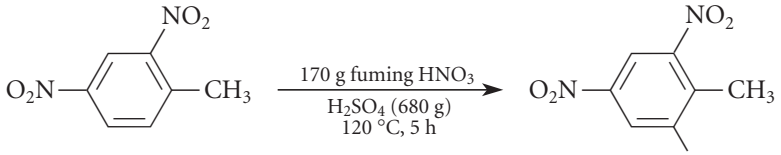
4-nitrotoluene



(16.43b)

4-nitrotoluene
50 g

2,4-dinitrotoluene
(90% yield)



(16.43c)

2,4-dinitrotoluene
50 g

2,4,6-trinitrotoluene
"TNT"
(90% yield)

Fuming nitric acid (Eq. 16.43c) is an especially concentrated form of nitric acid. Ordinary nitric acid contains 68% by weight of nitric acid; fuming nitric acid is 95% by weight nitric acid. It owes its name to the layer of colored fumes usually present in the bottle of the commercial product. Fuming nitric acid is a much harsher (that is, more reactive) nitrating reagent than nitric acid itself.

In contrast, when an activating group is introduced by electrophilic substitution, the products are *more reactive* than the reactants; consequently, additional substitutions can occur easily under the conditions of the first substitution and, as a result, mixtures of products are obtained. This is the situation in Friedel–Crafts alkylation. As noted in the discussion of Eq. 16.19 (p. 758), one way to avoid multiple substitution in such cases is to use a large excess of

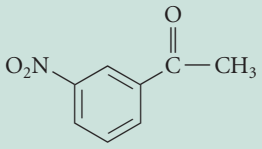
the starting material. (Friedel–Crafts alkylation is the only electrophilic aromatic substitution reaction discussed in this chapter that introduces an activating substituent.)

Some deactivating substituents retard some reactions to the point that they are not useful. For example, Friedel–Crafts *acylation* (Sec. 16.4F) does not occur on a benzene ring substituted *solely* with one or more meta-directing groups. In fact, nitrobenzene is so unreactive in the Friedel–Crafts acylation that it can be used as the solvent in the acylation of other aromatic compounds! Similarly, the Friedel–Crafts *alkylation* (Sec. 16.4E) is generally too slow to be useful on compounds that are more deactivated than benzene itself, even halobenzenes.

PROBLEMS

16.29 In each of the following sets, rank the compounds in order of increasing harshness of the reaction conditions required to accomplish the indicated reaction.
(a) sulfonation of benzene, *m*-xylene, or *p*-dichlorobenzene
(b) Friedel–Crafts acylation of chlorobenzene, anisole, or toluene.

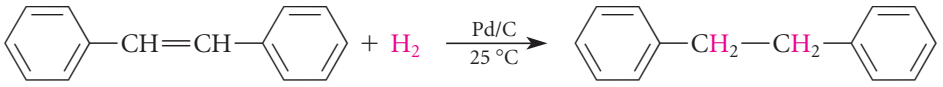
16.30 Outline a synthesis of *m*-nitroacetophenone from benzene; explain your reasoning.



***m*-nitroacetophenone**

16.6 HYDROGENATION OF BENZENE DERIVATIVES

Because of its aromatic stability, the benzene ring is resistant to conditions used to hydrogenate ordinary double bonds.

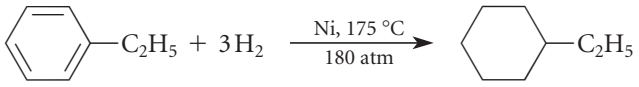


(16.44)

stilbene
(cis or trans)

(2-phenylethyl)benzene
(bibenzyl)
(95% yield)

Nevertheless, aromatic rings can be hydrogenated under more extreme conditions of temperature or pressure (or both), and practical laboratory apparatus that can accommodate these conditions is readily available. Typical conditions for carrying out the hydrogenation of benzene derivatives include Rh or Pt catalysts at 5–10 atm of hydrogen pressure and 50–100 °C, or Ni or Pd catalysts at 100–200 atm and 100–200 °C. For example, compare the conditions for the following hydrogenation with those for the hydrogenation in Eq. 16.44.



(16.45)

ethylbenzene

ethylcyclohexane
(93% yield)