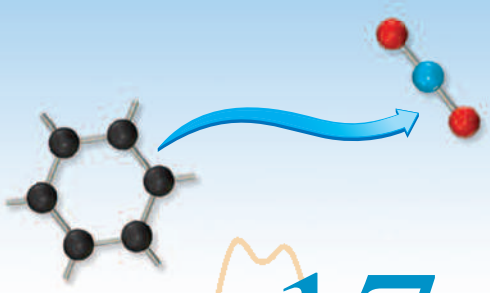

Aromatic Substitution Reactions

CHAPTER 17

Most of the reactions discussed in this chapter involve the attack of an electrophile on an aromatic compound. Although the initial step of the mechanism resembles that of the electrophilic addition reactions of carbon–carbon double bonds discussed in Chapter 11, the final product here results from substitution of the electrophile for a hydrogen on the aromatic ring rather than addition. Therefore, these reactions are called **electrophilic aromatic substitutions.**

First, the general mechanism for these reactions is presented. This is followed by a specific example, the substitution of a nitro group onto a benzene ring. Then the effect of a group that is already present on the ring on the rate of the reaction and its regiochemistry is discussed in detail. Next, reactions that add halogens, sulfonic acid groups, alkyl groups, and acyl groups to the aromatic ring are presented. In each case the required reagents, the mechanism for generating the electrophile, the usefulness, and the limitations of the reactions are discussed. These reactions are very important and constitute the majority of the chapter.

Next, three different mechanisms for nucleophilic substitutions on aromatic rings are presented. These are followed by several other reactions that are useful in synthesis because they interconvert groups attached to aromatic rings. Finally, the use of combinations of all of these reactions to synthesize a variety of substituted aromatic compounds is discussed.

Mastering Organic Chemistry

- Predicting the Products of Aromatic Substitution Reactions
- Understanding the Mechanisms of Aromatic Substitution Reactions
- Predicting the Effect of a Substituent on the Rate and Regiochemistry of an Electrophilic Aromatic Substitution Reaction
- Synthesizing Aromatic Compounds

17.1 Mechanism for Electrophilic Aromatic Substitution

A general mechanism for the electrophilic aromatic substitution reaction is outlined in Figure 17.1. The process begins by reaction of the electrophile with a pair of pi electrons of the aromatic ring, which acts as the nucle-

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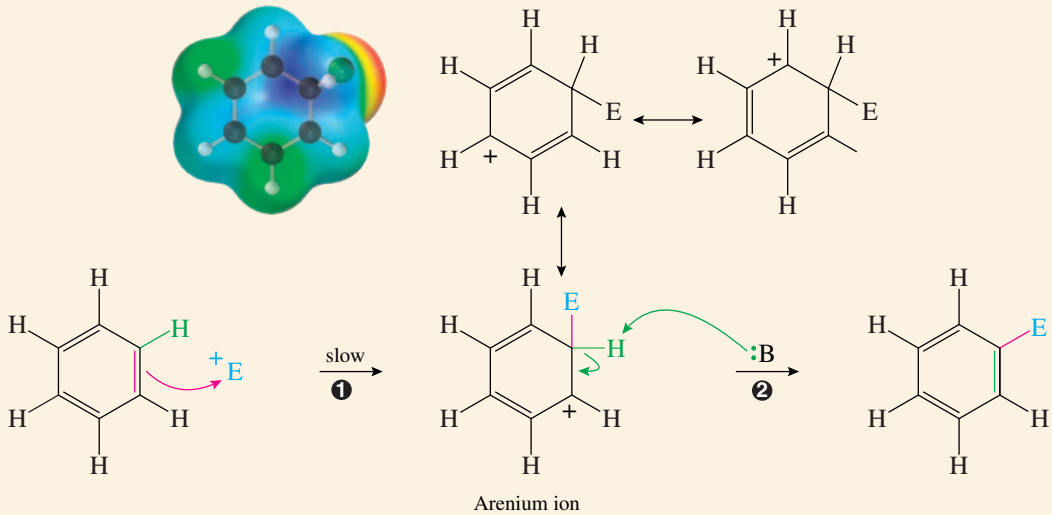


❶ The electrophile reacts with a pair of pi electrons of the aromatic ring. This step resembles the first step of the reaction in which electrophiles react with alkenes, described in Chapter 11. This is the slow step of the reaction.

This carbocation is called an arenium ion. Although it has considerable resonance stabilization, it has lost the aromatic resonance energy of benzene because the cycle of orbitals does not extend entirely around the ring. Note that the resonance structures have the positive charge located on the carbons ortho and para to the carbon that is bonded to the electrophile.

❷ Rather than add as a nucleophile to the positive carbon, a base removes a proton from the arenium ion to regenerate the aromatic ring with its large resonance stabilization.

Figure 17.1

MECHANISM OF A GENERAL ELECTROPHILIC AROMATIC SUBSTITUTION REACTION.

ophile, in a fashion very similar to the addition reactions described in Chapter 11, which begin by reaction of an electrophile with the pi electrons of an alkene. This results in the formation of a carbocation called an **arenium ion.** Removal of a proton from the arenium ion by some weak base that is present restores the aromatic ring and results in the substitution of the electrophile for a hydrogen on the aromatic ring.

It is instructive to examine the energetics of this reaction and compare them to those of the addition reactions of Chapter 11 (see Figure 17.2). Because of its aromatic resonance energy, benzene is considerably more stable than the alkene. Because of resonance, the arenium ion that is produced in the electrophilic aromatic substitution reaction is more stable than the carbocation produced in the addition reaction. However, the arenium ion is no longer aromatic, so its stabilization relative to the carbocation is less than the stabilization of benzene relative to the alkene. Because the transition states for both of these reactions resemble the carbocation intermediates (recall the Hammond postulate), the transition state leading to the arenium ion must have lost most of its aromatic stabilization also. This causes the activation energy for the electrophilic aromatic substitution reaction, $\Delta G_s^{\ddagger}$, to be larger than the activation energy for the addition reaction, $\Delta G_a^{\ddagger}$. In other words, the loss of aromatic resonance energy that occurs on going to the transition state for substitution results in a higher activation barrier. The substitution reaction usually requires much stronger electrophiles than the addition reaction.

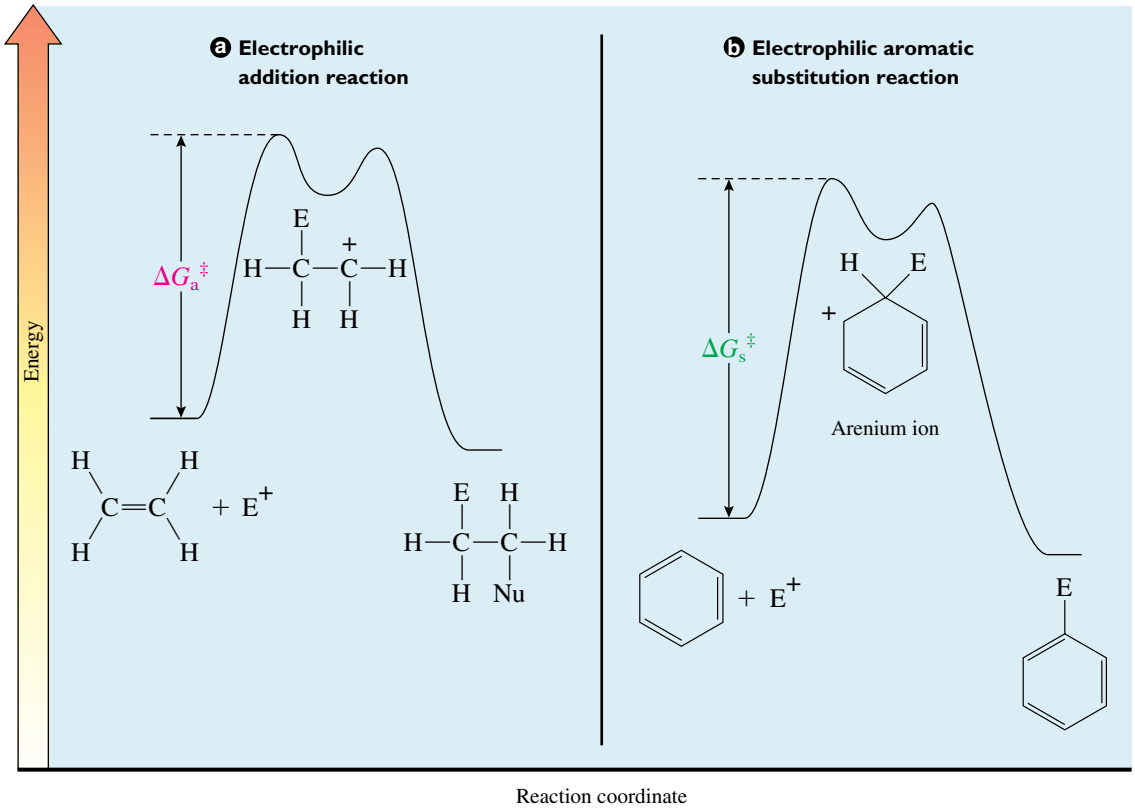
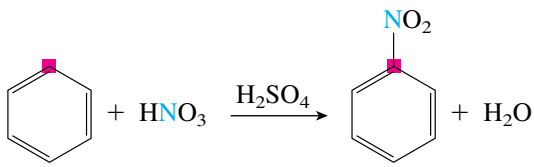


Figure 17.2

REACTION ENERGY DIAGRAMS FOR a AN ELECTROPHILIC ADDITION TO AN ALKENE AND b AN ELECTROPHILIC AROMATIC SUBSTITUTION REACTION.

The arenium ion, like any carbocation, has two reaction pathways available. It could react with a nucleophile to give an addition product, or it could lose a proton to some base in the system to give a substitution product. If addition were to occur, the product would be a cyclohexadiene, which is no longer aromatic because it has only two double bonds in the ring. It has lost at least 35 kcal/mol (146 kJ/mol) of stabilization, the difference in resonance energy between an aromatic ring and a cyclohexadiene. Obviously, the formation of the aromatic ring in the substitution product is greatly favored.

All of the electrophilic aromatic substitution reactions follow this same general mechanism. The only difference is the structure of the electrophile and how it is generated. Let's look at a specific example, the nitration of benzene. This reaction is accomplished by reacting benzene with nitric acid in the presence of sulfuric acid:



Benzene Nitrobenzene

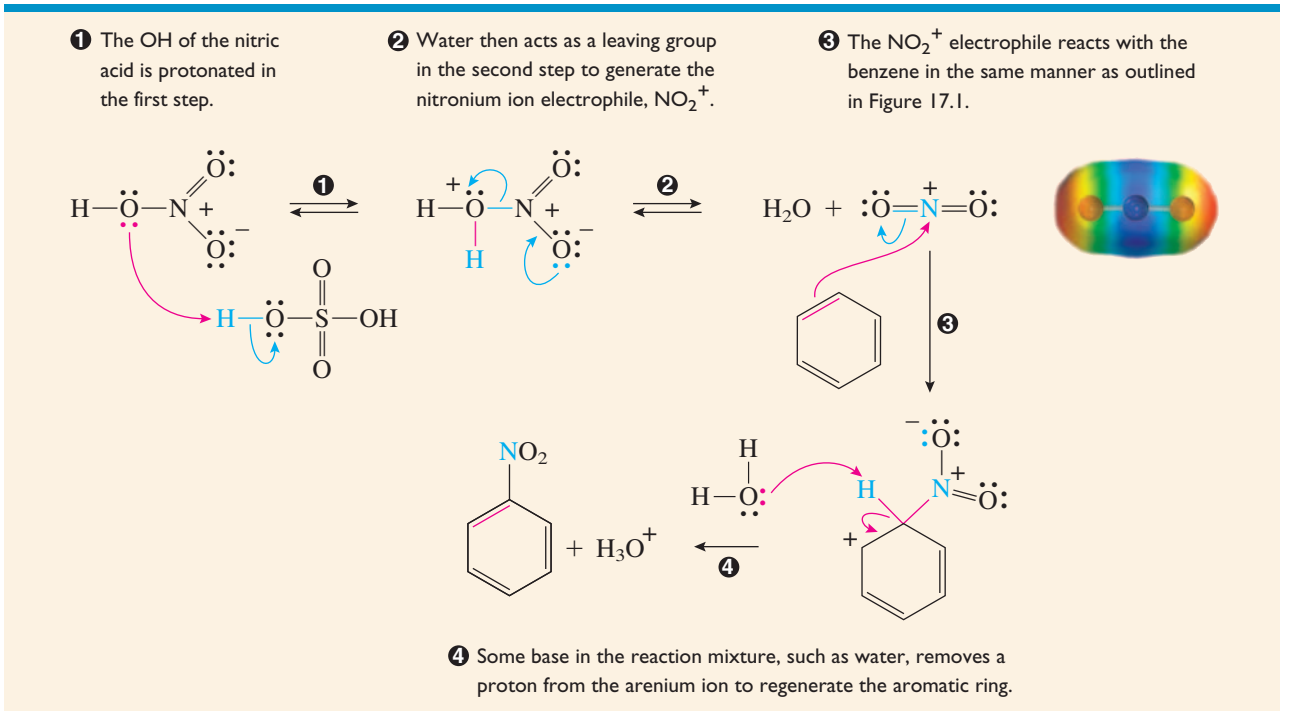


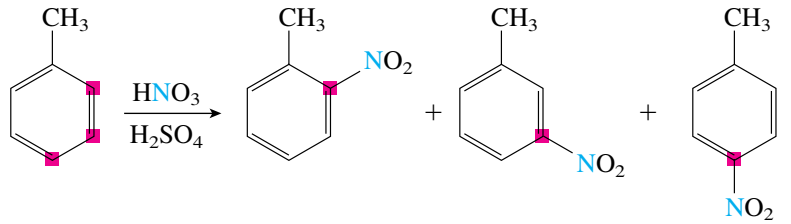
Figure 17.3

MECHANISM OF THE NITRATION OF BENZENE.

The mechanism for this reaction is presented in Figure 17.3. The electrophile, NO_2^+ (nitronium ion) is generated from the nitric acid by protonation of an OH group. Water then acts as a leaving group to generate the electrophile. The rest of the mechanism is identical to that outlined in Figure 17.1.

17.2 EFFECT OF SUBSTITUENTS

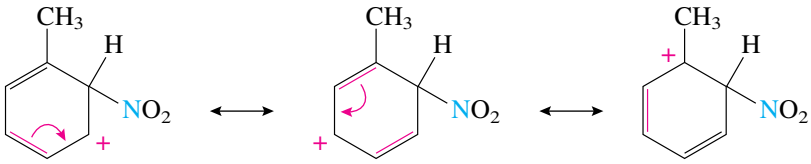
When a substituted benzene is nitrated, the substituent on the ring has an effect on the rate of the reaction. In addition, the NO_2^+ electrophile can attach ortho, meta, or para to the substituent. For example, when toluene is nitrated, it is found to react 17 times faster than benzene. Substitution occurs primarily ortho and para to the methyl group.



Toluene	60% *o*-Nitrotoluene	3% *m*-Nitrotoluene	37% *p*-Nitrotoluene

The methyl group accelerates the reaction compared to benzene and directs the incoming electrophile to the ortho and para positions. Both the rate enhancement and the

regiochemistry of the reaction can be understood by examination of the three possible arenium ions produced by attack of the electrophile at the positions ortho, meta, and para to the methyl group. Consider the case of attack at an ortho position first:

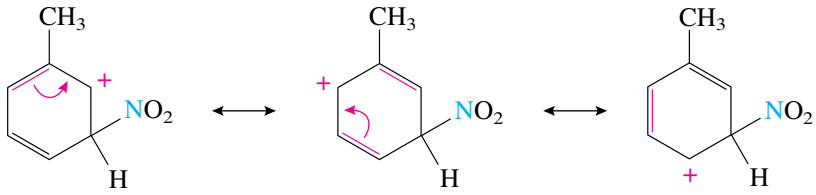


Most stable resonance structure

Arenium ion from ortho attack

In one of the resonance structures, the positive charge is located on the carbon bonded to the methyl substituent. As we are well aware, the methyl group will stabilize the carbocation, so this arenium ion is somewhat lower in energy (more stable) than the arenium ion produced in the nitration of benzene itself.

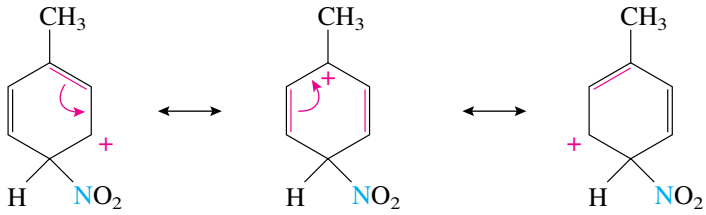
Consider next the arenium ion produced by attack of the electrophile at a position meta to the methyl group:



Arenium ion from meta attack

In this case, none of the resonance structures has the positive charge located on the carbon bonded to the methyl group. This ion has no extra stabilization when compared to the arenium ion formed from benzene.

Finally, consider the case of attack of the electrophile at the para position:



Most stable resonance structure

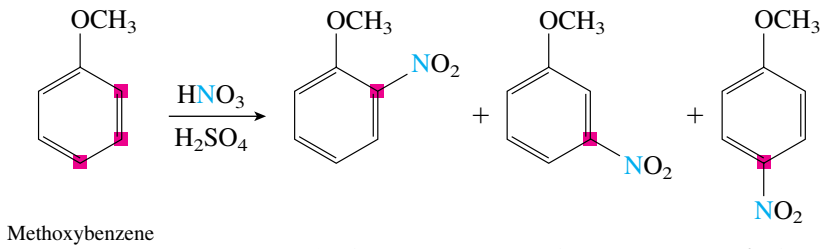
Arenium ion from para attack

This arenium ion is similar to that produced by attack at the ortho position in that the positive charge is located on the carbon bonded to the methyl group in one of the resonance structures. Therefore, it is more stable than the arenium ion formed from benzene.

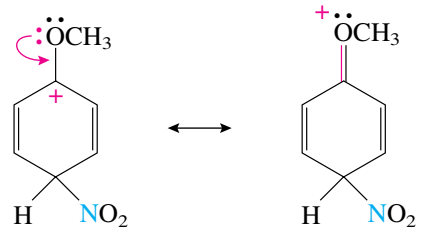
Although all arenium ions are unstable, reactive intermediates, those resulting from ortho and para attack of the electrophile on toluene, but not that from meta attack, are more stable than the arenium ion produced from benzene itself. Therefore, for toluene the transition states leading to the ortho and para ions are at lower energy than is the transition state leading to the meta ion or the transition state that is formed in the nitration of benzene. Thus, the methyl group accelerates the attack of the electrophile at the ortho and para positions. The methyl is an activating group (it makes the aromatic ring react faster), and it is an ortho/para directing group.

The effects of other groups can be understood by similar reasoning. When the electrophile bonds ortho or para to the substituent, the positive charge is located on the carbon that is bonded to the substituent in one of the resonance structures. If the substituent is one that can stabilize the carbocation, then it accelerates the reaction and directs the incoming electrophile to the ortho and para positions. If, on the other hand, the substituent is one that destabilizes the carbocation, then it slows the reaction and directs the electrophile to the meta position so that the positive charge is never on the carbon directly attached to the substituent. The meta arenium ion is less destabilized than the ortho or para ions in this case. Some other examples will help clarify this reasoning.

The nitration of methoxybenzene (anisole) proceeds 10,000 times faster than does nitration of benzene and produces predominantly the ortho and para isomers of nitroanisole.

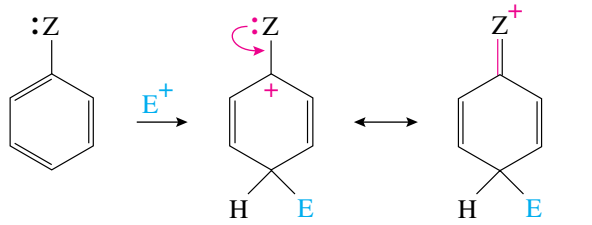


From these results it can be seen that the methoxy group is also an ortho/para director and is a much stronger activating group than is the methyl group. Examination of the resonance structure for the para arenium ion that has the positive charge located on the carbon bonded to the methoxy group explains these results.



Two electronic effects are operating in this case: an inductive effect and a resonance effect. Because of the high electronegativity of the oxygen, the methoxy group withdraws electrons by its inductive effect (see Section 4.5). If this were the only effect operating,

then it would be a deactivating group. However, in this case there is also a resonance effect. As shown in the resonance structure on the right, the methoxy group is a resonance electron-donating group. This resonance structure is especially stable because the octet rule is satisfied for all of the atoms. A similar, especially stable resonance structure can be written for the arenium ion that is produced by reaction of the electrophile at the ortho position. However, when the electrophile reacts at the meta position, the positive charge is never located on the carbon bonded to the methoxy group, so this especially stable resonance structure cannot be formed. Overall, the resonance effect dominates the inductive effect in this case so the methoxy group is a strongly activating group and an ortho/para director. With a few exceptions that are discussed shortly, any group that has an unshared pair of electrons on the atom bonded to the ring, represented by the general group Z in the following equation, has a similar resonance effect and acts as an activating group and an ortho/para director:



Especially stable resonance structure

PROBLEM 17.1

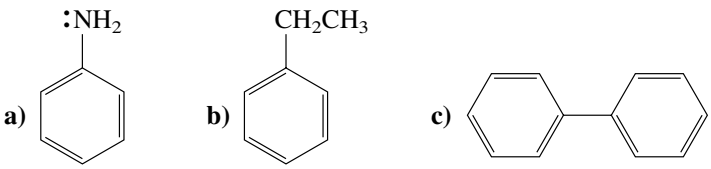
Show all of the resonance structures for the arenium ion that is produced by attack of the NO_2^+ electrophile at the ortho position of anisole. Which of these structures is especially stable?

PROBLEM 17.2

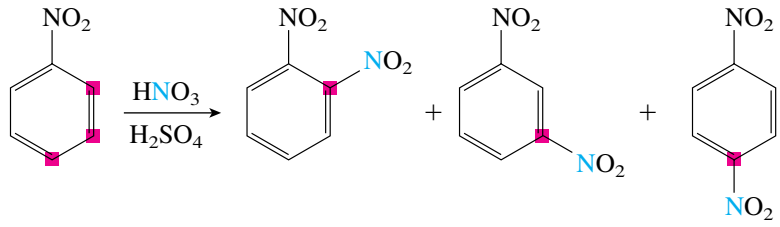
Show all of the resonance structures for the arenium ion that is produced by attack of the NO_2^+ electrophile at the meta position of anisole. Is there an especially stable resonance structure in this case?

PROBLEM 17.3

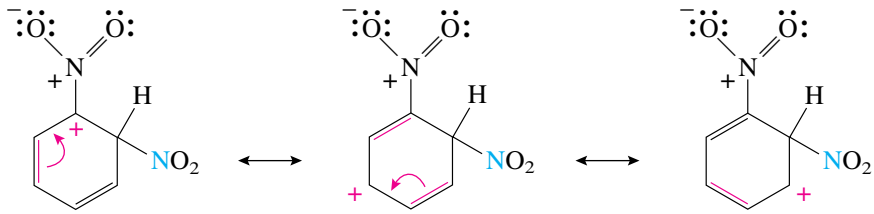
Explain why these compounds react faster than benzene in electrophilic aromatic substitution reactions and give predominantly ortho and para products:



Now let's consider an example where the substituent slows the reaction. The nitration of nitrobenzene occurs approximately 10^7 times more slowly than the nitration of benzene and gives predominantly the *meta*-isomer of dinitrobenzene.



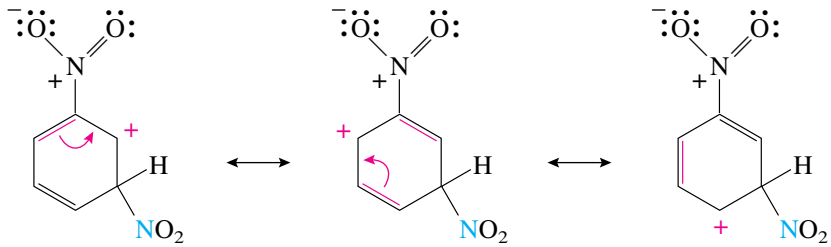
The nitro group is deactivating and directs the incoming electrophile to the meta position. Again, examination of the arenium ions provides an explanation for these results. First, consider the arenium ion produced by attack of the electrophile at an ortho position:



Arenium ion from ortho attack

The nitro group is an electron-withdrawing group both by its inductive effect and by its resonance effect. The first resonance structure is especially destabilized because the positive charge is located directly adjacent to the electron-withdrawing nitro group. Thus, the presence of the nitro group on the ring dramatically slows attack of an electrophile at the ortho position.

Now, consider attack of the electrophile at a meta position:



Arenium ion from meta attack

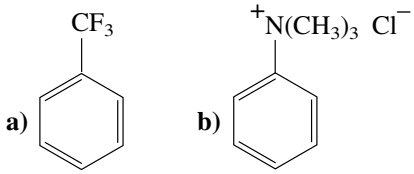
This time there is no resonance structure that has the positive charge on the carbon bonded to the nitro group. The arenium ion is still destabilized by the electron-withdrawing effect of the nitro group, but this ion is not destabilized as much as the ion produced by attack of the electrophile at the ortho position because the positive charge is never as close to the nitro group.

The arenium ion produced by attack of the electrophile at the para position resembles that produced by attack at the ortho position in that it also has a resonance structure that has the positive charge on the carbon that is bonded to the nitro group. The destabilization of this ion is comparable to that of the ortho ion.

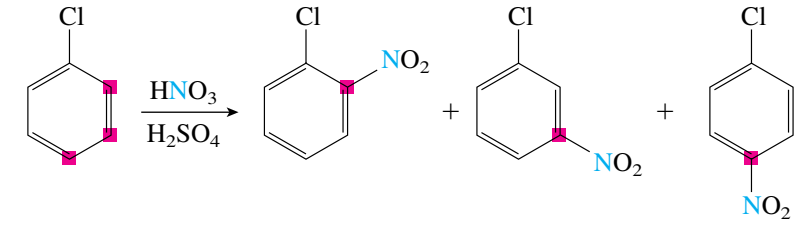
Overall, then, the nitro group slows the reaction, but it slows attack at the meta position less than it slows attack at the ortho and para positions. It is a deactivating group and a meta-directing group. In general, any group that withdraws electrons from the ring by an inductive and/or resonance effect behaves similarly.

PROBLEM 17.4

Explain why these compounds react more slowly than benzene in electrophilic aromatic substitution reactions and give predominantly meta products:



So far, groups have been either activating and ortho/para directors or deactivating and meta directors. The halogens are exceptions to this generalization. They are slightly deactivating compared to benzene but still direct to the ortho and para positions. For example, chlorobenzene is nitrated 17 times slower than benzene and produces predominantly *ortho*- and *para*-chloronitrobenzene.



Why do the halogens have this unusual behavior? Like the methoxy group, the inductive and resonance effects of the halogens are in competition. In the case of the halogens, however, the inductive electron-withdrawing effect is slightly stronger than the resonance electron-donating effect. The high electronegativity of fluorine is responsible for its inductive effect being stronger than its resonance effect. The other halogens are weaker resonance electron-donating groups because their *p* orbitals do not overlap well with the 2*p* AO of the ring carbon, owing to the longer length of the carbon–halogen bond and the size of the 3*p*, 4*p*, or 5*p* AO. As a result, the halogens are weakly deactivating groups. But because resonance electron donation is most effective at the ortho and para positions, these positions are deactivated less than the meta position. Therefore, the halogens are slightly deactivating ortho/para directors.

The effect of almost any substituent can be understood on the basis of similar reasoning. Table 17.1 lists the effect on both the reaction rate and the regiochemistry of the substituents most commonly found on benzene rings. Rather than just memorizing this table, try to see the reasons why each group exhibits the behavior that it does. The strongly activating, ortho/para directors all have an unshared pair of electrons on the atom attached to the ring that is readily donated by resonance. Alkyl and aryl groups

Table 17.1 Effect of Substituents on the Rate and Regiochemistry of Electrophilic Aromatic Substitution Reactions

Substituent	Rate Effect	Regiochemistry	Comments
—$\ddot{N}R_2$ —$\ddot{N}HR$ —$\ddot{N}H_2$ —$\ddot{O}H$	Strongly activating	ortho and para	Resonance donating effect is stronger than inductive withdrawing effect
—$\ddot{O}R$ —$\ddot{S}R$ —$\ddot{N}HCCH_3$ —$\ddot{O}CCH_3$	Moderately activating	ortho and para	Resonance donating effect is stronger than inductive withdrawing effect, but not as much so as above
—R Alkyl groups —Ar Aryl groups	Weakly activating	ortho and para	Weak inductive or resonance donors
—$\ddot{X}$: Halogens	Weakly deactivating	ortho and para	Resonance donating effect controls regiochemistry but is weaker than inductive withdrawing effect that controls rate
—CH —CR —COH —COR —CNH_2	Moderately deactivating	meta	Inductive and resonance withdrawers
—CN —SO_3H —CX_3 —$\overset{+}{N}R_3$ —$\overset{+}{N}H_3$ —NO_2	Strongly deactivating	meta	Inductive and/or resonance withdrawers

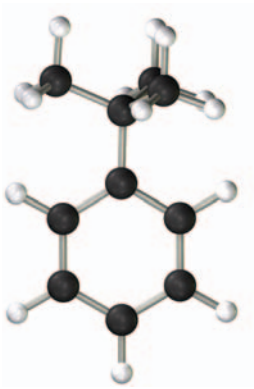
stabilize a positive charge on an adjacent carbon, so they are activating ortho/para directors, although they are less activating than the preceding groups. The deactivating meta-directing groups all have a positive or partial positive charge on the atom attached to the ring. The halogens are unusual because they are weakly deactivating, ortho/para directors.

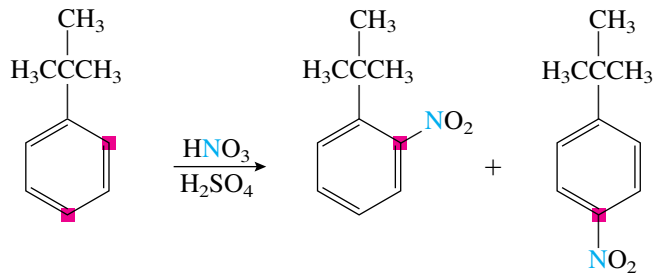
PROBLEM 17.5

Predict the effect of these substituents on the rate and regiochemistry of electrophilic aromatic substitution reactions:

a) —$\ddot{S}$—CH_3 **b)** —$\overset{O}{\overset{\|}{S}}(=O)$—$CH_3$ **c)** —$\overset{O}{\overset{\|}{C}}$—Cl

Finally, let's compare the amount of ortho product to the amount of para product produced in a reaction of an aromatic compound that has an ortho/para director on the ring. There are two ortho positions and only one para position, so if statistics were the only important factor, the ratio of ortho to para products should be 2 to 1. However, attack at the ortho position can be disfavored by the steric effect of the group. Obviously, this depends partly on the size of the group and the size of the electrophile. In addition, some reactions are more sensitive to steric effects than others. In general, then, the ratio of ortho to para product ranges from 2 to 1 in favor of the ortho product to predominantly para for reactions involving bulky substituents or reactions that are very sensitive to steric hindrance. An example of this steric effect can be seen by comparing the following reaction to the nitration of toluene presented earlier (page 674). The major product from toluene is the *ortho*- isomer (60% ortho and 37% para). In contrast, the bulky group of *t*-butylbenzene causes the major product from its nitration to be the *para*-isomer.

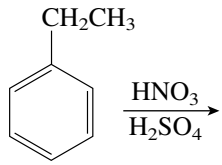




t-Butylbenzene 18% 82%

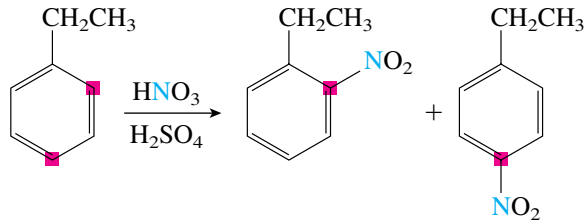
PRACTICE PROBLEM 17.1

Show the products of the reaction of ethylbenzene with nitric acid and sulfuric acid.



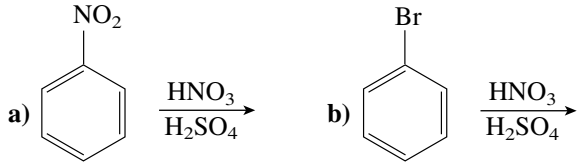
Solution

The ethyl group, like other alkyl groups, is weakly activating and directs to the ortho and para positions. The small amount of meta product that is formed is usually not shown.



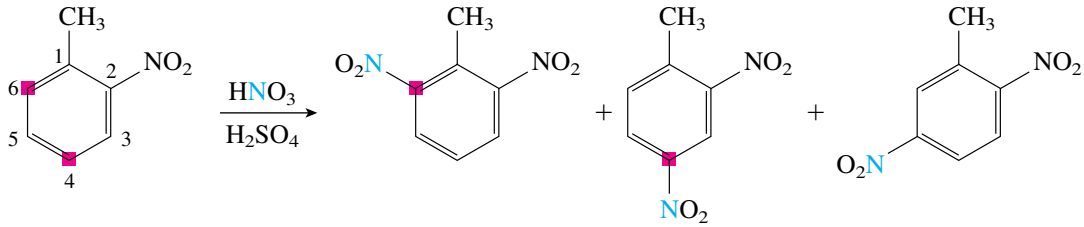
PROBLEM 17.6

Show the products of these reactions:



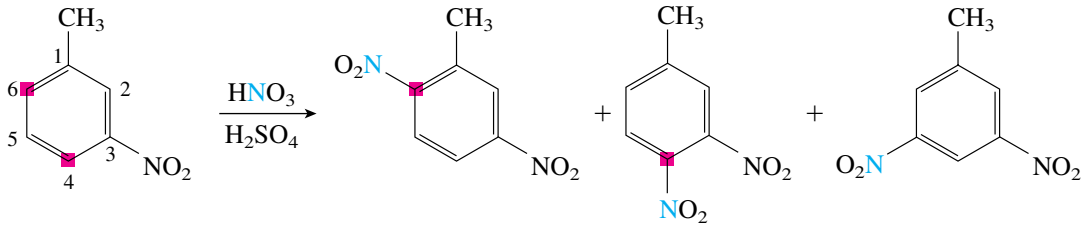
17.3 Effect of Multiple Substituents

The situation is more complicated if there is more than one substituent on the benzene ring. However, it is usually possible to predict the major products that are formed in an electrophilic aromatic substitution reaction. When the substituents direct to the same position, the prediction is straightforward. For example, consider the case of 2-nitrotoluene. The methyl group directs to the positions ortho and para to itself—that is, to positions 4 and 6. The nitro group directs to positions meta to itself—that is, also to positions 4 and 6. When the reaction is run, the products are found to be almost entirely 2,4-dinitrotoluene and 2,6-dinitrotoluene, as expected:



2-Nitrotoluene 29% 70% 1%

If the groups direct to different positions on the ring, usually the stronger activating group controls the regiochemistry. Groups that are closer to the top of Table 17.1 control the regiochemistry when competing with groups lower in the table. In the case of 3-nitrotoluene the methyl group directs to positions 2, 4, and 6 while the nitro group directs to position 5. Because the methyl group is a stronger activating group than the nitro group, it controls the regiochemistry:

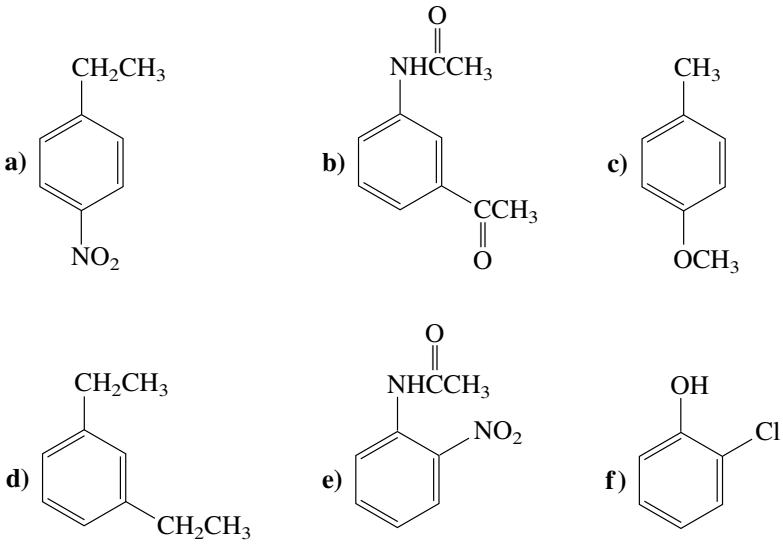


3-Nitrotoluene 38% 60% 1%

Note that none of the product where the new nitro group has been added to position 2, between the two groups, is formed. In general, the position between two groups that are meta to each other is not very reactive because of steric hindrance by the groups on either side of this position.

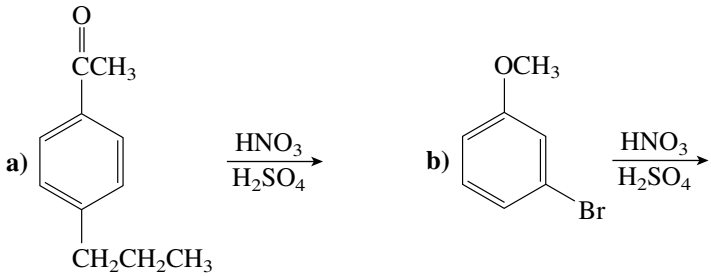
PROBLEM 17.7

Explain which positions would be preferentially nitrated in the reaction of these compounds with nitric acid and sulfuric acid:



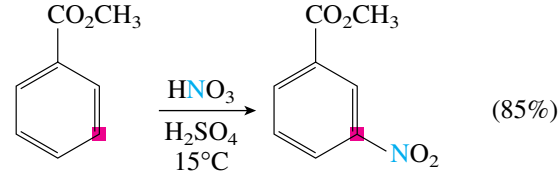
PROBLEM 17.8

Show the major products of these reactions:



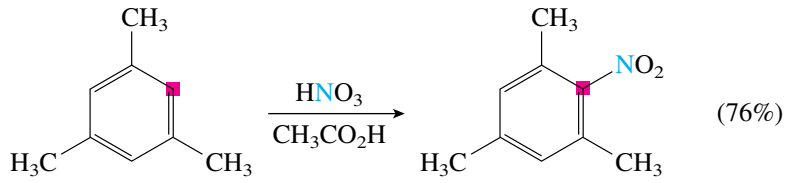
17.4 NITRATION

The reagents and the mechanism for the nitration of an aromatic ring have already been discussed. The reaction is very general and works with almost any substituent on the ring, even strongly deactivating substituents.



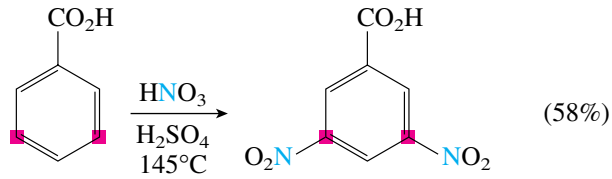
Methyl benzoate

The concentration of the NO_2^+ electrophile is controlled by the strength of the acid that is used in conjunction with nitric acid. Milder conditions, such as nitric acid without sulfuric acid, nitric acid and acetic acid, or nitric acid in acetic anhydride, are employed when the ring is strongly activated, as illustrated in the following example:



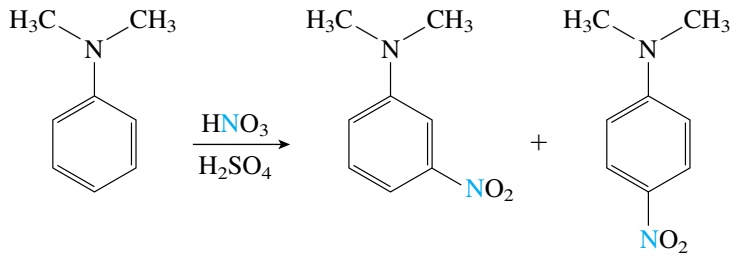
1,3,5-Trimethylbenzene

The nitro group that is added to the ring in these reactions is a deactivating group. This means that the product is less reactive than the reactant, so it is easy to add only one nitro group to the ring. However, it is possible to add a second nitro group, if so desired, by using more vigorous conditions. Thus, the reaction of benzoic acid using the same conditions as shown earlier for methyl benzoate (HNO_3, H_2SO_4, 15°C) results in the formation of the mononitration product, *m*-nitrobenzoic acid. Under more drastic conditions (higher temperature and higher sulfuric acid concentration), two nitro groups can be added, as illustrated in the following equation:



Benzoic acid

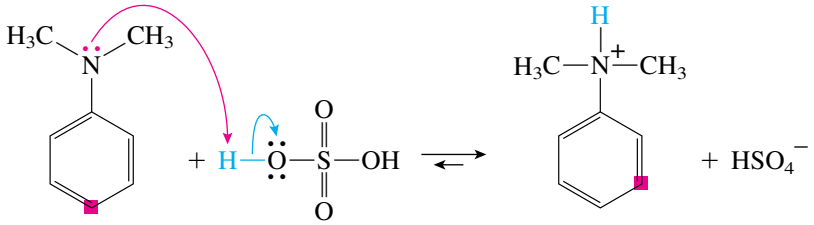
The following example illustrates a problem that sometimes occurs with amino substituents:



N,N-Dimethylaniline 63% 18%

The dimethylamino group is a strong activator and an ortho/para director, yet the major product from the reaction is the *meta*-isomer. This unexpected result is due to the

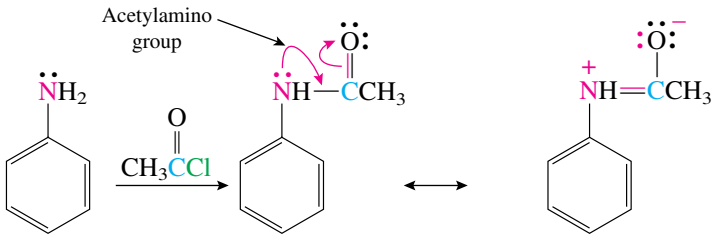
basicity of the amino group. In the strongly acidic reaction mixture, the nitrogen is protonated:



The $NH(CH_3)_2^+$ group deactivates the ring and directs to the meta position. The major product, the *meta*-isomer, results from the reaction of the protonated amine. The minor product, the *para*-isomer, results from the reaction of a very small amount of unprotonated amine. Although its concentration in the strongly acidic solution is extremely small, the unprotonated amine is many orders of magnitude more reactive than its conjugate acid, so some of the para product is formed.

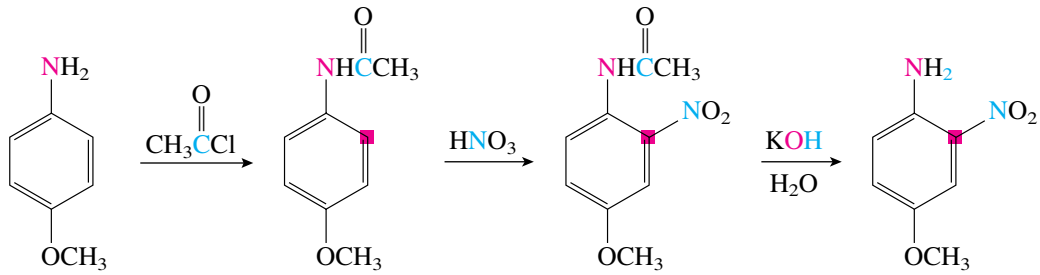
It is fairly common for the electron pair on an amino group, which is a good Lewis base, to react with a Lewis acid under the strongly electrophilic conditions of these substitution reactions. This changes the substituent from a strong activating group to a strong deactivating group. As a result, the reaction often has the undesired regiochemistry, and in some cases the desired reaction may not occur at all. Because the exact result is difficult to predict or control, the amino substituent is usually modified to decrease its reactivity. The strategy is similar to that employed in the Gabriel synthesis (see Section 10.6). A "protecting group" that makes the electrons on the nitrogen less basic is bonded to the amino group. After the desired substitution reaction has been accomplished, the protecting group is removed and the amino group is regenerated.

The most common method to decrease the reactivity of an unshared pair of electrons on an atom is to attach a carbonyl group to that atom. Therefore, the amine is first reacted with acetyl chloride to form an amide. (This reaction and its mechanism are described in detail in Section 19.6. To help you remember the reaction for now, note that the nitrogen nucleophile attacks the carbonyl carbon electrophile, displacing the chloride leaving group.)



Because of delocalization of the nitrogen's electron pair onto the carbonyl oxygen, the electrons of the acetylamino group are less available for delocalization into the ring by resonance. (This is why the acetylamino group is a weaker activator than the amino group.) In addition, the electron pair on the nitrogen of an amide is much less basic, and reactions with Lewis acids in the substitution reactions are not usually a problem. However, the acetylamino group is still an activator and an ortho/para director, so substitu-

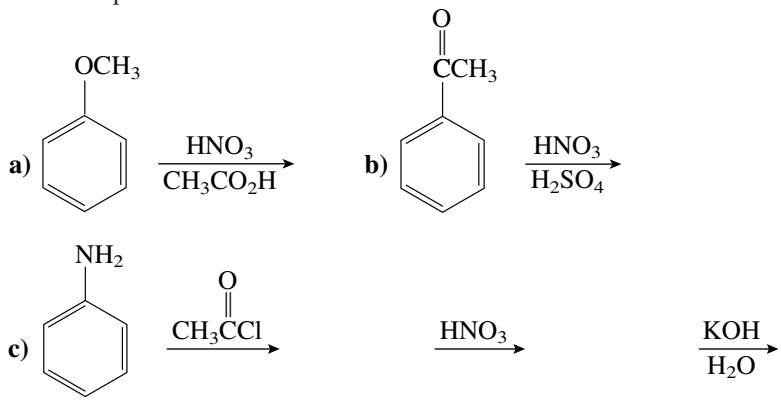
tion reactions work well. After the substitution has been completed, the acetyl group can be removed by hydrolysis of the amide bond (This reaction is very similar to the imide hydrolysis employed in the Gabriel synthesis [Section 10.6] and the ester hydrolysis used in the acetate method for the preparation of alcohols [Section 10.2].) An example of the use of this strategy is illustrated in the following synthesis. (Note that the acetylamino group controls the regiochemistry of the reaction, so it is a stronger activator than the methoxy group in this reaction.)



p-Methoxyaniline

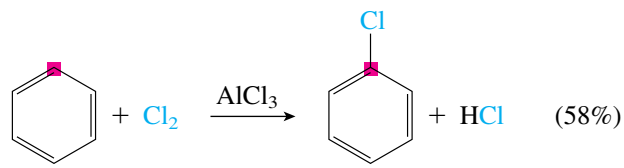
PROBLEM 17.9

Show the products of these reactions:



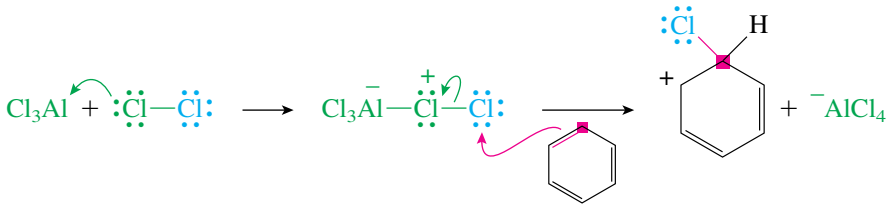
17.5 HALOGENATION

Chlorine and bromine can be substituted onto an aromatic ring by treatment with Cl_2 or Br_2. With all but highly activated aromatic rings (amines, phenols, polyalkylated rings), a Lewis acid catalyst is also required to make the halogen electrophile strong enough to accomplish the reaction. The most common catalysts are the aluminum and iron halides, $AlCl_3$, $AlBr_3$, $FeCl_3$, and $FeBr_3$. An example is provided by the following equation:



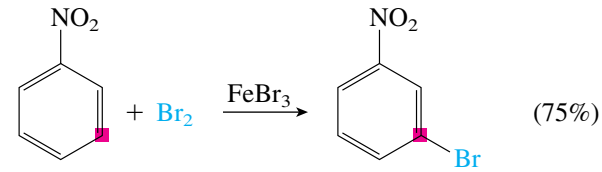
Chlorobenzene

As shown in the following equation, the Lewis acid, $AlCl_3$ in this case, bonds to one of the atoms of Cl_2 to produce the electrophilic species:



A pair of pi electrons of the aromatic ring then bonds to the electrophilic chlorine as $AlCl_4^-$ leaves. ($AlCl_4^-$ is a weaker base and a better leaving group than Cl^-.) The remainder of the mechanism is the same as that illustrated in Figure 17.1.

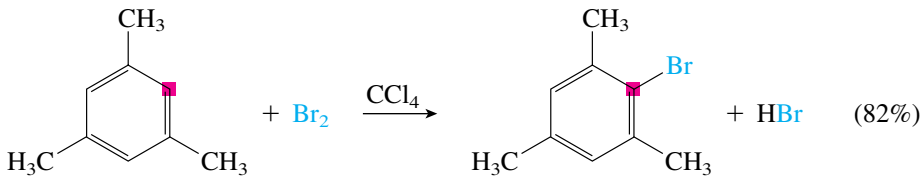
This substitution reaction provides a general method for adding chlorine or bromine to an aromatic ring. Because both are deactivating substituents, the product is less reactive than the starting aromatic compound, so it is possible to add a single halogen. The reaction works with deactivated substrates, as illustrated in the following example:



Nitrobenzene

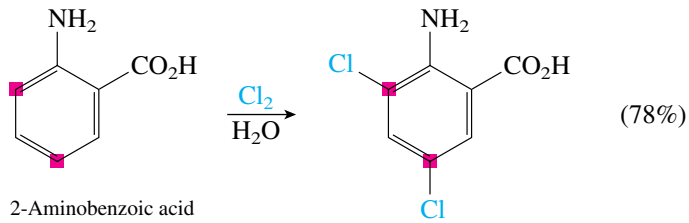
ORGANIC Chemistry Now™
Click *Mechanisms in Motion* to view **Electrophilic Aromatic Bromination.**

As mentioned previously, halogenation of highly reactive substrates can be accomplished without the use of a Lewis acid catalyst. Thus, the bromination of mesitylene (1,3,5-trimethylbenzene) is readily accomplished by reaction with bromine in carbon tetrachloride:



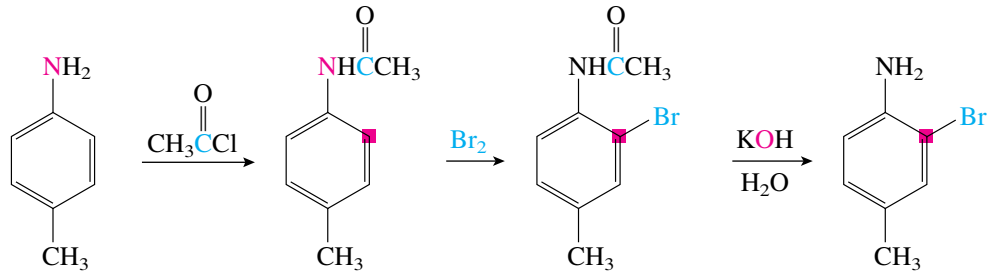
Mesitylene
(1,3,5-trimethylbenzene)

With very reactive compounds, such as anilines and phenols, it is often difficult to stop the reaction after only one halogen has added to the ring. In such cases the product that is isolated usually has reacted at all of the activated positions:



2-Aminobenzoic acid

If this is a problem, the solution again is to decrease the reactivity of the ring by modification of the activating group. The carbonyl protecting group is removed after the halogenation is accomplished.

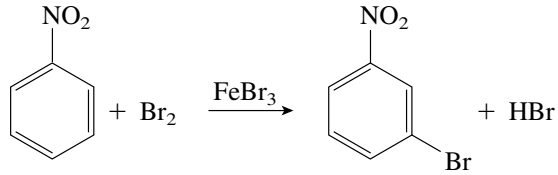


(67%)

p-Methylaniline

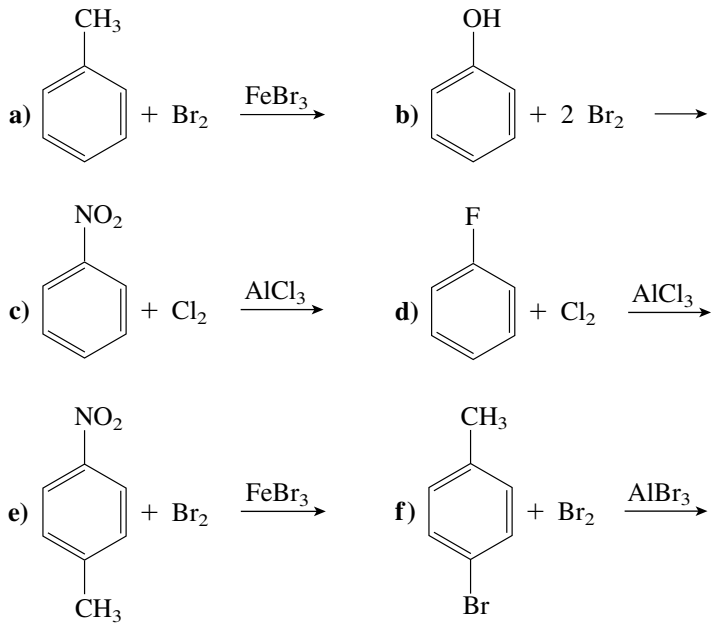
PROBLEM 17.10

Show all of the steps in the mechanism for this reaction:



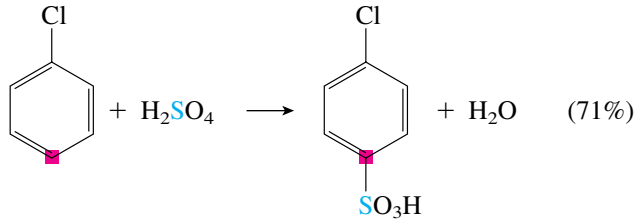
PROBLEM 17.11

Show the products of these reactions:



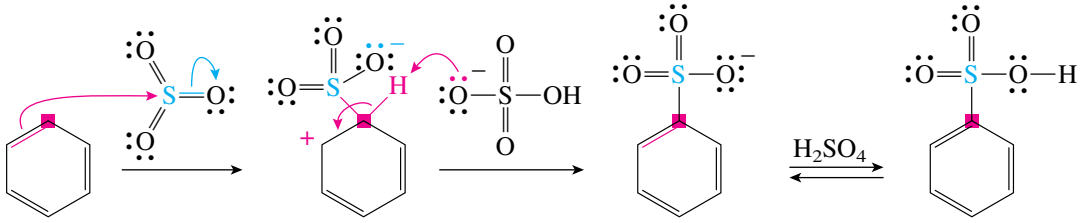
17.6 SULFONATION

A sulfonic acid group can be substituted onto an aromatic ring by reaction with concentrated sulfuric acid as shown in the following example:



Chlorobenzene *p*-Chlorobenzenesulfonic acid

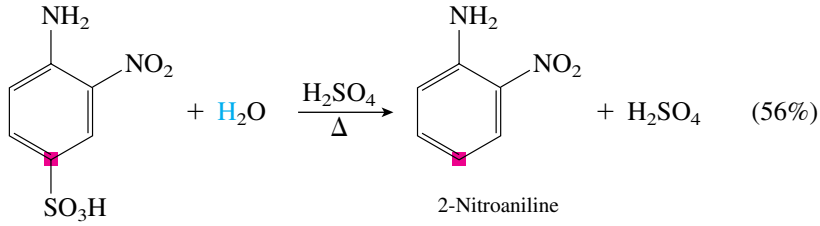
Although the electrophile varies depending on the exact reaction conditions, it is often sulfur trioxide, SO_3, that is formed from sulfuric acid by the loss of water. The mechanism for the addition of this electrophile proceeds according to the following equation:



Benzenesulfonic acid

Again, this is a general reaction that works for deactivated as well as activated rings. The SO_3H group that is added is a deactivator, so the reaction can be halted after the substitution of a single group.

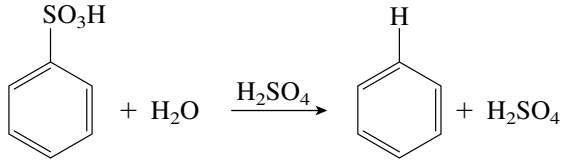
In contrast to the other reactions that have been presented so far, this substitution is readily reversible. Reaction of a sulfonic acid in a mixture of water and sulfuric acid results in removal of the sulfonic acid group. In this case a proton is the electrophile. An example is provided by the following equation:



2-Nitroaniline

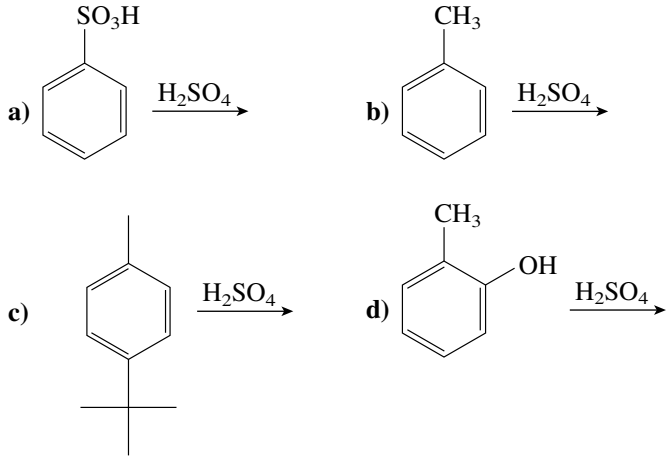
PROBLEM 17.12

Show all of the steps in the mechanism for this reaction:



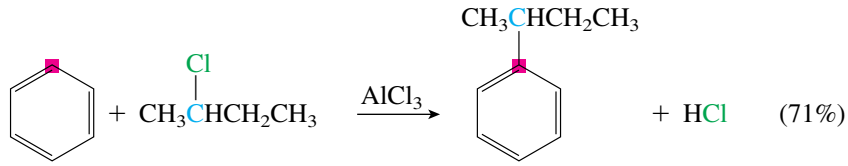
PROBLEM 17.13

Show the products of these reactions:



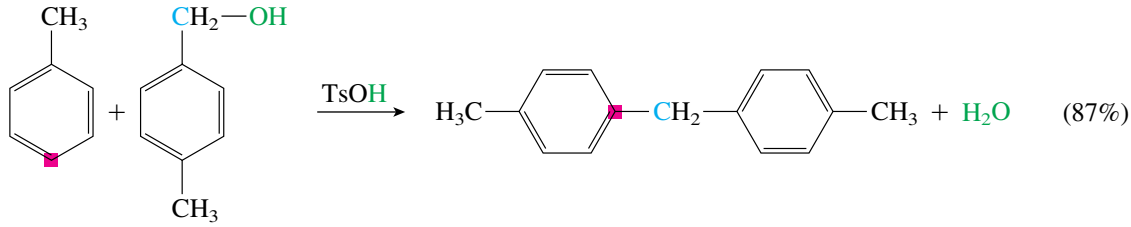
17.7 Friedel-Crafts Alkylation

Developed by C. Friedel and J. M. Crafts, the reaction of an alkyl halide with an aromatic compound in the presence of a Lewis acid catalyst, usually $AlCl_3$, results in the substitution of the alkyl group onto the aromatic ring:



In most cases the electrophile is the carbocation that is generated when the halide acts as a leaving group. The role of the aluminum chloride is to complex with the halogen to make it a better leaving group. From the point of view of the alkyl halide, the mechanism is an S_N1 reaction with the pi electrons of the aromatic ring acting as the nucleophile (see Figure 17.4).

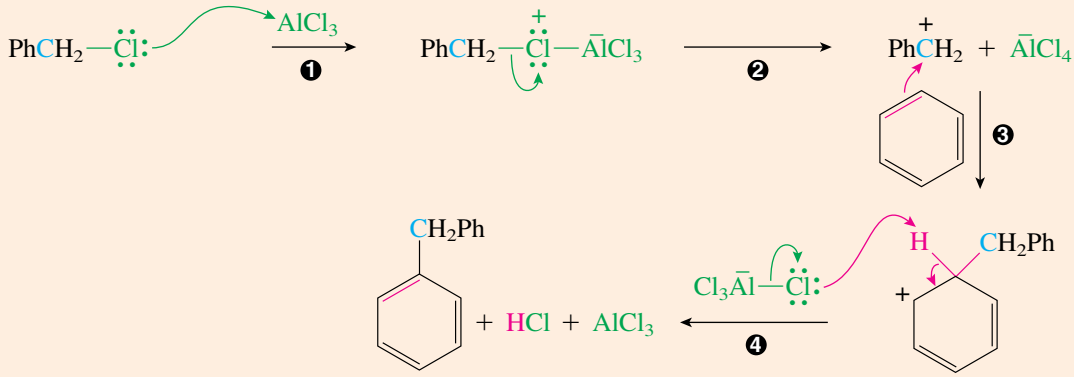
Although the most common method for generating the electrophile for the alkylation reaction employs an alkyl halide and aluminum trichloride, it can be generated in other ways also. For example, the reaction in the following equation uses the reaction of an alcohol and an acid to produce the carbocation:



❶ The aluminum trichloride bonds with an electron pair on the chlorine of the alkyl halide to form a Lewis acid–base adduct. This changes the leaving group to $AlCl_4^-$, which is a weaker base and a better leaving group than chloride anion.

❷ The $AlCl_4^-$ leaves, producing a carbocation intermediate.

❸ The carbocation acts as an electrophile and reacts with a pair of pi electrons of the aromatic ring. Or this can be viewed as an S_N1 reaction, with the weakly nucleophilic aromatic ring attacking the carbocation. The remainder of the mechanism is identical to the general mechanism outlined in Figure 17.1.

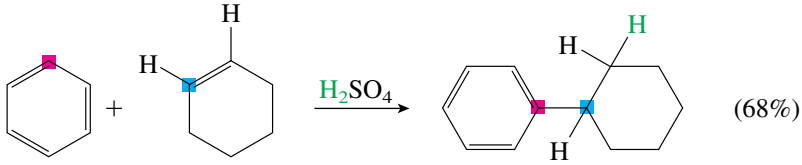


❹ A base in the reaction mixture, such as $AlCl_4^-$, removes a proton to produce the final product, HCl, and $AlCl_3$, which can begin the process anew.

Active Figure 17.4 ORGANIC Chemistry Now™

MECHANISM OF THE FRIEDEL-CRAFTS ALKYLATION REACTION. Test yourself on the concepts in this figure at **OrganicChemistryNow.**

Alternatively, the carbocation can be generated by protonation of an alkene. This reaction resembles the additions to alkenes discussed in Chapter 11. An example is provided by the following equation:

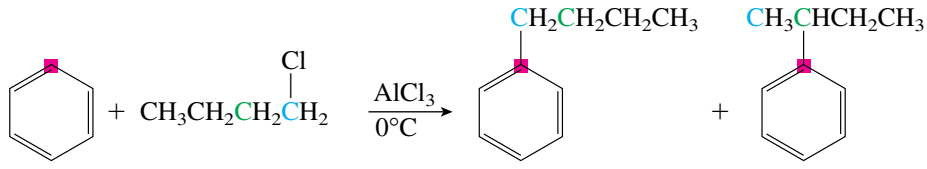


(68%)

Several limitations occur with the Friedel-Crafts alkylation reaction. First, the alkyl group that is added to the ring is an activating group. This causes the alkylated product to be more reactive (by a factor of about 2) than the starting aromatic compound. Therefore, a significant amount of product where two or more alkyl groups have been added is commonly formed. The best solution to this problem is to use a large excess of the aromatic compound that is to be alkylated. This can easily be accomplished for compounds that are readily available, such as benzene or toluene, by using them as the solvent for the reaction. Note that the Friedel-Crafts alkylation is the only one of these electrophilic aromatic substitution reactions in which the product is more reactive than the starting material. All of the other reactions put deactivating groups on the ring, so they do not suffer from the problem of multiple substitution.

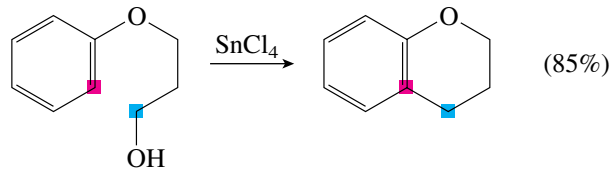
A second limitation is that aromatic compounds substituted with moderately or strongly deactivating groups cannot be alkylated. The deactivated ring is just too poor a nucleophile to react with the unstable carbocation electrophile before other reactions occur that destroy it.

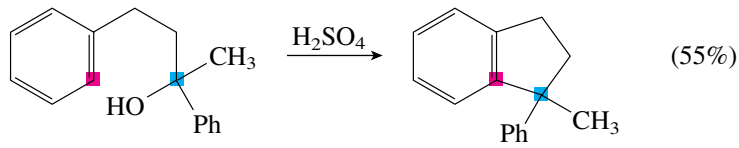
The final limitation is one that plagues all carbocation reactions: rearrangements. Because the aromatic compound is a weak nucleophile, the carbocation has a lifetime that is longer than is the case in most of the other reactions involving this intermediate, allowing ample time for rearrangements to occur. An example is provided by the following equation:



Butylbenzene 34% | *sec*-Butylbenzene 66%

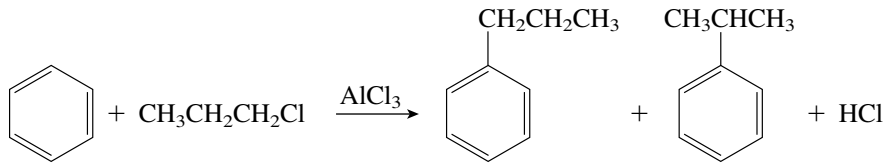
Despite these limitations, alkylation of readily available aromatic compounds, such as benzene and toluene, using carbocations that are not prone to rearrange, is a useful reaction. Intramolecular applications of this reaction have proven to be especially valuable.





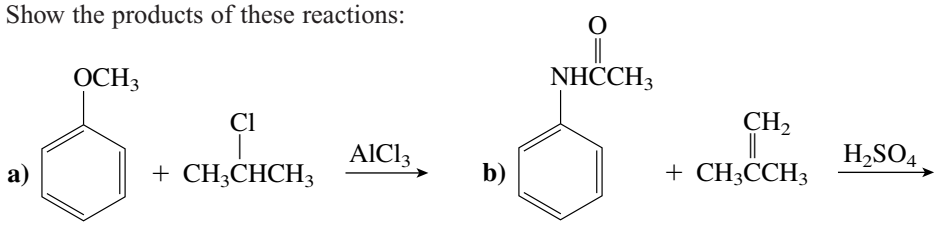
PROBLEM 17.14

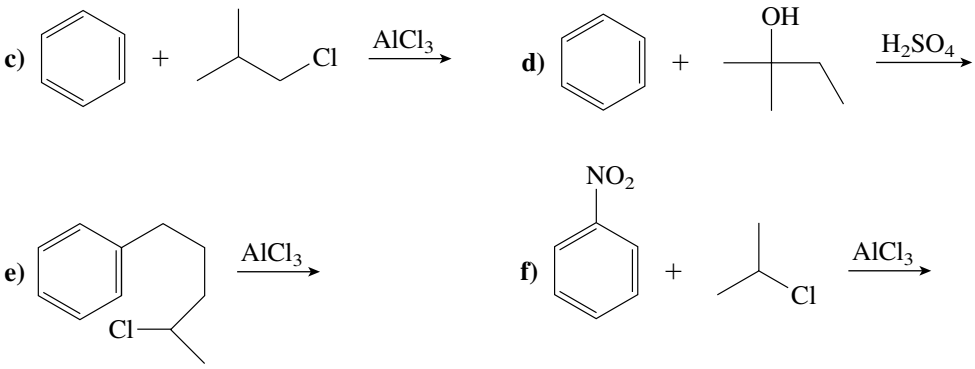
Show all of the steps in the mechanism for the formation of both products in this reaction:



PROBLEM 17.15

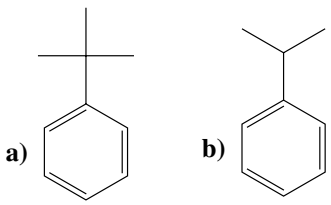
Show the products of these reactions:





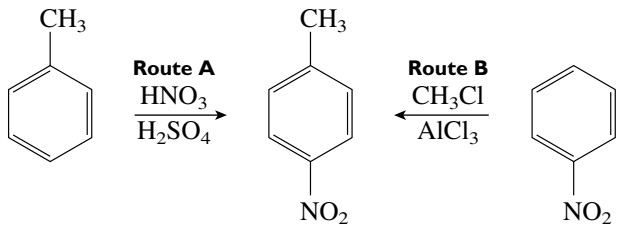
PROBLEM 17.16

Show syntheses of these compounds from benzene:



PRACTICE PROBLEM 17.2

Explain which of these routes would provide a better method for the preparation of *p*-nitrotoluene:



p-Nitrotoluene

Solution

Route A works fine. Toluene is readily nitrated, and the methyl group is an ortho/para director. The only problem is that both the desired compound and its *ortho*-isomer are produced and must be separated. (This is a common problem, and we usually assume that the separation can be accomplished, although it is not always easy in the laboratory.) Route B is unsatisfactory because the Friedel-Crafts alkylation reaction does not work with deactivated compounds such as nitrobenzene. Furthermore, even if the alkylation could be made to go, the nitro group is a meta director, so the desired product would not be formed.

Focus On

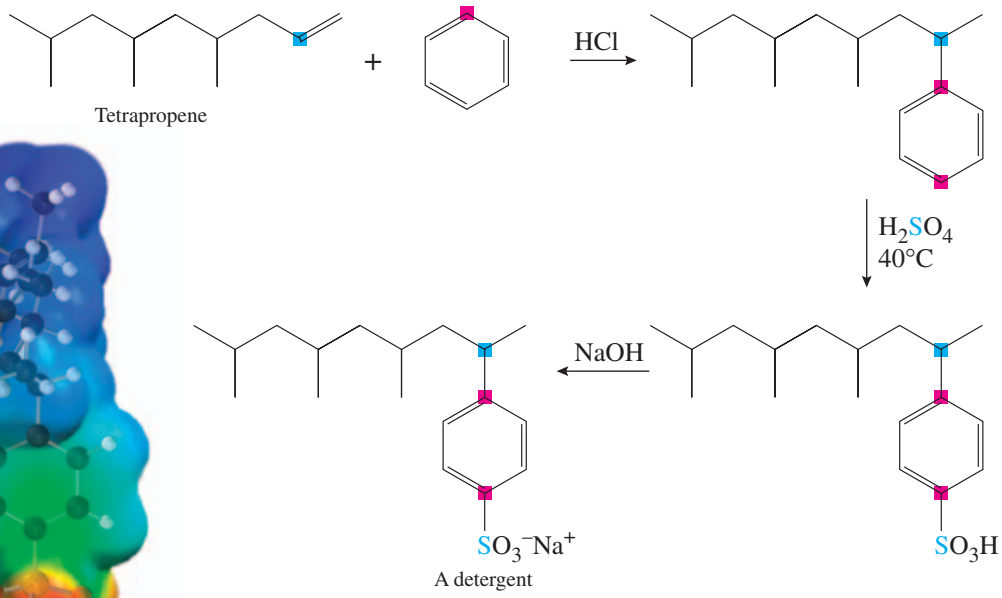
Synthetic Detergents, BHT, and BHA

A soap is the sodium salt of carboxylic acid attached to a long, nonpolar hydrocarbon chain. When a soap is placed in hard water, the sodium cations exchange with cations such as Ca^{2+} and Mg^{2+}. The resulting calcium and magnesium salts are insoluble in water and precipitate to form "soap scum."

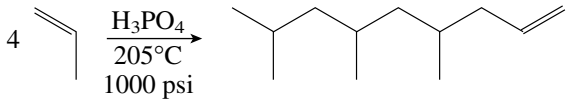
$$2\ CH_3(CH_2)_{16}CO_2^-\ Na^+ + Ca^{2+} \longrightarrow \underset{\text{Precipitates}}{[CH_3(CH_2)_{16}CO_2^-]_2\ Ca^{2+}} + 2\ Na^+$$

Synthetic detergents were invented to alleviate this problem. Rather than use the anion derived from a carboxylic acid with a large nonpolar group, detergents employ the anion derived from a sulfonic acid attached to a large nonpolar group. The calcium and magnesium salts of these sulfonic acids are soluble in water, so detergents do not precipitate in hard water and can still accomplish their cleaning function.

Two of the reactions that are used in the industrial preparation of detergents are electrophilic aromatic substitution reactions. First, a large hydrocarbon group is attached to a benzene ring by a Friedel-Crafts alkylation reaction employing tetrapropene as the source of the carbocation electrophile. The resulting alkylbenzene is then sulfonated by reaction with sulfuric acid. Deprotonation of the sulfonic acid with sodium hydroxide produces the detergent.

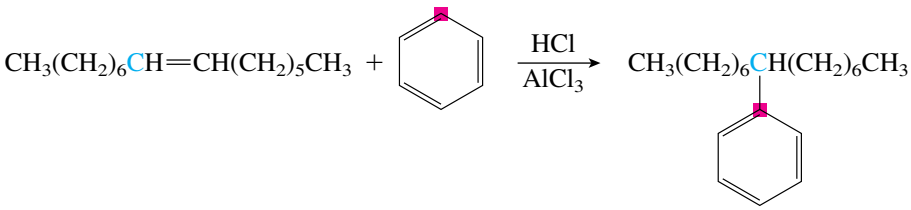


The exact structure of the alkyl group on the benzene ring is not important as long as it is large enough to confer the necessary hydrophobic character. Tetrapropene was used in the early versions of detergents because it was readily and cheaply available from the treatment of propene with acid. In this reaction, four propenes combine to form tetrapropene through carbocation intermediates. (In addition to the compound shown in the equation, an isomer with the double bond between carbon 2 and carbon 3 is also formed. If you are interested in the mechanism for this reaction, it is a variation of the cationic polymerization mechanism described later in Section 24.3.)



However, the detergent prepared from tetrapropene caused a problem in sewage treatment plants. The microorganisms that degrade such compounds start from the end of the hydrocarbon chain and seem to have trouble proceeding through tertiary carbons. The presence of several tertiary carbons in the tetrapropene chain slows its biodegradation to the point at which a significant amount passes through a treatment plant unchanged. This causes the resulting effluent and the waterways into which it is discharged to become foamy, an environmentally unacceptable result.

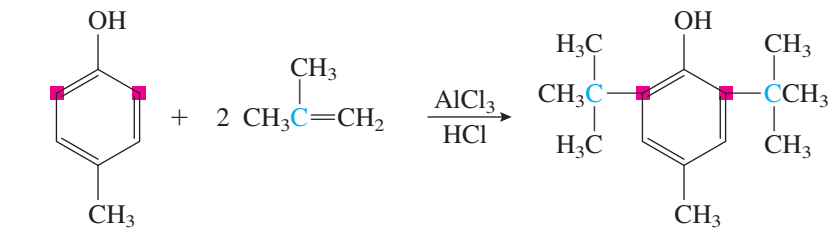
To solve this problem, most modern detergents are prepared from straight-chain alkenes. The resulting linear alkylbenzenesulfonate detergents are more easily degraded, and our rivers are no longer foamy. An example of a typical alkylation is shown in the following equation:



PROBLEM 17.17

What isomeric alkyl benzene should also be formed in this reaction?

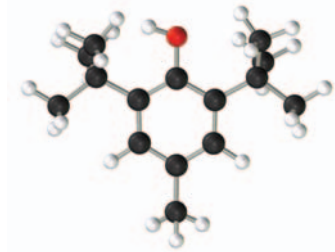
Butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) are antioxidants that are added to foods and many other organic materials to inhibit decomposition caused by reactions with oxygen. Perhaps you have seen these compounds listed among the ingredients on your cereal box at breakfast. (The mechanism of operation for these antioxidants is described in Section 21.8.) Both of these compounds are prepared by Friedel-Crafts alkylation reactions. BHT is synthesized by the reaction of *p*-methylphenol with 2-methylpropene in the presence of an acid catalyst.



p-Methylphenol (*p*-hydroxytoluene)

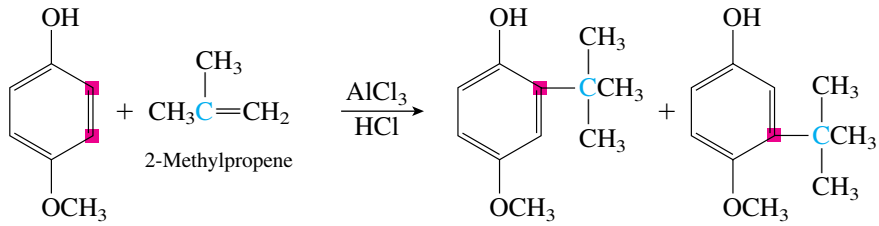
2-Methylpropene (isobutylene)

Butylated hydroxytoluene (BHT)



Continued

Addition of a proton to 2-methylpropene produces the *t*-butyl carbocation, which then alkylates the ring. Conditions are adjusted so that two *t*-butyl groups are added. BHA is prepared in a similar manner by the reaction of *p*-methoxyphenol with 2-methylpropene and an acid catalyst. In this case conditions are adjusted so that only one *t*-butyl group is added. Because the hydroxy group and the methoxy group are both activating groups, a mixture of products is formed in this case.

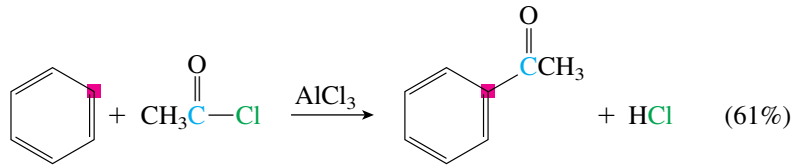


p-Methoxyphenol (*p*-hydroxyanisole)

Butylated hydroxyanisole (BHA)

17.8 Friedel-Crafts Acylation

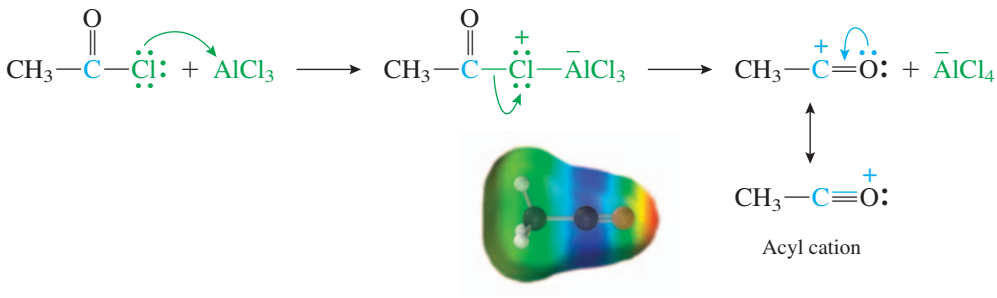
The reaction of an aromatic compound with an acyl chloride in the presence of a Lewis acid (usually $AlCl_3$) results in the substitution of an acyl group onto the aromatic ring. An example of this reaction, known as the Friedel-Crafts acylation, is provided by the following equation:



Benzene — Acetyl chloride — Acetophenone

ORGANIC Chemistry Now™ Click *Coached Tutorial Problems* to quiz yourself on **Mechanisms of Electrophilic Aromatic Substitution.**

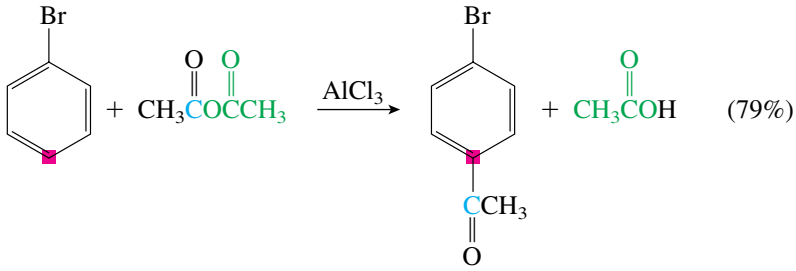
The electrophile, an acyl cation, is generated in a manner similar to that outlined in Figure 17.4 for the generation of the carbocation electrophile from an alkyl halide. First the Lewis acid, aluminum trichloride, complexes with the chlorine of the acyl chloride. Then $AlCl_4^-$ leaves, generating an acyl cation. The acyl cation is actually more stable than most other carbocations that we have encountered because it has a resonance structure that has the octet rule satisfied for all of the atoms:



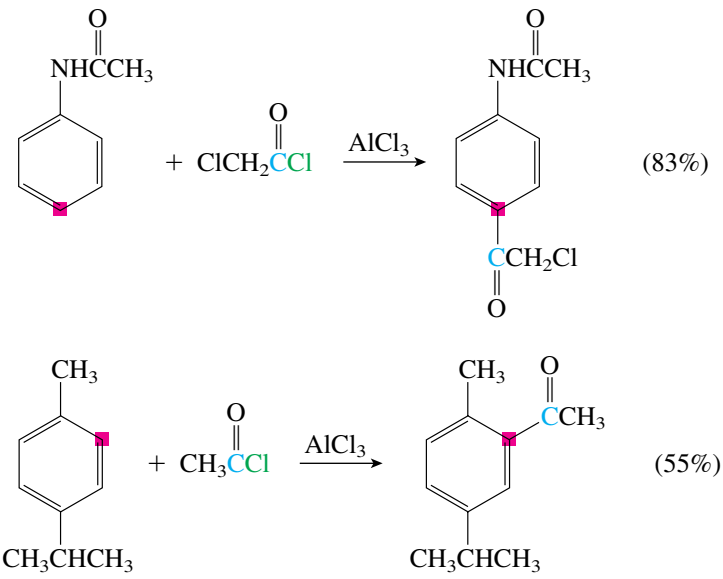
Acyl cation

The Friedel-Crafts acylation reaction does not have most of the limitations of the alkylation reaction. Because of the stability of the acyl cation, rearrangements do not occur in this reaction. In addition, the acyl group that is added to the ring is a deactivator, so the product is less reactive than the starting aromatic compound. Therefore, there is no problem with multiple acyl groups being added to the ring. However, like alkylations, the acylation reaction does not work with moderately or strongly deactivated substrates—that is, with rings that are substituted only with meta directing groups. As a consequence of fewer limitations, the Friedel-Crafts acylation reaction is more useful than the alkylation reaction.

Anhydrides can be used in place of acyl chlorides as the source of the electrophilic acyl cation:

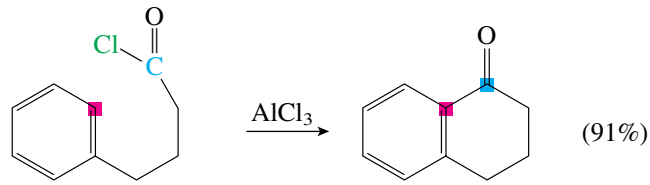


As seen in this example, the acylation reaction is more sensitive to steric effects than the other reactions that have been discussed so far and tends to give predominantly the para product. Some additional examples are provided by the following equations:



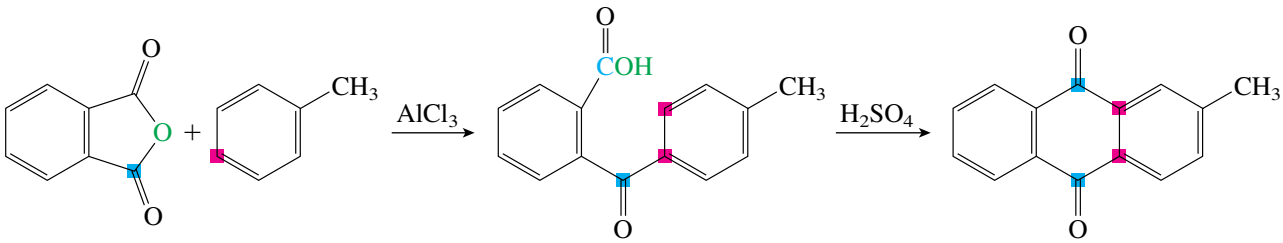
p-Isopropyltoluene

Finally, the intramolecular version of the Friedel-Crafts acylation reaction has proved to be very valuable in the construction of polycyclic compounds, as illustrated in the following equation:



(91%)

For intramolecular reactions, treatment of a carboxylic acid with sulfuric acid or polyphosphoric acid is sometimes used to generate the acyl cation electrophile. This method is usually too mild for intermolecular acylations but works well for intramolecular examples, as shown in the following equation:



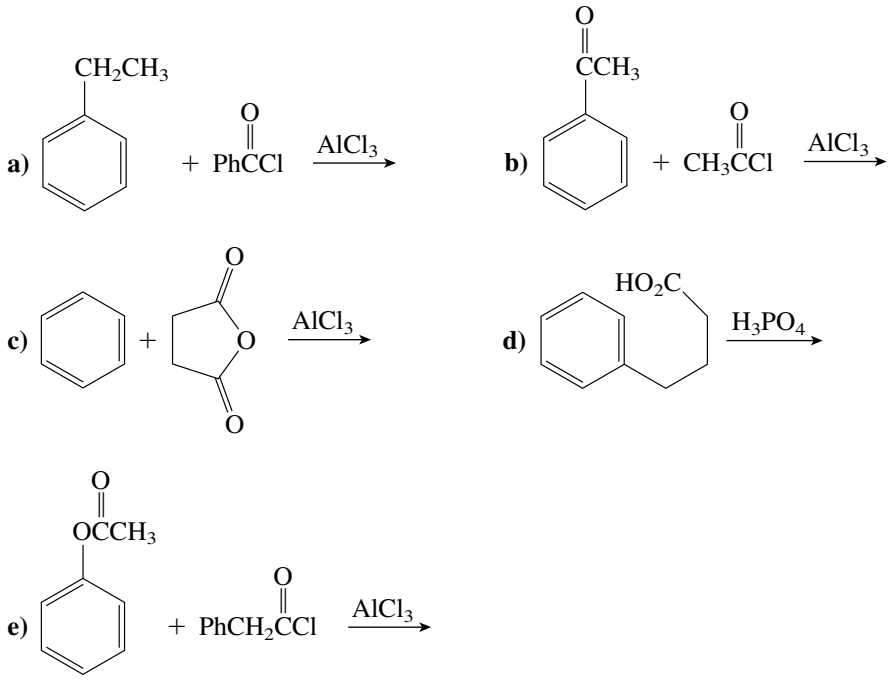
(90%)

PROBLEM 17.18

Explain why the Friedel-Crafts acylation of *p*-isopropyltoluene shown on the previous page results in the substitution of the acyl group at the position ortho to the methyl group.

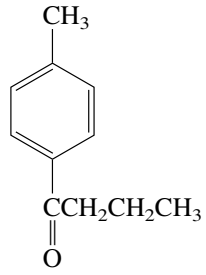
PROBLEM 17.19

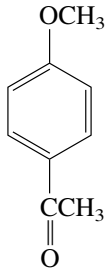
Show the products of these reactions:

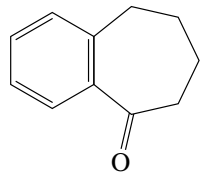


PROBLEM 17.20

Suggest syntheses of these compounds using Friedel-Crafts acylation reactions:

a) 

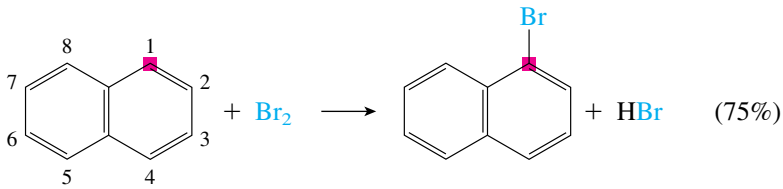
b) 

c) 

ORGANIC Chemistry Now™ Click *Coached Tutorial Problems* for additional practice showing the products of **Electrophilic Aromatic Substitution Reactions.**

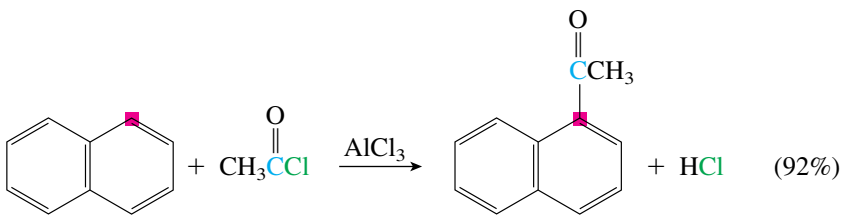
17.9 Electrophilic Substitutions of Polycyclic Aromatic Compounds

Polycyclic aromatic compounds also undergo electrophilic aromatic substitution reactions. Because the aromatic resonance energy that is lost in forming the arenium ion is lower, these compounds tend to be more reactive than benzene. For example, the bromination of naphthalene, like that of other reactive aromatic compounds, does not require a Lewis acid catalyst:



Naphthalene

Naphthalene also undergoes the other substitution reactions described for benzene. For example, it is acylated under standard Friedel-Crafts conditions:



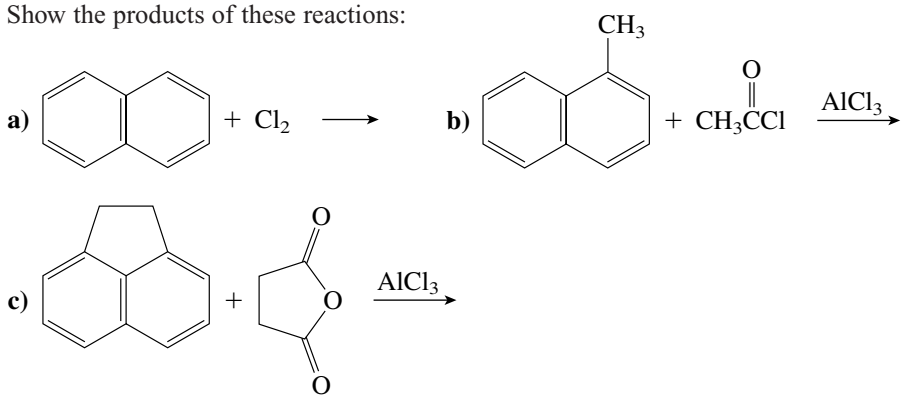
Note that both the bromination and the acylation of naphthalene result in the substitution of the electrophile at the 1 position. None of the isomeric product with the electrophile bonded to the 2 position is isolated in either case. The higher reactivity of the 1 position can be understood by examination of the resonance structures for the arenium ion. When the electrophile adds to the 1 position, the arenium ion has a total of seven resonance structures, whereas only six exist for the arenium ion resulting from addition of the electrophile to the 2 position.

PROBLEM 17.21

Draw the seven resonance structures for the arenium ion formed in the bromination of naphthalene at the 1 position and the six resonance structures formed in bromination at the 2 position.

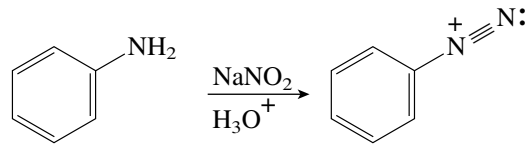
PROBLEM 17.22

Show the products of these reactions:



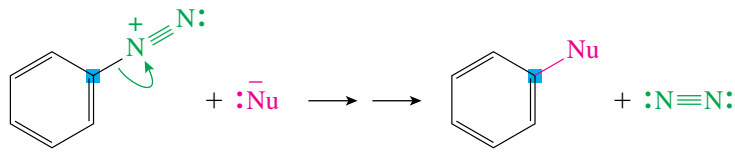
17.10 Nucleophilic Aromatic Substitution: Diazonium Ions

All of the reactions presented so far in this chapter have involved an electrophile reacting with an aromatic compound that acts as a nucleophile. Now we are going to consider several reactions that, at least on the surface, appear to involve attack by a nucleophile on the aromatic ring. The first of these involves aromatic diazonium ions, which are prepared from the reaction of amines with sodium nitrite and acid:



Aniline A diazonium ion

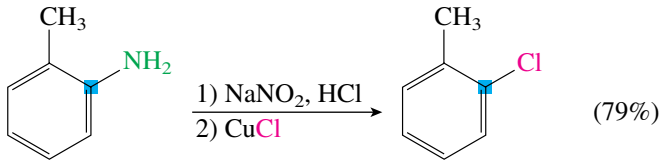
Although aromatic halides are inert to both S_N1 and S_N2 reactions (see Chapter 8), aromatic diazonium ions can act as the electrophilic partner in a nucleophilic substitution reaction. These ions are highly reactive because the leaving group, N_2, is an extremely weak base:



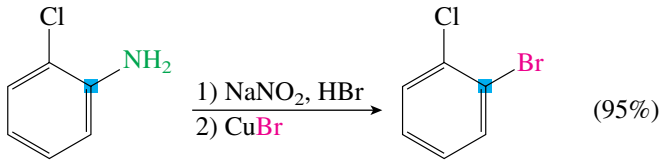
The mechanisms for these reactions are not well understood, but there is evidence that some actually follow an S_N1 pathway. Many others are known to involve radicals (odd electron species). We will not be concerned with the details of the various mechanisms here.

The diazo group can be replaced by a number of different nucleophiles. Although several different mechanisms may operate, it is easiest to remember the reactions if you consider them all to be simple nucleophilic substitutions, even though most are not. The following equations provide examples of the various substitutions that can be accomplished with diazonium ions.

The diazo group can be replaced with chlorine or bromine by reaction with cuprous chloride or cuprous bromide. [The Cu(I) aids in the formation of the radicals that are involved in these particular reactions.]

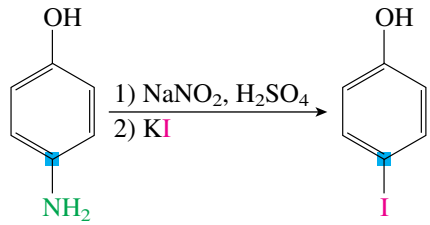


(79%)



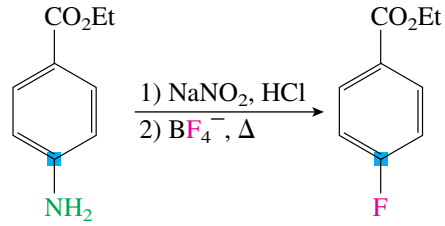
(95%)

The diazo group can be replaced with iodine by reaction with potassium iodide:



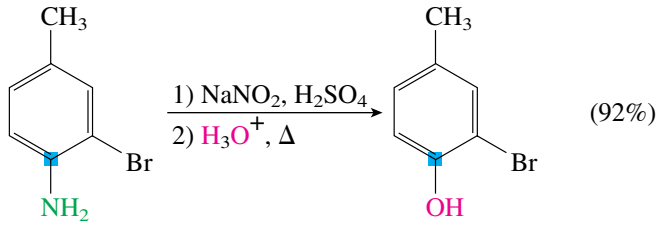
(72%)

If the diazonium ion is heated in the presence of tetrafluoroborate ion, the diazo group is replaced with a fluorine:



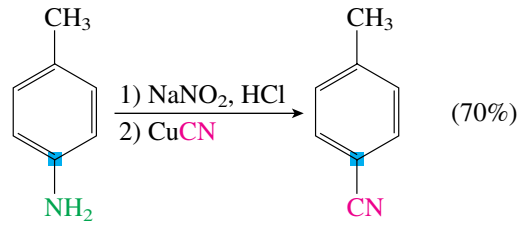
(69%)

If the diazonium ion is heated in aqueous acid, the diazo group is replaced with a hydroxy group:

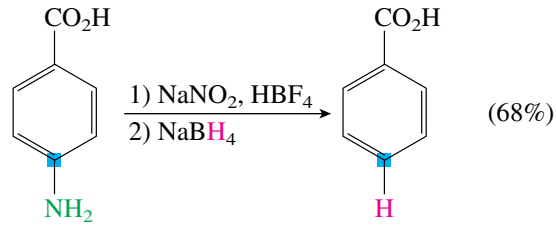


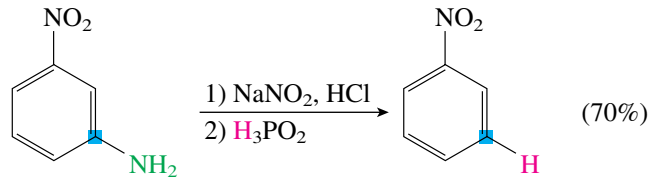
(92%)

The diazo group can be replaced with a cyano group by reaction with cuprous cyanide. This reaction is very similar to the reactions with cuprous chloride and cuprous bromide:



Finally, it is possible to replace the diazo group with a hydrogen. This is accomplished by reaction with sodium borohydride or hypophosphorous acid (H_3PO_2):

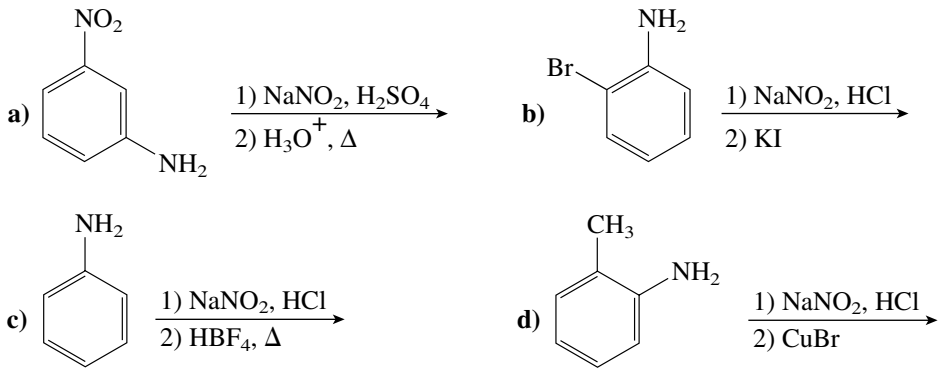


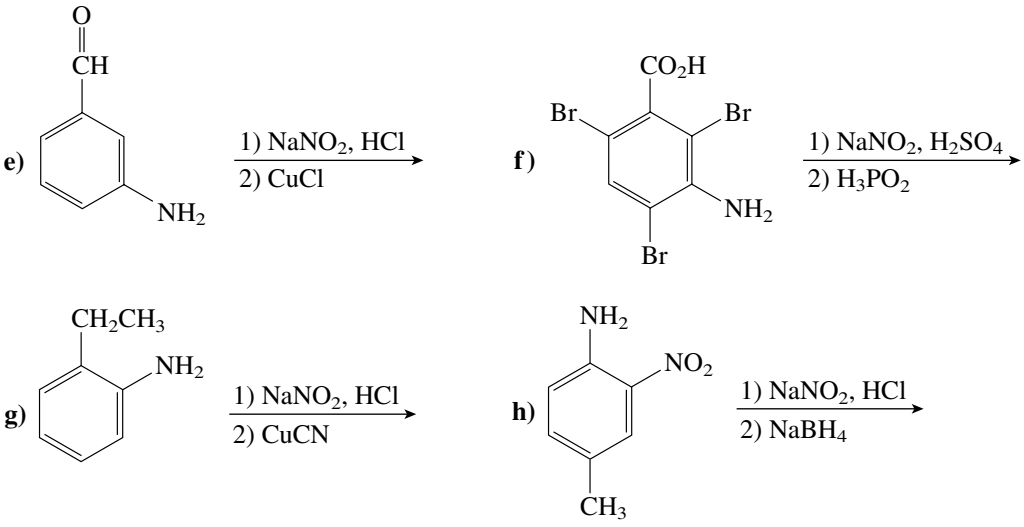


These substitution reactions are useful in synthesis because they are the only direct methods for adding several substituents (I, F, OH, CN) to an aromatic ring. (A method to introduce the precursor amino substituent onto the ring will be described shortly.) In addition, the ability to replace an amino group with a hydrogen can be very useful in obtaining an unusual orientation of the remaining substituents (see Section 17.14).

PROBLEM 17.23

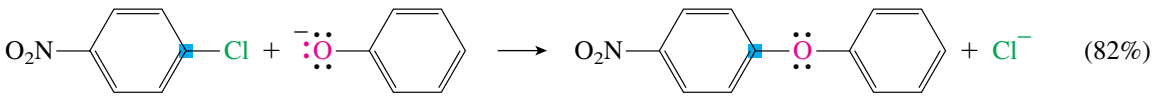
Show the products of these reactions:





17.11 Nucleophilic Aromatic Substitution: Addition–Elimination

The reaction of a nucleophile with an aromatic halide that has a strong electron withdrawing group ortho and/or para to the halogen results in substitution of the nucleophile for the halogen.



(82%)

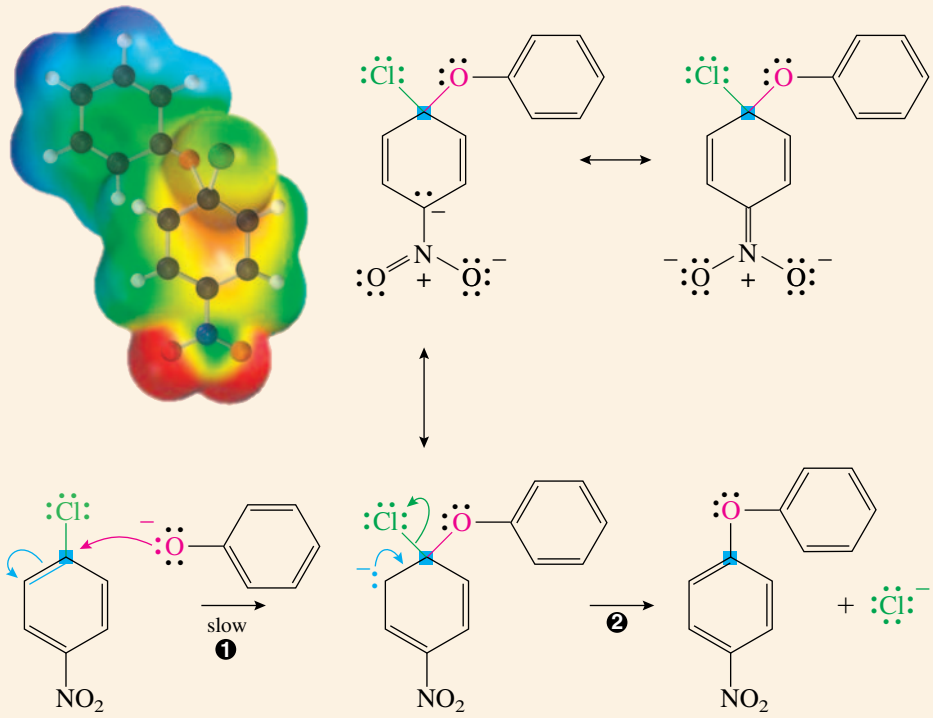
p-Chloronitrobenzene

This reaction at first might appear to be a normal S_N2 reaction because its rate depends on the concentration of both the nucleophile and the aromatic halide. However, experiments have shown that the mechanism consists of two steps. Addition of the nucleophile occurs in the first step, followed by departure of the leaving group in the second step, as shown in Figure 17.5. Therefore, this is called the **addition–elimination mechanism.**

One indication that this is not a normal S_N2 reaction is the requirement that electron-withdrawing groups be attached to the ring. As shown in Figure 17.5, the intermediate that is formed in this substitution reaction is a carbanion. This carbanion must have substituents, such as nitro or carbonyl groups, attached to the positions ortho or para to the leaving group so that they can delocalize the electron pair by resonance, thus stabilizing the anionic intermediate.

Another indication that the mechanism is different from those encountered in Chapter 8 is the effect of changing the leaving group. For this reaction the order of reactivity is

Fastest leaving group						Slowest leaving group
F	>	Cl	>	Br	>	I



❶ The nucleophile adds to the carbon bonded to the leaving group in the first step. This step is usually rate determining.

For the initial addition to occur, the anion that results must be stabilized. This stabilization is provided by the presence of substituents, such as nitro or carbonyl groups, that can delocalize the anionic pair of electrons by resonance. These groups must be attached ortho or para to the leaving group to have the necessary resonance interaction with the anion.

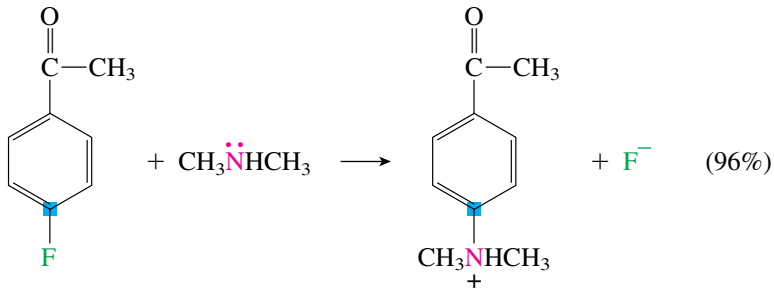
❷ The leaving group departs in the second step.

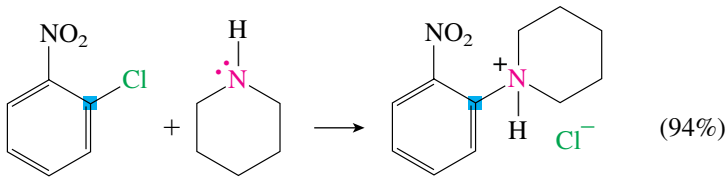
Figure 17.5

MECHANISM OF NUCLEOPHILIC SUBSTITUTION ON AN AROMATIC RING BY ADDITION–ELIMINATION.

Note that this is the opposite of the order found for S_N1 and S_N2 reactions. The reason for this reversal is that the leaving group does not depart in the rate-determining step in this reaction. Instead, the leaving group exerts its effect by helping stabilize the carbanion intermediate by its inductive effect. Because fluorine is the most electronegative of these atoms, it helps the most to stabilize the carbanion and the transition state leading to it.

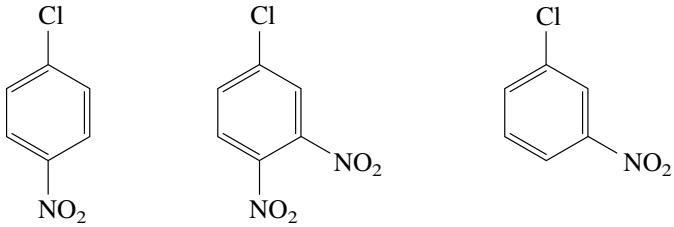
Although the requirement for the presence of certain electron-withdrawing groups ortho and/or para to the leaving group limits the generality of this reaction, it works well with appropriately substituted compounds. Additional examples are shown in the following equations:





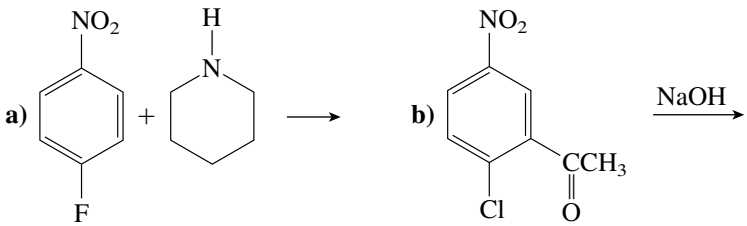
PROBLEM 17.24

Arrange these compounds in order of increasing rate of reaction with sodium hydroxide by the addition–elimination mechanism. Remember that the first step is rate determining.



PROBLEM 17.25

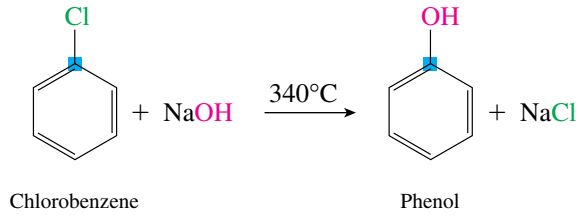
Show the products of these reactions:



17.12 Nucleophilic Aromatic Substitution: Elimination–Addition

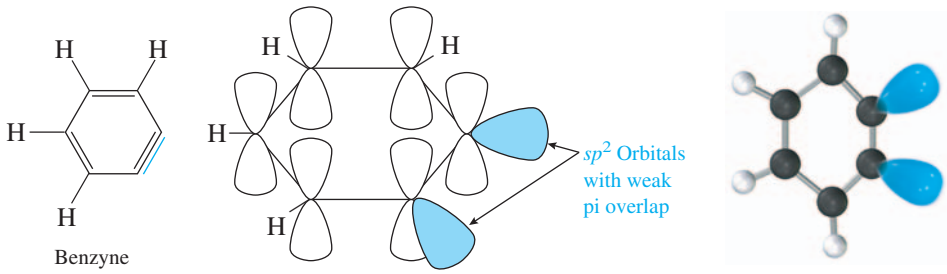
A final mechanism for nucleophilic aromatic substitution occurs when aromatic halides are reacted with very strong bases, such as amide anion, or with weaker bases, such as hydroxide ion, at high temperatures. For example, an older industrial method for the

preparation of phenol employed the reaction of chlorobenzene with sodium hydroxide at high temperature:



Although this reaction appears as though it might be a simple substitution, experiments indicate that it occurs by an elimination–addition mechanism. This mechanism is outlined in Figure 17.6 for the reaction of chlorobenzene with amide anion in liquid ammonia as solvent.

First, hydrogen chloride is lost by an E2 elimination to form an unusual, and highly reactive, compound called **benzyne:**



The elimination converts one of the "double bonds" of benzene into a "triple bond." This triple bond is quite different from a normal triple bond because of the angle constraints imposed by the six-membered ring. An orbital picture of benzyne shows the normal benzene arrangement of *p* orbitals perpendicular to the plane of the ring. The other bond of the triple bond results from two sp^2-hybridized AOs overlapping in pi fashion in the plane of the ring. Obviously, these orbitals do not overlap very well because they are not parallel. Although it is convenient to use a structure with a triple bond to represent benzyne, we must recognize that one bond of this triple bond is not a typical pi bond and is highly reactive.

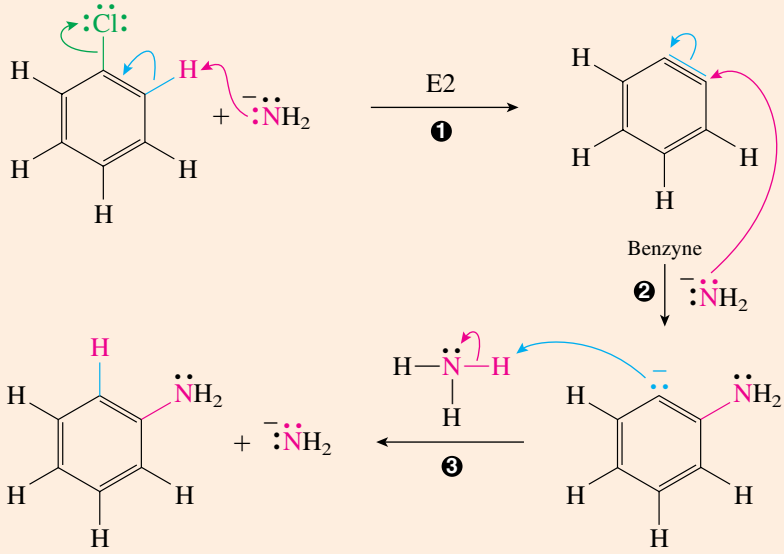
Benzyne is an extremely reactive compound. It cannot be isolated and exists only for a very short time before it reacts. Under the strongly nucleophilic conditions of these reactions, a nucleophile adds to the bond to generate a carbanion. The strongly basic carbanion then removes a proton from some weak acid in the reaction mixture to form the final product.

One of the characteristics of reactions involving benzyne intermediates is that the nucleophile can bond to the same carbon to which the leaving group was bonded, or it can bond to the carbon adjacent to the one to which the leaving group was bonded. This often results in the formation of isomeric products when substituted aromatic halides are used. For example, the reaction of *p*-bromotoluene with sodium dimethylamide in dimethylamine as the solvent gives a 50:50 mixture of the meta and para

❶ The strong base causes an E2 elimination of hydrogen chloride.

Because of its large amount of angle strain, benzyne is an extremely reactive molecule and has only a fleeting existence.

❷ Although normal triple bonds do not react with nucleophiles, the high reactivity of benzyne allows a nucleophile to attack to form a carbanion.

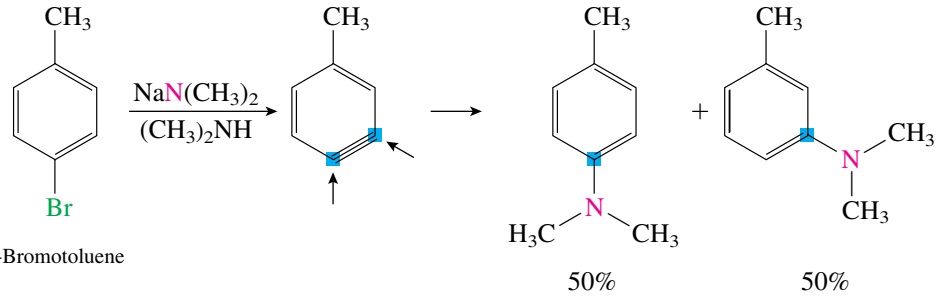


❸ The strongly basic carbanion removes a proton from the solvent, ammonia, to complete the reaction.

Figure 17.6

MECHANISM OF NUCLEOPHILIC AROMATIC SUBSTITUTION BY ELIMINATION–ADDITION (THE BENZYNE MECHANISM).

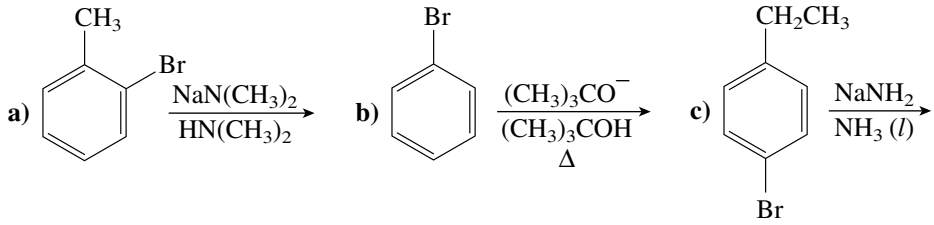
products because the nucleophile can bond to either carbon of the benzyne triple bond. Such a product mixture is common whenever an asymmetrical benzyne intermediate is formed.



p-Bromotoluene

PROBLEM 17.26

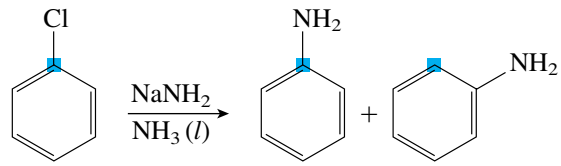
Show the products of these reactions:



Focus On

Experimental Evidence for the Benzyne Mechanism

After a new (and unusual) mechanism, such as the benzyne mechanism for nucleophilic aromatic substitution, is proposed, experiments are usually designed to test that mechanism. A classic experiment supporting the benzyne mechanism used a radioactive carbon label. Examination of the mechanism shown in Figure 17.6 shows that the carbon bonded to the leaving chlorine and the carbon ortho to it become equivalent in the benzyne intermediate. Consider what would happen if the carbon bonded to the chlorine were a radioactive isotope of carbon (^{14}C) rather than the normal isotope of carbon (^{12}C). If we follow the position of the radioactive carbon label through the mechanism of Figure 17.6, we find that the label should be equally distributed between the carbon attached to the amino group in the product and the carbon ortho to it.



When the experiment was conducted in the laboratory, this is exactly the result that was observed. Although it does not prove the benzyne mechanism, this experiment provides strong evidence supporting it.

It is one thing to conceive of such an experiment and another to carry it out in the laboratory. Let's see how the experiment was actually accomplished. First, chlorobenzene with a radioactive label at the carbon attached to the chlorine had to be obtained. Fortunately, this material was available from a commercial laboratory.