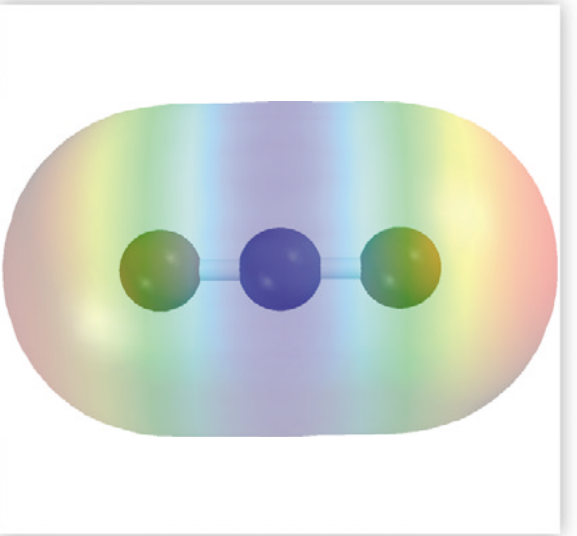
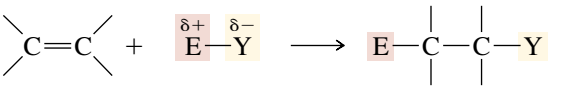


CHAPTER 12

REACTIONS OF ARENES: ELECTROPHILIC AROMATIC SUBSTITUTION

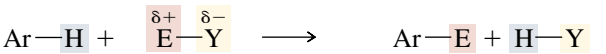
In the preceding chapter the *special stability* of benzene was described, along with reactions in which an aromatic ring was present as a substituent. In the present chapter we move from considering the aromatic ring as a substituent to studying it as a functional group. What kind of reactions are available to benzene and its derivatives? What sort of reagents react with arenes, and what products are formed in those reactions?

Characteristically, the reagents that react with the aromatic ring of benzene and its derivatives are *electrophiles*. We already have some experience with electrophilic reagents, particularly with respect to how they react with alkenes. Electrophilic reagents *add* to alkenes.



Alkene | Electrophilic reagent | Product of electrophilic addition

A different reaction takes place when electrophiles react with arenes. *Substitution is observed instead of addition.* If we represent an arene by the general formula ArH, where Ar stands for an aryl group, the electrophilic portion of the reagent replaces one of the hydrogens on the ring:



Arene | Electrophilic reagent | Product of electrophilic aromatic substitution

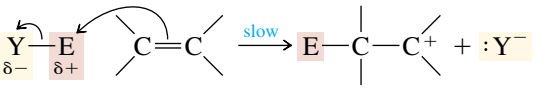
We call this reaction **electrophilic aromatic substitution;** it is one of the fundamental processes of organic chemistry.

12.1 REPRESENTATIVE ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS OF BENZENE

The scope of electrophilic aromatic substitution is quite large; both the arene and the electrophilic reagent are capable of wide variation. Indeed, it is this breadth of scope that makes electrophilic aromatic substitution so important. Electrophilic aromatic substitution is the method by which substituted derivatives of benzene are prepared. We can gain a feeling for these reactions by examining a few typical examples in which benzene is the substrate. These examples are listed in Table 12.1, and each will be discussed in more detail in Sections 12.3 through 12.7. First, however, let us look at the general mechanism of electrophilic aromatic substitution.

12.2 MECHANISTIC PRINCIPLES OF ELECTROPHILIC AROMATIC SUBSTITUTION

Recall from Chapter 6 the general mechanism for electrophilic addition to alkenes:

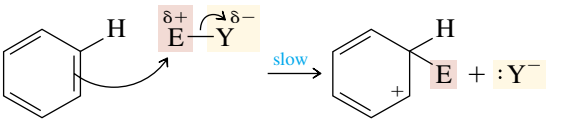


Alkene and electrophile — Carbocation

Carbocation — Nucleophile — Product of electrophilic addition

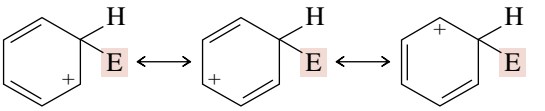
The first step is rate-determining. It is the sharing of the pair of π electrons of the alkene with the electrophile to form a carbocation. Following its formation, the carbocation undergoes rapid capture by some Lewis base present in the medium.

The first step in the reaction of electrophilic reagents with benzene is similar. An electrophile accepts an electron pair from the π system of benzene to form a carbocation:



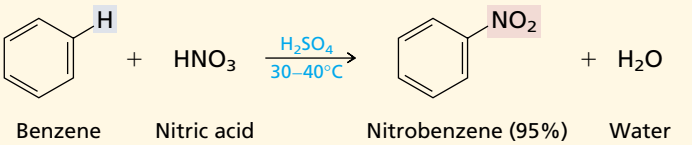
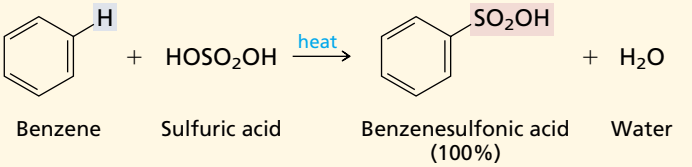
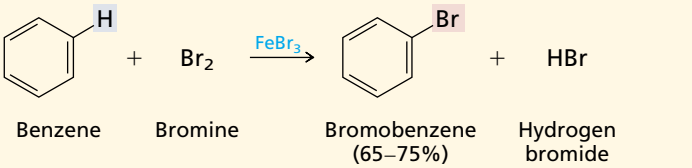
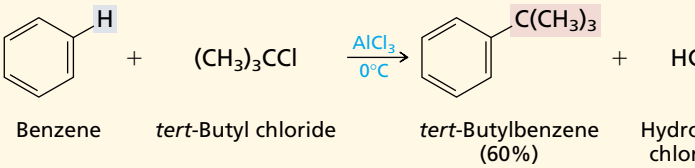
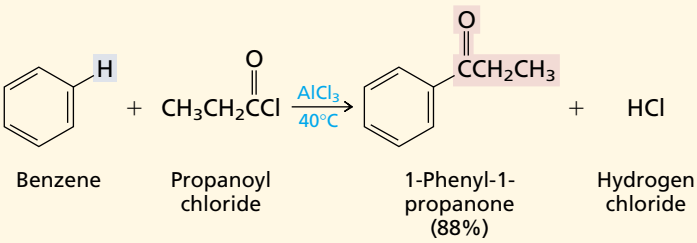
Benzene and electrophile — Carbocation

This particular carbocation is a resonance-stabilized one of the allylic type. It is a **cyclohexadienyl cation** (often referred to as an **arenium ion**).

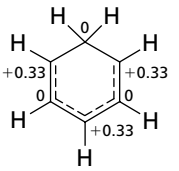


Resonance forms of a cyclohexadienyl cation

TABLE 12.1 Representative Electrophilic Aromatic Substitution Reactions of Benzene

Reaction and comments	Equation
1. Nitration Warming benzene with a mixture of nitric acid and sulfuric acid gives nitrobenzene. A nitro group (—NO_2) replaces one of the ring hydrogens.	
2. Sulfonation Treatment of benzene with hot concentrated sulfuric acid gives benzenesulfonic acid. A sulfonic acid group (—SO_2OH) replaces one of the ring hydrogens.	
3. Halogenation Bromine reacts with benzene in the presence of iron(III) bromide as a catalyst to give bromobenzene. Chlorine reacts similarly in the presence of iron(III) chloride to give chlorobenzene.	
4. Friedel–Crafts alkylation Alkyl halides react with benzene in the presence of aluminum chloride to yield alkylbenzenes.	
5. Friedel–Crafts acylation An analogous reaction occurs when acyl halides react with benzene in the presence of aluminum chloride. The products are acylbenzenes.	

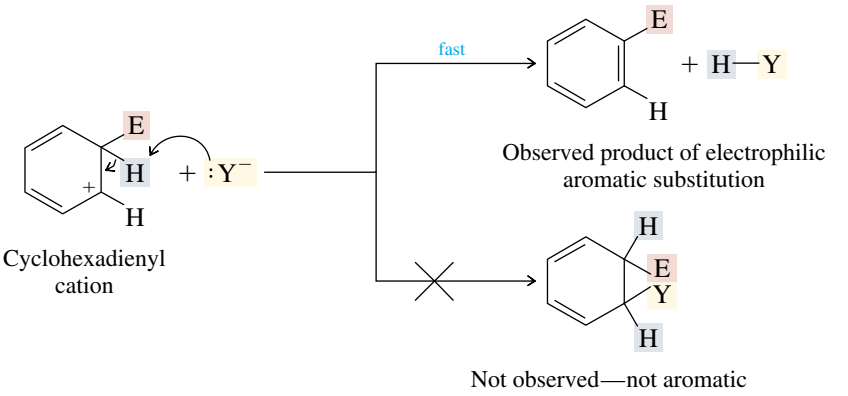
PROBLEM 12.1 In the simplest molecular orbital treatment of conjugated systems, it is assumed that the π system does not interact with the framework of σ bonds. When this MO method was used to calculate the charge distribution in cyclohexadienyl cation, it gave the results indicated. How does the charge at each carbon compare with that deduced by examining the most stable resonance structures for cyclohexadienyl cation?



A model showing the electrostatic potential of this carbocation can be viewed on *Learning By Modeling.*

Most of the resonance stabilization of benzene is lost when it is converted to the cyclohexadienyl cation intermediate. In spite of being allylic, a cyclohexadienyl cation

is *not* aromatic and possesses only a fraction of the resonance stabilization of benzene. Once formed, it rapidly loses a proton, restoring the aromaticity of the ring and giving the product of electrophilic aromatic substitution.



If the Lewis base ($:Y^-$) had acted as a nucleophile and added to carbon, the product would have been a nonaromatic cyclohexadiene derivative. Addition and substitution products arise by alternative reaction paths of a cyclohexadienyl cation. Substitution occurs preferentially because there is a substantial driving force favoring rearomatization.

Figure 12.1 is a potential energy diagram describing the general mechanism of electrophilic aromatic substitution. In order for electrophilic aromatic substitution reactions to overcome the high activation energy that characterizes the first step, the electrophile must be a fairly reactive one. Many electrophilic reagents that react rapidly with alkenes do not react at all with benzene. Peroxy acids and diborane, for example, fall into this category. Others, such as bromine, react with benzene only in the presence of catalysts that increase their electrophilicity. The low level of reactivity of benzene toward

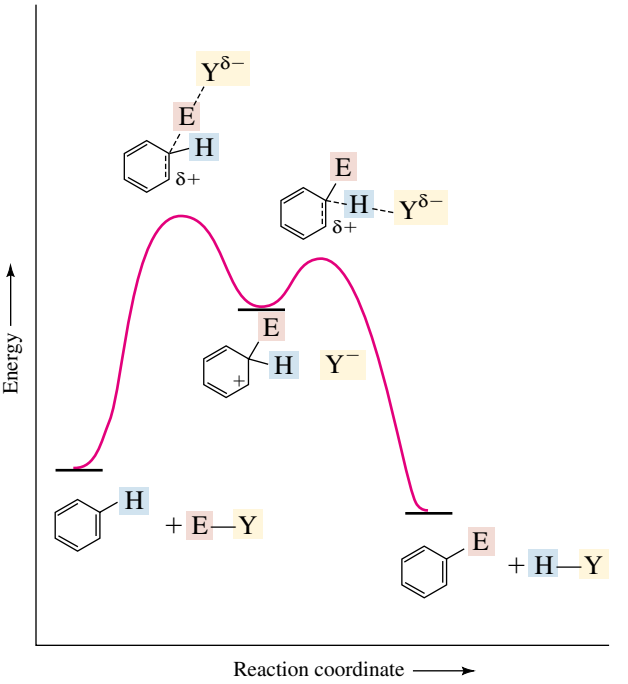


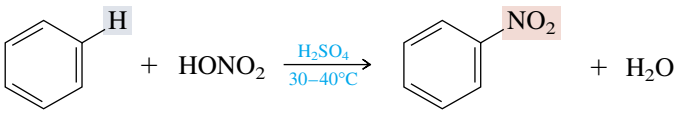
FIGURE 12.1 Energy changes associated with the two steps of electrophilic aromatic substitution.

electrophiles stems from the substantial loss of resonance stabilization that accompanies transfer of a pair of its six π electrons to an electrophile.

With this as background, let us now examine each of the electrophilic aromatic substitution reactions presented in Table 12.1 in more detail, especially with respect to the electrophile that attacks benzene.

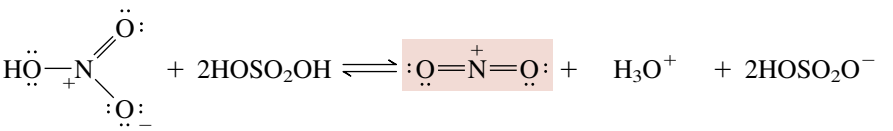
12.3 NITRATION OF BENZENE

Now that we've outlined the general mechanism for electrophilic aromatic substitution, we need only identify the specific electrophile in the nitration of benzene (see Table 12.1) to have a fairly clear idea of how the reaction occurs. Figure 12.2 shows the application of those general principles to the reaction:



Benzene Nitric acid Nitrobenzene (95%) Water

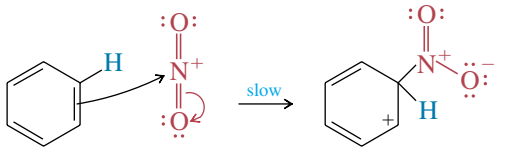
The electrophile (E^+) that reacts with benzene is *nitronium ion* ($^+NO_2$). The concentration of nitronium ion in nitric acid alone is too low to nitrate benzene at a convenient rate, but can be increased by adding sulfuric acid.



Nitric acid Sulfuric acid Nitronium ion Hydronium ion Hydrogen sulfate ion

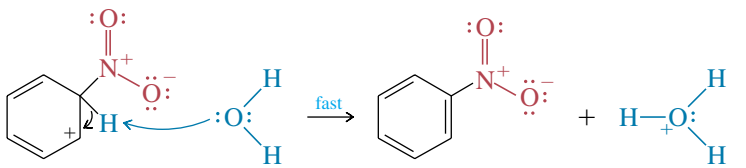
The role of nitronium ion in the nitration of benzene was demonstrated by Sir Christopher Ingold–the same person who suggested the S_N1 and S_N2 mechanisms of nucleophilic substitution and who collaborated with Cahn and Prelog on the *R* and *S* notational system.

Step 1: Attack of nitronium cation on the π system of the aromatic ring



Benzene and nitronium ion Cyclohexadienyl cation intermediate

Step 2: Loss of a proton from the cyclohexadienyl cation



Cyclohexadienyl cation intermediate Water Nitrobenzene Hydronium ion

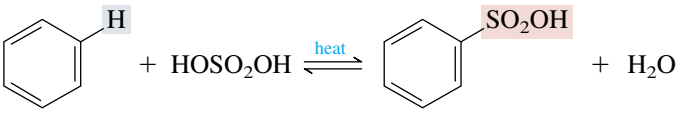
FIGURE 12.2 The mechanism of the nitration of benzene. An electrostatic potential map of nitronium ion can be viewed on *Learning By Modeling.*

Nitration of the ring is not limited to benzene alone, but is a general reaction of compounds that contain a benzene ring. It would be a good idea to write out the answer to the following problem to ensure that you understand the relationship of starting materials to products in aromatic nitration before continuing to the next section.

PROBLEM 12.2 Nitration of 1,4-dimethylbenzene (*p*-xylene) gives a single product having the molecular formula $C_8H_9NO_2$ in high yield. What is this product?

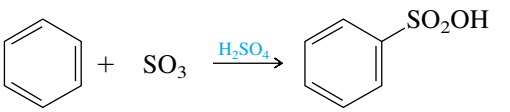
12.4 SULFONATION OF BENZENE

The reaction of benzene with sulfuric acid to produce benzenesulfonic acid,



Benzene Sulfuric acid Benzenesulfonic acid Water

is reversible but can be driven to completion by several techniques. Removing the water formed in the reaction, for example, allows benzenesulfonic acid to be obtained in virtually quantitative yield. When a solution of sulfur trioxide in sulfuric acid is used as the sulfonating agent, the rate of sulfonation is much faster and the equilibrium is displaced entirely to the side of products, according to the equation



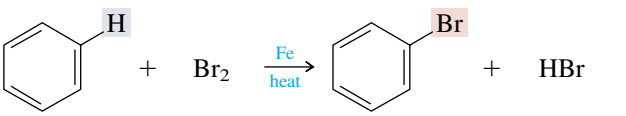
Benzene Sulfur trioxide Benzenesulfonic acid

Among the variety of electrophilic species present in concentrated sulfuric acid, sulfur trioxide is probably the actual electrophile in aromatic sulfonation. We can represent the mechanism of sulfonation of benzene by sulfur trioxide by the sequence of steps shown in Figure 12.3.

PROBLEM 12.3 On being heated with sulfur trioxide in sulfuric acid, 1,2,4,5-tetramethylbenzene was converted to a product of molecular formula $C_{10}H_{14}O_3S$ in 94% yield. Suggest a reasonable structure for this product.

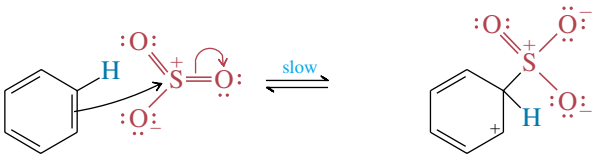
12.5 HALOGENATION OF BENZENE

According to the usual procedure for preparing bromobenzene, bromine is added to benzene in the presence of metallic iron (customarily a few carpet tacks) and the reaction mixture is heated.



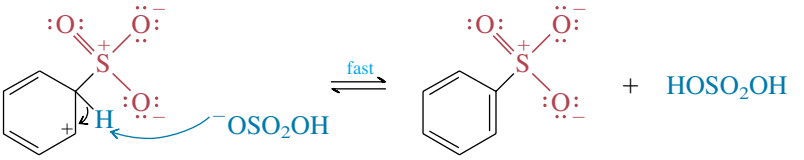
Benzene Bromine Bromobenzene (65–75%) Hydrogen bromide

Step 1: Sulfur trioxide attacks benzene in the rate-determining step



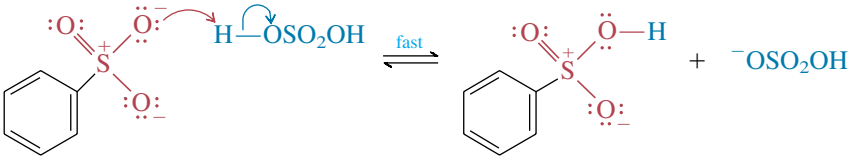
Benzene and sulfur trioxide — Cyclohexadienyl cation intermediate

Step 2: A proton is lost from the sp^3 hybridized carbon of the intermediate to restore the aromaticity of the ring. The species shown that abstracts the proton is a hydrogen sulfate ion formed by ionization of sulfuric acid.



Cyclohexadienyl cation intermediate — Hydrogen sulfate ion — Benzenesulfonate ion — Sulfuric acid

Step 3: A rapid proton transfer from the oxygen of sulfuric acid to the oxygen of benzenesulfonate completes the process.



Benzenesulfonate ion — Sulfuric acid — Benzenesulfonic acid — Hydrogen sulfate ion

FIGURE 12.3 The mechanism of sulfonation of benzene. An electrostatic potential map of sulfur trioxide can be viewed on *Learning By Modeling.*

Bromine, although it adds rapidly to alkenes, is too weak an electrophile to react at an appreciable rate with benzene. A catalyst that increases the electrophilic properties of bromine must be present. Somehow carpet tacks can do this. How?

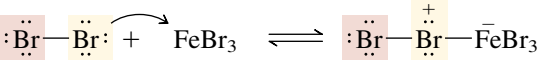
The active catalyst is not iron itself but iron(III) bromide, formed by reaction of iron and bromine.

$$2Fe + 3Br_2 \longrightarrow 2FeBr_3$$

Iron — Bromine — Iron(III) bromide

Iron(III) bromide ($FeBr_3$) is also called *ferric bromide.*

Iron(III) bromide is a weak Lewis acid. It combines with bromine to form a Lewis acid-Lewis base complex.



Lewis base — Lewis acid — Lewis acid-Lewis base complex

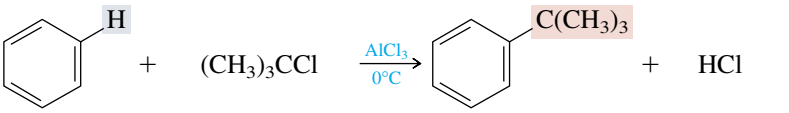
Complexation of bromine with iron(III) bromide makes bromine more electrophilic, and it attacks benzene to give a cyclohexadienyl intermediate as shown in step 1 of the mechanism depicted in Figure 12.4. In step 2, as in nitration and sulfonation, loss of a proton from the cyclohexadienyl cation is rapid and gives the product of electrophilic aromatic substitution.

Only small quantities of iron(III) bromide are required. It is a catalyst for the bromination and, as Figure 12.4 indicates, is regenerated in the course of the reaction. We'll see later in this chapter that some aromatic substrates are much more reactive than benzene and react rapidly with bromine even in the absence of a catalyst.

Chlorination is carried out in a manner similar to bromination and provides a ready route to chlorobenzene and related aryl chlorides. Fluorination and iodination of benzene and other arenes are rarely performed. Fluorine is so reactive that its reaction with benzene is difficult to control. Iodination is very slow and has an unfavorable equilibrium constant. Syntheses of aryl fluorides and aryl iodides are normally carried out by way of functional group transformations of arylamines; these reactions will be described in Chapter 22.

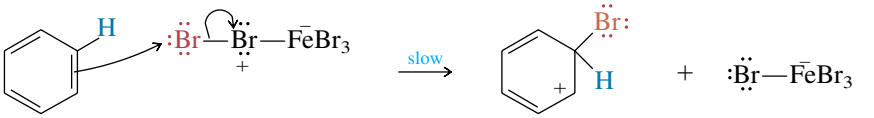
12.6 FRIEDEL–CRAFTS ALKYLATION OF BENZENE

Alkyl halides react with benzene in the presence of aluminum chloride to yield alkylbenzenes.



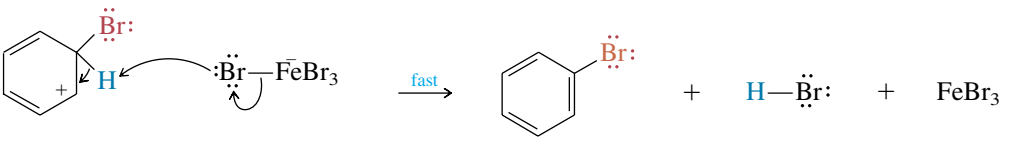
Benzene | *tert*-Butyl chloride | *tert*-Butylbenzene (60%) | Hydrogen chloride

Step 1: The bromine–iron(III) bromide complex is the active electrophile that attacks benzene. Two of the π electrons of benzene are used to form a bond to bromine and give a cyclohexadienyl cation intermediate.



Benzene and bromine–iron(III) bromide complex | Cyclohexadienyl cation intermediate | Tetrabromoferrate ion

Step 2: Loss of a proton from the cyclohexadienyl cation yields bromobenzene.

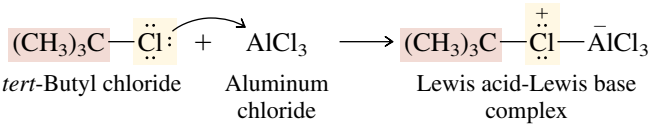


Cyclohexadienyl cation intermediate | Tetrabromoferrate ion | Bromobenzene | Hydrogen bromide | Iron(III) bromide

FIGURE 12.4 The mechanism of bromination of benzene.

Alkylation of benzene with alkyl halides in the presence of aluminum chloride was discovered by Charles Friedel and James M. Crafts in 1877. Crafts, who later became president of the Massachusetts Institute of Technology, collaborated with Friedel at the Sorbonne in Paris, and together they developed what we now call the **Friedel–Crafts reaction** into one of the most useful synthetic methods in organic chemistry.

Alkyl halides by themselves are insufficiently electrophilic to react with benzene. Aluminum chloride serves as a Lewis acid catalyst to enhance the electrophilicity of the alkylating agent. With tertiary and secondary alkyl halides, the addition of aluminum chloride leads to the formation of carbocations, which then attack the aromatic ring.



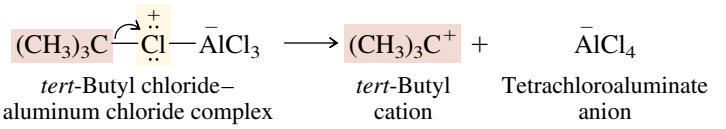
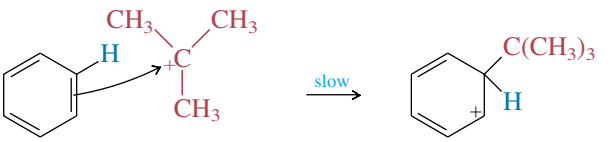


Figure 12.5 illustrates attack on the benzene ring by *tert*-butyl cation (step 1) and subsequent formation of *tert*-butylbenzene by loss of a proton from the cyclohexadienyl cation intermediate (step 2).

Secondary alkyl halides react by a similar mechanism involving attack on benzene by a secondary carbocation. Methyl and ethyl halides do not form carbocations when treated with aluminum chloride, but do alkylate benzene under Friedel–Crafts conditions.

Step 1: Once generated by the reation of *tert*-butyl chloride and aluminum chloride, *tert*-butyl cation attacks the π electrons of benzene, and a carbon-carbon bond is formed.



Step 2: Loss of a proton from the cyclohexadienyl cation intermediate yields *tert*-butylbenzene.

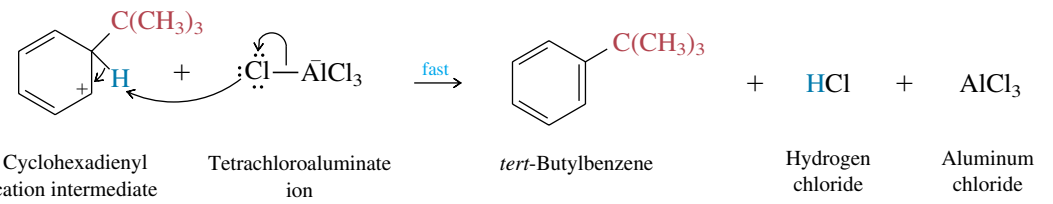
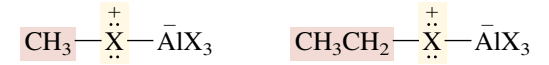


FIGURE 12.5 The mechanism of Friedel–Crafts alkylation. An electrostatic potential map of *tert*-butyl cation can be viewed on *Learning By Modeling.*

The aluminum chloride complexes of methyl and ethyl halides contain highly polarized carbon–halogen bonds, and these complexes are the electrophilic species that react with benzene.

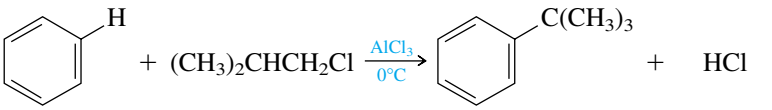


Methyl halide–aluminum halide complex

Ethyl halide–aluminum halide complex

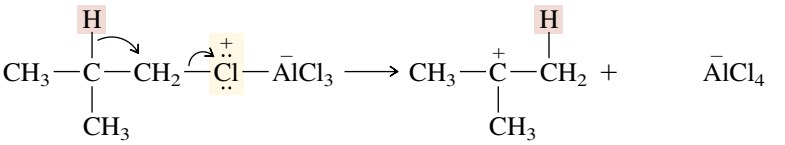
Other limitations to Friedel–Crafts reactions will be encountered in this chapter and are summarized in Table 12.4.

One drawback to Friedel–Crafts alkylation is that rearrangements can occur, especially when primary alkyl halides are used. For example, Friedel–Crafts alkylation of benzene with isobutyl chloride (a primary alkyl halide) yields only *tert*-butylbenzene.



Benzene | Isobutyl chloride | *tert*-Butylbenzene (66%) | Hydrogen chloride

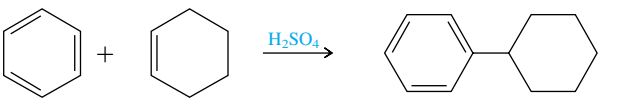
Here, the electrophile is *tert*-butyl cation formed by a hydride migration that accompanies ionization of the carbon–chlorine bond.



Isobutyl chloride–aluminum chloride complex | *tert*-Butyl cation | Tetrachloroaluminate ion

PROBLEM 12.4 In an attempt to prepare propylbenzene, a chemist alkylated benzene with 1-chloropropane and aluminum chloride. However, two isomeric hydrocarbons were obtained in a ratio of 2:1, the desired propylbenzene being the minor component. What do you think was the major product? How did it arise?

Since electrophilic attack on benzene is simply another reaction available to a carbocation, other carbocation precursors can be used in place of alkyl halides. For example, alkenes, which are converted to carbocations by protonation, can be used to alkylate benzene.

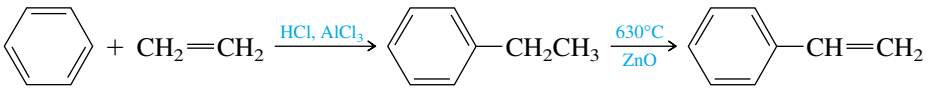


Benzene | Cyclohexene | Cyclohexylbenzene (65–68%)

PROBLEM 12.5 Write a reasonable mechanism for the formation of cyclohexylbenzene from the reaction of benzene, cyclohexene, and sulfuric acid.

Alkenyl halides such as vinyl chloride ($CH_2{=}CHCl$) do *not* form carbocations on treatment with aluminum chloride and so cannot be used in Friedel–Crafts reactions.

Thus, the industrial preparation of styrene from benzene and ethylene does not involve vinyl chloride but proceeds by way of ethylbenzene.



Benzene Ethylene Ethylbenzene Styrene

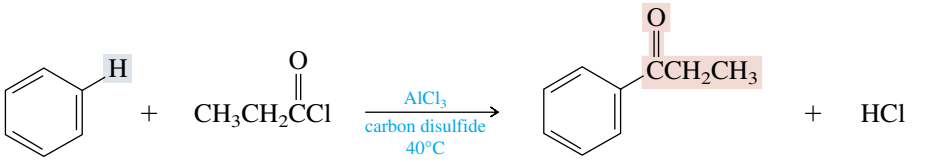
Dehydrogenation of alkylbenzenes, although useful in the industrial preparation of styrene, is not a general procedure and is not well suited to the laboratory preparation of alkenylbenzenes. In such cases an alkylbenzene is subjected to benzylic bromination (Section 11.12), and the resulting benzylic bromide is treated with base to effect dehydrohalogenation.

PROBLEM 12.6 Outline a synthesis of 1-phenylcyclohexene from benzene and cyclohexene.

12.7 FRIEDEL–CRAFTS ACYLATION OF BENZENE

Another version of the Friedel–Crafts reaction uses **acyl halides** instead of alkyl halides and yields **acylbenzenes.**

An acyl group has the general formula

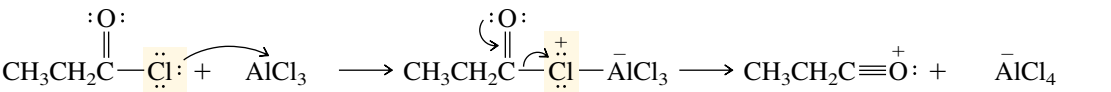


Benzene Propanoyl chloride 1-Phenyl-1-propanone (88%) Hydrogen chloride

The electrophile in a Friedel–Crafts acylation reaction is an **acyl cation** (also referred to as an **acylium ion).** Acyl cations are stabilized by resonance. The acyl cation derived from propanoyl chloride is represented by the two resonance forms

Most stable resonance form;
oxygen and carbon have octets of electrons

Acyl cations form by coordination of an acyl chloride with aluminum chloride, followed by cleavage of the carbon–chlorine bond.



Propanoyl chloride Aluminum chloride Lewis acid-Lewis base complex Propanoyl cation Tetrachloroaluminate ion

The electrophilic site of an acyl cation is its acyl carbon. An electrostatic potential map of the acyl cation from propanoyl chloride (Figure 12.6) illustrates nicely the concentration of positive charge at the acyl carbon. The mechanism of the reaction between this cation and benzene is analogous to that of other electrophilic reagents (Figure 12.7).

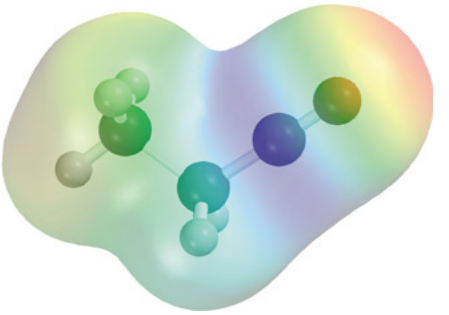
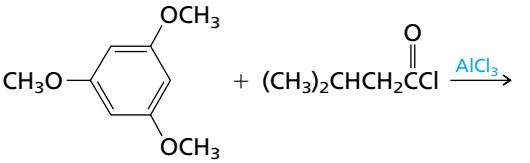


FIGURE 12.6 Electrostatic potential map of propanoyl cation [$(CH_3CH_2C{=}O)^+$]. The region of greatest positive charge (blue) is associated with the carbon of the C=O group.

PROBLEM 12.7 The reaction shown gives a single product in 88% yield. What is that product?



Acyl chlorides are readily available. They are prepared from carboxylic acids by reaction with thionyl chloride.

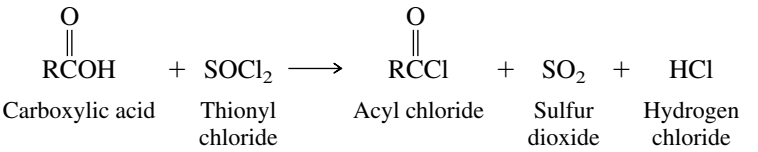
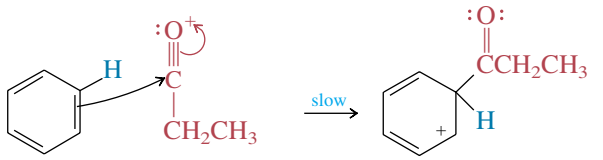
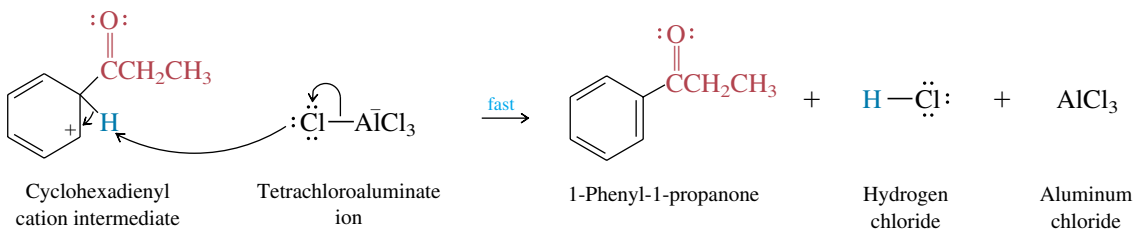


FIGURE 12.7 The mechanism of Friedel–Crafts acylation.

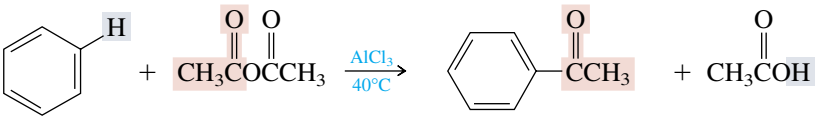
Step 1: The acyl cation attacks benzene. A pair of π electrons of benzene is used to form a covalent bond to the carbon of the acyl cation.



Step 2: Aromaticity of the ring is restored when it loses a proton to give the acylbenzene.



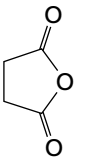
Carboxylic acid anhydrides, compounds of the type $RCOCR$ (with two carbonyl oxygens), can also serve as sources of acyl cations and, in the presence of aluminum chloride, acylate benzene. One acyl unit of an acid anhydride becomes attached to the benzene ring, while the other becomes part of a carboxylic acid.



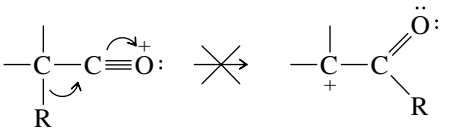
Benzene | Acetic anhydride | Acetophenone (76–83%) | Acetic acid

Acetophenone is one of the commonly encountered benzene derivatives listed in Table 11.1.

PROBLEM 12.8 *Succinic anhydride,* the structure of which is shown, is a cyclic anhydride often used in Friedel–Crafts acylations. Give the structure of the product obtained when benzene is acylated with succinic anhydride in the presence of aluminum chloride.



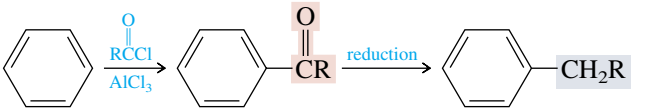
An important difference between Friedel–Crafts alkylations and acylations is that acyl cations do not rearrange. The acyl group of the acyl chloride or acid anhydride is transferred to the benzene ring unchanged. The reason for this is that an acyl cation is so strongly stabilized by resonance that it is more stable than any ion that could conceivably arise from it by a hydride or alkyl group shift.



More stable cation; all atoms have octets of electrons | Less stable cation; six electrons at carbon

12.8 SYNTHESIS OF ALKYLBENZENES BY ACYLATION–REDUCTION

Because acylation of an aromatic ring can be accomplished without rearrangement, it is frequently used as the first step in a procedure for the *alkylation* of aromatic compounds by *acylation–reduction.* As we saw in Section 12.6, Friedel–Crafts alkylation of benzene with primary alkyl halides normally yields products having rearranged alkyl groups as substituents. When a compound of the type $ArCH_2R$ is desired, a two-step sequence is used in which the first step is a Friedel–Crafts acylation.

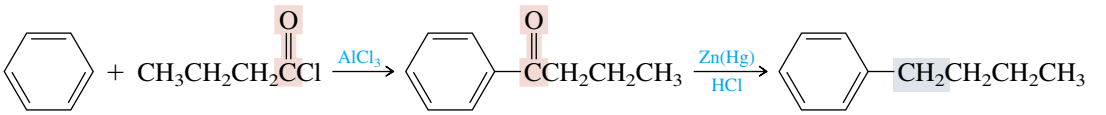


Benzene | Acylbenzene | Alkylbenzene

The second step is a reduction of the carbonyl group (C═O) to a methylene group (CH_2).

The most commonly used method for reducing an acylbenzene to an alkylbenzene employs a zinc–mercury amalgam in concentrated hydrochloric acid and is called the **Clemmensen reduction.**

The synthesis of butylbenzene illustrates the acylation–reduction sequence.



Benzene | Butanoyl chloride | 1-Phenyl-1-butanone (86%) | Butylbenzene (73%)

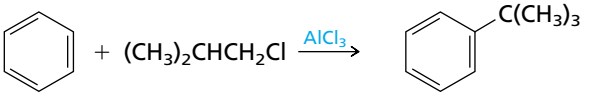
Direct alkylation of benzene using 1-chlorobutane and aluminum chloride would yield *sec*-butylbenzene by rearrangement and so could not be used.

PROBLEM 12.9 Using benzene and any necessary organic or inorganic reagents, suggest efficient syntheses of

(a) Isobutylbenzene, $C_6H_5CH_2CH(CH_3)_2$

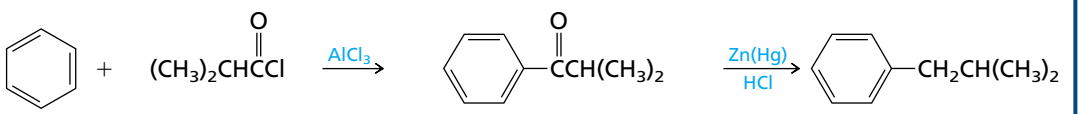
(b) Neopentylbenzene, $C_6H_5CH_2C(CH_3)_3$

SAMPLE SOLUTION (a) Friedel–Crafts alkylation of benzene with isobutyl chloride is not suitable, because it yields *tert*-butylbenzene by rearrangement.



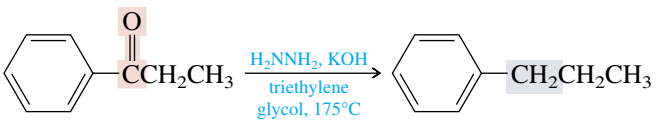
Benzene | Isobutyl chloride | *tert*-Butylbenzene (66%)

The two-step acylation–reduction sequence is required. Acylation of benzene puts the side chain on the ring with the correct carbon skeleton. Clemmensen reduction converts the carbonyl group to a methylene group.



Benzene | 2-Methylpropanoyl chloride | 2-Methyl-1-phenyl-1-propanone (84%) | Isobutylbenzene (80%)

Another way to reduce aldehyde and ketone carbonyl groups is by **Wolff–Kishner reduction.** Heating an aldehyde or a ketone with hydrazine (H_2NNH_2) and sodium or potassium hydroxide in a high-boiling alcohol such as triethylene glycol ($HOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$, bp 287°C) converts the carbonyl to a CH_2 group.



1-Phenyl-1-propanone | Propylbenzene (82%)

Both the Clemmensen and the Wolff–Kishner reductions are designed to carry out a specific functional group transformation, the reduction of an aldehyde or ketone carbonyl to a methylene group. Neither one will reduce the carbonyl group of a carboxylic acid, nor

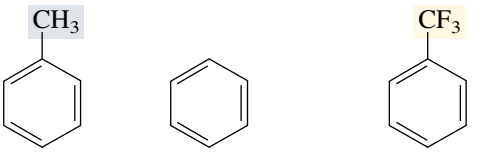
are carbon–carbon double or triple bonds affected by these methods. We will not discuss the mechanism of either the Clemmensen reduction or the Wolff–Kishner reduction, since both involve chemistry that is beyond the scope of what we have covered to this point.

12.9 RATE AND REGIOSELECTIVITY IN ELECTROPHILIC AROMATIC SUBSTITUTION

So far we've been concerned only with electrophilic substitution of benzene. Two important questions arise when we turn to analogous substitutions on rings that already bear at least one substituent:

1. What is the effect of a substituent on the *rate* of electrophilic aromatic substitution?
2. What is the effect of a substituent on the *regioselectivity* of electrophilic aromatic substitution?

To illustrate substituent effects on rate, consider the nitration of benzene, toluene, and (trifluoromethyl)benzene.



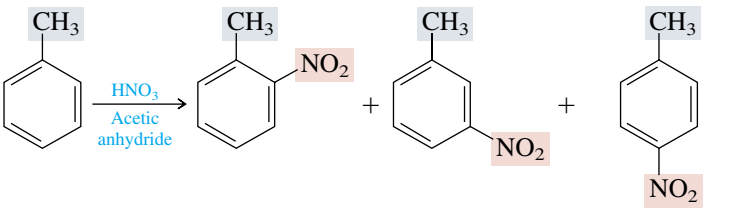
Toluene (most reactive) | Benzene | (Trifluoromethyl)benzene (least reactive)

Examine the molecular models of toluene and (trifluoromethyl)benzene on *Learning By Modeling*. In which molecule is the electrostatic potential of the ring most negative? How should this affect the rate of nitration?

Toluene undergoes nitration some 20–25 times faster than benzene. Because toluene is more reactive than benzene, we say that a methyl group *activates* the ring toward electrophilic aromatic substitution. (Trifluoromethyl)benzene, on the other hand, undergoes nitration about 40,000 times more slowly than benzene. We say that a trifluoromethyl group *deactivates* the ring toward electrophilic aromatic substitution.

Just as there is a marked difference in how methyl and trifluoromethyl substituents affect the rate of electrophilic aromatic substitution, so too there is a marked difference in how they affect its regioselectivity.

Three products are possible from nitration of toluene: *o*-nitrotoluene, *m*-nitrotoluene, and *p*-nitrotoluene. All are formed, but not in equal amounts. Together, the ortho- and para-substituted isomers make up 97% of the product mixture; the meta only 3%.

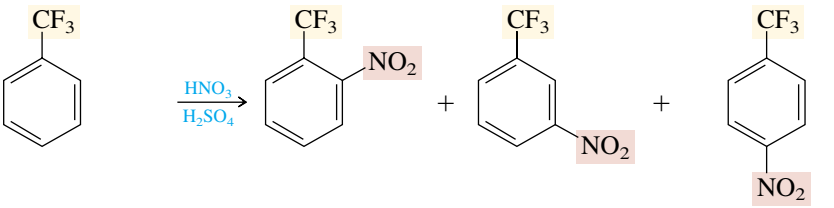


Toluene | *o*-Nitrotoluene (63%) | *m*-Nitrotoluene (3%) | *p*-Nitrotoluene (34%)

How do the charges on the ring carbons of toluene and (trifluoromethyl)benzene relate to the regioselectivity of nitration?

Because substitution in toluene occurs primarily at positions ortho and para to methyl, we say that *a methyl substituent is an* **ortho, para director.**

Nitration of (trifluoromethyl)benzene, on the other hand, yields almost exclusively *m*-nitro(trifluoromethyl)benzene (91%). The ortho- and para-substituted isomers are minor components of the reaction mixture.



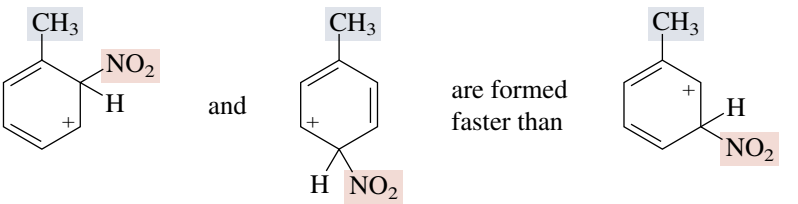
(Trifluoromethyl)benzene | *o*-Nitro(trifluoromethyl)benzene (6%) | *m*-Nitro(trifluoromethyl)benzene (91%) | *p*-Nitro(trifluoromethyl)benzene (3%)

Because substitution in (trifluoromethyl)benzene occurs primarily at positions meta to the substituent, we say that *a trifluoromethyl group is a* **meta director.**

The regioselectivity of substitution, like the rate, is strongly affected by the substituent. In the following several sections we will examine the relationship between the structure of the substituent and its effect on rate and regioselectivity of electrophilic aromatic substitution.

12.10 RATE AND REGIOSELECTIVITY IN THE NITRATION OF TOLUENE

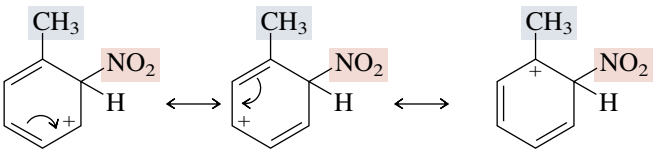
Why is there such a marked difference between methyl and trifluoromethyl substituents in their influence on electrophilic aromatic substitution? Methyl is activating and ortho, para-directing; trifluoromethyl is deactivating and meta-directing. The first point to remember is that the regioselectivity of substitution is set once the cyclohexadienyl cation intermediate is formed. If we can explain why



we will understand the reasons for the regioselectivity. A principle we have used before serves us well here: a *more stable carbocation is formed faster than a less stable one.* The most likely reason for the directing effect of methyl must be that the cyclohexadienyl cation precursors to *o*- and *p*-nitrotoluene are more stable than the one leading to *m*-nitrotoluene.

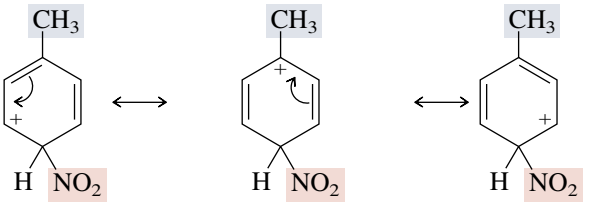
One way to assess the relative stabilities of these various intermediates is to examine electron delocalization in them using a resonance description. The cyclohexadienyl cations leading to *o*- and *p*-nitrotoluene have tertiary carbocation character. Each has a resonance form in which the positive charge resides on the carbon that bears the methyl group.

Ortho attack



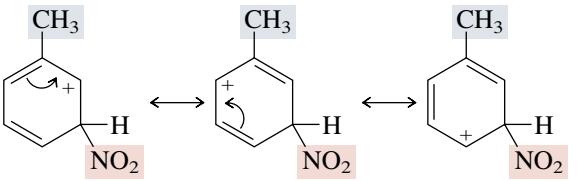
This resonance form is a tertiary carbocation

Para attack



The three resonance forms of the intermediate leading to meta substitution are all secondary carbocations.

Meta attack



Because of their tertiary carbocation character the intermediates leading to ortho and to para substitution are more stable and are formed faster than the one leading to meta substitution. They are also more stable than the secondary cyclohexadienyl cation intermediate formed during nitration of benzene. A methyl group is an activating substituent because it stabilizes the carbocation intermediate formed in the rate-determining step more than a hydrogen does. It is ortho, para-directing because it stabilizes the carbocation formed by electrophilic attack at these positions more than it stabilizes the intermediate formed by attack at the meta position. Figure 12.8 compares the energies of activation for attack at the various positions of toluene.

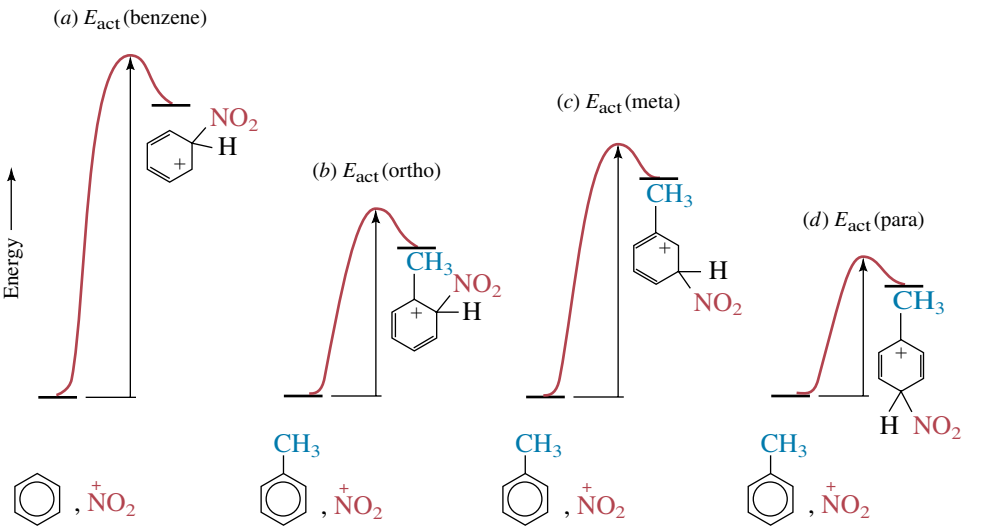
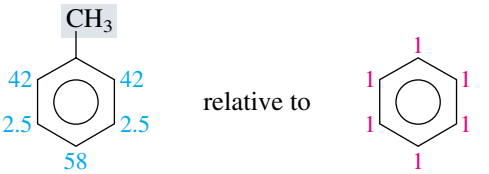


FIGURE 12.8 Comparative energy diagrams for nitronium ion attack on (*a*) benzene and at the (*b*) ortho, (*c*) meta, and (*d*) para positions of toluene. E_{act} (benzene) > E_{act} (meta) > E_{act} (ortho) > E_{act} (para).

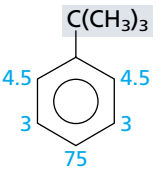
A methyl group is an *electron-releasing* substituent and activates *all* of the ring carbons of toluene toward electrophilic attack. The ortho and para positions are activated more than the meta positions. The relative rates of attack at the various positions in toluene compared with a single position in benzene are as follows (for nitration at 25°C):



These relative rate data per position are experimentally determined and are known as *partial rate factors.* They offer a convenient way to express substituent effects in electrophilic aromatic substitution reactions.

The major influence of the methyl group is *electronic.* The most important factor is relative carbocation stability. To a small extent, the methyl group sterically hinders the ortho positions, making attack slightly more likely at the para carbon than at a single ortho carbon. However, para substitution is at a statistical disadvantage, since there are two equivalent ortho positions but only one para position.

PROBLEM 12.10 The partial rate factors for nitration of *tert*-butylbenzene are as shown.



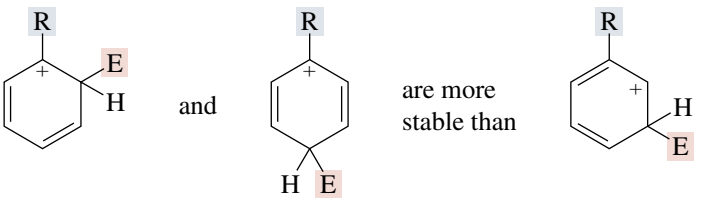
(a) How reactive is *tert*-butylbenzene toward nitration compared with benzene?
(b) How reactive is *tert*-butylbenzene toward nitration compared with toluene?
(c) Predict the distribution among the various mononitration products of *tert*-butylbenzene.

SAMPLE SOLUTION (a) Benzene has six equivalent sites at which nitration can occur. Summing the individual relative rates of attack at each position in *tert*-butylbenzene and benzene, we obtain

$$\frac{\textit{tert}\text{-Butylbenzene}}{\text{Benzene}} = \frac{2(4.5) + 2(3) + 75}{6(1)} = \frac{90}{6} = 15$$

tert-Butylbenzene undergoes nitration 15 times faster than benzene.

All alkyl groups, not just methyl, are activating substituents and ortho, para directors. This is because any alkyl group, be it methyl, ethyl, isopropyl, *tert*-butyl, or any other, stabilizes a carbocation site to which it is directly attached. When R = alkyl,

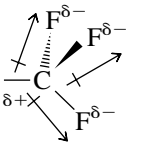


where E is any electrophile. All three structures are more stable for R = alkyl than for R = H and are formed more quickly.

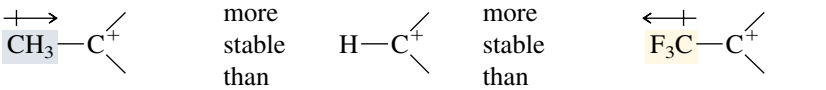
12.11 RATE AND REGIOSELECTIVITY IN THE NITRATION OF (TRIFLUOROMETHYL)BENZENE

Turning now to electrophilic aromatic substitution in (trifluoromethyl)benzene, we consider the electronic properties of a trifluoromethyl group. Because of their high electronegativity the three fluorine atoms polarize the electron distribution in their σ bonds to carbon, so that carbon bears a partial positive charge.

Recall from Section 4.10 that effects that are transmitted by the polarization of σ bonds are called *inductive effects.*



Unlike a methyl group, which is slightly electron-releasing, a trifluoromethyl group is a powerful electron-withdrawing substituent. Consequently, a CF_3 group *destabilizes* a carbocation site to which it is attached.

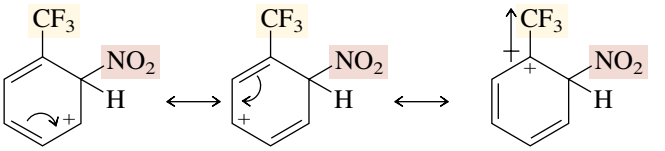


Methyl group releases electrons, stabilizes carbocation

Trifluoromethyl group withdraws electrons, destabilizes carbocation

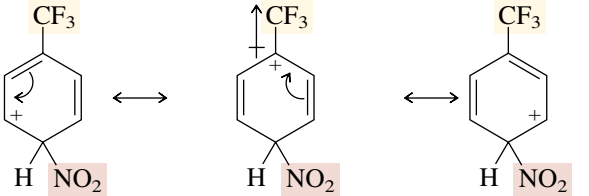
When we examine the cyclohexadienyl cation intermediates involved in the nitration of (trifluoromethyl)benzene, we find that those leading to ortho and para substitution are strongly destabilized.

Ortho attack



Positive charge on carbon bearing trifluoromethyl group; very unstable

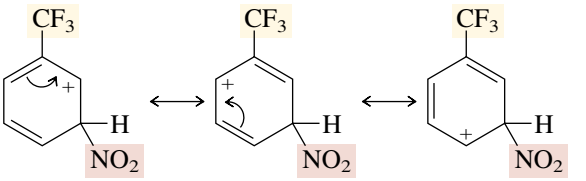
Para attack



Positive charge on carbon bearing trifluoromethyl group; very unstable

None of the three major resonance forms of the intermediate formed by attack at the meta position has a positive charge on the carbon bearing the trifluoromethyl substituent.

Meta attack



Attack at the meta position leads to a more stable intermediate than attack at either the ortho or the para position, and so meta substitution predominates. Even the intermediate corresponding to meta attack, however, is very unstable and is formed with difficulty. The trifluoromethyl group is only one bond farther removed from the positive charge here than it is in the ortho and para intermediates and so still exerts a significant, although somewhat diminished, destabilizing effect.

All the ring positions of (trifluoromethyl)benzene are deactivated compared with benzene. The meta position is simply deactivated *less* than the ortho and para positions. The partial rate factors for nitration of (trifluoromethyl)benzene are

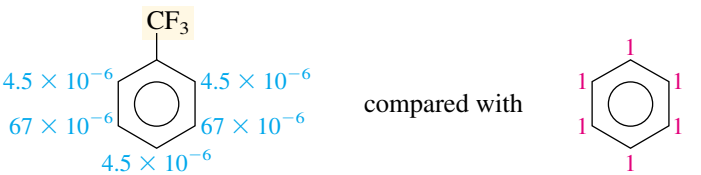


Figure 12.9 compares the energy profile for nitration of benzene with those for attack at the ortho, meta, and para positions of (trifluoromethyl)benzene. The presence of the electron-withdrawing trifluoromethyl group raises the activation energy for attack at all the ring positions, but the increase is least for attack at the meta position.

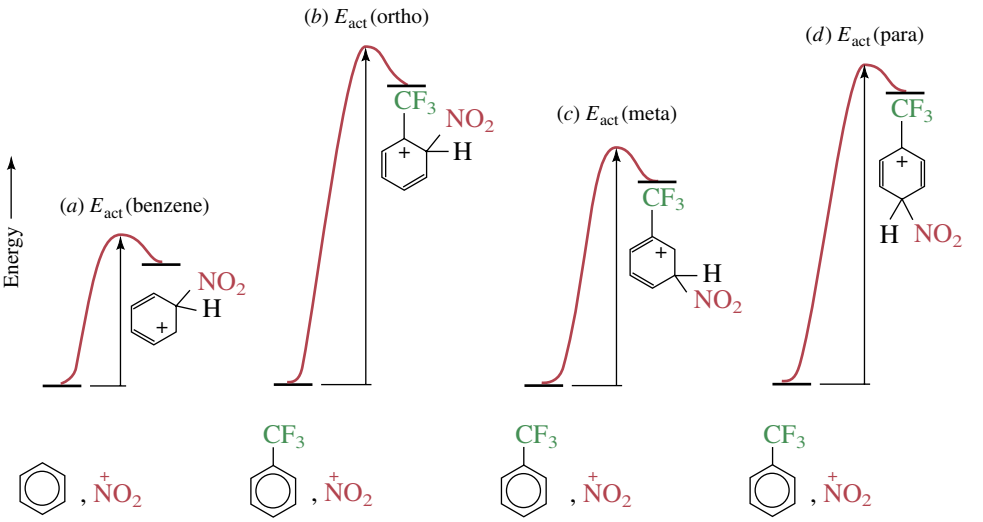


FIGURE 12.9 Comparative energy diagrams for nitronium ion attack on (*a*) benzene and at the (*b*) ortho, (*c*) meta, and (*d*) para positions of (trifluoromethyl)benzene. E_{act} (ortho) > E_{act} (para) > E_{act} (meta) > E_{act} (benzene).

PROBLEM 12.11 The compounds benzyl chloride ($C_6H_5CH_2Cl$), (dichloromethyl)benzene ($C_6H_5CHCl_2$), and (trichloromethyl)benzene ($C_6H_5CCl_3$) all undergo nitration more slowly than benzene. The proportion of *m*-nitro-substituted product is 4% in one, 34% in another, and 64% in another. Classify the substituents $—CH_2Cl$, $—CHCl_2$, and $—CCl_3$ according to each one's effect on rate and regioselectivity in electrophilic aromatic substitution.

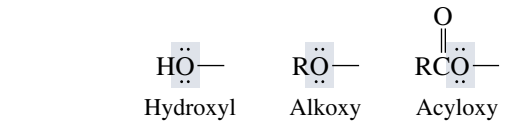
12.12 SUBSTITUENT EFFECTS IN ELECTROPHILIC AROMATIC SUBSTITUTION: ACTIVATING SUBSTITUENTS

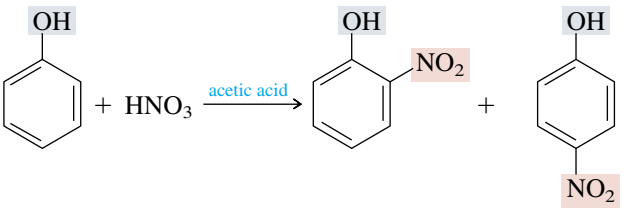
Our analysis of substituent effects has so far centered on two groups: methyl and trifluoromethyl. We have seen that a methyl substituent is activating and ortho, para-directing. A trifluoromethyl group is strongly deactivating and meta-directing. What about other substituents?

Table 12.2 summarizes orientation and rate effects in electrophilic aromatic substitution reactions for a variety of frequently encountered substituents. It is arranged in order of decreasing activating power: the most strongly activating substituents are at the top, the most strongly deactivating substituents are at the bottom. The main features of the table can be summarized as follows:

1. All activating substituents are ortho, para directors.
2. Halogen substituents are slightly deactivating but are ortho, para-directing.
3. Strongly deactivating substituents are meta directors.

Some of the most powerful *activating* substituents are those in which an oxygen atom is attached directly to the ring. These substituents include the hydroxyl group as well as alkoxy and acyloxy groups. All are ortho, para directors.





Phenol and *anisole* are among the commonly encountered benzene derivatives listed in Table 11.1. Electrophilic aromatic substitution in phenol is discussed in more detail in Section 24.8.

Hydroxyl, alkoxy, and acyloxy groups activate the ring to such an extent that bromination occurs rapidly even in the absence of a catalyst.

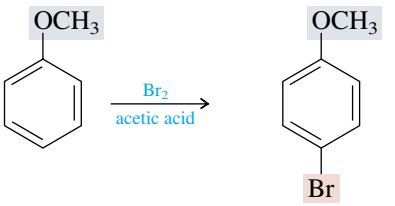
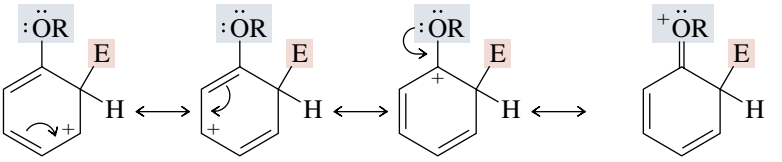


TABLE 12.2 Classification of Substituents in Electrophilic Aromatic Substitution Reactions

Effect on rate	Substituent		Effect on orientation
Very strongly activating	$-\ddot{N}H_2$	(amino)	Ortho, para-directing
	$-\ddot{N}HR$	(alkylamino)	
	$-\ddot{N}R_2$	(dialkylamino)	
	$-\ddot{O}H$	(hydroxyl)	
Strongly activating	$-\ddot{N}HC(=O)R$	(acylamino)	Ortho, para-directing
	$-\ddot{O}R$	(alkoxy)	
	$-\ddot{O}C(=O)R$	(acyloxy)	
Activating	$-R$	(alkyl)	Ortho, para-directing
	$-Ar$	(aryl)	
	$-CH{=}CR_2$	(alkenyl)	
Standard of comparison	$-H$	(hydrogen)	
Deactivating	$-X$ ($X = F, Cl, Br, I$)	(halogen)	Ortho, para-directing
	$-CH_2X$	(halomethyl)	
Strongly deactivating	$-CH(=O)$	(formyl)	Meta-directing
	$-CR(=O)$	(acyl)	
	$-COH(=O)$	(carboxylic acid)	
	$-COR(=O)$	(ester)	
	$-CCl(=O)$	(acyl chloride)	
	$-C{\equiv}N$	(cyano)	
	$-SO_3H$	(sulfonic acid)	
Very strongly deactivating	$-CF_3$	(trifluoromethyl)	Meta-directing
	$-NO_2$	(nitro)	

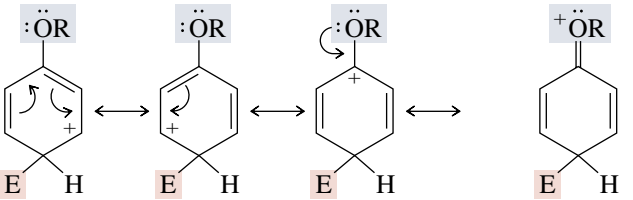
The inductive effect of hydroxyl and alkoxy groups, because of the electronegativity of oxygen, is to withdraw electrons and would seem to require that such substituents be deactivating. The electron-withdrawing inductive effect, however, is overcome by a much larger electron-releasing effect involving the unshared electron pairs of oxygen. Attack at positions ortho and para to a carbon that bears a substituent of the type $-\ddot{O}R$ gives a cation stabilized by delocalization of an unshared electron pair of oxygen into the π system of the ring (a *resonance* or *conjugation* effect).

Ortho attack



Most stable resonance form; oxygen and all carbons have octets of electrons

Para attack

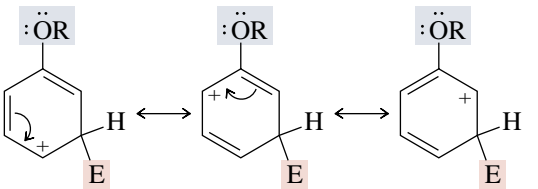


Most stable resonance form; oxygen and all carbons have octets of electrons

Oxygen-stabilized carbocations of this type are far more stable than tertiary carbocations. They are best represented by structures in which the positive charge is on oxygen because all the atoms have octets of electrons in such a structure. Their stability permits them to be formed rapidly, resulting in rates of electrophilic aromatic substitution that are much faster than that of benzene.

The lone pair on oxygen cannot be directly involved in carbocation stabilization when attack is meta to the substituent.

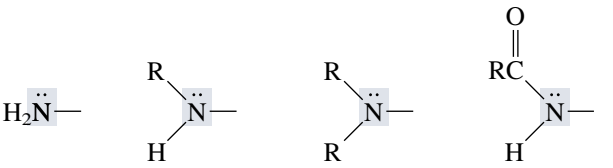
Meta attack



Oxygen lone pair cannot be used to stabilize positive charge in any of these structures; all have six electrons around positively charged carbon.

The greater stability of the carbocations arising from attack at the ortho and para positions compared with the carbocation formed by attack at the position meta to the oxygen substituent explains the ortho, para-directing property of hydroxyl, alkoxy, and acyloxy groups.

Nitrogen-containing substituents related to the amino group are even more strongly activating than the corresponding oxygen-containing substituents.



The nitrogen atom in each of these groups bears an electron pair that, like the unshared pairs of an oxygen substituent, stabilizes a carbocation site to which it is attached. Since nitrogen is less electronegative than oxygen, it is a better electron pair donor and stabilizes the cyclohexadienyl cation intermediates in electrophilic aromatic substitution to an even greater degree.

Aniline and its derivatives are so reactive in electrophilic aromatic substitution that special strategies are usually necessary to carry out these reactions effectively. This topic is discussed in Section 22.15.

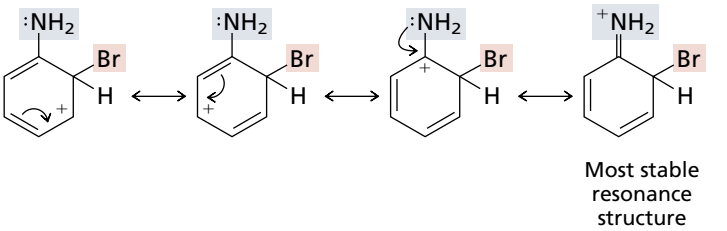
PROBLEM 12.12 Write structural formulas for the cyclohexadienyl cations formed from aniline ($C_6H_5NH_2$) during

(a) Ortho bromination (four resonance structures)

(b) Meta bromination (three resonance structures)

(c) Para bromination (four resonance structures)

SAMPLE SOLUTION (a) There are the customary three resonance structures for the cyclohexadienyl cation plus a resonance structure (the most stable one) derived by delocalization of the nitrogen lone pair into the ring.



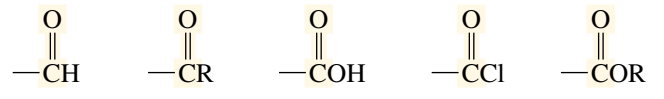
Alkyl groups are, as we saw when we discussed the nitration of toluene in Section 12.10, activating and ortho, para-directing substituents. Aryl and alkenyl substituents resemble alkyl groups in this respect; they too are activating and ortho, para-directing.

PROBLEM 12.13 Treatment of biphenyl (see Section 11.7 to remind yourself of its structure) with a mixture of nitric acid and sulfuric acid gave two principal products both having the molecular formula $C_{12}H_9NO_2$. What are these two products?

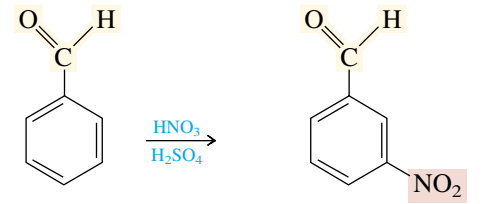
The next group of substituents in Table 12.2 that we'll discuss are the ones near the bottom of the table, those that are meta-directing and strongly deactivating.

12.13 SUBSTITUENT EFFECTS IN ELECTROPHILIC AROMATIC SUBSTITUTION: STRONGLY DEACTIVATING SUBSTITUENTS

As Table 12.2 indicates, a variety of substituent types are *meta-directing and strongly deactivating*. We have already discussed one of these, the trifluoromethyl group. Several of the others have a carbonyl group attached directly to the aromatic ring.

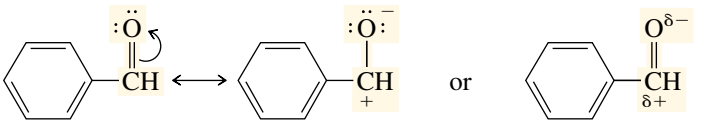


The behavior of aromatic aldehydes is typical. Nitration of benzaldehyde takes place several thousand times more slowly than that of benzene and yields *m*-nitrobenzaldehyde as the major product.



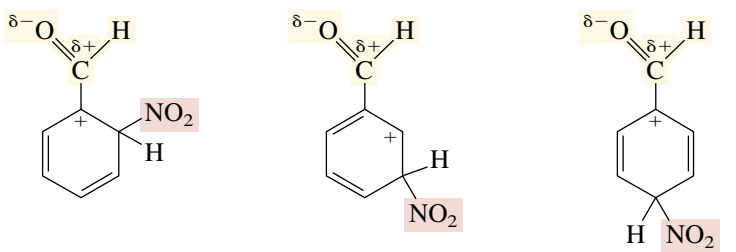
Benzaldehyde *m*-Nitrobenzaldehyde (75–84%)

To understand the effect of a carbonyl group attached directly to the ring, consider its polarization. The electrons in the carbon-oxygen double bond are drawn toward oxygen and away from carbon, leaving the carbon attached to the ring with a partial positive charge. Using benzaldehyde as an example,



Because the carbon atom attached to the ring is positively polarized, a carbonyl group behaves in much the same way as a trifluoromethyl group and *destabilizes* all the cyclohexadienyl cation intermediates in electrophilic aromatic substitution reactions. Attack at any ring position in benzaldehyde is slower than attack in benzene. The intermediates for ortho and para substitution are particularly unstable because each has a resonance structure in which there is a positive charge on the carbon that bears the electron-withdrawing substituent. The intermediate for meta substitution avoids this unfavorable juxtaposition of positive charges, is not as unstable, and gives rise to most of the product. For the nitration of benzaldehyde:

Ortho attack ***Meta attack*** ***Para attack***



Unstable because of adjacent positively polarized atoms

Positively polarized atoms not adjacent; most stable intermediate

Unstable because of adjacent positively polarized atoms

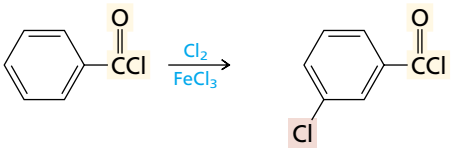
PROBLEM 12.14 Each of the following reactions has been reported in the chemical literature, and the principal organic product has been isolated in good yield. Write a structural formula for the isolated product of each reaction.

(a) Treatment of benzoyl chloride ($C_6H_5\overset{\overset{O}{\|}}{C}Cl$) with chlorine and iron(III) chloride

(b) Treatment of methyl benzoate ($C_6H_5\overset{\overset{O}{\|}}{C}OCH_3$) with nitric acid and sulfuric acid

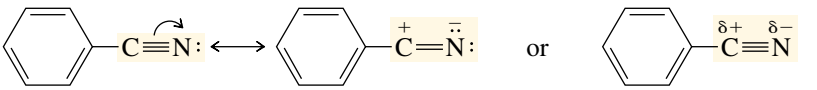
(c) Nitration of 1-phenyl-1-propanone ($C_6H_5\overset{\overset{O}{\|}}{C}CH_2CH_3$)

SAMPLE SOLUTION (a) Benzoyl chloride has a carbonyl group attached directly to the ring. A $-\overset{\overset{O}{\|}}{C}Cl$ substituent is meta-directing. The combination of chlorine and iron(III) chloride, introduces a chlorine onto the ring. The product is *m*-chlorobenzoyl chloride.



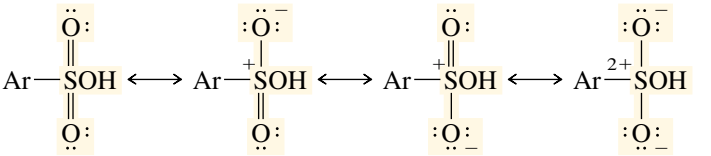
Benzoyl chloride — *m*-Chlorobenzoyl chloride (isolated in 62% yield)

A cyano group is similar to a carbonyl for analogous reasons involving resonance of the type

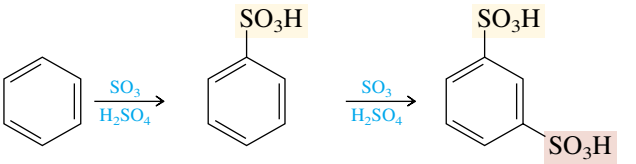


Cyano groups are electron-withdrawing, deactivating, and meta-directing.

Sulfonic acid groups are electron-withdrawing because sulfur has a formal positive charge in several of the resonance forms of benzenesulfonic acid.

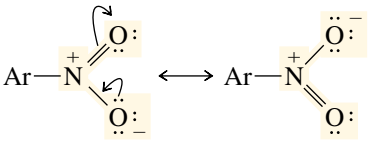


When benzene undergoes disulfonation, *m*-benzenedisulfonic acid is formed. The first sulfonic acid group to go on directs the second one meta to itself.

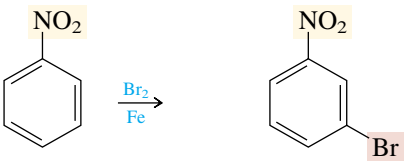


Benzene — Benzenesulfonic acid — *m*-Benzenedisulfonic acid (90%)

The nitrogen atom of a nitro group bears a full positive charge in its two most stable Lewis structures.



This makes the nitro group a powerful electron-withdrawing deactivating substituent and a meta director.

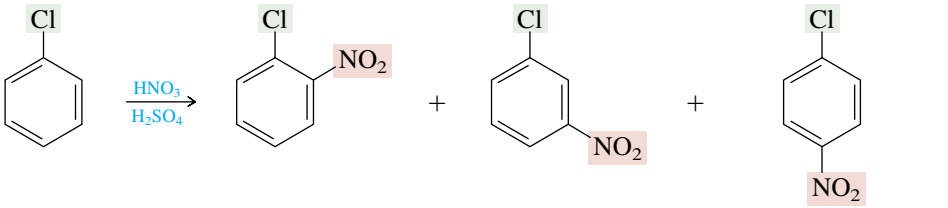


Nitrobenzene *m*-Bromonitrobenzene (60–75%)

PROBLEM 12.15 Would you expect the substituent $-\overset{+}{N}(CH_3)_3$ to more closely resemble $-\ddot{N}(CH_3)_2$ or $-NO_2$ in its effect on rate and regioselectivity in electrophilic aromatic substitution? Why?

12.14 SUBSTITUENT EFFECTS IN ELECTROPHILIC AROMATIC SUBSTITUTION: HALOGENS

Returning to Table 12.2, notice that *halogen substituents direct an incoming electrophile to the ortho and para positions but deactivate the ring toward substitution.* Nitration of chlorobenzene is a typical example of electrophilic aromatic substitution in a halobenzene; its rate is some 30 times slower than the corresponding nitration of benzene. The major products are *o*-chloronitrobenzene and *p*-chloronitrobenzene.



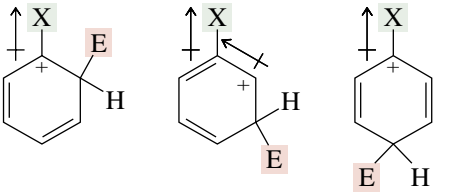
Chlorobenzene *o*-Chloronitrobenzene (30%) *m*-Chloronitrobenzene (1%) *p*-Chloronitrobenzene (69%)

PROBLEM 12.16 Reaction of chlorobenzene with 4-chlorobenzyl chloride and aluminum chloride gave a mixture of two products in good yield (76%). What were these two products?

Since we have come to associate activating substituents with ortho, para-directing effects and deactivating substituents with meta, the properties of the halogen substituents appear on initial inspection to be unusual.

This seeming inconsistency between regioselectivity and rate can be understood by analyzing the two ways that a halogen substituent can affect the stability of a cyclohexadienyl cation. First, halogens are electronegative, and their inductive effect is to draw

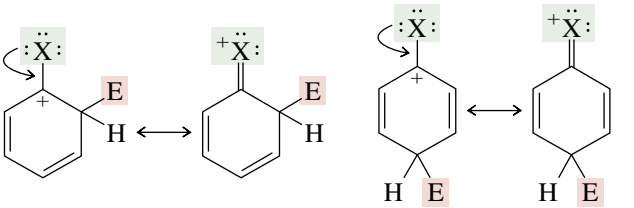
electrons away from the carbon to which they are bonded in the same way that a trifluoromethyl group does. Thus, all the intermediates formed by electrophilic attack on a halobenzene are less stable than the corresponding cyclohexadienyl cation for benzene, and halobenzenes are less reactive than benzene.



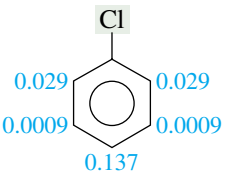
All these ions are less stable when X = F, Cl, Br, or I than when X = H

Like hydroxyl groups and amino groups, however, halogen substituents possess unshared electron pairs that can be donated to a positively charged carbon. This electron donation into the π system stabilizes the intermediates derived from ortho and from para attack.

Ortho attack ***Para attack***



Comparable stabilization of the intermediate leading to meta substitution is not possible. Thus, resonance involving halogen lone pairs causes electrophilic attack to be favored at the ortho and para positions but is weak and insufficient to overcome the electron-withdrawing inductive effect of the halogen, which deactivates all the ring positions. The experimentally observed partial rate factors for nitration of chlorobenzene result from this blend of inductive and resonance effects.



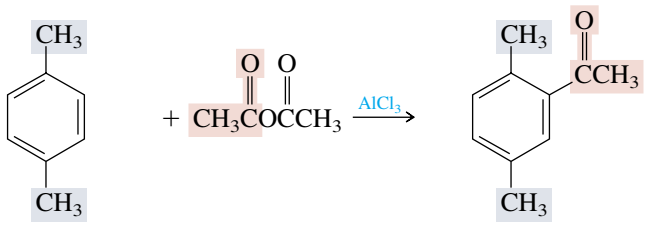
The mix of inductive and resonance effects varies from one halogen to another, but the net result is that fluorine, chlorine, bromine, and iodine are weakly deactivating, ortho, para-directing substituents.

12.15 MULTIPLE SUBSTITUENT EFFECTS

When a benzene ring bears two or more substituents, both its reactivity and the site of further substitution can usually be predicted from the cumulative effects of its substituents.

In the simplest cases all the available sites are equivalent, and substitution at any one of them gives the same product.

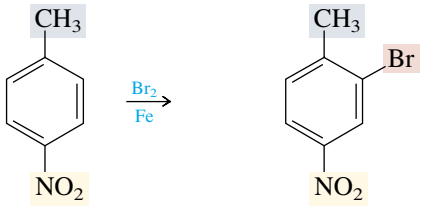
Problems 12.2, 12.3, and 12.7 offer additional examples of reactions in which only a single product of electrophilic aromatic substitution is possible.



1,4-Dimethylbenzene (*p*-xylene)

2,5-Dimethylacetophenone (99%)

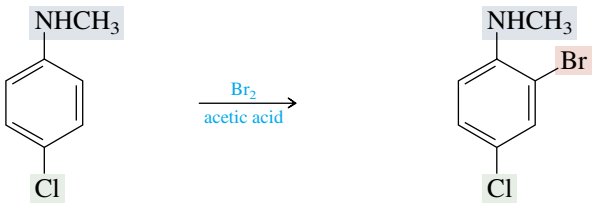
Often the directing effects of substituents reinforce each other. Bromination of *p*-nitrotoluene, for example, takes place at the position that is ortho to the ortho, para-directing methyl group and meta to the meta-directing nitro group.



p-Nitrotoluene

2-Bromo-4-nitrotoluene (86–90%)

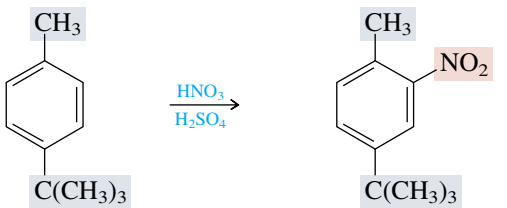
In almost all cases, including most of those in which the directing effects of individual substituents oppose each other, *it is the more activating substituent that controls the regioselectivity of electrophilic aromatic substitution.* Thus, bromination occurs ortho to the *N*-methylamino group in 4-chloro-*N*-methylaniline because this group is a very powerful activating substituent while the chlorine is weakly deactivating.



4-Chloro-*N*-methylaniline

2-Bromo-4-chloro-*N*-methylaniline (87%)

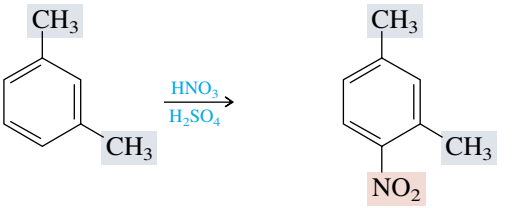
When two positions are comparably activated by alkyl groups, substitution usually occurs at the less hindered site. Nitration of *p-tert*-butyltoluene takes place at positions ortho to the methyl group in preference to those ortho to the larger *tert*-butyl group. This is an example of a *steric effect.*



p-tert-Butyltoluene

4-*tert*-Butyl-2-nitrotoluene (88%)

Nitration of *m*-xylene is directed ortho to one methyl group and para to the other.



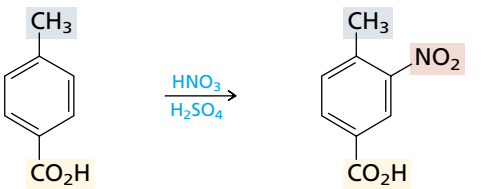
m-Xylene 2,4-Dimethyl-1-nitrobenzene (98%)

The ortho position between the two methyl groups is less reactive because it is more sterically hindered.

PROBLEM 12.17 Write the structure of the principal organic product obtained on nitration of each of the following:

(a) *p*-Methylbenzoic acid
(b) *m*-Dichlorobenzene
(c) *m*-Dinitrobenzene
(d) *p*-Methoxyacetophenone
(e) *p*-Methylanisole
(f) 2,6-Dibromoanisole

SAMPLE SOLUTION (a) Of the two substituents in *p*-methylbenzoic acid, the methyl group is more activating and so controls the regioselectivity of electrophilic aromatic substitution. The position para to the ortho, para-directing methyl group already bears a substituent (the carboxyl group), and so substitution occurs ortho to the methyl group. This position is meta to the *m*-directing carboxyl group, and the orienting properties of the two substituents reinforce each other. The product is 4-methyl-3-nitrobenzoic acid.



p-Methylbenzoic acid 4-Methyl-3-nitrobenzoic acid

Problem 12.38 illustrates how partial rate factor data may be applied to such cases.

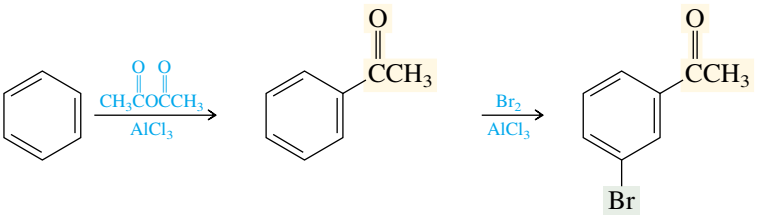
An exception to the rule that regioselectivity is controlled by the most activating substituent occurs when the directing effects of alkyl groups and halogen substituents oppose each other. Alkyl groups and halogen substituents are weakly activating and weakly deactivating, respectively, and the difference between them is too small to allow a simple generalization.

12.16 REGIOSELECTIVE SYNTHESIS OF DISUBSTITUTED AROMATIC COMPOUNDS

Since the position of electrophilic attack on an aromatic ring is controlled by the directing effects of substituents already present, the preparation of disubstituted aromatic compounds requires that careful thought be given to the order of introduction of the two groups.

Compare the independent preparations of *m*-bromoacetophenone and *p*-bromoacetophenone from benzene. Both syntheses require a Friedel–Crafts acylation step and a bromination step, but the major product is determined by the *order* in which the two

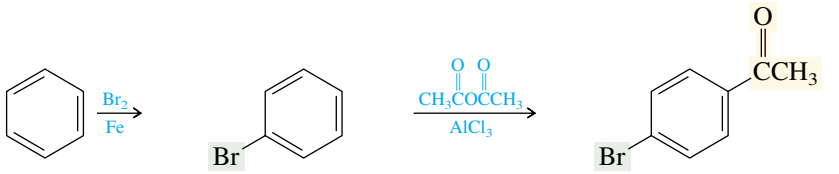
steps are carried out. When the meta-directing acetyl group is introduced first, the final product is *m*-bromoacetophenone.



Benzene — Acetophenone (76–83%) — *m*-Bromoacetophenone (59%)

Aluminum chloride is a stronger Lewis acid than iron(III) bromide and has been used as a catalyst in electrophilic bromination when, as in the example shown, the aromatic ring bears a strongly deactivating substituent.

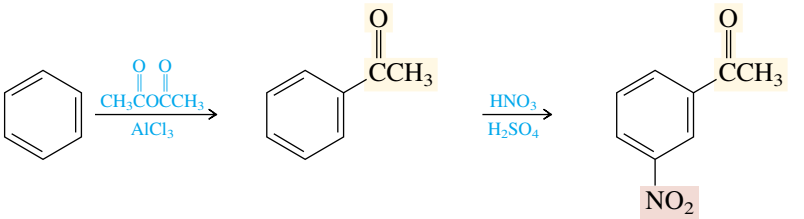
When the ortho, para-directing bromine is introduced first, the major product is *p*-bromoacetophenone (along with some of its ortho isomer, from which it is separated by distillation).



Benzene — Bromobenzene (65–75%) — p-Bromoacetophenone (69–79%)

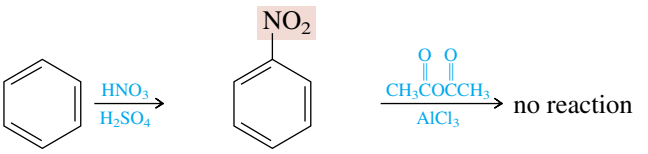
PROBLEM 12.18 Write chemical equations showing how you could prepare *m*-bromonitrobenzene as the principal organic product, starting with benzene and using any necessary organic or inorganic reagents. How could you prepare *p*-bromonitrobenzene?

A less obvious example of a situation in which the success of a synthesis depends on the order of introduction of substituents is illustrated by the preparation of *m*-nitroacetophenone. Here, even though both substituents are meta-directing, the only practical synthesis is the one in which Friedel–Crafts acylation is carried out first.



Benzene — Acetophenone (76–83%) — *m*-Nitroacetophenone (55%)

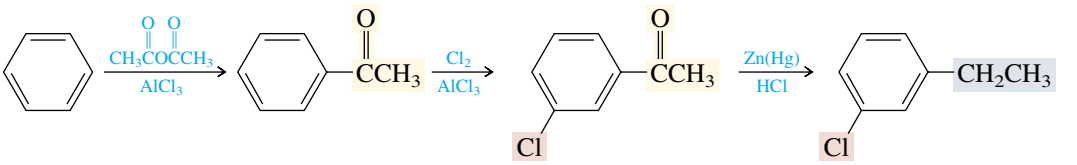
When the reverse order of steps is attempted, it is observed that the Friedel–Crafts acylation of nitrobenzene fails.



Benzene — Nitrobenzene (95%)

Neither Friedel–Crafts acylation nor alkylation reactions can be carried out on nitrobenzene. The presence of a strongly deactivating substituent such as a nitro group on an aromatic ring so depresses its reactivity that Friedel–Crafts reactions do not take place. Nitrobenzene is so unreactive that it is sometimes used as a solvent in Friedel–Crafts reactions. The practical limit for Friedel–Crafts alkylation and acylation reactions is effectively a monohalobenzene. *An aromatic ring more deactivated than a monohalobenzene cannot be alkylated or acylated under Friedel–Crafts conditions.*

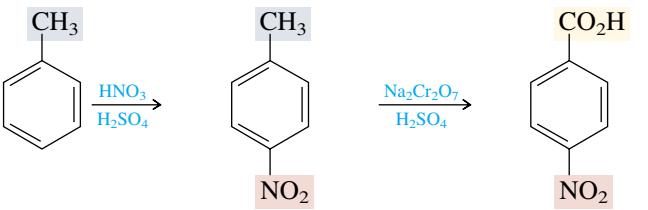
Sometimes the orientation of two substituents in an aromatic compound precludes its straightforward synthesis. *m*-Chloroethylbenzene, for example, has two ortho, para-directing groups in a meta relationship and so can't be prepared either from chlorobenzene or ethylbenzene. In cases such as this we couple electrophilic aromatic substitution with functional group manipulation to produce the desired compound.



Benzene | Acetophenone | *m*-Chloroacetophenone | *m*-Chloroethylbenzene

The key here is to recognize that an ethyl substituent can be introduced by Friedel–Crafts acylation followed by a Clemmensen or Wolff–Kishner reduction step later in the synthesis. If the chlorine is introduced prior to reduction, it will be directed meta to the acetyl group, giving the correct substitution pattern.

A related problem concerns the synthesis of *p*-nitrobenzoic acid. Here, two meta-directing substituents are para to each other. This compound has been prepared from toluene according to the procedure shown:



p-Nitrotoluene (separate from ortho isomer) | *p*-Nitrobenzoic acid (82–86%)

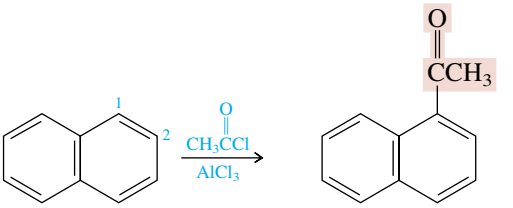
Since it may be oxidized to a carboxyl group (Section 11.13), a methyl group can be used to introduce the nitro substituent in the proper position.

PROBLEM 12.19 Suggest an efficient synthesis of *m*-nitrobenzoic acid from toluene.

12.17 SUBSTITUTION IN NAPHTHALENE

Polycyclic aromatic hydrocarbons undergo electrophilic aromatic substitution when treated with the same reagents that react with benzene. In general, polycyclic aromatic hydrocarbons are more reactive than benzene. Since, however, most lack the symmetry of benzene, mixtures of products may be formed even on monosubstitution. Among polycyclic aromatic hydrocarbons, we will discuss only naphthalene, and that only briefly.

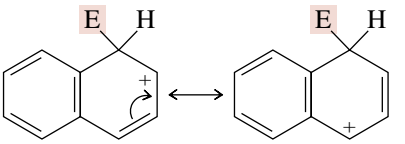
Two sites are available for substitution in naphthalene, C-1 and C-2, C-1 being normally the preferred site of electrophilic attack.



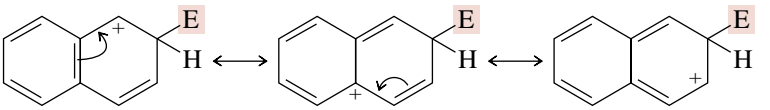
Naphthalene 1-Acetylnaphthalene (90%)

C-1 is more reactive because the arenium ion formed by electrophilic attack there is a relatively stable one. Benzenoid character is retained in one ring, and the positive charge is delocalized by allylic resonance.

Attack at C-1



Attack at C-2



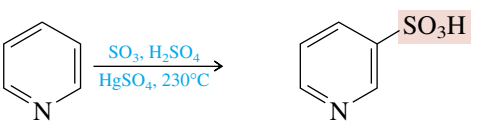
To involve allylic resonance in stabilizing the arenium ion formed during attack at C-2, the benzenoid character of the other ring is sacrificed.

PROBLEM 12.20 Sulfonation of naphthalene is reversible at elevated temperature. A different isomer of naphthalenesulfonic acid is the major product at 160°C than is the case at 0°C. Which isomer is the product of kinetic control? Which one is formed under conditions of thermodynamic control? Can you think of a reason why one isomer is more stable than the other? (*Hint:* Build space-filling models of both isomers.)

12.18 SUBSTITUTION IN HETEROCYCLIC AROMATIC COMPOUNDS

The great variety of available structural types causes heterocyclic aromatic compounds to range from exceedingly reactive to practically inert toward electrophilic aromatic substitution.

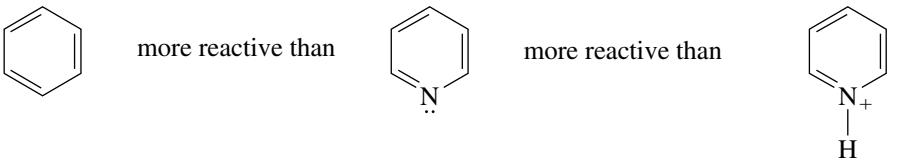
Pyridine lies near one extreme in being far less reactive than benzene toward substitution by electrophilic reagents. In this respect it resembles strongly deactivated aromatic compounds such as nitrobenzene. It is incapable of being acylated or alkylated under Friedel–Crafts conditions, but can be sulfonated at high temperature. Electrophilic substitution in pyridine, when it does occur, takes place at C-3.



Pyridine Pyridine-3-sulfonic acid (71%)

The electrostatic potential map of pyridine on *Learning By Modeling* clearly shows its decreased π electron density.

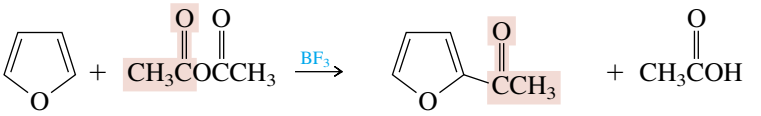
One reason for the low reactivity of pyridine is that its nitrogen atom, since it is more electronegative than a CH in benzene, causes the π electrons to be held more tightly and raises the activation energy for attack by an electrophile. Another is that the nitrogen of pyridine is protonated in sulfuric acid and the resulting pyridinium ion is even more deactivated than pyridine itself.



Benzene Pyridine Pyridinium ion

Lewis acid catalysts such as aluminum chloride and iron(III) halides also bond to nitrogen to strongly deactivate the ring toward Friedel–Crafts reactions and halogenation.

Pyrrole, furan, and thiophene, on the other hand, have electron-rich aromatic rings and are extremely reactive toward electrophilic aromatic substitution—more like phenol and aniline than benzene. Like benzene they have six π electrons, but these π electrons are delocalized over *five* atoms, not six, and are not held as strongly as those of benzene. Even when the ring atom is as electronegative as oxygen, substitution takes place readily.

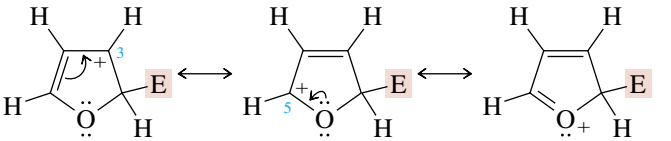


Furan Acetic anhydride 2-Acetylfuran (75–92%) Acetic acid

The regioselectivity of substitution in furan is explained using a resonance description. When the electrophile attacks C-2, the positive charge is shared by three atoms: C-3, C-5, and O.

Attack at C-2

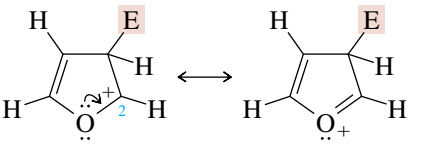
Carbocation *more stable;* positive charge shared by C-3, C-5, and O.



When the electrophile attacks at C-3, the positive charge is shared by only two atoms, C-2 and O, and the carbocation intermediate is less stable and formed more slowly.

Attack at C-3

Carbocation *less stable;* positive charge shared by C-2 and O.



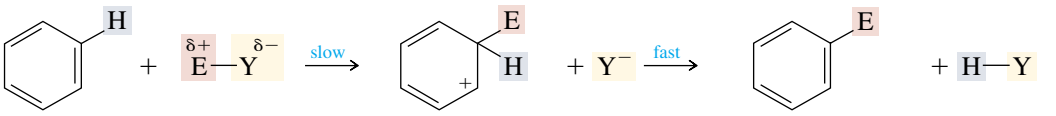
The regioselectivity of substitution in pyrrole and thiophene is like that of furan and for similar reasons.

PROBLEM 12.21 When benzene is prepared from coal tar, it is contaminated with thiophene, from which it cannot be separated by distillation because of very similar boiling points. Shaking a mixture of benzene and thiophene with sulfuric acid causes sulfonation of the thiophene ring but leaves benzene untouched. The sulfonation product of thiophene dissolves in the sulfuric acid layer, from which the benzene layer is separated; the benzene layer is then washed with water and distilled. Give the structure of the sulfonation product of thiophene.

12.19 SUMMARY

Section 12.1 On reaction with electrophilic reagents, compounds that contain a benzene ring undergo **electrophilic aromatic substitution.** Table 12.1 in Section 12.1 and Table 12.3 in this summary give examples.

Section 12.2 The mechanism of electrophilic aromatic substitution involves two stages: attack of the electrophile on the π electrons of the ring (slow, rate-determining), followed by loss of a proton to restore the aromaticity of the ring.

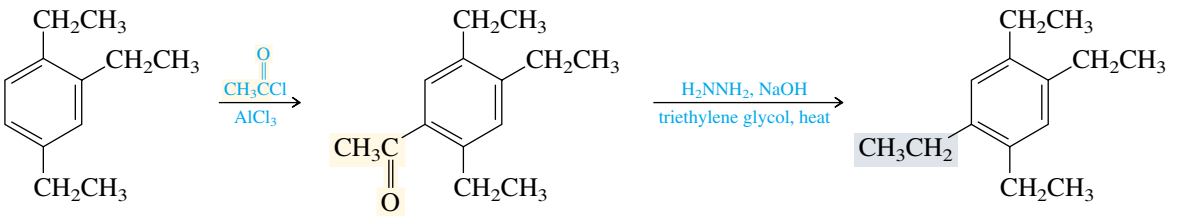


Benzene | Electrophilic reagent | Cyclohexadienyl cation intermediate | Product of electrophilic aromatic substitution

Sections 12.3–12.5 See Table 12.3

Sections 12.6–12.7 See Tables 12.3 and 12.4

Section 12.8 Friedel–Crafts acylation, followed by Clemmensen or Wolff–Kishner reduction is a standard sequence used to introduce a primary alkyl group onto an aromatic ring.



1,2,4-Triethylbenzene | 1,3,4-Triethylacetophenone (80%) | 1,2,4,5-Tetraethylbenzene (73%)

Section 12.9 Substituents on an aromatic ring can influence both the *rate* and *regioselectivity* of electrophilic aromatic substitution. Substituents are classified as *activating* or *deactivating* according to whether they cause the ring to react more rapidly or less rapidly than benzene. With respect to regioselectivity, substituents are either *ortho, para-directing* or *meta-directing*. A methyl group is activating and ortho, para-directing. A trifluoromethyl group is deactivating and meta-directing.

TABLE 12.3 Representative Electrophilic Aromatic Substitution Reactions

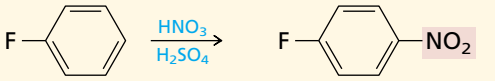
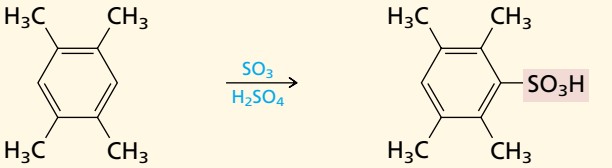
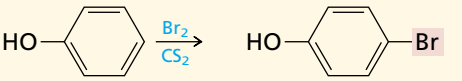
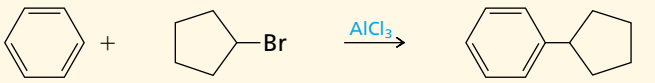
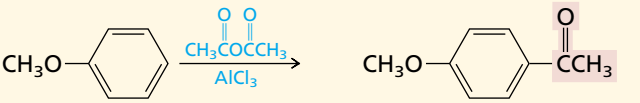
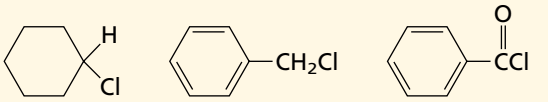
Reaction (section) and comments	General equation and specific example
Nitration (Section 12.3) The active electrophile in the nitration of benzene and its derivatives is nitronium cation ($:\ddot{O}{=}\overset{+}{N}{=}\ddot{O}:$). It is generated by reaction of nitric acid and sulfuric acid. Very reactive arenes those that bear strongly activating substituents undergo nitration in nitric acid alone.	$ArH + HNO_3 \xrightarrow{H_2SO_4} ArNO_2 + H_2O$ Arene Nitric acid Nitroarene Water  Fluorobenzene *p*-Fluoronitrobenzene (80%)
Sulfonation (Section 12.4) Sulfonic acids are formed when aromatic compounds are treated with sources of sulfur trioxide. These sources can be concentrated sulfuric acid (for very reactive arenes) or solutions of sulfur trioxide in sulfuric acid (for benzene and arenes less reactive than benzene).	$ArH + SO_3 \longrightarrow ArSO_3H$ Arene Sulfur trioxide Arenesulfonic acid  1,2,4,5-Tetramethylbenzene 2,3,5,6-Tetramethylbenzenesulfonic acid (94%)
Halogenation (Section 12.5) Chlorination and bromination of arenes are carried out by treatment with the appropriate halogen in the presence of a Lewis acid catalyst. Very reactive arenes undergo halogenation in the absence of a catalyst.	$ArH + X_2 \xrightarrow{FeX_3} ArX + HX$ Arene Halogen Aryl halide Hydrogen halide  Phenol *p*-Bromophenol (80 84%)
Friedel Crafts alkylation (Section 12.6) Carbocations, usually generated from an alkyl halide and aluminum chloride, attack the aromatic ring to yield alkylbenzenes. The arene must be at least as reactive as a halobenzene. Carbocation rearrangements can occur, especially with primary alkyl halides.	$ArH + RX \xrightarrow{AlCl_3} ArR + HX$ Arene Alkyl halide Alkylarene Hydrogen halide  Benzene Cyclopentyl bromide Cyclopentylbenzene (54%)
Friedel Crafts acylation (Section 12.7) Acyl cations (acylium ions) generated by treating an acyl chloride or acid anhydride with aluminum chloride attack aromatic rings to yield ketones. The arene must be at least as reactive as a halobenzene. Acyl cations are relatively stable, and do not rearrange.	$ArH + RCCl \xrightarrow{AlCl_3} ArCR + HCl$ Arene Acyl chloride Ketone Hydrogen chloride $ArH + RCOCR \xrightarrow{AlCl_3} ArCR + RCOH$ Arene Acid anhydride Ketone Carboxylic acid  Anisole *p*-Methoxyacetophenone (90 94%)

TABLE 12.4 Limitations on Friedel–Crafts Reactions

1. The organic halide that reacts with the arene must be an alkyl halide (Section 12.6) or an acyl halide (Section 12.7).

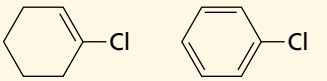
These will react with benzene under Friedel–Crafts conditions:



Alkyl halide | Benzylic halide | Acyl halide

Vinylic halides and aryl halides do not form carbocations under conditions of the Friedel–Crafts reaction and so cannot be used in place of an alkyl halide or an acyl halide.

These will not react with benzene under Friedel–Crafts conditions:

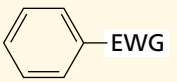


Vinylic halide | Aryl halide

2. Rearrangement of alkyl groups can occur (Section 12.6).

Rearrangement is especially prevalent with primary alkyl halides of the type RCH_2CH_2X and R_2CHCH_2X. Aluminum chloride induces ionization with rearrangement to give a more stable carbocation. Benzylic halides and acyl halides do not rearrange.

3. Strongly deactivated aromatic rings do not undergo Friedel–Crafts alkylation or acylation (Section 12.16). Friedel–Crafts alkylations and acylations fail when applied to compounds of the following type, where EWG is a strongly electron-withdrawing group:



EWG:

$-CF_3$, $-NO_2$, $-SO_3H$, $-C{\equiv}N$,

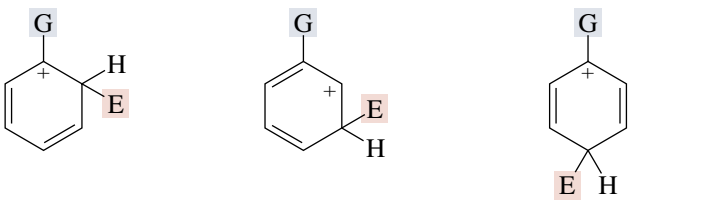
$-\overset{\overset{O}{\|}}{C}H$, $-\overset{\overset{O}{\|}}{C}R$, $-\overset{\overset{O}{\|}}{C}OH$, $-\overset{\overset{O}{\|}}{C}OR$, $-\overset{\overset{O}{\|}}{C}Cl$

4. It is sometimes difficult to limit Friedel–Crafts alkylation to monoalkylation.

The first alkyl group that goes on makes the ring more reactive toward further substitution because alkyl groups are activating substituents. Monoacylation is possible because the first acyl group to go on is strongly electron-withdrawing and deactivates the ring toward further substitution.

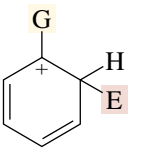
Sections 12.10–12.14

How substituents control rate and regioselectivity in electrophilic aromatic substitution results from their effect on carbocation stability. An electron-releasing substituent stabilizes the cyclohexadienyl cation intermediates corresponding to ortho and para attack more than meta.

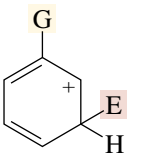


Stabilized when G is electron-releasing | Less stabilized when G is electron-releasing | Stabilized when G is electron-releasing

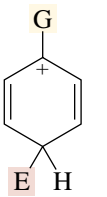
Conversely, an electron-withdrawing substituent destabilizes the cyclohexadienyl cations corresponding to ortho and para attack more than meta. Thus, meta substitution predominates.



Destabilized when G is electron-withdrawing



Less destabilized when G is electron-withdrawing



Destabilized when G is electron-withdrawing

Substituents can be arranged into three major categories:

1. **Activating and ortho, para-directing:** These substituents stabilize the cyclohexadienyl cation formed in the rate-determining step. They include $-\ddot{N}R_2$, $-\ddot{O}R$, —R, —Ar, and related species. The most strongly activating members of this group are bonded to the ring by a nitrogen or oxygen atom that bears an unshared pair of electrons.
2. **Deactivating and ortho, para-directing:** The halogens are the most prominent members of this class. They withdraw electron density from all the ring positions by an inductive effect, making halobenzenes less reactive than benzene. Lone-pair electron donation stabilizes the cyclohexadienyl cations corresponding to attack at the ortho and para positions more than those formed by attack at the meta positions, giving rise to the observed regioselectivity.
3. **Deactivating and meta-directing:** These substituents are strongly electron-withdrawing and destabilize carbocations. They include

$$-CF_3, \quad -\overset{\displaystyle O}{\overset{\|}{C}}R, \quad -C{\equiv}N, \quad -NO_2$$

and related species. All the ring positions are deactivated, but since the *meta* positions are deactivated less than the ortho and para, meta substitution is favored.

Section 12.15 When two or more substituents are present on a ring, the regioselectivity of electrophilic aromatic substitution is generally controlled by the directing effect of the more powerful *activating* substituent.

Section 12.16 The order in which substituents are introduced onto a benzene ring needs to be considered in order to prepare the desired isomer in a multistep synthesis.

Section 12.17 Polycyclic aromatic hydrocarbons undergo the same kind of electrophilic aromatic substitution reactions as benzene.

Section 12.18 Heterocyclic aromatic compounds may be more reactive or less reactive than benzene. Pyridine is much less reactive than benzene, but pyrrole, furan, and thiophene are more reactive.

PROBLEMS

12.22 Give reagents suitable for carrying out each of the following reactions, and write the major organic products. If an ortho, para mixture is expected, show both. If the meta isomer is the expected major product, write only that isomer.

(a) Nitration of benzene

(b) Nitration of the product of part (a)

(c) Bromination of toluene

(d) Bromination of (trifluoromethyl)benzene

(e) Sulfonation of anisole

(f) Sulfonation of acetanilide ($C_6H_5NHCCH_3$, with O double-bonded to the carbonyl C)

(g) Chlorination of bromobenzene

(h) Friedel–Crafts alkylation of anisole with benzyl chloride

(i) Friedel–Crafts acylation of benzene with benzoyl chloride

(j) Nitration of the product from part (i)

(k) Clemmensen reduction of the product from part (i)

(l) Wolff–Kishner reduction of the product from part (i)

12.23 Write a structural formula for the most stable cyclohexadienyl cation intermediate formed in each of the following reactions. Is this intermediate more or less stable than the one formed by electrophilic attack on benzene?

(a) Bromination of *p*-xylene

(b) Chlorination of *m*-xylene

(c) Nitration of acetophenone

(d) Friedel–Crafts acylation of anisole with CH_3CCl (O double-bonded to the carbonyl C)

(e) Nitration of isopropylbenzene

(f) Bromination of nitrobenzene

(g) Sulfonation of furan

(h) Bromination of pyridine

12.24 In each of the following pairs of compounds choose which one will react faster with the indicated reagent, and write a chemical equation for the faster reaction:

(a) Toluene or chlorobenzene with a mixture of nitric acid and sulfuric acid

(b) Fluorobenzene or (trifluoromethyl)benzene with benzyl chloride and aluminum chloride

(c) Methyl benzoate ($C_6H_5COCH_3$, with O double-bonded to the carbonyl C) or phenyl acetate ($C_6H_5OCCH_3$, with O double-bonded to the carbonyl C) with bromine in acetic acid

(d) Acetanilide ($C_6H_5NHCCH_3$, with O double-bonded to the carbonyl C) or nitrobenzene with sulfur trioxide in sulfuric acid

(e) *p*-Dimethylbenzene (*p*-xylene) or *p*-di-*tert*-butylbenzene with acetyl chloride and aluminum chloride

(f) Benzophenone ($C_6H_5CC_6H_5$, with O double-bonded to the carbonyl C) or biphenyl ($C_6H_5—C_6H_5$) with chlorine and iron(III) chloride

12.25 Arrange the following five compounds in order of decreasing rate of bromination: benzene, toluene, *o*-xylene, *m*-xylene, 1,3,5-trimethylbenzene (the relative rates are 2×10^7, 5×10^4, 5×10^2, 60, and 1).

12.26 Each of the following reactions has been carried out under conditions such that disubstitution or trisubstitution occurred. Identify the principal organic product in each case.

(a) Nitration of *p*-chlorobenzoic acid (dinitration)

(b) Bromination of aniline (tribromination)

(c) Bromination of *o*-aminoacetophenone (dibromination)

(d) Nitration of benzoic acid (dinitration)

(e) Bromination of *p*-nitrophenol (dibromination)

(f) Reaction of biphenyl with *tert*-butyl chloride and iron(III) chloride (dialkylation)

(g) Sulfonation of phenol (disulfonation)

12.27 Write equations showing how you could prepare each of the following from benzene or toluene and any necessary organic or inorganic reagents. If an ortho, para mixture is formed in any step of your synthesis, assume that you can separate the two isomers.

(a) Isopropylbenzene

(b) *p*-Isopropylbenzenesulfonic acid

(c) 2-Bromo-2-phenylpropane

(d) 4-*tert*-Butyl-2-nitrotoluene

(e) *m*-Chloroacetophenone

(f) *p*-Chloroacetophenone

(g) 3-Bromo-4-methylacetophenone

(h) 2-Bromo-4-ethyltoluene

(i) 1-Bromo-3-nitrobenzene

(j) 1-Bromo-2,4-dinitrobenzene

(k) 3-Bromo-5-nitrobenzoic acid

(l) 2-Bromo-4-nitrobenzoic acid

(m) Diphenylmethane

(n) 1-Phenyloctane

(o) 1-Phenyl-1-octene

(p) 1-Phenyl-1-octyne

(q) 1,4-Di-*tert*-butyl-1,4-cyclohexadiene

12.28 Write equations showing how you could prepare each of the following from anisole and any necessary organic or inorganic reagents. If an ortho, para mixture is formed in any step of your synthesis, assume that you can separate the two isomers.

(a) *p*-Methoxybenzenesulfonic acid

(b) 2-Bromo-4-nitroanisole

(c) 4-Bromo-2-nitroanisole

(d) *p*-Methoxystyrene

12.29 How many products are capable of being formed from toluene in each of the following reactions?

(a) Mononitration (HNO_3, H_2SO_4, 40°C).

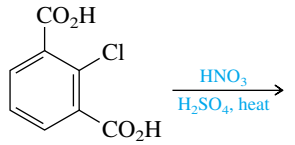
(b) Dinitration (HNO_3, H_2SO_4, 80°C).

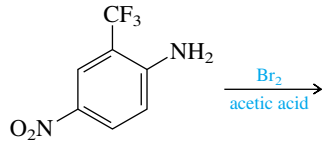
(c) Trinitration (HNO_3, H_2SO_4, 110°C). The explosive TNT (trinitrotoluene) is the major product obtained on trinitration of toluene. Which trinitrotoluene isomer is TNT?

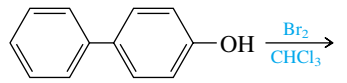
12.30 Friedel–Crafts acylation of the individual isomers of xylene with acetyl chloride and aluminum chloride yields a single product, different for each xylene isomer, in high yield in each case. Write the structures of the products of acetylation of *o-, m-,* and *p*-xylene.

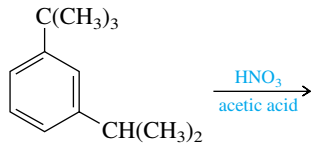
12.31 Reaction of benzanilide ($C_6H_5NHC(=O)C_6H_5$) with chlorine in acetic acid yields a mixture of two monochloro derivatives formed by electrophilic aromatic substitution. Suggest reasonable structures for these two isomers.

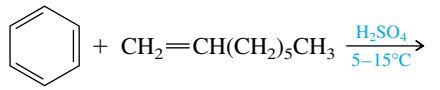
12.32 Each of the following reactions has been reported in the chemical literature and gives a predominance of a single product in synthetically acceptable yield. Write the structure of the product. Only monosubstitution is involved in each case, unless otherwise indicated.

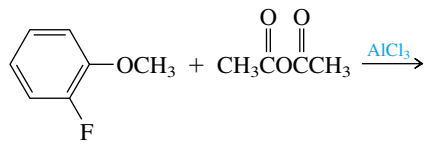
(a) 

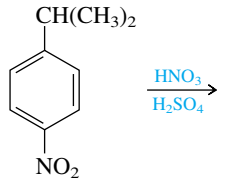
(b) 

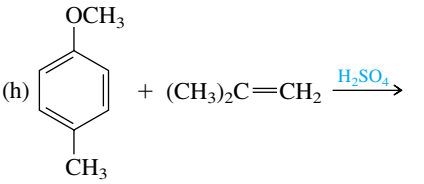
(c) 

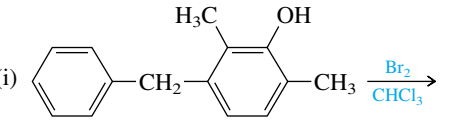
(d) 

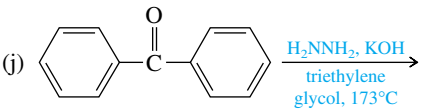
(e) 

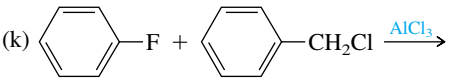
(f) 

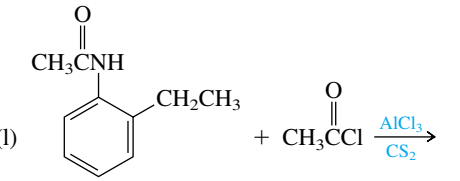
(g) 

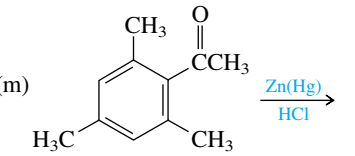
(h) 

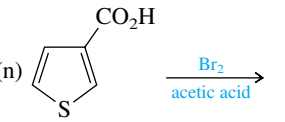
(i) 

(j) 

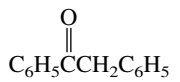
(k) 

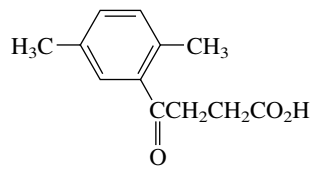
(l) 

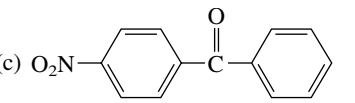
(m) 

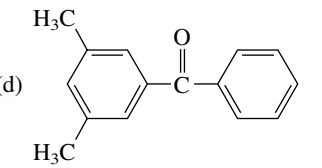
(n) 

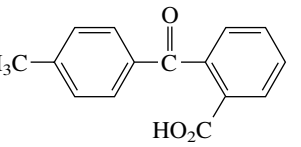
12.33 What combination of acyl chloride or acid anhydride and arene would you choose to prepare each of the following compounds by a Friedel–Crafts acylation reaction?

(a) 

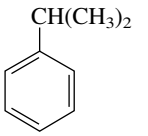
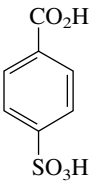
(b) 

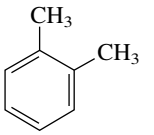
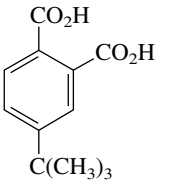
(c) 

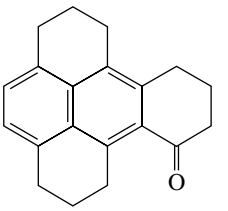
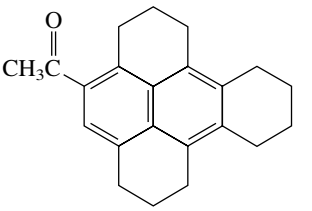
(d) 

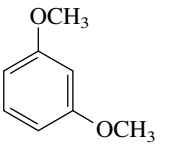
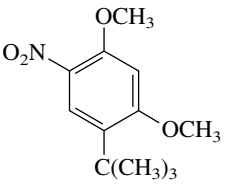
(e) 

12.34 Suggest a suitable series of reactions for carrying out each of the following synthetic transformations:

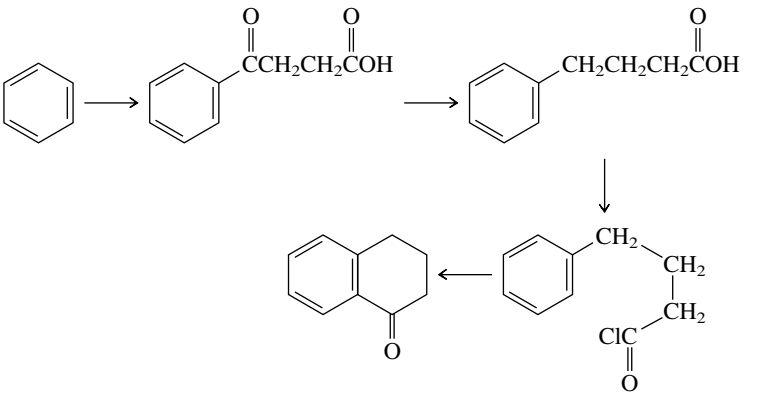
(a)  to 

(b)  to 

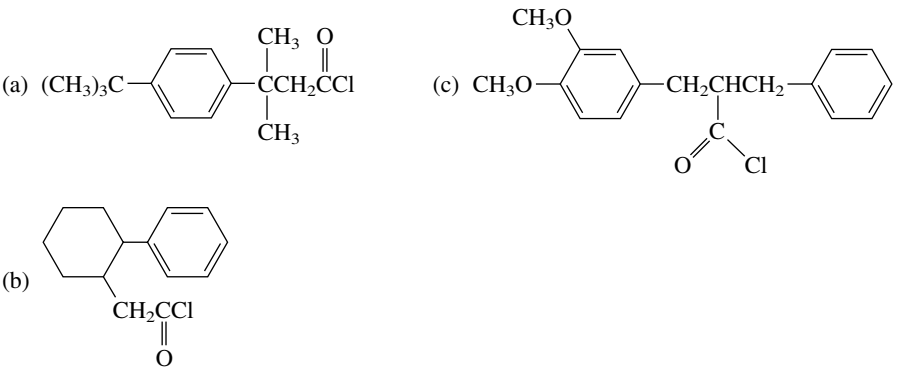
(c)  to 

(d)  to 

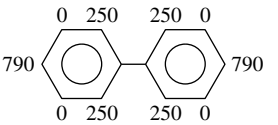
12.35 A standard synthetic sequence for building a six-membered cyclic ketone onto an existing aromatic ring is shown in outline as follows. Specify the reagents necessary for each step.



12.36 Each of the compounds indicated undergoes an intramolecular Friedel–Crafts acylation reaction to yield a cyclic ketone. Write the structure of the expected product in each case.



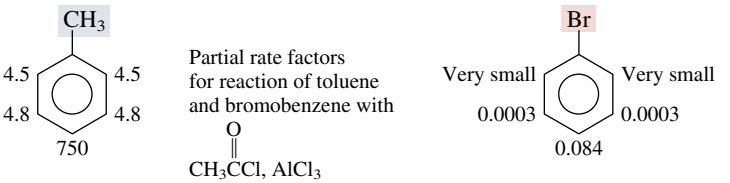
12.37 The partial rate factors for chlorination of biphenyl are as shown.



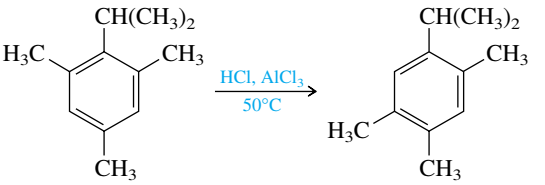
(a) What is the relative rate of chlorination of biphenyl compared with benzene?

(b) If, in a particular chlorination reaction, 10 g of *o*-chlorobiphenyl was formed, how much *p*-chlorobiphenyl would you expect to find?

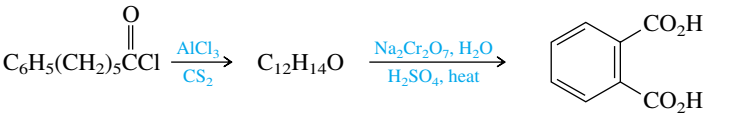
12.38 Partial rate factors may be used to estimate product distributions in disubstituted benzene derivatives. The reactivity of a particular position in *o*-bromotoluene, for example, is given by the product of the partial rate factors for the corresponding position in toluene and bromobenzene. On the basis of the partial rate factor data given here for Friedel–Crafts acylation, predict the major product of the reaction of *o*-bromotoluene with acetyl chloride and aluminum chloride.



12.39 When 2-isopropyl-1,3,5-trimethylbenzene is heated with aluminum chloride (trace of HCl present) at 50°C, the major material present after 4 h is 1-isopropyl-2,4,5-trimethylbenzene. Suggest a reasonable mechanism for this isomerization.



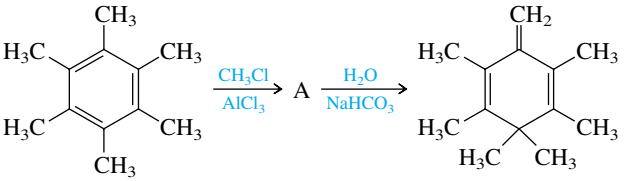
12.40 When a dilute solution of 6-phenylhexanoyl chloride in carbon disulfide was slowly added (over a period of 8 days!) to a suspension of aluminum chloride in the same solvent, it yielded a product A ($C_{12}H_{14}O$) in 67% yield. Oxidation of A gave benzene-1,2-dicarboxylic acid.



6-Phenylhexanoyl chloride | Compound A | Benzene-1,2-dicarboxylic acid

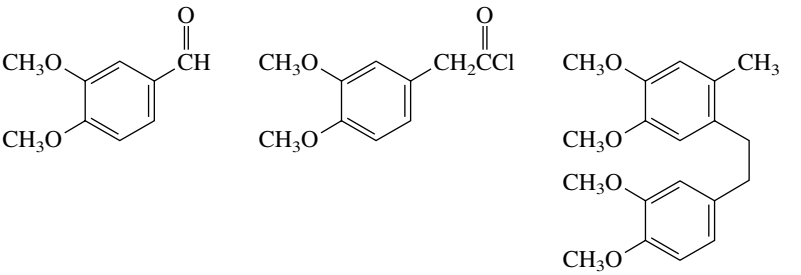
Formulate a reasonable structure for compound A.

12.41 Reaction of hexamethylbenzene with methyl chloride and aluminum chloride gave a salt A, which, on being treated with aqueous sodium bicarbonate solution, yielded compound B. Suggest a mechanism for the conversion of hexamethylbenzene to B by correctly inferring the structure of A.



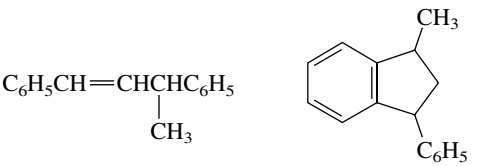
Hexamethylbenzene | Compound B

12.42 The synthesis of compound C was achieved by using compounds A and B as the sources of all carbon atoms. Suggest a synthetic sequence involving no more than three steps by which A and B may be converted to C.



Compound A | Compound B | Compound C

12.43 When styrene is refluxed with aqueous sulfuric acid, two "styrene dimers" are formed as the major products. One of these styrene dimers is 1,3-diphenyl-1-butene; the other is 1-methyl-3-phenylindan. Suggest a reasonable mechanism for the formation of each of these compounds.



1,3-Diphenyl-1-butene | 1-Methyl-3-phenylindan

12.44 Treatment of the alcohol whose structure is shown here with sulfuric acid gave as the major organic product a tricyclic hydrocarbon of molecular formula $C_{16}H_{16}$. Suggest a reasonable structure for this hydrocarbon.