CHAPTER

# 5

Alison Miksch/Jupiter Images

A fennel plant is an aromatic herb used in cooking. A phenyl group (pronounced exactly the same way) is the characteristic structural unit of "aromatic" organic compounds.

# Aromatic Compounds



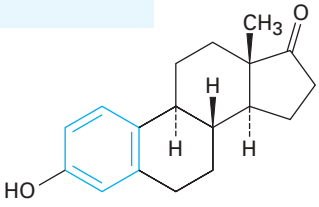
**In the early days of organic chemistry, the word *aromatic* was used to describe fragrant substances such as benzene (from coal distillate), benzaldehyde (from cherries, peaches, and almonds), and toluene (from tolu balsam).** It was soon realized, however, that substances classed as aromatic differed from most other organic compounds in their chemical behavior.

Today, the association of aromaticity with fragrance has long been lost, and we now use the word **aromatic** to refer to the class of compounds that contain six-membered benzene-like rings with three double bonds. Many valuable compounds are aromatic in part, such as the steroidal hormone estrone and the cholesterol-lowering drug atorvastatin, marketed as Lipitor. Benzene itself causes a depressed white blood cell count (leukopenia) on prolonged exposure and should not be used as a laboratory solvent.

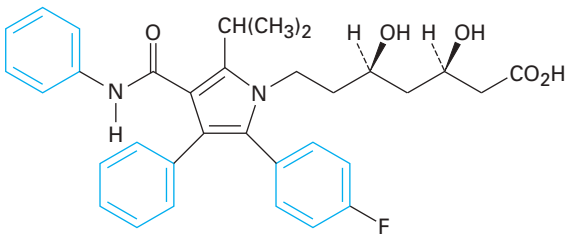
OWL

Online homework for this chapter can be assigned in OWL, an online homework assessment tool.

**Benzene**




**Estrone**



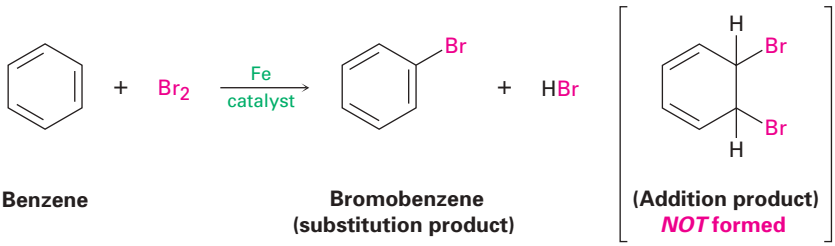

**Atorvastatin (Lipitor)**

## WHY THIS CHAPTER?

Aromatic rings are a common part of many organic structures and are particularly important in nucleic acid chemistry and in the chemistry of several amino acids. In this chapter, we'll find out how and why aromatic compounds are different from such apparently related compounds as alkenes.

# 5.1 Structure of Benzene

Benzene ($C_6H_6$) has eight fewer hydrogens than the corresponding six-carbon alkane ($C_6H_{14}$) and is clearly unsaturated, usually being represented as a six-membered ring with alternating double and single bond. Yet it has been known since the mid-1800s that benzene is much less reactive than typical alkenes and fails to undergo typical alkene addition reactions. Cyclohexene, for instance, reacts rapidly with $Br_2$ and gives the addition product 1,2-dibromocyclohexane, but benzene reacts only slowly with $Br_2$ and gives the *substitution* product $C_6H_5Br$.




Further evidence for the unusual nature of benzene is that all its carbon–carbon bonds have the same length—139 pm—intermediate between typical single (154 pm) and double (134 pm) bonds. In addition, the electron density in all six carbon–carbon bonds is identical, as shown by an electrostatic potential map (Figure 5.1a). Thus, benzene is a planar molecule with the shape of a regular hexagon. All C–C–C bond angles are 120°, all six carbon atoms are $sp^2$-hybridized, and each carbon has a $p$ orbital perpendicular to the plane of the six-membered ring.

Because all six carbon atoms and all six $p$ orbitals in benzene are equivalent, it's impossible to define three localized $\pi$ bonds in which a given $p$ orbital overlaps only one neighboring $p$ orbital. Rather, each $p$ orbital overlaps equally well with both neighboring $p$ orbitals, leading to a picture of benzene in which all six $\pi$ electrons are free to move about the entire ring (Figure 5.1b). In resonance terms (Sections 4.9 and 4.10), benzene is a hybrid of two equivalent forms. Neither form is correct by itself; the true structure of benzene is somewhere in between the two resonance forms but is impossible to draw with our usual conventions. Because of this resonance, benzene is more stable and less reactive than a typical alkene.

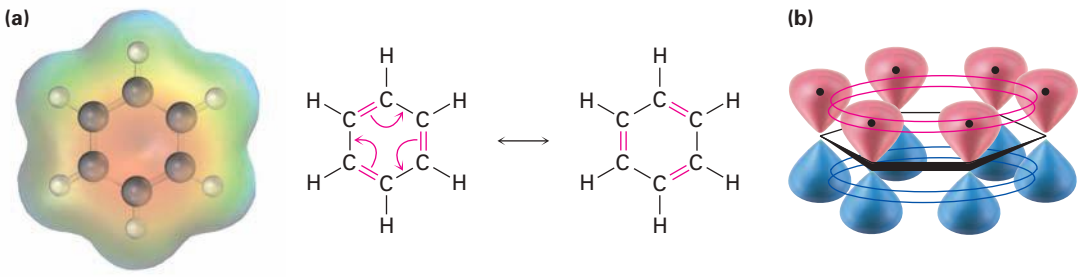
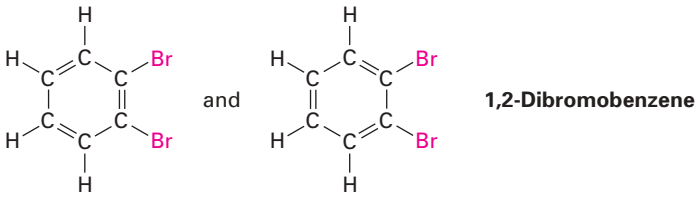



**Figure 5.1** **(a) An electrostatic potential map of benzene and (b) an orbital picture. Each of the six carbon atoms has a *p* orbital that can overlap equally well with neighboring *p* orbitals on both sides. The $\pi$ electrons are thus shared around the ring in two doughnut-shaped clouds, and all C–C bonds are equivalent.**

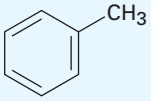
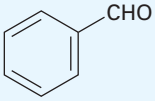
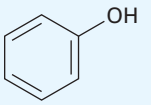
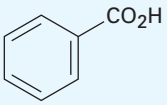
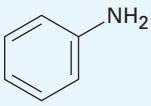
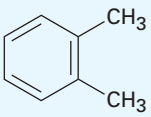
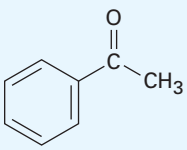
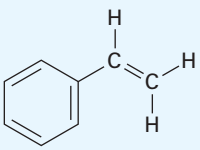
**Problem 5.1** Line-bond structures appear to imply that there are two different isomers of 1,2-dibromobenzene, one with the bromine-bearing carbon atoms joined by a double bond and one with the bromine-bearing carbons joined by a single bond. In fact, though, there is only one 1,2-dibromobenzene. Explain.




## 5.2 Naming Aromatic Compounds

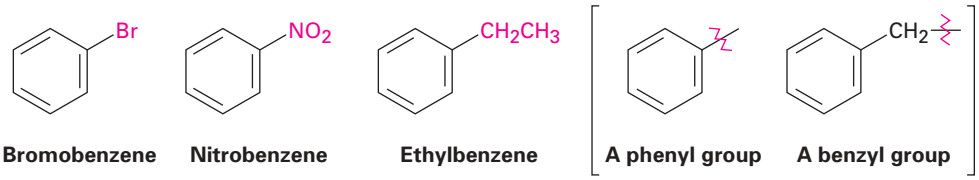
Aromatic substances, more than any other class of organic compounds, have acquired a large number of common names. IUPAC rules discourage the use of most such names but allow some of the more widely used ones to be retained (Table 5.1). Thus, methylbenzene is commonly known as *toluene,* hydroxybenzene as *phenol,* aminobenzene as *aniline,* and so on.

**Table 5.1 Common Names of Some Aromatic Compounds**

| Structure | Name | Structure | Name |
|---|---|---|---|
|  | Toluene (bp 111 °C) |  | Benzaldehyde (bp 178 °C) |
|  | Phenol (mp 43 °C) |  | Benzoic acid (mp 122 °C) |
|  | Aniline (bp 184 °C) |  | *ortho*-Xylene (bp 144 °C) |
|  | Acetophenone (mp 21 °C) |  | Styrene (bp 145 °C) |

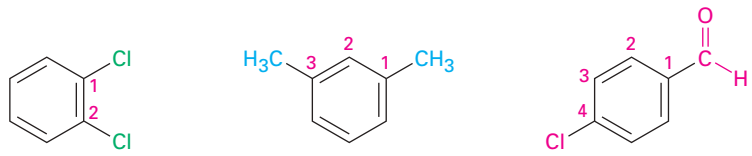
Monosubstituted benzenes are systematically named in the same manner as other hydrocarbons, with *-benzene* as the parent name. Thus, $C_6H_5Br$ is bromobenzene, $C_6H_5NO_2$ is nitrobenzene, and $C_6H_5CH_2CH_3$ is ethylbenzene. The name **phenyl**, pronounced **fen**-nil and sometimes abbreviated as Ph or Φ (Greek phi), is used for the $-C_6H_5$ unit when the benzene ring is considered as a substituent. In addition, a generalized aromatic substituent is called an

**aryl group**, abbreviated as Ar, and the name **benzyl** is used for the $C_6H_5CH_2$– group.




**Bromobenzene** **Nitrobenzene** **Ethylbenzene** **A phenyl group** **A benzyl group**

Disubstituted benzenes are named using one of the prefixes *ortho-* (*o*), *meta-* (*m*), or *para-* (*p*). An ortho-disubstituted benzene has its two substituents in a 1,2 relationship on the ring; a meta-disubstituted benzene has its two substituents in a 1,3 relationship; and a para-disubstituted benzene has its substituents in a 1,4 relationship.

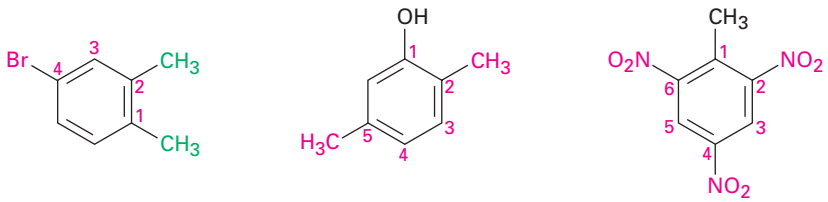



***ortho*-Dichlorobenzene**
**1,2 disubstituted**

***meta*-Dimethylbenzene**
**(*meta*-xylene)**
**1,3 disubstituted**

***para*-Chlorobenzaldehyde**
**1,4 disubstituted**

As with cycloalkanes (Section 2.7), benzenes with more than two substituents are named by choosing a point of attachment as carbon 1 and numbering the substituents on the ring so that the second substituent has as low a number as possible. The substituents are listed alphabetically when writing the name.



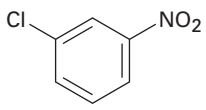

**4-Bromo-1,2-dimethylbenzene** **2,5-Dimethylphenol** **2,4,6-Trinitrotoluene (TNT)**

Note in the second and third examples shown that *-phenol* and *-toluene* are used as the parent names rather than *-benzene*. Any of the monosubstituted aromatic compounds shown in Table 5.1 can be used as a parent name, with the principal substituent (–OH in phenol or $-CH_3$ in toluene) considered as C1.

## Worked Example 5.1

### Naming an Aromatic Compound

What is the IUPAC name of the following compound?



**Solution** Because the nitro group ($-NO_2$) and chloro group are on carbons 1 and 3, they have a meta relationship. Citing the two substituents in alphabetical order gives the IUPAC name *m*-chloronitrobenzene.

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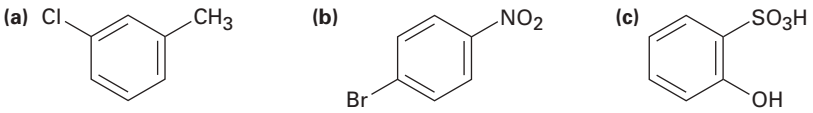
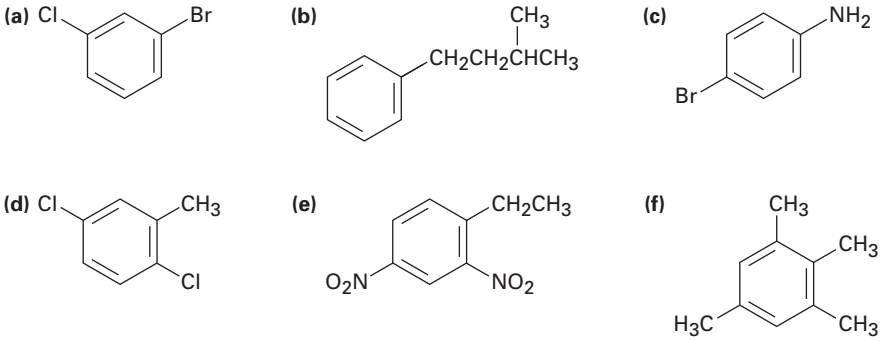
**Problem 5.2** Tell whether the following compounds are ortho, meta, or para disubstituted:




**Problem 5.3** Give IUPAC names for the following compounds:

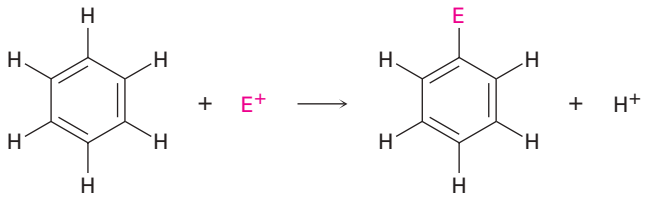



**Problem 5.4** Draw structures corresponding to the following IUPAC names:

**(a)** *p*-Bromochlorobenzene **(b)** *p*-Bromotoluene
**(c)** *m*-Chloroaniline **(d)** 1-Chloro-3,5-dimethylbenzene

## 5.3 Electrophilic Aromatic Substitution Reactions: Bromination

The most common reaction of aromatic compounds is **electrophilic aromatic substitution**, a process in which an electrophile ($E^+$) reacts with an aromatic ring and substitutes for one of the hydrogens.




Many different substituents can be introduced onto the aromatic ring by electrophilic substitution. To list some possibilities, an aromatic ring can be substituted by a halogen (–Cl, –Br, –I), a nitro group ($-NO_2$), a sulfonic acid group ($-SO_3H$), an alkyl group (–R), or an acyl group (–COR). Starting from

only a few simple materials, it's possible to prepare many thousands of substituted aromatic compounds (Figure 5.2).

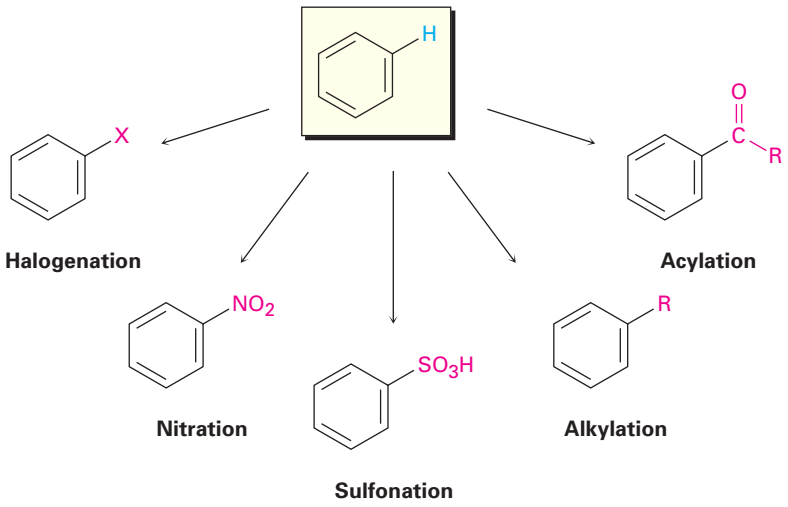
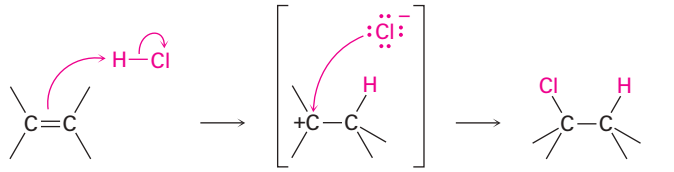
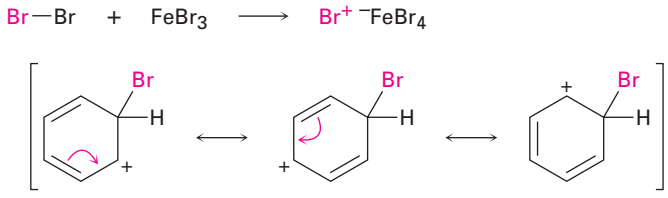



**Figure 5.2** Some electrophilic aromatic substitution reactions.

Before seeing how these electrophilic substitution reactions occur, let's briefly recall what was said in Sections 3.7 and 3.8 about electrophilic addition reactions of alkenes. When a reagent such as HCl adds to an alkene, the electrophilic $H^+$ approaches the $\pi$ electrons of the double bond and forms a bond to one carbon, leaving a positive charge at the other carbon. This carbocation intermediate then reacts with the nucleophilic $Cl^-$ ion to yield the addition product.




An electrophilic aromatic substitution reaction begins in a similar way, but there are a number of differences. One difference is that aromatic rings are less reactive toward electrophiles than alkenes are. For example, $Br_2$ in $CH_2Cl_2$ solution reacts instantly with most alkenes but does not react with benzene at room temperature. For bromination of benzene to take place, a catalyst such as $FeBr_3$ is needed. The catalyst makes the $Br_2$ molecule more electrophilic by reacting with it to give $FeBr_4^-$ and $Br^+$. The electrophilic $Br^+$ then reacts with the electron-rich (nucleophilic) benzene ring to yield a nonaromatic carbocation intermediate. This carbocation is doubly allylic (Section 4.9) and is a hybrid of three resonance forms.

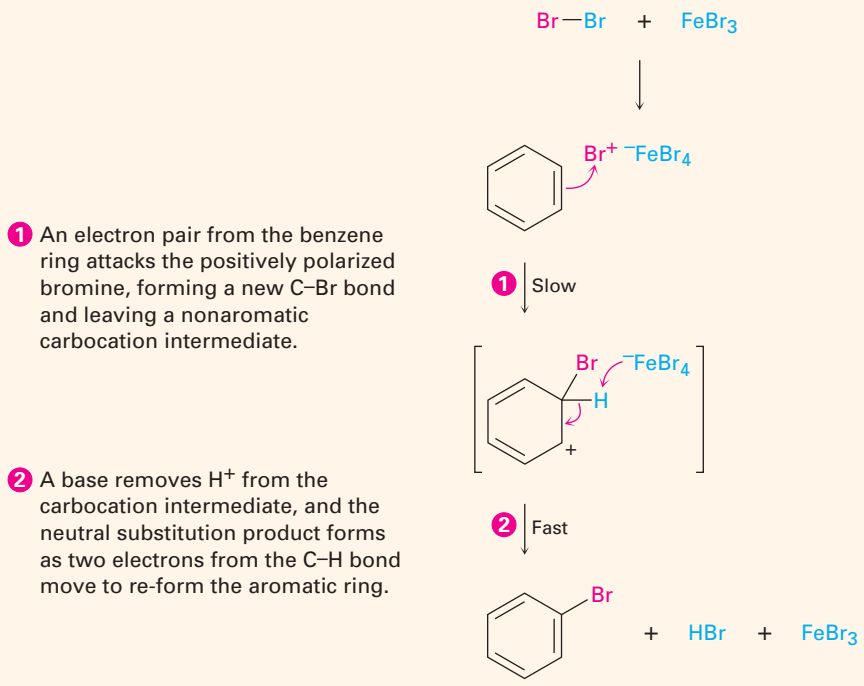


Although more stable than a typical nonallylic carbocation because of resonance, the intermediate in electrophilic aromatic substitution is much less stable than the starting benzene ring itself. Thus, reaction of an electrophile with a benzene ring has a relatively high activation energy and is rather slow.

Another difference between alkene addition reactions and aromatic substitution reactions occurs after the electrophile has added to the benzene ring and the carbocation intermediate has formed. Instead of adding $Br^-$ to give an addition product, the carbocation intermediate loses $H^+$ from the bromine-bearing carbon to give a substitution product. The net effect is the substitution of $H^+$ by $Br^+$ by the overall mechanism shown in Figure 5.3.

**MECHANISM**

**Figure 5.3** **The mechanism of the electrophilic bromination of benzene. The reaction occurs in two steps and involves a resonance-stabilized carbocation intermediate.**






Why does the reaction of $Br_2$ with benzene take a different course than its reaction with an alkene? The answer is straightforward: if *addition* occurred, the resonance stabilization of the aromatic ring would be lost and the overall reaction would be energetically unfavorable. When *substitution* occurs, though, the resonance stability of the aromatic ring is retained and

the reaction is favorable. An energy diagram for the overall process is shown in Figure 5.4.

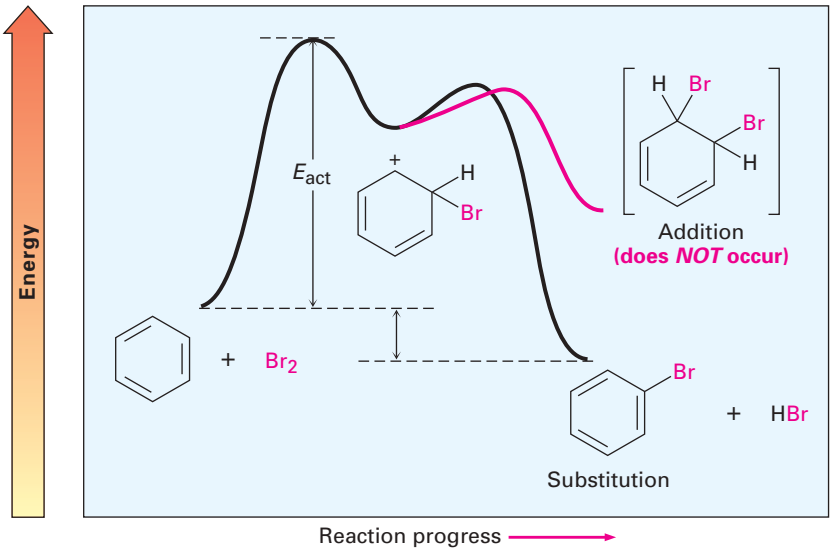



**Figure 5.4** An energy diagram for the electrophilic bromination of benzene. The reaction occurs in two steps and releases energy.

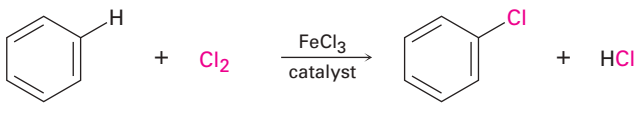
**Problem 5.5** There are three products that might form on reaction of toluene (methylbenzene) with $Br_2$. Draw and name them.

## 5.4 Other Electrophilic Aromatic Substitution Reactions

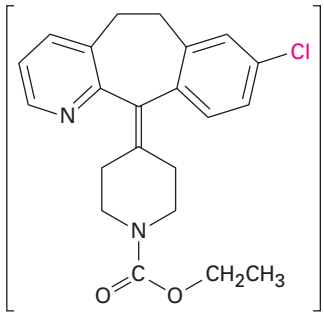
Many other electrophilic aromatic substitutions occur by the same general mechanism as bromination. Let's look at some briefly.

### Chlorination and Iodination

Aromatic rings react with $Cl_2$ in the presence of $FeCl_3$ catalyst to yield chlorobenzenes, just as they react with $Br_2$ and $FeBr_3$ to give bromobenzenes. This kind of reaction is used in the synthesis of numerous pharmaceutical agents, including the antiallergy medication loratadine, marketed as Claritin.



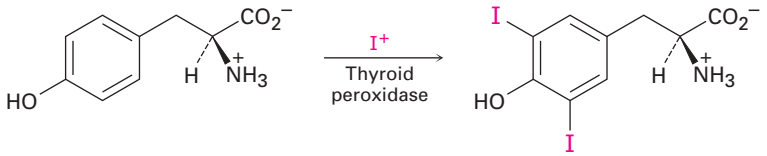

**Benzene** **Chlorobenzene (86%)**



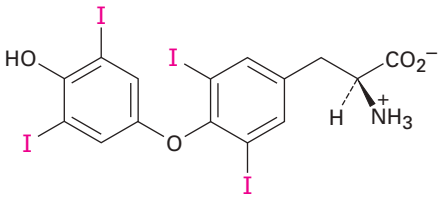

**Loratadine**

Electrophilic aromatic halogenations also occur in the biological synthesis of many naturally occurring molecules, particularly those produced by marine organisms. In humans, the best-known example occurs in the thyroid gland

during the biosynthesis of thyroxine, a thyroid hormone involved in regulating growth and metabolism. The amino acid tyrosine is first iodinated by thyroid peroxidase, and two of the iodinated tyrosine molecules then couple. The electrophilic iodinating agent is an $I^+$ species, perhaps hypoiodous acid (HIO), that is formed from iodide ion by oxidation with $H_2O_2$.




**Tyrosine** **3,5-Diiodotyrosine**

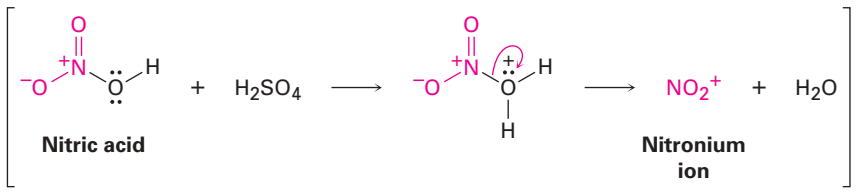



**Thyroxine**
**(a thyroid hormone)**

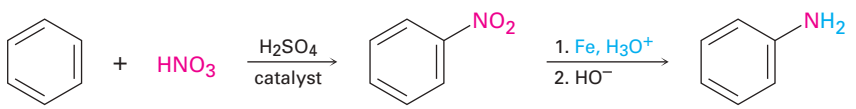
## Nitration

Aromatic rings are nitrated by reaction with a mixture of concentrated nitric and sulfuric acids. The electrophile is the nitronium ion, $NO_2^+$, which is formed from $HNO_3$ by protonation and loss of water and which reacts with benzene in much the same way $Br^+$ does.

Aromatic nitration does not occur in nature but is particularly important in the laboratory because the nitro-substituted product can be reduced by reagents such as iron, tin, or $SnCl_2$ to yield an amino-substituted product, or *arylamine,* $ArNH_2$. Attachment of an amino group to an aromatic ring by the two-step nitration/reduction sequence is a key part of the industrial synthesis of many dyes and pharmaceutical agents.



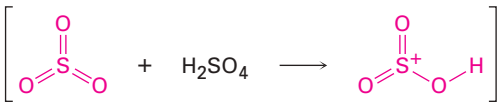

**Nitric acid** **Nitronium ion**

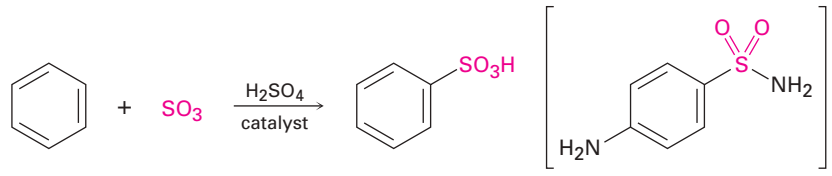



**Benzene** **Nitrobenzene** **Aniline (95%)**

## Sulfonation

Aromatic rings are sulfonated by reaction with so-called fuming sulfuric acid, a mixture of $SO_3$ and $H_2SO_4$. The reactive electrophile is $HSO_3^+$, and substitution occurs by the usual two-step mechanism seen for bromination. Aromatic sulfonation is a key step in the synthesis of such compounds as the sulfa drug family of antibiotics.






**Benzene** **Benzenesulfonic acid** **Sulfanilimide (a sulfa drug)**

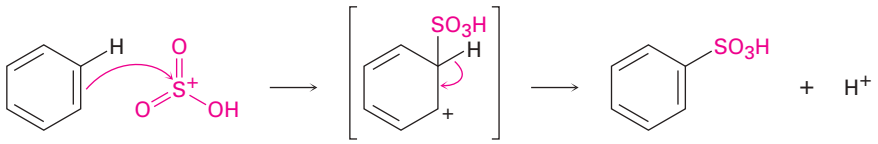
### Worked Example 5.2 Writing the Mechanism of an Electrophilic Aromatic Substitution Reaction

Show the mechanism of the reaction of benzene with fuming sulfuric acid to yield benzenesulfonic acid.

**Strategy**

The reaction of benzene with fuming sulfuric acid to yield benzenesulfonic acid is a typical electrophilic aromatic substitution reaction, which occurs by the usual two-step mechanism. An electrophile first adds to the aromatic ring, and $H^+$ is then lost. In sulfonation reactions, the electrophile is $HSO_3^+$.

**Solution**




**Carbocation intermediate**

---

**Problem 5.6** Show the mechanism of the reaction of benzene with nitric acid and sulfuric acid to yield nitrobenzene.

**Problem 5.7** Chlorination of *o*-xylene (*o*-dimethylbenzene) yields a mixture of two products, but chlorination of *p*-xylene yields a single product. Explain.

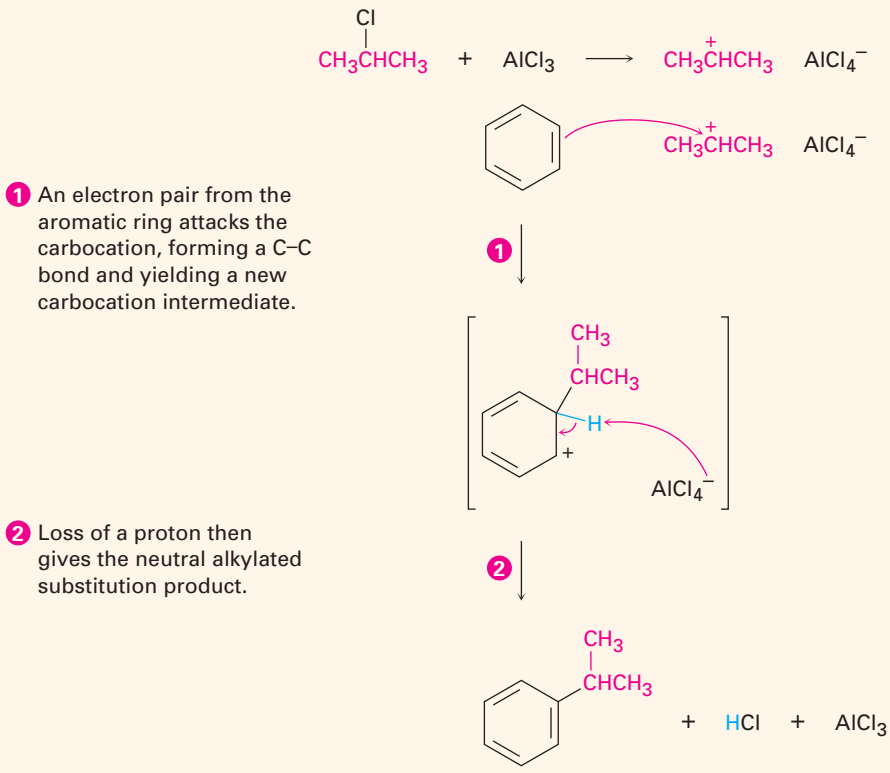
**Problem 5.8** How many products might be formed on chlorination of *m*-xylene?

# 5.5 The Friedel–Crafts Alkylation and Acylation Reactions

One of the most useful electrophilic aromatic substitution reactions is *alkylation*—the introduction of an alkyl group onto the benzene ring. Called the **Friedel–Crafts alkylation reaction** after its discoverers, the reaction is carried out by treating the aromatic compound with an alkyl chloride, RCl, in the presence of $AlCl_3$ to generate a carbocation electrophile, $R^+$. Aluminum chloride catalyzes the reaction by helping the alkyl halide to dissociate in much the same way that $FeBr_3$ catalyzes aromatic brominations by helping $Br_2$ dissociate (Section 5.3). Loss of $H^+$ then completes the reaction (Figure 5.5).

## MECHANISM

**Figure 5.5** Mechanism of the Friedel–Crafts alkylation reaction. The electrophile is a carbocation, generated by $AlCl_3$-assisted ionization of an alkyl chloride.

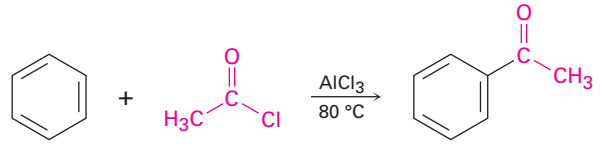





Despite its utility, the Friedel–Crafts alkylation reaction has several limitations. For one, only *alkyl* halides can be used. Aromatic (aryl) halides such as chlorobenzene don't react. In addition, Friedel–Crafts reactions don't succeed on aromatic rings that are already substituted by the groups $-NO_2$, $-C{\equiv}N$, $-SO_3H$, or $-COR$. Such aromatic rings are much less reactive than benzene for reasons we'll discuss in the next two sections.

Closely related to the Friedel–Crafts alkylation reaction is the **Friedel–Crafts acylation reaction**. When an aromatic compound is treated with a

carboxylic acid chloride (RCOCl) in the presence of $AlCl_3$, an **acyl** (**a**-sil) **group** (R—C═O) is introduced onto the ring. For example, reaction of benzene with acetyl chloride yields the ketone acetophenone.




**Benzene** **Acetyl chloride** **Acetophenone (95%)**

**Problem 5.9** What products would you expect to obtain from the reaction of the following compounds with chloroethane and $AlCl_3$?

**(a)** Benzene **(b)** *p*-Xylene

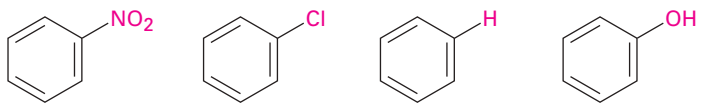
**Problem 5.10** What products would you expect to obtain from the reaction of benzene with the following reagents?

**(a)** $(CH_3)_3CCl$, $AlCl_3$ **(b)** $CH_3CH_2COCl$, $AlCl_3$

## 5.6 Substituent Effects in Electrophilic Aromatic Substitution

Only one product can form when an electrophilic substitution occurs on benzene, but what would happen if we were to carry out an electrophilic substitution on a ring that already has a substituent? A substituent already present on the ring has two effects:

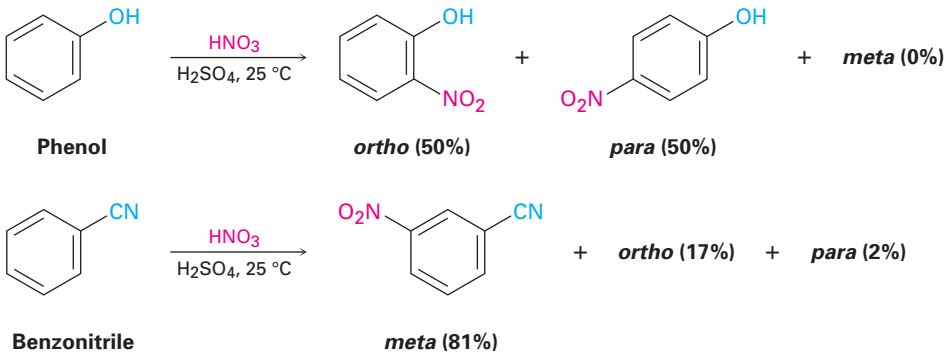
- **Substituents affect the *reactivity* of an aromatic ring**. Some substituents activate a ring, making it more reactive than benzene, and some deactivate a ring, making it less reactive than benzene. In aromatic nitration, for instance, the presence of an –OH substituent makes the ring 1000 times more reactive than benzene, while an $-NO_2$ substituent makes the ring more than 10 million times less reactive.




| | | | | |
|---|---|---|---|---|
| Relative rate of nitration | $6 \times 10^{-8}$ | 0.033 | 1 | 1000 |


- **Substituents affect the *orientation* of a reaction**. The three possible disubstituted products—ortho, meta, and para—are usually not formed in equal amounts. Instead, the nature of the substituent already present on the ring determines the position of the second substitution. An –OH group directs further substitution toward the ortho

and para positions, for instance, while a –CN directs further substitution primarily toward the meta position.




Substituents can be classified into three groups, as shown in Figure 5.6: *meta-directing deactivators, ortho- and para-directing deactivators,* and *ortho- and para-directing activators.* There are no meta-directing activators. Note how the directing effect of a group correlates with its reactivity. All meta-directing groups are deactivating, and all ortho- and para-directing groups other than halogen are activating. The halogens are unique in being ortho- and para-directing but deactivating.

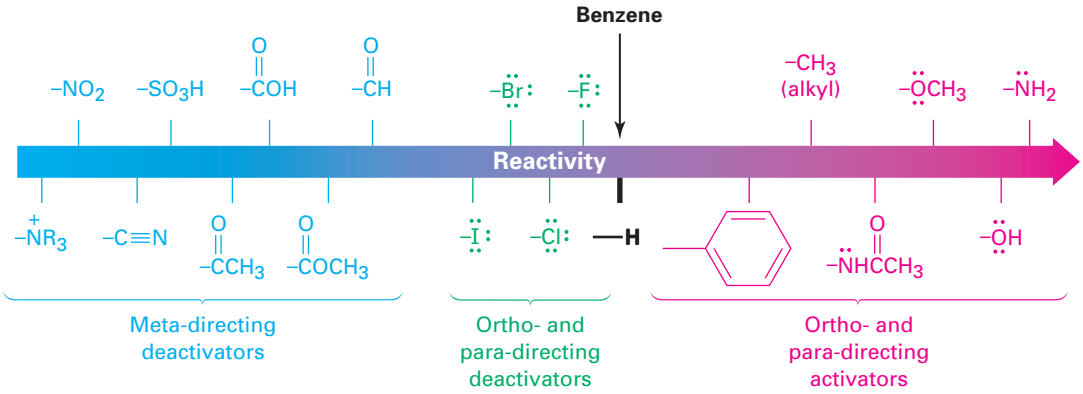



**Figure 5.6** Substituent effects in electrophilic aromatic substitutions. All activating groups are ortho- and para-directing, and all deactivating groups other than halogen are meta-directing. The halogens are unique in being deactivating but ortho- and para-directing.

## Worked Example 5.3

### Predicting Relative Reactivity in Electrophilic Aromatic Substitution Reactions

Which would you expect to react faster in an electrophilic aromatic substitution reaction, chlorobenzene or ethylbenzene? Explain.

**Strategy** Look at Figure 5.6, and compare the relative reactivities of chloro and alkyl groups.

**Solution** A chloro substituent is deactivating, whereas an alkyl group is activating. Thus, ethylbenzene is more reactive than chlorobenzene.

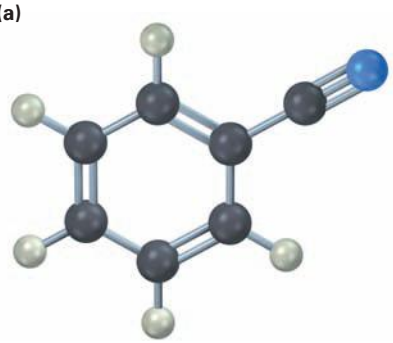
---

**Problem 5.11** Use Figure 5.6 to rank the compounds in each of the following groups in order of their reactivity toward electrophilic aromatic substitution:

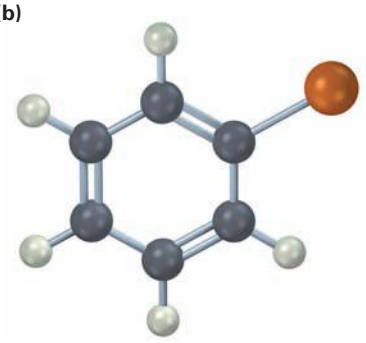
**(a)** Nitrobenzene, phenol (hydroxybenzene), toluene
**(b)** Phenol, benzene, chlorobenzene, benzoic acid
**(c)** Benzene, bromobenzene, benzaldehyde, aniline (aminobenzene)

**Problem 5.12** Draw and name the products you would expect to obtain by reaction of the following substances with $Cl_2$ and $FeCl_3$ (blue = N, reddish brown = Br):

(a)



(b)



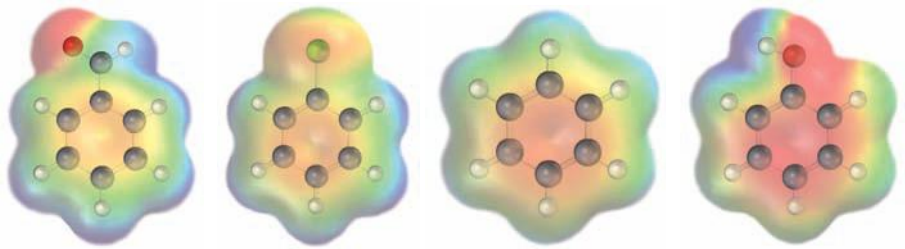
## 5.7 An Explanation of Substituent Effects

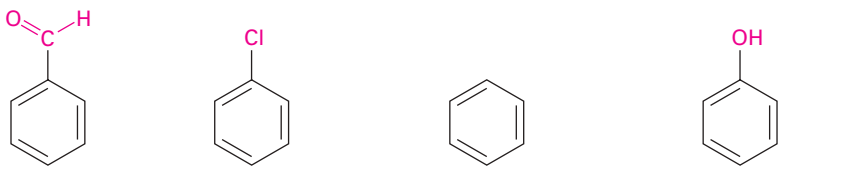
We saw in the previous section that substituents affect both the reactivity of an aromatic ring and the orientation of further aromatic substitutions. Let's look at the effects separately.

### Activating and Deactivating Effects in Aromatic Rings

What makes a group either activating or deactivating? The common characteristic of all activating groups is that they *donate* electrons to the ring, thereby making the ring more electron-rich, stabilizing the carbocation intermediate, and lowering the activation energy for its formation. Conversely, the common characteristic of all deactivating groups is that they *withdraw* electrons from the ring, thereby making the ring more electron-poor, destabilizing the carbocation intermediate, and raising the activation energy for its formation.

Compare the electrostatic potential maps of benzaldehyde (deactivated), chlorobenzene (weakly deactivated), and phenol (activated) with that of benzene. The ring is more positive (yellow) when an electron-withdrawing group such as –CHO or –Cl is present and more negative (red) when an electron-donating group such as –OH is present.






**Benzaldehyde** **Chlorobenzene** **Benzene** **Phenol**

Electron donation or withdrawal may occur by either an inductive effect (Section 1.9) or a resonance effect (Section 4.10). An inductive effect is the withdrawal

or donation of electrons through a $\sigma$ bond due to an electronegativity difference between the ring and the attached substituent atom, while a resonance effect is the withdrawal or donation of electrons through a $\pi$ bond due to the overlap of a $p$ orbital on the substituent with a $p$ orbital on the aromatic ring.

## Orienting Effects in Aromatic Rings: Ortho and Para Directors

Let's look at the nitration of phenol as an example of how ortho- and para-directing substituents work. In the first step, reaction with the electrophilic nitronium ion ($NO_2^+$) can occur either ortho, meta, or para to the –OH group, giving the carbocation intermediates shown in Figure 5.7. The ortho and para intermediates are more stable than the meta intermediate because they have more resonance forms—four rather than three—including a particularly favorable one that allows the positive charge to be stabilized by electron donation from the substituent oxygen atom. Because the ortho and para intermediates are more stable than the meta intermediate, they are formed faster.

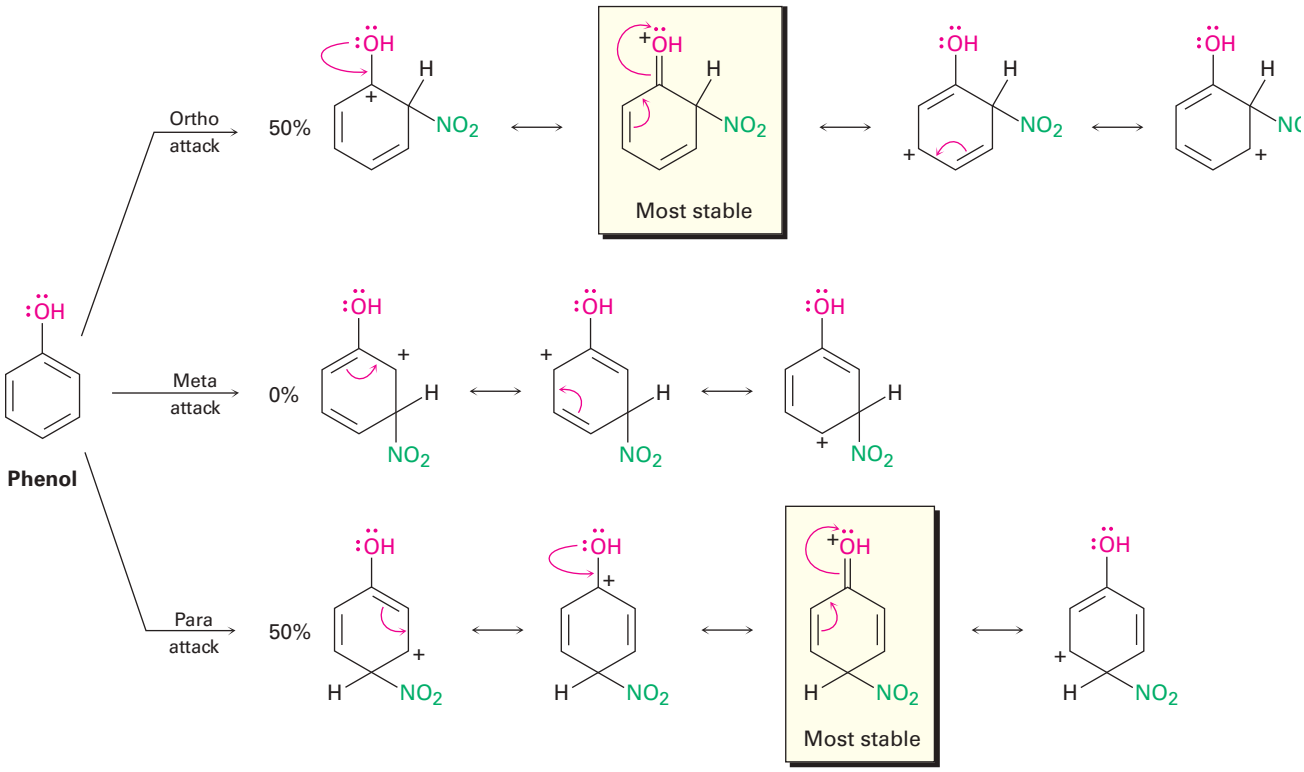
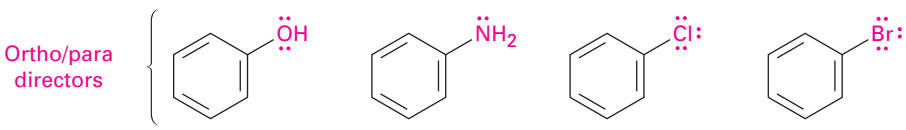



**Figure 5.7** Carbocation intermediates in the nitration of phenol. The ortho and para intermediates are more stable than the meta intermediate because they have more resonance forms, including a particularly favorable one that involves electron donation from the oxygen atom.

In general, any substituent that has a lone pair of electrons on the atom directly bonded to the aromatic ring allows an electron-donating resonance interaction to occur and thus acts as an ortho and para director.



## Orienting Effects in Aromatic Rings: Meta Directors

The influence of meta-directing substituents can be explained using the same kinds of arguments used for ortho and para directors. Look at the chlorination of benzaldehyde, for instance (Figure 5.8). Of the three possible carbocation intermediates, the meta intermediate has three favorable resonance forms, while the ortho and para intermediates have only two. In both ortho and para intermediates, the third resonance form is particularly unfavorable because it places the positive charge directly on the carbon that bears the aldehyde group, where it is disfavored by a repulsive interaction with the positively polarized carbon atom of the C=O group. Hence, the meta intermediate is more favored and is formed faster than the ortho and para intermediates.

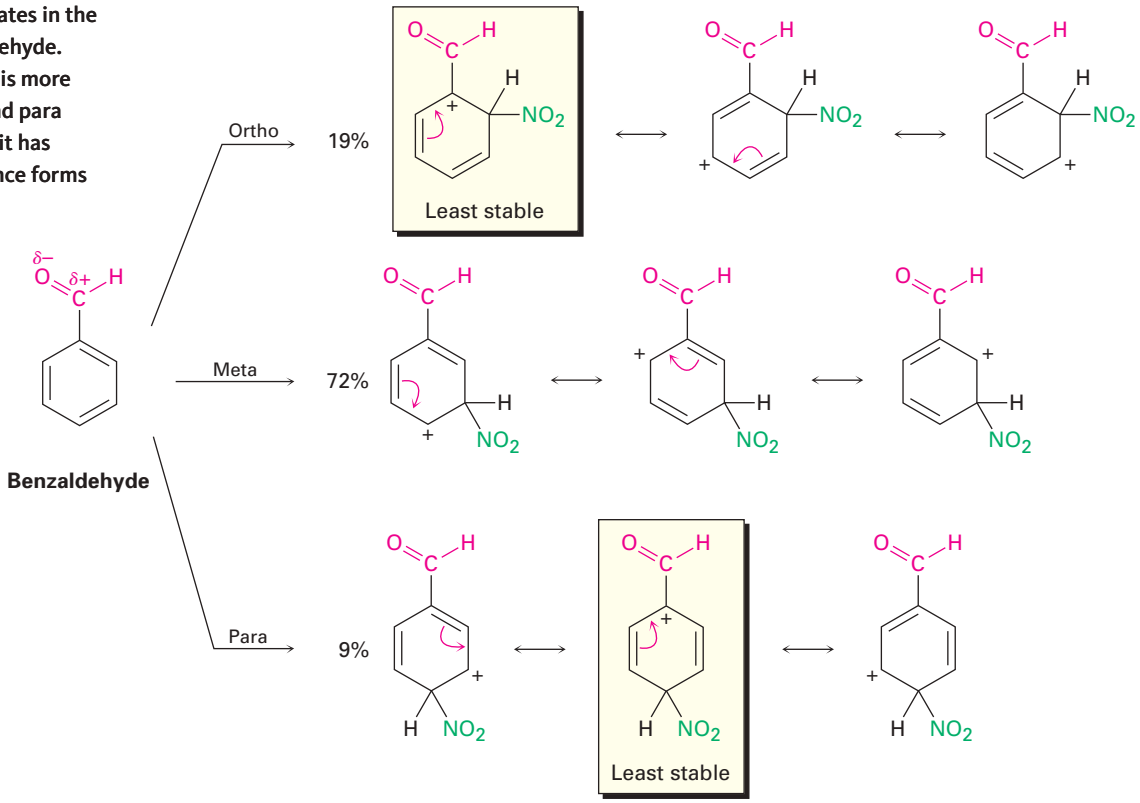
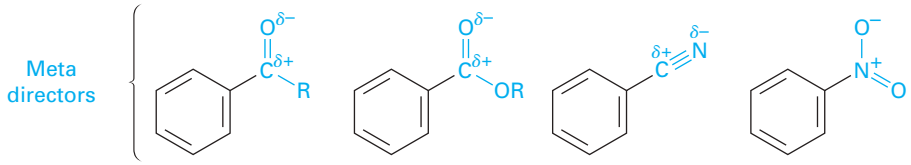



**Figure 5.8** Intermediates in the chlorination of benzaldehyde. The meta intermediate is more favorable than ortho and para intermediates because it has three favorable resonance forms rather than two.

In general, any substituent that has a positively polarized atom ($\delta+$) directly attached to the ring makes one of the resonance forms of the ortho and para intermediates unfavorable, and thus acts as a meta director.



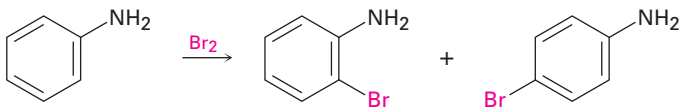
**Worked Example 5.4** **Predicting the Product of an Electrophilic Aromatic Substitution Reaction**

What product(s) would you expect from bromination of aniline, $C_6H_5NH_2$?

**Strategy**

Look at Figure 5.6 to see whether the $-NH_2$ substituent is ortho- and para-directing or meta-directing. Because an amino group has a lone pair of electrons on the nitrogen atom, it is ortho- and para-directing and we expect to obtain a mixture of *o*-bromoaniline and *p*-bromoaniline.

**Solution**




**Aniline** ***o*-Bromoaniline** ***p*-Bromoaniline**

---

**Problem 5.13** What product(s) would you expect from sulfonation of the following compounds?

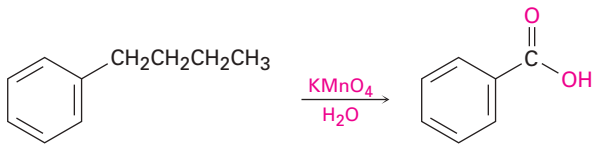
**(a)** Nitrobenzene **(b)** Bromobenzene **(c)** Toluene
**(d)** Benzoic acid **(e)** Benzonitrile

**Problem 5.14** Draw resonance structures of the three possible carbocation intermediates to show how a methoxyl group ($-OCH_3$) directs bromination toward ortho and para positions.

**Problem 5.15** Draw resonance structures of the three possible carbocation intermediates to show how an acetyl group, $CH_3C{=}O$, directs bromination toward the meta position.

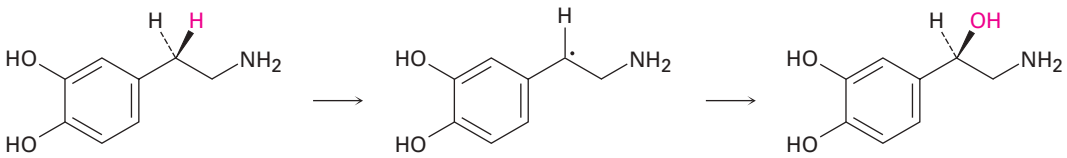
## 5.8 Oxidation and Reduction of Aromatic Compounds

Despite its unsaturation, a benzene ring does not usually react with strong oxidizing agents such as $KMnO_4$. (Recall from Section 4.6 that $KMnO_4$ cleaves alkene C=C bonds.) Alkyl groups attached to the aromatic ring are readily attacked by oxidizing agents, however, and are converted into carboxyl groups ($-CO_2H$). For example, butylbenzene is oxidized by $KMnO_4$ to give benzoic acid. The mechanism of this reaction is complex and involves attack on the side-chain C–H bonds at the position next to the aromatic ring (the **benzylic position**) to give radical intermediates.



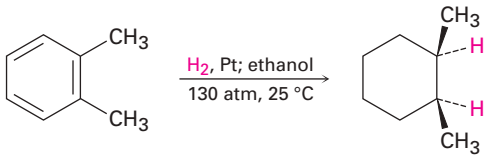

**Butylbenzene** **Benzoic acid (85%)**

Analogous oxidations occur in various biological pathways. The neurotransmitter norepinephrine, for instance, is biosynthesized from dopamine by a benzylic hydroxylation reaction. The process is catalyzed by the copper-containing enzyme dopamine $\beta$-monooxygenase and occurs by a radical mechanism.



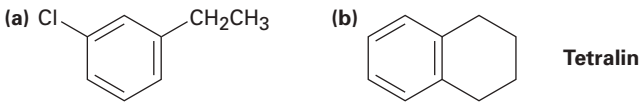

**Dopamine** **Norepinephrine**

Just as aromatic rings are usually inert to oxidation, they are also inert to reduction under typical alkene hydrogenation conditions. Only if high temperatures and pressures are used does reduction of an aromatic ring occur. For example, *o*-dimethylbenzene (*o*-xylene) gives *cis*-1,2-dimethylcyclohexane if reduced at high pressure.




***o*-Xylene** ***cis*-1,2-Dimethylcyclohexane**

**Problem 5.16** What aromatic products would you expect to obtain from oxidation of the following substances with $KMnO_4$?



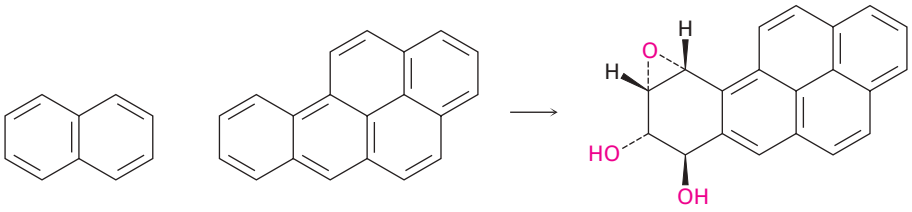

**Tetralin**

## 5.9 Other Aromatic Compounds

The concept of aromaticity—the unusual chemical stability present in cyclic conjugated molecules like benzene—can be extended beyond simple monocyclic hydrocarbons. Naphthalene, for instance, a substance familiar for its use in mothballs, has two benzene-like rings fused together and is thus a **polycyclic aromatic compound**.

Perhaps the most notorious polycyclic aromatic hydrocarbon is benzo[*a*]pyrene, which has five benzene-like rings and is a major carcinogenic (cancer-causing) substance found in chimney soot, cigarette smoke, and well-done barbecued meat. Once in the body, benzo[*a*]pyrene is

metabolically converted into a diol epoxide that binds to DNA, where it induces mutations.




**Naphthalene** **Benzo[*a*]pyrene** **A diol epoxide**

In addition to monocyclic and polycyclic aromatic hydrocarbons, some aromatic compounds are **heterocycles**—cyclic compounds that contain atoms of two or more elements in their rings. Nitrogen, sulfur, and oxygen atoms are all found along with carbon in various aromatic compounds. We'll see in Chapter 12, for instance, that the nitrogen-containing heterocycles pyridine, pyrimidine, pyrrole, and imidazole are aromatic, even though they aren't hydrocarbons and even though two of them have five-membered rather than six-membered rings (Figure 5.9). They are aromatic because they all, like benzene, contain a cyclic conjugated array of six $\pi$ electrons. Pyridine and pyrimidine have one $\pi$ electron on each of their six ring atoms. Pyrrole and imidazole have one $\pi$ electron on each of four ring atoms and an additional two $\pi$ electrons (the lone pair) on their N–H nitrogen.

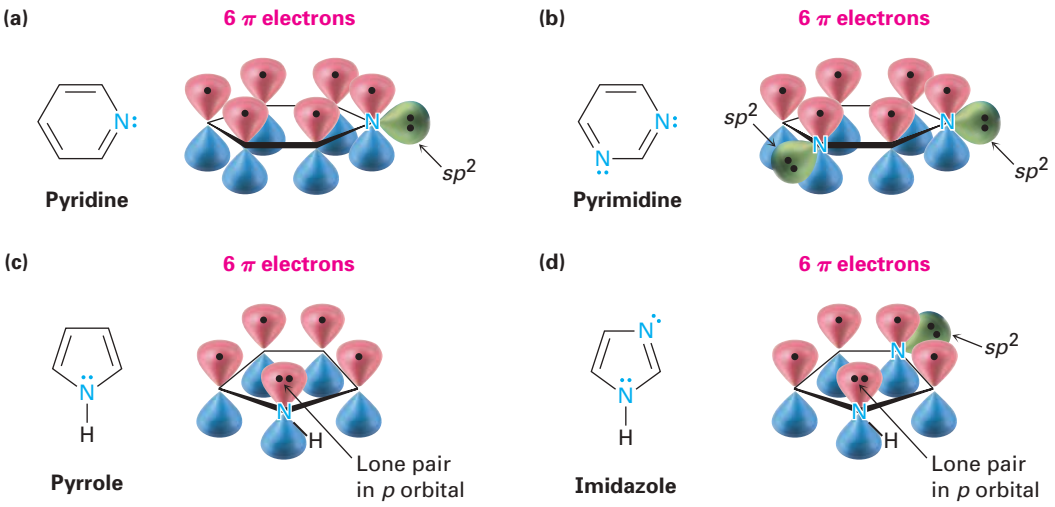
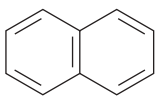



**Figure 5.9** Orbital views of the nitrogen-containing compounds **(a)** pyridine, **(b)** pyrimidine, **(c)** pyrrole, and **(d)** imidazole. All are aromatic because, like benzene, they contain a cyclic conjugated system of six $\pi$ electrons. Pyridine and pyrimidine have one $\pi$ electron on each of their six ring atoms. Pyrrole and imidazole have one $\pi$ electron on each of four ring atoms and an additional two $\pi$ electrons (the lone pair) on their N–H nitrogen.

**Problem 5.17** There are three resonance structures of naphthalene, of which only one is shown. Draw the other two.



**Naphthalene**

## 5.10 Organic Synthesis

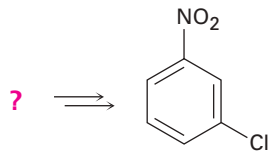
The laboratory synthesis of organic molecules from simple precursors might be carried out for many reasons. In the pharmaceutical industry, new organic molecules are often designed and synthesized for evaluation as medicines. In the chemical industry, syntheses are often undertaken to devise more economical routes to known compounds. In this book, too, we'll sometimes devise syntheses of complex molecules from simpler precursors, but the purpose here is simply to help you learn organic chemistry. Devising a route for the synthesis of an organic molecule requires that you approach chemical problems in a logical way, draw on your knowledge of organic reactivity, and organize that knowledge into a workable plan.

The only trick to devising an organic synthesis is to *work backward*. Look at the product and ask yourself, "What is the immediate precursor of that product?" Having found an immediate precursor, work backward again, one step at a time, until a suitable starting material is found. Let's try some examples.

### Worked Example 5.5 Synthesizing a Substituted Aromatic Compound

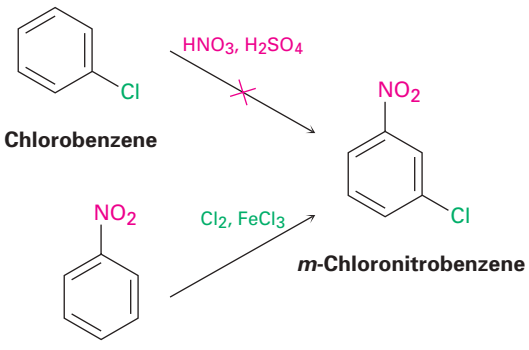
Synthesize *m*-chloronitrobenzene starting from benzene.

**Strategy** Work backward by first asking, "What is an immediate precursor of *m*-chloronitrobenzene?"




***m*-Chloronitrobenzene**

There are two substituents on the ring, a –Cl group, which is ortho- and para-directing, and an $-NO_2$ group, which is meta-directing. We can't nitrate chlorobenzene because the wrong isomers (*o*- and *p*-chloronitrobenzenes) would result, but chlorination of nitrobenzene should give the desired product.

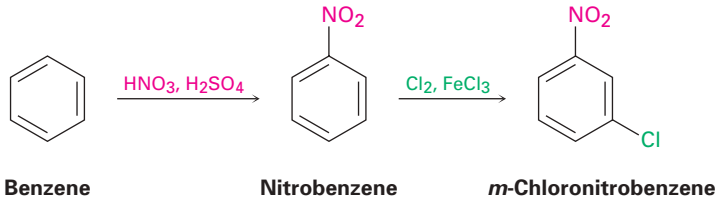



**Chlorobenzene** **m-Chloronitrobenzene**

**Nitrobenzene**

"What is an immediate precursor of nitrobenzene?" Benzene, which can be nitrated.

**Solution** We've solved the problem in two steps:

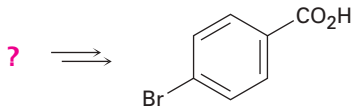



**Benzene** **Nitrobenzene** ***m*-Chloronitrobenzene**

## Worked Example 5.6 Synthesizing a Substituted Aromatic Compound

Synthesize *p*-bromobenzoic acid starting from benzene.

**Strategy** Work backward by first asking, "What is an immediate precursor of *p*-bromobenzoic acid?"

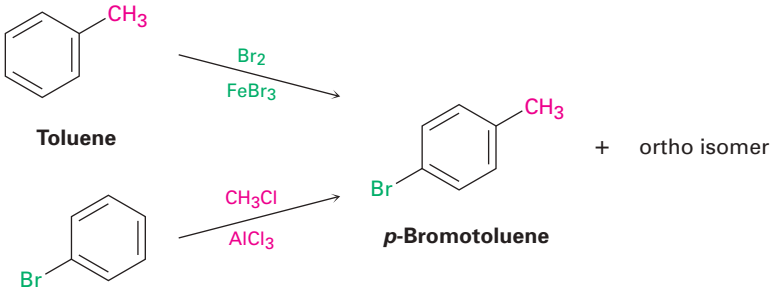



***p*-Bromobenzoic acid**

There are two substituents on the ring, a $-CO_2H$ group, which is meta-directing, and a –Br atom, which is ortho- and para-directing. We can't brominate benzoic acid because the wrong isomer (*m*-bromobenzoic acid) would be formed. We've seen, however, that oxidation of alkylbenzene side chains yields benzoic acids. An immediate precursor of our target molecule might therefore be *p*-bromotoluene.


***p*-Bromotoluene** ***p*-Bromobenzoic acid**

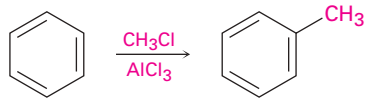
"What is an immediate precursor of *p*-bromotoluene?" Perhaps toluene, because the methyl group would direct bromination to the ortho and para positions, and we could then separate isomers. Alternatively, bromobenzene might be an immediate precursor because we could carry out a Friedel–Crafts alkylation and obtain the para product. Both methods are satisfactory.




**Toluene** ***p*-Bromotoluene**

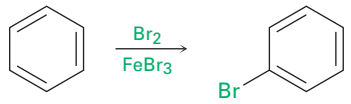
**Bromobenzene**

"What is an immediate precursor of toluene?" Benzene, which can be methylated in a Friedel–Crafts reaction.



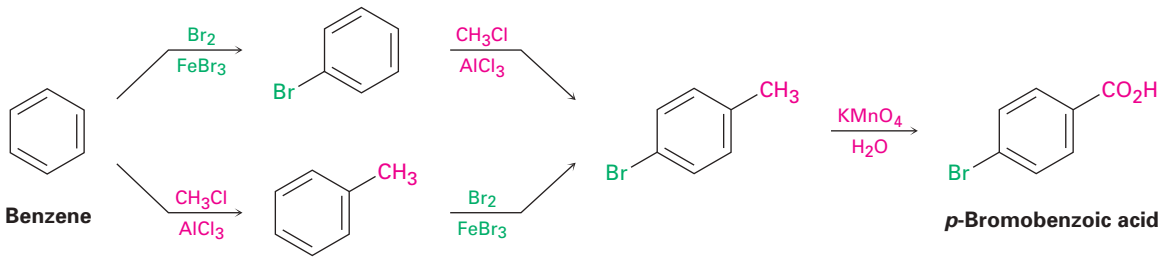

**Benzene** **Toluene**

"Alternatively, what is an immediate precursor of bromobenzene?" Benzene, which can be brominated.




**Benzene** **Bromobenzene**

**Solution** Our backward synthetic (*retrosynthetic*) analysis has provided two workable routes from benzene to *p*-bromobenzoic acid.

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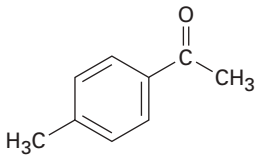
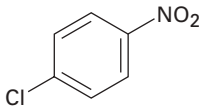
**Problem 5.18** Propose syntheses of the following substances starting from benzene:

**(a)**



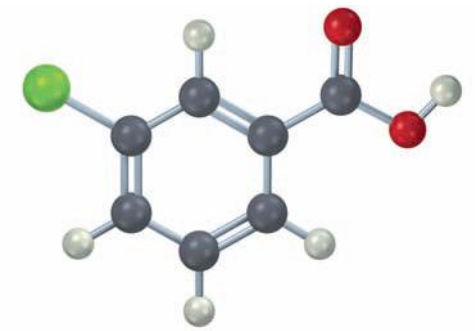

**(b)**




**Problem 5.19** Synthesize the following substances from benzene:

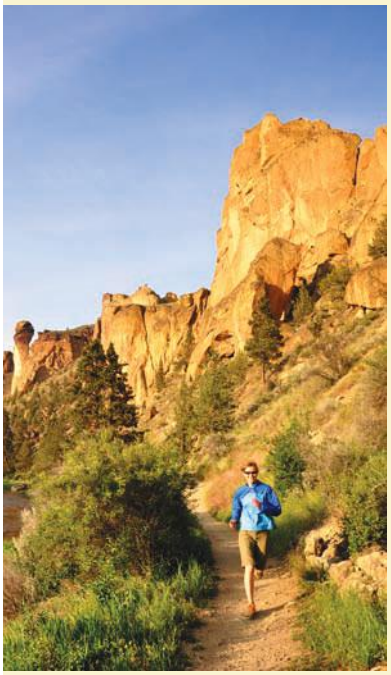
**(a)** *o*-Bromotoluene **(b)** 2-Bromo-1,4-dimethylbenzene

**Problem 5.20** How would you prepare the following substance from benzene? (Yellow-green = Cl.)



INTERLUDE

# Aspirin, NSAIDs, and COX-2 Inhibitors





**Long-distance runners sometimes call ibuprofen "the fifth basic food group" because of its ability to control aches and pains.**

Whatever the cause—tennis elbow, a sprained ankle, or a wrenched knee—pain and inflammation seem to go together. They are, however, different in their origin, and powerful drugs are available for treating each separately. Codeine, for example, is a powerful *analgesic,* or pain reliever, used in the management of debilitating pain, while cortisone and related steroids are potent *anti-inflammatory* agents, used for treating arthritis and other crippling inflammations. For minor pains and inflammation, both problems are often treated at the same time by using a common, over-the-counter medication called an *NSAID,* or nonsteroidal anti-inflammatory drug.

The most common NSAID is aspirin, or acetylsalicylic acid, whose use goes back to the late 1800s. It had been known from before the time of Hippocrates in 400 BC that fevers could be lowered by chewing the bark of willow trees. The active agent in willow bark was found in 1827 to be an aromatic compound called *salicin,* which could be converted by reaction with water into salicyl alcohol and then oxidized to give salicylic acid. Salicylic acid turned out to be even more effective than salicin for reducing fever and to have analgesic and anti-inflammatory action as well. Unfortunately, it also turned out to be too corrosive to the walls of the stomach for everyday use. Conversion of the phenol –OH group into an acetate ester, however, yielded acetylsalicylic acid, which proved just as potent as salicylic acid but less corrosive to the stomach.


**Salicyl alcohol** **Salicylic acid** **Acetylsalicylic acid (aspirin)**

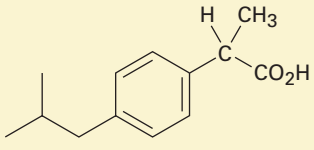
Although extraordinary in its powers, aspirin is also more dangerous than commonly believed. A dose of only about 15 g can be fatal to a small child, and aspirin can cause stomach bleeding and allergic reactions in long-term users. Even more serious is a condition called *Reye's syndrome,* a potentially fatal reaction to aspirin sometimes seen in children recovering from the flu. As a result of these problems, numerous other NSAIDs have been developed in the last several decades, most notably ibuprofen and naproxen.

Like aspirin, both ibuprofen and naproxen are relatively simple aromatic compounds containing a side-chain carboxylic acid group. Ibuprofen, sold under the names Advil, Nuprin, Motrin, and others, has

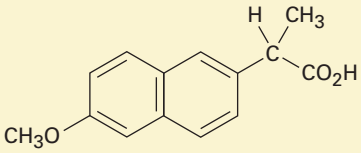
continued

INTERLUDE

roughly the same potency as aspirin but is less prone to cause stomach upset. Naproxen, sold under the names Aleve and Naprosyn, also has about the same potency as aspirin but remains active in the body six times longer.



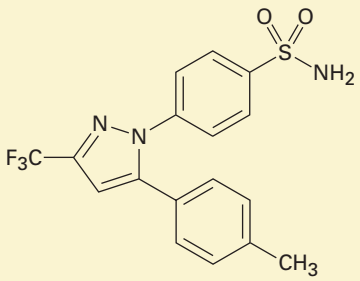

**Ibuprofen**
**(Advil, Nuprin, Motrin)**



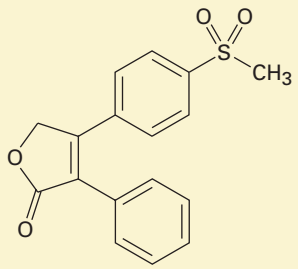

**Naproxen**
**(Aleve, Naprosyn)**

Aspirin and other NSAIDs function by blocking the cyclooxygenase (COX) enzymes that carry out the body's synthesis of compounds called prostaglandins (Section 6.3). There are two forms of the enzyme: COX-1, which carries out the normal physiological production of prostaglandins, and COX-2, which mediates the body's response to arthritis and other inflammatory conditions. Unfortunately, both COX-1 and COX-2 enzymes are blocked by aspirin, ibuprofen, and other NSAIDs, thereby shutting down not only the response to inflammation but also various protective functions, including the control mechanism for production of acid in the stomach.

Medicinal chemists have devised a number of drugs that act as selective inhibitors of the COX-2 enzyme. Inflammation is thereby controlled without blocking protective functions. Originally heralded as a breakthrough in arthritis treatment, the first generation of COX-2 inhibitors, including Vioxx, Celebrex, and Bextra, turned out to cause potentially serious heart problems, particularly in elderly or compromised patients. The second generation of COX-2 inhibitors now under development promises to be safer but will be closely scrutinized for side effects before gaining approval.




**Celecoxib**
**(Celebrex)**




**Rofecoxib**
**(Vioxx)**

## Summary and Key Words



Aromatic rings are a common part of many biological molecules and pharmaceutical agents and are particularly important in nucleic acid chemistry. In this chapter, we've seen how and why aromatic compounds are different from such apparently related compounds as alkenes, and we've seen some of their most common reactions.

The word **aromatic** refers to the class of compounds structurally related to benzene. Aromatic compounds are named according to IUPAC rules, with disubstituted benzenes referred to as either ortho (1,2 disubstituted), meta (1,3 disubstituted), or para (1,4 disubstituted). Benzene is a resonance hybrid of two equivalent forms, neither of which is correct by itself. The true structure of benzene is intermediate between the two.

The most common reaction of aromatic compounds is **electrophilic aromatic substitution**. In this two-step polar reaction, the $\pi$ electrons of the aromatic ring first attack the electrophile to yield a resonance-stabilized carbocation intermediate, which then loses $H^+$ to give a substituted aromatic product. Bromination, chlorination, iodination, nitration, sulfonation, **Friedel–Crafts alkylation**, and **Friedel–Crafts acylation** can all be carried out. Friedel–Crafts alkylation is particularly useful for preparing a variety of alkylbenzenes but is limited because only alkyl halides can be used and strongly deactivated rings do not react.

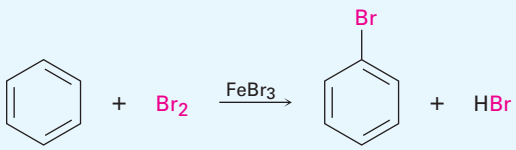
Substituents on the aromatic ring affect both the reactivity of the ring toward further substitution and the orientation of that further substitution. Substituents can be classified as either activators or deactivators, and as either ortho and para directors or meta directors.

The side chains of alkylbenzenes have unique reactivity because of the neighboring aromatic ring. Thus, an alkyl group attached to the aromatic ring can be degraded to a carboxyl group ($-CO_2H$) by oxidation with aqueous $KMnO_4$. In addition, the aromatic ring can be reduced to yield a cyclohexane on catalytic hydrogenation at high pressure.

In addition to substituted benzenes, polycyclic hydrocarbons such as naphthalene are also aromatic, and nitrogen-containing **heterocycles** such as pyridine, pyrimidine, pyrrole, and imidazole are aromatic because their rings have the same six-$\pi$-electron electronic structure as benzene.

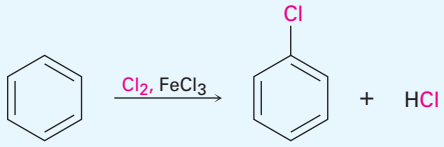
## Summary of Reactions

1. Electrophilic aromatic substitution
   **(a)** Bromination (Section 5.3)

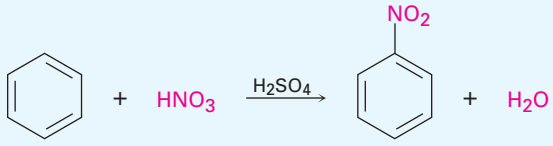



continued

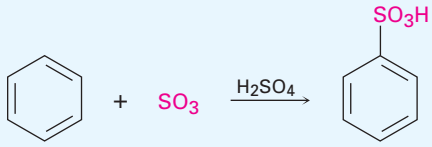
**(b)** Chlorination (Section 5.4)



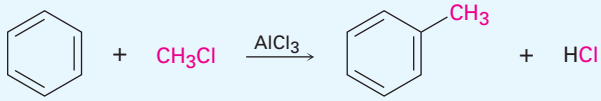

**(c)** Nitration (Section 5.4)



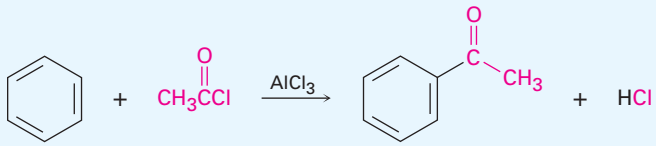

**(d)** Sulfonation (Section 5.4)




**(e)** Friedel–Crafts alkylation (Section 5.5)

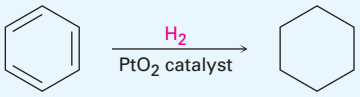



**(f)** Friedel–Crafts acylation (Section 5.5)




2. Oxidation of aromatic side chains (Section 5.8)


3. Hydrogenation of aromatic rings (Section 5.8)



# Exercises

## Visualizing Chemistry

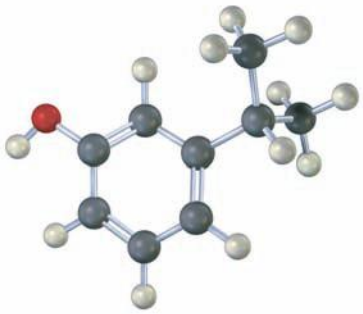
(Problems 5.1–5.20 appear within the chapter.)

OWL

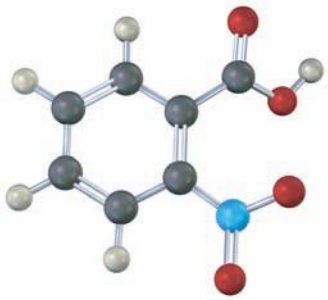
Interactive versions of these problems are assignable in OWL.

**5.21** Give IUPAC names for the following substances (red = O, blue = N).

(a)

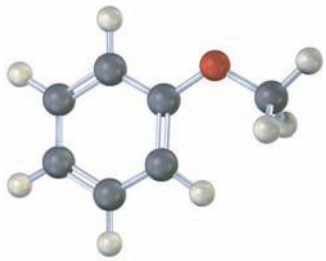


(b)

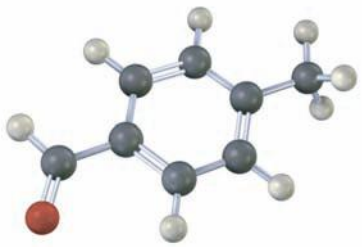


**5.22** Draw and name the product from reaction of each of the following substances with (i) $Br_2$, $FeBr_3$ and (ii) $CH_3COCl$, $AlCl_3$ (red = O):

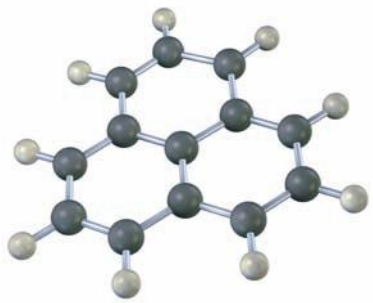
(a)



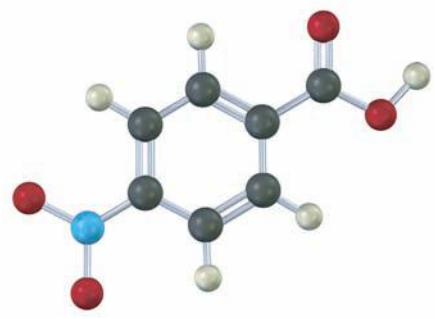
(b)



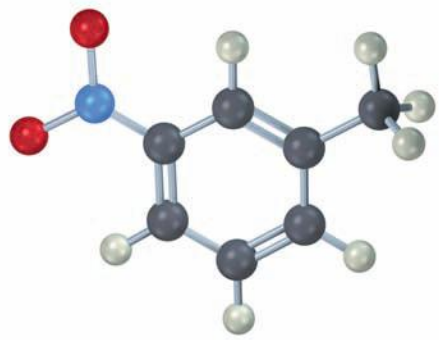
**5.23** The following structure represents a carbocation. Draw two resonance structures, indicating the positions of the double bonds.



**5.24** How would you synthesize the following compound starting from benzene? More than one step is needed.



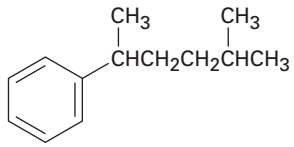
**5.25** The following compound can't be synthesized using the methods discussed in this chapter. Why not?

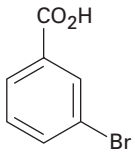


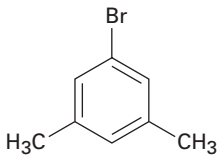
## Additional Problems

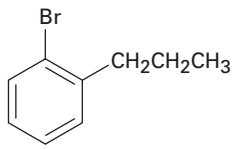
### Naming Aromatic Compounds

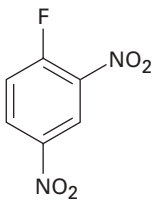
**5.26** Give IUPAC names for the following compounds:

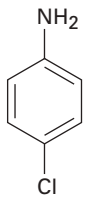
(a) 


(b) 


(c) 


(d) 


(e) 


(f) 

**5.27** Draw structures corresponding to the following names:

**(a)** *m*-Bromophenol **(b)** Benzene-1,3,5-triol
**(c)** *p*-Iodonitrobenzene **(d)** 2,4,6-Trinitrotoluene (TNT)
**(e)** *o*-Aminobenzoic acid **(f)** 3-Methyl-2-phenylhexane

**5.28** Draw and name all aromatic compounds with the formula $C_7H_7Cl$.

**5.29** Draw and name all isomeric bromodimethylbenzenes.

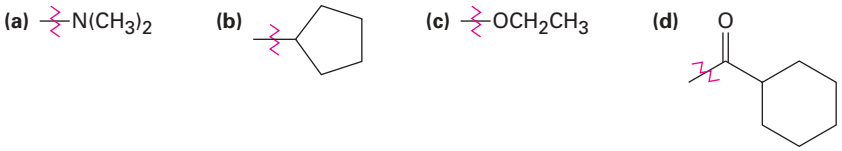
## Reactions and Substituent Effects

**5.30** Propose structures for aromatic hydrocarbons meeting the following descriptions:

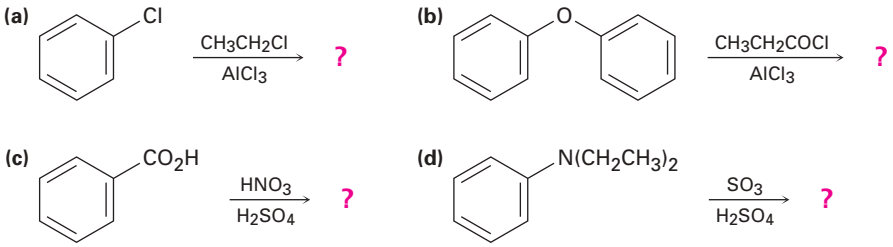
**(a)** $C_9H_{12}$; can give only one product on aromatic bromination
**(b)** $C_8H_{10}$; can give three products on aromatic chlorination
**(c)** $C_{10}H_{14}$; can give two products on aromatic nitration

**5.31** Formulate the reaction of benzene with 2-chloro-2-methylpropane in the presence of $AlCl_3$ catalyst to give *tert*-butylbenzene.

**5.32** Identify each of the following groups as an activator or deactivator and as an *o,p*-director or *m*-director:




**5.33** Predict the major product(s) of the following reactions:




**5.34** Predict the major product(s) of mononitration of the following substances:

**(a)** Bromobenzene **(b)** Benzonitrile (cyanobenzene)
**(c)** Benzoic acid **(d)** Nitrobenzene
**(e)** Phenol **(f)** Benzaldehyde

**5.35** Which of the substances listed in Problem 5.34 react faster than benzene and which react slower?

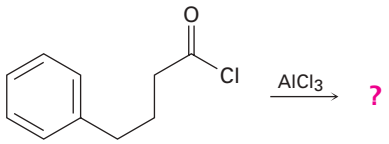
**5.36** Rank the compounds in each group according to their reactivity toward electrophilic substitution:
**(a)** Chlorobenzene, *o*-dichlorobenzene, benzene
**(b)** *p*-Bromonitrobenzene, nitrobenzene, phenol
**(c)** Fluorobenzene, benzaldehyde, *o*-dimethylbenzene

**5.37** The orientation of electrophilic aromatic substitution on a disubstituted benzene ring is usually controlled by whichever of the two groups already on the ring is the more powerful activator. Name and draw the structure(s) of the major product(s) of electrophilic chlorination of the following substances:
**(a)** *m*-Nitrophenol **(b)** *o*-Methylphenol **(c)** *p*-Chloronitrobenzene

**5.38** Predict the major product(s) you would expect to obtain from sulfonation of the following substances (see Problem 5.37):
**(a)** *o*-Chlorotoluene **(b)** *m*-Bromophenol **(c)** *p*-Nitrotoluene

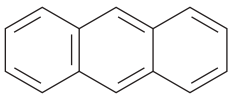
**5.39** Rank the following aromatic compounds in the expected order of their reactivity toward Friedel–Crafts acylation. Which compounds are unreactive?
**(a)** Bromobenzene
**(b)** Toluene
**(c)** Anisole ($C_6H_5OCH_3$)
**(d)** Nitrobenzene
**(e)** *p*-Bromotoluene

**5.40** In some cases, the Friedel–Crafts acylation reaction can occur *intramolecularly,* that is, within the same molecule. Predict the product of the following reaction:




**5.41** What is the structure of the compound with formula $C_8H_9Br$ that gives *p*-bromobenzoic acid on oxidation with $KMnO_4$?

**5.42** Draw the three additional resonance structures of anthracene.



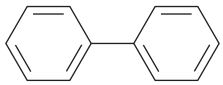
**Anthracene**

## MECHANISMS

**5.43** Show the steps involved in the Friedel–Crafts reaction of benzene with $CH_3Cl$.

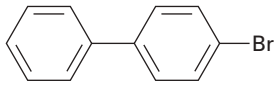
**5.44** Propose a mechanism to explain the fact that deuterium (D, $^2H$) slowly replaces hydrogen ($^1H$) in the aromatic ring when benzene is treated with $D_2SO_4$.

**5.45** Use resonance structures of the possible carbocation intermediates to explain why bromination of biphenyl occurs at the ortho and para positions rather than at the meta positions.



**Biphenyl**

**5.46** In light of your answer to Problem 5.45, at what position and on which ring would you expect nitration of 4-bromobiphenyl to occur?



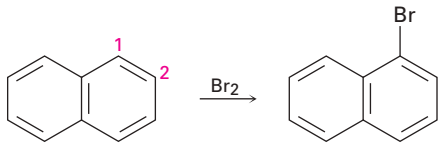

**4-Bromobiphenyl**

## Synthesis

**5.47** Starting with benzene, how would you synthesize the following substances? Assume that you can separate ortho and para isomers if necessary.
**(a)** *m*-Bromobenzenesulfonic acid **(b)** *o*-Chlorobenzenesulfonic acid
**(c)** *p*-Chlorotoluene

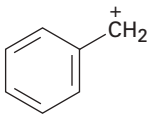
**5.48** Starting from any aromatic hydrocarbon of your choice, how would you synthesize the following substances? Ortho and para isomers can be separated if necessary.
**(a)** *o*-Nitrobenzoic acid **(b)** *p-tert*-Butylbenzoic acid

**5.49** Explain by drawing resonance structures of the intermediate carbocations why naphthalene undergoes electrophilic aromatic substitution at C1 rather than at C2.



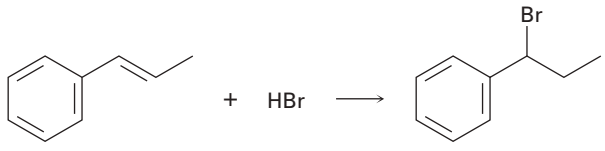

## General Problems

**5.50** We said in Section 4.9 that an allylic carbocation is stabilized by resonance. Draw resonance structures to account for the similar stabilization of a benzylic carbocation.

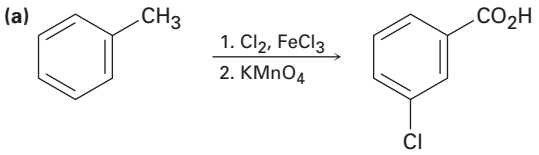


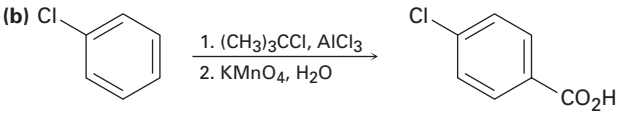

**A benzylic carbocation**

**5.51** Addition of HBr to 1-phenylpropene yields (1-bromopropyl)benzene as the only product. Propose a mechanism for the reaction, and explain why none of the other regioisomer is produced (see Problem 5.50).

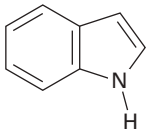


**5.52** The following syntheses have flaws in them. What is wrong with each?



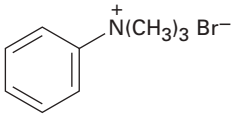




**5.53** Indole is an aromatic compound that has a benzene ring fused to a pyrrole ring. Look at the electronic structure of pyrrole in Figure 5.9c, and then draw an orbital picture of indole.
**(a)** How many $\pi$ electrons does indole have?
**(b)** What is the electronic relationship of indole to naphthalene?




**Indole**

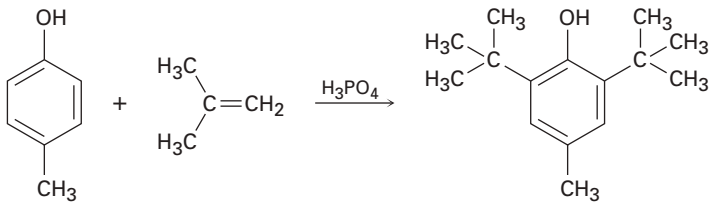
**5.54** Would you expect the trimethylammonium group to be an activating or deactivating substituent? Explain.




**Phenyltrimethylammonium bromide**

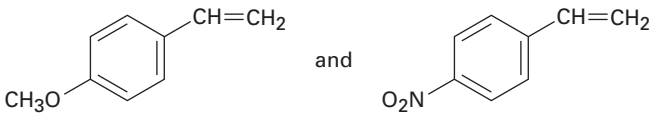
**5.55** Starting with toluene, how would you synthesize the three nitrobenzoic acids?

**5.56** Carbocations generated by reaction of an alkene with a strong acid catalyst can react with aromatic rings in a Friedel–Crafts reaction. Propose a mechanism to account for the industrial synthesis of the food preservative BHT from *p*-cresol and 2-methylpropene:

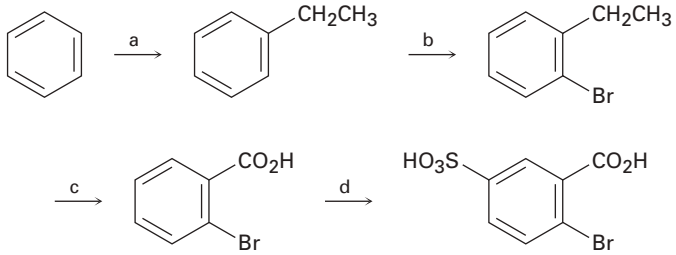



***p*-Cresol** **BHT**

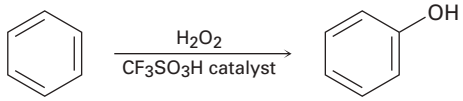
**5.57** You know the mechanism of HBr addition to alkenes, and you know the effects of various substituent groups on aromatic substitution. Use this knowledge to predict which of the following two alkenes reacts faster with HBr. Explain your answer by drawing resonance structures of the carbocation intermediates.




**5.58** Identify the reagents represented by the letters **a** through **d** in the following scheme:

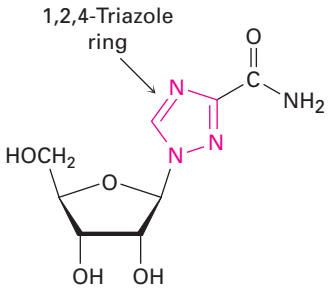



**5.59** Benzene can be hydroxylated by reaction with $H_2O_2$ in the presence of an acid catalyst. What is the likely structure of the reactive electrophile? Propose a mechanism for the reaction.




**IN THE MEDICINE CABINET**

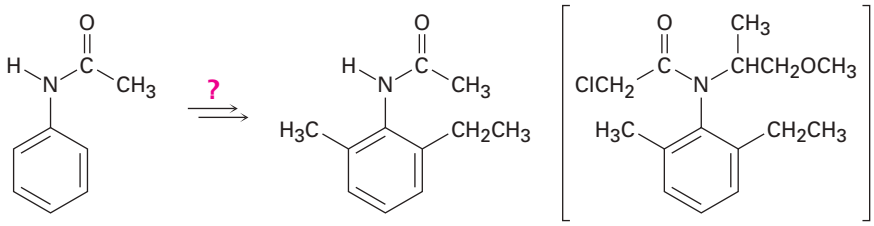
**5.60** Ribavirin, an antiviral agent used against hepatitis C and viral pneumonia, contains a 1,2,4-triazole ring. Look at the electronic structure of imidazole in Figure 5.9d, and then explain why the ring is aromatic.




**Ribavirin**

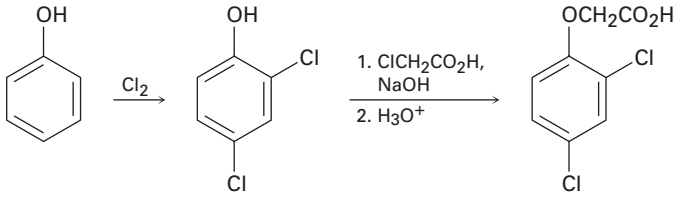
**IN THE FIELD**

**5.61** The herbicide metolachlor is broadly used in the United States to control weeds but is being phased out in Europe because of possible environmental risks. Usually marketed under the name Dual, approximately 50 million pounds of metolachlor are applied on crops each year in the United States. The preparation of metolachlor begins with the conversion of acetanilide to 2-ethyl-6-methylacetanilide. How would you accomplish this conversion?




**Acetanilide** **2-Ethyl-6-methyl-acetanilide** **Metolachlor**

**5.62** Synthesis of the herbicide 2,4-D begins with chlorination of phenol followed by reaction of the product with NaOH and chloroacetic acid. Name the chlorinated intermediate, and use resonance structures to explain the pattern of chlorination in the first step.




**Phenol** **2,4-D**