Basics of

Aromatic Chemistry

Prepared by

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Benzene and Its Derivatives

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show many of the reactions characteristic of alkenes. Yet, benzene is remarkably *un*reactive! It does not undergo the addition, oxidation, and reduction reactions characteristic of alkenes. For example, benzene does not react with bromine, hydrogen chloride, or other reagents that usually add to carbon–carbon double bonds. Nor is benzene oxidized by peracids under conditions that readily oxidize alkenes. When benzene reacts, it does so by substitution in which a hydrogen atom is replaced by another atom or a group of atoms.

The term *aromatic* was originally used to classify benzene and its derivatives because many of them have distinctive odors. It became clear, however, that a sounder classification for these compounds would be one based on structure and chemical reactivity, not aroma. As it is now used, the term **aromatic** refers instead to the fact that benzene and its derivatives are highly unsaturated compounds that are unexpectedly stable toward reagents that react with alkenes.

We use the term **arene** to describe aromatic hydrocarbons, by analogy with alkane and alkene. Benzene is the parent arene. Just as we call a group derived by the removal of an H from an alkane an alkyl group and give it the symbol R—, we call a group derived by the removal of an H from an arene an **aryl group** and give it the symbol **Ar**—.

Aromatic compound A term used to classify benzene and its derivatives.

Arene An aromatic hydrocarbon.

Aryl group A group derived from an aromatic compound (an arene) by the removal of an H; given the symbol Ar—.

Ar— The symbol used for an aryl group, by analogy with R— for an alkyl group.

9.1 What Is the Structure of Benzene?

Let us imagine ourselves in the mid-nineteenth century and examine the evidence on which chemists attempted to build a model for the structure of benzene. First, because the molecular formula of benzene is C_6H_6, it seemed clear that the molecule must be highly unsaturated. Yet benzene does not show the chemical properties of alkenes, the only unsaturated hydrocarbons known at that time. Benzene does undergo chemical reactions, but its characteristic reaction is substitution rather than addition. When benzene is treated with bromine in the presence of ferric chloride as a catalyst, for example, only one compound with the molecular formula C_6H_5Br forms:

$$\underset{\text{Benzene}}{C_6H_6} + Br_2 \xrightarrow{FeCl_3} \underset{\text{Bromobenzene}}{C_6H_5Br} + HBr$$

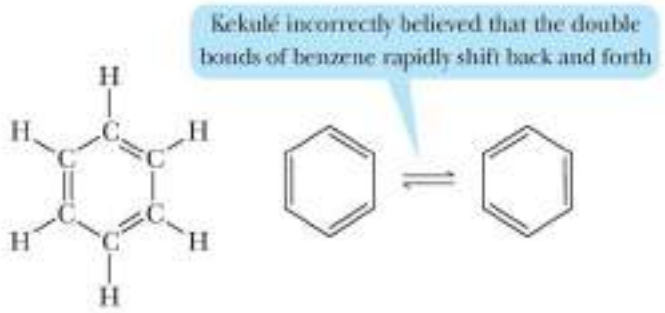
Chemists concluded, therefore, that all six carbons and all six hydrogens of benzene must be equivalent. When bromobenzene is treated with bromine in the presence of ferric chloride, three isomeric dibromobenzenes are formed:

$$\underset{\text{Bromobenzene}}{C_6H_5Br} + Br_2 \xrightarrow{FeCl_3} \underset{\substack{\text{Dibromobenzene}\\ \text{(formed as a mixture of}\\ \text{three constitutional isomers)}}}{C_6H_4Br_2} + HBr$$

For chemists in the mid-nineteenth century, the problem was to incorporate these observations, along with the accepted tetravalence of carbon, into a structural formula for benzene. Before we examine their proposals, we should note that the problem of the structure of benzene and other aromatic hydrocarbons has occupied the efforts of chemists for over a century. It was not until the 1930s that chemists developed a general understanding of the unique structure and chemical properties of benzene and its derivatives.

A. Kekulé's Model of Benzene

The first structure for benzene, proposed by August Kekulé in 1872, consisted of a six-membered ring with alternating single and double bonds and with one hydrogen bonded to each carbon. Kekulé further proposed that the ring contains three double bonds that shift back and forth so rapidly that the two forms cannot be separated. Each structure has become known as a **Kekulé structure**.

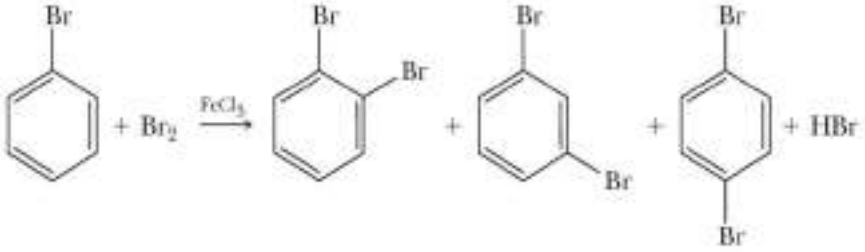


A Kekulé structure, showing all atoms

Kekulé structures as line-angle formulas

Because all of the carbons and hydrogens of Kekulé's structure are equivalent, substituting bromine for any one of the hydrogens gives the same compound. Thus, Kekulé's proposed structure was consistent with the fact that treating benzene with bromine in the presence of ferric chloride gives only one compound with the molecular formula C_6H_5Br.

His proposal also accounted for the fact that the bromination of bromobenzene gives three (and only three) isomeric dibromobenzenes:

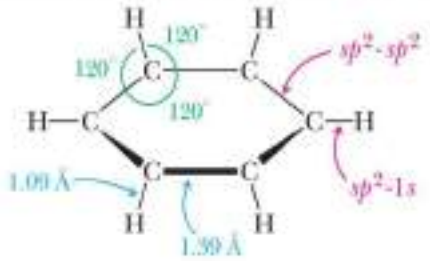


The three isomeric dibromobenzenes

Although Kekulé's proposal was consistent with many experimental observations, it was contested for years. The major objection was that it did not account for the unusual chemical behavior of benzene. If benzene contains three double bonds, why, his critics asked, doesn't it show the reactions typical of alkenes? Why doesn't it add three moles of bromine to form 1,2,3,4,5,6-hexabromocyclohexane? Why, instead, does benzene react by substitution rather than addition?

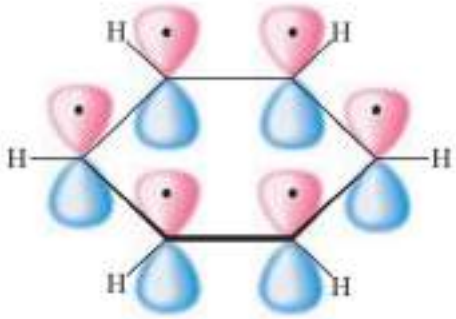
B. The Orbital Overlap Model of Benzene

The concepts of the **hybridization of atomic orbitals** and the **theory of resonance**, developed by Linus Pauling in the 1930s, provided the first adequate description of the structure of benzene. The carbon skeleton of benzene forms a regular hexagon with C—C—C and H—C—C bond angles of 120°. For this type of bonding, carbon uses sp^2 hybrid orbitals (Section 1.6E). Each carbon forms sigma bonds to two adjacent carbons by the overlap of sp^2–sp^2 hybrid orbitals and one sigma bond to hydrogen by the overlap of sp^2–1s orbitals. As determined experimentally, all carbon–carbon bonds in benzene are the same length, 1.39 Å, a value almost midway between the length of a single bond between sp^3 hybridized carbons (1.54 Å) and that of a double bond between sp^2 hybridized carbons (1.33 Å):

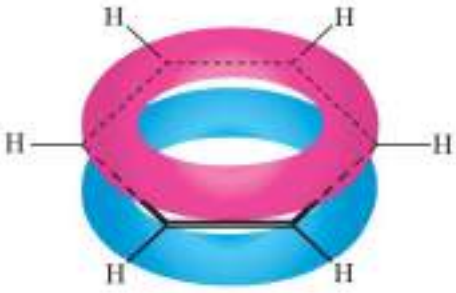


Each carbon also has a single unhybridized 2p orbital that contains one electron. These six 2p orbitals lie perpendicular to the plane of the ring and overlap to form a continuous pi cloud encompassing all six carbons. The electron density of the pi system of

a benzene ring lies in one torus (a doughnut-shaped region) above the plane of the ring and a second torus below the plane (Figure 9.1).



(a)



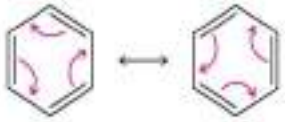
(b)

FIGURE 9.1
Orbital overlap model of the bonding in benzene. (a) The carbon, hydrogen framework. The six 2*p* orbitals, each with one electron, are shown uncombined. (b) The overlap of parallel 2*p* orbitals forms a continuous pi cloud, shown by one torus above the plane of the ring and a second below the plane of the ring.

Resonance energy The difference in energy between a resonance hybrid and the most stable of its hypothetical contributing structures.

C. The Resonance Model of Benzene

One of the postulates of resonance theory is that, if we can represent a molecule or ion by two or more contributing structures, then that molecule cannot be adequately represented by any single contributing structure. We represent benzene as a hybrid of two equivalent contributing structures, often referred to as *Kekulé structures*:

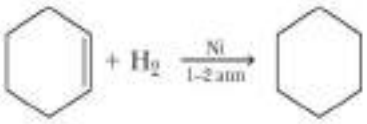


Benzene as a hybrid of two equivalent contributing structures

Each Kekulé structure makes an equal contribution to the hybrid; thus, the C—C bonds are neither single nor double bonds, but something intermediate. We recognize that neither of these contributing structures exists (they are merely alternative ways to pair 2*p* orbitals with no reason to prefer one over the other) and that the actual structure is a superposition of both. Nevertheless, chemists continue to use a single contributing structure to represent this molecule because it is as close as we can come to an accurate structure within the limitations of classical Lewis structures and the tetravalence of carbon.

D. The Resonance Energy of Benzene

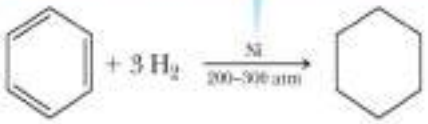
Resonance energy is the difference in energy between a resonance hybrid and its most stable hypothetical contributing structure. One way to estimate the resonance energy of benzene is to compare the heats of hydrogenation of cyclohexene and benzene (benzene can be made to undergo hydrogenation under extreme conditions). In the presence of a transition metal catalyst, hydrogen readily reduces cyclohexene to cyclohexane (Section 5.6):



$\Delta H^0 = -120$ kJ/mol (−28.6 kcal/mol)

By contrast, benzene is reduced only very slowly to cyclohexane under these conditions. It is reduced more rapidly when heated and under a pressure of several hundred atmospheres of hydrogen:

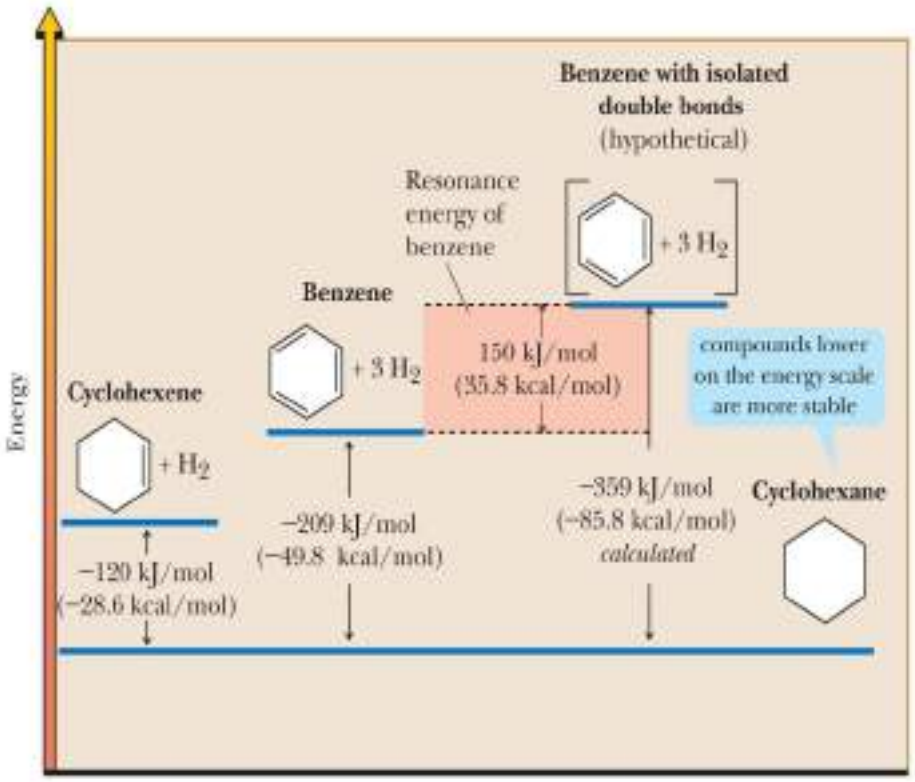
because benzene does not react readily with reagents that add to alkenes, hydrogenation of benzene must be performed at extremely high pressures



$\Delta H^0 = -209$ kJ/mol (−49.8 kcal/mol)

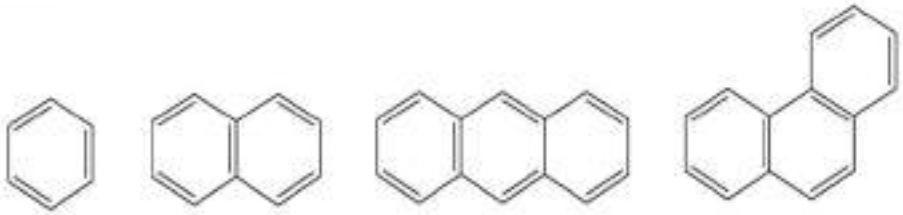
The catalytic reduction of an alkene is an exothermic reaction (Section 5.6B). The heat of hydrogenation per double bond varies somewhat with the degree of substitution of the double bond; for cyclohexene $\Delta H^0 = -120$ kJ/mol (−28.6 kcal/mol). If we imagine benzene in which the 2*p* electrons do not overlap outside of their original C—C double bonds, a hypothetical compound with alternating single and double bonds, we might expect its heat of hydrogenation to be $3 \times -120 = -359$ kJ/mol (−85.8 kcal/mol). Instead, the heat of hydrogenation of benzene is only −209 kJ/mol (−49.8 kcal/mol). The difference of 150 kJ/mol (35.8 kcal/mol) between the expected value and the experimentally observed value is the **resonance energy of benzene**. Figure 9.2 shows these experimental results in the form of a graph.

FIGURE 9.2
The resonance energy of benzene, as determined by a comparison of the heats of hydrogenation of cyclohexene, benzene, and the hypothetical benzene.



For comparison, the strength of a carbon–carbon single bond is approximately 333–418 kJ/mol (80–100 kcal/mol), and that of hydrogen bonding in water and low-molecular-weight alcohols is approximately 8.4–21 kJ/mol (2–5 kcal/mol). Thus, although the resonance energy of benzene is less than the strength of a carbon–carbon single bond, it is considerably greater than the strength of hydrogen bonding in water and alcohols. In Section 8.1C, we saw that hydrogen bonding has a dramatic effect on the physical properties of alcohols compared with those of alkanes. In this chapter, we see that the resonance energy of benzene and other aromatic hydrocarbons has a dramatic effect on their chemical reactivity.

Following are resonance energies for benzene and several other aromatic hydrocarbons:



Resonance energy [kJ/mol (kcal/mol)]	Benzene	Naphthalene	Anthracene	Phenanthrene
	150 (35.8)	255 (60.9)	347 (82.9)	381 (91.0)

9.2 What Is Aromaticity?

Many other types of molecules besides benzene and its derivatives show aromatic character; that is, they contain high degrees of unsaturation, yet fail to undergo characteristic alkene addition and oxidation–reduction reactions. What chemists had long sought to understand were the principles underlying aromatic character. The German chemical physicist Erich Hückel solved this problem in the 1930s.

Hückel's criteria are summarized as follows. To be aromatic, a ring must

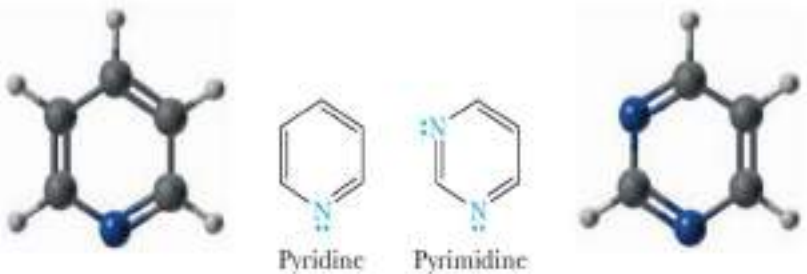
1. Have one $2p$ orbital on each of its atoms.
2. Be planar or nearly planar, so that there is continuous overlap or nearly continuous overlap of all $2p$ orbitals of the ring.
3. Have 2, 6, 10, 14, 18, and so forth pi electrons in the cyclic arrangement of $2p$ orbitals.

this criterion is also called the **4n + 2 rule** because the allowable numbers of pi electrons can be determined when n is substituted by any integer, including zero

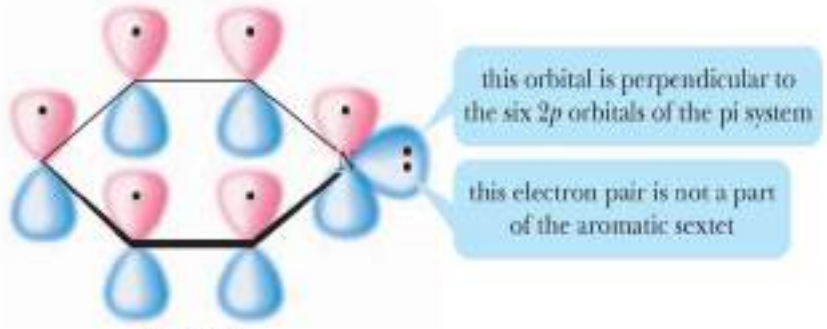
Benzene meets these criteria. It is cyclic, planar, has one $2p$ orbital on each carbon atom of the ring, and has 6 pi electrons (an aromatic sextet) in the cyclic arrangement of its $2p$ orbitals.

Let us apply these criteria to several **heterocyclic compounds**, all of which are aromatic. Pyridine and pyrimidine are heterocyclic analogs of benzene. In pyridine, one CH group of benzene is replaced by a nitrogen atom, and in pyrimidine, two CH groups are replaced by nitrogen atoms:

Heterocyclic compound
An organic compound that contains one or more atoms other than carbon in its ring.



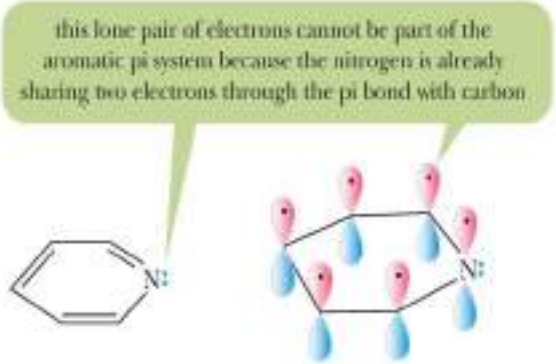
Each molecule meets the Hückel criteria for aromaticity: Each is cyclic and planar, has one $2p$ orbital on each atom of the ring, and has six electrons in the pi system. In pyridine, nitrogen is sp^2 hybridized, and its unshared pair of electrons occupies an sp^2 orbital perpendicular to the $2p$ orbitals of the pi system and thus is not a part of the pi system. In pyrimidine, neither unshared pair of electrons of nitrogen is part of the pi system. The resonance energy of pyridine is 134 kJ/mol (32.0 kcal/mol), slightly less than that of benzene. The resonance energy of pyrimidine is 109 kJ/mol (26.0 kcal/mol).



Pyridine

HOW TO 9.1 Determine Whether a Lone Pair of Electrons Is or Is Not Part of an Aromatic Pi System

(a) First, determine whether the atom containing the lone pair of electrons is part of a double bond. If it is part of a double bond, it is not possible for the lone pair to be part of the aromatic pi system.



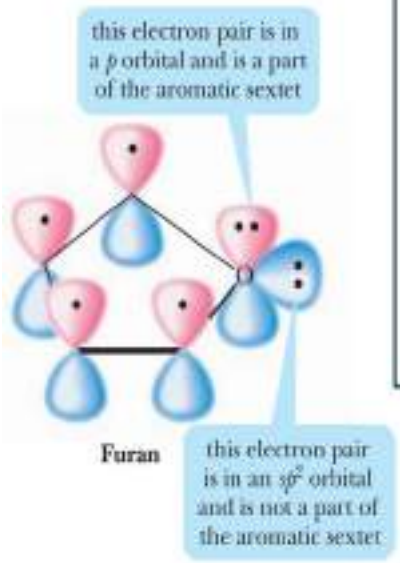
(b) If the atom containing the lone pair of electrons is not part of a double bond, it is possible for the lone pair of electrons to be part of the pi system.

Determine this by placing the atom in a hybridization state that places the lone pair of electrons in a *p* orbital. If this increases the number of aromatic pi electrons to either 2, 6, 10, 14, and so on, then the lone pair of electrons is part of the pi aromatic system. If placing the lone pair of electrons in the pi system changes the total number of pi electrons to any other number (e.g., 3–5, 7–9, etc.), the lone pair is not part of the aromatic pi system.

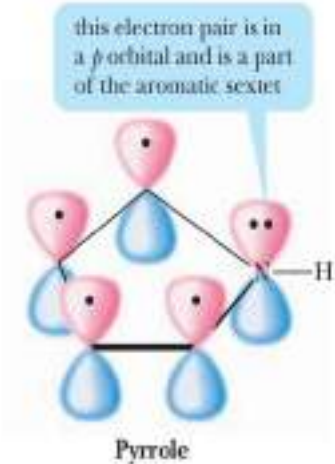
a nitrogen atom with three single bonds is normally sp^3 hybridized. However, to determine if the lone pair of electrons belongs in the pi system, we must change the hybridization of nitrogen to sp^2 so that the electrons can reside in a *p* orbital

The lone pair on nitrogen gives the pi system six electrons. Therefore, the nitrogen should be sp^2 hybridized.

The lone pair gives the pi system eight electrons. Therefore, the nitrogen should not be sp^2 hybridized.



Furan



Pyrrole

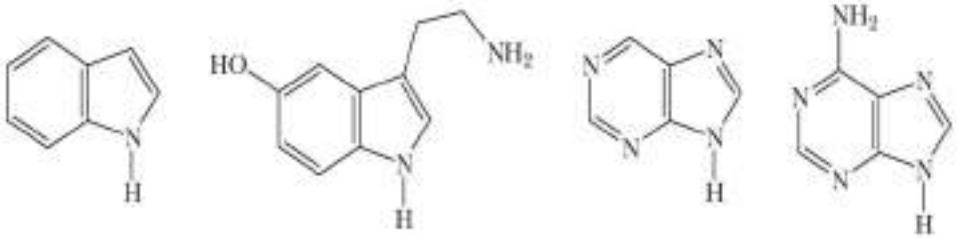
FIGURE 9.3
Origin of the six pi electrons (the aromatic sextet) in furan and pyrrole. The resonance energy of furan is 67 kJ/mol (16 kcal/mol); that of pyrrole is 88 kJ/mol (21 kcal/mol).

The five-membered-ring compounds furan, pyrrole, and imidazole are also aromatic:

Furan Pyrrole Imidazole

In these planar compounds, each heteroatom is sp^2 hybridized, and its unhybridized $2p$ orbital is part of a continuous cycle of five $2p$ orbitals. In furan, one unshared pair of electrons of the heteroatom lies in the unhybridized $2p$ orbital and is a part of the pi system (Figure 9.3). The other unshared pair of electrons lies in an sp^2 hybrid orbital, perpendicular to the $2p$ orbitals, and is not a part of the pi system. In pyrrole, the unshared pair of electrons on nitrogen is part of the aromatic sextet. In imidazole, the unshared pair of electrons on one nitrogen is part of the aromatic sextet; the unshared pair on the other nitrogen is not.

Nature abounds with compounds having a heterocyclic aromatic ring fused to one or more other rings. Two such compounds especially important in the biological world are indole and purine:

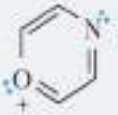


Indole Serotonin (a neurotransmitter) Purine Adenine

Indole contains a pyrrole ring fused with a benzene ring. Compounds derived from indole include the amino acid L-tryptophan (Section 18.2C) and the neurotransmitter serotonin. Purine contains a six-membered pyrimidine ring fused with a five-membered imidazole ring. Adenine is one of the building blocks of deoxyribonucleic acids (DNA) and ribonucleic acids (RNA), as described in Chapter 20. It is also a component of the biological oxidizing agent nicotinamide adenine dinucleotide, abbreviated NAD^+ (Section 21.1B).

EXAMPLE 9.1

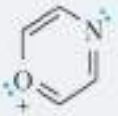
Which of the following compounds are aromatic?

(a) 
(b) 
(c) 

STRATEGY

Determine whether each atom of the ring contains a 2*p* orbital and whether the molecule is planar. If these criteria are met, determine the number of pi electrons. Those having 2, 6, 10, 14, and so on electrons are aromatic.

SOLUTION

(a) 

This molecule is planar, and each atom of the ring contains a 2*p* orbital. There is a total of 6 pi electrons. The molecule is aromatic.

(b) 

This molecule is planar, and each atom of the ring contains a 2*p* orbital. There is a total of 4 pi electrons. The molecule is not aromatic.

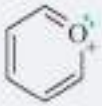
(c) 

Treat the molecule as planar for the purposes of determining aromaticity. Also, treat each carbon atom in the ring as containing a 2*p* orbital. That is, treat the oxygen atom as sp^2 hybridized, so that one of its lone pairs of electrons will enter the pi electron system (if we do not do this, the molecule cannot be aromatic because an oxygen atom with two lone pairs of electrons and two single bonds is normally sp^3 hybridized). Despite these special considerations, the molecule ends up with a total of eight pi electrons, so the molecule is not aromatic. Because it is not aromatic, the oxygen has no driving force to be sp^2 hybridized and is, in fact, sp^3 hybridized. Also, the molecule has no driving force to be planar, and in fact, the molecule is nonplanar.

See problem 9.11

PROBLEM 9.1

Which of the following compounds are aromatic?

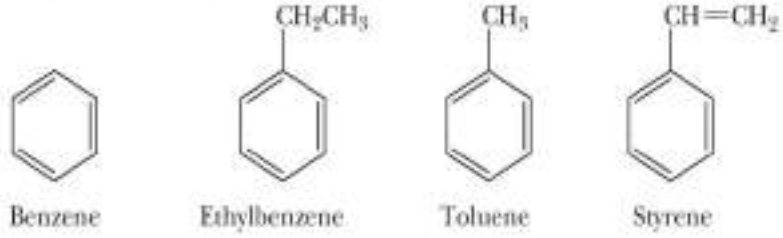
(a) 
(b) 
(c) 

9.3 How Are Benzene Compounds Named, and What Are Their Physical Properties?

A. Monosubstituted Benzenes

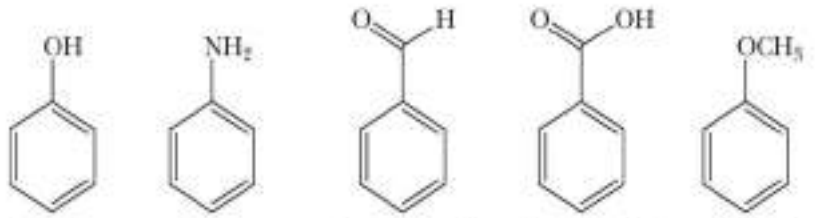
Monosubstituted alkylbenzenes are named as derivatives of benzene; an example is ethylbenzene. The IUPAC system retains certain common names for several of the simpler monosubstituted alkylbenzenes. Examples are **toluene** (rather than methylbenzene) and

styrene (rather than phenylethylene):



	Benzene	Ethylbenzene	Toluene	Styrene
mp (°C)	5.5	−95	−93	−31
bp (°C)	80	136	110	145

The common names **phenol**, **aniline**, **benzaldehyde**, **benzoic acid**, and **anisole** are also retained by the IUPAC system:



	Phenol	Aniline	Benzaldehyde	Benzoic acid	Anisole
mp (°C)	41	−6	−26	123	−37
bp (°C)	182	184	178	249	154

The physical properties of substituted benzenes vary depending on the nature of the substituent. Alkylbenzenes, like other hydrocarbons, are nonpolar and thus have lower boiling points than benzenes with polar substituents such as phenol, aniline, and benzoic acid. The melting points of substituted benzenes depend on whether or not their molecules can be packed close together. Benzene, which has no substituents and is flat, can pack its molecules very closely, giving it a considerably higher melting point than many substituted benzenes.

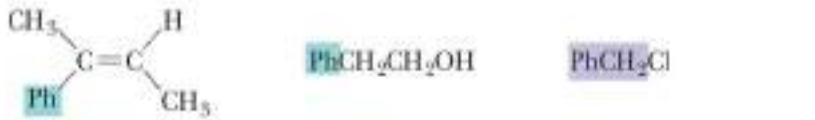
Phenyl group C_6H_5-, the aryl group derived by removing a hydrogen from benzene.

Benzyl group $C_6H_5CH_2-$, the alkyl group derived by removing a hydrogen from the methyl group of toluene.

As noted in the introduction to Chapter 5, the substituent group derived by the loss of an H from benzene is a **phenyl** group (Ph); that derived by the loss of an H from the methyl group of toluene is a **benzyl group** (Bn):

Benzene Phenyl group (Ph) Toluene Benzyl group (Bn)

In molecules containing other functional groups, phenyl groups and benzyl groups are often named as substituents:



(*Z*)-2-Phenyl-2-butene 2-Phenylethanol Benzyl chloride

Ortho (*o*) Refers to groups occupying positions 1 and 2 on a benzene ring.

Meta (*m*) Refers to groups occupying positions 1 and 3 on a benzene ring.

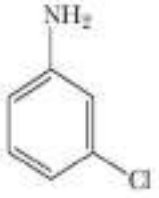
Para (*p*) Refers to groups occupying positions 1 and 4 on a benzene ring.

B. Disubstituted Benzenes

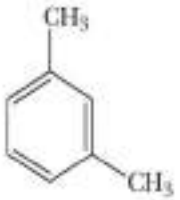
When two substituents occur on a benzene ring, three constitutional isomers are possible. We locate substituents either by numbering the atoms of the ring or by using the locators **ortho**, **meta**, and **para**. The numbers 1,2- are equivalent to *ortho* (Greek: straight); 1,3- to *meta* (Greek: after); and 1,4- to *para* (Greek: beyond).

When one of the two substituents on the ring imparts a special name to the compound, as, for example, toluene, phenol, and aniline, then we name the compound as a derivative of that parent molecule. In this case, the special substituent occupies ring position number 1. The IUPAC system retains the common name **xylene** for the three isomeric dimethylbenzenes. When neither group imparts a special name, we locate the two substituents and list them in alphabetical order before the ending *-benzene*. The carbon of the benzene ring with the substituent of lower alphabetical ranking is numbered C-1.

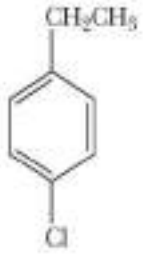
4-Bromotoluene
(*p*-Bromotoluene)



3-Chloroaniline
(*m*-Chloroaniline)



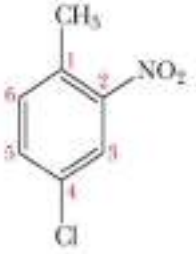
1,3-Dimethylbenzene
(*m*-Xylene)



1-Chloro-4-ethylbenzene
(*p*-Chloroethylbenzene)

C. Polysubstituted Benzenes

When three or more substituents are present on a ring, we specify their locations by numbers. If one of the substituents imparts a special name, then the molecule is named as a derivative of that parent molecule. If none of the substituents imparts a special name, we number them to give the smallest set of numbers and list them in alphabetical order before the ending *-benzene*. In the following examples, the first compound is a derivative of toluene, and the second is a derivative of phenol. Because there is no special name for the third compound, we list its three substituents in alphabetical order, followed by the word *benzene*.



4-Chloro-2-nitrotoluene

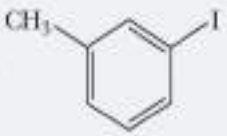
2,4,6-Tribromophenol

2-Bromo-1-ethyl-4-nitrobenzene

EXAMPLE 9.2

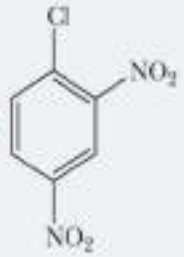
Write names for these compounds:

(a)

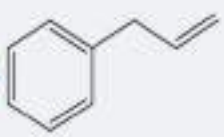


(b)

(c)



(d)



STRATEGY

First, determine whether one of the substituents imparts a special name to the benzene compound (e.g., toluene, phenol, aniline). Identify all substituents and list them in alphabetical order. Use numbers to indicate relative position. The locators *ortho*, *meta*, or *para* can be used for disubstituted benzenes.

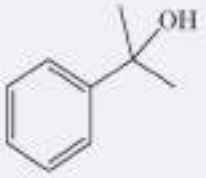
SOLUTION

(a) 3-Iodotoluene or *m*-iodotoluene (b) 3,5-Dibromobenzoic acid (c) 1-Chloro-2,4-dinitrobenzene (d) 3-Phenylpropene

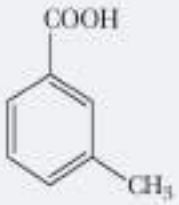
See problems 9.13, 9.14

PROBLEM 9.2

Write names for these compounds:

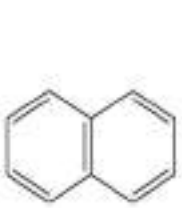
(a) 

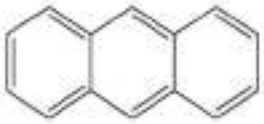
(b) 

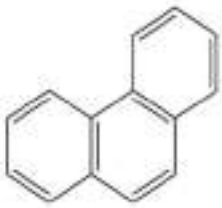
(c) 

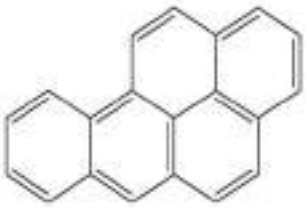
Polynuclear aromatic hydrocarbon A hydrocarbon containing two or more fused aromatic rings.

Polynuclear aromatic hydrocarbons (PAHs) contain two or more aromatic rings, each pair of which shares two ring carbon atoms. Naphthalene, anthracene, and phenanthrene, the most common PAHs, and substances derived from them are found in coal tar and high-boiling petroleum residues. At one time, naphthalene was used as a moth repellent and insecticide in protecting woolens and furs, but its use has decreased due to the introduction of chlorinated hydrocarbons such as *p*-dichlorobenzene. Also found in coal tar are lesser amounts of benzo[a]pyrene. This compound is found as well in the exhausts of gasoline-powered internal combustion engines (for example, automobile engines) and in cigarette smoke. Benzo[a]pyrene is a very potent carcinogen and mutagen.


Naphthalene


Anthracene


Phenanthrene

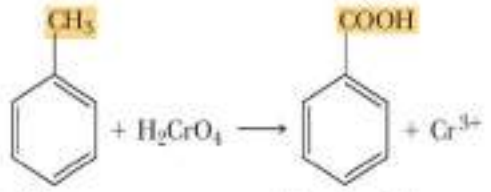

Benzo[a]pyrene

9.4 What Is the Benzylic Position, and How Does It Contribute to Benzene Reactivity?

Benzylic carbon An sp^3 hybridized carbon bonded to a benzene ring.

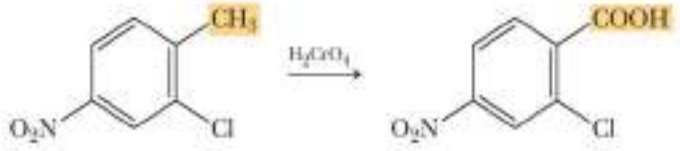
As we have mentioned, benzene's aromaticity causes it to resist many of the reactions that alkenes typically undergo. However, chemists have been able to react benzene in other ways. This is fortunate because benzene rings are abundant in many of the compounds that society depends upon, including various medications, plastics, and preservatives for food. We begin our discussion of benzene reactions with processes that take place not on the ring itself, but at the carbon immediately bonded to the benzene ring. This carbon is known as a **benzylic carbon**.

Benzene is unaffected by strong oxidizing agents, such as H_2CrO_4 and $KMnO_4$. When we treat toluene with these oxidizing agents under vigorous conditions, the side-chain methyl group is oxidized to a carboxyl group to give benzoic acid:



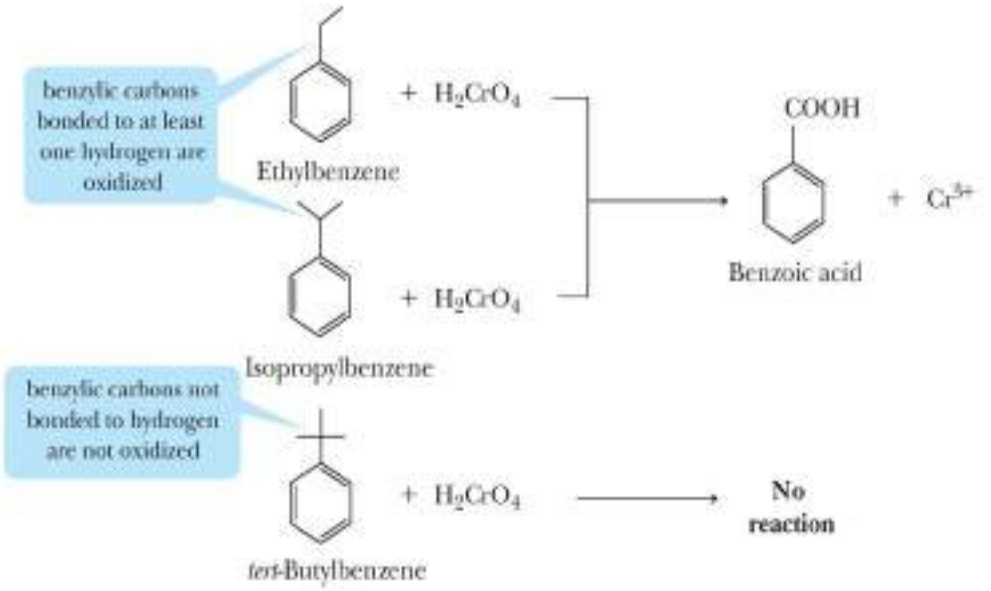
Toluene Benzoic acid

The fact that the side-chain methyl group is oxidized, but the aromatic ring is unchanged, illustrates the remarkable chemical stability of the aromatic ring. Halogen and nitro substituents on an aromatic ring are unaffected by these oxidations. For example, chromic acid oxidizes 2-chloro-4-nitrotoluene to 2-chloro-4-nitrobenzoic acid. Notice that in this oxidation, the nitro and chloro groups remain unaffected:



2-Chloro-4-nitrotoluene 2-Chloro-4-nitrobenzoic acid

Ethylbenzene and isopropylbenzene are also oxidized to benzoic acid under these conditions. The side chain of *tert*-butylbenzene, which has no benzylic hydrogen, is not affected by these oxidizing conditions.



From these observations, we conclude that, if a benzylic hydrogen exists, then the benzylic carbon (Section 9.3A) is oxidized to a carboxyl group and all other carbons of the side chain are removed. If no benzylic hydrogen exists, as in the case of *tert*-butylbenzene, then the side chain is not oxidized.

If more than one alkyl side chain exists, each is oxidized to —COOH. Oxidation of *m*-xylene gives 1,3-benzenedicarboxylic acid, more commonly named isophthalic acid:

m-Xylene

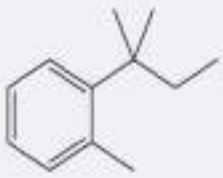
1,3-Benzenedicarboxylic acid (Isophthalic acid)

EXAMPLE 9.3

Predict the products resulting from vigorous oxidation of each compound by H_2CrO_4. The various by-products that are formed from benzylic oxidation reactions are usually not specified.

(a) 1,4 -dimethylbenzene (*p*-xylene)

(b)



STRATEGY

Identify all the alkyl groups in the reactant. If a benzylic hydrogen exists on an alkyl group, chromic acid will oxidize it to a —COOH group.

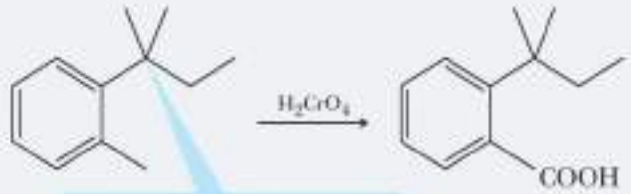
SOLUTION

chromic acid oxidizes both alkyl groups to —COOH groups, and the product is terephthalic acid, one of two compounds required for the synthesis of Dacron polyester and Mylar (Section 17.4B)

(a) 

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

1,4-Benzenedicarboxylic acid (Terephthalic acid)

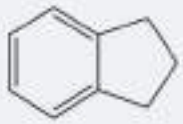
(b) 

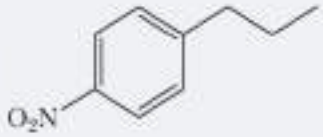
this alkyl group has no benzylic hydrogens and is not oxidized

See problem 9.30

PROBLEM 9.3

Predict the products resulting from vigorous oxidation of each compound by H_2CrO_4:

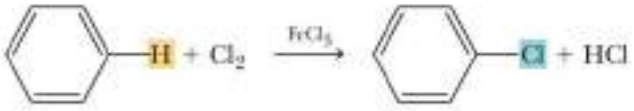
(a) 

(b) 

9.5 What Is Electrophilic Aromatic Substitution?

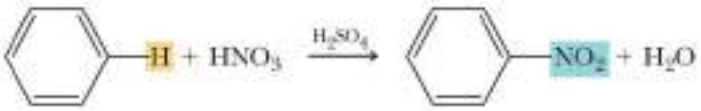
Although benzene is resistant to most of the reactions presented thus far for alkenes, it is not completely unreactive. By far the most characteristic reaction of aromatic compounds is substitution at a ring carbon. Some groups that can be introduced directly onto the ring are the halogens, the nitro ($-NO_2$) group, the sulfonic acid ($-SO_3H$) group, alkyl ($-R$) groups, and acyl ($RCO-$) groups.

Halogenation:



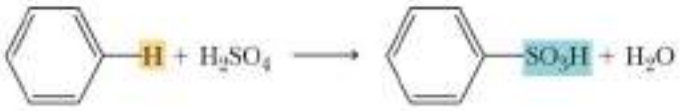
Chlorobenzene

Nitration:



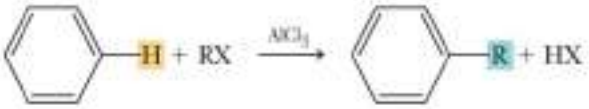
Nitrobenzene

Sulfonation:



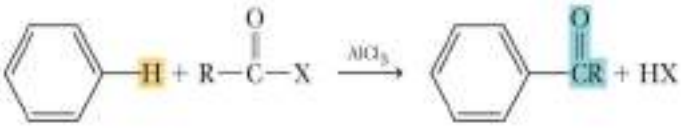
Benzenesulfonic acid

Alkylation:



An alkylbenzene

Acylation:



An acyl halide

An acylbenzene

9.6 What Is the Mechanism of Electrophilic Aromatic Substitution?

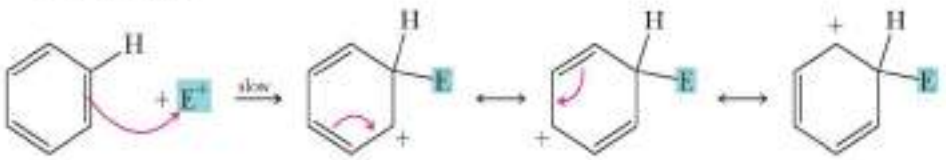
Electrophilic aromatic substitution A reaction in which an electrophile, E^+, substitutes for a hydrogen on an aromatic ring.

In this section, we study several types of **electrophilic aromatic substitution** reactions—that is, reactions in which a hydrogen of an aromatic ring is replaced by an electrophile, E^+. The mechanisms of these reactions are actually very similar. In fact, they can be broken down into three common steps:

Step 1: **Generation of the electrophile.** This is a reaction pattern specific to each particular electrophilic aromatic substitution reaction.

$$\text{Reagent(s)} \longrightarrow E^+$$

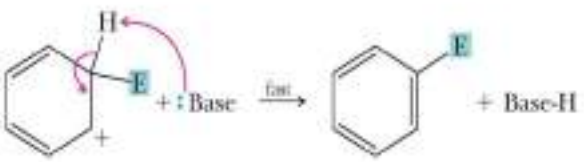
Step 2: **Reaction of a nucleophile and an electrophile to form a new covalent bond.** Attack of the electrophile on the aromatic ring to give a resonance-stabilized cation intermediate:



(the nucleophile)

Resonance-stabilized cation intermediate

Step 3: **Take a proton away.** Proton transfer to a base to regenerate the aromatic ring:



The reactions we are about to study differ only in the way the electrophile is generated and in the base that removes the proton to re-form the aromatic ring. You should keep this principle in mind as we explore the details of each reaction.

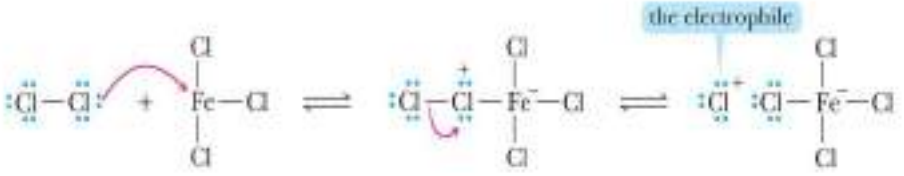
A. Chlorination and Bromination

Chlorine alone does not react with benzene, in contrast to its instantaneous addition to cyclohexene (Section 5.3C). However, in the presence of a Lewis acid catalyst, such as ferric chloride or aluminum chloride, chlorine reacts to give chlorobenzene and HCl. Chemists account for this type of electrophilic aromatic substitution by the following three-step mechanism:

Mechanism

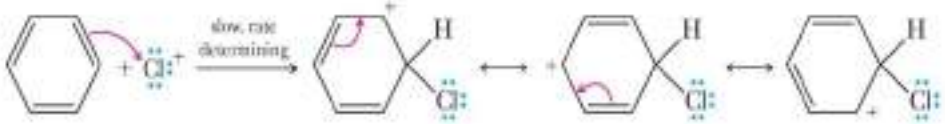
Electrophilic Aromatic Substitution—Chlorination

STEP 1: Formation of the Electrophile. Reaction between chlorine (a Lewis base) and $FeCl_3$ (a Lewis acid) gives an ion pair containing a chloronium ion (an electrophile):

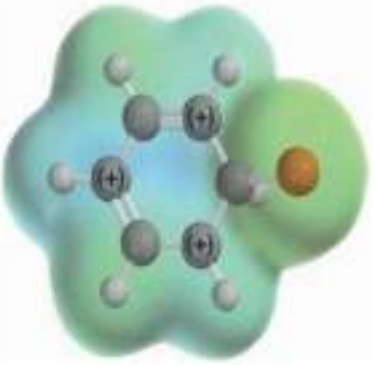


Chlorine (a Lewis base) | Ferric chloride (a Lewis acid) | A molecular complex with a positive charge on chlorine and a negative charge on iron | An ion pair containing a chloronium ion

STEP 2: Reaction of a nucleophile and an electrophile to form a new covalent bond. Reaction of the Cl_2–$FeCl_3$ ion pair with the pi electron cloud of the aromatic ring forms a resonance-stabilized cation intermediate, represented here as a hybrid of three contributing structures:

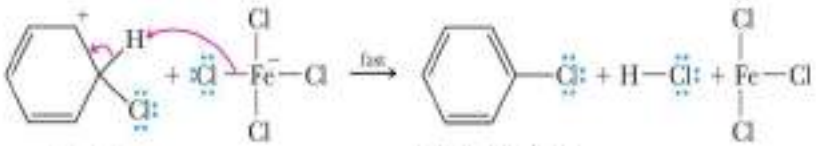


(the nucleophile) | Resonance-stabilized cation intermediate



The positive charge on the resonance-stabilized intermediate is distributed approximately equally on the carbon atoms 2, 4, and 6 of the ring relative to the point of substitution.

STEP 3: Take a proton away. Proton transfer from the cation intermediate to $FeCl_4^-$ forms HCl, regenerates the Lewis acid catalyst, and gives chlorobenzene:



Cation intermediate | Chlorobenzene

Treatment of benzene with bromine in the presence of ferric chloride or aluminum chloride gives bromobenzene and HBr. The mechanism for this reaction is the same as that for chlorination of benzene.

The major difference between the addition of halogen to an alkene and substitution by halogen on an aromatic ring is the fate of the cation intermediate formed after the halogen is added to the compound. Recall from Section 5.3C that the addition of chlorine to an alkene is a two-step process, the first and slower step of which

is the formation of a bridged chloronium ion intermediate. This intermediate then reacts with chloride ion to complete the addition. With aromatic compounds, the cation intermediate loses H^+ to regenerate the aromatic ring and regain its large resonance stabilization. There is no such resonance stabilization to be regained in the case of an alkene.

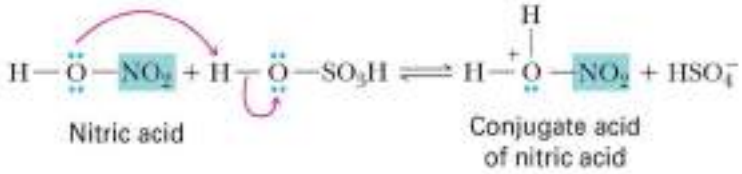
B. Nitration and Sulfonation

The sequence of steps for the nitration and sulfonation of benzene is similar to that for chlorination and bromination. For nitration, the electrophile is the **nitronium ion**, NO_2^+, generated by the reaction of nitric acid with sulfuric acid. In the following equations nitric acid is written $HONO_2$ to show more clearly the origin of the nitronium ion.

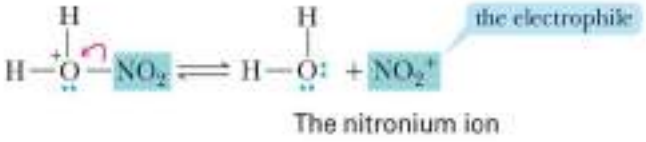
Mechanism

Formation of the Nitronium Ion

STEP 1: **Add a proton.** Proton transfer from sulfuric acid to the OH group of nitric acid gives the conjugate acid of nitric acid:



STEP 2: **Break a bond to form a stable ion or molecule.** Loss of water from this conjugate acid gives the nitronium ion, NO_2^+:

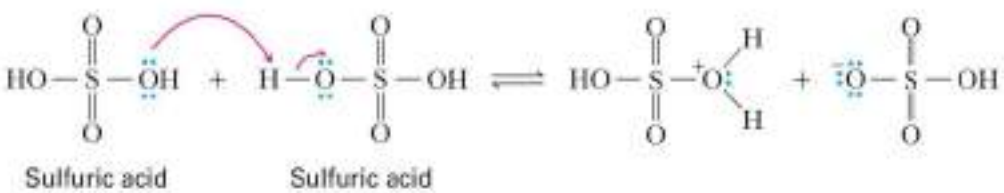


Mechanism

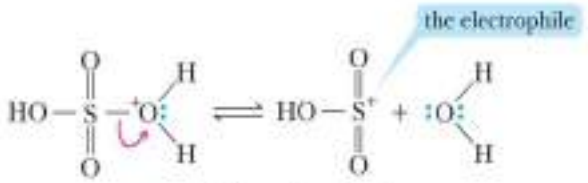
Formation of the Sulfonium Ion

The sulfonation of benzene is carried out using hot, concentrated sulfuric acid. The electrophile under these conditions is either SO_3 or HSO_3^+, depending on the experimental conditions. The HSO_3^+ electrophile is formed from sulfuric acid in the following way:

STEP 1: **Add a proton.** Proton transfer from one molecule of sulfuric acid to the OH group of another molecule of sulfuric acid gives the conjugate acid of sulfuric acid:



STEP 2: Break a bond to form a more stable ion or molecule. Loss of water from this conjugate acid gives the sulfonium ion as the electrophile:



The sulfonium ion

EXAMPLE 9.4

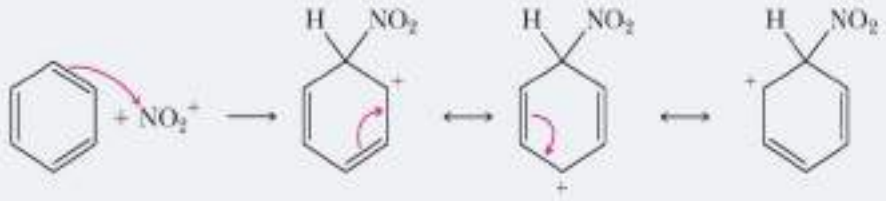
Write a stepwise mechanism for the nitration of benzene.

STRATEGY

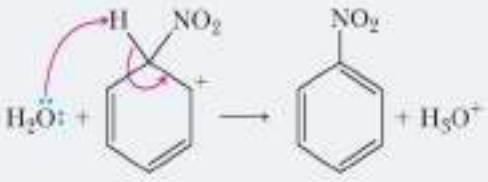
Keep in mind that the mechanisms of electrophilic aromatic substitution reactions are all very similar. After the formation of the electrophile, attack of the electrophile on the aromatic ring occurs to give a resonance-stabilized cation intermediate. The last step of the mechanism is proton transfer to a base to regenerate the aromatic ring. The base in nitration is water, which was generated in the formation of the electrophile.

SOLUTION

STEP 1: Reaction of a nucleophile and an electrophile to form a new covalent bond. Reaction of the nitronium ion (an electrophile) with the benzene ring (a nucleophile) gives a resonance-stabilized cation intermediate.



STEP 2: Take a proton away. Proton transfer from this intermediate to H_2O regenerates the aromatic ring and gives nitrobenzene:



Nitrobenzene

See problems 9.21, 9.22

PROBLEM 9.4

Write a stepwise mechanism for the sulfonation of benzene. Use HSO_3^+ as the electrophile.

C. Friedel–Crafts Alkylation

Alkylation of aromatic hydrocarbons was discovered in 1877 by the French chemist Charles Friedel and a visiting American chemist, James Crafts. They discovered that mixing benzene, a haloalkane, and $AlCl_3$ results in the formation of an alkylbenzene and

HX. **Friedel–Crafts alkylation** forms a new carbon–carbon bond between benzene and an alkyl group, as illustrated by reaction of benzene with 2-chloropropane in the presence of aluminum chloride:

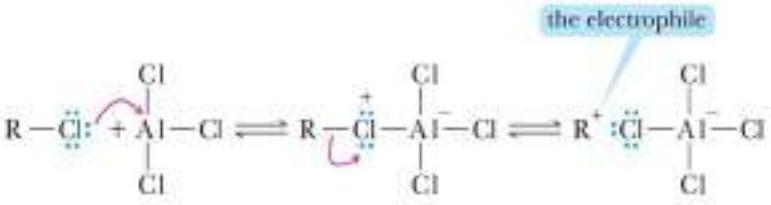
Benzene | 2-Chloropropane (Isopropyl chloride) | Isopropylbenzene (Cumene)

Friedel–Crafts alkylation is among the most important methods for forming new carbon–carbon bonds to aromatic rings.

Mechanism

Friedel-Crafts Alkylation

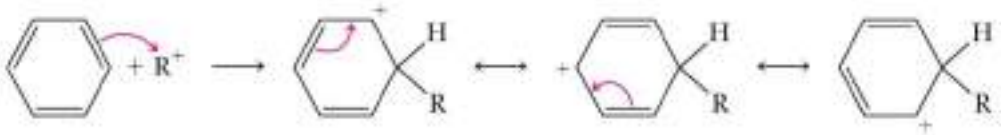
STEP 1: **Formation of an electrophile.** Reaction of a haloalkane (a Lewis base) with aluminum chloride (a Lewis acid) gives a molecular complex in which aluminum has a negative formal charge and the halogen of the haloalkane has a positive formal charge. Redistribution of electrons in this complex then gives an alkyl carbocation as part of an ion pair:



A molecular complex with a positive charge on chlorine and a negative charge on aluminum

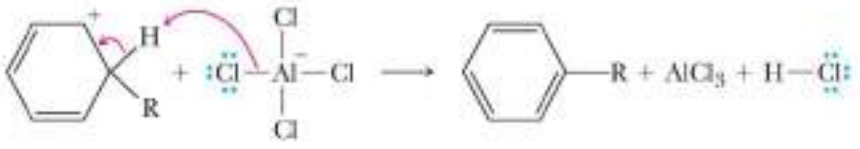
An ion pair containing a carbocation

STEP 2: **Reaction of a nucleophile and an electrophile to form a new covalent bond.** Reaction of the alkyl carbocation with the pi electrons of the aromatic ring gives a resonance-stabilized cation intermediate:



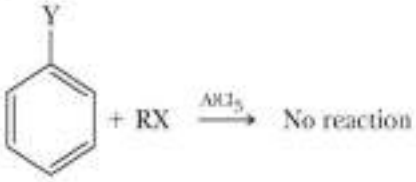
The positive charge is delocalized onto three atoms of the ring

STEP 3: **Take a proton away.** Proton transfer regenerates the aromatic character of the ring and the Lewis acid catalyst:



There are two major limitations on Friedel–Crafts alkylations. The first is that it is practical only with stable carbocations, such as 3° carbocations, resonance-stabilized carbocations, or 2° carbocations that cannot undergo rearrangement (Section 5.4). Primary carbocations will undergo rearrangement, resulting in multiple products as well as bonding of the benzene ring to unexpected carbons in the former haloalkane.

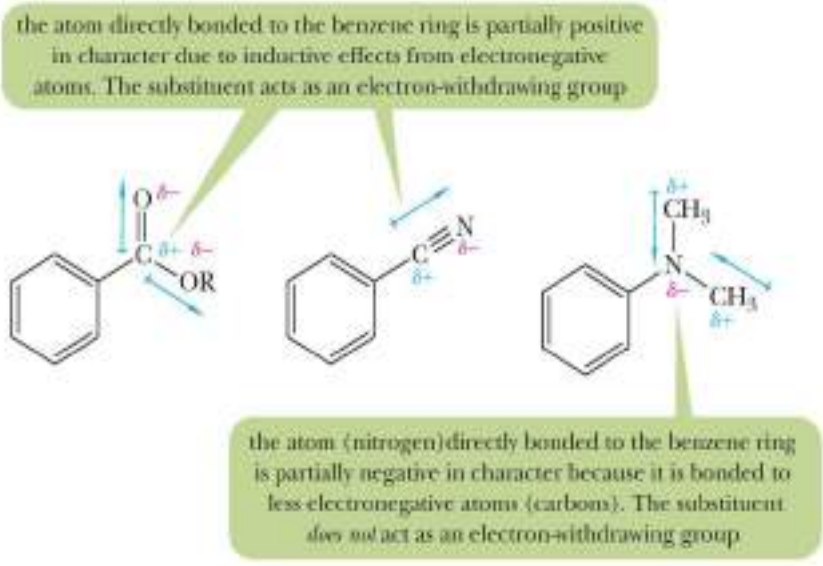
The second limitation on Friedel–Crafts alkylation is that it fails altogether on benzene rings bearing one or more strongly electron-withdrawing groups. The following table shows some of these groups:



When Y Equals Any of These Groups, the Benzene Ring Does Not Undergo Friedel–Crafts Alkylation				
$-\overset{O}{\overset{\|}{C}}H$	$-\overset{O}{\overset{\|}{C}}R$	$-\overset{O}{\overset{\|}{C}}OH$	$-\overset{O}{\overset{\|}{C}}OR$	$-\overset{O}{\overset{\|}{C}}NH_2$
$-SO_3H$	$-C{\equiv}N$	$-NO_2$	$-NR_3^+$	
$-CF_3$	$-CCl_3$			

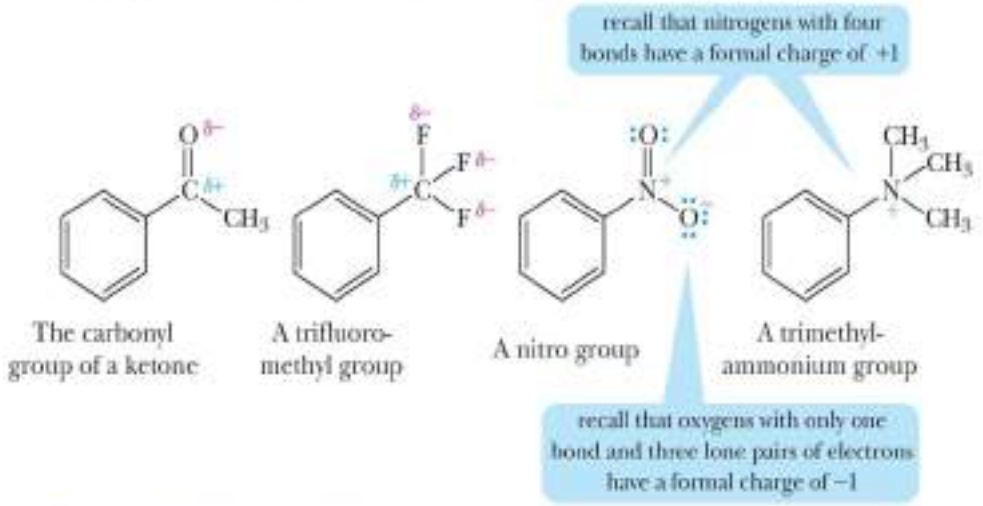
HOW TO 9.2 Determine Whether a Substituent on Benzene Is Electron Withdrawing

Determine the charge or partial charge on the atom directly bonded to the benzene ring. If it is positive or partially positive, the substituent can be considered to be electron withdrawing. An atom will be partially positive if it is bonded to an atom more electronegative than itself.



A common characteristic of the groups listed in the preceding table is that each has either a full or partial positive charge on the atom bonded to the benzene ring. For carbonyl-containing compounds, this partial positive charge arises because of the difference in electronegativity between the carbonyl oxygen and carbon. For $-CF_3$ and $-CCl_3$ groups, the partial positive charge on carbon arises because of the difference in electronegativity

between carbon and the halogens bonded to it. In both the nitro group and the trialkylammonium group, there is a positive charge on nitrogen:

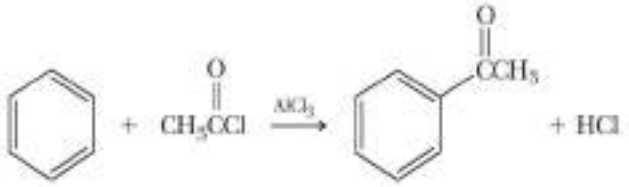


The carbonyl group of a ketone | A trifluoromethyl group | A nitro group | A trimethylammonium group

D. Friedel–Crafts Acylation

Acyl halide A derivative of a carboxylic acid in which the —OH of the carboxyl group is replaced by a halogen—most commonly, chlorine.

Friedel and Crafts also discovered that treating an aromatic hydrocarbon with an acyl halide in the presence of aluminum chloride gives a ketone. An **acyl halide** is a derivative of a carboxylic acid in which the —OH of the carboxyl group is replaced by a halogen, most commonly chlorine. Acyl halides are also referred to as acid halides. An RCO— group is known as an acyl group; hence, the reaction of an acyl halide with an aromatic hydrocarbon is known as **Friedel–Crafts acylation**, as illustrated by the reaction of benzene and acetyl chloride in the presence of aluminum chloride to give acetophenone:



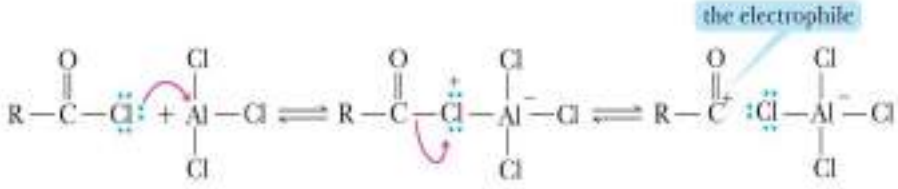
Benzene | Acetyl chloride (an acyl halide) | Acetophenone (a ketone)

In Friedel–Crafts acylations, the electrophile is an acylium ion, generated in the following way:

Mechanism

Friedel–Crafts Acylation—Generation of an Acylium Ion

STEP 1: **Formation of an electrophile.** Reaction between the halogen atom of the acyl chloride (a Lewis base) and aluminum chloride (a Lewis acid) gives a molecular complex. The redistribution of valence electrons in turn gives an ion pair containing an **acylium ion**:

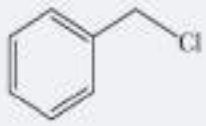


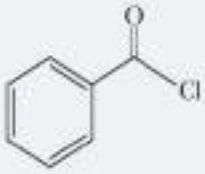
An acyl chloride (a Lewis acid) | Aluminum chloride (a Lewis acid) | A molecular complex with a positive charge on chlorine and a negative charge on aluminum | An ion pair containing an acylium ion

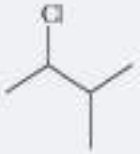
Steps 2 and 3 are identical to steps 2 and 3 of Friedel–Crafts alkylation (Section 9.6C).

EXAMPLE 9.5

Write a structural formula for the product formed by Friedel–Crafts alkylation or acylation of benzene with

(a) 

(b) 

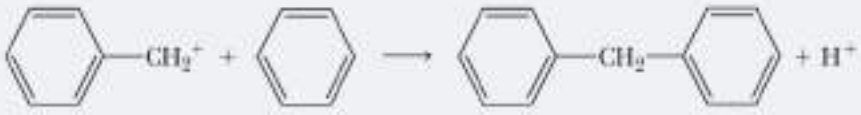
(c) 

STRATEGY

Utilize the fact that the halogenated reagent in Friedel–Crafts reactions will normally form a bond with benzene at the carbon bonded to the halogen (Br or Cl). Therefore, to predict the product of a Friedel–Crafts reaction, replace the halogen in the haloalkane or acyl halide with the benzene ring. One thing to be wary of, however, is the possibility of rearrangement once the carbocation is formed.

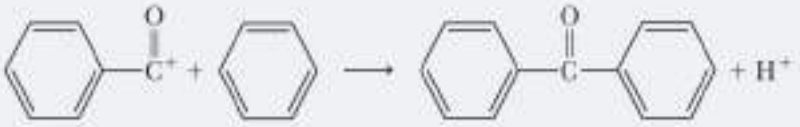
SOLUTION

(a) Treatment of benzyl chloride with aluminum chloride gives the resonance-stabilized benzyl cation. Reaction of this cation (an electrophile) with benzene (a nucleophile), followed by loss of H^+, gives diphenylmethane:



Benzyl cation (an electrophile) | (a nucleophile) | Diphenylmethane

(b) Treatment of benzoyl chloride with aluminum chloride gives an acyl cation. Reaction of this cation with benzene, followed by loss of H^+, gives benzophenone:



Benzoyl cation (an electrophile) | Benzophenone

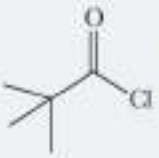
(c) Treatment of 2-chloro-3-methylbutane with aluminum chloride gives a 2° carbocation. Because there is an adjacent 3° hydrogen, a 1,2-hydride shift can occur to form the more stable 3° carbon. It is this carbon that reacts with benzene, followed by loss of H^+, to give 2-methyl-2-phenylbutane.

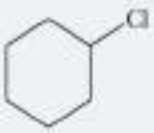
A 2° carbocation | A 3° carbocation | 2-Methyl-2-phenylbutane

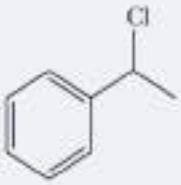
See problems 9.18, 9.19

PROBLEM 9.5

Write a structural formula for the product formed from Friedel–Crafts alkylation or acylation of benzene with

(a) 

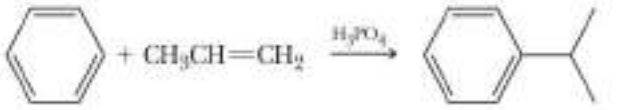
(b) 

(c) 

E. Other Electrophilic Aromatic Alkylations

Once it was discovered that Friedel–Crafts alkylations and acylations involve cationic intermediates, chemists realized that other combinations of reagents and catalysts could give the same intermediates. We study two of these reactions in this section: the generation of carbocations from alkenes and from alcohols.

As we saw in Section 5.3B, treatment of an alkene with a strong acid, most commonly H_2SO_4 or H_3PO_4, generates a carbocation. Isopropylbenzene is synthesized industrially by reacting benzene with propene in the presence of an acid catalyst:



Benzene Propene Isopropylbenzene (Cumene)

Carbocations are also generated by treating an alcohol with H_2SO_4 or H_3PO_4 (Section 8.2E):

Benzene 2-Methyl-2-phenylpropane (*tert*-Butylbenzene)

EXAMPLE 9.6

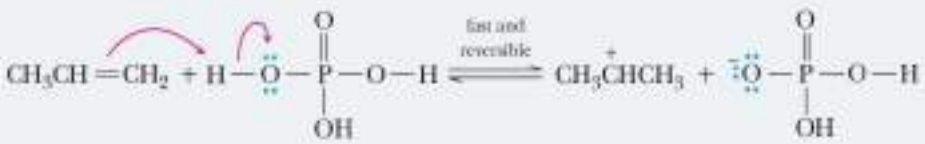
Write a mechanism for the formation of isopropylbenzene from benzene and propene in the presence of phosphoric acid.

STRATEGY

Draw the mechanism for the formation of the carbocation. This step constitutes the generation of the electrophile. The remaining steps in the mechanism are the usual: attack of the electrophile on benzene and proton transfer to rearomatize the ring.

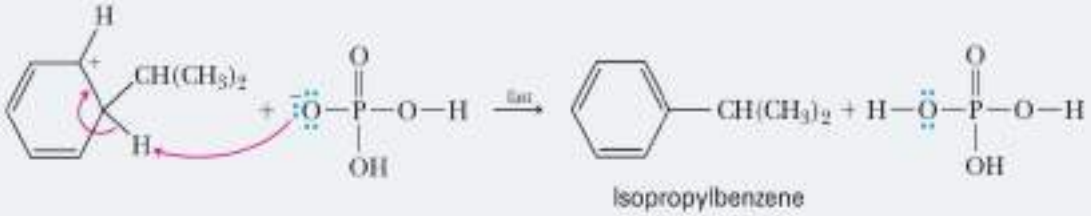
SOLUTION

STEP 1: **Add a proton.** Proton transfer from phosphoric acid to propene gives the isopropyl cation:



STEP 2: **Reaction of a nucleophile and an electrophile to form a new covalent bond.** Reaction of the isopropyl cation with benzene gives a resonance-stabilized carbocation intermediate:

STEP 3: Take a proton away. Proton transfer from this intermediate to dihydrogen phosphate ion gives isopropylbenzene:



Isopropylbenzene

See problems 9.18, 9.19, 9.33, 9.34

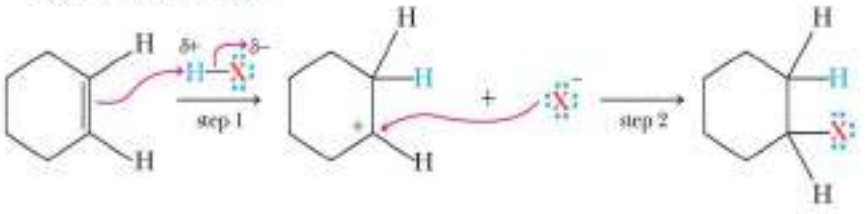
PROBLEM 9.6

Write a mechanism for the formation of *tert*-butylbenzene from benzene and *tert*-butyl alcohol in the presence of phosphoric acid.

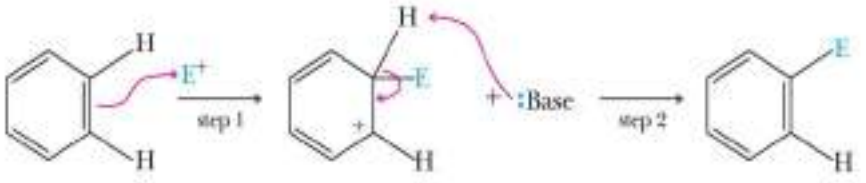
F. Comparison of Alkene Addition and Electrophilic Aromatic Substitution (EAS)

Electrophilic aromatic substitution represents the second instance in which we have encountered a C=C double bond attacking an electrophile. The first instance was in our discussion of alkene addition reactions in Section 5.3. Notice the similarities in the first step where a C=C double bond attacks an electrophilic atom (H^+ or E^+). In Step 2, however, alkene addition results in the attack of a nucleophile on the carbocation, while EAS results in abstraction of a hydrogen by base. In one reaction, the C=C double bond is destroyed, while in the other, the C=C double bond is regenerated.

Addition to an Alkene



Electrophilic Aromatic Substitution



9.7 How Do Existing Substituents on Benzene Affect Electrophilic Aromatic Substitution?

A. Effects of a Substituent Group on Further Substitution

In the electrophilic aromatic substitution of a monosubstituted benzene, three isomeric products are possible: The new group may be oriented ortho, meta, or para to the existing group. On the basis of a wealth of experimental observations, chemists have made the

following generalizations about the manner in which an existing substituent influences further electrophilic aromatic substitution:

1. *Substituents affect the orientation of new groups.* Certain substituents direct a second substituent preferentially to the ortho and para positions; other substituents direct it preferentially to a meta position. In other words, we can classify substituents on a benzene ring as **ortho–para directing** or **meta directing**.
2. *Substituents affect the rate of further substitution.* Certain substituents cause the rate of a second substitution to be greater than that of benzene itself, whereas other substituents cause the rate of a second substitution to be lower than that of benzene. In other words, we can classify groups on a benzene ring as **activating** or **deactivating** toward further substitution.

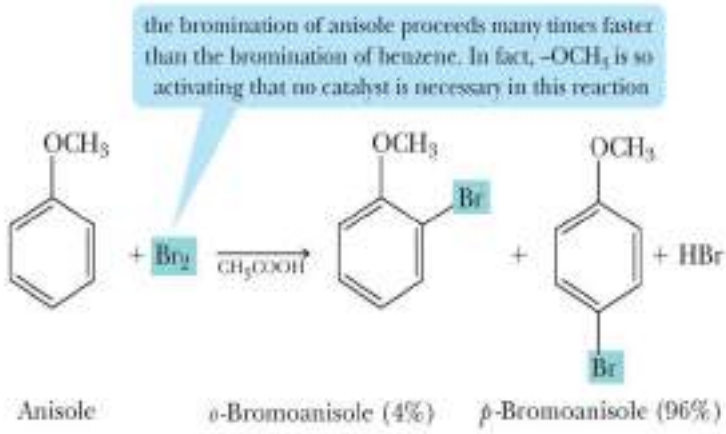
Ortho–para director Any substituent on a benzene ring that directs electrophilic aromatic substitution preferentially to ortho and para positions.

Meta director Any substituent on a benzene ring that directs electrophilic aromatic substitution preferentially to a meta position.

Activating group Any substituent on a benzene ring that causes the rate of electrophilic aromatic substitution to be greater than that for benzene.

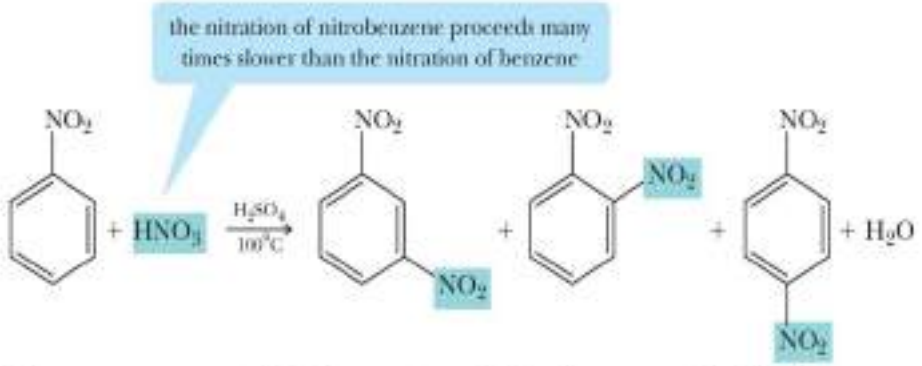
Deactivating group Any substituent on a benzene ring that causes the rate of electrophilic aromatic substitution to be lower than that for benzene.

To see the operation of these directing and activating–deactivating effects, compare, for example, the products and rates of bromination of anisole and nitrobenzene. Bromination of anisole proceeds at a rate 1.8×10^9 greater than that of bromination of benzene (the methoxy group is activating), and the product is a mixture of *o*-bromoanisole and *p*-bromoanisole (the methoxy group is ortho–para directing):



Anisole *o*-Bromoanisole (4%) *p*-Bromoanisole (96%)

We see quite another situation in the nitration of nitrobenzene, which proceeds 10,000 times slower than the nitration of benzene itself. (A nitro group is strongly deactivating.) Also, the product consists of approximately 93% of the meta isomer and less than 7% of the ortho and para isomers combined (the nitro group is meta directing):



Nitrobenzene *m*-Dinitrobenzene (93%) *o*-Dinitrobenzene *p*-Dinitrobenzene

Less than 7% combined

Table 9.1 lists the directing and activating–deactivating effects for the major functional groups with which we are concerned in this text.

TABLE 9.1 Effects of Substituents on Further Electrophilic Aromatic Substitution

Ortho–Para Directing	strongly activating	$-\ddot{N}H_2$	$-\ddot{N}HR$	$-\ddot{N}R_2$	$-\ddot{O}H$	$-\ddot{O}R$	
	moderately activating	$-\ddot{N}HCR$ (O)	$-\ddot{N}HCAr$ (O)	$-\ddot{O}CR$ (O)	$-\ddot{O}CAr$ (O)		
	weakly activating	$-R$					
	weakly deactivating	$-\ddot{F}:$	$-\ddot{Cl}:$	$-\ddot{Br}:$	$-\ddot{I}:$		
Meta Directing	moderately deactivating	$-CH$ (O)	$-CR$ (O)	$-COH$ (O)	$-COR$ (O)	$-CNH_2$ (O)	$-SOH$ (O, O)
	strongly deactivating	$-NO_2$	$-NH_3^+$	$-CF_3$	$-CCl_3$		

Relative importance in directing further substitution

increasing reactivity relative to benzene

decreasing reactivity relative to benzene

If we compare these ortho–para and meta directors for structural similarities and differences, we can make the following generalizations:

1. Alkyl groups, phenyl groups, and substituents in which the atom bonded to the ring has an unshared pair of electrons are ortho–para directing. All other substituents are meta directing.
2. Except for the halogens, all ortho–para directing groups are activating toward further substitution. The halogens are weakly deactivating.
3. All meta directing groups carry either a partial or full positive charge on the atom bonded to the ring.

We can illustrate the usefulness of these generalizations by considering the synthesis of two different disubstituted derivatives of benzene. Suppose we wish to prepare *m*-bromonitrobenzene from benzene. This conversion can be carried out in two steps: nitration and bromination. If the steps are carried out in just that order, the major product is indeed *m*-bromonitrobenzene. The nitro group is a meta director and directs bromination to a meta position:

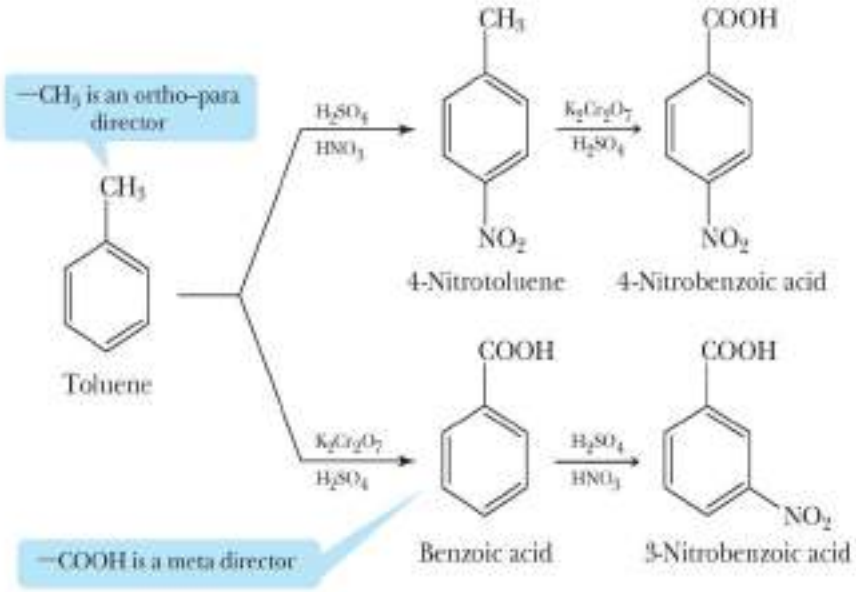
Nitrobenzene *m*-Bromonitrobenzene

If, however, we reverse the order of the steps and first form bromobenzene, we now have an ortho–para directing group on the ring. Nitration of bromobenzene then

takes place preferentially at the ortho and para positions, with the para product predominating:

Bromobenzene o-Bromonitrobenzene p-Bromonitrobenzene

As another example of the importance of order in electrophilic aromatic substitutions, consider the conversion of toluene to nitrobenzoic acid. The nitro group can be introduced with a nitrating mixture of nitric and sulfuric acids. The carboxyl group can be produced by oxidation of the methyl group (Section 9.4).



Nitration of toluene yields a product with the two substituents para to each other, whereas nitration of benzoic acid yields a product with the substituents meta to each other. Again, we see that the order in which the reactions are performed is critical.

Note that, in this last example, we show nitration of toluene producing only the para isomer. In practice, because methyl is an ortho–para directing group, both ortho and para isomers are formed. In problems in which we ask you to prepare one or the other of these isomers, we assume that both form and that there are physical methods by which you can separate them and obtain the desired isomer.

EXAMPLE 9.7

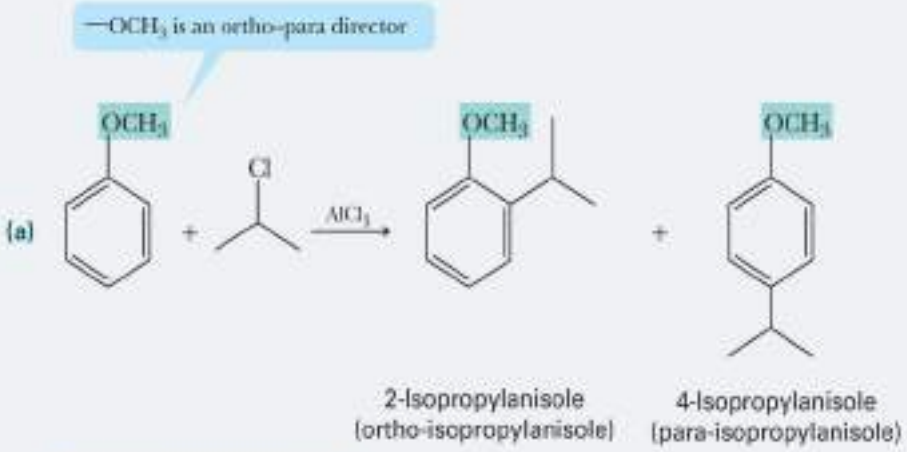
Complete the following electrophilic aromatic substitution reactions. Where you predict meta substitution, show only the meta product. Where you predict ortho–para substitution, show both products:

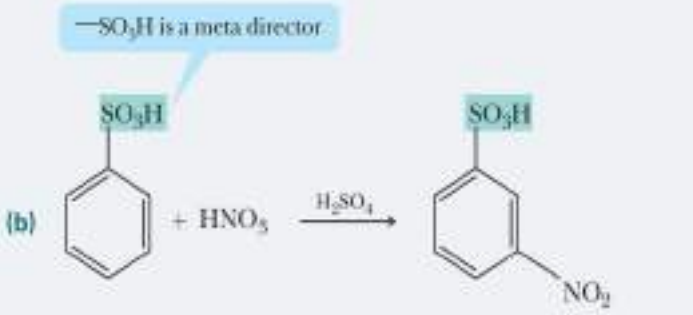
STRATEGY

Determine whether the existing substituent is ortho–para or meta directing prior to completing the reaction.

SOLUTION

The methoxyl group in (a) is ortho–para directing and strongly activating. The sulfonic acid group in (b) is meta directing and moderately deactivating.





See problems 9.24–9.26, 9.31, 9.32, 9.42–9.44, 9.46, 9.47

PROBLEM 9.7

Complete the following electrophilic aromatic substitution reactions. Where you predict meta substitution, show only the meta product. Where you predict ortho–para substitution, show both products:

B. Theory of Directing Effects

As we have just seen, a group on an aromatic ring exerts a major effect on the patterns of further substitution. We can make these three generalizations:

1. If there is a lone pair of electrons on the atom bonded to the ring, the group is an ortho–para director.
2. If there is a full or partial positive charge on the atom bonded to the ring, the group is a meta director.
3. Alkyl groups are ortho–para directors.

We account for these patterns by means of the general mechanism for electrophilic aromatic substitution first presented in Section 9.5. Let us extend that mechanism to consider how a group already present on the ring might affect the relative stabilities of cation intermediates formed during a second substitution reaction.

We begin with the fact that the rate of electrophilic aromatic substitution is determined by the slowest step in the mechanism, which, in almost every reaction of an electrophile with the aromatic ring, is attack of the electrophile on the ring to give a resonance-stabilized cation intermediate. Thus, we must determine which of the alternative carbocation intermediates (that for ortho–para substitution or that for meta substitution) is the more stable. That is, we need to show which of the alternative cationic intermediates has the lower activation energy for its formation.

Nitration of Anisole

The rate-determining step in nitration is reaction of the nitronium ion with the aromatic ring to produce a resonance-stabilized cation intermediate. Figure 9.4 shows the cation intermediate formed by reaction meta to the methoxy group. The figure also shows the cationic intermediate formed by reaction para to the methoxy group. The intermediate formed by reaction at a meta position is a hybrid of three major contributing structures: (a), (b), and (c). These three are the only important contributing structures we can draw for reaction at a meta position.

The cationic intermediate formed by reaction at the para position is a hybrid of four major contributing structures: (d), (e), (f), and (g). What is important about structure (f) is that all atoms in it have complete octets, which means that this structure contributes more to the hybrid than structures (d), (e), or (g). Because the cation formed by reaction at an ortho or para position on anisole has a greater resonance stabilization and, hence, a lower activation energy for its formation, nitration of anisole occurs preferentially in the ortho and para positions.

Nitration of Nitrobenzene

Figure 9.5 shows the resonance-stabilized cation intermediates formed by reaction of the nitronium ion meta to the nitro group and also para to it.

Each cation in the figure is a hybrid of three contributing structures; no additional ones can be drawn. Now we must compare the relative resonance stabilizations of each

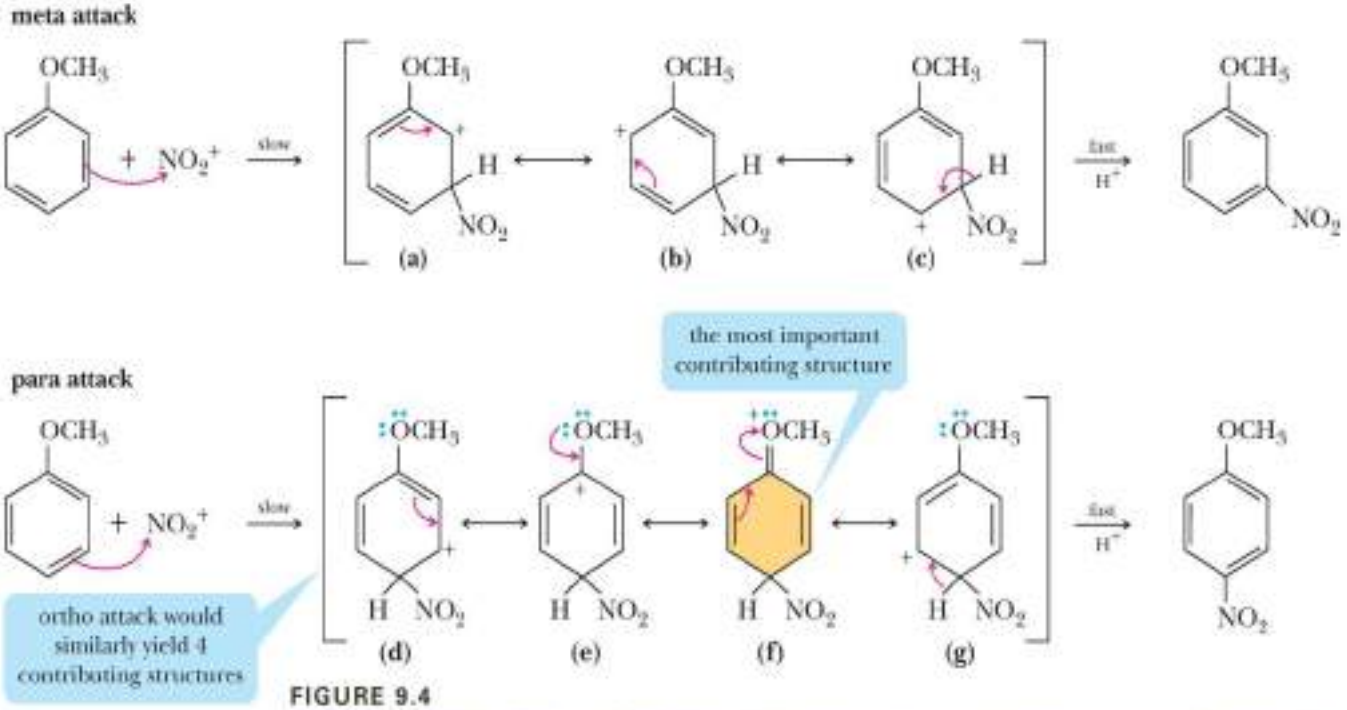


FIGURE 9.4
Nitration of anisole. Reaction of the electrophile meta and para to a methoxy group. Regeneration of the aromatic ring is shown from the rightmost contributing structure in each case.

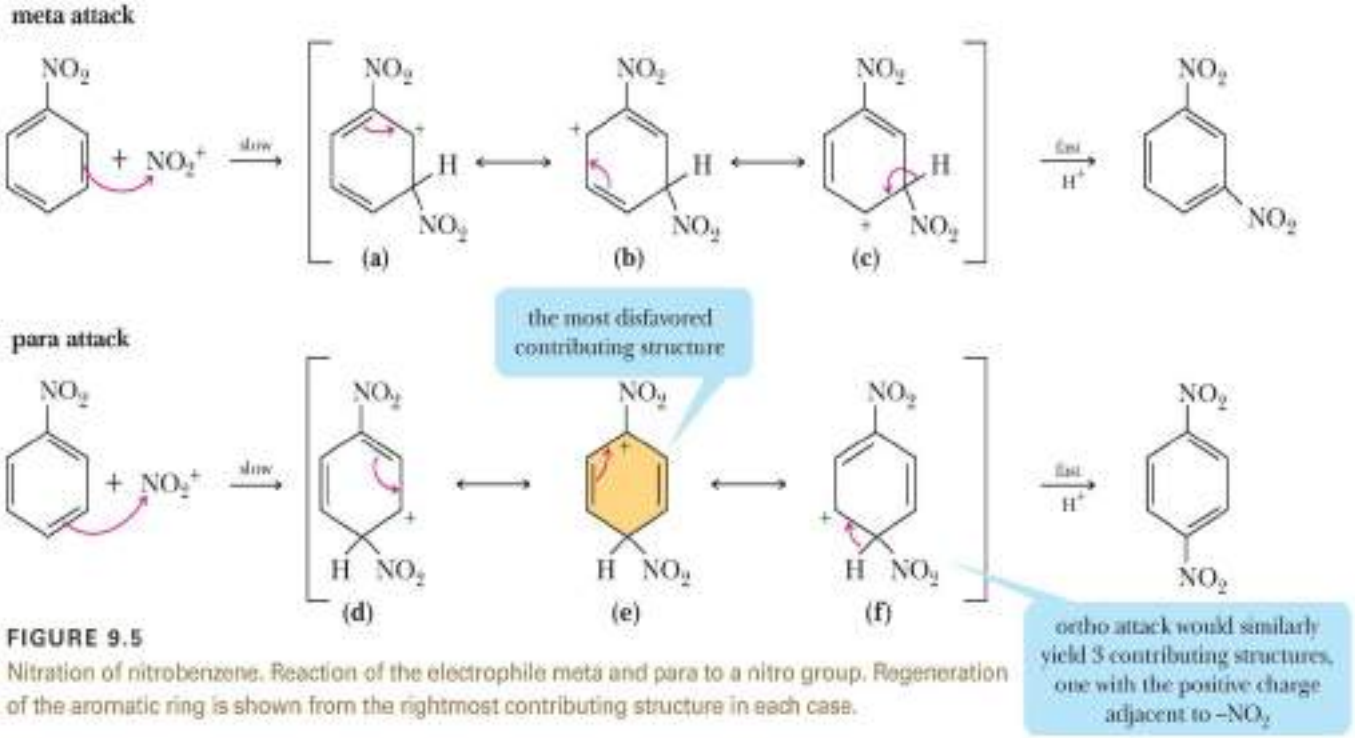
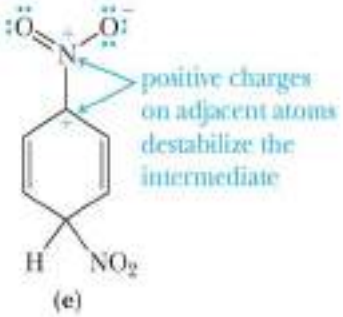


FIGURE 9.5
Nitration of nitrobenzene. Reaction of the electrophile meta and para to a nitro group. Regeneration of the aromatic ring is shown from the rightmost contributing structure in each case.

hybrid. If we draw a Lewis structure for the nitro group showing the positive formal charge on nitrogen, we see that contributing structure (e) places positive charges on adjacent atoms:



Because of the electrostatic repulsion thus generated, structure (e) makes only a negligible contribution to the hybrid. None of the contributing structures for reaction at a meta position places positive charges on adjacent atoms. As a consequence, resonance stabilization of the cation formed by reaction at a meta position is greater than that for the cation formed by reaction at a para (or ortho) position. Stated alternatively, the activation energy for reaction at a meta position is less than that for reaction at a para position.

A comparison of the entries in Table 9.1 shows that almost all ortho–para directing groups have an unshared pair of electrons on the atom bonded to the aromatic ring. Thus, the directing effect of most of these groups is due primarily to the ability of the atom bonded to the ring to delocalize further the positive charge on the cation intermediate.

The fact that alkyl groups are also ortho–para directing indicates that they, too, help to stabilize the cation intermediate. In Section 5.3A, we saw that alkyl groups stabilize carbocation intermediates and that the order of stability of carbocations is 3° > 2° > 1° > methyl. Just as alkyl groups stabilize the cation intermediates formed in reactions of alkenes, they also stabilize the carbocation intermediates formed in electrophilic aromatic substitutions.

To summarize, any substituent on an aromatic ring that further stabilizes the cation intermediate directs ortho–para, and any group that destabilizes the cation intermediate directs meta.

EXAMPLE 9.8

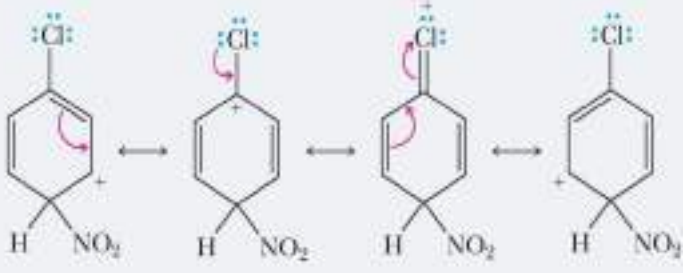
Draw contributing structures formed during the para nitration of chlorobenzene, and show how chlorine participates in directing the incoming nitronium ion to ortho–para positions.

STRATEGY

Draw the intermediate that is formed initially from para attack of the electrophile. Then draw a contributing structure by moving electrons from the pi bond adjacent to the positive charge. Repeat for all contributing structures until all resonance possibilities have been exhausted. *Note:* Be sure to look for resonance possibilities outside of the benzene ring.

SOLUTION

Contributing structures (a), (b), and (d) place the positive charge on atoms of the ring, while contributing structure (c) places it on chlorine and thus creates additional resonance stabilization for the cation intermediate:

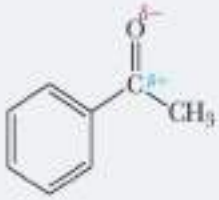


(a) (b) (c) (d)

See problem 9.29

PROBLEM 9.8

Because the electronegativity of oxygen is greater than that of carbon, the carbon of a carbonyl group bears a partial positive charge, and its oxygen bears a partial negative charge. Using this information, show that a carbonyl group is meta directing:



C. Theory of Activating–Deactivating Effects

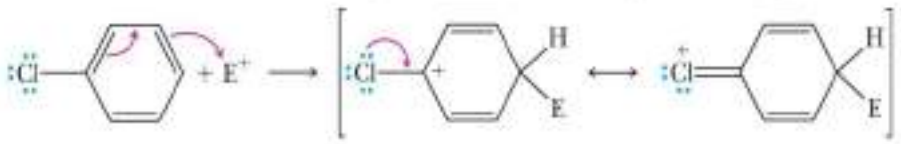
We account for the activating–deactivating effects of substituent groups by a combination of resonance and inductive effects:

1. Any resonance effect, such as that of $-NH_2$, $-OH$, and $-OR$, which delocalizes the positive charge of the cation intermediate lowers the activation energy for its formation and is activating toward further electrophilic aromatic substitution. That is, these groups increase the rate of electrophilic aromatic substitution, compared with the rate at which benzene itself reacts.
2. Any resonance or inductive effect, such as that of $-NO_2$, $-C{=}O$, $-SO_3H$, $-NR_3^+$, $-CCl_3$, and $-CF_3$, which decreases electron density on the ring, deactivates the ring to further substitution. That is, these groups decrease the rate of further electrophilic aromatic substitution, compared with the rate at which benzene itself reacts.
3. Any inductive effect (such as that of $-CH_3$ or another alkyl group), which releases electron density toward the ring, activates the ring toward further substitution.

In the case of the halogens, the resonance and inductive effects operate in opposite directions. As Table 9.1 shows, the halogens are ortho–para directing, but, unlike other ortho–para directors listed in the table, the halogens are weakly deactivating. These observations can be accounted for in the following way.

1. *The inductive effect of halogens.* The halogens are more electronegative than carbon and have an electron-withdrawing inductive effect. Aryl halides, therefore, react more slowly in electrophilic aromatic substitution than benzene does.

2. *The resonance effect of halogens.* A halogen ortho or para to the site of electrophilic attack stabilizes the cation intermediate by delocalization of the positive charge:



EXAMPLE 9.9

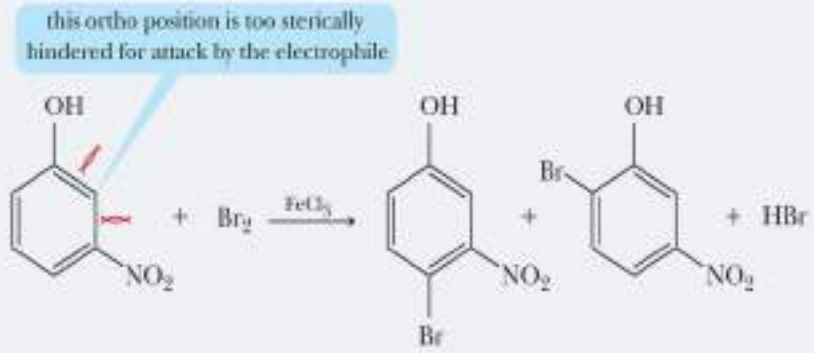
Predict the product of each electrophilic aromatic substitution.

STRATEGY

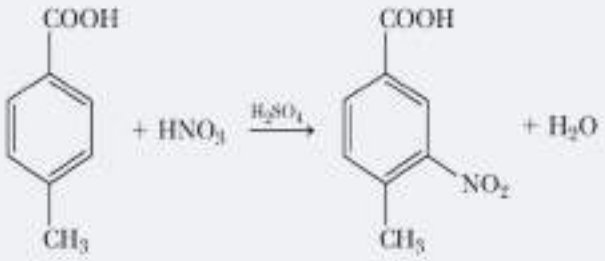
Determine the activating and deactivating effect of each group. The key to predicting the orientation of further substitution on a disubstituted arene is that ortho–para directing groups are always better at activating the ring toward further substitution than meta directing groups (Table 9.1). This means that, when there is competition between ortho–para directing and meta directing groups, the ortho–para group wins.

SOLUTION

(a) The ortho–para directing and activating —OH group determines the position of bromination. Bromination between the —OH and $-NO_2$ groups is only a minor product because of steric hindrance to attack of bromine at this position:



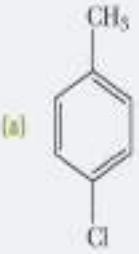
(b) The ortho–para directing and activating methyl group determines the position of nitration:

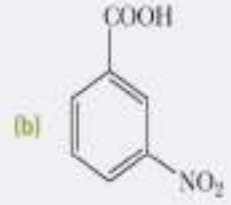


See problems 9.24–9.26, 9.31, 9.32, 9.42–9.44, 9.46, 9.47

PROBLEM 9.9

Predict the product of treating each compound with HNO_3/H_2SO_4:



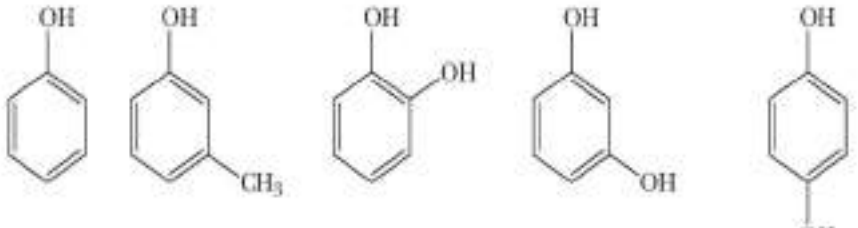


9.8 What Are Phenols?

A. Structure and Nomenclature

Phenol A compound that contains an —OH group bonded to a benzene ring.

The functional group of a **phenol** is a hydroxyl group bonded to a benzene ring. We name substituted phenols either as derivatives of phenol or by common names:

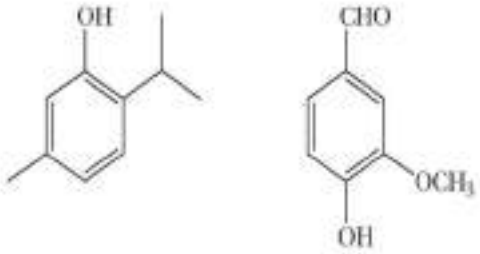


Phenol | 3-Methylphenol (*m*-Cresol) | 1,2-Benzenediol (Catechol) | 1,3-Benzenediol (Resorcinol) | 1,4-Benzenediol (Hydroquinone)

Erika Koga/Digital Vision/Getty Images, Inc

Thymol is a constituent of garden thyme, *Thymus vulgaris*.

Phenols are widely distributed in nature. Phenol itself and the isomeric cresols (*o*-, *m*-, and *p*-cresol) are found in coal tar. Thymol and vanillin are important constituents of thyme and vanilla beans, respectively:

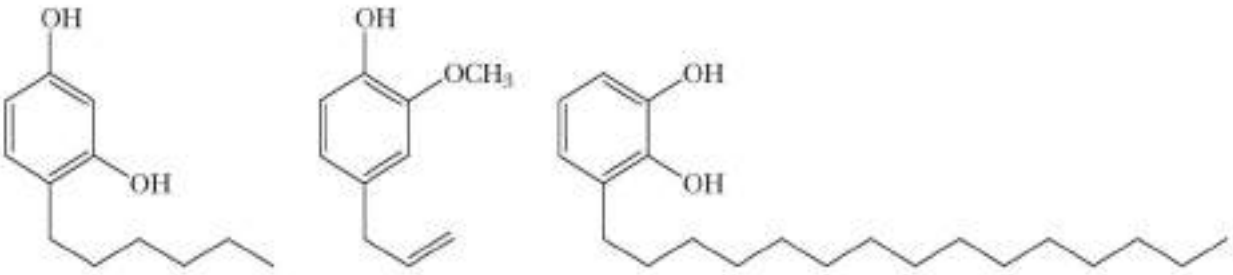


2-Isopropyl-5-methylphenol (Thymol) | 4-Hydroxy-3-methoxybenzaldehyde (Vanillin)

Charles D. Winters

Poison ivy.

Phenol, or carbolic acid, as it was once called, is a low-melting solid that is only slightly soluble in water. In sufficiently high concentrations, it is corrosive to all kinds of cells. In dilute solutions, phenol has some antiseptic properties and was introduced into the practice of surgery by Joseph Lister, who demonstrated his technique of aseptic surgery in the surgical theater of the University of Glasgow School of Medicine in 1865. Nowadays, phenol has been replaced by antiseptics that are both more powerful and have fewer undesirable side effects. Among these is hexylresorcinol, which is widely used in nonprescription preparations as a mild antiseptic and disinfectant.

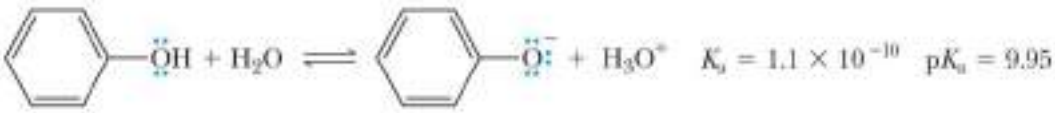


Hexylresorcinol Eugenol Urushiol

Eugenol, which can be isolated from the flower buds (cloves) of *Eugenia aromatica*, is used as a dental antiseptic and analgesic. Urushiol is the main component in the irritating oil of poison ivy.

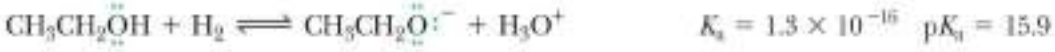
B. Acidity of Phenols

Phenols and alcohols both contain an —OH group. We group phenols as a separate class of compounds, however, because their chemical properties are quite different from those of alcohols. One of the most important of these differences is that phenols are significantly more acidic than are alcohols. Indeed, the acid ionization constant for phenol is 10^6 times larger than that of ethanol!



Phenol Phenoxide ion

$K_a = 1.1 \times 10^{-10}$ $pK_a = 9.95$



Ethanol Ethoxide ion

$K_a = 1.3 \times 10^{-16}$ $pK_a = 15.9$

Another way to compare the relative acid strengths of ethanol and phenol is to look at the hydrogen ion concentration and pH of a 0.1-M aqueous solution of each (Table 9.2). For comparison, the hydrogen ion concentration and pH of 0.1 M HCl are also included.

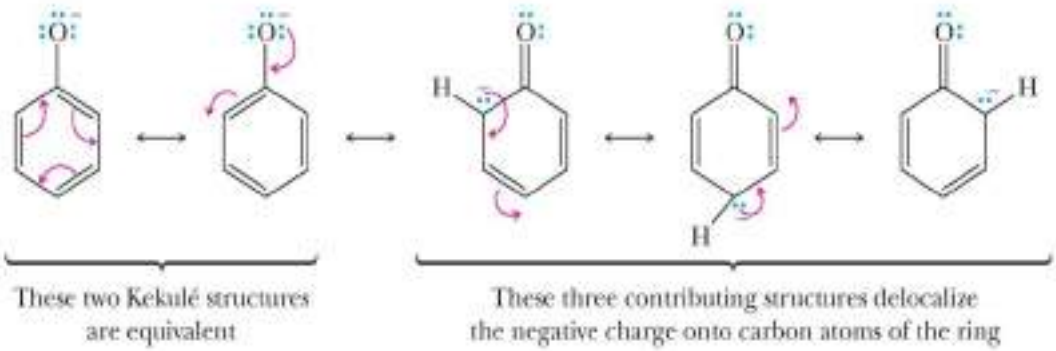
In aqueous solution, alcohols are neutral substances, and the hydrogen ion concentration of 0.1 M ethanol is the same as that of pure water. A 0.1-M solution of phenol is slightly acidic and has a pH of 5.4. By contrast, 0.1 M HCl, a strong acid (completely ionized in aqueous solution), has a pH of 1.0.

The greater acidity of phenols compared with alcohols results from the greater stability of the phenoxide ion compared with an alkoxide ion. The negative charge on the phenoxide ion is delocalized by resonance. The two contributing structures on the left for the phenoxide ion place the negative charge on oxygen, while the three on the right place the negative charge on the ortho and para positions of the ring. Thus, in the resonance hybrid, the negative charge of the phenoxide ion is delocalized over four atoms,

TABLE 9.2 Relative Acidities of 0.1-M Solutions of Ethanol, Phenol, and HCl

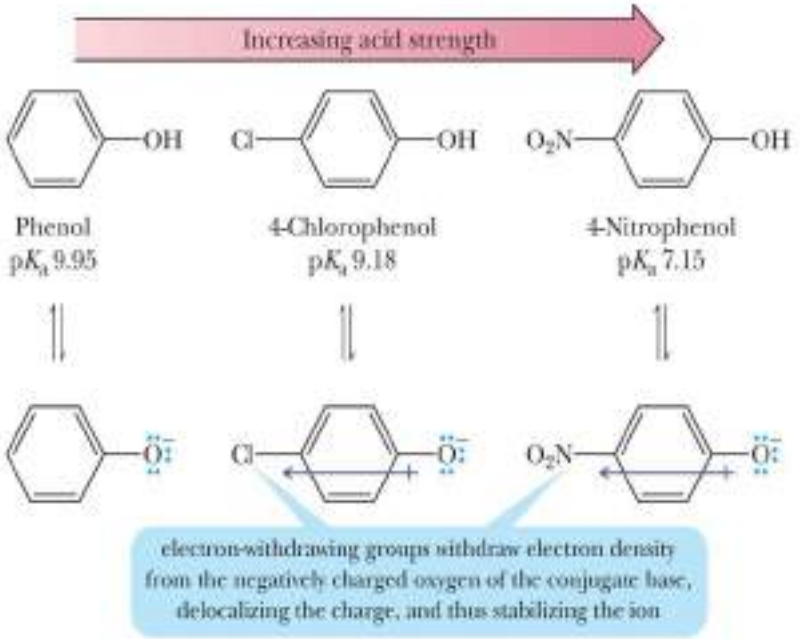
Acid Ionization Equation	$[H^+]$	pH
$CH_3CH_2OH + H_2O \rightleftharpoons CH_3CH_2O^- + H_3O^+$	1×10^{-7}	7.0
$C_6H_5OH + H_2O \rightleftharpoons C_6H_5O^- + H_3O^+$	3.3×10^{-6}	5.4
$HCl + H_2O \rightleftharpoons Cl^- + H_3O^+$	0.1	1.0

which stabilizes the phenoxide ion realtive to an alkoxide ion, for which no delocalization is possible:



Note that, although the resonance model gives us a way of understanding why phenol is a stronger acid than ethanol, it does not provide us with any quantitative means of predicting just how much stronger an acid it might be. To find out how much stronger one acid is than another, we must determine their pK_a values experimentally and compare them.

Ring substituents, particularly halogen and nitro groups, have marked effects on the acidities of phenols through a combination of inductive and resonance effects. Because the halogens are more electronegative than carbon, they withdraw electron density from the negatively charged oxygen in the conjugate base, stabilizing the phenoxide ion. Nitro groups have greater electron-withdrawing ability than halogens and thus have a greater stabilizing effect on the phenoxide ion, making nitrophenol even more acidic than chlorophenol.



EXAMPLE 9.10

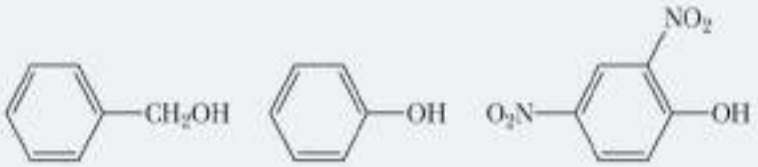
Arrange these compounds in order of increasing acidity: 2,4-dinitrophenol, phenol, and benzyl alcohol.

STRATEGY

Draw each conjugate base. Then determine which conjugate base is more stable using the principles of resonance and inductive effects. The more stable the conjugate base, the more acidic the acid from which it was generated.

SOLUTION

Benzyl alcohol, a primary alcohol, has a pK_a of approximately 16–18 (Section 8.2A). The pK_a of phenol is 9.95. Nitro groups are electron withdrawing and increase the acidity of the phenolic —OH group. In order of increasing acidity, these compounds are:



Benzyl alcohol
pK_a 16–18

Phenol
pK_a 9.95

2,4-Dinitrophenol
pK_a 3.96

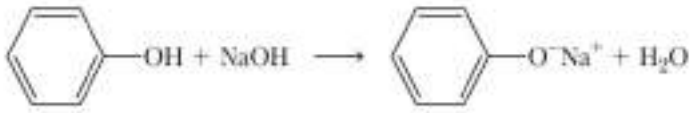
See problems 9.36–9.38

PROBLEM 9.10

Arrange these compounds in order of increasing acidity: 2,4-dichlorophenol, phenol, cyclohexanol.

C. Acid–Base Reactions of Phenols

Phenols are weak acids and react with strong bases, such as NaOH, to form water-soluble salts:



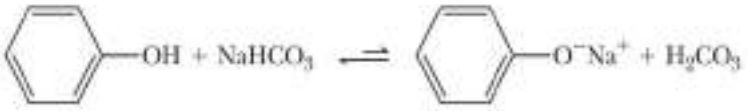
Phenol
pK_a 9.95
(stronger acid)

Sodium hydroxide
(stronger base)

Sodium phenoxide
(weaker base)

Water
pK_a 15.7
(weaker acid)

Most phenols do not react with weaker bases, such as sodium bicarbonate, and do not dissolve in aqueous sodium bicarbonate. Carbonic acid is a stronger acid than most phenols, and, consequently, the equilibrium for their reaction with bicarbonate ion lies far to the left (see Section 2.4):



Phenol
pK_a 9.95
(weaker acid)

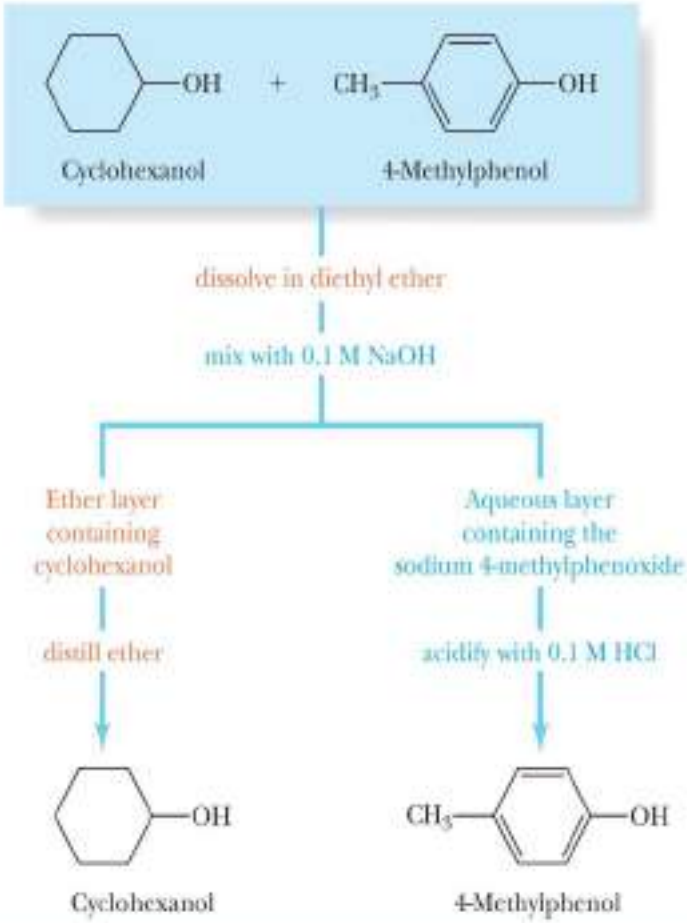
Sodium bicarbonate
(weaker base)

Sodium phenoxide
(stronger base)

Carbonic acid
pK_a 6.36
(stronger acid)

The fact that phenols are weakly acidic, whereas alcohols are neutral, provides a convenient way to separate phenols from water-insoluble alcohols. Suppose that we want to separate 4-methylphenol from cyclohexanol. Each is only slightly soluble in water; therefore, they cannot be separated on the basis of their water solubility. They can be separated, however, on the basis of their difference in acidity. First, the mixture of the two is dissolved in diethyl ether or some other water-immiscible solvent. Next, the ether solution is placed in a separatory funnel and shaken with dilute aqueous NaOH. Under these conditions, 4-methylphenol reacts with NaOH to give sodium 4-methylphenoxide, a water-soluble salt. The upper layer in the separatory funnel is now diethyl ether (density 0.74 g/cm^3), containing only dissolved cyclohexanol. The lower aqueous layer contains dissolved sodium 4-methylphenoxide. The layers are separated, and distillation of the ether (bp 35°C) leaves pure cyclohexanol (bp 161°C). Acidification of the aqueous phase with 0.1 M HCl or another

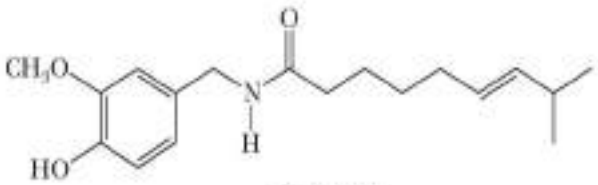
strong acid converts sodium 4-methylphenoxide to 4-methylphenol, which is insoluble in water and can be extracted with ether and recovered in pure form. The following flowchart summarizes these experimental steps:



Chemical Connections 9B

CAPSAICIN, FOR THOSE WHO LIKE IT HOT

Capsaicin, the pungent principle from the fruit of various peppers (*Capsicum* and *Solanaceae*), was isolated in 1876, and its structure was determined in 1919:



Capsaicin
(from various types of peppers)

The inflammatory properties of capsaicin are well known; the human tongue can detect as little as one drop of it in 5 L of water. Many of us are familiar with the burning sensation in the mouth and sudden tearing in the eyes caused by a good dose of hot chili peppers. Capsaicin-containing extracts from these flaming foods are also used in sprays to ward off dogs or other animals that might nip at your heels while you are running or cycling.

Ironically, capsaicin is able to cause pain and relieve it as well. Currently, two capsaicin-containing creams, Mioton and Zostrix®, are prescribed to treat the burning pain associated with postherpetic neuralgia, a complication of shingles. They are also prescribed for diabetics, to relieve persistent foot and leg pain.

The mechanism by which capsaicin relieves pain is not fully understood. It has been suggested that, after it is applied, the nerve endings in the area responsible for the transmission of pain remain temporarily numb. Capsaicin remains bound to specific receptor sites on these pain-transmitting neurons, blocking them from further action. Eventually, capsaicin is removed from the receptor sites, but in the meantime, its presence provides needed relief from pain.

Questions

Would you predict capsaicin to be more soluble in water or more soluble in 1-octanol?

Would your prediction remain the same if capsaicin were first treated with a molar equivalent of NaOH?

D. Phenols as Antioxidants

An important reaction in living systems, foods, and other materials that contain carbon–carbon double bonds is **autoxidation**—that is, oxidation requiring oxygen and no other reactant. If you open a bottle of cooking oil that has stood for a long time, you will notice a hiss of air entering the bottle. This sound occurs because the consumption of oxygen by autoxidation of the oil creates a negative pressure inside the bottle.

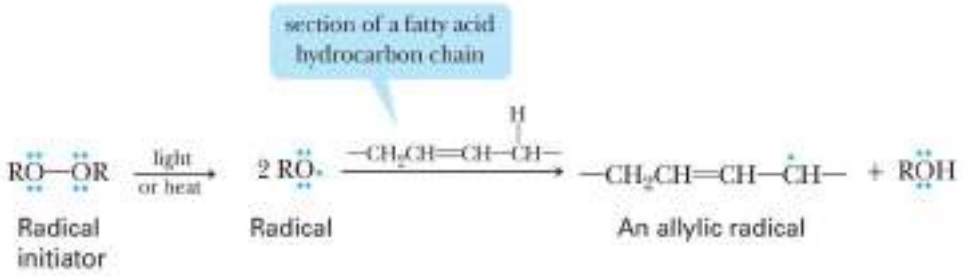
Cooking oils contain esters of polyunsaturated fatty acids. You need not worry now about what esters are; we will discuss them in Chapter 14. The important point here is that all vegetable oils contain fatty acids with long hydrocarbon chains, many of which have one or more carbon–carbon double bonds. (See Problem 4.44 for the structures of three of these fatty acids.) Autoxidation takes place at a carbon adjacent to a double bond—that is, at an **allylic carbon**.

Autoxidation is a radical chain process that converts an R—H group into an R—O—O—H group, called a *hydroperoxide*. The process begins when energy in the form of heat or light causes a molecule with a weak bond to form two **radicals**, atoms, or molecules with an unpaired electron. This step is known as **chain initiation**. In the laboratory, small amounts of compounds such as peroxides, ROOR, are used as initiators because they are easily converted to RO· radicals by light or heat. Scientists are still unsure precisely what compounds act as initiators in nature. Once a radical is generated, it reacts with a molecule by removing the hydrogen atom together with one of its electrons (H·) from an allylic carbon. The carbon losing the H· now has only seven electrons in its valence shell, one of which is unpaired.

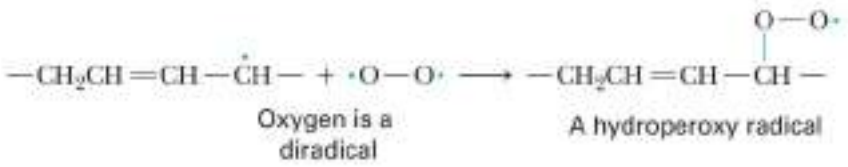
Mechanism

Autoxidation

STEP 1: Chain Initiation—Formation of a Radical from a Nonradical Compound. The radical generated from the exposure of the initiator to light or heat causes the removal of a hydrogen atom (H·) adjacent to a C=C double bond to give an allylic radical:



STEP 2a: Chain Propagation—Reaction of a Radical and Oxygen to Form a New Radical. The allylic radical reacts with oxygen, itself a diradical, to form a hydroperoxy radical. The new covalent bond of the hydroperoxy radical forms by the combination of one electron from the allylic radical and one electron from the oxygen diradical:

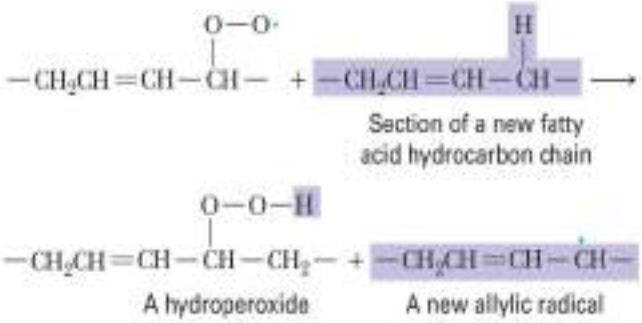


STEP 2b: Chain Propagation—Reaction of a Radical and a Molecule to Form a New Radical. The hydroperoxy radical removes an allylic hydrogen atom (H·) from a new fatty

(a) (b)

Although we represent molecular oxygen with the Lewis structure shown in (a), oxygen has long been known to exist and behave as a diradical, as shown in (b).

acid hydrocarbon chain to complete the formation of a hydroperoxide and, at the same time, produce a new allylic radical:



Charles D. Winters

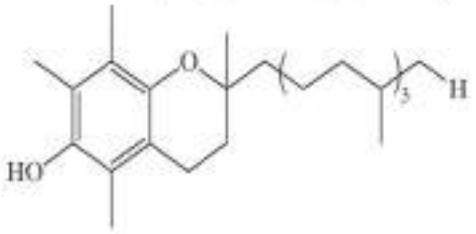
Butylated hydroxytoluene (BHT) is often used as an antioxidant in baked goods to "retard spoilage."

The most important point about the pair of chain propagation steps is that they form a continuous cycle of reactions. The new radical formed in Step 2b next reacts with another molecule of O_2 in Step 2a to give a new hydroperoxy radical, which then reacts with a new hydrocarbon chain to repeat Step 2b, and so forth. This cycle of propagation steps repeats over and over in a chain reaction. Thus, once a radical is generated in Step 1, the cycle of propagation steps may repeat many thousands of times, generating thousands and thousands of hydroperoxide molecules. The number of times the cycle of chain propagation steps repeats is called the **chain length**.

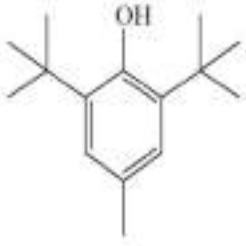
Hydroperoxides themselves are unstable and, under biological conditions, degrade to short-chain aldehydes and carboxylic acids with unpleasant "rancid" smells. These odors may be familiar to you if you have ever smelled old cooking oil or aged foods that contain polyunsaturated fats or oils. A similar formation of hydroperoxides in the low-density lipoproteins deposited on the walls of arteries leads to cardiovascular disease in humans. In addition, many effects of aging are thought to be the result of the formation and subsequent degradation of hydroperoxides.

Fortunately, nature has developed a series of defenses, including the phenol vitamin E, ascorbic acid (vitamin C), and glutathione, against the formation of destructive hydroperoxides. The compounds that defend against hydroperoxides are "nature's scavengers." Vitamin E, for example, inserts itself into either Step 2a or 2b, donates an H· from its phenolic —OH group to the allylic radical, and converts the radical to its original hydrocarbon chain. Because the vitamin E radical is stable, it breaks the cycle of chain propagation steps, thereby preventing the further formation of destructive hydroperoxides. While some hydroperoxides may form, their numbers are very small and they are easily decomposed to harmless materials by one of several enzyme-catalyzed reactions.

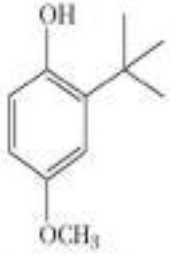
Unfortunately, vitamin E is removed in the processing of many foods and food products. To make up for this loss, phenols such as BHT and BHA are added to foods to "retard [their] spoilage" (as they say on the packages) by autoxidation:



Vitamin E



Butylated hydroxy-toluene (BHT)



Butylated hydroxy-anisole (BHA)

Similar compounds are added to other materials, such as plastics and rubber, to protect them against autoxidation. The protective properties of phenols may explain why the health benefits of foods such as green tea, wine, and blueberries (each of which contains large amounts of phenolic compounds) have been lauded by nutritionists and others in the medical community.

SUMMARY OF KEY QUESTIONS

9.1 What Is the Structure of Benzene?

- **Benzene** is a molecule with a high degree of unsaturation possessing the molecular formula C_6H_6. Each carbon has a single unhybridized 2*p* orbital that contains one electron. These six 2*p* orbitals lie perpendicular to the plane of the ring and overlap to form a continuous pi cloud encompassing all six carbons.
- Benzene and its alkyl derivatives are classified as **aromatic hydrocarbons,** or **arenes.**

9.2 What Is Aromaticity?

- According to the **Hückel criteria for aromaticity**, a cyclic compound is aromatic if it (1) has one 2*p* orbital on each atom of the ring, (2) is planar so that overlap of all *p* orbitals of the ring is continuous or nearly so, and (3) has 2, 6, 10, 14, and so on, pi electrons in the overlapping system of *p* orbitals (i.e., it has $4n + 2$ π electrons).
- A **heterocyclic aromatic compound** contains one or more atoms other than carbon in an aromatic ring.

9.3 How Are Benzene Compounds Named, and What Are Their Physical Properties?

- Aromatic compounds are named by the IUPAC system. The common names **toluene**, **xylene**, **styrene**, **phenol**, **aniline**, **benzaldehyde**, and **benzoic acid** are retained.
- The C_6H_5- group is named **phenyl**, and the $C_6H_5CH_2-$ group is named **benzyl**.
- To locate two substituents on a benzene ring, either number the atoms of the ring or use the locators **ortho (*o*)**, **meta (*m*)**, and **para (*p*)**.
- **Polynuclear aromatic hydrocarbons** contain two or more fused benzene rings.

9.4 What Is the Benzylic Position, and How Does It Contribute to Benzene Reactivity?

- The **benzylic position** is the carbon of an alkyl substituent immediately bonded to the benzene ring.
- The benzylic position of a benzene ring can be oxidized by chromic acid without affecting any of the benzene ring atoms.

9.5 What Is Electrophilic Aromatic Substitution?

- A characteristic reaction of aromatic compounds is **electrophilic aromatic substitution**, which involves the substitution of one of the ring hydrogens of benzene for an electrophilic reagent.
- The five types of electrophilic aromatic substitution discussed here are **nitration**, **halogenation**, **sulfonation**, **Friedel–Crafts alkylation**, and **Friedel–Crafts acylation**.

9.6 What Is the Mechanism of Electrophilic Aromatic Substitution?

- The mechanism of electrophilic aromatic substitution can be broken down into three common steps: (1) generation of the electrophile, (2) attack of the electrophile on the aromatic ring to give a resonance-stabilized cation intermediate, and (3) proton transfer to a base to regenerate the aromatic ring.
- The five electrophilic aromatic substitution reactions studied here differ in their mechanism of formation of the electrophile (Step 1) and the specific base used to effect the proton transfer to regenerate the aromatic ring (Step 3).

9.7 How Do Existing Substituents on Benzene Affect Electrophilic Aromatic Substitution?

- Substituents on an aromatic ring influence both the rate and site of further substitution.
- Substituent groups that direct an incoming group preferentially to the ortho and para positions are called **ortho–para directors**. Those that direct an incoming group preferentially to the meta positions are called **meta directors**.
- **Activating groups** cause the rate of further substitution to be faster than that for benzene; **deactivating groups** cause it to be slower than that for benzene.
- A mechanistic rationale for directing effects is based on the degree of resonance stabilization of the possible cation intermediates formed upon reaction of the aromatic ring and the electrophile.
- Groups that stabilize the cation intermediate are ortho–para directors; groups that destabilize it are deactivators and meta directors.

Summary

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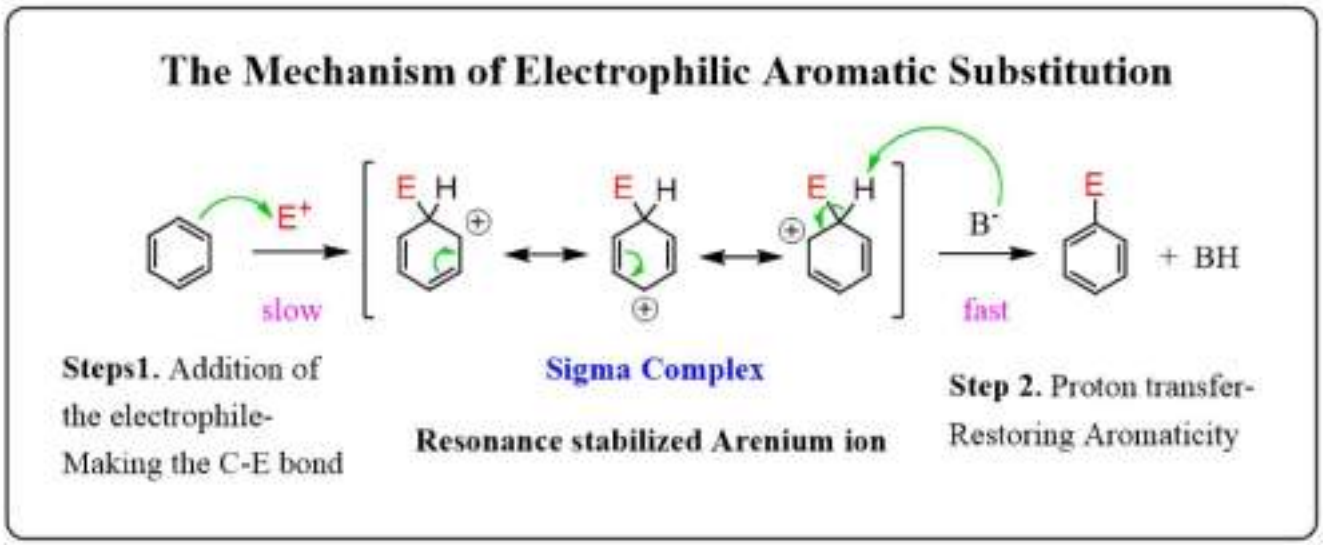
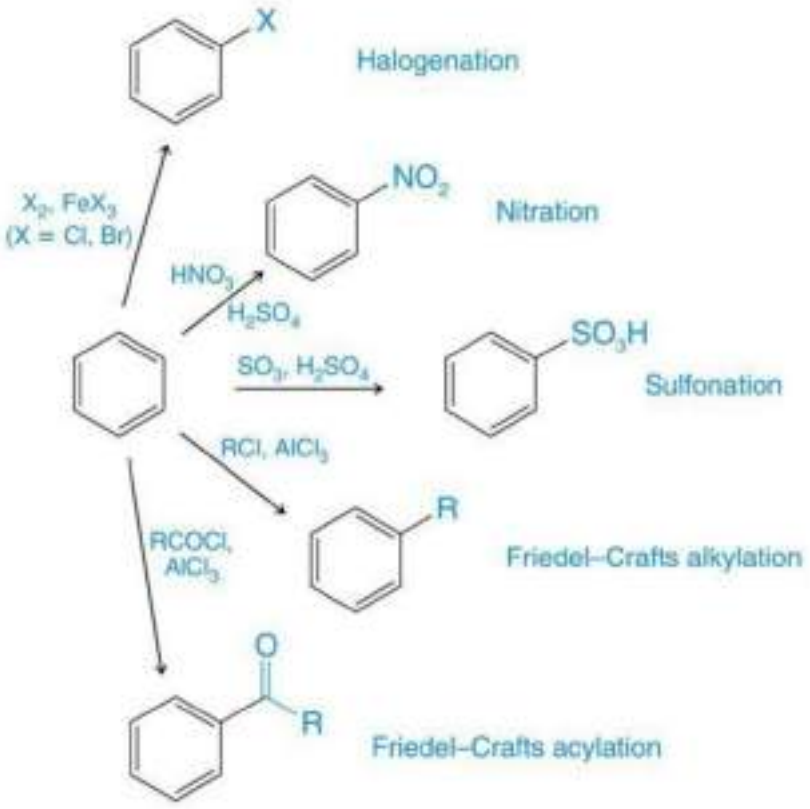
Faculty of Science, Chemistry Department

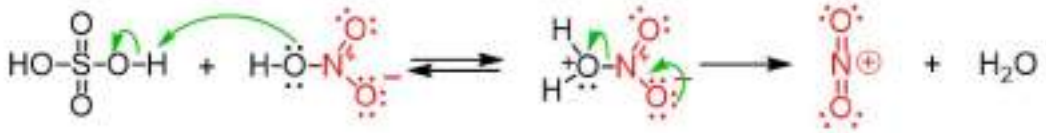
Electrophilic Substitution reactions



Examples of Electrophilic Aromatic Substitution



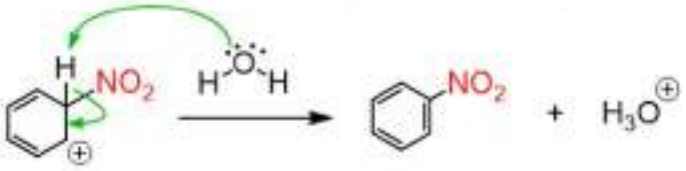
The stronger sulfuric acid protonates the nitric acid to form $^{+}NO_2$ electrophile



Nitronium ion

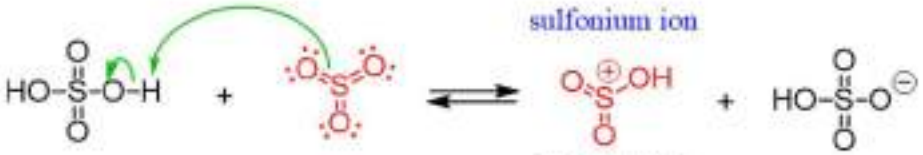
Addition of the electrophile Sigma Complex **hybrid**

Loss of a proton - restoring the aromaticity



nitrobenzene

The $^{+}SO_3H$ strong electrophile is from by protonation of SO_3

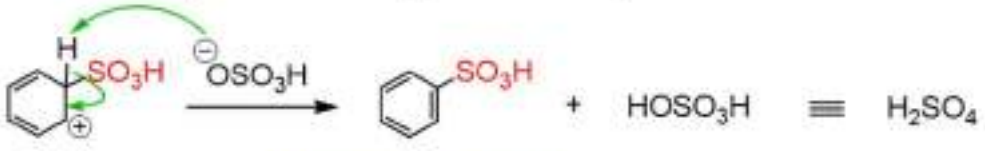


sulfonium ion

electrophile

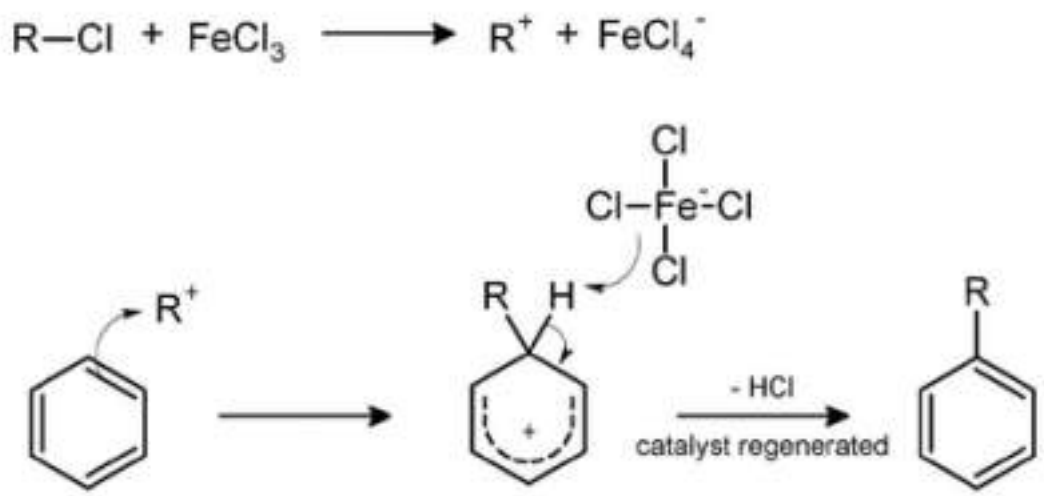
Addition of the E^{+} Sigma Complex **hybrid**

Loss of a proton - restoring the aromaticity

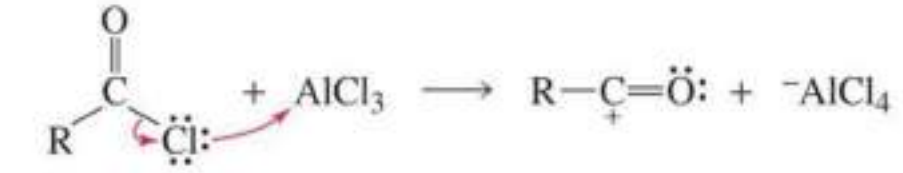


benzenesulfonic acid

Friedel-Crafts Alkylation of Benzene

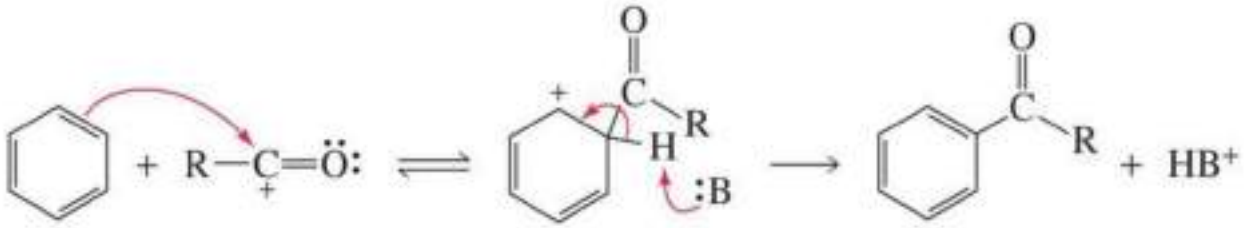


Friedel-Crafts Acylation of Benzene

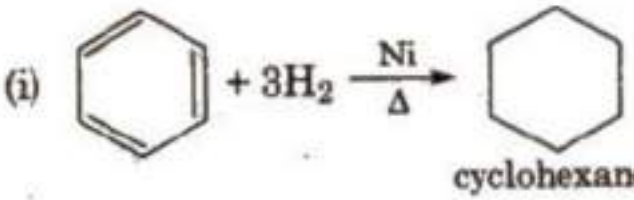


an acyl chloride

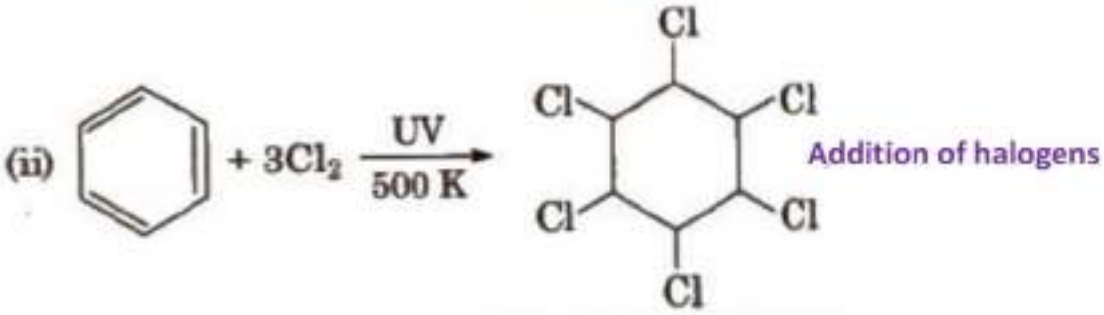
an acylium ion



Addition Reactions of Benzene



Addition of hydrogen

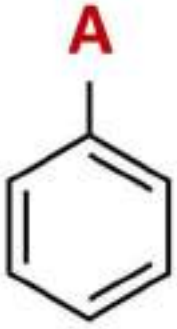


Addition of halogens

Benzene hexachloride **(BHC)**
or **Gammexane**

Orientation of Electrophilic Aromatic Substitution

Monosubstituted benzene derivatives



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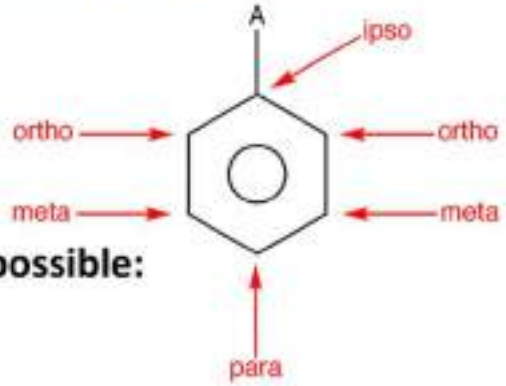
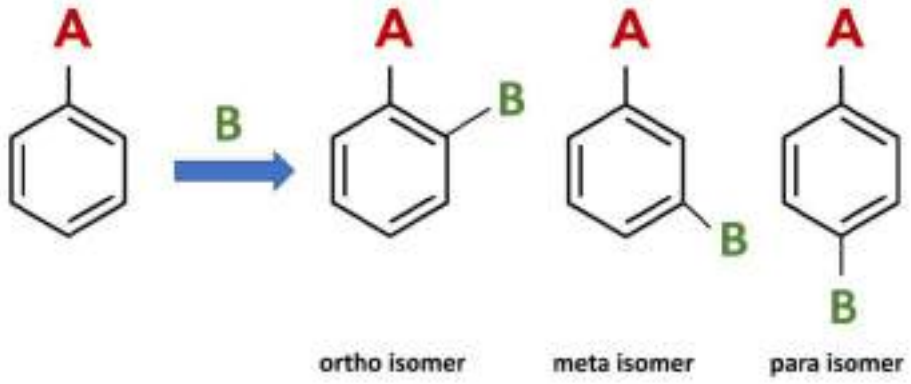
Positions name of monosubstituted benzene



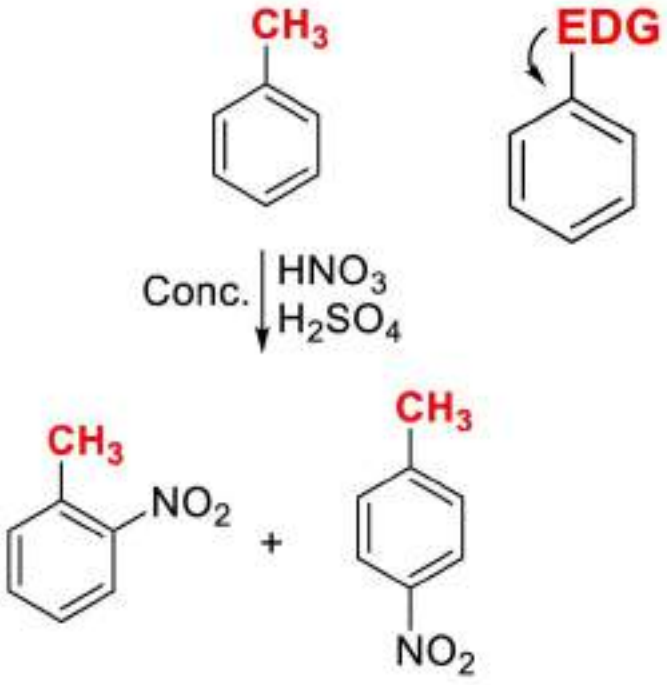
There are three isomeric products are possible:

ortho-, meta- and para-

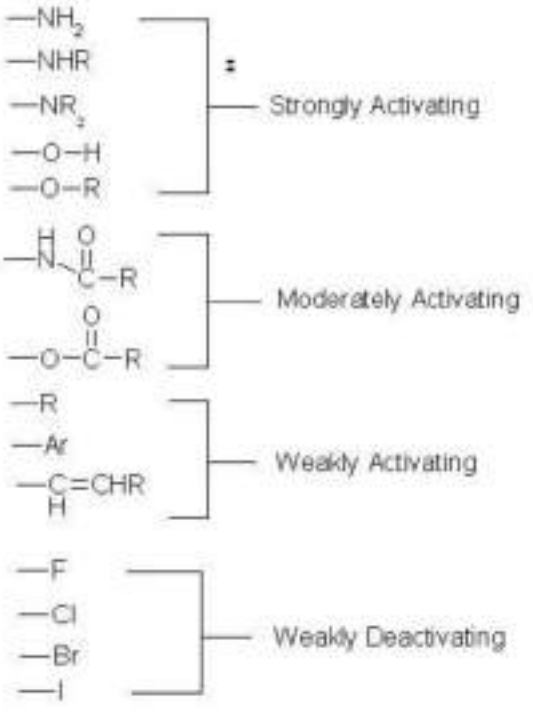


Classification of Group A

1) ortho-, para- Directing groups

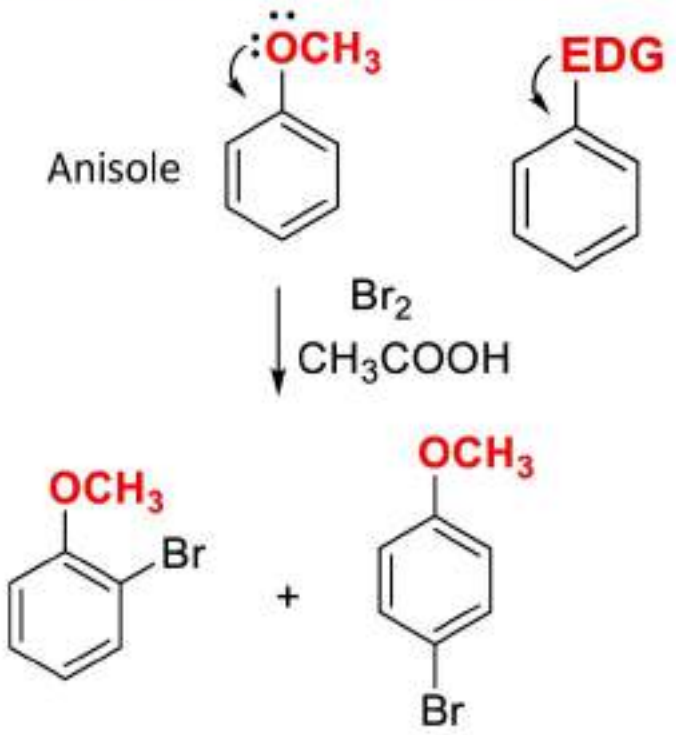


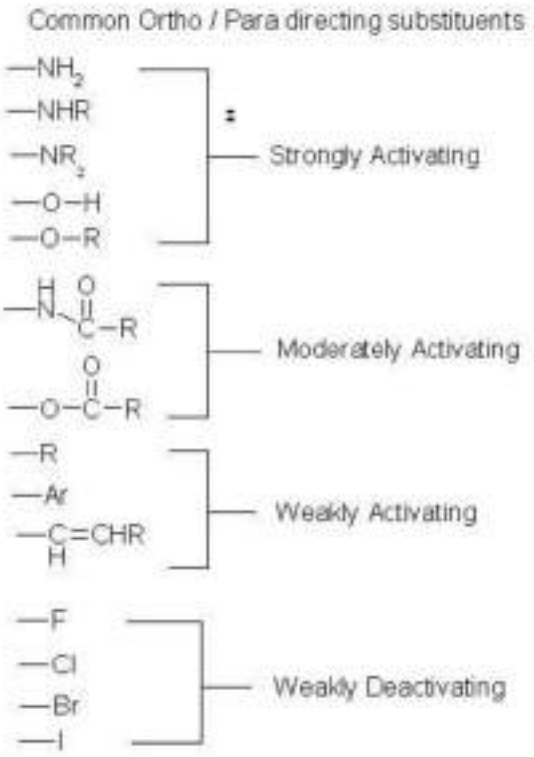
Common Ortho / Para directing substituents



Classification of Group A

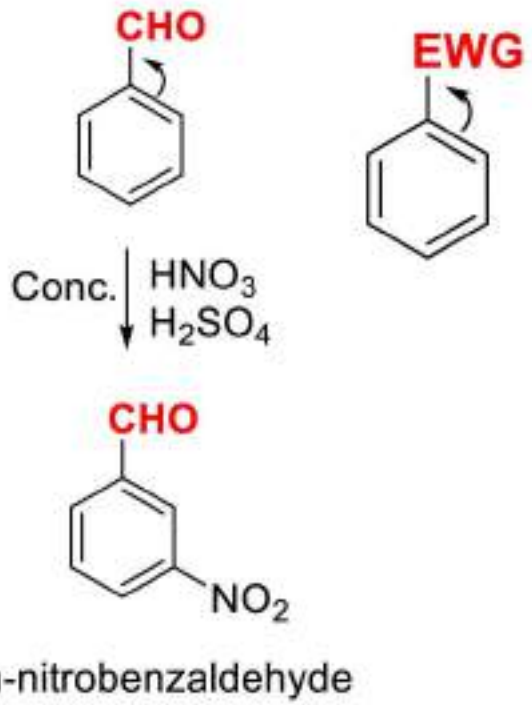
1) ortho-, para- Directing groups



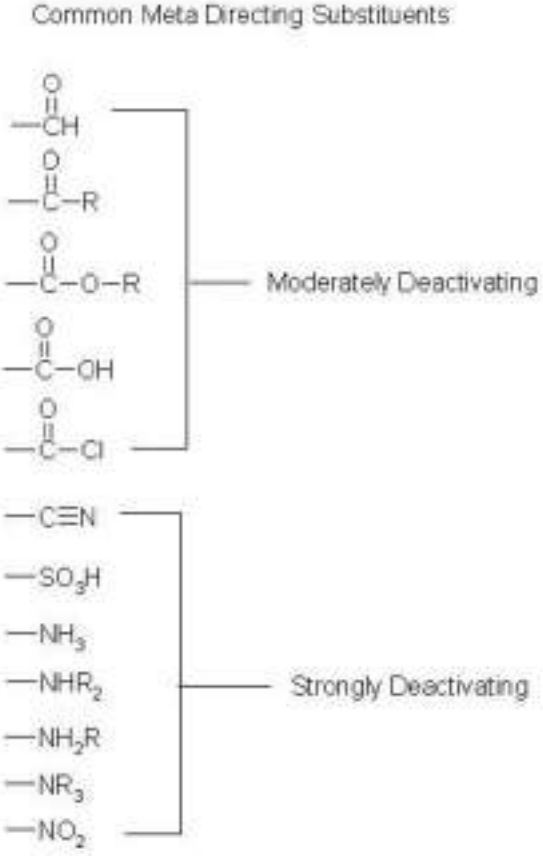


Classification of Group A

2) meta- Directing groups

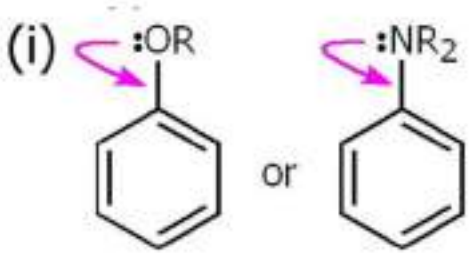


m-nitrobenzaldehyde



Inductive and Resonance Effects:
Theory of Orientation

Two types of EDG

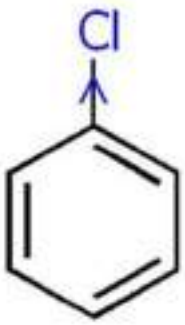
(i) 

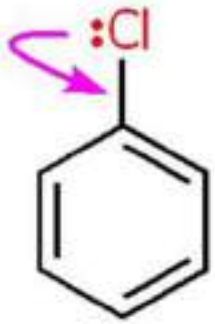
(donates electron towards the benzene ring through resonance effect)

(ii) 

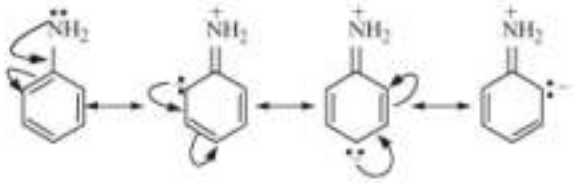
by positive inductive effect (donates electron towards the benzene ring through σ bond)

❖ For halogens, two opposing effects:



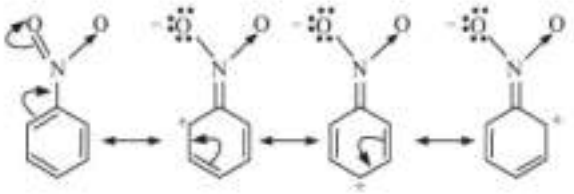


Positive Resonance Effect (+R Effect): Transfer of electrons is away from an atom or substituent group attached to the conjugated system.



+ R effect showing groups: – halogen, – OH, – OR, – OCOR, – NH_2, – NHR, – NR_2, – NHCOR

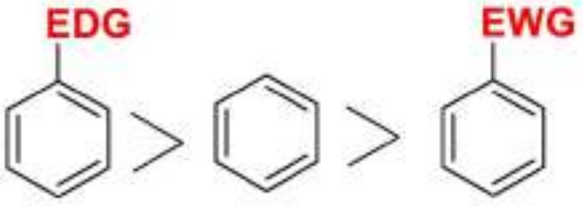
Negative Resonance Effect (– R Effect): Transfer of electrons is towards the atom or substituent group attached to the conjugated system.

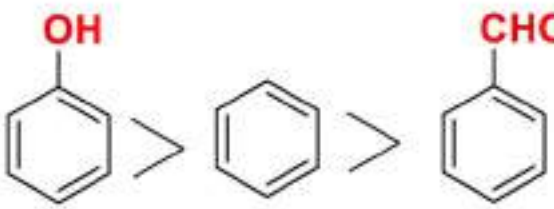


– R effect showing groups: – COOH, – CHO, >C = O, – CN, – NO_2

Rate of reaction (Reactivity)

- **[Benzene + EDG] > benzene alone in reactivity**
  Because EDG increase the Nucleophilicity of benzene ring
- **[benzene + EWG] < benzene alone in reactivity**
  Because EWG decrease the Nucleophilicity of benzene ring
- **[benzene +EDG] > Benzene > [benzene +EWG] in reactivity**

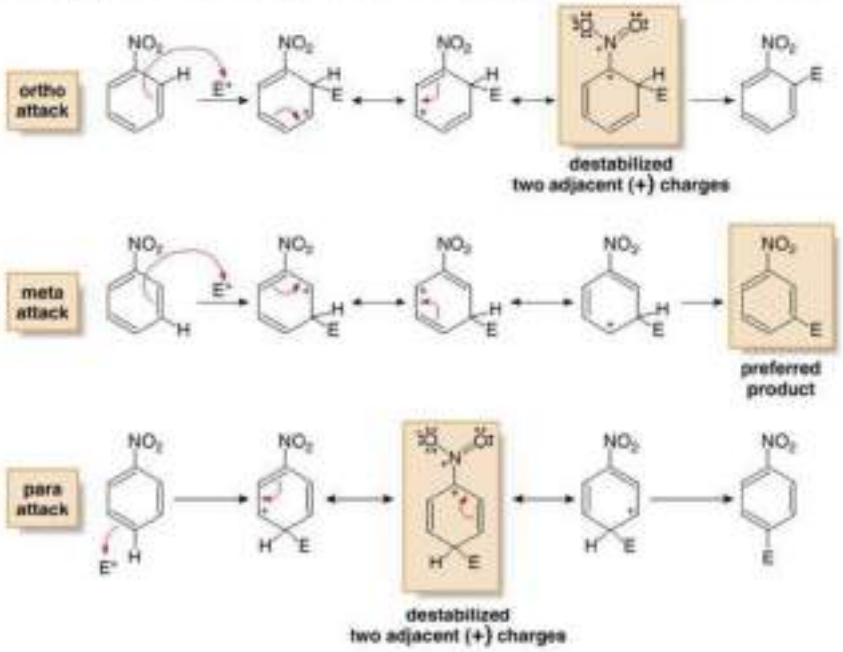




Electrophilic Aromatic Substitution

Orientation Effects in Substituted Benzenes:

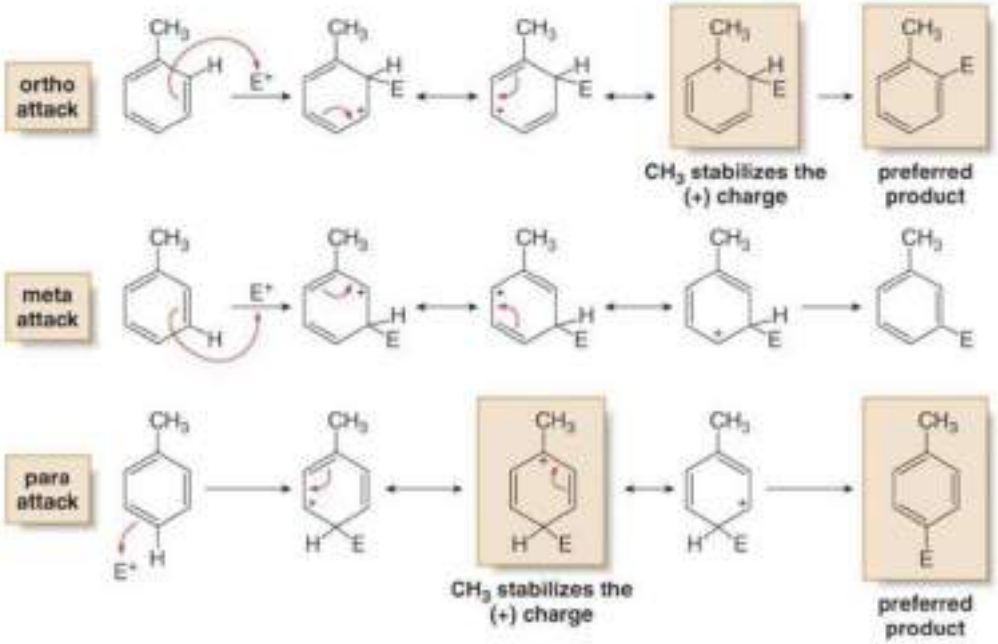
- **With the NO_2 group (and all meta directors) meta attack occurs because attack at the ortho and para position gives a destabilized carbocation intermediate.**



Electrophilic Aromatic Substitution

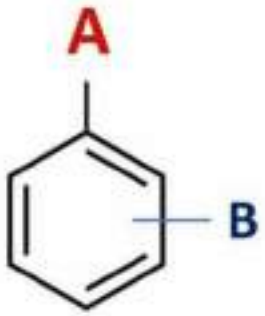
Orientation Effects in Substituted Benzenes

- A CH_3 group directs electrophilic attack ortho and para to itself because an electron-donating inductive effect stabilizes the carbocation intermediate.



Orientation of Electrophilic Aromatic Substitution

Disubstituted benzene derivatives



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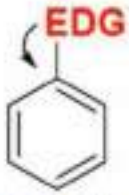
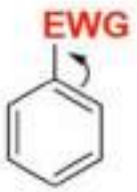
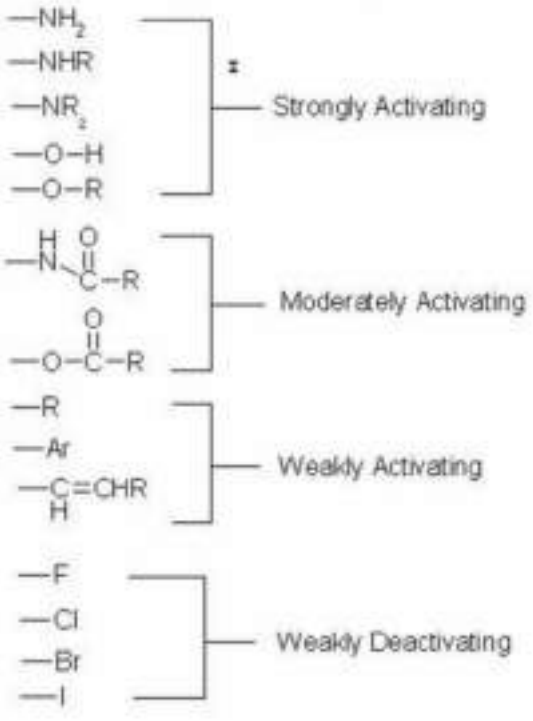
Directing groups

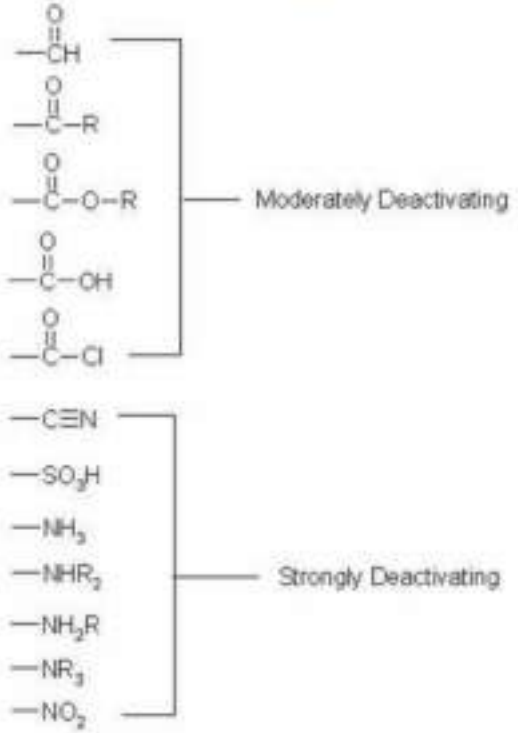




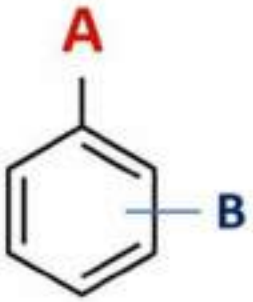
1) ortho-, para- Directing groups



2) meta- Directing groups



Orientation priority

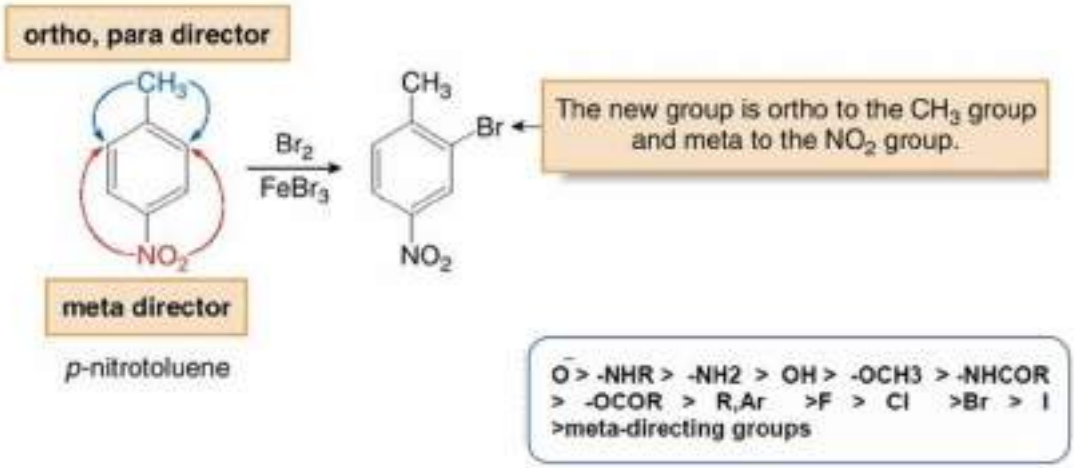


O⁻ > -NHR > -NH2 > OH > -OCH3 > -NHCOR > -OCOR > R,Ar >F > Cl >Br > I >meta-directing groups

Electrophilic Aromatic Substitution

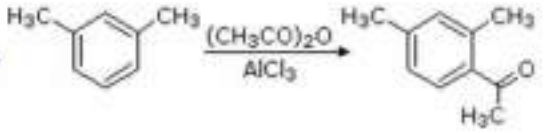
Disubstituted Benzenes

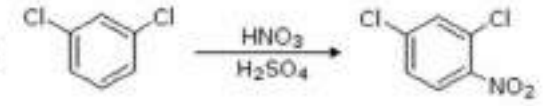
1. **When the directing effects of two groups reinforce, the new substituent is located on the position directed by both groups.**

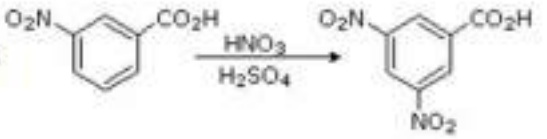


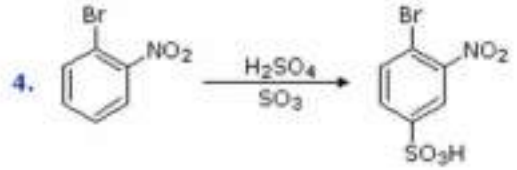
Examples

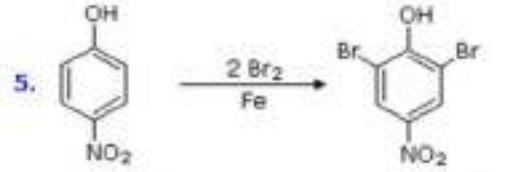
O⁻ > -NHR > -NH2 > OH > -OCH3 > -NHCOR > -OCOR > R,Ar >F > Cl >Br > I >meta-directing groups

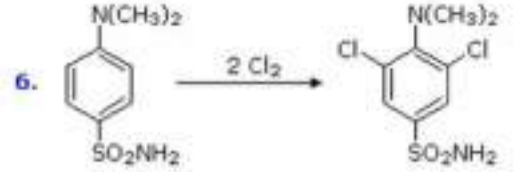
1. 

2. 

3. 

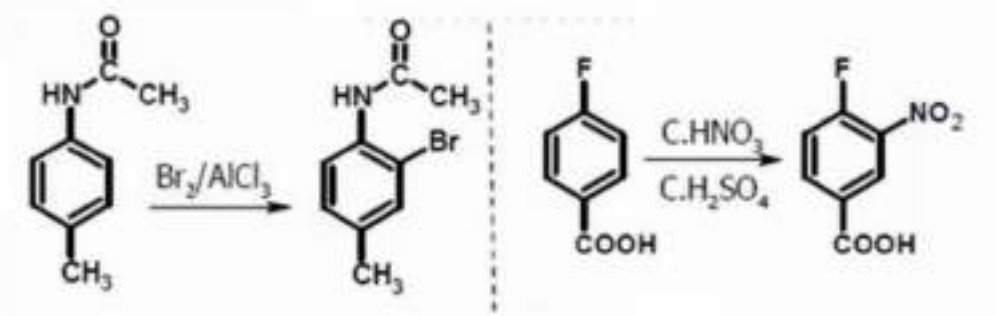
4. 

5. 

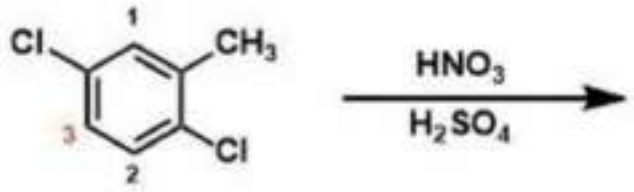
6. 

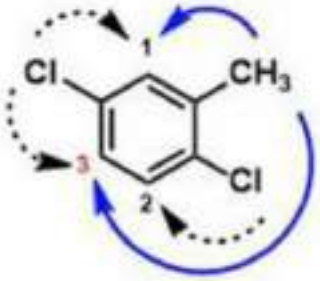
Examples

O⁻ > -NHR > -NH2 > OH > -OCH3 > -NHCOR > -OCOR > R,Ar >F > Cl >Br > I >meta-directing groups



What is the **product** of this reaction?





The solid arrows indicate the preference of the methyl group, the activating and strongest directing group present. Dashed arrows indicate the preferences of the chlorine substituents, which are deactivating.
Because -CH_3 is the most activating group, it decides where the nitro group will substitute.
Out of positions 1 and 3, 1 is more sterically hindered, so the reaction will preferentially occur at position 3. Also, one of the -Cl groups directs there, so there is a partial additive effect.

9.8 What Are Phenols?

- The functional group of a **phenol** is an —OH group bonded to a benzene ring.
- Phenol and its derivatives are weak acids, with pK_a approximately 10.0, but are considerably stronger acids than alcohols, with pK_a 16–18.
- Various phenols are used to prevent autoxidation, a radical chain process that converts an R—H group into an R—O—O—H (hydroperoxide) group and causes spoilage in foods.

QUICK QUIZ

Answer true or false to the following questions to assess your general knowledge of the concepts in this chapter. If you have difficulty with any of them, you should review the appropriate section in the chapter (shown in parentheses) before attempting the more challenging end-of-chapter problems.

1. The mechanism of electrophilic aromatic substitution involves three steps: generation of the electrophile, attack of the electrophile on the benzene ring, and proton transfer to regenerate the ring. (9.6)
2. The C—C double bonds in benzene do not undergo the same addition reactions that the C—C double bonds in alkenes undergo. (9.1)
3. Friedel–Crafts acylation is not subject to rearrangements. (9.5)
4. An aromatic compound is planar, possesses a 2*p* orbital on every atom of the ring, and contains either 4, 8, 12, 16, and so on, pi electrons. (9.2)
5. When naming disubstituted benzenes, the locators para, meta, and ortho refer to substituents that are 1,2, 1,3, and 1,4, respectively. (9.3)
6. The electrophile in the chlorination or bromination of benzene is an ion pair containing a chloronium or bromonium ion. (9.6)
7. An ammonium group ($-NH_3^+$) on a benzene ring will direct an attacking electrophile to a meta position. (9.7)
8. Reaction of chromic acid, H_2CrO_4, with a substituted benzene always oxidizes every alkyl group at the benzylic position to a carboxyl group. (9.4)
9. Benzene consists of two contributing structures that rapidly interconvert between each other. (9.1)
10. The electrophile in the nitration of benzene is the nitrate ion. (9.6)
11. A benzene ring with an —OH bonded to it is referred to as "phenyl." (9.3)
12. Friedel–Crafts alkylation of a primary haloalkane with benzene will always result in a new bond between benzene and the carbon that was bonded to the halogen. (9.5)
13. Resonance energy is the energy a ring contains due to the stability afforded it by its contributing structures. (9.1)
14. A phenol will react quantitatively with NaOH. (9.8)
15. The use of a haloalkane and $AlCl_3$ is the only way to synthesize an alkylbenzene. (9.6)
16. Phenols are more acidic than alcohols. (9.8)
17. Substituents of polysubstituted benzene rings can be numbered according to their distance from the substituent that imparts a special name to the compound. (9.3)
18. If a benzene ring contains both a weakly activating group and a strongly deactivating group, the strongly deactivating group will direct the attack of an electrophile. (9.7)
19. Oxygen, O_2, can be considered a diradical. (9.8)
20. The contributing structures for the attack of an electrophile to the ortho position of aniline are more stable than those for the attack at the meta position. (9.7)
21. A deactivating group will cause its benzene ring to react slower than benzene itself. (9.7)
22. Friedel–Crafts alkylation is promoted by the presence of electron-withdrawing groups. (9.5)
23. Autoxidation takes place at allylic carbons. (9.8)
24. The contributing structures for the attack of an electrophile to the meta position of nitrobenzene are more stable than those for the attack at the ortho or para position. (9.7)

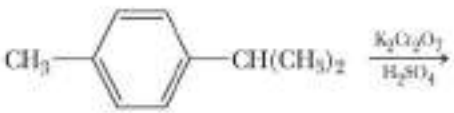
Answers: (1) T (2) T (3) T (4) F (5) F (6) T (7) T (8) F (9) F (10) F (11) F (12) F (13) F (14) T (15) F (16) T (17) T (18) F (19) T (20) T (21) T (22) F (23) T (24) T

Detailed explanations for many of these answers can be found in the accompanying Solutions Manual.

KEY REACTIONS

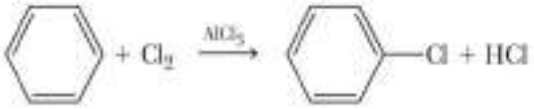
1. Oxidation at a Benzylic Position (Section 9.4)

A benzylic carbon bonded to at least one hydrogen is oxidized to a carboxyl group:



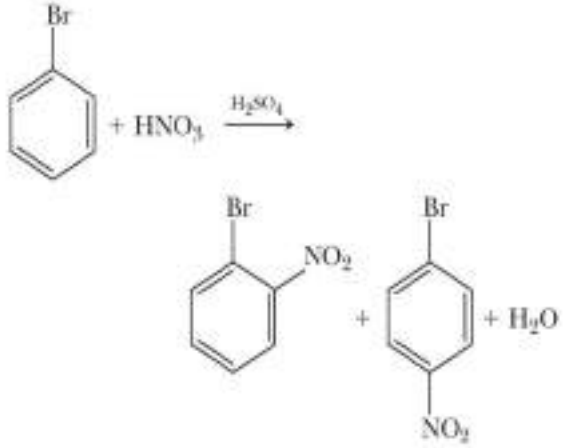
2. Chlorination and Bromination (Section 9.6A)

The electrophile is a halonium ion, Cl^+ or Br^+, formed by treating Cl_2 or Br_2 with $AlCl_3$ or $FeCl_3$:



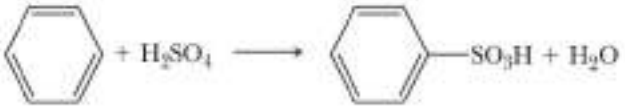
3. Nitration (Section 9.6B)

The electrophile is the nitronium ion, NO_2^+, formed by treating nitric acid with sulfuric acid:



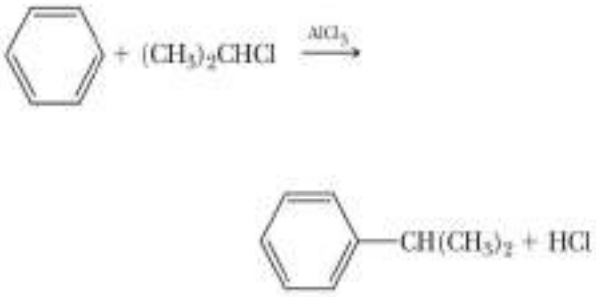
4. Sulfonation (Section 9.6B)

The electrophile is HSO_3^+:



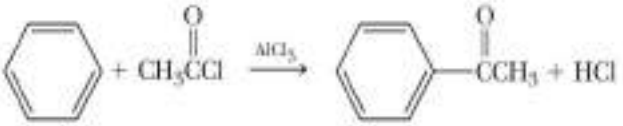
5. Friedel–Crafts Alkylation (Section 9.6C)

The electrophile is an alkyl carbocation formed by treating an alkyl halide with a Lewis acid:



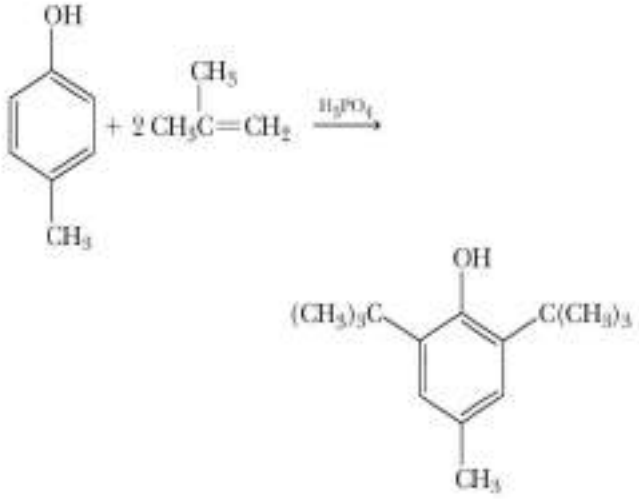
6. Friedel–Crafts Acylation (Section 9.6D)

The electrophile is an acyl cation formed by treating an acyl halide with a Lewis acid:



7. Alkylation Using an Alkene (Section 9.6E)

The electrophile is a carbocation formed by treating an alkene with H_2SO_4 or H_3PO_4:

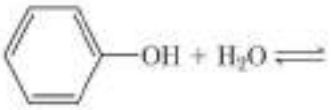


8. Alkylation Using an Alcohol (Section 9.6E)

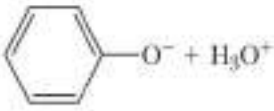
The electrophile is a carbocation formed by treating an alcohol with H_2SO_4 or H_3PO_4:

9. Acidity of Phenols (Section 9.8B)

Phenols are weak acids:



Phenol



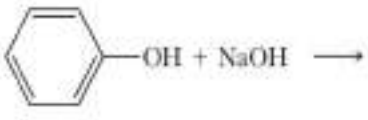
$K_a = 1.1 \times 10^{-10}$
$pK_a = 9.95$

Phenoxide ion

Substitution by electron-withdrawing groups, such as the halogens and the nitro group, increases the acidity of phenols.

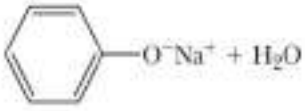
10. Reaction of Phenols with Strong Bases (Section 9.8C)

Water-insoluble phenols react quantitatively with strong bases to form water-soluble salts:



Phenol
pK_a 9.95
(stronger acid)

Sodium
hydroxide
(stronger base)



Sodium
phenoxide
(weaker base)

Water
pK_a 15.7
(weaker acid)

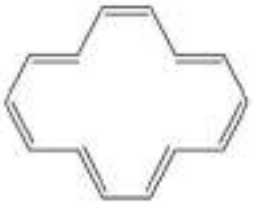
PROBLEMS

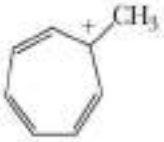
A problem marked with an asterisk indicates an applied "real-world" problem. Answers to problems whose numbers are printed in blue are given in Appendix D.

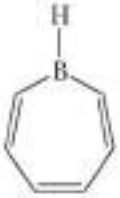
Section 9.2 Aromaticity

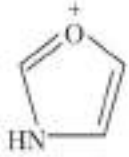
9.11 Which of the following compounds or chemical entities are aromatic? **(See Example 9.1)**

(a) 

(b) 

(c) 

(d) 

(e) 

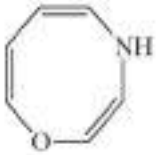
(f) 

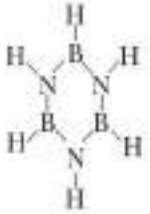
(g) 

(h) 

(i) 

(j) 

(k) 

(l) 

9.12 Explain why cyclopentadiene (pK_a 16) is many orders of magnitude more acidic than cyclopentane ($pK_a > 50$). (*Hint:* Draw the structural formula for the anion formed by removing one of the protons on the —CH_2— group, and then apply the Hückel criteria for aromaticity.)

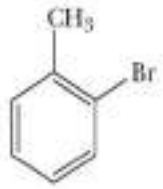
Cyclopentadiene

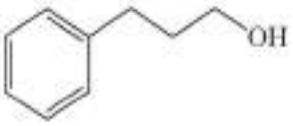
Cyclopentane

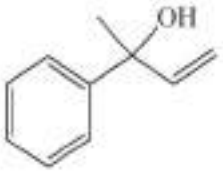
Section 9.3 Nomenclature and Structural Formulas

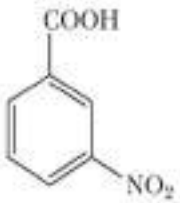
9.13 Name these compounds: **(See Example 9.2)**

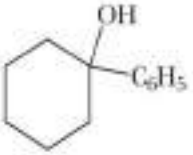
(a) 

(b) 

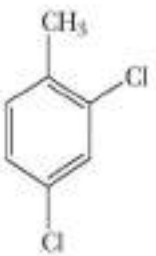
(c) 

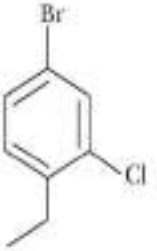
(d) 

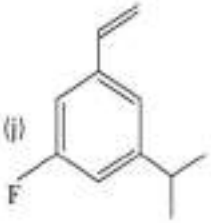
(e) 

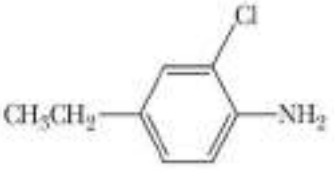
(f) 

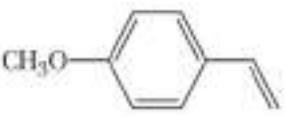
(g) 

(h) 

(i) 

(j) 

(k) 

(l) 

9.14 Draw structural formulas for these compounds: **(See Example 9.2)**

(a) 1-Bromo-2-chloro-4-ethylbenzene
(b) 4-Iodo-1,2-dimethylbenzene
(c) 2,4,6-Trinitrotoluene (TNT)
(d) 4-Phenyl-2-pentanol
(e) *p*-Cresol
(f) 2,4-Dichlorophenol
(g) 1-Phenylcyclopropanol
(h) Styrene (phenylethylene)
(i) *m*-Bromophenol
(j) 2,4-Dibromoaniline
(k) Isobutylbenzene
(l) *m*-Xylene
(m) 4-Bromo-1,2-dichlorobenzene
(n) 5-Fluoro-2-methylphenol
(o) 1-Cyclohexyl-3-ethylbenzene
(p) *m*-Phenylaniline
(q) 3-Methyl-2-vinylbenzoic acid
(r) 2,5-Dimethylanisole

9.15 Show that pyridine can be represented as a hybrid of two equivalent contributing structures.

9.16 Show that naphthalene can be represented as a hybrid of three contributing structures. Show also, by the use of curved arrows, how one contributing structure is converted to the next.

9.17 Draw four contributing structures for anthracene.

Section 9.5 Electrophilic Aromatic Substitution: Monosubstitution

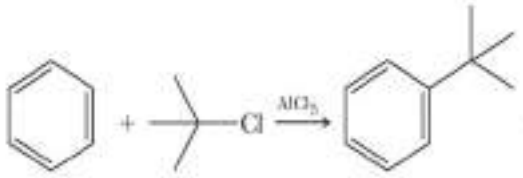
9.18 Draw a structural formula for the compound formed by treating benzene with each of the following combinations of reagents: **(See Examples 9.5, 9.6)**

(a) $CH_3CH_2Cl/AlCl_3$ (b) $CH_2{=}CH_2/H_2SO_4$
(c) CH_3CH_2OH/H_2SO_4 (d) CH_3OCH_3/H_2SO_4

9.19 Show three different combinations of reagents you might use to convert benzene to isopropylbenzene. **(See Examples 9.5, 9.6)**

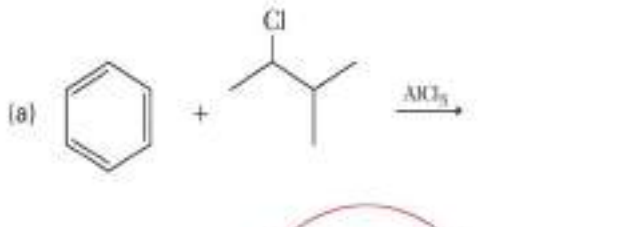
9.20 How many monochlorination products are possible when naphthalene is treated with $Cl_2/AlCl_3$?

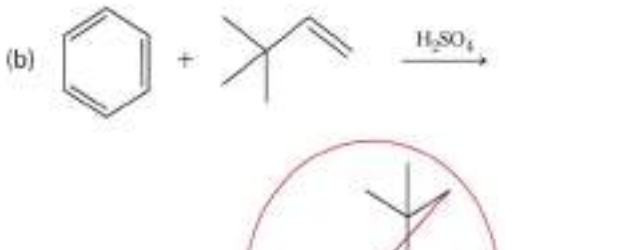
9.21 Write a stepwise mechanism for the following reaction, using curved arrows to show the flow of electrons in each step: **(See Example 9.4)**



9.22 Write a stepwise mechanism for the preparation of diphenylmethane by treating benzene with dichloromethane in the presence of an aluminum chloride catalyst. **(See Example 9.4)**

9.23 The following alkylation reactions do not yield the compounds shown as the major product. Predict the major product for each reaction and provide a mechanism for their formation.

(a)


(b)


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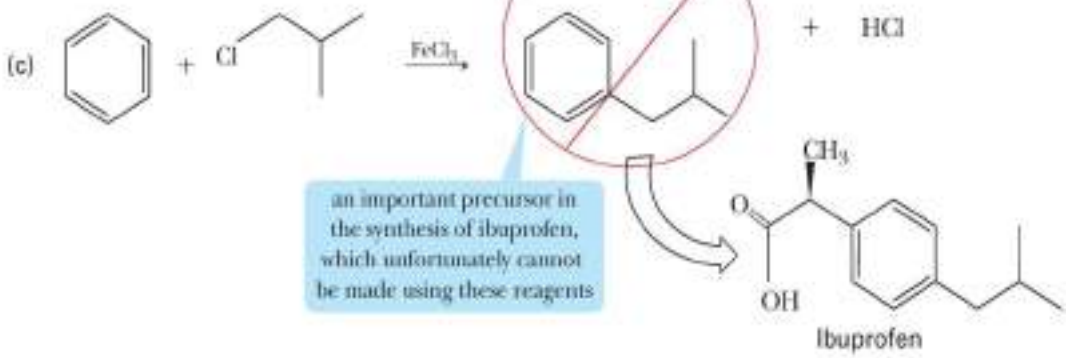


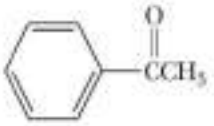
Section 9.7 Electrophilic Aromatic Substitution: Substitution Effects

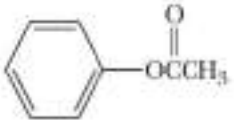
9.24 When treated with $Cl_2/AlCl_3$, 1,2-dimethylbenzene (*o*-xylene) gives a mixture of two products. Draw structural formulas for these products. **(See Examples 9.7, 9.9)**

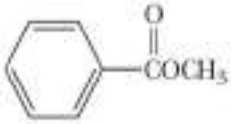
9.25 How many monosubstitution products are possible when 1,4-dimethylbenzene (*p*-xylene) is treated with $Cl_2/AlCl_3$? When *m*-xylene is treated with $Cl_2/AlCl_3$? **(See Examples 9.7, 9.9)**

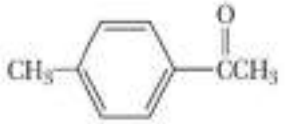
9.26 Draw the structural formula for the major product formed upon treating each compound with $Cl_2/AlCl_3$: **(See Examples 9.7, 9.9)**

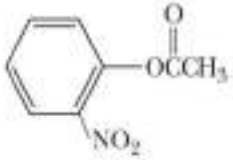
(a) Toluene (b) Nitrobenzene
(c) Chlorobenzene (d) *tert*-Butylbenzene

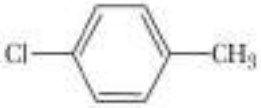
(e) 

(f) 

(g) 

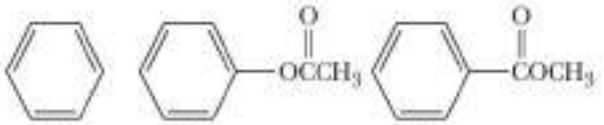
(h) 

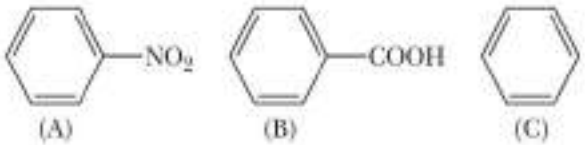
(i) 

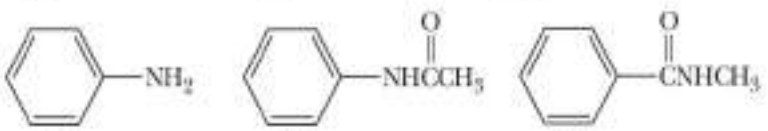
(j) 

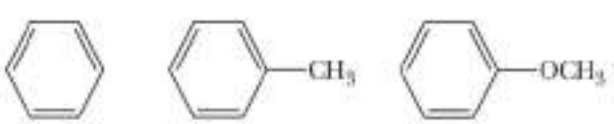
9.27 Which compound, chlorobenzene or toluene, undergoes electrophilic aromatic substitution more rapidly when treated with $Cl_2/AlCl_3$? Explain and draw structural formulas for the major product(s) from each reaction.

9.28 Arrange the compounds in each set in order of decreasing reactivity (fastest to slowest) toward electrophilic aromatic substitution:

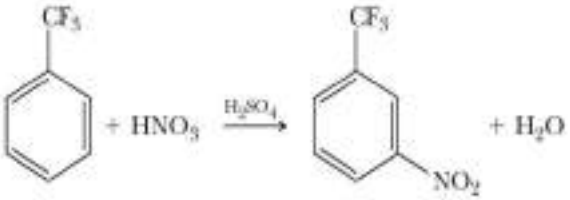
(a) 
(A) (B) (C)

(b) 
(A) (B) (C)

(c) 
(A) (B) (C)

(d) 
(A) (B) (C)

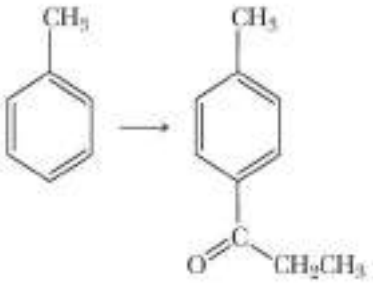
9.29 Account for the observation that the trifluoromethyl group is meta directing, as shown in the following example: **(See Example 9.8)**

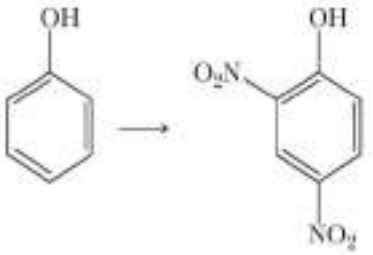


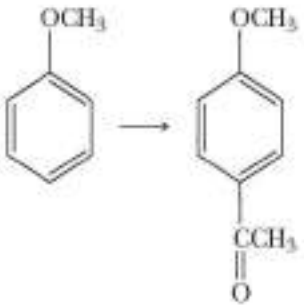
9.30 Show how to convert toluene to these carboxylic acids: **(See Example 9.3)**

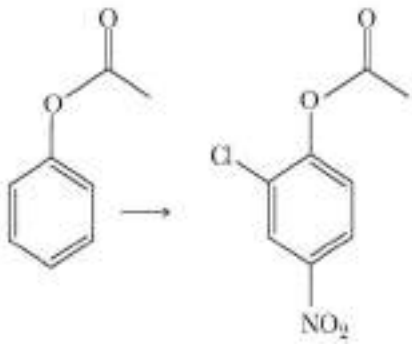
(a) 4-Chlorobenzoic acid (b) 3-Chlorobenzoic acid

9.31 Show reagents and conditions that can be used to bring about these conversions: **(See Examples 9.7, 9.9)**

(a) 

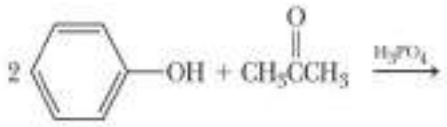
(b) 

(c) 

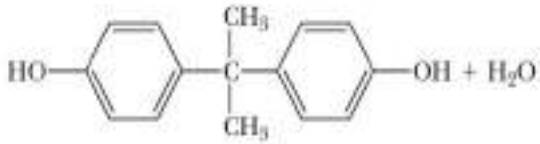
(d) 

9.32 Propose a synthesis of triphenylmethane from benzene as the only source of aromatic rings. Use any other necessary reagents. **(See Examples 9.7, 9.9)**

***9.33** Reaction of phenol with acetone in the presence of an acid catalyst gives bisphenol A, a compound used in the production of polycarbonate and epoxy resins (Sections 16.4C and 16.4E): **(See Example 9.6)**



Acetone

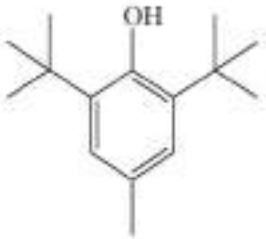


Bisphenol A

Propose a mechanism for the formation of bisphenol A. (*Hint:* The first step is a proton transfer from phosphoric acid to the oxygen of the carbonyl group of acetone.)

*9.34 2,6-Di-*tert*-butyl-4-methylphenol, more commonly known as butylated hydroxytoluene, or BHT, is used as an antioxidant in foods to "retard spoilage." BHT is synthesized industrially from 4-methylphenol (*p*-cresol) by reaction with 2-methylpropene in the presence of phosphoric acid: **(See Example 9.6)**

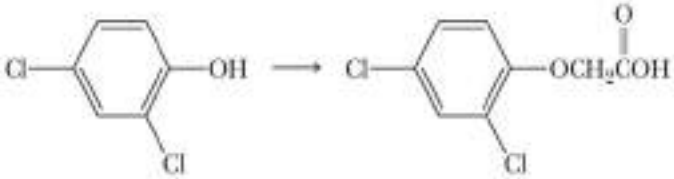
4-Methylphenol 2-Methylpropene



2,6-Di-*tert*-butyl-4-methylphenol (Butylated hydroxytoluene, BHT)

Propose a mechanism for this reaction.

***9.35** The first herbicide widely used for controlling weeds was 2,4-dichlorophenoxyacetic acid (2,4-D). Show how this compound might be synthesized from 2,4-dichlorophenol and chloroacetic acid, $ClCH_2COOH$:

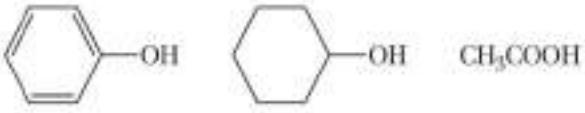


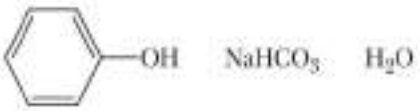
2,4-Dichlorophenol 2,4-Dichlorophenoxyacetic acid (2,4-D)

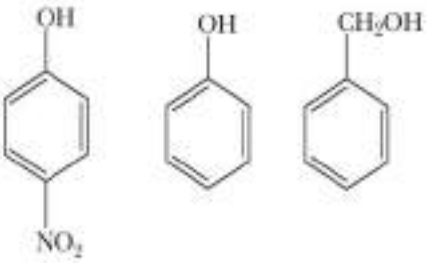
Section 9.8 Acidity of Phenols

9.36 Use resonance theory to account for the fact that phenol (pK_a 9.95) is a stronger acid than cyclohexanol (pK_a 18). **(See Example 9.10)**

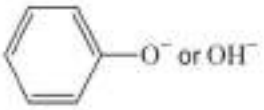
9.37 Arrange the compounds in each set in order of increasing acidity (from least acidic to most acidic): **(See Example 9.10)**

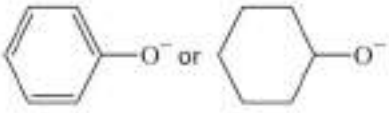
(a) 

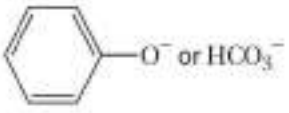
(b) 

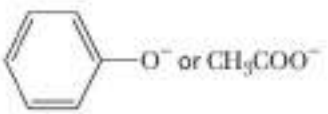
(c) 

9.38 From each pair, select the stronger base: **(See Example 9.10)**

(a) 

(b) 

(c) 

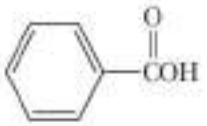
(d) 

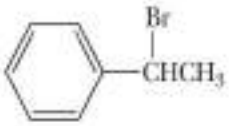
9.39 Account for the fact that water-insoluble carboxylic acids (pK_a 4–5) dissolve in 10% sodium bicarbonate with the evolution of a gas, but water-insoluble phenols (pK_a 9.5–10.5) do not show this chemical behavior.

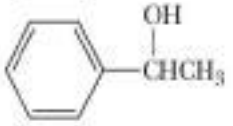
9.40 Describe a procedure for separating a mixture of 1-hexanol and 2-methylphenol (*o*-cresol) and recovering each in pure form. Each is insoluble in water, but soluble in diethyl ether.

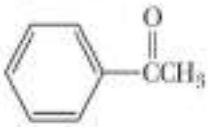
Syntheses

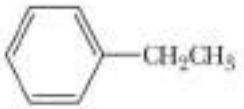
9.41 Using styrene, $C_6H_5CH{=}CH_2$, as the only aromatic starting material, show how to synthesize these compounds. In addition to styrene, use any other necessary organic or inorganic chemicals. Any compound synthesized in one part of this problem may be used to make any other compound in the problem:

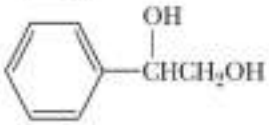
(a) 

(b) 

(c) 

(d) 

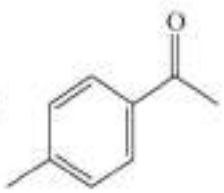
(e) 

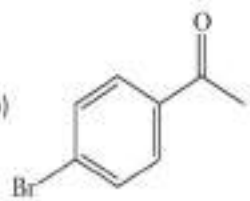
(f) 

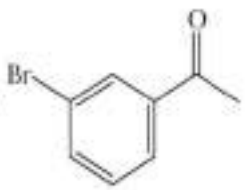
9.42 Show how to synthesize these compounds, starting with benzene, toluene, or phenol as the only sources of aromatic rings. Assume that, in all syntheses, you can separate mixtures of ortho–para products to give the desired isomer in pure form: **(See Examples 9.7, 9.9)**

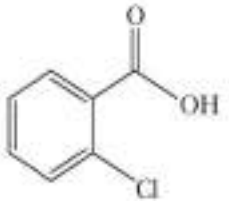
(a) *m*-Bromonitrobenzene
(b) 1-Bromo-4-nitrobenzene
(c) 2,4,6-Trinitrotoluene (TNT)
(d) *m*-Bromobenzoic acid
(e) *p*-Bromobenzoic acid
(f) *p*-Dichlorobenzene
(g) *m*-Nitrobenzenesulfonic acid
(h) 1-Chloro-3-nitrobenzene

9.43 Show how to synthesize these aromatic ketones, starting with benzene or toluene as the only sources of aromatic rings. Assume that, in all syntheses, mixtures of ortho–para products can be separated to give the desired isomer in pure form: **(See Examples 9.7, 9.9)**

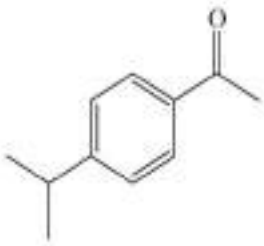
(a) 

(b) 

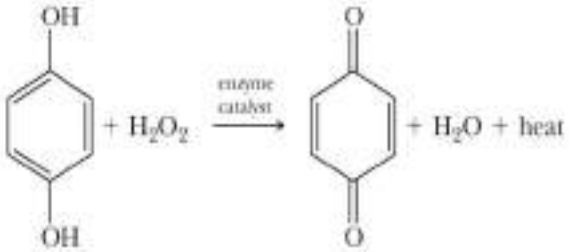
(c) 

(d) 

***9.44** The following ketone, isolated from the roots of several members of the iris family, has an odor like that of violets and is used as a fragrance in perfumes. Describe the synthesis of this ketone from benzene. **(See Examples 9.7, 9.9)**

4-Isopropylacetophenone 

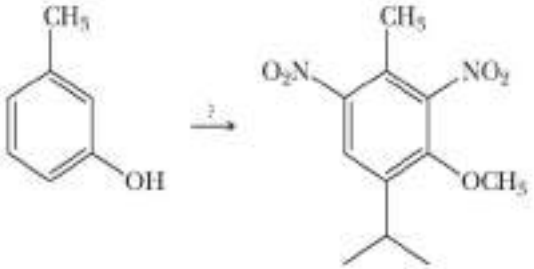
***9.45** The bombardier beetle generates *p*-quinone, an irritating chemical, by the enzyme-catalyzed oxidation of hydroquinone, using hydrogen peroxide as the oxidizing agent. Heat generated in this oxidation produces superheated steam, which is ejected, along with *p*-quinone, with explosive force.



Hydroquinone *p*-Quinone

(a) Balance the equation.
(b) Show that this reaction of hydroquinone is an oxidation.

***9.46** Following is a structural formula for musk ambrette, a synthetic musk used in perfumes to enhance and retain fragrance: **(See Examples 9.7, 9.9)**

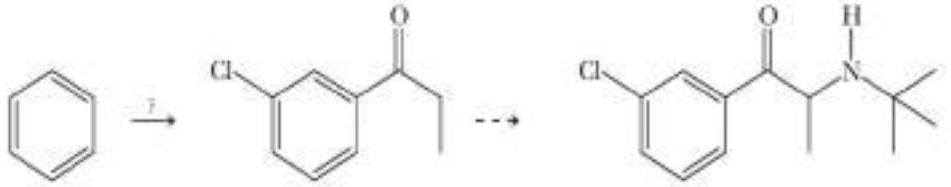


m-Cresol Musk ambrette

Propose a synthesis for musk ambrette from *m*-cresol.

***9.47** [3-Chlorophenyl]propanone is a building block in the synthesis of bupropion, the hydrochloride salt of which is the antidepressant Wellbutrin. During clinical trials, researchers discovered that smokers

reported a diminished craving for tobacco after one to two weeks on the drug. Further clinical trials confirmed this finding, and the drug is also marketed under the trade name Zyban® as an aid in smoking cessation. Propose a synthesis for this building block from benzene. (We will see in Section 12.8 how to complete the synthesis of bupropion.) **(See Examples 9.7, 9.9)**



Benzene (3-Chlorophenyl)-1-propanone Bupropion (Wellbutrin, Zyban)

CHEMICAL TRANSFORMATIONS

9.48 Test your cumulative knowledge of the reactions learned thus far by completing the following chemical transformations. *Note: Some will require more than one step.*

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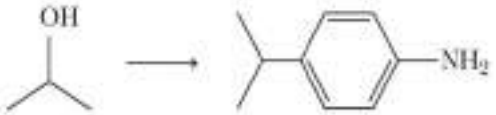

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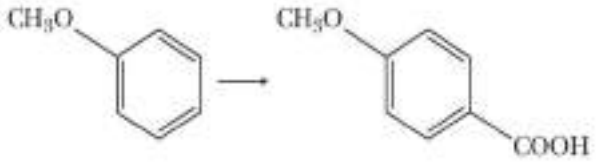

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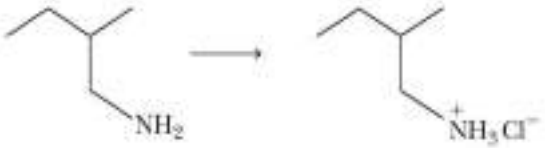

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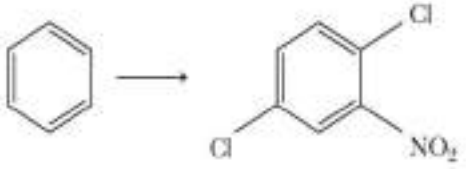

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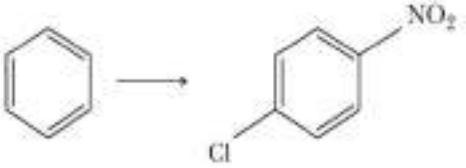

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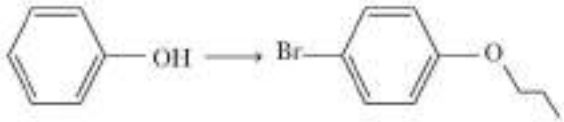
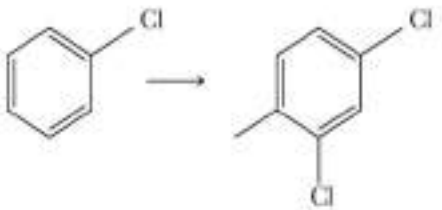
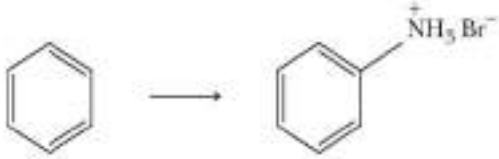
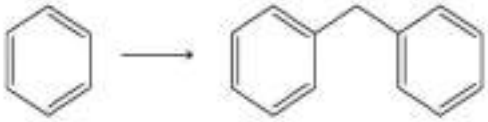
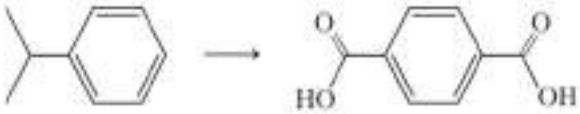
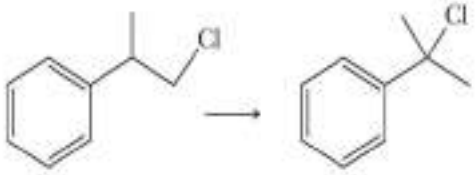


(g)


(h)


(i)


(j)


(k)


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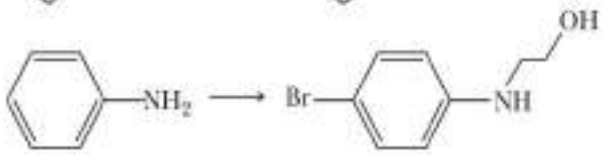

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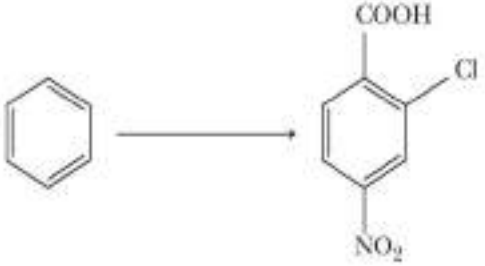
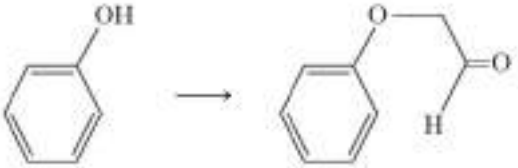
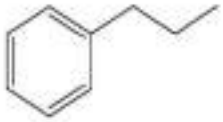
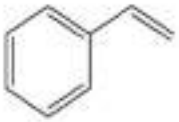


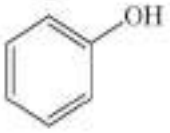
(n)


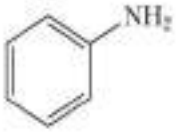
LOOKING AHEAD

9.49 Which of the following compounds can be made directly by using an electrophilic aromatic substitution reaction?

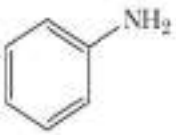
(a) 

(b) 

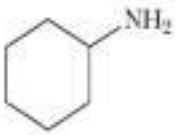
(c) 

(d) 

9.50 Which compound is a better nucleophile?

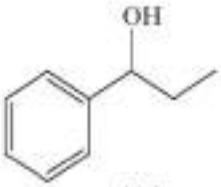


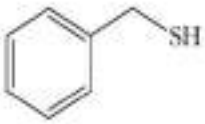
or

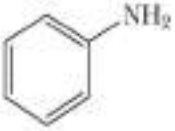


Aniline Cyclohexanamine

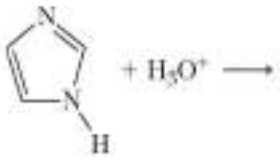
9.51 Suggest a reason that the following arenes do not undergo electrophilic aromatic substitution when $AlCl_3$ is used in the reaction:

(a) 

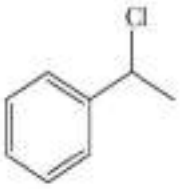
(b) 

(c) 

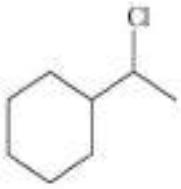
9.52 Predict the product of the following acid–base reaction:



9.53 Which haloalkane reacts faster in an S_N1 reaction?



or



9.54 Which of the following compounds is more basic?

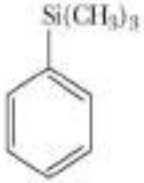
Furan or

Tetrahydrofuran

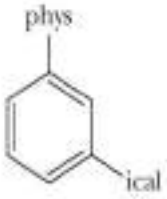
GROUP LEARNING ACTIVITIES

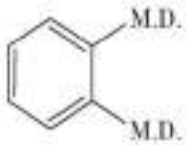
9.55 Following are benzene compounds with substituents we have yet to encounter. As a group, decide whether each ring will be activated or deactivated. Then determine whether each substituent is ortho–para or meta directing by analyzing their intermediates in an electrophilic aromatic substitution reaction.

(a) 

(b) 

9.56 The following structures represent a play on words when named. Can you name them? Can you come up with other funny names?

(a) 

(b) 

Amines

KEY QUESTIONS

10.1 What Are Amines?
10.2 How Are Amines Named?
10.3 What Are the Characteristic Physical Properties of Amines?
10.4 What Are the Acid–Base Properties of Amines?
10.5 What Are the Reactions of Amines with Acids?
10.6 How Are Arylamines Synthesized?
10.7 How Do Amines Act as Nucleophiles?

HOW TO

10.1 How to Predict the Relative Basicity of Amines

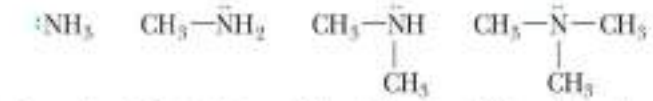
CHEMICAL CONNECTIONS

10A Morphine as a Clue in the Design and Discovery of Drugs
10B The Poison Dart Frogs of South America: Lethal Amines

CARBON, HYDROGEN, and oxygen are the three most common elements in organic compounds. Because of the wide distribution of amines in the biological world, nitrogen is the fourth most common element in organic compounds. The most important chemical properties of amines are their basicity and their nucleophilicity.

10.1 What Are Amines?

Amines are derivatives of ammonia (NH_3) in which one or more hydrogens are replaced by alkyl or aryl groups. Amines are classified as primary (1°), secondary (2°), or tertiary (3°), depending on the number of hydrogen atoms of ammonia that are replaced by alkyl or aryl groups (Section 1.7B). As we saw with ammonia, the three atoms or groups bonded to the nitrogen in amines assume a trigonal pyramidal geometry:

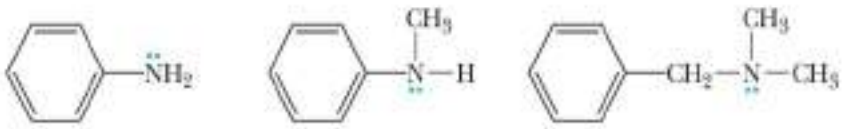


Ammonia | Methylamine (a 1° amine) | Dimethylamine (a 2° amine) | Trimethylamine (a 3° amine)

Amines are further divided into aliphatic amines and aromatic amines. In an **aliphatic amine**, all the carbons bonded directly to nitrogen are derived from alkyl groups; in an **aromatic amine**, one or more of the groups bonded directly to nitrogen are aryl groups:

Aliphatic amine An amine in which nitrogen is bonded only to alkyl groups.

Aromatic amine An amine in which nitrogen is bonded to one or more aryl groups.

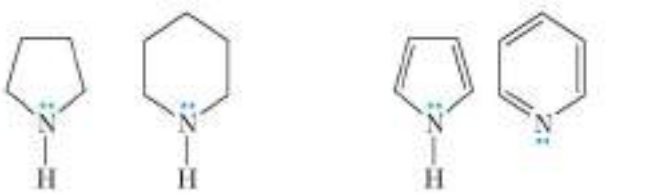


Aniline (a 1° aromatic amine) | *N*-Methylaniline (a 2° aromatic amine) | Benzyldimethylamine (a 3° aliphatic amine)

An amine in which the nitrogen atom is part of a ring is classified as a **heterocyclic amine**. When the nitrogen is part of an aromatic ring (Section 9.2), the amine is classified as a **heterocyclic aromatic amine**. Following are structural formulas for two heterocyclic aliphatic amines and two heterocyclic aromatic amines:

Heterocyclic amine An amine in which nitrogen is one of the atoms of a ring.

Heterocyclic aromatic amine An amine in which nitrogen is one of the atoms of an aromatic ring.



Pyrrolidine Piperidine (heterocyclic aliphatic amines) | Pyrrole Pyridine (heterocyclic aromatic amines)

EXAMPLE 10.1

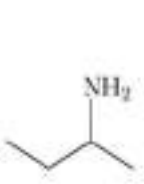
PROBLEM 10.1

Identify all carbon stereocenters in coniine, nicotine, and cocaine.

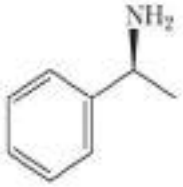
10.2 How Are Amines Named?

A. Systematic Names

Systematic names for aliphatic amines are derived just as they are for alcohols. The suffix *-e* of the parent alkane is dropped and is replaced by *-amine*; that is, they are named alkanamines:



2-Butanamine



(*S*)-1-Phenylethanamine

$H_2N(CH_2)_6NH_2$

1,6-Hexanediamine

EXAMPLE 10.2

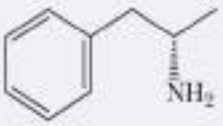
Write the IUPAC name or provide the structural formula for each amine:

(a) 

(b) 2-Methyl-1-propanamine

(c) 

(d) *trans*-4-Methylcyclohexanamine

(e) 

STRATEGY

When naming, look for the longest chain of carbons that contains the amino group. This will allow you to determine the root name. Then identify and name the substituents, the atoms or groups of atoms that are not part of that chain of carbons.

To translate a name to a structure, identify the carbon chain from the root name and add the substituents to the correct position on the chain.

SOLUTION

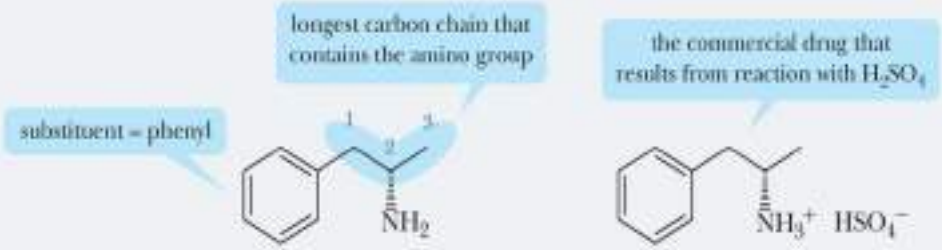
(a) 1-Hexanamine

(b) 

(c) 1,4-Butanediamine

(d) 

(e) The systematic name of this compound is (*S*)-1-phenyl-2-propanamine. Its common name is amphetamine. The dextrorotatory isomer of amphetamine (shown here) is a central nervous system stimulant and is manufactured and sold under several trade names. The salt with sulfuric acid is marketed as Dexedrine sulfate.



(*S*)-1-Phenyl-2-propanamine Dexedrine sulfate

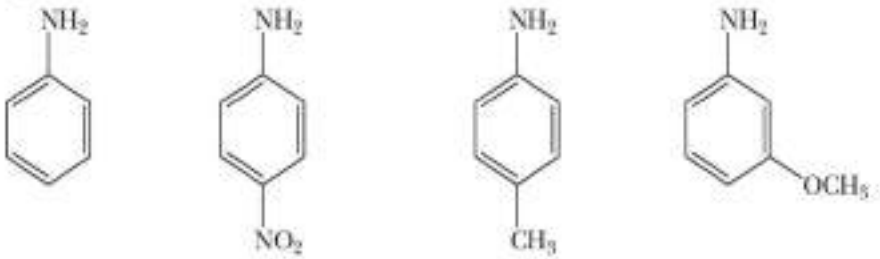
See problems 10.11, 10.12, 10.16

PROBLEM 10.2

Write a structural formula for each amine:

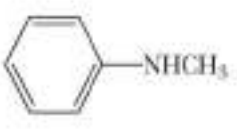
(a) 2-Methyl-1-propanamine (b) Cyclohexanamine (c) (*R*)-2-Butanamine

IUPAC nomenclature retains the common name **aniline** for $C_6H_5NH_2$, the simplest aromatic amine. Its simple derivatives are named with the prefixes *o*-, *m*-, and *p*-, or numbers to locate substituents. Several derivatives of aniline have common names that are still widely used. Among these are **toluidine**, for a methyl-substituted aniline, and **anisidine**, for a methoxy-substituted aniline:

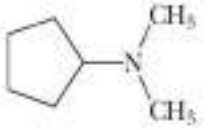


Aniline 4-Nitroaniline (*p*-Nitroaniline) 4-Methylaniline (*p*-Toluidine) 3-Methoxyaniline (*m*-Anisidine)

Secondary and tertiary amines are commonly named as *N*-substituted primary amines. For unsymmetrical amines, the largest group is taken as the parent amine; then the smaller group or groups bonded to nitrogen are named, and their location is indicated by the prefix *N* (indicating that they are bonded to nitrogen):

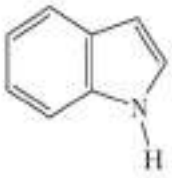


N-Methylaniline

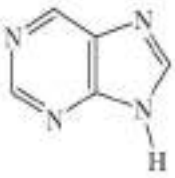


N,*N*-Dimethylcyclopentanamine

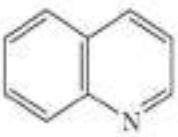
Following are names and structural formulas for four heterocyclic aromatic amines, the common names of which have been retained by the IUPAC:



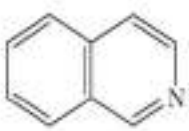
Indole



Purine



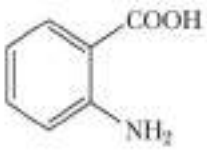
Quinoline



Isoquinoline

Among the various functional groups discussed in this text, the $-NH_2$ group has one of the lowest priorities. The following compounds each contain a functional group of higher precedence than the amino group, and, accordingly, the amino group is indicated by the prefix *amino-*:

2-Aminoethanol
(Ethanolamine)

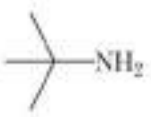


2-Aminobenzoic acid
(Anthranilic acid)

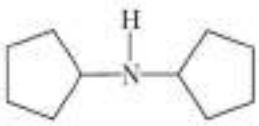
B. Common Names

Common names for most aliphatic amines are derived by listing the alkyl groups bonded to nitrogen in alphabetical order in one word ending in the suffix *-amine*; that is, they are named as **alkylamines**:

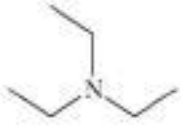
Methylamine



tert-Butylamine



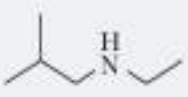
Dicyclopentylamine



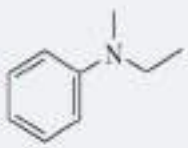
Triethylamine

EXAMPLE 10.3

Write the IUPAC name or provide the structural formula for each amine:

(a) 

(b) Cyclohexylmethylamine

(c) 

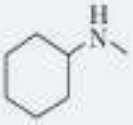
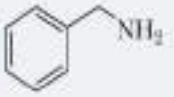
(d) Benzylamine

STRATEGY

When naming, look for the longest chain of carbons that contains the amino group. This will allow you to determine the root name. If the longest chain of carbons is a benzene ring, the amine may be named as an aniline derivative. When identifying the substituents, remember that substitutents bonded to a nitrogen are preceded by "*N*-."

To translate a name to a structure, identify the carbon chain from the root name and add the substituents to the correct position on the molecule.

SOLUTION

(a) *N*-ethyl-2-methyl-1-propanamine (b)  (c) *N*-ethyl-*N*-methylaniline (d) 

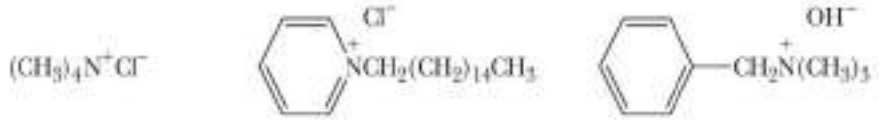
See problems 10.11, 10.12, 10.16

PROBLEM 10.3

Write a structural formula for each amine:

(a) Isobutylamine (b) Triphenylamine (c) Diisopropylamine

When four atoms or groups of atoms are bonded to a nitrogen atom, we name the compound as a salt of the corresponding amine. We replace the ending *-amine* (or aniline, pyridine, or the like) by *-ammonium* (or *anilinium, pyridinium,* or the like) and add the name of the anion (chloride, acetate, and so on). Compounds containing such ions have properties characteristic of salts, such as increased water solubility, high melting points, and high boiling points. Following are three examples (cetylpyridinium chloride is used as a topical antiseptic and disinfectant):



Tetramethylammonium chloride

Hexadecylpyridinium chloride (Cetylpyridinium chloride)

Benzyltrimethylammonium hydroxide

Charles D. Winters

Several over-the-counter mouthwashes contain *N*-alkylatedpyridinium chlorides as an antibacterial agent.

10.3 What Are the Characteristic Physical Properties of Amines?

Amines are polar compounds, and both primary and secondary amines form intermolecular hydrogen bonds (Figure 10.1).

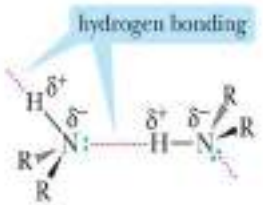


FIGURE 10.1

Intermolecular association of 1° and 2° amines by hydrogen bonding. Nitrogen is approximately tetrahedral in shape, with the axis of the hydrogen bond along the fourth position of the tetrahedron.

TABLE 10.1 Physical Properties of Selected Amines

Name	Structural Formula	Melting Point (°C)	Boiling Point (°C)	Solubility in Water
Ammonia	NH_3	−78	−33	very soluble
Primary Amines				
methylamine	CH_3NH_2	−95	−6	very soluble
ethylamine	$CH_3CH_2NH_2$	−81	17	very soluble
propylamine	$CH_3CH_2CH_2NH_2$	−83	48	very soluble
butylamine	$CH_3(CH_2)_3NH_2$	−49	78	very soluble
benzylamine	$C_6H_5CH_2NH_2$	10	185	very soluble
cyclohexylamine	$C_6H_{11}NH_2$	−17	135	slightly soluble
Secondary Amines				
dimethylamine	$(CH_3)_2NH$	−93	7	very soluble
diethylamine	$(CH_3CH_2)_2NH$	−48	56	very soluble
Tertiary Amines				
trimethylamine	$(CH_3)_3N$	−117	3	very soluble
triethylamine	$(CH_3CH_2)_3N$	−114	89	slightly soluble
Aromatic Amines				
aniline	$C_6H_5NH_2$	−6	184	slightly soluble
Heterocyclic Aromatic Amines				
pyridine	C_5H_5N	−42	116	very soluble

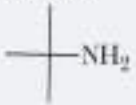
Both compounds have polar molecules and interact in the pure liquid by hydrogen bonding. Methanol has the higher boiling point because hydrogen bonding between its molecules is stronger than that between molecules of methylamine.

All classes of amines form hydrogen bonds with water and are more soluble in water than are hydrocarbons of comparable molecular weight. Most low-molecular-weight amines are completely soluble in water (Table 10.1). Higher-molecular-weight amines are only moderately soluble or insoluble.

EXAMPLE 10.4

Account for the fact that butylamine has a higher boiling point than *t*-butylamine.

Butylamine
bp 78 °C



t-Butylamine
bp 46 °C

STRATEGY

Identify structural differences that might affect the intermolecular attractions between the molecules of each compound.

SOLUTION

Both molecules can participate in hydrogen bonding. However, the *t*-butyl group is larger and bulkier, making it more difficult for the molecules of *t*-butylamine to hydrogen bond to each other.

See problems 10.18–10.20

Aromatic carboxylic acids

Properties of carboxylic acids

Acidity

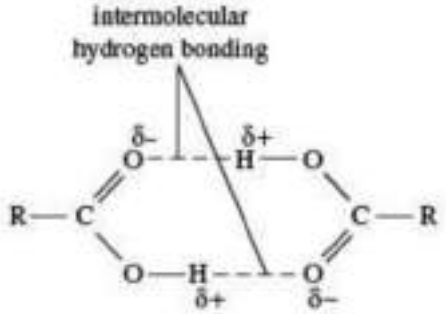
The most important property of carboxylic acids, and the one that is responsible for naming them such, is their acidity. An acid is any compound that donates a hydrogen ion, H^+ (also called a proton), to another compound, termed a base. Carboxylic acids do this much more readily than most other classes of organic compounds, so they are said to be stronger acids, even though they are much weaker than the most important mineral acids sulfuric (H_2SO_4), nitric (HNO_3), and hydrochloric (HCl). The reason for the enhanced acidity of this group of compounds can best be demonstrated by a comparison of their acidity with that of alcohols, both of which contain an ^-OH group. Alcohols are neutral compounds in aqueous solution. When an alcohol donates its proton, it becomes a negative ion called an alkoxide ion, RO^-. When a carboxylic acid donates its proton, it becomes a negatively charged ion, $RCOO^-$, called a carboxylate ion.

Solubility

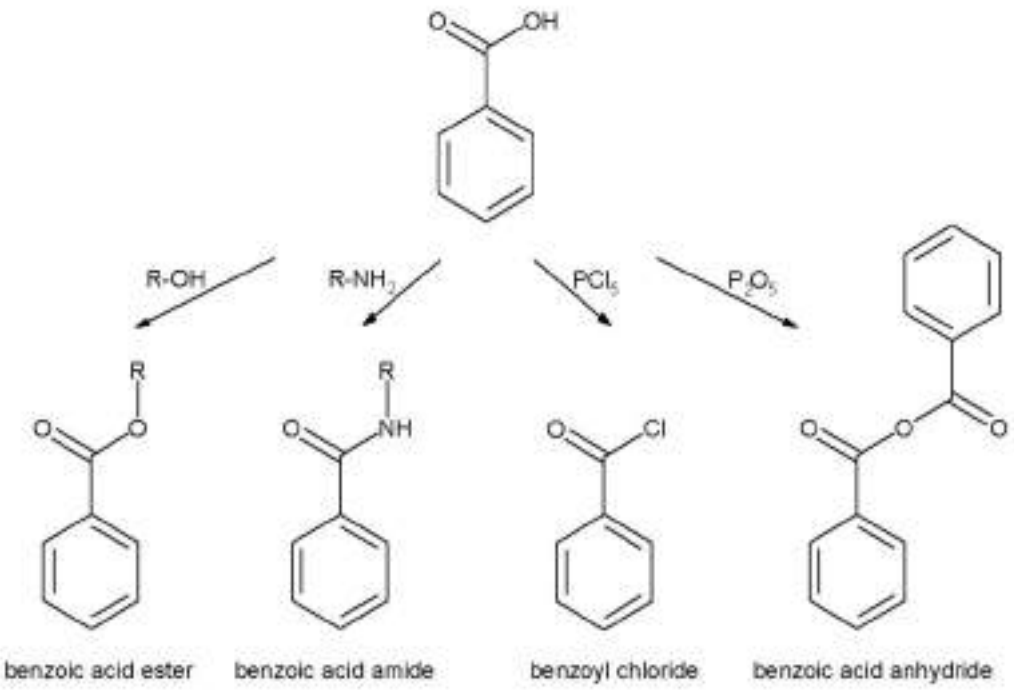
The solubility of carboxylic acids in water is similar to that of alcohols, aldehydes, and ketones. Acids with fewer than about five carbons dissolve in water; those with a higher molecular weight are insoluble owing to the larger hydrocarbon portion, which is hydrophobic. The sodium, ammonium, and potassium salts of carboxylic acids, however, are generally quite soluble in water. Thus, almost any carboxylic acid can be made to dissolve in water by converting it to such a salt, which is easily done by adding a strong base—most commonly sodium hydroxide (NaOH) or potassium hydroxide, (KOH). The calcium and sodium salts of propanoic (propionic) acid are used as preservatives, chiefly in cheese, bread, and other baked goods.

Boiling point

Carboxylic acids have much higher boiling points than hydrocarbons, alcohols, ethers, aldehydes, or ketones of similar molecular weight. The difference is that two molecules of a carboxylic acid form two hydrogen bonds with each other (two alcohol molecules can only form one). Thus, carboxylic acids exist as dimers (pairs of molecules), not only in the liquid state but even to some extent in the gaseous state.

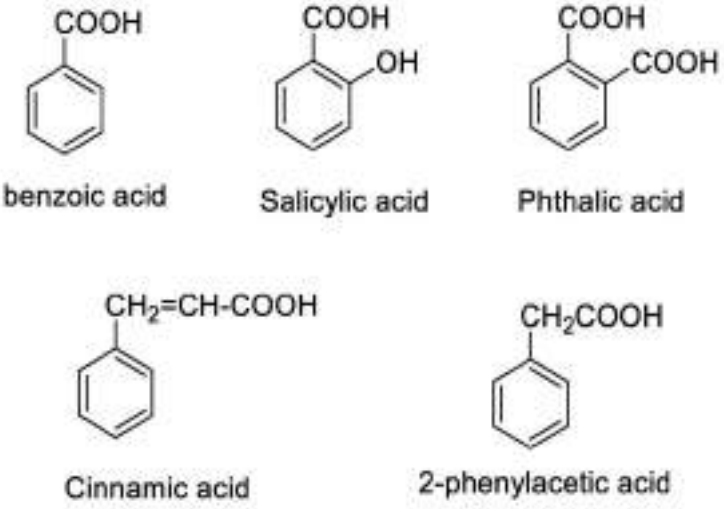


Therefore, boiling a carboxylic acid requires the addition of more heat than boiling the corresponding alcohol, because (1) if the dimer persists in the gaseous state, the molecular weight is in effect doubled; and, (2) if the dimer is broken upon boiling, extra energy is required to break the two hydrogen bonds. Carboxylic acids with higher molecular weights are solids at room temperature (e.g., benzoic and palmitic acids). Virtually all salts of carboxylic acids are solids at room temperature, as can be expected for ionic compounds.



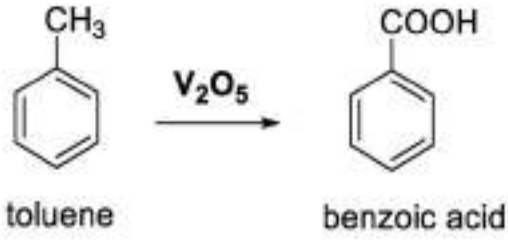
Aromatic carboxylic acids

Aromatic carboxylic acids are compounds containing one or more carboxylic group attached to the benzene ring, Benzoic acid is an example of monocarboxylic (monobasic acid), Phthalic acid is an example of dicarboxylic (dibasic) aromatic acids, Aromatic acids are stronger than aliphatic acids due to the acidity of the benzene ring.



Preparation of benzoic acid

Benzoic acid can be prepared by the oxidation of toluene or benzaldehyde by the proper oxidizing agent, It is prepared commercially by the oxidation of toluene in atmospheric air at 400°C and in the presence of vanadium pentoxide V_2O_5.



Aromatic acids are generally stronger, less soluble in water and less volatile than aliphatic acids, The reaction of the carboxylic group resembles the aliphatic acids, this can be by the formation of salts with metals, their hydroxides or carbonates and the formation of esters with alcohols.

Physical properties of Benzoic acid

Benzoic acid is less soluble in water than acetic acid because the molecular weight of benzoic acid is more than that of acetic acid and as the molecular mass increases, the solubility decreases.

Benzoic acid is less volatile, it has a high boiling point than acetic acid because the molecular mass of benzoic acid is more than that of acetic acid.

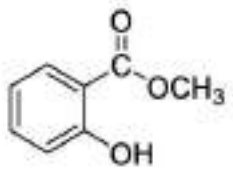
Benzoic acid is stronger in acidity than acetic acid.

Carbolic acid < Acetic acid < Benzoic acid < Salicylic acid < Phthalic acid

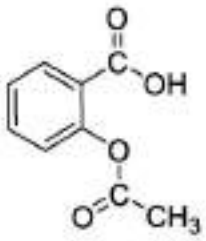
The organic acids in our life

Benzoic acid (C_6H_5COOH) is sparingly soluble in water, It is converted to its sodium or potassium salts to become soluble in water and to be easily absorbed in the human body, sodium benzoate of concentration 0.1% is used as a preservating substance for foods because it prevents the growth of fungi on foods.

Salicylic acid is used in the manufacture of cosmetics specific to skin because it makes it softer, flexible and protect it against sun rays, and It is used in the elimination of skin warts and acne, It is also used in preparation of Aspirin and Marookh, It was used in the treatment of cold diseases and headache since 1829, before using Aspirin, but it caused bleeding of stomach.



Methyl salicylate



Acetylsalicylic acid
(Aspirin)

Three of the most important aromatic dicarboxylic acids are called phthalic, isophthalic, and terephthalic acid, for the ortho, meta, and para isomers, respectively. Phthalic acid is converted to its anhydride simply by heating (see

below Polycarboxylic acids). Phthalic anhydride is used to make polymeric resins called alkyd resins, which are used as coatings, especially for appliances and automobiles. The para isomer, terephthalic acid, is also used to make polymers—namely, polyesters

Organic Chemistry in Our Life

Products With Common Organic Chemicals

These common products make use of organic chemistry:

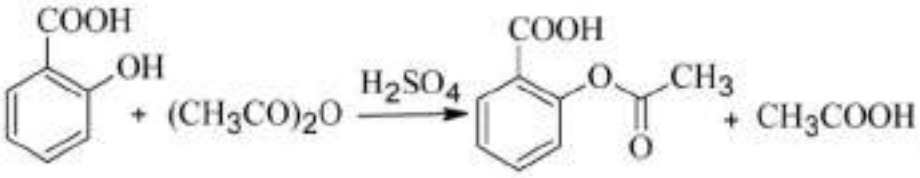
Shampoo, Perfume, Lotion, Detergents, Cosmetics, Gasoline, Drugs, Food and food additives, Plastics, Paper, Insect repellent, Synthetic fabrics (nylon, polyester, rayon), Paint, Mothballs (naphthalene), Enzymes, Nail polish remover, Wood, Coal, Natural gas, Solvents, Fertilizers, Vitamins, Dyes, Soap, Candles, Asphalt ..... ect.

Most products you use involve organic chemistry. Your computer, furniture, home, vehicle, food, and body contain organic compounds. Every living thing you encounter is organic. Inorganic items, such as rocks, air, metals, and water, often contain organic matter, too.

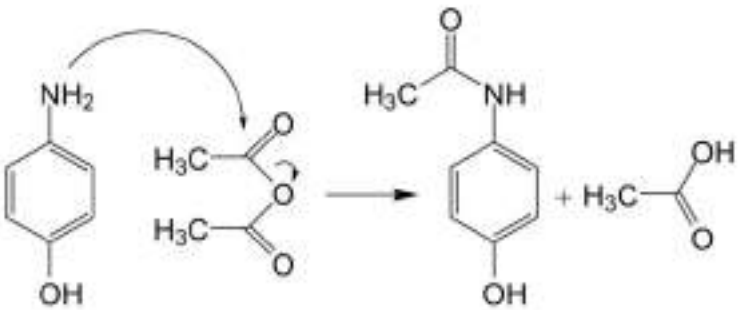
Organic Chemistry in Our Life

Drugs

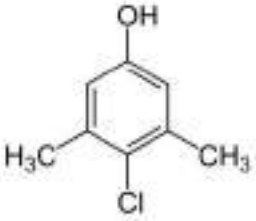
Synthesis of Aspirin



Synthesis of Paracetamol

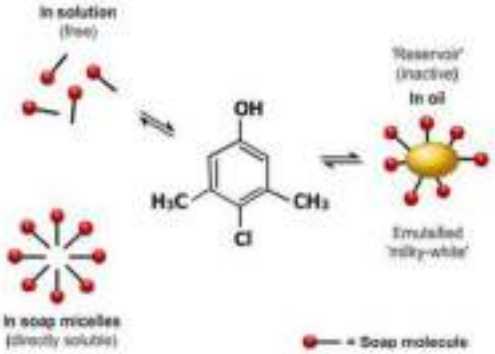


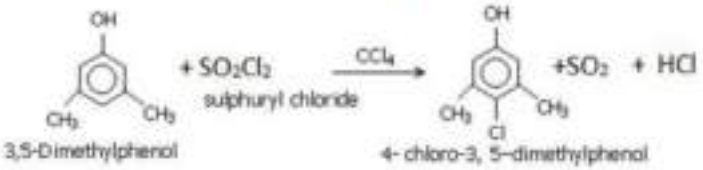
Organic Chemistry in Our Life



Antiseptic

Para chloro meta xylenol- PCMX





Chemical Name	CAS No	Proportion (%w/w)
Chloroxylenol	88-04-0	4.8 (%w/v)
Pine Oil	8002-09-3	<10
Isopropyl alcohol	67-63-0	10 - 30
Other ingredients classified as not hazardous according to NOSCH		to 100

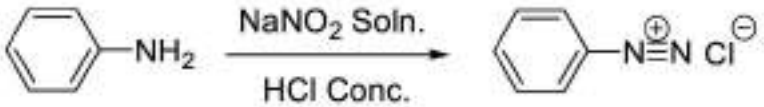
Adapted from Chemistry in the cupboard; RSC chemistry, UK , 2010

Organic Chemistry in Our Life

Azo days

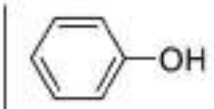
Ar-N=N-Ar

Ex:

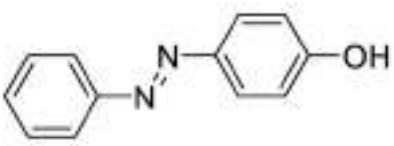


Aniline

Diazonium salt



Phenol



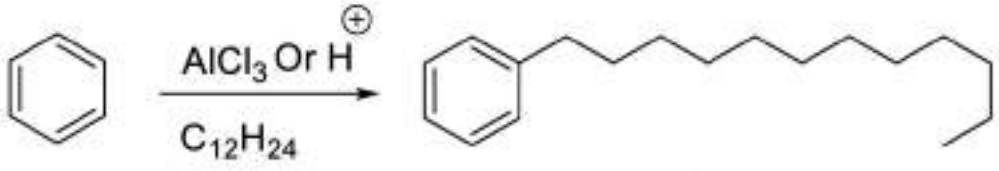
phenyldiazenyl phenol

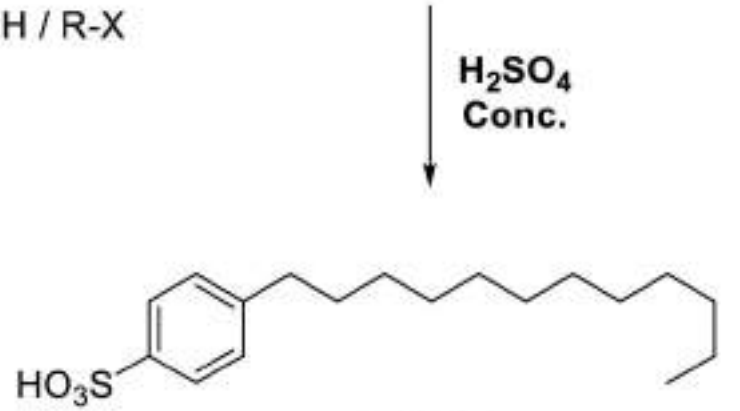
Orange clour azo day

Organic Chemistry in Our Life

Detergents

Ex:





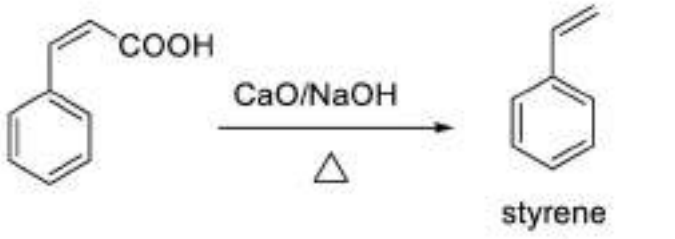
LABSA

Liner Alkyl Benzene Sulphonic Acid

Organic Chemistry in Our Life

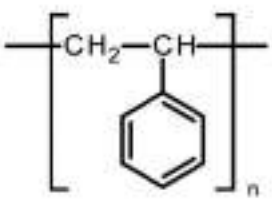
Detergents

Ex:



styrene

Polymerization



Polystyrene

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Organic Chemistry : Structure, Mechanism, Synthesis, Robert J. Ouellette , By (author) J. David Rawn